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Silica-Bound Homogenous Catalysts as Recoverable and Reusable Catalysts in Organic Synthesis

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Abstract: Very frequently the most costly components in a chemical reaction are not the starting materials or the reaction products, but the catalyst. In addition to the advantages from the economic point of view, recovery and reuse of the catalyst is equally important in order to avoid wastes, so improving the greenness of the process. There is a current tendency to transform homogeneous into heterogeneous catalysis, that will even be accelerated in the near future. Starting from a successful homogeneous catalyst, one general methodology allowing its recovery and reuse is to immobilize a suitable derivative of the active catalyst on an insoluble solid support. When the catalyst does not deactivate and is sufficiently stable under the reaction conditions, the ultimate immobilization methodology is to attach covalently the catalytically active species to the support. In this contribution, after introducing some general principles describing the fundamentals of the covalent anchoring, the emphasis is placed more on giving an overview of the most important types of covalently anchored catalysts, including Brönsted and Lewis acids, covalently anchored bases and hydrogenation complexes. Hot topics such as silica-bound organocatalysts and the application of periodic mesoporous organosilicas as heterogeneous catalysts is also covered.

Keywords: Brönsted acids covalently anchored to silica; covalently-anchored catalysts; from homogeneous to heterogeneous catalysis; periodic mesoporous organosilicas as catalysts; silica as support; silica-bound organocatalysts; supported catalysts

1 Introduction

The classical natural product syntheses developed in the first half of the 20th century were based on the use of highly reactive reagents that spontaneously transform into products at moderate temperature, and the vast majority of the organic syntheses up to 1980s rarely contained catalytic reactions.[1–5] Grignard synthesis and transition metal oxidations are paradigmatic examples of this type of organic chemistry.

The under use of catalysis in organic synthesis was in sharp contrast with the remarkable development of heterogeneous catalysis in oil refining and petrochemistry.[6–8] Starting in the mid 1950s, petrochemical processes were making ample use of solid acids. It was, however, a turning point when organic synthesis became deeply focused on asymmetric synthesis. For the preparation of enantiomerically pure substances, the superior methodology based on the use of asymmetric catalysis was clearly established in the

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1980s.[9–11] At this time, the general applicability of homogeneous asymmetric hydrogenations and enantioselective allylic alcohol epoxidation was firmly established.[12,13] Latter, the field of enantioselective epoxidation was considerably expanded to non-activated alkenes using easily available, enantioselectively pure metallosalen complexes.[14] The extremely high enantioselectivity of many of these catalytic processes and their applicability to a wide range of substrates constituted a breakthrough in chemistry that changed the scenario in organic synthesis, increasing considerably the interest for introducing catalysis in organic reactions.

In addition to the practical advantages of enantioselective catalysis with respect to alternatives requiring stoichiometric amounts of chiral reagents, a research field that is currently exerting a strong influence and forcing organic synthesis to a profound change is green chemistry. Sustainability and an environmental benign character have become necessary prerequisites that are pushing us to abandon traditional organic reagents and conventional solvents.[15,16] This tendency derived from the application of the green chemistry principles will grow in importance in very near future, leading to a new reaction toolbox for organic synthesis. Notably, the first and fifth principles of green chemistry refer to the "*minimization of wastes*" and the "*replacement of stoichiometric by catalytic reactions*".[15] Obviously, all reactions consume stoichiometric amounts of reagents, and the fifth principle (directly related to the subject of this review) points out the necessity to substitute those reactions that use highly reactive and environmentally unacceptable reagents by others that are tolerable but do not react due to kinetic reasons. One clear example of how application of the fifth principle influences organic reactions is the replacement of alcohol oxidations to ketones with permanganate by oxidations with benign oxidizing reagents including H_2O_2, hydroperoxides and O_2. The use of permanganate does not require any catalyst and certainly works well, but produces stoichiometric amounts of manganese oxide and other by-products that strongly limit the sustainability of the process. In contrast, the use of ambient oxygen as oxidant is challenging since it requires the development of a catalyst that should exert a total control on the oxidation mechanism, thus avoiding overoxidation.[17]

As a consequence of the factors considered above, it can be foreseen that catalysis will continue to grow in importance in organic synthesis in the near future to levels that were not predictable twenty years ago.

2 Homogeneous *versus* Heterogeneous Catalysis

A general trend in catalysis is to transform a successful homogeneous catalyst into a heterogeneous catalytic system (Scheme 1).[6,18] The use of heterogeneous solid catalysts being in a different phase than the reagents and products has an obvious advantage in terms of easy separation from the reaction mixture, allowing the recovery of the solid and eventually its reuse, provided that the solid has not become deactivated during the course of the reaction.

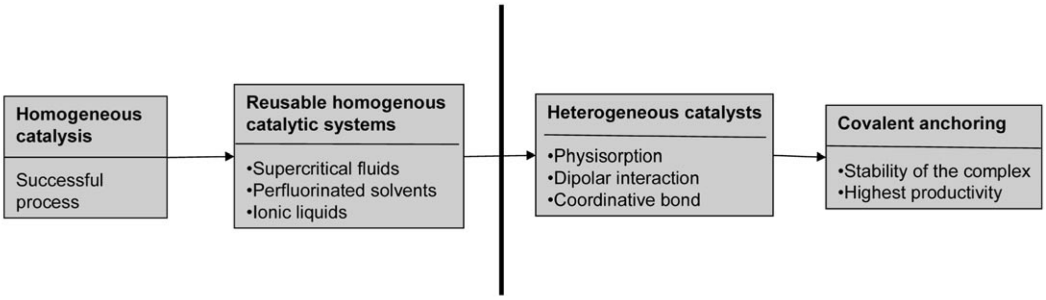
The development of selective and reusable solid catalysts for organic reactions has been a very active area of research.[19] Thus, in addition to easy separation,[20–22] the use of insoluble solid catalysts has the extra bonus of minimizing wastes derived from catalyst separation and disposal, fulfilling the principle of recyclability. In addition, solid catalysts allow the design of continuous flow processes that are economically very attractive at the industrial scale.

Normally, homogeneous catalysts are developed earlier than heterogeneous catalysts. This is mainly due to the fact that homogeneous catalysts based on molecular species usually contain a single site that is well defined and characterizable by solution spectroscopy. Then, by organic synthesis it is possible to obtain a series of catalysts with optimized catalytic properties. In contrast to this, solid catalysts may contain a wide distribution of catalytic sites differing in their intrinsic activity and selectivity, and they are some times difficult to characterize at the molecular level.

A scientifically rewarding methodology could, therefore, be to transform a successful homogeneous catalyst into a heterogeneous solid catalyst. The simplest strategy to perform this task is by supporting the soluble metallic complex or molecule on the surface of an insoluble solid.[23–26] The highest level of evolution in the surface immobilization strategy is the covalent attachment of the organic compound or ligand to the solid surface.

It is the purpose of this review to illustrate with some representative examples the current methodologies to transform a homogeneous into a heterogeneous catalyst by supporting it on different type of silicas. The specific aim of this account is to bring to the attention of synthetic organic chemists the state of the art in the field of covalent anchoring of metallic complexes and active molecules on silicas. To achieve this task we have selected mainly systems developed in our laboratory, although occasionally we also include relevant catalysts from other research groups. It is not the purpose of this article to provide a comprehensive coverage of all the covalently attached silica catalysts and the reader is referred to earlier reviews in the literature for an in-depth coverage of this area.[6,25–29]

We will comment briefly on the advantages/disadvantages of the covalent immobilization with respect to alternative methodologies of heterogenization, providing examples on the role that the support can play in the reaction and, then, the main body of this report will focus on the description of covalently anchored homogeneous catalysts on silicas. We have organized the central sections on silica-bound catalysts according to the reaction type being catalyzed.



Scheme 1. Evolution from a homogeneous catalyst into a covalently attached heterogeneous catalyst.

3 Covalent Immobilization as the Definite Methodology for Converting a Homogeneous Catalyst into a Heterogeneous Catalyst

The general purpose of supporting active sites on an insoluble solid is to make heterogeneous a homogeneous catalytic process. This can be achieved in many different ways that vary from mere physisorption (adsorption by physical forces) onto the solid surface to the most sophisticated covalent anchoring to the solid surface. Covalent anchoring constitutes generally the last generation in a series of catalysts that typically start from a highly active soluble catalyst. Among the disadvantages of covalent anchoring to the silica support, the main one is that catalyst preparation adds complexity to the homogeneous phase catalyst.

Covalent immobilization requires functionalization of the catalytically active complex or molecule through a peripheral position that does not hamper the catalytic activity. Also, in many cases, the solid support has to be functionalized and modified either prior to the key step of covalent anchoring or after it. Thus, covalent anchoring of a metallic complex or an active molecule often requires dedicated organic synthesis. The only way to compensate this synthetic effort is by producing a solid catalyst that is durable and reusable for many runs, exhibiting a total productivity that compensates for all this effort. Productivity, i.e., the maximum number of kg of products produced by a kg of catalyst, has to be very high to overbalance and compensate the synthetic effort. This prerequisite needs to be demonstrated and checked for every system, since it may occur that the anchored catalytic sites are not robust enough for a large number of reuses, and they may become irreversibly deactivated.

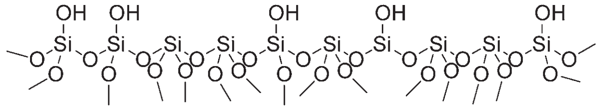
Among the reasons for deactivation of a covalently anchored catalyst, the most common ones are degradation of the organic molecule or ligand under the reaction conditions, leaching of the active metal in the case of metallic complexes, and adsorption of poisons onto the active site. Covalent anchoring of the complex to a support does not prevent all those deactivation pathways, since it only ensures that no desorption of the covalently attached molecule from the support will occur. Therefore, it may be that covalent anchoring on a solid support would not be worthwhile because the resulting solid would lose catalytic activity, and the reusability and productivity would be unsatisfactorily low.

The lack of stability of a highly active homogeneous catalyst is not so uncommon as it may appear at first sight. For instance, all the highly active homogeneous palladium catalysts that are widely used for cross-coupling reactions are suspected of being highly unstable.[30,31] Also, salen-manganese complexes for enantioselective alkene epoxidation are not very stable in the presence of oxidizing reagents.[32,33]

Concerning the procedure of immobilization and, particularly, if there are some advantages derived from covalent binding, Dioos and Jacobs have shown in the case of a chiral salen-chromium complex that adsorption of the complex from a solution onto the surface of amorphous silica provides a solid that can be used as a heterogeneous catalysts for epoxide ring opening.[34,35] The complex does not leach into the solution during the course of the catalytic reaction and the supported salen-chromium can be reused indefinitely with fresh substrates. Given a situation like this, there will not be an evident advantage of producing an analogous catalyst covalently bound to the silica,[36] particularly considering that covalent immobilization will require organic synthesis and further preparation steps than just mere physisorption. However, this situation is not common and, depending on the solvent and reaction conditions, physisorption of a soluble catalyst on the silica surface is inefficient to immobilize species that easily become desorbed and migrate into the liquid phase under the reaction conditions.

