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DEVELOPMENT OF SELECTIVE AND ECO-EFFICIENT SYNTHETIC PROCESSES PROMOTED BY HETEROGENEOUS CATALYSTS OR IONIC LIQUIDS

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Alla mia famiglia

Content

General Introduction

Sustainable development and Green chemistry

Historically society and industry in particular developed with more or less complete disregard for the environment consequences. The environmental problems we have today and predict for the future are, at least in part, due to society's collective pursuit of short term economic growth.

One of the conclusion from the 1992 United Nations Conference on Environment and Development in Rio de Janeiro was the urgent need to find a more sustainable way of life, based on careful use of resources and a reduction in environmental emissions. There was also a call to move towards a model in which environmental enhancement is fully integrated with economic development. But current thinking on sustainable development already came out of United Nations Commission on Environment and Development in 1987 (Brundtland Commission), which defined sustainable development as development that "meets the needs of the present without compromising the ability of future generations to meet their own needs." Sustainable development is a use of resource that aims to meet human needs while preserving the environment so that these needs can be met not only in the present, but also for future generations. Since 1987 Governments, society and industry have started to consider what sustainable development really means and how best to start to achieve it from their own standpoint.

Two of the key aspects of sustainable development from an energy and chemical perspective are to develop more renewable forms of energy and to reduce pollution.

During the twentieth century chemistry changed forever the way we live. Probably the greatest perceived benefits, to the general public, have come from pharmaceutical industry with development of painkillers, antibiotics or anticancer drugs. In addition our life-style would be completely different without the development of polymeric materials.

However the chemical industry is often viewed as causing more harm than good by general public. The major reason is that the industry is perceived as being polluting and causing significant environmental damage. As well as specific disasters, general pollution came to the public attention in the 1960s and 70s through eutrophication, foaming rivers, the discovery of persistent organic pollutants. Chemists and engineers engaged in development of chemical products and processes have not set out to cause damage to the environment or human health. These have occurred largely through a lack of knowledge, especially of the long term effects of products entering the environment, even if some irresponsible industrial behavior occurred.

The challenge for the chemical industry in the twenty-first century is to continue to provide the benefits we have come to rely on, in a economically viable manner, but without the adverse environmental side effects.

During the early 1990s the US Environmental protection Agency (EPA) coined the concept of Green Chemistry as a chemistry able to promote innovative chemical technologies that reduce or eliminate the use or generation of hazardous substances in the design, manufacture and use of chemical products. Over the last ten years Green Chemistry has gradually become recognized as both a culture and a methodology for achieving sustainability [1].

P. C. Anastas [2] defined the 12 principles of Green Chemistry:

- **Prevention**

It is better to prevent waste than to treat or clean up waste after it has been created.

- **Atom Economy**

Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product.

- **Less Hazardous Chemical Syntheses**

Wherever practicable, synthetic methods should be designed to use and generate substances that possess little or no toxicity to human health and the environment.

- **Designing Safer Chemicals**

Chemical products should be designed to effect their desired function while minimizing their toxicity.

- **Safer Solvents and Auxiliaries**

The use of auxiliary substances (*e.g.*, solvents, separation agents, etc.) should be made unnecessary wherever possible and innocuous when used.

- **Design for Energy Efficiency**

Energy requirements of chemical processes should be recognized for their environmental and economic impacts and should be minimized. If possible, synthetic methods should be conducted at ambient temperature and pressure.

- **Use of Renewable Feedstocks**

A raw material or feedstock should be renewable rather than depleting whenever technically and economically practicable.

- **Reduce Derivatives**

Unnecessary derivatization (use of blocking groups, protection/ deprotection, temporary modification of physical/chemical processes) should be minimized or avoided if possible, because such steps require additional reagents and can generate waste.

❖ **Catalysis**

Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.

❖ **Design for Degradation**

Chemical products should be designed so that at the end of their function they break down into innocuous degradation products and do not persist in the environment.

❖ **Real-time analysis for Pollution Prevention**

Analytical methodologies need to be further developed to allow for real-time, in-process monitoring and control prior to the formation of hazardous substances.

❖ **Inherently Safer Chemistry for Accident Prevention**

Substances and the form of a substance used in a chemical process should be chosen to minimize the potential for chemical accidents, including releases, explosions, and fires.

First, Green Chemistry addresses the problem of efficient utilisation of raw materials and the concomitant elimination of waste. Second, it deals with the health, safety and environmental issues associated with the manufacture, use and disposal or re-use of chemicals [3]. A direct consequence of this trends towards 'green chemistry' is that traditional concepts of process efficiency are changing from an exclusive focus on chemical yield to one that assigns economic value to eliminating waste and avoiding the use of toxic and/or hazardous chemicals [4]. Through application of Green Chemistry concepts significant savings can be made, arising from reduced raw material use, lower capital expenditure, lower costs of waste treatment and disposal, for example. The fundamental challenge for the chemical industry is to continue to provide the benefits to society without causing damage to the environment [1]. The concept of atom efficiency and the E-factor have proven to be popular tools in the evaluation of the "greenness" of a chemical process [5]. They also permit to compare sectors of chemical manufacturing. Roger Sheldon's **E factor** [5][6] calculates the amount of waste for any Kg of product. Assumptions on solvent and other factors can be made or a total analysis can be performed. The E-factor calculation is defined by the ratio of the mass of waste per unit of product:

E Factor = Total Waste (kg) / Product (kg)

The metric is very simple to understand and to use. It highlights the waste produced in the process as opposed to the reaction, thus helping those who try to fulfill one of the twelve principles of green chemistry to avoid waste production. E factors ignore recyclable factors

such as recycled solvents and re-used catalysts, which obviously increases the accuracy but ignores the energy involved in the recovery (these are often included theoretically by assuming 90 % solvent recovery).

Table 1. E Factors across the chemical industry

Industry Sector	Annual Production (t)	E Factor	Waste Produced (t)
Oil Refining	10^6-10^8	Ca. 0.1	10^5-10^7
Bulk Chemicals	10^4-10^6	<1-5	10^4-5×10^6
Fine Chemicals	10^2-10^4	5-50	5×10^2-5×10^5
Pharmaceuticals	10-10^3	25-100	2.5×10^2-10^5

Crucially, this metric is simple to apply industrially, as a production facility can measure how much material enters the site and how much leaves as product and waste, thereby directly giving an accurate global E-factor for the site. Table 1 shows that oil companies produce a lot less waste than pharmaceuticals as a percentage of material processed. This reflects the fact that the profit margins in the oil industry require them to minimize waste and find uses for products which would normally be discarded as waste. By contrast the pharmaceutical sector is more focused on molecule manufacture and quality. The currently high profit margins within the sector mean that there is less concern about the comparatively large amounts of waste that are produced (especially considering the volumes used) although it has to be noted that, despite the percentage waste and E factor being high, the pharmaceutical section produces lower tonnage of waste than any other sector. This table encouraged a number of large pharmaceutical companies to commence "green" chemistry programs. The E factor takes only the mass of waste generated into account. However, what is important is the environmental impact of this waste, not just its amount, *i.e.* the nature of the waste must be considered. One kg of sodium chloride is obviously not equivalent to one kg of a chromium salt. Hence, Sheldon introduced the term 'environmental quotient', EQ, obtained by multiplying the E factor with an arbitrarily assigned unfriendliness quotient, Q. For example,

one could arbitrarily assign a Q value of 1 to NaCl and, say, 100-1000 to a heavy metal salt, such as chromium, depending on its toxicity, ease of recycling, etc. The magnitude of Q is obviously debatable and difficult to quantify but, importantly, 'quantitative assessment' of the environmental impact of chemical processes is, in principle, possible. It is also worth noting that Q for a particular substance can be both volume-dependent and influenced by the location of the production facilities.

Another fundamental concept is atom efficiency. Most people would associate oil refining more than pharmaceutical manufacturing with dirty processes and waste, yet, while the sheer scale of the former leads to the largest volume of waste, the ratio of waste to product is greater for the latter by a factor of 102–103. In pharmaceutical and fine chemicals manufacturing, the high value of the product has been a particularly significant feature in the establishment of many highly (atom) inefficient processes. Stoichiometric reagents (*e.g.*, chromate oxidants), catalysts that cannot easily be recovered and reused, and large volumes of volatile organic solvents are routinely used with all the consequential waste at the end of the reaction when the organic products need to be separated from the inorganic reagents, catalysts, and solvents (typically by an aqueous quench). Some of the biggest problem areas in synthetic methodology in this context are:

• acid-catalyzed reactions
• selective oxidations
• halogenations
• base-catalyzed reactions
• reductions
• metal-catalyzed reactions
• phase-transfer-catalyzed reactions

In tackling these problem areas, we should not be afraid to strive toward the "ideal synthesis" which would be

• atom efficient
• safe
• one step
• involving no wasted reagents
• based on renewable resources
• environmentally acceptable (including product fate considerations).

Step changes that move toward the ideal synthesis can be achieved with the application of several technologies including catalysis, process intensification, alternative energy sources and supercritical fluids. Since the major source of waste from a chemical process is the separation stage, it would seem sensible to focus heavily on that. The heterogenization of catalysts so that they can easily be separated and reused at the end of a process, is a logical and versatile approach to simplifying the process, removing the need for an aqueous quench or other destructive separation step and reducing the demand for raw materials [7].

So considering these points in this dissertation we reported the development of selective and eco-efficient processes. Particularly we focussed our attention on:

- ❖ oxidation processes promoted by supported catalysts
- ❖ enantioselective oxidation processes promoted by ionic liquids
- ❖ C-C bond formation reactions promoted by supported ionic liquids or commercial clays.

Catalysis

Catalysis, which has played such a vital role in the success of the industry in the 20th century, will also play a very important role in the new greener industry of the new century.
Reducing the environmental impact of chemical processes (*e.g.*, by replacing reagents or by enabling more efficient processes), catalysis will catalyze the greening of chemistry [7]. Today it is estimated that 90% of chemicals used have come into contact with a catalyst at some stage in their manufacture. All major bulk chemical and refining processes employ catalysts. The number of fine and pharmaceutical processes currently using catalysts is still relatively small by comparison, but a combination of economic and environmental factors is focusing much research on this area. There are important parameters that impact on both the commercial viability and the greenness of a catalyst:

- Selectivity: a catalyst will be of limited benefit if it also enhances the rate of by-product formation.
- Turnover frequency and Turnover number: they are related to catalyst lifetime and hence to cost and waste. Low turnover number and low turnover frequency will mean large that amount of catalyst is required, increasing the cost and the amount of waste.

Catalysts are extensively used and play a huge role in making bulk chemical manufacture technology more competitive and environmentally friendly. They are now needed by the fine chemical and pharmaceuticals industries and they need to be selective, robust, recoverable and reusable.

Catalysis as a whole comprises the varieties of heterogeneous, homogeneous, and biological (enzyme) catalysis. In agreement with its historical development, heterogeneous catalysis was applied first commercially to a large extent. Enzymatic catalysis is the most recent discipline and has developed explosively, being included in many commercial applications. In between is homogeneous catalysis, which in fact started with the action of nitrous oxides in the lead chamber process and thus prior to the recognition of the effects of heterogeneous catalysts. Now it is estimated that 85% of all chemical processes are run catalytically, with a ratio of applications of heterogeneous to homogeneous catalysis of appoximately 75:25. It is true that homogeneously catalyzed processes such as hydroformylation, carbonylation, oxidation, hydrogenation, metathesis, and hydrocyanation contribute with millions of tons to the bulk chemicals, but on the other hand the progress of homogeneous catalysis is also going on with fine chemicals, *i.e.*, with products the manufacture of which ensures high atom economies or *E* factors [8].

There are some differences between heterogeneous and homogeneous catalysts that have a significant impact on their greenness (Table 1).

Table 1. Comparison of heterogeneous and homogeneous catalysts.

Heterogeneous	*Homogeneous*
Usually distinct solid phase	Same phase as reaction medium
Readily separated	Often difficult to separate
Readily regenerated and recycled	Expansive/ difficult to recycle
Rates not usually as fast as homogeneous	Often very high rates
May be diffusion limited	Not diffusion controlled
Quite sensitive to poisons	Usually robust to poisons
Lower selectivity	High selectivity
Longer service life	Short service life
Often high- energy process	Often takes place under mild conditions
Poor mechanistic understanding	Often mechanism well understood

In term of total tonnage and dollar value the contribution of homogeneous catalytic processes is significantly smaller than that of heterogeneous catalytic reactions. All the basic raw materials or building blocks for chemicals are manufactured by a small but very important set of heterogeneous catalytic reactions [9]. Heterogeneous catalysts have been used the first time industrially 100 years ago. Amongst the first processes was the catalytic hydrogenation of oils and fats to produce margarine using finely divided nickel. It is quite likely that when this process was first operated in the late nineteenth century unhealthy amounts of nickel remained in the product. The issue of leaching and the avoidance of trace catalyst residues are still important aspects of research from both human health, economic and environmental point of view. In contrast to refinery and bulk chemical operations, heterogeneous catalysts are not widely employed in the manufacture of fine chemicals and pharmaceuticals. With increasing concern over waste by-products from these industries, as well as the increasing cost of waste treatment and disposal, considerable effort is now being put into using heterogeneous catalysts to improve efficiency and reduce the environmental impact of these sectors.

Although the fundamental processes for refining petroleum and its conversion to basic building blocks are based on heterogeneous catalysts, many important value-added products are manufactured by homogeneous catalytic processes [9].

Homogeneous catalysts have been well researched, since their catalytic centres can be relatively easily defined and understood, but difficulties in separation and catalyst regeneration prevent their wider use. These challenges are the focus of current research. The most widely used homogeneous catalysts are simple acids or bases which catalyze well-known reactions such as ester and amide hydrolysis or esterification. Such catalysts are inexpensive enough that they can be neutralized, easily separated from organic materials and disposed of. This contributes to the huge quantity of aqueous salt waste generated by industry. Many of the green benefits of homogeneous catalysts, especially high selectivity, arise from tailored made catalysts involving transition metals and appropriate ligands [1].

Immobilized catalysts

The ultimate goal of many researchers working in the field of catalysis is to combine the fast rates and high selectivity of homogeneous catalysts with the easy recovery and recycle of heterogeneous catalysts. In the majority of cases this results in studies aiming to heterogenize a homogeneous catalyst.

Immobilised heterogeneous catalysts should exhibit all mentioned advantages of both homogeneous and heterogeneous catalysts [10], such as comparable performance to that of the free catalyst, simple and efficient preparation, general applicability of the procedures and sufficient chemical and thermal stability of the support. When used in batch operation, leaching of catalyst elements into the reaction medium should be minimal, while its separation from the products should be possible with simple techniques such as filtration. Finally, reuse without activity and selectivity loss should be possible as well. In continuous flow operation with a fixed bed of immobilised catalyst, stability in time of both activity and selectivity is a prerequisite. Present-day requirements imply that such catalyst preparation and operation should be designed to cope with the concept of sustainability and in an industrial environment to show minimal energy consumption [11]. However the creation of the ideal supported catalyst is related to the need of new technologies and new supports since they have an important role in the outcome of the process.

In fact, normally, the heterogenization procedure causes a decreasing in activity and stereoselectivity in comparison with the homogeneous catalyst. Besides the solid support determines limited diffusion of reactants to the active sites and this results in lower reaction rates.

There are several general applicable methods for the transformation of major homogeneous catalysts to give recyclable heterogeneous catalysts:

- impregnation
- steric hinderance-occlusion in porous systems (ship in the bottle)
- "mobile support" technique
- grafting or tethering (covalent bond).

Impregnation is based on the immobilisation of complexes via electrostatic interactions with a solid support. As an example, cationic Rh-diphosphine cationic complexes are retained on anionic resins via ion-pair formation, yielding recyclable catalysts devoid of metal leaching [12]. Although all inorganic or organic supports with ion exchange properties can be used, such as anion and cation exchange resins, clays, and zeolites, the retention of such complexes is governed by mere ion-exchange equilibria between the complex and the support. Multivalent metal complexes show good retention, provided that the active form of the complex does not undergo reduction.

Heterogenisation via complex entrapment is a typical method that occurs with zeolite supports. The term "ship-in-bottle" catalysis has been coined for this method. The strategy consists in the in situ synthesis of the transition metal complex in support cages, assuring

retention for steric reasons [13]. Alternatively, functionalised ligands can be prepared that are soluble in the reaction medium but allow the catalyst complexes to be separated from the reaction medium by extraction, filtration or precipitation after temperature or pH change [14]. In an other approach, the functionalised complexes allow one to perform the reactions in two-phase conditions [15]. This development found industrial applications in the case of olefin hydroformylation [16]. In this biphase technique the homogeneous catalyst is dissolved in water, acting as the "mobile support". Simple decantation allowing phase separation, results in the separation of the catalyst present in the aqueous phase from the organic phase containing the products. All these approaches yield an immobilised catalyst, which is not anchored chemically to any support.

A straightforward strategy to combine the best properties of homogeneous and heterogeneous catalysts, allowing efficient catalyst separation from product mixture, is to immobilise irreversibly the suitably ligated catalyst on a solid support [17]. The numerous attempts combining the best properties of homogeneous and heterogeneous catalysts involve as catalyst support either organic polymers such as

- linear, non-cross-linked polymers soluble in suitable solvents
- swellable, slightly cross-linked polymers
- highly crosslinked polymers

or porous inorganic solids such as

- Amorphous oxides (silica, alumina, zirconia)
- Clays, pillared clays
- Zeolites
- MCM.

This kind of immobilization can be performed by tethering or grafting techniques. When grafting technique is applied [18], the catalytic site is directly anchored on the support (Figure 1). This procedure is used for supporting organometallic complexes, in those cases by ligand exchange reaction, deprotonated Si-OH complete the metal coordination first sphere.

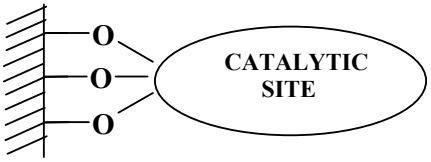

Figure 1. Grafting technique

In Tethering technique, a spacer is introduced between the support and the catalytic site. The nature and the length of the spacer can be tuned in order to minimize the steric hindrance of the support. Furthermore the catalytic site is in a similar condition to homogeneous phase, so the steric hindrance of the support is usually less important than in grafted catalyst [19].

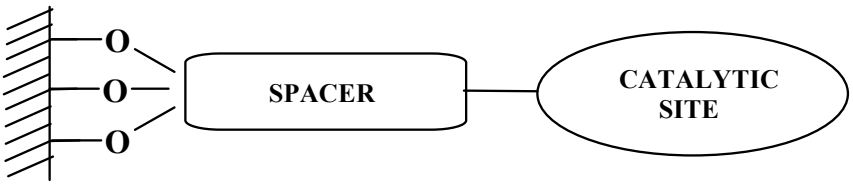

Figure 2. Tethering technique

Even if the support is inert, its structure is of vital importance to the efficiency of the catalyst reaction. The support acts like many small molecular reactors and modifies the characteristics of free catalysts increasing the steric constraints and enhancing the local concentrations of reagents near the surface where the reaction takes place. Since the reactants are in a different phase to the catalyst both diffusion and adsorbsion influence the overall rate. Many modern inorganic supports have surface areas of 100 to ›1000 m^2g^{-1}, the vast majority of this area is due to the presence of internal pores.

Materials with an average pore size of less than 1.5-2 nm are called microporous, while materials with very large pore sizes (›50nm) are called macroporous materials; those with intermediate pore sizes are called mesoporous. The support can be a siliceous or a organic polymeric material. In many cases, mesoporous and macroporous silica gel have been used as support. As far as the anchoring of catalytic moieties is concerned, the key step consists in the functionalisation of the silica surface, populated with silanol groups. The pre-treatment temperature of the parent silica determines the nature of the hydroxy groups (isolated, geminal, hydrogen bound), their location and reactivity. In nanostructured mesoporous silica of the MCM-41-type, the reactivity of the siloxanes is considered to be sufficient for covalent linking with a tether [20]. The transformation of the silica surface is possible via a pleiade of

commercially available silylating agents, yielding the same functionalities mentioned also for polymeric supports. Concomitant or subsequent silylation with trimethylchlorosilane makes possible to ensure the neutralisation of residual hydroxyl groups.
The versatility of functional groups for reaction with tethering groups on siliceous materials (surface silanols) is distinctly lower than that on the organic polymeric supports. With the advent of hierarchically ordered silica materials, however, such supports show a wide variety in porosity [21]. Next to the nature of the support, its degree of loading and the nature of the solvent used, the length and flexibility of the spacer require fine tuning to reach optimal catalytic behaviour [22]. Polystyrene cross-linked for a few percent with 1,4-divinylbenzene, although readily filtered, should be used in swellable solvents, the nature of which is determining diffusion behaviour. On the other hand, highly cross-linked polystyrene or polyacrylate as well as inorganic supports like silica, show permanent and fixed porosity and can be used in presence of a large variety of solvents [23].

In this dissertation the tethering approach has been followed to immobilize different homogeneous catalysts on amorphous silica.
The immobilization has been achieved using trialkoxysilyl compounds giving intermediate species for a further functionalization in order to prepare the catalysts.
The obtained catalysts have been used for oxidation processes and for carbon-carbon bond formation reactions.

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Chapter 1

Silica-bound decatungstates as heterogeneous catalysts for H_2O_2 activation in selective oxidation reactions

1.1 Introduction

Oxidation reactions are some of the most useful chemical transformations despite the fact that they are among the most problematic processes, due mainly to the production of large amounts of pollutant materials [1]. At the international level, significant effort has been devoted to substituting the traditional stoichiometric inorganic oxidants such as Cr(VI) and Mn(VII) with cleaner catalytic systems. The heavy metal oxidants give toxic wastes, organic stoichiometric oxidants are usually very expensive [2], and nitric acid unavoidably forms various nitrogen oxides. Therefore, the need for cleaner and safer oxidation procedures has prompted industrial and academic researchers to investigate the use of benign, easy-to-handle oxidants, such as hydrogen peroxide and molecular oxygen. Indeed, the use of hydrogen peroxide as an oxidant has attracted considerable attention in recent years [3]. Aqueous hydrogen peroxide is an ideal oxidant for liquid-phase reactions because it produces only harmless water by reaction, is safe to store and use, and is cheap and readily available [4]. Among the different metal catalysts, various types of tungsten-based catalytic systems have been reported to be used in the activation of H_2O_2 [5]. Recently, Noyori and co-workers described the activity of sodium tungstate combined with phenylphosphonic acid and a quaternary ammonium hydrogen sulfate as a phase-transfer catalyst [3] in the oxidation of alcohols, olefins, and sulfides. A further step in the development of environmentally benign chemical processes is the replacement of current homogeneous oxidation procedures for the synthesis of fine chemicals by heterogeneous processes. Immobilized catalysts are receiving great interest due to several advantages, such as simplified product work-up, separation, isolation, and catalyst reuse [7]. Indeed, chemical processes with little waste are expected from using immobilized catalysts, because these catalysts can be easily recovered and reused.
Further developing the interest of our group in heterogeneous catalysis [8], in this chapter we present the preparation of alkyl ammonium decatungstates chemically bound to silica support. We explore the activity of these hybrid catalysts in H_2O_2 activation, examining the oxidation of different substrates.
Polyoxometalates (POMs, transition metal oxygen–anion clusters) are a large and rapidly growing class of inorganic compounds with significant applications in a range of areas. Such materials have been studied in detail over the past decades with some of them possessing interesting applications in catalysis [9]. Among them, decatungstate anion ($W_{10}O_{32}^{4-}$) is one of the most promising examples.

The structure of this polyoxoanion has been determined by Fuchs [10]. It is reported to have a D_{4h} symmetry. Two W_5O_{18} units are bonded mirror-simmetrically through four common oxygen atoms with formation of an octahedral space (Figure 1).

The activity of the decatungstate anion $W_{10}O_{32}^{4-}$ in promoting photo-oxygenation of various substrates has been studied extensively [11]. Recently, hexadecyl trimethyl ammonium decatungstate was reported to catalyze hydrogen peroxide activation for the oxidation of alcohols [12], and a paper dealing with lacunary polyoxotungstate for microwave-assisted H_2O_2 activation has been published recently [13]. Surfactant-type decatungstates were prepared and used as catalysts in oxidative desulfurization of fuel oils employing H_2O_2 as oxidant [14]. Indeed this polyoxoanion looks really active in homogeneous catalysis in the oxidation of dibenzothiofene and its derivatives, really difficult to remove by typical hydrodesulfurization.

Heterogenized alkylammonium decatungstates were previously reported in the literature as catalysts for photo-oxidation reactions, but the immobilization of such catalysts was usually performed by impregnation of the solid support [8] or by embedding in different polymeric membranes [15] or inside the silica network [16]. To enhance the activity and stability, it may be preferable to anchor the metal catalyst to the support through a chemical bond. Thus, we designed an ammonium cation covalently bound to the solid support and then we introduced the polyoxoanion via an exchange reaction [17]. The anchoring of the metal catalyst through a chemical bond should expand the range of possible reaction solvents including those solvents able to dissolve and to remove the ammonium decatungstate from the support. Furthermore, the chemical bond, stronger than electrostatic interactions, should increase the robustness of the catalyst, making it reusable.

The ability of different type of alkylammonium decatungstates (**CAT I-IV** in figure 1**)** in the activation of H_2O_2 has been studying in the oxidation of different substrates.

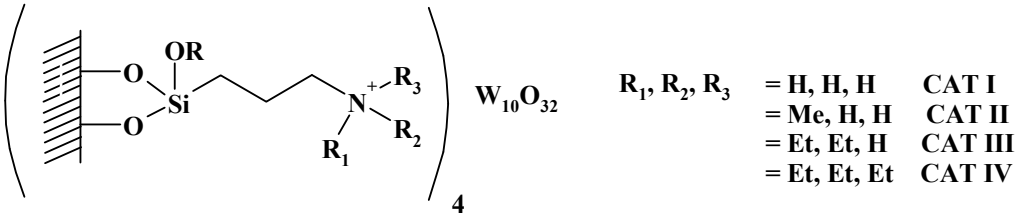


Figure 1. Ammonium decatungstates bound to silica.

First we investigated the oxidation of sulfides to sulfoxides. Organosulfur compounds are versatile and useful intermediates in organic synthesis for the preparation of biologically active products [18]. The sulfoxide group is present in well-known drugs, the proton-pump inhibitors omeprazole and lansoprazole, as well as in the pesticide fipronil and various insecticides. The selective oxidation of sulfides to sulfoxides is a problem that remains the subject of intensive study [3].

More recently, the oxidation of secondary amines to nitrones has been studied as well. Nitrones are really important compounds. They were originally developed as free radical-trapping agents in free radical chemistry. Two decades later, it was realized that nitrones could protect biological systems from oxidative stress.

Therefore nitrones have been tested as therapeutic agents for neuraland systemic dysfunctions including atherosclerosis, septicemia, stroke, and Alzheimer's disease. Some derivatives of α-phenyl-*tert*-butylnitrone (PBN) have undergone extensive commercial development as therapeutics for acute ischemic stroke. Also, in recent observations nitrones have been shown to act synergistically in combination with antioxidants in the prevention of acute acoustic-noise-induced hearing loss [19].

Moreover they have been widely employed either as 1,3-dipoles in [3+2] cycloaddition reactions with alkenes [20] or as electrophilic acceptors towards organometallic reagents [21].

So the selective oxidation of secondary amines to nitrones represents a really important target.

1.2 Results and discussion

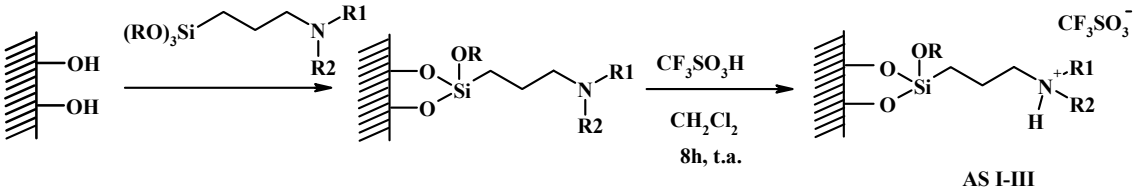
1.2.1 Catalyst preparation and characterization

The preparation of catalysts **CAT I–IV** involved two main steps: (a) silica functionalization anchoring ammonium salts to surface silanols and (b) anion exchange with sodium decatungstate (Scheme 1).

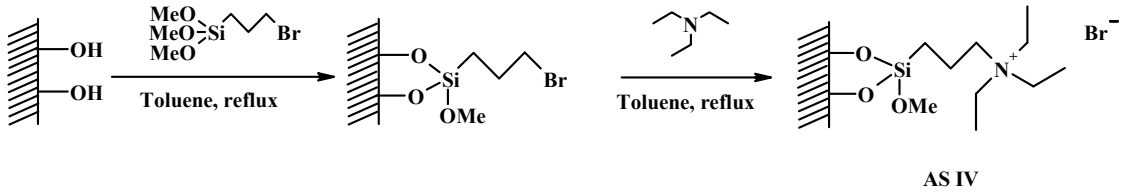
Scheme 1.

