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Ph.D. Thesis in Chemical Science

HETEROGENEOUS BASIC CATALYSTS FOR FINE CHEMICAL PRODUCTION: FROM TRADITIONAL BATCH TO CONTINUOUS FLOW SYSTEM

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A tutte le persone che mi vogliono bene

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CHAPTER 1

Selective Nitroaldol, Michael reactions catalyzed by organic bases supported on silica under batch conditions.

1a. Heterogeneous Catalysis.

1a.1 General Introduction.

Nowadays, increasing demanding in environmental legislation, public and corporate pressures have forced chemists to develop cleaner technologies[1]. This need will provide the study for new catalysts and new environmental friendly catalytic processes[2,3,4]. The possibility to easily recover and reuse catalysts is very important as well because very frequently the component most expensive in a chemical reaction is the catalyst and not the reagents or the products[5].

The ideal catalyst[6] should follow some requirements:

1) produce a infinite amount of product, without encountering deactivation conditions or poisoning under reaction conditions; 2) effect a rapid reaction without external eating or cooling; 3) have no need to work in inert atmosphere; 3) be readily available and inexpensive; 4) be not toxic and non hazardous, 5) not require activation or initiation step.

In recent years two preferential tendencies have been developed: polymer-supported catalysts and inorganic oxides heterogenised catalysts[7,8]. In particular the general area of crosslinked polymer supports showed an explosive growth connected with the development of new macroporous materials, that are characterized by a rigid porous matrix that persists even in the dry state[9]. These polymers are typically produced as spherical beads by a suspension polymerization process, which is based on the mixture of cross-linking monomer, inert diluent and the porogen. Otherwise it has been reported the preparation of “molded” porous materials with high characteristic for catalysis and asymmetric catalysis too. On the other hand inorganic oxides show several advantages, such as more mechanical stability, easier handling and a wider range of solvents that can be used. Furthermore the zeolites, that present regular crystalline structure with high specific surface and periodic regular cavities and pores of molecular dimensions, are the support of election for tuning activities and selectivities. The support acts like many small molecular reactors and modifies the characteristics of free catalysts increasing the steric constraints and enhancing the local concentrations of reagents near the surface where the reaction takes place.

In the class of solid catalysts, particularly interesting are the supported homogeneous catalysts as they combine the potential versatility and selectivity of homogeneous catalysts with the practical advantages of solid materials, such as easy separation of the catalyst from the reaction medium, recovery and use of a large variety of reaction conditions.

However the creation of the ideal supported catalyst is related to the need of new technologies and new supports since they have an important role in the outcome of the process.

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

The support surface and the catalyst site surrounding can influence the extent of the reaction.

The focus of this dissertation regards the immobilization of organic base onto solid supports for the production of fine chemical in batch and continuous flow set up.

1a.2 Solid base catalysts for the synthesis of fine chemicals.

Although catalysis by solid acids has received much attention due to its importance in petroleum refining and petrochemical processes, relatively few studies have focused on catalysis by bases[10]; base catalysts, however, play a decisive role in a number of reactions essential for fine-chemical synthesis. Solid-base catalysts have many advantages over liquid bases in many respects. The state of the art of basic catalysts up to the mid of the 1990s has been presented in the excellent reviews by Hattori[11] and Barthomeuf[12] which also contributed to a much understanding of the "basicity" of zeolitic materials.

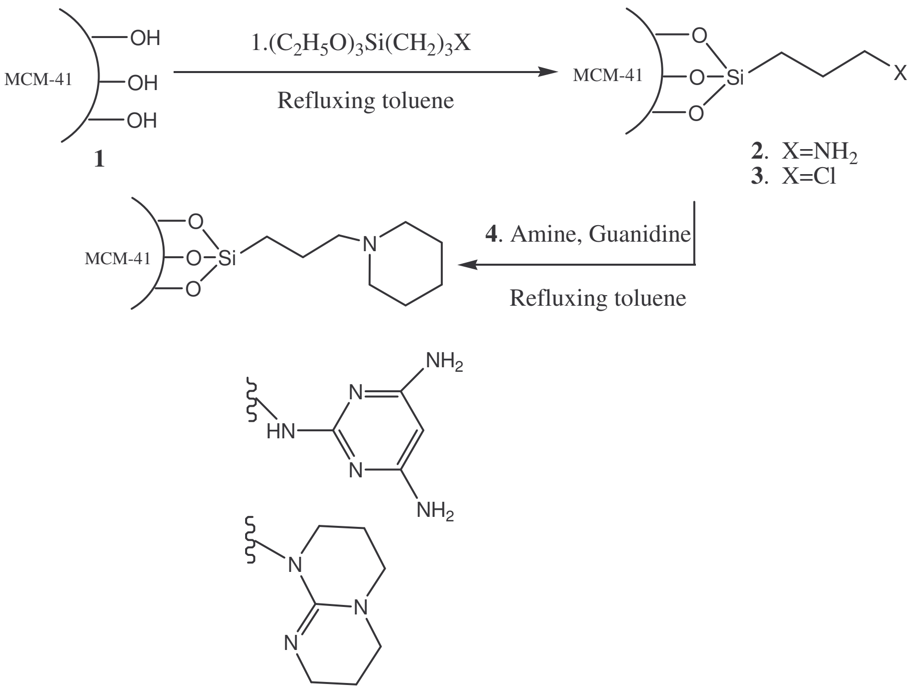
In fact many organic reactions mechanism, for fine-chemical synthesis, involved carbanions intermediates. They are formed by abstraction of a proton from a C–H bond of an organic molecule by a base. Many organic reactions often require a stoichiometric amount of liquid base to generate carbanions and produce a stoichiometric amount of metal salts as by products. Heterogeneous base catalysts present fewer disposal problems, while allowing easier separation from the reaction medium and in the same time easier recovery of the products and solvent. A fundamental feature from an industrial point of view is that they are non corrosive. So solid-base catalysts offer environmentally benign and more economical pathways for the synthesis of fine chemicals. Because of these advantages, research on the synthesis of fine chemicals using solid bases as catalyst has increased over the past decade. The recent development of solid-base materials and the reactions catalyzed by solid bases are published recently and describe more detail of some aspects of catalysis by solid bases [13,14,15,16,17,18,19,20]. In Refs.[15,17], the industrial processes using solid-base catalysts are listed.

Solid-base reactions can also replace organometallic reagents such as Grignard reagents and alkyl lithium to form C–C and Si–C bonds, and so forth. They can also replace organo-transition metal catalysts. For example, dimerization of phenylacetylene, is usually carried out using organo-transition metals, such as Ru and Rh, as catalysts. Novel reactions should be found and explored not only from the known homogeneous base-catalyzed reactions, but also from a wider range of reactions which might proceed through “anionic or anion” like intermediates. Of course, there are problems to be solved. Though a variety of methods have been applied, there is no definitive or unified way of characterizing solid bases, especially base strength[15,21]. Many of spectroscopic methods are not easily applicable to characterize solid bases. For example, the XPS binding energy of O1*s* can be a good measure for determining the electron density of zeolite surfaces[22]. This technique cannot be used for most of base catalysts, since the basic sites are often only a very small fraction of oxygen anions on the surface. The temperature-programmed desorption of carbon dioxide is often utilized for determining base strength, because of technical easiness. It is, however, hard to rationalize the desorption temperature to the strength as Brønsted base, that is, to abstract a proton from a substrate, since the adsorption of carbon dioxide does not involve the proton-transfer step. At present, we have to rely on model reactions such as alkene isomerization and Knoevenagel condensation. The base strength could be conjectured from the p*K*a values of the reactants. However, it should be noted that the base strength is dependent on reaction conditions. Corma et al. estimated the base strength of alkali-exchanged Y–zeolites from the Knoevenagel reactions[23]. Na-exchanged Y–zeolite has the basic strength of a pH value of 10.3 and cannot activate ethyl malonate (p*K*a =13.3*)* at 413 K. The same catalyst can activate phenylacetonitrile (p*K*a =21.9*)* to react with methanol, reaction (1’), at 533 K. In addition, as in the homogeneous reactions, the reaction rates are often very much dependent on the solvent used.

Recently, some groups have described the preparation of simple solid catalysts based on zeolite and their successful application as base catalysts in organic reactions[24,25,26]. In particular after the first approach “impregnation method” by Hathaway and Davis[27], a new way of modifying zeolites was developed by Ono and Baba. In order to obtain basic materials[28] alkali-exchanged zeolite Y was immersed in a solution of metallic Na, Yb or Eu in liquid ammonia and dried before by solvent evacuation and finally by heating at 450 K. The base sites were created on the impregnated zeolite and they showed catalytic activity in the double bond isomerization of but-1-ene to but-2-ene.

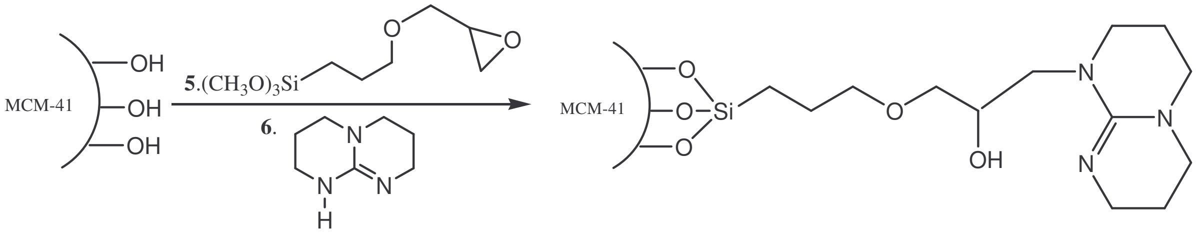
In the 1990s, a different kind of solid base catalyst with high specific surface area was developed, which contains nitrogen rather than oxygen atoms as basic sites. Treating amorphous aluminium orthophosphate[29,30,31,32,33], zirconium phosphate[34], aluminium vanadate[35,36] or galloalumino-phosphate[37] with ammonia at temperatures of 973-1273 K, the oxygen was replaced by nitrogen in a three step process[38]. The amorphous oxynitrides are active in base-catalyzed reactions. They are considered to be more strongly basic than alkali ion-exchanged zeolites and comparable to hydrotalcites or MgO[39].

One reason for the limited application of zeolite catalysts in the synthesis of fine chemicals resides in their small pore openings which prevent bulky molecules from reaching the active sites. As a logical remedy, the use of mesoporous materials MCM-41 as carriers for basic guest species has been proposed[40,41], by impregnation with cesium acetate in aqueous or methanolic solution and subsequent calcinations. Recently a new way of modifying MCM-41 has been described. The material was functionalized by anchoring organic bases at the silanol groups[42,43]; Chauvel and coworkers[38,44] developed procedures for anchoring primary **2** and tertiary amines **4** at the silanol groups **1** of MCM-41 (Scheme 1).



Scheme 1.

Subba Rao et all pointed out that the route described above will lead to immediate poisoning of the strongest base sites due to the HCl liberated in the synthesis. To avoid this problem, 3-methoxysilylpropoxymethyloxirane **5** with a glicidyl group can be used in the anchoring reaction, as showed in Scheme 2:



Scheme 2.

The organic-inorganic hybrid materials are less strongly basic than the corresponding free organic molecules and posses a wide distribution of the base sites with different strengths, which has been explained by an H-bonding interaction of the amine function with residual silanol groups[45,46]. The incorporation of an organic base into the pores of zeolite Y has been attempted by using the "ship-in-the-bottle" synthesis method[47]. Moreover hydrotalcite-derived[48] basic catalysts continue to attract research interest as well, for example the mixed oxide was more active in Knöevenagel condensations than ion-exchanged zeolites[49,50].

1a.3 Hybrid Basic Catalysts.

Different amines have been successfully tethered on MCM-41. Trying to combine the basicity of amino groups with the shape-selectivity effects, amorphous silica have been imprinted with amines covalently linked to the silicon atoms of the silicate[51,52,53].

Cauvel et all synthesized [54] mesoporous silica functionalized with primary and tertiary amines following Mobil's method[55]. In the same year P. A. Jacobs and co-workers obtained a MCM-TBD material used as catalyst for Michael reactions and Robinson annulation[56].

Guanidines represent a class of strongly basic compounds widely utilized as reagents as well as catalysts in organic synthesis. During the last decade different research groups turned their interest into the anchoring of efficient homogeneous catalysts on the surface of various supports with the aim of producing the corresponding heterogeneous efficiently reusable counterparts[57]. Among these catalysts guanidines received particular attention. TBD is a versatile guanidine with nucleophilic and basic properties which render this compound an extremely useful catalyst for many organic transformations.

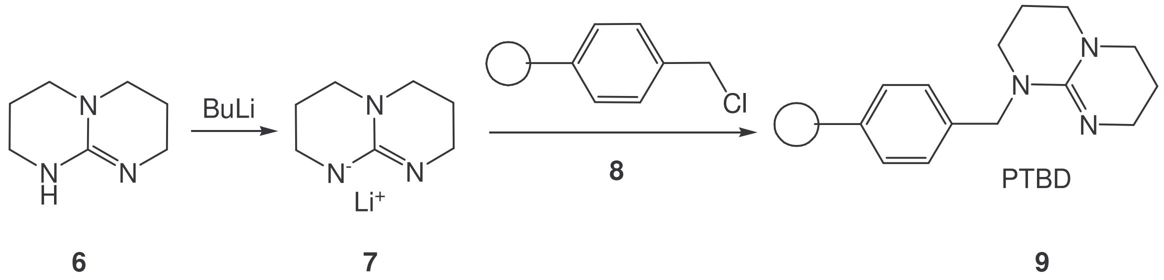
One of the first supported organic bases utilized as catalyst for synthetic purposes was the propylamine tethered onto amorphous silica employed to perform the Knoevenagel reaction. After this early study a growing number of papers has been published describing the preparation of different organic bases anchored to solid supports including guanidines[58].

Strong organic bases such as tetramethylguanidine (TMG) that are able to stabilize intermediate anions *via* hydrogen bonds or hydrophobic interactions have been used as catalysts for carbon-carbon bond formation and known reactions catalyzed by guanidines include Michael additions[59], aldol-like condensations[60] and Strecker reactions[61].

Guanidines have been supported onto different organic and inorganic supports with the aim of preparing and applying solid basic reusable catalysts.

1,5,7-Triazabicyclo[4.4.0]dec-5-ene (TBD) represents the prototype for a group of strong guanidine bases which have been previously utilized as homogeneous catalysts[62]. The pK_{BH+} values of these compounds are about 26, ensuring a strong basicity[63], about 100 times more basic than tetramethylguanidine[64]. Moreover, TBD contains a reactive NH group which can be covalently linked by nucleophilic attack to a previously immobilized electrophile.

The first support utilized to the above mentioned purpose for guanidine immobilization was an organic polymer, namely a chloromethylated polystyrene crosslinked with 2 mol% of divinylbenzene, reported in 1992 by Tomoi et al.[65]. Tomoi et al. described the immobilization of TBD **6** by using a strategy involving the reaction of the lithium-TBD salt **7** with a chloromethylated polystyrene **8**: various polystyrene supported TBD materials (PTBD) **9** with degrees of base functionalization ranging from 1.12 to 2.40 mmol/g were prepared (Scheme 3).



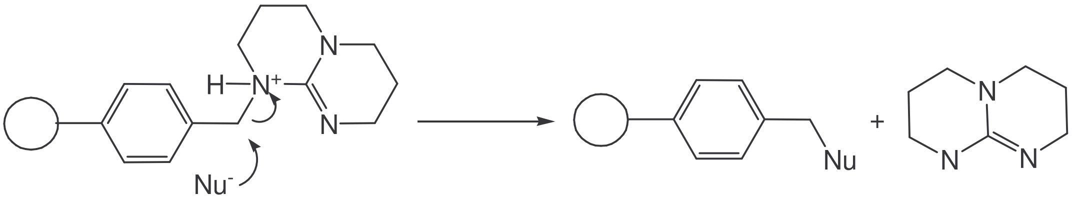
Scheme 3.

Nowadays the polymer supported guanidine (with a base loading up to 3.5 mmol/g) is a commercially available material, mainly used as basic scavenger to trap acidic species. Nevertheless, some research groups have utilized this material as heterogeneous catalyst for organic transformations.

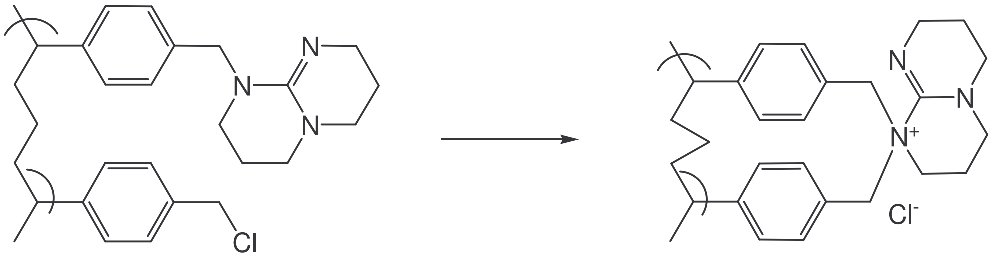
The polymer supported TBD has been used in the last years for many organic transformations which involved a basic or nucleophilic catalysis:

- Esterification reactions (benzoic acid[62], glycerol[66], synthesis 1-acyl L-α-glycerophosphorylcholine[67])
- Alkylation reactions (alkylation of ethylcyanoacetate, phenols alkylation[68])
- Nucleophilic aromatic substitution of activated aryl halides with *para*-chlorophenol nucleophile[65]
- Addition of diethylphosphate to imines[69]
- Addition of nitromethane to alicyclic ketones and aldehydes[66]
- Transesterification of soybean oil with methanol[70]
- Condensation reaction between benzaldehyde and heptanal to produce jasminaldehyde[71]

However polymer supported TBD usually suffers from the drawback of being little recyclable because of leaching of the guanidine into the crude (Scheme 4) and deactivation by guanidine alkylation (Scheme 5).



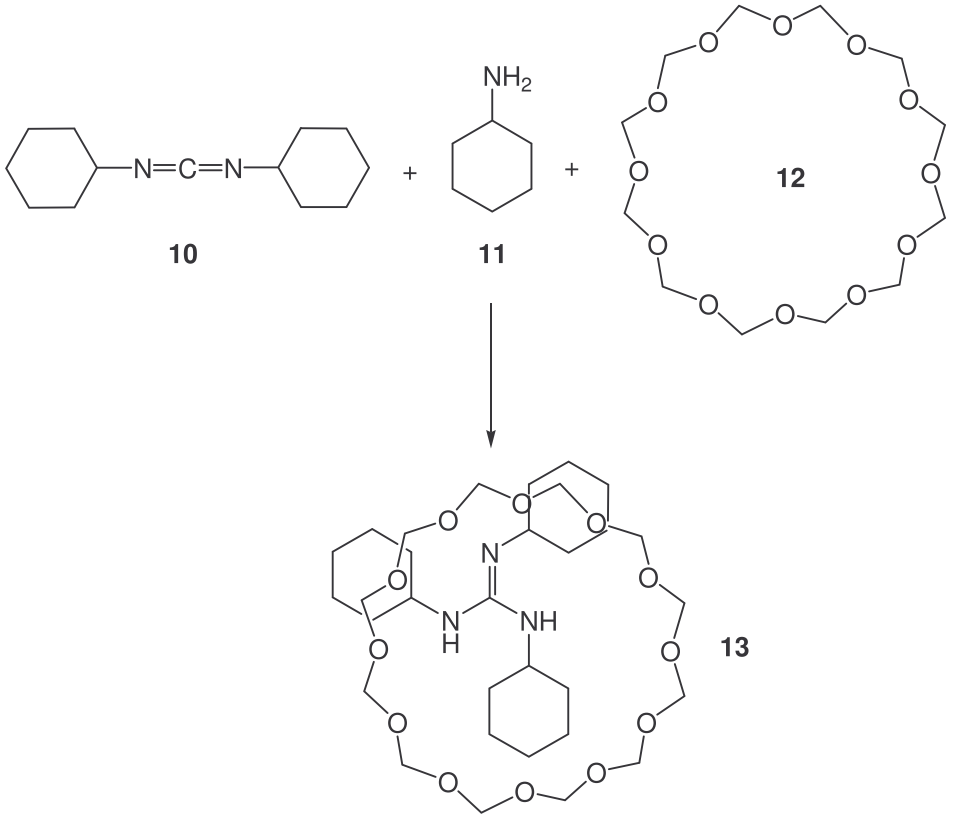
Scheme 4. Possible mechanism of guanidine leaching



Scheme 5. Possible mechanism of guanidine deactivation

All these problems derive from the preparation procedure of the supported catalyst which involves nucleophilic substitution of a supported halides by means of TBD. To overcome these downsides some authors have adopted a different approach to heterogenization, namely the preparation of "ship in a bottle" guanidines by encapsulation in the supercages of zeolite Y. Schuchardt et al.[72] were able to incapsulate *N,N',N"*-tricyclohexylguanidine (TCG) in Wessalith® DAY (with FAU structure, 7.4 Å channels and 13.0 Å supercages) by reacting

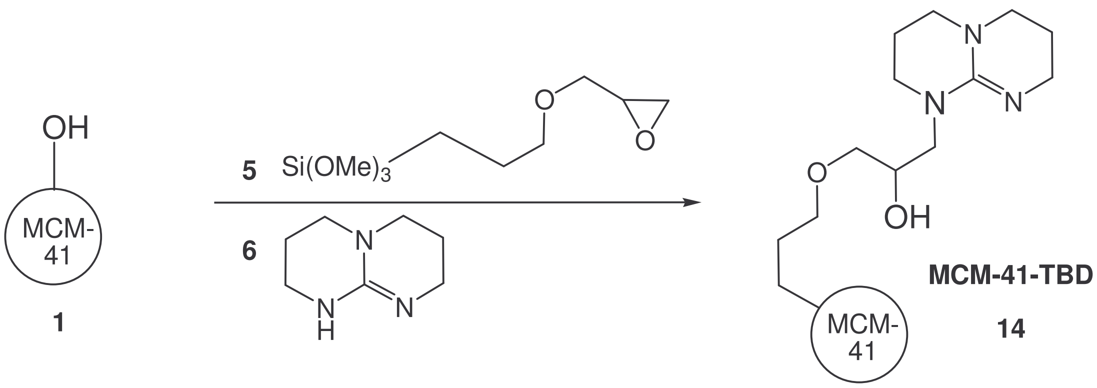
N,N'-dicyclohexylcarbodiimide **10** with cyclohexylamine **11** inside the supercages of this hydrophobic zeolite **12** (Scheme 6).



Scheme 6.

The catalytic activity of this material was tested in the condensation of acetone with benzaldehyde to give 4-phenyl-3-buten-2-one however the product was obtained only in small amount (10%) in respect to the yield under homogeneous conditions (with TCG 94% yield). The conclusion is that guanidine TCG encapsulated in Wessalith® (**13**) is not an effective catalyst for organic syntheses, as the smaller pores make the diffusion of reactants and products more difficult.

A heterogeneous and strongly basic catalyst constituted by TBD covalently coupled to a siliceous MCM-41 support was prepared by Jacobs et al.[54] by functionalizing the inner surface of the mesoporous siliceous MCM-41 support **1**[73] with oxirane group through reaction of 3-trimethoxylsilylpropoxymethyloxirane **5** with the surface silanol groups. Then TBD **6** was allowed to react with the epoxide group avoiding the formation of quaternary guanidinium salts which may poison the base sites (Scheme 7).



Scheme 7.

Quaternarization of the amine and guanidine bases can be the consequence of the reaction of liberated HCl or HBr when chloro- or bromopropyl groups are utilized instead of the glycidyl groups as immobilized electrophiles[74].

The so obtained hybrid organic-inorganic material MCM-41-TBD **14** was used as catalyst in the Michael reaction between 2-cyclopenten-1-one and ethylcyanoacetate. The catalyst accelerates only the desired 1,4-addition and bypasses all possible side reactions: thus the product was obtained in 52% yield and 100% selectivity by carrying out the reaction at 80 °C for 30 minutes. MCM-41-TBD could also be successfully utilized to promote the Knoevenagel condensation of aromatic aldehydes with ethylcyanoacetate and malononitrile. The selectivity was excellent, usually over 90% and in several cases (i.e. *p*-nitrobenzaldehyde) yields approach 100%.

The same catalyst has been utilized in the jasminaldehyde synthesis by condensation of benzaldehyde with heptanal under true batch reactor conditions[15]. The target compound was isolated in lower yield (79%) with respect to that obtained by carrying out the reaction with PTBD (99%) but with a considerably higher selectivity (70% vs 49%). This result suggests that TBD immobilized on MCM-41 results in a catalyst that is considerably more thermally stable, and shows a better selectivity than PTBD. This is probably an indication for a shape selective reaction in the pore system.

Finally it is interesting to consider the possibility to apply heterogenised amines on asymmetric synthesis.

A. Corma et all found that some heterogenised chiral amines, based on cinchonine and cinchonidine, are active in Michael addition of nucleophiles to enones[75], although the enantioselectivity of the reaction was moderat. So taking this into account they tried to improve the enantioselectivity preparing new chiral amines, having a chiral environment instead of a chiral base centre. They report a very feasible methodology to synthesize and heterogenize new amines, having a chiral environment, on inorganic supports such as amorphous silica, mesoporous silica MCM-41 and delaminated zeolite ITQ-2, and their use as ‘‘green’’ and reusable catalysts in the enantioselective Michael addition of ethyl 2-oxocycloalkanecarboxylates to acrolein.[76]

In this dissertation the tethering approach has been followed to support organic bases on amorphous silica.

The immobilization has been achieved using a trialkoxysilyl compound, in some cases as precursor of the catalyst in other cases as intermediate species for a further functionalization (Section **1b**).

The catalysts prepared have been used in carbon-carbon bond formation, in particular in reactions such as nitroaldol and Michael addition.

1a.4. References.

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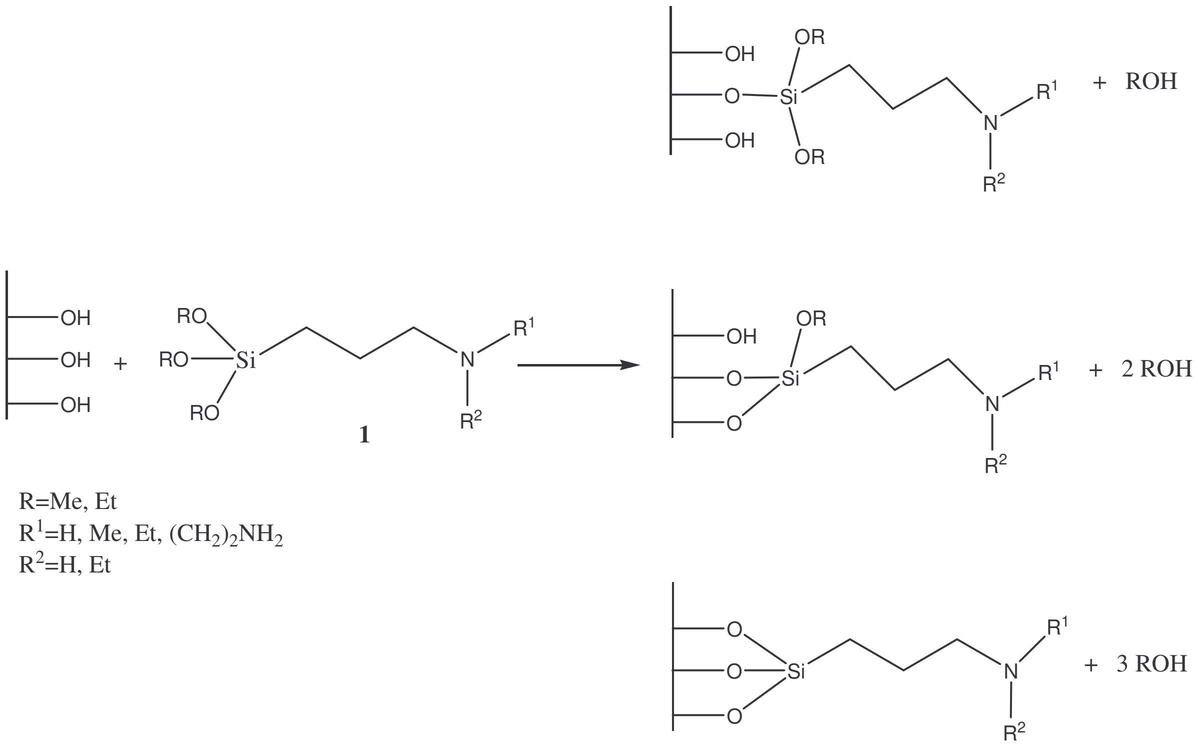
1b. Silica supported bases preparation.

1b.1. Preparation of KG-60-supported alkyl-amines.

Silica-supported organic catalysts can be prepared by sol-gel or post-modification method. We have utilized the post-modification approach for the preparation of all silica supported bases[1] since catalysts with lower base loading values gave better yields in shorter reaction times[2]. The higher activity of the catalysts prepared by post-modification method in comparison to the sol-gel method is probably due to the larger surface area (~250 m^2/g for post-modification method versus ~135 m^2/g for the sol-gel method[3]).

Catalysts were prepared according to the methods reported in the literature by grafting the organic groups to the surface silanols of the KG-60 silica, previously dried at 350 °C overnight, using trialkoxyorganosilanes.

In particular 3-aminopropyltriethoxysilane, *N*-methyl-3-aminopropyltrimethoxysilane, *N*,*N*-diethyl-3-aminopropyltrimethoxysilane and 3-(2-aminoethylamino)propyl-trimethoxysilane gave solid basic catalysts called KG-60-NH_2[4], KG-60-NHMe[5], KG-60-NEt_2[6] and KG-60-$NH(CH_2)_2NH_2$[7] respectively. The materials (amorphous or mesoporous silica), carrying an amino group on carbon 3, are achieved by tethering of propyltrialkoxysilanes **1**. The process involves the reaction of the alkoxy groups (Scheme 1) with the surface silanols: compounds **1** can react with one, two or three alkoxy groups giving rise to a soft, robust and very robust anchorage, respectively.



1

R=Me, Et
R^1=H, Me, Et, $(CH_2)_2NH_2$
R^2=H, Et

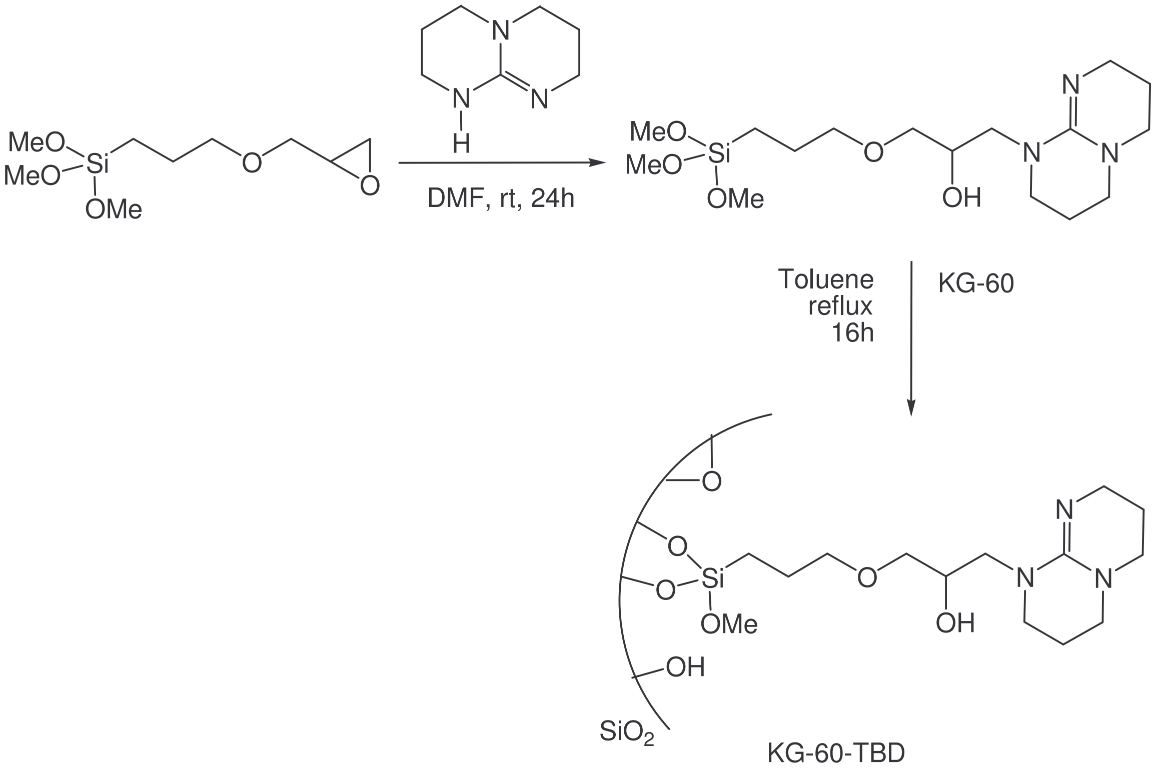
Scheme 1.

A typical preparation was as follows: dried silica (10 g) was added to toluene (150 ml), followed by the selected trialkoxysilane (30 mmol). The mixture was refluxed for 18 hours with mechanical stirring. The resulting slurry was cooled to room temperature and the modified silica was filtered, washed with toluene (50 ml), acetone (50 ml), water (50 ml) and finally with acetone (2 x 50 ml). After allowed to dry at room temperature under vacuum, the modified silica was dried in an oven at 100 °C for 10 hours.

1b.2. Preparation of KG-60-supported 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD).

A different methodology for the guanidine TBD is following explained:
the tethering of 3-trimethoxysilylpropoxymethyloxirane to the surface of siliceous materials and successive functionalization with an organic compound able to add to the epoxide moiety is usually utilized for the tethering of strong bases [i.e. 1,5,7-triazabicyclo[4.4.0]dec 5-ene (TBD)] in order to avoid the production of the corresponding supported guanidinium salts (Scheme 2)
The preparation of the supported catalyst was performed by modifying the method described by Jacobs[8,9] et all through two steps: 1) (3-glycidyloxypropyl) trimethoxysilane (10 ml, 46.5

mmol) was added dropwise under nitrogen to a solution of TBD (6.5 g, 46.9 mmol) in dry DMF (65 ml). The mixture was stirred for 24 hours at room temperature. 2) A suspension of KG-60 silica (20.1 g previously sieved and dried) in dry toluene (150 ml) was refluxed for 1 hour under nitrogen; then the solution obtained by the first step was added to the suspension and refluxed for additional 16 hours under nitrogen. The modified silica obtained was filtered and washed with toluene (120 ml), dichloromethane (200 ml) and methanol (100 ml), then extracted with a diethyl ether dichloromethane mixture (150/150 ml) in a Soxhlet apparatus overnight. Finally, the modified silica was dried.



Scheme 2

1b.3 Catalysts characterisation.

All materials, with different supported bases, were characterised with respect to their compositional, textural and surface properties.

The loading of the organic groups was calculated from the nitrogen content by elemental analysis performed with CARLO ERBA CHNS-0 EA1108 ELEMENTAL ANALYZER.

The N_2 adsorption-desorption isotherms, carried out at -196 °C on a Micromeritics ASAP 2010, were used to determine the specific surface areas S.A.$_{B.E.T.}$. Before each measurement the samples were out-gassed at 110 °C and $1.33 \cdot 10^{-4}$ Pa for 12 hours.

All the results obtained are summarized in Table 1:

Entry	**Catalyst**	**Loading (mmol/g)**	**Surface area (m^2/g)**
1	KG-60-NH_2	1.06	254
2	KG-60-$NH(CH_2)_2NH_2$	1.24	225
3	KG-60-NHMe	0.88	245
4	KG-60-NEt_2	1.12	210
5	KG-60-TBD	0.67	260

Table 1

Thermogravimetric analyses, performed with a Universal V4 2E TA, revealed that all these materials are thermally stable and thus do not release organic fragments almost until 200 °C.

The results are represented in Figure 1-9.

KG-60-NH_2

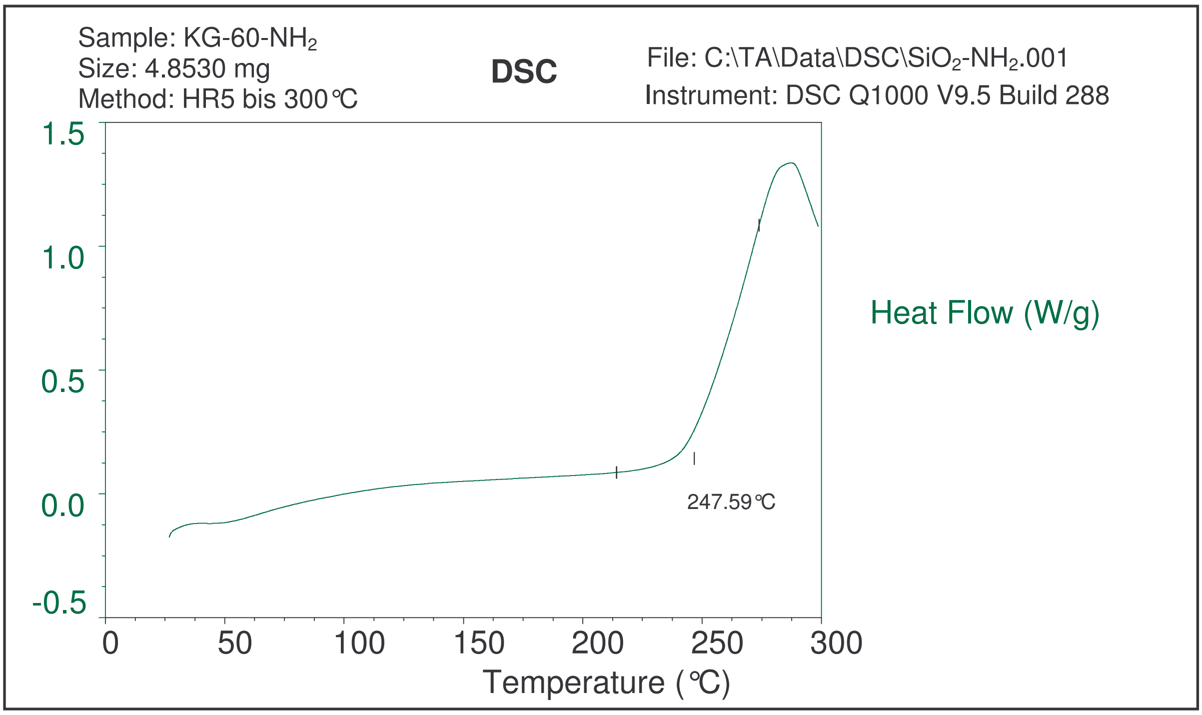


Figure 1. DSC of KG-60-NH_2.