4 Silanol Groups and Covalent Binding

Covalent anchoring on silica surfaces is based on the presence of silanol groups (≡Si−OH in Scheme 2). The existence of these silanol groups can be easily determined by IR spectroscopy of the silica samples previously submitted to water removal.[37]



Scheme 2. Structure of silica surface containing silanoxy bridges and silanol groups.

The specific density of the silanol groups per gram of silica depends on many factors including surface area, procedure of silica formation, incomplete condensation of neighbouring silanols and thermal pretreatment of the silica at high temperatures. Even though silanol groups can also be in the interior of the silica particles, silanols together with silanoxy groups (≡Si−O−Si≡ bridges), are the natural terminal groups of the silicas at the solid surface. Since the silanol groups are located at the surface, the population of silanols increases along with the total surface area.

Also, silica samples obtained by sol-gel synthesis have a considerably higher population of silanol groups, due to incomplete condensation of the molecular precursors, than pyrogenic silicas produced at high temperatures. Treating silicas at temperature about 900 °C produces the condensation of two neighbouring silanol groups to form a silanoxy bridge (Figure 1).[38,39] Ideally, the maximum achievable loading of catalytic sites on the solid is desired and, therefore, a large population of silanol groups is convenient to effect the anchoring of a sufficiently high amount of catalyst. On the other hand, after having performed the covalent anchoring, the presence of residual silanol groups may be negative and detrimental for the catalytic performance of the solid, and it could be even necessary to mask these free silanol groups.

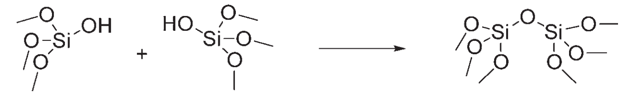
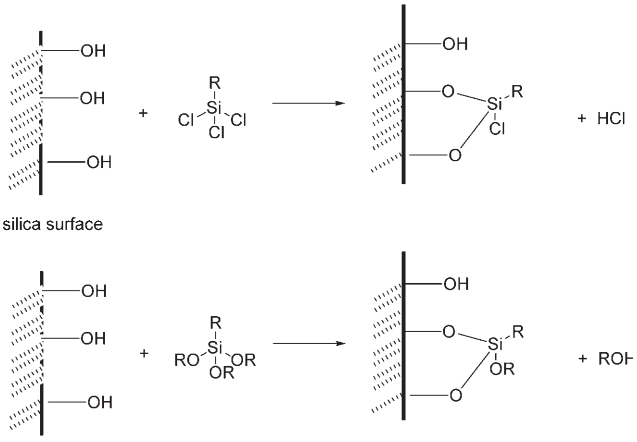
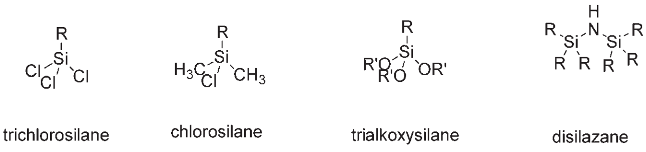


Figure 1. Formation of silanoxy bridges by thermal condensation of neighbouring silanol groups.

The most widely used methodology to anchor on silica surfaces is the reaction of surface silanol groups with silylating reagents. Chlorosilanes were initially used, but condensation of chlorosilanes with surface silanol groups evolves HCl that may cause some damage to the structure of the silica or have other undesired effects on the organic component (Scheme 3). Hydrochloric acid may be especially damaging in the case of mesoporous silicas, which may undergo extensive collapse of their structure upon reacting with chlorosilanes. For this reason, current silylating agents are mainly trialkoxysilanes or disilazane which upon reaction evolve alcohols or ammonia (Scheme 4). Also, in those cases in which the silylating agent has three leaving groups, anchoring usually involves the substitution of one or two but rarely the three groups. This is simply due to the difficulty of having three surface silanol groups close enough to bind with a single silicon atom. Substitution of one or two of the silylating agent leaving groups already produces one or two covalent bonds with the solid surface that are sufficient for having a robust anchoring to the surface. Mono- and bipodal anchoring of the silylating agent leaves some leaving groups that eventually will hydrolyze with the ambient moisture.



Scheme 3. Surface reactions leading to covalent anchoring of organic R groups.



Scheme 4. Most common silylating reagents.

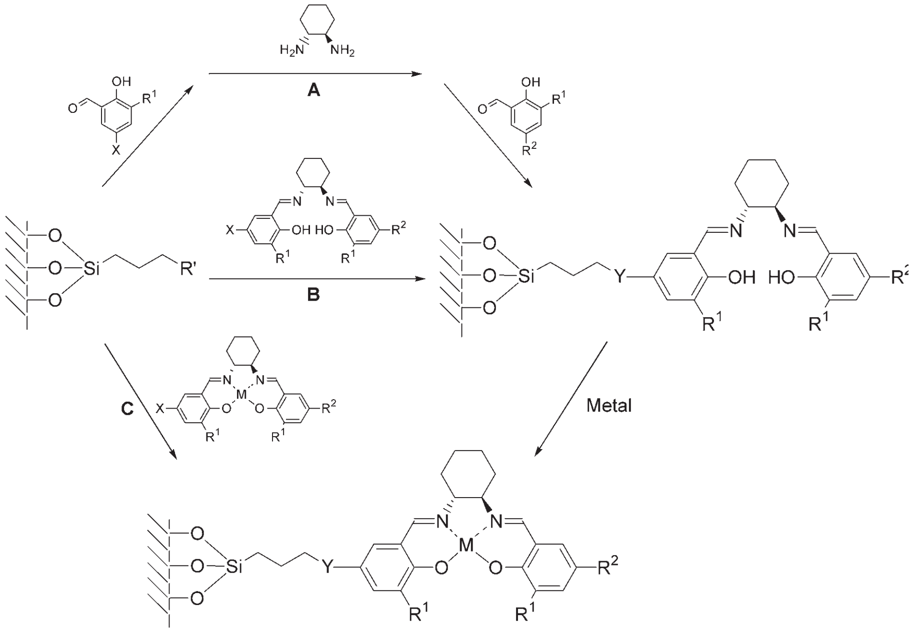
The above methodology is based on the strength and inertness of the Si–C bond that is assumed to be stable during manipulation of the sample. However, under certain circumstances, particularly for good leaving organic groups, the stability of the Si–C bond may not be sufficient and the system should be surveyed for the stability of the silylating agent throughout all the process.[40,41] This can be done by means of solid-state ^{29}Si or ^{13}C NMR spectroscopy that allows to follow the presence of the Si–C atoms that appear at very specific chemical shifts, different from other Si or C atoms.

It has to be remarked that although many other alternatives can be envisioned for functionalization of the silanol OH groups such as, for instance, forming $\equiv$Si–O–CH$_2$, other strategies different from silanization have been rarely used and certainly would deserve further study to show the strength of the corresponding covalent anchoring.

5 Alternative Synthetic Procedures for Covalent Anchoring to Silica

There are several strategies to covalently anchor a homogeneous catalyst to the solid surface through silanoxy bridges. One of them is based on the extensive use of solid-phase reactions. Starting from the support, several consecutive reactions are performed to synthesize the desired compound. An example related to the anchoring of salen-metal complexes is illustrated in Scheme 5, path A. While this methodology offers a simple separation procedure from the reaction mixture, this approach has the severe disadvantage of a poor characterization of the organic anchored material.

A second alternative consists in performing the synthesis of the suitable compound or complex in solution and performing its anchoring onto the solid sur-



Scheme 5. Different strategies reported to anchor covalently salen-metal complexes to silica.

face in the final reaction (Scheme 5, path C). Reaction mixtures can be purified by standard chromatography and the purity assessed unambiguously. Then, the very last step consists in the anchoring of these soluble catalysts on the insoluble support. While the advantage of this methodology is a more convincing characterization of the synthetic intermediates, it is still possible that some adventitious sites develop in the last reaction. In addition, this methodology does not take advantage of solid phase synthesis. Intermediate situations between a stepwise solid phase synthesis and solution synthesis with final covalent anchoring are also possible (Scheme 5, path B). We have successfully used these methodologies in a variety of heterogenized homogeneous catalysts.[42–44]

In view of the above comments, when reviewing the catalytic results on silica-bound catalysts one has to carefully consider the catalyst preparation procedure. It may happen that the catalytic activity tests give results that are negatively disguised and influenced by the lack of purity or by the imperfect preparation procedure of the anchored catalyst. In other words, an optimized material in terms of preparation could exhibit an improved catalytic performance that would have been difficult to foresee from the reported results.

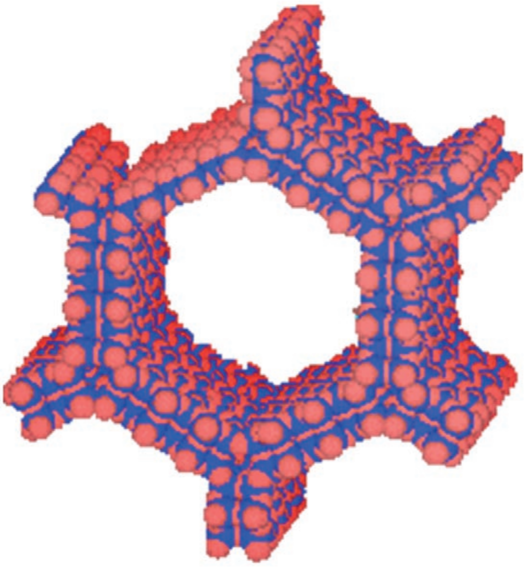
6 Sulfonic Groups Covalently Anchored to Silicas as Solid Brönsted Acids

Acids (either Brönsted or Lewis) are the most important and common catalysts.[45] Many organic reactions such as aldol condensations, nucleophilic additions, hydrolysis, acylations, etc. are catalyzed by acids. There are many problems associated to the use of liquid or soluble acids, including a difficult separation from the reaction mixture, the need of neutralization, the impossibility of reuse and reactor corrosion among others. It would be very useful to have a solid acid that can be separated by filtration and reused.[46]

Zeolites in their H^+ form are the most widely used solid acids in petrochemistry and gas phase reactions.[47] Zeolites working in gas-phase, continuous-flow processes are the paradigmatic examples of non-toxic, reusable, highly selective solid catalysts. However, when moving to fine chemistry and for liquid phase, batch wise reactions typical of organic synthesis, zeolites are not the universal acid catalysts. The main drawback of zeolites as general solid acids is the small pore size available (<1.0 nm even for the so-called large-pore zeolites) that imposes a severe restriction for the accessibility of larger molecules to the internal surface of the catalyst.

