# Catalysis by Sol-Gels: An Advanced Technology for Organic Chemistry

Rosaria Ciriminna and Mario Pagliaro*

*Istituto per lo Studio dei Materiali Nanostrutturati, CNR, via Ugo La Malfa 153, 90146 Palermo, Italy*

**Abstract:** Catalysis by sol-gel doped materials -- chemical conversions mediated by porous glassy matrices containing actives entrapped within their *internal* huge porosity -- is now a developed chemical technology offering unique advantages in terms of catalyst stability, selective activity and versatility which include ease of materials production and application.

In general, the performance of these materials is largely superior compared to other catalytic solids obtained by traditional support impregnation methods, while they offer entirely new possibilities prior unavailable in catalysis. Selective activities higher than in solution; mutually destructive catalysts in one pot; fast conversions in carbon dioxide; smooth reactions in water with hydrophobic catalysts; entrapped enzymes 10 times more active than in solution; asymmetric syntheses with full recovery of the precious catalyst: These are just a few examples of the chemical wonders made possible by these materials.

The reactivity of sol-gel catalysts can indeed be controlled and tailored to meet the requirements of largely different chemical conversions either by varying their structural properties (surface polarity, porosity, surface area, morphology etc.) or even the chemical activity of the encapsulated active. The technology is being increasingly adopted by industry while intense researches are carried out worldwide in several academy and industry laboratories. In order therefore to prevent its rapid obsolescence, this review intends to outline the general findings emerging from research on catalysis by sol-gels to help the reader organic chemist in adopting a sol-gel catalyst as a viable and practical tool to achieve the desired products.

*"This article is dedicated to the memory of Dr. Giancarlo Gulì."*

## 1. INTRODUCTION
### 1.1 Scope of the Review

Catalysis by sol-gel doped materials -- porous metal oxides confining an active specie, obtained by an hydrolysis-condensation reaction of suitable precursors -- has become in the last 20 years a prominent tool to synthesize a vast number of useful molecules both in the laboratory and in industrial plants [1]. The initial burst came by Avnir and Reisfeld who first conceived in 1984 the idea to add a dopant solution (a dye molecule) at the early stage of a silicon alkoxide gelation process and to verify the activity of the glass (xerogel) resulting by mild essiccation of the intermediate alcogel [2]. It was rapidly established that *any* organic molecules, including enzymes, could be entrapped and dispersed within the *inner* porosity of such glasses with full retention of the chemical activity and marked stabilization of the entrapped dopant molecules. The domains of organic chemistry and ceramic materials were merging and the new era of inorganic-organic hybrid materials had started [3].

Since then, a worldwide interest for such materials literally exploded as much in academy as in industry as witnessed by the number of research papers (>22,000) and patents (7,420 issued in the US only) appeared in the international literature [4].

Besides chemical catalysis, applications of sol-gels include sensoristics [5], optics [6], biotechnology [7], electrochemistry [8], chromatography [9] and even cosmetics [10], and while a thorough review on sol-gel catalysts was recently published [1a], there still seems to be a need for a review capable to offer organic chemists a *general grasp of what it is possible* using these materials, both in replacing classic solution chemistry syntheses and in exploiting the new possibilities unavailable prior to their introduction. This is the aim of this account, which will be refered throughout the whole text to the physical and chemical properties of sol-gels, which originate the cornucopia of their applications.

### 1.2 Sol-Gel Catalytic Materials

The underlying basic concept to all sol-gels applications is unique: One or more host molecules are entrapped by a sol-gel process within the cages of an amorphous metal oxide where they are accessible to diffusible reactants through the inner pore network and give place to chemical interactions and reactions [3].

Despite its simplicity, the concept has shown tremendous implications and the field has rapidly evolved into the so called "Sol-Gel Science and Technology" [11]: An advanced domain of chemical research capable to afford sophisticated catalytic materials offering unique versatility and many new useful properties.

Surface of several hundreds square meters per gram are typical for these reactive materials, which are microporous (pore size<20 Å) if drying of the intermediate gel is carried out by conventional (thermal) essiccation at mild temperatures when capillary effects force the pores in the alcogel to collapse; or mesoporous (20 Å<pore size<500 Å) if the extraction of the solvent filling the gel network is done using supercritical $CO_2$.

*Address correspondence to this author at the Istituto per lo Studio dei Materiali Nanostrutturati, CNR, *via* U. La Malfa 153, 90146 Palermo, Italy; Tel: + 39 091 680 93 70; Fax: + 39 091 680 93 99, E-mail: mario.pagliaro@ismn.cnr.it; Web: qualitas1998.net/ismn

In both cases, the resulting materials are *chemical sponges*: Chromatographic materials, which adsorb and concentrate the reagents at the cages surface where reactions take place while the adsorbed molecules promote further diffusion of incoming reactants [3a]. When the dopant is a catalytic species (or a precursor) the chemical behavior of the resulting catalyst is affected by four main fundamental factors:

1.  The hydrophilic-lipophilic balance (HLB).
2   The flexibility of the sol-gel cages.
3.  The accessibility of the entrapped species.
4.  The presence of entrapped co-dopants.

Remarkably, all these properties can be subtly controlled and tailored in a vast range of values enabling the preparation of catalysts capable to meet demanding requirements in terms of selective activity, stability and versatility.

### 1.3 Heterogeneous Catalysis in Organic Chemistry

Today only 20% of the fine chemicals production processes are catalytic and a common rule of thumb is that 15-20 kg of by-products are normally generated with 1 kg of useful product [12]. A truly major goal of modern chemical research is, therefore, to render catalytic these organic syntheses as sustainability [13] and economic pressure on the pharmaceutical industry in today's hypercompetitive market are determining a huge interest for heterogeneous catalytic conversions.

a-bottle, grafting and anchoring techniques [15]. In general all these traditional methods are surface heterogenizations in which one organic or inorganic polymer is mixed with a solution of the catalyst (or a precursor). Results are varying but reduced catalytic activity, slower reaction rates due to transport limitations, lack of accessibility of the active sites, and leaching of the supported species are commonly observed problems.

Indeed, a main concept of heterogeneous catalysis -- which is crucial to all applications of solid catalysts to organic chemistry -- is that while derivatizations of materials surface require the formation of a new covalent bond through a slow heterogeneous reaction that leaves the anchored molecules unprotected at the material pores surface, *confinement* of an active species within a material's pores restricts the possible orientations that reactants can assume approaching the catalytic center so that, in general, a sol-gel entrapped catalysts shows *higher* (enantio)selectivity in comparison to both homogeneous catalyst in solution surface-bounded to a non porous material [16].

