



Sol-gel catalysts for synthetic organic chemistry: milestones in 30 years of successful innovation

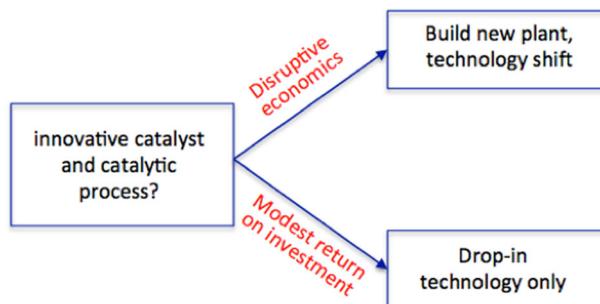
Mario Pagliaro¹

Received: 21 September 2019 / Accepted: 24 February 2020
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Abstract

First commercialized in the second half of the 1990s as organosilica-entrapped lipases, sol-gel catalysts share several unique properties that make them ideally suited for process chemistry, namely synthetic organic chemistry in the fine chemicals industry. Is their application potential fully realized? What are the obstacles to their widespread uptake in the specialty and fine chemicals industry? Can they also be employed in visible-light photocatalysis?

Graphical Abstract



Keywords Sol-gel catalyst · Heterogeneous catalysis · Synthetic organic chemistry · Flow chemistry

Highlights

- Sol-gel catalysts share several unique properties that make them ideally suited for process chemistry.
- With their high activity and ultralow leaching, these catalysts can often displace homogeneous catalysts as drop-in replacements, requiring little or no changes to existing processes.
- Production costs lower, thanks to streamlined chemical processes requiring no expensive catalyst-product separation.
- Sol-gel catalysts are increasingly used by industry but their application potential is far from being fully realized.

1 Introduction

From metal nanoparticles to organometallic catalysis, from biocatalysis through to organo-, electro-, and photocatalysis, virtually all domains of catalysis have been affected by the introduction of sol-gel entrapped catalysts more than 25 years ago. Surprisingly, the first catalytic species to be encapsulated in the early 1990s were various

✉ Mario Pagliaro
mario.pagliaro@cnr.it

¹ Istituto per lo Studio dei Materiali Nanostrutturati, CNR, via U. La Malfa 153, 0146 Palermo, Italy

methanol-resistant enzymes entrapped in transparent silica xerogels obtained by mixing a solution of an enzyme with tetramethyl orthosilicate at room temperature followed by gelation and drying [1].

In the same year, López et al. in Mexico reported a hydrogenation catalyst comprised of “ruthenium incorporated in the silica network” [2]. Comparing its performance in the hydrogenation of *o*-xylene with that of Ru impregnated on silica and observing enhanced stability for the sol–gel catalyst, the team still used the Ru/SiO₂ formula to refer to the sol–gel catalyst. Surface impregnation and sol–gel encapsulation, however, are “completely different phenomena” [3]. Hence, shortly afterward Avnir introduced the more informative “catalyst@SiO₂” formula to indicate sol–gel entrapped catalysts [3].

In 1993, Rosenfeld et al. reported the first transition metal (Rh, Pt, and Co) quaternary ammonium ion pairs entrapped in SiO₂ as hydrogen transfer catalysts in a number of different reactions [4]. The catalysts were found to be highly efficient and recyclable, a most important feature in light of forthcoming practical applications.

The use of the sol–gel process to prepare high surface area metal oxides to be used as catalyst supports had been widely investigated in the 1980s. In 1992, scholars in Spain published one of the first reviews on the application of the sol–gel methods to catalyst preparation [5]. “The method,” the team emphasized, “allows control of the texture, composition, homogeneity, and structural properties of solids, and makes possible the production of tailored materials such as dispersed metals, oxidic catalysts and chemically modified supports” [5].

We briefly recall that in 1990, Yanagisawa et al. had published the synthesis of mesoporous silica using the surfactant-template sol–gel process [6]. The “1 nm prison” of zeolite microporosity was finally escaped by obtaining calcined SiO₂ networks with “micro pores 2–4 nm in diameter” and surface area of 900 m² g⁻¹ [6].

Six years later, Kröcher et al. reported a periodic mesoporous “hybrid” silica functionalized with a Ru catalyst, obtained via sol–gel co-condensation of RuCl₂X₃ [X = Ph₂P(CH₂)₂Si(OEt)₃, Me₂P(CH₂)₂Si(OEt)₃] with Si(OEt)₄, capable of mediating the synthesis of *N,N*-dimethylformamide from CO₂, H₂, and dimethylamine under supercritical conditions with full selectivity at turnover numbers of up to 110,800 [7].

In early 1995, Reetz’s et al. reported the discovery that lipases entrapped in organically modified silica (ORMOSIL) produced by the fluoride-catalyzed hydrolysis of mixtures of RSi(OCH₃)₃ and Si(OCH₃)₄ and additives such as polyvinyl alcohol or proteins yield solid catalysts with esterification activities close to hundredfold (88) higher when compared with free enzyme powders [8, 9]. The same team found that to be easily recycled, the lipase@ORMOSIL material needs to be fixed on a stable porous carrier. A few months later, these materials became the first sol–gel catalysts to be successfully commercialized [10].

Excellent reviews [11] and book chapters [12] have been published and continue to regularly appear in the literature [13] following rapid advances in the field. Table 1 summarizes selected milestones in the development of sol–gel catalysts that will be crucially important for synthetic organic chemistry.