In order to overcome the problem of pore size, the synthesis of mesoporous materials by Mobil researchers[48] constituted a breakthrough due to the possibility of opening the catalysis by solid acids to the large molecules characteristic of organic synthesis.[49] The most widely used mesoporous silica is known as MCM-41 (Scheme 6). However, it was realized soon that the use of mesoporous silicas and aluminosilicates as solid acids will not meet the initial expectations due to the low acid strength of their acid sites.

An alternative to the use of the mild acid sites of their aluminosilicate framework is to employ these mesoporous silicas as supports to which strong acid



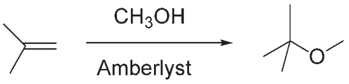
Scheme 6. Pictorial representation of the hexagonal channels of a mesoporous MCM-41 structure.

sites can be covalently anchored. Sulfonic acids are organic compounds that exhibit an acid strength comparable to those of sulfuric acid and benzenesulfonic acid is a strong acid frequently used in organic solvents.[50]

Jacobs et al. prepared a strong acid catalyst consisting of a mesoporous silica containing alkanesulfonic acid groups.[51,52] The synthesis of this MCM-41/SO_3H was achieved by anchoring 3-mercaptopropyltrialkoxysilane to the silanol groups of MCM-41 followed by oxidation of the terminal mercapto groups to sulfonic acid with hydrogen peroxide (Scheme 7). Subsequently other groups have introduced variations in the preparation of this type of MCM-41/SO_3H materials.[53–55] These improvements have focused on the synthesis of MCM-41/SO_3H in a single step (instead of preparing a MCM-41 to which the alkylmercapto group is anchored), optimization of the mercapto to sulfonic oxidation step, control of the MCM-41 pore size, protection of the residual silanol groups, etc. The use of different structure-directing agents different from cetyltrimethylammonium leads to the formation of other mesoporous silicas besides MCM-41, such as those with structure of SBA-15 and SBA-12 using Pluronics 123 and Brij-76 as structure-directing agents, respectively.

Analogous to alkanesulfonic acids, arenesulfonic acids covalently anchored to mesoporous silicas have also been prepared. They can be obtained by sulfonation of phenyl groups linked to silica frameworks including MCM-41 and SBA-15.[55–58] The catalytic activity of the alkanesulfonic was found to be higher than that of the arenesulfonic acid for esterification reactions.

In many respects, particularly for those containing arenesulfonic groups, MCM-41/SO_3H can be considered as the inorganic counterpart of polystyrenes and related polymers having phenylenesulfonic groups, a widely-used example of them being Amberlyst.[59,60] There are many acid-catalyzed reactions, including some large-scale industrial processes, that can be promoted using polystyrene bearing sulfonic groups.[61,62] The room temperature addition of alcohols to isobutene to form *tert*-butyl ethers used as isooctane number boosters is an example of a industrial process that can be performed with polyarenesulfonic resins (Scheme 8).[63–65]



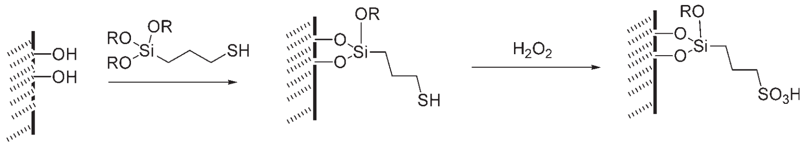
Scheme 8. Industrial use of Amberlyst polystyrenic resin for the preparation of *tert*-butyl methyl ether.

With respect to polymeric arenesulfonic acids, the obvious advantage of MCM-41/SO_3H is the large surface area of mesoporous silicas (~1000 m^2g^{-1}) compared to cross-linked polystyrene (~50 m^2g^{-1}), this factor being reflected in a higher catalytic activity as a result of the easier accessibility of substrates to the acid sites.

Several groups[50,54,55,66,67] have used this type of MCM-41/SO_3H solid as catalysts for the esterification of fatty acids (lauric and oleic acids), the monoesterification of glycerol and sorbitol, the alkylation of benzene by 1-dodecene, the acylation of anisole and the formation of bis-phenol A among other process.

7 Perfluoroalanesulfonic Groups Covalently Anchored to Silicas as Solid Brönsted Superacids

Alkane- and arenesulfonic groups are strong acids, but their pK_a values are higher than that of sulfuric acid. These acids or mixture of acids that have lower



Scheme 7. Procedure for the preparation of alkanesulfonic acid covalently anchored to mesoporous silicas.

pK_a values than pure sulfuric acid (pK_a −12) are known as superacids.[68,69] Some reactions, particularly those that are carried out at low temperatures, require acid sites reaching the superacidic region. The interest of having solid acids with an acidity comparable to or even stronger than that of sulfuric acid is obvious considering that the previously commented advantages of solid acids with respect to liquid or soluble acids in terms of corrosion, waste minimization and reuse are even more necessary in this case.

The most important example of an insoluble strong solid acid is Nafion.[70] Nafion is a polymeric perfluoroalanesulfonic acid. The electronegativity of fluorine substituents increases the acid strength of the sulfonic group, that now becomes comparable to that of sulfuric acid and to that of trifluoromethanesulfonic acid. There has been some debate and controversy about whether or not trifluoromethanesulfonic acid and Nafion are superacids in the strict sense.[71] What is important anyway is that the acidity of these acids is close to that of sulfuric acid and stronger than that of alkanesulfonic acids.

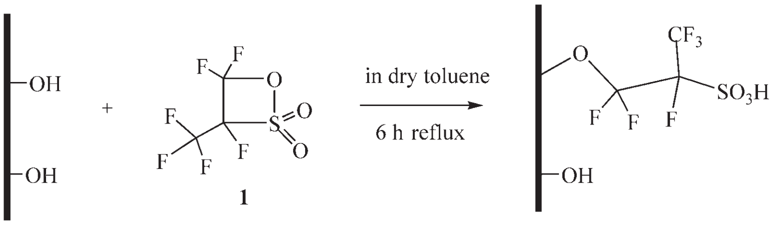
In a series of classical articles, Olah and co-workers developed a multitude of organic reactions that can be catalyzed by Nafion as a heterogeneous solid acid.[70] The outcome of this research is that Nafion is an extremely acidic and stable catalyst. However, the catalytic activity of Nafion was far from optimal due to the small surface area of the perfluoroalkanesulfonic sites. In order to increase the catalytic activity of Nafion-like resins, Harmer and co-workers supported depolymerized Nafion onto high surface area silica (about $200\,m^2g^{-1}$).[60,72] This certainly was a step forward since due to the increase in surface area the catalytic activity of solid acid sites increases, and it was shown to be active, among others, for acylation and alkylation reactions.[73]

A further development was achieved by anchoring in a single step, and starting from preformed MCM-41, a perfluoralkanesulfonic group. The resulting material (denoted as Nafion@MCM-41) exhibits a significant catalytic activity enhancement of about one order of magnitude with respect to silica-supported Nafion.[74,75] This activity increase is even more remarkable considering that the loading of sulfonic groups of Nafion@MCM-41 has a maximum of about 1.5 wt%, that is much smaller than that of silica-depolymerized Nafion composite (15–20 mol% of sulfonic groups). The key point in the preparation of Nafion@MCM-41 was the reaction of perfluoromethyl β-sulfone with the free silanol groups of MCM-41 (Scheme 9).

Compared to the multistep procedure followed to prepare MCM-41/SO_3H, reaction with perfluorinated β-sulfone presents obvious advantages in terms of synthetic economy. Also compared to MCM-41/SO_3H, as expected in view of the general stability of perfluoro compounds, the thermal stability of Nafion@MCM-41 was considerable higher. Thus, no significant decomposition of sulfonic groups took place upon heating Nafion@MCM-41 at temperatures below 350 °C. In contrast, MCM-41/SO_3H undergoes extensive SO_2 evolution at temperatures between 300 and 350 °C as determined by mass spectrometry coupled with thermoprogrammed desorption apparatus.

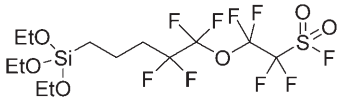
Nafion@MCM-41 exhibits a remarkable catalytic activity for the esterification of carboxylic acids including long chain aliphatic alcohols.[74] Working in batches of 2 mmoles of alcohol per 50 mg of catalyst, Nafion@MCM-41 was found to be reusable without observing an activity decrease for the esterification of octanoic and dodecanoic acids with ethanol and 1-dodecanol. Nafion@MCM-41 was also an active catalyst for the acylation of anisole with acetic anhydride at moderate temperatures, although in this case the catalyst undergoes deactivation by poisoning arising from subsequent reaction of methoxyacetophenones.[74]

The reason for the remarkable catalytic activity of Nafion@MCM-41 is the combination of strong Brönsted acid sites together with a support with a large surface area and porosity. The surface area decreases with the loading of perfluoralkanesulfonic groups and varies from 1000 to $650\,m^2g^{-1}$. However, a problem that still has to be solved is the limited stability of Nafion@MCM-41 in terms of the collapse of the mesoporous structure and hydrolysis of the covalent bond. The first problem can be solved by using SBA-15 or other more robust mesoporous silica materials as supports. The second problem arises from the hydrolysis of the $\equiv Si{-}O{-}CF_2{-}$bond. This may require the introduction of a convenient tether between the perfluorinated alkanesulfonic group and the silyloxy bond.



Scheme 9. Structure and preparation procedure of Nafion@MCM-41.

Recently, Macquarrie, Harmer and co-workers have reported a porous silica that contains a perfluorinated sulfonic acid that does not contain such labile silyloxy groups (Scheme 10).[76] The material was prepared in a single step by sol-gel synthesis using tetraethyl orthosilicate or trimethoxypropylsilane in combination with a perfluorinated sulfonic acid. The preparation of this fluorosulfonic silane is, however, not trivial and was not disclosed in the publication. This material was found stable and reusable for the acylation of anisole with benzoyl chloride.[76]



Scheme 10. Structure of the fluorous sulfonic acid that can be covalently anchored to mesoporous silicas.[76]

There is no doubt that a strong perfluorinated Brönsted solid acid such as Nafion@MCM-41 will be of general applicability provided that its stability is high and will have multitude of applications in organic synthesis. The problem will be catalyst regeneration in the case that deactivation occurs before a certain turnover number has been achieved.

