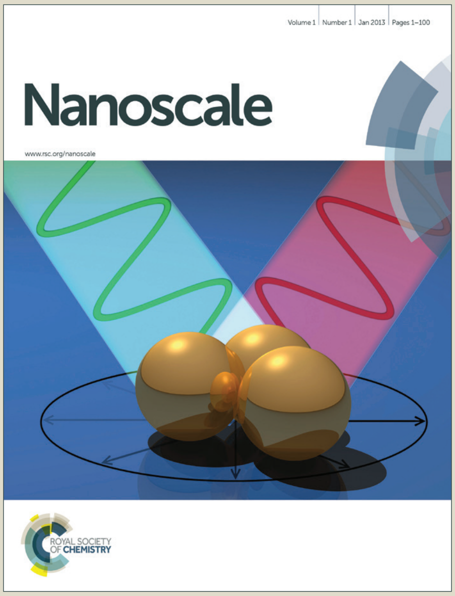
Nanoscale

Accepted Manuscript



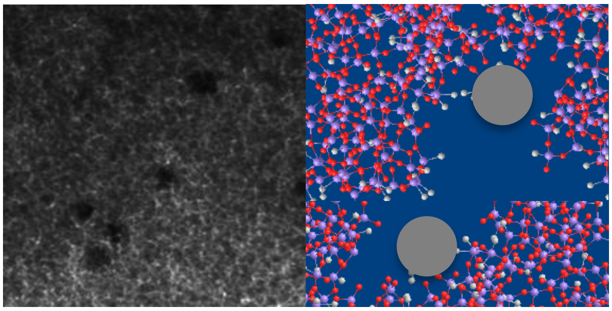
ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/nanoscale

Towards waste free organic synthesis via nanostructured hybrid silicas

Rosaria Ciriminna, Laura M. Ilharco, Valerica Pandarus, Alexandra Fidalgo, François Béland, Mario Pagliaro

Immobilization and stabilization of metal nanoparticles within an ORMOSIL amorphous structure, for highly efficient and selective heterogeneous solid catalysis.



Nanoscale (Themed collection "Hybrid Materials", 9-Jan-2014)

Towards waste free organic synthesis via nanostructured hybrid silicas

Rosaria Ciriminna,[1] Laura M. Ilharco,[2] Valerica Pandarus,[3] Alexandra Fidalgo,[2] François Béland,[3] Mario Pagliaro[1]*

[1]Istituto per lo Studio dei Materiali Nanostrutturati, CNR, via U. La Malfa 153, 90146 Palermo, Italy; [2]Centro de Química-Física Molecular and IN-Institute of Nanoscience and Nanotechnology, Instituto Superior Técnico, Complexo I, Av. Rovisco Pais 1, 1049-001 Lisboa, Portugal; [3]SiliCycle Inc., 2500, Parc-Technologique Blvd, Quebec City, Quebec Canada G1P 4S6.

Abstract

As catalysis and organic synthesis come together again, the need for stable, selective and truly heterogeneous solid catalysts for clean and efficient synthetic organic chemistry becomes urgent. Hybrid silica glasses obtained by the sol-gel nanochemistry approach can be successfully used for the waste-free synthesis of valued chemicals in various applications. This success derives from the deliberate chemical design of the hybrid nanostructures capable to immobilizing and stabilizing organocatalytic species and unstable metal nanoparticles. The highly selective activity along with broad scope and ease of application of these mesoporous materials to high-throughput reactions opens the route to faster, cleaner and more convenient processes for both small and large scale manufacturing of useful molecules.

Introduction

In an interesting historic account, Sheldon and co-workers explain how, under the mounting pressure of environmental legislation, organic synthesis and catalysis, after 150 years in isolation, have come together again.[i] Put briefly, catalysis developed as a subdiscipline of physical chemistry. With the advent of the petrochemicals industry in the 1930s, catalysis was widely used in oil refining and bulk chemicals manufacture. The fine chemicals and pharmaceuticals industries, however, remained primarily the domain of synthetic organic chemists, who were reluctant to apply catalytic alternatives to classical stoichiometric methodologies originating from the autonomous evolution of organic chemistry.

Aware of the high economic costs associated to its atom inefficient synthetic processes, affording >200 kg of waste for every kilogram of active pharmaceutical ingredient (API) manufactured,[ii] the fine chemicals and pharmaceutical industries are switching to biocatalysis and to heterogeneous catalysis.[iii] The ultimate goal of ideal organic synthesis is to replace multistep batch processes with continuous catalytic conversions that are atom,[iv] step[v] and redox[vi] economic, namely using catalysis to minimize wasteful steps, reducing the overall number of steps and also to minimize redox manipulations within a synthesis.

These are indeed the features of heterogeneous selective catalysis under flow in which the solid catalyst rapidly mediates the desired reaction, avoiding waste generation and contamination of the product with toxic catalyst residues, while the efficient mixing and excellent heat transfer in heterogeneosuly catalyzed reactions carried out in flow microreactors often lead to much higher conversions, selectivity and yields than reaction under batch.[vii]

Industry, therefore, needs supported catalysts. A question arises, however: which one to choose among the numerous different materials developed by chemists in the last five decades? Introducing a comprehensive review volume of the 2002 state of the art of recoverable catalysts, Gladysz underlined[viii] that, from the standpoint of a synthetic or process chemist, the ideal recoverable catalyst would have outstanding selective activity, not be subject to leaching and degradation, and would be easily recovered.