In this account, we offer a critical and practice-oriented perspective on the development of sol–gel catalysts for synthetic organic chemistry.

What are the main advantages of these materials? Do they only stem from the possibility to heterogenize homogeneous catalysts and streamline synthetic processes? Is the application potential of these materials fully realized? What are the obstacles to their widespread uptake in the specialty and fine chemicals industry?

Besides substantiating the arguments of nanochemistry pioneers calling for the obsolescence of the single discipline “silos” approach to research in chemistry [14, 15], the historical development of sol–gel catalysis has numerous

Table 1 Selected milestones in the development of sol–gel catalysts for synthetic organic chemistry

Year	Catalyst	Reaction/New route
1992	Glucose oxidase, peroxidase, etc.@SiO ₂	First report of enzyme sol–gel entrapment [1]
1992	Ru@SiO ₂	<i>ortho</i> -Xylene hydrogenation [2]
1993	[R ₄ N] ⁺ [MX _n] ⁻ @SiO ₂ (M = Rh, Pt, Co, X = halide, and [R ₄ N] ⁺ = tetraalkylammonium ion)	Hydrogenation of olefins, hydroformylation of cyclohexene, double bond migration in allylic compounds, etc. [4]
1995	Lipase@ORMOSIL	Esterification of lauric acid with <i>n</i> -octanol, kinetic resolution of 1-phenylethanol [8]
1996	RuCl ₂ X ₃ (X = Me ₂ P(CH ₂) ₂ SiO _n)@SiO ₂	Synthesis of <i>N,N</i> -dimethylformamide from CO ₂ , H ₂ , and dimethylamine [7]
2000	TEMPO-4-imino-(3-(CH ₂) ₃ SiO _n)@SiO ₂	Selective oxidation of glucose to glucuronate [19]
2002	TEMPO-4-imino-(3-(CH ₂) ₃ SiO _n)@ORMOSIL	Anelli–Montanari selective oxidation of alcohols [20, 21]
2002	Horseradish peroxidase@SiO ₂	General route for sol–gel encapsulation of labile enzymes [32]

lessons to teach to scholars engaged in reshaping chemistry education [16].

2 Heterogeneous catalysis for synthetic organic chemistry

The transition from homogeneous to heterogeneous catalysis, possibly under flow conditions, is highly desirable, but most solid catalysts available for synthetic organic chemistry applications are unstable (leaching active species) and considerably less active than their homogeneous counterparts. In a highly cited recent study devoted to identifying the reasons why industry would not use immobilized transition metal catalysts, industrial and academic researchers emphasized for instance that immobilized palladium catalysts used for C–C bond-forming reactions are “invariably converted to nanoparticles after the first run” [17].

“To my knowledge”, Cole-Hamilton wrote 13 years ago in a study summarizing new approaches to catalyst separation and recovery, “the only commercial example of a homogeneous catalyst heterogenized on a solid support is the carbonylation of methanol using $[\text{RhI}_2(\text{CO})_2]^-$ electrostatically bound to an ion exchange resin. However, in this case leaching cannot be avoided. The plant in Japan therefore uses a guard bed of fresh ion exchange resin downstream of the reaction bed to readsorb any $[\text{RhI}_2(\text{CO})_2]^-$ that dissolves. After a period of time, the guard-bed resin, now loaded with rhodium, is cycled to become the catalyst bed” [18].

Following the discovery that the nitroxyl radical TEMPO (2,2,6,6-tetramethylpiperidine 1-oxyl) moiety entrapped in sol–gel silica is an excellent recyclable catalyst for the selective oxidation of glucose to glucuronic acid [19], we were convinced that sol–gel technology could provide the required robust and active catalysts to actually produce fine chemicals.

Called SiliaCat TEMPO, the first such catalytic ORMOSIL is a versatile, selective, and stable alcohol oxidation catalyst [20, 21]. The catalyst, for example, quickly affords almost quantitative (97%) conversion of benzyl alcohol to pure benzaldehyde at room temperature, without the need for corrosive KBr as a cocatalyst at low temperature (0 °C) [22]. For comparison, the same oxidative reaction over resin-immobilized TEMPO under flow required cooling at 0 °C and the use of KBr as a cocatalyst for optimal yields and selectivity.

In a number of fundamental studies coauthored together with Ilharco, Fidalgo, Pandarus, Béland, Avnir, Bolm, and Kaliaguine, we identified the reasons for the enhanced activity of the stable, ORMOSIL-entrapped catalyst when compared with the latter and other surface-derivatized TEMPO-based catalysts [23, 24]. What is relevant here is that such enhanced stability and unique versatility continues

to be reported in independent studies aimed at applying the catalyst for new conversions of practical synthetic relevance.

For example, during recent doctoral work, scholars in the UK reported that in the aerobic oxidation of 1-phenylethanol, and 2-octanol to the respective aldehyde and keto derivatives carried out in the presence of 0.1 mol% nitric acid under 40 bar air at 60 °C, SiliaCat TEMPO is more selective and stable than most other heterogeneous TEMPO catalysts (Fig. 1) [25].

“Very little loss in activity” is observed when recycling the catalyst over three consecutive runs, for both 1-phenylethanol, and 2-octanol, leading authors to conclude that “SiliaCat TEMPO is more stable than covalently tethered TEMPO prepared by the method of immobilizing 3-aminopropyltriethoxysilane on silica, and then tethering TEMPO via reductive amination” [25].