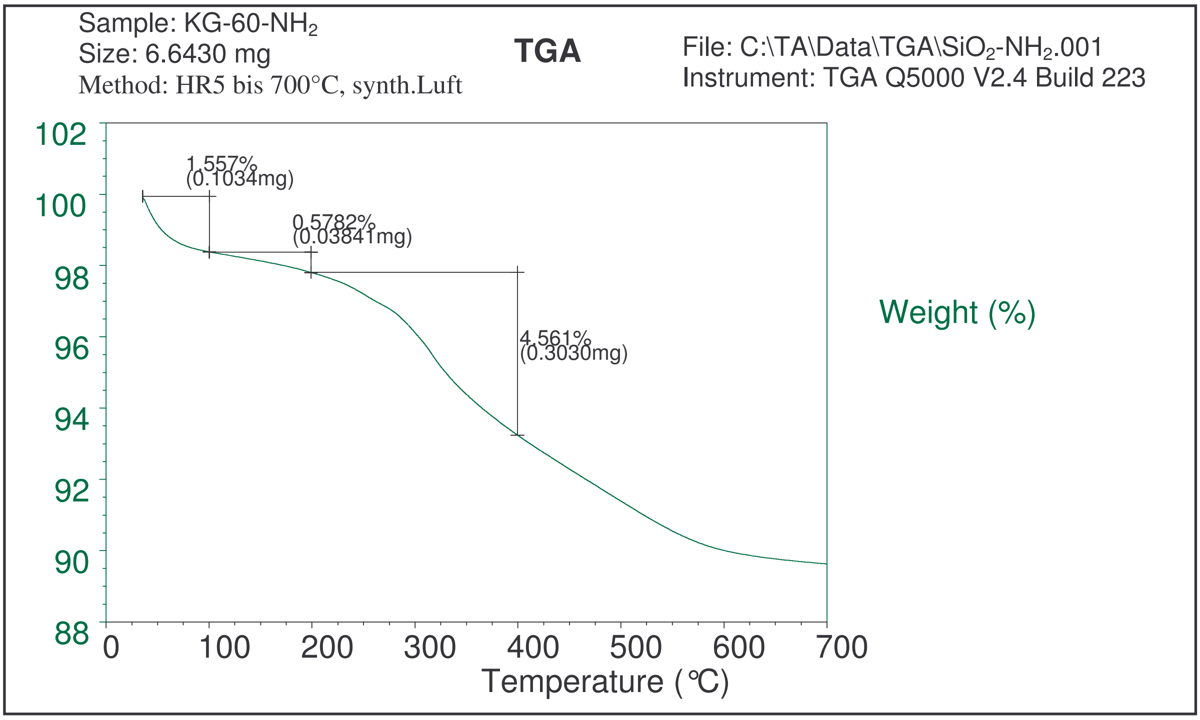


Figure 2. TGA of KG-60-NH_2.

KG-60-NH$(CH_2)_2NH_2$

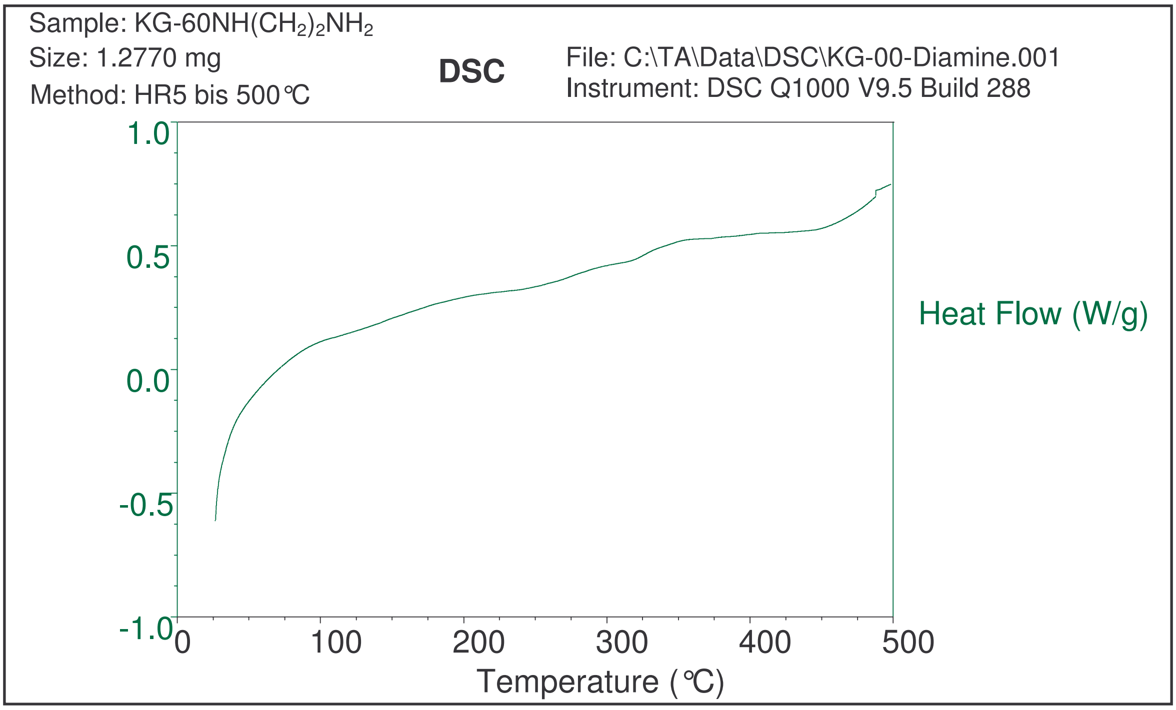


Figure 3. DSC of KG-60-NH$(CH_2)_2NH_2$.

KG-60-NHCH_3

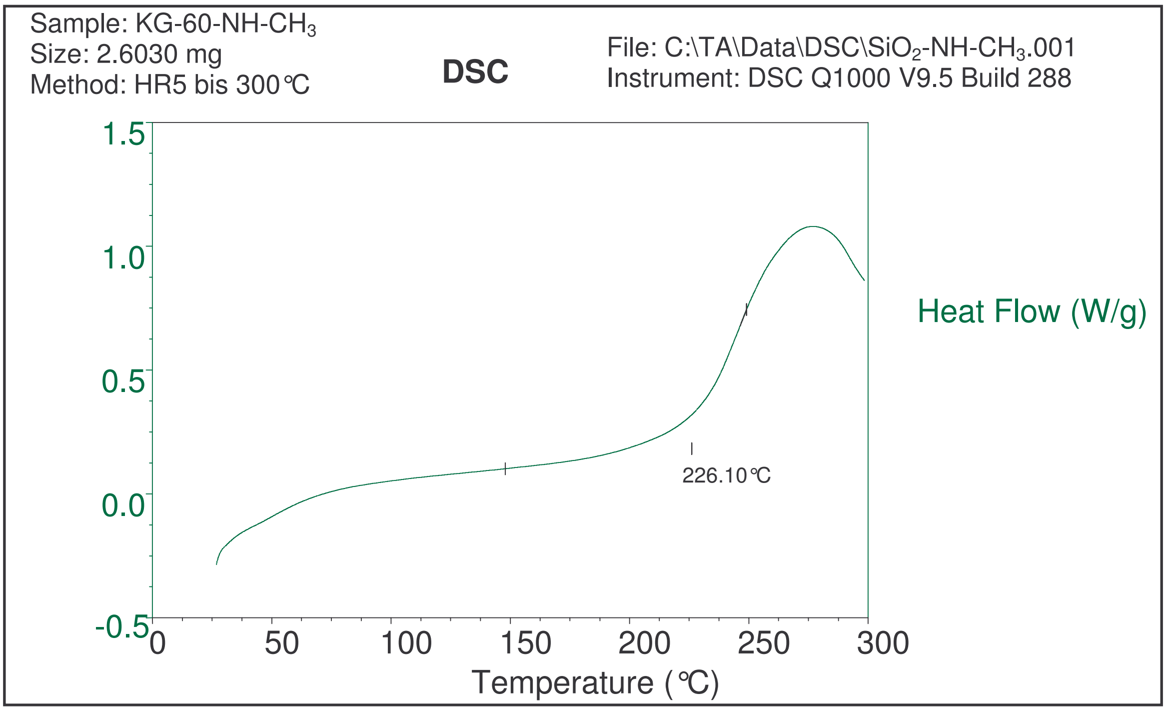


Figure 4. DSC of KG-60-NHCH_3

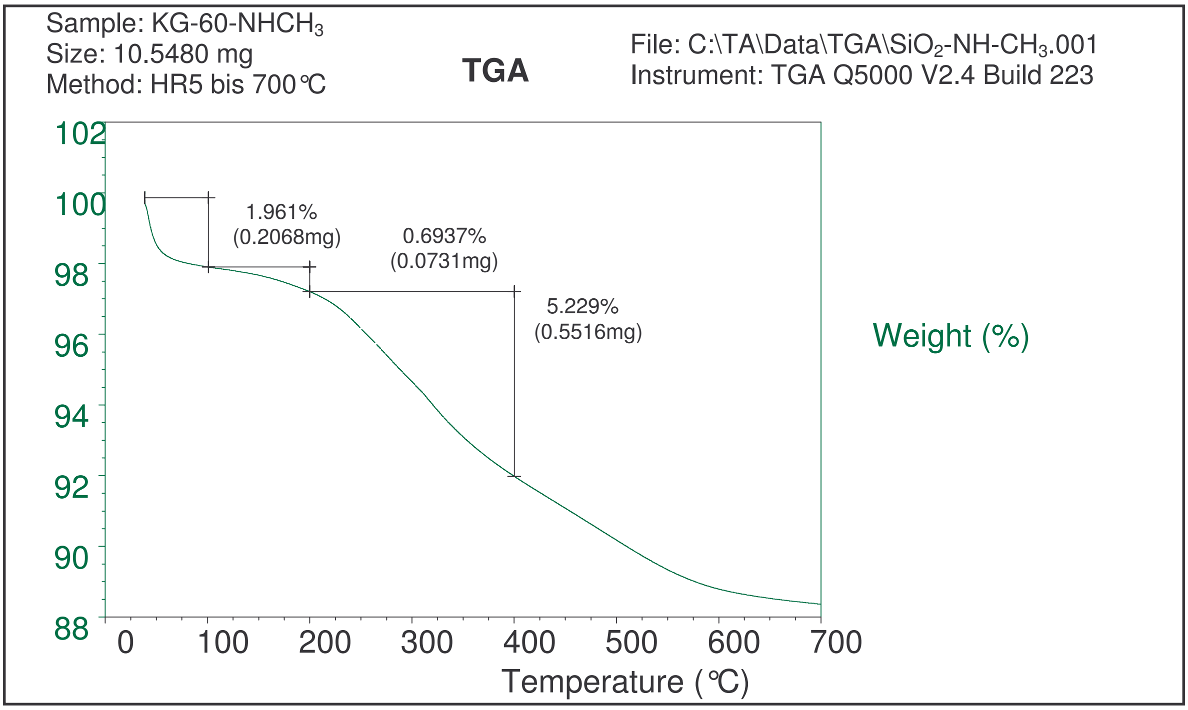


Figure 5. TGA of KG-60-$NHCH_3$.

KG-60-NEt_2

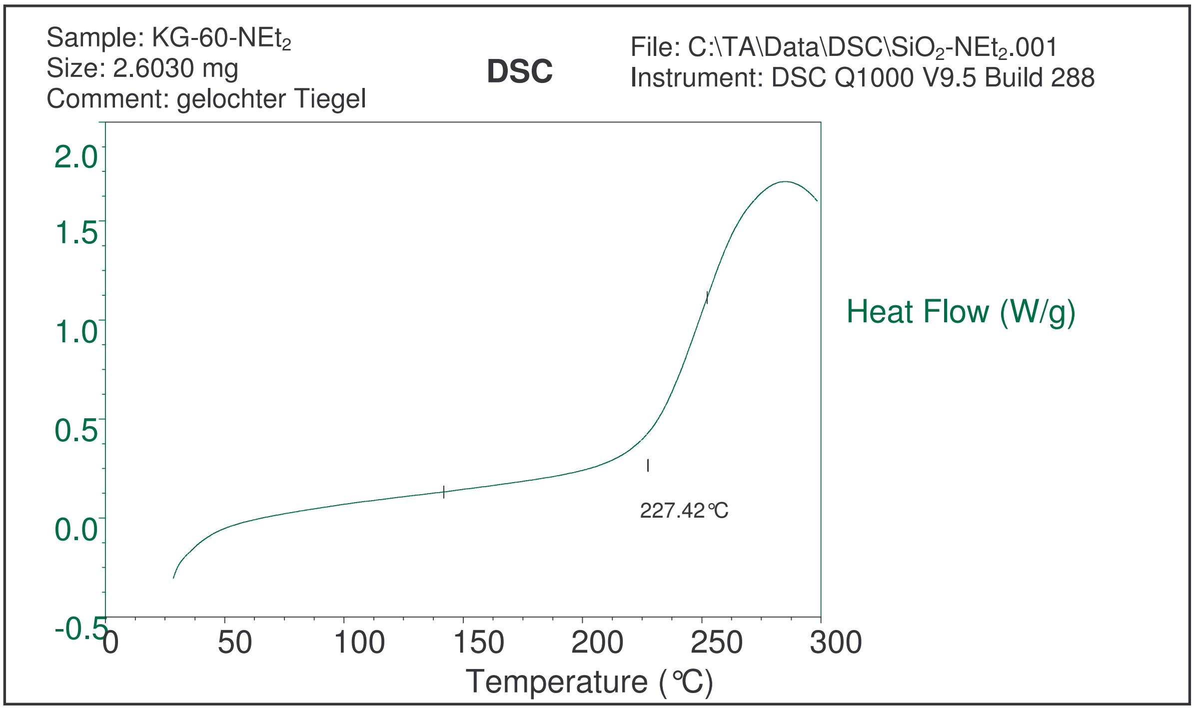


Figure 6. DSC of KG-60-NH_2.

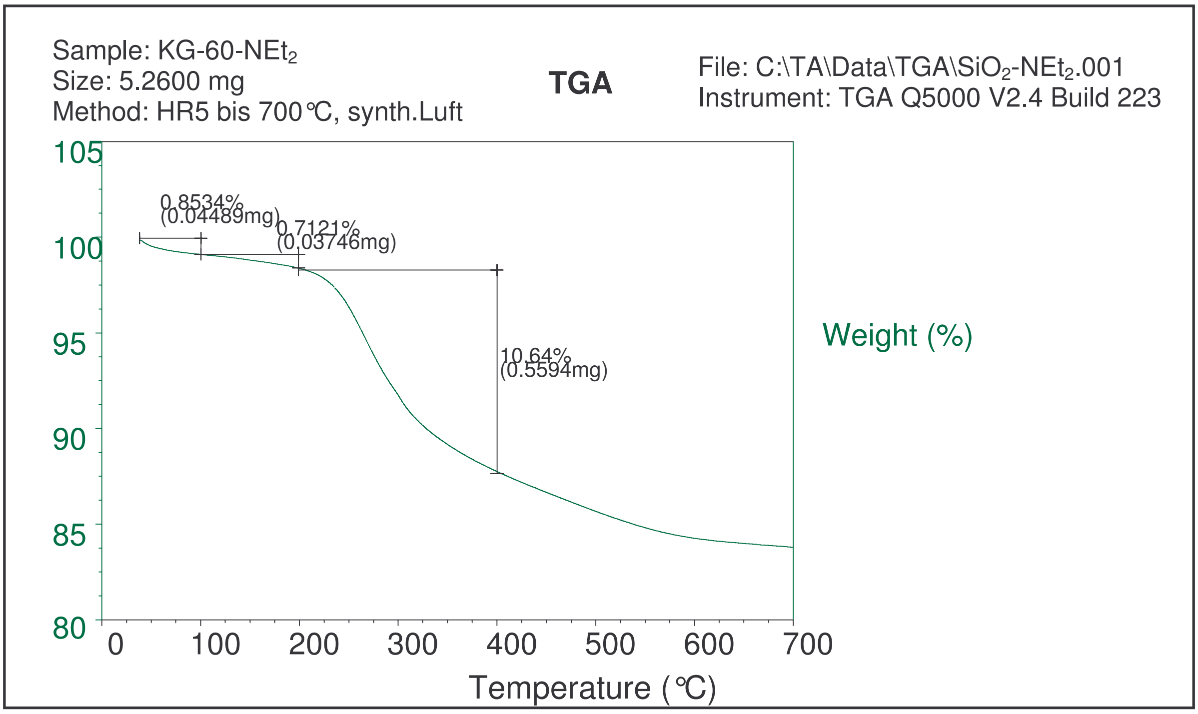


Figure 7. TGA of KG-60-NEt$_2$.

KG-60-TBD

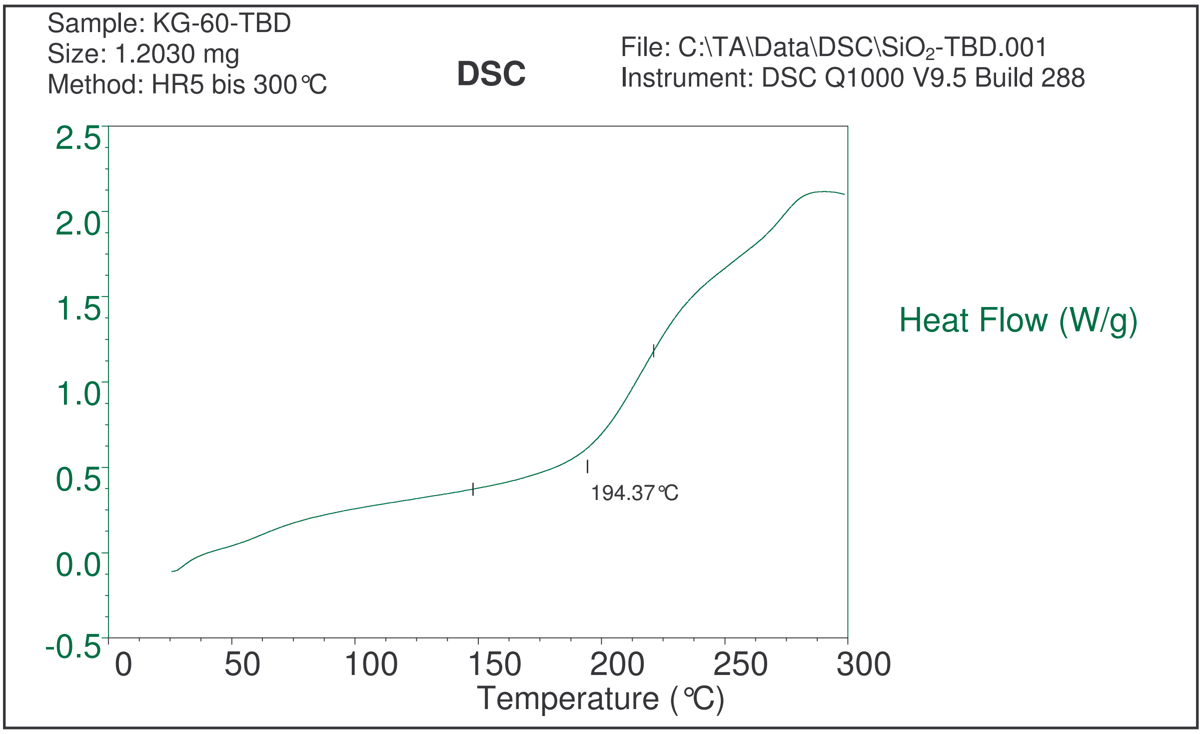


Figure 8. DSC of KG-60-TBD.

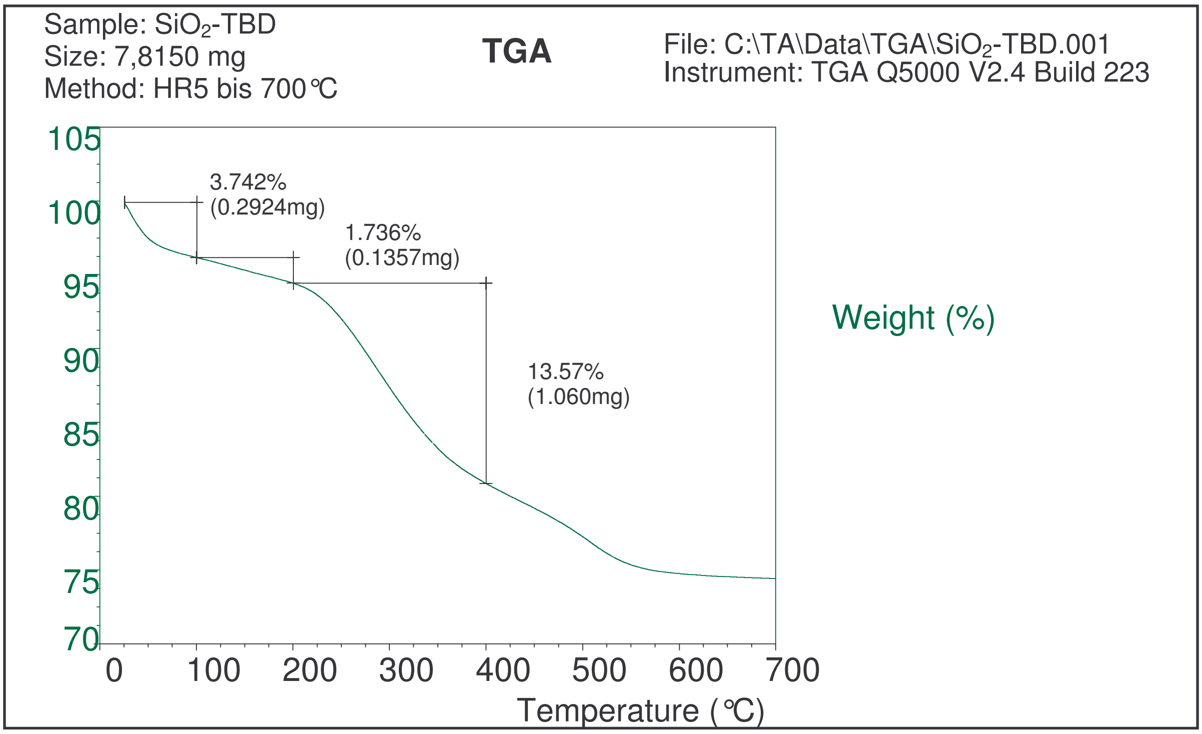


Figure 9. DSC of KG-60-TBD.

A short summary about DSC analysis is reported in order to have a direct comparison between the catalysts prepared.

The first mass-loss should be due to water desorption.

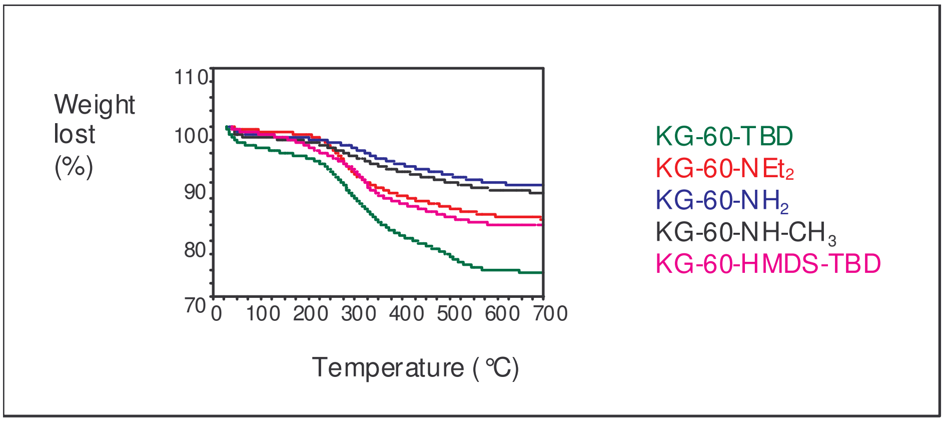


Figure 10. Summary of DSC analysis.

The different amount of weight lost % could be connected with the hydroscopic of the silica and so with the samples storage between the analysis.

Moreover the most significant result is that until 200°C all the samples gave no thermal decomposition.

1b.4. References

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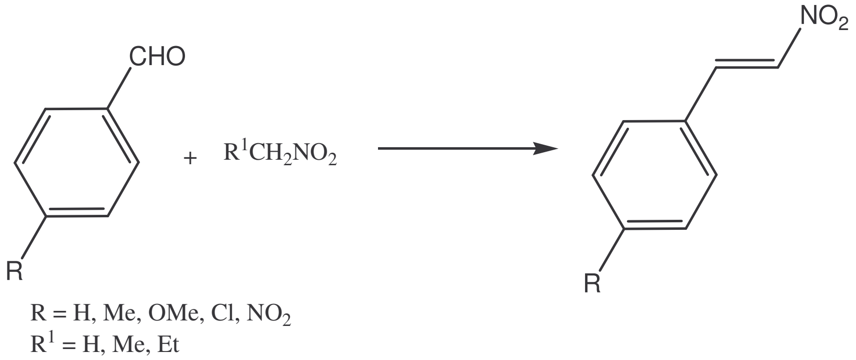
1c. Nitroaldol reaction.

1c.1 Introduction.

The nitroaldol condensation[1] between nitroalkanes and aromatic aldehydes to give (*E*)-nitrostyrenes (Scheme 1) (0.05 g catalyst/2.5 mmol carbonyl compound), routinely performed in the presence of a wide range of base catalysts, was studied in the presence of aliphatic amines supported on MCM-41 silica[2] prepared according to methodology explained in **1b** chapter.



Scheme 1

The inert nature of the amine-free material suggested that the supported amines were responsible for the activity. Their efficiency follows the trend primary>>secondary>tertiary, in disagreement with the tabulated basicity order of aliphatic amines in polar solvents[3]. These features, along with the reported remarkable ease with which aromatic aldehydes give rise to the supported imines by reaction with aminopropylsilica[4], allowed the authors to formulate a mechanistic hypothesis involving a supported imine intermediate, according to that already reported for the reaction of benzaldehyde and ethyl cyanoacetate in the presence of supported primary amino groups[5]. Repeated condensation tests in the reaction between benzaldehyde and nitromethane were successively performed for five cycles affording nitrostyrene in 98, 95, 95, 90 and 84% yield respectively. The reaction was extended to different aromatic aldehydes and nitroalkanes giving the corresponding nitrostyrenes in high yield (92-98%) and excellent selectivity (97-99%). In all cases the (*E*)-stereoisomer was the sole product detected. Nucleophilic reactions of unmodified aldehydes are usually difficult to control, affording complex mixture of products often due to the high reactivity of the formyl group under either basic or acidic reaction conditions The activity order, classified by the nature of amino groups, was secondary> primary>tertiary, which may suggest the intervention of enamine pathway[6]; the enals were exclusively obtained as (*E*) isomers. It should be noted that FSM-16-$(CH_2)_3$-NHMe exhibited higher activity than conventional solid bases such as MgO and Mg-Al-hydrotalcite (hexanal self-aldol condensation: FSM-16-$(CH_2)_3$-NHMe 97% conversion and 85% yield in 2 hours, MgO 56% conversion and 26% yield in 20 hours, Mg-Al-hydrotalcite 22% conversion and 11% yield in 24 hours). The leaching test allowed to exclude the possible migration of any active catalytic species in solution. The catalyst on recycling showed a decrease in the catalytic activity (60% yield after 2 h). However, the activity was comparable to that observed for the first run when the filtered catalyst was simply dispersed in diluted aqueous solution of K_2CO_3 followed by washing with distilled water, and subsequent drying. Moreover, the catalyst supported on mesoporous silica showed higher activity than that supported on amorphous silica: the initial rate of the former catalyst was 2.2 times higher than that of the latter one. In addition FSM-16-$(CH_2)_3$-NHMe exhibited much higher activity than the homogenous amine catalyst in terms of both initial rate and yield. This behaviour can be ascribed to the enrichment of the reactants inside the well ordered pores of mesoporous silica. The reaction could be more efficiently promoted by using ionic liquid ($[bmim]PF_6$) instead of toluene[7]. Hexamethylphosphoric triamide (HMPA) has been extensively used in organic synthesis because of its superior solvation and coordination properties[8]. Unfortunately, HMPA is also toxic and a potential carcinogenic reagent; this limits its broad utility in organic synthesis. To address the toxicity problems of HMPA, while maintaining its excellent synthetic utility, a polymer-supported HMPA-type derivative (PS-HMPA) (Fig. **1**) was prepared by a multistep methodology involving the treatment of methylamino polypolystyrene with tetramethylphosphorodiamidic chloride.

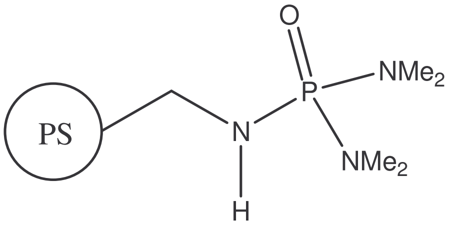
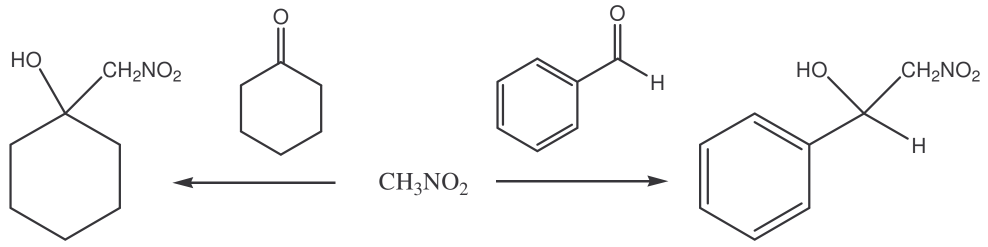


Figure 1

This supported amide was utilized for catalytic aldol reactions between trichlorosilyl enol ethers of ketones and aldehydes for the synthesis of β-hydroxy ketones (0.15 g catalyst/2 mmol carbonyl compound)[9]. The model reaction between trichlorosilyl enol ether of cyclohexanone and benzaldehyde, carried out at -78°C in the presence of PSHMPA, was complete within 3 hours and afforded the aldol product in 80% yield and 1:1 diastereoselectivity; when the temperature was increased to -23°C, the reaction time for the complete conversion was shortened to 2 hours, and the diastereoselectivity was improved to 9:1 (*syn*/*anti*). The aldol products in the present reaction showed an opposite configuration to that of the products obtained with homogeneous, chiral phosphoramide catalysts[10]. This observation suggests that this reaction can proceed through two possible pathways: the first involves the formation of a pre-aldol complex responsible for an open-chain mechanism, the second involves a closed, boat-like transition state. The first hypothesis is the more likely, due to the bulky environment on the polymer; this hypothesis was indirectly supported by the fact that the use of Denmark's bulky chiral phosphoramide catalyst resulted in the prevalent *syn* selectivity[11]. The polymer could be reused in a second run but, however, its effectiveness was somewhat diminished (about 15 % lower then the original reaction). The diminished catalytic activity was presumably due to slow destruction of the polymer when subjected to the vigorous magnetic stirring. Commercially available TBD supported on polystyrene [PS-TBD] was utilized to promote the Henry reaction (Scheme 2) (10% mol supported base/carbonyl compound)[12].

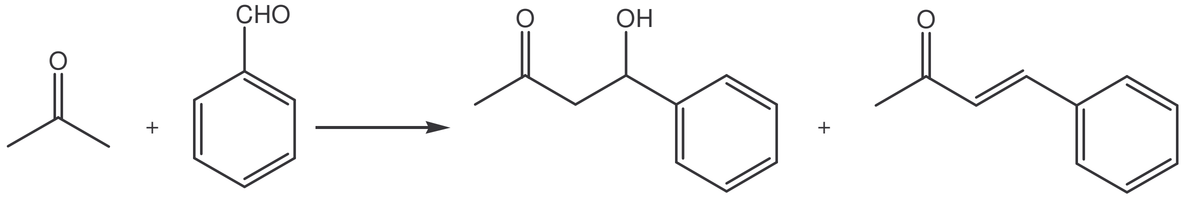


1 **2**

Scheme 2.

The addition of nitromethane to cyclohexanone was completed in 1 hour at 0 °C affording product **1** in 82% yield; as expected the reaction with benzaldehyde afforded the corresponding product **2** in 95% yield in only 5 minutes at the same temperature. However, the reaction was not generally applicable as other aliphatic ketones and acetophenone did not react. The same catalyst was also utilized in the condensation reaction between benzaldehyde and heptanal to produce jasminaldehyde (0.2 g catalyst/15 mmol carbonyl compound)[13]. This reaction could afford the heptaldehyde self-condensation product, some benzyl alcohol and benzoic acid (from the Cannizzaro reaction) as by-products. A high temperature favours the jasminaldehyde formation. By slowly adding heptaldehyde in order to keep its concentration low, a 99% conversion accompanied by a 91% selectivity could be reached; on the contrary, when the heptaldehyde was added in one portion, a much lower selectivity was obtained (49%) at the same conversion (95%). In addition the catalyst suffered from severe deactivation and consequently it could not be successfully recycled.

Since alkyl substituted guanidines heterogenized on organic polymers were found to undergo some leaching during reactions of considerable practical importance such as transesterification of soybean oil with methanol[14], some authors adopted a different approach to heterogenization, namely the preparation of "ship in a bottle". TCG, tricyclohexylcarbodiimide was encapsulated in the supercages of Wessalith® zeolite and the catalytic activity of this material was tested in the condensation of acetone with benzaldehyde to give the α,β-unsaturated ketone **4** (Scheme 3)[15].



3 **4**

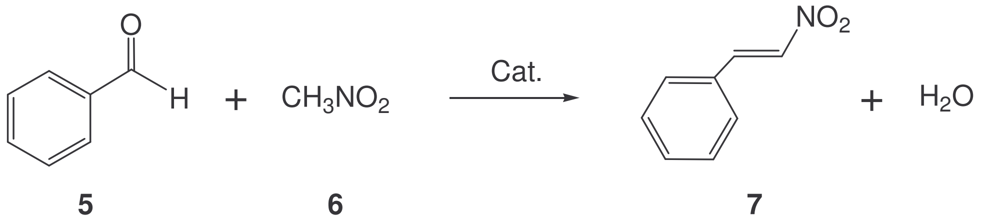
Scheme 3

In the presence of 10% mol of TCG under homogeneous conditions benzaldehyde was quantitatively converted after 2 hours and compound **4** was obtained with 94% yield, whereas 10% mol TCG encapsulated in zeolite Wessalith® afforded **4** with 8% yield accompanied by compound **3** with 48% yield.

By using TCG supported on MCM-41 silica[16], the total yield (**3** + **4** products) ranged from 31 to 89%, and the amount of the addition product **3** depended on the alcohol solvent utilized (**4**/**3**:MeOH 89/0, PriOH 40/22, ButOH 20/11).

1c.2 Results and discussion.

Our attention was focused on the nitroaldol condensation between benzaldehyde and nitromethane[17] (Scheme 4), we applied primary, secondary and tertiary amines as well as TBD as catalysts supported on amorphous silica KG-60 through a convenient spacer (Table 1).



Scheme 4

Catalyst	Functionalizing agent
KG-60-NH_2	3-aminopropyl-triethoxysilane
KG-60-$NHCH_2(NH_2)$	[3-(2-aminoethylamino)propyl]trimethoxysilane
KG-60-CH_3	[3-methylaminopropyl]trimethoxysilane
KG-60-NEt_2	(3-diethylaminopropyl)trimethoxysilane
KG-60-TBD	1,5,7-triazabicyclo[4.4.0.]dec-5-ene

Table 1

Batch reactions were carried out by stirring freshly distilled benzaldehyde **5** (2.46 mmol) in nitromethane **6** (3 ml) utilized as solvent-reagent for 1 hour at 75 °C in the presence of 3% mol catalyst (with respect to benzaldehyde) under nitrogen to avoid oxidation of the benzaldehyde to benzoic acid that could react with the supported amine giving the amide and definitively poisoning the catalyst. The reaction gave directly (*E*)-nitrostyrene **7** as the sole isomer accompanied by polynitroderivative by-products due to the polymerization of **7** and/or addition of a second molecule of nitromethane to **7** and or nitroalcohol formation by nucleophilic direct addition of nitromethane to **5**.