Yet, a decade later Cole-Hamilton could notice that most of the catalysts developed thus far suffer from severe leaching, which compromises catalyst lifetime and contaminates reaction products.[ix] One of the few large-scale processes applying supported catalysts is from the Japanese company Chiyoda that uses supported rhodium for methanol carbonylation. Leaching occurs; the rhodium is trapped on a guard bed and then the flows are reversed so that the guard bed becomes the catalyst bed.[x]

It is in this context that Avnir and coworkers in the 1985-1995 decade developed the new field of «organic chemistry within ceramic matrixes»,[xi] namely the first chemical (analytical and synthetic) applications of doped silica glasses, doped with enzymes, photoprobes and organometallic catalysts. Once sol-gel entrapped within the inner porosity of amorphous silicas, organic molecules, biomolecules, metal nanoparticles and even cells are physically and chemically stabilized, while being accessible to external reactants for chemical interaction.

Almost concomitantly, in 1995 Reetz and coworkers in Germany discovered that lipases sol-gel encapsulated in organically modified silicas (ORMOSILs), were also active and recyclable in fat esterification reactions carried out in organic solvents, with activities up to 10 times higher compared to the free enzymes in suspension.[xii] Readily commercialized by Fluka in 1996, the latter materials were the first commercial sol-gel catalysts to reach the market.

Numerous examples of green synthetic methodologies using sol-gel entrapped catalysts followed,[xiii] until the first sol-gel entrapped catalytic nanomaterials that combine the advantages of homogeneous catalysis (reactivity and selectivity) and heterogeneous catalysis (recovery and recyclability) were made commercially available.

These hybrid catalysts (trade-named Silia*Cat*) include oxidation organocatalyst TEMPO[xiv] and a series of organosilica-entrapped metal nanoparticles that open the route to nanoparticle metal catalysis of unprecedented performance, with applications including stereoselective hydrogenation of vegetable oils,[xv] carbon-carbon bond formation with ligand-free and not air sensitive catalysis,[xvi] ultraselective hydrosilylation[xvii] and hydrogenation[xviii] of alkenes, and many other reactions. In this account, we show how their successful application derives from the deliberate chemical design of the right hybrid nanostructures capable to immobilize and stabilize organocatalytic species and unstable metal nanoparticles (MNPs). We present some recent results obtained using these solid-supported catalysts under flow, and show how they allow the synthesis of fine chemicals at low cost, with minimal or no environmental impact, opening the route to truly sustainable organic synthesis. The conclusions place this progress in the context of materials chemistry actual development.

Hybrid, encapsulated catalysts

The ORMOSIL-based Silia*Cat* catalyst family is one notable example of nanochemistry in action,[xix] namely the application of synthetic chemistry to make nanostructured materials with special properties, by the merging of those porous materials with the chemistry of the encapsulated species. Their synthesis is an alternate general method whereby organometallic species, organocatalysts and noble metal nanoparticles are encapsulated within porous organosilica in a simple one-pot synthesis.

In the encapsulation of MNPs, for example, the synthetic method is similar to the biocompatible bottom-up routes for sol-gel enzymes encapsulation in biohybrid silica-based materials.[xx] It consists in a mild entrapment process, which starts with controlled distillation, in a rotavapor, of the alcohol released during the hydrolysis and co-condensation of two organosilane monomers, such as methyltriethoxysilane, $MeSi(OEt)_3$, and tetraethoxysilane, $Si(OEt)_4$. The resulting alcohol-free sol is doped with a metal salt (M^{n+}) and undergoes further polycondensation to yield a microporous hydrogel that is dried under mild conditions. The latter material undergoes reduction, also under mild conditions, to yield a nanostructured xerogel doped with M^0 nanoparticles trade-named Silia*Cat* M(0).

Sintering of traditional supported metal catalysts is caused by the mobility of the metal nanoparticles on the supporting material's surface.[xxi] The sol-gel encapsulation within the organosilica architecture prevents that mobility, because the active nanoparticles are encapsulated individually within the ORMOSIL amorphous structure of the embedding matrix (Figure 1).