8 Solid Lewis Acids Derived from Covalently Attached Silicas

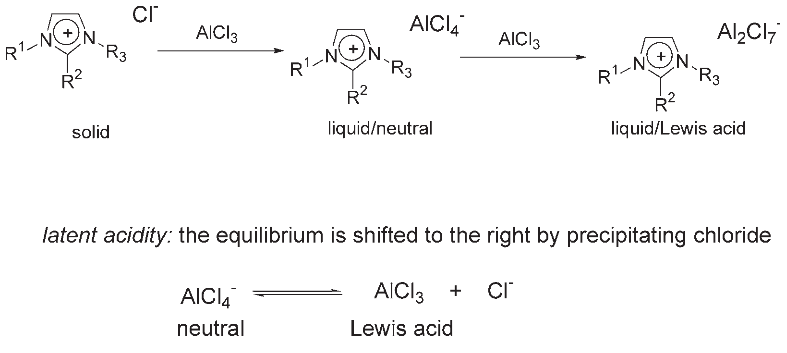
Common Lewis acids such as $AlCl_3$, BF_3, $ZnCl_2$ etc. are inorganic halides that do not contain organic components able to be covalently anchored to silica. Clark and co-workers have deposited $AlCl_3$ and BF_3 in mesoporous MCM-41 and used these solids as recoverable Brönsted and Lewis solid acids.[77–80] However, based on the work with ionic liquids, there is an elegant alternative strategy to support Lewis acids on silicas by covalent attachment of an organic cation.

Ionic liquids are ionic organic compounds that are molten at temperatures below 100 °C.[81,82] Normally they are formed from an organic cation and an inorganic anion. The most common organic cations are *N,N′*-dialkylimidazolium and typical inorganic anions are $[BF_4]^-$ and $[PF_6]^-$. The anion cannot usually be a halide, since they form high-melting solid compounds. However, when dissolving $AlCl_3$ in these solid imidazolium halides a series of chloroaluminate species are developed and the resulting mixture becomes liquid at room temperature.[6] When $AlCl_3$ and halide are mixed in a 1-to-1 stoichiometry, the resulting molten salt is neutral although it can exhibit "*latent acidity*". However, the ionic liquid becomes acidic when an excess of $AlCl_3$ is used, a singular case being a 2-to-1 stoichiometry. In these ionic liquids the predominant species is known to be $[Al_2Cl_7]^-$, that behaves as $AlCl_3$. Many other polyaluminium halides have been determined, all of them being Lewis acids. Scheme 11 indicates some of the reactions that take place.

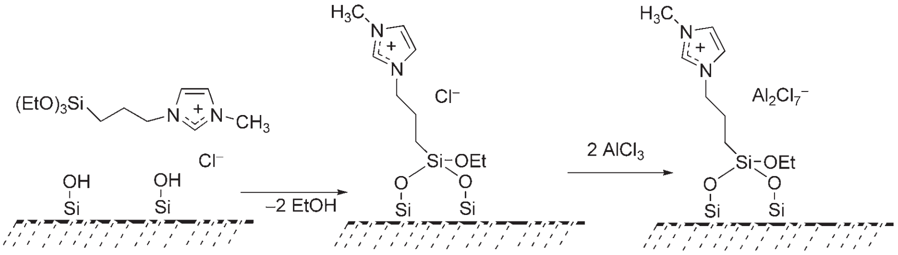
Hölderich and co-workers anchored an imidazolium tag covalently to the solid silica surface, representing a silica-supported ionic liquid.[83–85] Scheme 12 presents the preparation procedure. Addition of $AlCl_3$ to this silica-supported imidazolium affords strong solid Lewis acids that exhibit a remarkable activity towards alkylation of benzene.

Thus, alkylation by 1-dodecene of benzene derivatives and naphthalene has been used as model reactions to test the catalytic activity and reusability of related solid-supported $AlCl_3$ systems.[85] For the liquid phase alkylation of benzene by 1-dodecene catalyzed by $[Al_2Cl_7]^-$ associated to covalently linked imidazolium cation, working at a conversion of 90% of 1-dodecene, a high selectivity towards monoalkylation (95%) with a minor percentage of isomerized by-product (10%) was attained (Scheme 13).

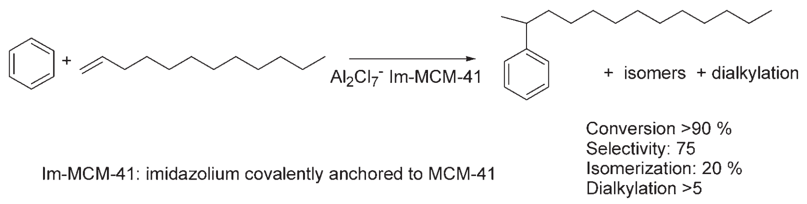
Likewise, anchoring $SnCl_4$ on silica functionalized with organic quaternary ammonium chloride renders a solid in which the pentacoordinated anionic $[SnCl_5]^-$ species is formed (Scheme 14).[86] The resulting ionic pair $[NR_4]^+[SnCl_5]^-$ resembles again an



Scheme 11. Lewis acid aluminium species associated to organic cations.



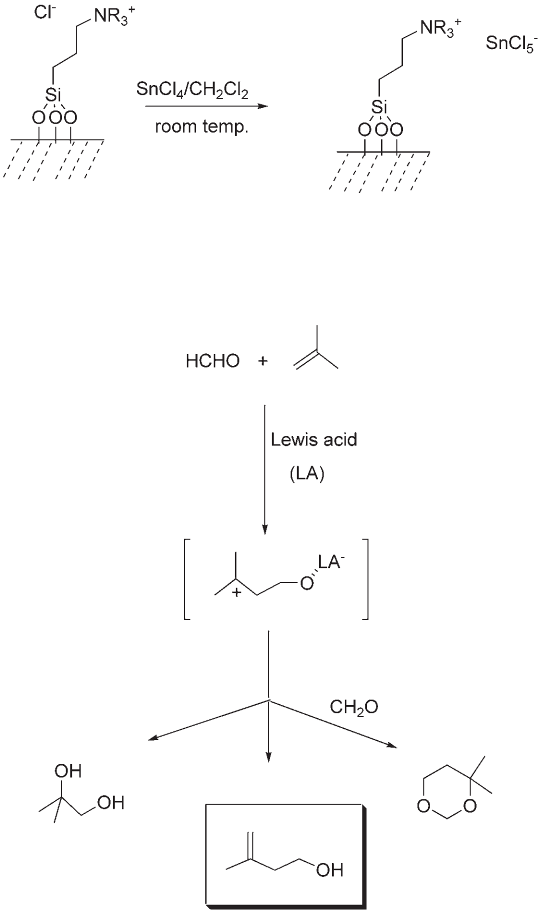
Scheme 12. Lewis acid solid obtained by covalent anchoring of an imidazolium cation (based on ref.[85]).



Scheme 13. Product distribution for the Friedel–Crafts alkylation of benzene with 1-dodecene catalyzed by anionic aluminium species associated to imidazolium ion covalently bonded to mesoporous MCM-41.

ionic liquid exhibiting "*latent acidity*" except that the organic cation is covalently bound to silica.

The $[SiO_2\text{-}NR_4]^+$ $[SnCl_5]^-$ catalyst has been found to be active for the Prins reaction of isobutene and paraformaldehyde (Scheme 14).[86] Furthermore, the selectivity towards the desired 3-methyl-3-buten-1-ol, which is a valuable building block for the synthesis of terpenes, largely improves with respect to unsupported $SnCl_4$. The anchored $[SnCl_5]^-$ catalyst was reused three times with a very minor decrease in conversion and selectivity (Table 1).[86] No bleeding of tin(IV) from the solid to the solution was observed. Simple adsorption of tetrapropylammonium tin pentachloride exhibits somewhat lower catalytic activity than the anchored analogue and significantly poorer reusability.[86]



Scheme 14. Preparation and structure of the solid catalyst $SiO_2\text{-}NR_4^+$ $[SnCl_5]^-$ and the products obtained in the reaction of formaldehyde with isobutene (based on ref.[86]).

Table 1. Prins condensation of isobutene and paraformaldehyde in chloroform at 60 °C after 2 h reaction time in the presence of tin(IV) chloride catalysts (data taken from ref.[86]).

Catalyst	Formaldehyde Conversion [%]	3-Methyl-3-buten-1-ol Yield [%]
None	0	–
$SnCl_4$	97.4	54.6
SIL-NR_4^+ $[SnCl_5]^-$[a]	64.6	92.8
Recycle 1[b]	63.3	91.1
Recycle 2[b]	61.9	91.0

[a] SIL-NR_4^+ $[SnCl_5]^-$ stands for tripropylammoniumpropylsilyl anchored on silica acting as heterogeneous catalyst.

[b] Used solid recovered by filtration and employed as catalyst in a subsequent run under the same conditions.

Given the importance of conventional Lewis acids in organic synthesis, there is no doubt that these types of reusable and recoverable solid acids can be of great interest. However, the main problem that needs to be addressed is the long-term stability of the inorganic Lewis acid. In this regard, it has to be remarked that particularly by exploiting the concept of *latent acidity*, the *neutral* species of the Lewis acid is much more moisture-stable than the *active* Lewis form of the pair, this fact being positive to produce more reusable and storable materials.