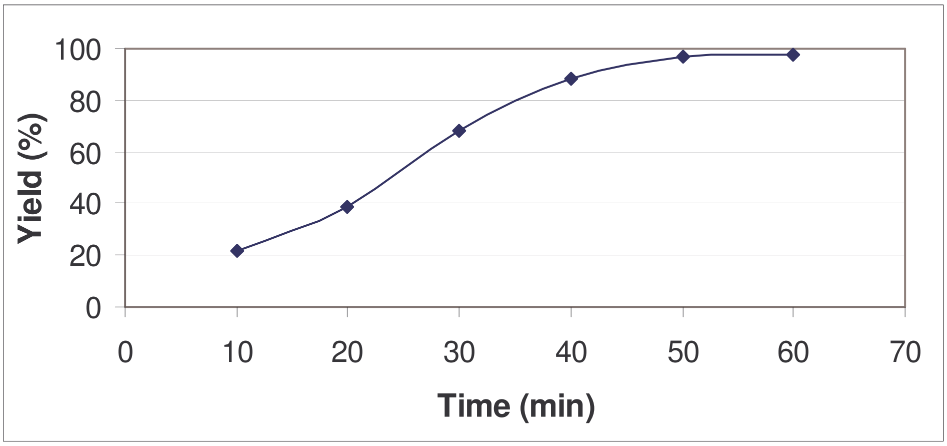
Results reported in Table 2 confirm that the yield and selectivity of product **7** are mainly affected by the nature of the supported amine rather than by the physico-chemical parameters of the catalysts such as the surface area or the basic strength.

Entry	**Catalyst**	**Loading [mmol/g]**	**Surface area (m^2/g)**	**Conv. 5 [%]**	**Yield 7 (Sel.[a]) [%]**
1	KG-60-NH_2	1.06	254	100	98 (98)
2	KG-60-$NH(CH_2)_2NH_2$	1.24	225	52	36 (70)
3	KG-60-NHMe	0.88	245	75	28 (37)
4	KG-60-NEt_2	1.12	210	28	4 (15)
5	KG-60-TBD	0.67	260	67	26 (38)
6	KG-60-NH_2-HMDS	1.16	250	9	9 (100)

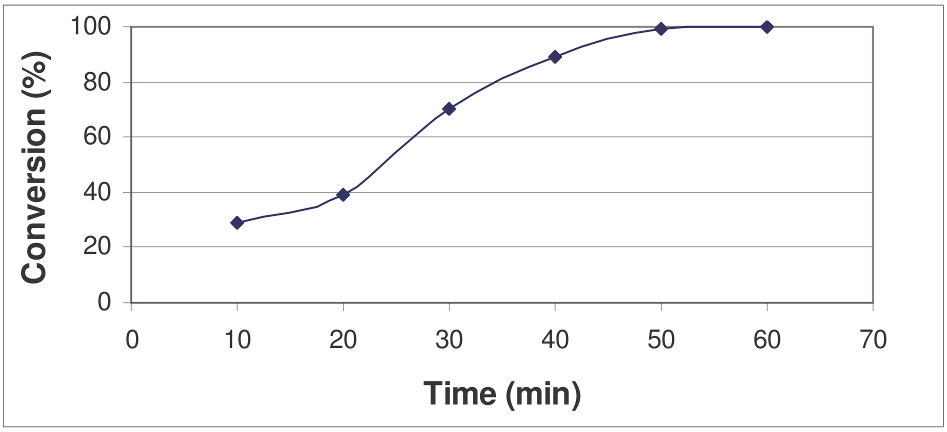
Table 2. [a] (Yield/Conversion)x100

Indeed, different supported amine catalysts with comparable surface area and similar amine loading gave product **7** with completely different yield and selectivity (Table 2, entries 1 and 3). Moreover, the supported propylamine gave product **7** with yield and selectivity greater than that of the more basic supported TBD (propylamine pK_b = 3.4, **7** yield = 98%, **7** selectivity = 98%; TBD pK_b = -11.0, **7** yield = 26%, **7** selectivity = 38%) (Table, entries 1 and 5).

This behaviour was attributed by us and others to the fast initial production of a supported reactive imine intermediate by reaction of the supported propylamine with benzaldehyde as it can be easily verified by FT-IR spectra[18]. Product **7** arises from the nitro-Mannich addition of nitromethane (activated as nitronate anion) to the supported imine followed by the β-scission[19]. We also analyzed the progress of benzaldehyde **5** conversion versus time in the model reaction performed in the presence of KG-60-NH_2 catalyst. The conversion reaches 100% after 60 min (Graphic 2); the data were better described by a first order irreversible kinetic with $k = 1.2 \times 10^{-2} (1.9 \times 10^{-3})$ min^{-1}. The yield trend versus time is reported in Graphic 1 as well.



Graphic 1.



Graphic 2.

Concerning the effect of the supported base, it is well recognised that different basic catalysts such as KG-60-NHMe, KG-60-NEt_2 and KG-60-TBD, that exhibit basic sites with medium and high basic strength, can promote the reaction through a typical nitroaldol mechanism involving addition of the nitronate anion to the aldehyde[20]. The great difference of the two chemical pathways (namely the nitro Mannich and the nitroaldol mechanisms) is the main reason to account for the different catalytic activities.

The reaction mechanism trough imine-intermediate alone doesn't explain completely the great reactivity of the supported primary amine (Table 2, Entry 1), in fact this type of organic, inorganic catalyst has a bifunctional activity. In particular by silylating the free silanol groups of silica the yield showed a drastic decrease (Table 2, Entry 6). It is clear the double role played by the primary amine like basic catalytic site and the role played by free silanol groups like acidic sites. The hole reaction mechanism is showed in Figure 2:

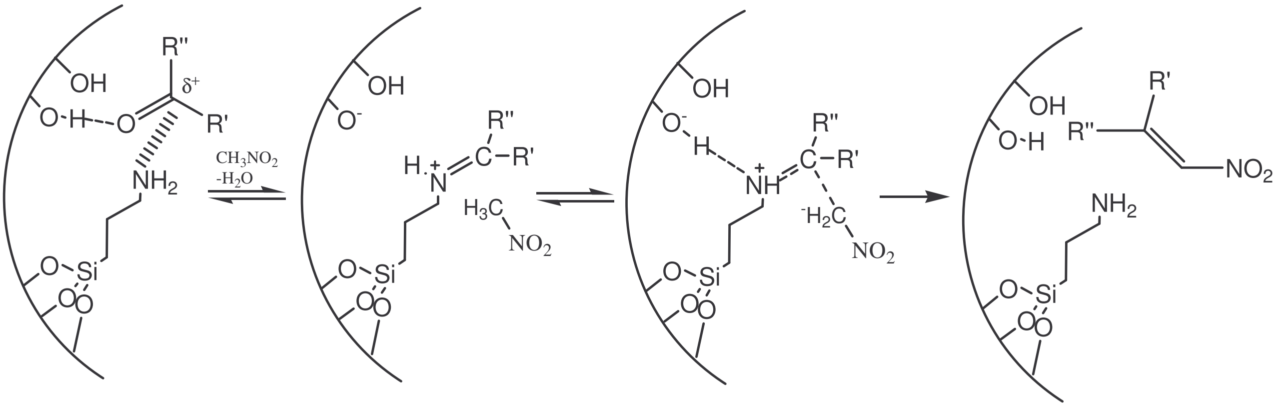


Figure 2.

The matrix structure of the silica plays an important role too in order to impose this cooperativety. The silylation step was made by using a typical silylating agent such as hexamethyldisilazane, at 60°C for 2 hours. The different reactivity (Table 2, Entry 6) is due to the different polarity of the silica surface and to the less number of silanol groups available for the benzaldehyde activation. Other groups have proved the same concept in parallel during the last three years providing some interesting papers[21,22].

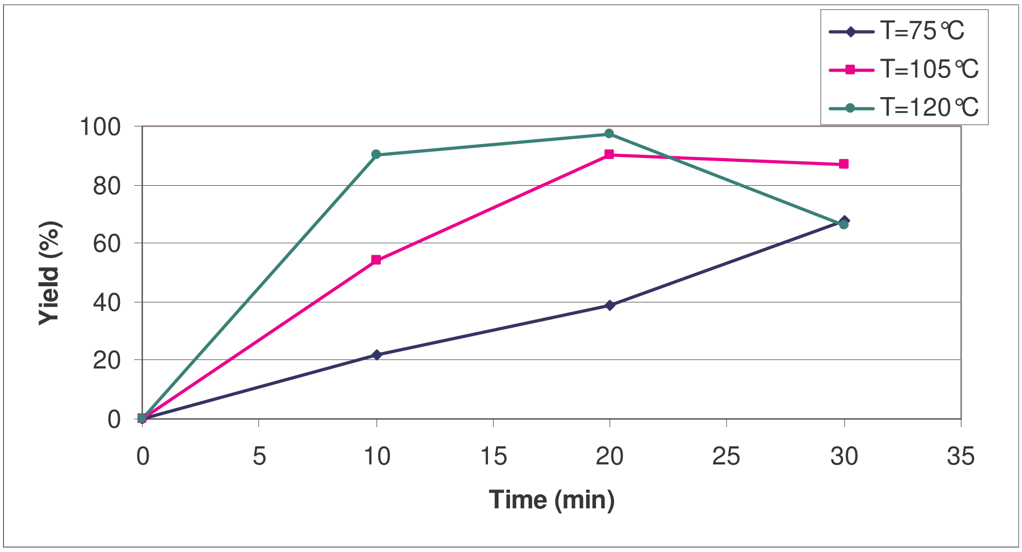
The temperature effect on the reaction trend was evaluated; all the parameters used have been already explained above. The results obtained, by performing the reaction at 85, 95 and 105°C during 30 minutes reaction are reported in Table 3.

Entry	Temperature (°C)	Yield (%)	Conversion 5 (%)	Selectivity (%)[a]
1	85	75	85	88
2	95	86	98	88
3	105	87	100	87

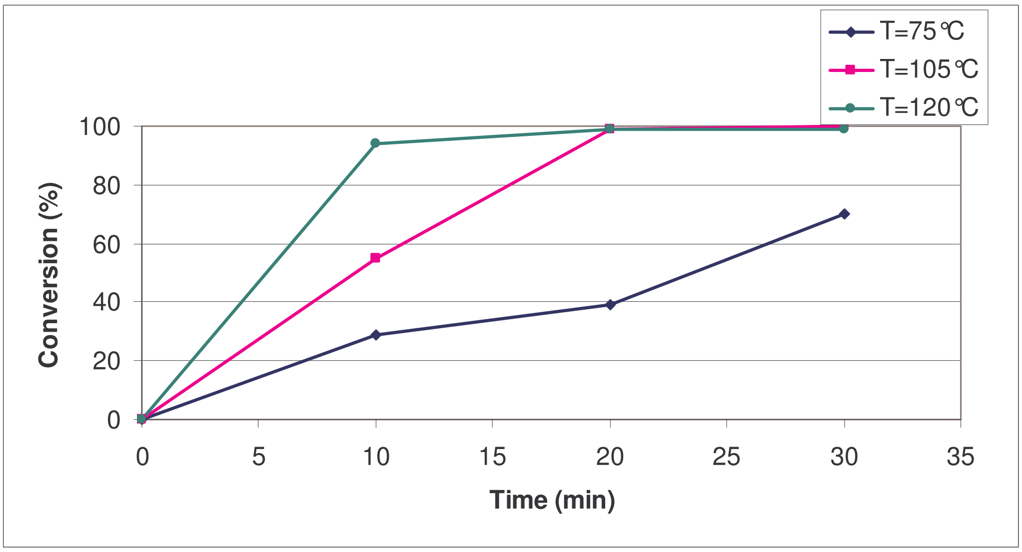
Table 3. [a] (Yield/Conversion)x100

Results from Table 3 show the possibility to achieve high conversion values in shorter time (30 minutes) but some problems about the selectivity arise. In fact at higher reaction temperatures the formation of the byproduct 1,3-dinitroalkane, due to the double attach of nitromethane to **5**, is favorite.

So the temperature effect was investigated at 75, 105, 120°C monitoring the conversion (Graphic 3) and selectivity (Graphic 4) trend versus time until 30 minutes in order to find out the best condition.



Graphic 3



Graphic 4

In particular at 120°C the desired product nitrostyrene **7** was obtained in optimum yield (97%) in only 20 minutes of reaction time.

1c.3 Experimental section.

Nitroaldol Reaction procedure

In a glass tubular reactor fresh benzaldehyde (0.261g; 2,46 mmol) is added to a suspension of the selected catalyst (3% mmol) in 3 ml of nitromethane (55.38 mmol). The mixture is heated at the selected temperature and reaction time. At the end of the reaction the crude is filtrated and the catalyst recovered after washing with 20 ml of ethyl acetoacetate. Finally yield, conversion and selectivity are determined by GC through internal standard analysis.

The reactions performed at higher temperatures are carried out in a steel reactor.

KG-60-NH_2 Silylation

The catalyst (500 mg) KG-60-NH_2 (see section **1b.1**) was inserted under nitrogen atmosphere in a flask and HMDS (16 mmol) was added like reagent/solvent. The mixture was magnetically stirrer for 2 hours at 60°C, then the powder was filtered washed with dichloromethane and acetone and dried under vacuum. Finally the catalyst obtained was characterized by elemental analysis (loading 1.16 mmol/g) and by FT-IR (Figure 3).

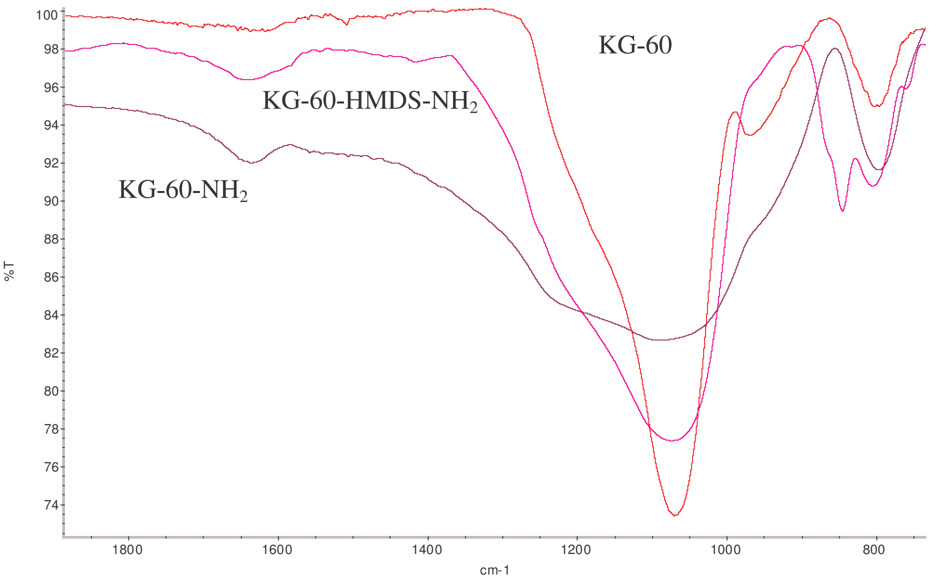


Figure 3.

The FT-IR spectra showed the band (1650-1580 cm^{-1}) typical for primary amine and different bands between 900-700 cm^{-1} due to the successful silylation of the free silanol groups.

1c.4 References.

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1d. Michael Addition.

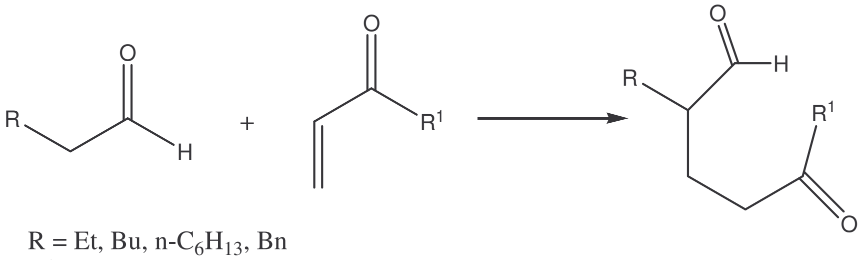
1d.1 Introduction.

The Michael addition[1] of nitroalkanes to electron-poor olefins (Scheme 1) was investigated in the presence of SiO_2-$(CH_2)_3$-NEt_2 (0.42 g catalyst/2.1 mmol olefin) prepared following the methodology explained in section **1b**[2].

R= Me, Et, Pr, n-C_5H_{11}
R^1 = H, Me
EWG = MeCO, EtCO, $PhSO_2$, CN, MeOCO

Scheme 1

A wide range of nitroalkanes underwent Michael addition to electron poor olefins by this procedure affording the products in good to excellent yield (56-90%); the different reactivity was ascribed to the different activation of the electronpoor carbon-carbon double bond. The catalyst could be utilized with similar results for at least two further cycles in the model reaction between 1-nitropropane and methyl vinyl ketone (reaction: 80%; 1st recycle 78%; 2nd recycle: 79%). Secondary amines, immobilized on mesoporous FSM-16, were utilized to obtain substituted 5-ketoaldehydes, important synthons for the preparation of natural products such as terpenoids, by direct 1,4-conjugate addition of unmodified aldehydes to vinyl ketones (1% mol supported base/carbonyl compound) (Scheme 2)[3].



R = Et, Bu, n-C_6H_{13}, Bn
R^1 = Me, Et

Scheme 2

The reaction, that could not be catalyzed by ordinary basic metal oxides such as MgO and Mg-Al-hydrotalcite, was efficiently promoted by FSM-16-$(CH_2)_3$-NHMe, suggesting the intervention of the enamine pathway.
Elemental analysis showed that the nitrogen content of the catalyst did not decrease after the reaction, confirming that the leaching of amino groups during the reaction was negligible. The catalyst could be recycled showing a decrease of activity in the reaction between decanal and methyl vinyl ketone (from 70 to 43% yield). However, the activity of the recovered catalyst was restored by treatment with a dilute aqueous solution of K_2CO_3 followed by washing with water. The reaction even with a small amount of catalyst could be applied to different aldehydes and vinyl ketones giving the corresponding products in 37-93% yield.

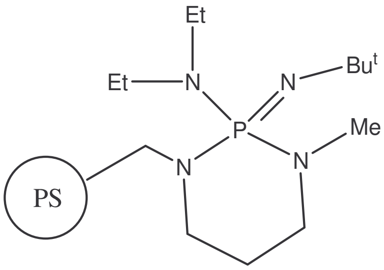
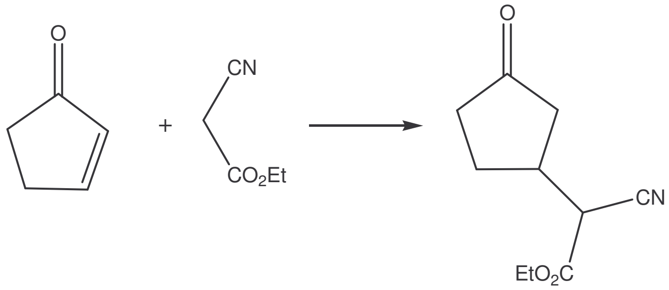


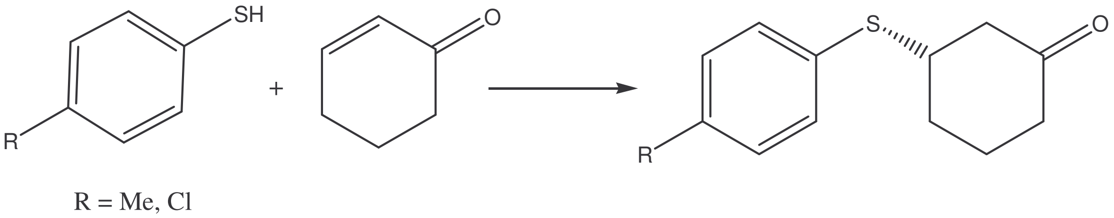
Figure 1

The commercially available polystyrene supported iminophosphorane (Fig. **1**) was utilized to promote the Michael addition of acyclic- and cyclic-1,3-dicarbonyl compounds, including those substituted at the active methylene, to electron-poor olefins (5% mol supported base/carbonyl compound)[4]. The reaction did not require dry solvents or inert atmosphere and afforded the desired adducts in 42-98% yield. As expected the more reactive acrolein and methyl vinyl ketone gave very good results with both acyclic and cyclic β-ketoesters and β-diketones and, surprisingly, acrylonitrile and methyl acrylate, reported to be totally inactive under Lewis acid catalysis[5], afforded the corresponding adducts with α-acetylbutyrolactone in high yield (77 and 98% respectively). In the reaction with crotonaldehyde, a 1:1 mixture of diasteroisomers was detected. The catalyst could be recycled three times without significant lowering of product yield, although the reaction time increased from 4 to 7 and to 16 hours; however, after three cycles the catalyst beads were crunched by mechanical stirring leading to an inactive powder. MCM-41-TBD catalyst was used in the Michael reaction between 2-cyclopenten-1-one and ethyl cyanoacetate (0.02 g catalyst/ 1 mmol carbonyl compound) (Scheme **3**)[6]

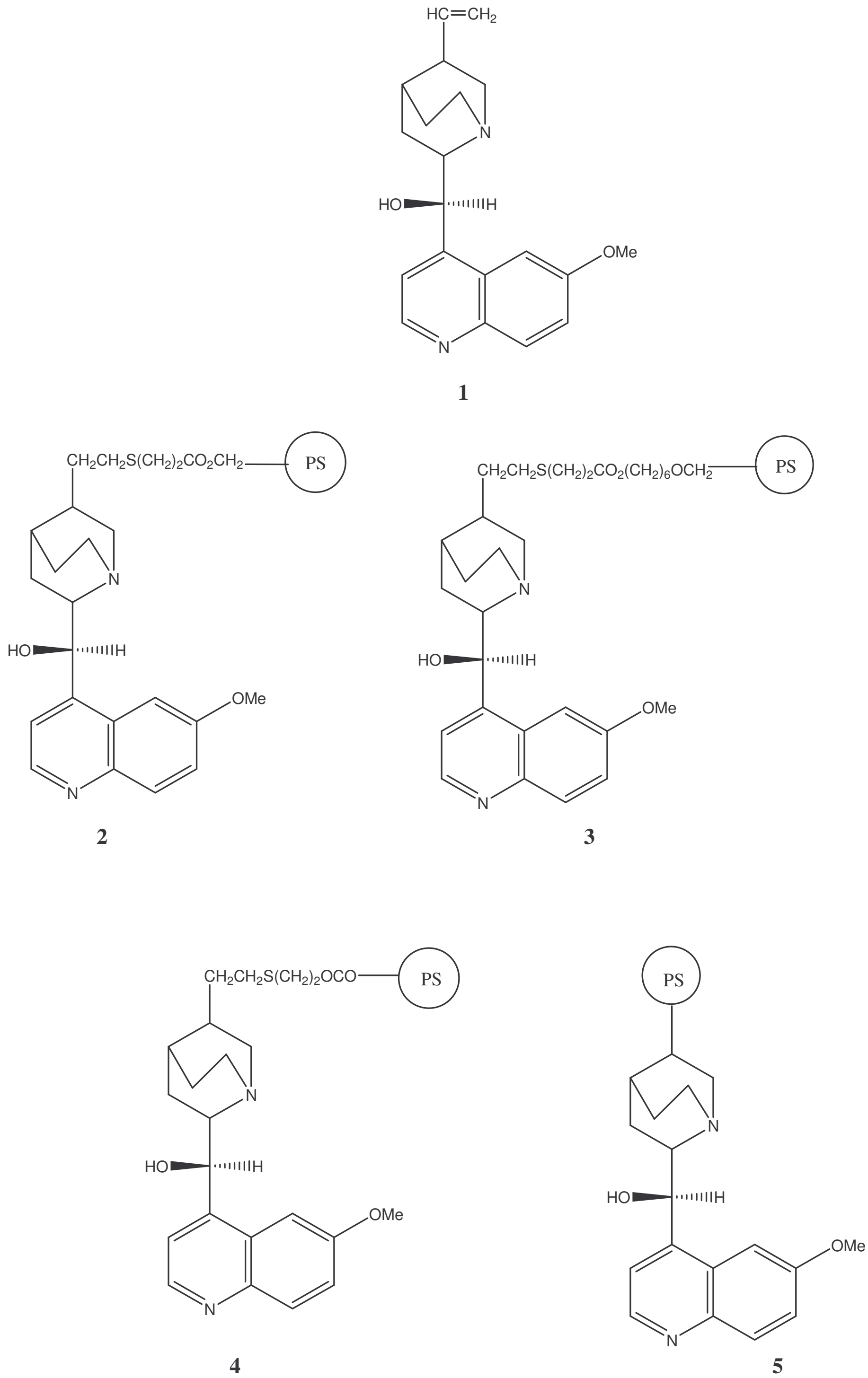


Scheme 3

The product was obtained in 52% yield and 100% selectivity. Differences in reactivity were observed, related to the nature of the reagents: thus diethyl malonate reacted with methyl vinyl ketone affording the Michael adduct in 34% yield after 30 minutes, whereas the adduct with 2- cyclohexen-1-one was obtained in 15% yield after 60 hours. Cinchonidine, cinchonine, quinine and quinidine, bonded to crosslinked polystyrene (Fig. **2**), were compared as solid catalysts in the enantioselective addition of thiophenols to 2-cyclohexen-1-one (0.02 g catalyst/2.57 mmol carbonyl compound) (Scheme **4**)[7].



Scheme 4



1

2

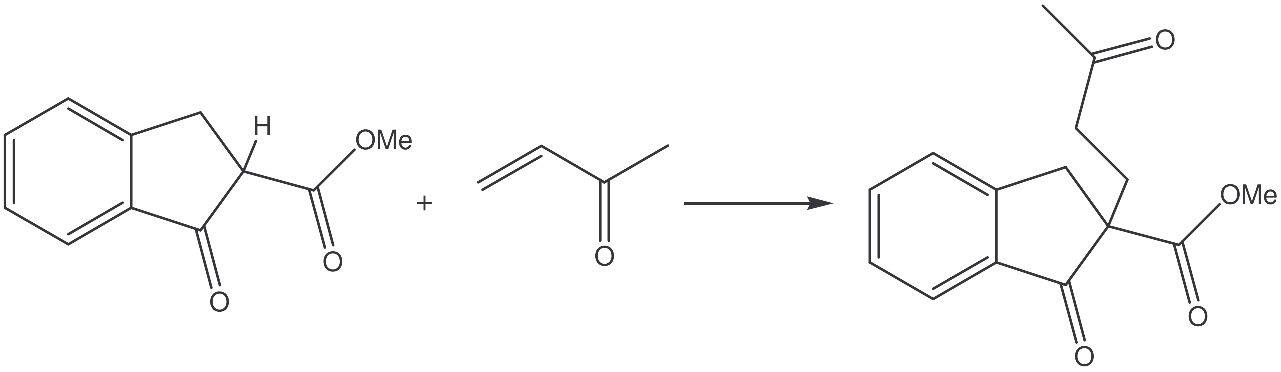
3

4

5

Figure 2

The reaction did not occur in the presence of unfunctionalized polystyrene and, as expected, cinchonidine and quinine gave predominantly the *R* enantiomer, whilst cinchonine and quinidine afforded the *S* one. The enantiomer obtained with each polymer-supported alkaloid was the same as that obtained under homogeneous conditions; nevertheless, the optical yields were always less and the best result was achieved with supported cinchonine (81% yield, 45% ee). The catalyst could be recovered and reused in successive reactions for at least three times affording chemical and optical yields similar to those obtained with the fresh catalyst. As the reactivity of supported alkaloids was often reduced in comparison to that of their homogeneous counterparts, a spacer could be introduced between the catalytic centre and the polymer matrix to overcome this drawback.



Scheme 5

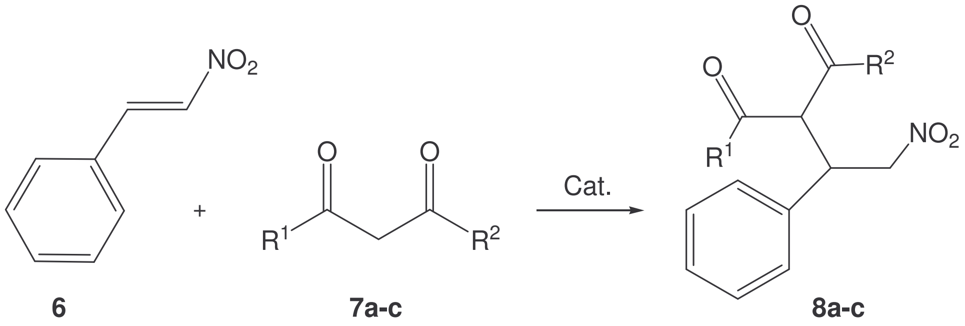
To this end polymer-supported quinine derivatives with spacers of different length were prepared (Fig. **2**) and tested in the Michael addition of methyl 1-oxo-2-indancarboxylate to methyl vinyl ketone (0.06 g catalyst/0.25 mmol methyl 1-oxo-2-indancarboxylate) (Scheme **5**)[8].

Catalysts **2** and **3** with spacer groups containing eight and fifteen atoms respectively, showed comparable stereoselectivity (62 and 65% ee respectively) and higher than that showed by **5** with no spacer (49% ee); the reaction carried out in the presence of homogeneous quinine **1** afforded the adduct with 76% ee. Quite surprisingly catalyst **4**, with a seven-atom spacer containing an acryloyl moiety, showed a lower activity but, when the reaction temperature was raised from -48 to 25 °C, the product was isolated with 92% yield and 45% ee, confirming that the configurational environment reaction in spite of the low catalytic activity. When the recovered polymers **2** and **3** were utilized in successive reactions, they exhibited lower catalytic activity but the stereoselectivity was comparable to that of the first use.

In this dissertation heterogeneous catalysts were applied for studying and optimizing the Michael addition, between β-dicarbonyl compounds and nitrostyrene derivates.

1d.2 Results and discussion.

In the present dissertation the Michael addition[9,10] of β-dicarbonyl compounds **7** to the electronpoor carbon-carbon double bond of compounds **6** (Scheme 6) was studied.



7a: $R^1=R^2=CH_3$; **7b**: $R^1=CH_3$, $R^2=OEt$; **7c**: $R^1=R^2=OEt$

Scheme 6

At first the model reaction between nitrostyrene **6** and acetylacetone **7a** was studied using different supported amines and the β-dicarbonyl compound as reagent/solvent (**6**:**7a** : 1:16 mmol); the results obtained in 4 hours are summarized in Table 1.

Entry	**Catalyst**	**Yield 8a (%)**	**Conversion 6 (%)**	**Selectivity (%)**
1	KG-60-NH_2	31.5	49	64
2	KG-60-$NHCH_2(NH_2)$	84	87	96
3	KG-60-$NHCH_3$	≥98	100	≥98
4	KG-60-NEt_2	≥98	100	≥98
5	KG-60-TBD	≥98	100	≥98

Table 1

The use of secondary, tertiary amine and TBD supported leads to optimum results in terms of yield and selectivity (Table 1, Entry 3-5), which are respectively 98 and 100%.

Only in the case of the primary amine (Table 1, Entry 1) the conversion is only 49% and the selectivity 64% because of nitrostyrene telomerization on silica matrix. In all the other cases the great excess of **7** allows to achieve very good results by using different types of supported-amine.

Studies were successively made with the goal to reduce the amount of β-dicarbonyl compound **7** and to achieve more efficient synthetic process. The reactions were performed with the strongest basic catalyst KG-60-TBD by using stoichiometric ratio between the reagents **6** and **7**, in the presence of solvents (1.5 ml) with different polarity at room temperature. Results are collected in Table 2.

Entry	**Solvent**	**Conversion 6** (%)	**Yield 8a** (%)	**Selectivity** (%)
1	CH_2Cl_2	88	70	79
2	EtOH	92	67	73
3	Toluene	63	40	63
4	EtOAc	90	92	98
5	CH_3CN	89	69	78
6	Tert-butanolo	53	53	>99
7	THF	86	73	85

Table 2

Ethyl acetate was the best solvent (Table 2, Entry 4) but for solubility reason and with the aim to transfer the synthetic process to a continuous flow system THF (Table 2, Entry 7) was selected as reaction solvent for further investigation. In particular the use of THF allows to obtain good value of yield 73% but a decrease selectivity in comparison with ethyl acetate, respectively 98 and 85%; even if we didn't observed any by-product.

In order to understand the selectivity decrease reagent **6,** dodecane and KG-60-TBD were inserted in a flask and the mixture was stirred for 1 hour at room temperature. The amount of nitrostyrene was monitored by GC and NMR-^{1}H showing a 10% losing. After this test it was more clear the problem connected with the reactivity of nitrostyrene on siliceous material due to telomerization giving short polymers.

Different catalysts were studied, under the same conditions, in order to improve the result obtained by using stoichiometric ratio between **6** and 7 and THF as solvent, the results are reported in Table 3:

Entry	Catalyst	Conversion 6 (%)	Yield 8a (%)	Selectivity (%)
1	KG-60-NH_2	73	8	11
2	KG-60-$NHCH_3$	92	76	82
3	KG-60-NEt_2	81	43	53
4	KG-60-TBD	86	73	85
5	KG-60-HMDS-TBD	88	82	95

Table 3

The higher yield and selectivity observed with TBD supported catalysts are mainly ascribable to the higher basicity resulting in a higher concentration of the active acetylacetone carbanion[11]. This promotes an increase of the Michael addition rate and shortens the permanence time of the very reactive nitrostyrene in contact with the siliceous material, thus minimising the by-product formation (Table 3, entry 4). For the same reason similar results are obtained with KG-60-$NHCH_3$ (Table 3, Entry 2).

Entry 5 shows an improvement of selectivity reaction using KG-60-TBD-HMDS (loading 0.73 mmol/g), in particular after 4 hour, yield and conversion were achieved respectively: 82 and 88%.

In conclusion the activity of KG-60-TBD catalyst was strongly affected by the polarity of the solvent, since the reaction involves charged species in the transitions state (Table 2, entries 1, 3 and 7). In particular, it was found that the higher the polarity of the solvent, the higher the nitrostyrene conversion and product yield.

The maximum catalytic efficiency was observed when acetylacetone was utilised as solvent-reagent, since in these conditions the concentration of the acetylacetone anion reaches the maximum value (Table 1, entry 3, 4, 5).

A seemingly anomalous behaviour was observed when the reaction was carried out in ethanol (Table 2, entry 2): indeed the high nitrostyrene conversion (92%) was accompanied by a surprisingly low yield value of product **8** (67%). However, this result can be rationalised taking into account that ethanol is a protic solvent able to catalyse the nitrostyrene polymerisation, that can also be promoted by the silica surface free silanols[12].

Interesting results were achieved by preventing the negative effect of the surface silanols through silanization with hexamethyldisilazane (HMDS) using KG-60-HMDS-TBD as catalyst with a molar ratio acetylacetone/nitrostyrene = 1:1 (Table 3, entry 5)[13].

This result can be improved by using the molar ratio 3:1 acetylacetone/nitrostyrene, under these conditions the product **8a** was obtained in good yield and selectivity, respectively of 87 and 89% (Table 4, Entry 1), in 1 hour at room temperature.

The procedure could be efficiently applied to other β-dicarbonyl compounds such as ethyl acetoacetate **7b** and diethylmalonate **7c** (Scheme 6) using KG-60-HMDS-TBD as catalyst. Illustrative synthetic results are reported in Table 4.

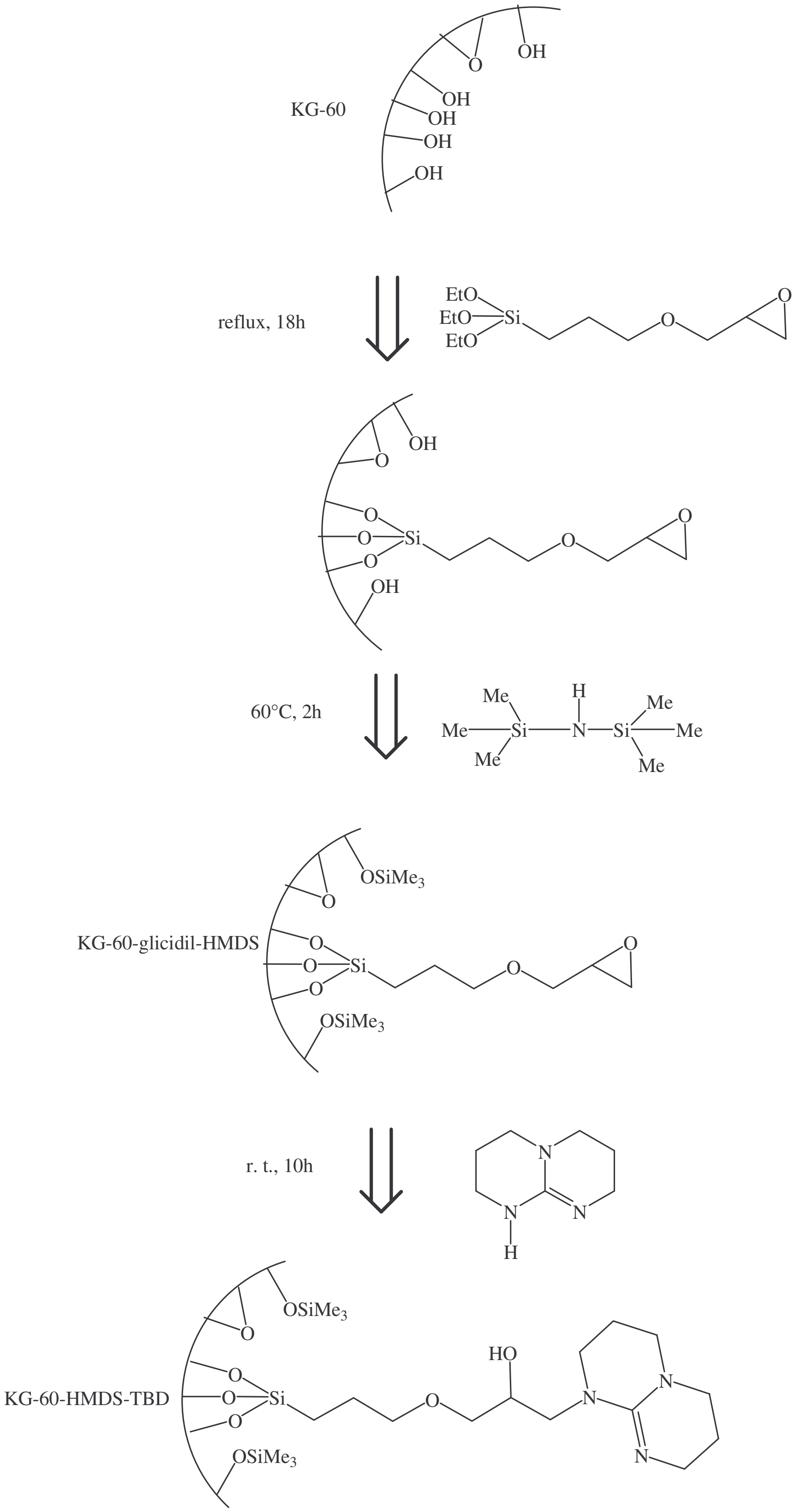
Entry	**R^1**	**R^2**	**Yield (%)**	**Conversion 6 (%)**	**Selectivity (%)**
1	CH_3	CH_3	87	89	98
2	CH_3	OEt	90	93	97
3	OEt	OEt	62	85	73

Table 4

The lower reactivity observed with diethyl malonate (Table 9, entry 3) is likely ascribable to the lower pK_a value of the active methylene function[14].