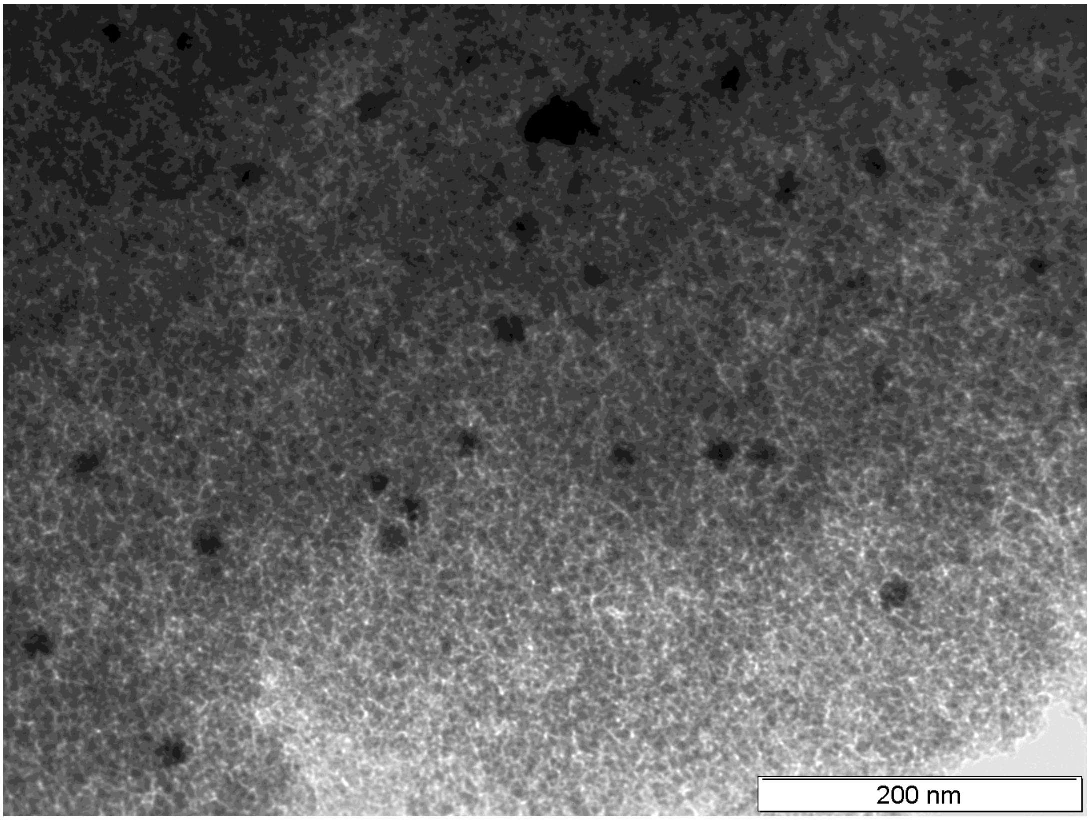


Figure 1. TEM image of Silia*Cat* Pt^0 microstructure.

The metal nanocrystallites vary in size and in density, depending on the metal, but they are very small (average diameter below 16 nm in Figure 1; but smaller by changing the sol-gel process parameters), without aggregation.

As a consequence, coalescence of small particles to larger ones, which leads to deactivation of these catalysts with typical decrease in surface area and attendant reduction in the number of active sites, is not possible. No agglomerated particles are present on the outer surfaces of the organosilica xerogel. The metal nanoparticles are accessible to reactant molecules in the encapsulated system with reduced mass transfer limitations, due to this mesoporous nature of the organosilica matrix. Overall, this allows to chemically exploiting the metal special properties that occur at the nano scale.[xxii]

The 3-D sol-gel encapsulation drastically differs from 2-D surface adsorption. In the case of entrapped molecular species, for example the stable nitroxyl radical TEMPO (2,2`,6,6`-tetramethylpiperidine-N-oxyl), degradation of the supported catalyst is due to oxoammonium ion mediated cleavage of amino bonds, and consequent quenching of the active species that are bound and left unprotected at the material's external surface. This neighboring effect has been observed both for polystyrene[xxiii] and silica-tethered[xxiv] TEMPO (Figure 2).

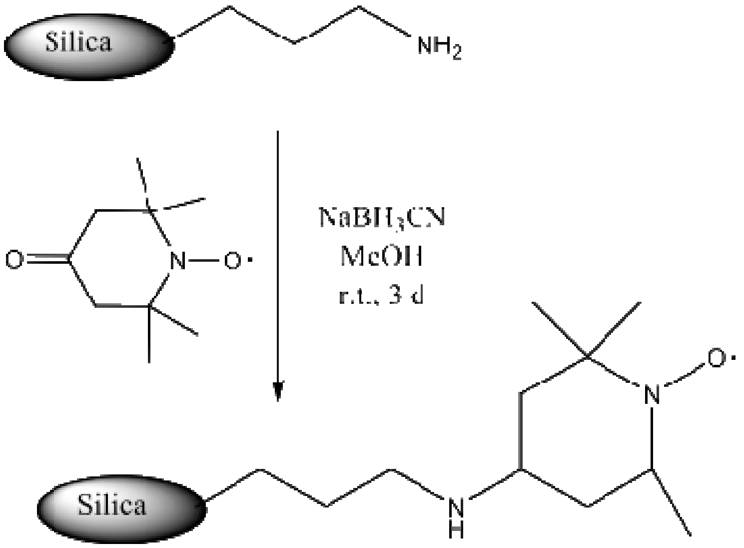


Figure 2. Synthesis of a TEMPO catalyst bound onto silica using commercial aminopropyl-functionalized silica according to Fey et al., Ref.24.

In the ORMOSIL-entrapped catalyst, the radical moieties are immobilized and protected in the material's sol-gel cages, avoiding cleavage of the amino bond and thus intrinsically preventing degradation. Accordingly, the Silia*Cat* material is generally recyclable in the biphasic Anelli-Montanari oxidation of an ample variety of alcohols in batch.[13]

Structural Investigations on Silia*Cat* Materials

The outstanding catalytic properties of these hybrid materials are supported by their structure at molecular level, and by their microstructure. The mesoporous structure of Silia*Cat* M(0) materials has been proved by nitrogen adsorption-desorption isotherms at 77 K (Figure 3).

