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Preparation, characterization and use of hybrid heterogeneous catalysts supported on silica or magnetic nanoparticles for eco-efficient processes

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General introduction

Sustainable development and Green Chemistry

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.

The concept of the sustainable development was proposed by the United Nations/International Committee on Environment and Development(ICED, 1987) as ''development which meets the needs of the present without compromising the ability of future generations to meet their own needs''. This concept was gained acceptance at the United Nations Conference on Environment and Development (Rio-de-Janeiro, 1992) it lies not in the notion of a sustained character of the development but in an understanding of the development as a steadily and long existing and maintained process that is in advocating the stability of the development. Such an understanding of the development should be well represented in the action initiated in the framework of national and international state ecological policies. Since 1987 Government, 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 most important aspect of sustainable development are develop a renewable forms of energy and reduce pollution: chemists and engineer engaged in development of chemical products and processes have not set out to cause damage to the environment or human health.

In the twenty century there was a most challenge in chemical industry due to reduce the adverse environmental side effects and during the 1990s the 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.

P. C. Anastas (EPA) defined the 12 principles of Green Chemistry:

1) Prevention

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

2) Atom Economy

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

3) Less hazardous chemical syntheses;

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

4) Designing safer chemicals;

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

5) 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

6) Design of energy efficiency;

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

7) Use of renewable feedstock;

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

8) Reduce derivates;

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

9) Catalysis;

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

10) Design of degradation;

Chemicals product 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

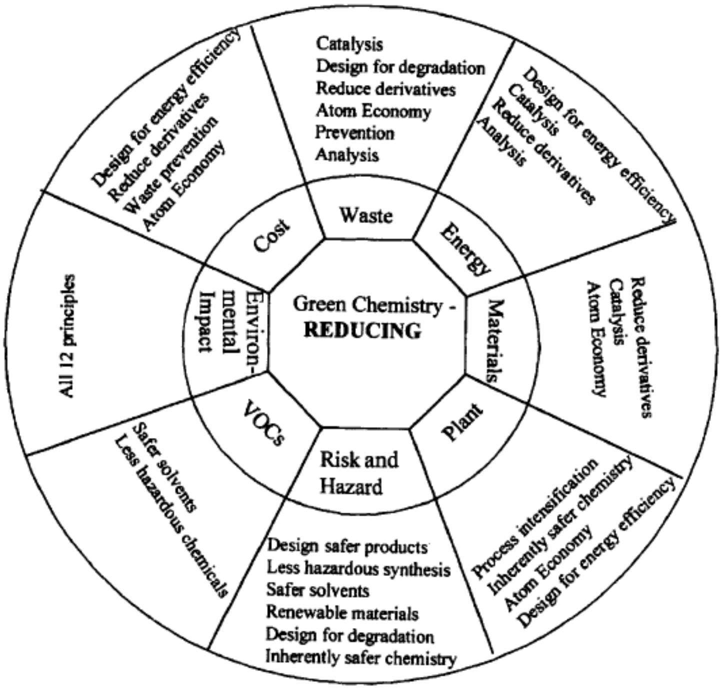
11) Real-time analysis pollution prevention;

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

12) 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 chemicals accidents, including release, explosion.

The Green Chemistry can be thought as a ‘reducing’ approach. In fact, application of the 12 principles reduce the environmental impact of a process, the costs, the waste, the energy, materials, volatile organic solvents, and risk and hazard as well depicted. In following figure.



The fundamental challenge for the chemical industry is to continue to provide the benefits to society without causing damage to the environment [1]. One of the most important parameters for the evaluation of green process is the E factor, introduced by Roger Sheldon [2][3] to calculate the amount of waste for Kg of product. Assumption on the 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:

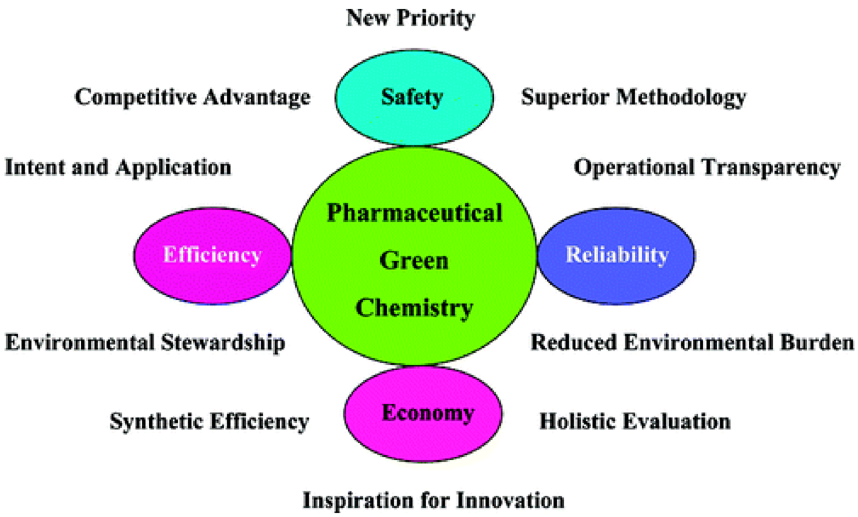
E factor = Total waste (Kg) / Product (Kg)

This is a simple method for to evaluate the environmental impact of a process. But the E-Factor ignore recyclable factors such as recycled solvent and re-used catalysts, which obviously increase the accuracy but ignores the energy involved in the recovery (these are often theoretically by assuming 90% solvent recovery)

Table 1

Industry Sector	Annual Productio (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

The application of this metric in industrial field, is very simple and the measurement of the materials *in* and *out* is direct and accurate. In table 1 are showed the E factor of chemical industry: the first important data is the low value of waste in oil refining, and the high value of pharmaceutical industry. This reflect the fact that the profit margins in the oil industry require them to minimize waste and find uses for products which would normally discarded as waste. By contrast the pharmaceutical sector is more focused on molecular manufacture and quality. Another aspect is the high volume of materials producted by oil industry, in comparison with the low tonnage of pharmaceutical industry. This table encouraged a number of large pharmaceutical companies to begin a green chemistry program. In fact in the last years this industry start to open their research opening to a new greener processes [4]



Sheldon introduced another factor to evaluated the environmental impact of industrial process: EQ (environmental quotient). In fact 1 kg of sodium chloride is quite different from the same of 1 kg of Cr(VI). This parameters is assigned multiplying the E factor with an arbitrarily assigned unfriendliness quotient, Q. For example for NaCl, Q is 1,for heavy metal salts are 100-1000.

Catalysis

Catalysis played a fundamental role in chemical industry of 20th century. In fact catalysis reduce the environmental impact and for the future will can increase the success of Green Chemistry approach [5] Today it is estimate that 85% of chemicals used have come into contact with a catalyst at some stage in their manufacture. The parameters for to know the commercial viability and the greenness of a catalyst are:

1) Selectivity;
2) TON (turnover number), TOF (turnover frequency);

Indeed, the formation of by-products inorganic or organic should be avoided and the catalyst lifetime long enough to reduce the cost and waste amount. For bulk chemical manufacture, catalysts play a huge role and they were largely used. Meanwhile in pharmaceutical and fine chemical industry the catalyst role ar, have increase the applications in more recent years.

There are three kind of catalysis: homogeneous, heterogeneous and biological.

The first application of a catalyst in industrial chemistry was an heterogeneous catalyst, meanwhile the enzymatic catalysts was the more recent discipline and has developed explosively, being included in many commercial applications. Homogeneous catalysis started its life in industrial chemistry with nitrous oxides in the lead chamber process and thus prior to the recognition of the effects of heterogeneous catalysts. Now homogeneous catalysis is applied in hydroformilations, carbonylation, oxidations, metathesis, hydrocyanations, hydrogenations and for fine chemicals production.

The differences between homogeneous catalysis and heterogeneous catalysis are showed in table 1.

Table 2

Heterogeneous	Homogeneous
Usually distinct solid phase	Same phase as reaction medium
Readily separated	Often difficult to separate
Readily regenerated and recycled	Expensive / 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

From the point of view of contribution of tonnage and dollars, heterogeneous catalysis have the major part of contribute: all the basic raw materials or building blocks for chemicals are manufactured by a small but very important set of heterogeneous catalytic processes [6].

Nickel was the first heterogeneous catalyst and it was used more than 100 years ago for hydrogenation of oils and fats to produce margarine. Unfortunately unhealthy amounts of nichel contaminated the product. The issue of leaching and the avoidance of trace of catalyst residue are still important aspects of research from both human health, economic and environmental point of view.

In pharmaceutical and fine chemical industry heterogeneous catalysis is less used: out the increasing costs for disposal and treatment of waste and by-products are pushing toward a reduction of environmental impact.

The most used catalysts are basic or acid, and the possibility to have heterogeneous catalysts with this properties can reduce the aqueous waste and the inorganic or organic salts contained into the aqueous solution due to neutralization processes.

Many of the green benefits of homogeneous catalysts, especially high selectivity, arise from tailored made catalysts involving transition metals and appropriate ligands [7].

Immobilized catalysts

One of the most important approach to realize new heterogeneous catalysts is the heterogeneization of active homogeneous catalyst to a solid support. The target is to combine the selectivity and rate of homogeneous catalyst with the simple recovery of heterogeneous catalyst [8]. Using this kind of catalyst the leaching in batch condition should be minimal and the separation can be obtained by a simple filtration and finally the catalyst can be reused. The heterogeneized catalysts can be used in continuous flow system in order to obtain a process with a minimal energy consumption [9].

Normally the heterogeneization caused a decrease of catalyst activity in comparison with the corresponding homogeneous catalyst for the problem connected to the diffusion of the substrate to the catalytic sites.

There are four method for heterogeneize an homogeneous catalyst:

1. Impregnation
2. Steric hindrance-occlusion in porous system (ship in the bottle)
3. Grafting or tethering (covalent bound)
4. Ion pair formation

Methods 3 and 4 are the most used approaches, because the catalyst is anchored to the support with a chemical bound.

For grafting or tethering approach the supports are organic polymers (linear, non cross-linked polymers in suitable solvent; swellable, slighty cross-linked polymers; highly cross-linked polymers), or ‘porous inorganic solids (amorphous oxides such silica, alumina, zirconia; clays or pillared clays; zeolites, MCM).

When the grafting tecniques is applied [10], the catalytic site is directly anchored on the support. This procedure is used for supporting the organometallics complexes, in those cases by ligand anion exchange reaction, deprotonated Si-OH complete the metal coordination first sphere. In tethering technique, a spacer is introduced between the support and 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 similar condition to homogeneous phase, so the steric hindrance of the support is usually less important than in grafted catalyst.

The nature of the support is a very important aspect: superficial area, polarity. The support can be a siliceous or 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 consist in the functionalization of silica surface, populated by silanols groups. This groups can be obtained by a pre-treatment of the silica, and than the functionalization of the silica can be obtained via a pleiade of commercially available silylating agents. 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 hierarchical ordered silica materials, however, such support show a wide variety in porosity [11]. Next to the nature of the support, its degree of loading and the nature of the solvent used, the length and the flexibility of the spacer require fine tuning to reach optimal catalytic behavior [12].

In this dissertation the tethering approach has been followed to immobilize different homogeneous catalysts on amorphous silica. Moreover another type of support was prepared and used, magnetite nanoparticles in order to obtain a magnetic catalyst recoverable by a simple magnetic decantation.

The obtained catalysts have been used for oxidation processes and for carbon-carbon bond formation reactions.

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Chapter 1

Silica-bound and magnetic nanoparticles-bound decatungstate, as heterogeneous catalyst for green oxidation reactions

1.1 Introduction

Oxidation reactions are one of the most studied and important reactions in organic chemistry. The great problems with this kind of reaction is selectively, production of large amount of pollutant material. Traditionally oxidations were carried out with stoichiometric amount of metal salts such as Mn(VII), Cr(VI) and strong acids such as nitric acid. This processes involve an economical and processes problems for the waste's elimination. In the last decades legislations call for the lowering of waste production and the use more of more friendly alternative reagent and catalysts. This goal can be achieved through the application of the principles of green Chemistry that provide a framework for designing more eco-compatible routes to fine chemicals production. In the our laboratory we focused the attention on two principles of Green Chemistry: use of heterogeneous catalysts and use of less hazardous synthesis process. For Chemistry industries the use of non-toxic solvents, non-toxic reagents, simple implants and green condition is a great attractive from an economical viewpoint. The use of heterogeneous catalysts in the liquid phase offers advantages over homogeneous ones, such as easy recovery and recycling, stability.

Recently we have demonstrated the activity of decatungstate anion supported on silica for the sulfide oxidation [1]. Polyoxometallates (POMs) are a large and rapidly growing class of inorganic compound 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 [2]. Among them, decatungstate anion in one of the most promising examples. We investigated the oxidations of alcohol to corresponding aldehyde and ketones, and epoxidation of cycloottene to corresponding epoxide.

The oxidation of alcohol to their corresponding aldehydes and ketones is of significant importance in organic chemistry, both for fundamental research and industrial manufacturing [3]. This kind of oxidation is carried out with stoichiometric amount of oxidants generating a lot of waste and pollutants. From an economical and environmental viewpoint, catalytic processes are thus valuable, and those employing green oxidants such us hydrogen peroxide are particular attractive.

In the present work we report about the reactivity of decatungstate grafted on silica and a study about decatungstate grafted on magnetite nanoparticles.

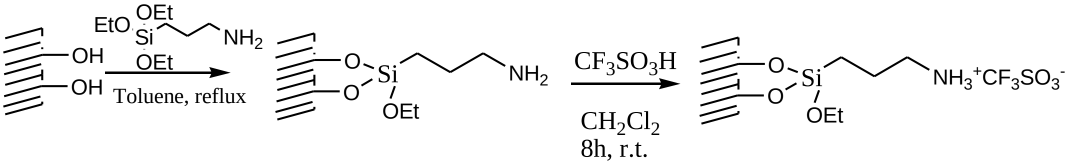
1.2 Results and Discussion

1.2.1Catalyst preparation: silica bound decatungstate

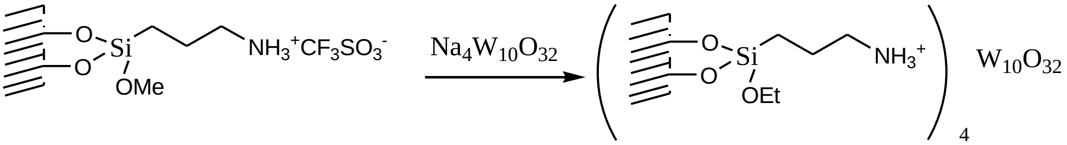
Following the procedure reported by our group [1] the preparation of the catalyst involved two main steps: a) silica functionalization anchoring ammonium salt to surface silanols and b) anion exchange with sodium decatungstate (scheme 1).

Scheme 1

a) Heterogenization of primary ammonium salt:



b) decatungstate anchoring:



Anchored primary ammonium salt was prepared by refluxing silica and 3-(aminopropyl)-triethoxy silane in toluene, under stirring overnight. The cooled functionalized silica was filtered off, washed with toluene and dried under high vacuum to give the surface-bound alkylamine groups with a loading of 1,2 mmol/g. The resulting material were reacted with trifluoromethane sulfonic acid for 8 hours at r.t., filtered off, washed with DCM and dried under high vacuum. Elemental analysis revealed an organic loading of 0,9 mmol/g. The final catalyst was prepared disperding the anchored ammonium salt in water for 30 minutes at r.t. The catalyst was filtered off, washed with water, ethanol and diethyl ether and dried under high vacuum. Then the solid was washed in continuous with hot acetonitrile for 12 hours in a Soxhlet apparatus. After drying under high vacuum the catalyst was completely characterized. The final loading of W was 0,15 mmol/g, as determined by ICP-AES analysis of the catalyst.

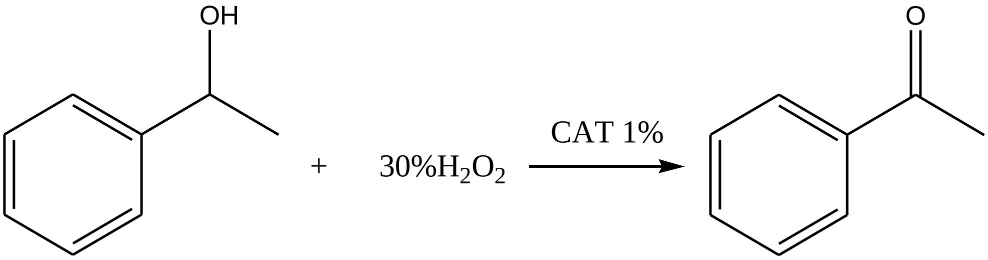
1.2.2 Alcohol oxidation

The obtained catalyst was tested in oxidation of benzylic alcohol to the corresponding aldehydes and ketones. This oxidation is very studied and in literature numerous of procedure were reported. Recently was reported a procedure using a POM in heterogeneous conditions with hydrogen peroxide as oxidant.[4].

Oxidation of alcohol is important because the obtained products (aldehydes and ketones) are important intermediates for synthesis.

The oxidation of phenyl ethanol to acetophenone was selected as the model reaction (scheme 2):

Scheme 2



1 **2a**

For the preliminary study we tested the catalyst in refluxing methanol, overnight with ratio alcohol/hydrogen peroxide 1/1. In this condition the product was obtained in 30% yield. In table 1 there are the results obtained in different conditions (solvents, reagent ratio, time)

Table 1

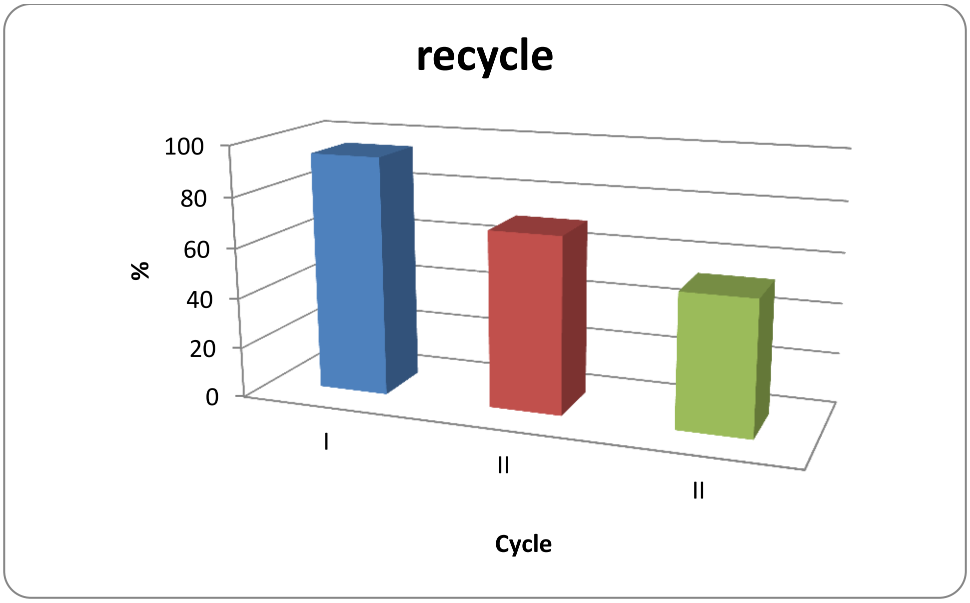
Entry	Solvent	Ratio **1**/H_2O_2	Time (h)	Yield (%)	Sel (%)
1	MeOH	1	5	20	99
2	MeOH	1	12	30	99
3	MeOH	3	12	40	99
4	t-BuOH	3	12	33	99
5	H_2O (0,3 ml)	3	3	80	99
6	H_2O (0,3 ml)	3	4	95	99

Reaction conditions: benzylic alcohol (1mmol), catalyst (1% mmol) in the solvent (3 ml otherwise stated)

The first solvent used was methanol for its green properties, but the conversion of benzyl alcohol was low.

Using water the reaction worked very well in concentrated conditions (entry 5) and with an excess of oxidant. But, in this condition, the ion pair of the catalyst could be disturbed by the dissociative property of water. In fact test of recycle (figure 1) showed the non-recyclability of the catalyst.

Figure 1



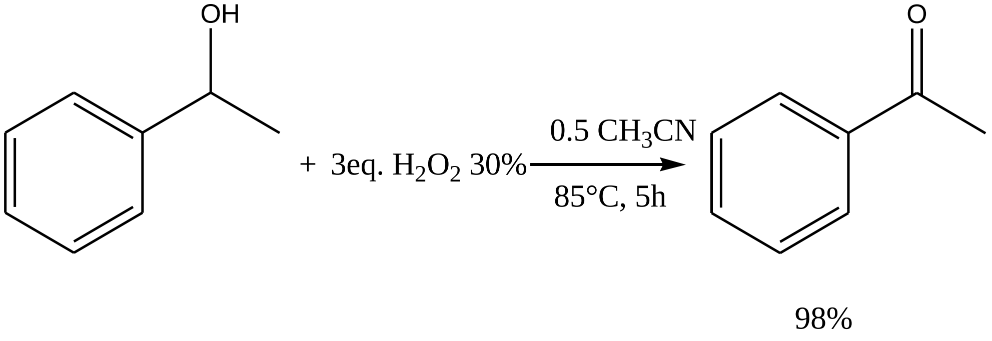
After 3 cycle the yield decrease to 53 %, and it was attributed to the high dissociating charactestics of water, that cause dissociation of ion pair of the heterogeneized catalyst.

To overcome this problem we employed as acetonitrile, obtaining good results. In table 2 we reported the results:

Table 2

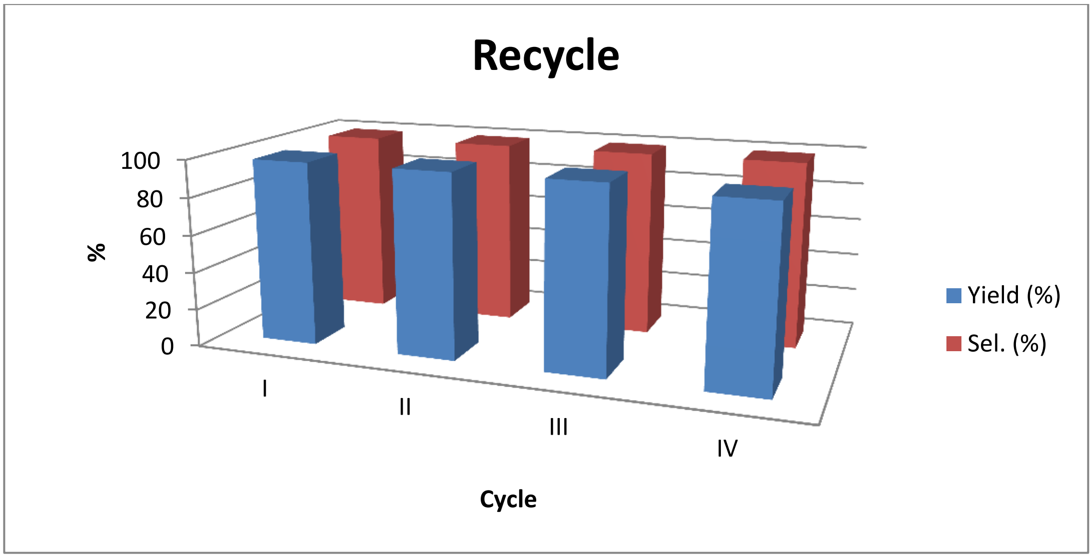
Entry	Acetonitrile (ml)	cycle	Yield 1 (%)	Sel 1 (%)
1	0,3	1	99	99
2	0,3	2	93	99
3	0,3	3	62	99
4	0,5	1	90	99
5	0,5	2	88	99
6	0,5	3	89	99
7	0,5	4	86	99

Yield and selectivity was calculated using GC analysis with t-butyl phenol as internal standard. Reaction: 1mmol of alcohol, 1% of catalyst in acetonitrile, at 85°C



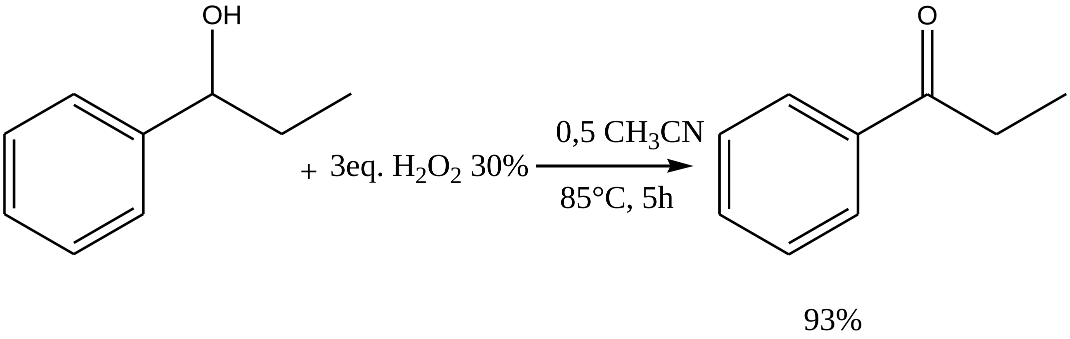
Reacting 1 mmol of benzylic alcohol in 0.5 ml of refluxing acetonitrile in the presence of 1% of catalyst, after 5h we obtained the product in yield 98%and 99% selectivity. Moreover, the catalyst recyclability showed that the catalyst was used for at least 4 times without any loss of activity.

Figure 2



To extend the applicability of the reaction to others benzylic alcohol we applied the optimized conditions using ethyl-phenyl alcohol such a substrate (scheme 3).

Scheme 3

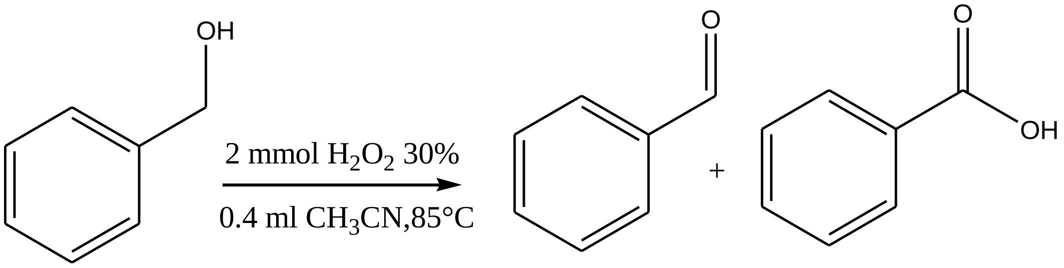


3 **2b**

Propiophenone was obtained in 70% yield and 99% selectivity.