The ORMOSIL network is open to external reactants and is mesoporous. Hence, it can be accessed by polymeric molecules. This was demonstrated in 2019 by researchers at a healthcare company in South Korea who reported the successful conversion of bacterial cellulose into cellulose nanofiber (CNF) [26].

The conventional method of synthesizing CNF, namely TEMPO-oxidized cellulose fibers, uses aqueous hypochlorite buffered at pH 10–11 and a catalytic amount of homogeneous TEMPO and NaBr [27]. The method, the industrial team noted, “can be scaled but with significant limitations due to difficult washing process via repetitive centrifugation to separate the product from reactants when treating large amounts of cellulose” [26].

The complete removal of the reactants is especially important in any healthcare or cosmetic application, which will preferably use bacterial cellulose due to its unique properties such as biocompatibility, high crystallinity, large surface area, and elasticity.

The one-pot synthesis of CNF over SiliaCat TEMPO employs simple filtration instead of centrifugation after the oxidation reaction (Fig. 2). Comparison of CNFs obtained via the heterogeneous and homogeneous routes clearly shows enhanced physical and chemical properties for CNF obtained over SiliaCat TEMPO.

Indeed, while the average diameter of the bacterial CNFs in the conventional homogeneous oxidation process decreased from ~100 nm to 30–50 nm after oxidation, the average diameter of CNF obtained using SiliaCat TEMPO was found to be about 80 nm (Fig. 3), much closer to the diameter of the original cellulose fibers, with significant improvement of the rheological and flow properties of a material that will find widespread application in fields as diverse as cosmetics, electric vehicle manufacturing, and flexible electronics [28].

For example, the ability to block particulate matter (PM) on the skin surface is due to the nanofibrous structure of CNF

Fig. 1 Conversion of 2-octanol and 1-phenylethanol over SiliaCat TEMPO (top) and recycling of the catalyst in three consecutive reaction runs (bottom). [Image courtesy of Dr N. Hughes, reproduced from [25], with kind permission]

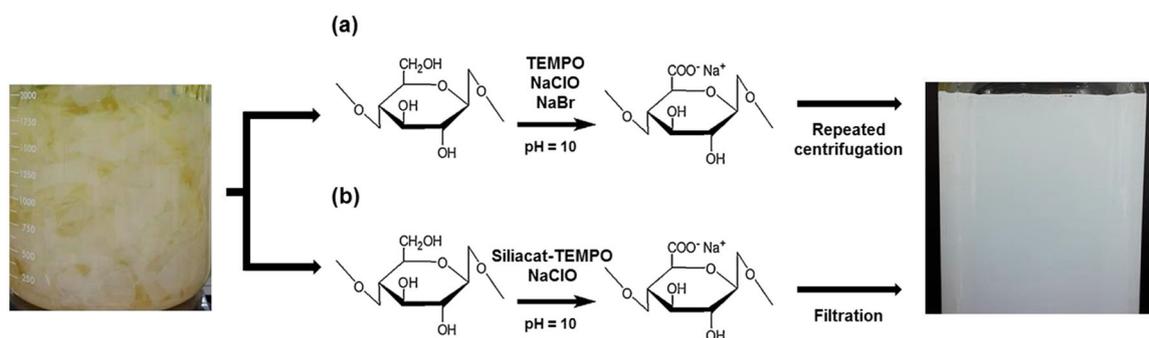
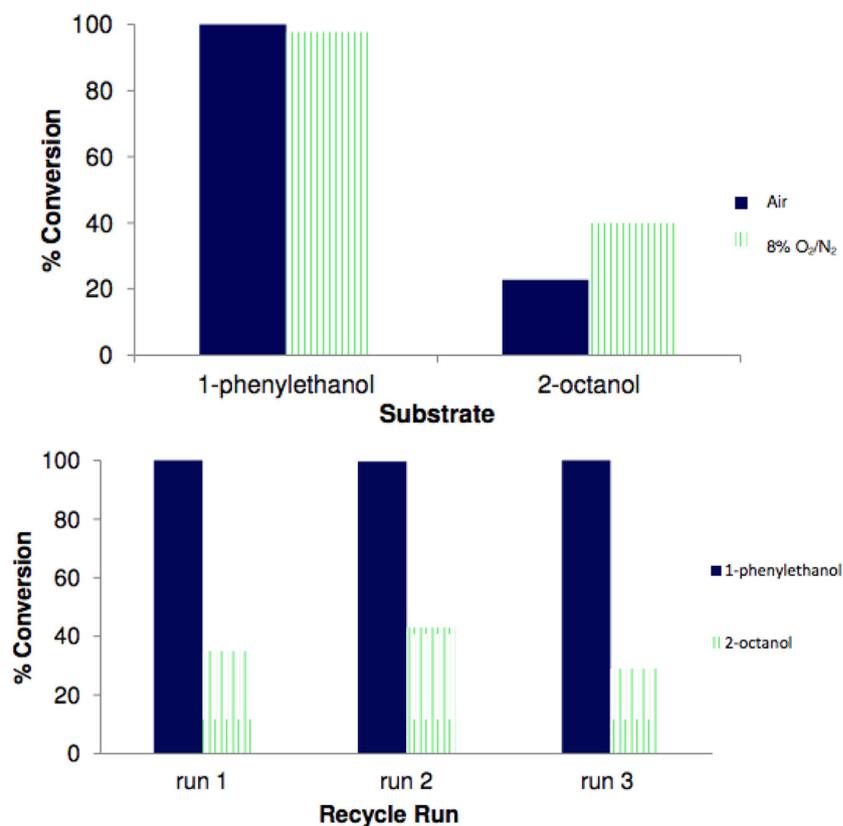


