

See discussions, stats, and author profiles for this publication at: <https://www.researchgate.net/publication/227998178>

# Catalysis with Doped Sol–Gel Silicates

ARTICLE *in* ADVANCED SYNTHESIS & CATALYSIS · MARCH 2011

Impact Factor: 5.66 · DOI: 10.1002/adsc.201000731

---

CITATIONS

21

---

READS

47

4 AUTHORS, INCLUDING:



**Rosaria Ciriminna**

Italian National Research Council

161 PUBLICATIONS 3,063 CITATIONS

SEE PROFILE



**Piera Demma Carà**

University of Liverpool

13 PUBLICATIONS 161 CITATIONS

SEE PROFILE



**Mario Pagliaro**

Italian National Research Council

180 PUBLICATIONS 3,460 CITATIONS

SEE PROFILE

# Catalysis with Doped Sol-Gel Silicates

Rosaria Ciriminna,<sup>a</sup> Piera Demma Carà,<sup>b</sup> Marzia Sciortino,<sup>b</sup> and Mario Pagliaro<sup>a,\*</sup>

<sup>a</sup> Istituto per lo Studio dei Materiali Nanostrutturati, CNR, via U. La Malfa 153, 90146 Palermo PA, Italy

Fax: (+39)-091-680-9247; e-mail: mario.pagliaro@cnr.it

<sup>b</sup> Dipartimento di Ingegneria e Tecnologie Agro Forestali, Università degli Studi, viale delle Scienze 13, 90128 Palermo, Italy.

Received: September 24, 2010; Revised: December 21, 2010; Published online: March 16, 2011

This paper is dedicated with affection to Professor Laura M. Ilharco for many years of fruitful collaboration, and for all she has done at the Instituto Superior Técnico de Lisboa for the progress of sol-gel science and technology.

**Abstract:** Silicates doped with catalytic species have only been slowly adopted by the fine chemicals and pharmaceutical industries, in spite of their remarkable and unique properties such as pronounced physical and chemical stability; high (enantio)selective activity and ease of materials production and application. This is now changing thanks to stricter safety regulations and to concomitant success of the first commercial catalysts. In this account we tell the story of these materials and identify some deficiencies in the innovation process that may serve as lesson in guiding the future management of innovation in these relevant industries.

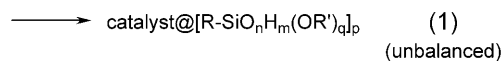
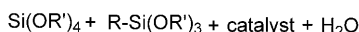
1 Introduction

- 2 Sol-Gel Silicate Catalysts: An Emerging Technology
- 3 Amorphous Silicates vs. Polymers and Periodic Silicates
- 4 New Catalyst for the Selective Oxidation of Alcohols
- 5 Entrapped Pd Catalysts for Carbon-Carbon Bond Formation
- 6 Economic Insights
- 7 Outlook and Conclusions

**Keywords:** fine chemistry; heterogeneous catalysis; organically modified silica (ORMOSIL); sol-gel chemistry; xerogels

## 1 Introduction

The first physically entrapped organometallic catalysts in a sol-gel silica matrix (Rh, Pt and Co ammonium ion pairs for hydrogen transfer catalysis) were described by Avnir and co-workers in 1993.<sup>[1]</sup> Generally obtained by sol-gel physical or chemical encapsulation of the active species in the inner porosity of an organosilica matrix [Eq. (1), which illustrates the essential Si–R bond in the organosilica product], these materials remained a chemical curiosity for the whole 1995–2005 decade in spite of their impressive level of performance.<sup>[2]</sup>



The catalytic material thereby obtained is a new *chemical system* with new and usually enhanced chemical and physical properties, exactly in the same sense for which, in systems theory,<sup>[3]</sup> the properties of a system encompass and go beyond the properties of the comprising elements.