(A) heterogenisation of ammonium salts

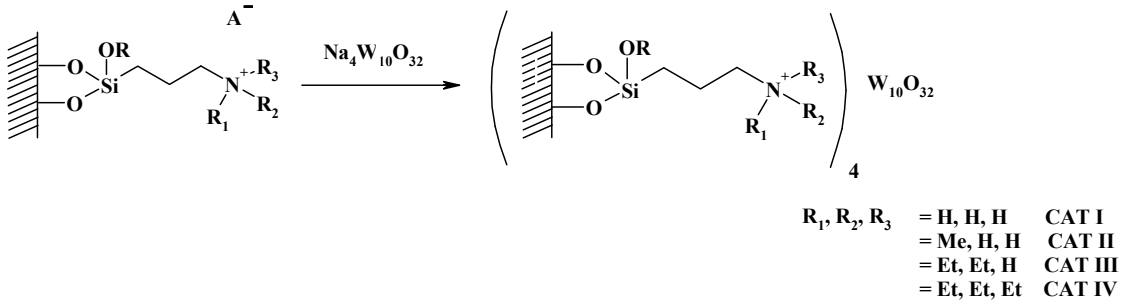
i)



ii)



(B) decatungstate anchoring



Alkylammonium heterogenization was done by one of two procedures depending on the type of ammonium cation. Anchored primary, secondary, and tertiary ammonium salts were prepared by refluxing silica and the suitable (alkylaminopropyl)trialkoxysilane in toluene under stirring for few hours. The cooled functionalized silica was filtered off, washed and then dried under high vacuum to give the surface-bound alkylamine groups with a loading of 0.8–0.9 mmol/g. The resulting materials in dry dichloromethane were reacted with trifluoromethane sulfonic acid for 8 h at room temperature, filtered off, washed and then

dried under vacuum affording the corresponding alky-ammonium salts bound to the solid surface (**AS I–III** in Scheme 1, Ai). Elemental analyses revealed a sulfur loading of 0.8–0.9 mmol/g. To prepare supported quaternary ammonium bromide, (3-bromopropyl)trimethoxysilane was condensed with silica silanols by refluxing in toluene following the procedure described above. The bromopropylated silica (0.5 mmol/g loading) was then treated with triethylamine in refluxing toluene for 24 h, affording the corresponding supported quaternary ammonium bromide (**AS IV** in Scheme 1, Aii) [22]. After cooling, the solid was filtered on a Büchner funnel and carefully washed with toluene, then dried at 60 ˚C under high vacuum. The amount of bromide ions present on the functionalized silica after the reaction with triethylamine was determined by titration [23] according to the method described by Volhard, giving a bromide loading of 0.43 mmol/g. The catalysts **CAT I–IV** were prepared by stirring a mixture of the selected surface-bound alkylammonium salt and an aqueous solution of sodium decatungstate in distilled water at room temperature for 30 min (Scheme 1, B). The choice of the reaction time is important to ensure the anion exchange avoiding the degradation of sodium decatungstate in water, as evidenced by following the variation of the UV absorption band at 323 nm in two hours time (Figure 2).

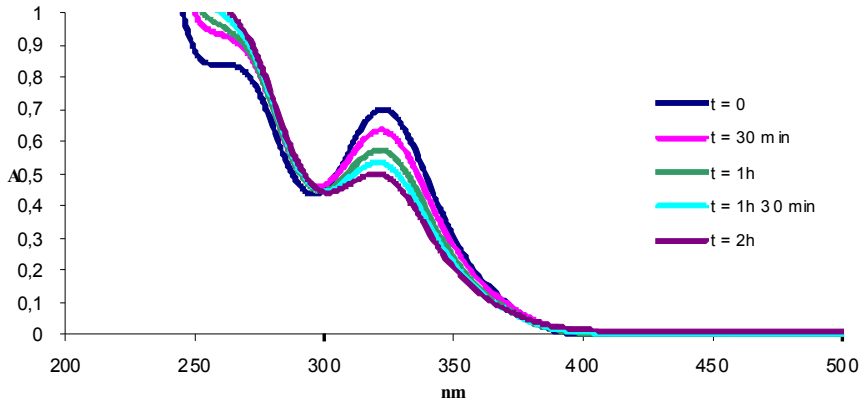


Figure 2. Uv spectrum of Sodium Decatungstate in H_2O.

Then the solids were washed in continuous with hot acetonitrile for 12 h using a Soxhlet apparatus. After drying under high vacuum for 3 h, the catalysts were completely characterized. All functionalized materials were characterized with respect to compositional, structural, and surface properties.

Table 1. Surface area (SA_{BET}), A^- loading in precursor **AS**, N and decatungstate loading of catalysts **CAT I-IV.**

Catalyst		$SA_{BET.}$ (m^2/g)	A^- load. in AS (mmol/g)	N loading (mmol/g)	W_{10} loading (mmol/g)
CAT I	$\{SiO_2-(CH_2)_3NH_3\}_4W_{10}O_{32}$	190	0.80	0.7	0.12
CAT II	$\{SiO_2-(CH_2)_3NH_2Me\}_4W_{10}O_{32}$	173	0.92	0.7	0.16
CAT III	$\{SiO_2-(CH_2)_3NHEt_2\}_4W_{10}O_{32}$	185	0.81	0.6	0.13
CAT IV	$\{SiO_2-(CH_2)_3NEt_3\}_4W_{10}O_{32}$	313	0.43	0.3	0.06

As expected, a general decrease in surface area was found due to functionalization, and a more pronounced effect was observed with increasing of loading. Elemental analysis of the materials obtained at each step of functionalization allowed us to evaluate the loading of the supported organic moieties, which was found to be 0.3–0.9 mmol/g. The higher values of loading observed at the first step when propylamino groups were present could be ascribed to base catalyzed condensation. The absence of sulphur atoms after the exchange process is noteworthy, indicating the complete substitution of trifluoromethane sulfonate with decatungstate anions. ICP-AES analyses of the catalysts allowed us to evaluate the W loading. The W_{10} loading of catalysts **CAT I–IV** are reported in Table 1. The simultaneous ICP-AES analyses of W and Na demonstrated that practically all of the sodium of $Na_4W_{10}O_{32}$ was exchanged. The complete substitution of sodium in supported decatungstate was confirmed by EDS microanalysis. The discrepancy between nitrogen and W_{10} loadings is not as high as it might appear, because one decatungstate unit requires four ammonium cations. In addition, we verified that silica treated with $Na_4W_{10}O_{32}$ and washed according to the exchange procedure did not present any amount of tungsten. This result indicates that the only species present on silica are alkylammonium decatungstates bound to the support.

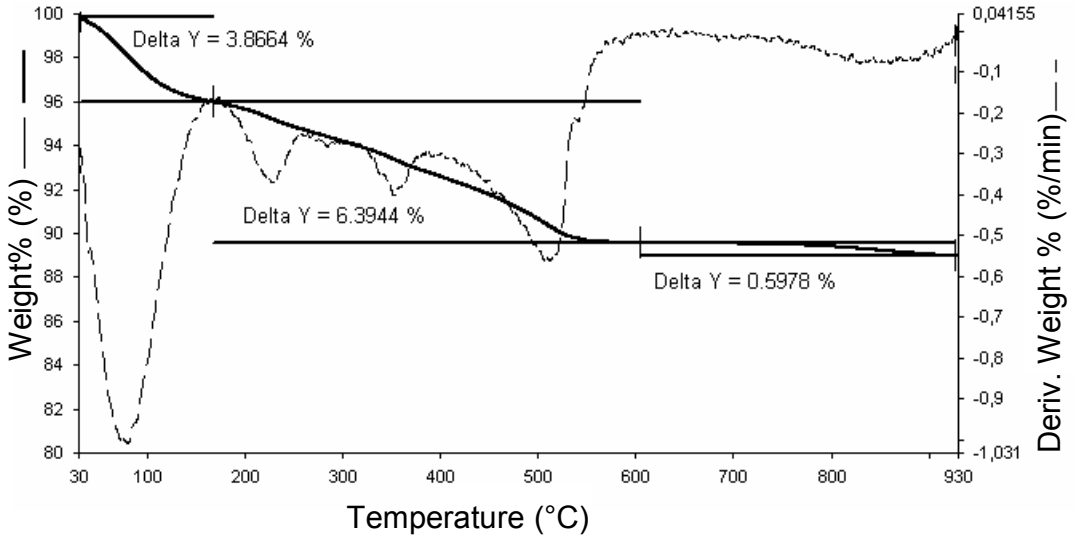


Figure 3. TGA/ DTG analysis of **CAT I**.

TGA/DTG of all the catalysts (Figure 3) revealed that the first step of thermal decomposition, from room temperature to 170 °C, corresponds to removal of the surface-adsorbed water, and that the major weight loss occurs at high temperature, as expected for chemisorbed materials, confirming that ammonium groups are covalently bound on the surface of silica.

FTIR spectra (Figure 4) demonstrate that the structure of decatungstate was still preserved on the silica surface. The characteristic frequencies of W–O stretching modes [24] were observed for all the catalysts. Fig. 3 shows the spectra of the bare SiO_2 (a), $(n\text{-}Bu_4N)_4W_{10}O_{32}$ (b), and **CAT I** (c), in which the three bands at 945, 893, and 803 cm^{-1} are readily distinguishable.

UV–vis spectroscopy is reported highly diagnostic for decatungstate polyanion, showing a characteristic absorption at 324 nm (in addition to the band at 268 nm) in solution assigned to oxygen-to-tungsten charge transfer (O→W CT) transition (Figure 5). The UV–vis diffuse reflectance spectra of all of the catalysts showed this typical band. Fig. 6 illustrates the spectrum of **CAT IV** [25].

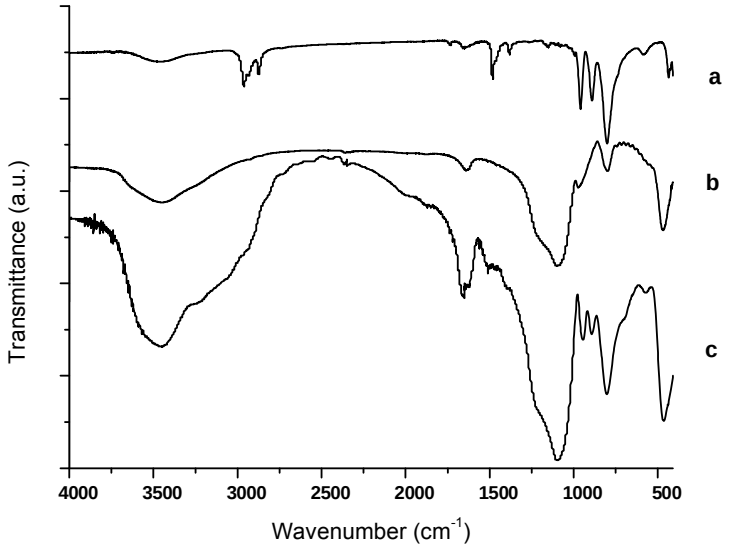


Figure 4. FT-IR spectrum of **CAT I.**

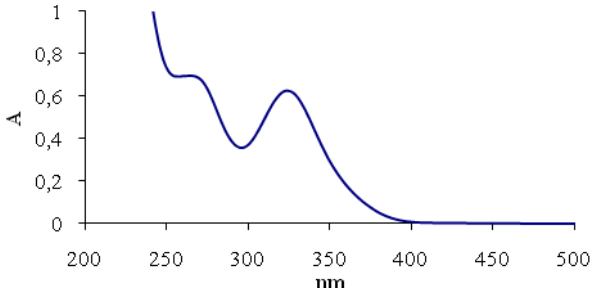


Figure 5. UV spectrum of $Na_4W_{10}O_{32}$ in CH_3CN.

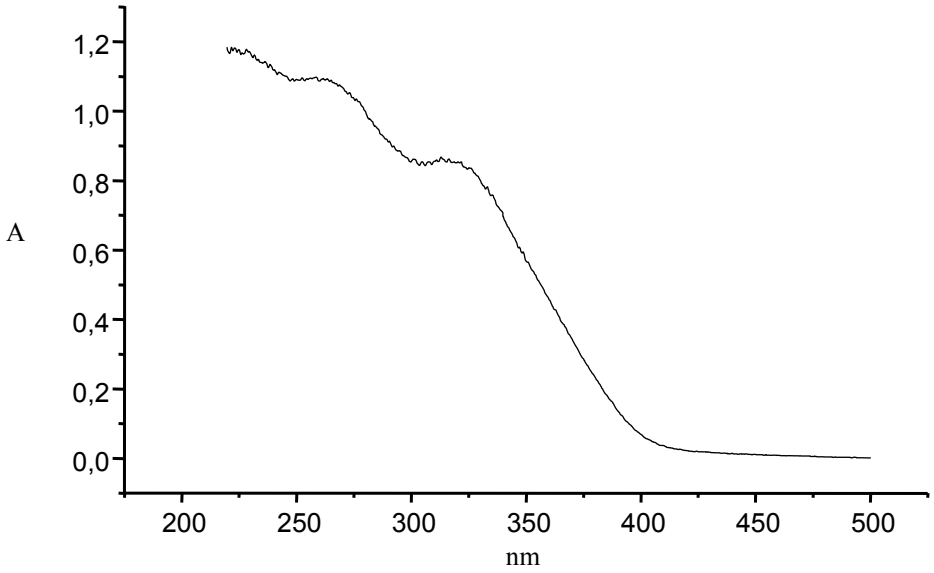
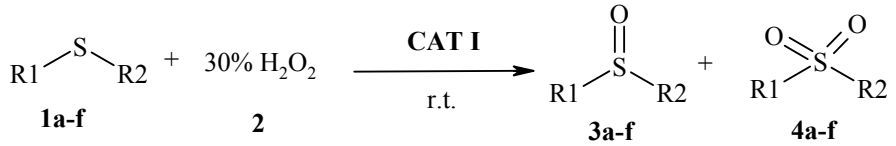


Figure 6. Diffuse reflectance UV–vis spectrum of **CAT IV**.

1.2.2 Catalytic activity: oxidation of sulfides to sulfoxides

The catalytic activity of the heterogenized decatungstates was at first tested in the oxidation of sulfides. The oxidation of phenyl methyl sulfide with 30% H_2O_2 was selected as the model reaction (Scheme 2).



Scheme 2.

A CH_2Cl_2/CH_3OH (1:1) mixture was first chosen as reaction solvent because it gives a homogeneous phase with the reagents, increasing the accessibility to the catalyst, and avoids reagent/product adsorption on the solid support, as was reported recently [17]. We examined the catalytic activity of **CAT I** reacting methyl phenyl sulfide (2 mmol) and 30% H_2O_2 in CH_2Cl_2/CH_3OH (1:1) (10 mL) at room temperature for 1.5 h. The amounts of catalyst and hydrogen peroxide were varied to use the minimum amount of each. The data, reported in Table 2, reveal that **CAT I** is very active.

Table 2. Methyl phenyl sulfoxide synthesis[a] catalysed by **CAT I.**

Entry	CAT I (mol%)	Ratio 1: 2	3 Yield (%)	3 Selectivity (%)	TON[b]
1	2	1:1.0	93	94	49
2	0.5	1:1.1	88	96	185
3	0.2	1:1.1	85	96	445
4	0.1	1: 3.0	89[c]	91[c]	980
5	0,1	1:1.15	92	95	960
6	SiO_2	1:1.15	2	-	-

[a] Reactions were performed reacting sulfide 2 mmol and 30% H_2O_2 in CH_2Cl_2/CH_3OH (1:1) (10 mL) for 90 min.
[b] Turnover number calculated as products (mol)/catalyst (mol).
[c] Reaction time 60 min., then the selectivity decreased.

Indeed, using a very low quantity (0.1 mol%) of decatungstate with respect to sulfide, methyl phenyl sulfoxide was obtained in 92% yield and 95% selectivity (Table 2, entry 5). A slight excess of H_2O_2 (1.15 equiv.) was used when the amount of catalyst was decreased. Using a

larger amount of H_2O_2 (3 equiv.) 89% of yield was obtained with 91% of selectivity in a shorter time (1 h) (Table 2, entry 4). Prolonging the reaction time, the selectivity decreased due to further oxidation to sulfone. Aiming to reduce the waste of reagent, we used 1.15 equiv. of H_2O_2. To investigate the possible influence of the solid support on the reaction outcome, a blank reaction was carried out adding unfunctionalized silica. Only traces (2%) of sulfoxide were obtained (Table 2, entry 6).

The different catalysts **CAT I–IV** were tested to examine the possible influence of the ammonium cation on the polyoxometalate activity. The amount of catalyst used in each experiment was determined on the basis of the loading value to introduce the same supported decatungstate equivalents (0.1 mol%). The data reported in Table 3 demonstrate a strong effect of the ammonium cation.

Table 3. Effect of ammonium cation in **CAT I-IV** activity[a]

Entry	CAT	3 Yield (%)	TON[b]
1	**CAT I**	92	960
2	**CAT II**	49	515
3	**CAT III**	32	333
4	**CAT IV**	30	315
5	**CAT IV**	87[c]	50

[a] Reactions were performed reacting sulfide 2 mmol, 30% H_2O_2 2.3 mmol, catalyst 0.1 mol% (0.002 mmol of W_{10}) in CH_2Cl_2/CH_3OH (1:1) (10 mL) for 90 min.
[b] Turnover number calculated as products (mol)/catalyst (mol).
[c] Catalyst 2 mol%.

The catalyst containing primary ammonium cation, **CAT I**, is the most active, giving phenyl methyl sulfoxide at a very high yield and selectivity, followed by **CAT II**, which contains a secondary ammonium group. We can attribute this effect to the increasing steric hindrance of the ions surrounding decatungstate, which make it less accessible. Prompted by the high selectivity (95%) observed for all of the catalysts, we checked whether increasing the amount of **CAT IV** (2 mol%) would produce more sulfoxide **3a** in a shorter time, due to the increased number of catalytic sites in the reaction. After 45 min, the conversion was 95 with 96% selectivity. The selectivity decreased during the time due to overoxidation; after 90 min, it

was 87% with complete conversion (Table 3, entry 5). However, the TON values indicate that increasing the amount of catalyst decreased the efficiency, as sometimes occurs [26]. Therefore, we found that all of the catalysts prepared were able to promote the oxidation of sulfide **1** by hydrogen peroxide, increasing only the relative amount.

In an attempt to develop an environmentally friendly process, we tried to avoid using chlorinated solvent. We succeeded in accomplishing the reaction solely in methanol with good results, obtaining the solfoxide at 92% yield and 97% selectivity (Table 4, entry 1).We also carried out the model reaction in isopropanol and acetonitrile as solvents and achieved the expected sulfoxide **3a** yields of 86 and 80%, respectively. These findings demonstrate that methanol was the best reaction solvent. We performed some experiments using 10% H_2O_2 and obtained lower conversions (75% after 90 min and 83% after 120 min) with high selectivity (96%). This negative role of water can be attributed to competitive interaction with the metal and to modification of the polarity of the catalyst surface. Indeed, the increased surface hydrophobicity can decrease the reactivity of the hydrophobic sulfide reagent. The conversion and product distribution of the model reaction were determined as functions of the reaction time (Fig. 5).

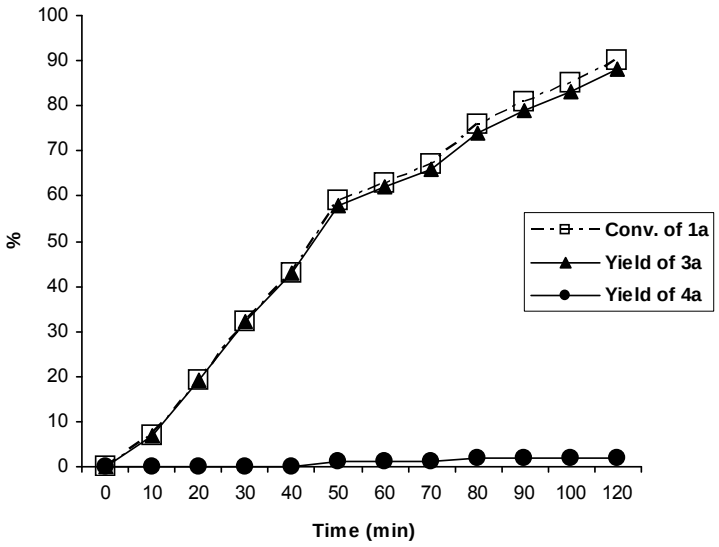
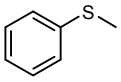
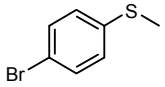
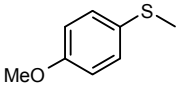
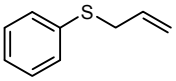
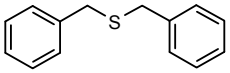
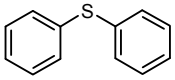
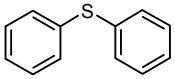


Figure 5. Reaction profile of the oxidation of methyl phenyl sulfide **1a** over **CAT I**.

The results demonstrate that sulfoxide **3a** was formed selectively and the amount of sulfone **4a** slightly increased over time. It is interesting to note that sulfone **4a** can be obtained selectively (100%) in a quantitative yield reacting the sulfide **3a** with 3 equivalents of 30% H_2O_2 in the presence of **CAT I** (1 mol%) for 4 h (Table 4, entry 2).

Table 4. Oxidation of Sulfides **1** to Sulfoxides **3** using 30% H_2O_2 catalyzed by **CAT I** in MeOH[a].

Entry	Sulfide	Product	3 Yield (%)	3 Selectivity (%)	TON[b]
1		**3a**[c]	92	97	953
2		**3b**	80	95	842
3		**3c**	86	97	890
4		**3d**	83	96[d]	865
5		**3e**	94[e]	94[e]	995
6		**3f**	56	95	588
7		**3f**	90[f] (85)[g]	90[f] (96)[g]	995 (443)

[a] Reactions were performed reacting sulfide 2 mmol, 30% H_2O_2 (1.15 equiv.), catalyst 0.1 mol% in CH_3OH (10 mL) for 90 min.
[b] Turnover number calculated as products (mol)/catalyst (mol).
[c] When the reaction was carried out using 30% H_2O_2 (3 equiv) and catalyst 1 mol% for 4 h the corresponding sulfone **4a** was obtained in 99% yield and 100% selectivity.
[d] No epoxidation product was detected.
[e] Evaluated by ^1H NMR.
[f] Reaction time 24 h.
[g] Reaction time 6 h using catalyst 0.2 mol%.

The possible hydrogen peroxide decomposition was examined both in the reaction mixture and in a blank experiment in which hydrogen peroxide was stirred in the presence of **CAT I** in methanol for 90 min. A hydrogen peroxide efficiency of 95–98% was found, indicating that unproductive decomposition was negligible.

To explore the general applicability of this reaction, we examined various sulfides. As reported in Table 4, variously substituted aryl methyl sulfides underwent smooth oxidation to selectively afford the corresponding sulfoxides in high yields (Table 4, entries 1–3).

The selective oxidation of allyl phenyl sulfide to the corresponding sulfoxide (Table 4, entry 4) is noteworthy. Epoxidation of the double bond was not observed and the corresponding sulfoxide was obtained in good yield and selectivity. A surprising result was the selective oxidation of dibenzyl sulfide (Table 4, entry 5). Indeed, it has been reported that the oxidation of dialkyl sulfides leads to the formation of sulfones along with sulfoxides with poor selectivity [3]. It is known that the formation of sulfoxides from diaryl sulfides is difficult to achieve using 30% H_2O_2 [27]. Interestingly, under the described reaction conditions, even diaryl sulphide furnished the corresponding sulfoxides in very good yield in a reaction carried out for 24 h, or for 6 h in the presence of 0.2 mol% of catalyst (Table 4, entry 7).

A possible mechanism of this reaction involves the formation of peroxotungstate species [13] and the subsequent nucleophilic attack of the sulfur atom in the thioether on the peroxo species. Indeed, it is known that thioethers are oxidized to sulfoxides by electrophilic oxidants [28], which explains the minor reactivity of aromatic thioethers, as found in other studies [29], due to delocalization of the electron density on the sulfur.

Considering our results all together, we can conclude that heterogenized decatungstate **CAT I** is very efficient in the activation of hydrogen peroxide in sulfide oxidation. This catalyst also shows high hydrogen peroxide efficiency for the reaction studied.

To verify the heterogeneity of the catalytic process, we performed the leaching test suggested by Lempers and Sheldon [30]. The reaction was filtered after 15 min, and stirring was continued for 75 min after the catalyst was removed. The reaction yield did not change significantly (from 18 to 21%), indicating that no leaching of the active catalytic species occurred during the reaction. It is noteworthy that in contrast, the $(Bu_4N)_4W_{10}O_{32}$ adsorbed on silica gave a positive leaching test, with the product yield increasing from 20 to 60% after filtration.

Finally, we carried out recycling experiments for the oxidation of methyl phenyl sulfide **1a** in methanol (Fig. 5).

The filtered catalyst was dried after washing and reused without further activation. Interestingly, the recycled catalyst could be reused for at least five reaction cycles with almost unchanged results. For comparison, the adsorbed decatungstate demonstrated a dramatic drop in yield (from 92 to 16%) during the second cycle (Figure 7).

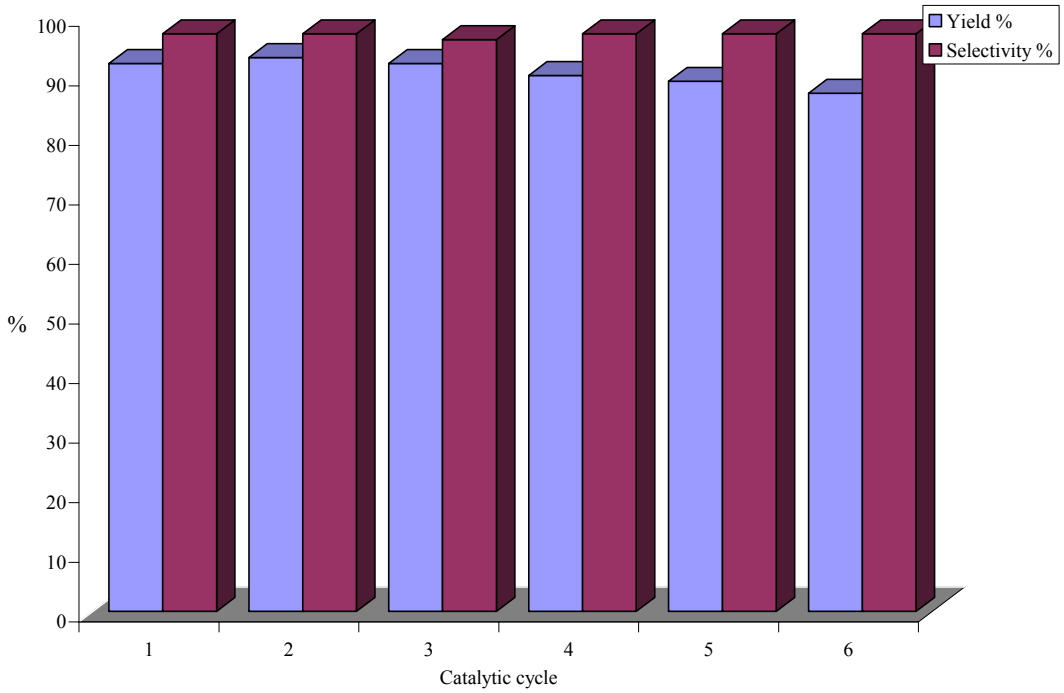


Figure 7. Catalyst recycling of **CAT I** in methyl phenyl sulfide oxidation.

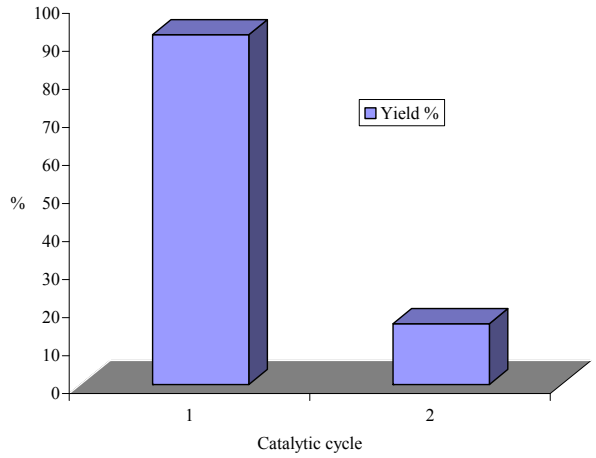


Figure 8. Catalyst recycling of **ADS CAT** in methyl phenyl sulfide oxidation.

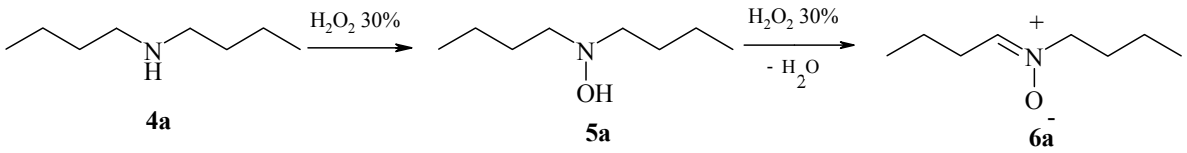
1.2.3 Catalytic activity: oxidation of secondary amines to nitrones

In order to further explore the potential of the catalyst in H_2O_2 activation, the oxidation of secondary amine to nitrones was studied.

Nitrones are synthesized in different ways among which condensation of carbonyl compounds with N-monosubstituted hydroxylamines, N-alkylation of oximes and zinc-mediated reduction of nitroalkanes and nitroarenes, in the presence of aldehydes [31]. An important synthetic procedure is of the oxidation of secondary amines [32], hydroxylamines [33] or imines [34]. The oxidative approach, using hydrogen peroxide (or urea hydrogen peroxide) or alkyl hydroperoxide starting from corresponding secondary amines, provides the most direct and general method for preparing nitrones [35]. Different examples are reported in literature using homogeneous catalysts (1–8% mol) such as Na_2MoO_4, Na_2WO_4, CH_3ReO_3 or SeO_2 and hydrogen peroxide (2– 7 equiv.) as primary oxidant. Good yields have been obtained for the catalytic oxidation of certain amines. However, other cases suffer from limited chemoselectivity: a significant amount of hydroxylamine is recovered, overoxidation and hydrolysis of the products can be observed [32].