Fig. 2 Schematic showing the synthesis of TEMPO-oxidized cellulose nanofibers (TOCNs) via the (a) conventional process and (b) one-pot heterogeneously catalyzed process. [Reproduced from [26], with kind permission]

and to the high carboxylate content, which confers to the carboxy CNFs excellent water-absorbing ability, resulting in a low resistance to water, as well as the ability to form a network of nanofibers on the skin surface, blocking PM.

Testing an oil-in-water (o/w) emulsion containing the newly obtained CNF (TOCNs) at different concentration (the contact angle of the water over time rapidly decreased as the TOCNs' content in the o/w emulsion increases, Fig. 4a), the team found that the said emulsion prevents carbon black from entering into the microgrooves on the surface of the skin, and at the same time allows it to be easily removed (Fig. 4b).

“It is anticipated—wrote the aforementioned researchers at the healthcare company—that due to its simplicity,

efficiency, and ease of use, the proposed one-pot synthesis method will be employed in production scenarios to prepare production quantities of bio-based polymer nanofibers” [26].

The homogeneously catalyzed process affords CNF at a cost of \$90–100/kg [28]. Said high cost is also due to the high cost of processing the hypochlorite dilute solution containing dissolved TEMPO and sodium bromide after reaction. Separating the nitroxyl radicals in solution after the oxidation, in fact, is an expensive, multistep task [29].

Thanks to SiliaCat TEMPO or to another sol-derived material such as Karimi's catalyst (TEMPO@SiO₂@Fe₃O₄) [30], CNF manufacturers can now switch to heterogeneous catalysis, thereby dramatically reducing production costs

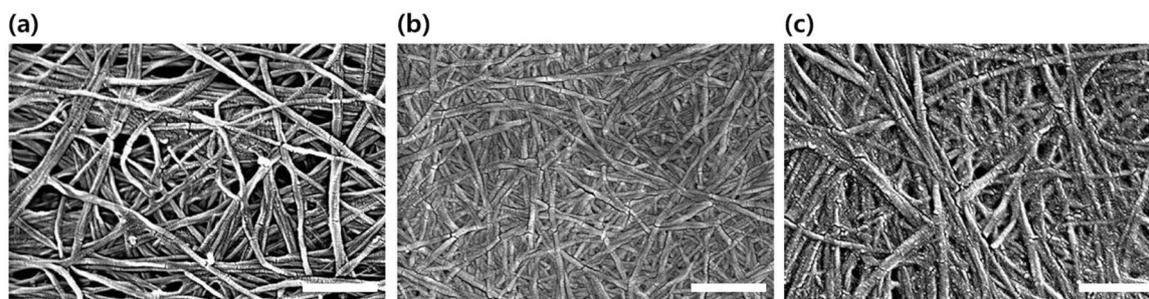


Fig. 3 SEM images of (a) pure bacterial cellulose, (b) TEMPO-oxidized cellulose nanofibers via conventional synthesis (C-TOCNs), and (c) TEMPO-oxidized cellulose nanofibers obtained after the one-

pot synthesis over SiliaCat TEMPO (O-TOCNs). Scale bar = 500 nm. [Reproduced from [26], with kind permission]

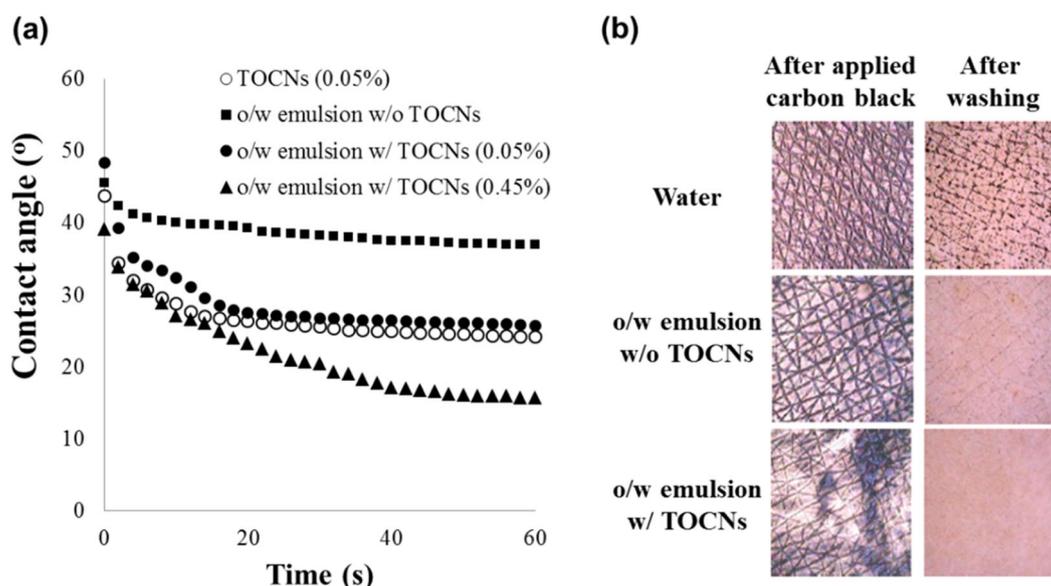


Fig. 4 a Changes in the contact angle of various concentrations of TEMPO-oxidized cellulose nanofibers (TOCNs) obtained via heterogeneous oxidation over SiliaCat TEMPO in o/w emulsion at different

concentrations over time and b the washing experiment conducted to remove the carbon black from porcine skin. [Reproduced from [26], with kind permission]

while improving the properties of the resulting CNF, and opening the route to new, high value applications of this exceptional material [31].