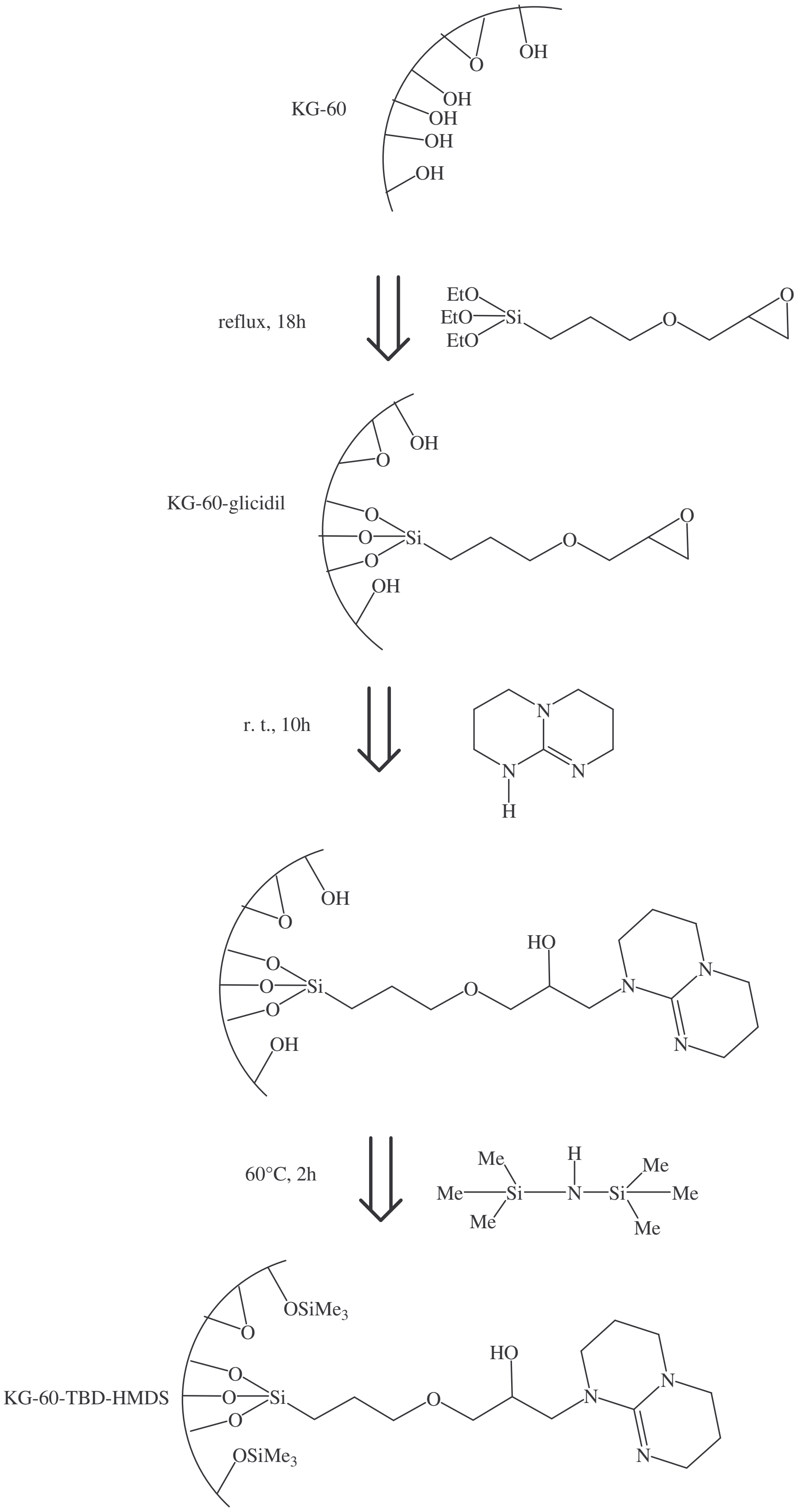
The preparation of KG-60-HMDS-TBD was optimized after some tries, in fact the silica capped can be prepared following two different pathways A and B (Scheme 7, 8):

Pathway A



Scheme 7

Pathway B



Scheme 8

The catalyst KG-60-HMDS-TBD synthesized by following way A is able to catalyze the Michael reaction with good results in terms of yield (82%) and selectivity (95%) (Table 3, Entry 5). On the other side if the silanol groups capping is performed before TBD binding (Scheme 9) the catalyst activity showed a drastically decrease in terms of selectivity (85%) and similar yield (80%). This result seems to be due to a cooperative role played by the OH group formed during the reaction between TBD and the epoxide moiety (Figure 3).

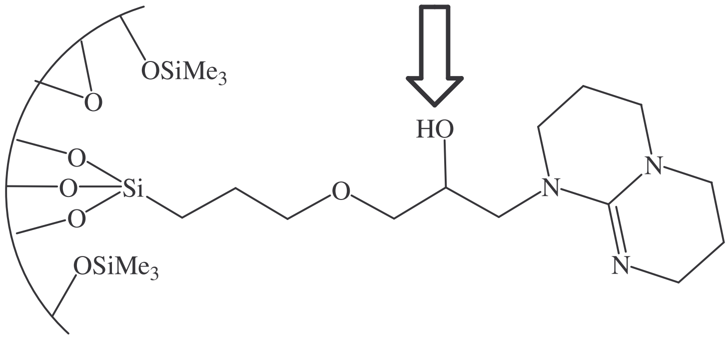


Figure 3

The hypothesis is partially confirmed by two additional tests based on different capping conditions following Pathway B:

1. double amount of HMDS, 60°C and 2h;
2. same amount of HMDS, reflux, 12 h.

In both cases the nitrostyrene conversion is high and the yield value lower, respectively 30 and 48 % in comparison with the result previously achieved. So stronger reaction conditions in terms of molar ratio and temperature lead to less active catalysts for the Michael addition between nitrostyrene and β-dicarbonyl compounds.

All the catalysts were characterized by FT-IR technique.

In particular the FT-IR spectra collected on KG-60-TBD, KG-60-HMDS-TBD and KG-60-TBD-HMDS, show the band 1636 cm^{-1} which is diagnostic of the stretching of the double bond carbon nitrogen of the guanidine species (Figure 4). Comparing FT-IR spectra recorded on KG-60-HMDS-TBD and KG-60-TBD-HMDS materials the unchanged band corresponding to the guanidine confirms the presence of the base. Besides the spectra recorded on KG-60-TBD-HMDS looks more similar to that obtained with KG-60-TBD.

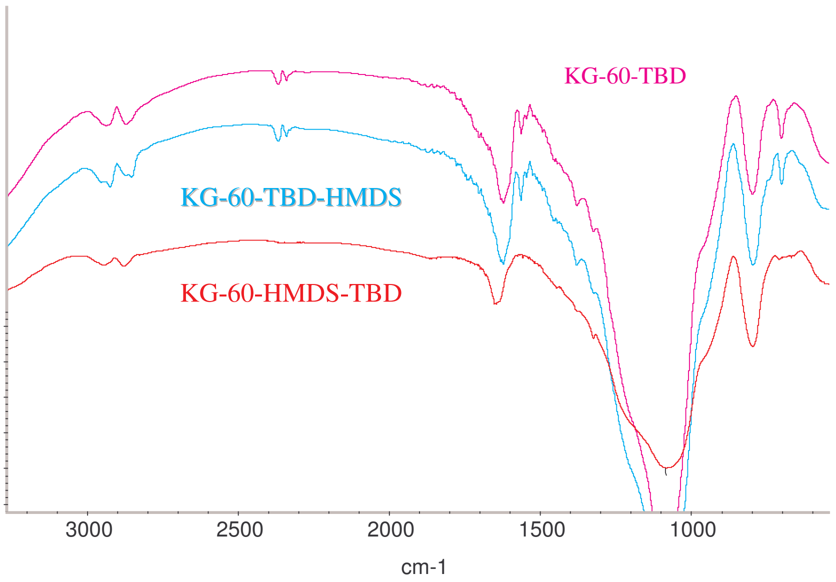


Figure 4

The catalyst preparation was monitored by FT-IR during the following steps, in Figure 5 are reported the FT-IR spectra recorded by using pathway A:

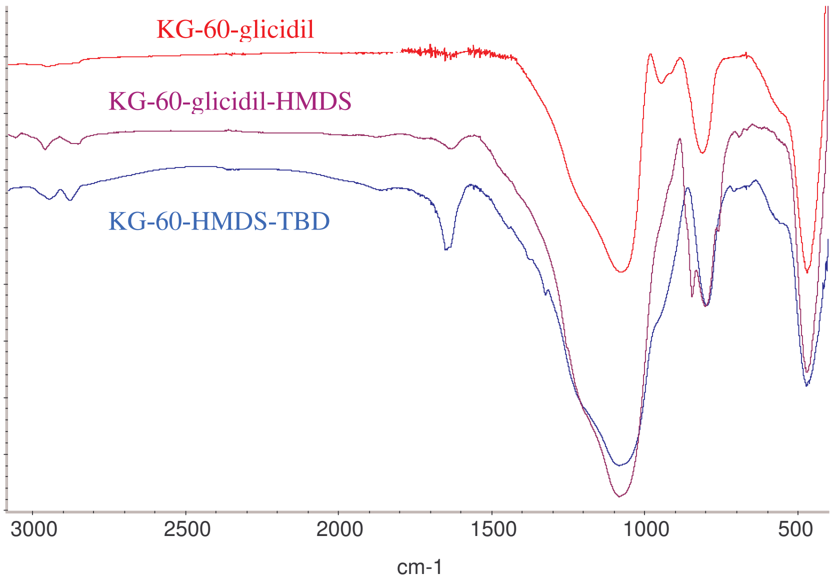


Figure 5

Finally the FT-IR spectra recorded for KG-60-TBD- HMDS synthesis (Pathway B) are collected in the following Figure:

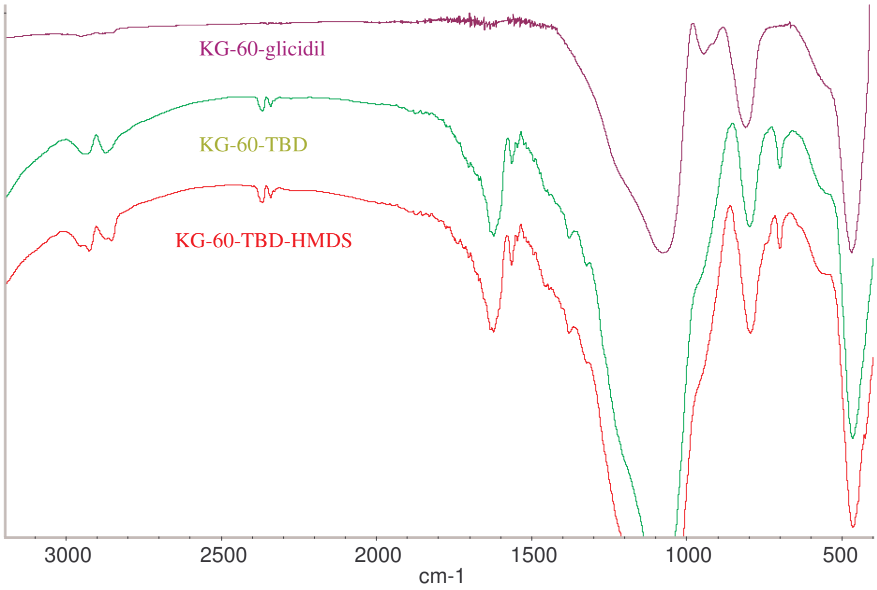


Figure 6

These spectroscopic data, correlated with the catalyst activity above explained, strongly support the hypothesis that the catalyst KG-60-HMDS-TBD is bifunctional.

Products **8a-c** gave melting points and spectral data consistent with the reported ones[15,16,17]

1d.3 Experimental section.

Michael Addition

1. β-dicarbonyl compound as reagent/solvent

In a tubular reactor nitrostyrene **6** (0.298g, 2 mmol) was inserted under nitrogen, then the selected catalyst (10% mmol) and finally the Michael donor **7** as reagent solvent (3.3 ml, 32 mmol). The mixture was stirred at room temperature for 4 hours. After that the catalyst was filtered, washed with ethyl acetate (15 ml) and recovered while the crude was collected and analyzed by GC instrument.

2. Molar ratio 1:1 nitrostyrene: β-dicarbonyl compound

To a solution of nitrostyrene (0.30 g, 2.0 mmol) in the selected solvent (1.5 ml), β-dicarbonyl compound (2.0 mmol) and the catalyst (10% mmol) were added. The mixture was stirred at room temperature under nitrogen for 4 hours. The catalyst was filtered and washed with ethyl acetate (15 ml) and the crude was collected.

KG-60-HMDS-TBD Silylation[18]

Silica gel KG-60 (8 g), previously heated at 350 °C for 3 hours and dried by vacuum at room temperature for 2 hours, was introduced into a flask containing dry toluene (120 ml). (3-glycidyloxy-propyl)trimethoxysilane (4.0 ml, 17 mmol) was added and the mixture was heated at reflux under stirring for 18 hours. The modified silica was filtered and washed with dichloromethane (20 ml). The powder was then mixed with HMDS (19.4 g, 120 mmol) and the mixture was heated at 60 °C under stirring for 2 hours. The powder was filtered and washed with dichloromethane (20 ml). The powder was then introduced into a flask containing a solution of TBD (2.45 g, 17.58 mmol) in dry toluene (120 ml) and the mixture was stirred at room temperature for 10 hours. The catalyst was filtered, washed with dichloromethane (20 ml) and extracted by Soxhlet apparatus for 10 hours by using dichloromethane/diethyl ether 1:1 solution (200 ml). Finally, the catalyst was filtered and dried under vacuum at room temperature.

For Michael addition we have performed the Sheldon test[19] confirming the inactivity of the filtered reaction mixture and the reusability of the catalyst in both cases.

1d.4 References.

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[11] The high catalytic activity of the silica-supported strongly basic TBD catalyst was shown in carbamate and carbonate synthesis: S. Carloni et al., *J. Catal.*, **2002**, 205, 199.

[12] Blank experiment confirmed that nitrostyrene was telomerized in ~15% yield upon prolonged stirring with KG-60 silica at room temperature

[13] It is indeed reported that the surface of pure silica gel is covered with silanol groups, at a maximum concentration of 8 Brönsted acid OH groups per nm^2 with a pK_a value ≈6: G. Fink et al., *Chem. Rev.*, **2000**, *100*, 1377.

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CHAPTER 2

Organic synthesis using catalysts supported onto different materials in simple laboratory and micro-structured flow system.

2a. Continuous flow systems.

2a.1. General Introduction

In recent years the synthesis of organic compounds using polymer-supported catalysts (PS) or reagents[1,2] has been of great interest in flow system[3,4,5,6,7,8,9,10].

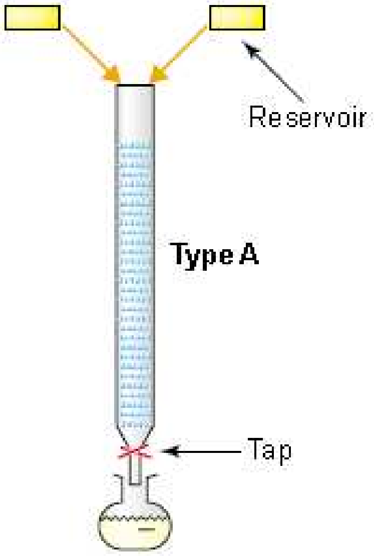
This approach represents a relatively new area of study in rapid progress and it promises to improve the ease, efficiency and automation of liquid-phase synthesis.

Flow system have several advantages over conventional batch reactions.

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

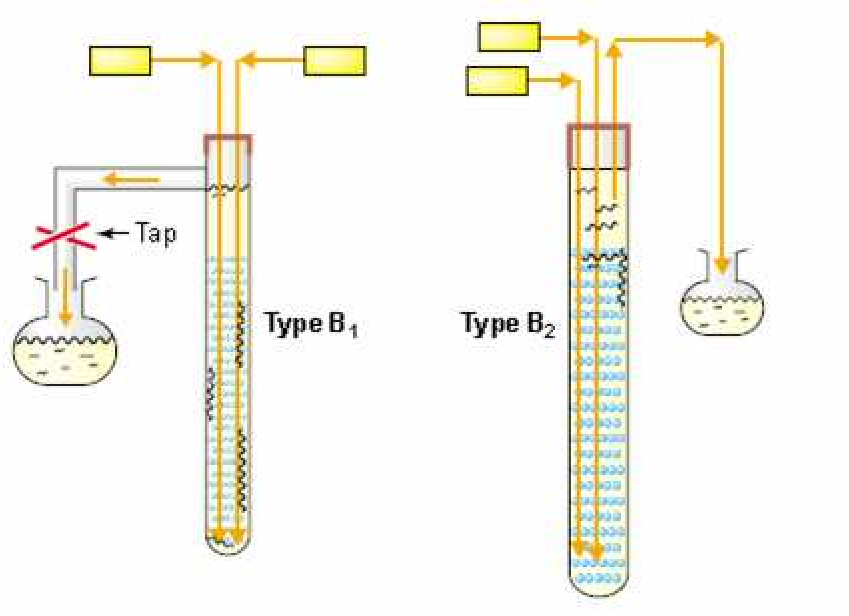
There are three different possibilities of working in flow system:

A)



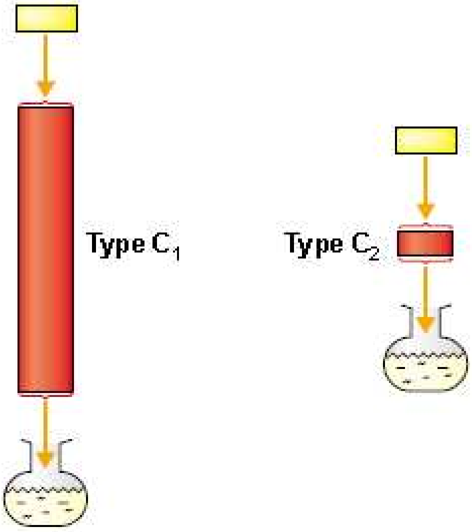
Type A is constituted by a simple packed catalytic bed (powder or beads polymer) in a glass column that is equipped with a jacket for column heating and cooling. The reactant solution is introduced to the column by gravity feed or by pumping through a syringe or peristaltic pump. The elute flow trough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

B)



<u>Type B</u> has the feature that the solution is pumped down from the top via long syringe needles into the bottom of the glass tube containing powdered or beads polymer. The product flow upwards or overflow trough a side arm into a receiver (B_1) or is pumped out from the top of the column (B_2).

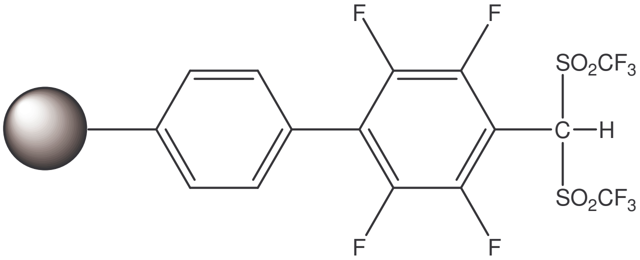
C)



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

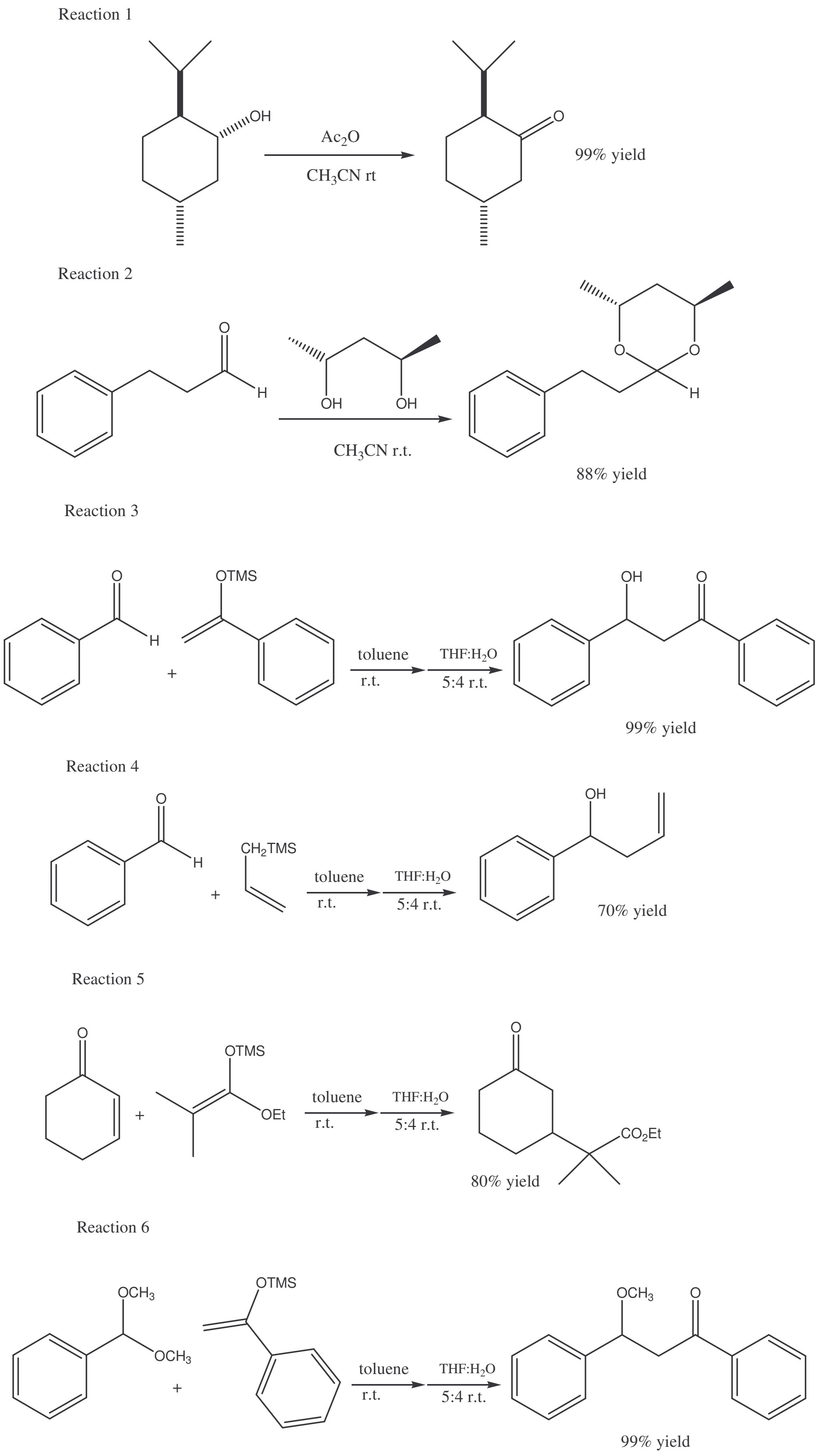
All these systems have the advantages above reported but some drawbacks too. For example if the catalytic bed has swelling proprieties that change markedly as the reaction proceeds or as the solvent changes, the column can be destructed or not tighten anymore to the external cover. Besides it is well known the possible formation of preferential pathways when the catalytic bed is packed that decreases the catalyst accessibility and the productivity.

The first use of a PS catalyst in a solution phase system was almost certainly the use of column of acidic or basic ion-exchange resins[11].
In Scheme 1 are reported important examples of organic reaction performed using PS super Bronsted acid (**1**) in Flow System; the support is constituted by microporous 2% crosslinked polystyrene beads[12] mixed with celite and packed into a 2 mL syringe.



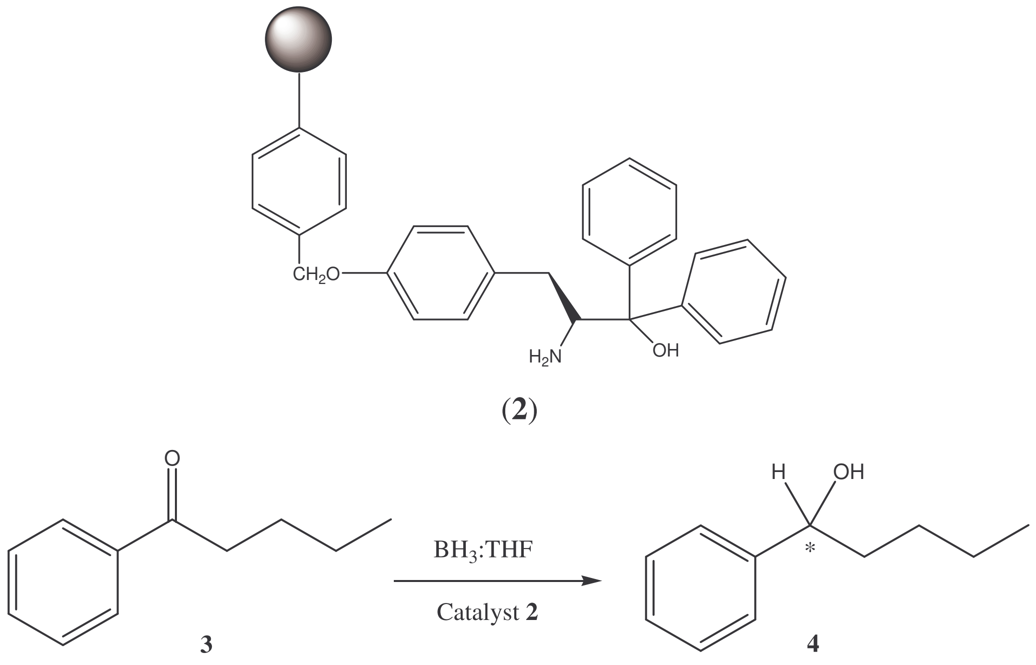
(**1**)

Many different reactions, such as ester formation, synthesis of cyclic acetals, the Mukaiyama aldol reaction, the Sakurai-Hosomi reaction, the Mukaiyama-Michael addition reaction were performed achieving very good results. When a mixture of L-menthol and acetic anhydride in acetonitrile was passed once through the column over 1 h at ambient temperature, the ester was formed in 99% yield: see Reaction 1 (Scheme 1). Other esters were synthesized similarly. Other acid-catalyzed reactions carried out were the synthesis of cyclic acetals (Reaction 2), the Mukaiyama aldol reaction (Reaction 3), the Sakurai-Hosomi reaction (Reaction 4), the Mukaiyama-Michael addition reaction (Reaction 5), and the Mukaiyama aldol-type reaction (Reaction 6).


Reaction 1
OH
Ac$_2$O
CH$_3$CN rt
O
99% yield
Reaction 2
O
H
OH
OH
CH$_3$CN r.t.
O
O
H
88% yield
Reaction 3
O
H
OTMS
+
toluene
r.t.
THF:H$_2$O
5:4 r.t.
OH
O
99% yield
Reaction 4
O
H
CH$_2$TMS
+
toluene
r.t.
THF:H$_2$O
5:4 r.t.
OH
70% yield
Reaction 5
O
+
OTMS
OEt
toluene
r.t.
THF:H$_2$O
5:4 r.t.
O
CO$_2$Et
80% yield
Reaction 6
OCH$_3$
OCH$_3$
+
OTMS
toluene
r.t.
THF:H$_2$O
5:4 r.t.
OCH$_3$
O
99% yield

Scheme 1

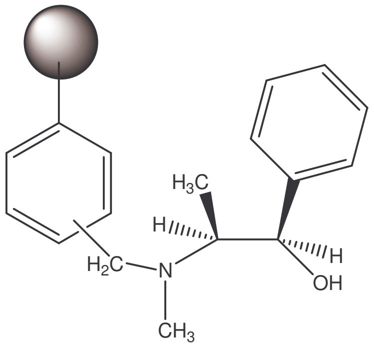
There are specific studies of PS catalyst (**2**) [13, 14, 15, 16 17] in flow system involving enantioselective reactions (Scheme 2) as following showed:



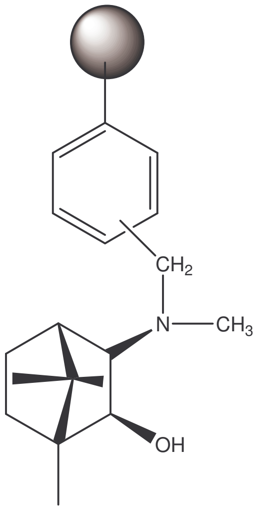
Scheme 2

The valerophenone **3** was reduced to the corresponding alcohol **4** using a PS chiral amino-alcohol **2** in a fluid-bed reactor. In particular with flow rates of 0.4 and 0.8 ml/min, corresponding to residence times of 30-60 min, the desired product **4** was obtained with *ee* of 83-93% similar to the results achieved under batch conditions.

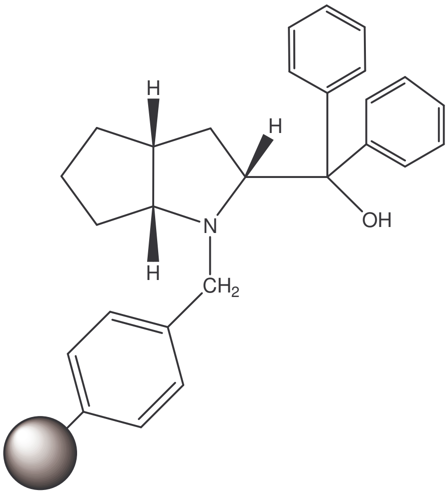
Itsuno et all developed a flow system for the production of chiral alcohols **9** from aldehydes **8,** with diethylzinc and different catalysts as: PS-ephedrine **5**, crosslinked polystyrene with camphor-derived residues **6**. The research group of Luis and Martens used a flow system based on 90% mol of divinylbenzene containing 10% mol of the catalysts residues **7** (Scheme 3), for the synthesis of (R)-1-phenylpropanolo in 85% yield and 99% *ee*.



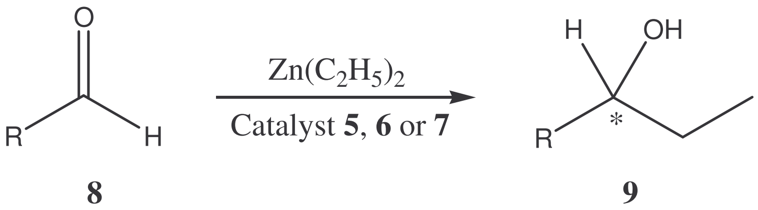
(5)



(6)



(7)

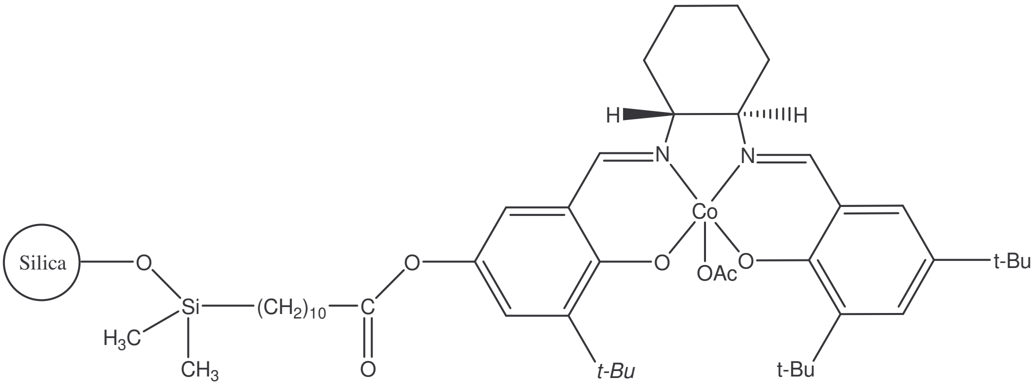


Scheme 3

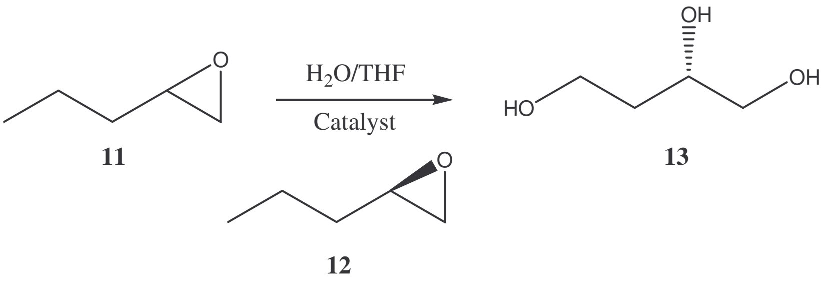
With optimum conditions for example benzaldehyde, using catalyst **5**, gave the corresponding alcohol in 98% yield and 98% *ee*, which are values substantially better than those obtained from similar batch reactions.

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

Annis and Jacobsen studied the hydrolytic kinetic resolution of epoxides (39% yield, *ee* 94%) by using the chiral catalyst supported on silica gel **10** (Scheme 4). The column could be regenerated successfully.



(**10**)



Scheme 4

Frechet's group performed different types of reactions[18,19,20] by grafting the functionalities to polymer tubular monoliths with excellent flow proprieties.

Kirschning[21] developed new monolithic materials (polymer/glass) composites and a new technique, named Passflow, applied to microreactor devices. Besides the same research group combined important different concepts such as heterogeneous catalysis, reaction microwave assisted, microreactors and non classical solvents[22].

It is important underline that ideally a reaction using a catalyst would go to completion with only one pass through the system. However it should be take in count that the most organic reactions are quite slow, so it will be necessary use low flow rate in order to along the residence time. If the reaction is not fast enough the output of the reactor will be recycle round the system.

The catalyst regeneration could be considered convenient if it occurs in one easy reaction.

2a.2. References.

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2b. Silica coated ceramic honey comb cube.

2b.1. State of the art and applications.

According to some authors, development of monolithic catalysts and/or reactors represents one of major achievements in the field of heterogeneous catalysis and chemical reaction engineering of the recent years. The term ''monolith'' has its origin in Greek language. It is a combining form of mono ''single'' and lithos ''stone''[1].

With respect to their basic construction material there are ceramic (mainly cordierite) and metallic (stainless steel, metal alloys, etc.) monoliths[2,3,4,5,6,7,8,9,10,11].

Schematic presentation of a ceramic monolithic catalyst is shown in Figure 1.

A monolithic catalyst is most commonly made by applying the layer of a catalytically active component or appropriate support (e.g. g-Al_2O_3, SiO_2, ZrO_2, carbon, zeolites, etc.) containing one or more catalytically active components (Pt, Pd, Rh, zeolites, etc.) to the walls (or inside the walls) of the basic, most frequently inert monolith structure. This process is known as coating or washcoating. If the monolith structure is available in the required support material, the catalytically active phase can be directly deposited on the monolith. However, if the monolith is not available in the required support material, this support material should be coated on the monolithic substrate first.

It is crucial that the support of a catalytically active component(s) adheres strongly to the basic inert monolith structure.

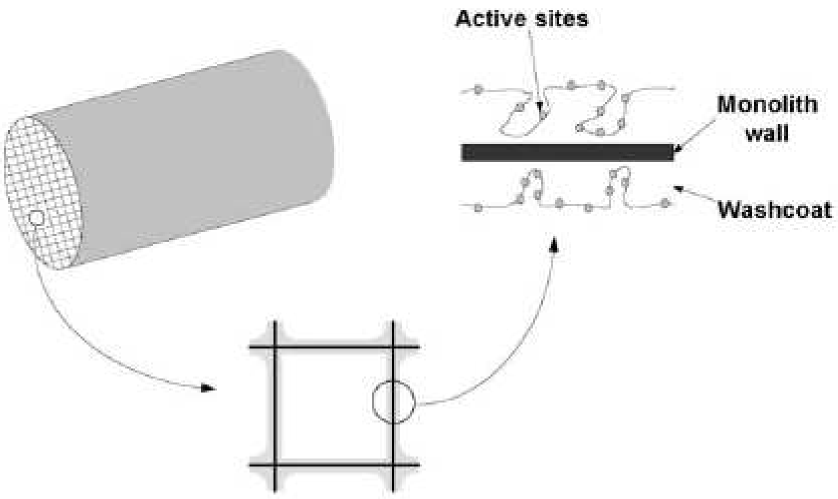


Figure 1.

