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Reviews

Recent Uses of Sol–Gel Doped Catalysts in the Fine Chemicals and Pharmaceutical Industry

Rosaria Ciriminna and Mario Pagliaro*

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

Abstract:

A number of sol–gel-entrapped catalysts are eventually being commercialised due to unique advantages offered to organic synthesis and to biotechnology applications. Yet, the examples reviewed in this paper are the very first ones of a technology now in the commercial pipeline that will have an impact on the way organic synthesis and biotechnology are practiced in the fine chemicals and pharmaceutical industry.

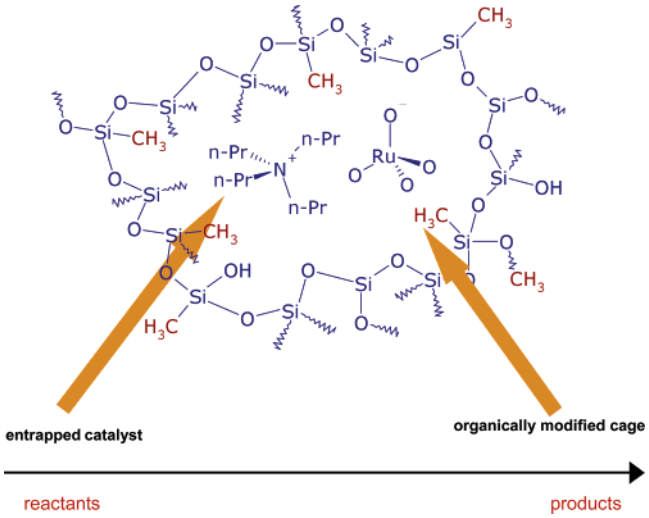
Introduction

The pharmaceutical industry produces between 25 and 100 kg or more of waste for every kilogram of active pharmaceutical ingredient (API) manufactured.[1] According to a leading practitioner of the industry, "the potential waste coproduced with APIs is in the range of 500 million to 2 billion kg per year. Even at a nominal disposal cost of $1 per kg, the potential savings just in waste avoidance is significant"[2] compared to the pharmaceutical industry annual sales (almost $500 billion in 2003[2]).

Catalysis over heterogenized catalysts enabling *one-pot, multistep synthesis*[3] would offer a solution to most of these problems (Scheme 1), eliminating the large amounts of solvents and purification media currently employed by industry. Yet "many homogeneous catalytic systems cannot be commercialised because of difficulties associated with separating the products from the catalyst."[4]

Until recently, indeed, heterogeneous catalysts in the fine chemicals industry were remarkable for a disappointingly poor achievement, if any. "To my knowledge—as Cole-Hamilton put it in 2003—the only commercial example of a homogeneous catalyst heterogenized on a solid support is the carbonylation of methanol using $[RhI_2(CO)_2]^-$ electrostatically bound to an ion-exchange resin";[4] and even in that single case, the author pointed out that "leaching cannot be avoided".[4]

Scheme 1. **Systems approach to organic synthesis with doped sol–gel nanocomposites**



The reason for this obsolescence is mostly rooted in the fact that the fine chemicals industry is a product (and not process)-oriented industry, i.e., it focuses on the development of new products to maximize revenues in the time span in which exclusive rights are granted by patenting innovation.

As a result, traditional heterogenization technologies of homogeneous catalysts were characterized by a poor level of performance in terms of activity, selectivity, and stability.

Current economic hypercompetition, however, and ever stricter environmental regulations are bringing about a radical change, with industry (often small, knowledge-intensive companies) and academy working together to develop a variety of solid-phase catalytic technologies for high-throughput organic synthesis.[5]

Some of the most remarkable achievements include microencapsulation in polystyrenes such as entrapped OsO_4 for olefin hydroxylation (exploiting the interaction between π electrons of benzene rings of the polystyrenes used as polymer backbones and the vacant orbitals of the catalysts),[5] polyurea-entrapped Pd (PdEnCat) for a multiplicity of C–C bond-forming reactions,[6] and the use of carboxylic acid functionalised polymer (FibreCat).[7] In general, however,

* To whom correspondence should be addressed. E-mail: mario.pagliaro@ismn.cnr.it. Web: www.qualitas1998.net/ismn.

(1) This accounts for the importance of the concept of atom efficiency pioneered by Barry Trost and Roger Sheldon in the early 1990s. For an essay on sustainability applied to chemical synthesis, see: Collins, T. *Science* **2001**, *291* (5501), 48.

(2) Cue, B. W. *Chem. Eng. News* **2005**, *83* (39), 46.