Being five times stronger and one fifth lighter than steel, CNF in principle could replace steel and even aluminum in making new, mechanically strong and ultralight composite materials. Dispersed in water, CNF affords transparent films with high optical transparency and low haze called “transparent nanopaper” and is ideally suited as a substrate for flexible electronics devices.

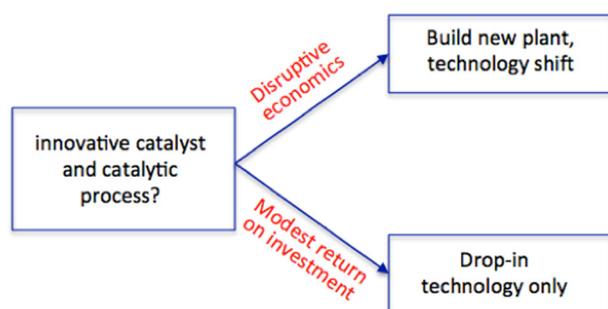
3 A nanochemistry tour-de-force

The sol–gel route for the entrapment of metal nanoparticles in ORMOSIL matrices is similar to the biocompatible route

for sol–gel enzyme encapsulation in biohybrid silica developed by Ferrer et al. [32]. The resulting catalytic ORMOSILs doped with palladium [33] and platinum [34] NPs are broad scope heterogeneous catalysts for synthetic organic chemistry.

The chemical and physical origins of the superior activity of these catalysts has been at least partly identified [35, 36], including the enhanced performance under continuous-flow conditions [37]. Their use in reactions as diverse as highly selective hydrogenation, C–C cross coupling, hydrogenolysis, and oxidation reactions was reviewed in 2015 [38].

What is relevant to this account focusing on practical applicability is a number of subsequent advances that make them suitable as drop-in replacements for many homogeneously and heterogeneously catalyzed processes of relevance to the fine and specialty chemicals industries.



Scheme 1 Two options exist for any newly developed catalyst and catalytic process of relevance to the chemical industry

Coauthoring along with Teles and Della Pina one of the first reviews on the industrial applications of gold catalysts [39], we highlighted that there are only two possible options for a new catalyst seeking commercial use (Scheme 1). Either the new catalyst enables the development of an entirely new process with different raw materials and breakthrough economics, which will lead to construction of a dedicated plant, or the new catalyst uses the same raw materials as the conventional catalyst and offers a moderate economic improvement. In the latter case, the catalyst will be used by industry only if it can be developed as a drop-in for existing processes.

Silica-based sol–gel entrapped catalysts offer several key advantages that make them relevant for practical applications [38]. Their synthesis is easily scalable from mg up to multiton scale with high and reproducible catalyst loading.

The resulting glasses are chemical sponges (reagent concentrated at the surface of the material) featuring uniquely high thermal stability and robustness due to the rigid and highly porous structure favoring reactant diffusion. Finally, silica and ORMOSIL do not swell in organic solvent or in water, are air stable, require no inert conditions, and are easily removed by simple filtration, being free flowing powders without any static charge. Furthermore, these catalysts are nonpyrophoric. For example, while frequently used palladium on charcoal (Pd/C) hydrogenation and hydrogenolysis catalyst is highly pyrophoric, SiliaCat Pd(0) is nonpyrophoric [40].

Returning to the industrial relevance of newly developed catalysts, replacing low-cost (but toxic) Ni catalysts commonly used in commercial squalene hydrogenation with a solid palladium catalyst would be highly desirable. Extensive purification is required to remove most Ni leached into the squalane product to meet maximum acceptable levels of Ni compounds (Ni^{2+} and Ni^0) in a cosmetic product (0.2 ppm). Indeed, very often cosmetic products contain much higher (9–10 ppm) amounts of Ni [41].

Derived from squalene via catalytic hydrogenation, squalane is a nonirritant oil with a unique ability to penetrate the human skin, imparting flexibility and smoothness without an unpleasant greasy feel. Currently, the manufacturing

process of squalane via squalene hydrogenation accounts for ~40% of the overall production cost [41].

A lower cost hydrogenation process would allow wider utilization of sustainable phytosqualene from olive oil and farnesene (sugar cane).

The SiliaCat Pd(0) xerogel powder is capable of mediating the highly selective hydrogenation of 92% pure squalene dissolved in ethanol (but not of 82% olive squalene) with ultralow leaching of Pd in the isolated crude product (less than 0.002% Pd) under mild conditions (1 mol % Pd catalyst, 0.33 M squalene in EtOH, 5 h, 1 atm H_2 at 50 °C). Furthermore, the catalyst reused in five consecutive reaction runs retains its full activity, achieving each time complete conversion in 5 h [42].