Relevant to wall porosity two different types of ceramic monoliths can be distinguished: porous monoliths and monoliths of a limited porosity. Most metallic monoliths are nonporous. There is a third group of monolithic catalysts distinguished by their basic structure (e.g. integral or incorporated monoliths). The examples are monolithic catalysts constituted of a single catalytic active component or appropriate mixtures of catalytically active components (V_2O_5/TiO_2, zeolites, combinations such as TiO_2, V_2O_5 and WO_3, VOx/ TiO_2/SiO_2, etc.)[8,10,12,13]. Such monoliths are often used in the treatment of exhaust gases generated in the stationary sources (e.g. during selective reduction of nitrogen oxides (NOx) with ammonium as a reductant)[13,14].

Specific surface of the ceramic and metallic monolith support is very small (in the case of cordierite ceramic monolith it is ca. 2 $m^2 \cdot g^{-1}$)[14].

The procedures that utilise cordierite as a raw material consists in kneading together cordierite powder, water and an agglomerating agent, which can be polyethylene oxide, cellulose, methylcellulose or their mixtures[15,16,17]. The paste thus formed is extruded in the desired shape, dried and calcined at 1300–1400 ◦C for 3–4 h. Sometimes, in the composition of the dough small quantities of carbonates, saw-dust or starch are added in order to improve the macroporosity of the final product[18,19].

Likewise, other additives have been used with higher thermal expansion coefficients, such as spinels, mullite or zirconia[20,21,22] to improve the mechanical properties of the monolith.

The most common application of monolithic catalysts and reactors is in abatement of pollution from non-stationary sources (treatment of exhaust gases Fig. 2 from cars and other vehicles, decomposition of ozone in aircrafts, etc.) and from stationary sources (selective reduction of NOx, destruction of volatile organic compounds (VOC), catalytic combustion). More details about commercial application of monolith structures in the above processes can be found in the literature[23,11,13,14,24,25,26,27].

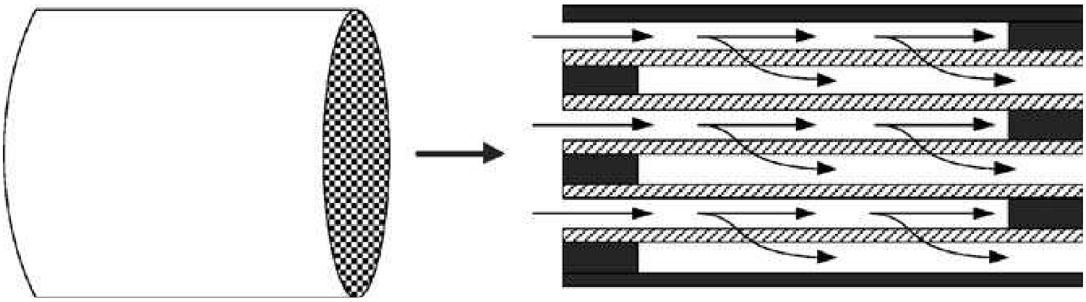


Figure 2.

However every decision about the use of ceramic monolith catalysts must take into consideration their disadvantages which are generally[24,9,10]: (a) in the ceramic monoliths with almost nonporous walls of the channels the radial mass transfer between adjacent channels is very limited and the radial heat transfer occurs only by conduction through the solid walls; (b) due to low thermal conductivity ceramic monoliths are operated at nearly adiabatic conditions; (c) the risk of cracking of the ceramic monolith structure under conditions of rapidly changing temperatures; (d) basic design and preparation of monolithic catalysts, versus conventional ones, is more complex and costly (this disadvantage equally refers to ceramic and metallic monolith catalysts). Therefore, for chemical controlled reactions the monolith may not contain sufficient catalyst to yield the desired conversion efficiencies.

Anyway, synthetic processes performed in a continuous flow system made with monolithic reactors show great potentialities and possible improvements by environmental and so economical point of view. Consequently many research groups are focusing their efforts to exploit this topic.

In this project we decided to investigate the immobilization of organic catalyst on ceramic monoliths useful for realizing continuous flow process.

2b.2. Silica coating and catalyst immobilization.

The immobilization of 3-aminopropyltriethoxysilane, as basic catalyst, performed directly on the ceramic material by tethering technique. was unsuccessful. This result can be easily explained considering the low number of free silanol groups present on the ceramic surface.
So a coating technique, ''dipping technique''[28], was performed on honeycomb monolithic supports (dimensions 1.5, 1.5, 1.6 cm) like a distribution of 16 channels.
A commercial colloidal silica solution, named Ludox AS-30, was utilized showing the following features:

- Solids (wt%): 30
- Density (g/ml): 1.2 a 25°C
- pH: 9.1
- Surface Area (m^2/g): 230

The washcoating method applied is based on a methodology reported in literature[29] and it involves some steps, such as plunging, drying, calcinations, et. At first all monoliths were dried at 120°C for 2 hours, and each one was weighted. Then they were plunged into the selected colloidal solution, Ludox AS-30, respectively for 5, 10, 15, 20 seconds. The excess of silica solution was eliminated by pressured air and the monoliths were horizontally rotated around their axes for 1 hour at room temperature in order to obtain a well distributed coating. The progressive drying of the monolith surface can be observed. Finally they are calcined at 450°C for 1 hour.
In the following table are reported some results about coating tests obtained with 5 seconds of immersion, in particular the weight increasing after calcinations was evaluated.

Entry	Δg (g)	% W[a]
Mono3	0.253	11
Mono7	0.2799	10.8
Mono 13	0.2246	9.7
Mono 31	0.1789	10.9
Mono 32	0.223	10
Mono 33	0.2017	11
Mono 34	0.1903	9
Mono 39	0.1855	10.8
Mono 40	0.2065	11
Mono 41	0.2375	12
Mono 42	0.1986	10.3

Table 1. Coating step (immersion time:5s).

[a] % weight of coating respect of initial monolithic weight.

The coating step showed a quite regular trend. Some tests of coating with AS-30 silica colloidal solution and 10 seconds of immersion are shown in Table 2.

Entry	Δg (g)	% W
Mono4	0.230	9.7
Mono8	0.2477	10.8

Table 2. Coating step (immersion time:10s).

A longer immersion time didn't improve the amount of silica coating and in particular for 15 and 20 seconds immersion no regular trend was obtained.

Following these results other coating tests with different silica colloidal solutions were performed (see Table 3); the main Ludox features were reported:

i) Ludox AM-30:

Solids (wt%): 30

Density (g/ml): 1.21 a 25°C

pH: 8.9

Surface Area (m^2/g): 220

ii) Ludox AS-40:
Solids (wt%): 40
Density (g/ml): 1.295 a 25°C
pH: 9.1
Surface Area (m^2/g):135

Entry	Ludox	Δg (g)	% W	Immersion time
Mono 11	AM-30	0.1901	8.2	5
Mono 12[a]	AM-30	0.2169	8.3	10
Mono 27	AS-40	0.251	15	5
Mono 28	AS-40	0.2783	14	5

Table 3. Coating by different silica colloidal solution Ludox.
[a]Immersion time didn't have any influence.

The mechanical stability of the coated monolith was checked by immersion in water ultrasonic bath (15 seconds). A medium weight lowering calculated around 2 % confirmed the mechanical stability of the samples analyzed.

Double coating.

A double coating, using AS-30 silica colloidal solution and immersion time of 5 seconds for both plugging, was performed. The results obtained are reported in Table 4:

Entry	Δg (g)	% W
Mono 17	0.2477	16
Mono 18	0.2559	16
Mono 19	0.2744	15
Mono 20	0.3225	16.7
Mono 21	0.437	14
Mono 22	0.2897	16.8

Table 4. Double coating.

The first coating represented the 9% of the total value.

The mechanical stability of the coated monolith was checked by ultrasonic test (in water for 15 seconds). A weight lowering of 10% was observed indicating that it is not convenient to perform a double coating in terms of time and material consuming.

Surface Activation.

Some information in literature[30] are presented concerning surface activation of materials, such as cordierite or in general ceramic foams. In fact to slightly increase both the ceramic surface area and a certain surface activation (by inducing the formation of silanol groups), the monolith was placed into an alkaline solution (1 M NaOH) and heated at 110 °C for 2 h. The aim of this activation step was to favour the monolith surface coating by facilitating the formation of links (covalent Si-O-Si bonds) with colloidal silica particles.

After basic treatment the monolith was washed with deionizated water within neutral PH then dried for 2 hours at 150°C.

Finally the surface was coated by AS-30 silica colloidal solution and then the catalyst tethered (Mono 25); in the same time the direct catalyst tethering was tested (Mono 30).

Catalyst Immobilization.

In the preliminary stage the weight difference before and after coating was evaluated.

The silica-coated monoliths were modified by 3-aminopropyltrietoxysilane tethering following the classical approach by De Vos et all[31]. The procedure is partially modified using a great excess of silane agent in order to use the same concentration and to cover the monolith structure. The coated monolith was heated at reflux in toluene$_{dry}$ (35 ml) for 1 hour and then the 3-aminopropyltriethoxysilane was added (3.20 ml, 3.033g) dropwise. The mixture was stirred at the same temperature for 18 hours. The monolith was then washed in a Soxhlet apparatus for 24 hours (solvents CH_2Cl_2:Et_2O 1:1, 300 ml) and dried under vacuum.

In order to avoid mechanical abrasion of the ceramic material the monolith was suspended, by using a metallic net, inside the reaction mixture under magnetic stirring.

The loading value of significant samples was calculated by elemental analysis (Table 5).

The ceramic support was completely destroyed because only a portion of the sample didn’t afford a correct and reproducible loading value. This fact is due to a not uniform silica coating or catalyst anchoring, but it could be also connected with the sensibility of the analysis itself. In fact the inorganic support composed the major part of the sample.

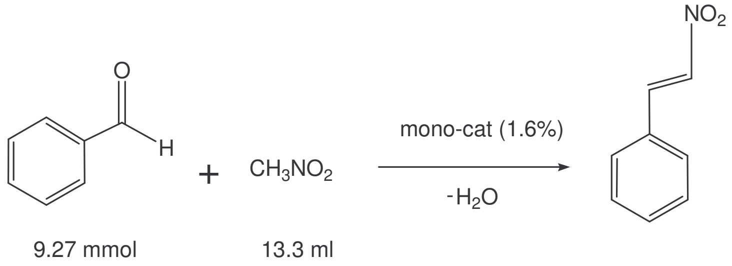
Entry	**%N**	**%C**	**%H**	**Loading (mmol/g)**
Blanc	0	0	0	-
AS-30	0.22	0.69	0.17	0.157
AS-40	0.21	0.68	0.17	0.15

Table 5. Loading value.

The %N values showed a little amount of catalyst anchored to the support and it is not proportional to the silica coating amount, which is higher with the Ludox AS-40. The low catalyst concentration value obtained in comparison with the powder silica is probably due to the Surface Area of the monolith. It is reasonable to think that the number of the preformed channels is too low (see future tests).

2b.3. Results and discussion

The monolithic catalysts were tested in the model nitroaldol reaction (see Reaction Scheme 1) between benzaldehyde and nitromethane (reagent/solvent) in a batch system:



Scheme 1

First the blanc test, performed by using the silica coated ceramic monoliths without catalyst tethering, was negative. Moreover the monolith, after to be removed from the reaction medium and to be dried on air atmosphere, showed a significantly weight increasing due to the reagents absorption (~20%mmol).

In order to compare the results obtained with the powder silica catalyst (see section **1c**) the reactant solution concentration used was the same (73.7g/l) but the reaction time necessary to achieve significant conversion was 5h at 75°C.

The results were reported in the following Table:

Mono	**Ludox**	**Dipping time (sec)**	**Yield (%)**	**Conversion (%)**	**Selectivity* (%)**
3	AS-30	5	55	80	69
13	AS-30	5	59	77	77
8	AS-30	10	30	42	71
11	AM-30	5	13	30	43
12	AM-30	10	<5	-	-
21	AS-30	5	6	26	23
22	AS-30	5	<10	-	-
25	AS-30	5	43	62	69
30	AS-30	5	2	33	6

Table 6. Reactions test.

*The selectivity is calculated like ratio between yield and conversion.

The monoliths coated with Ludox AS-30 solution for a dipping time of 5 seconds achieved good conversion value 62-80% even if the catalyst amount was only 1.6%mol in respect of 9.27 mmol of benzaldehyde. The reaction scale was almost 4 times the batch reaction scale used. However the system showed immediately some drawbacks because the reaction selectivity (64-69%) is low and the reproducibility was not excellent (see mono 3, 13, 25).

The first point could be probably due to the lower reaction rate and the consequent longer reaction time; trace of by-product due to the CH_3NO_2 addition to the nitrostyrene already present in the reaction medium were detected by GC analysis.

The catalytic monolith 3 was reused in the same reaction conditions described above without washing or thermal pre-treatment giving 54% conversion and 17% yield.

Finally the recycle was performed following a solvent washing with EtOAc at 80°C for 2h (Mono 13), or a thermal pre-treatment at T=100°C for 2h (Mono 8) but results were unsatisfactory:

Mono	**Yield (%)**	**Conversion (%)**
13	22	57
8	17	43

Table 7. Recycling results.

The reagents/product absorption was evident by observing the monolith colour after reaction (Figure 3 block on the right side), showing some orange spots inside the modified channel.

Figure 3. Respectively from the left site: ceramic honey comb cube, silica coated ceramic cube, silica coated modified ceramic cube after use.

Leaching Test.

The definitive test for leaching[32] is performed by filtering the catalyst, at the reaction temperature, during the course of the reaction and allowing the filtrate to react further. If no further reaction is observed this is a strong evidence in support of heterogeneous catalysis. In traditional batch the catalyst filtration is done after cooling at room temperature, while the catalytic monolith, which is a unique block, can be easy removed from the reaction mixture. The test was negative in fact the reaction stopped when the monolith is removed.

Continuous Flow Process.

The reaction was performed using a triple bed of monoliths already modified (see Catalyst Immobilization) inserted in a special glass reactor which has the same cubic shape. It was equipped with a tap in the bottom and with an electrical heating belt. The reactant solution was passed trough the catalytic monolith by gravimetric feed at 75 °C for a total time of 1 hour. The product was collected in a receiver and analyzed by gaschromatography. The yield value was 10%.

Ceramic monolith powdered.

The monolith was powdered in a mortar and then was used in the nitroaldol model reaction without giving any benzaldehyde conversion. This results underlined the importance of the monolithic pre-formed structure in the reaction success.

In conclusion the present work described the use of a monolithic ceramic cube as catalytic reactor for organic synthesis catalyzed by heterogenised organic base. The system showed stable silica coating and following catalyst immobilization, otherwise the low surface area value of the cordierite affords to very low loading value. The small catalyst amount is strictly connected with the slow reaction rate, that represents together with the reagents adsorption, two important limitations for catalytic application up to now.

2b.4. References.

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2c. Packed-bed Silica Powdered Reactor

2c.1 Introduction

Use of catalysts immobilized onto solid supports for the liquid-phase fine chemical synthesis allows their easy separation from the reaction mixture and reuse for many runs, finally reaching great advantages such as saving energy, minimizing waste production and delivering products of higher purity[1]. Moreover, supported catalysts can be applied in packed-bed or monolithic reactors for continuous-flow processes[2,3].

These relatively new technologies offer many fundamental and practical advantages of relevance to the pharmaceutical and fine chemical industries such as facile automation, reproducibility, safety and process reliability[3,4,5]. The improved performance of these catalytic reactors is attributed to faster heat transfer and mixing as a result of the increased surface area-to-volume ratio[6].

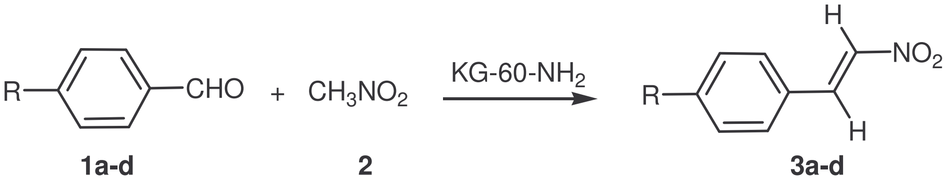
Despite the growing number of studies on this topic, only few reports discuss the use of catalytic packed-bed (micro)reactors applied to continuous-flow synthetic chemistry[7,8].

As a result of a more general project aimed at achieving basic information to design micro- and monolithic reactors for organic syntheses, we have recently patented the continuous-flow synthesis of enatiomerically enriched (*R*,*R*)-chrysanthemic acid through a tubular reactor packed with silica supported chiral copper(II)-BOX catalyst[9].

Besides a great number of products for fine, pharmaceutical and material chemistry with an ever increasing level of complexity has been developed over the past several decades through multistep synthetic methods. In multistep synthesis the preparative difficulties increase significantly with the number of steps mainly due to extensive isolation and purification operations. These drawbacks can be overcome by exploiting a multistep-sequential synthetic methodology, namely by adding reagents and/or catalysts in a sequential manner, without isolation of the previously formed intermediates[10]. Moreover, in many cases, multicomponent reactions can be utilized to assemble three or more starting compounds into the final target molecule in a one reaction vessel. The successful outcome of a given multistep sequential or multicomponent process depends on a fine balance of equilibria and a convenient sequence of reversible and irreversible steps[11]. In principle, the preparation of complex organic compounds can be also performed by employing a combination of column reactors with supported catalysts and/or reagents[12]. This approach makes use of columns packed with immobilized organic or inorganic catalysts/reagents. Starting materials are added to the top of the column and by means of gravity or pressure passed through the packing where they react giving the product recovered at the bottom of the setup[13]

2c.2. Nitroaldol Condensation under continuous-flow conditions.

Our studies were first focused on the set up of a catalytic reactor to perform the nitroaldol condensation under continuous-flow conditions (Scheme 1)[14].



1a R=H, **1b** R=Me, **1c** R=OMe, **1d** R=Cl

Scheme 1

The nitroaldol condensation (Scheme 1) was studied by using a tubular reactor. The reactor was prepared with an oil jacketed glass column (6.0 cm length x 0.8 cm inner diameter) packed with 0.23 grams of KG-60-NH_2 “diluted” into 0.77 grams of KG-60 silica previously heated at 350 °C for 3 hours. Both siliceous materials were sieved at 80 mesh before use.

The reactor was equipped with a tap and an electric belt for heating the column at the selected temperature; a thermoregulator directly inserted in the oil was applied in order to keep constant the temperature (Figure 1).

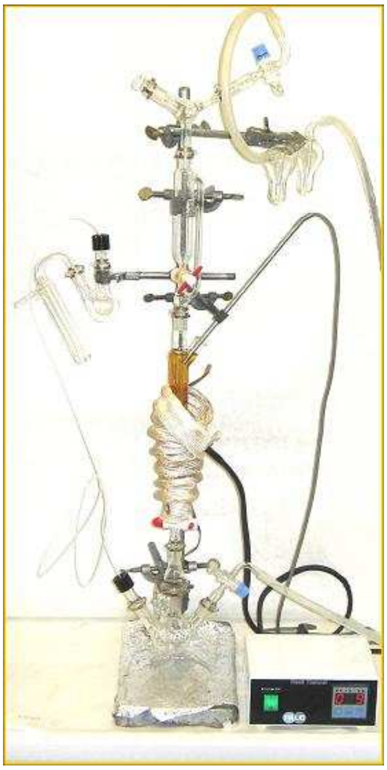


Figure 1

This simple laboratory flow system allowed to perform the reaction under inert atmosphere with recycling when necessary. Otherwise the reactant solution inserted by gravimetric feed or under nitrogen pressure was passed trough the packed bed and was collected in the down reservoir for being analyzed by gas-chromatography.

The column reactor was previously treated with nitromethane and successively utilized taking into account the optimum conditions found in the previous batch experiments (see section **1c**).

A solution of benzaldehyde (0.87g, 8.2 mmol) in nitromethane (4.2 ml) was passed through the column at different elution times.

Results are reported in Table 1.

Entry	Cat. mmol (%)	Time (min)	Temperature (°C)	Yield 3a (%)	Conversion 1a (%)	Selectivity[a] (%)
1	3	40	56	33	35	94
2	3	60	56	45	52	86
3	3	80	56	50	55	91
4	3	60	75	70	76	92
5	3	60	80	62	84	74
6	4.5	50	65	80	87	92
7	6	50	65	72	98	73

Table 1. Continuous-flow nitroaldol condensation of benzaldehyde and nitromethane (solvent-reagent) over KG-60-NH_2 catalyst (1.06 mmol/g propylamine loading), [a] (Yield/Conversion)x100.

A low pressure (by N_2 flow) was applied at the top of the column in order to keep the flow constant during the entire residence time.

Benzaldehdye **1a** (R=H) conversion and nitrostyrene **3a** yield were evaluated from the entire reaction mixture recovered at the end of the flow-through process.

By using 3% mol of KG-60 -NH_2 with respect to benzaldehyde passed, the conversion of **1a** and the yield of **3a** increased by increasing the reaction time from 40 to 80 minutes, reaching modest values at 56°C in all cases (35-55% **1a** conversion, 86-94% **3a** selectivity) (Table 1, entries 1-3).

Ideally the flow rate should be slow enough to guarantee full conversion of the starting materials and to give only the desired product at the end of the reaction. However, by directly applying to the column reactor the best reaction parameters achieved with batch experiments, the selectivity towards nitrostyrene **3a** dropped down mainly due to the production of 1,3-dinitro-2-phenylpropane by further addition of nitromethane to nitrostyrene. To overcome this drawback, the residence time was shortened to 50 minutes and the catalyst amount was increased to 4.5%; under these conditions a low pressure was applied in order to have a regular flow inside the column. The efficiency of the column reactor was greatly enhanced and product **3a** was obtained with 80% yield and 92% selectivity without need to isolate the intermediate nitroalcohol (Table 1, entry 6)[15].

The catalytic reactor can be efficiently reused after simple rinsing with nitromethane. A second reaction mixture was then passed through the reactor under the same previous conditions giving product **3a** in 76% yield and 96% selectivity.

The continuous-flow condensation process was extended to some aromatic aldehydes under the optimized conditions of 50 minutes elution time and 65 °C, giving the small series of substituted nitrostyrenes reported in Table 2 with interesting yields and selectivities.

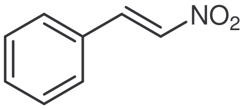
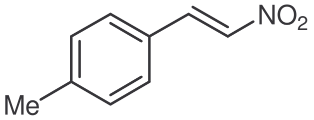
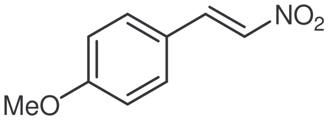
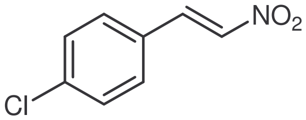
Entry[a]	**Product**	**3**	**Yield (Sel.**[b]**)** **[%]**
1		**3a**	80 (92)
2		**3b**	81 (93)
3		**3c**	83 (96)
4		**3d**	65 (93)

Table 2. Preparation of substituted nitrostyrenes *via* continuous-flow nitroaldol condensation over KG-60-NH_2 catalyst (1.06 mmol/g propylamine loading). [a]Experimental conditions: all reactions were performed using 8.2 mmol of the selected benzaldehyde in 4.2 ml of nitromethane in the presence of 0.35 g of KG-60-NH_2 and 0.65 g of KG-60; elution time: 50 min, temperature: 65 °C, [b](Yield/Conversion)x100.

From results reported in Table 2, it comes that the introduction of an electronwithdrawing substituent at the *para* position of the aromatic aldehyde results in a lower yield of the corresponding nitrostyrene (Table 2, entry 4). This phenomenon is in good agreement with the presence of supported imine intermediate. Indeed, in an early comparative study Santerre et al. reported that the rate of imine formation from substituted aromatic aldehydes and aliphatic amines greatly diminishes as the electronwithdrawing power of the substituent on the aromatic ring increases[16].

General procedure: Nitroaldol condensations under continuous-flow conditions:

KG-60 silica (0.77 or 0.65 g depending on KG-60-NH_2 amount), previously sieved to 80 mesh and dried at 350 °C for 3 hours, was mixed with the catalyst KG-60-NH_2 (0.23 g, 0.25 mmol or 0.35 g, 0.37 mmol, 3.0% and 4.5% mol with respect to benzaldehyde). The powder was packed in the reactor, an oil jacketed steel HPLC column (6.0 cm length x 0.8 cm inner diameter), together with nitromethane (10 ml). The jacketed column was heated to the selected temperature and a solution of the aromatic aldehyde (8.20 mmol) in dry nitromethane (4.2 ml) was passed under pressure at a selected flow rate by using a syringe pump. The crude was collected at the bottom of the column after rinsing with ethyl acetate (20 ml).

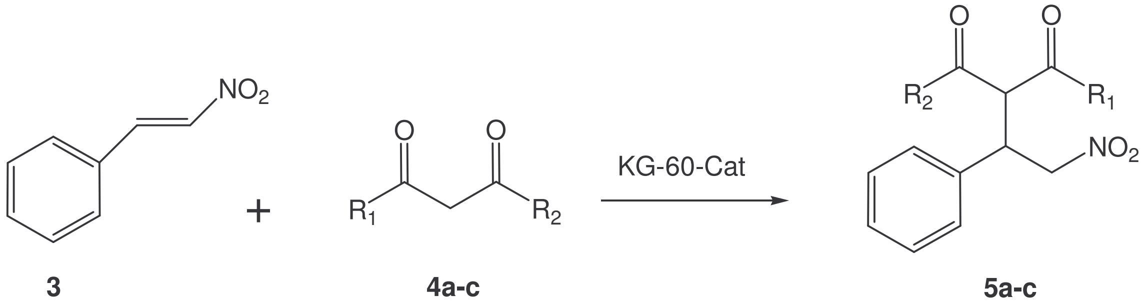
2c.3 Michael addiction under continuous-flow conditions.

We next investigated the continuous-flow Michael addition of acetylacetone to nitrostyrene by taking into account the preliminary studies made in the batch experiments (see Chapter **1d**). In particular the reaction was performed at different reaction conditions in order to achieve a real improvement in terms of productivity or space time yield.

The reaction was performed over KG-60-NEt_2 catalyst (1 g, 20%mol) using the Michael donor (Scheme 2) as reagent/solvent. The catalyst was packed into the column that was heated at 80°C by an external oil coating. The nitrostyrene (1.22 g, 8.2 mmol) was dissolved in Michael donor compounds (5mL, 49 mmol) and passed through the catalytic column by gravimetric feed in 1 hour. The crude was collected at the end of the column and analyzed by gas chromatography.
The results obtained were reported in Table 3:

Entry[a]	**R_1**	**R_2**	**Yield (%)**	**Selectivity[b] (%)**
1	OEt	CH_3	98	96
2	OEt	OEt	51	72
3	CH_3	CH_3	98	97

Table 3. [a] Experimental conditions: all reactions were performed using 8.2 mmol of nitrostyrene, 49 mmol of the β-dicarbonyl compound in the presence of 1.00 g of KG-60-NEt_2; elution time: 60 min, temperature: 80 °C, [b] (Yield/Conversion)x100.



4a R_1=R_2=CH_3; **4b** R_1=CH_3, R_2=OEt; **4c** R_1=R_2=OEt

Scheme 2

The same experiments were developed by trying to use a stechiometric ration between the reagents **3/4a-c** and THF like solvent, the temperature was decreased to 64°C, for 1 hour of elution time.(Table 4)

Entry[a]	**R_1**	**R_2**	**Yield (%)**	**Selectivity[b] (%)**
1	OEt	CH3	48	65
2	OEt	OEt	20	45
3	CH3	CH3	33	53

Table 4. [a] Experimental conditions: all reactions were performed using 6.66 mmol of nitrostyrene, 6.66 mmol of the β-dicarbonyl compound in 14 ml of THF in the presence of 1.00 g of KG-60-NEt_2; elution time: 60 min, temperature: 64 °C, [b](Yield/Conversion)x100.

The selectivity values suggest that these reaction conditions favoured the formation of byproducts due to a low reaction rate.

The Michael reaction was performed by using KG-60-TBD and then KG-60-TBD-HMDS (see Chapter **1b**) catalysts in order to improve the reaction selectivity (Table 5).

Entry[a]	**Catalyst**	**Yield 5a (%)**	**Selectivity (%)**
1	KG-60-TBD	67	73
2	KG-60-TBD-HMDS	53	95
3[b]	KG-60-TBD-HMDS	60	95
4[c]	KG-60-TBD-HMDS	54	96
5[d]	KG-60-TBD-HMDS	24	37
6[e]	KG-60-TBD-HMDS	62	87

Table 5. [a] Experimental conditions: all reactions were performed using 6.66 mmol of nitrostyrene, 6.66 mmol of the β-dicarbonyl compound in 14.0 ml of THF in the presence of 1.00 g of KG-60-TBD-$SiMe_3$; elution time: 60 min, temperature: 25 °C, [b] Temperature 50°C, [c] 2.0g KG-60-TBD-HMDS, [d] 1.0g of KG-60-TBD-$SiMe_3$ dispersed in 1.0g of SiO_2, , [e] 1.0g of KG-60-TBD-$SiMe_3$ dispersed in 1.0g of Al_2O_3 neutral.

From entry 4 it comes that the reaction didn't improve by using the double amount of the catalyst. So we tried different dispersing materials (Table 5, entry 5 and 6) to improve the contact with the catalyst maybe too hard packed (the preparation required many steps and so the powder can be more fine too).
Moreover any useful dispersing material was found out.

Finally the reaction tests were performed with an excess of Michael donors (**3/4a-c** 1/3) at room temperature and in the presence of THF, for a shorter reaction time achieving very interesting results (Table 6):

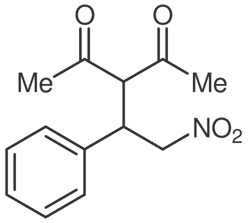
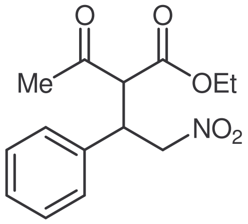
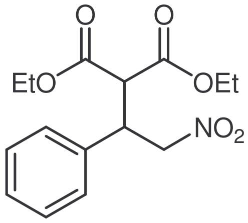
Entry[a]	**Product**	**5**	**Yield (Sel.**[b]**) [%]**
1		**5a**	90 (98)
2		**5b**[c]	92 (98)
3		**5c**	60 (72)

Table 6. [a]Experimental conditions: all reactions were performed using 7.3 mmol of nitrostyrene, 22.0 mmol of the β-dicarbonyl compound in 14.0 ml of THF in the presence of 1.00 g of KG-60-TBD-SiMe$_3$; elution time: 60 min, temperature: 25 °C., [b](Yield/Conversion)x100, [c]48:52 diastereomeric mixture.

The lower reactivity observed with diethyl malonate (Table 6, entry 3) is likely ascribable to the lower pK_a value of the active methylene function[17].

The same column-reactor can be utilized, after accurate rinsing with ethyl acetate, for the preparation of some other Michael adducts between nitrostyrene and β-dicarbonyl compounds.

A comparison was made in terms of Space Time Yield between all the different reaction conditions tested in flow and batch conditions, it showed (Table 7) clearly the set up potentiality even if for practical reasons the reaction scale in flow system was bigger.

Entry	**Cat. (%mmol)**	**Temperature (°C)**	**Ratio 3/4a**	**Flow/batch STY g/l*h**
1	KG-60-NEt$_2$ (20)	80	1/6	26 (4*scale)
2	KG-60-TBD-HMDS (10)	r.t.	1/1	13 (2*scale)
3	KG-60-TBD-HMDS (10)	r.t.	1/3	22 (3*scale)

Table 7. Space time yield comparison.

General procedure: Michael addition of β-dicarbonyl compounds to nitrostyrene under continuous-flow conditions:

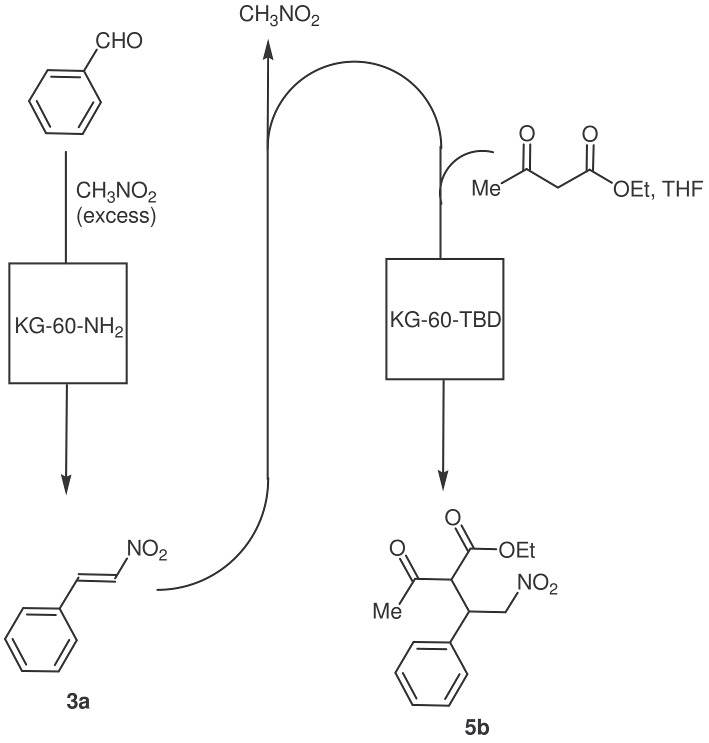
KG-60-TBD-SiMe$_3$ catalyst sieved at 80 mesh (1.00 g, 0.73 mmol) was packed in an oil jacketed glass column with THF (10 ml). Then a solution of the β-dicarbonyl compound (22.0 mmol) and nitrostyrene (1.08 g, 7.3 mmol) in THF (14 ml) was passed through under low pressure at room temperature in a fixed elution period. The crude was collected at the bottom of the column.

Multistep process

Finally, the preparation of the multifunctional compound **5b** was studied by sequential two-step column catalytic methodology (Scheme 3). The first step was performed as described giving product **3a** in 80% yield. The solution coming from the first reactor was directly passed trough the second reactor after addition of the ethylacetoacetate **4b**. Unfortunately the selectivity of the process was poor due to the competitive addition of excess nitromethane to the C-C electronpoor double bond of nitrostyrene. Thus we decided to remove the excess nitromethane by distillation and to replace the solvent with THF. Under these conditions the product **5b** was obtained in75% yield.

General procedure: multistep reaction.

Benzaldehyde (0.9 g, 8.6 mmol) diluted in nitromethane (5 ml) was reacted through the KG-60-NH_2 column-reactor at 110 °C during 12 minutes residence time under nitrogen affording nitrostyrene **3a** in 80% yield. The reaction mixture was then subjected to distillation to remove the excess of nitromethane (to avoid formation of by-products derived from further addition of nitromethane to nitrostyrene). The resulting oil was diluted in THF (16 ml) containing ethyl acetoacetate (3.3 g, 25.2 mmol) and passed at room temperature through the second column-reactor filled with KG-60-TBD-$SiMe_3$, previously washed with THF, with residence time of 60 minutes. The final reaction mixture was collected giving compound **5b** in 75% overall yield with respect to benzaldehyde.



Scheme 3

In conclusion, in this study we have described the preparation of two packed-bed column reactors containing propylamine (KG-60-NH$_2$) and guanidine TBD (KG-60-TBD-SiMe$_3$) immobilized onto amorphous silica KG-60.

The first catalyst, KG-60-NH$_2$, was efficiently utilized for performing the continuous-flow nitroaldol condensation between nitromethane and aromatic aldehydes giving a small series of (*E*)-nitrostyrenes variously substituted on the aromatic ring (65-80% yield, 93-98% selectivity).

The second catalyst, KG-60-TBD-SiMe$_3$, gave Michael addition of β-dicarbonyl compounds to nitrostyrenes affording polyfunctional compounds under continuous-flow conditions (60-92% yield, 72-98% selectivity).

The combination of both processes allows the production of multifunctional compounds **5** that represent valuable intermediates in fine and pharmaceutical chemistry, since nitrocompounds can be transformed into amines, ketones, carboxylic acids, etc[18,19].

According to Scheme 3, multifunctional compounds **5** can be produced by nitroaldol condensation between aromatic aldehydes **1** and nitromethane **2** directly giving nitrostyrenes **3** (step 1) followed by Michael addition of β-dicarbonyl compounds **4** to the electronpoor carbon-carbon double bond of compounds **3** (step 2)[20,21].

Compounds like **5** represent useful precursors to various complex organic molecules of industrial interest [22] having functionalities that can be derived from both nitro group and β-dicarbonyl system[23].

2c.4. References

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[22] Michael adducts **5** can be converted (through conventional methods) into γ-aminocarbonyl compounds which constitute valuable intermediates for the preparation of a variety of 1,4-difunctionalized derivatives. As an example, compound **5b** was hydrolyzed and decarboxylated by treatment with aqueous sodium hydroxide at room temperature affording 4-phenyl-5-nitro-2-pentanone in 90% yield (from **5b**) that was then reduced to 4-phenyl-5-amino-2-pentanone hydrochloride in 88% yield by treatment with hydrogen over Pt-S-C in EtOH/HCl: R. Tamura, D. Oda, H. Kurokawa, *Tetrahedron Lett.*, **1986**, *27*, 5759.