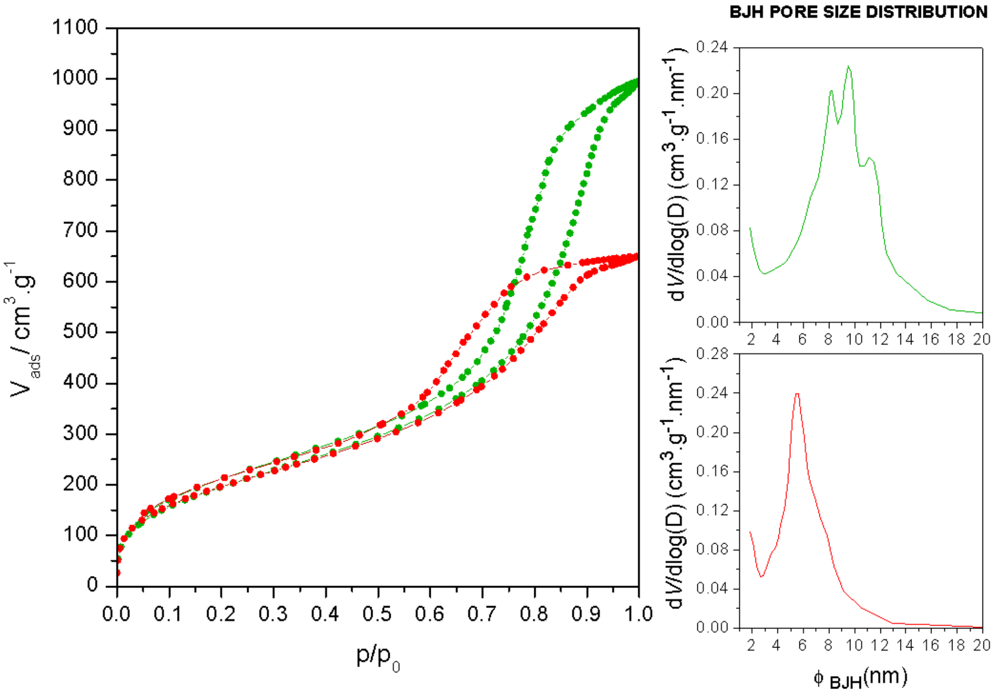


Figure 3. N_2 adsorption-desorption isotherms of Silia*Cat* Pt^0 (green) and Silia*Cat* Pd^0 (red), and corresponding mesopore size distributions from BJH analysis of the desorption isotherms.

The materials possess large surface areas (above 700 m^2 g^{-1}), with total pore volumes in the range 1.0-1.6 cm^3 g^{-1}. The isotherms are type IV with hysteresis loops close to type H1, characteristic of capillary condensation in open cylindrical mesopores between spheroidal particles of fairly uniform array.[xxv]

The mesopore size distribution using the BJH algorithm on the desorption isotherms showed a maximum population with average diameter depending on the metal, but below 10 nm, with no contribution from micropores (indicated by the t-plot analysis and by the values of parameter c in the BET equation).

The molecular structure of these materials has been characterized both by solid state NMR and FTIR spectroscopies. Solid state NMR show that the degree of cross-linking does not correlate with the catalytic activity,[xxvi] while the diffuse reflectance infrared spectra (Figure 4) have shown that these catalysts are both hydrophobic (low relative intensities of the νOH and νSi-OH bands) and lipophilic (high relative intensities of the CH_3 related bands).