Alas (see Scheme 1), also in the case of squalane manufacturing via squalene hydrogenation, industry is interested in drop-in replacement technology only. Industrial hydrogenation of squalene over Ni-based catalysts takes place under solvent-free conditions, the only approach of practical relevance to industry.

Squalene of even low purity, such as 82% olive-derived squalene, can be selectively and entirely converted to squalane under solvent-free and mild reaction conditions of 3 bar H_2 and 70 °C using the spherical version of the sol–gel-entrapped Pd catalyst SiliaCat Pd(0) [43]. Reused successfully in eight consecutive cycles, with very low palladium leaching (<2 ppm), the new spherical catalyst opens the route to the hydrogenation of sustainable phytosqualene in place of shark liver oil squalene.

First suggested in 2011 (“the fabrication of organosilica materials in nanospherical morphology is of even higher interest in catalysis, drug delivery, and biochemistry” [44]), ORMOSIL sol–gel catalysts with spherical morphology enable also the solvent-free hydrosilylation of a variety of olefins, opening the route to lower cost Pt-free silicones.

Directly demonstrated on a 150 mmol scale using an ultralow amount (0.025 mol% Pt) of spherical SiliaCat Pt(0) with the silane in a slight excess (1.25–1.50 equiv.), under mild reaction conditions (75 °C), catalysis is truly heterogeneous, with palladium leaching values < 5 ppm [45].

Employed in the hydrosilylation of 1-octene with triethoxysilane, with complete conversion of olefin in silylated product with 98% yield within 1 h, the spherical sol–gel catalyst affords significantly higher yield in functionalised silane than 5 wt% Pt/C and 5 wt% Pt/ Al_2O_3 commercial catalysts; and significantly higher activity than both 5 wt% Pt/ SiO_2 (Escat 2351) and 2.3 wt% Pt EnCat 40.

In four consecutive multigram catalytic syntheses starting from 660 mmol of 1-octadecene (167 g) with 1.25 equiv. of chlorodimethylsilane over 0.025 mol% Pt of SiliaCat Pt(0) (0.66 g) under optimized reaction conditions, no significant decrease in yield was observed for three

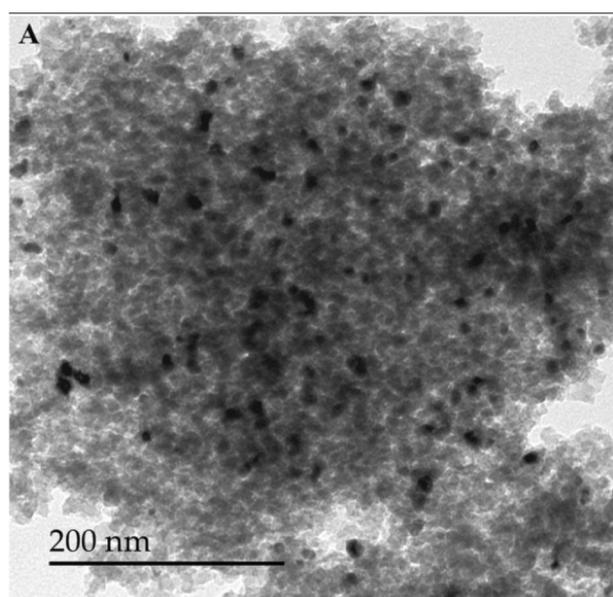


Fig. 5 TEM image of spherical SiliaCat Pt after the reusability test. [Reproduced from [45], with kind permission]

consecutive reaction runs. The fourth reaction run proceeded with a significant decrease in yield (65%).

The latter deactivation is not due to sintering of the Pt nanoparticles whose size even after the fourth reaction run is almost unchanged (from 5–7 to 6–8 nm, Fig. 5), but rather to poisoning by HCl produced in the reaction mixture by the decomposition of excess chlorodimethylsilane.

Similarly, functionalized with Au nanoparticles, the spherical organosilica glass allows the direct, solvent-free conversion of benzyl alcohol to benzaldehyde and benzyl benzoate [46]. The process is carried out in one pot starting from benzyl alcohol using oxygen as the only oxidant under mild conditions (2 bar O₂, 100 °C) along with an ultralow amount (0.02 mol%) of Au catalyst.

Contrary to what happens with Au deposited over TiO₂ or over zeolites employed in the same solvent-free aerobic oxidation of benzyl alcohol, no toluene forms via disproportionation of benzyl alcohol into benzaldehyde, toluene, and water. Benzaldehyde is a valued fragrance and aroma, whereas benzyl benzoate is still today among the best drugs for the treatment of scabies.

Again, the spherical ORMOSIL tested for stability in six consecutive reaction runs retained its original high activity, with a slight yield reduction after the fifth cycle, mainly due to catalyst loss on filtration and washing.

4 The case for heterogeneous catalysis via sol-gel entrapped metal complexes

SiliaCat DPP-Pd is an orange powder with high selective activity in a wide variety of C–C cross-coupling reactions

[47]. The material is synthesized from a diphenylphosphine-functionalized silane, (2-(diphenylphosphino)ethyl)triethoxysilane, and methyltriethoxysilane via sol-gel hydrolysis and polycondensation in the presence of Pd(II).