(3) Broadwater, S. J.; Roth, S. L.; Price, K. E.; Kobašlija, M.; Tyler McQuade, D. *Org. Biomol. Chem.* **2005**, *3*, 2899.

(4) Cole-Hamilton, D. J. *Science* **2003**, *299*, 1702.

(5) Kobayashi, S.; Akiyama, R. A renaissance of immobilized catalyst. *Chem. Commun.* **2003**, 449.

(6) Detailed information on the technology and its applications are available at the URL: http://www.reaxa.co.uk.

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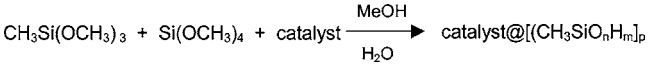
10.1021/op050211u CCC: $33.50

Scheme 2



metal leaching cannot be avoided. The PdEnCat catalyst, for instance, leaches <4% of Pd per catalytic reaction run.

Along with these recent technologies, sol−gel-entrapped catalysts made of doped organically modified silicates (ORMOSIL) doped with one or more catalytic species enable heterogeneous conversions that are *more* selective and active than conventional homogeneous catalyses.[8]

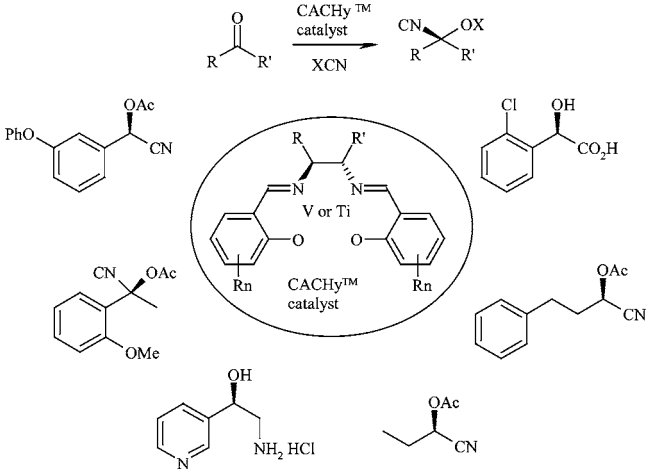
A number of recent studies have proved that catalysts encapsulated in the inner porosity of ORMOSIL (Scheme 2), in fact, are much more efficient than other supported catalysts and even more than homogeneous catalysts in a wide variety of reactions, under largely different conditions.[8a]

The trend was studied and verified, for instance, for reactions catalysed by transition metal, organo-, and enzyme catalysts entrapped in ORMOSIL prepared by copolymerization of tetramethoxysilane (TMOS) and the modifying co-precursor methyltrimethoxysilane (MTMS) and has been correlated with the encapsulation itself but also with the structure of the sol−gel matrix, namely the HLB (hydrophobicity−lipophilicity balance) and the textural properties of the materials.[9]

Furthermore, the use of a silica-based ceramic matrix as the functional support has a number of practical, unique advantages including stability towards harsh conditions, low swelling, and consistent binding sites for the catalyst.[10]

In this report we highlight some of the main achievements using sol−gel-entrapped catalysts in a number of commercially relevant reactions. As progress in the fine chemicals industry "depends strongly on novel synthetic chemistry carried out in the academy",[11] this account aims to reinforce such a collaborative approach by providing information on a key chemical technology whose potential, in terms of benefits to society, is far from being realized.

Scheme 3. **Cyanohydrins are precursors for hydroxy- and amino acids and amino alcohols**[a]



[a] New sol−gel CACHy catalysts convert aldehydes and ketones into valued chiral building blocks.

Ti/V(salen)@silica: CTIS−CACHy

Titanium and vanadium salen complexes of vanadium or titanium developed by North and Belokon[12] entrapped in organic−inorganic silica hybrid gels are commercialised by Avecia under the trademark CACHy (Catalysts for Asymmetric CyanoHydrin sYnthesis). Hence, silica xerogels doped with chiral ligands complexed to V or to Ti catalyse the asymmetric addition of different cyanide-functionalised organic molecules to aldehydes and ketones to afford enantiomerically enriched cyanohydrins (Scheme 3).[13]

Chiral cyanohydrins are high-value building blocks and useful precursors for hydroxyamino acids and amino alcohols. This sol−gel immobilisation technology licensed from Johnson Matthey and named CTIS CACHy (CTIS: Chiral Technologies Interface System) 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 above 90%.