Getting back to the activity of these chemical systems, apparently not even their selective activities higher than those in solution,<sup>[4]</sup> enantioselective catalysis with insoluble organometallic complexes in water,<sup>[5]</sup> highly efficient asymmetric epoxidation of alkenes,<sup>[6]</sup> high-yield aerobic oxidations in carbon dioxide,<sup>[7]</sup> selective hydrogenations,<sup>[8]</sup> and asymmetric syntheses with enhanced enantioselectivity<sup>[9]</sup> and with full recovery of the precious catalyst, were sufficient to cause their adoption by the pharmaceutical and fine chemicals industries. Thus, for years, lipases entrapped in organically modified silicates (ORMOSIL) as discovered by Reetz in 1995<sup>[10]</sup> were the only sol-gel catalysts available on the market thanks to the 10-fold improvement in activity upon encapsulation and

*Piera Demma Carà* is currently a PhD student in sustainable technologies at the University of Palermo's Itaf Department. Her work, carried out also at Palermo's CNR Institute of nanostructured materials, aims at the development of new heterogeneous sol-gel Pd catalysts for cross-coupling reactions. In 2009 she spent a 6-months internship at Québec City's Silicycle Inc.



*Marzia Sciortino* is currently completing her PhD in sustainable technologies at the University of Palermo's Itaf Department. Her work, carried out also at Palermo's CNR Institute of nanostructured materials, aims at the development of new silica-based microparticles for catalytic and cosmetic applications. In 2009 she was at Southern Illinois University (Carbondale, USA) working in the laboratories of Professor Bakul Dave.



*Rosaria Ciriminna* is a research chemist at Palermo's CNR Institute of nanostructured materials. Her interests span from catalysis and green chemistry, to natural products sol-gel materials and supercritical carbon dioxide as alternative reaction solvent. Her work has resulted in numerous achievements, including more than 60 research papers on these topics and the recent commercialization of a Ru-based hybrid sol-gel catalyst for highly selective aerobic oxidations.



*Mario Pagliaro* is a research chemist at Italy's CNR based in Palermo and the head of Sicily's Photovoltaics Research Pole where he teaches new energy technologies. His research interests are in materials chemistry, sustainability, science methodology and management. Mario is the author of a large body of research papers as well as of scientific and management books. He regularly organizes conferences and gives courses, seminars and tutorials on the topics of his research. In 2009 he chaired the highly successful 10<sup>th</sup> edition of FIGIPAS Meeting in Inorganic Chemistry held in Palermo.



to Fluka, the company which commercialized these hybrid bio-glasses shortly after discovery.

Today, the pharmaceutical industry is among the world's largest industries with a global market expected to exceed \$ 825 billion in 2010.<sup>[11]</sup> The industry certainly plays a central role in maintaining our health,<sup>[12]</sup> but it does so generally by producing between 25 and 100 kg or more of waste for every kilogram of active pharmaceutical ingredient (API) manufactured. For comparison, the petrochemicals sector produces 0.1 kg of waste for every kilogram of product.<sup>[13]</sup> API molecular structures are generally complex, the syntheses are lengthy, and patient safety demands very high purity. Waste is generally made up of large amounts of solvent, metals, acids, bases and other reactants that are employed in the typical consecutive reaction and purification steps of homogeneous syntheses, including large amounts of purification media such as silica gels.

Of course, commercial volumes of drugs are relatively low, with an annual production between 1,000

to 1 million kg per compound, compared with basic chemicals that are produced in billions of kilograms per year. Nevertheless, even at a nominal disposal cost of \$1 per kg, the potential savings just in waste avoidance are significant (in the range of \$ 500 million to 2 billion per year).<sup>[13]</sup>

How can we then achieve the same end product using a different set of inputs and reactions such that we eliminate waste from the process? By developing new, effective *solid* catalysts allowing the elimination of the separation step of the catalyst from the reaction mixture, to recover the costly catalyst, and to conduct consecutive conversions in one-pot with no lengthy intermediate separation steps.<sup>[14]</sup>

In 2004, some of us published an account<sup>[2]</sup> aimed to show the large applicative potential of catalysis by sol-gel doped materials. Shortly afterwards, we investigated the structural origins of the superior performance of these solids<sup>[15]</sup> and then, almost concomitantly, the first sol-gel catalysts for the fine chemicals industry were commercialized.<sup>[16]</sup> Yet, their potential

in terms of benefits to industry and the environment remains far from being fulfilled. In this report we critically assess the state of a field that has evolved into a well established sector of chemical research, also at the industrial level, with forthcoming applications also in the biofuel industry.<sup>[17]</sup> We use two examples to show the advanced level of the technology and conclude the review with an analysis putting the technology in the context of contemporary fine chemicals business.