As put by Juan et al. when reporting new results concerning continuous Sonogashira reaction under flow in 2012, the catalyst “costs less than other commonly used palladium sources, such as palladium acetate or Pearlman’s catalyst, while providing increased yields of valued cross-coupled products at a much faster rate than any homogeneously catalyzed process in a batch reactor” [48]. The Sonogashira reaction under flow, indeed, does not require catalyst separation from the product, drastically reducing solvent utilization in a process that quickly affords valued products thereby isolated at far lower cost.

Alcázar’s team went on to report in 2014 good to excellent conversions in several Negishi and Suzuki–Miyaura cross-coupling reactions. In most cases, products were isolated directly without chromatographic purification, whereas the use of SiliaCat DPP-Pd reduced the leaching of palladium in the final product to parts per billion [49].

In 2015, Greco et al. published a comparative study of the most common immobilized diarylphosphine- and triarylphosphine-based palladium catalysts used in C–C coupling reactions by carrying out two model Mizoroki–Heck and Suzuki–Miyaura reactions in an X-Cube flow reactor (polymer-bound Pd Tetrakis, FiberCat 1001, EnCat TPP30, and SiliaCat DPP-Pd) [50].

SiliaCat DPP-Pd showed superior leaching resistance and stability with respect to the other three catalysts, with very low levels of leached Pd (332 μg for the Mizoroki–Heck reaction and 39 μg for the Suzuki–Miyaura reaction).

Packed in a column reactor during the processing of a Mizoroki–Heck reaction using acetonitrile as solvent and triethanolamine as base, the powder SiliaCat DPP-Pd in contact with hot solvent after 120 min eventually turned black in color, pointing to the formation of metallic Pd. However, leaching was extremely low.

Indeed, Welch’s team in Canada in the course of the last 5 years (2015–2019) has demonstrated how the direct hetero(arylation) synthesis of molecular dyes used as semiconductors in organic electronics is best carried out over robust and reusable SiliaCat DPP-Pd, affording excellent yields and high-purity materials with negligible Pd-metal contamination [51].

The method, they recently wrote, can be successfully extended “to a range of different substrates and operates effectively on milligram to multigram scale reactions using reagent-grade solvents in air” [51]. The organic materials resulting from pairing of an efficient cross-coupling direct hetero(arylation) protocol and SiliaCat DPP-Pd can be dissolved in a solution and printed on substrates, including plastics and foils, with which to make either flexible organic

photovoltaic solar cells or even organic light emitting diodes for incorporation in the screens of mobile phones, laptop computers, and electronic tablets.

The need for greener syntheses in organic processes carried out by the fine chemicals industries is evident for instance by the recent case of contaminated sartans batches (angiotensin receptor blockers widely employed since the late 1980s to treat high blood pressure and congestive heart failure) recently recalled in USA [52].

The Valsartan patent, in particular, expired in 2012, opening the route to the introduction of generic alternatives, which are today widely manufactured in India and in China. The synthetic pathway to Valsartan originally published by industry includes a homogeneous Suzuki–Miyaura coupling reaction. In 2013, we reported the synthesis of the biphenyl moiety present in all sartans, carrying out the heterogeneous Suzuki–Miyaura coupling reaction mediated by 0.7 mol% SiliaCat DPP-Pd between 2-chlorobenzonitrile and 4-tolylboronic acid at 77 °C under reflux, directly scaled up from 1 to 100 g of aryl halide [53].

The yield in a coupled product achieved in 1 h by simply stirring the mixture at 700 rpm in the presence of K₂CO₃ (1.1 equiv) is 100%. The catalyst was not recyclable but leaching once again was low (<5 ppm), well below the maximum acceptable limit for palladium in parenteral drugs (10 ppm).

Two years later, Martin et al. reported the telmisartan synthesis from two different functionalized benzimidazole fragments and the biphenyl moiety [54]. Following alkylation and saponification reactions under flow, the Suzuki–Miyaura reaction is carried out over SiliaCat DPP-Pd under continuous-flow conditions at 180 °C, at a flow rate of 0.1 mL/min at 40 bar affording pure telmisartan in 81% yield in 5 min residence time. The convergent synthesis requires no intermediate purifications or solvent exchange.

5 Main obstacles to industrial adoption

To identify the main obstacles to industrial uptake of sol–gel entrapped catalysts, it is instructive to review the case of industry's adoption of heterogeneous catalysis in supercritical carbon dioxide (scCO₂).

In 2006, the excellent performance of a sol–gel entrapped ionic liquid and perruthenate (supercritical SILC, [55]), as well as that of a fluorinated sol–gel ORMOSIL doped tetrapropylammonium perruthenate (FluoRuGel), as broad scope catalysts for alcohol aerobic oxidation carried out in scCO₂ was reported [56]. The world's first continuous, multipurpose reactor for heterogeneously catalyzed fine chemicals productions conducted in scCO₂ opened at a fine chemicals company in Britain on July 2002. The first

industrial reaction run at the plant was the hydrogenation of isophorone, affording trimethylcyclohexanone whose quality (haze, acidity, residual substrate, and trimethylcyclohexanol) largely exceeded customer specifications [57]. However, the process was discontinued and the plant is not currently operational because, as explained by a company's managers, “there is no current commercial advantage” for the company “in using this green technology for the manufacture of specialty chemicals at present” [57].