P450@ORMOSIL: MetaChip

A new sol−gel-entrapped catalyst that will largely speed up the drug discovery process is made of ORMOSIL-entrapped cytochrome P450 enzymes put on a chip. The system allows the creation of liver metabolites of drug candidates and rapid testing of them for toxicity against specific types of cell, thus identifying those activated by the liver and weeding out those made toxic earlier in the drug discovery process.[14]

P450 enzymes are the liver's major detoxification enzymes, iron-containing proteins responsible for the initial

(7) This catalyst consists of polymer fibre functionalised via graft copolymerisation to which metal species are covalently bound, resulting in a high density of active and accessible functional sites enabling efficient heterogenization of a number of homogeneous catalyst with high loading (~2−3 mmol g^{-1}). The fiber are commercalised by Johnson Matthey in a variety of lengths (0.25 mm is standard), giving materials with different physical characteristics suited to a variety of reactor and filter combinations. One example is: Gilhespy, M.; Lok; M.; Baucherel, X. *Chem. Commun.* **2005**, 1085.

(8) (a) Ciriminna, R.; Pagliaro, M. *Curr. Org. Chem.* **2004**, *8*, 1851. (b) Avnir, D.; Blum, J.; Lev, O. *The Encyclopedia of Materials: Science and Technology*; Buschow, K. H. J., Flemings, M. C., Kramer, E. J.. Cahn, R. W., Ilschner, B., Mahajan S., Eds.; Elsevier Science: Amsterdam, 2001; pp 8040−8049.

(9) (a) Ciriminna, R.; Ilharco, L. M.; Fidalgo, A.; Campestrini, S.; Pagliaro, M. *Soft Matter* **2005**, *1*, 231. (b) Fidalgo, A.; Ciriminna, R.; Ilharco, L. M.; Pagliaro, M. *Chem. Mater.* **2005**, *17*, 6686.

(10) These advantages include *fast kinetics* (silica is surface functionalised and reacts much faster than conventional polymer-bound reagents where the reaction is slowed by the rate of diffusion through the polymer and can be slowed further by the polymer ability to swell); *versatility* (works under a wide range of conditions: in all solvents, organic and aqueous. It has a high thermal stability and can be used in microwave applications); and *ease of use* (unlike polymer, silica is easy to weigh and handle with no static issues and is easily amendable to automation. It is mechanically stable, works in any format, and is easily scaled. It requires little or no washing because it does not swell in any solvent). The Canada-based company SiliCycle Inc., for instance, commercialises a vast variety of functionalised silica gels as advanced reagents of the pharmaceutical and fine chemicals industry.

(11) Laird, T. *Org. Process Res. Dev.* **2005**, *9*, 1

(12) Blacker, A. J.; North, M.; Belokon, Y. N. Chiral Catalysis: C−C Coupling and Oxidation Supplement. *Chem. Today* **2004**, *22*, 30−32.

(13) (a) Rouhi, M. *Chem. Eng. News* **2004**, *82* (7), 20. (b) See also the Avecia website at the URL: www.avecia.com.

(14) Lee, M.-Y.; Park, C. B.; Dordick, J. S.; Clark, D. S. *Proc. Natl. Acad. Sci. U.S.A.* **2005**, *102*, 983.

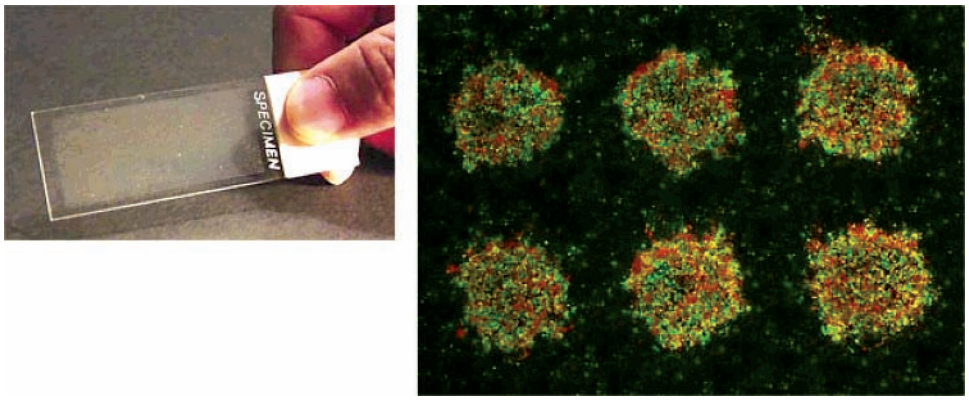


Figure 1. **MetaChip (left) can do rapid toxicity testing of potential drug candidates. The colored spots correspond to regions of dead cells resulting from contact with a toxic product of P450 metabolism generated on the MetaChip (reproduced from Lee, M.-Y.; Park, C. B.; Dordick, J. S.; Clark, D. S.** ***Proc. Natl. Acad. Sci. U.S.A.*** **Copyright (2003) National Academy of Sciences, U.S.A. with permission).**

clearance of drugs from the body and the activation of prodrugs, that work by oxidizing chemicals to make them more water soluble so that potentially harmful substances can be eliminated more easily from the body.