## 2 Sol-Gel Silicate Catalysts: An Emerging Technology

Catalysis with doped sol-gel silicates is an emerging technology. Out of the 1526 papers dealing with silica-based catalysts in the Boolean search using a scientific database,<sup>[18]</sup> it is interesting to notice that 692 articles were published in the last five years (2005–June 2010) pointing to an increasing interest in the scientific community. Remarkably, only 30 papers were published dealing with sol-gel catalytic ORMOSILs (Figure 1), despite the fact that these materials were profitably marketed by Fluka as early as 1995. In contrast to these figures, the number of papers dealing with catalytic periodic mesoporous silica exceeds 2,300.

In principle, efficient catalysis over doped silicates replacing both catalytic or stoichiometric homogeneous conversions with solid-state syntheses offers a solution to most problems encountered in pharmaceutical syntheses. SiO<sub>2</sub> is an optimal commercial support

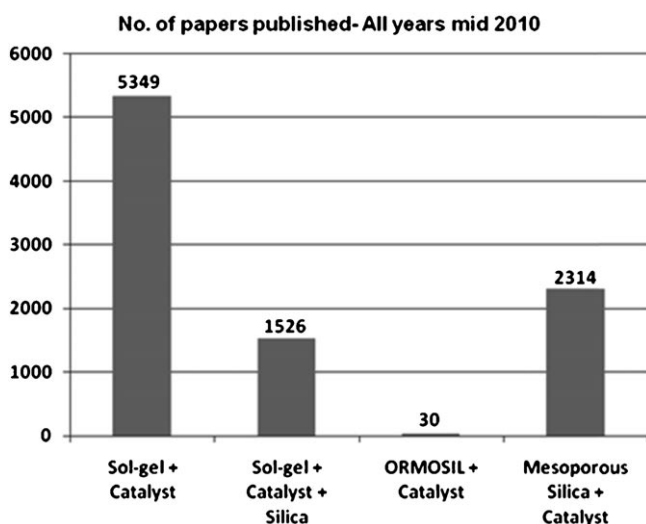
for industrial syntheses, thanks to its stability towards harsh conditions, low swelling, accurate loading, fast kinetics, easy filtration, and high mechanical and thermal stability (Table 1).

By further applying the “green chemistry” principles<sup>[19]</sup> to redesign existing manufacturing processes companies are provided with a double economic benefit because more of the raw materials they purchase end up in the products *and* less waste needs to be disposed of. Yet, until the early 2000s not only heterogeneous but also homogeneous catalysts in the fine chemicals industry were notable, if at all, for their absence.<sup>[20]</sup>

The reason for this absence was mostly rooted in the fact that this industry is a product (and not a process) oriented business, namely it focuses on the development of new products to maximize revenues in the time span in which exclusive royalties are granted by patented innovation.<sup>[21]</sup>

Current economic hypercompetition, however, and ever stricter safety regulations (Table 2),<sup>[22]</sup> are causing a radical change in the fine chemical industry and its main customers, namely the pharmaceutical and cosmetic companies.

Efficient solid catalysts for clean, high-yield organic syntheses are now in demand. This, in practice, excludes traditional heterogeneous catalysts that for decades have been prepared by surface heterogenization



**Figure 1.** Number of papers published related to sol-gel catalyst. The keywords used for the Boolean search are shown in the abscissa axis. [Date range: All years to June 20, 2010; Source: Scopus.]