Then we studied the catalyst activity in the oxidation of primary benzylic alcohol to the corresponding aldehyde. In this reactions is more difficult to obtain the complete selectivity because the obtained aldehyde is sensitive to over oxidation. The reaction was carried out in the conditions optimized for secondary alcohol giving benzaldehyde in good yield (78%), along with 5% of benzoic acid (scheme 4):

Scheme 4

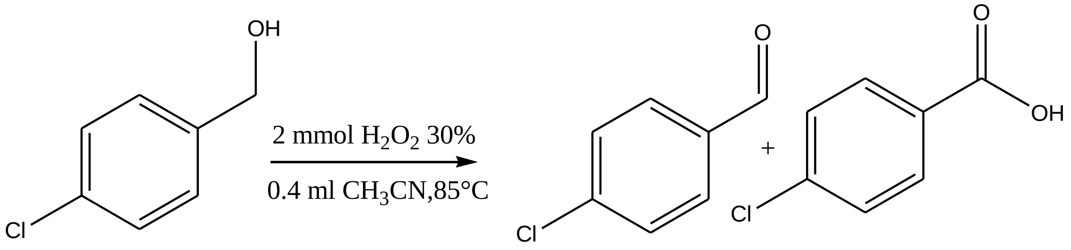


4 5a 6a

1 mmol 80% 5%

Operating at 85°C with 0,4 ml of acetonitrile we obtain a good yield but with a 5% of corresponding acid. Using p-chlorobenzyl alcohol as substrate, the corresponding aldehyde was obtained in 80% yield accompanied by a small amount (2%) of the corresponding acid (scheme 5):

Scheme 5

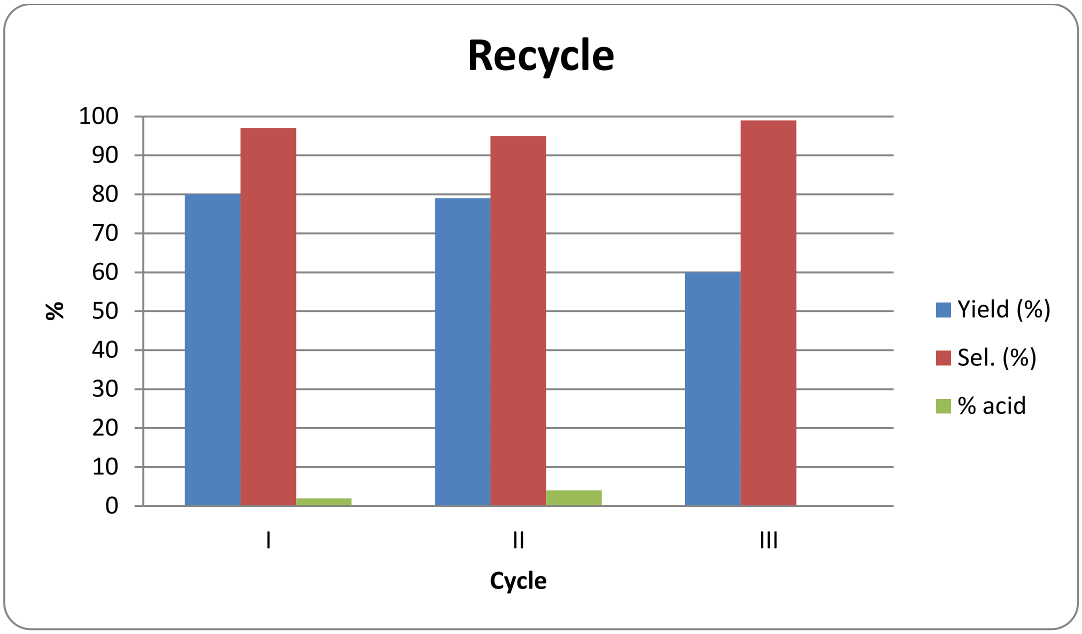


6 5b 6b

1 mmol 80% 2%

We examined the recyclability of the catalyst in this last reaction (fig. 3):

Fig. 3



The recycle test was conducted for three cycles: in the first cycle the aldehyde was obtained in good yield and 2% of corresponding acid was detected. In the second cycle the yield was good but a little increase of acid was observed. In the third cycle the yield decrease but conserving high selectivity. This partial deactivation of the catalyst could be attributed to the interaction of the acidic by-product with the catalyst, probably causing some leaching. The problem of benzoic acid formation was avoided carrying out the reaction in larger volume of solvent (i.e. 1 mmol in 5 ml) and for shorter time (2 h), but the yield decrease (10%). On the basis of these results, we are planning to study this reaction in a continuous flow system.

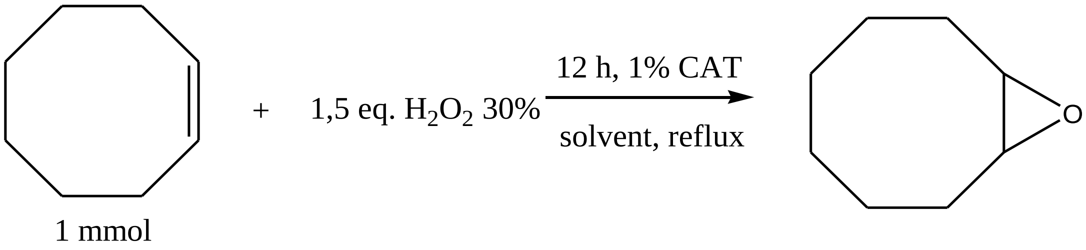
1.2.3 Epoxidation of *cis*-cyclooctene

In order to explore the catalytic activity of the supported decatungstate in other oxidation reactions, we tested the catalyst in alkene epoxidation.

Epoxidation is an important reaction to synthetize intermediate for fine chemicals. In literature there are a lot of publication for this kind of reaction and in the last two decades some groups reported the reactivity of POMs for this process in homogeneous condition[5]. Interesting paper was published byR. Hajian et al using a POM in heterogeneous condition [6].

The preliminary study was performed using *cis*-cycloottene as a model substrate, in methanol, and the reaction's condition are showed in scheme 6:

Scheme 6



7 **8**

In methanol conditions the product was detected in traces, and we have recovered all cycloottene . We tested other solvents and the results are showed in table 3

Table 3

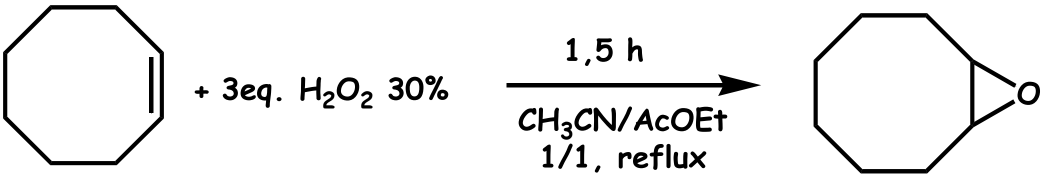
Entry	Solvent	H_2O_2 (mmol)	Time (h)	Yield 8 (%)	Selectivity 8 (%)
1	MeOH	1,5	12	traces	99
2	CH_3CN	1,5	12	traces	99
3	THF	1,15	3	30	99
4*	THF	1,15	3	30	99
5	THF	1,5	24	60	99
6	THF	3	6	72	99
7	THF	3	12	82	99
8	dimethoxyethane	1,5	6	45	99
9	dimethoxyethane	2	6	95	99
10**	dimethoxyethane	2	6	95	99
11	dioxolane	3	3	80	99

Reaction conditions: 1 mmol of substrate, reflux condition, 1% of catalyst;
Yield and selectivity was calculated using GC analysis with t-butyl phenol as internal standerd. *5% of catalyst;**recycle of entry 8.

Using acetonitrile the reaction didn’t work, probably due to the low solubility of cyclooctene in CH_3CN and in MeOH; the effort was to find a solvent which was able to dissolve the hydrogen peroxide and the cyclooctene. Using THF the product was detected after 3 hours in 30% of yield (entry 3), that did not change increasing the catalyst amount (entry 4) from 1% to 5%. In order to increase the yield we increased the reaction time to six hours and the amount of hydrogen peroxide obtaining a yield 72% with a complete selectivity. A further yield (82%) increase was obtained carrying out the reaction for 12 hours. We explore other solvents such as dimethoxyethane carrying out the reaction for 6 hours. The product was obtained in very good yield (95%) and excellent selectively. This solvent was able to dissolve the reagents, and has an high boiling point. Further in this conditions the catalyst was recyclable. However the real problem was the toxicity of dimethoxyethane: for a green synthesis is inacceptable to use this kind of solvent. We tested the dioxolane, a special solvent for synthesis, that recently was considered an alternative green solvent of the toxic glymes. The reaction showed good yield and selectively, but in GC analysis we detected some amount of ethylene glycol evidencing some decomposition of the solvent in glycol and formaldehyde. This is not acceptable in a green synthesis.

Aiming at finding a good medium able to dissolve both the reagents a mixture of acetonitrile and ethyl acetate was tested:

Scheme 7

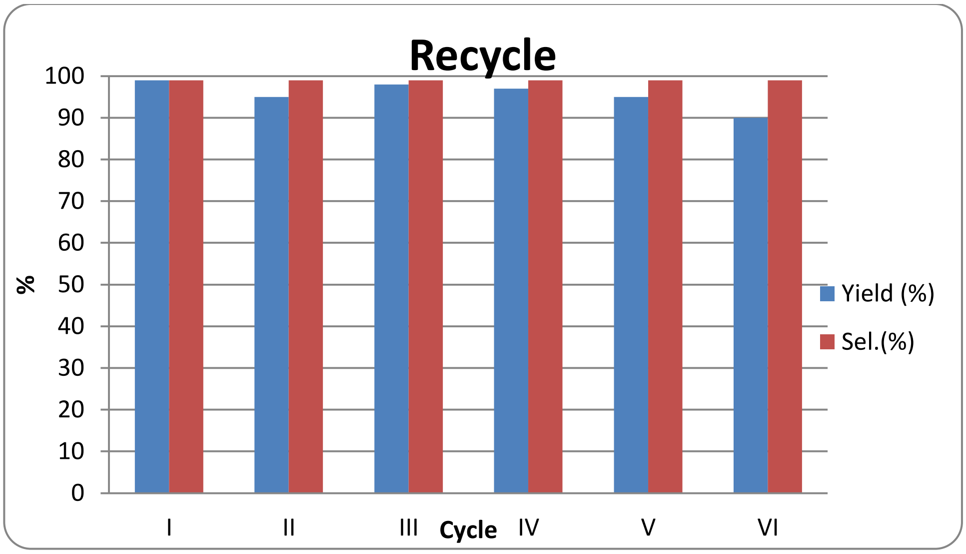


7 **8**

99%

Using this unusual solvent the reaction was carried out for 1,5 hours, and the product was obtained in excellent yield (99%) and selectively (99%). We tested the recyclability of the catalyst showed in figure 4:

Fig. 4



As shown in figure 4, the catalyst is recyclable, giving only a slight yield decrease in the sixth cycle (90% yield). Work in progress to extend the applicability of the catalyst to other substrate.

Study of a magnetic support: preparation of decatunstate supported on core-shell magnetite nanoparticles

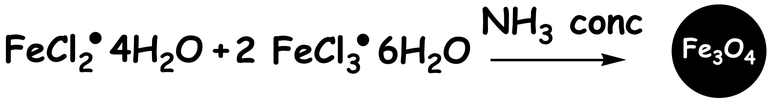
In the last decades numerous research groups have focused their attention to the preparation of nanoparticles, in particular to superparamagnetic nanoparticles. In literature it is possible to see a lot of publications, because magnetic nanoparticles (MNPs) have great potential for biological application such as hyperthermia, cancer therapy, drug delivery [7-9].

Another important application was the use of MNP as support for heterogeneous catalysts due to the easy separation of the catalyst from the reaction by a simple magnetic decantation [10].

Therefore, we choose to explore this type of material as support to heterogenize decatungstate. In particular we choose to prepare nanoparticles of Fe_3O_4, since magnetite NP have good magnetic properties and different procedure for their synthesis and functionalization are reported in the literature.

To synthetize the magnetite NPs we choose the modified Massart's method [10] consisting in co-precipitation of the iron salts in aqueous solution, adding ammonia.

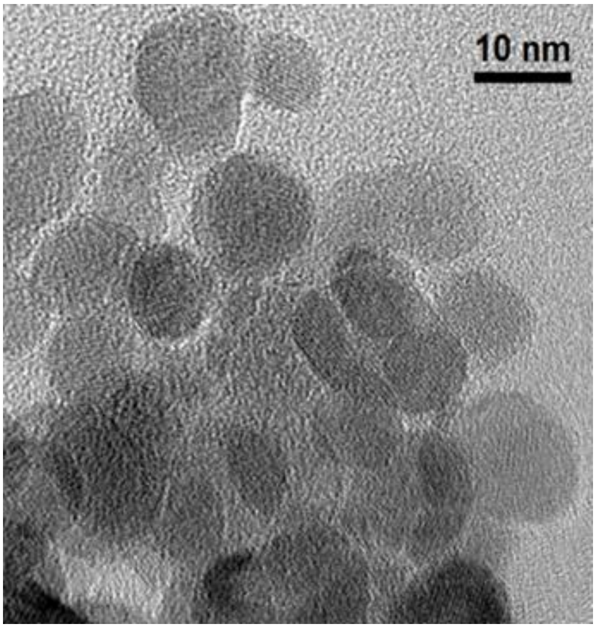
Scheme 8



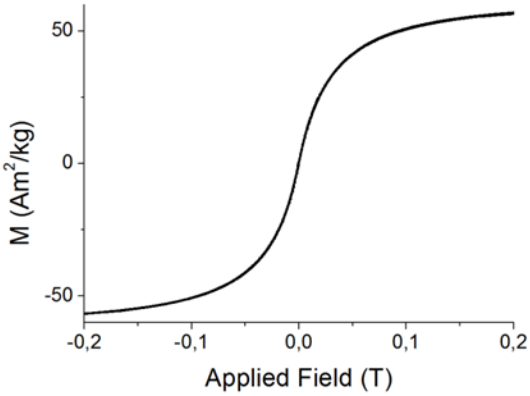
The reaction was carried out under Ar atmosphere, using deionized water (previously deoxygenated) for four hours. After then the magnetite was cooled at room temperature, washed several times with distilled water and dried overnight under high vacuum.

The obtained NPs were examined by TEM microscopy to study dimensional distribution and crystallinity.

Fig 5



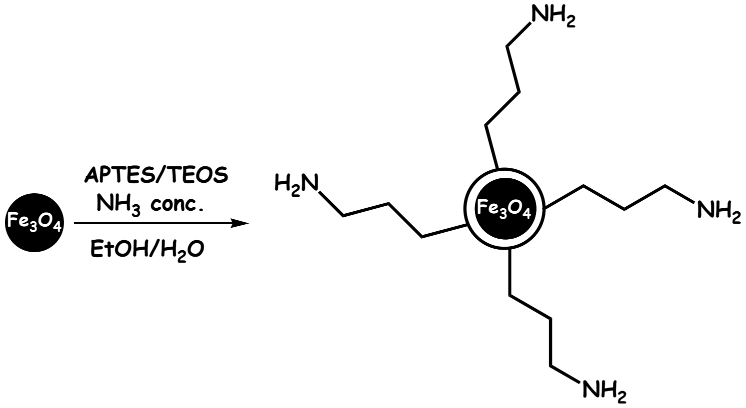
In fig.5 was reported a TEM image that shows the small dimension of the NPs centered between 6-8 nm. A study of magnetic properties was performed. The saturation of magnetization and the results are showed in figure 6:



This kind of study was performed applying a magnetic field on the sample due to align the spin of the nanoparticles. After the field was eliminated and the spin return to original position. If the NP are superparamagnetic a residual magnetization must be not detected. In fact in figure 6 it is possible to see the total absence of hysteresis. We can conclude the superparamagnetic character of the synthetized magnetite NPs since any residue magnetization is absent.

The next step was the functionalization of this NPs. We performed a study testing numerous procedures reported in literature to obtain core shell Fe_3O_4. The experimental conditions influence the formation of aggregate and the thickness of the coating. Indeed, using the NPs obtained by co-precipitation method, there is the problem of great aggregation. The better result was obtained following the procedure shown in scheme 9:

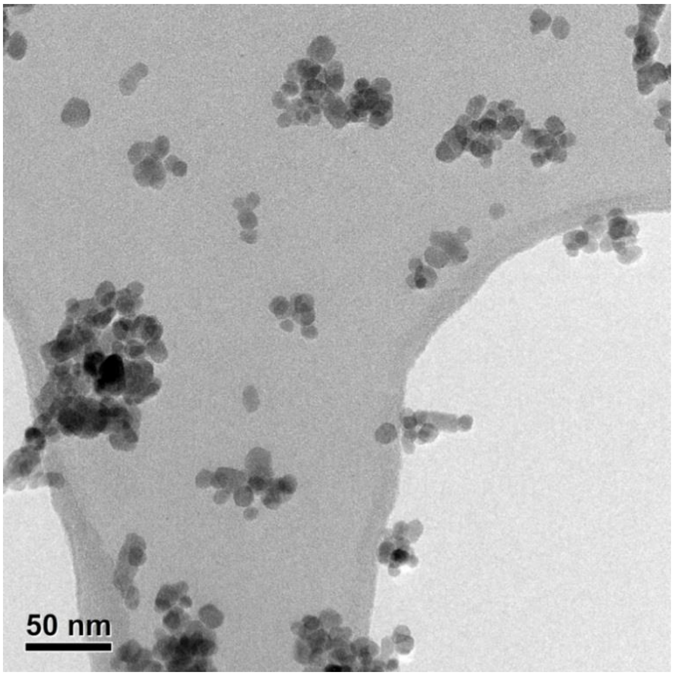
Schema 9



The reaction was carried out overnight using mechanical stirrer at 60°C. The ratio water/EtOH was 1/1 to obtain a good solvent for disperding the NPs. After then the functionalized NP were cooled to room temperature and decanted using a permanent magnete, washed several times with ethanol and dried overnight under high vacuum.

The nanoparticle with silica coating and bearing amino groups was examined by TEM spectroscopy (fig. 7):

Fig. 7



It is possible to observe the presence of very small and larger aggregate.

Now the functionalized NPs were ready for the next step, that is the decatungstate anion anchoring. We followed the same procedure employed to support decatungstate on silica gel:

- Reaction with trifluoromethansulfonic acid giving ammonium salt
- Anion exchange in water to introduce decatungstate

All the reactions were carried out with mechanical stirrer.

The NPs were examined by TEM microscopy:

Fig. 8a

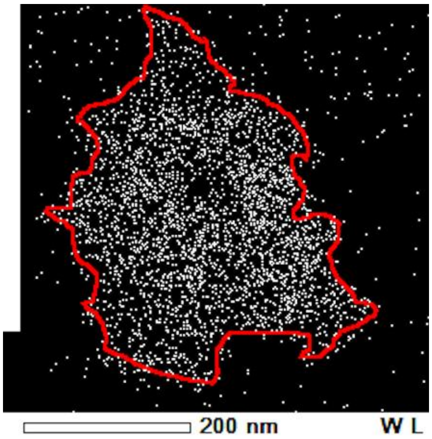
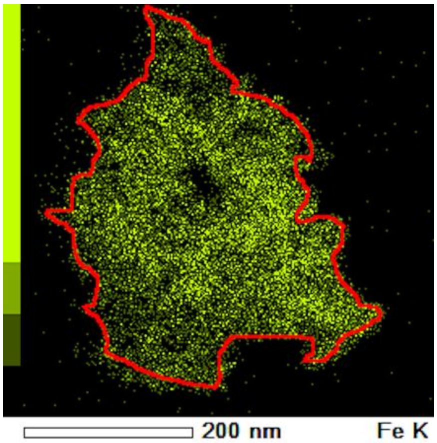


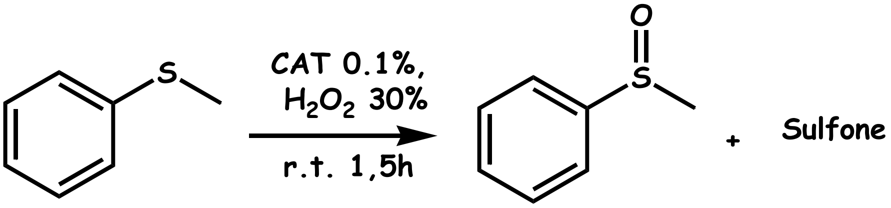
Fig 8b



During the catalyst preparation, larger aggregates were obtained. In fig. 8a is showed the distribution of tungsten in the aggregate, and the distribution of iron (8b) in the same aggregate. On the basis of these images, we can state that decatungstate was successfully anchored and it was homogeneously distributed on the aggregate.

The obtained magnetic catalyst was tested in the sulfide oxidation as a model reaction employing the same condition previously reported for decatungstate bound to silica gel.

Scheme 10:



90% 5%

The catalyst showed the same reactivity of silica supported decatunstate, but with the advantage of catalyst recovery by magnetic decantation.

The studies for extend the applicability of this catalyst in others reaction are in progress in the our laboratory.

1.3 Experimental section

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 (Merk) (size 0.040-0.063 mm; surface area 480-530 m^2/g; pore volume 0.74-0.84 cm^3/g). The starting material of alcohol oxidation were hydrogen peroxide (30% Carlo Erba), methyl-phenyl alcohol (99%, Aldrich), ethyl-phenyl alcohol (99% Aldrich), Benzyl alcohol (99% Aldrich), *p*-Chloro-benzyl alcohol (99% Aldrich), methyl benzyl alcohol (99% Aldrich).

The starting material of cyclooctene epoxidation were hydrogen peroxide (30% Carlo Erba), cyclooctene (95%, Aldrich).

APTES (97% Aldrich), $Na_2WO_4*2H_2O$ (98% Aldrich)

1.3.2 Synthesis of Sodium tungstate

$Na_4W_{10}O_{32}$ was prepared following a literature procedure [12],adding 260 ml of boiling aqueous 1M HCl solution to a boiling solution containing $Na_2WO_4*2H_2O$ (44 g) in distilled water. The resulting solution was allowed to boil for 40 seconds, after which it was transferred into 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 with a small amount of cool water, ethanol and diethyl ether and transferred to a 250 ml beaker. The of non-metallic spatula is recommended to avoid the formation of a blue color. The 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 crystal of sodium decatungstate were collected on a fritted funnel and dried under vacuum (9,4 g). From the mother liquor, it was possible to obtain more crystals on concentration. The absorbance spectrum in acetonitrile or in water showed characteristic well-defined maximum at 324 or 323 nm, respectively.

1.3.3 Catalyst preparation

The preparation of catalyst involved two main steps: (a) silica functionalization anchoring ammonium salts to surface silanols and (b) anion exchange with sodium decatungstate. Silica was activated by refluxing in HCl conc. For 4 h, followed by washing until neutral with distilled water and then drying. Anchored primary ammonium salt was prepared by refluxing activate silica (5 g) and 3-(aminopropyl)-triethoxysilane (10 mmol) in toluene (30 ml) under stirring overnight. The cooled functionalized silica was filtered off, washed with toluene, diethyl ether and dichlomethane (2x25 ml each) and dried under high vacuum overnight. The loading of amino group was detected by elemental analysis (0,8-1,2 mmol/g). The resulting material in dry dichloromethane (5 g in 25 ml)were reacted with trifluoromethane sulfonic acid (two equivalents with respect the supported amino group) for 8 h at room temperature, filtered off, washed successively with dichloromethane, ethanol and diethyl ether (2 x 25 ml each).Then it was dried under high vacuum overnight. The loading was detected by elemental analysis (0,8-0,9mmol/g).

The catalyst was prepared stirring the surface bound ammonium salt in distilled water with sodium decatungstate at room temperature for 30 min. After stirring the white solid was filtered off, carefully washed with 700 ml of distilled water, 50 ml of ethanol and 50 ml of diethyl ether. Then it was washed in continuous with hot acetonitrile for 12 hours using a Soxhlet apparatus. After drying under high vacuum the catalyst was ready to use.

The loading of W was determined by ICP-AES analysis (0.15 mmol/g)

1.3.4 Synthesis of magnetite nanoparticles

I step: synthesis of magnetite nanoparticles

In a 500 ml 3 necked round bottom flask 11g of $FeCl_3$ $*6H_2O$ (40.7 mmol) was dissolved in 120 ml of deionized water. Then 4 g of $FeCl_2$$*4H_2O$ (20.1 mmol) was added and the solution was heated at 85 °C under argon atmosphere. The pH value of the solution was adjusted to 10 by the addition of concentrated aqueous ammonia. The magnetite formation started immediately. After stirring for 4 hours under argon atmosphere the reaction was cooled. The nanoparticles were washed several times with deionized water to pH=7, removing the excess of ammonia. The black precipitate was collected by magnetic decantation and dried under high vacuum overnight.

1.3.5 Functionalization of magnetite nanoparticle

In two neck round bottom flask 0.5 g of magnetite nanoparticles was dispersed in 100 ml of a mixture EtOH/H_2O 1/1, sonicating for 10 minutes. After then the mixture was stirred with mechanical stirrer and heating at 60°C. After 5 minutes a mixture of APTES/TEOS 9/1 was added. The reaction was carried out overnight. After than the mixture was cooled and the nanoparticles were washed for several times with EtOH and dried under high vacuum.

The resulting material in dry dichloromethane (0.5 g in 50 ml) were reacted with trifluoromethane sulfonic acid (two equivalents with respect to the supported amino group) for 8 h at room temperature, magnetically decanted, washed several times successively with ethanol. Then it was dried under high vacuum overnight

The catalyst was prepared stirring the surface bound ammonium salt in distilled water with sodium decatungstate at room temperature for 30 min. After stirring the brown solid was magnetically decanted, carefully washed with distilled water, 50 ml of ethanol. After drying under high vacuum the catalyst was ready to use.

The loading of W was determined by ICP-AES analysis (0,08 mmol/g)

The identity of the produced aldehydes and ketones were attribute by comparison of spectra with authentic samples or with data reported in the literature.

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Chapter 2

Decatungstate supported on magnetite nanoparticles for hydroquinone oxidation

2.1 Introduction

The oxidation is one of the most important reaction in industrial chemistry. In the last decades new green legislations call for the lowering of waste production and the use more of more friendly alternative reagents and catalysts. This goal can be achieved through the application of the principles of Green Chemistry that provide a framework for designing more eco-compatible routes to fine chemicals production [1].

Oxidation of phenols and hydroquinones affords quinones which are found as structural unit in a great variety of natural compounds, showing antifungal, antibacterical, antiviral activity. Furthermore, benzoquinones are important as intermediates for preparation of fine chemicals and pharmaceuticals [2-4].