## 2. CATALYSIS BY SOL-GELS

Sol-gel catalysts are heterogenous materials employing solid-liquid interphases [1a]: A mobile and a stationary component penetrate each other at molecular level with the catalytic species being well-defined, highly *mobile* and *homogeneously* distributed across an highly porous chemically and thermally inert network, thus combining the



**Fig. (1).** The alcogels in this picture are ormosils doped with the Ru species TPAP. Upon a mild heat treatment these materials become more active than TPAP in solution.

Stoichiometric conversions in solution, which consume large amounts of solvents and heavy metals are to be replaced with clean catalytic processes using atom-efficient reagents and solid catalysts [12] allowing the elimination of the separation step of the catalyst from the reaction mixture; to recover the costly catalysts (in which the chiral ligands may be even more expensive than the precious metal); and to conduct fast combinatorial conversions with easy separation (and detection) of products in the reaction mixture [14].

Several methodologies have been developed to entrap organometallic catalysts in solid materials including ship-in-

advantages of homogeneous (high selective activity and reproducibility) and heterogeneous (stabilization and easy separation and recovery of the catalyst) catalysis.

Four main methods are in use to prepare sol-gel catalysts:

i)  Physical entrapment of organometallic species (including enzymes);

ii) polymerization of trialkoxysilyl derivatives of metal ligands;
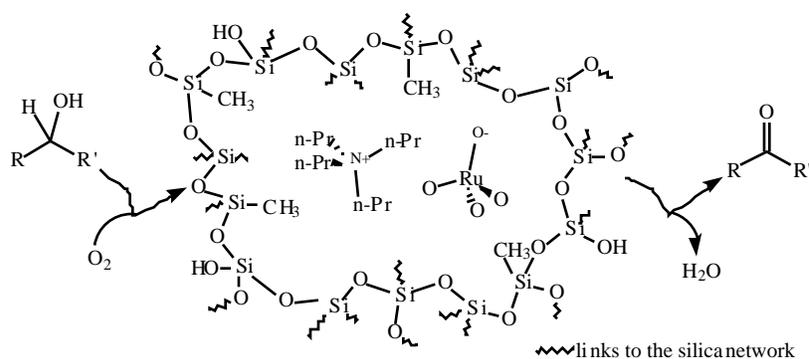
**Fig. (2).** Sol-gel caging of a dopant (TPAP, in this case) is versatile. And a methylated ormosil such as the one here represented is an ideal aerobic catalyst.

   iii)   entrapment of metal nanoparticles, and

   iv)   mixed inorganic oxides.

Both the latter sol-gel supported metallites [17] and sol-gel mixed oxides offer several advantages with mixed zirconia-based oxides up to reach the automotive market [18]; the following discussion, however, will be limited to the first two methodologies, which are of direct relevance to the organic chemist.

## 2.1 Physically Entrapped Catalysts

In most applications, silica was the sol-gel matrix of choice due to a number of advantageous properties of $SiO_2$ that make it an optimal commercial support for solid-phase syntheses [19]. Hence, a variety of organometallic catalysts soluble in methanol or in aqueous THF have been physically entrapped in leach-proof silica gels showing enhanced activity and opening new possibilities [1b].

A general finding emerging from these researches is that *only* the physically entrapped quaternary onium ion pairs of transition metal catalysts do not leach in solution during catalysis. Furthermore, when the entrapped catalyst is insoluble in the solvent in use, its encapsulation enables smooth, leach-proof catalysis. Enantioselective hydrogenation mediated by sol-gel entrapped Ru-BINAP, for instance, can now be carried out in water where Ru-BINAP is entirely unsoluble, reusing the catalyst at length [1b].

As mentioned above, the sol-gel entrapment largely enhances both *physical* and *chemical* stability of the dopant. For instance, while fresh $RuCl_2(PPh_3)_3$ exposed to air gradually loses its high efficiency in mediating the double-bond migration in allylbenzene, the entrapped version can be used many times without any loss in activity [1b].

Finally, in contrast to zeolites and other crystalline porous materials, amorphous sol-gel materials show a *distribution* of porosity, which does not restrict the scope of application of sol-gel catalysts to substrates under a threshold molecular size. Hence, a Rh-doped silica gel can be used to catalyze the disproportionation of vic-dihydroarenes [1b] as well a Ru-doped xerogel can be used for the oxidative dehydrogenation of largely different alcohol substrates [20].

The efficiency of the latter catalyst -- an hybrid organic-inorganic silica xerogel -- shows another possibility disclosed by the organic modification of the inorganic polymeric network, a feature exploited since the early studies of sol-gel doped materials [3a].

The intimate mixing of molecular alkoxide precursors in organic solvents, in fact, allows organic and inorganic components to be associated at the molecular level in order to form real organic–inorganic nanocomposites.

In the case of silicon, a multiplicity of organically modified silicon alkoxides are available that are hydrolytically-stable, and several sol-gel organically modified silicates (ormosils) have shown their high potential as catalysts for selective conversions in advanced organic chemistry.

Silica alkylation with an octyl or phenyl residue, for example, induces hydrophobicity of the sol-gel material opening the route to the use of water as reaction medium for organic reactions by simply emulsifying the organic reactants. In this manner, a general procedure for hydrogenations converting alkenes, alkynes, C=C aromatic bonds, cyano and nitro groups is achieved, which uses a rhodium doped 10-20% alkylated silica matrix – an hybrid polymer in which 10 to 20 per cent of the silicon atoms bear attached an organic group -- in an elegant three-phase emulsion-solution-transfer (EST, Fig. **3**) process [21].

The surfactant molecules, which carry the hydrophobic substrate, adsorb/desorb reversibly on the surface of the sol-gel matrix breaking the micellar structure and spilling their substrate load into the sol-gel cages where the catalytic reaction takes place to form the desired product, which is thus extracted by the desorbing surfactant carrying the emulsified product back into solution.

Interestingly, a partially (10 to 20%) hydrophobized sol-gel yields optimal reactivity, a result due to the fact that the organic groups tend to concentrate at the surface of the sol-gel cages impairing high degree of lipophilic character to the material even at low concentration [22]. An hydrophilic unmodified $SiO_2$ sol-gel matrix doped with the same catalyst indeed restricts reactants from being spilled *into* the sol-gel matrix (yielding abundant isomerization product); while a more hydrophobic substrate readily adsorbs the reactants but does not *desorb* the products into the emulsion [21].