Hence, by simply spotting a precursor solution of recombinant P450 enzymes in MTMS and aqueous HCl over a MTMS-coated glass slide, a device is obtained (MetaChip, short for Metabolizing Enzyme Toxicology Assay) that combines high-throughput P450 catalysis with cell-based screening on a microscale platform, so that many drug candidates can be tested simultaneously at early phases of drug development. This provides a high-throughput microscale alternative to currently used in vitro methods for human metabolism and toxicology screening based on liver slices, cultured human hepatocytes, or isolated P450 itself.

The MetaChip device is made of sol−gel spots (volume varied from 5 to 100 nL) arrayed in any number of spatially addressable arrangements (Figure 1). The second component is a human cell monolayer housed in a chamber slide, which is used for cytotoxicity screening of the P450-generated metabolite. A solution of lead compound is applied to the sol−gel spots by using the microarrayer, followed by stamping of the cell monolayer onto the sol−gel array. After incubation for sufficient time to allow the synthesis of P450-generated metabolites, the cell monolayer slide is removed, and the cells are stained to determine the percentage of dead cells by using a microarray scanner.

Sol−Gel Encapsulation of Cytochromes P450. Sol solution was prepared by mixing 250 μL of methyltrimethoxysilane (MTMOS) (Aldrich) with 100 μL of HCl (5 mM), followed by sonication for 10 min. The MTMOS/HCl sol solution (40 μL) was mixed with 60 μL of CYP3A4 baculosomes (1.1 nmol of P450 per mL, Invitrogen) and 10 μL of regeneration system (333 mM glucose-6-phosphate/40 units/mL glucose-6-phosphate dehydrogenase in 100 mM potassium phosphate buffer, pH 8). To prevent detachment of sol−gel spots from the glass slide and to ensure hemispherical spots, MTMOS sol solution (2 mL, pH 7) was spin-coated (at 50 × *g* for 30 s) onto the slide. The MTMOS sol solution containing CYP3A4 was then spotted onto the MTMOS-coated glass slide by using a MicroSys 5100-4SQ microarrayer (Cartesian Technologies, Irvine, CA) and allowed to gel for 24 h at 4 °C. A similar method was used to encapsulate other P450 isozymes in the sol−gels. P450 reactions were performed in 525-spot arrays consisting of 15 × 35 spots (30 nL each) by dispensing 60 nL of substrate solution (see below) on top of each sol−gel spot with the microarrayer.

Lipase@ORMOSIL

The mild preparation conditions of ORMOSIL are compatible with the effective entrapment of transition metal catalyst, enzymes, or even living cells in silica-based materials (with minor or no loss of biological activity), i.e., the *merger* of chemistry, biology, and materials science.

For example, Fluka commercialised a vast set of catalytic sol−gel lipase immobilizates that rapidly reached the market after their invention in 1995 because of their remarkable activity in esterification reactions (but also in the kinetic resolution of chiral alcohols and amines) and stability (residual activity of 70% even after 20 reaction cycles is common).

The original procedure for the encapsulation produced by the fluoride-catalysed 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, and these materials have now reached a second-generation level of performance.[15]

On a lab scale, the best performing catalyst for esterification requires double immobilization of lipase within the cages of an ORMOSIL (iBTMS:TMOS = 5:1 with iBTMS = *i*-C_4H_9) and further coating on the external surface of Celite along with co-entrapment of 18-crown-6 ether in the presence of small amounts of polyvinyl and isopropyl alcohol.

General Procedure for Sol−Gel Entrapment of Lipases. A commercial lipase powder (lyophilizate) such as AnL (150 mg), BcL (150 mg), CaLB (125 mg), CrL (150 mg), CrL type VII (60 mg), MmL (150 mg), PfL (150 mg), PpL (150 mg), PrL (150 mg), or TIL (70 mg) was placed in

(15) Reetz, M. T.; Tielmann, P.; Wiesenhofer, W.; Konen, W.; Zonta, A. *Adv. Synth. Catal.* **2003**, *345*, 717.