The synthesis of nitrones is formally a two-step process involving the initial oxidation to secondary hydroxylamines followed by further oxidation and water elimination to nitrones (Scheme 3). For any mol of amine 2 mol of H_2O_2 are needed, so 1 eq. of H_2O_2 corresponds to 2 mol of H_2O_2.

The oxidation of dibutyil amine to the correspondent nitrone was selected as model reaction.



Scheme 3. Model reaction

As it is shown in Table 5 **CAT I** is really active in the oxidation of the dibutyl amine to the corresponding nitrone **6a**. We started our study using 0.5 mol% of catalyst and 1.5eq. of 30% H_2O_2 in MeOH for 1.5h (Table 5, entry 1), obtaining 86% of yield and 86% of selectivity. Increasing the reaction time to 3h (Table 5, entry 2), 90% of yield with 95% of selectivity has been achieved. Performing the reaction without catalyst (Table 5, entry 3) 15% of nitrone **6a** was obtained.

Table 5.

Entry[a]	CAT (%)	Time (h)	Yield (%)	Select. (%)[c]
1	0.5	1.5	86 [b]	86 [b]
2	0.5	3	90 [b]	95 [b]
3	-	3	15	100

[a] Reaction conditions: **CAT I**, H_2O_2 30%, MeOH, room temperature;
[b] Yield and selectivity determined by ^1H NMR using 1,1,2,2-tetracloroethane as internal standard;
[c] Yield and selectivity determined by GC-fid using 1,4-dimethoxybenzene as internal standard.

The order of reagent addition was studied as well. Two different procedures were followed: in the first the catalyst and H_2O_2 were added in the flask in presence of the solvent and stirred for 10 minutes, then the amine was added. In the second procedure the catalyst and the amine were added in the flask in presence of the solvent, after stirring for 10 minutes H_2O_2 was added. The first procedure gives a 10% higher yield than the second one. Probably the first procedure helps the formation of a peroxotungstate species, which will act as active species for the oxidation of secondary amine to nitrone as described by Murahashi [32].

In the optimised reaction conditions (0.5 mol% of **CAT I**, 1.5 eq. H_2O_2 30%, MeOH, 3h) conversion and product distribution of the model reaction have been studied as functions of the reaction time (Fig. 9). The results demonstrate that nitrone **6a** was formed with complete selectivity. It is interesting to note that hydroxylamine **5a** formation was not observed in the reaction course.

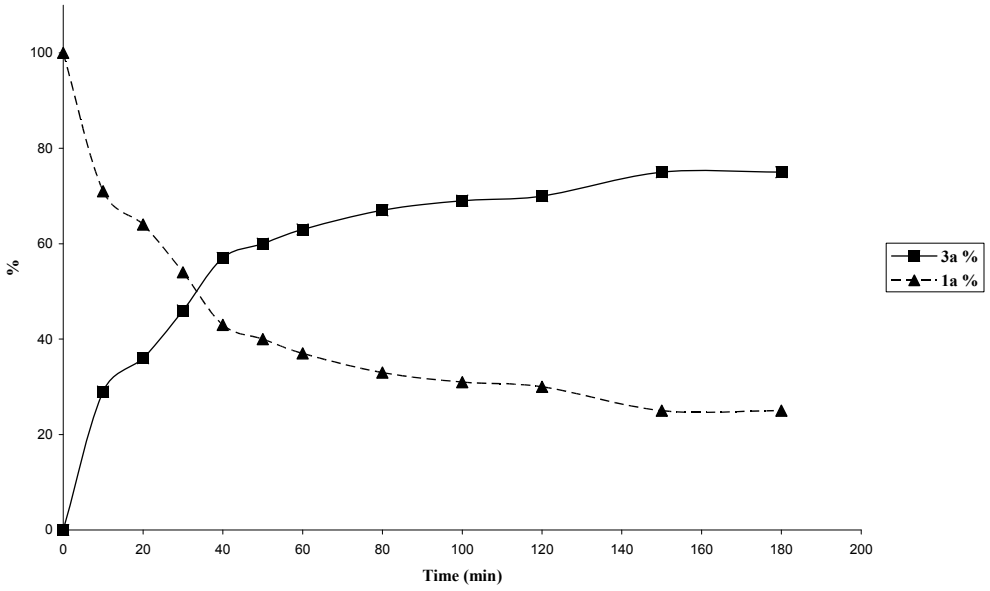
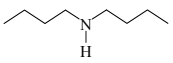
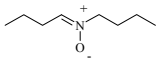
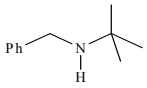
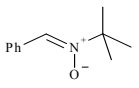
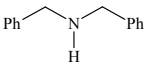
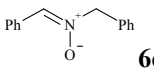
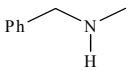
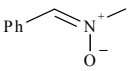


Figure 9. Reaction profile of the oxidation of dibutylamine **4a** over **CAT I**; yield and conversion determined by ^{1}H NMR.

Table 6. Oxidation of secondary amines **4a-d** by aqueous 30% H_2O_2 (1.5eq.) catalyzed by **CAT I** at room temperature in MeOH.

Entry	Substrate	Product	Cat. (%)	Time	Yield (%)	Select.(%)
1	 **4a**	 **6a**	0.5	3 h	90[a]	95[a]
2	 **4b**	 **6b**	1.5	21 h	99[b](63)[c]	100(97)[c]
3	 **4c**	 **6c**	1	15 h	94[d](99)[e]	99[d](99)[e]
4	 **4d**	 **6d**	0.75	20 min	85[d]	91[d]

[a] Based on the substrate, determined by GC-FID using internal standard method.
[b] Isolated product.
[c] After 3 cycles.
[d] Based on the substrate, determined by ^{1}H NMR using internal standard method.
[e] Results obtained using 2eq. of 30% H_2O_2.

To explore the general applicability of this reaction, we examined various secondary amines. As reported in Table 6, variously substituted secondary amines underwent smooth oxidation to selectively afford the corresponding nitrones in high yields (Table 6, entries 1–4).

As reported in literature, the oxidation of more hindered secondary amines occurs in longer reaction times and requires a larger amount of catalyst (Entries 2 and 3).

A worth of note is the result obtained in the oxidation of benzyl-*tert*-butyl amine **4b** to N-benzylidene-*tert*-butylamine N-oxide **6b** (PBN). 99% yield of weighed product was achieved using 1% of heterogeneous catalyst and 1.5 eq. of 30% H_2O_2 at room temperature in 21 hours. Many studies clearly demonstrate that PBN-related nitrones have potent biological activity. Different authors confirmed the activity of PNB and PBN-related nitrones against degenerative diseases such as Alzheimer and Parkinson [19].

Floyd and Carney in 1988–1992 made the original discoveries in experimental stroke and subsequential studies, funded by Centauar Pharmaceuticals and Astra-Zeneca, demonstrated the high therapeutic activity of PBN-related nitrones against acute ischemic stroke [19]. This has been lately confirmed by Sun et al. evidencing that TBN, a PBN-related nitrone, is strongly effective for treatment of ischemic stroke [19].

R.A. Floyd et al. discovered as well the anticancer activity of PBN-related nitrones, especially against liver neoplastic lesions. Kawai et al. demonstrated that PBN certainly has scavenging activity against $^1O_2$ and it is able to attenuate $^1O_2$-induced neuronal cell death [36].

The obtained results in the oxidation of benzyl-*tert*-butyl amine **4b** is particularly interesting if compared with those reported in the literature. PBN is usually synthesised by oxidation of N-benzyl-*tert*-butyl amine with H_2O_2. Different examples are reported in homogeneous catalysis. S. Murahashi et al. obtained PBN with 95% of yield in presence of Na_2WO_4 and 1.5 eq. of oxidant at room temperature [32]. More recently M. Colladon et al. synthesised PBN using a Pt complex. Carrying out the reaction in CH_2Cl_2, with 10% of catalyst, at 50 °C, for 24 hours, 15% of yield was obtained [37]. C. Zonta et al. reported 92% of yield using 5% of a Ti based complex as catalyst, 70% H_2O_2 at 65 °C, in 45 hours [38]. No data are reported in heterogeneous catalysis. This procedure allows to obtain the useful compound with 99% of yield, using a small amount of catalyst (1%), a slightly excess of the green oxidant at usual concentration (1.5eq. 30% H_2O_2) at room temperature. So in this thesis we report the first synthetic procedure for the preparation of PBN in heterogeneous catalysis and the obtained result is better than those reported in the literature under homogeneous catalysis.

Good results were obtained as well in the oxidation of dibenzyl amine **4c** to the corresponding nitrone **6c**. Using just 1% of heterogeneous catalyst, 1.15eq. of 30% H_2O_2 in 21h, 94% of yield and 98% of selectivity were obtained. Only 1% of benzaldehyde was observed as by-product. Increasing the amount of 30% H_2O_2 to 2eq., 99% of yield was obtained. Our

procedure is particularly interesting if compared with those reported in literature. Different examples are reported in homogeneous catalysis. C. Zonta et al. obtained 92% of yield at 60 °C using 5% of Ti complex and 4eq. of 70% H_2O_2 [38]. It is important to take into account that the use of higher than 35% of hydrogen peroxide is strongly discouraged, since it can lead to the formation of detonable compositions [39].
Only 15% yield of nitrone **6c** was obtained by M. Colladon et al. in dichloromethane, in presence of a Pt complex as catalyst (10%), using 35% H_2O_2 [37]. Only one example of secondary amine oxidation to nitrones is reported in heterogeneous catalysis. Employing a tungstate-exchanged Mg-Al Layered double hydroxides, B.M. Choudary reported good results in the oxidation of dibutyl amine, but just 60% yield was obtained in the oxidation of dibenzyl amine [40]. So the result we obtained in the oxidation of dibenzylamine is comparable to those reported in literature under homogeneous catalysis and better than the result reported under heterogeneous catalysis.

Our procedure worked well also for the preparation of C-Phenyl-N-methylnitrone **6d** and to our knowledge it is the first oxidative preparation of this compound.
Using 0.75% of **CAT I** and 1.5eq. of 30% H_2O_2 in 20min, 85% of yield and 91% of selectivity were achieved.
This nitrone **6d** is widely used in 1,3-dipolar cycloaddition reaction for synthesis of five-members heterocyclic rings. Up to now it was prepared by condensation reaction between benzaldehyde and N-methyl-hydroxyl-amine hydrochloride in chloroform, performing the work-up in benzene 78% of yield was obtained [41]. So the procedure we reported allows the synthesis of nitrone **6d** gives us higher yield than that reported in literature, using a small amount of an heterogeneous catalyst and avoiding chlorinated and carcinogenic solvents, such as chloroform and benzene.

Finally, the recyclability of the catalytic system was studied in the oxidation of benzyl-*tert*-butyl amine **4b** to PBN **6b**. After 3 cycles 63% of product **6b** was obtained (Figure 10). In order to understand the decrease of yield in the recycle, ICP analysis of tungsten has been performed on **CAT I** after the second cycle. A considerable decrease of tungsten content was detected (about 50%). Considering that in sulphide oxidation there was no leaching of the active species employing the same solvent and the same oxidant (MeOH and 30% H_2O_2), we supposed that secondary amine or the nitrone could be able to remove W from the supported catalyst. Thus **CAT I** (1.5% mol) was stirred in presence of amine **4b** (1mmol) or PBN **6b**

(1mmol) in MeOH at room temperature, after 21h **CAT I** was filtered off, dried and analised by ICP analysis.

When **CAT I** was treated with the product PBN, no leaching occurred, while after treating **CAT I** with the secondary amine **4b**, 0.09 mmol of W_{10}/g were detected.

These data indicate that the secondary amine is responsible for W leaching.

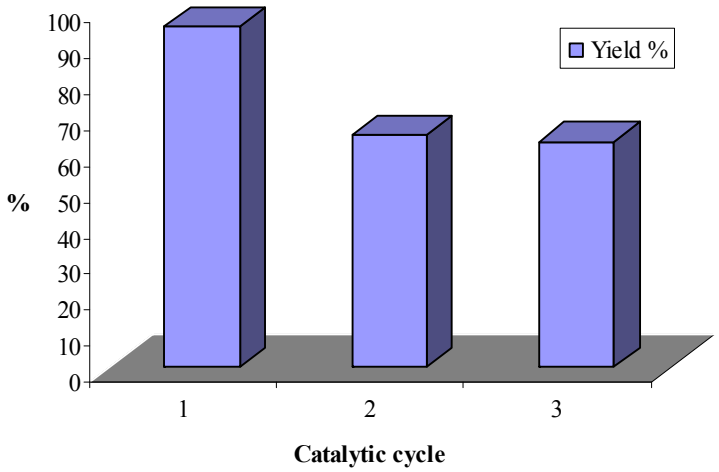


Figure 10. Catalyst recycling of **CAT I** in benzyl-*tert*-butyl amine **4b** oxidation. Reaction conditions: 1.5 mol% of **CAT I**, 1.5 eq. 30% H_2O_2, MeOH, 21h, r.t..

1.3 General information

1.3.1 Materials

All materials purchased were used as such unless otherwise stated. Starting materials for catalyst preparation: silica gel KG60 for column chromatography (Merck) (size 0.040–0.063 mm; surface area, 480–540 m^2/g; pore volume 0.74–0.84 cm^3/g), (3-aminopropyl)triethoxysilane (99%, Aldrich), (3- diethylaminopropyl)trimethoxysilane (90%, Fluka), (3-methylaminopropyl)trimethoxysilane (97%, Fluka), (3-bromopropyl) trimethoxysilane (97%, Fluka), trifluoromethanesulfonic acid (98%, Fluka), sodium tungstate dihydrate (Aldrich). $(n\text{-}Bu_4N)_4W_{10}O_{32}$ was prepared according to a literature procedure [24] and the adsorbed catalyst was prepared following an "impregnation" procedure described previously [8]. The starting materials for sulfide oxidation were hydrogen peroxide (30%, Carlo Erba), methyl phenyl sulfide (99%, Aldrich), methyl-4-methoxyphenyl sulfide (97%, Aldrich), methyl-4-bromophenyl sulfide (97%, Aldrich), dibenzyl sulphide (95%, Fluka; it was recrystallized from diethyl ether), diphenyl sulfide (98%, Aldrich), and allyl phenyl sulphide (96.5%, Fluka).

1.3.2 Sodium decatungstate ($Na_4W_{10}O_{32}$) preparation

$Na_4W_{10}O_{32}$ was prepared following a literature procedure [15], adding 260 mL of a boiling aqueous 1M HCl solution to a boiling solution containing $Na_2WO_4 \cdot 2H_2O$ (44 g) in distilled water (250 mL). The resulting solution was allowed to boil for 40 seconds, after which it was transferred to a 2L beaker and rapidly cooled to 0 °C in a liquid nitrogen/acetone bath under stirring. Solid NaCl was added to saturation while the temperature was maintained at 0 °C. A precipitate formed that was collected on a fritted funnel; washed in a small amount of cold water, ethanol, and diethyl ether; and transferred to a 250mL beaker. (The use of non-metallic spatula is recommended to avoid the formation of a blue colour). This precipitate was suspended in hot acetonitrile (130 mL); then the suspension was filtered, and the filtrate was placed in a freezer overnight. Large pale-lime crystals of sodium decatungstate were collected on a fritted funnel and dried (9.4 g). From the mother liquor, it was possible to obtain more crystals on concentration. The absorbance spectrum in acetonitrile or in water comprised a well-defined maximum at 324 or 323 nm, respectively.

1.3.3 Catalyst preparation

The preparation of catalysts **CAT I–IV** involved two main steps: (a) silica functionalization anchoring ammonium salts to surface silanols and (b) anion exchange with sodium decatungstate (Scheme 1). Silica was activated by refluxing in HCl conc. for 4 h, followed by washing until neutral with distilled water and then drying [42]. Alkylammonium heterogenization was done by one of two procedures depending on the type of ammonium cation. Anchored primary, secondary, and tertiary ammonium salts were prepared by refluxing activated silica (5 g) and the suitable (alkylaminopropyl)trialkoxysilane (10 mmol) in toluene (30 mL) under stirring for 1 h. After distillation of a toluene fraction containing ethanol, the refluxing was continued. After 1 h, this second procedure was repeated and refluxing continued for 0.5 h [23]. The cooled functionalized silica was filtered off, washed with toluene, diethyl ether, and dichloromethane (2 × 25 mL each) and then dried under high vacuum at 60 °C for 3 h to give the surface-bound alkylamine groups with a loading of 0.8–0.9 mmol/g. The resulting materials in dry dichloromethane (5 g in 25 mL) were reacted with trifluoromethane sulfonic acid (two equivalents with respect to the supported amino group) for 8 h at room temperature, filtered off, washed successively with dichloromethane, ethanol and diethyl ether (2 × 25 mL each) [17]. Then they were dried under vacuum at 60 °C for 3 h,

affording the corresponding alkylammonium salts bound to the solid surface (**AS I–III** in Scheme 1, Ai). Elemental analyses revealed a sulfur loading of 0.8–0.9 mmol/g.

To prepare supported quaternary ammonium bromide, (3-bromopropyl)trimethoxysilane (2.43 g, 10 mmol) was condensed with 5 g of silica silanols by refluxing in 30 mL of toluene following the procedure described above. The bromopropylated silica (5 g, 0.5 mmol/g loading) was then treated with triethylamine (1.01 g, 50 mmol) in 30 mL of refluxing toluene for 24 h, affording the corresponding supported quaternary ammonium bromide (**AS IV** in Scheme 1, Aii) [22]. After cooling, the solid was filtered on a Büchner funnel and carefully washed with toluene (5×20 mL), then dried at 60 °C under high vacuum. The amount of bromide ions present on the functionalized silica after the reaction with triethylamine was determined by titration [23] according to the method described by Volhard, starting from 0.30 g of immobilized salt in 10 mL of ethanol, 10 mL of 0.1 N $AgNO_3$ solution, and 5 mL of HNO_3 6 N were added, and the suspension was stirred in the dark for 0.5 h at room temperature. Then the solid was filtered off, and the excess $AgNO_3$ was titrated with 0.1 N ammonium thiocyanate, giving a bromide loading of 0.43 mmol/g.

The catalysts **CAT I–IV** were prepared by stirring a mixture of the selected surface-bound alkylammonium salt (4 mmol) and an aqueous solution of sodium decatungstate (4 mmol) in distilled water at room temperature for 30 min (Scheme 1, B). For example, supported propylammonium triflate **AS I** (5 g, loading 0.80 mmol/g) was stirred with sodium decatungstate (9.77 g, 4.0 mmol) in 30 mL of distilled water. The choice of the reaction time is important to ensure the anion exchange avoiding the degradation of sodium decatungstate in water as evidenced by following the variation of the UV absorption band at 323 nm. After stirring, the white solids were filtered off, carefully washed with 700 mL of distilled water, 50 mL of ethanol, and 50 mL of diethyl ether. Then they were washed in continuous with hot acetonitrile for 12 h using a Soxhlet apparatus.

After drying at 60 °C under high vacuum for 3 h, the catalysts were completely characterized.

1.3.4 Catalyst characterization

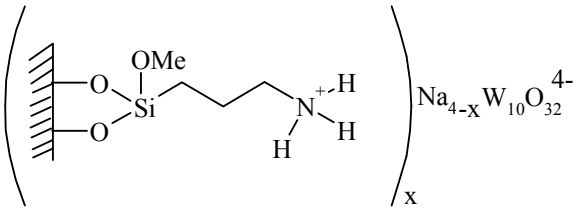
All functionalized materials were characterized with respect to compositional, structural, and surface properties. The loading of the organic groups was calculated by elemental analysis performed with a Carlo Erba CHNS-O EA1108 elemental analyzer.

Metal elemental analyses were performed by ICP-AES on an Ultima 2 Jobin Yvon HORIBA instrument, with testing solutions prepared by dissolving about 5 mg of the catalyst in 10 mL of 10% dilute NH_4OH and further diluting by 1:10 with distilled water. (It is important that

these solutions be transferred quickly in PE vials when Na is determined, to avoid contamination from glass). EDS analyses of the catalysts, in a windowless configuration, to determine the presence of sodium and tungsten were performed in a Philips 515 scanning electron microscope equipped with an EDAX Phoenix microanalyzer.

Thermogravimetric analysis and differential thermal analysis (TGA–DTA) were carried out on a Perkin–Elmer TGA7 analysis system. N_2 adsorption–desorption isotherms, obtained at 77 K using a Micrometrics PulseChemiSorb 2705, were used to determine specific surface areas, SA_{BET}. Before each measurement, the samples were outgassed at 383 K for 1 h. FTIR spectra of all of the catalysts (KBr pellets) were recorded on a Nicolet FTIR Nexus spectrophotometer (resolution 4 cm^{-1}) in the range of 4000–400 cm^{-1}. DRS-UV measurements were performed using a Varian 2390 UV–vis spectrophotometer equipped with an integrating sphere in the range of 220– 500 nm.

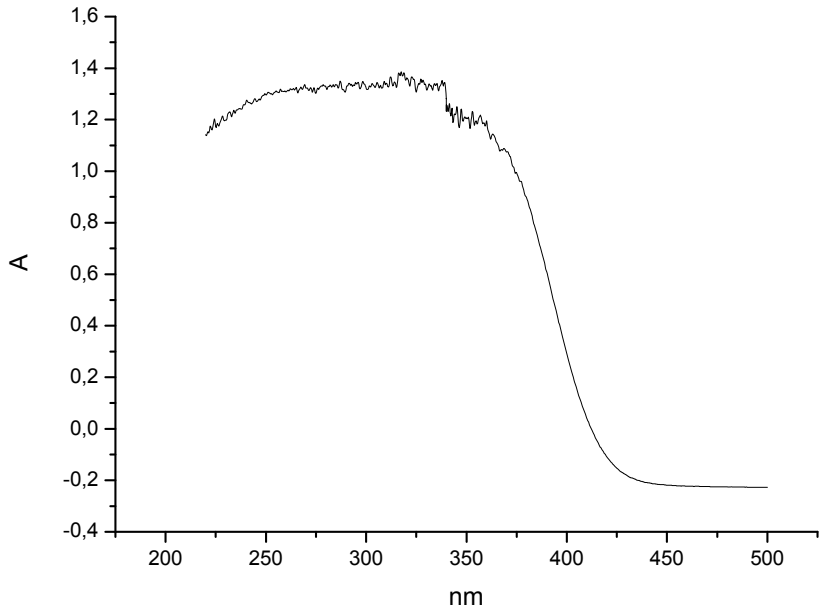
Cat I



ICP-AES (W)

Loading W_{10}: 0.123 mmol/g

UV-Vis diffuse reflectance spectrum



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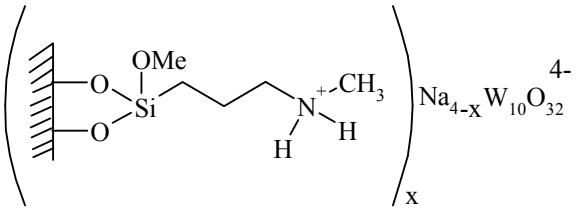
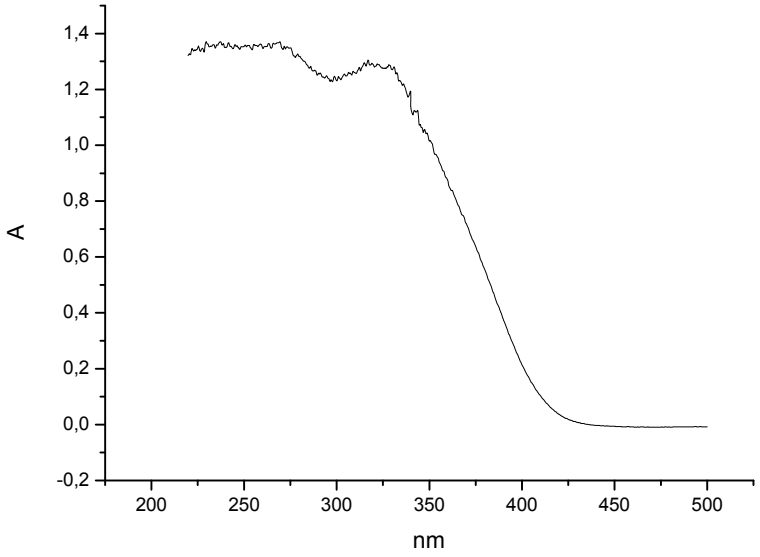


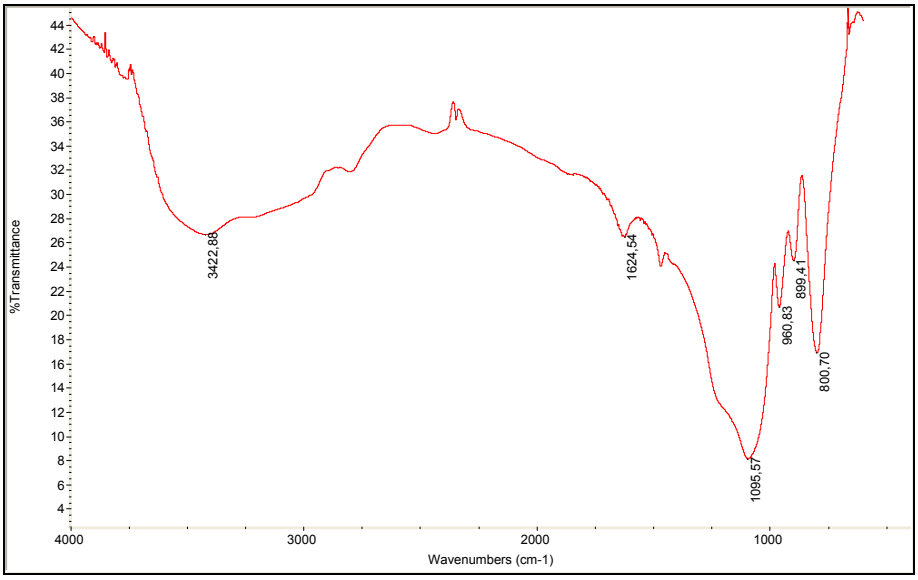
ICP-AES (W)

Loading W_{10}: 0.143 mmol/g

UV-Vis diffuse reflectance spectrum



FT-IR spectrum (KBr)



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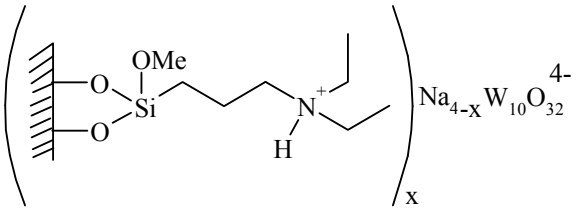
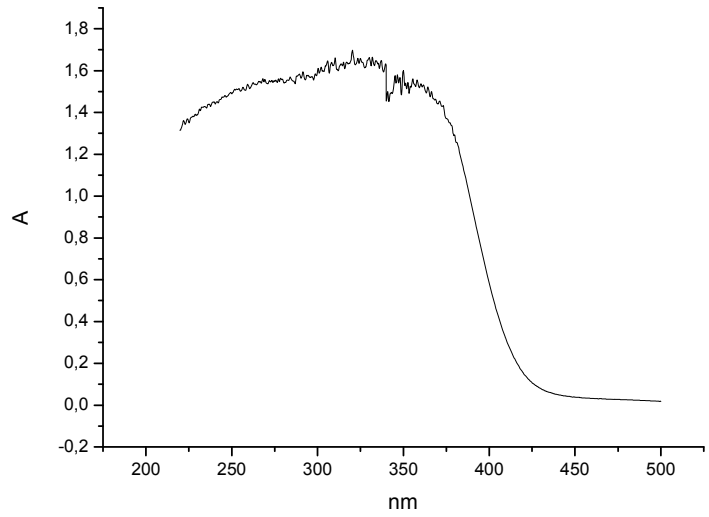


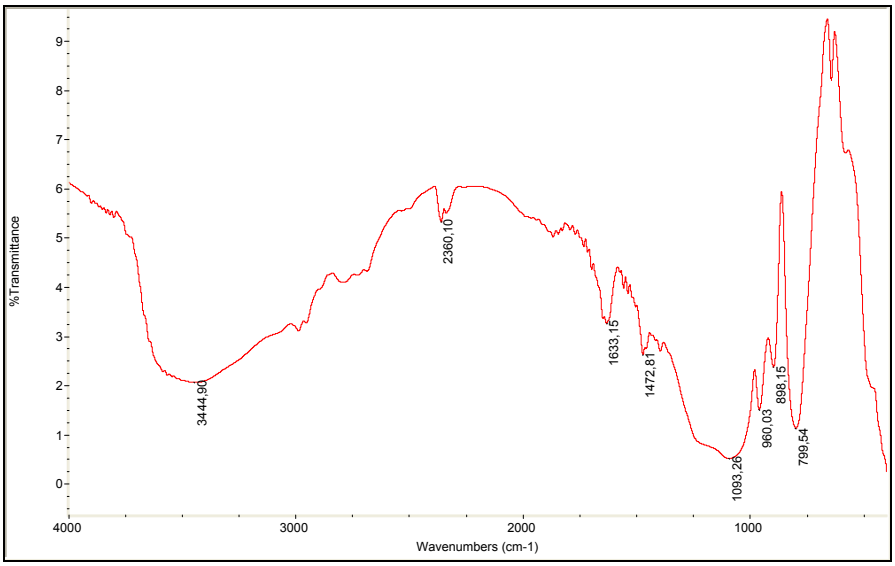
ICP-AES (W)

Loading W_{10}: 0.115 mmol/g

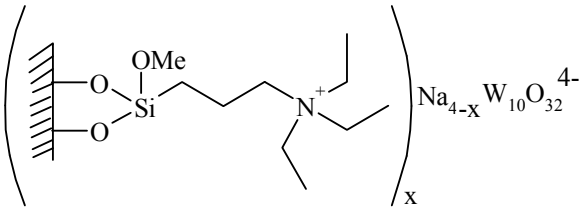
UV-Vis diffuse reflectance spectrum



FT-IR spectrum (KBr)



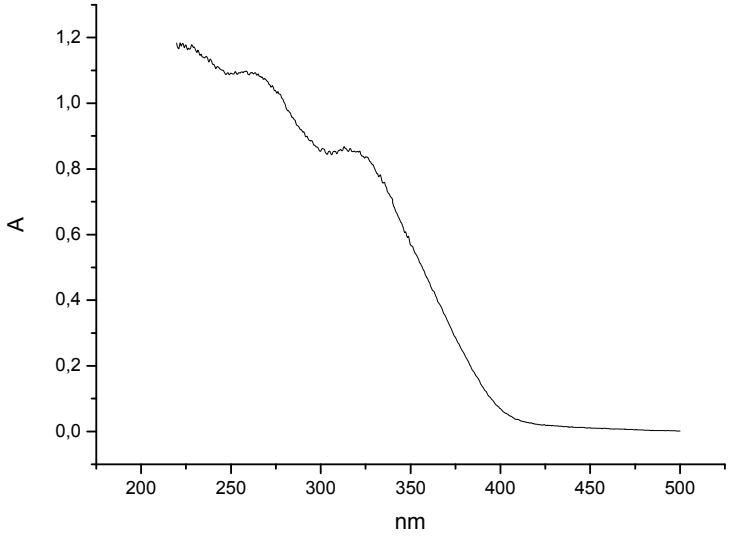
Cat IV



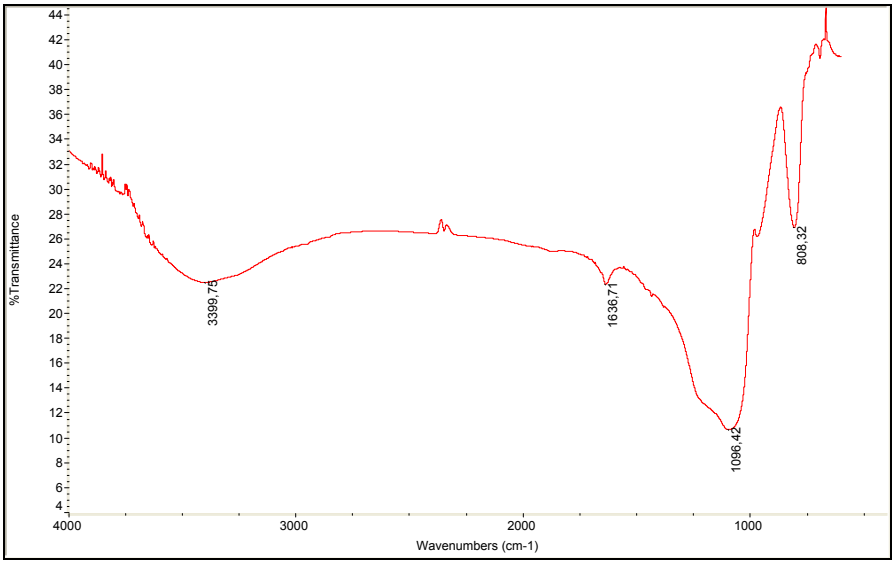
ICP-AES (W)

Loading W_{10}: 0.012-0.054 mmol/g

UV-Vis diffuse reflectance spectrum



FT-IR spectrum (KBr)

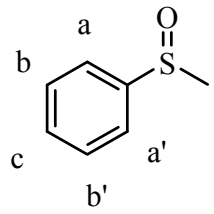


1.3.5 Reaction procedure for sulfide oxidation

Typical oxidation of methyl phenyl sulfide with hydrogen peroxide as model reaction was performed using a round-bottomed flask. The selected catalyst (the amount of which was evaluated on the basis of loading values for introducing the specified amount of decatungstate) and 30% H_2O_2 (0.23 ml, 2.30 mmol) were added to a solution of methyl phenyl sulphide (0.25 g, 0.23 ml, 2.0 mmol) in the specified solvent (10 m).