The key, thus, is a careful control of the hydrophilic-lipophilic balance (HLB) of the solid itself along with the *structural similarity* between the component of the catalyst and the substrate, which seems to be necessary for successful catalytic reactions in the EST system. Hence, in the last example, hydrogenation of the arene was found to proceed best when the sol-gel matrix contained a phenyl ring, while
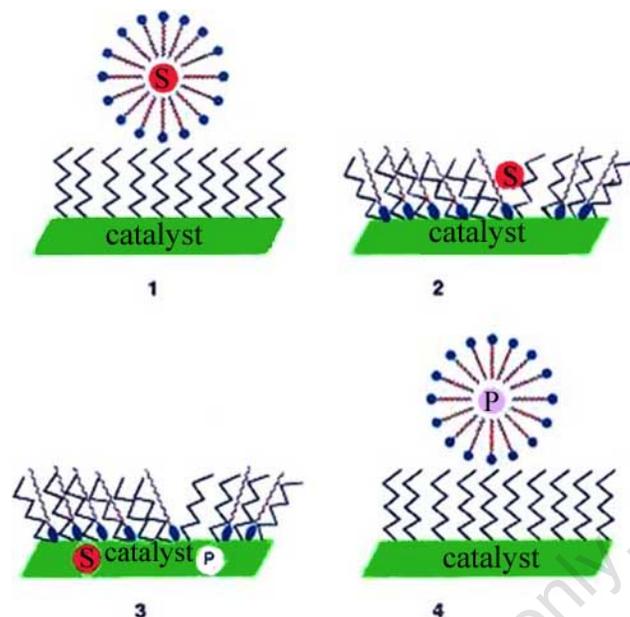
**Fig. (3).** Illustration of the transport, reaction, and adsorption/desorption steps of the EST process. The emulsion which contains the substrate (**1**) spills its content into the catalyst material (**2**), the catalytic process takes place (**3**), and then the adsorbed surfactant carries the product back into solution (**4**).
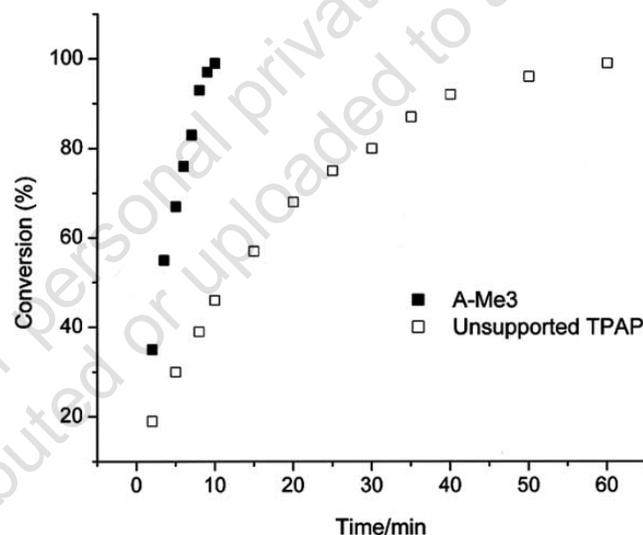


**Fig. (4).** Oxidation kinetics in the aerobic conversion of benzyl alcohol to benzaldehyde in toluene mediated by 10 mol % TPAP encapsulated in the sol-gel hydrophobic matrix **A-Me3** (■) and unsupported (□).

an octyl-modified matrix was more suitable for the reduction of long chained 1-octene [21].

The HLB, however, is not the unique factor affecting reactivity of sol-gel catalysts, in that the *accessibility* and the *flexibility* of the cages entrapping the dopants are also relevant. For example, the versatile aerobic oxidation catalysts TPAP (tetra-*n*-propylammonium perruthenate), which shows a modest activity in promoting alcohols oxidation when entrapped in a pure $SiO_2$ matrix, entrapped in partially hydrophobized silica xerogels becomes *more* active than the catalyst dissolved in toluene [20] (Fig. **4**) or suspended in $CO_2$ in supercritical state [23].

Along with hydrophobicity, high amounts both of water (to promote hydrolysis) and of methanol employed as co-solvent in the catalyst preparation (to promote homogeneity), are needed to ensure optimal reactivity [20], showing the number of experimental parameters of the sol-gel synthesis, which can be controlled independently to optimize the performance of the resulting catalyst.

## 2.2 Chemically Entrapped Catalysts

Covalent bond immobilization of the catalyst to the sol-gel matrix is usually sought to prevent leaching of the entrapped catalyst into the reaction medium. As mentioned
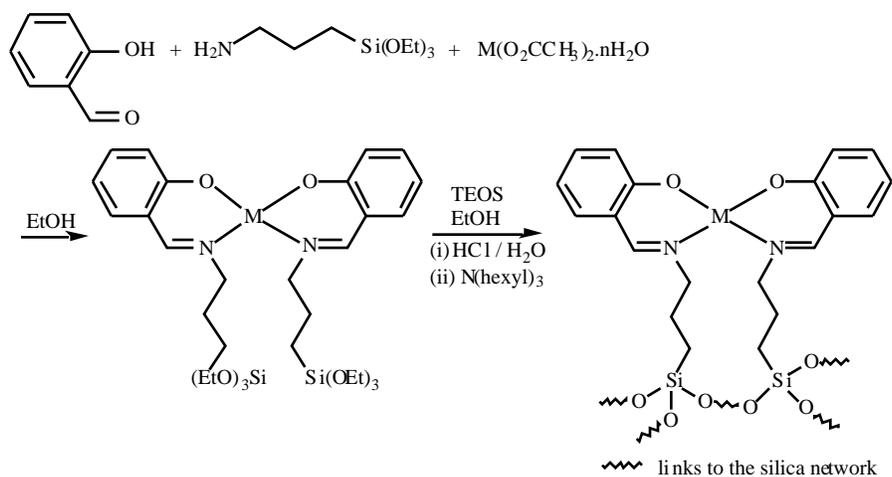
**Fig. (5).** Sol-gel chemical encapsulation of a manganese-complex requires previous modification of the ligand.
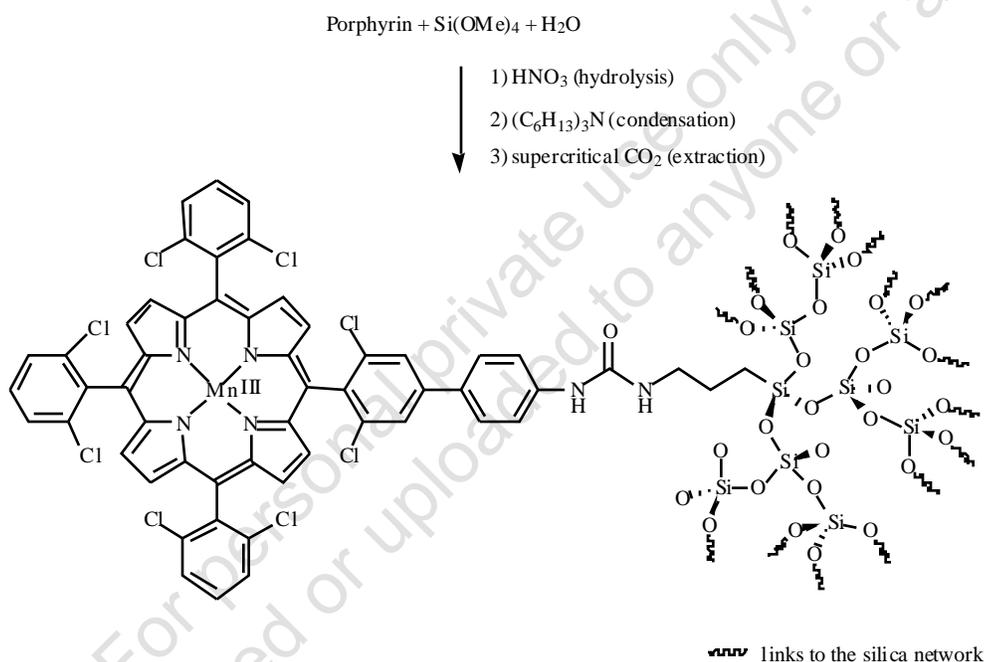