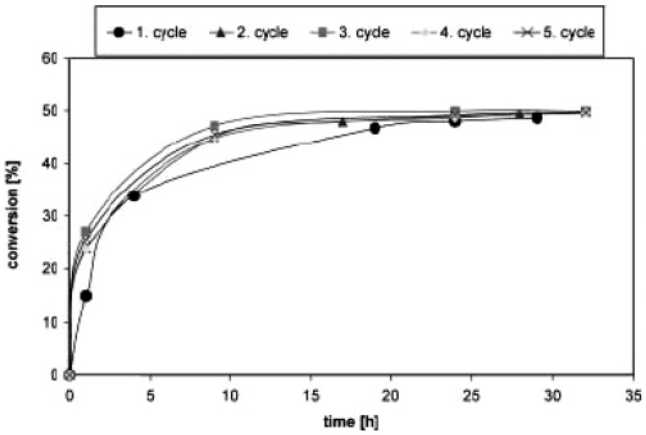


Figure 2. **Recycling experiments in the kinetic resolution of racemic amine using the sol−gel CaLB-immobilizate prepared with 18-crown-6 as an additive (reproduced from Reetz, M. T.; Tielmann, P.; Wiesenhofer, W.; Konen, W.; Zonta, A. *Adv. Synth. Catal.* 2003, *345*, 717 with permission from Wiley-VCH).**

a 50-mL Falcon tube (Corning) together with Tris/HCl buffer (390 μL; 0.1 M; pH 7.5) and 50 mg of Celite after which the mixture was vigorously shaken with a vortex mixer. Then aqueous PVA (100 μL of a 4% w/v), aqueous sodium fluoride (50 μL of a 1 M solution), and isopropyl alcohol (100 μL) were added, and the mixture was homogenized using a vortex mixer. Then the alkylsilane (2.5 mmol) and TMOS (0.5 mmol; 74 μL; 76 mg) were added, and the mixture was agitated once more for 10−15 s. Gelation was usually observed within seconds or minutes while gently shaking the reaction vessel. Following drying overnight in the opened Falcon tube, isopropyl alcohol (10 ± 15 mL) was added to facilitate removal of the white solid material (filtration). The gel was successively washed with distilled water (10 mL), isopropyl alcohol (10 mL), and *n*-pentane (10 mL). During this process a spatula was used to crush the gel. Thereafter, the lipase immobilizate was placed in an open 2-mL plastic vessel and dried in the air at room temperature. The resulting material showed a 30-fold improvement in activity compared to non-immobilised lipase powder.

Using sol−gel encapsulated lipase B (from CaLB, *Candida antarctica*) prepared in the presence of 18-crown-6 in the acylating kinetic resolution of racemic 1-phenylethylamine with methoxyacetic acid ethyl ester as acylating agent, the desired (*S*)-amine was isolated enantiomerically pure (ee >99%) while the 50% conversion was reached within 29 h, i.e. the highly enantioselective reaction ideally stops when the (*R*)-enantiomer has been consumed.[15]

Figure 2, showing the results of five cycles, demonstrates constant performance with respect to activity with no reduction in enantioselectivity in any of the runs.

Finally, the high catalyst loading typical of sol−gel entrapped catalysts ensures a desirable high S/C (substrate/catalyst ratio) as the major part of the heterogeneous catalyst weight originates from the silicate matrix. For example, in a preparative-scale reaction of the alcohol *rac*-1-(2-naphthyl)-ethanol only 250 mg of sol−gel CaLB-immobilizate could be used per 10 g of substrate. For comparison, all this makes the process based on sol−gel immobilizate lipase largely competitive with the commercial BASF process using lipase immobilised on Amberlite to produce the amine at a scale of 1000 tons/year.

Cells@ORMOSIL (Biosil Method)

A number of pharmaceutical molecules, including valued paclitaxel (Taxol) are currently being produced in small scale over cells entrapped in a thin siliceous layer, thanks to the Biosil method (Figure 3), obtained by spraying aqueous TEOS over a suspension of living cells.[16]

The conceptual base of the approach—the use of functional cells or cell aggregates as a highly specialised laboratory for producing the desired substances—has enormous practical consequences; the cells, in fact, are a complete and natural system encompassing, per se, the entire enzymatic chain and yielding specific molecules from elemental substrates.

Furthermore, the process is general and versatile: gas-phase silicon alkoxides react with the wet surface of cells, affording a mechanically stable and homogeneous layer of amorphous SiO_2 modified by Si−R and Si−H bonds; the layer does not suppress cell viability or functionality (allowing porosity control) while it provides important immunological protection (by tailored exclusion of access to macromolecules above a certain threshold pore size).

Representative Example with *Coronilla vaginalis* L Cells. An ordinary fabric of glass fibers was cut into disks of about 25-mm diameter. These were hydrolysed by fluxing steam for 2 h. A 1/1 $Si(OEt)_4/CH_3SiH(OEt)_2$ ethanol solution with nominal SiO_2 concentration = 100 g/dm^3 was hydrolysed with stoichiometric H_2O, OR/H_2O = 0.5 molar ratio, and set aside until achievement of viscosity = 100 Pas.