Oxidation of hydroquinones to their corresponding benzoquinones can be achieved by a variety of methods: with Fremy's salt (potassium dinitrosulfonate [5], sodium dichromate/sulfuric acid mixtures[6], benzyltrimethylammonium tribromide [7], iodine or hydroiodic acid/hydrogen peroxide mixtures [8], diphenyl diselenide/hydrogen peroxide mixtures [9] ammonium ceric nitrate/Montmorilonite K10 mixtures[9], phenyl iodose acetate on alumina under microwawe irradiation [10], and a variety of metal derivates [11] have been exploited.

Recently, our group have demonstrated the ability of polyoxoanion decatungstate bound to silica to activate hydrogen peroxide as green oxidant in the oxidation of sulfides to sulfoxides with high yields and selectivity [12]. The catalyst was demonstrated to be completely recyclable for at least six times without loss of activity.

In this PhD thesis we planned to heterogenize the polyoxoanion decatungstate by anchoring to magnetic nanoparticles as support.

In the last years nanoparticles were increasingly studied for their potential use in biomedical applications and also for their use such a support for catalysts in order to increase the superficial area. The most studied nanoparticles were magnetite nanoparticles for their magnetical property and their compatibility in biological systems, and also for their simple preparation.

In addition, magnetite nanoparticles (Fe_3O_4) of small size (< 20 nm) are superparamagnetic. It means that they respond to an external magnetic field without retaining any magnetization when it is removed. This behavior adds a further advantage to heterogeneous catalysis since the catalyst can be easily separated from crude reaction by magnetic decantation, recovered and immediately reused.

In this work we present the preparation of decatungstate bound to superparamagnetic magnetite nanoparticles and the use of this catalyst in the reaction of hydroquinone oxidation with hydrogen peroxide aq. 30%.

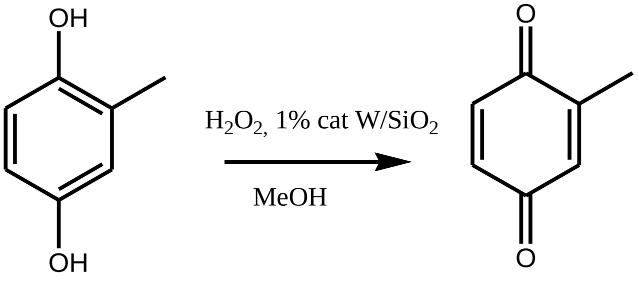
2.2 Results and discussion

2.2.1 Preliminary study

The goal to reach hydroquinone oxidation is to obtain a selective oxidation without any by-product. In fact the formation of by-product due to coupling between reagent and product is very easy to occur. Also oligomers can be formed with the progress of the reaction.

A preliminary study was performed using the POM decatungstate anchored on silica support described in chapter 1 (1.2.1). The reaction was carried out with 1% mmol of catalyst in methanol at room temperature (scheme 1):

Scheme 1

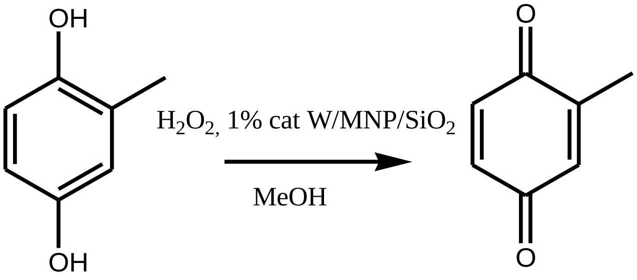


1a 2a

In this condition the product was obtained in 50% of yield after 6 hours, but the selectivity was low: in fact the conversion was quantitative. At short time (2 hours) the selectivity was quantitative but yield was unsatisfactory (50%). Increasing the reaction time the conversion increased but selectivity drop down. Similary results were obtained using other solvents and higher amount of catalyst.

Then we employed the decatungstate anchored on core-shell magnetite nanoparticle ($W/MNP/SiO_2$) previously functionalized with primary ammonium cation: in chapter 1 (1.2.4) we have shown the reactivity of this catalyst in oxidation of sulphides. The reaction was carried out with 1% mmol of W/SiO_2catalyst in methanol at room temperature (scheme 2):

Scheme 2



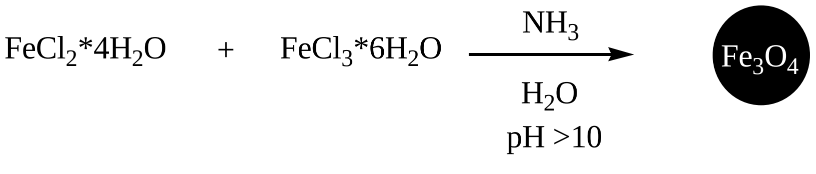
1 2a

In this conditions the product was obtained in 50% yield and 50% selectivity, but the reaction time was shorter, 30 minutes. In order to modulate the polarity of the support to limit the formation of polar by-products we changed the counter ion of the catalyst. We decided to anchor a tetralkyl phosphonium salt on magnetite nanoparticles.

2.2.2 Synthesis of catalyst

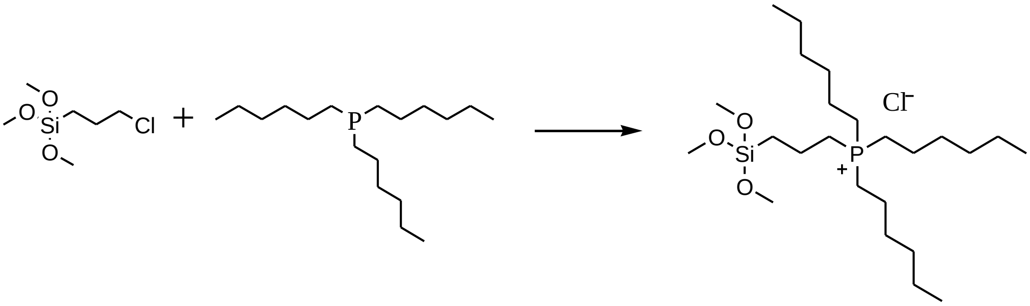
The catalyst preparation involves three steps: 1) Synthesis of magnetite nanoparticles; 2) Synthesis of ionic liquid; 3) anchoring the ionic liquid on magnetite nanoparticles; 4) anion exchange.

1) Magnetite nanoparticles were synthetized via co-precipitation procedure, applying a modified Massarth method (1);

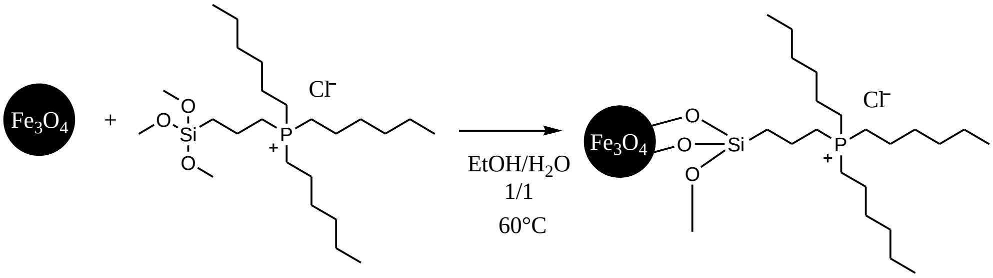


$$FeCl_2{*}4H_2O \quad + \quad FeCl_3{*}6H_2O \xrightarrow[H_2O \\ pH>10]{NH_3} Fe_3O_4$$

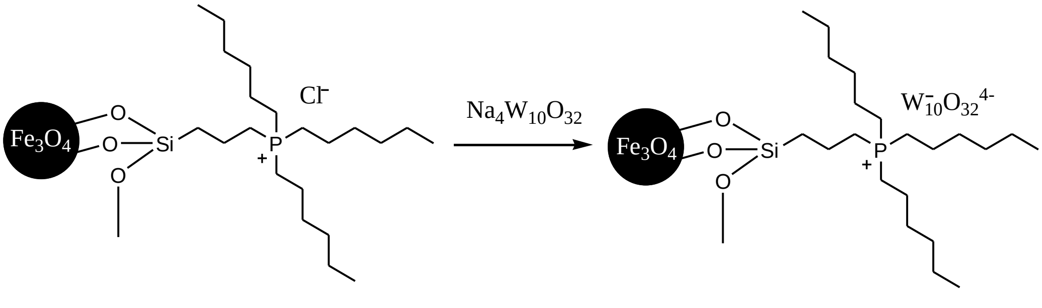
2) The ionic liquid was synthetized in solvent free condition at 120°C overnight, under nitrogen atmosphere reacting choropropyltrimethoxy silane and trihexylphosphine;



3) For ionic liquid anchoring 0,5 g of magnetite nanoparticles was sonicated for 10 minutes in 10 ml of water; 90 ml of ethanol was added and the suspension was sonicated for 5 minutes. After then the ionic liquid was added. The solution was heated at 60°C in oil bath and was stirred overnight by mechanical stirrer.

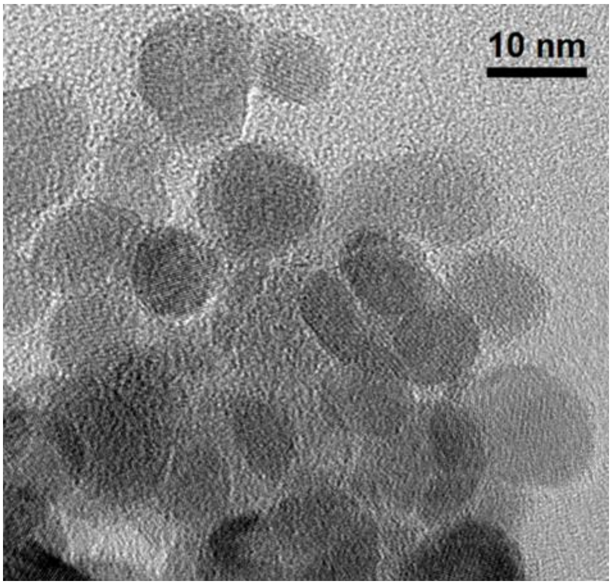


4) For the anion exchange the functionalized magnetite was sonicated for 5 minutes in methanol and the solution was stirred by mechanical stirrer. $Na_4W_{10}O_{32}$ was added and the reaction was carried for 1 h at room temperature. After washing with deionized water (to eliminate the unreacted decatungstate) and methanol, the catalyst was dried under high vacuum.



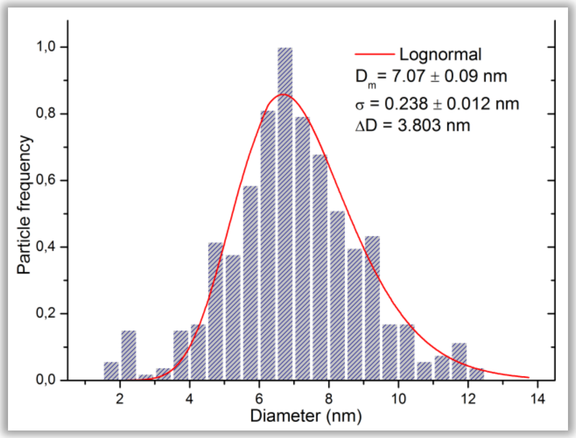
In collaboration with institute IMEM (CNR) the catalyst supported on MNP was characterized by magnetic and spectroscopy measures. The catalyst was characterized by TEM microscopy to determine the nanoparticle size distribution and to study the composition of the catalyst by microanalysis.

Fig 1



In figure 1 a TEM image of magnetite nanoparticles obtained is shown. The obtained MNP are crystalline with size distribution centred at 6-8 nm.

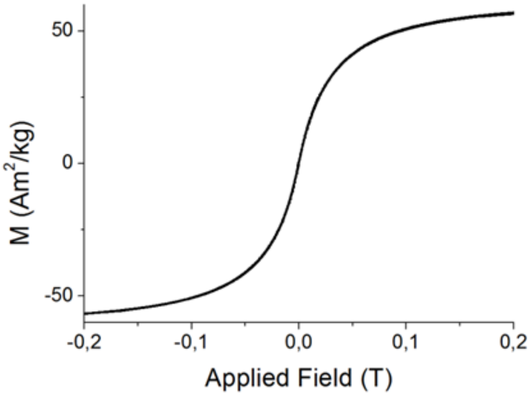
Fig 2



Obviously there are large aggregates because this MNPs were not stabilized and aggregation occurs also during distribution of the sample on the supporte gride.

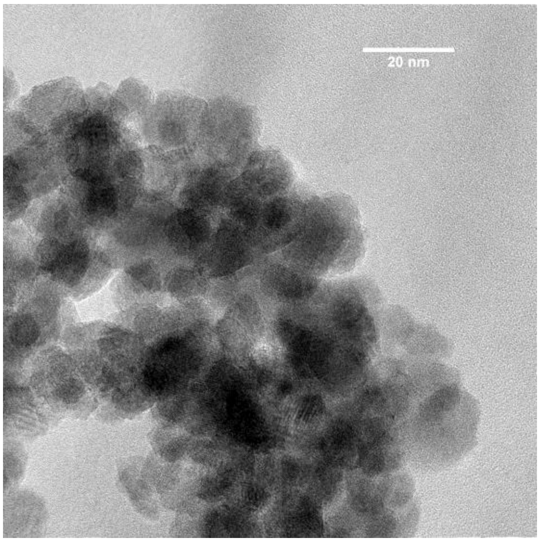
To complete the characterization, magnetic measurement were performed:

Figure 3



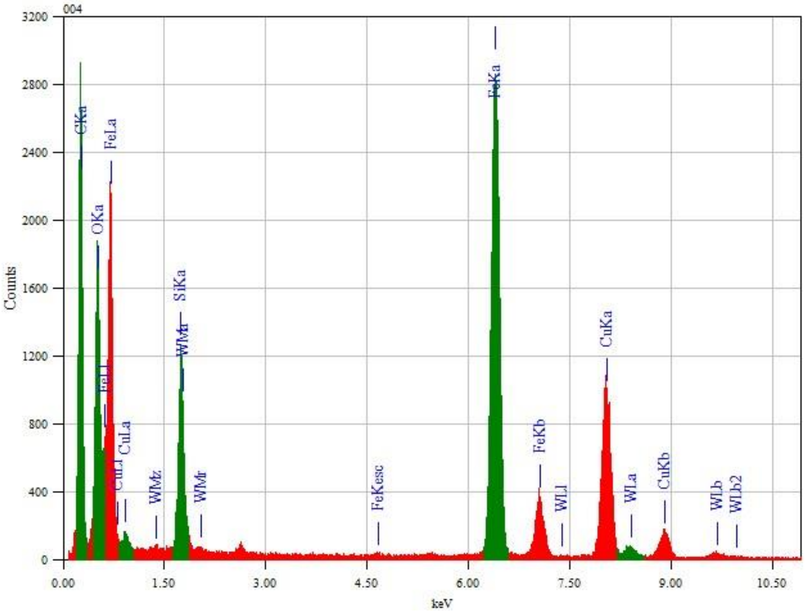
In figure 3 is shown the magnetization of saturation of the synthetized NPs and the graphic evidenced the superparamagnetic property of the magnetite. When the nanoparticles were exposed on magnetic field, and that field was successively removed, there is not a residue magnetization. In fact hysteresis isn’t observed. After the decatungstate anchorage on the MNP, the resulting catalyst was examined by TEM (figure 4).

Fig. 4



The catalyst presents large aggregate (100-500 nm), and the TEM microanalysis (figure 6) revealed the presence of W, even if in small amount, confirming the W anchorage. This result was confirmed by ICP-AES analysis, that gave a W catalyst loading of 0,003 mmol/g.

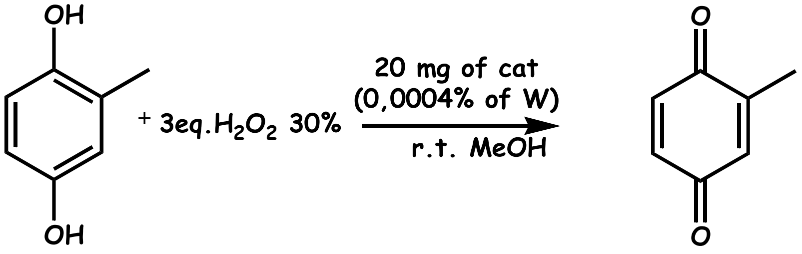
Figure 6



2.2.3 Catalytic test

The catalytic activity of the above described catalyst was tested in hydroquinones oxidation to afford the corresponding benzoquinones, important intermediates for fine chemicals synthesis. One of most important benzoquinone is trimethylbenzoquinone, a precursor of the vitamin K. Methyl hydroquinone oxidation was studied as a model reaction. The reaction conditions was illustrated in scheme 3:

Scheme 5



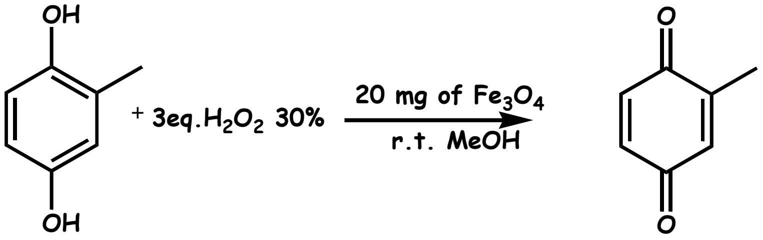
1 0.5 mmol 2a 99%

The reaction was carried out for 45 minutes in methanol at room temperature using 3 equivalents of H_2O_2, under mechanical stirring. It is noteworthy that the catalyst is very active and selective. Indeed, a very small amount of catalyst (0.0004%) was able to afford the methyl quinone in quantitative yield.

Taking into account that iron oxide itself could activate hydrogen peroxide, we examined the activity of the nude nanoparticles.

The reaction was carried out in the same condition employed for the supported catalyst (scheme 6)

Scheme 6



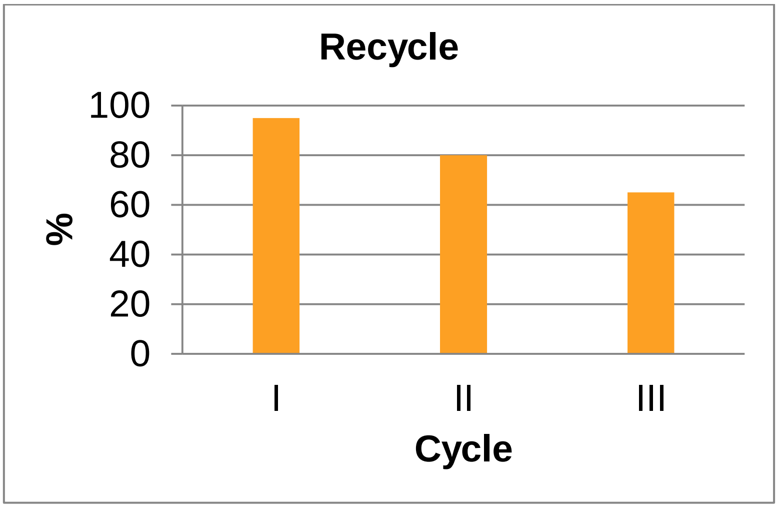
1 2a

0.5 mmol

After 45 minutes the product was obtained in lower yield (i.e 70%) and 99% of selectivity.

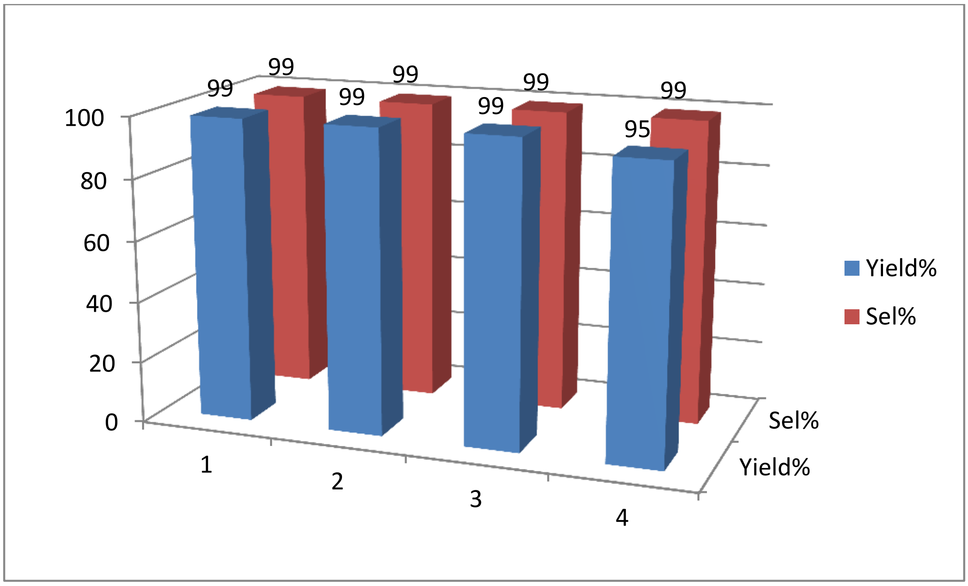
We examined the recyclability of nude magnetite NPs in this reaction (fig 7)

Fig 7



The magnetite nanoparticles showed a progressive loss of activity in any cycle, probably due to modification of the iron oxide.

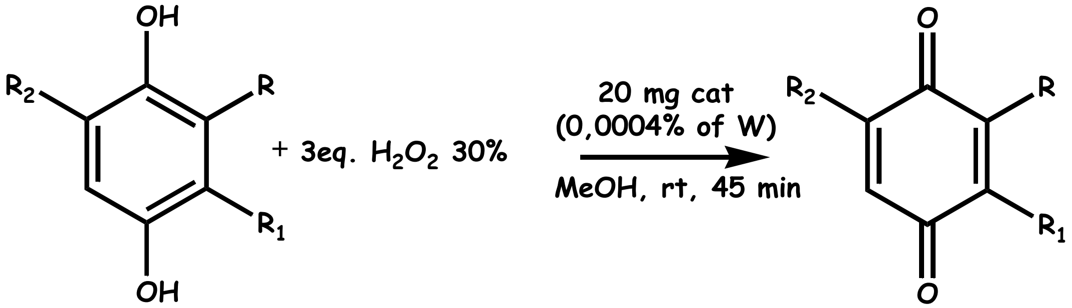
The supported catalyst recyclability was studied in the model reaction under the optimized reaction conditions (20 mg of cat, 7 ml of methanol, r.t, 45 min). After any cycle the catalyst was recovered by magnetic decantation, washed with methanol, dried under vacuum and immediately reused in the following cycle in the same round bottom flask. The good results obtained are shown in figure 8:



For three cycle 99% of yield and selectivity were obtained; in the fourth cycle was obtained 95% yield and 99% of selectively, evidencing the perfect recyclability of catalyst It is not possible to exclude a combined effect of magnetite support and decatungstate, but we can state that the presence of W is fundamental to obtain a highly active, and recyclable catalyst. To evaluate the contribution of a radical mechanism, we will examine the reaction in presence of a radical scavenger, such as BHT.

The general applicability of the reaction was then studied and the results were showed in table 2:

Table 2:



1

2

Entry	R	R_1	R_2	Time (min)	Yield 2(%)	Sel. 2(%)
1	Me	H	H	45	99	99
2	Me	Me	Me	45	98	99
3	OMe	H	H	45	98	99
4	t-Bu	H	H	120	99	98
5	H	H	H	45	93	98

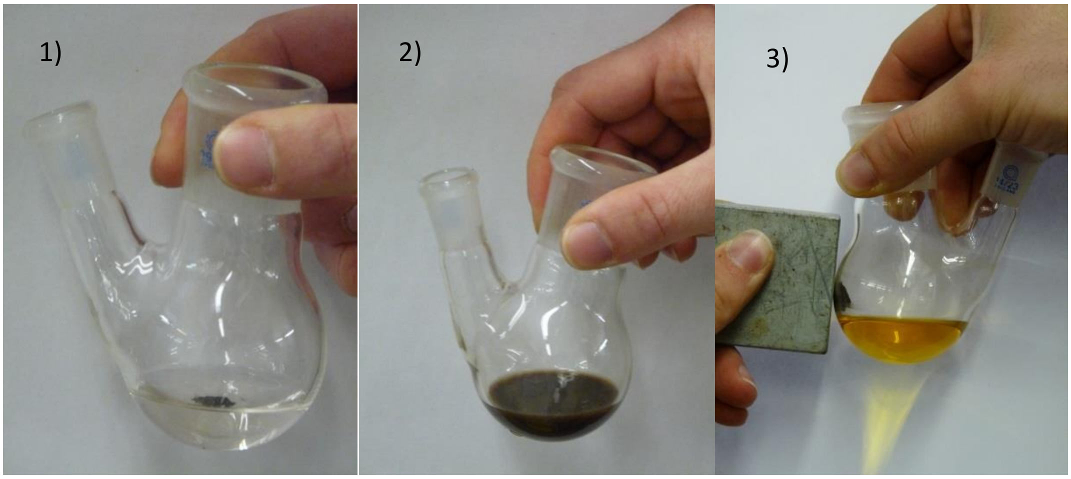
Rection conditions: 0.5 mmol of hydroquinone, 1.5 mmol of H_2O_2, in 6 ml of methanol, 20 mg of catalyst

[1] Yield determined by GC using method of internal standard;

[2] Isolated yield;

As evidenced by the results shown in table 2 the supported phosphonium decatunstate was a catalyst able to promote the oxidation of hydroquinones bearing various substituents with high yields and selectivities. The most important quinone, trimethylhydroquinone (entry 2) was obtained with excellent yield(98%) and selectivity (99%). This results are comparable or superior with the data reported in literature.

In figure 9 we show the further advantage of supeparamagnetic catalyst, magnetic decantation:



1) This picture shows a round bottom flask containing methylhydroquinone, H_2O_2, solvent and catalyst (colourless solution); 2) the same flask after sonication; 3) at the end of reaction the product was in solution and the catalyst was magnetically decanted (yellow solution, for the presence of methylbenzoquinone) and easily separated. After the separation the catalyst was washed with methanol, dried quickly and reused in the same flask.

Experimental section

2.3 General information

2.3.1 Materials

All materials purchased were used as such unless otherwise stated. Starting materials for catalyst preparation: $FeCl_2$ *$4H_2O$, $FeCl_3$ *$6H_2O$, (3-chloropropyl) trimethoxysilane (97% Aldrich), trihexyl phosphine (>90% TCI), Sodium tungstate dehydrate (Aldrich), ammonia solution 30% (Carlo Erba reagenti). The starting material for hydroquinone oxidation were hydrogen peroxide (30% Carlo Erba), 2-methyl-1,4-hydroquinone (98%, Aldrich) recrystallized from toluene, trimethyl-1,4-hydroquinone, *tert*-butyl-1,4-hydroquinone (97%, Aldrich), 2-methoxy-1,4-hydroquinone (97%, Aldrich), 1,4-hydroquinone (97% Aldrich).