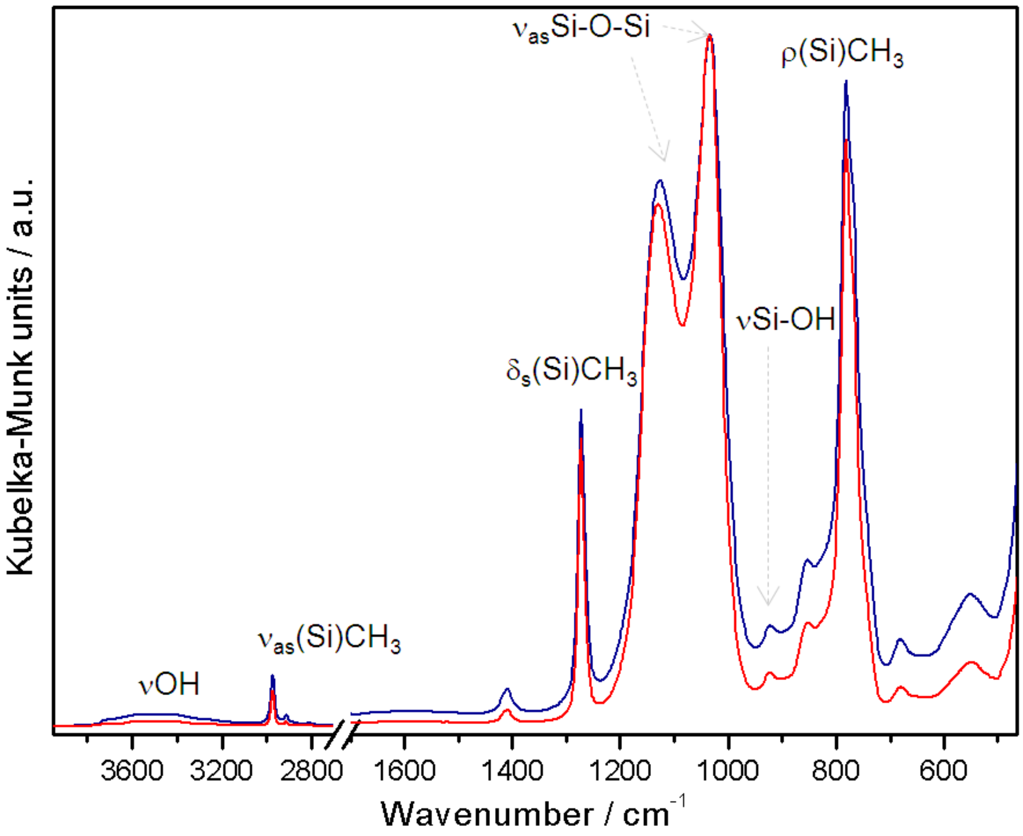
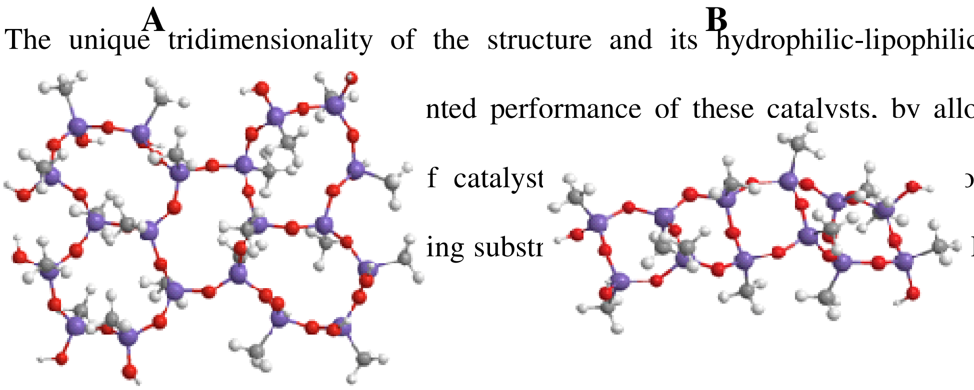


Figure 4. DRIFT spectra of Silia*Cat* Pd^0 (black line) and Silia*Cat* Pt^0 (red line), normalized to the maximum.

A quantitative analysis of the split ν_{as}Si-O-Si band has shown that both ORMOSIL structures contain ~80% of six-member siloxane rings (Scheme 1A) and ~20% of four-member siloxane rings (Scheme 1B), yielding an extremely three dimensional network.[xxvii]

Scheme 1. Schematic representation of a silica cluster containing five cyclic siloxane units: A- six-member [$(SiO)_6$]; B - four member [$(SiO)_4$].



The unique tridimensionality of the structure and its hydrophilic-lipophilic balance
nted performance of these catalysts, by allowing the
f catalyst orption of
ing substr Pd and Pt

A flow nanochemistry approach to catalysis

At least 50% of the reactions used in the fine chemical and pharmaceutical industry could be improved by switching from batch to flow chemistry using the microreactor technology.[xxviii] However, in more than 60% of the reactions studied, a solid is present, (whether as reactant, catalyst or product), which is difficult to handle in flow.

In principle, the use of immobilized chemicals overcomes this common issue encountered in flow chemistry. With solid-supported reagents no work-up is required (all reagent excess remains on the solid support), while the higher exposure of reagents to catalyst improves the reaction rate compared with traditional batch chemistry.

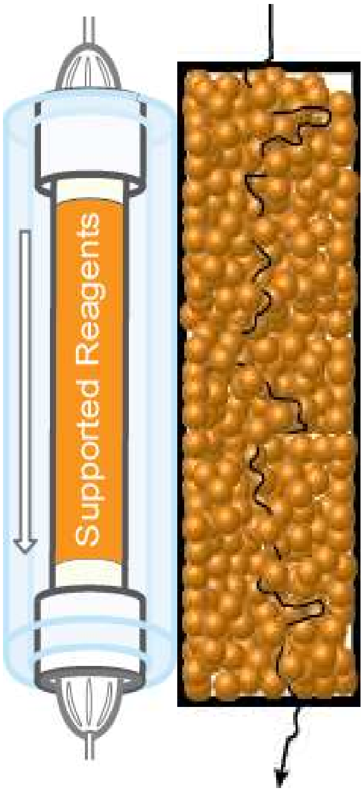


Figure 5. Polymer beads where fluid flows around beads, and not through them. [Adapted from Prof. D. T. McQuade, with kind permission].