The disks dipped into the solution were extracted at a rate of 1 mm/s. These materials, consolidated over 15 days at 40 °C, show that the glass fibers are coated by a deposit of amorphous and porous SiO_2-like material still holding Si−H and $Si-CH_3$ moieties. A cell suspension culture of *C. vaginalis* L. was used to soak the sterile disks; the operation was performed under sterile conditions, leaving the single disks in Petri dishes filled with the cell culture for 3 days on a rotary shaker at 90 rpm, at 25°C, with a 12-h photoperiod.

Single disks were washed on the surface, to eliminate any nontrapped cell load. The disks were dipped into a SiO_2 sterile sol suspension. This colloidal suspension, with a particle diameter of 40 nm, was buffered at pH 5.7 with phosphatic alkaline salts and diluted with distilled water to a nominal SiO_2 concentration of 20 g/dm^3.

The disks, extracted at a rate of 1 mm s^{-1}, were mounted on a rack and introduced into a glass reactor. The reactor was supplied with a gas flow of air saturated by $Si(OEt)_4$ and $CH_3SiH(OEt)_2$ from an 80/20 molar ratio solution thermostated at 85 °C. Total gas flow was 15 mL min^{-1} per

(16) (a) Cappelletti, E. M.; Carturan, G.; Piovan, A. Production of secondary metabolites with plant cells immobilized in a porous inorganic support. U.S. Patent 5,998,162, December 7, 1999. See also the recent review: (b) Carturan, G.; Dal Toso, R.; Boninsegna, S.; Dal Monte, R. *J. Mater. Chem.* **2004**, *14*, 2087.

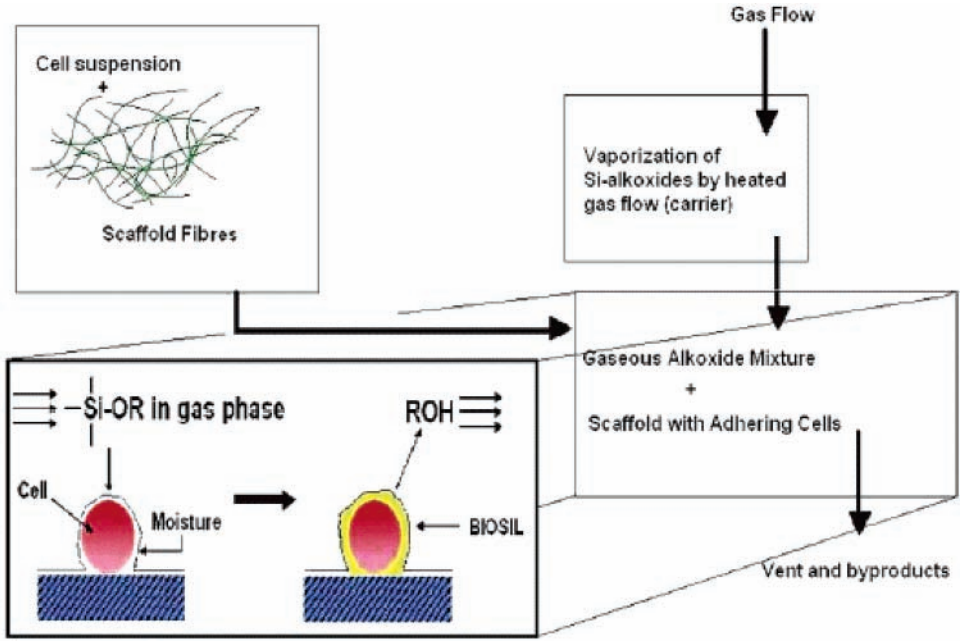
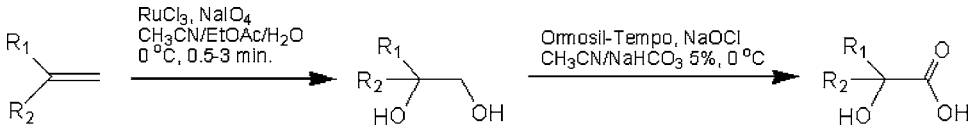


Figure 3. **Biosil process; Si−OR = alkoxide precursors, ROH = reaction byproducts (reproduced from Carturan, G.; Dal Toso, R.; Boninsegna, S.; Dal Monte, R. *J. Mater. Chem.* 2004, *14*, 2087 with permission from the Royal Society of Chemistry).**

Scheme 4. **Readily available olefins converted to valued α-hydroxyacids in two catalytic steps only (reproduced from Gancitano, P.; Ciriminna, R.; Testa, M. L.; Fidalgo, A.; Ilharco, L. M.; Pagliaro, M. *Org. Biomol. Chem.* 2005, *3*, 2389 with permission from the Royal Society of Chemistry)**



125 cm^2 of the geometrical surface of the disks. Treatment was continued for 3 min; then, using the same total gas flow, disks were treated for 2 min with air saturated with steam by bubbling into water thermostated at 70 °C. Cells in the glass fiber disk were observed by SEM and appeared to be immobilised by the SiO_2-like deposit.