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2d. Silica-based monoliths

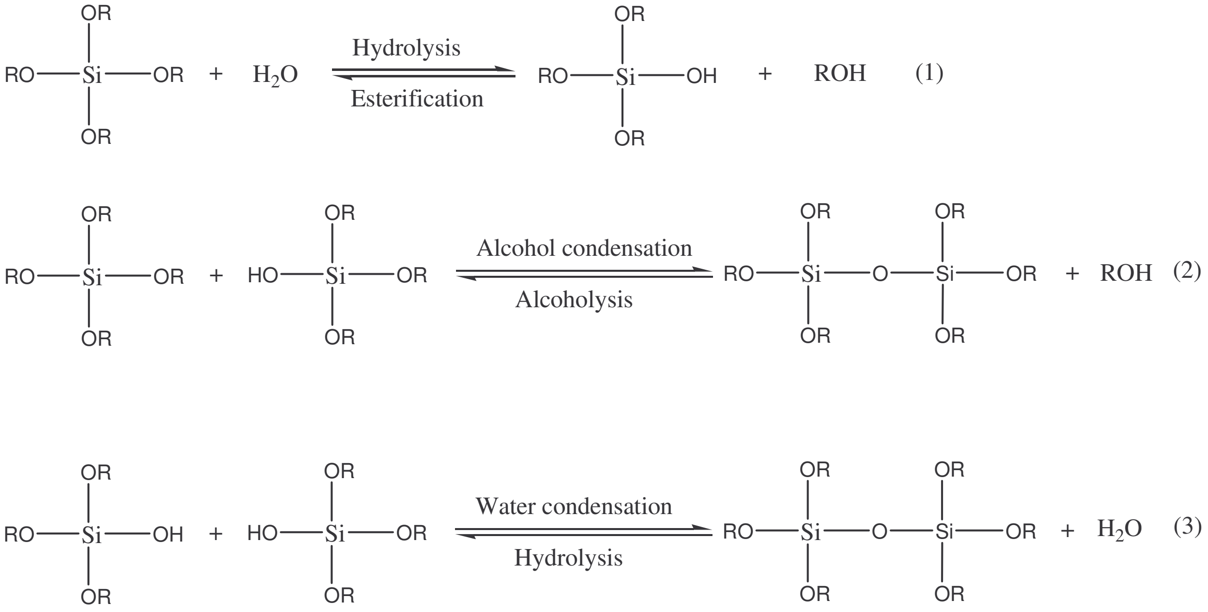
2d.1. State of the art and applications

Silica-based monoliths[1] include any column that incorporates one continuous piece (or rod) of porous silica. They can be generated by the polymerization of sol-gel precursors (sol-gel monoliths)[2] or by the immobilization of silica particles (particle-fixed monoliths)[3]

The popularity of silica monoliths can be linked to the wide variety of highly characterized packing materials available, in addition to the availability of different chemical methods that can be used for surface modification and ligand attachment.

Silica monoliths generated by the sol-gel process usually involve the catalytic hydrolysis, condensation, and subsequent polycondensation of silica alkoxide precursors (*e.g.*, TMOS, TEOS) to form a macroporous gel network. These reactions can be catalyzed by acids [4,5], bases[6,7], ions[8,9] or light[10,11] and often involve the use of additives (*e.g.*, PEG) to favour phase separation and thus to control macropore size and volume. Monoliths thus formed generally possess high throughpore-to-skeleton size ratios that can lead to a 10-fold improvement in column permeability as compared to packed columns in addition to provide high separation efficiency.

Scheme 1 shows the reaction schemes involved in the sol-gel process using a silica alkoxide precursor in aqueous media.



Scheme 1. Hydrolysis and condensation reactions involved in the sol-gel process.

In the other case the fabrication of continuous beds by thermal treatment of packing materials involves the fusion of the porous silica particles at high temperatures (*e.g.*, 250°C) in the presence of water. Usually an additive (*e.g.*, $NaHCO_3$) is included to facilitate the agglomeration of the microparticles. Sintering temperatures must be high enough to partially dissolve the silica particles, but low enough to prevent changes in the pore characteristics of the packing material[12]. Formation of the monolith is achieved when the grain boundaries of particles and the capillary wall are joined together after deposition of the previously dissolved silica upon cooling[13]. The resulting porous matrix provides a higher surface area than its sol-gel counterpart without requiring the problematic frits used in traditional packed columns.

Merck company (Merck KGaA, Darmstadt, Germany) has developed a new type of monolithic material named Chromolith[14], which is a porous material containing a network of pores defined by macropores, which provide approximately 80% of the total porosity, and mesopores, which represent 10–15% of the total porosity[15,16]. The column permeability calculated from the pressure drop over monolithic and packed columns suggests that the C18 silica monolith column with macropore channels of 2µm corresponds to a conventional column packed with 11µm particles. The problem of contact with the wall was solved and Merck produced a corresponding PEEK column housing. The invention of monolithic silica based columns can be regarded as a major technological change in column technology. The most important characteristics[17] are reported as follow:

Chromatographic features of the chromatographic columns studied

Features	Chromolith Performance Symmetry C18
Silica type	High purity
Structure type	Monolithic
Particle size (µm)	–
Total porosity (%)	>80
Median pore diameter (Å)	–
Macropore size (µm)	2
Mesopore size (Å)	130
Surface area ($m^2\ g^{-1}$)	300
Pore volume ($ml\ g^{-1}$)	1
Total carbon	18
Endcapped	yes
Column length (mm)	100

Column diameter (mm)	4.6
pH stability range	2–7.5
Temperature stability (°C)	max. 45
Pressure stability (bar)	max. 200
Optimum flow rate (ml min^{-1})	2

The bimodal internal structure is clearly shown in the following SEM pictures:

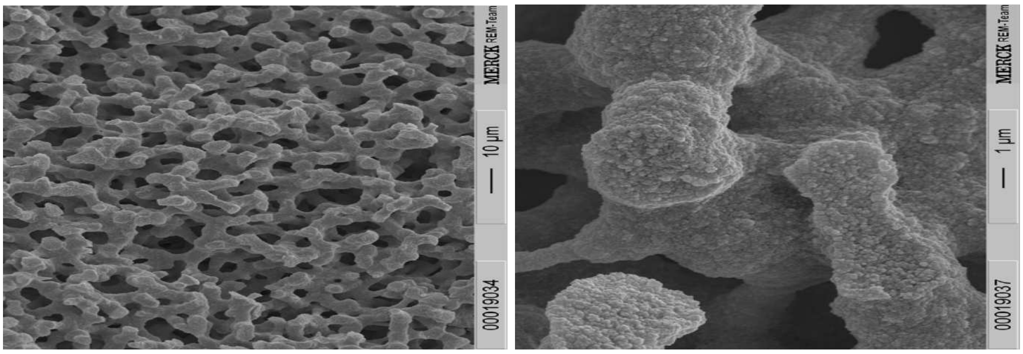


Figure 1. SEM picture of the monolithic silica column.

The most important applications of this monolithic column are divided into two main topics:

- Chromatographic Separation
- Bioreactor Applications

In the first case the improvement is correlated with the possibility to obtain the same performance, reproducibility, and sensibility in comparison with conventional HPLC packed columns but operating at lower pressure and in a shorter time[18,19,20]. This allows working in a more automated and efficient system without using expensive apparatus needed for high pressures.

Moreover, the monolithic column properties have been of great interest in recent years, especially in connection with enzyme immobilization. For example a new type of penicillin G acylase[21] (PGA)-based monolithic silica support was developed and evaluated for the chiral separation by HPLC. The enzyme, chiral selector, was covalently immobilized to the surface of the derivatized monolithic column. The enantioselectivity and the performance of the developed column compared to the corresponding experimental data obtained with a PGA-based microparticulate (5µm) silica column were really satisfying.

In literature the use of monolithic columns as bioreactors is reported[22]. A bioreactor composed of Trypsin immobilized on an epoxy-modified silica monolithic column was coupled to an analytical reactor for the on-line digestion, peptide separation and identification of test proteins by ESI-MS–MS. The influence of various parameters (flow rate, temperature, buffer pH and molarity, etc.) on enzymatic activity was investigated by an experimental design and the most significant factor was found to be the flow rate. The efficiency of the reported on-line bioreactor for tryptic mapping is reported for somatostatin and myoglobin, selected as model compounds. The equipment used showed all the potentiality of this system in terms of automation:

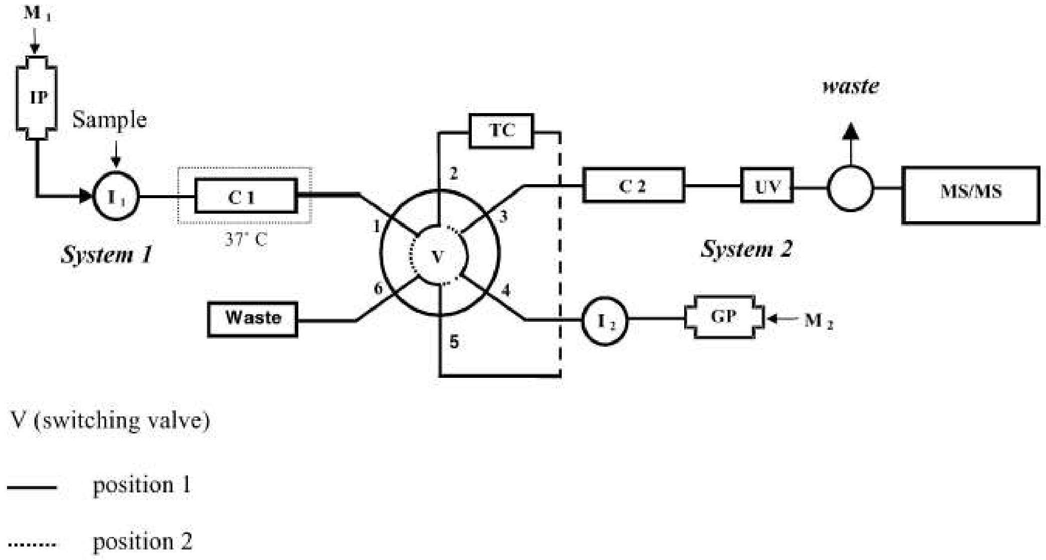


Figure 2. Scheme of the chromatographic set-up for performing the on-column digestion and ESI-MS–MS analysis of peptide mixtures from the trypsin bioreactor. IP: isocratic pump, I1: thermostated column oven autosampler set at 37.0 ± 0.1°C, M1: 100 mM phosphate buffer (pH 7.0) delivered at 1.0 ml/min, C1: trypsin bioreactor, TP: C18 trapping column, GP: quaternary gradient pump, M2: gradient mobile phase delivered at a flow rate of 0.3 ml/min, C2: analytical column, UV: diode array detector, MS–MS: ion trap mass spectrometer with electrospray ionization ion source and V: automatically controlled six-port Rheodyne sample valve.

In this dissertation, the possibility to develop a new monolithic and catalytic reactor for fine chemicals synthesis has been investigated.

The project was divided in four parts:

1. Catalyst immobilization and quantification.
2. Activity evaluation as micro-structured reactor for nitroaldol synthesis.
3. Synthetic process repeatability and reproducibility.
4. Monolith characterizations after use.

At the end the performance of the process has been compared to the traditional batch approach in order to exploit the potentiality of continuous processes employing micro-structured reactors.

2d.2. Results and Discussion

It was decided to focus the experimental studies on the nitroaldol reaction which was already studied in traditional batch reactors (see **1c**) and a continuous flow system based on a silica-packed bed (see **2c**).

A new flow system apparatus was realized in order to insert a monolithic silica column which had to be modified to be used such as a catalytic reactor. The flow system used (Figure 3) is based on a monolithic silica bed on which the organic catalyst (propylamine) is covalently bonded. It consists of a commercial Chromolith Performance Column (Merck) of 10 cm length and 4.6 mm width that is immersed in a constant temperature bath. The reactant solutions are first mixed in a stirred and atmospheric inert box and then introduced into the reactor by using a continuously operating syringe pump. System pressure is permanently monitored by online pressure sensor. The eluate is collected as fractions. A T-valve is inserted in order to have the possibility to exchange the fluid and to eliminate air bubbles present in the solution without removing the rest of the apparatus.

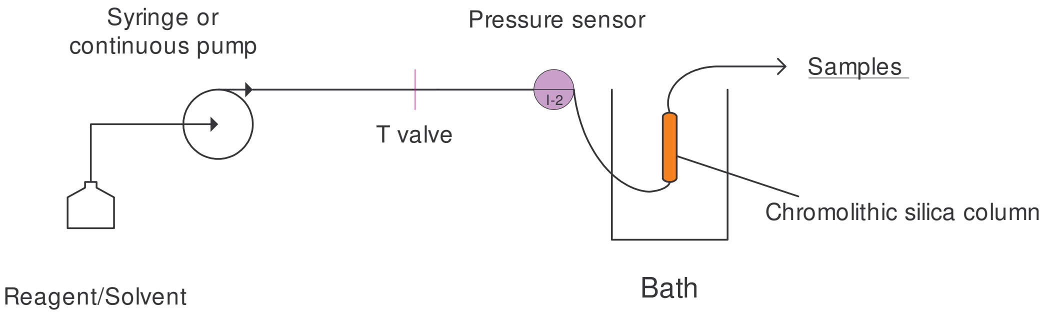
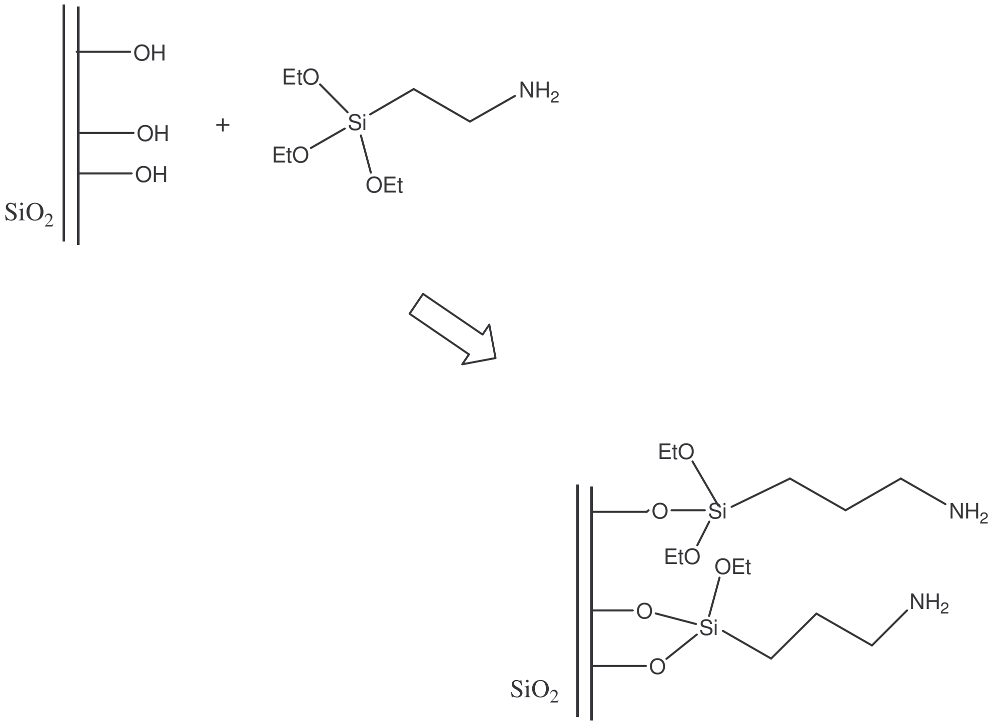


Figure 3. Schematic continuous flow apparatus.

At first the catalyst immobilization was realized in accordance to some previously mentioned papers in chapter **2d.1**. The bifunctional catalyst (see chapter **1c.2**) needs no complete column uncapping, that can be realized by anchoring 3-amino-propyltriethoxisylane to the surface silanol groups.

The silica monolith activation with aminopropyl groups is illustrated in Scheme 2 according to the tethering methodology:



Scheme 2. Catalyst immobilization by tethering technique.

Different procedures were applied in order to control the catalyst amount anchored and to evaluate the efficiency and reproducibility of the immobilization.

Normally the amount of 3-aminopropyl tethered on silica powder is determined by simple elemental analysis in order to know the weight% of nitrogen contained in the sample.

The subsequent device for catalyst immobilization needs a technique being able to quantify the amount of 3-aminopropyl in a closed system which is passed through by the sylilating solution (Figure 4).

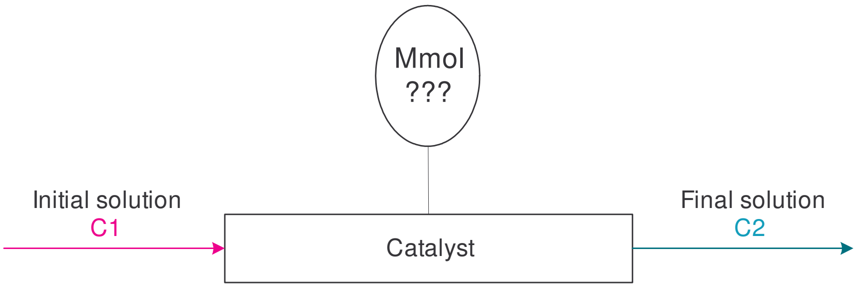


Figure 4. Device.

The catalyst amount or the loading value were determined by using two non destructive and spectroscopic techniques, namely UV-Vis and (ATR)-FT-IR spectroscopy.

In literature[23] the application of a modified Gisin's method is reported, used for the quantification of the amino groups content anchored on a resin or a capillary silica column.

This method is based on the reaction between Picric Acid (2,4,6-trinitrophenol) and the primary amine to form the corresponding salt which can be eluted by using a solution of N,N-di-isopropylamine in EtOH. The solution eluted is analyzed by UV-Vis assuming that the value of the molar extinction coefficient $\varepsilon_{,EtOH,358.30,25°C}$ (14500) is constant in the considered concentration range of 1.10^{-5}-20.10^{-5}M. This method can be successfully applied to the system used in this study even if the absorption on silica must be overcome by copious cleaning between the procedures steps. The absorbance value is easy correlated by Lambert-Beer law with the solution concentration and finally with the amount of picric acid present which corresponds to the amount of aminopropyl anchored inside the column.

The Gisin's method was first tested with amino propylamine anchored on silica powdered with a loading of 1.14 mmol/g (elemental analysis). In particular the catalyst powder (0.25g) was dispersed in a bed of glass beads and inserted in a glass column connected with a syringe pump.

The eluted solution concentration obtained is 0.0109M which corresponds to a value of 0.274 mmol of amino groups in a good accordance with the elemental analysis (0.285 mmol).

The second analytical method is based on the calibration of a solution of 3-aminopropyltriethoxysilane in dry toluene by using FT-IR spectroscopy. The data were statistically elaborated with TQ-Analyst and Unscramble programs.

Two spectral ranges (3100-2800 cm^{-1} and 1200-800 cm^{-1}) showed characteristic absorption bands of the examined compound and a good linearity for different solution concentrations.

The catalyst amount is determined by measuring the initial solution concentration and the concentration after passing the solution through the column, and by considering the cleavage necessary for removing the free amino-propyl still present in solution and not really anchored.

The results obtained and the main reaction conditions applied are summarized in Table 2.

The first immobilization test (Table 2, Column 1) is explained in detail to provide an in depth understanding of the entire process operation.

Prior to the reaction, a Chromolith® Performance column (containing approximately 0.5 g of silica gel), encased in a PEEK plastic housing, was pretreated with a nitrogen flow (maximum pressure: 10 bar) without rinsing out the storage solvents (mixture of n-Heptane/Dioxane

95/5, v/v). Therefore, the column was dried overnight at 60°C under vacuum (120 mbar). The modification of the dried Chromolith® Si column was carried out by pumping dry toluene through the monolith at a volumetric flow rate of 0.02 ml/min for 80 minutes. After that interval time which corresponds to a volume of 1.6 ml, the solvent dropped out the column. The monolithic silica column was stored inside a thermostatic bath at 60°C and passed by dry toluene for two hours at different flow rates for silica activation and for back pressure check. The pressure values are reported as a function of the flow rate (Figure 5), and that trend confirms a linear flow regime.

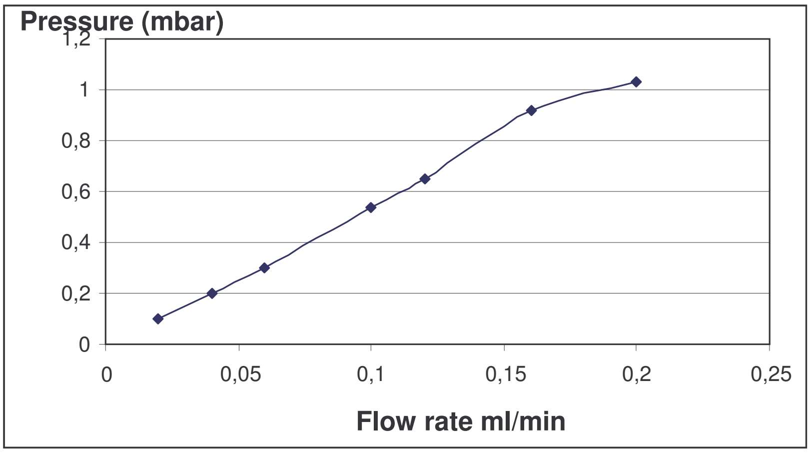


Figure 5. Pressure as a function of the flow rate.

Then a solution of 3-aminopropyltriethoxysilane (1.2g) in 25 ml of dry toluene (50.2g/l) was pumped at a volumetric rate of 0.14 ml/min at 60°C. The eluate was collected in fractions every 10 minutes and analyzed by FT-IR spectroscopy. The aminopropyl modified silica column was washed with dry toluene for 4 h at room temperature at a volumetric flow rate of 0.2 ml/min and two additional hours with a mixture of toluene/CH_2Cl_2 (3/1 v/v) at a volumetric flow rate of 0.4 ml/min. The eluted solutions were collected respectively in a volumetric flask of 50 ml (Cleavage 1, Cleavage 2) and analyzed by FT-IR.

The results obtained are summarized in Table 1 and shown in Figure 6.

Time (min)	Concentration (g/l)
0	48,71
10	-1,89
20	-0,84
30	-12,63
40	23,19
50	34,78
60	44,75
70	41,39
80	39,63
90	43,06
Cleavage 1	-32.60
Cleavage 2	-18.824

Table 1. Experimentally determined concentration of 3-amino-propyltriethoxisilane in toluene as a function of time.

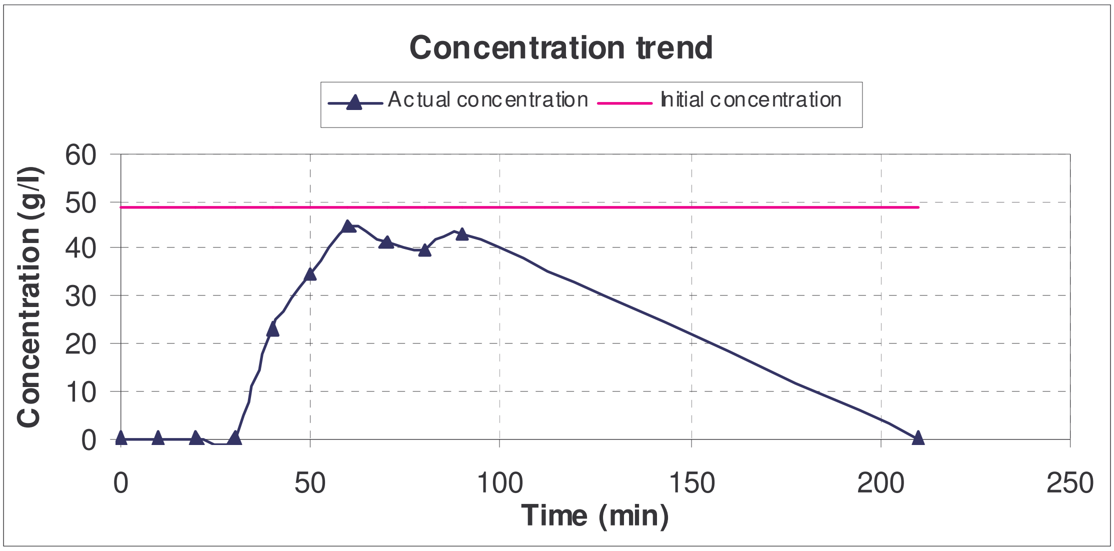


Figure 6. Experimentally determined concentration as a function of time.

The negative values suggested to extend the calibration at lower concentration values and to replace the program TQ-Analyst by the program Unscrambler for data elaboration. However, the data show that the silylation test was successful.

The catalyst's amount determined by Gisin's method is 0.364 mmol.

Finally the column was backed in an oven for 3 h at 60 °C and stored in a drier under vacuum.

The reproducibility of the uncapping method has been already proved in previous paper[18] so it was not evaluated again.

Different possibilities to improve and control the catalyst amount anchored inside the column reactor were tested. In particular four different procedures were performed using different conditions summarized in the following table.

Monolithic Column	**Flow rate (ml/min)**	**Time (h)**	**Temperature (°C)**	**Contact Time (min)**	**Loading by UV-Vis (mmol/g)**	**Loading by FT-IR (mmol/g)**
1	0.14	2	60	11	0.7	-
2	0.07	4	60	22	0.5	0.6
	0.026	15	60	53	0.8	1.2
3*	-	15	r.t.	-	-	0.4

Table 2. Catalyst amount (mmol) evaluated by UV-Vis and ATR-IR spectroscopy.

*Solution concentration 10% v/v (105 g/l)

A contact time of 22 minutes (twice the contact time of column 1) was used for column 2 modification without changing the total volume of 3-aminopropyltriethoxysilane solution and the reaction temperature (60 °C).

The loading value obtained by Gisin's method modified was 0.5 mmol/g, which is not higher as the initially determined value. Therefore a subsequent immobilization procedure was repeated on the same column 2.

In this case the flow rate applied was 0.026 ml/min, which corresponds to a contact time of 53 minutes, and the total volume was increased. At the end the amount of catalyst was similar to the one obtained for column 1. Besides, the reactor was stored between different test runs, in degassed ethylacetate to avoid the presence of CO_2 and the use of protic solvents.

Finally, column 3 was rinsed with a solution of 3-aminopropyltriethoxysilane (double concentration), closed and washed with dry toluene only after 15 h at room temperature.

This approach did also not improve the first results obtained.

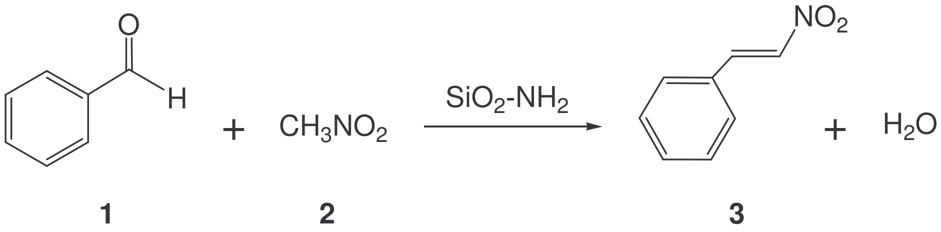
There was no clear correlation found between process parameters such as flow rate, contact time, solution volume and the uncapped value obtained.

The only useful consideration for a continuous flow procedure seems to be applying flow rates around 0.5 ml/min and maybe higher temperatures.

Reaction Tests

Column 1

The nitroaldol reaction (Scheme 3) between benzaldehyde **1** and nitromethane **2** catalyzed by a supported primary amine on silica was previously studied in batch (see **1c**) and under continuous flow conditions (see **2c**) employing packed-bed reactors with good results.



Scheme 3

The new flow apparatus, shown in Figure 7, was evaluated to perform the same reaction (Scheme 3) by changing reaction parameters during one continuous experiment.

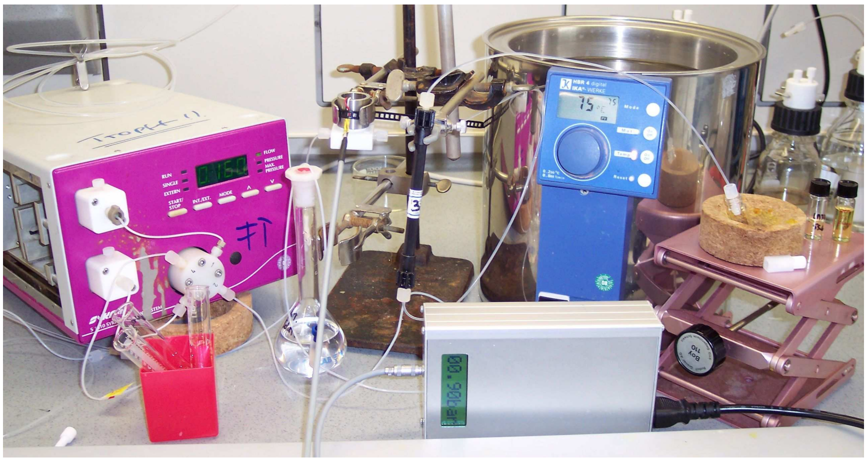


Figure 7. Picture of the continuous flow apparatus.

The apparatus has a specific total volume which is composed by the volume of the fittings, tubes, syringe pump, pressure sensor and finally the reactor itself. This value is important in order to define the dead volume which has to be considered before collecting the first reaction samples. The time steps for taking subsequent samples are depending on the applied flow rate. Moreover the influence of flow rate and thus residence time on the chemistry can be systematically investigated.

The reactor or chromatographic column conditioning might have a significant impact on both the column life time and the reaction selectivity. Consequently, this parameter has been studied, too.

Preliminary Studies-Test 1

The nitroaldol reaction (Scheme 3) was performed by changing reaction parameters during one continuous experiment (total time 3,33 h). The solution concentration (c=82.8 g/l) used in the flow experiments is equal to the batch conditions. The main system features can be summarized as follows

Total volume system (ml)	1.9
Column conditioning	CH_3NO_2, 2.9 ml, 75°C,
Dead time (min)	12
Experimental Column Volume (ml)	1.25 (column not completely dry)
Pump type	TSE Syringe Pump

Table 3. The main system features.

Experimental plan

At first different residence time were evaluated at 75°C (Test 1a-c) and then the increasing temperature effect was studied using the same residence time (Test 1c-d) and a shorter residence time as well (Test 1e).

Flow rate (ml/min) / Temperature (°C)	0.08	0.16	0.32	0.64	Residence time (min)	Solution Volume (ml)
75	Test1b				**20**	4.3
75		Test1a			**10**	10.7
75			Test1c		**5**	14.1
85			Test1d		**5**	8.3
85				Test1e	**2.5**	6.4

Table 4. Experimental plan.

The conversion and yield tendencies obtained, following the experimental plane explained above, are reported in diagrams 1-5 and summarized in tables 5-9.

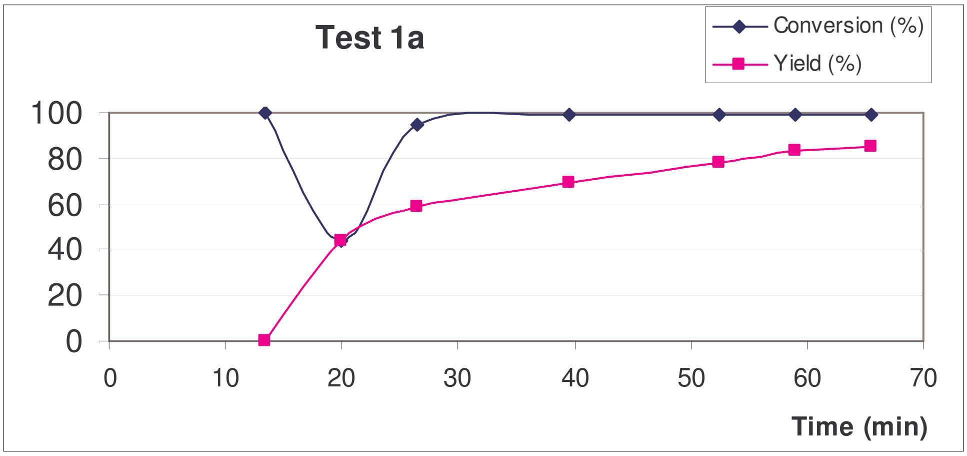


Diagram 1. The conversion and yield tendencies as a function of the time under Test 1a conditions.

Conversion **1** (%)	Yield **3** (%)	Selectivity (%)	Time (min)
100	0	0	14
44	44	100	20
99	59	59	27
99	69	69	40
99	78	79	53
99	84	84	59
99	86	86	66

Table5. Conversion, yield and selectivity values obtained.

The selectivity values were influenced by some factors like reagent/product absorption and 1,3-dinitro-2-phenyl-propane by-product formation, which is faster eluted from the system. In addition, it must be considered that a dilution effect occurs due to nitromethane present inside the column coming from previous experiments or pre-conditioning measures.

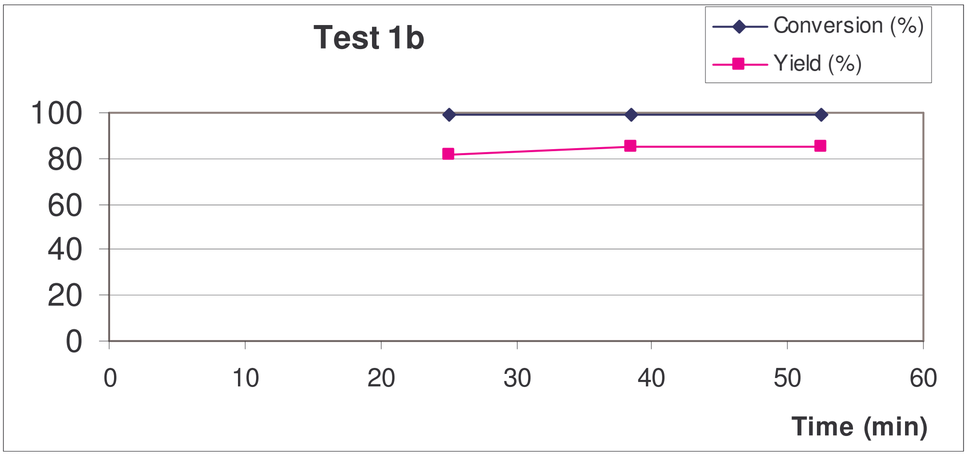


Diagram 2. The conversion and yield tendencies as a function of the time under Test 1b conditions.

Conversion **1** (%)	Yield **3** (%)	Selectivity (%)
99	81	82
99	85	85
99	85	86

Table 6. Conversion, yield and selectivity values obtained.

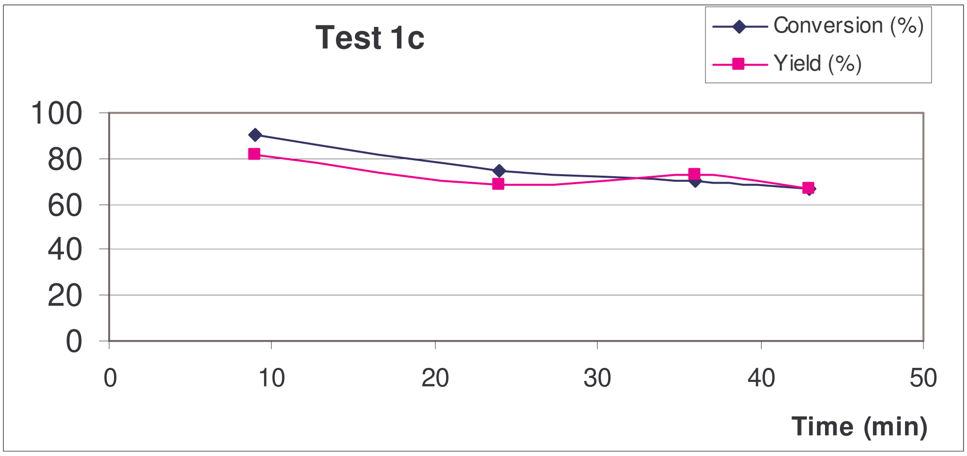


Diagram 3 The conversion and yield tendencies as a function of the time under Test 1c conditions.

Conversion **1** (%)	Yield **3** (%)	Selectivity (%)
90	82	91
75	68	91
70	73	-
67	67	100

Table 7. Conversion, yield and selectivity values obtained.

At the same reaction temperature (75 °C) and different residence times of 10 and 20 minutes the conversion is almost quantitative and the selectivity is influenced by the presence of the by-product due to the double attach of the nitromethane to the desired product **3** already formed.

Moreover, with a contact time of only 2.5 minutes the conversion was still around 70 % and the selectivity was optimum.