**Fig. (6).** Entrapped in a silica aerogel, this manganese porphyrin is 9 times more active than in solution.

above, binding of the catalyst is easily accomplished by using a silicon alkoxide derivatized with a suitable ligand or with a functional group reacting with the dopant species.

Again, site isolation of the entrapped catalyst offers unexpected properties for the supported homogeneous catalysts in a number of different conversions. Hence, for instance, in the synthesis of *N,N*-diethylformamide from $CO_2$, $H_2$ and diethylamine, a mesoporous silica hybrid aerogel doped with bidentate $RuCl_2[Ph_2P(CH_2)_3PPh_2]_2$ complexes exhibits excellent selectivities (100%) and turnover frequencies up to $18,400 \ h^{-1}$, more than six times *higher* than the corresponding homogeneous catalyst [24]. Furthermore, the mesoporous areogel catalyst is almost *nine* times more active compared to a similarly doped microporous xerogel due to the high porosity of the first material, which enables easy access of the substrate to the active sites.

Similar enhancements in both catalyst selectivity and activity upon sol-gel encapsulation are common: A silica areogel doped with a phosphino-rhodium catalyst, for instance, is a far more active and selective hydroformylation catalyst compared both to a silica-supported and to the homogeneous analog [25]; while another xerogel doped with a chiral Rh hydrogenation catalyst led to chiral alcohol with ee up to 58% in the reduction of acetophenone (and up to 98% in the case of the more hindered ketones), which is *higher* than the ee given by the same chiral rhodium catalysts dissolved in solution or adsorbed at the surface of a commercial silica gel [26].

On the other hand, a similarly doped cobalt(salen) aerogel (Fig. **5**) was *slow* in catalyzing the oxidation of ethylbenzene to acetophenone despite showing quantitative conversion of ethylbenzene, a yield unaccessible with a similar heterogenized system obtained by conventional impregnation when a drastic reduction in activity is observed after 50% conversion [27].

This result clearly shows how the ligand silylation, affecting the *electronic* properties of the complex, may

indeed result in marked change of the entrapped complex activity.

Silylation therefore, should be planned carefully synthesizing the most suitable structure as shown in the example following by the hybrid organic-inorganic material resulting from the covalent attachment of manganese(III) porphyrin to a silica aerogel network (Fig. **6**).

The macrocycle features three electron-withdrawing meso-2,6-dichlorophenyl groups, which stabilize metalloporphyrins against oxidative decomposition through steric and electronic effects, while the well distanced aminopropyl triethoxysilyl-functionalized linker ensures optimal covalent attachment to the final aerogel. As a result, the hybrid catalyst was highly active in the epoxidation of various olefins and in the hydroxylation of an alkane while, again, its activity was enhanced in comparison to the performance of the same porphyrin in homogenous solution [28].

As mentioned above referring to entrapped TPAP, the flexibility of the encaging silica sol-gel cavities has a crucial role in ensuring optimal reactivity and several examples show the general validity of this concept. Thus, nine phosphine-ruthenium complexes were chemically entrapped in silica and in different ormosils and invariably the activity of the resulting catalysts in the hydrogenation of *n*-butanal increased with increasing mobility of the entrapped Ru complex [29], that is with the alkylation degree of the ormosil.

Notably, the organosilane $(CH_3)_2Si(OCH_3)_2$ was used as co-condensation precursor, which is particularly effective in releasing the constraint imposed to the entrapped dopant by the silica sol-gel cage. By the same token, the sol-gel encapsulation of a phosphine-rhodium complex resulted in several selective hydrogenation catalytic ormosils whose activity raised significantly raising the amount of the co-polycondensation agent $MeSi(OMe)_2$-$(CH_2)_6$-$(MeO)_2SiMe$ [30].

The sol-gel entrapment phenomenon can be further exploited to carry out in one pot reactions with *mutually destructive* reactants while still allowing these reagents to activate and participate in desired reactions [31]. In fact, doped sol-gel materials contain a negligible amount of the entrapped molecules at the outer reaches of the particulate or monolithic material since, compared to 1-2 $m^2$ $g^{-1}$ of external surface, a sol-gel has hundreds of square meters per gram of internal surface area.

Hence, for instance, an oxidant (pyridinium dichromate) and a reducing species $(RhCl[P(C_6H_5)_3]_3)$ were entrapped in *separate* sol-gel matrices and with these entrapped reagent and catalyst three different one-pot redox reactions were carried out in sequence -- up to four reactions in one pot [31a] -- without their mutual destruction and with no need for separation steps (Fig. **7**).

The concept at the base of the method, once again, is *general* and one-pot acid/base and enzyme/catalyst enantioselective solid-state syntheses are easily achieved by entrapment of the mutual destructive reagents in two different sol-gel silicas [31b].