The overall cost of a chemical process (*C*) to manufacture a chemical product includes the intrinsic process cost (*C*_i) plus the cost of producing unwanted by-products (price of nonconformance, PONC) [58]

$$C = C_i + \text{PONC}. \quad (1)$$

To reduce cost, a company will undertake action to eliminate waste (the PONC term in the above equation) achieving a lower overall cost. In case of no effluents, such as in the zero-emission heterogeneously catalyzed hydrogenation in scCO₂ mentioned above, there is no PONC adding to the overall cost of the process. Industry will adopt the new and greener process provided that the cost of the process is significantly lower than that of the conventional process.

Otherwise, either the process will not be adopted, or it will be discontinued. This explains, for example, why selective alcohol oxidation over the FluoRuGel catalyst was not adopted or selective hydrogenation discontinued.

6 Outlook and perspectives

The fine chemical industry, including suppliers of active pharmaceutical ingredients (APIs), widely uses homogeneous catalysis to manufacture its valued products, most often relying on metal catalysts purchased by chemical companies owning proprietary metal ligands and related transition metal catalysts (used for example in asymmetric hydrogenation). Catalytic hydrogenation or hydrogenolysis over Pd/C, or over supported Ni in the case of squalene or fats and vegetable oils, are the main heterogeneously catalyzed processes in industry.

Stable, versatile, low cost, easy to handle, and safe sol–gel catalysts fit both main requirements that, in my opinion, will reshape the industry in the course of the next two decades (2020–2040) driven by societal and technology megatrends [59]: (i) the global demand for better, lighter, more durable, healthier, and greener functional products by the industry's largest customers (automotive, paints, cosmetics, personal care, and pharmaceutical sectors), and (ii) the uptake of decentralized production based on clean chemical technology.

In general, robust and mesoporous sol–gel entrapped organosilica-based catalysts are ideally suited for use in new

generation flow reactors, to which most fine chemical productions will shortly transition [60].

“The immobilization of catalysts,” as recently emphasized by a team of industrial research chemists at different pharmaceutical companies, “remains an exciting area particularly with the growth of interest in continuous manufacturing” [61].

Sol–gel catalysts comprised of enzyme, organocatalyst, and metal nanoparticle entrapped in silica and hybrid organosilica matrices briefly described in this study are increasingly being adopted by fine chemicals industries. With their high activity and ultralow leaching, these catalysts can often displace homogeneous catalysts as drop-in replacements, requiring little or no changes to existing processes, cutting production costs, thanks to streamlined chemical processes requiring no expensive catalyst–product separation. At the same time, being mesoporous, non-swelling, robust, and easily assembled in a packed bed, catalytic sol–gel glasses are uniquely well suited for application to continuous-flow chemistry processes avoiding “fouling and clogging” identified by Jensen as a crucial requirement for the uptake of solid reagents in flow catalytic processes [62].

Once again, change is not driven by environmental or safety factors, but rather by economics. Continuous-flow processing, indeed, allows production costs to be reduced to such an extent that fine chemical and pharmaceutical companies based in western Europe and North America can restart manufacturing in their home countries, after three decades in which fine chemicals and APIs were imported at low cost from India’s and China’s companies using standard batch-type reactors.

For example, switching to flow chemistry a leading API manufacturer found that “after an initial R&D approach, easy scalability at industrial plant” was possible and “with minimal investment, it has been possible to insource 100% of production volumes (instead of 40% as classical batch reactions), with negligible impact from regulatory point of view and improvement into quality and cost associated” [63].

Finally, transparent silica and organosilica glasses doped with visible-light photocatalysts hold the potential to make convenient the adoption of solar photocatalysis in the fine chemicals industry. Early examples include the SiliaSun catalyst comprised of an ORMOSIL encapsulating flower-like, nanostructured bismuth wolframate for the improved aerobic oxidation of dissolved glycerol to dihydroxyacetone [64], or of ferulic acid to vanillic acid under visible light [65] in water using only oxygen or even air at ambient pressure as the sole oxidant species.

Writing with Xu about the waste-free synthesis of fine chemicals on an industrial scale with visible light in a 2016 issue of the main process chemistry journal could seem far-fetched [66]. Three years later, the first reaction vessels

coated with a polymer photoredox catalyst enabling prolonged batch and flow photocatalysis with excellent yields, even with opaque reaction mixtures, via backside irradiation were reported [67].

Considering that the first electrocatalytic applications for highly selective and waste-free alcohol oxidations have already been reported [68], sol–gel technology is the first to make available a complete off-the-shelf catalyst platform for many types of catalytic reactions.

Acknowledgements Thanks to Rosaria Ciriminna, CNR, Valeria Pandarus and François Béland, SiliCycle, Laura M. Ilharco and Alexandra Fidalgo, Instituto Superior Técnico, David Avnir, Hebrew University of Jerusalem, Sandro Campestrini, University of Padova, Serge Kaliaguine, Université Laval, Massimo Carraro, now at the University of Sassari, Giovanni Palmisano, now at Khalifa University of Science and Technology, Francesco Parrino, now at University of Trento, Babak Karimi and Mina Ghahremani, Institute of Advanced and Basic Studies, Yi-Jun Xu, Fuzhou University, and Leonardo Palmisano, University of Palermo. Well beyond scientific collaboration I am privileged to enjoy the friendship of these eminent scholars over several years. Thanks to the organizers of the 20th International Sol-Gel Conference, St. Petersburg, August 25–30, 2019, for inviting me to give a plenary lecture on the topics of this study.

Compliance with ethical standards

Conflict of interest The author declares that he has no conflict of interest.

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