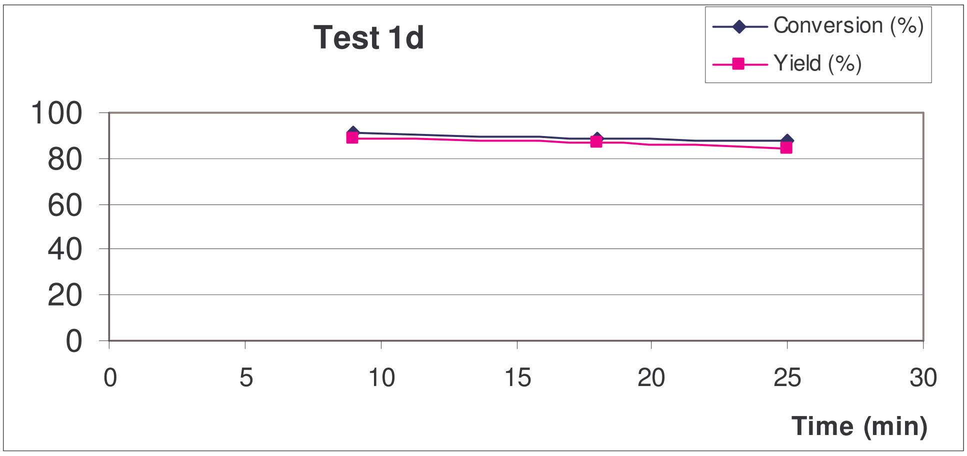


Diagram 4. The conversion and yield tendencies as a function of the time under Test 1d conditions.

Conversion **1** (%)	Yield **3** (%)	Selectivity (%)
91	88	97
89	87	98
88	84	96

Table 8. Conversion, yield and selectivity values obtained.

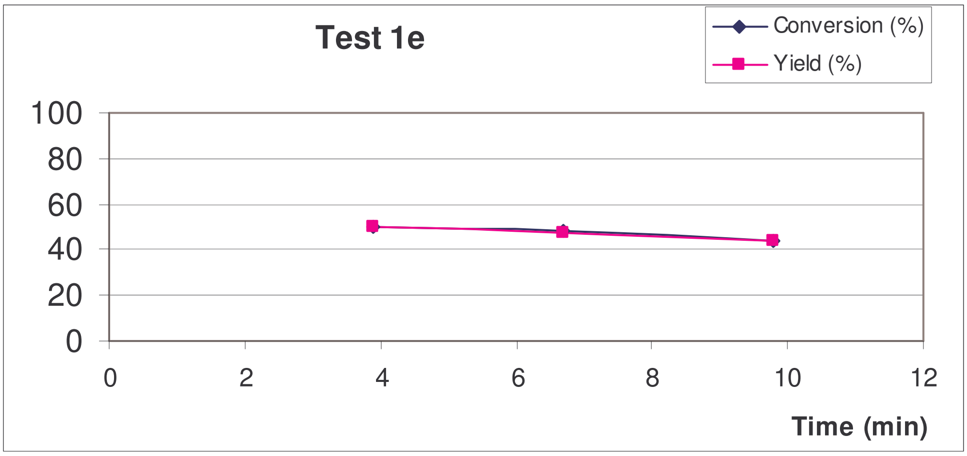


Diagram 5. The conversion and yield tendencies as a function of the time under Test 1e conditions.

Conversion **1** (%)	Yield **3** (%)	Selectivity (%)
50	50	100
49	47	98
44	44	100

Table 9. Conversion, yield and selectivity values obtained.

By applying higher flow rates (0.32, 0.64 ml/min) the conversion obviously decreased. However the values obtained are still very positive for the short contact times applied (5 and 2.5 minutes respectively) and the selectivity is optimum.

Test 1 confirmed clearly the possibility to build up an automated and pressure-driven reaction system.

In particular, the experimental data show that while operating at constant temperature an increasing flow rate and thus decreasing contact time leads to decreasing conversion values whereas the reaction selectivity improved.

Reaction Reproducibility-Test 2

Test 2 was performed after 30 days (column was stored under vacuum inside a drier) in order to prove the test 1 reproducibility and investigate performance under a varied flow rate of 0.48 ml/min.

Total volume system (ml)	2.1
Column conditioning	CH_3NO_2, 3.1 ml, 75°C,
Dead time (min)	12
Experimental Column Volume (ml)	1.8
Pump type	Harvard Syringe Pump

Table 10. The main system features.

Experimental plan

Flow rate (ml/min) / Temperature (°C)	0.16	0.32	0.48	0.64	Residence time (min)	Solution Volume (ml)
75	Test2a				**10**	12.3
75		Test2b			**5**	4.3
85		Test2c			**5**	8.6
85			Test2d		**3.33**	8.6
85				Test2e	**2.5**	-

Table 11. Experimental plan.

The first part of the experiments (Diagram 6, Table 10) was compared with the results obtained in Test 1 and it showed a drastical decrease in benzaldehyde conversion from 90% to 40%.

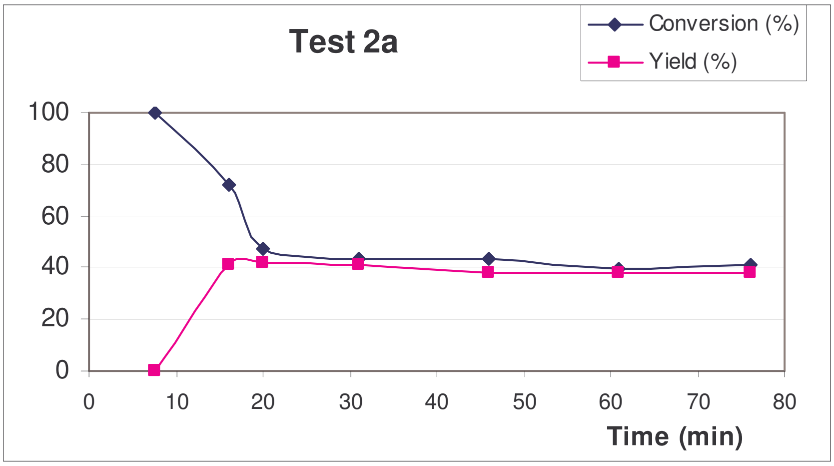


Diagram 6. The conversion and yield tendencies as a function of the time under Test 2a conditions.

Conversion **1** (%)	Yield **3** (%)	Selectivity (%)
100	0	100
72	41	72
47	42	47
44	41	44
44	38	44
39	38	39
41	38	92

Table 12 Conversion, yield and selectivity values obtained**..**

Although the catalyst activity was so different in comparison to the previous results the reaction was controlled by changing the same process parameters such as flow rate and temperature. The results from the single continuous experiment under systematic variation of process parameters are summarized in Diagram 7.

(It was not possible to perform test 2e because the pump stalled.)

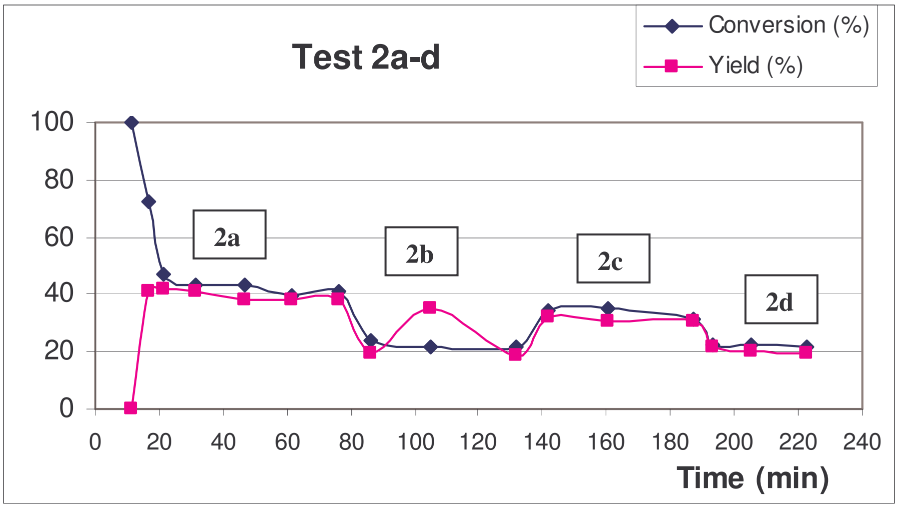


Diagram 7. The conversion and yield tendencies as a function of the time under Test 2a-d conditions

The observed catalyst poisoning could be due to different reasons (see Catalyst Regeneration Test 3).

The reactant solution retention and interaction with the polar silica support was evaluated.
The experiment was performed by using a UV-Vis flow cell connected with the column outlet and by manually injecting 0.5 ml of reactant solution (benzaldehyde concentration in CH_3NO_2 82.8 g/l) in three minutes. The reactor was heated at 75°C and connected with a syringe pump (flow rate 0.16 ml/min) for purging with CH_3NO_2. The benzaldehyde and the nitrostyrene product dropped out the column in a time interval starting 22 minutes and ending 24 minutes after injection.
This means that 3.52 ml of CH_3NO_2 (about twice of the reactor volume) were necessary for the complete elution; it was not possible to spilt up the signal due to overlapping absorption peaks of benzaldehyde and nitrostyrene and because of the strong nitromethane absorption in the spectral range investigated (220-340 nm^{-1})
The conversion and yield obtained were 32% and 29%, respectively.

Catalyst Regeneration Test 3

After Test 2 the column was regenerated with 5 ml 10%vol $N(Et)_3$ in EtOH and washed with 20 ml EtOH. In test 3 the catalyst activation was further investigated.

Total volume system (ml)	1.889
Column conditioning	CH_3NO_2, 3.89 ml, 75°C
Dead time (min)	24
Pump type	Harvard Syringe Pump

Table 13. The main system features.

Experimental plan

Flow rate (ml/min) / Temperature(°C)	0.08	0.08	Residence time (min)	Solution Volume (ml)
75	Test3a		**20**	11.52
85		Test3b	**20**	7.2

Table 14. Experimental plan.

The results obtained are reported in the diagram 8 below.

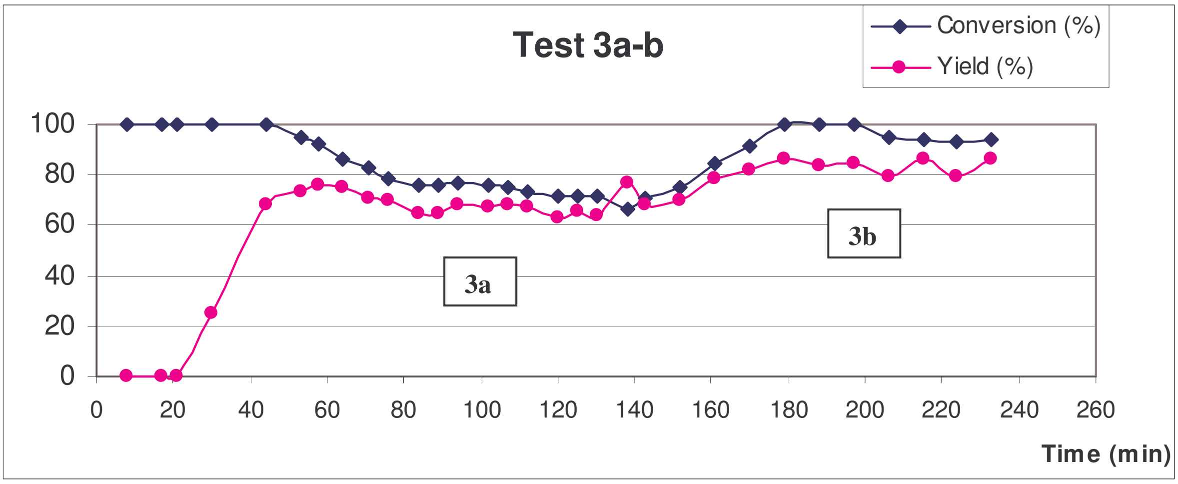
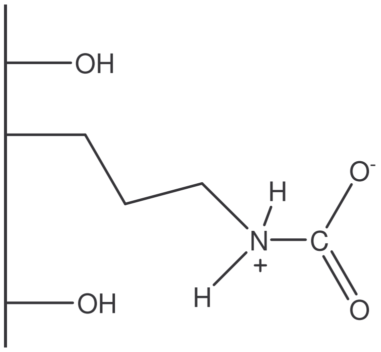


Diagram 8. The conversion and yield tendencies as a function of the time under Test 3a-b conditions.

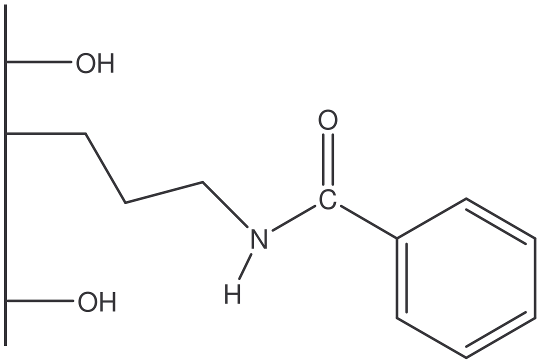
The product samples contained traces of nitro alcohol, apart from other by-products which might be due to the presence of residual Et_3N and to the dilution effect at a very low flow rate of 0.08 ml/min.

Moreover, the results show the possibility to regenerate, even if not completely, the catalyst and to achieve benzaldehyde conversion between 75% and 95% at 75°C and 85°C, respectively.

Therefore the catalyst poisoning can be partially overcome by treating it with a solution of tertiary amine such as triethylamine. This result confirms the hypothesis about the catalyst poisoning, which is due to the reaction between CO_2 and primary amine to give a carbonate or carbamate derivative (Scheme 4) or between benzoic acid (benzaldehyde oxidation) and the active site amine (Scheme 5).



Scheme 4



Scheme 5

Moreover, after some reaction runs carbon deposits (coke) could change the catalyst site surround and the role played by free silanol groups as co-catalysts for the nitroaldol reaction could be influenced as well.

Column Conditioning-Test 4

Test 4 was performed by modifying the column conditioning.

Total volume system (ml)	1.9
Column conditioning	Reactant solution, 1.6 ml, r.t.
Dead time (min)	24
Pump type	Harvard Syringe Pump

Table 15. The main system features.

Experimental plan

Flow rate (ml/min) / Temperature(°C)	0.08	0.08	Residence time (min)	Solution Volume (ml)
85	Test4a		**20**	7.1
95		Test4b	**20**	5.4

Table 16. Experimental plan.

The results obtained are reported in Diagram 9.

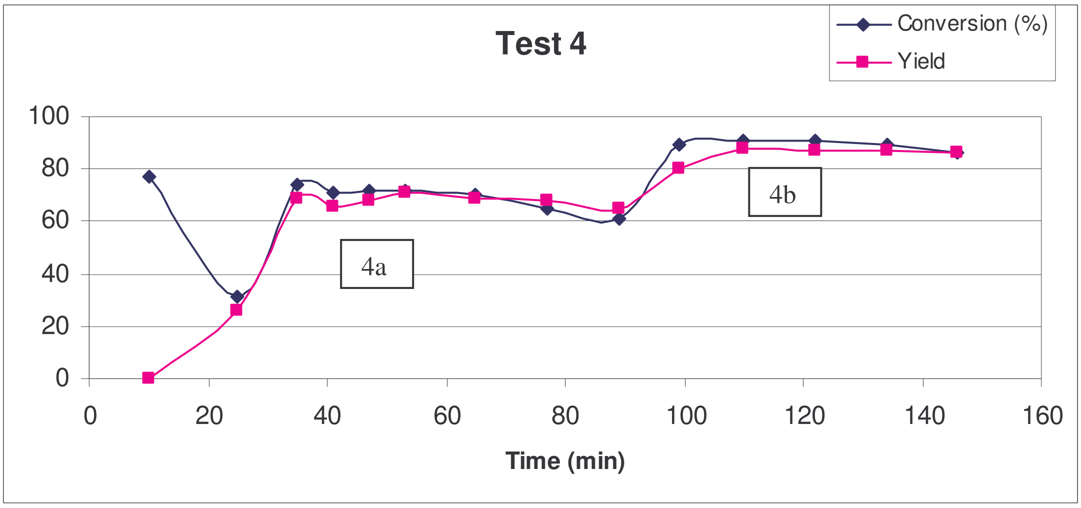


Diagram 9. The conversion and yield tendencies as a function of the time under Test 4 conditions.

The reaction performance is not strongly affected by the column conditioning with the reactant solution instead of the CH_3NO_2, even if the reaction selectivity is higher than the values expected while operating at 85 and 95°C..

By considering the global mass balance of the process, sampled during the entire run, the total yield and conversion were 79% and 91%, respectively.

These results show the great improvement in terms of flow process productivity in comparison with the batch process. Here a productivity value of 0.14 was obtained, which increases as the scale of reaction increases (Table 15). The productivity is defined as:

$$\text{Productivity}=\frac{moles\ product}{reactor\ volume \times time \times moles\ catalyst}$$

Nitroaldol Reaction	Flow productivity	Batch productivity	Flow/batch productivity
—	0.14	0.08	1.7
Double scale	0.32	0.03	9.7
Global process Test 4	0.74	-	-

Table 17. Comparison of productivity values obtained.

STY (Space Time Yield) represents another important parameter in order to make a comparison between the two different process systems; in particular the parameter space can be either defined as the reactor volume (STY 1) or as the reactant solution volume (STY 2):

$$\text{STY}=\frac{g\ product}{volume\ (l) \times time\ (h)}$$

Nitroaldol Reaction	Flow STY 1	Batch STY 1	Flow STY 2	Batch STY 2
	1030	22	232	169

Table 18. Comparison of STY values obtained.

Test 4 was repeated and similar results were obtained.

After that the monolithic column reactor was tested at higher flow rate (0.64 ml/min) but only very low conversion was obtained (approx. 12% at 95°C) and some problems with increasing back pressure were detected.

The catalyst regeneration was repeated twice but without recovering the initial activity.

Therefore, the lifetime of the catalytic system was 16 h, which is approximately 4 times longer in comparison with the same catalyst system used under batch conditions.

Catalyst amount evaluation by Modified Gisin's method-Test 5

When the catalyst life was anymore recoverable the Gisin's method (Figure 17) was performed in order to compare directly the catalyst amount still present inside the reactor (Pink Line) with the value obtained after catalyst immobilization (Blue line) (see Table 2, Column 1).

The maxima absorptions are similar but with a dilution factor ten times bigger for the blue line; so the amine content found is 0.035, which is 10 times less in comparison with the fresh catalytic column.

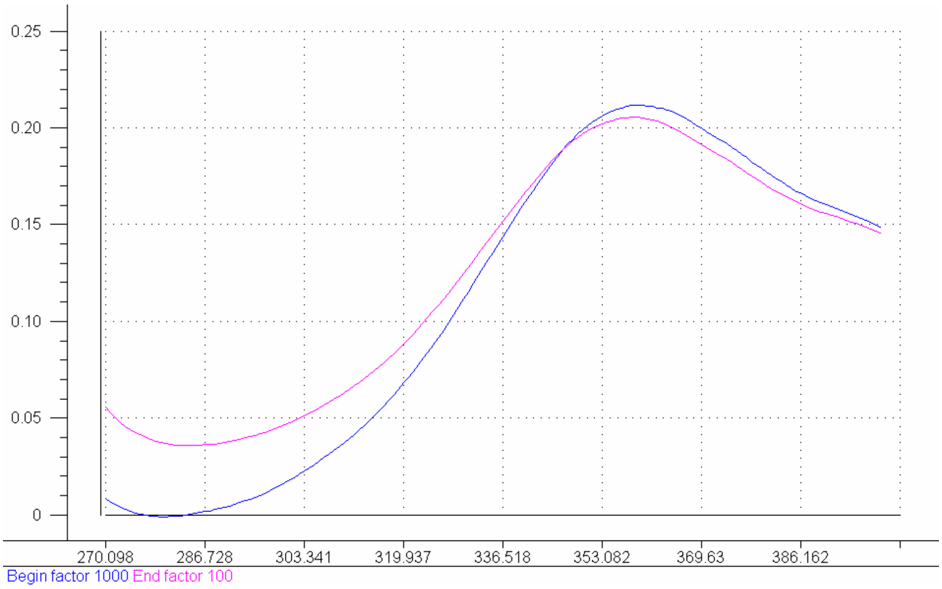
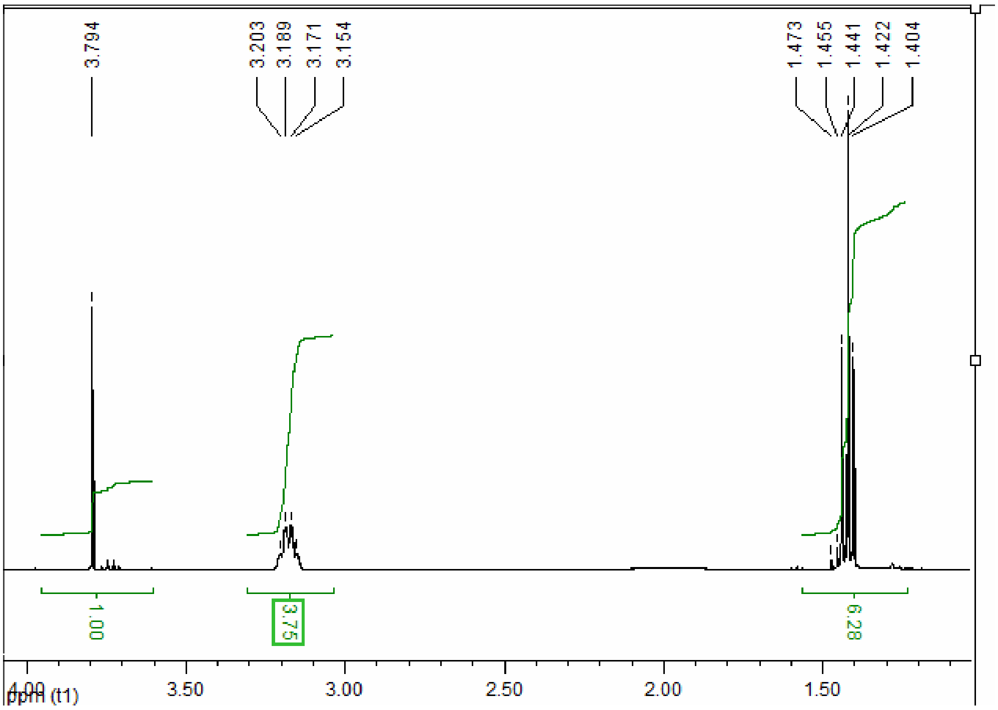


Figure 8. Maxima absorption band of fresh and used (pink line) catalytic column.

This result can be explained by the catalyst leaching occurred progressively during the reaction tests or by the active sites inaccessibility.

It is important to underline that during the experiments the back pressure was higher than usual and not constant.

Besides the Et_3N solutions used for the catalyst reactivation were analyzed by ^{1}H-NMR (see Spectrum 1) showing that they contain only tertiary amine or ammonium salt.



Spectrum 1

In the same way the samples collected during the reaction tests did not contain any propylamine as it was investigated by HPLC and HPLC-MS analysis (see Experimental Part); so the catalyst leaching (or free propylamine) was never detected.

Column 2

Reaction Repeatability-Test 6

Fresh monolithic column 2 (see Table 2) was also tested in order to study the reaction repeatability. The column conditioning was performed by using the reactant solution to investigate more deeply the reasons of a better selectivity obtained in Test 4 in comparison with the CH_3NO_2 conditioning:

Total volume system (ml)	1.9
Column conditioning	Reactant solution, 1.6 ml, 85°C
Dead time (min)	24
Pump type	Harvard Syringe Pump

Table 19. The main system features.

Experimental plan

Flow rate (ml/min) Temperature (°C)	0.08	0.16	Residence time (min)	Solution Volume (ml)
85	Test6a		**20**	4.4
85		Test6b	**20**	9.6

Table 20. Experimental plan.

The results are shown in diagram 10:

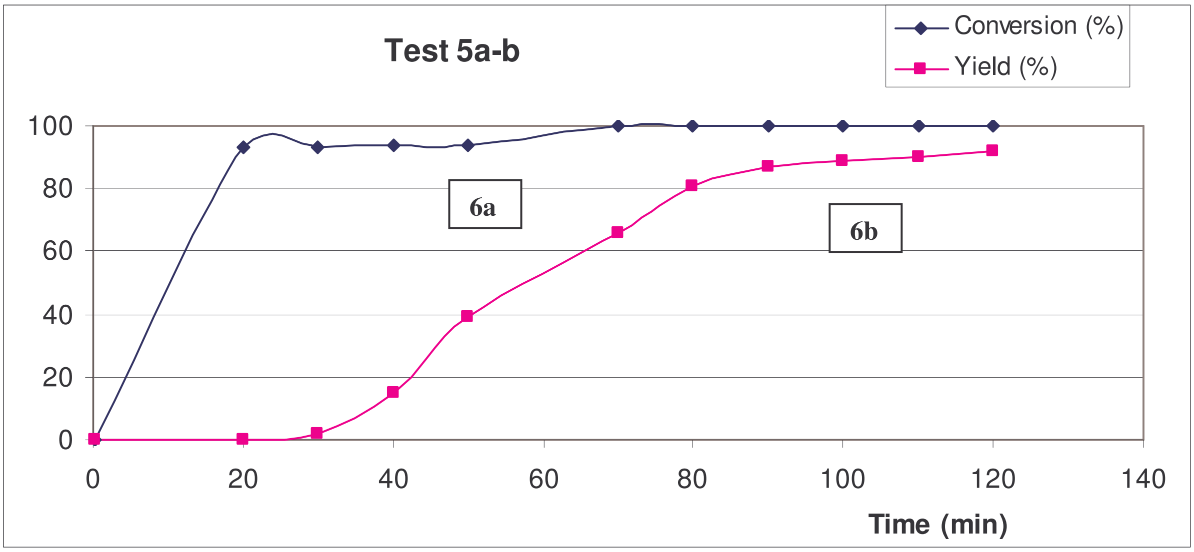


Diagram 10. The conversion and yield tendencies as a function of the time under Test 5a-b conditions.

The great reactivity of the fresh catalytic column was confirmed in terms of benzaldehyde conversion (93-100%) and by-product formation present in high amount at a flow rate of 0.08 ml/min.

Therefore, the column conditioning seems not to be the main factor that influences the reaction selectivity which was approx. 90% after 100 minutes of processing even if the flow rate was increased to 0.16 ml/min and thus the contact time was reduced.

Lower Reaction Temperatures-Test 7

The reaction was performed at room temperature and 65°C by flowing the reactant solution at 0.08ml/min (Test 7a, Test 7b).

Flow rate (ml/min) / Temperature(°C)	0.08	0.08	0.08	Residence time (min)	Solution Volume (ml)
r.t.	Test7a			20	9.6
65		Test7b		20	3.2
75			Test7c	20	3.2

Table 21. Experimental plan.

The conversion obtained is 3% and 62%, respectively.

Finally, Test 7c showed a good reactivity (84% conversion) and optimum selectivity (95%) although the conversion is lower in comparison with the fresh column (100%, see Test 1).

Catalytic Reactor Efficiency Test 8

The experiments were run consecutively for 7.33 hours at a flow rate of 0.08 ml/min at two different temperatures of 75°C and 85°C, respectively. The results are summarized in the following diagram:

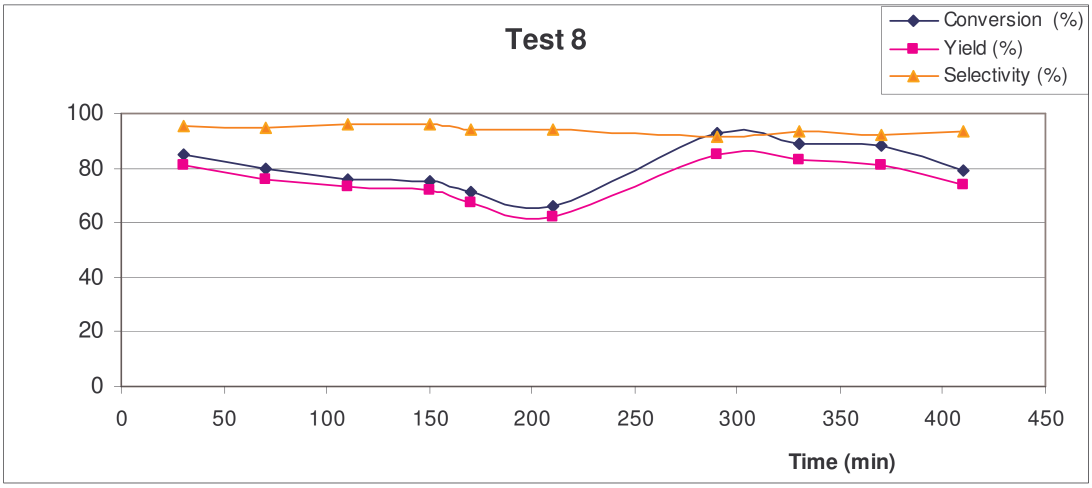


Diagram 11. Catalytic reactor efficiency.

The process selectivity obtained in all runs is very good (approx.95%).

The efficiency decreased after three hours, but by increasing the temperature a good conversion could be achieved again (82%) without stopping the flow system. In total, the reactor could be successfully operated over 6 hours.

The good performance of the entire flow process is shown in the following table, by using parameters such as Space Time Yield (STY) and productivity which have been already defined above:

Temperature (°C)	**STY (g/h·l)**	**Productivity**
75	2971.93	835.56
85	2769.33	793.01

Table 22. Process performance.

However, at a fixed reaction temperature and flow rate the fresh catalytic column is more active (see Test 6).

Different Reaction Conditions-Test 9

Reactant Solution Pumping

The reaction was tested under conditions of constant concentration by pulsing the solution of benzaldehyde in nitromethane in 50.26μl aliquots followed by CH_3NO_2 purging for 90 minutes at a flow rate of 0.08 ml/min. The obtained conversion was 12% and even after increasing the temperature from 75°C to 85°C no significant improvement was observed.

Double Reactant Solution Concentration

The concentration of benzaldehyde is 160 g/l in
nitromethane, exactly the double value used previously in order to reduce the nitromethane amount. Unfortunately, the conversion obtained was only 40% at 75°C and 0.08 ml/min.

Column 3

Reaction Repeatability-Test 10

The reaction repeatability was tested once more (see Test 6) performing the nitroaldol reaction with the fresh monolithic column 3 (Table 2) and conditioned by CH_3NO_2 at reaction temperature.

The catalyst amount anchored inside the column 3 was evaluated only by FT-IR spectroscopy in order to avoid the use of solvent such as CH_2Cl_2, which is problematic for the silica monolithic column stability.

Total volume system (ml)	1.9
Column conditioning	CH_3NO_2, 3.9 ml, r.t.
Dead time (min)	24
Pump type	Harvard Syringe Pump

Table 23. The main system features.

Experimental plan

Flow rate (ml/min) Temperature(°C)	0.08	0.16	0.32	Residence time (min)	Solution Volume (ml)
75	Test10a			**20**	10.72
75		Test10b		**10**	4.32
85		Test10c		**5**	14.08
85			Test10d	**5**	8.32

Table 24. Experimental plane

The results are shown in diagram 12:

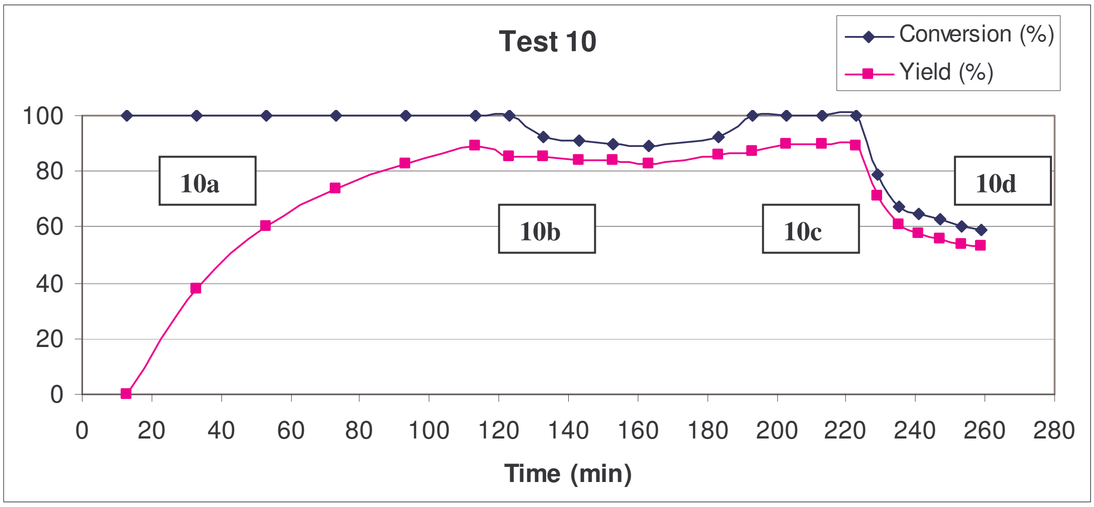


Diagram 12. The conversion and yield tendencies as a function of the time under Test 10a-d conditions.

Once more the repeatability of the process was proved, by using three different monolithic silica columns conveniently modified (see Table 2).

Loop Reactions-Test 11

Finally, the reaction was performed at a small scale (~4 ml) by employing a loop system. High flow rates were tested in order to benefit from the good selectivity normally obtained under these conditions of short residence time and to exploit the advantages at 85°C detected up to now.

Flow rate (ml/min)	**Cycles number**	**Residence time (min)**	**Yield 3 (%)**	**Conversion 1 (%)**
0.32	4	5	95	99
0.48	7	3.33	95	99

Table 25. Results obtained under loop reaction system.

The results were very positive in terms of yield and selectivity, the comparison in terms of Space Time Yield is impressive.

Reaction System	**STY** **(g/h·l)**
Batch	129
Monolithic Column	3804

Table 26. Batch and flow system STY.

In conclusion, a catalytic and monolithic reactor has been successfully realized for the selective synthesis of β-nitrostyrene from benzaldehyde and nitromethane through nitroaldol condensation. The catalyst, a primary amine, was covalently bonded to the silica monolith by tethering technique and the catalyst loading obtained (0.7 mmol/g) is comparable with the value normally obtained for silica powder (1.1 mmol/g). However, the tethering technique requires less time and reagent consuming than the conventional approach. The reaction was performed in single continuous experiment and worked very well. By changing reaction parameters such as flow rate and temperature the conversion could be optimized. In particular the fresh catalytic reactors allow achieving quantitative conversion during contact times of 10 to 20 minutes at 75°C. By further increasing the flow rate a conversion of 50 % in only 2.5 minutes is possible. The process reproducibility was proved by performing the reaction with three different monolithic column previously modified, following the same procedures. The reaction tendencies showed the same dependence on flow rate and temperature in all three column processes. In the case of loop reaction processes it was also possible to influence the process performance by the number of loops.

The performance of continuous catalytic process expressed by STY (Space Time Yield) and/or productivity was 30 times greater than the performance of the corresponding batch process. These results represent a powerful improvement which can be exploited by using larger reaction scales. The process repeatability has been extensively studied for all three column reactors. In particular, at the same reaction conditions the performance was constant for 3 hours, after that time the conversion started to decrease. By increasing the temperature without stopping the process the conversion could be enhanced again. The catalytic system undergoes a significant catalyst poisoning which can be easily regenerated in an one step reaction until 16 h of total run time. Therefore, the column life time needs to be further improved, for instance by considering more accurately the structural stability of the monolith provided by Merck KGaA which has some limitations with respect to the solvent used (CH_2Cl_2) and the operative temperature (40°C).

Finally, the good results obtained open the possibility to extend the use of the silica monolithic column as a powerful support/reactor powerful for other fine chemical productions under conditions of heterogeneous catalysis.

Characterization

The project was completed by characterizing the monolithic silica column structure after use. The Chromolith Performance Column 1 was cut in seven equal parts (of 1cm length) without scratching the internal siliceous material and were analyzed by:

- ✓ SEM-EDX
- ✓ ATR-FTIR spectroscopy
- ✓ EGA (Evolved Gas Analysis)
- ✓ Elemental Analysis

SEM-EDX

The samples numbered consecutively according to their position along the flow direction (1 to 7) showed approximately the same structure and porosity until sample No. 5, while in sample No. 6 and 7 some areas of aggregation are present. It is not clear whether these agglomerates are due to precipitation phenomena or structural rearrangement, even if the second assumption seems to be more likely. The following SEM-pictures show as examples the structures detected for samples 1 and 5 and that of sample 7 which is clearly different.