Isolated and stable Lewis acid sites in a silica matrix have been achieved by introducing transition metals such as Ti, Fe, Cr, Co, Zn and Sn, as well as Zr, in the framework of silica zeolites and mesoporous materials.[87–99] These elements when tetrahedrally coordinated with silicon through oxygen bridges were able to act as a Lewis acid catalysts for selective oxidations using H_2O_2, cyclization of citrollenal to isopulegol, for Merwein–Ponndorf reactions and hydroxylation of benzene, among others.[100–112] Further information on these types of Lewis acid catalysts can be found in a recent review.[18]

9 Hybrid Basic Catalysts

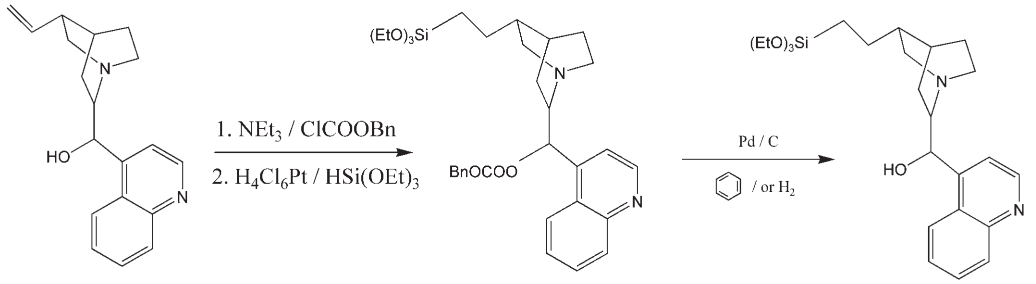
The development of environmentally friendly basic catalysts involves the preparation of materials that can successfully replace alkaline hydroxides and alkali metals in methanol during the synthesis of fine chemicals. Nevertheless, one should be aware that alkaline hydroxides are inexpensive and their effluents are relatively easy for disposal by acid neutralization and consequently they are highly competitive as catalysts. Thus, finding special selectivity and activity effects should be the main driving force to develop inorganic solid base[113–115] and hybrid organic-inorganic base catalysts.

Concerning hybrid catalysts, it was possible to prepare strong Brönsted basic catalysts by anchoring an organic ammonium quaternary salt to the surface of pure silica MCM-41 mesoporous material.[116] This was done by reacting 3-trimethoxysilylpropyl(trimethyl)ammonium chloride ($SiNR_4Cl$) with hydroxy groups located at the surface of a dehydrated MCM-41. The final exchange of chloride by hydroxide anions was carried out by contacting the grafted salt with a methanolic solution of Me_4NOH at room temperature. The resultant hybrid MCM-41-quaternary organic tetraalkylammonium hydroxide catalyst shows high activity for a variety of carbon-carbon forming bond reactions such as Knoevenagel condensations, Michael additions and aldol condensations. Very high selectivities to the desired products were observed in all cases, the activity being much higher than for other solid base catalysts such as hydrotalcites or Cs-MSM-41 materials. It has to be remarked, however, that when the Knoevenagel condensations were carried out using Me_4NOH as homogeneous basic catalyst a higher initial rate per mol of OH^- was found. Taking into account that the accessibility of the reactants to the active sites in the grafted MCM-41 is not limited, it would appear that the anchored OH^- groups might be interacting with the remaining silanol groups located on the inner part of the MCM-41 channels. It would then be most interesting to prepare new materials in which free silanol groups are silylated. This will avoid not only undesired interactions between the OH^- and surface silanol groups, but also the preparation of highly hydrophobic materials that will avoid the competitive adsorption of water.

While the basicity of amines is lower than that of the tetraalkylammonium hydroxides, the former may allow special selectivity effects. Thus, different amines have been successfully grafted on MCM-41.[117,118] Trying to combine the basicity of amino groups with shape-selectivity effects, amorphous silicas have been imprinted with amines covalently linked to the silicon atoms of the silicate.[119–123] This is an excellent idea that has shown some success and will require further work in order to either avoid mass transfer limitations, to maximize TOF, or to use diffusion restrictions for achieving diffusion shape-selectivity effects.

Owing to the fact that L-proline has shown good enantioselectivity for base-catalyzed reactions in the homogeneous phase such as aldol reactions, Katz et al. have prepared a series of proline-derived catalysts as a general structure motif for heterogeneous enantioselective catalysts.[122,123] However, enantioselectivity was not observed in this case.

In the case of base catalysis, the number of enantioselective base-catalyzed reactions is small. More specifically, chiral Michael additions can allow the formation of C–C bonds with one or two pairs of enantiomers. Chiral Michael reactions were already achieved more than 30 years ago[124] using homogeneous catalysts. More recently, homogeneous catalysts such as lanthanum-sodium-BINOL complexes,[125] chiral crown ethers incorporating a D-glucose unit in the presence of a base,[126,127] have achieved high enantioselectivities for Michael additions. *Cinchona* alkaloids have also been used since a long time, as chiral homogeneous catalysts for the Michael reaction.[128–130] First attempts to prepare organic-inorganic *Cinchona*-based catalysts showed very low diastereoisomeric excesses for the Michael addition of alkyl and aryl mercaptans to racemic 5-methoxy-2-(5*H*)-furanone.[131] However, a different catalyst preparation method has been used and yields better results (see Scheme 15). In this way the cinchonidine grafted on MCM-41 gave enantioselectivities of ~50% for the Michael addition of ethyl 2-oxocyclopentanecarboxylate and vinyl ketone, while in the homogeneous phase an *ee* of



Scheme 15. Preparation of a triethoxysilyl derivative of a *Cinchona* alkaloid.

65% was achieved.[132] Interestingly, it was found that the unprotected cinchonidine exhibits higher enantioselectivity than the protected, suggesting that the interaction between the free OH groups of the alkaloid and the reagents in the transition state favours preferentially the formation of one of the isomers. This opens the possibility for improving the catalytic behaviour of hybrid catalysts by stabilizing specific transition states through cooperative interactions with the hydroxy groups of the inorganic counterpart.

In the case of silica hybrid basic catalysts, special attention should be paid to hydrolysis of the anchored base, especially when water is present or formed during the reaction. Hydrolysis can be diminished by improving the silica surface with organic chains,[133] or by the use of a TiO_2 over-layer on which phosphonate functions are the coupling groups.[134]

10 Silica-Bound Enantioselective Hydrogenation Catalysts

Chiral metal-salen complexes of noble metals have been used as heterogeneous catalysts for enantioselective hydrogenations.[135–137] Hydrogenation of imines is an important synthetic reaction that transforms carbonyl compounds into primary and secondary amines and can serve to prepare chiral α- and β-amino acids. Commonly, homogeneous imine hydrogenation catalysts are Ir and Rh complexes and require relative high H_2 pressures.[138,139] There is an incentive to develop heterogeneous, highly active catalysts based on less expensive metals that work under lower hydrogen pressures. Corma and co-workers have reported chiral palladium- and nickel-salen complexes covalently anchored to a series of silica supports that are able to effect the hydrogenation of imines at 4 bar.[140,141]

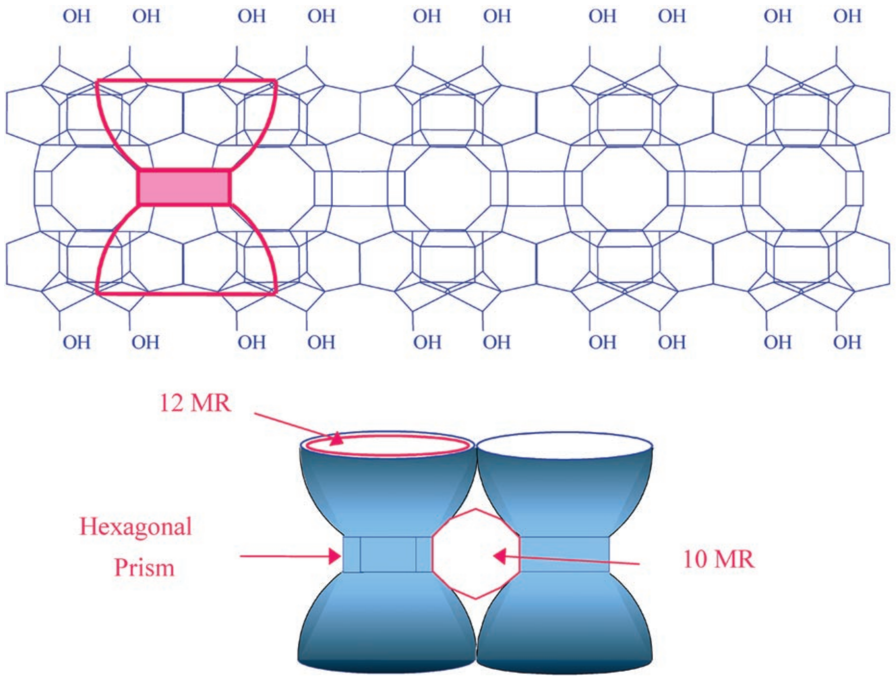
A careful comparison of the catalytic activity of the same salen complex on different supports has served to establish that the support can play a positive role on the catalysis by increasing the concentration of reactants near to the catalytic site, thus contributing to the success of the hydrogenation. This idea is certainly original since in most of the work on supported catalysts, the role of the support surface in the reaction mechanism is ignored.[142] The results obtained in terms of initial activity point to the importance of the nature and properties of the support on the catalysis. Thus, the activity of the identical salen complex increases on going from amorphous silica to mesoporous MCM-41, being higher using delaminated ITQ-2.[140,141]

ITQ-2 is a delaminated zeolite formed by layers (2.5 nm depth) of crystalline material whose surface defines cups (0.8 × 0.8 nm) as shown in Scheme 16.[143] The main advantage of ITQ-2 as support is its large surface area ($\sim 700\ m^2 g^{-1}$) that is all accessible and mostly external as compared to microporous zeolites.[143]

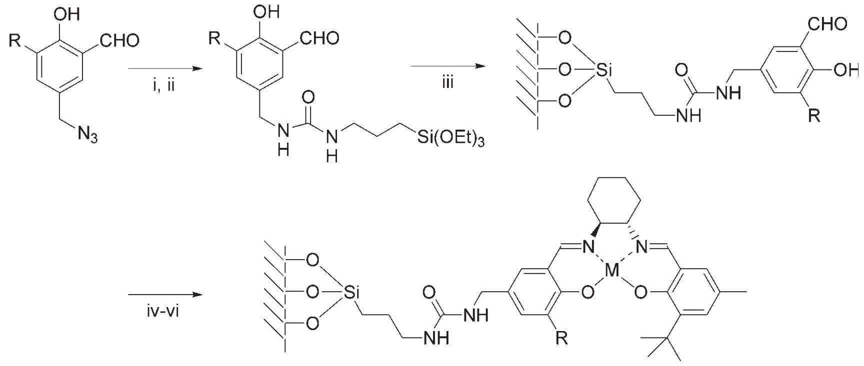
When the complex is anchored on ITQ-2, its activity is even double the activity of the unsupported complex in the homogeneous phase. This has been interpreted as a preferential adsorption of hydrogen and reactants inside the cup-like holes of the ITQ-2 surface, since these cups create a potential well for adsorbing guest molecules.