2.3.2 Synthesis of catalyst

2.3.2.1 Sodium decatungstate

$Na_4W_{10}O_{32}$ was prepared following a literature procedure. Adding 260 ml of boiling aqueous 1M HCl solution to a boiling solution containing Na_2WO_4*$2H_2O$ (44 g) in distilled water. The resulting solution was allowed to boil for 40 second, 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 and that was collected on a fritted funnel; washed with a small amount of cool water, ethanol and diethyl ether and transferred to a 250 ml beaker. The use of non-metallic spatula is recommended to avoid the formation of a blue colour. The precipitate was suspended in hot acetonitrile (130 ml); then suspension was filtered, and the filtrate was placed in a freezer overnight. Large pale-lime crystal of sodium decatungstate were collected on a fritted funnel and dried (9,4 g). From the mother liquor, it was possible to obtain more crystal on concentration. The absorbance spectrum in acetonitrile or in water comprised a characteristic well-defined maximum at 324 or 323 nm, respectively.

2.3.2.2 Anchoring of decatungstate

I step: synthesis of magnetite nanoparticles

In a 500 ml 3 neck round bottom flask 11g of $FeCl_3$ $*6H_2O$ (40.7 mmol) was dissolved in 120 ml of deionized water. Then 4 g of $FeCl_2*4H_2O$ (20.1 mmol) was added and the solution was heated at 85 °C under argon atmosphere. The pH value of the solution was adjusted to 10 by the addition of concentrated aqueous ammonia. The magnetite formation started immediately. After stirring for 4 hours under argon atmosphere the reaction was cooled. The nanoparticles were washed several time with deionized water to pH=7 removing the excess of ammonia. The black precipitate was collected by magnetic decantation and dried under high vacuum overnight.

II step: Syntesys of phosphonium salt;

In 25 ml Schlenk the 3-(chloropropyl) trymethoxy silane and trihexyl phosphine were added under nitrogen atmosphere. The mixture was heated in solvent free condition for 4 h. The crude product was characterized by ESI-MS and used in the next step.

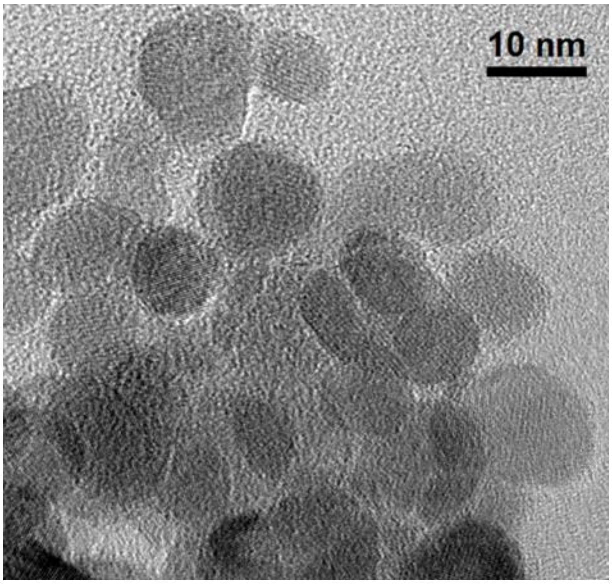
III step: Anchorage of phosphonium salt

In a 250 ml round bottom flask 0.5 g magnetite nanoparticles was sonicated for 15 minute into the solvent reaction, and 10 mmol of phosphonium salt were added. The mixture was stirred by mechanical stirrer and heated at 60°C overnight. After then the magnetic supported phosphonium salt was magnetically decantedl and washed with methanol several times using the magnetic decantation. The functionalized MNP was dried under high vacuum and the loading of organic group was determined by elemental analysis (in progress).

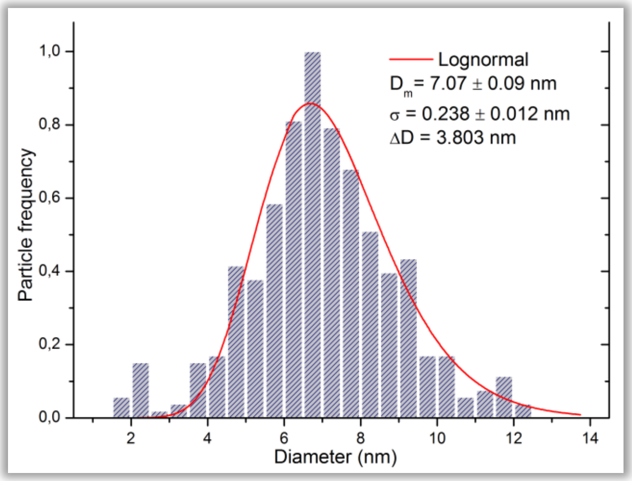
IV step: Anion exchange

In 250 ml of round bottom flask, 0.5 g of supported phosphonium salt was suspended in 150 ml of MeOH. The sodium decatungstate was added in ratio 4/1 respect to the mmol of supported salt, and the mixture was stirred for 2 h at r.t. After then the catalyst was washed with MeOH for several times using magnetic decantation in order to eliminate the unreacted sodium salt. The powder was dried under high vacuum and the loading of organic group was determined by elemental analysis, and the W loading was determined by ICP-AES (0.002 mmol/g).

Magnetite nanoparticles

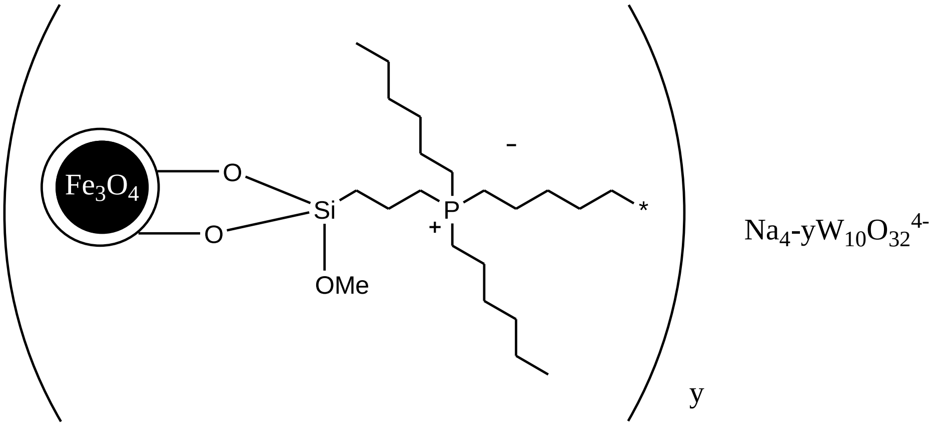


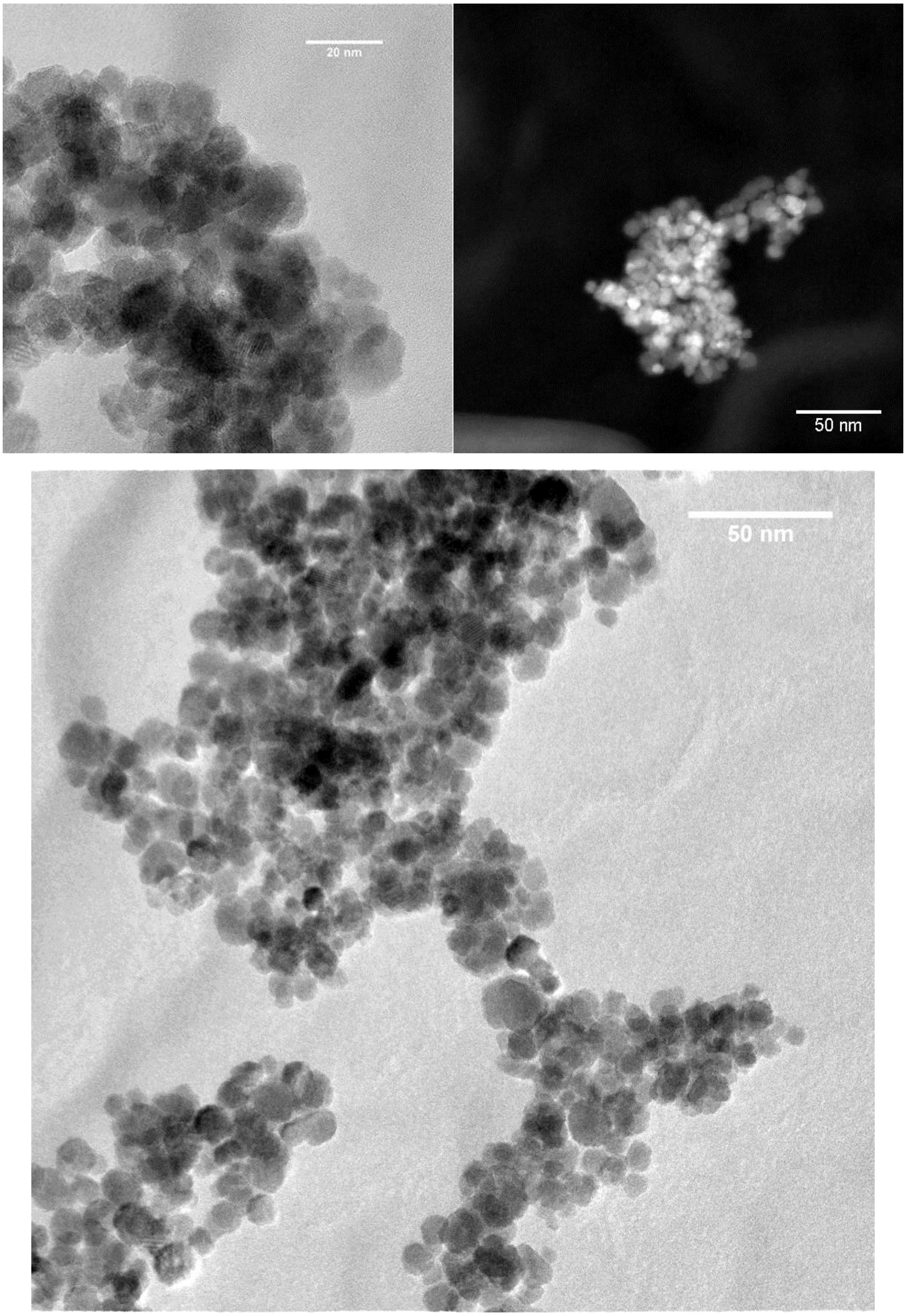
This picture shows the magnetite nanoparticles.



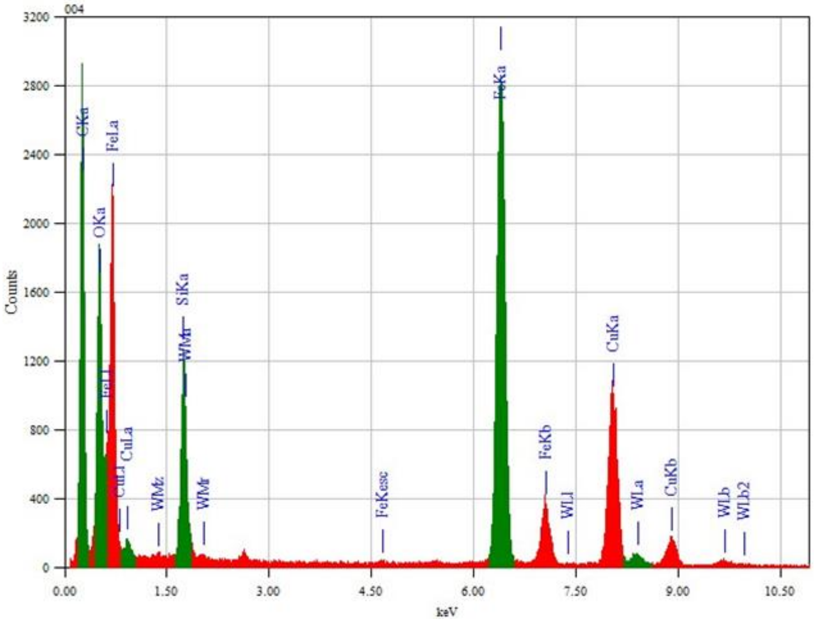
The istogram shows the size distribution of magnetite nanoparticles (centered on 6-8 nm)

Magnetic Catalyst





The final catalyst present large aggregates (100-500 nm).



Elemental analysis detect a loading of W 0.004 mmol/g. This is in accordance with the microanalysis TEM: this graphic shows the presence in low amount of W in the analyzed aggregate. Some signals are high for the overlap of L line of silica.

2.3.3 Reaction procedure for hydroquinone oxidation

Typical oxidation of methyl hydroquinone with hydrogen peroxide as model reaction was performed using a 100 ml round bottomed flask. The 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 (1.5 mmol, 0,15 ml) were added to methanol (6 ml) sonicated for 5 minutes and stirred by mechanical stirrer. The hydroquinone was added after 5 minutes.

The reaction was stirred for 45 minutes. The progress of oxidation reaction was monitored by GC and TLC. After 45 minutes, the mixture was magnetically decanted using a permanent magnete (Nd-Fe-B). The solid catalyst was washed with 5 ml of methanol and recovered. The solution was examined by GC. The GC analysis were performed on a Trace GC ThermoFinnigan instrument with a Supelco SPB-20 fused silica capillary column (30 mx0.25 mm) with helium as a carrier, adding 4-tert-butyl phenol as internal standard. The model reaction of methyl hydroquinone was monitored between 15 and 60 min. Samples were obtained periodically, and the course of reaction was followed by GC using 4-tert-butyl phenol as internal standard added to the samples. The same methodology was followed in the synthetic application to different hydroquinone the different catalysts. The product was purified by extraction adding 30 ml of diethyl ether to a methanolic solution, and washed with distilled water two times. The organic phase was evaporated on rotavapor and the solid was examined by NMR.

The identity of the produced and benzoquinones were attribute by comparison of spectra with authentic samples or with data reported in the literature.

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Chapter 3

Chiral complex anchored on silica gel for enantioselective sulfide oxidation

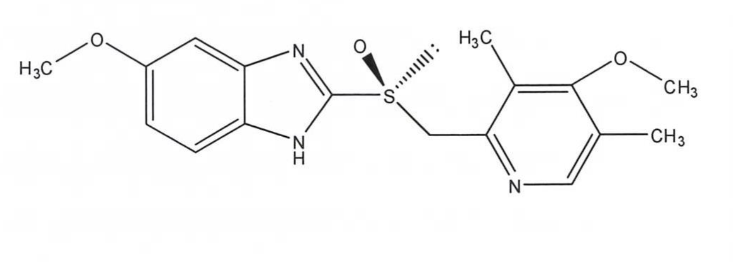
3.1 Introduction

Development of new catalytic processes for enantioselective synthesis is one of the most important objective in synthetic chemistry. Catalysis play a fundamental role for ecocompatible processes and heterogeneous catalysis is widely applied in industrial synthesis for the simple separation of the catalyst, recover and reuse and adaptability in continuous flow processes.

Chiral sulfoxides are used as auxiliaries in asymmetric synthesis and as a ligand in enantioselective catalysis.[1]. The use of sulfinyl group as a chiral controller is based on the high optically stability (200°C are necessary for the stereomutation), accessibility in both enantiomeric form, and high efficiency as a carrier of chiral information. The large stereoelectronic differences between the three substituents at the sulfinyl sulphur (the lone pair of electrons, the oxygen atom and the two alkyl 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, allow both the oxygen and the sulfur atoms to coordinate Lewis acids and transition metals, leading higly rigid and ordered transition-state geometries that permit effective transfer of the chiral information to the alkyl or the aryl groups or more distant positions. [1].

Some pharmaceutically important drugs contain asymmetric sulfynil moieties [2]: esomeprazole(fig 1) is the most important one.

Fig.1

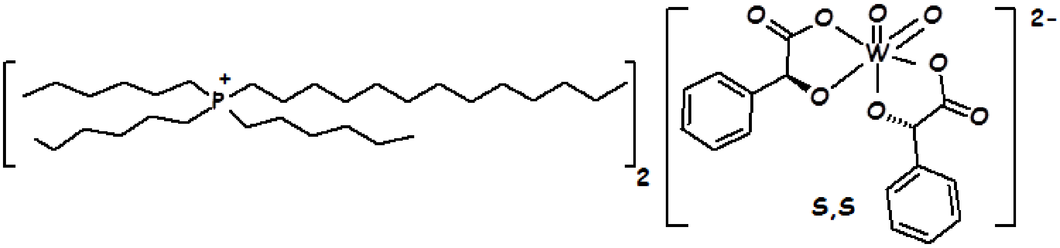


Enantioselective oxidations of sulfides can be performed by biocatalysis [3] or by chemical oxidation, the latter occurring in the presence of chiral oxidizing species, or by using a chiral oxidants and chiral metal complexes [4].

For the chemical oxidation, the most studied catalysts was based on titanium and vanadium complexes. An example is titanium (IV) isopropylate with optically active diethyl tartrate and an oxidant such as tert-butyl hydroperoxyde [5-6]. In those works, dry atmosphere is request in order to avoid humidity.

Complexes of $VO(acac)_2$ with chiral Schiff bases work in asymmetric oxidation with hydrogen peroxide such as oxidant, the humidity is not a problem, but the enantioselectivity is not very high [7].

The good results obtained using tungsten-based catalyst in hydrogen peroxide activation [8] have prompted our group, in collaboration with prof. Seddon's group of QUILL centre at Belfast University, to prepare new chiral ionic liquids containing a chiral complex of tungsten as anion. In particular, the ionic liquid formed by a tetralkyl phosphonium cation and tungsten (S)-mandelate as chiral anion (fig. 2), was able to promote the enantioselective oxidation of tioanisole to the corresponding sulfoxide with high e.e (up 96%). and moderate yield, using UHP as a oxidant. [9] (fig 2)



However the enantioselectivity drop after 1 hour of reaction and it was not possible to increase the yield over 50% without observing a drop of enantioselectivity.

On the basis of those results we decided to anchor the tungsten complex with mandelate as ligand, on a silica support in order to obtain a heterogeneous catalyst for enantioselective oxidation of sulfide.

3.2 Results and discussion

Asimmetric oxidation in heterogeneous catalysis is one more interesting field in industrial chemistry.

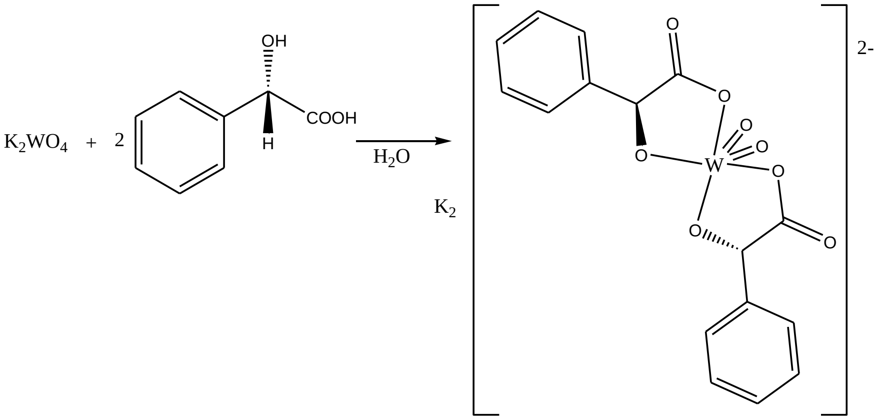
There are numerous papers in literature which show that tungsten is able to activate hydrogen peroxide for oxidation of sulfides. Recently some papers with chiral catalysts based on tungsten were published.

> In one case the catalyst was a chiral polyoxotungstophosphonate, derivated by the reaction between polyoxotungstate and a chiral phosphonate [10]. This catalyst was used in sulfide oxidation showing high activity but low enantioselectivity (e.e. <8%).
>
> Another work shown the activity of dendrimeric polyoxometallate [11] tesi angelica): the model reaction was the thioanisole oxidation, using hydrogen peroxide such a oxidant in bifasic system. The e.e. obtained was <14%.

In this work we studied the anchorage of the chiral tungsten mandelate complex on silica support in order to obtain an heterogeneous catalyst for enantioselective oxidation of sulfide to sulfoxide.

For the synthesis of the tungsten complex we followed a procedure reported in literature:

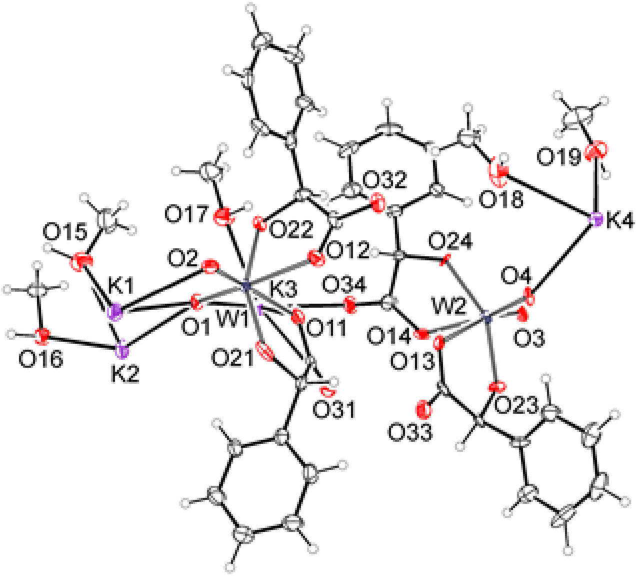
Scheme 1



For the sodium salt of this complex [11] that was characterized by Zhou and co-workers [12]. We synthetized the potassium salt using tungstate/ mandelic acid ratio of 1/2 in water at 85°C.

We choose the potassium salt because the crystallization of the sodium complex required several days. The crude complex was analyzed with ^{1}H-NMR spettroscopy showing the formation of the complex in high yield; the benzylic proton was monitored and a low residue of free mandelic acid (3-5%) was detected. The complex was purified by crystallization and crystals obtained in methanol were suitable for RX analysis. The crystal structure is shown in figure 3:

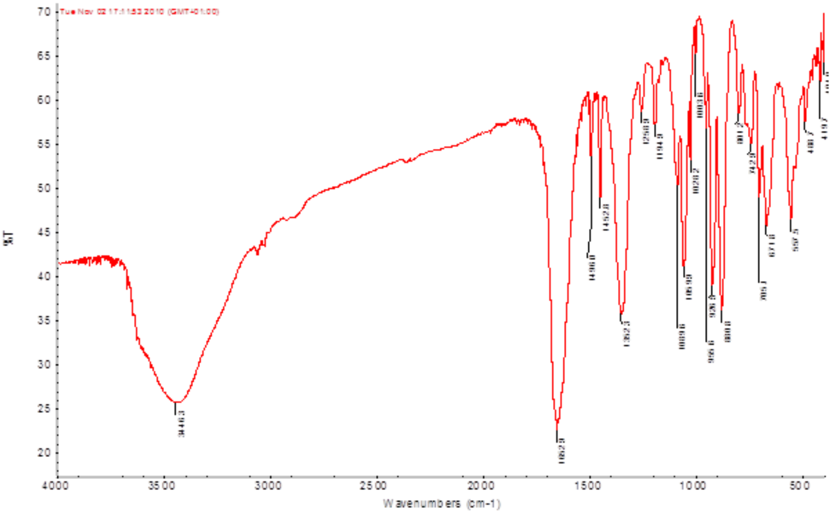
Fig. 3



The XRD analysis was performed at low temperature in order to preserve the crystal (the solid was deliquescent). A dimeric structure was evidenced , and metal centre and ligands shown a Λ and S configuration respectively. W(1) and W(2) showed octahedric distorted coordination, with the two oxygen were in *cis* positions.

In figure 4 the FT-IR of the complex is reported:

Fig. 4

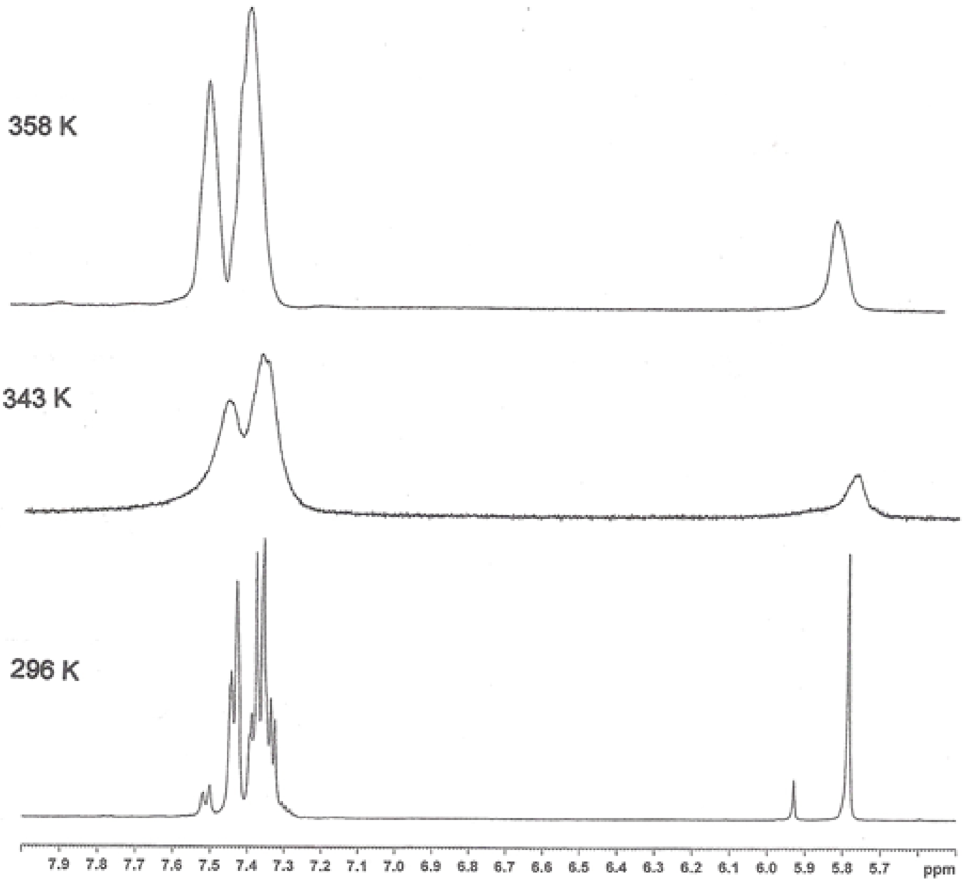


It is possible to see the signal of carboxylate groups, ν_{as} at 1653 cm^{-1} and ν_{sym} at 1352 cm^{-1}, double bond W-O at 926 and 880 cm^{-1}, in accordance with results reported for sodium complex [12].