However, problems generally arise with polymer beads because fluid flows around beads, and not through them (Figure 5) as many particles are closed and not accessible to reactants. Second-generation heterogeneous catalytic systems must be used to overcome these relevant practical issues.[xxix]

One approach, widely pursued by McQuade and coworkers, makes use of porous polymer microcapsules.[25] Another approach recently developed by Nandini Nevi and coworkers,[xxx] utilises microporous catalysts such as SiO_2 nanospheres encapsulating Pd NPs. Finally, we use the mesoporous ORMOSILs described herein to afford high-yield waste-free processes that can be easily scaled up to multikilogram-scale syntheses, opening also the way for reactions that were previously difficult to perform in batch.

Selective oxidation in flow. A clean catalytic oxidation method, which is now widely employed in fine chemicals manufacture as alternative to stoichiometric oxidations using toxic and dangerous oxidants such as $Na_2Cr_2O_7$, $KMnO_4$, MnO_2 and $NaIO_4$, employs a catalytic amount of the stable free radical TEMPO in the organic phase, and NaOCl as primary oxidant in the aqueous phase.[xxxi]

Silia*Cat* TEMPO is a well known recyclable TEMPO effective catalyst for the oxidation of alcohols with bleach; whose original batch reaction at low temperature (0 °C) typically yields the desired carbonyl product in 97% yield.[14] When performed in flow (Figure 6) the same reaction is considerably improved.[xxxii] Hence, the solid phase reactor is packed with Silia*Cat* TEMPO, and dichloromethane (solvent 1) and water (solvent 2) are pumped independently to inject a solution of the alcohol in organic solvent (Loop 1) and an aqueous solution of NaOCl (Loop 2) into the system.

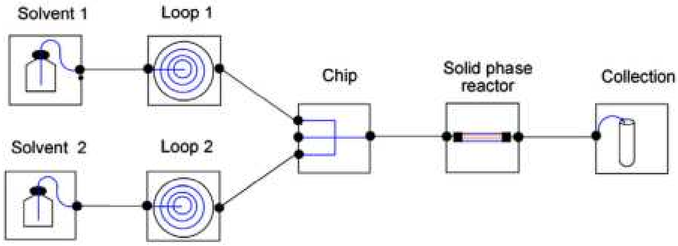


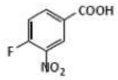
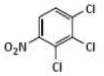
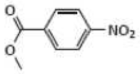
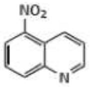
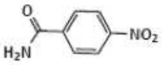
Figure 6. Fluidic set-up for TEMPO oxidation in flow Using Silia*Cat* TEMPO. Under flow the selective oxidation of alcohols with bleach can be performed at room temperature, and does not require the use of corroding KBr as co-catalyst. [Reproduced from Ref.36, with kind permission].

A residence time in the solid phase reactor of two minutes is now enough to achieve full conversion (100% conversion) to pure benzaldehyde (100% selectivity). By contrast, in batch conditions, it took 60 min to achieve 97% conversion.

Under flow, the reaction can be performed at room temperature, is much quicker and does not require corroding KBr co-catalyst (10 mol%). No post-reaction clean up is required to remove the catalyst. For comparison, when an epoxy resin functionalized with TEMPO is used to carry out the same reaction in flow, again corrosive KBr as co-catalyst and low temperature (0 °C) are required for acceptable reaction rate attaining a maximum 95% yield.[xxxiii]

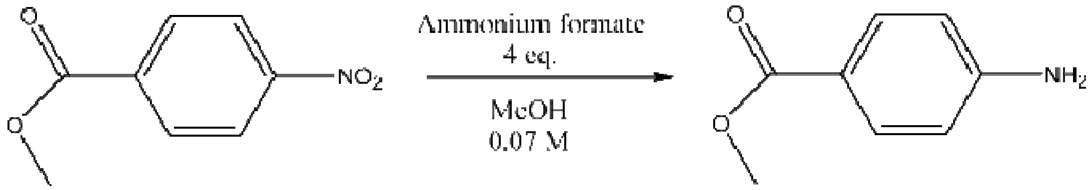
Selective hydrogenation in flow. The selective hydrogenation of nitro compounds in the presence of different functionalities including carboxylic acid, ester, amide, and halide groups can be carried out over Silia*Cat* Pd(0) catalyst under remarkably mild conditions, namely 1 atm of H_2 at room temperature (Table 1).

Table 1. Hydrogenation of nitroarenes to nitroamines over Silia*Cat* Pd(0)

Substrate	Catalyst (mol%)	Time (min)	Solvent (M)	Conversion (%) (Selectivity %)
	0.5	60	MeOH (0.1 M)	100 (100)
	0.5	60	MeOH (0.1 M)	100 (97)
	0.5	30	MeOH (0.1 M)	100 (99)
	0.5	60	MeOH (0.1 M)	100 (100)
	1.0	60	MeOH (0.07 M)	100 (100)

The process is eminently clean, and selectively runs under ultra mild conditions at full (1) atom efficiency with no by-products (no waste). No post-reaction work-up is required to remove the catalyst besides simple filtration.

At the laboratory scale, the use of hydrogen gas may be replaced by an alternate hydrogen source such as, for example, ammonium formate. We thus investigated the hydrogenation reaction using ammonium formate (Scheme 2) both in batch and in flow using the Syrris Asia 220 system, in order to demonstrate the versatility of the nitroarene hydrogenation in flow.