It is worth to note that while acids and bases adsorbed at the surface of *polymers* are left partly exposed and consequently require acid/base solid-state syntheses to be carried out consecutively [32], their sol-gel entrapment
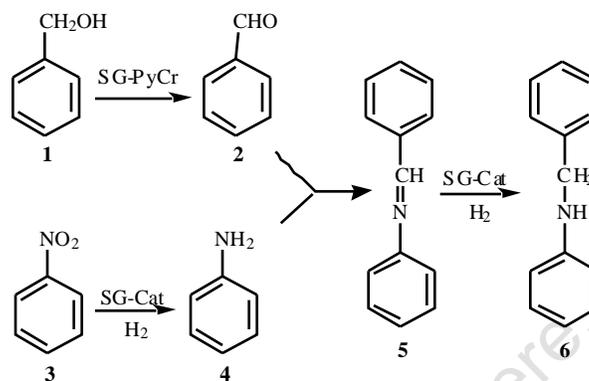


**Fig. (7).** In this one-pot multistep synthesis benzyl alcohol is first oxidized to benzaldehyde in a hydrogen-purged autoclave at 1 bar $H_2$. Raising the $H_2$ pressure to 13 bar nitrobenzene is reduced to aniline which rapidly reacts with the aldehyde to form the Schiff base 5 in 91% yield.

allows smooth reaction in one pot and full recovery of the catalyst by simple filtration with recycle in further runs without loss in catalytic activity [31c].

Similarly, when the entrapped enantioselective natural catalyst lipase is added in one pot to the sol-gel entrapped hydrogenation catalyst (and enzyme poison) $RhCl[P(C_6H_5)_3]_3$, easy one pot esterification and C-C double bond hydrogenation was achieved leading to saturated esters in good yields. Thus, when 10-undecenoic acid and (*S*)-(-)-2-methylbutanol were subjected in one pot to entrapped lipase and rhodium phosphine catalyst, the saturated *optically pure* chiral ester (*S*)-(-)-2-methylbutyl undecanoate was obtained in 91% yield (since the heterogenized lipase is capable of inducing asymmetry during esterification with a prochiral alcohol) [31b].

In other cases, organic modification of the sol-gel cages markedly protects the entrapped molecular dopant from degradation by external reactants, as shown for instance (Fig. **8**) by the entrapment of the radical TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl) -- an highly active catalyst, which in the NaOCl oxidation of alcohols to carbonyls in a $CH_2Cl_2/H_2O$ biphasic system becomes highly stabilized upon sol-gel entrapment (Fig. **9**) in a ormosil matrix [33] -- while it progressively loses its activity when entrapped at the external surface of commercial silica [34].
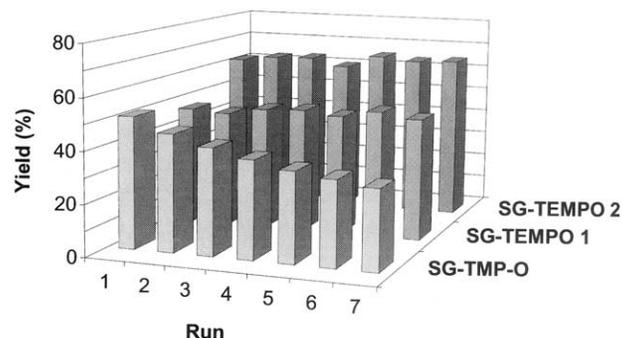


**Fig. (8).** Yields in the Montanari-Anelli oxidation of 1-nonanol to give nonanal in the presence of silica-supported TEMPO (SG-TMP-O, front row), and of sol-gel ormosils doped with TEMPO [SG-TEMPO-1 is 25% and SG-TEMPO-2 is 100% methylated (middle and back row, respectively)].
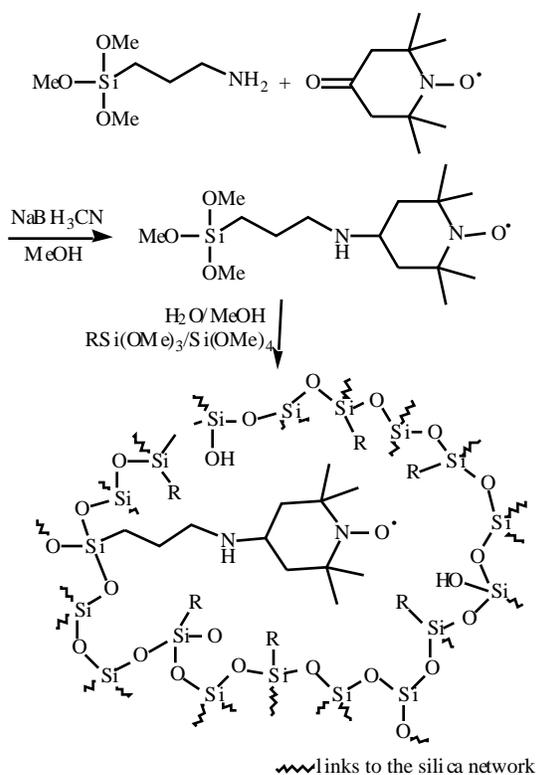
**Fig. (9).** Sol-gel immobilize TEMPO is an "off-the-shelf" alcohol oxidation catalyst: In a bi-phasic reaction system and in organic solvent it yields carbonyls; in water it affords carboxylates.

Encapsulation starting from the easily available triacetonamine derivative 4-oxo-TEMPO and propylamine-trimethoxysilane, in fact, prevents the *intermolecular* quenching of the radicals bounded at the silica surface, which has been found responsible for the loss of activity of TEMPO tethered at the surface of commercial silica [34]; moreover, a *positive feedback* effect is observed by using the doped ormosils (Fig. **8**) in which the catalytic activity actually *increases* upon each run due to reactants adsorption during catalysis [33].

Once again encapsulation of the dopant does the trick by restricting the modes of access of incoming reactants to the catalyst entrapped at the cage surface.

Thus, while homogeneous TEMPO *fails* to oxidize benzylic aminoalcohols to aminohydroxyacids, a fully methylated sol-gel ormosil doped with TEMPO selectively affords these valuable pharmaceutical precursors in high yields (60-80%, Fig. **10**) by isolating the nitroxyl radicals within the hydrophobized pores [35].

Finally, the sol-gel process versatility can be exploited to observe a significant effect on catalysis caused by modifications of the *acidity* of the silica cages surrounding each active site, as shown by modification of the silica sol-gel cages imprinted with an aminopropyl site originally carrying a moiety similar to the substrate to convert, and eventually rendered hydrophilic (**6**) or hydrophobic (**5**) (Fig. **11**).