Moreover, it is known that the presence of acids increases the hydrogenation activity of homogeneous catalysts. Given the important role of the adsorption of reagents in mesoporous and delaminated zeolites, it was also observed that the use of acidic MCM-41 and ITQ-2 supports even increases the activity of the anchored complex due to the presence of Brönsted acid sites on the support.[140,141] The stability of covalently anchored Pd- and Ni-salen complexes toward recycling was good and no decrease in activity was observed after four reuses, the solids acting really as a heterogeneous catalyst since leaching was not observed.

The main drawback of these covalently anchored Pd- and Ni-salen catalysts is that in spite of their very high catalytic activity they exhibit a low enantioselectivity (~10–15%), far away from the 80% obtained for the enantioselective imine hydrogenation with Ir complexes. Also the strategy followed for the preparation of the anchored complex, that is based on three consecutive reactions carried out on supported reactants and without a possibility of purification (Scheme 17), may need to be revisited and improved.



Scheme 16. Pictorial representation of the layered structure of delaminated ITQ-2 zeolite showing the presence of silanol groups on the upper and lower surface of the layers (taken from ref.[143]).



i) H_2, Pd/C; ii) $OCN(CH_2)_3Si(OEt)_3$; iii) support, toluene, 110 °C; iv) cyclohexanediamine;
v) 6-tert-butyl-4-methylsalicylaldehyde; vi) $M(OAc)_2$ (M= Pd, Ni)

Scheme 17. Preparation of covalently anchored Pd- and Ni-salen imine hydrogenation catalysts (based on ref.[140]).

Following a route analogous to that shown in Scheme 17, Corma et al. have also prepared several heterogeneous catalysts with manganese- and copper-salen complexes as catalysts and MCM-41 or silica as supports. This catalyst series was used for the chiral oxidation of phenyl sulfides.[144,145] The *ee*s achieved with the heterogeneous catalysts were similar to the values obtained in homogeneous phase. After using the catalysts, the resultant solution exhibited no colour and no metal was detected in the solution by atomic absorption spectroscopy. The catalysts were recovered by filtration and reused at least four times, retaining most of their initial catalytic activity.[144,145]

Very recently gold complexes anchored on different silica supports have shown high activity and good enantioselectivity for hydrogenation of olefins and imines.[44,146]

11 Periodic Mesoporous Silicas as C−C Coupling Catalysts

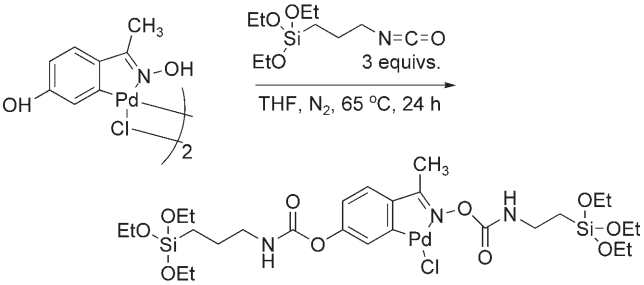
The synthesis of mesoporous MCM-41 and related materials constituted a breakthrough in materials science, because it offered promises to overcome the limitations of classical zeolites in terms of the available pore dimensions.[48,147] The large specific surface area of mesoporous MCM-41, reaching values of 1000 $m^2 g^{-1}$, determines that approximately one fifth of all the silicon atoms are located at the surface. As commented earlier, terminal coordination positions of silicons are occupied by hydroxy residues forming silanol groups. The large population of these silanol groups renders MCM-41 and related materials highly hydrophilic and not so adequate for adsorption of lipophilic organic molecules. With the initial purpose of controlling the hydrophilicity/hydrophobicity of the internal MCM-41 surface, silylation procedures in which an aliphatic alkyl group was covalently attached to the silica surface became widely used.[148] As commented above, a step forward was to use this methodology to attach to the silica walls any other organic molecule or metallic complex that can be used as catalyst. In these solids, the catalytic sites are connected to the walls through a single tether and the species is occupying space in the channel system.

A novel concept in mesoporous materials was developed by Stein, Ozin and Inagaki in which an organosilane containing at least two terminal trialkoxysilane groups able to condense and form a hybrid polymeric material is used as the exclusive silicon source to form mesoporous solids using the MCM-41 procedure.[149–153] The resulting hybrid organic/inorganic material was termed as periodic mesoporous organosilica (PMOs). In these materials, the framework of the solid can be formed exclusively by an organosilane that will be the only silicon source.

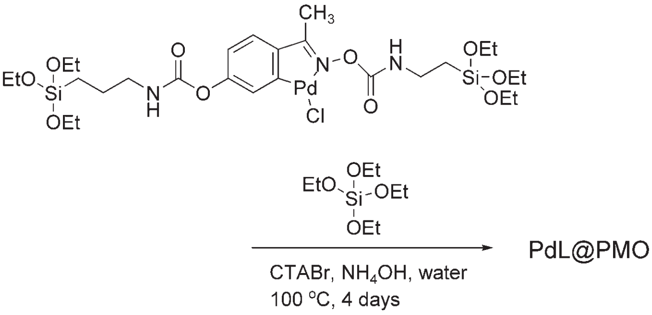
However, the concept of PMOs was proved with very simple organosilanes containing methylene, ethylene, phenylene and other organic moieties of a few carbon atoms. When a functionality derived from the presence of an organic moiety is desired, more complex organic moieties with a larger number of carbon atoms are necessary.

In these cases using complex organosilanes, it is impossible to obtain a well-structured PMO using the organosilane as the sole silicon source, since this renders amorphous organosilicas. To avoid the formation of non-porous materials that would be devoid of the advantages of PMOs, an alternative is the addition of variable amounts (typically from 50 to 95 wt%) of tetraalkoxysilane as co-condensating agent, in order to permit some relaxation of the hybrid framework that would allow the templating effect of the structure-directing agent used during the synthesis of the PMO.

Thus, we have applied the concept of PMOs to develop heterogeneous catalysts in which the active sites are forming part of the framework connected by two tether units. One of these materials contains a carbapalladacycle forming part of the structure.[154] Palladium-catalyzed coupling reactions are among the most powerful transformations due the high yields obtained, the wide scope, the mild conditions and the compatibility with many functional groups that do not interfere in the coupling.[155–159] Among the successful homogeneous palladium catalysts, carbapalladacycles derived from electron-rich aromatics having a heteroatom in a position allowing formation of a ring encompassing the palladium atom are known to be very active. One of the simplest examples of highly active carbapallacycles is the complex of 4-hydroxyacetophenone oxime with palladium(II) reported by Najera and co-workers.[160,161] Using the two available hydroxy groups of the oxime, we have functionalized in a simple way this complex by two terminal triethoxysilane groups and prepared a PMO containing up to 15 wt% of this complex. Scheme 18 and Scheme 19 describe the routes followed for the preparation of the silanized palladium complex and the PdL@PMO catalyst.



Scheme 18. Synthesis of a carbapalladacycle derived from 4-hydroxyacetophenone oxime having two terminal triethoxysilyl groups.



Scheme 19. Synthesis of a periodic mesoporous silica through co-condensation of a carbapalladacycle complex and tetraethoxysilane.

PdL@PMO containing up to a maximum of about 0.1 mmol of palladium complex per gram of solid and surface areas of about 1000 $m^2 g^{-1}$ and uniform pore size about 3.0 nm were obtained.[154] Figure 2 shows a transmission electron micrograph in which the pore openings of regular size distribution can be clearly seen. The outcome of this research is an interesting

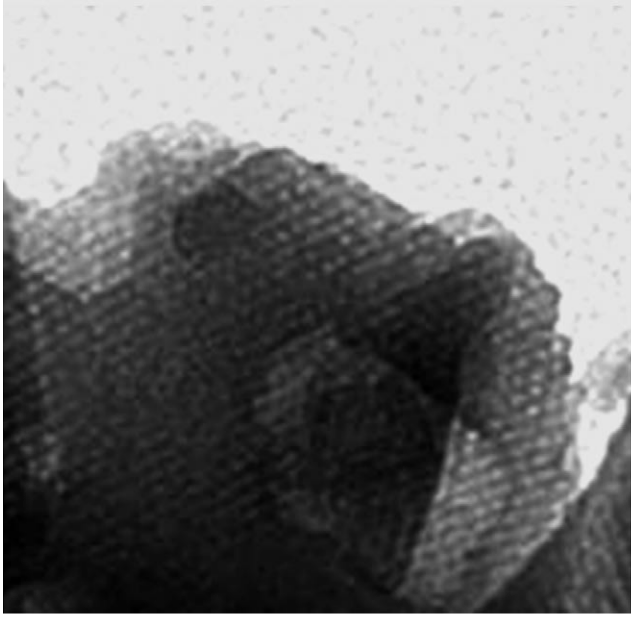


Figure 2. TEM image of PdL@PMO showing the mesoporous structure of the solid.

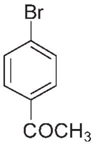
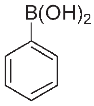
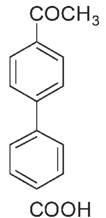
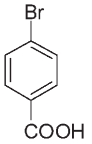
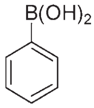
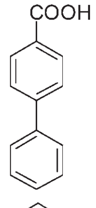
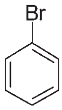
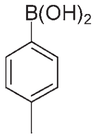
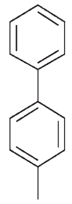
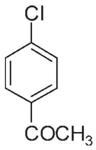
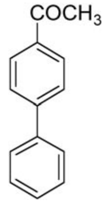
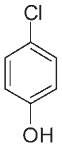
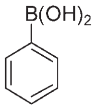
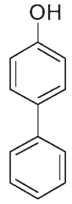
porous material in which the catalytic palladium sites are distributed in a highly porous inert silica framework.

The catalytic activity of PdL@PMO was tested for the Suzuki coupling of a series of aryl halides (including bromides and chlorides) and phenylboronic acid in water in the presence of larger equivalent amounts of potassium carbonate as base. Table 2 presents some of the results attained. While the carbapalladacycle anchored to the PMO showed activity for aryl bromides, it was inactive for aryl chlorides. In this regard, it is worth mentioning that the reported activity in the homogeneous phase for the cross-coupling of phenylboronic acid and 4-chloroacetophenone with the parent oxime carbapalladacycle at 0.1 mol% in water at 100°C in the presence of K_2CO_3 and tetrabutylammonium bromide in one hour, is higher than 99%. It appears, then, that the intrinsic catalytic activity of the carbapalladacycle is somehow reduced upon immobilization.