The reaction was stirred at room temperature for 1.5 h. The progress of the oxidation reaction was monitored by GC and TLC. After 1.5 h, the mixture was filtered on Büchner funnel. The solid catalyst was washed with 5 ml of methanol and recovered. When the CH_2Cl_2/MeOH mixture was used as reaction solvent, distilled water was added to the solution to obtain phase separation, and further extraction was accomplished with CH_2Cl_2 (2 × 10 mL). When the reaction solvent was MeOH, the solution was rapidly evaluated by gas chromatography; otherwise, $Na_2S_2O_3$ was added to the solution to consume the excess H_2O_2 (verified by an iodinated paper test) and filtered off [27]. The gas-chromatographic analyses were performed on a Trace GC ThermoFinnigan instrument with a Supelco SPB-20 fused silica capillary column (30 m×0.25 mm) with helium as a carrier, adding 4-*tert*-butylphenol as an internal standard. The hydrogen peroxide content in the reaction mixture was measured following a standard iodometric titration method with sodium thiosulfate [43]. The model reaction of methyl phenyl sulfide and hydrogen peroxide was monitored between 10 and 120 min. Samples were obtained periodically, and the course of the reaction was followed by gas chromatography using 4-*tert*-butylphenol as the internal standard added to the samples. The same methodology was followed in the synthetic application to different sulfides using the best catalyst **CAT I**. The products were purified by flash chromatography over silica gel column, using hexane–ethyl acetate mixtures as eluants. All products gave melting points and spectral data consistent with those reported.

Characterization of methyl phenylsulfoxide (3a).

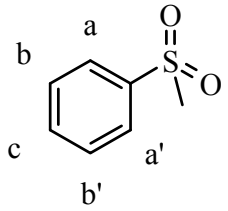


Trasparent oil, m.w. 140.21, C_7H_8OS.

^{1}H NMR ($CDCl_3$, 300MHz), δ(ppm): 3.06 s, 3H (CH_3), 7.55-7.60 m, 2H (Hc and Hc'), 7.64-7.66 m, 1H (Hc), 7.94-7.96 m, 2H (Hb and Hb').

MS-EI (m/z): 140 M+ (98%), 125 (100%), 97 (45%).

Characterization of methyl phenylsulfone (4a).

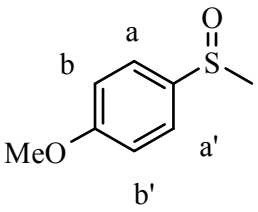


White solid, m.w. 156.20, $C_7H_8O_2S$.

^{1}H NMR ($CDCl_3$, 300MHz), δ(ppm): 3.06 s, 3H (CH_3); 7.55-760 m, 2H (Hc and Hc'); 7.64-7.66 m, 1H (Hb); 7.94-7.96 m, 2H (Ha and Ha').

MS-EI (m/z): 156 M+ (50%), 141 (55%), 94 (45%).

Characterization of 4-methoxy-phenyl methyl sulfoxide (3c).

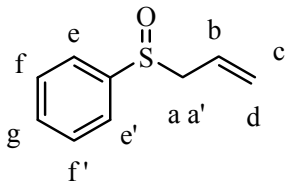


Trasparent oil, m.w. 170.23, $C_8H_{10}O_2S$.

^{1}H NMR ($CDCl_3$, 300MHz), δ(ppm): 2.67 s, 3H (CH_3); 3.82 s, 3H (OCH_3); 7.00 d, 2H (Hb and Hb') ½ para system, J= 8.8 ; 7.56 d, 2H (Ha and Ha') ½ para system, J= 8.8.

MS-EI (m/z): 170 M+ (20%), 155 (100%), 139 (10%).

Characterization of 4-methoxy-phenyl methyl sulfoxide (3d). [44]

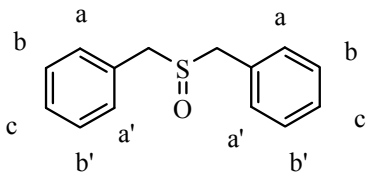


Trasparent oil, m.w. 166.24, $C_9H_{10}OS$.

^{1}H NMR ($CDCl_3$, 300MHz), δ(ppm): 3.46 dd, 1H (1/2 CH_2) J= 12.8, 7.6; 3.53 dd, 1H (1/2 CH_2) J=12.8, 7.6; 5.18 ddd, 1H (Hd) J=17.2, 1.6, 1.2; 5.32 ddd, 1H (Hc) J=9.6, 1.2, 1.2; 5.61 ddt, 1H (Hb) J= 17.2, 9.6, 7.6; 7.44-7.54 m, 3H (Hf, Hf' and Hg); 7.56-7.62 m, 2H (He and He').

MS-EI (m/z): 166 M^+ (26%), 125 (100%), 117 (35%).

Characterization of dibenzyl sulfoxide (3e).

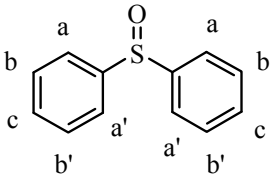


White solid, m.w. 230.33, $C_{14}H_{14}OS$.

^{1}H NMR ($CDCl_3$, 300MHz), δ(ppm): 3.60 s, 4H (2 CH_2), 7.20-7.35 m, 10H (2Ha, 2Ha', 2Hb, 2Hb', 2Hc).

MS-EI (m/z): 230 M+ (2%), 180 (5%), 91 (100%).

Characterization of diphenyl sulfoxide (3f).



White solid, m.w. 202.28, $C_{12}H_{10}OS$.

^{1}H NMR ($CDCl_3$, 300MHz), δ(ppm): 7.44-7.47 m, 6H (2Hb, 2Hb', 2Hc), 7.63-7.66 m, 4H (2Ha, 2Ha').

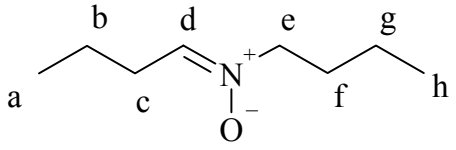
MS-EI (m/z): 202 M^+ (100%), 154 (80%), 109 (95%), 97 (35%).

1.3.6 Reaction procedures for secondary amines oxidation

Procedure for the synthesis of N- butylidenebutyl amine N-oxide (6a).

In a 25ml round bottom flask **CAT I** (0.75% mol, 0.055 g, loading 0.135 mmol/g) was suspended in 5ml of MeOH. Under nitrogen flow 30% H_2O_2 (0.304 ml, 3 mmol) is added. The mixture is stirred for 10min. To the stirred solution *sec*-amine (129 mg, 0.168 ml, 1 mmol) is added. The reaction was allowed to stir at room temperature. After completion of the reaction (followed by TLC), the catalyst was filtered off and a small amount of sodium bisolfite was added to decompose the unreacted hydrogen peroxide. The treated reaction mixture was filtered to remove solid salt. The yield and the selectivity were determined by GC-FID using the internal standard method (1,4-dimethoxybenzene). The product was isolated by distillation under high vacuum (0.01mmHg) at 50 °C or by chromatography on silica gel plates and characterised by ^{1}H NMR and GC-MS.

Characterization of N- butylidenebutyl amine N-oxide (6a) [32].



Yellow oil, $C_8H_{17}NO$, m.w. 143. 24.

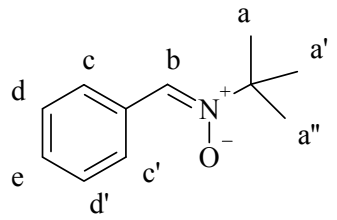
^{1}H NMR ($CDCl_3$, 300MHz), δ(ppm): 0.94 m, 6H, (Ha and Hh); 1.30 hexaplet, 2H (Hg) J=7; 1.53 hexaplet, 2H (Hb) J=7 Hz; 1.86 quintuplet, 2H (Hf); J=7; 2.47 quartuplet, 2H (Hc); J=6 and 7 Hz; 3.74 t, 2H (He) J=7 Hz; 6.66 t, 1H (Hd) J=6 Hz.

MS-EI (m/z): 143 M^+ (9%), 128 (16%), 100 (100%), 84 (28%), 72 (36%).

Procedure for the synthesis of N-benzylidene-*tert*-butyl amine N-oxide (6b).

In a 25ml round bottom flask **CAT I** (1.5% mol, 0.108 g, loading 0.135 mmol/g) was suspended in 5ml of MeOH. Under nitrogen flow 30% H_2O_2 (0.304ml, 3mmol) was added. The mixture was stirred for 10min. *Sec*-amine (163mg, 0.185ml, 1mmol) was added and reaction was allowed to stir at room temperature. After completion of the reaction (followed by TLC), the catalyst was filtered off and a small amount of sodium bisolfite was added to decompose the unreacted hydrogen peroxide. The treated reaction mixture was filtered to remove solid salt. The solvent was removed under reduced pressure giving a almost pure solid product that was weighted to determine the yield. The product can be crystallized from exane.

Characterization of N-benzylidene-*tert*-butyl amine N-oxide (6b) [32].



White solid, $C_{11}H_{15}ON$, m.w. 177.26.

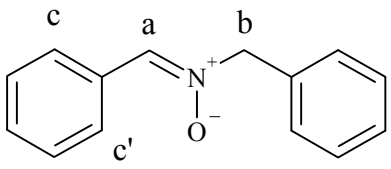
^{1}H NMR ($CDCl_3$, 300MHz), δ(ppm): 1.62 s, 9H (Ha); 7.40-7.42 m, 3H (He and Hd); 7.55 s, 1H (Hb)**;** 8.27-8.31 m, 2H (Hc).

MS-EI (m/z): 177 M+(20%), 121(22%), 89 (16%), 57 (100%).

Procedure for the synthesis of N-benzylidenebenzyl amine N-oxide (6c).

In a 25ml round bottom flask the **CAT I** (1.0% mol, 0.068 g, loading 0.208 mmol/g) was suspended in 5ml of MeOH. Under nitrogen flow 30% H_2O_2 (0.304ml, 3mmol) was added. After stirring for 10 min., the *sec*-amine (197mg, 0.192ml, 1mmol) was added. The reaction was allowed to stir at room temperature. After completion of the reaction (followed by TLC), the catalyst was filtered off and a small amount of sodium bisolfite was added to decompose the unreacted hydrogen peroxide. The treated reaction mixture was filtered to remove solid salt and the solvent was removed under reduced pressure. The yield and the selectivity were determined by ^{1}H NMR, using 1,1,2,2-tetrachloroethane as internal standard. The product was isolated by chromatography on silica gel plates and characterised by ^{1}H NMR and GC-MS.

Characterization of N-benzylidenebenzyl amine N-oxide (6c) [32].



White solid, m.p. 81-82°C (lit. [32] 81-83 °C), $C_{14}H_{13}ON$, m. w. 211.28.

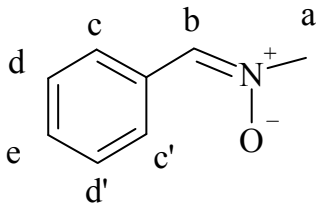
^{1}H NMR ($CDCl_3$, 300MHz), δ(ppm): 5.06 s, 2H (Hb); 7.36-7.51 m, 9H (ArH and Ha); 8.17-8.25 m, 2H (Hc e Hc').

MS-EI (m/z): 211 M+ (70%), 105 (100%), 91 (28%), 77 (83%).

Procedure for the synthesis of N-benzylidenemethyl amine N-oxide (6d).

In a 25ml round bottom flask the **CAT I** (0.75% mol, 0.035 g, loading 0.208 mmol/g) was suspended in 5ml of MeOH. Under nitrogen flow 30% H_2O_2 (0.304ml, 3mmol) was added. After stirring for 10 min., *sec*-amine (121 mg, 0.129 ml, 1mmol) was added. The reaction was allowed to stir at room temperature. After completion of the reaction (followed by TLC), the catalyst was filtered off and a small amount of sodium bisolfite was added to decompose the unreacted hydrogen peroxide. The treated reaction mixture was filtered to remove solid salt and the solvent was removed under reduced pressure. The yield and the selectivity were determined by ^{1}H NMR, using 1,1,2,2-tetrachloroethane as internal standard. The product was isolated by chromatography on silica gel plates and characterised by ^{1}H NMR and GC-MS.

Characterization of N-benzylidenemethyl amine N-oxide (6d) [41].



Yellow oil, C_8H_9ON, m.w.135.18.

^{1}H NMR ($CDCl_3$, 300MHz), δ(ppm): 3.83 s, 3H (Ha); 7.28 s, 1H (Hb); 7.30-7.35 m, 3H (Hd); 8.12-8.15 m, 2H (Hc).

MS-EI (m/z): 135 M+ (69%), 134 (100%), 107 (16%), 89 (25%), 77 (64%).

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Chapter 2

Chiral catalytic ionic liquids for enantioselective sulfide oxidation.

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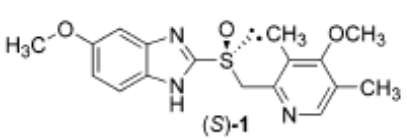
This work was mainly performed during the six month Marie Curie fellowship at QUILL.

2.1 Introduction

The heterogeneous catalytic system described in the first chapter gave us good results in the oxidation of sulfides to sulfoxides, but obviously only racemic sulfoxides could be obtained.
Since sulfoxides are chiral molecules and enantiopure sulfoxides are really interesting compounds, we planned to develop a tungsten-based catalytic system able to achieve enantioselectivity.
Chiral sulfoxides are used as auxiliaries in asymmetric synthesis and as ligands in enantioselective catalysis [1]. There are basically three factors that form the basis of the success and effectiveness of the sulfinyl group as a chiral controller: (i) its high optical stability since the thermal stereomutation of sulfoxides occurs at a significant rate only at about 200 °C; (ii) its efficiency as a carrier of the chiral information. The large stereoelectronic differences between the three substituents at the sulfinyl sulphur (the lone pair of electrons, the oxygen atom, and two alkyl or aryl groups) allow the creation of a well-defined chiral environment around the sulfur atom. Additionally, the polarized S-O bond, with a net positive charge on sulfur, allows both the oxygen and sulfur atoms to coordinate to Lewis acids and transition metals, leading to highly rigid and ordered transition-state geometries that permit effective transfer of the chiral information to the alkyl or aryl groups or more distant positions; (iii) its accessibility in both enantiomeric forms [1]. The synthesis of chiral non-racemic sulfoxides with high enantiomeric purity has been a subject of constant interest over the past two decades. A real breakthrough occurred in the synthesis of chiral sulfoxides at the beginning of the 1990s, when various new methodologies appeared. The new methods allow access to a large number of sulfoxides with different steric and stereoelectronic characteristics, generally in both enantiomeric forms.
Moreover, a number of pharmaceutically important drugs contain asymmetric sulfinyl moieties [2]. The most common one is omeprazole (Figure 1). It was marketed under the names of Losec and Prisolec, is the leading gastric proton pump inhibitor (PPI) used as an antiulcer agent. Consequently, a large number of pharmaceutical companies seek to develop their own gastric acid secretion inhibitors based on the framework of omeprazole (Figure 1). In recent years there has been great interest in the synthesis of optically pure (S)-omeprazole (esomeprazole) in relation of the chiral switch to single enantiomer launching of omeprazole. Accordingly, esomeprazole (S-1, Figure 1) was launched throughout Europe in August 2000 and in the United States in February 2001 under the trade name of Nexium as new PPI. Other

important sulfoxides include inhibitors of uric acid biosynthesis, potassium channel activators, calcium channel antagonists [1].



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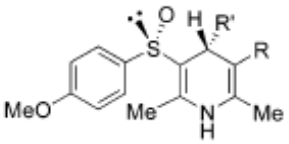

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Figure 1. Esomeprazole (1) and Calcium channel activator (2).

Enantioselective oxidations of sulfides can be performed either by biocatalysis [3] or by chemical oxidation, the latter occurring in the presence of chiral oxidising species, or by using a chiral oxidants and chiral metal complexes [5].

The asymmetric oxidation of sulfides by metal catalysts is one of the most attractive routes to optically active sulfoxides so far reported [10]. Nowadays the most well studied and versatile catalytic systems for asymmetric sulfides oxidation are those utilizing titanium and vanadium complexes. The use of Kagan [11] and Modena [12] reagents containing titanium(IV) isopropylate, optically active diethyl tartrate, and an oxidant (commonly cumene hydroperoxide or *tert*-butyl hydroperoxide, more seldom substituted furyl hydroperoxides) enables to prepare in good yields and high enantioselectivity optically active sulfoxides from a wide range of aryl alkyl sulfides. The drawbacks of these reagents are the necessity to carry out the reactions in inert atmosphere, with controlled humidity, and frequently with equimolar amount of the oxidizing system with respect to sulfides. These systems are poorly suitable for asymmetric oxidation of dialkyl sulfides and sulfides containing functional groups. In these cases it is necessary to choose ligands from a large number (because the oxidation of each sulfide might require one definite ligand, and the slightest changes in the sulfide structure can demand looking for another ligand). The other kind of catalysts often employed are vanadium-based systems. Complexes of $VO(acac)_2$ with chiral Schiff bases are used in asymmetric oxidation of sulfides in catalytic quantities (1%), permit application of aqueous hydrogen peroxide as oxidant, and the reaction can be carried out in the air presence. The system is sufficiently versatile and often is efficient where the titanium-containing systems give negative results.

However with catalytic systems utilizing vanadium the enantioselectivity as a rule is not very high [8].

On the basis of the good results obtained in the oxidation of sulphides to sulfoxides using tungsten-based catalysts, we planned to combine the properties of chiral tungsten catalysts with those of tailored or functionalized ionic liquids [13].

So we prepared a new class of chiral ionic liquids in which the catalytic metal centre and chirality are located in the anion and the cation was chosen for its imparted hydrophobicity.

In recent years, significant progress has been made in the application of room temperature ionic liquids in catalytic processes. Ionic liquids (ILs) are salts which exist in the liquid state at ambient temperatures. The advantages that ionic liquids due to their properties are here reported:

- a wide liquid range of about 300 °C with a melting point around room temperature;
- a wide range of materials (including inorganic, organic and even polymeric materials) are soluble in ionic liquids
- excellent and variable Lewis/Brönsted acidity
- high polarity
- negligible vapor pressure
- potential to be reused and recycled.

Ionic liquid are generally thought to have another advantage in that they display a low coordination tendency, however, direct experimental evidence of this is still lacking, that is to say, the structure of the solute entities in ionic liquids is still unclear. Interconversion of coordinatively unsaturated–saturated species is a key feature in catalyst function. Studies on the coordination behaviour of ionic liquids with different materials such as metal clusters, oxides nanoparticles and coordination complexes are required in order to understand this area more clearly [14].

From these benefits, it is reasonable to expect that ionic liquids could also play a significant role in asymmetric synthesis, one of the prime concerns for industry and academia. Their polar and non-coordinating properties hold considerable potential for enantioselective reactions since profound effects on reactivities and selectivities can be expected. Surprisingly, it is only very recently that attention has really been focused on the application of ILs for enantioselective processes. Three different strategies may be envisioned to perform an asymmetric reaction involving ILs: (i) the chirality can arise from a chiral substrate or a chiral reagent and the ionic liquid is used to replace with benefit the environmentally unfriendly organic solvent; (ii) the chirality can arise from a catalyst (transition-metal catalyst or biocatalyst) and the ionic liquid is used to stabilize and/or to allow the recovery of the chiral catalyst. With respect to reactions carried out in conventional solvents, reactions in ILs have

different thermodynamic and kinetic behaviours, which often lead to improved process performance. Better selectivity and/or conversion have been demonstrated. Furthermore, ionic liquids allow an enhanced stability of organometallic reagents and biocatalysts, an easy product recovery as well as possible recycling of homogeneous catalysts. It is noteworthy the ease to separate organic products from the ionic liquid phase by extraction, using immiscible solvents. IL phase containing the active catalyst could be readily reused without significant loss of catalytic activity, fact particularly interesting for asymmetric catalysis, due to the high-added value of the chiral catalysts. (iii) The chiral discrimination is promoted by the ionic liquid itself (*e.g.* a chiral ionic liquid) which acts as a chiral promoter [15].

The first example in asymmetric synthesis was proposed by Chauvin in 1995 however, most of the related studies were published after 2000.

Luo et al. [16] reported a chiral pyrrolidine unit covalently tethered to an IL moiety, so that the former can serve as a catalytic site and the latter as both the phase tag and a chiral-induction group. For the first time it has been reported that ionic-liquid type organocatalysts would still maintain the unique properties of an ionic liquid and would also serve as an efficient catalyst for judiciously selected reactions. They underlined that the role of imidazolium as a chiral-induction goup considering that the bulky and planar organic cation may impart space shielding to the reaction intermediate and the proximity of the ionic-liquid unit to the active site may create a microenvironment that is favorable for the reaction. In fact, the high polarity and ionic character of the ILs exert synergistic effects on many organic reactions [16].

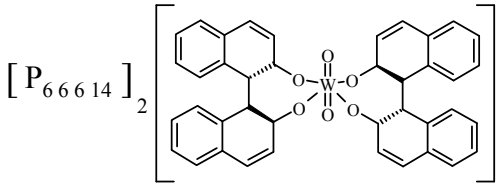
In this thesis work we prepared chiral ionic liquids (CILs) containing chiral anions. They are viscous liquids at room temperature and are soluble in moderately polar solvents, such as chloroform, dichloromethane, and methanol, but insoluble in less polar solvents, such as diethyl ether, ethyl acetate, and hexane. These properties, together with the straightforward synthesis, satisfied the requirements for practical applications in asymmetric synthesis [17].

These ionic liquids show to be able to catalyze the enantioselective oxidation of sulfides to sulfoxides.

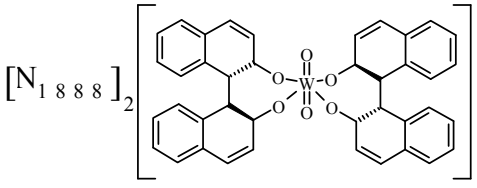
2.2 Results and discussions

Combining the areas of chiral tungsten catalysts with tailored or functionalised ionic liquids, a new class of chiral ionic liquids has been prepared, in which the catalytic metal centre and chirality are focussed in the anion and the cation was chosen for its imparted hydrophobicity. These ionic liquids were prepared incorporating trihexyltetradecylphosphonium $[P_{6\,6\,6\,14}]^+$ and methyltrioctylammonium $[N_{1\,8\,8\,8}]^+$ cations to improve organic miscibility. These ionic liquids were synthesised using tungstate(VI) complexes containing *(S)*-mandelic acid (Hmand) and (*S*)-1,1'-binaphthol (H_2binol) as chiral ligands. To the best of our knowledge, these anions have not been utilised previously for promoting chiral sulfide oxidations. Enantioselective oxidation of sulfides to sulfoxides using hydrogen peroxide or urea hydrogen peroxide (UHP) [18] as the sacrificial oxidant was demonstrated, with good yields and selectivity, with enantiomeric excesses up to 96%, using the ionic liquids as chiral catalysts. These results indicate that efficient chiral induction was promoted by the presence of both the catalytic site and the stereogenic centre in the anion.

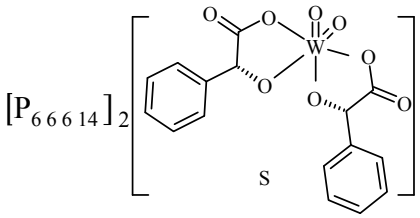
Two new salts containing the tungsten(VI)-2,2'-(*S*)-binaphthol complex were prepared *via* a two step process. The first step involved preparation of the salt $Na[N_{4\,4\,4\,4}][WO_2(S\text{-binol})_2]$ [19] and in the next step cation exchange was performed by a simple metathesis in either CH_2Cl_2 or $CHCl_3$ with $[P_{6\,6\,6\,14}]Cl$, or $[N_{1\,8\,8\,8}]Br$. The removal of tetraalkylammonium halides yielded $[P_{6\,6\,6\,14}]_2[WO_2(S\text{-binol})_2]$ and $[N_{1\,8\,8\,8}]_2[WO_2(S\text{-binol})_2]$ (Figure 1) as pale yellow solids possessing low melting points (54 °C and 116-117 °C respectively). Similarly, two other ionic liquids containing a tungsten(VI)-(*S*)-mandelate complex were prepared *via* $Na_2[WO_2(S\text{-mand})_2]$[20] following a similar experimental procedure. $[P_{6\,6\,6\,14}]_2[WO_2(S\text{-mand})_2]$ and $[N_{1\,8\,8\,8}]_2[WO_2(S\text{-mand})_2]$ were obtained (Figure 1).



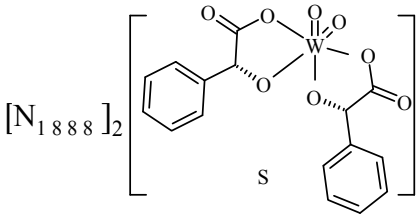
$[P_{6\,6\,6\,14}]_2[WO_2\text{-(S-binol)}_2]$ **CIL1**



$[N_{1\,8\,8\,8}]_2[WO_2\text{-(S-binol)}_2]$ **CIL2**



$[P_{6\,6\,6\,14}]_2$



$[N_{1\,8\,8\,8}]_2$

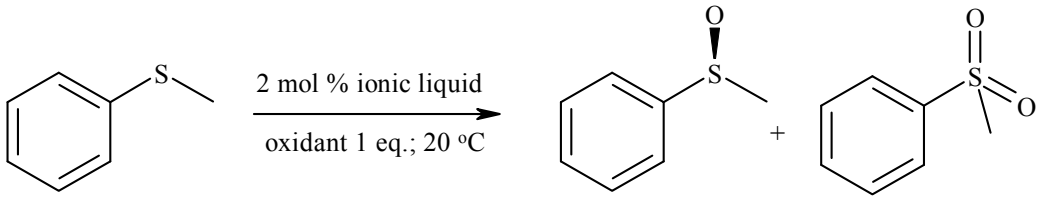
$[P_{6\,6\,6\,14}]_2[WO_2\text{-(S-mandelate)}_2]$ **CIL3**

$[N_{1\,8\,8\,8}]_2[WO_2\text{-(S-mandelate)}_2]$ **CIL4**

Figure 1. Structures of ionic liquids used in this study.