The ^{1}H NMR showed two signals at 5.78 and 5.93 ppm due to the benzylic carbon CH(O) group.

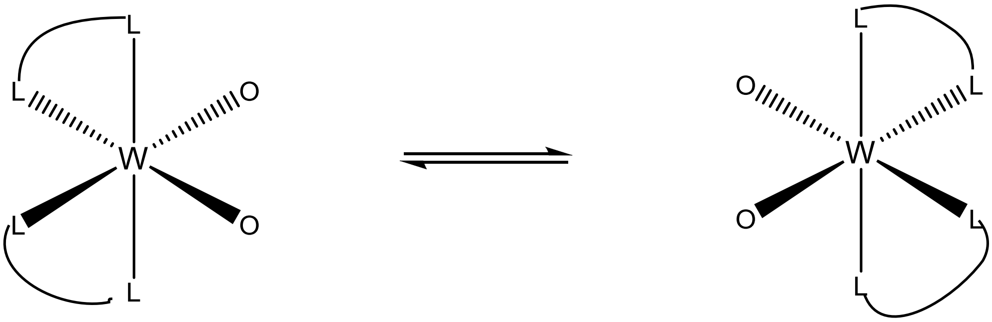
Also in the ^{13}C NMR spectrum there are two signals at 89.8 and 88.5 ppm due to the benzylic carbon. This signals could be attributed to equilibrium between the Λ_{ss} and $\Delta_{s,s}$ form of the complex. This hypothesis was supported by the ^{1}H-NMR study at increasing temperature shown in figure 5:

Fig. 5



Increasing the temperature, the two signals gave coalescence, and a single signal was observed at 85°C. It was not possible to reach higher temperature to have a sharp signal, expected for a very fast exchange equilibrium, for technical reasons, and also taking into account that the solvent was D_2O.

Fig. 6

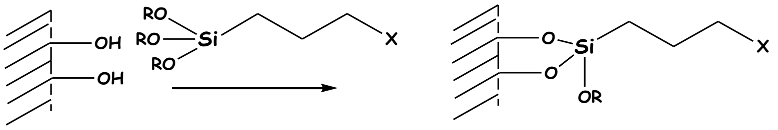


a b

3.2.1 Synthesis of catalysts

The first step was the functionalization of silica support with the appropriate alchoxy silane: to obtain tetralkyl ammonium salt or tetra alkyl phosphonium salt, the silica was functionalized using 3-(bromopropyl)trimethoxy silane. For the primary ammonium salt we used the 3-(aminopropyl)triethoxy silane.

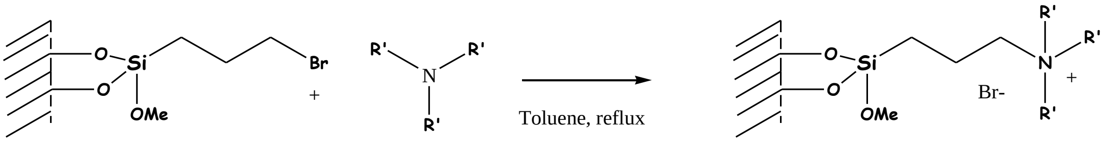
Scheme 2



X = Br, R = OMe
X = NH_2 R = OEt

The second step was the formation of ammonium salts. The quaternary salts were obtained reacting the alkyl bromide with a tertiary amine, in particular tripentyl amine.

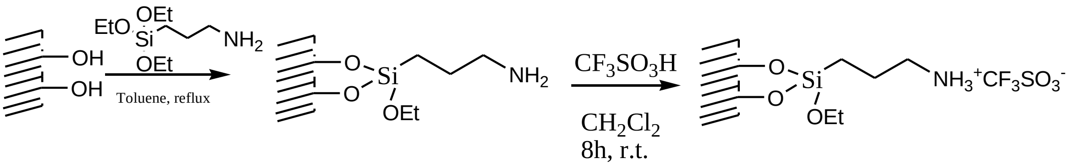
Scheme 3



R' = pentyl

The primary ammonium salt was prepared by protonation of the anchored amine with trifluoromethane sulfonic acid in dicholomethane (scheme 4):

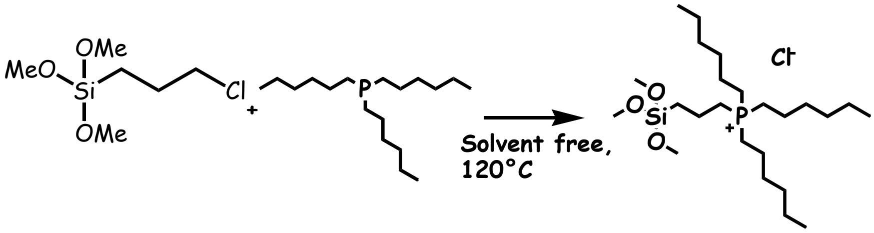
Scheme 4



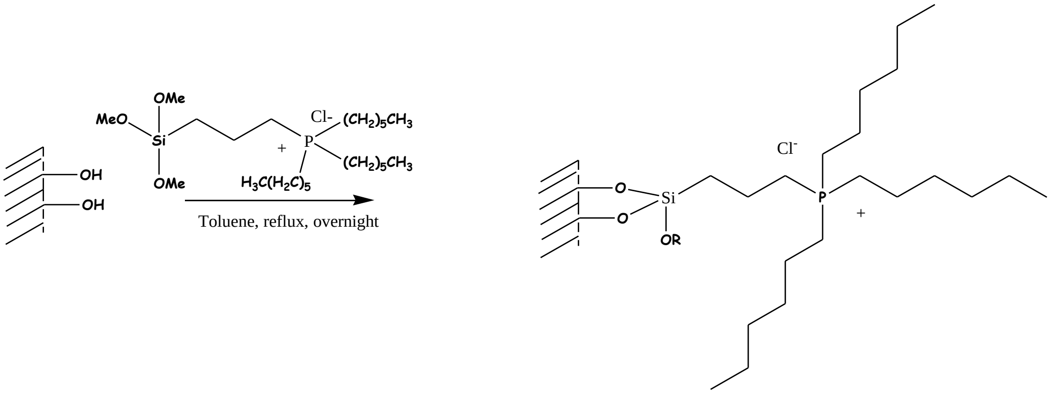
The anchored phosphonium salt was prepared in two steps (scheme 5):

Scheme 5

I Synthesis of phosphonium ionic liquid:

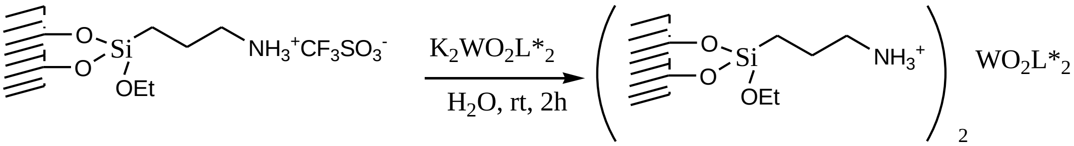


II Anchorage on silica:



The last step was the anion exchange to introduce the chiral tungstate; the reaction was carried out in water at room temperature for 2 hours.

Scheme 6

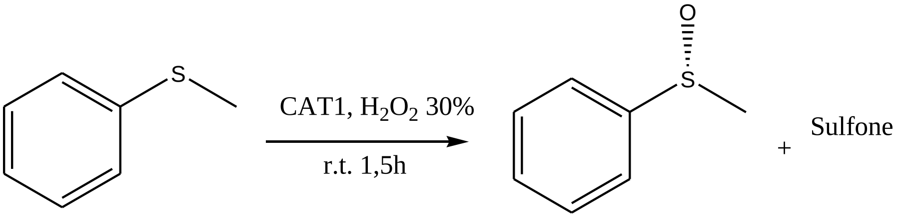


The loading of organic parts was determined by elemental microanalysis, and the W amount was detected by ICP-AES (0.36 mmol/g).

3.2.2 Catalytic test

The catalysts reactivity was tested in the oxidation of thioanisole as a model reaction.

Scheme 7



1 2a

The first reaction was carried out in homogeneous conditions using the potassium chiral complex ($K_2WO_2L^*_2$), with methanol as a solvent, 1,15 meq. of H_2O_2 at room temperature with 5% mol of catalyst. The yield was 75% and the e.e. 30%.
Using the supported catalyst with the primary ammonium salt (CAT1) we obtained the results showed in table 1

Table 1

Entry	Solvent	CAT1 (%)	Yield (%)	Sel. (%)	e.e. (%)
1	MeOH	5	77	78	16
2	CH_2Cl_2/MeOH 8/2	5	83	91	18
3	CH_3CN	5	64	88	4
4	CH_2Cl_2/CH_3CN 6/4	5	53	69	13
5	CH2Cl_2/H_2O 1/1	2	8	82	12

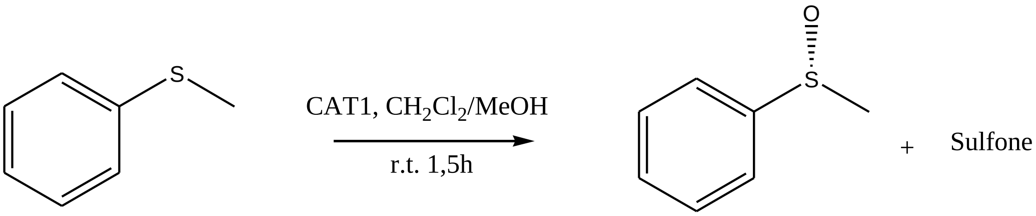
Reaction conditions: o.5 mmol of thioanisole, o.575 of H_2O_2 , 3 ml of solvent, 1.5 h, r.t.

Yield and selectivity were determined by ^{1}H NMR analysis using p-tert butyl phenol as a internal standard. Enantiomeric excess was detected by HPLC analysis.

Using a mixture CH_2Cl_2/MeOH 8/2 as solvent good a yield (83%) and selectivity (91%) were obtained,.but e.e. value was modest. The choise of the reaction solvent is restricted due to miscibility problems with aqueous H_2O_2. In order to increase the e.e. we decided to decrease the amount of protic solvent, but using a CH_2Cl_2/MeOH 9/1 ration hydrogen peroxide was not soluble. Acetonitrile was not a good solvent to obtain high asymmetric induction. (entry3, 5). The problem in bifasic system (entry5) was the compatibility of the catalyst in aqueous phase, and in this case the real solvent of the oxidation was water.

We decided to study another oxidant and other solvent in order to obtain higher e.e.

Scheme 8



1 2a

Table 2

Entry	Solvent	oxidant	Yield (%)	Sel (%)	e.e.
1	CH_2CL_2/MeOH 8/2	H_2O_2	83	91	18
2	CH_2CL_2/MeOH 95/5	UHP	72	85	15

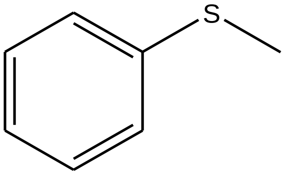
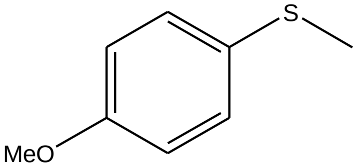
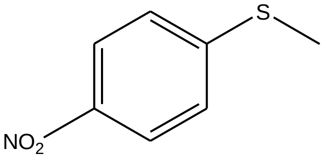
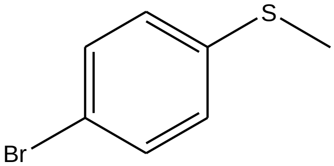
Reaction conditions: o.5 mmol of thioanisole, o.575 of H_2O_2 , 3 ml of solvent, 1.5 h, r.t.

Yield and selectively was determined by ^{1}HNMR analysis using p-tert butyl phenol as a internal standard. Enantiomeric excess was evaluated by HPLC analysis.

The use of UHP, complex between H_2O_2 and urea, was suggested by the good results reported for the chiral ionic liquid [9]. But with the supported catalyst CAT1 UHP did not gave better results.

We extended the reaction to other tioanisoles (Table 3):

Table 3

Entry	Substrate	Yield (%)	Sel (%)	e.e.
1	 2a	83	91	18
2	 2b	75	99	15
3	 2c	51	87	12
4	 2d	70	87	14

Reaction conditions: o.5 mmol of thioanisole, o.575 of H_2O_2 , 3 ml of solvent, 1.5 h, r.t.

Yield and selectively was determined by 1HNMR analysis using p-tert butyl phenol as a internal standard. Enantiomeric excess was detected by HPLC analysis.

We studied the effect of counter ion of the catalyst. In fact we used tetralkyl ammonium (CAT 2) or phosphonium salt (CAT 3) such a cation in order to modify the polarity of the catalyst.

Scheme 9

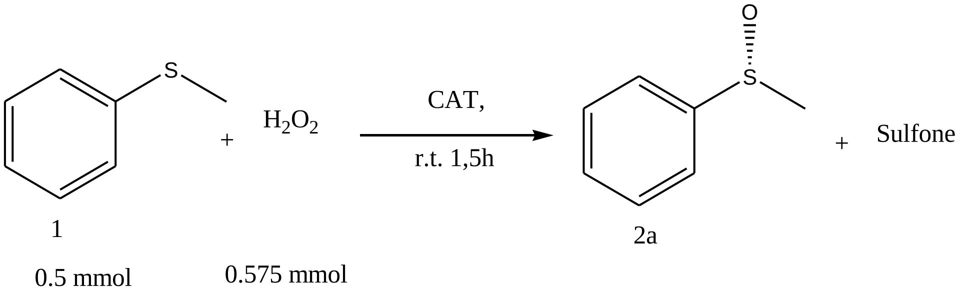


Table 4

Entry	Cat	Solvent	Yield (%)	Sel (%)	e.e. (%)
1	$K_2[WO_2$-$(L^*_2)]$	MeOH	75	82	30
2	CAT1	CH_2Cl_2/MeOH 8/2	83	91	18
3	CAT2	CH_2Cl_2/MeOH 8/2	65	95	11
4	CAT3	CH_2Cl_2/MeOH 8/2	22	99	10

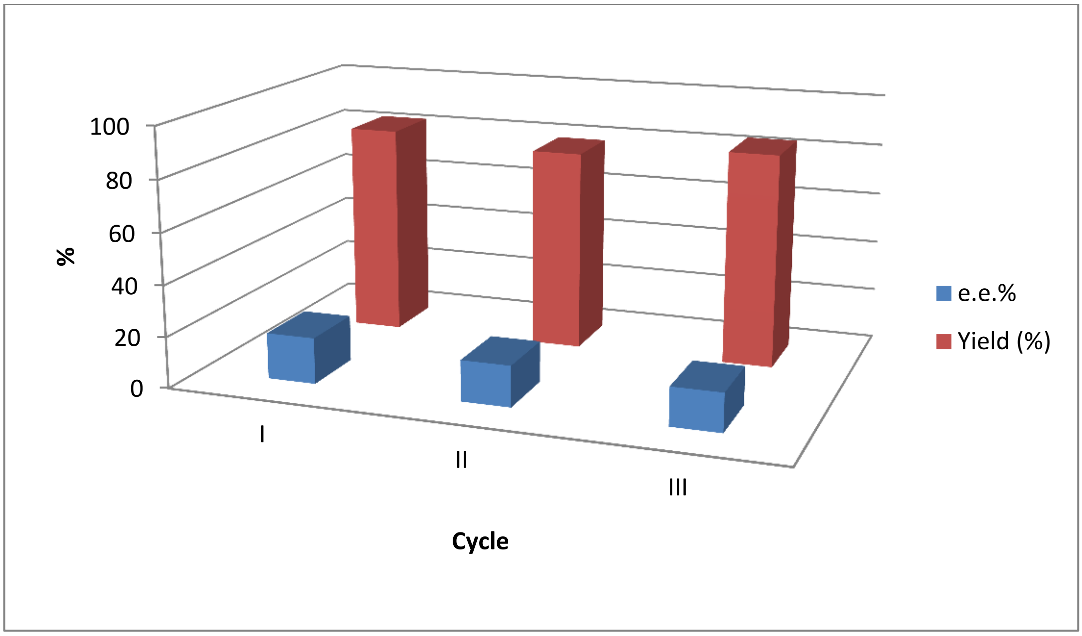
Reaction conditions: o.5 mmol of thioanisole, o.575 of H_2O_2 , 3 ml of solvent, 1.5 h, r.t.

Yield and selectivity were determined by ^{1}HNMR analysis using p-tert butyl phenol as a internal standard. Enantiomeric excess was evaluated by HPLC analysis.

With quaternary catalysts the yield decreased probably because the steric inderance of the counter ion cause the difficulty for the access of the substrate to the catalyst. The e.e. decrease too.

The last study was the catalyst recyclability. We use the CAT1 such a catalyst for the model reaction and the results are showed in figure 4

Figure 4



The figure 4 shows the perfect recyclability of the CAT1, but the e.e. slightly decreased (18-15%). To understand the reason, we analyzed the catalyst after three uses. The loading of W remain constant after the catalyst reuse. This explain the yield reproducibility during reuse. Probably the problem was the water adsorbed to the support that could modify the coordination around the metal.

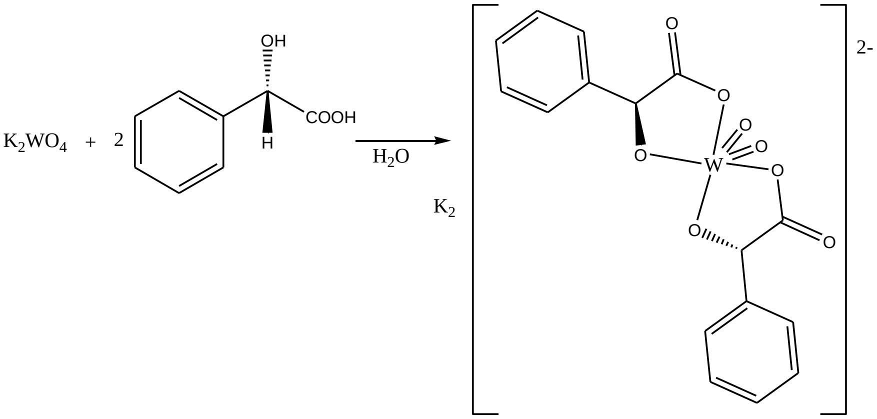
3.3 Experimental section

3.3.1 General informations

All materials purchased were used as such unless otherwise stated. Starting materials for catalyst preparation: silica gel KG60 for column chromatography (Merk) (size 0.040-0.063 mm; surface area 480-530 m^2/g; pore volume 0.74-0.84 cm^3/g). The starting material of alcohol oxidation were hydrogen peroxide (30% Carlo Erba), thioanisole (99% Aldrich), *p*-bromo thioanisole (99% Aldrich), *p*-nitro thioanisole (98% Aldrich), p-methoxy thioanisole (99% Aldrich).

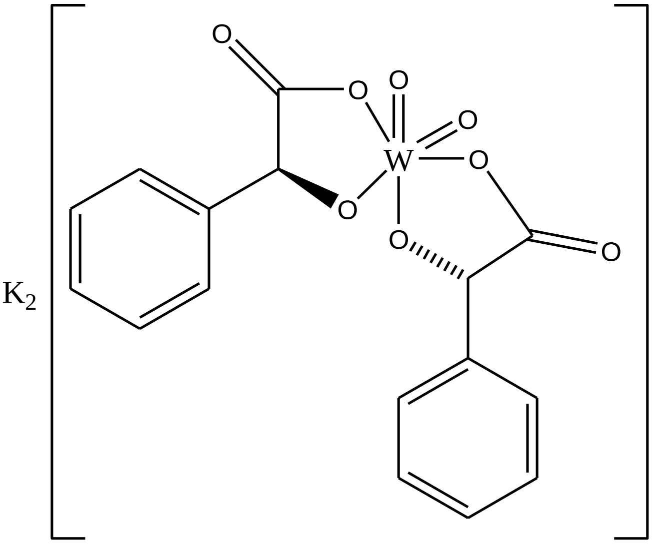
3.3.2 Catalyst preparation

3.3.2.1 Preparation of complex $K_2WO_2L_2$



In a one neck round bottom flask 8,5 mmol of potassium tungstate was dissolved in 7,5 ml of deionized water and successively 17 mmol of (S)-(+)-mandelic-acid were added. The reaction was carried out at 85°C overnight under magnetical stirrer. After then the solvent was removed under vacuum and the obtained solid was checked on NMR. This analysis show a residual of mandelic acid(3%).

Characterization of Complex $K_2[WO_2(S\text{-}MANDELATE)_2]$



^{1}H NMR (D_2O, 400 MHz)

δ(ppm)

5.95, 5.81 d, 1H, CH

7.36-7.64, 5H, Ph

^{13}C NMR (D_2O)

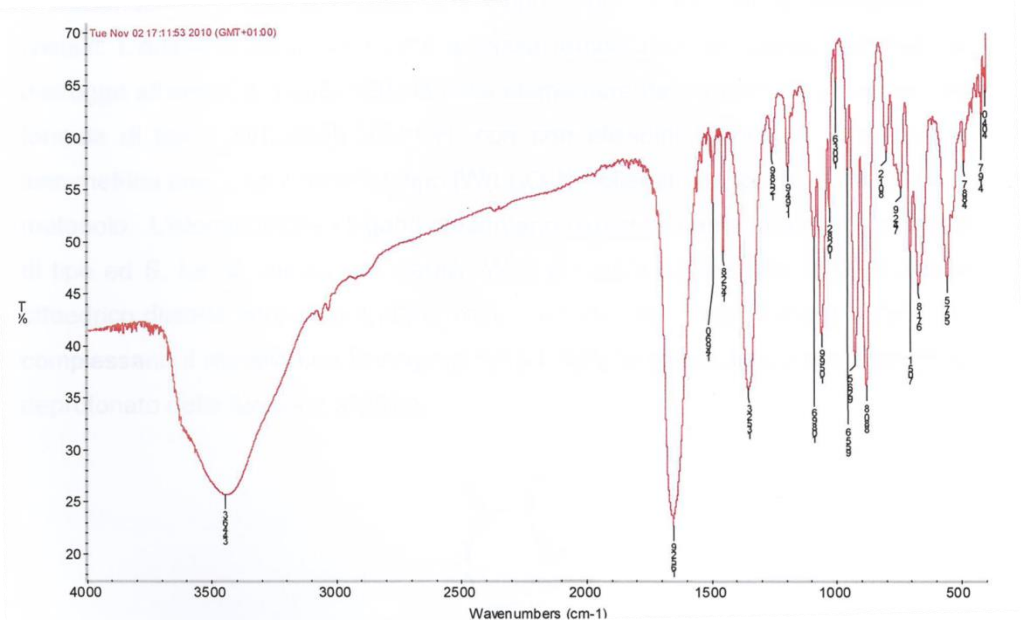
δ(ppm)

89.77, 88.49 ($HCO^{-)}$

143.3, 131.95, 131.73, 131.56, 130.95, 130.01 (Ph)

187.59 (C=O)

IR (KBr)

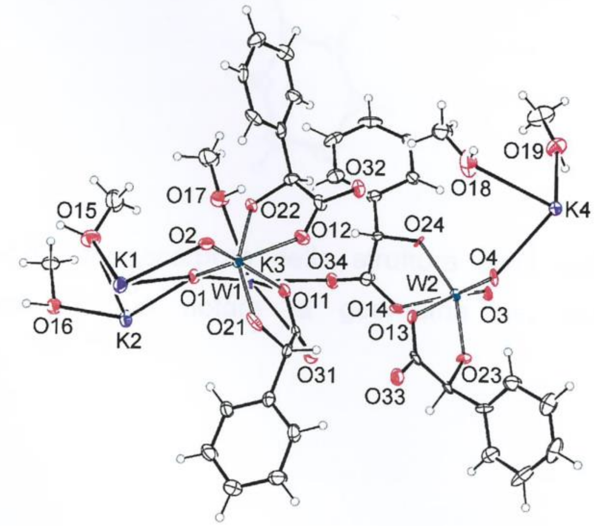


1653 cm^{-1} ν_{as} (C=O)

1352 cm^{-1} ν_{sim} (C=O)

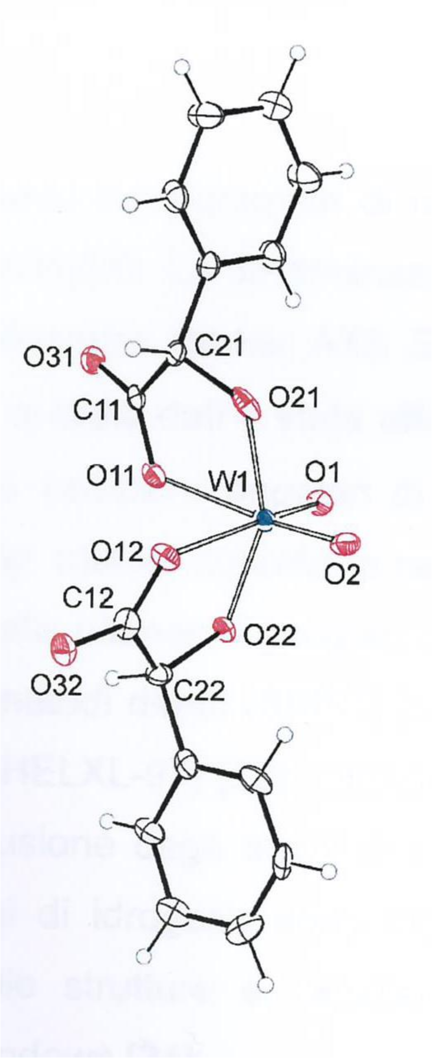
926 and 880 v (W=O)

XRD: (figure 5)



(figure 5) ORTEP drawing of $K_4\{[W(L)_2O_2]\}_2 \cdot 5CH_3OH$, with thermal ellipsoids at the 30% probability level. The asymmetric unit is represented by two $[W(L)_2O_2]^{2-}$ complex anions linked by K^+ and methanol molecules. The W atoms and the ligands exhibit the Λ and S configurations, respectively. The metal geometry of W(1) and W(2) is distorted octahedral with the two oxo group in *cis* position. The ligands behave as O,O bidentate with the oxygen atoms of the deprotonated carboxylic and alcoholic functions.