With respect to the palladium loading in PdL@PMO, the turnover numbers measuring the intrinsic catalytic activity per palladium atom, decrease upon Pd loading in the solid. In this respect, a compromise between low loading (highest turnover numbers), while still having sufficient palladium to achieve high conversion with the minimum amount of solid catalyst has to be reached.[154]

Interestingly, the beneficial influence of the mesoporosity of PdL@PMO was demonstrated by comparing the catalytic activity of one of these PdL@PMO with an analogous catalysts in which a carbapalladacycle was covalently anchored to amorphous silica.[154]

Table 2. Results of the Suzuki coupling of aryl halides with phenylboronic acids (1.5 equivalents) in water using potassium carbonate (2 equivalents) catalyzed by PdL@PMO (Pd 10 mol%) at reflux temperature for 24 h.

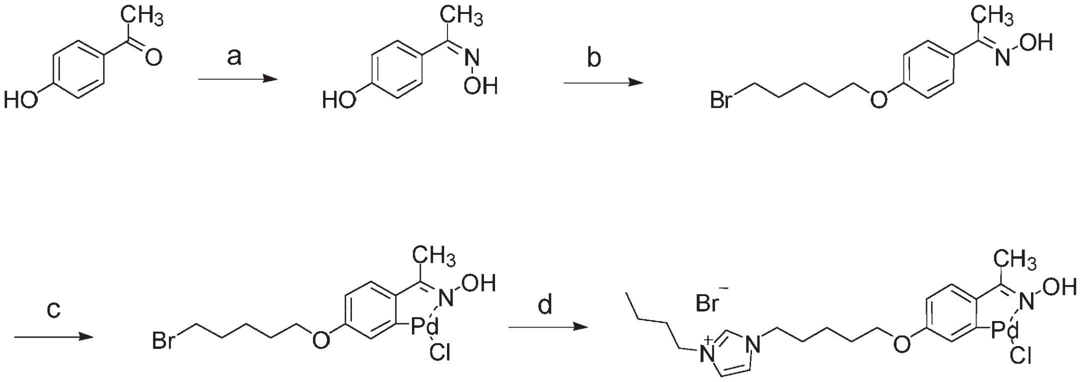
Aryl halide	Arylboronic acid	Product	Yield [%]
			>99
			>99
			>99
	$NaBPh_4$		12
			5

Although at long reaction times the conversions attained with both solids for the Suzuki coupling of bromobenzoic acid and phenylboronic were coincident (as they probably should be), the initial reaction rates were considerably higher for PdL@PMO than for PdL@SiO_2. This result, together with the fact that PdL@PMO and an analogous material in which PdL was anchored to a preformed MCM-41 silica[162,163] gave similar results, indicates that having the catalyst anchored on the high surface area support plays a favourable role in the catalytic activity of the sites.

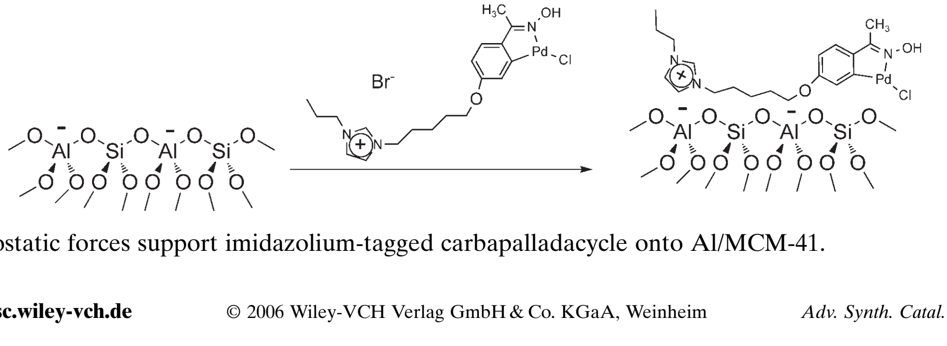
When studying the occurrence of leaching, either hot filtration of the solid catalyst or the three-phase test[164,165] designed by Davies and Lipshutz, showed the occurrence of palladium leaching. The three-phase test involves performing the Suzuki reaction as usual in the presence of the solid catalyst, but adding also a silica containing a covalently bound organic compound able to undergo the C–C coupling with the reagents present in the liquid phase. If some palladium becomes dissolved, then the silica-bound substrate should also react at the same time that the reaction in the liquid phase proceeds. If no leaching occurs, the product in the liquid phase should be formed and the substrate anchored to the silica should remain unreacted. Actually, it was quantified that about 50 % of the total conversion using PdL@PMO can be attributed to some palladium species present in the liquid phase by leaching from the solid into the solution.[154] Nevertheless, the total palladium content of the PdL@PMO upon reuse was maintained as determined by chemical analysis, indicating that either the amount of palladium leaching is undetectable or that the palladium species becomes re-adsorbed onto the PdL@PMO upon cooling the reaction mixture.[154]

An alternative strategy to the covalent anchoring for binding active catalytic sites to the surface of mesoporous silicas is the Coulombic interaction between negative charges of the aluminosilicate framework and positively charged species. $[SiO_4]^{4-}$ tetrahedra sharing the edges are neutral, but when an Si atom is isomorphically substituted by an Al atom to form $[AlO_4]^{5-}$, a negative charge is introduced in the framework. Each negative charge of the framework requires the presence of a charge compensating cation in order to ensure the electroneutrality of the solid. Thus, a carbapalladacycle having a tag with an imidazolium unit was adsorbed by electrostatic interaction on Al/MCM-41 (Si/Al ratio 13) and the solid used as a heterogeneous catalyst.[166] Scheme 20 and Scheme 21 show the synthetic route of this *ionophilic* palladacyle and the resulting electrostatic binding between this organometallic complex and the aluminosilicate support.

Am imidazolium-tagged carbapalladacycle electrostatically bound to Al/MCM-41 was used as a heterogeneous catalyst for the Suzuki coupling in toluene and DMF.[166] Better results were obtained in the latter aprotic polar solvent, in good agreement with the general behaviour of the catalytic activity of the soluble parent carbapalladacycle. In DMF, the supported cyclopalladated complex was able to promote the cross-coupling of bromo- and even chlorobenzenes, the supported palladium catalyst exhibiting an activity similar to that of the soluble analogue.[166] The solid can be recovered by filtration and reused. However, problems arise from the fact that about 30 % of the catalytic activity is due to palladium species leached from the solid under the reaction conditions and to the gradual decomposition of the organometallic complex leading to palladium nanoparticles that gradually loose the catalytic activity.[166] There



Scheme 20. Synthetic route followed for the preparation of oxime carbapalladacycle. a) NH_2OH, NaOAc, H_2O, reflux, 1 h; b) 1,5-dibromopentane, K_2CO_3, acetone, reflux, 48 h; c) Li_2PdCl_4, NaOAc, methanol, r.t., 72 h; d) 1-methylimidazole, THF, 50 °C, 72 h.



Scheme 21. Electrostatic forces support imidazolium-tagged carbapalladacycle onto Al/MCM-41.

are several ways to prove the occurrence of leaching, the simplest one being filtration of the solid at the reaction temperature at half of the total conversion and surveying the resulting clear solution for further product formation upon heating. Comparison between twin reactions submitted or not to removal of the solid catalyst provides a quantitative estimation of the contribution of homogeneous catalysis of the leached species to the overall process. The gradual decomposition of the carbapallacycle can be quantitatively assessed by following the intensity decrease of the characteristic ligand-to-metal charge transfer band at 350 nm in the diffuse reflectance optical spectrum of the solid.

12 Design of Hybrid Organic-Inorganic Catalysts for Cascade Reactions

The fast development of materials synthesis techniques make it possible to introduce various functionalities in a single catalyst. In this way it should be possible to prepare on the same support enzymes, mimics of enzymes, imprinted transition state analogues, metal complexes acid, base, redox sites. Very recently metal nanoparticles within organic-inorganic hybrid materials have been prepared that open the possibility of combining metal catalysis with acid, base, and organometalic functionalities.[167]

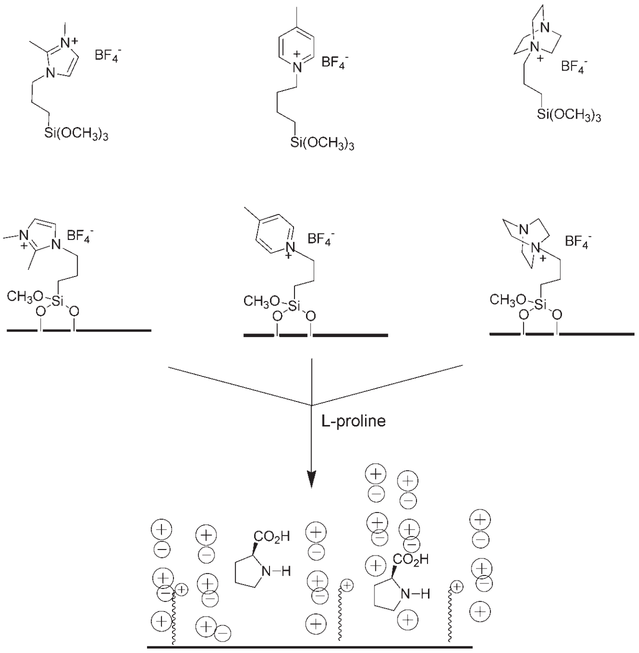
Using all the above materials, and assuming that a common window of reaction conditions could be achieved, multisite catalysts for cascade-type reactions could be obtained.

13 Silica-Bound Organocatalysts

Organocatalysis is a topic of much current importance. The interest in developing organocatalysts to promote organic reactions derives on one hand from the green chemistry principles, since avoidance of the use of metals in catalysts should increase the environmentally benign nature and sustainability of the process, and on the other hand, some of these catalysts are designed by bioinspiration trying to mimic in a simplified way active centres of enzymes.