All the ionic liquids were characterised by ^{1}H and ^{13}C NMR spectroscopy, ESI-mass spectrometry, DSC, CD spectroscopy and microanalysis. $[P_{6\,6\,6\,14}]_2[WO_2(S\text{-mand})_2]$ was a room temperature ionic liquid with a broad glass transition (DSC), whereas $[N_{1\,8\,8\,8}]_2[WO_2(S\text{-mand})_2]$ was a solid (m.p. 69 ^{o}C) at room temperature.

The catalytic activity of these ionic liquids was tested in a model reaction, the oxidation of phenyl methyl sulfide (Scheme 1).



Scheme 1. Model test reaction

Table 1. Enantioselective oxidation of methyl phenyl sulfide catalysed by $[P_{6\,6\,6\,14}]_2[WO_2(S\text{-binol})_2]$.

Entry[a]	Solvent	Oxidant	Time (h)	Sulfoxide Yield (%)[b]	Select. (%)	e.e. (%)[c]
1	CH_2Cl_2	UHP	6	5	100	95
2	solventless	UHP	4	50	58	6
3	[bmpyrr][NTf_2]	UHP	4	29	60	10
4	[C_6mim]Cl	UHP	4	62	75	5
5	H_2O	30% H_2O_2	1	12	100	25
6	aq. Na[AOT][c]	30% H_2O_2	1	64	82	6

[a] Reaction conditions: 2% mol **CIL1**, 1.15 eq. oxidant, r. t..
[b] Yield determined by HPLC.
[c] e.e. value determined by chiral HPLC.
[c] 5 mol %, 25 mM (sodium diisooctylsulfosuccinate).

The reaction was screened using $[P_{6\,6\,6\,14}]_2[WO_2(S\text{-binol})_2]$ **CIL1** as catalyst in a range of solvents with UHP or aqueous hydrogen peroxide as oxidants (Table 1).

When the reaction was performed using 2 mol % of **CIL1** at room temperature in CH_2Cl_2, with 1.15 equivalent of UHP, after 6 h very high enantioselectivity (95% e.e.) was observed, but the sulfoxide was just 5% (Table 1, entry 1) [21].

Similar results were obtained using aqueous 30% H_2O_2. Under the same reaction conditions, using UHP as oxidant $[N_{1\,8\,8\,8}]_2[WO_2(S\text{- binol})_2]$ was tested as a catalyst, but changing the cation made no difference to the catalytic activity. With the aim to increase the sulfide conversion, the reaction was performed in absence of solvent, using both the oxidants. With UHP as oxidant, 50% of sulfoxide yield was observed with 58% of selectivity and 6% of enantiomeric excess after 4 h (Table 1, entry 2). Similar results were obtained using aqueous 30% H_2O_2.

The reaction was then performed using the ionic liquids 1-butyl-1-methylpyrrolidinium bis{(trifluoromethyl)sulfonyl}amide ($[C_4mpyrr][NTf_2]$) or 1-hexyl-3-methylimidazolium chloride ($[C_6mim]Cl$) as solvent and UHP as oxidant. Low selectivities and enantiomeric excesses were obtained (Table 1, entries 3 and 4). Using water as a solvent and aq. 30% H_2O_2 as oxidant, after 1 h, 12% sulfoxide was obtained in a 25% enantiomeric excess (Table 1, entry 5). Adding Na[AOT], as a surfactant phase transfer reagent, an increase of conversion was observed with a decrease of the enantiomeric excess (Table 1, entry 6). $[P_{6\,6\,6\,14}]_2[WO_2(S\text{-binol})_2]$ was shown to promote the oxidation of sulfide to sulfoxide with low enantioselectivity.

In order to study the effect of changing the chiral ligand on the catalytic ability of these ionic liquids, the catalytic activity of $[P_{6\,6\,6\,14}]_2[WO_2(S\text{-mand})_2]$ was tested in the model reaction. A preliminary study was performed using $Na_2[WO_2(S\text{-mand})_2]$ as catalyst at room temperature, aq. 30% H_2O_2 or UHP as oxidant, in MeOH. After one hour, high sulfide conversion was observed, 91% and 89% respectively, with 100% of selectivity in both cases, but low enantiomeric excess (17%).

Using CH_2Cl_2 instead of MeOH, and 30% H_2O_2 as oxidant, a high enantiomeric excess was observed, $\geq$ 98%, although only a low sulfoxide yield of 12% was obtained. Furthermore, the sodium salt is not completely soluble in CH_2Cl_2. In order to increase the sulfide conversion without compromising the excellent enantiomeric excess, the reaction was performed using the hydrophobic ionic liquid, $[P_{6\,6\,6\,14}]_2[WO_2(S\text{-mand})_2]$ instead of the sodium salt. With a chiral tungstate(VI) complex in ionic liquid form, a completely homogeneous system was

obtained. As shown in the Tables 2 and 3, using this system, a high enantiomeric excess with good conversion and selectivity was achieved.

Table 2. Effect of the nature of oxidant on enantioselective oxidation of methyl phenyl sulfide catalysed by $[P_{6\,6\,6\,14}]_2[WO_2(S\text{-mand})_2]$.

Entry[a]	Oxidant	Sulfoxide yield (%)[b]	Select. (%)	e.e. (%)[c]
1	UHP	10	100	95
2	aq. 30% H_2O_2	44	100	30

[a] Reaction conditions: 1% mol **CIL3**, 1.15 eq. oxidant, r. t., 1h, CH_2Cl_2.
[b] Yield determined by HPLC.
[c] e.e. value determined by chiral HPLC.

Using UHP as oxidant in CH_2Cl_2, only 10% of sulfide conversion to sulfoxide with 95% enantiomeric excess was obtained, after 1 h (Table 2, entry 1). Using 30% H_2O_2 as oxidant, 44% of sulfide conversion and 30% enantiomeric excess was obtained (Table 2, entry 2). UHP is the oxidant that gave the highest enantiomeric excess. The slow release of H_2O_2 from UHP appears to play an important role in this oxidation resulting in a dramatic increase of the e.e.. Furthermore water can coordinate the metal and modify the chiral complex. In order to increase the sulfide conversion, without compromising the high enantiomeric excess, the amount of the catalyst was increased to a desired level.

Table 3. Effect of the amount of catalyst, $[P_{6\,6\,6\,14}]_2[WO_2(S\text{-mand})_2]$ **CIL3**, on enantioselective oxidation of methyl phenyl sulfide.

Entry[a]	Cat. (mol %)	Sulfoxide yield (%)[b]	Select. (%)	ee (%)[c]
1	1	10	100	95
2	2	36	78	95
3	5	58	82	95

[a] UHP 1.15 eq., room temperature, CH_2Cl_2 , 1 h.
[b] Yield determined by HPLC.
[c] ee value determined by chiral HPLC.

Using UHP as oxidant in CH_2Cl_2 and increasing the amount of catalyst from 1 to 5%, the sulfoxide yield increased from 10 to 58% with high enantiomeric excess (95%). A good selectivity was also maintained, as shown in Table 3.

Improved results were also obtained adding a small percentage of ethanol, 2%, to CH_2Cl_2 and using just 1% of $[P_{6\,6\,6\,14}]_2[WO_2(S\text{-mand})_2]$ as catalyst: the sulfide conversion increased from 10 to 41%, with 98% of selectivity and 88% of enantiomeric excess (Table 4, entry 2).

As expected, decreasing the reaction temperature to 10 °C led to an increase of the enantiomeric excess to 96% with 53% sulfoxide yield and 95% selectivity (Table 4, entry 10). However, a further increase of the reaction time did not give better results. Different solvent systems such as tetrahydrofuran (THF), MeOH, cyclohexane, $[C_4mpyrr][NTf_2]$, water and water with an added phase transfer reagent were also tested, giving unsatisfactory results. CH_2Cl_2-2% EtOH is the solvent system that gave the best results, as shown in Table 4.

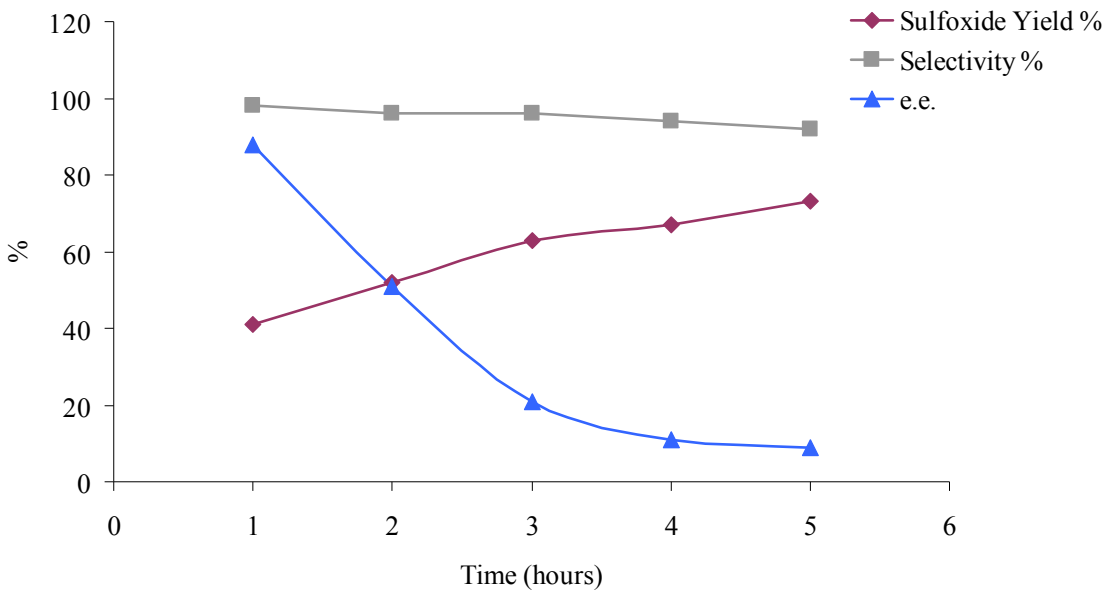
Table 4. Solvent effects on enantioselective oxidation of methyl phenyl sulfide with $[P_{6\,6\,6\,14}]_2[WO_2(S\text{-mand})_2]$ **CIL3**.

Entry[a]	Solvent	Cat. (mol %)	Sulfoxide Yield (%)[b]	Select. (%)	e.e. (%)[c]
1	CH_2Cl_2	1	10	100	95
2	CH_2Cl_2-2% EtOH	1	41	98	88
3	THF	1	85	100	<10
4	MeOH	1	93	84	<10
5	Cyclohexane	1	8	67	<10
6	$[C_4mpyrr][NTf_2]$	1	51	84	<10
7	H_2O	1	94	96	<10
8	aq. Na[AOT]	1	86	90	<10
9	Solventless	1	76	85	<10
10[e]	CH_2Cl_2-2% EtOH	1	53	95	96
12	CH_2Cl_2	5	58	82	95

[a] UHP 1.15 eq., room temperature, 1 h.
[b] Yield determined by HPLC.
[c] e.e. value determined by chiral HPLC.
[d] 5 mol %, 25mM.
[e] 10 ^oC/ 3 h.

Also the solvents would play an important role in organising the substrate at the ligating site of the complex.

Over a longer reaction time, an increase in the sulfide conversion was observed associated with high selectivity, but resulting in a drop of the enantiomeric excess (Graph 1). It is possible that the increased amount of water generated in the system may have an effect on the tungsten(VI) complex anion.



Graph 1. Time effect. Reaction conditions: 1% **CIL3**, 1.15eq. UHP, r.t., CH_2Cl_2, 2% EtOH.

In conclusion, a new class of catalytic ionic liquids containing a tungsten(VI) metal centre bearing chiral ligands has been prepared. These ionic liquids are shown to promote enantioselective oxidation of sulfides to sulfoxides with hydrogen peroxide related oxidants. A simple protocol for achieving high enantioselectivities and conversions is presented. The versatility of bulky and hydrophobic $[P_{6\,6\,6\,14}]^+$ and $[N_{1\,8\,8\,8}]^+$ cations for constructing ionic liquids with complex catalytic anions is also demonstrated. These types of ionic liquids containing other desirable metals could pave the way for further developments in other forms of oxidations. The synthesis of chiral catalytic ionic liquids for other enantioselective oxidation reactions, such as epoxidation is currently under way.

2.3 Experimental section

2.3.1 General Information:

Commercial reagents were used as received, unless otherwise stated. ^{1}H NMR and ^{13}C NMR spectra were carried out on a BRUKER AC 300 MHz, using $CDCl_3$ as solvent (at 300 MHz for ^{1}H and 75 MHz for ^{13}C). The multiplicity of the carbon atoms was determined by the DEPT 135 (DEPT = Distortionless Enhancement by Polarisation Transfer) experiments and quoted as CH_3, CH_2, CH and C for primary, secondary, tertiary and quaternary carbon atoms. ESI mass spectra were carried out on + ESI method on Waters SQ Detector; CD spectra were carried out on Jasco Spetctropolarimeter J-715; $[\alpha]_D^{20^\circ}$ were carried out on Perkin Elmer Model 341 Spectropolarimeter.

2.3.2 Procedure for the synthesis of the catalysts:

Preparation of $[P_{66614}]_2[WO_2(S\text{-Binol})_2]$ (**CIL1)** and $[N_{8881}]_2[WO_2(S\text{-Binol})_2]$ (**CIL2)**

The preparation of $[P_{66614}]_2[WO_2(S\text{-Binol})_2]$ and $[N_{1888}]_2[WO_2(S\text{-Binol})_2]$ involves two steps: preparation of the tungsten complex and exchange of the cation. The first step was the preparation of the ammonium salt $Na[N(Butyl)_4][WO_2(S\text{-Binol})_2]$, following the procedure reported in literature [19]. The cation exchange was realized in dichloromethane. The complex and the phosphonium salt $[P_{66614}]Cl$ (2 equivalents) or the ammonium salt $[N_{1888}]Br$ (2 equivalents) are dissolved in dichloromethane and the solution is stirred. The precipitation of $[N(Butyl)_4]Cl$ and NaCl or $[N(Butyl)_4]Br$ and NaBr respectively were observed. After the filtration of the solid salt, the solvent was removed under reduced pressure, and the product was dried and characterized.

$[P_{66614}]_2[WO_2(S\text{-Binol})_2]$ CIL1: ^1H NMR (300 MHz, $CDCl_3$) δ_H ppm: 7.85-7.79 (m, 8H, H_{ar}), 7.59 (d, 2H, H_{ar}, J= 8.9Hz), 7.29-7.09 (m, 12H, ar. H), 2.98-2.03 (m, 8H), 2.20-2.16 (m, 8H), 1.36-1.22 (m, 98H), 0.90-0.83 (m, 24H); ^{13}C NMR δ_C (300 MHz, $CDCl_3$) ppm: 156.24 (C), 134.34 (C), 128.96 (CH), 128.10 (CH), 127.83 (CH), 125.69 (CH), 125.38 (CH), 121.80 (CH), 120.62 (CH), 115.72, 58.17, 31.85 (CH_2), 30.94 (CH_2), 30.27 (CH_2), 30.08 (CH_2), 29.59 (CH_2), 29.44 (CH_2) , 29.30 (CH_2), 29.22 (CH_2), 28.83 (CH_2), 23.47 (CH_2), 22.62 (CH_2), 22.25 (CH_2), 21.53 (CH_2), 21.47 (CH_2), 19.34 (CH_2), 18.91 (CH_2), 18.29 (CH_2), 13.86 (CH_3), 13.51(CH_3); $[\alpha]_D^{20°}$= +35.8 (c= 0,39, EtOH); $[\Theta]^{20°}$= -98536 (λ= 322nm, EtOH); DSC: m.p. 54°C, g.t. -73°C; MS (+ESI) m/z: 483(M); MS (-ESI) m/z: 784 (M).

$[N_{1888}]_2[WO_2(S\text{-Binol})_2]$ CIL2: ^1H NMR (300 MHz, $CDCl_3$) δ_H ppm: 7.79-7.75 (m, 8H, H_{ar}), 7.47 (d, 4H, H_{ar}, J= 8.7Hz), 7.26-7.08 (m, 12H, ar. H), 2.94-2.92 (m, 21H), 2.73 (s, 3H, CH_3), 1.38-1.20 (m, 66H), 0.90-0.84 (m, 18H); ^{13}C NMR δ_C (300 MHz, $CDCl_3$) ppm: 153.58 (C), 133.96 (C), 129.80 (CH), 128.75 (CH), 127.96 (CH), 126.33 (CH), 124.93 (CH), 122.88 (CH), 118.81 (CH), 113.46 (Cq), 61.16 (CH_2), 58.78 (CH_2), 48.59 (CH_3) 31.55 (CH_2), 28.99 (CH_2), 26.09 (CH_2) , 23.87 (CH_2), 22.51 (CH_2), 22.09 (CH_2), 19.55 (CH_2), 14.00 (CH_3), 13.58 (CH_3); $[\alpha]_D^{20°}$= +26.0 (c= 0,31, EtOH), $[\Theta]^{20°}$= -68937 (λ= 322nm, EtOH); DSC: m.p. 116-117°C; MS (+ESI) m/z: 368 (M); MS (-ESI) m/z: 784 (M).

Preparation of $[P_{66614}]_2[WO_2(S\text{-Mandelate})_2]$(**CIL3**) and $[N_{1888}]_2[WO_2(S\text{-Mandelate})_2]$(**CIL4**)

The preparation of $[P_{66614}]_2[WO_2(S\text{-Mandelate})_2]$ and $[N_{1888}]_2[WO_2(S\text{-Mandelate})_2]$ involves two steps: preparation of the tungsten complex and exchange of the cation. The first step was the preparation of the sodium salt $Na_2[WO_2(S\text{-Mandelate})_2]$, following the procedure reported in literature [20]. The cation exchange was realized in the biphasic system water/ dichloromethane, dissolving the sodium complex in water and the phosphonium salt $[P_{66614}]Cl$ (2 eq.) or the ammonium salt $N_{1888}Br$ (2 eq.) in dichloromethane. After the extraction the organic phase is collected and dried (Na_2SO_4). The solvent is removed under reduced pressure, and the product is dried and characterized.

$[P_{66614}]_2[WO_2(S\text{-Mandelate})_2]$ CIL3: ^{1}H NMR (300 MHz, $CDCl_3$) δ_H ppm: 7.70 (d, 4H, J= 60Hz, H_{ar}), 7.26-7.10 (m, 6H, H_{ar}), 5.67 (s, 1H, CH), 2.32-2.28 (m, 16H), 1.36-1.21 (m, 98H), 0.89-0.82 (m, 24H); ^{13}C NMR δ_C (300 MHz, $CDCl_3$) ppm: 181.73 (C=O), 143.95 (C), 127.40 (CH), 126.39 (CH), 126.01(CH), 84.99, 31.86 (CH_2), 31.12 (CH_2), 30.74 (CH_2), 30.55 (CH_2) , 30.42 (CH_2), 30.23 (CH_2), 29.59 (CH_2), 29.50 (CH_2), 29.30 (CH_2), 29.22 (CH_2), 29.01 (CH_2), 22.63 (CH_2), 21.91 (CH_2), 19.14 (CH_2), 18.52 (CH_2), 13.90 (CH_3); $[\alpha]_D^{20°}$= +12.3 (c= 0,75, EtOH); $[\Theta]^{20°}$= -11752 (λ= 244nm, EtOH); DSC: glass; MS (+ESI) m/z: 483 (M); MS (-ESI) m/z: 516 (M).

$[N_{1888}]_2[WO_2(S\text{-Mandelate})_2]$ CIL4: ^{1}H NMR (300 MHz, $CDCl_3$) δ_H ppm: 7.78-7.67 (m, 4H, H_{ar}), 7.26-7.10 (m, 6H, H_{ar}), 5.85 (s, 1H, CH), 5.67 (s, 1H, CH), 3.22-3.17 (m, 18H), 3.07 (s, 6H, CH_3), 1.47-1.20 (m, 66H), 0.88-0.83 (m, 18H); ^{13}C NMR δ_C (300 MHz, $CDCl_3$) ppm: 181.88 (C=O), 144.36, 144.03, 127.97 (CH), 127.50 (CH), 127.37 (CH), 126.51 (CH), 126.16 (CH), 126.04 (CH), 85.43, 85.09, 61.02 (CH_2), 48.70 (CH_3), 31.60 (CH_2), 29.09 (CH_2), 28.93 (CH_2) , 26.14 (CH_2), 22.51 (CH_2), 22.24 (CH_2), 13.99 (CH_3); $[\alpha]_D^{20°}$= +17.2 (c= 0,95, EtOH); $[\Theta]^{20°}$ = -18024 (λ= 242, EtOH); DSC: m.p. 69 °C; MS (+ESI) m/z: 368 (M); MS (-ESI) m/z: 516 (M).

2.3.3 Catalytic test

The solvent, the catalyst and thioanisole (5mmol) were put in a round bottom flask, the mixture was stirred and the oxidant, 30% H_2O_2 or UHP (1.15 equivalent) was added. The mixture was stirred at room temperature. Aliquots were taken during the reaction course, treated with sodium sulphite in order to destroy the oxidant, and analyzed by HPLC equipped with a C_{18} column, in order to establish the conversion of thioanisole and the yield and selectivity of the sulfoxide; Column Agilent Zorbax C18 column (150mm) was employed with 50:50 CH_3CN/H_2O as eluent, flow of 1ml/min with isocratic elution, UV lamp 256nm. A HPLC equipped with a chiral column was employed to establish the enantiomeric excess: Column OB-H CHIRACEL 250mm, 80:20 Hexane/IPA, flow of 1.5 ml/min isocratically, UV lamp 256nm.

2.4 Notes and references

[1] For reviews on the use of chiral sulfoxides, see: a) I. Fernandez, N. Khiar, Chem. Rev. 103 (2003) 3651–3705; b) M. C. Carreno, Chem. Rev. 95 (1995) 1717–1760.

[2] One of the most popular drugs in the world (with total sales in 2002 of US$ 6.6 Billion) is the chiral sulfoxide Omeprazole (used in the treatment of dyspepsia, peptic ulcer disease (PUD), gastroesophageal reflux disease (GORD/GERD) and Zollinger-Ellison syndrome). Its enantioselective synthesis involves an asymmetric sulfide oxidation. a) For a summary of recent developments and data, see: A. M. Rouhi, Chem. Eng. News 81 (2003) 56–61; b) for a general overview on asymmetric syntheses of biologically active chiral sulfoxides, see: J. Legros, J. R. Dehli, C. Bolm, Adv. Synth. Catal. 347 (2005) 19–31.

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Chapter 3

Heterogeneization of a basic ionic liquid and its use as catalyst in Knoevenagel and Michael reactions.

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3.1 Introduction

Environmental concern associated with chemical synthesis has posed stringent and compelling demands for greener processes, and the development of cost-effective and environmentally benign catalytic systems has become one of the main themes of contemporary synthetic chemistry. In this context, developments of highly active and selective catalysts are of prime importance. As we highlighted in Chapter 1, heterogeneous catalysis is preferred in industrial processes to homogeneous catalysis as the extraction of the product and recovery of the catalyst are relatively easier. However, in various examples of heterogeneous catalysis, mass or heat transfer limitations in the solid catalyst may lead to decreased activity. Furthermore, compared with homogeneous catalysis, lower chemo- and stereoselectivities are often obtained. Obviously, a catalytic system, which makes it possible to secure the advantages of both homogeneous and heterogeneous catalysis (*i.e.*, good activity, high selectivity, easy extraction of the product and recovery of the catalyst) would greatly enhance the interest of industry in catalysis.

In the past 15 years, ionic liquids (ILs) have gained great attention due to their unique properties, as evidenced by their increasing popularity as innovative and environmentally benign reaction media as well as by their use as new vehicles for the immobilization of transition metal-based catalysts. From a chemical point of view, some characteristics of ILs, such as thermal stability and very low vapor pressure, address the problem of emission of volatile organic solvents (VOCs) in the atmosphere, thus making these liquids environmentally attractive alternatives to classical organic solvents. Moreover, the physical properties of ILs can be finely tuned by changing either the anion, the cation or the attached substituents. Thus ILs exhibit an excellent ability to dissolve polar and non-polar organic, inorganic and polymeric compounds, allowing substantial applications of ILs in various types of catalytic and synthetic reactions. There are many reviews in the literature which give comprehensive overviews about the topics related to ILs such as synthesis in ILs, catalysis with ILs, and non-solvent utilizations of ILs [1]. Numerous chemical reactions, such as polymerization, hydrogenation, regioselective alkylation, Friedel–Crafts reactions, dimerization of alkenes, Diels–Alder reactions, Michael reactions, cross-coupling reactions and some enzymic reactions can be carried out in ionic liquids or using ionic liquids as catalysts [2].

However, in homogeneous catalysis, there are many problems when ILs are used as reaction media: (i) a large amount of IL is required, this makes them unattractive based on economic

considerations since ILs are still expensive, even though being commercially available today; (ii) in order to separate organic products from the ionic phase, extraction with solvents which are immiscible with the ILs has to be used in the most cases; this procedure causes a drawback concerning the extraction of small amounts of the ILs and of the catalyst; (iii) using ILs as solvents will generate inevitably a large amount of waste at the end of their valid life, however, their potential toxicity and the lack of data about their biodegradability will render the disposal of waste ILs very difficult especially under the pressure of environmental protection; (iv) in some reactions, bulk IL systems may suffer from slow substrate diffusion due to the relatively high viscosities of the ILs, causing the main part of the reaction to proceed in the inter-phase or in the diffusion layer of the catalyst, rather than in the bulk solvent as would be strongly preferred. Thereby, the productivity of the process is limited since a large part of the catalytically active species is not participating in the reaction; (v) in order to minimize the effects of impurities in ILs on the catalysis, it requires generally the use of a very pure IL, which is, however, at this moment, very difficult to obtain. These aspects may be sufficient to explain why, although ILs have shown great potential on the homogeneous catalysis in laboratory scale, there has not yet been any known large-scale industrial application in catalysis. In order to advance catalysis with ILs, a new strategy which utilizes the advantageous properties of ILs and, at the same time, minimizes the negative effects, would be highly desirable. A particularly promising concept is represented by supported ionic liquids. This involves coating a solid support with a thin layer of an ionic liquid. The chemical reaction of the starting material to the product is catalysed by a chemical group associated with the cation or the anion of the ionic liquid, so called task specific ionic liquid (TSIL), or the catalyst is dissolved in the ionic liquid as reaction medium. The solid support locks the ionic liquid into position and stabilises a large interphase area between the ionic liquid and the reactant phase. As each component (ionic liquid, catalyst, additives and support) can be chosen indipendently, concept allows assembling a catalyst readily from predefined building blocks [3]. Solid catalysis with ILs appears to be an ideal choice because of the fact that ILs here are used in small amounts, while their efficiencies are as good as for the utilizations of bulk solvents. Recently, ready-made solid catalysts with ILs, in which the surface of the solid catalyst was coated by IL, offered a new method for re-investigations of many ready-made solid catalysts. Covalently grafting imidazolium cations onto the surface of solid materials not only heterogenizes the expensive IL, but also offers a lot of opportunities to investigate immobilizations of homogeneous metal complexes or metal nanoparticles. Recycling functionalized IL by this method is also possible.

C. Aprile et al. [4] recently reported an ionic liquid moiety covalently attached as a monolayer to the surface of a silica gel support. Indeed, ionic liquids are expensive, hence it is desirable to minimize the quantity used in typical biphasic reaction systems. To the covalently-attached ionic liquid monolayer, the organocatalyst (*e.g.* L-proline) was supported with or without additional adsorbed ionic liquid. Good enantioselectivities and yields were reported in the reaction between acetone and several aldehydes. The catalytic system was recovered easily by conventional filtration and later re-used. Moreover, since proline is adsorbed, it could be removed and replaced with fresh proline, allowing the catalyst recyclability [4].

Base-catalyzed reactions are not often required in the production of bulk chemicals but they are highly useful in the synthesis of many fine chemicals. A whole variety of solid base catalysts are available, ranging from simple metals, metal oxides, exchanged zeolites and tailored catalyst having specific organic base functionality tethered to an inert backbone.

Many basic transformations such as esterifications, Michael reactions and Knoevenagel reactions are carried out under basic conditions, some using aqueous base and other strong soluble organic bases such as guanidines. The base is not usually recovered, producing either salt or organic waste. In case of expansive organic bases, difficulty in recovery often prevents commercialization of the process. Several methods have now been developed to heterogenize organic bases on supports such as silica or polymeric material. For acceptable catalytic system it is important to maximize the amount of basic sites on the catalyst and at the same time maintaining an open structure for access of reagents [5].