Scheme 2 – Selective catalytic hydrogenation of methyl-1-carboxy-4-nitrobenzene mediated by Silia*Cat* Pd(0) with ammonium formate as hydrogen source.

The solid phase reactor was packed with wet Silia*Cat* Pd(0) and encased on the Asia module. The conversion and selection rate were measured by gas chromatography–mass spectrometry (GC-MS, Table 2).

Table 2. Catalytic Transfer Hydrogenation in Batch and Flow Chemistry over Silia*Cat* Pd(0)[a]

Catalyst (mol%)	T (°C)	Time (min)	Conditions			% Conversion (% Selectivity)
1	20	60		Batch		95 (100)
		-	**Flow (mL/min)**	**Volume reactor (mL)**	**Residence time**	
15	20		50	0.7	14	100
			100		7	(100)

[a]Conversions and selectivity evaluated by GC-MS analysis

Compared to the same process run under batch conditions, the process under flow affords full selective conversion in 14 minutes only, versus 60 minutes required for maximum 95% selectivity under batch.

Perspectives and Conclusions

In 2010, concluding a presentation dealing with the first 25 years of research in the field of sol-gel functional silicas, Avnir was challenging materials chemists to ask themselves what *they* could do for chemistry,[xxxiv] rather than chemistry for materials science. Chemistry indeed has originated the second largest global industry, one that along with prosperity and a myriad of useful products has brought about serious chemical contamination of the biosphere.[xxxv] Now, the whole green chemistry movement calls for a paradigm shift from traditional concepts of process efficiency, that focus largely on chemical yield, to one that assigns economic value to eliminating waste at source and to avoiding the use of toxic or hazardous substances.[1]

Sol-gel silica-based glasses are functional materials whose increasing utilization in disparate applications results in dramatic improvement in the sustainability profile of many existing chemical products and processes.[xxxvi] Sol-gel hybrid molecular, biomolecular and metal catalysts are no exception as they allow cleaning chemical synthesis by minimizing the use and generation of hazardous substances.

These porous yet highly stable materials are ideally suited to be coupled to flow chemistry techniques resulting in reactions which are faster and cleaner than the analogous reactions in batch, as shown above for two representative oxidation and hydrogenation reactions.

Today’s flow reaction systems, such as the Asia system used for the experiments described herein, are modular and can be upgraded to enable scale up, while the addition of modules can expand the scope of the chemistry achievable in the future. In brief, the process can be accomplished at scales from milligrams to grams to kilograms, all on the same instrument. Sol-gel entrapped hybrid glasses – and not polymer beads -- will be one of the enabling technologies of the forthcoming manufacturing of valued molecules[xxxvii] in high-throughput continuous processes, as silica-based glasses offer the high selective activity *and* long term stability required by practical application.

The high cross linked organoceramic matrix framework of the hybrid organic-inorganic material presents an excellent resistance, significantly better than the usual post-synthesis functionalized materials commonly used in heterogeneous catalysts. Opposite to traditional polymer-supported catalysts, the rigid and highly porous glassy structure is compatible with a wide range of solvents (no swelling); it offers an excellent resistance to high temperatures and pressure, while minimal static charge ensures ease of handling of a free-flowing powder. The sol-gel synthesis, furthermore, allows reproducible accurate loading, while the huge (several hundreds m^2/g) accessible surface area leads to high turn over number (TON). The examples presented in this report are only a brief selection out of many reactions widely employed in synthetic organic chemistry that are efficiently catalyzed by the Silia*Cat* catalysts. Sol-gel catalysis over nanostructured hybrid silicas, in conclusion, adds to the first successful nanochemistry technologies.[xxxviii]

Acknowledgements

This article is dedicated to Gino Nicolais, president of Italy’s Research Council. May the new CNR’s Institute of Solar Energy and Sustainable Development soon be operational. Prof. David Avnir’s science has been a constant source of insight and inspiration.

References

i. R. A. Sheldon, I. Arends, U. Hanefeld, *Green Chemistry and Catalysis*, Wiley-VCH, Weinheim: 2007.

ii. P. J. Dunn, *Chem. Soc. Rev.* **2012**, *41*, 1452-1461.

iii. R. Ciriminna, M. Pagliaro, *Org. Process Res. Dev.* **2013**, *17*, 1479-1484.

iv. B. M. Trost, *Angew. Chem. Int. Ed.* **1995**, *34*, 259-281.

v. P. A. Wender, M. P. Croatt, B. Witulski, *Tetrahedron* **2006**, *62*, 7505–7511.

vi. N. Z. Burns, P. S. Baran, R. W. Hoffmann, *Angew. Chem. Int. Ed.* **2009**, *48*, 2854-2867.

vii. S. G. Newman, K. F. Jensen, *Green Chem.* **2013**, *15*, 1456-1472

viii. J. A. Gladysz, *Chem. Rev.* **2002**, *102*, 3215.

ix. D. J. Cole-Hamilton In *Heterogenized Homogeneous Catalysts for Fine Chemicals Production* (eds P. Barbaro and F. Liguori), Springer, Dordrecht: 2010; pp v-x.

x. Chiyoda, Production of acetic acid, JP 235250 (1997).