Figure 6



(figure 6) Coordination environment of the W(1) atom. Thermal ellipsoids at drawn at the 30% probability level. The complex molecule containing the W(2) atom exhibits a similar geometry. The metal geometry of W(1) and W(2) is distorted octahedral with the two oxo group in *cis* position. The ligands behave as O,O bidentate with the oxygen atoms of the deprotonated carboxylic and alcoholic functions

Figure 7

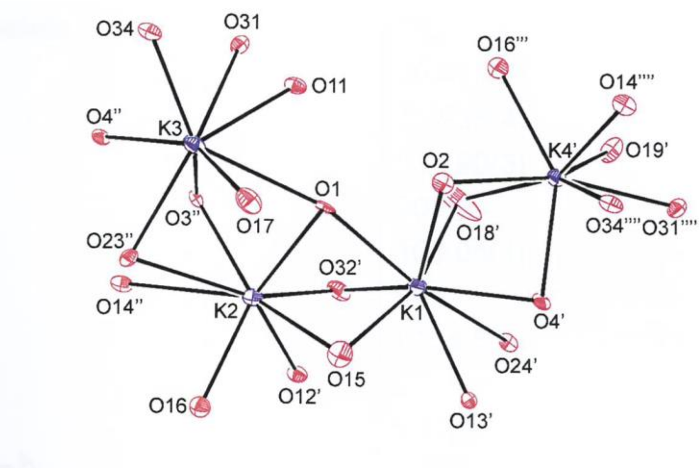


Figure 7: coordination sphere of cation K^+. Symmetry code: ‘-x, y+1/2, -z; ‘’=1-x,y+1/2,-z; ‘’’=-x, y-1/2, -z; ‘’’’=x-1, y,z.

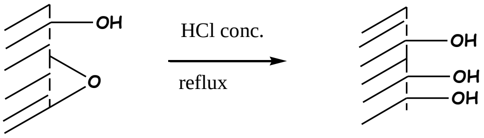
Empirical formula	C37 H44 K4 O21 W2
Formula weight	1348.82
Temperature	205(2) K
Wavelength	0.71073 A
Crystal system, space group	Monoclinic, P21
Unit cell dimensions	a = 10.489(2) A alpha = 90 deg.
b = 16.938(4) A	beta = 106.05(1) deg.
c = 13.790(3) A	gamma = 90 deg.
Volume	2354.5(9) A^3
Z, Calculated density	2, 1.903 Mg/m^3
Absorption coefficient	5.312 mm^-1

F(000)	1316
Crystal size	0.41 x 0.37 x 0.21 mm
Theta range for data collection	1.95 to 26.24 deg.
Limiting indices	-13<=h<=5, -13<=k<=19, -16<=l<=17
Reflections collected / unique	6363 / 5726 [R(int) = 0.0288]
Completeness to theta = 26.24	93.1 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.000 and 0.151
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5726 / 1 / 576
Goodness-of-fit on F^2	1.001
Final R indices [I>2sigma(I)]	R1 = 0.0531, wR2 = 0.1404
R indices (all data)	R1 = 0.0560, wR2 = 0.1429
Absolute structure parameter	0.004(14)
Largest diff. peak and hole	4.004 and -3.231 e.A^-3

$R1 = \Sigma||F_0|-|F_c||/\Sigma|F_0|$. $wR2 = [\Sigma[w(F_0^2-F_c^2)^2]/\Sigma[w(F_0^2)]]$

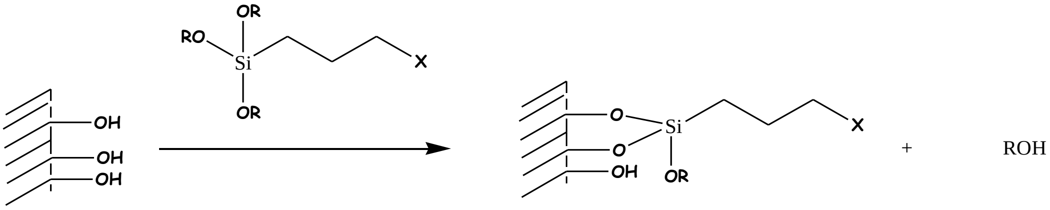
3.3.2.2 Synthesis of catalysts

Silica activation



In a 250 ml round bottom flask, 5 g of silica KG60 was added to 150 ml concentrated of HCl at 37%. The suspension was heated at reflux for 4 hours under vigorous stirring. The obtained silica was filtered off, washed to neutrality and dried under high vacuum and heated to 350 °C for 24 hours.

Silica functionalization

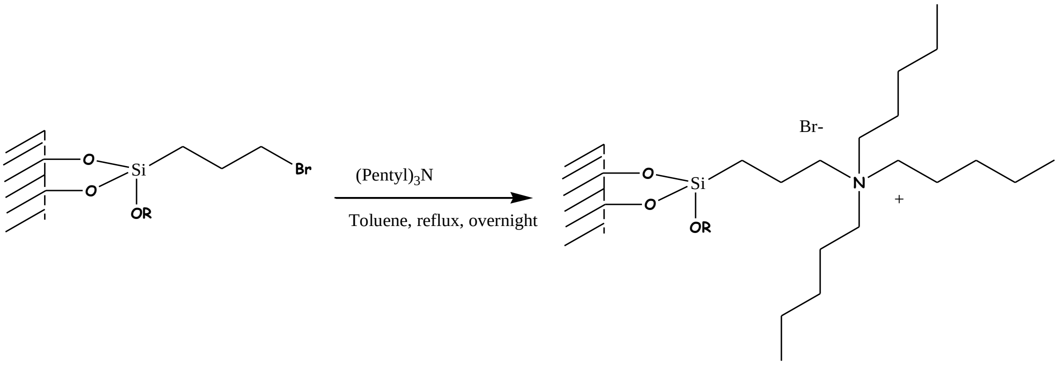


R= Me, X = Br

R = Et, X = NH_2

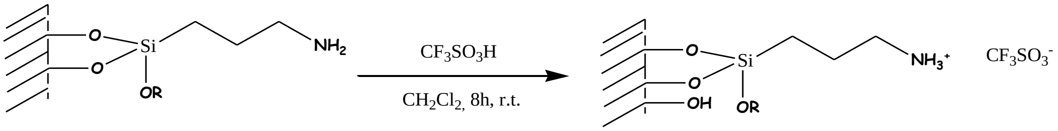
In a 100 ml round bottom flask 5 g of activated silica was suspended in30 ml of toluene, and 10 mmol of silane was added. The mixture was stirred and heated at reflux overnight. After then the solid was filtered by Buchner funnel and washed with 30 ml of toluene. The functionalized silica was dried under high vacuum and the loading of organic group was determined by elemental analysis (0.9 mmol/g).

Synthesis of quaternary ammonium salt



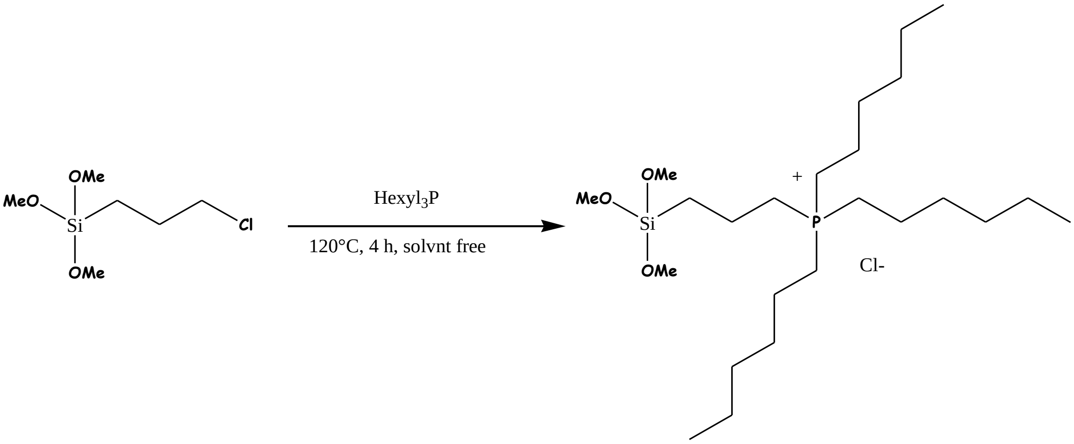
In a 100 ml round bottom flask 5 g of bromo-propylated silica was suspended in30 ml of toluene, and 50 mmol of tripentylamine was added.The mixture was stirred and heated at reflux overnight. After then the supported ammonium salt was filtered by Buchner funnel and washed with 30 ml of toluene. The functionalized silica was dried under high vacuum and the loading of organic group was determined by elemental analysis.

Synthesis of primary ammonium salt



In a 100 ml round bottom flask 5 g of amino-propylated silica was suspended in30 ml of toluene, and 10 mmol of trifluoromethansulfonic acid was added. The mixture was stirred for 8 hours a room temperature. After then the obtained solid was washed with 30 ml of dichloromethane. The supported primary ammonium salt functionalized silica was dried under high vacuum and the loading of organic group was determined by elemental analysis.

Preparation of anchored phosphonium salt



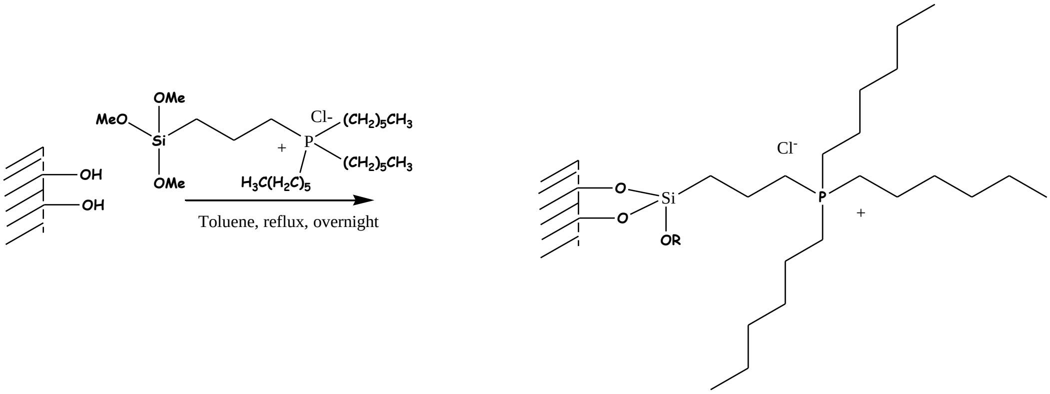
In 25 ml schlenk the 3-(chloropropyl) trymethoxy silane and trihexyl phosphine was added under nitrogen atmosphere. The mixture was heated in solvent free condition for 4 h. After the crude product was checked by ESI-MS.

ESI-MS

(Esi+) m/z : 450 (P4-Br$^-$); 551 (P4+Na$^+$); 567 (P4+K$^+$)

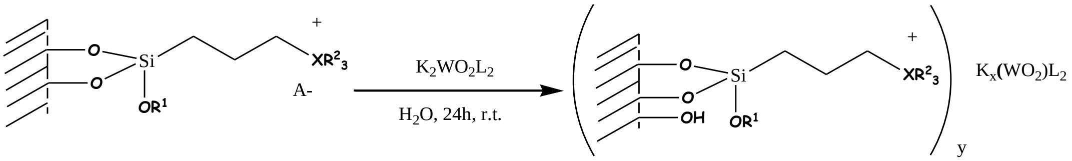
(Esi-) m/z : 607, 609, 611, 613, (M+2Br$^-$); 78,80(Br$^-$)

Sopporting of phosphonium salt



In a 50 ml round bottom flask 5 g of activated silica was suspended in30 ml of toluene, and 50 mmol of phosphonium salt was added.The mixture was stirred and heated at reflux overnight. After then the supported phosphonium salt was filtered by Buchner funnel and washed with 30 ml of toluene. The functionalized silica was dried under high vacuum and the loading of organic group was determined by elemental analysis.

Anion exchange



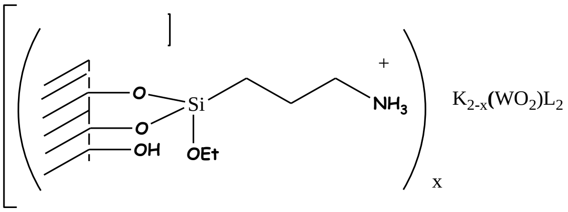
X= N, R^2= pentyl, R^1 = Me

X = N, R^2 = H, R^1 = Et

X= P, R_2= Hexyl, R^1 =Me

In 50 ml of round bottom flask, 5 g of supported ammonium or phosphonium salt was suspended in 50 ml of deionized water. The complex was added in ratio 1/1,15 respect to the mmol of supported salt, and the mixture was stirred for 24 h at r.t. After then the catalyst was washed with 30 ml of water, 30 ml of ethanol and 15 ml of diethyl ether in order to remove the water. The powder was drien under high vacuum and the loading of organic group was determined by elemental analysis. The W loading was determined by ICP-AES (0.36 mmol/g).

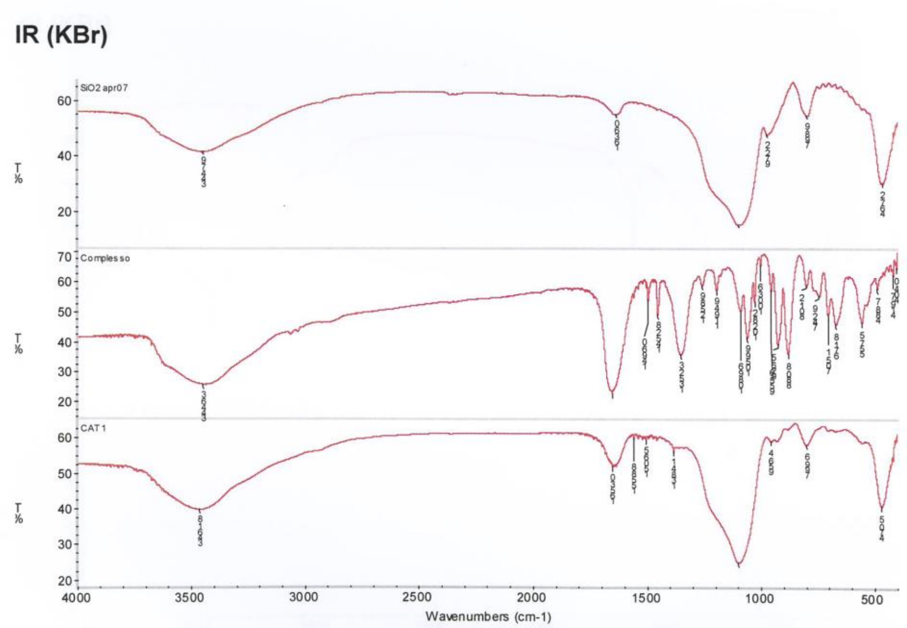
CAT 1



ICP-AES (W)

Loading W: 0,36 mmol/g

IR KBr

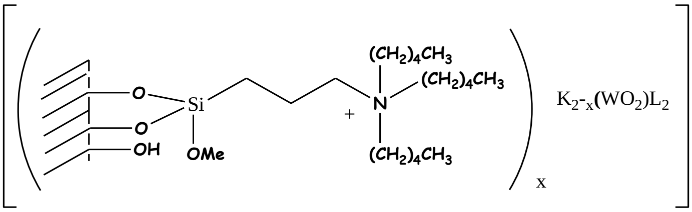


In order: IR of silica gel, IR of potassium complex, IR of CAT1

For CAT1

1653 cm^{-1} ν_{as} (C=O)

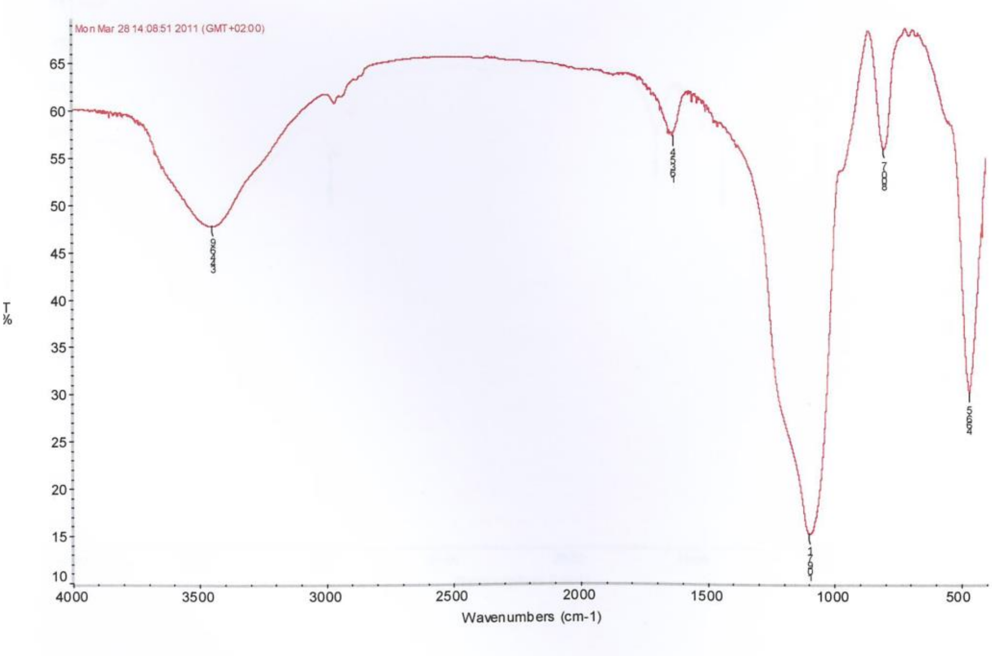
CAT 2



ICP-AES (W)

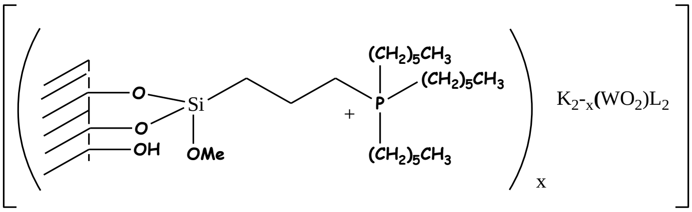
Loading W: 0,11 mmol/g

IR (KBr)



1654 cm^{-1} ν_{as} (C=O)

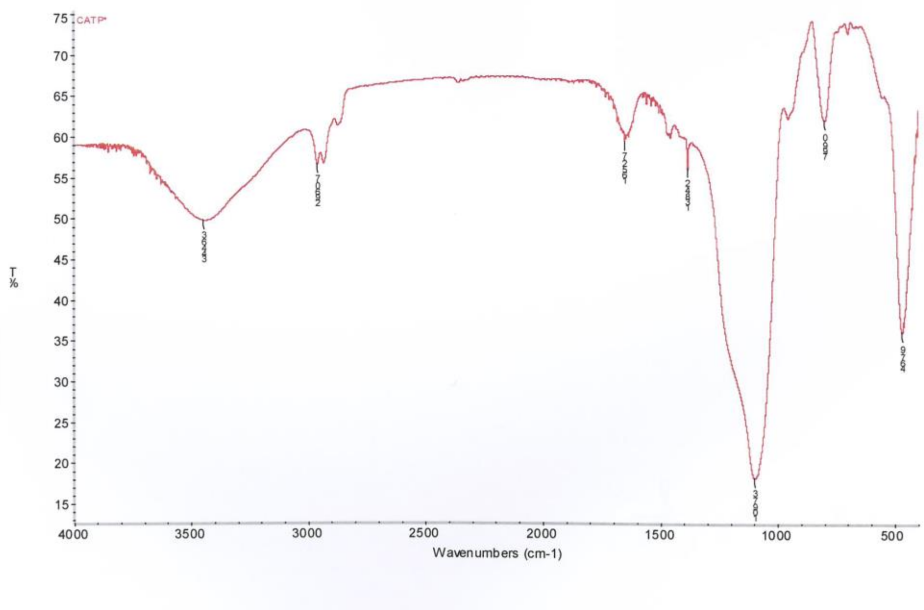
CAT 3



ICP-AES (W)

Loading W: 0,16 mmol/g

IR (KBr)



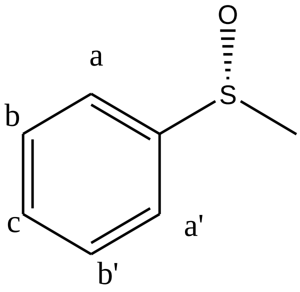
1652 cm^{-1} v_{as} (C=O)

3.3.3 Reaction procedure for sulfide oxidation

Typical oxidation of methyl phenyl sulfide with hydrogen peroxide as model reaction was performed using a 25 ml round bottomed flask. The selected catalyst (the amount of which was evaluated on the basis of loading values for introducing the specified amount of chiral tungstate) and 30% H_2O_2 (0,575 mmol, 0,058 ml) were added to the specified solvent (3 ml). The thioanisole was added (0.06 ml 0.5 mmol) after 5 minutes.

The reaction was stirred for 1,5 h. The progress of oxidation reaction was monitored by GC and TLC. After 1,5 h, the mixture was filtered on Buchner funnel. The solid catalyst was washed with 5 ml of methanol and recovered. The solution of crude reaction was examined by GC ; $Na_2S_2O_3$ was added to the solution to consume the excess of hydrogen peroxide and filtered off. The GC analysis 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*-butyl phenol as a internal standard. The model reaction of methyl phenyl sulfide was monitored between 30 and 90 min. Samples were obtained periodically, and the course of reaction was followed by GC using 4-*tert*-butyl phenol as a internal standard added to the samples. The same methodology was followed in the synthetic application to different sulfides and using the different catalysts. The product was purified by preparative silica plates, using hexane/ethyl acetate 1/1 as eluants. The pure product was analyzed by HPLC Agilent 1100 series with chiral column Chiralcel OD-H using hexane/isopropanol as eluants, in order to determine the enantiomeric excess. For determine the enantiomeric purity the pure products was analyzed on a spettrometer Perkin-elmer model 341 with Na and Hg lamp with polarimetre Glan-Taylor.

Characterization of methyl phenyl sulfoxide (2a)

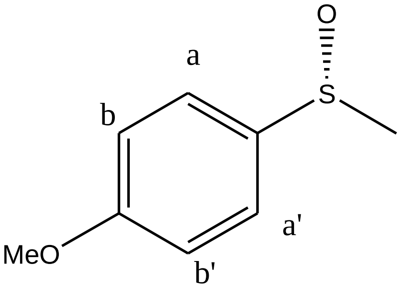


Transparent oil at 25°C, m.w. 140.21, C_7H_8S.

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

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

Characterization of 4-methoxy-methyl phenyl sulfoxide (2b)

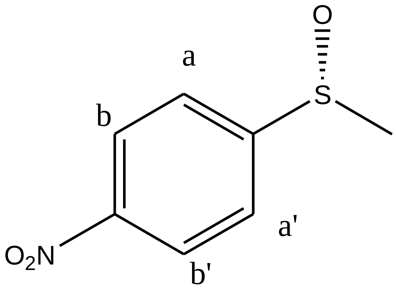


Transparent oil, m.w. 170.23, $C_8H_{10}S$.

1H NMR (CDCl3, 300 MHz) 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%)

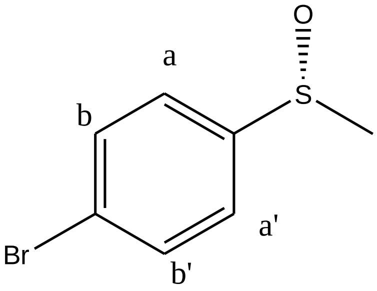
Characterization of 4-nitro-methyl phenyl sulfoxide (2c)



Transparent oil, m.w. 185, $C_7H_7SNO_2$.

1H NMR (CDCl3, 300 MHz) δ(ppm): 2,83 s, 3H (CH3); 7.87 d, 2H (Hb and Hb') ½ para system, J=8.8; 8.19 d, 2H (Ha and Ha') ½ para system, J=8,8

Characterization of 4-bromo-methyl phenyl sulfoxide (2d)



Transparent oil, m.w. 220, C_7H_7SBr.

1H NMR (CDCl3, 300 MHz) δ(ppm): 2,76 s, 3H (CH3); 7.52 d, 2H (Hb and Hb') ½ para system, J=8.8; 7.53 d, 2H (Ha and Ha') ½ para system, J=8,8

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C

Chapter 4

Heterogenized basic ionic liquid as a catalyst for nitro-Michael reaction and synthesis of 4-H-pyrans

4.1 Introduction

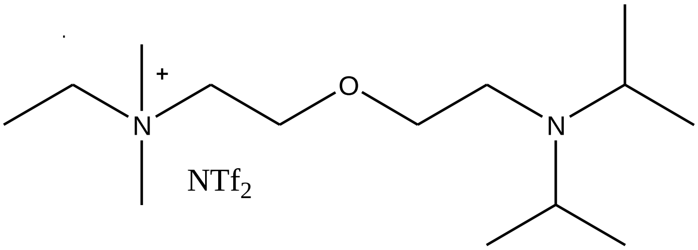
Environmental concern associated with chemical synthesis has posed stringent and compelling demands for greener processes, and development of cost-effective and environmentally benign catalytic systems has become one of main themes of contemporary synthetic chemistry. In this context, development of highly active and selective catalyst is of prime importance. Heterogeneous catalysis is preferred in industrial processes to homogeneous catalysis because the extraction of the product and recovery of the catalyst is relatively easier. However mass or heat transfer limitations in the solid catalyst may lead to decreased activity. Furthermore, lower chemo- and stereoselectivities are often obtained compared to homogeneous catalysis. Obviously, a catalytic system, which makes to secure the advantages of both heterogeneous and homogeneous 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 two decades, 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 this liquids environmentally attractive alternative 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 application of ILs in various type of catalytic and synthetic reactions. There are many review in the literature which give comprehensive overviews about the topics related to ILs such as synthesis in ILs, catalysis with ILs, and no-solvent utilization of ILs [1]. Numerous chemical reactions, such as polymerization, hydrogenations, regioselctive alkylations, Friedel-Crafts reactions, dimerizations of alkenes, Diels-Alder reactions, Michael reactions, cross-coupling reactions and some enzymatic reactions can be carried out in ionic liquid or using ionic liquid as catalyst [2].

However, in homogeneous catalysis there are many problems when ILs as used as reaction media: a large amount of ILs are required, (ILs are still expensive), there are problem for the extraction of the product from the ionic phase, , the viscosity of ILs caused diffusion problem of substrate, for optimal use of ILs maximal purity are request moreover the biodegradability of ILs and their toxicity is not clear. Another approach is to use ionic liquid such a catalyst of reaction: in fact is possible to realize a new classes of ionic liquid with a functional group tethered to the cation or anion. The incorporation of this functionally should imbue the ionic liquid with a capacity to behave not only as a reaction medium but also as a reagent or catalyst in some reaction or processes [20].

A particular promising concept is represented by supported ionic liquids. This involves coating a solid support with a thin layer of ionic liquid. The solid support locks the ionic liquid into position and stabilizes a large interphase area between the ionic liquid and the reactant phase. As each component (ionic liquid, catalyst, additives and support) can be chosen independently, concept allows assembling a catalyst readly 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 amount, while their efficiencies are as good as for the utilizations of bulk solvent.