Exploiting the technology, the Italy-based company IRB (Istituto di ricerche biotecnologiche) aims to license the technology and start production of taxol and other anticancer drugs over sol−gel-entrapped cells of *Taxus brevifolia*.

Promising Catalysts

Several sol−gel entrapped catalysts are likely to soon find commercial applications. A variety of transition metal catalysts physically entrapped in silica matrixes as ion pairs generated from the metal halides and quaternary ammonium or phosphonium salts, developed in the mid 1990s by Avnir and Blum, resulted in truly heterogeneous, stable, and selective mediators for a number of reactions, including hydrogenation, hydroformylation, and double bond migration conversions.[17]

The resulting sol−gel catalysts usually proved more stable and *versatile* under ambient conditions than their homogeneous analogues. For example, a remarkable asymmetric hydrogenation of prochiral itaconic acid over sol−gel entrapped (−)-Ru−BINAP in water becomes possible[18] which cannot occur with the non-entrapped, water-insoluble catalyst.

Another important highly selective and stable hydroformylation sol−gel catalyst is made of silica-supported Rh covalently bound to supported Xantphos family of ligands.[19] By incorporating monoliths of the sol−gel doped material into the paddles of an autoclave stirrer, the catalyst (Rotacat) can be used in a *continuous* liquid flow process. A single sample of this catalyst was used for a variety of different hydroformylation reactions under widely varying conditions over a period of more than a year, still retaining its selective activity.

Finally, extremely valuable α-hydroxy acids can now be conveniently synthesised with relevant selectivity enhancement using a sol−gel hydrophobized nanostructured silica matrix doped with the organocatalyst TEMPO (TEMPOrGel), coupled with rapid RuO_4-mediated olefin dihydroxylation (Scheme 4).[20]

The porous structure of the fully methyl-modified silica xerogel dictates accessibility of the diol molecules to the

(17) Blum, J.; Avnir, D.; Schumann, H. *CHEMTECH* **1999**, *29* (2), 32.

(18) See ref 17. In a typical series of experiments at 80 °C and 10 atm H_2, using 2.2 mmol substrate and 3.1 × 10^{-2} mmol sol−gel-entrapped (−)-Ru−BINAP in 4 mL of H_2O, the yields (and op) of the resulting (+)-2-methylsuccinic acid in the first four runs of 24 h were 100 (52), 98 (50), 95 (46), and 90% (41%), respectively.

(19) Sandee, A. J.; Reek, J. N. H.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *J. Am. Chem. Soc.* **2001**, *123*, 8468.

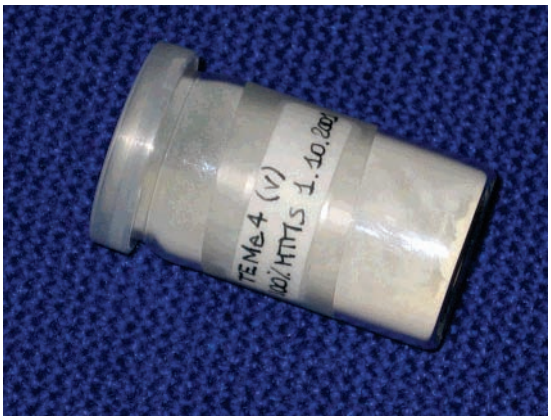


Figure 4. **TEMPOrGel: an off-the-shelf oxidation catalyst yielding valuable aldehydes, ketones, or carboxylates, depending on the reaction conditions.**

entrapped catalyst, limiting oxidative cleavage, and at the same time prevents catalyst deactivation (Figure 4).