xi. D. Avnir, *Acc. Chem. Res.* 1995, **28**, 328.

xii. M. T. Reetz, A. Zonta, J. Simpelkamp, *Angew. Chem. Int. Ed.* **1995**, *34*, 301-303.

xiii. For example: R. Abu-Reziq, D. Avnir, J. Blum, *Angew. Chem. Int. Ed.* **2002**, *41*, 4132-4134.

xiv. A. Michaud, G. Gingras, M. Morin, F. Béland, R. Ciriminna, D. Avnir, M. Pagliaro, *Org. Process Res. Dev.* **2007**, *11*, 766-768.

xv. V. Pandarus, G. Gingras, F. Béland, R. Ciriminna, M. Pagliaro, *Org. Process Res. Dev.* **2012**, *16*, 1307-1311.

xvi. M. Pagliaro, V. Pandarus, F. Béland, R. Ciriminna, G. Palmisano, P. Demma Carà, *Catal. Sci. Technol.* **2011**, *1*, 736-739.

xvii. R. Ciriminna, V. Pandarus, G. Gingras, F. Béland, M. Pagliaro, *ACS Sustain. Chem. Engineer.* **2013**, *1*, 249-253.

xviii. V. Pandarus, G. Gingras, F. Béland, R. Ciriminna, M. Pagliaro, *Org. Process Res. Dev.* **2012**, *16*, 1230-1234.

xix. G. A. Ozin, A. Arsenault, *Nanochemistry*, RSC Publishing: 2008.

xx. M.□L. Ferrer, F. del□Monte, D. Levy, *Chem. Mater.* **2002**, *14*, 3619-3621.

xxi. (a) R-J. Liu, P. A. Crozier, C. M. Smith, D. A. Hucul, J. Blackson, G. Salaita, *Microsc. Microanal.* **2004**, *10*, 77; (b) J. Liu, *Microsc. Microanal.* **2003**, *9*, 290; (c) A. K. Datye, Q. Xu, K. C. Kharas, J. M. McCarty, *Catal. Today.* **2006**, *111*, 59; (d) J. P. Gabaldon, M. Bore, A. K. Datye, *Top. Catal.* **2007**, *44*, 253; (e) I. S. Altman, I. E. Agranovski, *Appl. Phys. Lett*. **2005**, *87*, 053104.

xxii J. M. Campelo, D. Luna, R. Luque, J. M. Marinas, A. A. Romero, *ChemSusChem* **2009**, *2*, 18-45.

xxiii T. Miyazawa, T. Endo, *J. Polym. Sci. Polym Chem. Ed.* **1985**, *23*, 2487-2497.

xxiv T. Fey, H. Fisher, S. Bachmann, K. Albert, C. Bolm, *J. Org. Chem.* **2001**, *66*, 8154-8159.

xxv. S. J. Gregg, K. S. W. Sing, *Adsorption, Surface Area, and Porosity*, 2nd edition, Academic Press: New York, 1982.

xxvi. V. Pandarus, F. Béland, R. Ciriminna, P. Demma Carà, M. Pagliaro, *Catal. Letters* **2012**, *142*, 213-217.

xxvii A. Fidalgo, R. Ciriminna, L. Lopes, V. Pandarus, F. Béland, L. M. Ilharco, M. Pagliaro, *Chem. Central J.* **2013**, *7*, 161.

---

xxviii. D. M. Roberge, L. Ducry, N. Bieler, P. Cretton, B. Zimmermann, *Chem. Eng. Technol.* **2005**, *28*, 318-323.

xxix. D. T. McQuade, P. H. Seeberger, *J. Org. Chem.*, **2013**, *78*, 6384-6389

xxx. A. Samanta, R. Nandini Devi, *ChemCatChem* **2013**, *5*, 1911-1916.

xxxi. R. Ciriminna, M. Pagliaro, *Org. Process Res. Dev.* **2010**, *14*, 245-251.

xxxii. V. Pandarus, R. Ciriminna, G. Gingras, G., F. Béland, M. Drobod, O. Jima, M. Pagliaro, *Tetrahedron Lett.* **2013**, *54*, 1129-1132.

xxxiii. A. Bogdan, D T. McQuade, *Beilstein J Org Chem.* **2009**, *5*, 17.

xxxiv D. Avnir, “25 Years of Sol-Gel Research. Contributions to Chemistry”, 75th Israel Chemical Society, Tel Aviv, 25-26 January 2010.

xxxv R. M. Harrison, *Understanding Our Environment: An Introduction to Environmental Chemistry and Pollution*, RSC Publishing, Cambridge: 1999.

xxxvi R. Ciriminna, A. Fidalgo, F. Béland, V. Pandarus, L. M. Ilharco, M. Pagliaro, *Chem. Rev.* **2013**, *113*, 6592-6620.

xxxvii For example, 400 microreactors producing 800 g of artemisinin per day in 69% yield would meet the world demand of this powerful anti-malaria drug: F. Lévesque, P. H. Seeberger, *Angew. Chem. Int. Ed.* **2012**, *51*, 1706-1709.

xxxviii G. A. Ozin, L. Cademartiri, *Small* **2009**, *5*, 1240-1244.