Recently, ionic liquid technology has been utilized to enable base catalysed reactions to occur allowing the base to be recycled and, in some cases, showing higher selectivities compared with molecular solvents. For example, L-proline has been reported to act as a recyclable chiral base in ionic liquids in the chiral aldol condensations between propanone and a range of aromatic and aliphatic aldehydes. In addition, Forsyth and co-workers [6] have demonstrated that in ionic liquids based on $[NTf2]^-$ and $[FAP]^-$ significantly higher selectivities are found at high conversion for aldol condensation of 4-*t*-butylbenzaldehyde and propanal to form 3 (4-*t*-butyl-phenyl)-2-methyl-propenal, using piperidine compared with either the industrial process or using piperidine in molecular solvents. Ionic liquids have also been used in combination with solid supports. The Knoevenagel reaction has been performed in ionic liquids catalysed by hydrotalcite achieving excellent conversions after 1 h [7]. Shen et al. [8] immobilized a functionalized imidazolium ionic liquid on to silica gel, producing a solvent free recyclable system for the Knoevenagel condensation and for the cycloadditon of CO_2 with propylene. For each reaction conversions higher than 90% were reported with a slight

decrease upon recycle. Recently, guanidine based ionic liquids have been developed and employed as catalysts for the aldol [9], Henry [10], and Knoevenagel [11] reactions without any loss in catalytic activity after 15 runs. Amino-acids such as glycine and proline have also been used as a promoter in imidazolium ionic liquids for the condensation of aliphatic and aromatic aldehydes with malononitrile and diethylmalonate at 35–55 °C leading to high conversions albeit over a period of 12–48 h. Recently C. Hardacre and co-workers [13] reported a new class of ionic liquids derivatives of the non-nucleophilic Hünig's base tethered to an alkyl ammonium side chain. One of the ionic liquid is shown in Figure 1 and in each case the counter ion used was bis{(trifluoromethyl)sulfonyl}imide ([NTf2]$^-$).

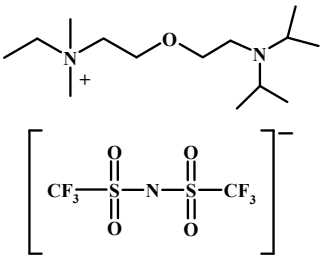


Figure 1. Basic ionic liquid (BIL) containing Hünig Base

These ionic liquids were employed for promoting Knoevenagel reaction. That basic ionic liquid (BIL) was reported to have similar activity to Hünig base. Carrying out the reaction without solvent 89% of conversion has been reported after 20 minutes of reaction between belzaldehyde and ethyl cyanoacetate. But many problems were found in the product extraction. So BIL was employed as catalyst, supported on silica by simple impregnation and suspended in an organic solvent or as a biphasic system with BIL in catalytic amounts [13].

However, in both cases various drawbacks were observed. The only usable solvent was cyloexene, so the reaction could be performed only with aldehydes soluble in that solvent; thermic degradation and deactivation were observed in both cases so the catalysts are not reusable; the highest yield observed with the adsorbed ionic liquids is 70% and it could not be increased due to deactivation of the catalytic system with time.

So in collaboration with QUILL (Queen's University Ionic Liquid Laboratories), we decided to anchor the ionic liquid on the silica support by the tethering technique, in order to improve the catalytic activity of these basic ionic liquids. The ionic liquid (Figure 1) was bound to the solid support by covalent bond with the purpose of increasing the robustness of the catalyst, making it reusable and expanding its applicability.

The catalytic activity of the obtained supported ionic liquid has been tested in Knoevenagel and Michael reactions.

The Knoevenagel condensation is one of the most important carbon–carbon bond forming reactions in organic synthesis. There has been extensive interest in Knoevenagel products in recent years as they have very important industrial applications. For example, coumarin derivatives which are basically derived from Knoevenagel condensation products have extensive applications in cosmetics, perfumes and several therapeutic drugs. This reaction is generally carried out by condensation of a carbonyl compound with an active methylene compound using any organic base such as ethylenediamine, piperidine, dimethylamino pyridine or corresponding ammonium salts, amino acids as catalysts. The notable disadvantage observed with many of the reported catalysts is that they were used in stoichiometric amounts or even large excess to effect complete conversion of the substrate [14]. So, there is still a quest for development of more efficient and simple methods and recently heterogeneous catalysts have also been used for the Knoevenagel reaction. Thus, the reaction has been catalyzed by heterogeneous catalysts based on alumina, silica, zeolite, zinc and magnesium oxides, resins and other catalysts with more or less success [15].

With the increasing public concern over environmental degradation, one of the challenges for chemists is to come up with new approaches that are less hazardous to human health and environment. The solvents used in organic synthesis are high in the list of environmental pollutants, because they are employed in large amounts and are usually volatile liquids. For overcoming this problem one approach is selecting water as a green medium. Another approach is carrying out reactions under solvent-free conditions. These methods have many advantages, such as reduced pollution, lower cost, and simplicity in processing which are beneficial to the industry as well as to the environment [15].

For these reasons, in this thesis we examined the possibility of performing solvent-free reactions.

The Michael reaction as well is generally regarded as one of the most efficient carbon–carbon bond forming reactions and can be easily applied to compounds having different functional groups. Apart from its versatile applications in synthetic organic chemistry, it has found multiple industrial applications. This reaction is industrially catalyzed by liquid or solid bases and remarkable progress has been made recently in developing new methodology for Michael addition. However, there are various drawbacks with the reported methodologies such as long reaction times, use of halogenated solvents, difficulty in recovery of high boiling solvents, high temperatures, requirement of special efforts to prepare catalysts, use of costly catalysts,

and moderate yields. Although transition metal-catalyzed Michael addition in organic solvent and water have been developed with a great deal of success, catalytic efficiency, substrate scope and reaction rate have been limited so far [16].

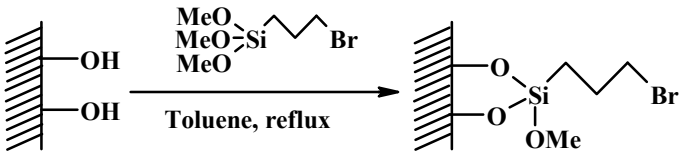
A number of reagents have been developed for the Michael mono-addition reaction. To date, a few reagents, such as ruthenium complex and basic ionic liquid, have been reported for the Michael bis-addition of active methylene compounds to conjugated carboxylic esters and nitriles. Moreover, these reagents failed to initiate the Michael bis-addition of active methylene compounds to conjugated ketones even at elevated temperature. Thus, there is a demand for the development of a milder reagent for a general Michael bis-addition of active methylene compounds to α,β- unsaturated ketones, esters, and nitriles in a single step [17].

3.2 Results and discussion

3.2.1 Catalyst preparation

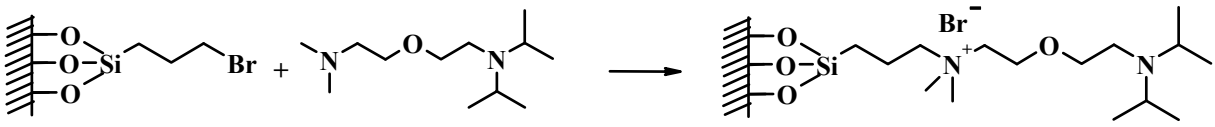
The catalyst preparation involved three main steps: (**a**) silica functionalization anchoring the spacer 3-bromopropyl group to surface silanols; (**b**) nucleofilic substitution between the supported propyl bromine and the tertiary amine; (**c**) anion exchange with litium bis-triflamate (Scheme 1).

a. First step: silica functionalization



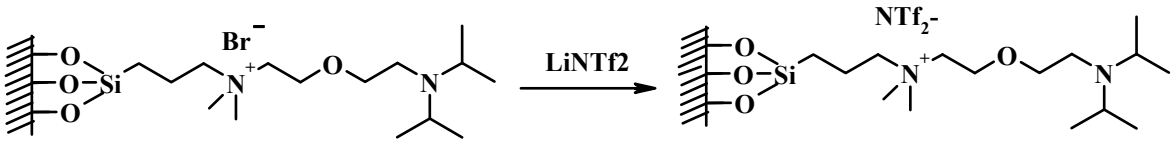
Loading ~0.9 mmol/g.

b. Second step: anchoring of the basic ionic liquid



SIL Br
Loading 0.64-0.75 mmol/g.

c. Third step: anion exchange



SIL
Loading 0.48-0.56 mmol/g.

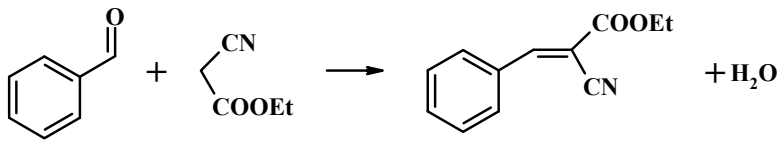
Scheme 1: Preparation of supported ionic liquid (SIL).

In the fist step (3-bromopropyl)trimethoxysilane was condensed with silica silanols by refluxing in toluene under stirring. The cooled functionalized silica was filtered off, washed and then dried under high vacuum to give the surface-bound alkyl bromide groups with a loading of 0.9 mmol/g detrmined by Elemental analysis. The bromide loading was determined by Volhard method, obtaining 0.83 mmol/g. In the second step the bromopropylated silica

was treated with the suitable tertiary amine (Scheme 1, **b**) in refluxing toluene for 24 h, affording the corresponding supported quaternary ammonium salt. After cooling, the solid was filtered off and carefully washed with toluene, then dried at 60 °C under high vacuum. The amount of bromide ions present on the functionalized silica at this step was determined by titration [18] according to the Volhard method, giving a bromide loading of 0.62 mmol/g. In the third step the Br^- anion was exchange with the NTf_2^- anion treating the solid with $LiNtf_2$ in order to obtain the supported basic ionic liquid corresponding to the published BIL. After stirring for 1 hour in water, the supported ionic liquid was filtered off, washed and dried under vacuum. The loading of the obtained material determined by Elemental analysis was 0.48-0.56 mmol/g. The amount of bromide ions still present on the functionalized silica after the exchange reaction was determined by titration [18] according to the method described by Volhard, the amount of bromine anions found was of 0.11 mmol/g, showing the almost complete anion exchange. Then the solid was washed in continuous with hot acetonitrile for 12 h using a Soxhlet apparatus.
In the prepared catalyst, the solid support is expected to have a sort of liquid film on the surface [19].

3.2.2 SIL catalytic activity: Knoevenagel reaction

The catalytic activity of SIL was tested in Knoevenagel reaction between belzaldehyde **1a** and ethyl cyanoacetate **2** in order to obtain compound **3a** (Scheme 2).



1a **2** **3a**

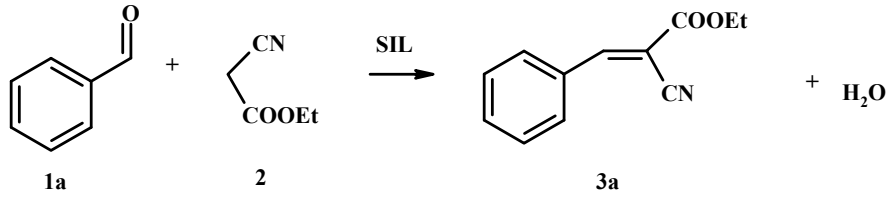
Scheme 2. Model reaction.

Product **3a** belongs to the class of α-cyanocynnamic acids. These compounds and their derivatives present high biological activity and they are used in polymeric, pharmaceutical and cosmetic industries. For example 3-nitro-ethyl-cinnamate is used as photo-sensibiliser [20] and Trimethoprim, well-known anti-bacteric agent, is synthesised by condensation of

ethyl cyanoacetate and 3,4,5-trimethoxybenzaldehyde, followed by reduction of the double bond [21].

The reaction was at first carried out in CH_3CN, using 10% mol of SIL and 1:1 ratio of the reagents for 48 hours and just 30% yield of **3a** was obtained. In order to increase the conversion, the reaction was carried out solvent less, using 5% mol of **SIL**. After 12 hours 92% yield of **3a** was obtained (Table1).

Table 1.



1a **2** **3a**

Entry	SIL (%)	Solvent	Time (h)	Yield 3a (%)
1	10	CH_3CN	48	30
2	5	-	12	92

Reaction condition: room temperature, **1a**/**2** ratio =1:1; yield and conversion were determined by GC analysis and ^{1}H-NMR spectroscopy.

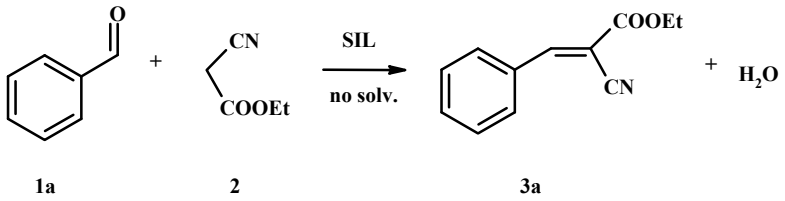
When the reaction was carried out without solvent high yield of compound **3a** was obtained in shorter time and using lower amount of catalyst.

Various reaction parameters (*i.e.* time, temperature and amount of catalyst) were varied to optimize the reaction. The obtained results are shown in Table 2. After reaction completion ethyl acetate was added to the mixture, the catalyst was filtered off and recovered. Yield and conversion were determined by ^{1}H-NMR and GS analysis giving comparable results. In GC analysis 1,4-dimethoxy benzene was employed as internal standard.

For ^{1}H-NMR analysis, the solvent was evaporated under vacuum giving a crude, that was weighted and analyzed by NMR.

When the reaction was carried at room temperature almost quantitative yield of compound **3a** was obtained in 18 hours (Table 2, entry 1). In order to reduce the reaction time the temperature was increased to 60 °C. After 6 hours 97% of product **3a** in high selectivity was obtained (Table 2, entry 4). Then the amount of catalyst was varied. Even decreasing the amount of **SIL** to 2%, 92% of yield was achieved in 6h (Table 2, entry 8).

Table 2. Optimization of reaction parameters.



1a **2** **3a**

Entry	SIL (%)	Time (h)	Temp. (°C)	Yield 3a (%)	Conv. 2 (%)
1	5	18	t.a.	97	97
2	5	12	t.a.	92	95
3	5	6	t.a.	68	75
4	5	6	60	97	98
5	5	3	60	96	98
6	5	1	60	73	80
7	2.5	3	60	86	87
8	2	6	60	92	96
9	2	3	60	84	85
10	1	3	60	35	40

Reaction condition: room temperature, **1a**/**2** ratio =1:1; yield and conversion were determined by GC analysis and ^{1}H-NMR spectroscopy.

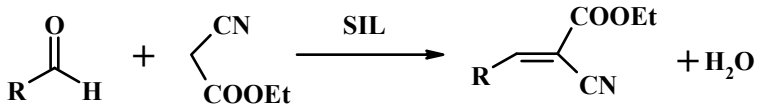
The general applicability of the reaction was then studied. As evidenced by the results shown in Table 3, the prepared supported catalyst was able to promote efficiently Knoevenagel condensation in presence of both aromatic (Table 3, entry 1-4) and aliphatic aldehydes (Table 3, entry 5) with high yields and selectivities. The presence of electron-withdrawing or elettron-donor groups (Table 3, entry 2, 3 and 4 respectively) on the aromatic ring increases the reactivity. Infact, almost quantitative yield of compounds **3b-d** were obtained in shorter time (3h *vs.* 6h).

We can conclude that the basic ionic liquid supported by chemical bond displays many advantages. When the ionic liquid heterogenised by simple impregnation was employed [13], only cyclohexene could be used as reaction medium. On the contrary, employing **SIL**, the reaction could be carried out in different solvents or without solvent with increased yield and selectivity. In the model reaction, compound **3a** was obtained in quantitative yield using just 2% mol of catalyst, while 10% mol of the adsorbed catalyst is reported to give not more than

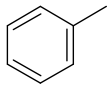
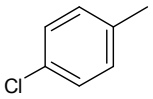
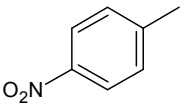
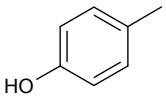
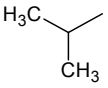
70% of yield. We did not observe the catalyst deactivation, that was observed in both the cases of homogeneous catalyst and adsorbed catalyst.

Furthermore our catalytic system permits to employ both liquid and solid aldehydes, overcoming the limit of solubility in cycloexene required by the published catalytic system [13].

Table 3. Reaction extension to various aldehydes.



1a-e **2** **3a-e**

Entry	Time (h)	SIL (%)	R	Yield 3 (%)	Conv. 2 (%)
1	6	2	 **3a**	94	96
2	3	2	 **3b**	98	99
3	3	2	 **3c**	99	99
4	3	2	 **3d**	99	99
5	6	5	 **3e**	88	94

Reaction conditions: 60 °C, solvent less, **1a**/**2** ratio =1:1; yield and conversion were determined by GC analysis and ^{1}H-NMR spectroscopy.

The catalyst recyclability was studied in the model reaction under the optimized reaction conditions (2% **SIL**, solvent less, 60 °C, 6h).

After any cycle the catalyst was recovered by Buchner funnel filtration, dried under vacuum and used in 2% mol in the following cycle. The obtained results are shown in Figure 2.

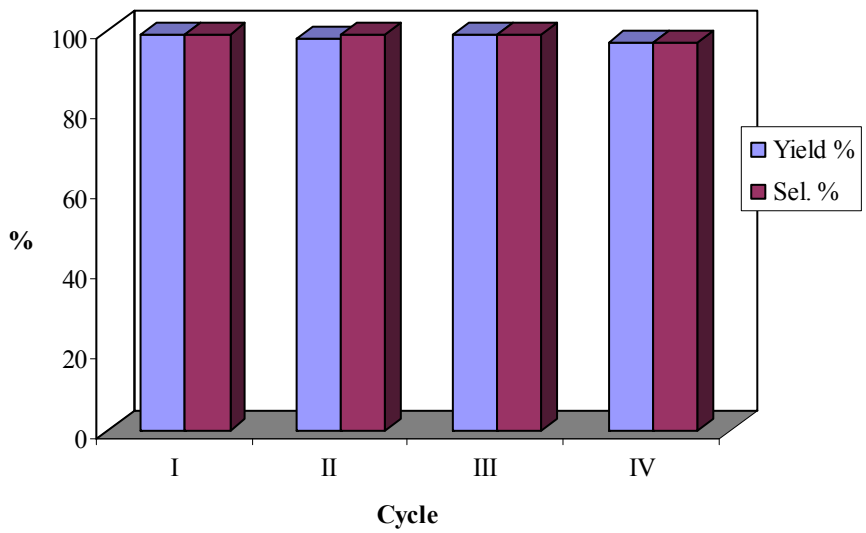
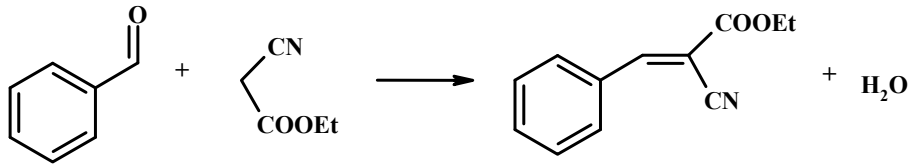


Figure 2. Study on **SIL** recyclability. Reaction conditions: 2% **SIL**, 60 °C, solvent less, 3 hours, **1a**/**2** ratio =1:1; yield and conversion were determined by ^{1}H-NMR spectroscopy.

In the forth cycle 97% of yield was obtained, evidencing the perfect recyclability of SIL.
This is a further advantage compared to the adsorbed ionic liquid and the ionic liquid in homogenous phase. On the basis of ^{1}H-NMR studies the Authors explained the non recyclability due to thermal degradation of the basic ionic liquid. They supposed that this occurs even if the catalyst is used at room temperature. Since the reaction is exothermic, the temperature arises to 65 °C. The prepared catalyst supporting the ionic liquid by chemical bond has been used in a reaction carried out at 60 °C and it could be recycled for at least four cycles. So we can affirm that our heterogeneous catalyst is more active and more robust than the homogenous and the adsorbed catalysts reported in literature [13].

Then we decided to evaluate the anion effect on activity of the supported ionic liquid. So **SIL Br** and **SIL** were tested in the model reaction. Results are shown in Table 4.

Table 4. Anion effect on the catalytic activity.



1a **2** **3a**

Entry	CAT	Yield (%)
1	SIL	84
2	SIL Br	75

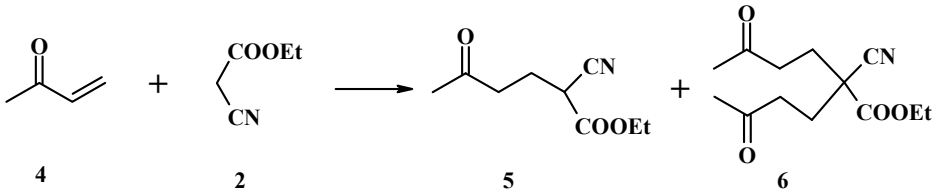
Reaction conditions: 60 °C, 2% catalyst, solvent less, 3 hours, **1a**/**2** ratio =1:1; yield and conversion were determined by GC analysis and ^{1}H-NMR spectroscopy.

As expected, using **SIL** bearing NTf_2^- anion (entry 1), higher yield and selectivity were obtained. When the ionic liquid is supported on a surface it forms a liquid film on the supported surface. The presence of an interphase area between the ionic liquid and the reactant phase makes easier the interaction between the reagents and the catalytic sites [3]. This effect is probably stronger when the ionic liquid contains NTf_2^- as anion, because of the property of the ionic liquid. Indeed, almost all the ionic liquid reported in literature containing NTf_2^- as anion are in liquid state at room temperature due to the highly delocalised negative charge in NTf_2^-.

Furthermore we started the study of **SIL Br** recyclability and already at the second cycle a decrease of yield was observed. Further studies are currently under way.

3.2.2 SIL catalytic activity: Michael reaction

The activity of **SIL** in promoting C-C bond formation reactions was studied as well in Michael addition. The reaction between ethyl cyanoacetate and methyl vinylketone was chosen as model (Scheme 3).

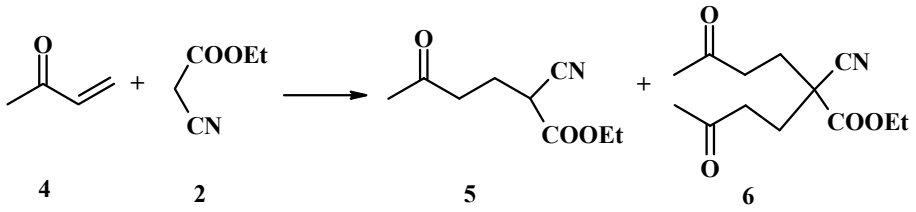


Scheme 3. Model reaction

Our purpose was to obtain a selective processes toward the formation Michael mono-addition product **5** or bis-addition product **6**.

Indeed preliminary reaction carried out using 1:1 ratio of reagents **4** and **2**, 5% mol of **SIL** in toluene for 12 hours gave high conversion (84%), but unsatisfactory selectivity. Compounds **5** and **6** were obtained in ratio 83:17. Two equivalents of reagent **4** were employed and reaction conditions were varied in order to obtain selectively compound **6**, which is reported in literature [22] as the most difficult to synthesise even using strong basic catalysts.

Table 5. Synthesis of compound **6**.



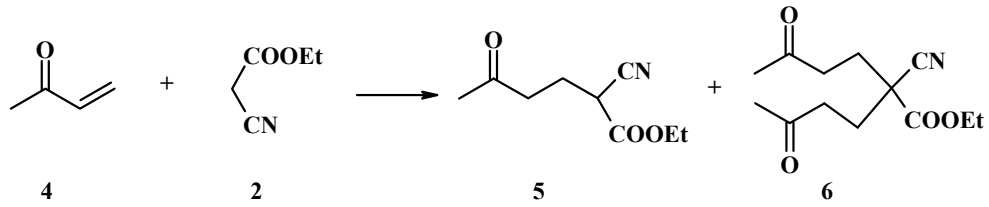
Entry	4:2 Ratio	Solvent	Temp. (°C)	Time (h)	Yield 5 (%)	Yield 6 (%)	Selec. 6 (%)
1	1:1	Toluene	25	12	70	14	17
2	2:1	-	25	12	11	85	88
3	2:1	-	60	3	14	81	85
4	2:1	-	60	4	11	84	88
5	2:1	-	60	12	10	86	89
6	4:1	-	80	12	2	98	98

Reaction conditions: 5% mol of **SIL**, solvent less, room temperature; yield and conversion determined by GC analysis.

When the reaction was carried out at room temperature using 5% of SIL in 12 hours without solvent, high yield (85%) of compound **6** was obtained with 88% selectivity (Table 5, entry 2). Increasing the temperature to 60 °C, in 4 hours the same results were obtained (Table 5, entry4). Excellent result was achieved using an excess (two fold) of reagent **4** at 80 °C for 12 hours (Table 5, entry 6), obtaining compound **6** in 98% yield and selectivity. This result is noteworthy considering that it is reported in literature that even a strong basic ionic liquid such as [bmIm]OH is not able to promote the formation of Michael bis-addition product [22].

Then we started to study the conditions to obtain selectively the Michael mono-addition product **5**. Different solvents and temperature were tested and a slightly excess of reagent **2** was used, as reported by other Authors [22]. The results are shown in Table 7.

Table 6.



4 2 5 6

Entry	4:2 Ratio	Solvent	Temp. (°C)	Yield 5 (%)	Yield 6 (%)	Selec. 5 (%)
1	1:1	Toluene	25	70	14	83
2	1:1.25	Cyclohexane	60	79	15	84
3	1:1.25	Ethylacetate	60	74	12	86

Reaction conditions: 5% mol of **SIL**, room temperature for 12 hours; yield and conversion determined by GC analysis.

In cyclohexane an increase of yield was observed (79%), but the selectivity of product **5** was still unsatisfactory (Table 6, entry 2) .

On the basis of the good results achieved in compound **6** preparation operating in solvent less conditions, the reaction for the synthesis of compound **5** was carried out without solvent as well. Results are depicted in Table 8.

Table 7. Synthesis of compound **5**.

Entry	4:2 Ratio	Time (h)	Yield 5 (%)	Yield 6 (%)	Selec. 5 (%)
1	1:2	1	78	2	98
2	1:3	1	81	0	100
3	1:3	2	84	6	91
4	1:3	3	84	8	91
5	1:5	2	99	0	100

Reaction conditions: 5% mol **SIL**, solvent less, room temperature; yield and conversion determined by GC analysis.

Employing an excess of reagent **2**, 100% of selectivity in product **5** was achieved in short reaction time (Table 7, entry 2). Prolonging the reaction time the conversion increased, but a small amount of product **6** (6-8%) was observed as well (Table 7, entry 3-4).
Quantitative conversion of reagent **4** in product **5** was observed employing 4 eq. of reagent **2** and by adding slowly in 2 hours time (Table 7, entry 5).
We can conclude that **SIL** is able to promote Michael addition reaction. Indeed using 5% mol of heterogeneous catalyst in the appropriate reaction conditions reaction, mono-addition product **5** and bis-addition product **6** were both obtained selectively in high yield.

3.3 Experimental section

3.3.1 General Information:

Commercial reagents were used as received, unless otherwise stated. ^{1}H NMR and ^{13}C NMR spectra were carried out on a BRUKER AC 300 MHz, using $CDCl_3$ as solvent. (at 300 MHz for ^{1}H and 75 MHz for ^{13}C). Mass spectra were obtained by the + ESI and - ESI methods on Waters SQ Detector or by GC-MS.

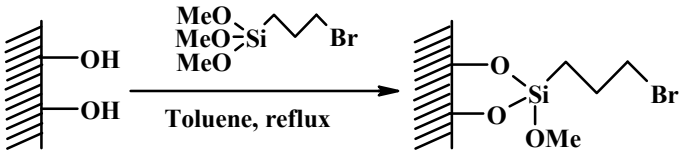
GC chromatograms were obtained by Trace GC Thermo Finnigan coupled with FID detector (Chromatography column Supelco SPB-20).

Preparative chromatographic plates were made using "Merck 60 PF254" silica (20 x 20 cm, thickness 1 mm).

Elemental analyses were performed with a Carlo Erba CHNS-O EA1108 elemental analyzer.

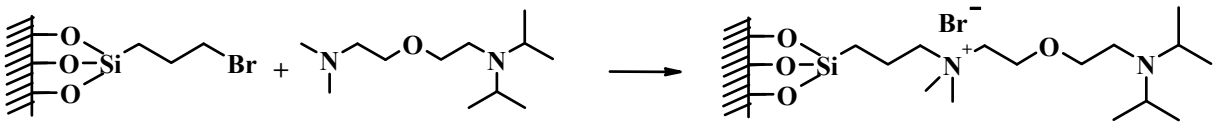
3.3.2 Heterogeneous catalyst preparation (SIL)

I step: silica functionalization



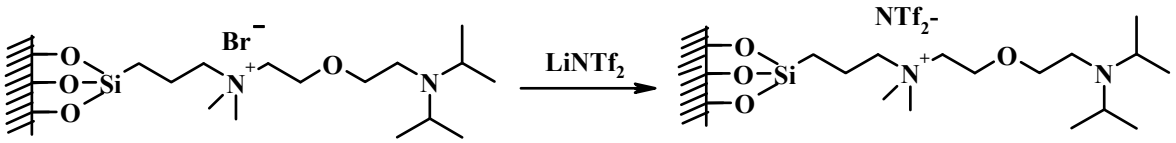
In a 100ml round bottom flask 5g of silica was heated to reflux in 30 ml of toluene for two hours in order to remove the adsorbed water. After changing the condenser, (3-bromopropyl) trimethoxysilane (2.43 g, 10 mmol) was added. The mixture was refluxed for 12 hours. The cooled functionalized silica was filtered off, washed with toluene, diethyl ether, and dichloromethane (2 × 25 ml each); then it was dried under high vacuum at 60 °C for 3 h to give the surface-bound bromopropylic group. The loading of the organic moieties was determined by elemental analysis (~0.9 mmol/g), the bromide loading was determined by Volhard method (0.83 mmol/g).