In the Knoevenagel condensation of isophthalaldehyde with malononitrile -- which is known to be favoured in protic solvents as well as when using acid-base bifunctional catalysts -- the acidic outer sphere surrounding the primary amine in **6** gave rate enhancements of about 50 and 30 relative, respectively, to **5** *and* to a commercially available catalyst consisting of a monolayer of 3-aminopropyl groups on silica [36].

## 2.3 Biocatalysis

Biological species such as enzymes, whole cells, antibodies and even bacteria [37] can all be entrapped in silica sol-gel matrix with only minor loss of activity: An almost incredible result considering the amount of toxic alcohols, which is released in conventional sol-gel processes based on the hydrolysis of alkoxides.

Shortly after the patent reporting their invention [38] and encapsulation of GOD (glucose oxidase) for use in glucose sensing [39], in 1995 lipase-entrapped ormosils were invented with activity even 8 times (!) higher with respect to the enzyme powders used in organic solvent [40].

Here, again, the higher activity was crucially due to the flexibility impaired to the entrapped enzyme by the hydrophobized sol-gel cages and the materials -- that today have reached a 2$^{nd}$-generation level of performance [41] --



**a:** R= $C_3H_7$, R'= Boc, R''= Me

**b:** R = p-$NO_2C_6H_4$, R'= COCHCl$_2$, R''= H

**c:** R = p-$NO_2C_6H_4$, R'= Boc, R''= H

\* In case of oxidation of **2b** and **2c**
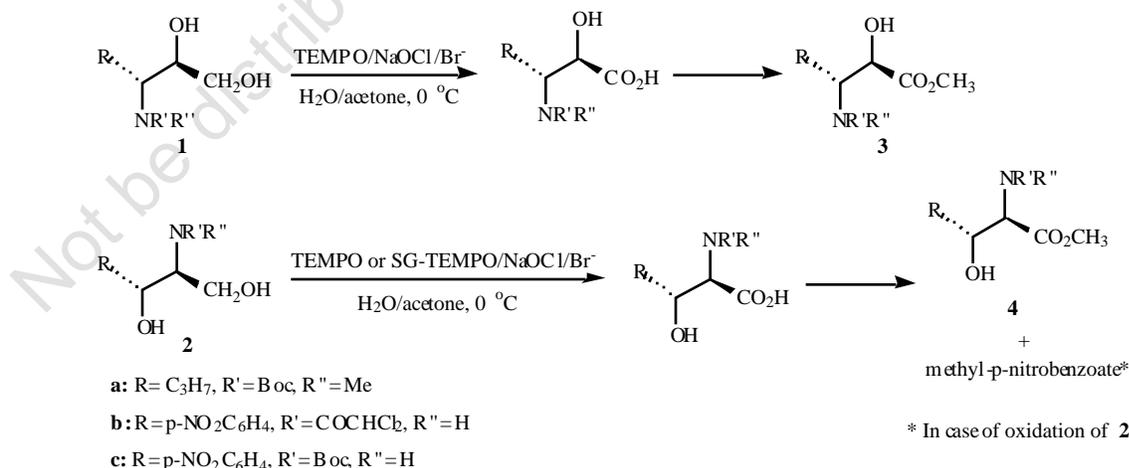
**Fig. (10).** Aminoalcohols are converted to valuable aminohydroxyacids over ormosil-entrapped TEMPO with good selectivity, while TEMPO in solution is entirely unselective.
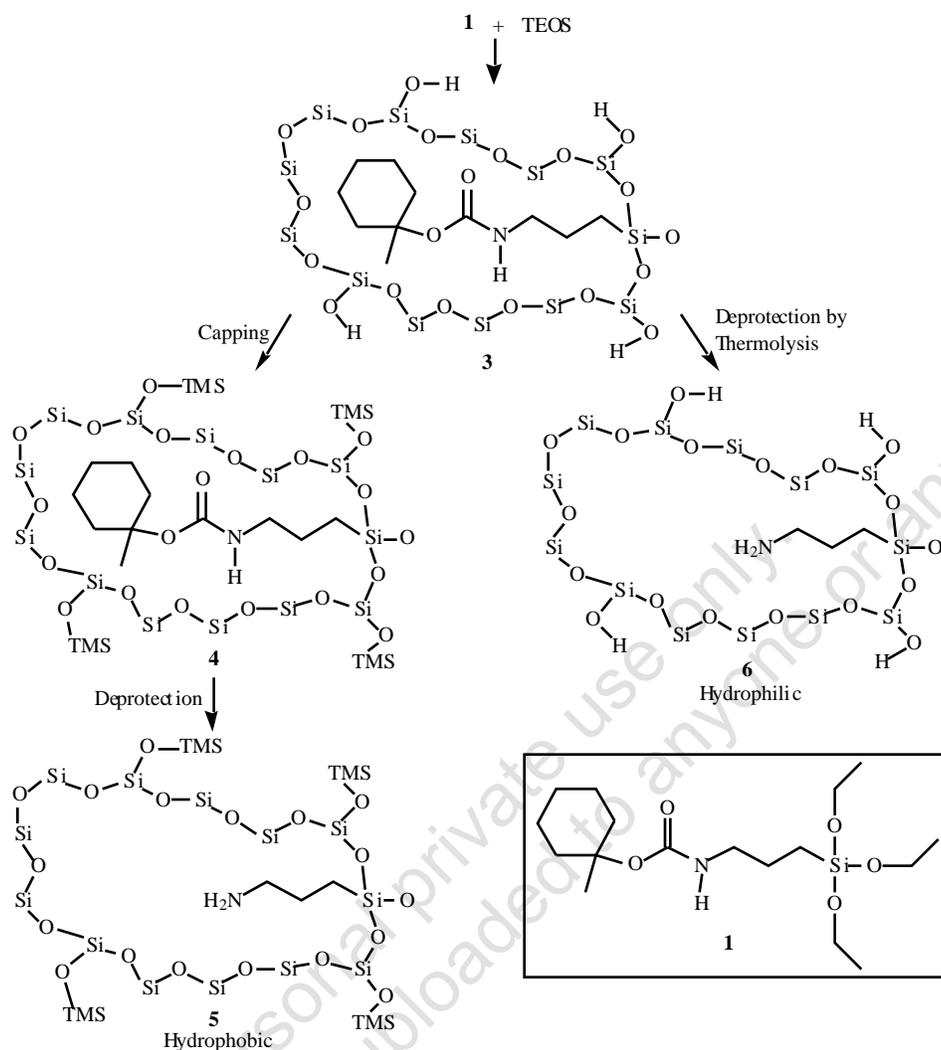
**Fig. (11).** Imprinting a sol-gel cage is simple. Further tailoring the microstructure to yield an hydrophilic material affords an highly active condensation catalyst.

rapidly reached the market, lipase being the most used enzyme in the chemical industry.