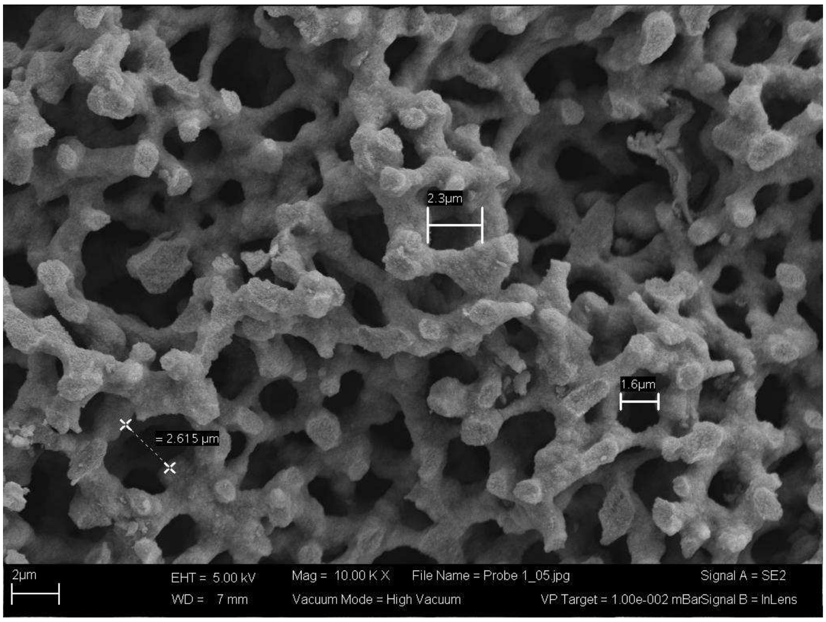


Figure 9. SEM picture of column sample No. 1

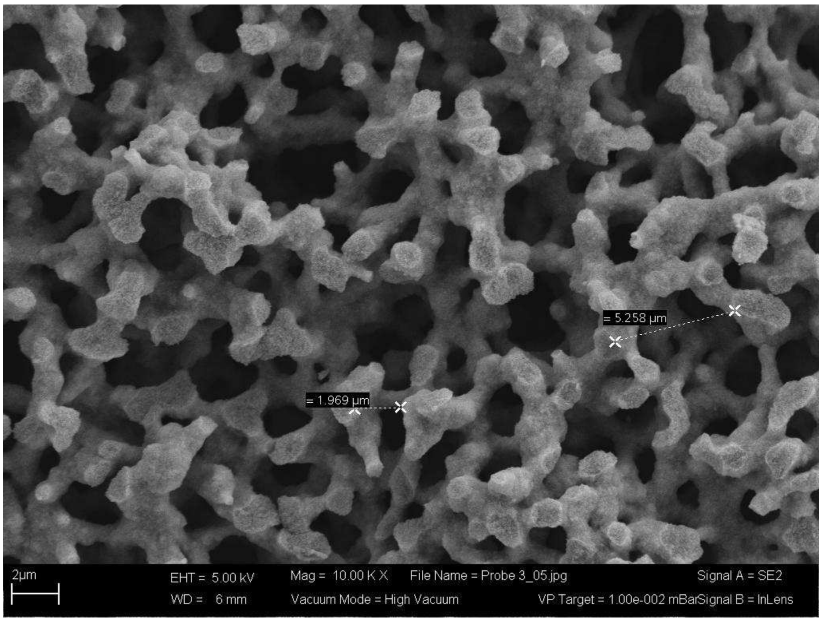


Figure 10. SEM picture of column sample No. 5

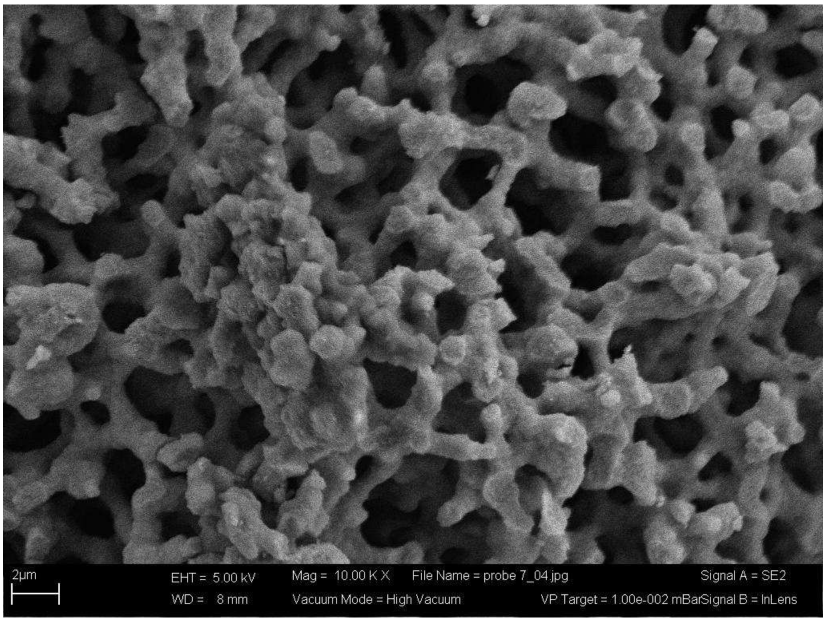
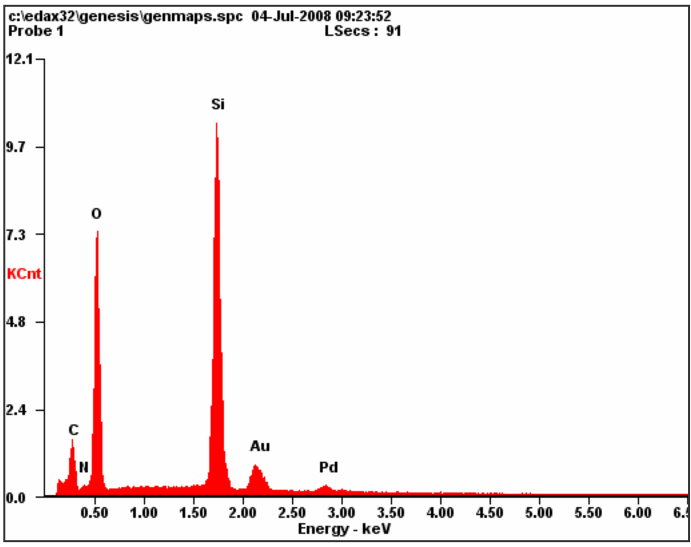


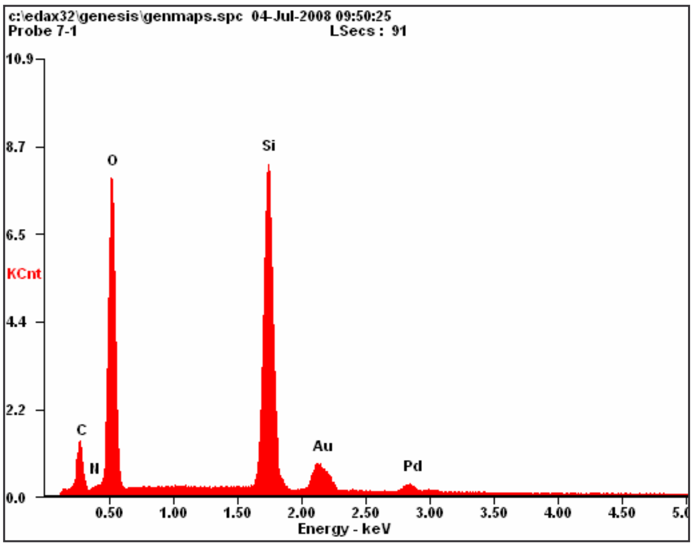
Figure 11. SEM picture of column sample No. 7

Analysis by coupled SEM and EDX gave no evidence for a different composition of these aggregates detected in sample 7 in comparison to the bulk column material. All seven samples show identically EDX data as illustrated below for Sample No.1 and Sample No. 7.



Element	*Wt%*	*At%*
CK	23.01	34.19
NK	02.18	02.77
OK	32.32	36.04
SiK	42.49	27.00
Matrix	Correction	ZAF

Figure 12. EDX analysis of sample No. 1



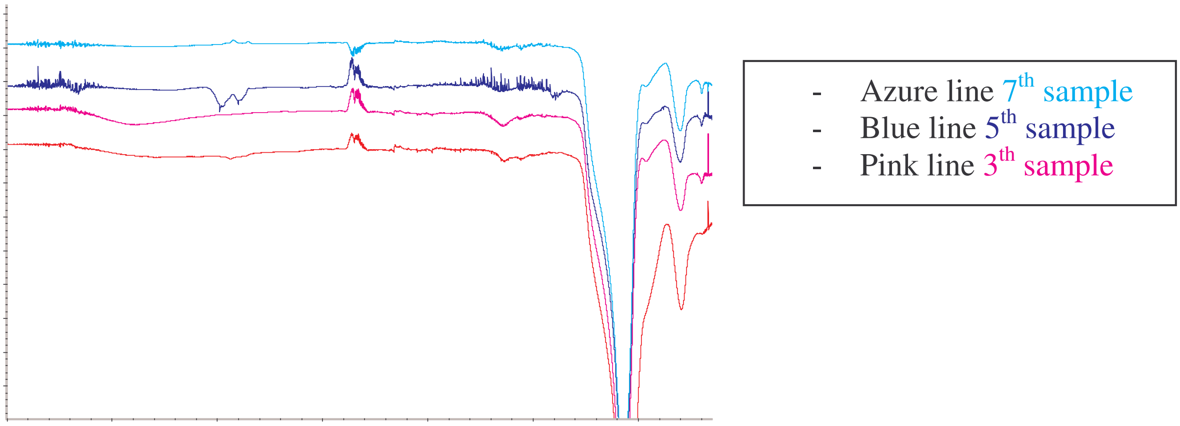
Element	*Wt%*	*At%*
CK	21.53	31.51
NK	02.37	02.98
OK	37.88	41.60
SiK	38.22	23.91
Matrix	Correction	ZAF

Figure 13. EDX analysis of sample No. 7

ATR-IR spectroscopy

This technique gave only partial information because it has a low sensitivity when applied to organic molecules dispersed on an inorganic surface.

However, by making a comparison of the KG-60-NH_2 catalyst (red line) spectrum with the spectra obtained from the cut samples it is obvious that a primary amine is present on the column as it can be detected by its characteristic absorption band at 1650-1500 cm^{-1}.



Spectra 2. FT-IR recorded on column samples No. 3, 5, 7

Elemental Analysis.

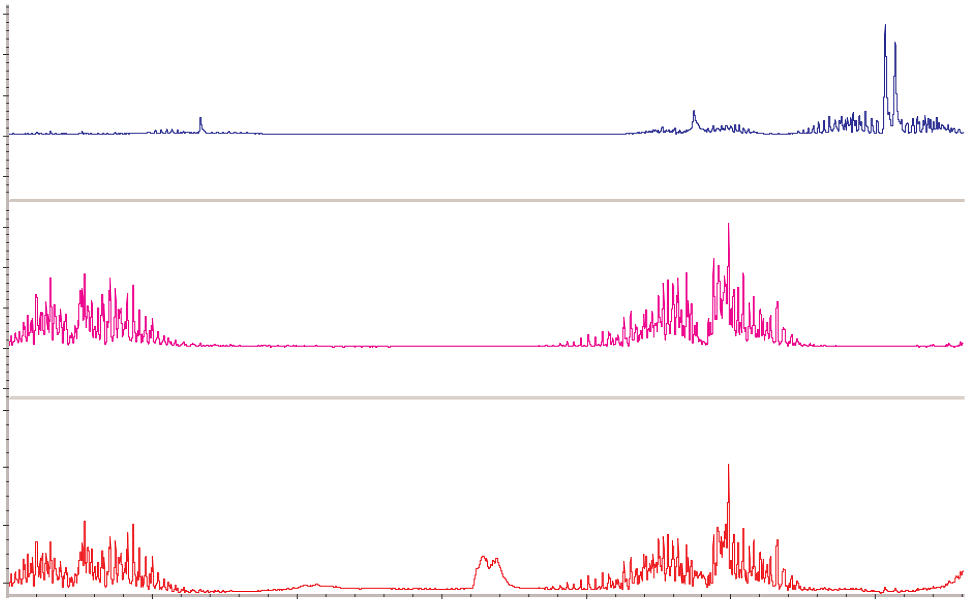
Elemental analysis also confirmed the presence of the catalytic site with a medium content of nitrogen which corresponds to a loading value of 0.88 mmol/g.

Element	Molecular weight	Sample No. 2	Sample No. 3	Sample No. 5	Sample No. 6	Sample No. 7
%N	14	1,26	1,20	1,22	1,26	1,25
%C	12	9,13	9,19	12,53	10,19	10,07
%H	1	1,21	1,24	1,68	1,3	1,19

Table 27. Elemental analysis values.

EGA

Evolved Gas Analysis is performed by heating the sample in an inert cell with a linear heating rate of 20 K/min until 400°C and simultaneously monitoring the gas phase by FT-IR spectroscopy.



Spectra 3. EGA analysis of the column.

The only evolved gases that were detected are NH_3 from amine functionalities, H_2O, and CO_2 at 230°C, which is the decomposition temperature of the powder catalyst KG-60-NH_2 (see TG and DSC data). By further increasing the temperature traces of N_2O as well as CO formation is observed due to subsequent decomposition reactions.

There is also a broad band at 2800-3000 cm^{-1} that could be assigned to alkyl C-H bonds.

2d.3. Experimental Part

The thermal stability of reagents, product and catalysts was tested by using thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC) in order to verify the possibility to perform the nitroaldol reaction between benzaldehyde and nitrostyrene at higher temperatures without any decomposition or explosive phenomena.

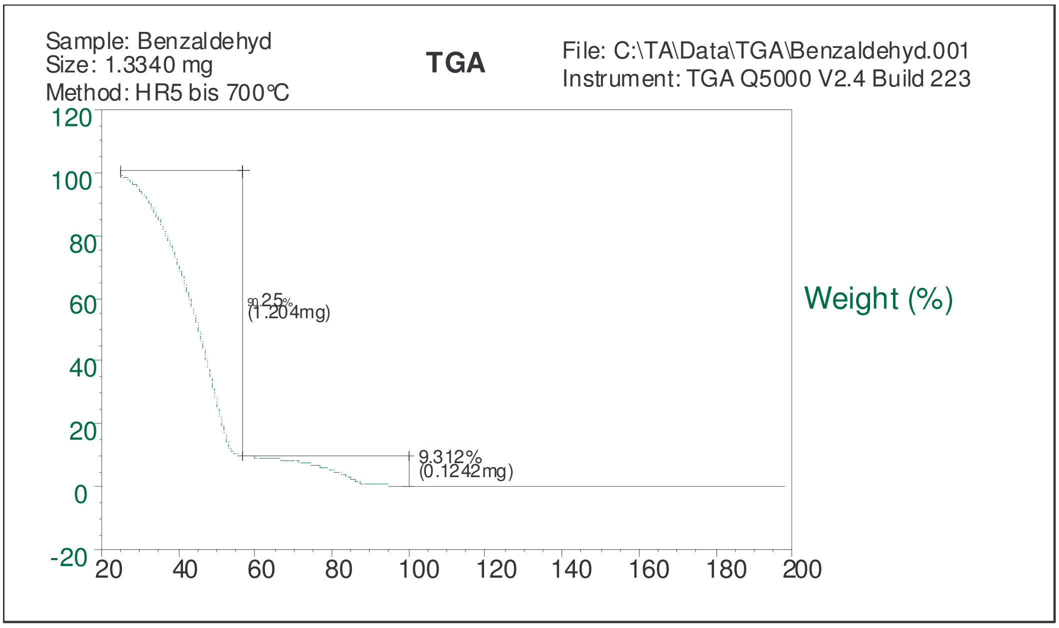


Figure 14. TGA of Benzaldehyde.

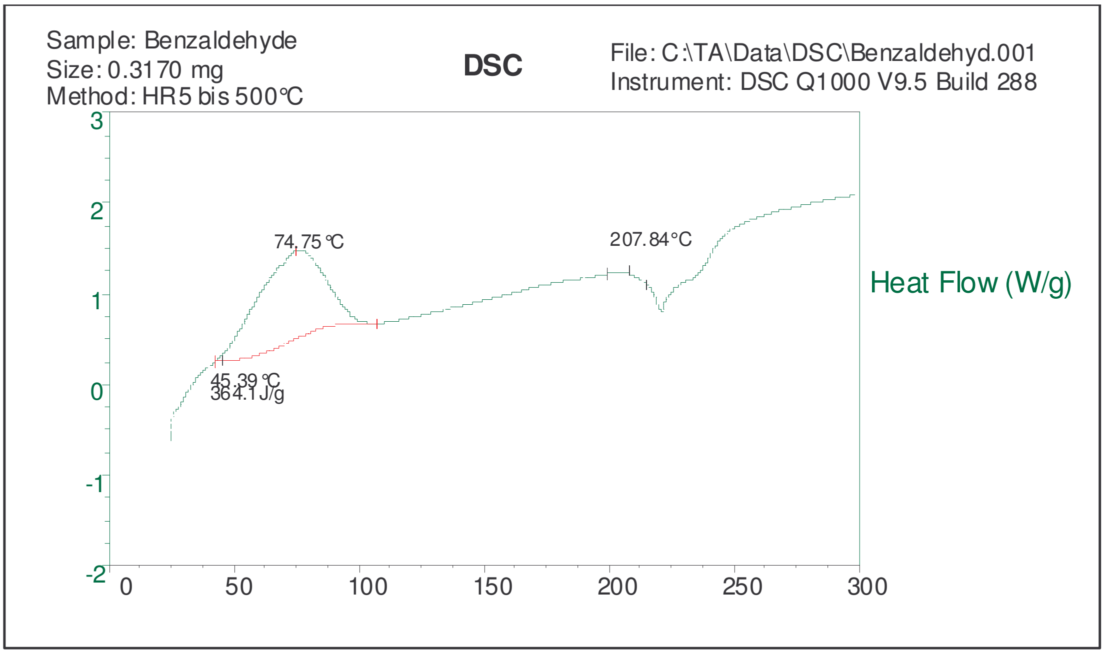


Figure 15. DSC of Benzaldehyde.

In an open TGA pan, benzaldehyde exhibits a significant mass loss between 30-55°C as a result of low vapour pressure (45°C, 4 mmHg). However, within an hermetically sealed DSC pan a slight exothermic decomposition reaction under high vapour pressure could be observed.

<u>Nitromethane</u> (Fluka≥97%)

Flash Points: 35°C closed pan; 44.44°C open pan

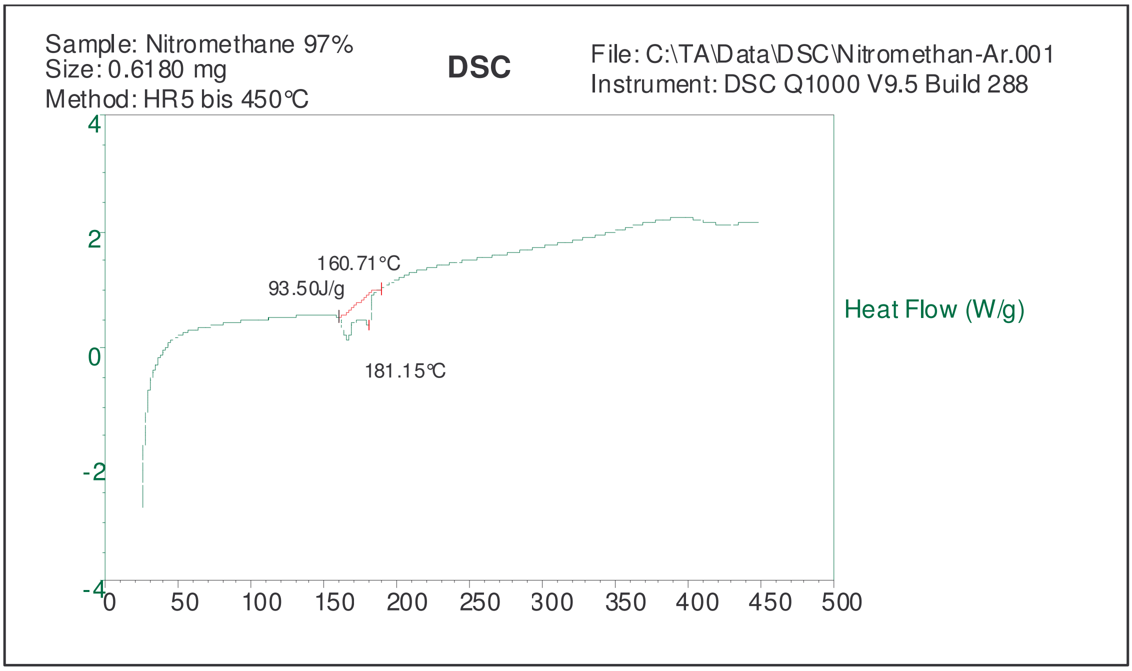


Figure 16. DSC of nitromethane.

It was not possible to perform the analysis in a closed system (like shown in Figure 17); The substance did not show any exothermic transition.

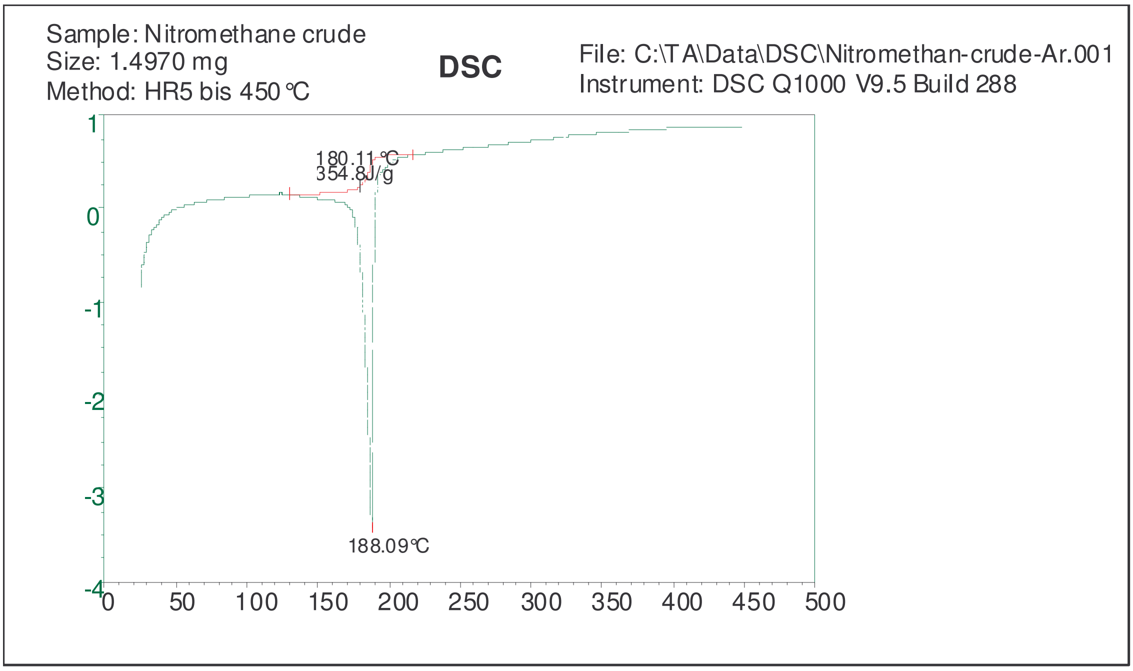


Figure 17. DSC of nitromethane crude.

<u>Trans nitrostyrene</u> (Aldrich 99%),

Melting point: 55-58°C

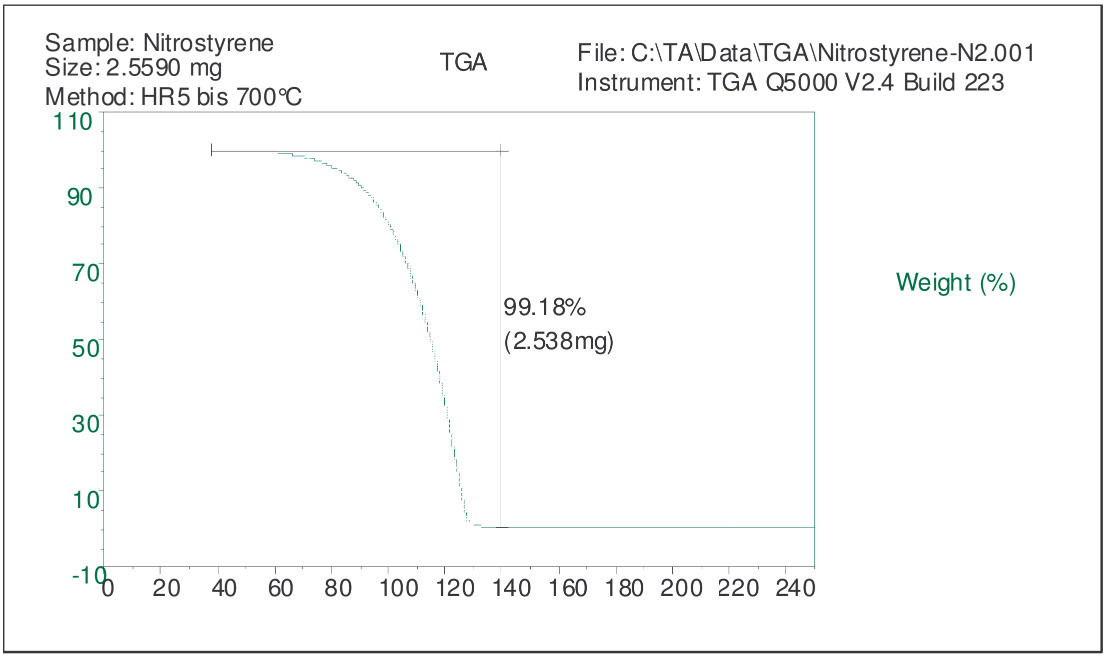


Figure 18. TGA of trans nitrostyrene

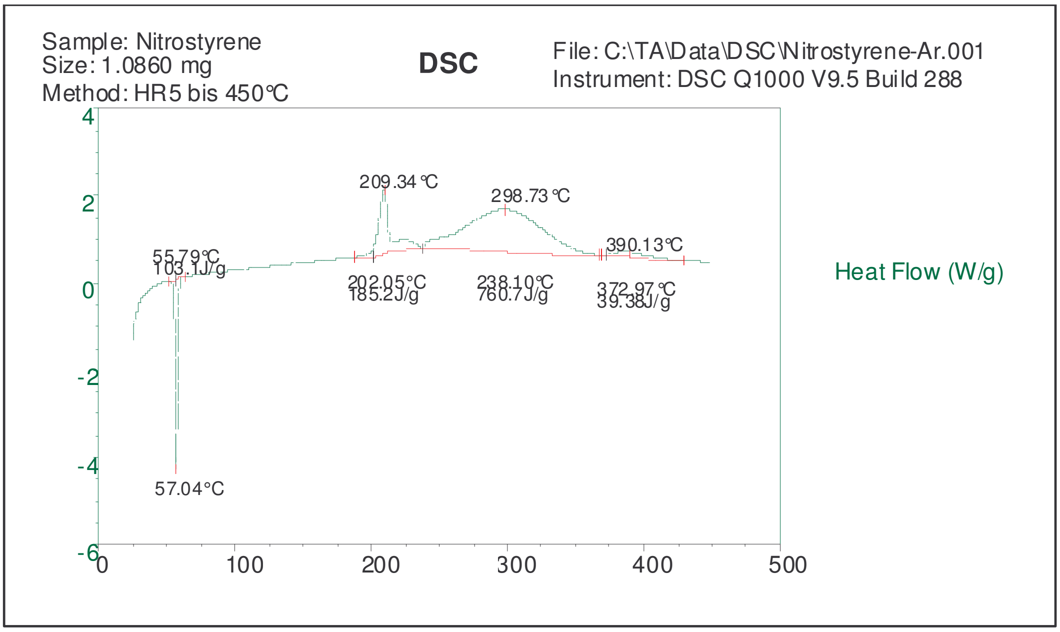


Figure 19. DSC of nitrostyrene.

The DSC data show a sharp endothermic melting peak at 56°C but no exothermic decomposition until 200°C.

Modified Gisin's method

The picric acid (aqueous solution 35% w) was filtered and placed in a drier under vacuum overnight. A 25 ml 0.1 M (0.5736 g) solution in CH_2Cl_2 was prepared and the molar extinction coefficient (14500, EtOH, $1 \cdot 10^{-5}$-$20 \cdot 10^{-5}$M) reported in literature was verified at the maximum absorption wavelength of 358.30 cm^{-1}. In particular two dilutions (factor 100, 50) were necessary to keep in the indicated concentration range and have not more than 20% of CH_2Cl_2 in the samples.

The column was purged with 5 ml 5% v/v diisopropylethylamine dissolved in CH_2Cl_2 (0.1 ml/min, pH = 7) for neutralizing the reaction medium as well as with 10 ml CH_2Cl_2 using a syringe pump.

Then, a 10 ml aliquot of the 0.1 M picric acid solution was pumped through the column at a flow rate of 0.2 ml/min. It was followed by copious washing (total 270 ml) monitored by UV-Vis spectrscopy to ensure that all free picric acid has been removed. Afterwards, the picric acid salt formed with the primary amine was removed by 10 ml of the diisopropylethylamine (5% v/v) solution in CH_2Cl_2. The eluate was collected in a volumetric flask with the last washing (15 ml CH_2Cl_2) and analyzed by UV-Vis spectroscopy in order to determine the molar concentration of picric acid present and thus indirectly the catalyst content.

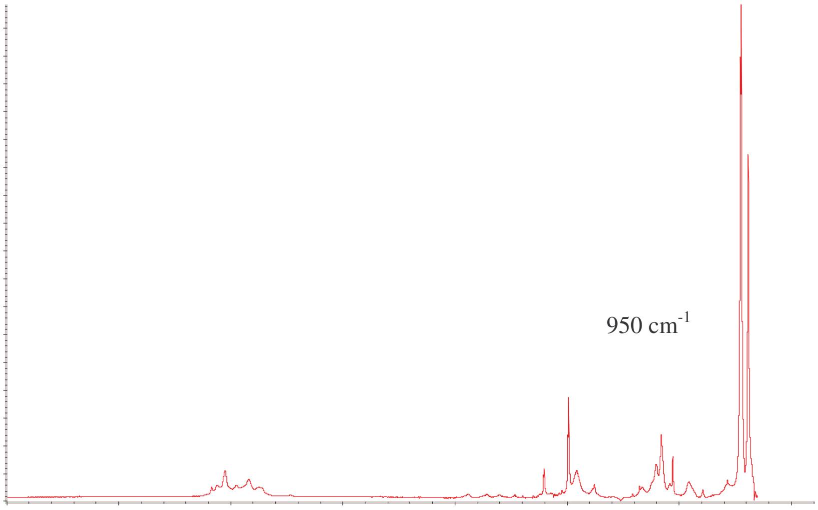
Catalyst Quantification by ATR-IR Spectroscopy

A solution of 3-aminopropyltriethoxysilane (Solution A) was prepared by weighting 1.25g in 25 ml volumetric flask filled with toluene. From this stock solution five different concentrations (Solution B-G, Table 14) were generated within one dilution step. All solutions were analyzed by ATR-IR spectroscopy (three replicates) and the spectra were elaborated by the Unscrambler software program.

Solution	Dilution Factor	Concentration (g/l)
A	1	50.60
B	1.25	40.48
C	1.66	30.36
D	2.5	20.24
E	3.33	15.18
F	5	10.12
G	10	5.06
Toluene	-	0

Table 28. Calibration solutions.

The calibration of the sylilating agent solution allowed estimating the content of 3-aminopropyltriethoxysilane present in the solution before and after passing through the silica reactor and consequently allowed determination of the amount of catalyst anchored. The absorbance value used is indicated in the following representative spectrum.



Spectra 4. FT-IR spectrum of 3-aminopropyltriethoxysilane in toluene

Acquisition parameters and Instrument Features:

Durascope diamond ATR-IR

Number of samples scans: 24

Number of background scans: 24

Resolution: 1.000

Sample gain: 1.0

Mirror velocity: 1.8988

Aperture: 34.00

Detector: MCT/A

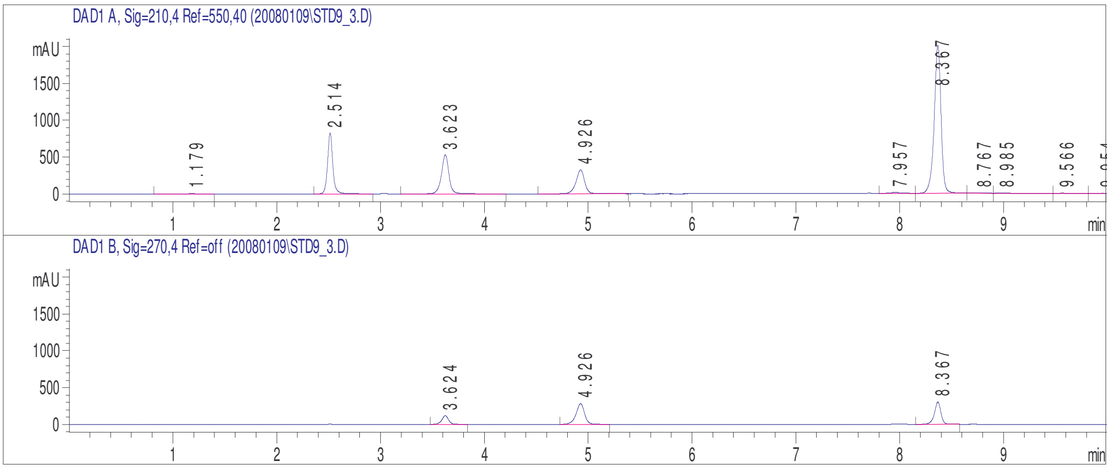
Beamsplitter: XT-KBr

Source: IR

HPLC Method

All reaction samples were analyzed by HPLC (Agilent) equipped with autosampler and diode array detector (A 210; B 270 nm). The chromatographic column used is LiChrospher 100, rpC18e, 5μ, 250X4, and the gradient is 60%CH_3CN e 40%H_2O (flow 1ml/min).

A standard solution containing nitrostyrene (99%), benzaldehyde (99%), CH_3NO_2 (>99%), and methyl-naphthalene (>97%) in CH_3CN were analyzed (see following chromatogram) at different concentrations and calibrated by using external standard mode. Each sample was injected without any pre-treatment but only after suitable dilution (0.1-0.4 g/l).



Representative Flow Nitroaldol Procedure.

The reactant solution composed of benzaldehyde and nitromethane was placed in a screw cap box previously dried.

Prior to reaction start the column was flashed with nitromethane at the desired temperature in order to condition the column and check the flow rate.

The reactant solution was transferred to a 50 ml syringe placed on the syringe pump and flow was initiated by following the experimental plan.

The reaction mixture was collected as fractions in a screw cap vial and injected after dilution in HPLC. After the entire run the column was washed with degassed EtOAc (25ml), closed and stored inside a drier. Conversions and yields were calculated from the HPLC analysis data after linear calibration of reagents and product. The selectivity values were obtained as ratio between conversion and yield.

Representative Catalyst Regeneration Procedure

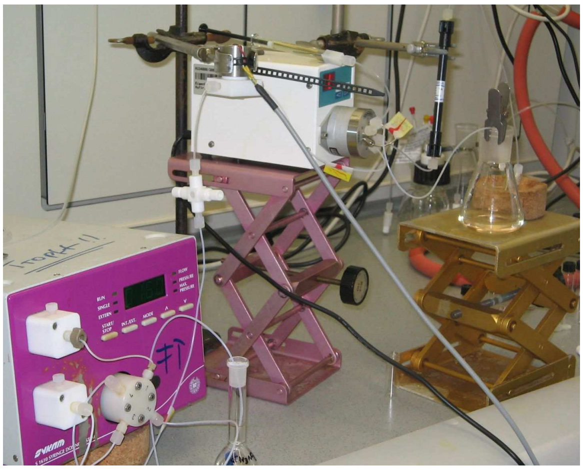
A 5 ml aliquot of triethylamine in absolute EtOH (10% v) was prepared in a volumetric flask and transferred into a syringe for passing through the column. The eluate (yellow solution) was collected in three fractions and followed by 20 ml of absolute EtOH. For each fraction the solvent was evaporated and the residue analyzed by NMR-^{1}H. Finally, the column was stored in degassed EtOAc.

Representative Pulsing Reaction

A set up with two syringes pumps has been tested (Harvard), one for reactant solution and one for the nitromethane (Picture 1). A switching valve was inserted in front of the monolithic reactor in order to pass a small volume only. The valve did not work properly under these conditions, maybe because of the back pressure which was not compatible with the switching valve hardware.

Picture 1.

Pulsing of the reactant solution was successfully conducted by using a steel loop (calculated volume: 50 μl) filled manually by using a glass syringe (5 ml) and automatically injected (Picture 2). The injection was followed by pure nitromethane (~5ml) at 0.08 ml/min flow rate and finally the elute was collected in a volumetric flask and analyzed by HPLC.



Picture 2

Representative Loop Reaction

The reaction set up was developed for having the minimum cycle volume solution. The column was previously flashed with CH_3NO_2 by using Syringe Dosing System (1ml) and then the inlet connected (via needle) with a graduate test-tube, containing the reactant solution, and the outlet inserted in the same one.

In this way the total volume was approx. 5 ml and the time necessary to run a cycle was defined. The intermediate samples were taken after each cycle by using a small syringe (100µl) and the last sample was taken after cleaning with CH_3NO_2 until a fixed volume of 7 ml was obtained.

2d.4. References.

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Curriculum vitae

Laura Soldi was born in 1979 in Monza (MI).

She went to school in Viadana where she received her high school degree from the *Liceo Scientifico P. Maggi* in 1998.

She attended Chemistry classes at the local city University of Parma. In 2004 she graduated (overall marks 105/110) in Industrial Chemistry in the laboratory of Prof. M. Costa studying the preparation of 2-oxalidinones derivates from N-alkylamine in supercritical carbon dioxide.

In October 2004 she won a grant for funding young researcher in technological transfer knowledge between University of Parma and the Endura Spa, a leading Company in the R&D Chemical Italian industry. Between 2004 and 2005 she worked at the Organic Department of the University of Parma under the supervision of Prof. Sartori and Dot. Valerio Borzatta, as industrial referee, about the eco-friendly synthesis of aliphatic-aril ketones by using carboxylic acid and heterogeneous catalysis.

After one year of research she began a Doctorate in Chemistry Science in the research group of Prof. Sartori, focusing her scientific interest in selective heterogeneous catalysis in continuous flow systems on the development of environmentally “clean” process for fine chemical.

During her Ph.D. from October 2007 to August 2008, she spent 10 months of research as guest scientist in Germany at the Fraunhofer Institute for Chemical Technology (ICT) of Pfinztal.

Under the supervision of Dot. Stefan Loebbecke she studied catalytic micro-structured flow system for the synthesis of pharmaceutical intermediates.

Ringraziamenti

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