II step: anchoring of the IL



The bromopropylated silica (2.5 g, 0.9 mmol/g loading) was then treated with the depicted tertiary amine (2.16 g, 10 mmol) in 30 mL of refluxing toluene for 24 h, affording the corresponding supported quaternary ammonium bromide. After cooling, the solid was filtered on a Büchner funnel and carefully washed with toluene (5×20 mL), then dried at 60 °C under high vacuum. The loading determined by elemental analysis was in the range 0.64-0.75 mmol/g. The amount of bromide ions present on the functionalized silica after the reaction with the tertiary amine was determined by titration [18] according to the method described by Volhard. Starting from 0.30 g of immobilized salt in 10 mL of ethanol, 10 mL of 0.1 N $AgNO_3$ solution, and 5 mL of HNO_3 6 N were added, and the suspension was stirred in the dark for 0.5 h at room temperature. Then the solid was filtered off, and the excess $AgNO_3$ was titrated with 0.1 N ammonium thiocyanate, giving a bromide loading of 0.62 mmol/g.

III step: anion exchange

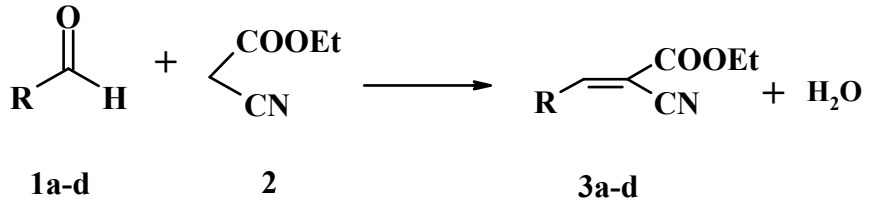


SIL

The catalysts **SIL** was prepared by stirring a mixture of the surface-bound ammonium bromide salt (2 g, 1.3 mmol) and an aqueous solution of $Li^{+}NTf_2^{-}$ (0.75 g, 2.6 mmol) in distilled water at room temperature for 2 hours. After stirring, the solid was filtered off, carefully washed with 50 ml of distilled water, 50 ml of ethanol, and 50 ml of diethyl ether. Elemental analyses revealed a loading of 0.48-0.56 mmol/g. The amount of bromide ions present on the functionalized silica after the reaction with triethylamine was determined by titration [18] according to the method described by Volhard. Starting from 0.30 g of immobilized salt in 10 mL of ethanol, 10 mL of 0.1 N $AgNO_3$ solution, and 5 mL of HNO_3 6 N were added, and the suspension was stirred in the dark for 0.5 h at room temperature. Then the solid was filtered off, and the excess $AgNO_3$ was titrated with 0.1 N ammonium thiocyanate, giving a bromide loading of 0.11 mmol/g, showing the almost complete anion exchange. Then the solid was washed in continuous with hot acetonitrile for 12 h using a Soxhlet apparatus.

3.3.3 Knoevenagel reaction procedure

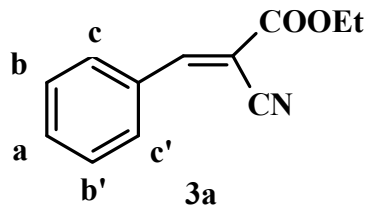
General procedure for the synthesis of ethyl (E)-2-cyano-3-aryl-acrilate (3a-d).



1a-d **2** **3a-d**

In one-neck flask a mixture of ethyl cyanoacetate (0.5 mmol) and **SIL** (2-5% mol as indicated in Table 3) were stirred at room temperature for 15 minutes. Then the selected aldehyde **1a-d** (0.5 mmol) was added and the mixture was heated at 60 °C for 3 h without solvent. After completion of reaction (as indicated by TLC, eluent *n*-hexane-ethyl acetate 40%), the reaction mixture was cooled to room temperature. Then ethyl acetate (3 ml) was added to the solid. The catalyst was simply removed by Büchner filtration and washed with ethyl acetate (8 ml). Yield and conversion were determined by GC analysis and ^{1}H-NMR spectroscopy obtaining the same results. For the GC analysis 1,4-dimethoxybenzene was used as internal standard. For ^{1}H-NMR analysis, the solution was concentrated under vacuum and the crude was weighted. The ratio between reagents and product **3** was determined by integration of the corresponding signals in the ^{1}H-NMR spectrum. Knowing the ratio and the crude weight, yield and conversion were determined. The products **3a-d** were purified by chromatography plates and characterized by ^{1}H NMR and GC-Mass analyses.

Characterization of ethyl (E)-2-cyano-3-phenylacrilate (3a).

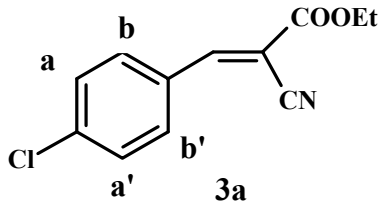


White solid, m.w. 201.23, $C_{12}H_{11}NO_2$.

^{1}H NMR ($CDCl_3$, 300MHz) δ (ppm): 8.25 s, 1H (CH=C); 7.99 d, 2H (Hc, Hc'), J = 7.1 Hz; 7.5-7.2 m, 3H (H_a, H_b, $H_{b'}$); 4.39 q, 2H (CH_2-CH_3), J= 7.1 Hz; 1.40 t, 3H (CH_2-CH_3), J= 7.1 Hz.

MS-EI (m/z): 201 [M^+ (90%)], 172 [M^+-Et (85%)], 156 [M^+-OEt] (100%), 128 [M^+-COOEt] (75%), 102 (43%).

Characterization of ethyl (E)-3-(4-chorophenyl)-2-cyanoacrilate (3b).

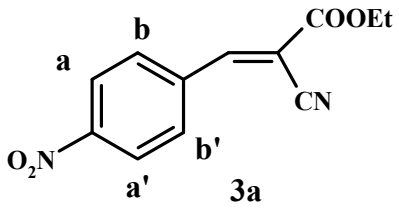


White solid, m.w. 235.67, $C_{12}H_{10}NO_2Cl$.

^{1}H NMR ($CDCl_3$, 300MHz) δ (ppm): 8.19 s, 1H, (CH=C); 7.93 d, 2H (H_c, $H_{c'}$), ½ para system, J = 8.5 Hz; 7.48 d, 2H (H_b, $H_{b'}$), ½ para system, J = 8.5 Hz; 4.39 q, 2H (CH_2-CH_3), J= 7.1 Hz; 1.40 t, 3H (CH_2-CH_3), J= 7.1Hz.

MS-EI (m/z): 235 M^+ (80%), 207 M^+-CH_2=CH_2 (60%), 190 M^+-OEt (100%), 162 M^+-COOEt (55%), 127 (47%).

Characterization of ethyl (E)-2-cyano-3-(4-nitrophenyl)acrilate (3c).

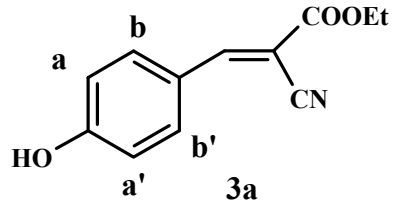


Yellow solid, m.w. 246.22, $C_{12}H_{10}N_2O_4$.

^{1}H NMR ($CDCl_3$, 300MHz) δ (ppm): 8.37 d, 2H (H_b, $H_{b'}$), ½ para system, J = 8,8 Hz; 8.30 s, 1H (CH=C); 8.14 d, 2H (H_a, $H_{a'}$), ½ para system, J = 8,8 Hz; 4.38 q, 2H (CH_2-CH_3), J= 7.1 Hz; 1.38 t, 3H (CH_2-CH_3), J= 7.1 Hz.

MS-EI (m/z): 246 M^+ (45%), 218 M^+-CH_2=CH_2 (100%), 201 M^+-OEt (90%), 155 (70%), 127 (56%).

Characterization of ethyl (E)-2-cyano-3-(4-hydroxyphenyl)acrilate (3d).



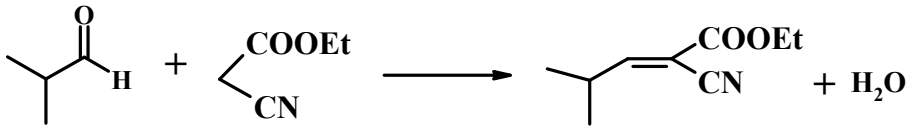
White solid, m.w. 217.23, $C_{12}H_{11}NO_3$.

^{1}H NMR (CD_3OD, 300MHz) δ (ppm): 8.25 s, 1H (CH=C); 8.02 d, 2H (H_b, $H_{b'}$), ½ para system, J = 9.0 Hz; 6.97 d, 2H (H_a, $H_{a'}$), ½ para system, J = 9.0 Hz; 4.39 q, 2H (CH_2-CH_3), J=6.0 Hz; 1.42 t, 3H (CH_2-CH_3), J= 6.0 Hz.

MS-EI (+ESI) (m/z): 218.09 ($M+H^+$) 10%, 239.79 ($M+Na^+$) 100%.

MS-EI (-ESI) (m/z): 216.00 ($M-H^+$) 100%.

Procedure for the synthesis of ethyl (E)-2-cyano-3-isopropylacrilate (3e).



1e **2** **3e**

In 2 ml pyrex reactor with screw stopper, a mixture of ethyl cyanoacetate (0.113 g, 1 mmol) and **SIL** (5% mol, 0.078 g, loading 0.57 mmol/g) were stirred at room temperature for 15 minutes. Then the isobutyl aldehyde **1e** (0.072 g, 1 mmol) was added and the mixture was heated under stirring at 60 ^{0}C for 6 h without solvent. After completion of reaction (as indicated by TLC, eluent *n*-hexane-ethyl acetate 40%), the reaction mixture was cooled to room temperature. Then ethyl acetate (3 ml) was added to the solid. The catalyst was simply removed by Büchner filtration, washed with ethyl acetate (8 ml). Yield and conversion were determined by GC analysis using 1,4-dimethoxybenzene as internal standard. The product **3e** was purified by chromatography plates and characterized by ^{1}H NMR, GC-Mass analyses.

Characterization of ethyl (E)-2-cyano-3-isopropylacrilate (3e).

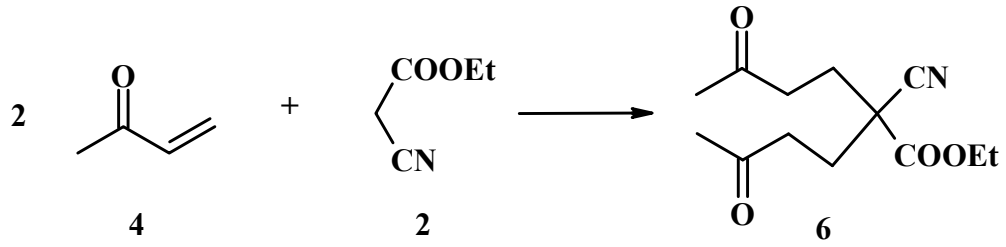
Transparent oil, m.w. 167.21, $C_9H_{13}NO_2$.

^{1}H NMR ($CDCl_3$, 300MHz) δ (ppm): 7,45 d, 1H (CH=C), J = 7.5 Hz; 4.30 q, 2H (CH_2 CH_3), J = 7.1 Hz; 3.0-2.9 m, 1H (H); 1.34 t, 3H (CH_2-CH_3), J = 7.1 Hz; 1.14 d, 6H (CH-CH_3), J= 7.1 Hz.

MS-EI (m/z): 152 M^+- CH_3 (10%),139 M^+- CH_2=CH_2 (100%),121 (40%), 111 (28%), 106 (30%).

3.3.4 Michael reaction procedure

Procedure for the synthesis of bis-addition product 6.



4 2 6

In one-neck flask a mixture of ethyl cyanoacetate **2** (0.060 g, 0.5 mmol) and **SIL** (5% mol, 0.044 g, loading 0.57mmol/g) were stirred at room temperature for 15 minutes. Then methyl vinylketone **4** (0.140 g, 2 mmol) was added and the mixture was heated at 80 °C and stirred for 12 h without solvent. After completion of reaction, the reaction mixture was cooled to room temperature. Then ethyl acetate (3 ml) was added to the solid. The catalyst was simply removed by Büchner filtration and washed with ethyl acetate (8 ml). Yield and conversion were determined by GC analysis.

The product **5** was purified by preparative chromatographic plates and characterized by ^{1}H NMR, GC-Mass analyses.

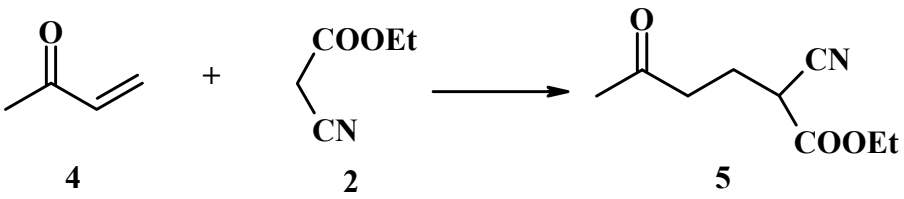
Characterization of product 6.

Transparent oil, m.w. 253.30, $C_{13}H_{18}NO_4$.

^{1}H NMR ($CDCl_3$, 300MHz) δ (ppm): 4.25 q, 2H ($O\underline{CH_2}$-CH_3), J= 7.1Hz; 2.75-2.48 m, 8H (4 CH_2-$\underline{CH_2}$); 2.10 s, 6H (2 CH_3); 1.32 t, 3H (OCH_2-$\underline{CH_3}$), J= 7.1Hz.

MS-EI (m/z): 183 (100%), 180 (43%), 137 (49%), 124 (35%), 111 (42%), 109 (26%).

Procedure for the synthesis of mono-addition product 5.



4 **2** **5**

In one-neck flask a mixture of ethyl cyanoacetate **2** (0.105 g, 1.5 mmol) and **SIL** (0.044 g, 5% mol, loading 0.57mmol/g) were stirred at room temperature for 15 minutes. Then methyl vinylketone **4** (0.035 g, 0.5 mmol) was added and the mixture was stirred for 1 h without solvent. After completion of reaction ethyl acetate (3 ml) was added to the solid. The catalyst was simply removed by Büchner filtration and washed with ethyl acetate (8 ml). Yield and conversion were determined by GC analysis using internal standard method.

3.4 References

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Chapter 4

Eco-efficient synthesis of 1,8-dioxo-octahydroxanthenes catalyzed by Montmorillonite KSF under solvent-free conditions.

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4.1 Introduction

The development of eco-efficient synthesis for fine chemicals production is a research area which has been attracting growing interest. In particular, the use of environmentally friendly heterogeneous catalysts (possibly commercially available) as well as the choice of safer solvents have to be considered in order to obtain environmentally acceptable processes [1], as pointed out in the Green Chemistry principles [1]. Heterogeneous catalysts, mainly clays and zeolites, have been employed for numerous acid-catalyzed organic reactions, offering several advantages over classical acids such as strong acidity, non-corrosive properties, high yields and selectivities in addition to the easy reaction work-up and catalyst reusability. In addition, a particular mention deserves the avoidance of salt formation due to usual quenching procedures. In particular, the interest in clays [2] as heterogeneous catalysts for organic synthesis is ascribable to both the 'green' properties and the cheapness.

Clays are characterised by two-dimensional *sheets* of corner sharing SiO_4 and AlO_4 tetrahedra, like all phyllosilicates. These tetrahedral sheets have the chemical composition $(Al,Si)_3O_4$, and each tetrahedron shares 3 of its vertex oxygen atoms with other tetrahedra forming a hexagonal array in two-dimensions. Clays can be classified depending on the way that tetrahedral and octahedral sheets are packaged into *layers*. These sheets could have a 1:1 (*i.e.* kaolin) or 2:1 (*i.e.* montmorillonite) structure (Figure 2); in the latter case, a central layer of alumina in octahedral coordination with oxygen is sandwiched between two layers of silicon tetrahedrally coordinated with oxygen.

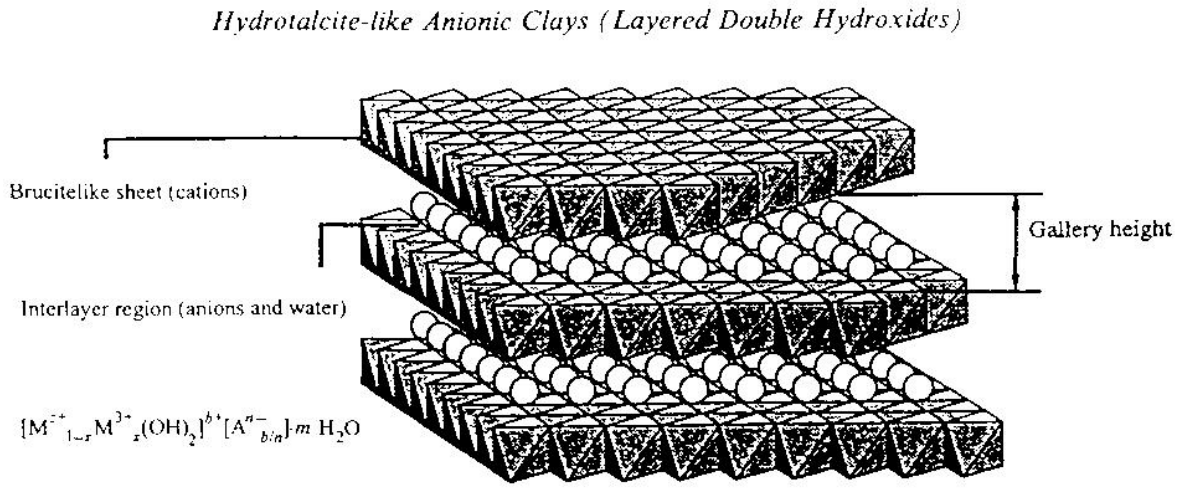


Figure 1. Hydrotalcite structure.

Although the ideal aluminosilicate is electrically neutral, random substitutions for the aluminum and silicon resulted in a net negative charge or net positive charge within the sheets; typical substitutions include Al^{3+} for Si^{4+} or Si^{4+} for Al^{3+} and Mg^{2+} for Al^{3+}.

When a net positive charge is delocalized on the layer, clays are classified as 'anionic clay' since they contain anionic species in the interlayer region, such as carbonate anions or nitrate anions, to balance the positive charge on the layers. Hydrotalcite (Figure 1), manasseite, pyroaurite, takovite are some examples of minerals of the anionic clay family.

When a net negative charge is delocalized on the layer clays are classified as 'cationic clays'. The term 'cationic clay' refers to natural or synthetic layered structures whose interlayers contain cations to balance the negative charge on the layers and these cations are exchangeable with other cations [4].

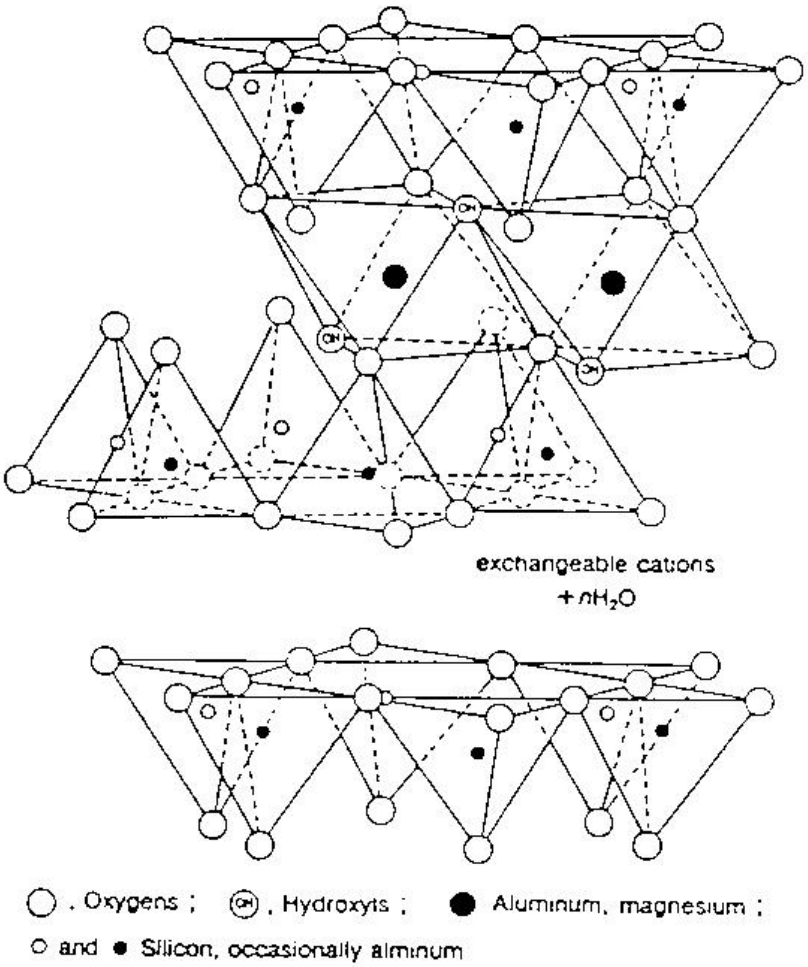


Figure 2. Montmorillonite structure.

To balance this negative charge, cations such as Na^+, K^+, or Ca^{2+} are located in an interlayer between the sheets. The interlayer also includes water molecules, some of which are complexed to the interlayer cations. Different clay materials (natural, acid-treated, cation-exchanged, and pillared clays) are effective catalysts for a wide variety of organic reactions. It is know that both Bronsted and Lewis acidity play a role in the catalytic activity [5].

Xanthenes and derivatives are a class of important compounds with biological activities [6] (*e.g*. antibacteria, anti-inflammatory, antiviral properties).

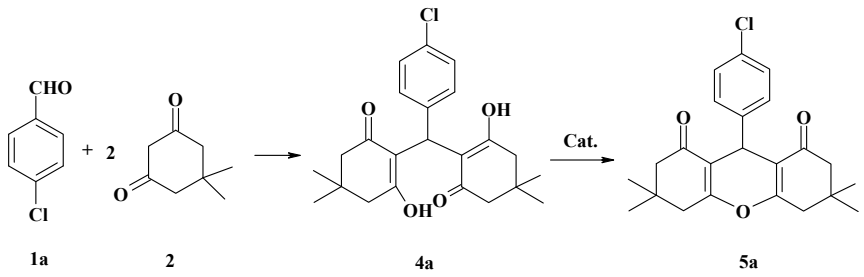
A variety of procedures have been reported to synthesize 1,8-dioxo-octahydroxanthene derivatives [7] and, recently, several methods have been developed using heterogeneous catalysts such as silica supported sodium hydrogen sulfate or silica chloride [8], polyphosphoric acid supported on silica [9], polyaniline-*p*-toluenesulphonate [10], Amberlyst-15 [11], Dowex-50W [12], Scandium cation-exchanged montmorillonite [13]. The use of ionic liquid as catalyst under ultrasound irradiation in methanol has just been published [14].

In spite of potential utility of aforementioned routes for the synthesis of xanthene derivatives, many of these methods involve expensive reagents, strong acidic conditions, long reaction times, low yields, use of excess of reagents/catalysts, use of toxic organic solvents and use of appositely prepared catalysts. Therefore, the search for reaction conditions overcoming these restrictions is still an open problem.

In continuation of the research group work on eco-efficient organic synthesis [15], in particular employing clay catalysts [16], here we report the preparation of 1,8-dioxo-octahydroxanthene derivatives by condensation of aromatic, heteroaromatic, α,β-unsaturated and aliphatic aldehydes with 5,5-dimethyl-1,3-cyclohexanedione (dimedone) under heterogeneous catalysis and in solvent-free conditions.

4.2 Results and Discussion

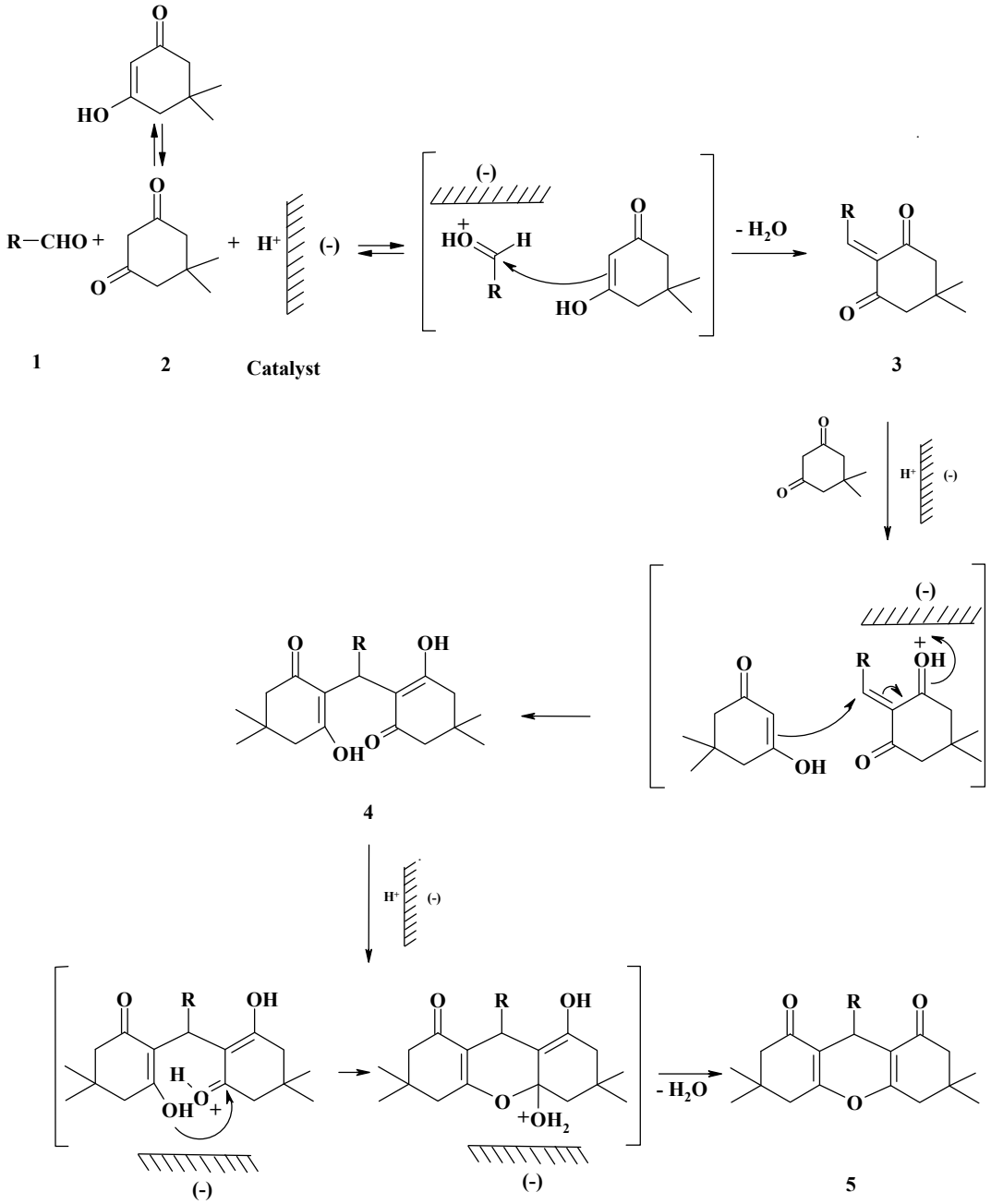
First, we carried out preliminary reactions in aqueous medium using 4-chlorobenzaldehyde and 5,5-dimethyl-1,3-cyclohexanedione as model reagents (Scheme 1) in the presence of various kinds of heterogeneous catalysts, with different acid properties.



Scheme 1. Model reaction.

Various clays (Na- and Ca-montmorillonites, kaoline, K10, KSF, Bieliaca) and zeolites (NaX, HSZ-330, HSZ-360 and HSZ-390) were employed in water at 90 °C, but in all the cases we observed the formation of the compound **4a,** which was obtained in almost quantitative yield also in the absence of any catalyst. It is interesting to observe that the intermediate Knoevenagel product **3** (Scheme 2) was not detected even employing the reagents in 1:1 ratio, due to the easy Michael addition of dimedone to the electron-poor alkene formed, as observed by other Authors [17]. In our opinion, the formation of two intramolecular hydrogen bonds in the bis-adduct **4**, as shown by Kaupp [17], accounts for this general behavior of cyclic 1,3-diketones to give immediately Michael addition. Recently, the formation of Knoevenagel product **3** (R = 4-Me-C_6H_4) in 60% yield was reported, carrying out the reaction in water at room temperature for 30 min [18], but this procedure failed in our hands, giving only small amount (< 20 %) of bis-adduct **4**.

In order to convert compounds **4** into the xanthene derivatives **5**, we decided to work under solvent free conditions and in the presence of a catalyst able to promote the intramolecular condensation. Indeed, the solventless uncatalyzed reaction carried out at 90 °C for 2 h still gave quantitatively the open product **4a** [17], showing that the crucial step which requires catalytic activation is the ring closure. Taking into account that the cyclisation process is the result of the nucleophylic attack of the enolic oxygen to a carbonyl group, followed by dehydration of the rearranged keto-tautomer (Scheme 2), we decided to use various type of acid catalysts.



Scheme 2. Reaction mechanism.

Thus, clays and HY zeolites with different acid properties were employed in the model reaction. In particular, KSF [19], K10 [20], and Na-montmorillonite [21] are smectite-type laminar silicates characterised by different chemical composition determining different acid-base properties [22]; HSZ-330 [23], HSZ-360 [24] and HSZ-390 [25] are acid faujasitic-type zeolites (HY) characterized by a different SiO_2/Al_2O_3 ratio determining their acidity [26].

Table 1. Catalyst effect in the synthesis of 1,8-dioxo-octahydroxanthene **(5a)**.

Entry[a]	Catalyst	Yield[b] (%)	Ratio[c] 5a : 4a
1	KSF	97	100 : 0
2	K10	92	23 : 69
3	Na-Mont.	91	2 : 98
4	HSZ-330	91	0 : 100
5	HSZ-360	89	2 : 98
6	HSZ-390	94	5 : 95

[a] Reaction conditions: 4-Chlorobenzaldehyde **1a** (1 mmol) and dimedone **2** (2 mmol) were reacted in the presence of 100 mg of catalyst under solvent free conditions at 90 °C for 2 h.
[b] Isolated yields.
[c] Determined by ^{1}H NMR evaluating the integral ratio of methine signals at δ 4.70 and 5.47 respectively.