**Table 1.** Advantages of using silica as catalyst support.

Fast kinetics	Silica is surface functionalized 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's ability to swell.
Versatility	Silica 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.
Ease of use	Unlike polymer, silica is easy to weigh and handle with no static issues and is easily amenable 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.

**Table 2.** Limits in metal residue levels in drug products.<sup>[a]</sup>

Metal	Concentration (ppm)	
	Oral	Parenteral
Pt, Pd, Ir, Rh, Ru, Os	5	0.5
Mo, V, Ni, Cr	10	1
Cu, Mn	15	1.5
Zn, Fe	20	2

<sup>[a]</sup> Source: European Agency for Evaluation of Medicinal Products.

reactions in which one organic or inorganic polymer is mixed with a solution of a catalyst precursor. Such derivatization of a material's surface leaves the anchored catalytic molecules unprotected at the material pore's surface. As a consequence, commonly observed results are reduced catalytic activity, slower reaction rates due to transport limitations, lack of accessibility of the active sites, and leaching of the supported species.

Starting in the late 1990s, new academic research in heterogeneous catalysis for fine chemicals, often financed by industry, underwent a renaissance.<sup>[23]</sup> Periodic mesoporous organosilicas (PMOs) doped with organometallic species;<sup>[24]</sup> polyurea encapsulated metal catalysts,<sup>[25]</sup> heteropoly acids-anchored chiral catalysts<sup>[26]</sup> and high molecular weight functionalized resins<sup>[27]</sup> are just a few representative outcomes of these efforts mainly carried out since the late 1990s. Sol-gel silicates doped with entrapped catalysts are another.

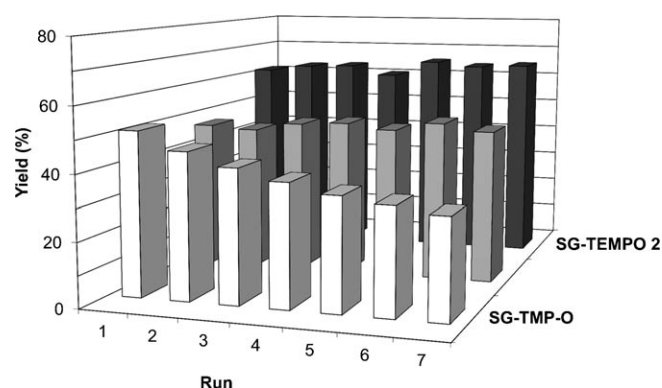
### 3 Amorphous Silicates vs. Polymers and Periodic Silicates

Sol-gel organosilica glasses are chemical sponges that adsorb and concentrate reactants at their inner surface.<sup>[28]</sup> They encompass the advantages offered by inorganic and organic (polymer) materials used for decades as supports in heterogeneous catalysis, and go beyond the limitations of said materials that have limited applications. Hence, in contrast to zeolites and to PMOs, amorphous silicates show a *distribution* of porosity which does not restrict the scope of application of sol-gel catalysts to substrates under a threshold molecular size, and allow us even to surpass the severe mass transfer limitations posed by narrow micropores (pore size <2 nm) in the liquid-phase synthesis of fine chemicals.

On the other hand, whereas flexible organic networks such as those of resins are often unstable giving rise to catalyst leaching,<sup>[29]</sup> sol-gel silicates share the high mechanical and chemical stability of glass. Furthermore, the sol-gel entrapment takes place in the inner porosity where the catalyst is protected and stabilized.