Many basic transformations such as esterification, Knoevenagel condensations, Michael additions are carried out under basic conditions, some using aqueous base and other strong soluble organic bases such as Guanidine. The base is not usually recovered, producing either salt or organic waste. Recently, guanidine basic ionic liquid have been developed and employed as catalyst in the aldol [4], Henry [5], and Knoevenagel condensation[6] reaction without any loss activity after 15 runs. Recently Hardacre and co-workers [7]reported a new class of ionic liquid derivates of the non-nucleophilic Hunig'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 (NTf_2).



These ionic liquid were employed for promoting Knoevenagel reaction. That basic ionic liquid (BIL) was reported to have similar activity to Hunig's base. Carring the reaction without solvent 89% of conversion has been reported after 20 minutes of reaction between benzaldehyde and ethyl cyaneacetate. But many problems were found in the product extraction. Using cyclohexene as solvent the products were extracted with a facile method but only aldehyde soluble in cyclohexene could be used. Hardacre's group tested the catalyst adsorbed on silica but the product was obtained in 70% of yield and there was release of active phase in solution.

In collaboration with Seddon's group of QUILL centre of Belfast, we planned 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 catalytic activity of the obtained supported ionic liquid was studied in Michael reactions. Coniugate addition of carbon nucleophiles to electron poor alkenes is of great importance among the large body of synthetic processes devoted to carbon-carbon bond formation.[9] This process is usually referred as Michael addition, and ever since the number of carbanionic species that have been used for conjugate has considerably increasing to includes various enolate systems and strong nucleophilic species such as organometallic reagents.

Nitroalkanes are a valuable source of stabilized carbanions since the high electron-withdrawing power of the nitro group provides an outstanding enhancement of the hydrogen acidity at the α position [10-13]. The final product of nitro-Michael reaction can be transformed thank to the versatility of nitro group because it is simple to remove, to reduce to primary amine, to convert a carbonyl group [14]. We also tested the catalyst in Michael reaction to obtain 4-*H*-benzopyrans In recent years, 4H-benzopyran and its derivates have attracted strong interest due to their useful biological and pharmacological properties, such as anticoagulant, spasmolytic, diuretic, anticancer, antianaphylactin agents. Substituted 4H-pyrans constitute a structural unit of a series of natural products [15].

Recent works has been reported using DBU[17], TBAB[18] or heteropoly acids[19]. Water has been applied to organic reactions as a solvent, and it has several advantages such as its low costs, safety, non-polluting nature and operational simplicity. Ten years ago we discovered that the Knoevenagel condensation between malononitrile and aldehydes can be performed in water without catalyst or additive. To date, many more organic reactions have been carried out in water.

We also tested the catalyst in a one pot reaction to obtain the same products.

4.2 Results and discussion

4.2.1 Catalyst preparation

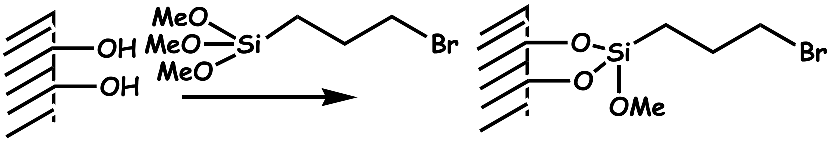
In a previous PhD thesis the anchorage of the basic ionic liquid on silica support has been realized. To compare the activity of the anchored catalyst with the results reported in the literature for the ionic liquid in homogeneous phase or adsorbed on silica, NTf_2 was introduced as anion. The basic ionic liquid bound to silica revealed to give better results in Knoevenagel condensation, than those published

In the present work we studied the effect of the anion on the activity.

The preparation of the catalyst involves two main steps: a) silica functionalization anchoring the spacer 3 bromopropyl silane group to surface silanols; b) nucleofilic substitution between the supported propyl bromine and the tertiary amine and subsequent anion exchange.

a) Anchorage of bromo-propyl group:

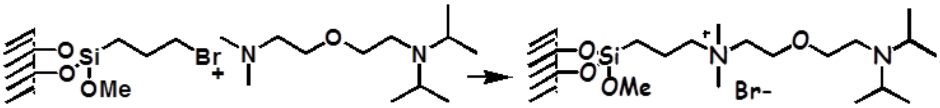
scheme 1



Loading 0.9mmol/g

b) Nucleophilic substitution with pre-synthetized diamine:

Scheme 2



SIL Br

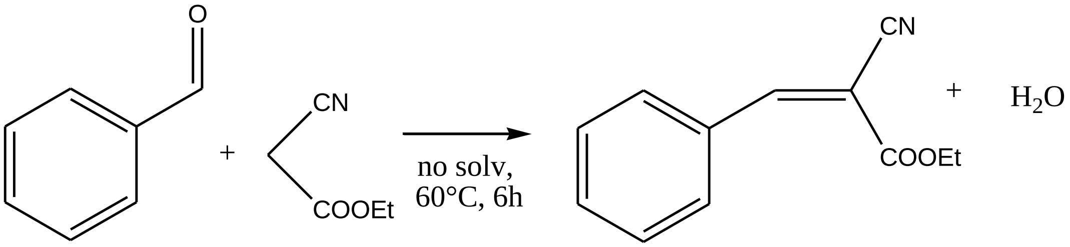
Loading 0.64-0.75 mmol/g

In the first step (3-bromopropyl)trimethoxysilane was condensed with silica silanols by refluxing in toluene under stirring. The cooled functionalized silica was filtered off, washed and dried under high vacuum to give the surface-bond alkyl bromide groups with a loading of 0.9 mmol/g. 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 amine, in refluxing toluene for 24 h, affording the corresponding supported quaternary ammonium salt. After cooling, the solid was filtered off and throughly washed with toluene, then dried at 60°C under high vacuum. Then the solid was washed in continuous with hot acetonitrile in a Soxhlet apparatus.

The amount of bromide ions present on the functionalized silica at this step was determined by titrations according to the Volhard method, giving a bromide loading of 0,62 mmol/g.

The catalyst activity was tested in Knoevenagel condensation of benzaldehyde and ethyl cyanoacetate, following the procedure previously employed, that is operating in solvent-free conditions, at 60°C (scheme 3)

Scheme 3

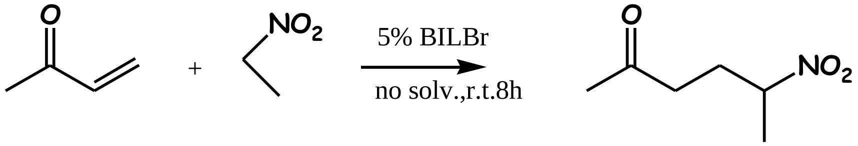


In this condition the product was obtained in 97% yield and 99% selectivity. Moreover we examined the recyclability of the catalyst and we obtained perfect recyclability in four cycle without any loss of activity. These results indicated that it is not necessary to exchange the Br^- with NTf_2^- to obtain a very active catalyst. Thus we decided to explore the activity of this basic supported catalyst (BIL-Br) in other reactions. In particular, the reactions examined were the coniugate addition of nitro-alkanes to electronwithdrawing olefins and the addition of ethyl acetoacetate to pre-sythetized electronpoor olefins for synthesis of 4-H-pyrans.

4.2.2 Catalytic test

4.2.2.1 Nitro Michael addition

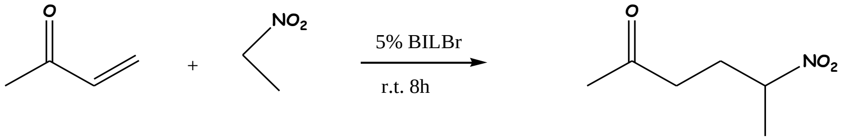
The activity of SIL Br in promoting C-C bond formation reactions was studied as well in nitro-Michael addition. The reaction between nitroethane and methyl vinil ketone was chosen as model (scheme 4)



1 2 3a

Indeed preliminary reaction carried out using 1:1 ratio of reagents 1 and 2, 5% mol of SIL Br for 8 h at room temperature gave high conversion but unsatisfactory selectivity mainly due to of double attack. Then we carried out the reaction using a slight excess of nitroalkane (5 eq.) without any solvent and we obtained the product in high yield (81 %) and selectivity 99%.

Scheme 5

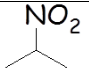
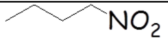
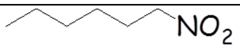


1 2 3a 81%

The obtained crude reaction was treated with ethyl acetate and the catalyst was recovered by filtration and reused. The purification of the obtained product was performed with a simple distillation in low vacuum, in order to eliminate the excess of nitroalkane and the unreacted methyl vinyl ketone.

We examined the general applicability of the reaction to other nitroalkanes and the results are shown in table 1.

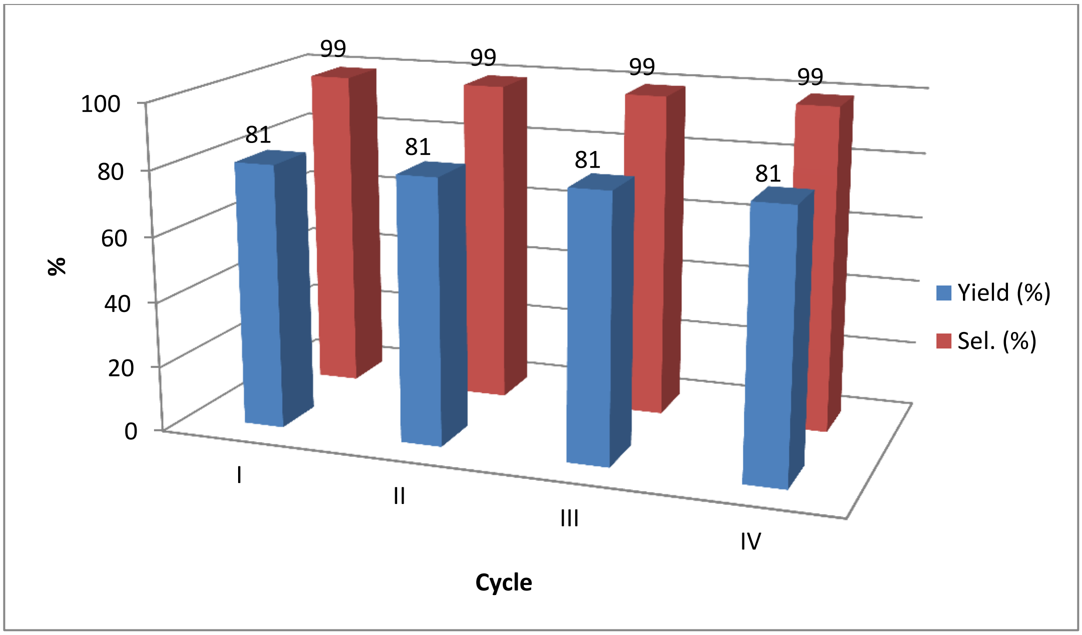
Table 1

Entry	Nitroalkane (2)	Yield (%)	Sel. (%)
1		81 3a	99
2		83 3b	99
3		90 3c	99
4		90 3d	99

Reaction condition: room temperature 1/2 ratio= 1:5; yield and conversion were determined by GC analysis with internal standard.

The last study concerned the catalyst recyclability in the model reaction under the optimized conditions (5% SIL, solvent less, r.t., ration methyl vinil ketone:nitroalkane 1:5). The results reported in figure 1 clearly show the recyclability of the catalyst, which can be used for at least four times without any loss of yield (81%), and selectivity (99%)

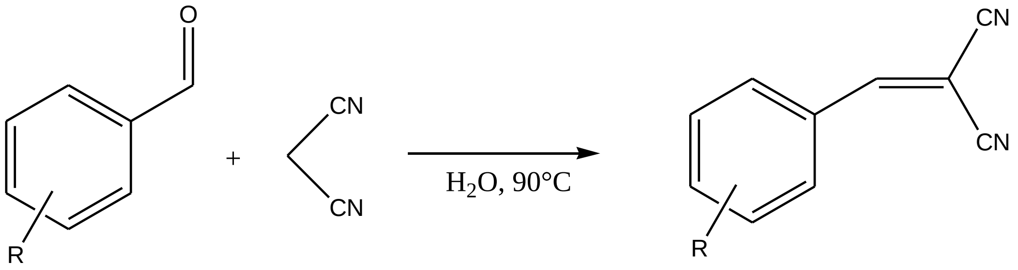
Fig. 1 (recyclability of the catalyst BILBr in model reaction



4.2.2.2 Synthesis of 4-H-pyrans

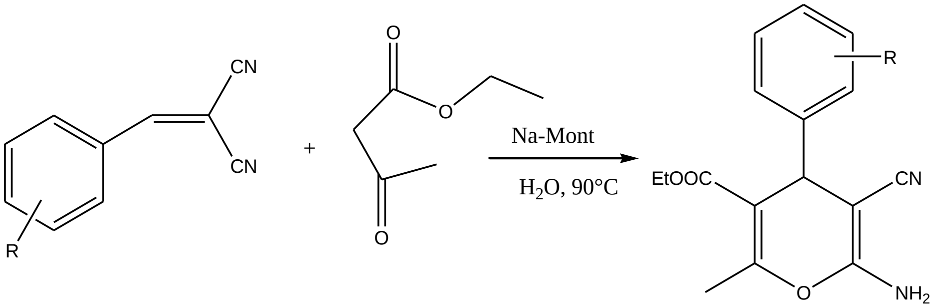
We tested the catalyst in another Michael reaction affording 4-H-pyrans, important compounds which showed a biological activity and activity such as erbicide and fungicide.[15]. In a previous study performed in our laboratory, this reaction was carried out using Na-Montmorillonite as catalyst following or two steps synthesis (scheme 6 and 7) or the one-pot synthesis (scheme 8)

Scheme 6



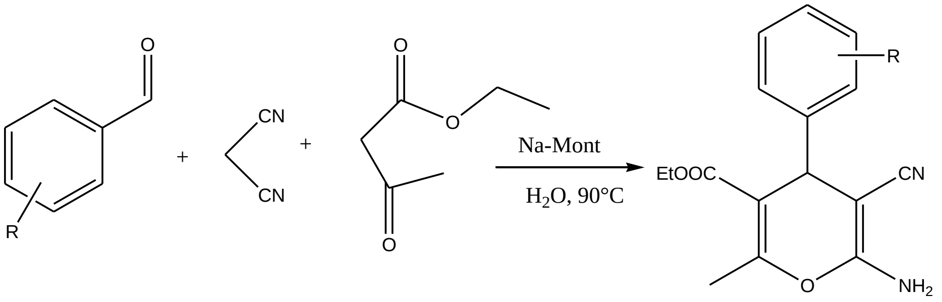
This reaction was accomplished without catalyst, according with our published procedure.[16]

Scheme 7



One-pot synthesis

Scheme 8

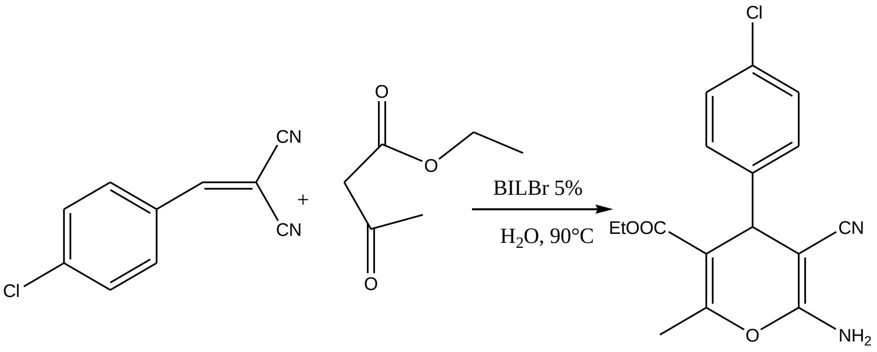


In the two-step synthesis the product was obtained in 50-97% depending on the R subsituent, meanwhile in one pot synthesis the yields were lower.

We tested the supported catalyst BILBr in this synthesis examining the Michael addition.

The preliminary study was performed using water as solvent, 90°C, for 2 hours. The results are showed in scheme 9:

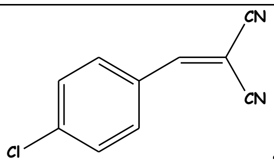
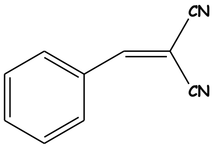
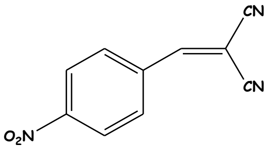
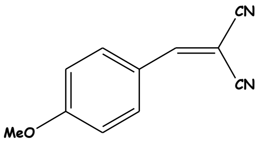
Scheme 9



72%

After two hours the product was obtained in 72% yield, and the selectively was quantitative since only the reagent and the product were detected. In order to increase the yield the reaction was carried out for 3 hours and the product was obtained in 97% yield. We extend the reaction to other alkenes:

Table 2

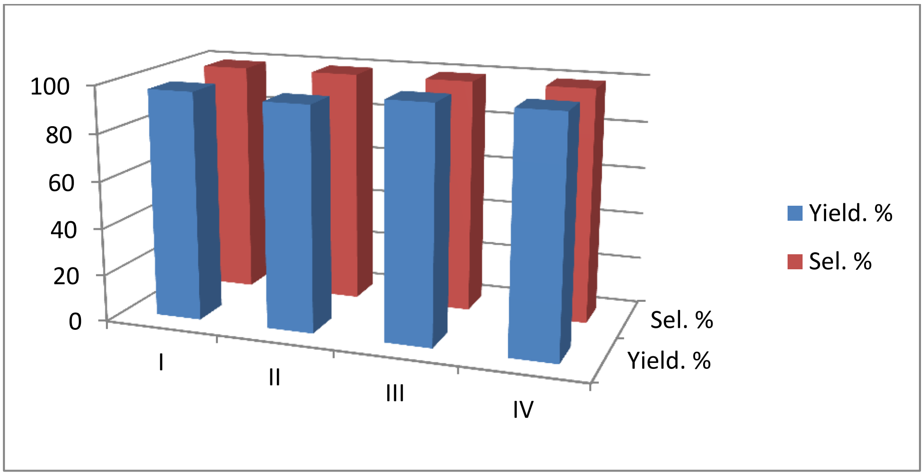
Entry	R	Yield 4 (%)	Sel. 4 (%)
1	 4a	97	99
2	 4b	65	99
3	 4c	97	99
4	 4d	35	99

Reaction: 5% of BILBr in H_2O, 3h, yield and sel. was determined by ^{1}H-NMR analysis using t-butyl phenol as standard

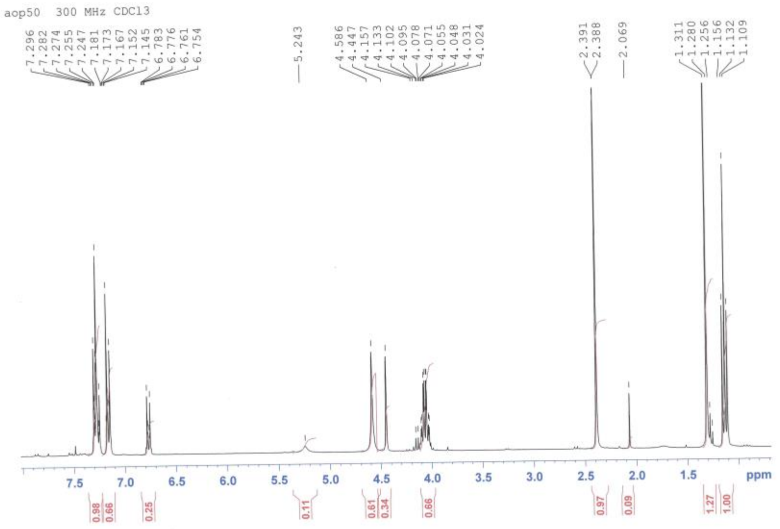
Using different substrate the yield was from good to very high depending on the with presence of electron withdrawing or electron donor group.

We tested the recyclability of the catalyst as shown in figure 2:

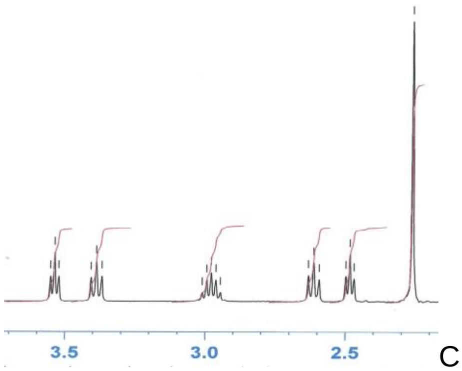
Fig. 2



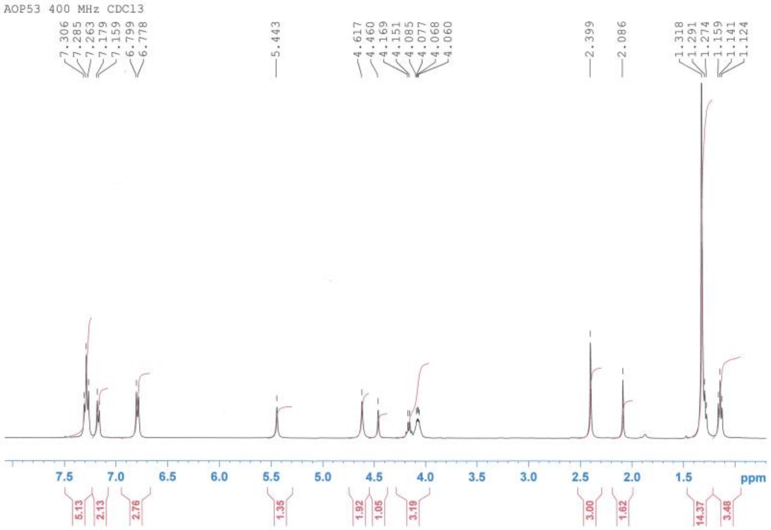
In at least four cycle the catalyst was able to promote the reaction without loss of activity. In figure 3 the ^{1}H-NMR spectra of the crude reaction after 4 h first cycle (A) and the fourth are showed (B):


aop50 300 MHz CDCl3
7.296
7.282
7.274
7.255
7.247
7.181
7.173
7.167
7.152
7.145
6.783
6.776
6.761
6.754
5.243
4.586
4.447
4.157
4.133
4.102
4.095
4.078
4.071
4.055
4.048
4.031
4.024
2.391
2.388
2.069
1.311
1.280
1.256
1.156
1.132
1.109
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm
0.98
0.66
0.25
0.11
0.61
0.34
0.66
0.97
0.09
1.27
1.00

A


3.5
3.0
2.5

C

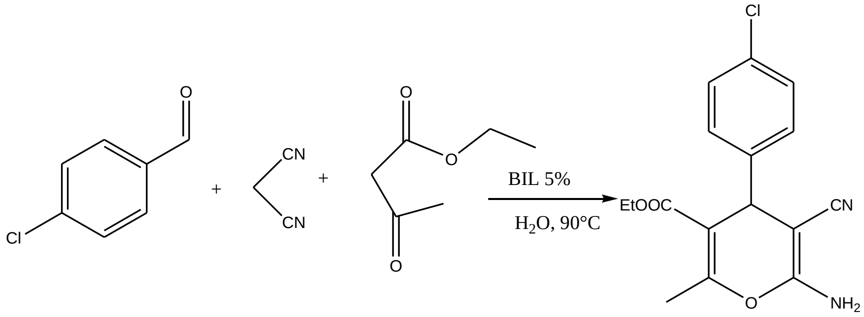

AOP53 400 MHz CDCl3
7.306
7.285
7.263
7.179
7.159
6.799
6.778
5.443
4.617
4.460
4.169
4.151
4.085
4.077
4.068
4.060
2.399
2.086
1.318
1.291
1.274
1.159
1.141
1.124
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm
5.13
2.13
2.76
1.35
1.92
1.05
3.19
3.00
1.62
14.37
3.48

B

The ^{1}H-NMR spectra of the crude reactions revealed the absence of the catalyst's signals (fig C), evidencing the robustness of the catalyst since any leaching does not occur. Further it is possible to observe the complete conversion and selectivity of the reaction since only the product signals (except signals of the standard) are present.

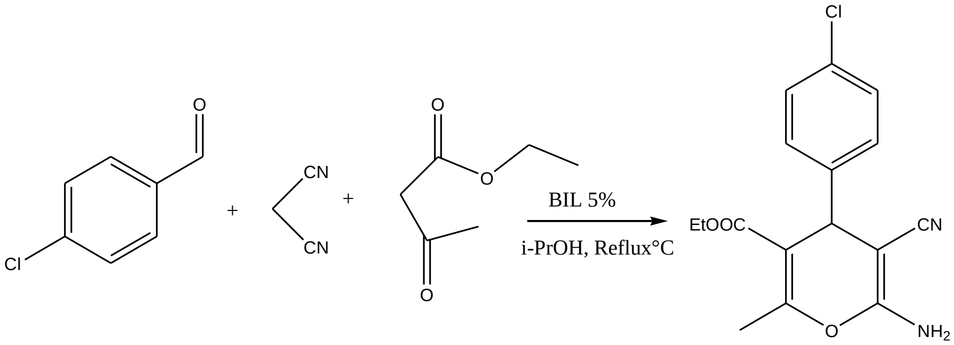
Taking into account that reduction of the reaction steps increases the environmental acceptability of a process, we studied the three component reaction, (scheme 10).