It is interesting to observe that KSF clay catalyzed the quantitative formation of the target compound **5a,** working under solvent free conditions at 90° C for two hours (Table 1, entry 1).

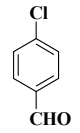
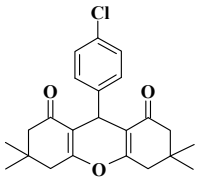
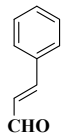
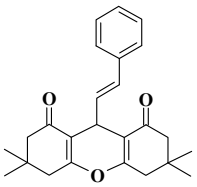
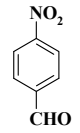
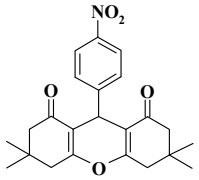
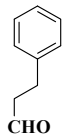
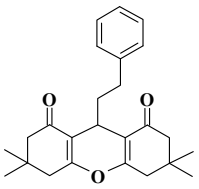
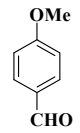
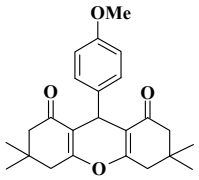
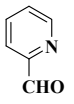
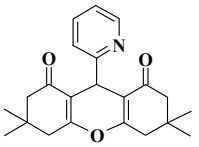
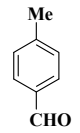
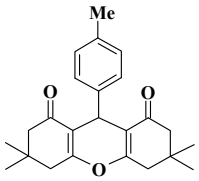
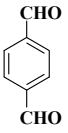
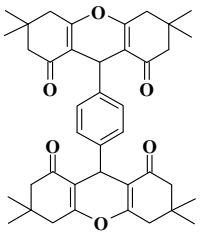
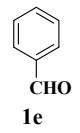
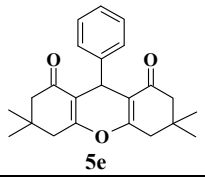
The reactions were performed at 90 °C since preliminary experiments evidenced that at lower temperature the yield of the cyclic product **5a** decreased and that the aldehyde sublimation occurs at 100 °C. Using the weak acidic Na-montmorillonite the cyclic compound was not obtained whereas K10-montmorillonite gave a mixture of open and cyclic products (**4a** and **5a)** (Table 1, entries 3 and 2).

Regarding the zeolites tested, they were less efficient than clays in promoting the cyclisation process (Table 1, entries 4-6). In our opinion, the main reason is ascribable to the HY zeolite channel dimension (7.4 Å) that hamper the formation of 1,8-dioxo-octahydroxantenes. The formation of traces of product **5a** can be attributed to the reaction promoted by external surface of the catalyst, as observed in other reactions [27].

The role of the clay surface acidity was evidenced using KSF washed with water in order to remove any traces of the inorganic acid employed in the industrial production. Indeed, almost complete conversion was obtained with high selectivity of cyclic compound **5a** (87%), increased to 95% after 3h reaction time.

In order to optimize the reaction conditions, the catalyst amount and reaction time were examined. We observed that mixtures of open (**4a**) and cyclic (**5a**) compounds were formed reducing the time to 1 h or the catalyst amount to 50 mg/mmol. Thus, we extended the study of this reaction to other aldehydes using a catalyst/aldehyde ratio of 100 mg/mmol for 2 h.

Table 2. Montmorillonite KSF catalyzed synthesis of 1,8-dioxo-octahydroxanthenes **(5 a-i).**

Entry	Aldehyde	Product[a]	Yield (%)[b]	Entry	Aldehyde	Product[a]	Yield (%)[b]
1	 **1a**	 **5a**	97	**6**	 **1f**	 **5f**	89
2	 **1b**	 **5b**	98	**7**	 **1g**	 **5g**	96
3	 **1c**	 **5c**	97	**8**	 **1h**	 **5h**	94
4	 **1d**	 **5d**	99	**9**	 **1i**	 **5i**	99[c]
5	 **1e**	 **5e**	99				

[a] Reaction conditions: aldehyde **1** (1 mmol), dimedone **2** (2 mmol) were reacted in the presence of 100 mg of KSF under solvent free conditions at 90 °C for 2 h.
[b] Isolated yields.
[c] Reaction conditions: similar to a) using aldehyde **1i** (0.5 mmol) at 120 °C for 10 h. The reaction conducted at 90°C gave a mixture of mono and bis-xantene derivatives.

The results reported in Table 2 show that the present procedure is of general validity for aromatic, heteroaromatic, aliphatic and α,β-unsaturated aldehydes. In particular, aromatic aldehydes gave excellent yields (97-99%) of xanthene derivatives **5** without formation of any by-product, regardless of the nature of the substituent (Table 2, entries 1-5). Also heteroaromatic reagent, 2-pyridinecarbaldehyde, reacted smoothly giving the corresponding 1,8-dioxo-octahydroxanthene **5h** in almost quantitative yield (Table 2, entry 8).

The reaction was successfully extended to 3-phenylpropionaldehyde as well as to cinnamaldehyde affording excellent yields of the compounds **5g** (new) and **5f** (96 and 89 % respectively, Table 2, entries 7 and 6). In the case of terephthalaldehyde (**1i**) the new bis-xanthene derivative **5i** was obtained in excellent yield (Table 2, entry 9) reacting the aldehyde with four equivalents of reagent **2** at 120 °C. The use of two equivalents of dimedone gave a mixture of mono- and bis-xanthene derivatives along with unreacted aldehyde.

The results obtained with the procedure here reported are better or comparable with the best ones reported in the literature under heterogeneous conditions, which employed refluxing solvents for longer time (noxious acetonitrile for 5 [11] or 6 h [8], water for 6 h [10]) or without solvent at higher temperature (140 °C for 0.5 h [9], 100 °C for 1.5 h [12]) often using appositely prepared catalysts ($NaHSO_4$-SiO_2 and silica chloride [8], PPA-SiO_2 [9], polyaniline-*p*-toluenesulfonate salt [10]).

Further, our synthetic approach has the advantages of using lower amount of a less expensive catalyst as well as not involving chlorinated solvent in the work-up procedure [12] or in the catalyst preparation [9], and not requiring chromatographic separation [8].

Finally, we investigated the KSF reusability. The catalyst, simply recovered by Büchner filtration and washed with ethyl acetate, was reused in the model reaction for at least three times (Table 3) without significant decrease in activity, by slightly increasing the reaction time to three hours in order to obtain complete conversion of reagents into product **5a.**

Table 3. Reusability of the catalyst in the preparation of **5a.**

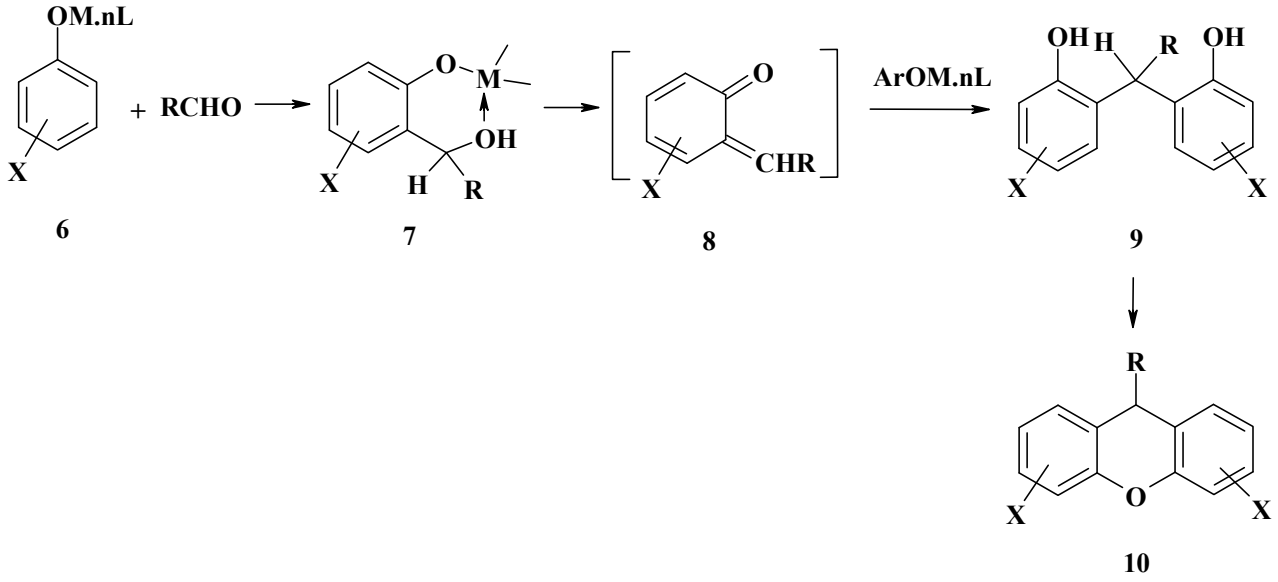
Entry	Number of cycles	Time (h)	Yield[b] (%)
1	1st	2	97
2	2nd	3	95
3	3rd	3	97
4	4th	3	94

Reaction conditions: Reaction conditions: aldehyde **1a** (1 mmol), dimedone **2** (2 mmol) were reacted in the presence of 100 mg of KSF under solvent free conditions at 90 °C for 2 h.

It is surprising that ^{1}H NMR spectra of xanthene derivatives **5** were not well described in the literature, despite their characteristic signals. Indeed, the methylenic proton signals at higher field, accounting for 4H, are two doublets at δ ~ 2.24 and 2.15 ppm with J~ 16.3 Hz (AB system), due to diastereotopic geminal protons, but they were previously reported as quartet (J= 16.6) [9] or doublet of doublet (J= ~ 2.4 and 1.6 Hz) [7] at δ ~ 2.2 ppm, although the spectra were recorded at the same or higher magnetic field. A TOCSY experiment recorder on

the new compound **5g** permitted to attribute these signals to the methylene groups near the carbonyl functions [28]. In our opinion, the ^{1}H NMR spectra of crude reactions are very useful to observe the possible presence of open compounds **4**, which are characterized by a low field singlets (δ > 11 ppm) due to enolic hydroxyl groups involved in intramolecular hydrogen bonds and by a methine signal at lower field than the corresponding **5** compounds [29].

Last, it is quite interesting to observe a close analogy between the enol-chemistry and the phenol-chemistry. It should not be so surprising since phenol can be regarded as a specially stabilized enol. Indeed, the mechanism depicted in Scheme 2 is similar to that reported [30] for metal-template reaction of phenol with aldheydes. 2,2'-Alkylidene-bis(phenols) **9**, similar to compounds **4,** were obtained through the formation of *o*-quinone methides **8**, which are similar to intermediates **3** (Scheme 3). Further, compounds **9** can be converted in xanthene derivatives **10**, as described in the literature [31].



6 **7** **8** **9** **10**

Scheme 3.

In conclusion, we have developed a simple, efficient and green methodology for the one-pot synthesis of 1,8-dioxo-octahydroxanthenes **5** using montmorillonite KSF under solvent-free conditions. Thus, five cascade reactions of addition-elimination-Michael addition-addition-elimination could be performed in excellent yields. This method is applicable to a wide range of aldehydes, including aromatic, aliphatic, α,β-unsaturated and heteroaromatic ones. The use of eco-friendly, commercially available and inexpensive heterogeneous catalyst under mild

reaction conditions, simple work-up in isolation of the products with high purity and recyclability of catalyst are features of this procedure.

4.3 Experimental section

4.3.1 General methods

^{1}H and ^{13}C NMR spectra were recorded on Bruker AC300 spectrometer in $CDCl_3$ (at 300 MHz for ^{1}H and 75 MHz for ^{13}C). The multiplicity of the carbon atoms was determined by the DEPT 135 (DEPT = Distortionless Enhancement by Polarisation Transfer) technique and quoted as CH_3, CH_2, CH and C for primary, secondary, tertiary and quaternary carbon atoms. FT-IR spectra (KBr pellets) were recorded on a Nicolet FT-IR Nexus spectrophotometer.
Mass spectra were obtained by the + ESI method on Waters SQ Detector. Melting points are uncorrected and were measured using a Gallenkamp apparatus. Elemental analyses of new compounds **5g** and **5h** were carried out with a Carlo Erba CHNS-0 EA12108 elemental analyzer. TLC analyses were performed on Merck 60 PF254 silica gel plates. KSF is a commercial (Fluka) montmorillonite and it was utilized without any previous treatment.
All the reagents were of commercial quality from freshly opened containers.

4.3.2 General procedure for the synthesis of 3,3,6,6-tetramethyl-1,8-dioxo-octahydroxanthenes (5).

In one-neck flask, fitted with a condenser, a mixture of aldehyde (1 mmol), 5,5-dimethyl-1,3-cyclohexanedione (0.280 g, 2 mmol) and montmorillonite KSF (0.10 g) were stirred at 90 ^{0}C for 2 h without solvent. After completion of reaction (as indicated by TLC, eluent *n*-hexane-ethyl acetate 40%), the reaction mixture was cooled to room temperature. Then ethyl acetate (15 ml) was added to the solid and refluxed for 5 min. The catalyst was simply removed by Büchner filtration, washed with ethyl acetate (10 ml), and the solution was concentrated under vacuum affording crude product **5** in high yield (Table 2). The crude products **5** were purified, if necessary, by crystallization from ethanol unless otherwise stated. Compounds **5g-i** were characterized by ^{1}H, ^{13}C NMR, IR spectroscopies, ESI-Mass and elemental analyses. ^{1}H and ^{13}C NMR spectra of the other products are reported.

Characterization of 9-(4-chlorophenyl)-3,3,6,6-tetramethyl-1,8-dioxo-octahydroxanthene (5a).

White solid, mp 236-237 °C (crystallized from ethanol)(lit. [10] 231-233 °C); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.23 and 7.17 (2d, 2x 2H, *J*= 6.5 Hz, AB *para*-system), 4.70 (s, 1H, CH), 2.46 (ψs, 4H, 2 x CH_2), 2.24 (d, 2H, 2 x ½CH_2, *J*= 16.3 Hz, AB system), 2.16 (d, 2H, 2 x ½CH_2, *J*= 16.3 Hz, AB system), 1.10 (s, 6H, 2 x CH_3), 0.98 (s, 6H, 2 x CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 196.4 (C), 162.4 (C), 142.6 (C), 131.9 (C), 129.7 (CH), 128.1 (CH), 115.2 (C), 50.6 (CH_2), 40.7 (CH_2), 32.1 (C), 31.4 (CH), 29.2 (CH_3), 27.2 (CH_3); EIMS: *m/z* (rel.int.) 386 (M^++2, 14), 384 (M^+, 40), 349 (15), 273 (100), 217 (25).

Characterization of 9-(4-nitrophenyl)-3,3,6,6-tetramethyl-1,8-dioxo-octahydroxanthene (5b).

Yellow solid, mp 226-227 °C (crystallized from ethanol)(lit. [9] 225-227 °C) ;^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.08 (d, 2H, Ar, H-3 and H-5, *J*=8.7 Hz), 7.47 (d, 2H, Ar, H-2 and H-6, *J*=8.7 Hz), 4.81 (s, 1H, CH), 2.52 (d, 2H, 2 x ½CH_2, *J*= 18.3 Hz, AB system), 2.46 (d, 2H, 2 x ½CH_2, *J*= 18.3 Hz, AB system), 1.11 (s, 6H, 2 x CH_3), 0.98 (s, 6H, 2 x CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 196.3 (C), 162.9 (C), 151.5 , 146.4 (C), 129.3 (CH), 123.4 (CH), 114.4 (C), 50.5 (CH_2), 40.7 (CH_2), 32.3 (CH), 32.2 (C), 29.2 (CH_3), 27.2 (CH_3).

Characterization of 9-(4-methoxyphenyl)-3,3,6,6-tetramethyl-1,8-dioxo-octahydroxanthene (5c).

Pale yellow solid, mp 249-250 °C (crystallized from ethanol) (lit. [9] 242-245 °C); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.20 (d, 2H, Ar, H-2 and H-6, *J*= 8.6 Hz,), 6.75 (d, 2H, Ar, H-3 and H-5, *J*= 8.6 Hz), 4.69 (s, 1H, CH), 2.45 (s, 4H, 2 x CH_2), 2.23 (d, 2H, 2 x ½CH_2, *J*= 16.3 Hz, AB system), 2.15 (d, 2H, 2 x ½CH_2, *J*= 16.3 Hz, AB system), 1.09 (s, 6H, 2 x CH_3), 0.98 (s, 6H, 2 x CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 196.5 (C), 162.0 (C), 157.8 (C), 136.4 (C), 129.2 (CH), 115.7 (C), 113.4 (CH), 55.0 (OCH_3), 50.7 (CH_2), 40.8 (CH_2), 32.1 (C), 30.9 (CH), 29.2 (CH_3), 27.3 (CH_3).

Characterization of 9-(4-methylphenyl)-3,3,6,6-tetramethyl-1,8-dioxo-octahydroxanthene (5d).

White solid, mp 208-209 °C (crystallized from ethanol)(lit. [14] 210-212 and [10] 216-218 °C); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.17 (d, 2H, Ar, H-2 and H-6, *J*= 8.0 Hz), 7.01 (d, 2H, Ar, H-3 and H-5, *J*= 8.0 Hz), 4.70 (s, 1H, CH), 2.45 (s, 4H, 2 x CH_2), 2.24 (s, 3H, CH_3), 2.23 (d, 2H, 2 x ½CH_2, *J*= 16.2 Hz, AB system), 2.16 (d, 2H, 2 x ½CH_2, *J*= 16.2 Hz, AB system), 1.09 (s, 6H, 2 x CH_3), 0.99 (s, 6H, 2 x CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 196.4 (C), 162.0 (C), 141.1 (C), 135.7 (C), 128.7 (CH), 128.2 (CH), 115.7 (C), 50.7 (CH_2), 40.8 (CH_2), 32.1 (C), 31.4 (CH), 29.2 (CH_3), 27.3 (CH_3), 21.0 (CH_3).

Characterization of 9-phenyl-3,3,6,6-tetramethyl-1,8-dioxo-octahydroxanthene (5e).

White solid, mp 204-205 °C (crystallized from ethanol)(lit. [7] 205-206 °C); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.0-7.4 (m, 5H, Ph), 4.74 (s, 1H, CH), 2.46 (s, 4H, 2 x CH_2), 2.23 (d, 2H, 2 x ½CH_2, *J*= 16.3 Hz, AB system), 2.15 (d, 2H, 2 x ½CH_2, *J*= 16.3 Hz, AB system), 1.09 (s, 6H, 2 x CH_3), 0.98 (s, 6H, 2 x CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 196.3 (C), 162.2 (C), 144.0 (C), 128.3 (CH), 128.0 (CH), 126.3 (CH), 115.6 (C), 50.7 (CH_2), 40.8 (CH_2), 32.1 (C), 31.8 (CH), 29.2 (CH_3), 27.3 (CH_3).

Characterization of 9-(2-phenylethenyl)-3,3,6,6-tetramethyl-1,8-dioxo-octahydroxanthene (5f).

White solid, 175-177 °C (crystallized from ethanol)(lit. [14] 175-177 °C); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.1-7.3 (m, 5H, Ph), 6.33 (dd, 1H, CH=C, *J*= 16.0 and 5.7 Hz), 6.24 (d, 1H, CH=C, *J*= 16.0 Hz), 4.39 (d, 1H, CH, *J*= 5.7 Hz), 2.43 (s, 4H, 2 x CH_2), 2.30 (s, 4H, 2 x

CH_2), 1.12 (s, 12H, 4 x CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 196.5 (C), 162.9 (C), 137.1 (C), 131.2 (CH), 130.3 (CH), 128.2 (CH), 127.0 (CH), 126.3 (CH), 114.4 (C), 50.8 (CH_2), 40.9 (CH_2), 32.2 (C), 29.2 (CH_3), 27.8 (CH), 27.5 (CH_3).

Characterization of 9-(2-phenylethyl)-3,3,6,6-tetramethyl-1,8-dioxo-octahydroxanthene (5g).

White solid, mp 103-104 °C (crystallized from hexane); ^1H NMR ($CDCl_3$, 300 MHz): δ 7.0-7.3 (m, 5H, Ph), 3.89 (t, 1H, CH, *J*= 4.2 Hz), 2.4 2.5 (m, 2H, CH_2), 2.36 (s, 4H, 2 x CH_2), 2.26 (d, 2H, 2 x ½CH_2, *J*= 16.1 Hz, AB system), 2.19 (d, 2H, 2 x ½CH_2, *J*= 16.1 Hz, AB system), 1.8-2.0 (m, 2H, CH_2, $\underline{CH_2}$-CH), 1.12 (s, 6H, 2 x CH_3), 1.10 (s, , 6H, 2 x CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 197.1 (C), 163.9 (C), 142.3 (C), 128.2 (CH), 125.5 (CH), 114.5 (C), 50.8 (CH_2), 40.8 (CH_2), 34.4 (CH_2), 31.92 (C), 31.88 (CH), 29.2 (CH_3), 27.6 (CH_3), 25.6 (CH); IR (KBr) 2956, 1679, 1665, 1651, 1619, 1378, 1201, 1161, 1137 cm^{-1}; MS (+ESI) *m/z* (relative intensità) 779.4($2M+Na^+$, 30), 401.2 ($M+Na^+$, 100), 379.2 ($M+H^+$,14); anal. calcd. for $C_{25}H_{30}O_3$: C, 79.33; H, 7.99; found: C, 79.34; H, 8.04.

Characterization of 9-(2-pyridyl)-3,3,6,6-tetramethyl-1,8-dioxo octahydroxanthene (5h).

White solid, mp 198-199 °C (crystallized from ethanol) (lit. [7] 188-190 °C); ^1H NMR ($CDCl_3$, 300 MHz): δ 8.36 (d, 1H, H-6, *J*= 4.4 Hz), 7.60 (d, 1H, H-3, *J*= 7.6 Hz), 7.53 (t, 1H, H-4 *J*= 7.6 Hz), 6.98 (ψt, 1H, H-5), 4.85 (s, 1H, CH), 2.52 (d, 2H, 2 x ½CH_2, *J*= 17.6 Hz, AB system), 2.43 (d, 2H, 2 x ½CH_2, *J*= 17.6 Hz, AB system), 2.23 (d, 2H, 2 x ½CH_2, *J*= 16.2 Hz, AB system), 2.14 (d, 2H, 2 x ½CH_2, *J*= 16.2 Hz, AB system), 1.09 (s, 6H, 2 x CH_3), 0.99 (s, 6H, 2 x CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 196.8 (C), 163.3 (C), 161.6 (C), 148.8 (CH), 135.6 (CH), 124.8 (CH), 121.3 (CH), 114.3 (C), 50.7 (CH_2), 40.8 (CH_2), 34.4 (CH), 32.2 (C), 29.3 (CH_3), 27.1 (CH_3); IR (KBr) 2963, 1681, 1658, 1626, 1367, 1197, 1165, 1137 cm^{-1}; MS (+ESI) *m/z* (relative intensity) 725.6 ($2M+Na^+$, 18), 374.2 ($M+Na^+$, 35), 352.3 ($M+H^+$,100); anal. calcd. for $C_{22}H_{25}NO_3$:C, 75.18; H, 7.17; N, 3.99; found: C, 74.92; H, 7.19; N, 3.89.

Characterization of 9-[4-(3',3',6',6'-tetramethyl-1',8'-dioxo-octahydroxanthen-9'-yl)-phenyl]-3,3,6,6-tetramethyl-1,8-dioxo-octahydroxanthene (5i).

Reacting terephthalaldheyde (benzene-1,4-dicarboxaldehyde) (0.067 g, 0.5 mmol) and 5,5-dimethyl-1,3-cyclohexane6dione (0.280 g, 2 mmol) in the presence of montmorillonite KSF (0.10 g) at 120 °C for 10 h, crude compound **4i** was isolated as a yellowish solid (0.309 g,

99%) by adding dichloromethane to the catalyst; after washing with ethyl acetate a white solid was obtained; crystals decomposed without melting (crystallized from CH_2Cl_2/ethyl acetate). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.07 (s, 4H), 4.70 (s, 2H, CH), 2.47 (d, 4H, 4 x ½CH_2, *J*= 17.6 Hz, AB system), 2.37 (d, 4H, 4 x ½CH_2, *J*= 17.6 Hz, AB system), 2.17 (s, 8H, 4 x CH_2), 1.07 (s, 12H, 4 x CH_3), 0.97 (s, 12H, 4 x CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 196.4 (C), 162.41 (C), 141.7 (C), 127.9 (CH), 115.68 (C), 50.8 (CH_2), 40.8 (CH_2), 32.3 (C), 30.71 (CH), 28.9 (CH_3), 27.7 (CH_3). IR (KBr) 2958, 1666, 1366, 1202, 1167 cm^{-1}; MS (+ESI) *m/z* (relative intensity) 661.5 ($M+K^+$, 11), 646.4 ($M+1+Na^+$, 42), 645.4 ($M+Na^+$, 100); anal. calcd. for $C_{40}H_{46}O_6$:C, 77.14; H, 7.45; found: C, 76.88; H, 7.40.

4.4 References and notes

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[19] KSF (Fluka) is a commercial acid montmorillonite with surface area 15 ± 10 m^2/g, acidity 0.85 mequiv H^+/g [determined in our laboratory by temperature-programmed desorption of ammonia gas (NH_3-TPD)] and with the following chemical composition (average value): SiO_2 (54.0%), Al_2O_3 (17.0%), Fe_2O_3 (5.2%), CaO (1.5%), MgO (2.5%), Na_2O (0.4%), K_2O (1.5%).

[20] K10 (Fluka) is a commercial acid montmorillonite with surface area 200 ± 10 m^2/g, acidity 0.70 mequiv H^+/g [determined in our laboratory by temperature-programmed desorption of ammonia gas (NH_3-TPD)] and with the following chemical composition (average value): SiO_2 (73.0%), Al_2O_3 (14.0%), Fe_2O_3 (2.7%), CaO (0.2%), MgO (1.1%), Na_2O (0.6%), K_2O (1.9%).

[21] Na-Montmorillonite (Source Clay Repository)is a natural sodium montmorillonite with surface area 32 ± 1 m^2/g, acidity 0.10 mequiv H^+/g [determined in our laboratory by temperature-programmed desorption of ammonia gas (NH_3-TPD)] and with the following chemical composition (average values): SiO_2 (58.7%), Al_2O_3 (18.9%), TiO_2 (0.2%), Fe_2O_3 (4.0%), CaO (0.8%), MgO (2.7%), Na_2O (1.2%), K_2O (0.3%).

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[23] Zeolite HSZ-330 (Tosoh Corp.) is a commercial acid faujasitic-type catalyst with 5.9 SiO_2-Al_2O_3 molar ratio, pore size 7.4 Å, surface area 460± 10 m^2/g (determined in our laboratory by the BET method), acidity 1.39 mequiv. H^+/g [determined in our laboratory by temperature-programmed desorption of ammonia gas (NH_3-TPD)] and with the following chemical composition (wt% dry basis): SiO_2 86.1, Al_2O_3 13.7, Na_2O 0.19.

[24] Zeolite HSZ-360 is a commercial (Tosoh Corp.) acid faujasitic-type catalyst with 13.9 SiO_2-Al_2O_3 molar ratio, pore size 7.4 Å, surface area 500± 10 m^2/g (determined in our laboratory by the BET method), acidity 0.51 mequiv. H^+/g [determined in our laboratory by temperature-programmed desorption of ammonia gas (NH_3-TPD)] and with the following chemical composition (wt% dry basis): SiO_2 89.0, Al_2O_3 10.9, Na_2O 0.06.

[25] Zeolite HSZ-390 is a commercial (Tosoh Corp.) acid faujasitic-type catalyst with 390 SiO_2-Al_2O_3 molar ratio, pore size 7.4 Å, surface area 590± 10 m^2/g (determined in our laboratory by the BET method), acidity 0.10 mequiv mequiv. H^+/g [determined in our laboratory by temperature-programmed desorption of ammonia gas (NH_3-TPD)] and with the following chemical composition (wt% dry basis): SiO_2 99.6, Al_2O_3 0.43, Na_2O <0.01.

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[28] ^{1}H-^{13}C heterocorrelated 2D experiment on compound **5a** showed the correlation between these proton signals at higher field and the carbon signal at lower field (δ 50.6 ppm), which was thus attributed with certainty to the methylene groups near the carbonyls.

[29] For example, the methine signals show the following δ values (ppm): 5.47 in **4a** and 4.70 in **5a**; 5.5 in **4d** and 4.7 in **5d**; 4.9 in **4f** and 4.39 in **5f**.

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Curriculum Vitae

Carla Quarantelli was born in 1983 in Parma.

She received her Bachelor degree in 2004 in chemistry and her Master degree in chemistry in 2006 in University of Parma choosing organic chemistry as a major research area. During her master project she worked under the supervision of Prof. Bigi on eco-efficient Knoevenagel reactions for the synthesis of electron-poor olefins.

Since January 2007 she had been a PhD student under the supervision of Prof. Bigi working on the development of selective and eco-efficient processes promoted by heterogeneous catalysts or ionic liquids.

In 2008 she was awarded with a six month Marie Curie fellowship at QUILL (Queen's University Ionic Liquid Laboratories) in Belfast, UK. Under the supervision of Prof. Ken Seddon and Dr. Nimal Gunaratne, she worked on the preparation of a new class of chiral ionic liquids employed as catalysts in enantioselective oxidation reactions. In February 2010 she will start working as post doc for Bayer Materials at CAT Catalytic Center ITMC, RWTH Aachen, Germany.

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