As mentioned above, when catalyst molecules are adsorbed at the external surface of polymers as well as of silica gel, they are partly exposed and unprotected. Hence, for example, the highly active organocatalyst TEMPO entrapped in an ORMOSIL matrix entirely retains its oxidation activity (Figure 2),<sup>[30]</sup> while it progressively loses activity when tethered at the external surface of commercial silica gel.<sup>[31]</sup>

The underlying concept common to all applications of catalytic sol-gel glasses is unique.<sup>[32]</sup> A mobile and



**Figure 2.** Yields in the Montanari–Anelli oxidation of 1-nonanol to give nonanal in the presence of silica-supported TEMPO (SG-TMP-O, *front row*), and of sol-gel ormosils doped with TEMPO [SG-TEMPO-1 is 25% and SG-TEMPO-2 is 100% methylated (*middle and back rows*, respectively)]. (Reproduced from ref.<sup>[30]</sup>, with permission).

a stationary component penetrate each other at the molecular level with the catalytic species being well-defined, highly mobile and homogeneously distributed within the inner porosity of a chemically and thermally inert network, thus combining the advantages of homogeneous (high selective activity and reproducibility) and heterogeneous (stabilization and easy separation and recovery of the catalyst) catalysis.

Such as in the case of periodic mesoporous organosilicas (PMOs, pore size 2–50 nm)<sup>[33]</sup> in which organometallic species are immobilized at the inner walls of mesoporous silica affording single-site solid catalysts,<sup>[24]</sup> spatial confinement governs the performance of sol-gel entrapped catalysts. However, it is not only the ease with which the pore diameter of these solids may be readily controlled that confers upon them such attractive opportunities.

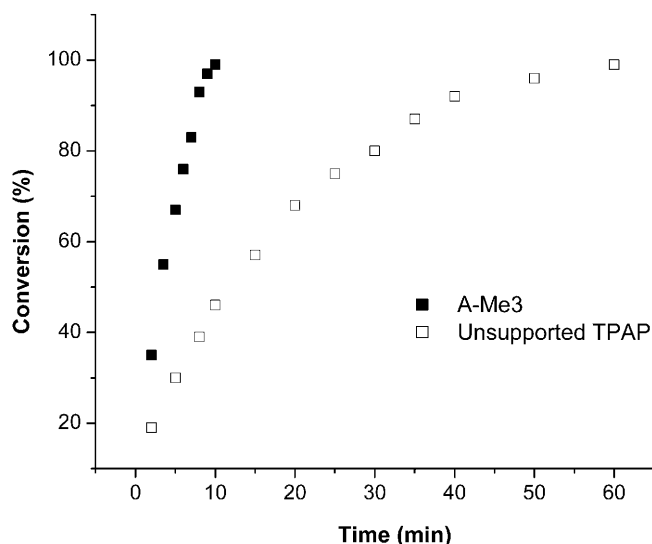
ORMOSILs (Scheme 1) doped with catalytic species, for example, enable heterogeneous conversions that are *more* selective and active than with conventional homogeneous catalyses. For example, the versatile aerobic oxidation catalyst TPAP (tetra-*n*-propylammonium perruthenate) entrapped in partially hydrophobized silica xerogel becomes *more* active than the homogeneous catalyst dissolved in toluene (Figure 3).<sup>[4]</sup>

In these nanohybrid glasses the alkyl-alkoxide precursor has a crucial role on the structure and catalytic properties of hybrid sol-gel catalysts, by affecting the mobility of the entrapped dopant.<sup>[34]</sup> In detail, the important factors affording optimal catalytic performance are two: predominance of six-membered siloxane rings (above 80% alkylation) and a low hydrophilicity-lipophilicity balance (HLB). Other relevant parameters of the sol-gel process such as the amount of co-solvent and the water/Si alkoxide ratio (to promote hydrolysis) can be controlled independently to





**Scheme 1.** Organically modified silica are sol-gel hybrid organic-inorganic material. Sol-gel process: hydrolysis and co-polycondensation.