Generally, however, conventional sol-gel entrapment may largely reduce the original enzyme activity. A major point, in fact, concerns the secondary and tertiary structures of these giant molecules, which is often altered (denaturated) by the constraints imposed by confinement in the sol-gel cages and by the alcohol released in the condensation process.

Showing its unmatched potential in materials synthesis, the sol-gel method profound versatility was recently exploited to solve the problem by simply replacing the silicon alkoxides precursors with glycerol-derived polyol silicates [42]. In this manner, enzymes and *cells* are easily immobilized in biosilica gels, which display activities approaching those of the free biologicals, together with the high stabilities and robustness that characterize sol-gel bioceramics. The method can be extended to metallosilicate, alkylsiloxane, functionalized siloxane and composite sol-gels, allowing the fabrication of a physicochemically diverse range of bio-doped polymers, which will find a multitude of applications in the near future.

## 3. TAILORING THE PROPERTIES OF SOL-GEL CATALYSTS

A true control and tailor of the chemical and physical properties of sol-gel molecular catalysts is the unique feature of these materials and is due to the versatile solution chemistry of metal alkoxides, and of organosilicon compounds in particular [3b].

The materials grow up of kinetic control [43], and not thermodynamic, resulting often in "living" materials that undergo structural modifications, and thus changes in reactivity, even months after preparation.The catalyst textural properties, HLB, shape and composition are thus to be planned by a rational choice of the preparation conditions based on the fundamental knowledge accumulated in the last 20 years.

Indeed, while in 1995 it was "remarkable to see how many applications of the entrapment have been developed, without fully understanding the picture at molecular level" [3a], ten years later we have a better understanding of both the sol-gel polycondensation process as well as of the resulting materials.
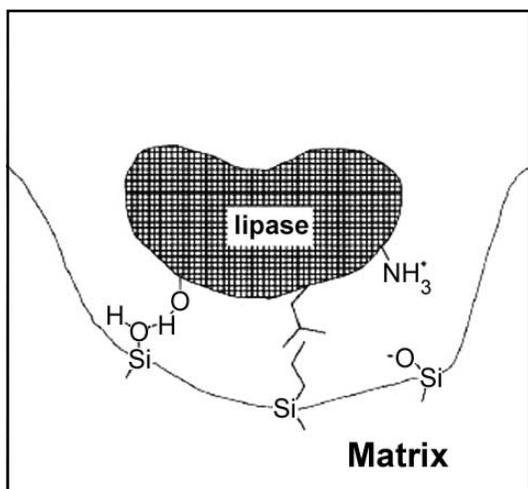
**Fig. (12).** Schematic view of non-covalent interactions between the gel matrix and the lipase.

A quantum study of the dynamic behavior of the hydrolysis reaction of $Si(OCH_3)_4$ under neutral, basic, and acidic conditions conducted at the atomic level with short time intervals [44] recently showed evidence that a flank-side attack mechanism is favored, in all the three cases, for the hydrolysis process; and that pentacoordinate silicon intermediates are easy pathways for the displacement of -$OCH_3$ by -OH on silicon. Moreover, the presence of the acid or the base as catalyst promotes the hydrolysis by rapid formation of Si-OH bond in comparison to the hydrolysis under neutral condition.

The protecting properties of the sol-gel caging are well established as it is the delicate balance between good isolation and protection and accessibility of the entrapped molecule. High acidity and low water/silane ratio were thought to be required in achieving such balance [3a]; and a closer look unveiled that what is actually demanded is a thorough hydrolysis of the alkoxides in order to ensure an open cross-linked final network in which the active molecules are entrapped at the cages surface, and not buried in bulk of the material [20].

During the growing of the material, in the mono-mer oligomer sol gel xerogel transition, micelles tend to form which may segregate the (generally hydrophobic) organometallic catalyst within their core and the polar head at the interface of the growing material [45]. Therefore, in order to disrupt any intermediate micelles and to ensure homogeneous dispersion of the catalyst across the polymeric network, an high amount of co-solvent and high water/silane are instrumental to afford highly active entrapped catalysts.

As shown extensively throughout the text, the *mobility* of the entrapped dopant is crucial in promoting the reactivity of the final materials; thus, provided that the dopant molecules are at the surface and enjoy enough freedom, high porosity will certainly promote reactivity by limiting intraparticle diffusion; but that will *not* be the case if microporous xerogels of different HLB are compared (cf. entrapped lipase and TPAP where the ormosils with the smaller pores are *more* reactive).

It is therefore, truly important for future practical applications of sol-gels to catalysis, that silica xerogels of increased porosity can now be produced by a novel 2-step process in which the alkoxides are first hydrolized in a strong acidic medium, and subsequently neutralized to promote condensation of the cross-linked clusters to yield a highly cross-linked gel, which is essentially pure silica of high porosity [46].

Finally, while the sol-gel matrix can usefully preserve the properties of the dopant, the reverse is also true in that changing the sol-gel cage environment can influence the properties of the dopant itself, and actually the fundamental potential of creating a *library of reactivities* from a single specific compound has been demonstrated by careful co-entrapment in a single sol-gel interphase of a surfactant and a dopant [47].

In other words, different reactivities for the *same* molecule can be accessed by tailoring the heterogeneous microenvironment of the molecule and catalytic reactions are probably the most important processes that will be revolutionized by this novel *molecular tailoring* approach, which awaits further exploitation. In place of applying synthetic methods to alter a catalyst reactivity, this new means of control involves choosing an appropriate solid micellar system (from the available multitude) and exploiting it in manipulating the chemistry of the entrapped compound. The sol-gel matrix and the micellar solubi-lization, in fact, have a synergetic effect: Their combination produces effects stronger and more tuneable than in solution, so that a careful selection of sol-gel entrapped surfactants allows to induce changes in the dopant properties from large magnitudes to delicate fine-tuning [47b].

## 4. PRACTICAL APPLICATIONS

### 4.1 Limits and Advantages of Sol-Gel Catalysts

The main limit of sol-gel entrapped catalyst is economic and resides in their high cost compared to traditional polymer-supported catalysts. Not only the price of silicon alkoxides is high, but very often industry cartel practices prevent economic supply of the alkoxide [48]. High cost will thus preclude applications unless a significant performance benefit is demonstrated.