Preparation of TEMPOrGel. The molar ratio in the precursor sol was set at Si:MeOH:H_2O:F^- = 1:3:8:0.017. **TEMPOrGel** was prepared by dissolving APTMS (1.25 mL, 6.9 mmol) in MeOH (2.6 mL) in a double-necked round-bottom flask, bringing the pH to 7 with concentrated HCl (10 μl, 1 M) followed by the addition of 4-oxo-TEMPO (189 mg, 1 mmol) and $NaBH_3CN$ (33 mg, 0.5 mmol), keeping the mixture under N_2 atmosphere. After 48 h under fast stirring at room temperature, the $NaBH_3CN$ excess was destroyed by adding aqueous HCl (143 μl, 7 M) followed by MTMS (5.82 mL, 40 mmol), MeOH (1 mL), H_2O (5.8 mL, 322 mmol), and aqueous NaF (0.75 mL, 1 M). The mixture, stirred using a Vortex agitator, gelled rapidly. The alcogel obtained was cooled at 0 °C in an ice bath for 30 min, sealed, and left to age at room temperature for 24 h after which it was dried in an oven at 60 °C for 5 days. The resulting orange xerogel was washed three times with dichloromethane under reflux, dried again at 60 °C, and powdered in a mortar. The catalytic load was 0.67 mmol radical/g.

Doped ORMOSIL recently opened the route to the use of water as reaction medium for catalytic organic reactions by simply emulsifying the organic reactants (all hydrophobic). The hydrophobic substrate is emulsified in water and subjected to an organometallic catalyst, which is entrapped within a partially hydrophobized sol−gel matrix. The surfactant molecules, which carry the hydrophobic substrate, adsorb/desorb reversibly on the surface of the sol−gel matrix, breaking the micellar structure, spilling their substrate load into the porous medium that contains the catalyst. A catalytic reaction then takes place within the ceramic material to form the desired products that are extracted by the desorbing surfactant, carrying the emulsified product back into the solution.

Preparation of the ORMOSIL-Entrapped Catalyst $RhCl_3$. A solution of ethyltriethoxyorthosilicate (0.36 mL, 1.68 mmol; ETOS) in EtOH (2.0 mL) was hydrolysed by vigorous stirring with triply distilled water (0.12 mL; TDW) and HCl (0.018 mL; 1 M) at 60 °C for 20 h. The resulting solution was added to (5.0 mL, 33.6 mmol) of tetramethyl orthosilicate {[ETOS]:[TMOS] = 1:20} that was prehydrolysed with TDW (4.0 mL) at 25 °C for 2 h. Methyltrioctylammonium chloride (65 mg, 0.16 mmol; Aliquat 336) and $RhCl_3 \cdot 3H_2O$ (43 mg, 0.16 mmol) in MeOH (5.0 mL) was added to the combined solutions. Gelation occurred within 1−2 days, and the resulting material was dried at 0.5 mmHg for 24 h at 25 °C and for an additional 12 h at 78 °C. The xerogel formed was heated under reflux for 30 min with CH_2Cl_2 (20 mL), dried at 0.5 mm for 3 h, sonicated with the same solvent for 30 min, and dried again (3 h), which yielded the final ceramic catalyst **1** (2.64 g).

In this manner, a *general* reaction procedure using a rhodium-doped 10−20% alkylated silica matrix in an elegant three-phase emulsion solid transfer process (EST) was demonstrated for hydrogenations converting alkenes, alkynes, aromatic C=C bonds, cyano and nitro groups and recently extended to hydrophormylation of alkenes with reaction yields from ca. 62 to 99%.[21] Upon reaction, the heterogenized catalyst can be easily separated from the reaction mixture by filtration and recycling.

Outlook and Conclusions

In a recent review[3] Tyler McQuade emphasized how "inorganic supports, as a rule, lack the synthetic *flexibility* of organic shells. This deficiency may limit their broad use".

By overcoming exactly *this* limitation, ORMOSIL affords a sort of ideal integration between the excellent physical and chemical stability of silica with the immense versatility provided by the organic modification of the inorganic silica structure.[22]

In practice, pharmaceutical companies can now rely on sol−gel-entrapped catalysts both for rapidly generating new drug candidates and to screen these candidates for toxicity. Yet much awaits to be accomplished.

For instance, the EST method needs urgent extension to other catalytic reactions under different conditions with the development of different sol−gel catalysts for other relevant conversions employed in fine chemicals production besides reduction.

Similarly, enzymes do not merely complement the transition states of the uncatalysed reactions, but rather they enter into reactions with substrates by covalent bond formation.[23] Our current broader picture of the physicochemical factors governing the chemical behaviour of ORMOSIL reveals that chemical modification of the sol cage does indeed alter the chemical properties of the entrapped dopant.[22] Learning to master *this* interaction for different enzymes might thus lead to replicating the outstanding results obtained with entrapped lipase.

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In conclusion, sol−gel ORMOSIL-entrapped catalysts are emerging as an advantageous technology capable of providing the fine chemicals and pharmaceutical industry with a number of efficient new solutions to face the challenges posed by the enhanced pace of innovation *and* sustainability, and eventually to make chemistry not only environmentally benign but also more efficient.

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