Among the different organocatalysts, the most successful is L-proline and derivatives, which are able to catalyze cross-aldol condensations.[168–171] The resulting aldols are frequently obtained in good to high enantiomeric excess, without the need to prepare an unnecessary intermediate such as silyl enol ether or enolates. The efficiency of proline and derivatives to catalyze enantioselectively aldol reactions is believed to arise from its amphoteric nature, the amine forming an enamine nucleophile whereas the carboxylic group activates the aldehyde by proton donation.[172]

The main problem in organocatalysis is the separation of the catalyst from the reaction products. In the case of proline this has been achieved in different ways including homogeneous (using of ionic liquids and polyethylene glycols as solvents) and heterogeneous (use of organic solvents that do not dissolve proline and adsorption on silica gel) methodologies.[169] Adsorption on silica gel leads to a significant decrease in the enantioselectivity of the process. In contrast, Gruttadauria and co-workers have reported a supported ionic liquid methodology in which the surface of silica gel is functionalized with an ionic organic group with imidazolium, pyridinium and 4-aza-1-azoniabicyclo[2.2.2]octane accompanied by different charge balancing anions (Scheme 22).[173,174]



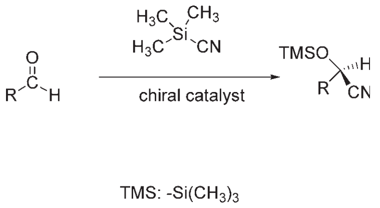
Scheme 22. Heterogeneous organocatalyst for enantioselective cross aldol condensation based on silica-bound organic cation and a film of non-covalently attached ionic liquid. L-Proline is dissolved in this interphase and retained at the end of the reaction.

These surface-modified silicas, in combination or not with an additional, non-covalently attached ionic liquid, adsorb and retain proline, the system acting as a reusable (seven times) and highly enantioselective (in some cases 86% *ee*) at high conversions.[173,174] The results have shown that covalent attachment of the organic cation is vital for attaining a high enantiomeric excess. Furthermore, upon deactivation the solid based on silica-bound imidazolium containing extra amounts of imidazolium $[BF_4]^-$ can be reactivated by further addition of proline in methanol.[173]

A further development of this system would consist in attaching covalently proline to the surface of mesoporous silica and to use the resulting solid as a heterogeneous catalyst. Although this material would certainly require complex synthetic work to obtain derivatized L-proline, the reusability of the system may in the long-term overcompensate this effort leading to a higher productivity per proline molecule.

14 Silica-Bound Heterogeneous Catalysts for Enantioselective Cyanosilylation of Aldehydes

Cyanohydrins are versatile synthetic intermediates that can be transformed straightforwardly into α,β-unsaturated nitriles, α-hydroxy acids, β-amino alcohols and other derivatives. Cyanohydrins can be obtained at room temperature by nucleophilic addition of HCN to aldehydes. A reaction that is closely related is the cyanosilylation of aldehydes using trimethylsilyl cyanide as reagent (Scheme 23). This reaction advantageously avoids the use of highly toxic hydrogen cyanide and also stabilizes the hydroxy group by silylation. Low-temperature cyanosilylation of aldehydes can be catalyzed in solution by Lewis acids. More recently, North and co-workers have reported the asymmetric version of this reaction using chiral dichlorotitanium- and vanadyl-salen complexes.[175–178]

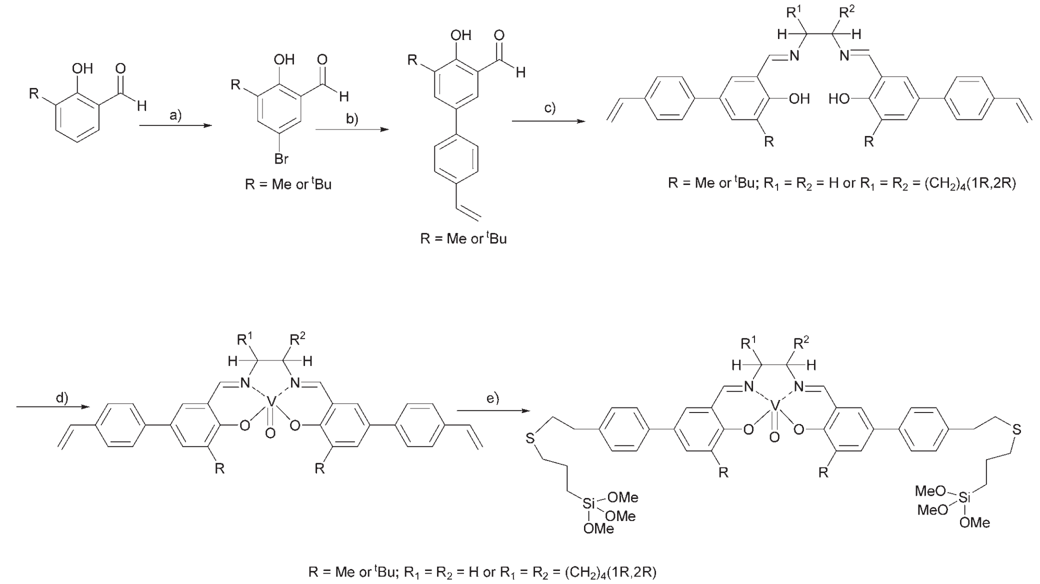


Scheme 23. Asymmetric cyanosilylation of aldehydes by trimethylsilyl azide.

A mesoporous hybrid organosilica containing a disilyl derivative of a vanadyl-salen complex has been synthesized using as silicon sources tetraethyl orthosilicate and a disilyl derivative of a vanadyl-salen complex.[179] The solid containing the vanadyl-salen complex results when both sources of silicon co-condense in the presence of cetyltrimethylammonium as structure-directing agent.

The synthesis of the required disilyl complex was accomplished starting from a bis-styryl-salen ligand that was complexed with the vanadyl cation. Subsequently, this bis-styryl-salen complex was reacted with 3-mercaptopropyltrimethoxysilane using a radical initiator under an inert atmosphere. The actual steps of the synthesis are shown in Scheme 24.

The resulting PMO-containing vanadyl-salen complexes prepared using the bis-silylated vanadyl-salen complexes and tetraethyl orthosilicate were characterized by powder X-ray diffraction and isothermal gas adsorption.[179] In the first technique the expected peaks corresponding to a well-ordered mesoporous hexagonal organosilica were observed, while isothermal nitrogen adsorption determined a total surface area of 900 $m^2 g^{-1}$ and a pore size of 42 nm. The loading of vanadium in the solids was about 17 $\mu mol \times g^{-1}$ and probably it will be desirable to optimize the va-



Scheme 24. Preparation of VO-salen intermediates. *Conditions*: a) Br_2, CH_2Cl_2, 0°C, 1 h; b) 4-vinylphenylboronic acid, $[Pd(PPh_3)_4]$, 2M Na_2CO_3, THF, 70°C, 3 h; c) diamine, EtOH, reflux, 1 h; d) VOacac, MeOH, r.t., overnight; e) 3-mercaptopropyltrimethoxysilane, AIBN, $CHCl_3$ (degassed), 70°C, 20 h.

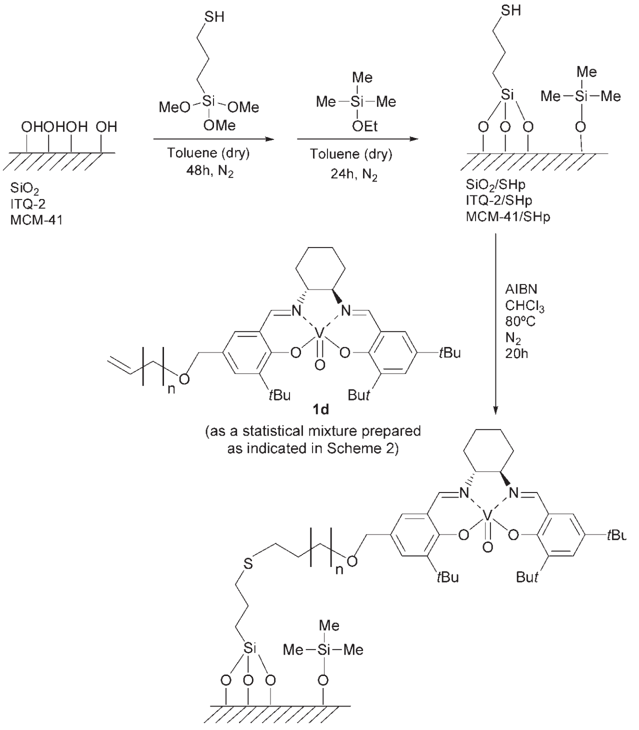
nadyl complex loading without compromising the surface area and the structure of the material.

These vanadyl-containing PMOs exhibit high activity as heterogeneous catalysts for the cyanosilylation of aldehydes at room temperature or below.[179] The solid was recovered and reused four times with a marginal decrease in the catalytic activity (Table 3).

Table 3. Results of the room temperature cyanosilylation of aldehydes (RCHO, R see Table) in $CHCl_3$ under N_2 atmosphere after 48 h using VO(salen)@PMO (0.25 mol%) as heterogeneous catalyst. The selectivity towards silylated cyanohydrin was higher than 98%.

R in Aldehyde RCHO	Reuse	Conversion [%]
C_6H_5-	0	82
C_6H_5-	1	79
C_6H_5-	2	83
C_6H_5-	3	71
p-F-C_6H_4-	-	86
p-CH_3O-C_6H_4-	-	81
n-C_5H_{11}-	-	79

Moreover, the enantiomeric version of using chiral vanadyl-salen complex anchored to silica, either through one or two covalent tethers has also been reported.[179–181] In this case, the material obtained by anchoring an asymmetric chiral vanadyl-salen to a preformed mesoporous MCM-41 is the one that gives higher enantiomeric excesses (>85%) almost comparable to those obtained using a soluble chiral complex. Moreover, an influence of the length of the tether connecting the complex with the solid surface was observed, longer tethers given catalysts with higher asymmetric induction capability, particularly if the residual silanol groups are protected by silylation with trimethylsilyl groups after anchoring the metal complex (Scheme 25).[180] This was interpreted by assuming that long tethers permit the chiral complex to move far from the solid surface, attaining a situation similar to the one occurring in solution (in which *ee*> 90% is obtained) and avoiding the unfavourable distortions in the transition state that could arise from the proximity of the solid surface.



Scheme 25. Preparation procedure for the covalent attachment of a chiral vanadyl-salen complex on the surface of mesoporous silica and delaminated ITQ-2 zeolite.

15 Concluding Remarks and Future Prospects

As commented above, it is evident that the tendency in the near future is that organic chemistry will make an even wider use of heterogeneous catalysis. This introduction will be progressive owing to the need to develop green processes. Synthetic organic chemists will rely more on the use of these silica-bound catalysts as they become commercially available. Most probably suitably functionalized silica supports will be of general use and, from them, anchoring of the required catalyst will be accomplished in a reliable way[182] even for non-specialized organic chemists. In addition, it can also be anticipated that the toolbox of heterogeneous catalysis will be expanded to virtually any organic reaction. Also more examples of the cooperation of the support to the success of the heterogeneous catalysis will be disclosed and a rationale for this effect, its scope and limitations set up.

Acknowledgements

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