Scheme 10



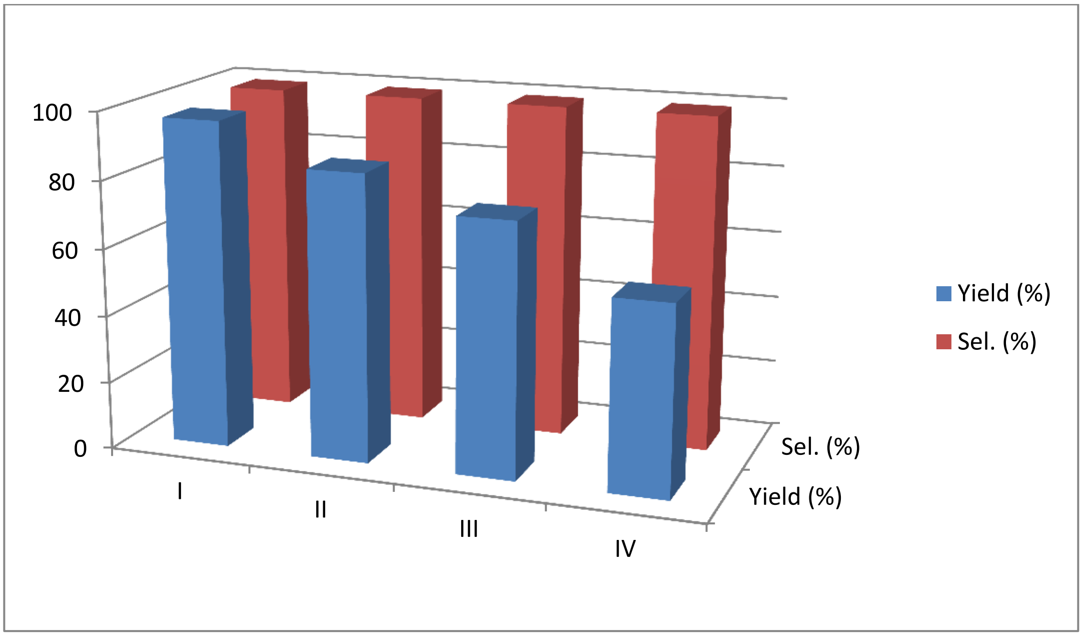
The reaction was first carried out in water at 90°C. In these conditions the product was obtained in lower yield (<60%) even if the aldehyde reacted completely with malononitrile. Indeed, the product was accompanied by large amount of unreacted alkene intermediate, that is not soluble in water. The core of the aggregates is not accessible to the reagent and catalyst, therefore unreactive. Then the reaction was carried out in i-PrOH, a green solvent who was able to dissolve both the intermediate and the product:

Scheme 11



The reaction was carried out for 6 hours, in refluxing i-PrOH with 5% of catalyst. In this conditions the product was obtained in 97% yield. We tested the catalyst recyclability also in this one-pot condition (figure 4):

Fig 4



Progressive yield decrease was observed. Further studies are required to optimize this three component reaction, such as to find a way to well disperse the intermediate in water.

4.3 Experimental section

4.3.1 General informations

All materials purchased were used as such unless otherwise stated. Starting materials for catalyst preparation: silica gel KG60 for column chromatography (Merk) (size 0.040-0.063 mm; surface area 480-530 m^2/g; pore volume 0.74-0.84 cm^3/g). The starting material for catalyst preparation were 3-(bromopropyl)-trimethoxy silane (97% Aldrich), and diamine that was prepared following the reported literature procedure[7]. For two step synthesis, the staring material were benzaldehyde (99% Aldrich), p-chloro-benzaldehyde (97% Fluka), p-nitrobenzaldehyde (97% Fluka), p-methoxybenzaldehyde (98% Fluka), malononitrile (Aldrich), ethyl acetoacetate (Riedel DeHaen).

For synthesis of γ-nitroalkane the starting material were: methyl vinil ketone (97% Aldrich), nitroethane (Fluka 98%), 2-nitropropane (Aldrich 98%), nitrobutane (Aldrich 99%), nitrohexane (Aldrich 99%)

4.3.2Catalyst preparation

Heterogeneous catalyst preparation

I step: silica functionalization

In a 100 ml round bottom flask 5g of silica was heated to reflux in 30 ml of toluene two hours in order to remove the adsorbed water. After changing the condenser, (3-bromopropyl) trimethoxysilane (2,43g, 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, (2x25 ml each); then it was dried under high vacuum at 60 °C for 3 hours to give the surface bond bromopropylic group. The loading of the organic moieties was determined by elemental analysis (-0,9 mmol/g), the bromide group was determined by Volhard method (0,83 mmol/g).

II step: anchoring of the Hunig's base

The bromopropylated silica (2,5g, 0,9 mmog/g loading) was treated with the depicted tertiary amine (2,16g 10 mmol) in 30 ml of refluxing toluene for 24 hours, affording the correspondent supported quaternary ammonium bromide. After cooling, the solid was filtered on a Buchner funnel and carefully washed with toluene (5x20 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 was determined by titration according to the method described by Volhard. Starting from a 0,30 g f immobilized salt in 10 ml of ethanol, 10 ml of 0,1 N $AgNO_3$ solution, and 5 ml of HNO_3 6N were added, and the suspension was stirred in the dark room for 0,5 h at room temperature. Then the solid was filtered off, and the excess of $AgNO_3$ was titrated with ammonium thiocyanate, giving a bromide loading of 0,62 mmol/g.

4.3.3 General procedure for nitro-Michael addition

In two ml round bottom flask the catalyst was added and stirred with 5 equivalents of nitroalkane. After 5 minutes the methyl vinil ketone (1 equivalent) was added and the reaction was stirred for 8 h at room temperature. At the end, the catalyst was filtered off with a Buchner funnel and washed with 15 ml of ethyl acetate. The yield was calculated with internal standard method by GC analysis. The pure product was obtained with distillation under vacuum by the residue reagents.

4.3.4 General procedure for synthesis of 4-H-pyrans

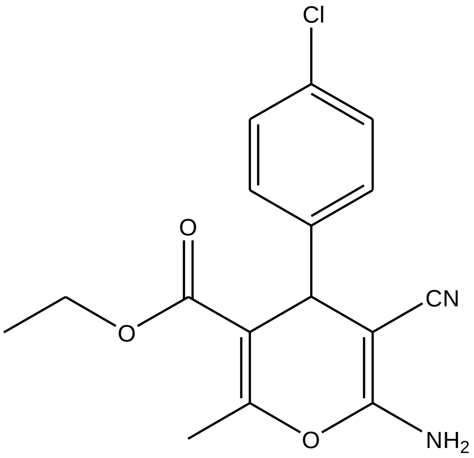
In a two ml round bottom flask the catalyst was dissolved in 2 ml of distilled water and the two reagents (1 mmol) was added. The suspension was vigorous stirred for 3 hours at 90°C. After then the solution was cooled at room temperature and methanol was added in order to dissolve the water insoluble product. The catalyst was filtered by Buchner funnel and washed with 20 ml of methanol. NMR was used to calculate the yield and t-butyl-phenol was used as internal standard. The pure product was obtained with chromatographic separation using silica plates with 8/2 hexane/acetate mixture preparative eluted.

One pot synthesis of 4-H-pyrans

In 25 ml round bottom flask the catalyst was suspended in i-PrOH and the reagents were added in order: malononitrile (1 mmol), aldehyde 1 mmol), ethyl acetoacetate (1 mmol). The reaction was stirred for 6 hours. At the end of reaction the crude was cooled and filtered by Buchner funnel and the catalyst was washed with 15 ml of ethyl acetate.

The product was purified by silica plates using ethyl acetate/hexane 2/8 mixture preparative.

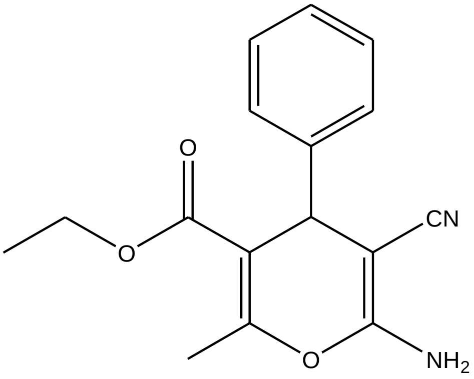
Characterization of 6-amino-5-cyano-4-(4-chlorophenyl)-2-ethyl-4H-pyrane-3-carboxylic acid methyl ester (4a)



White solid. m.w. 318.76

^{1}H NMR ($CDCl_3$, 400 MHz), δ(ppm): 7.26, d, 2H, (Hb, Hb'), 7.15, d, 2H, (Ha, Ha'), 4.55, br, s,1H (NH_2) 4.42, br s, (1H H-4pyran), 4.06, dq, (½ CH_2 AB system)J = 10.9 and 7.1 MHz,2.58, 4.01, dq, (½ CH_2 AB system) J = 10.9 and 7.1 MHz,2.36, s, 3H, (CH_3), 1.10, t, (CH_3-CH_2).

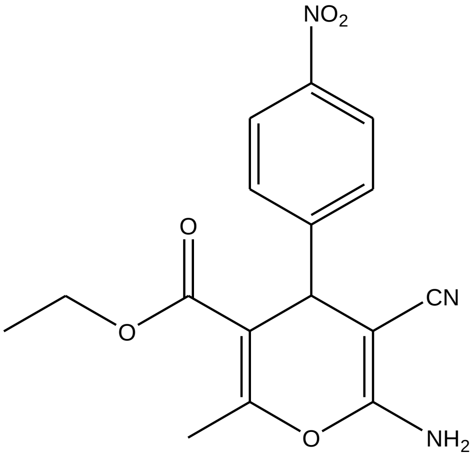
Characterization of 6-amino-5-cyano-4-phenyl-2-methyl-4H-pyrane-3-carboxylic acid ethyl ester (4b)



White solid. m.w. 318.76

^{1}H NMR ($CDCl_3$, 400 MHz), δ(ppm): 7.30-7.34, m, 2H, (H2, H6), 7.18-7.27, m, 3H, (H3’, H4’, H5’), 4.54, br, s,1H (NH_2) 4.44, br s, (1H H-4pyran), 4.06, dq, (½ CH_2 AB system)J = 10.9 and 7.1 MHz,2.58, 4.00, dq, (½ CH_2 AB system) J = 10.9 and 7.1 MHz,2.36, s, 3H, (CH_3), 1.08, t, (CH_3-CH_2).

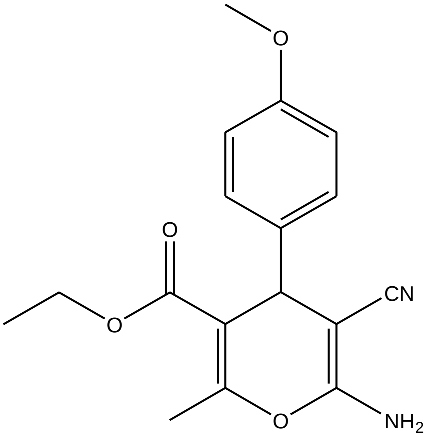
Characterization of 6-amino-5-cyano-4-(4-nitrophenyl)-2-methyl-4H-pyrane-3-carboxylic acid ethyl ester (4c)



Yellow solid. m.w. 329.31

^{1}H NMR ($CDCl_3$, 400 MHz), δ(ppm): 7.37, d, 2H, (Hb, Hb’), 7.26, d, 2H, (Ha, Ha’), 4.64, br, s,1H (NH_2) 4.55, br s, (1H H-4pyran), 4.03, dq, (½ CH_2 AB system)J = 10.9 and 7.1 MHz,2.58, 4.01, dq, (½ CH_2 AB system) J = 10.9 and 7.1 MHz,2.41, s, 3H, (CH_3), 1.10, t, (CH_3-CH_2).

Characterization of 6-amino-5-cyano-4-(4-methoxyphenyl)-2-methyl-4H-pyrane-3-carboxylic acid ethyl ester (4d)



White-yellow solid. m.w. 314.34
^{1}H NMR ($CDCl_3$, 400 MHz), δ(ppm): 7.10, d, 2H, (Hb, Hb'), 6.81, d, 2H, (Ha, Ha'), 4.38, br, s,1H (NH_2) 4.05, br s, (1H H-4pyran), 4.00, dq, (½ CH_2 AB system)J = 10.9 and 7.1 MHz,2.58, 4.01, dq, (½ CH_2 AB system) J = 10.9 and 7.1 MHz, 3.76, s, £H (OCH_3), 2.33, s, 3H, (CH_3), 1.11, t, (CH_3-CH_2).

The identity of the produced γ-nitroketones were attribute by comparison of spectra with authentic samples or with data reported in the literature.

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Chapter 5

Synthesis of a new basic ionic liquid for a multicomponent reaction

In collaboration with Prof. Kenneth R. Seddon[a] and Dr Nimal Gunaratne[a]

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5.1 Introduction

This chapter present the work performed during my stage at QUILL center of the Queen University of Belfast.

It deals with the preparation and use of task specific ionic liquid in homogeneous catalysis.

In recent years, significant progress has been made in the application of room temperature ionic liquids in catalytic processes. Ionic liquids (ILs) are organic salts which melt below ~100°C.

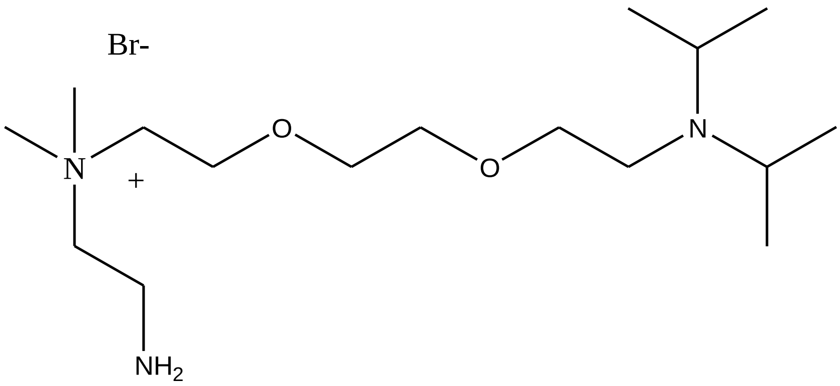
In the past ILs were introduced and received great attention as the solvents for their advantages respect to volatile organic solvents (VOCs):

1) A wide liquid range of about 300°C with a melting point around room temperature
2) A wide range of materials (including inorganic, organic and even polymeric materials) are soluble in ionic liquids
3) Excellent Lewis/Bronsted acidity
4) High polarity
5) Negligible vapor pressure
6) Potential to be reused and recycled.

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 stillexpensive; (ii) separation of IL by the crude reaction is very difficult; (iii) using IL as a solvent 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) diffusion problems for the viscosity of ILs; generally the ILs must be pure, without any impurity for their application.

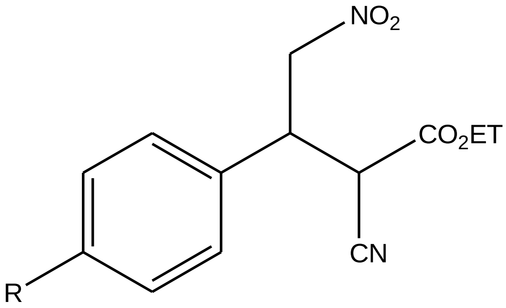
A more recent field of application of some ILs is the catalysis.

In collaboration with Prof. Seddon's group at QUILL centre of Queen's University of Belfast, we have study the synthesis and application of a new IL with two basic functional group (figure 1). Indeed it contains a tertiary amine, the Hunig's base, and a primary amine:



The choose of the anion and cation was decided in order to obtain a IL active as catalyst and with the feature to be easily separated by extraction: the counter anion is Br^-, and the cation contains two atoms of oxygen in addition to the two atoms of nitrogen. This kind of ionic liquid is hydrophilic and it is insoluble in the major parts of organic solvent. In chapter 4 we presented the catalytic activity of supported basic ionic liquid (SILBr) in heterogeneous phase to promote both Knoevenagel and Michel reaction. The activity of IL containing Hunig's base in the Knoevenagel reaction was published [1]. In that work the products was extracted by the crude reaction with cyclohexene, but in the case of aromatic aldehyde the extraction was very difficult. Some products were distilled but in some cases the distillation was difficult. The aim of the present work is to combine the activity of two different amine linked in the same IL to improve the activity of previous basic IL and to make easier the catalyst separation.

As model reaction we choose a three component reaction involving aromatic aldehyde, activated methylene compound and a nitroalkane. The product expected by subsequent Knoevenagel and Michael additions presents multifunctional groups, which can be transformed make it a usefull intermediate for fine chemicals and pharmaceutical compounds [2].



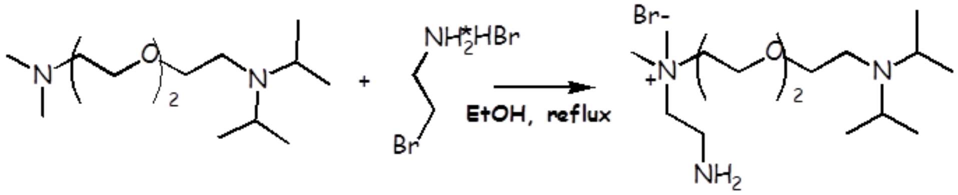
In the literature this kind of reaction was catalyzed by triethylamine [2], and the product was obtained in modest yield (47%). Michaud et al. [3] reported this reaction using various organic bases under microwaves irradiations and the results were not good.

Other strategy reported was to carrying out the reaction in two separate steps, the Knoevenagel and Michael reaction, with intermediate isolation and purification.

Our approach is to perform a one-pot reaction using the IL aiming to obtain a selective reaction without by-products and a facile separation of IL from the crude reaction.

5.2 Results and discussion

To synthetize this new ionic liquid we a followed procedure reported in literature[4] Scheme 1



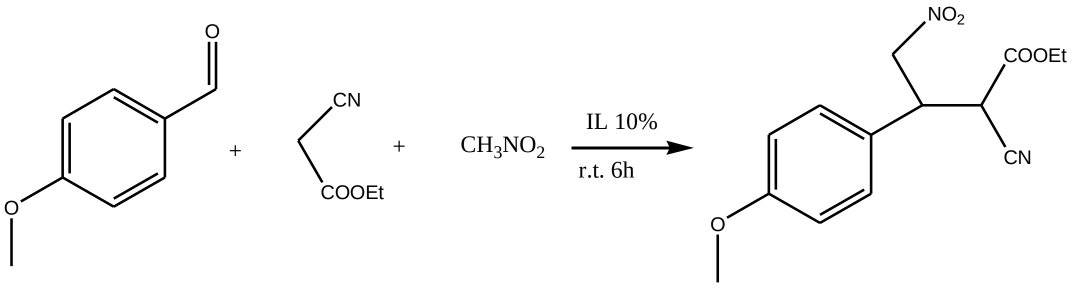
The diamine was synthetized with a published [1]. This reaction was carried out in EtOH at reflux overnight. Then the obtained ionic liquid was treated with a small portion of KOH in order to eliminate the HBr following a reported procedure [4].

The ionic liquid was dried overnight at 60°C degree under high vacuum and after that was ready to use.

5.2.2Catalytic test

To test the activity of this basic IL we studied the reaction between p-methoxybenzaldehyde, ethyl cynoacetate and nitromethane. The reaction was carried out at room temperature, for 6 hours, using 10% in mol of catalyst and a small excess of nitromethane.

Scheme 2:

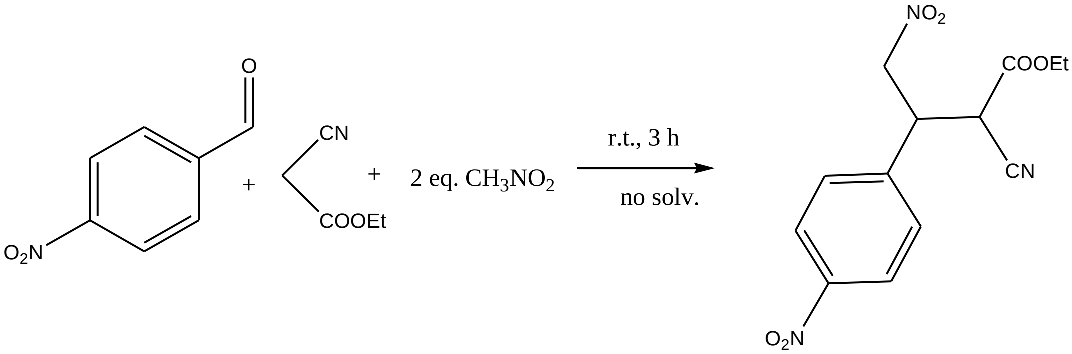


1a 2 3 4a (93%)

The product was obtained in high yield (93%) and complete selectively. The reactants were added in this order: nitromethane, activated methylene compound and aldehyde at last. The excess of nitromethane helps the mixing of the mixture. In fact the Knoevenagel reaction occurs in only 20 minutes, and the viscosity of the crude reaction increases. The treatment of the crude was a simple extraction with diethyl ether and water: in the organic phase we recovered the product and in the aqueous phase the ionic liquid. We checked the organic phase, after solvent removal, with ^{1}H NMR analysis and only the presence of the product was detected. Both the possible diastereoisomers were observed in similar amount. It is important to note the complete absence of the signals of the ionic liquid evidencing that the catalyst was completely removed. The aqueous phase was examined at ^{1}H-NMR and only the ionic liquid signals were detected.

We tested the catalytic activity using benzaldehydes of different reactivity i.e. with electronwithdrawing or electrondonor substituent.

Scheme 3



1b 2 3 4b 93%

In the case of 4-nitrobenzaldehyde, the same high yield (93%) was reached in shorter time (3 h).

We extend the applicability of the reaction to other aromatic aldehydes.

Scheme 4

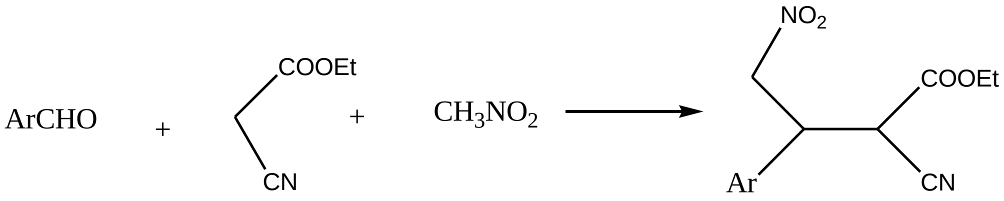
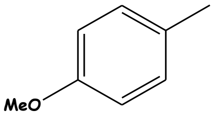
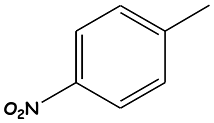
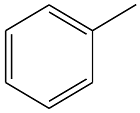
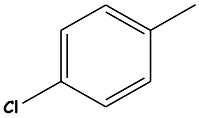
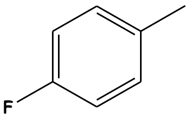


Table 1

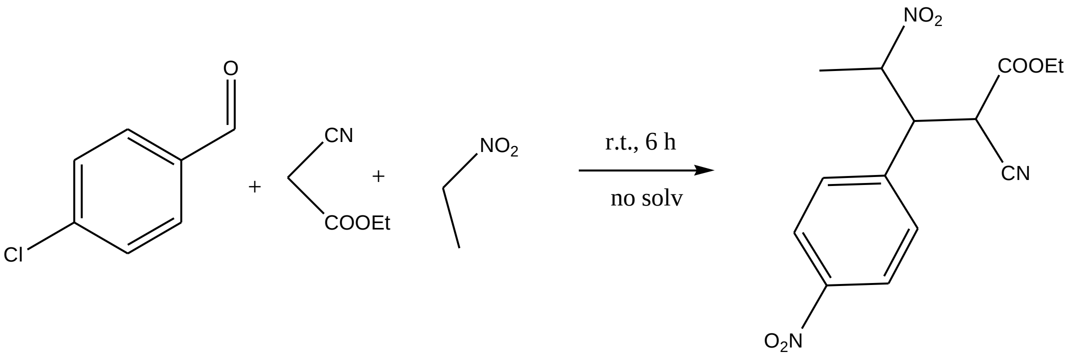
Entry	Ar	Time (h)	BIL(%)	Yield (%)	Sel. (%)
1	 3a	6	10	93	99
2	 4b	3	10	93	99
3	 4c°	6	10	90	99
4	 4d	6	10	90	99
5	 4e	6	10	91	99

Yield and selectivity are obtaining isolating the products with silica column using hexane/acetate 9/1 as eluant

In all the cases the conversion of aldehyde and activated methylene compound was complete, and the only by-product observed was the unreacted Knoevenagel intermediate. Another important aspect was the selectivity: in fact the addition of nitromethane to aldehyde or double nitromethane addition were not detected. The only by-product is the alkene formed by Knoevenagel, evidencing that first occurs the reaction with cyanoacetate and then the reaction with nitromethane.

We examined the possibility to extend the reaction to others nitroalkanes. As reported in scheme 4 nitroethane was employed:

Scheme 4



1d 2 5 6 70%

Carrying out the reaction in slight excess of nitroethane the IL catalyst afforded the expected product in good yield (70%) and complete selectivity.

This compound has three stereogenic centres, thus four diastereoisomers appears in ^{1}H-NMR spectra.

Using the BIL reported in literature [1] in the same conditions the reaction was less selective and the yield was lower.

Studies are in progress to extend the applicability of the catalyst to others activate methylene compounds.

5.3 Experimental section

5.3.1General informations

All materials purchased were used as such unless otherwise stated. Starting materials for catalyst preparation: silica gel KG60 for column chromatography (Merk) (size 0.040-0.063 mm; surface area 480-530 m^2/g; pore volume 0.74-0.84 cm^3/g). The starting material for catalyst preparation were bromo ethanamine (98% Aldrich) and diamine that prepared following the reported literature procedure[7]. For one pot synthesis, the staring material were benzaldehyde (99% Aldrich), p-chloro-benzaldehyde (97% Fluka), p-nitrobenzaldehyde (97% Fluka), p-methoxybenzaldehyde (98% Fluka), p-fluoro benzaldehyde (98% Aldrich), nitromethane (Aldrich 95%), nitroethane (Fluka 98%),

General procedure

In 10 ml round bottom flask the reagents were introduced in this order: catalyst (10% in mol), nitrocompound (6 mmol), aldehyde (3 mmol) and ethyl cyanoacetate (3 mmol). The reaction was carried out for 6 hours (in case of p-nitro benzaldehyde 3 hours). After then dichoromethane was added and the catalyst was extracted with water. The product was purified by column cromatographic using hexane/ethyl acetate 9/1 as eluant.

The identity of the produced products were attribute by comparison of spectra with authentic samples or with data reported in the literature.

References

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[2] Applied Catalysis A: General 445-446 (2012) 128-132.

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[4] E. D. Bates, R D. Mayton, I. Ntai, and J H. Davis, Jr. VOL. 124, N°. 6, 2002 9 J. AM. CHEM. SOC

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Thanks to my family for all the help, and thanks to my love Daniela.

Curriculum Vitae

Mega Antonio was born in 1984 in Gallipoli (LE).
He received his Bachelor degree in 2007 in industrial Chemistry and his Master degree in Science and Technologies of Industrial Chemistry. During his master project he worked under the supervision of Prof Catellani on synthesis of Phanatridines with the catalytic system Pd-norbonene.
In December 2009 he had win a fellowship under the supervision of Prof. Franca Bigi working on the development of selective and eco-efficient processes promoted by heterogeneous catalysts.
Since January 2011 he 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.
In 2013 he work at QUILL (Queen's University Ionic Liquid Laboratories) in Belfast UK. Under the supervision of Prof. Ken Seddon and Dr. Nimal Gunaratne, he worked on the preparation and use of a new basic ionic liquid employed in a multicomponent reaction.