From a technical viewpoint, both the porosity and mechanical stability of sol–gels need to be improved. These are especially important for achieving rapid catalysis in high-throughput reactors in which the intraparticle diffusional resistance of low-porosity sol–gels will not affect the catalytic efficiency. The difficulty here is that the greater the porous volume and pore size, the more brittle and fragile the polymer generally is, especially for amorphous pore structures.

To solve this problem, for instance, sol–gel lipase has been coated over beads of sinterized porous glass and certainly the ease of manipulation of the alcogel along with the versatility of the process offer other technical solutions [41].

On the other hand, along with frequent higher activity, selectivity and stability of sol-gel molecular catalysts reported above, another major advantage, which adds value to the performance of these materials is their broad applicability to novel reaction systems.
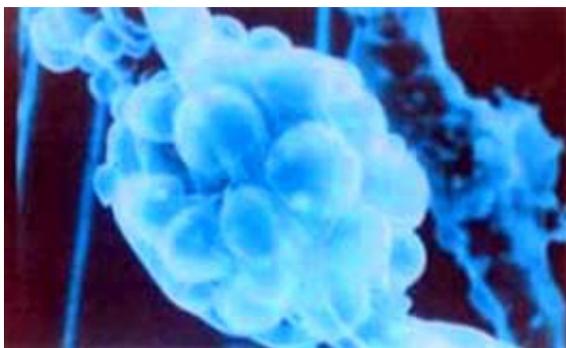
**Fig. (13).** Sol-gel silica entrapped cells such as those of *saccharomyces cerevisiae* shown here are highly stabilized and freely accessible to external nutrients acting as potent bioreactors (*photo courtesy of Giovanni Carturan*).

Industrial conversions in supercritical carbon dioxide, for instance, are carried out in a relatively small, high-throughput continuous reactor in which the catalyst is packed at the bottom of the reactor and the solvent continuously recycled [49].

In the case of this known fluorophilic solvent, the sol-gel process may easily afford an hydrophobized *fluorinated* catalytic silica gel, which can be shaped in practically any form (film, coating, fiber, foam, powders etc) to meet the engineering requirements of a continuous process, and then applied to the aerobic oxidation of alcohols into valuable carbonyls eliminating *any* by-products while carrying out the reaction in a non-flammable, non toxic and recyclable reaction medium [50]

### 4.2 Catalysts on the Market

Catalytic sol-gel lipase immobilizates rapidly reached the market after their invention in 1995 because of their remarkable activity and stability. The original procedure for the encapsulation produced by the fluoride-catalyzed hydrolysis of mixtures of $RSi(OCH_3)_3$ and $Si(OCH_3)_4$ has

been improved considerably with higher enzyme loading, variation of the alkylsilane precursor, and the use of additives [41]. Fluka commercializes a vast set of these sol-gels which are also excellent catalysts in the kinetic resolution of chiral alcohols and amines, and are recyclable without any substantial loss in enantioselectivity (residual activity of 70% even after 20 reaction cycles).

Another fundamental sol-gel biocatalytic process is commercially carried out by the Italian company Indena, which produces taxol (paclitaxel) over silica-entrapped *Taxus* cells, using the process developed by Carturan in 1989 in which an aqueous TEOS sol is sprayed over a suspension of living cells [51] resulting, in this case, in a bioreactor system which affords the synthesis of a precious anticancer drug without destroying the *Pacific yew* trees from whose bark the compound was extracted in very low yields.

The process is general in that it prevents the cells death and affords a whole set of bioactive materials (Fig. **13**) whose enormous potential awaits full exploitation in catalysis and in many other fields.

More recently, the British fine chemicals manufacturer Avecia (ex Zeneca) licensed the Johnson Matthey's sol-gel technology for preparing organic-inorganic silica hybrid gels doped with chiral ligands (CACHy - Catalytic Asymmetric CyanoHydrin) [52]. These catalysts allow easy conversion of aldehydes and ketones into chiral cyanohydrins, high value building blocks and useful pre-cursors for hydroxyamino acids and amino alcohols (Fig. **14**).

The new sol-gel technology -- named CTIS CACHy™ (CTIS: Chiral Technologies Interface System) -- dramatically improves process economics for large scale pharmaceutical manufacturing as it raises the turnover number of the catalyst compared with its homogeneous version, while maintaining enantiomeric excess (ee) above 90%.

Clearly, the competitive advantage offered here by these sol-gel catalysts -- new and lower cost cyanide reagents -- will push many other companies to adopt commercial sol-gel catalysts for their fine chemicals productions, while Johnson-
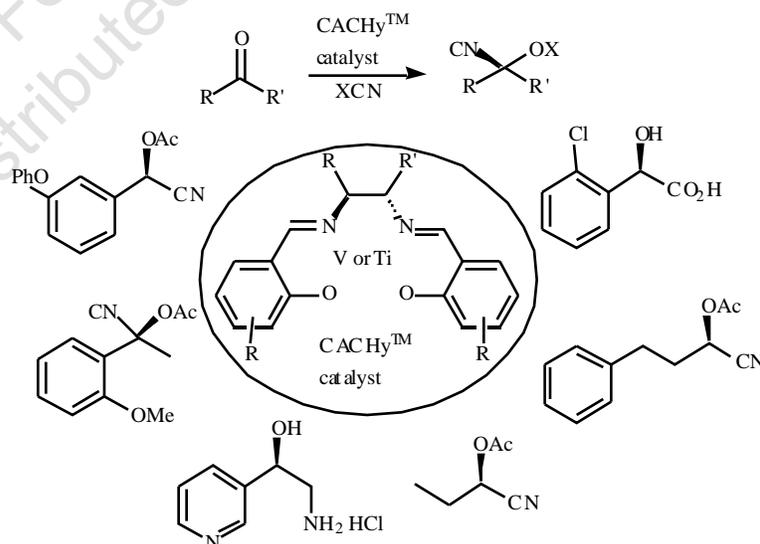


**Fig. (14).** Cyanohydrins are precursors for hydroxy- and amino acids and amino alcohols. And the new sol- gel CACHy catalysts convert aldehydes and ketones into these high value chiral building blocks.

Matthey itself is continuing to develop a line of chiral sol-gel catalytic materials in joint development with Avecia [53].

Companies such as BASF, for instance, operate large units of research working on sol-gel catalysts, and are easily envisaged to reach the market with proprietary technology to deliver more economic and sustainable manufacture of chiral compounds and fine chemicals by molecular sol-gel catalysts.

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