**Figure 3.** Oxidation kinetics in the aerobic conversion of benzyl alcohol to benzaldehyde in toluene mediated by 10 mol% TPAP encapsulated in the sol-gel hydrophobic matrix **A-Me3** (■) and unsupported (□). (Reproduced from ref.<sup>[4]</sup>, with permission).

optimize the performance of the resulting catalyst, affording a true control and tailoring of the chemical and physical properties of sol-gel molecular catalysts.<sup>[15]</sup>

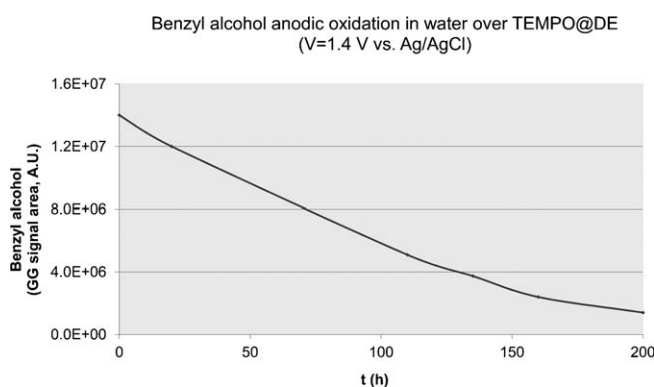
## 4 New Catalyst for the Selective Oxidation of Alcohols

SiliaCat TEMPO (Table 3) is a commercial solid catalyst that can efficiently be used in the selective oxidation of alcohols to carbonyl compounds. We have described elsewhere<sup>[35]</sup> its structure and preparation along with the large applicative potential of this material due to its high activity, reusability, selectivity towards the oxidation of alcohols into aldehydes/ketones, and its capacity to carry out the oxidation in either organic solvents or water.

In brief, the catalyst can smoothly afford high yields of aldehydes (Table 4) under extremely mild conditions (0 °C) in a biphasic water/solvent mixture (Scheme 2), with full recovery and recycle of the cata-

**Table 3.** SiliaCat TEMPO characteristics. (Reproduced from ref.<sup>[35]</sup>, with permission).

Accurate loading: 0.8–0.9 mmol g <sup>-1</sup>
High reactivity and TON
Leach-resistant & reusable
Air stable, inert conditions not needed
Does not require activation prior to use
No swelling, solvent independency
Easy purification (filtration)



**Figure 4.** Benzyl alcohol oxidation in water mediated by the electrode TEMPO@DE ( $V = 1.4$  V vs. Ag/AgCl). (Reproduced from ref.<sup>[39]</sup>, with permission).

lyst at the end of the reaction and without the serious drawbacks in terms of selectivity, metallic wastes, safety and harsh conditions posed by older processes used for this fundamental transformation (Scheme 3).

Indeed, the oxidation of primary and secondary alcohols is one of the main transformations in organic chemistry, that is widely employed in the pharmaceutical and cosmetic industry for the synthesis of drugs and fragrances. Yet, as recently remarked with surprise by Sheldon,<sup>[36]</sup> the three most popular oxidants used by Pfizer's medicinal chemists to oxidize alcohols to aldehydes identified in a 2008 publication<sup>[38]</sup> were the Dess–Martin periodinane (explosive and very expensive), the Swern reagent (evil-smelling and generating toxic by-products) and TPAP in a stoichiometric amount (extremely expensive).

Table 5 shows the high TON (turnover number) achievable with this material in the oxidation protocol of Scheme 2, while Table 6 displays the remarkable

**Table 4.** Oxidation of alcohol substrates with SiliaCat TEMPO. (Reproduced from ref.<sup>[35]</sup>, with permission).

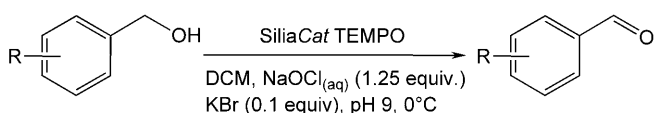
Entry	Substrate (R)	Si-TEMPO (mol%)	Time [min]	Conversion <sup>[a]</sup> [%]
1	4-NO <sub>2</sub>	0.2	60	49
			90	74
2	4-NO <sub>2</sub>	0.4	60	89
			90	98
3	4-MeO	0.4	60	36
			90	36
4	4-MeO	0.4	60	79 <sup>[b]</sup>
5	4Cl	0.4	60	70
			90	95
6	3-phenyl-1-propanol	0.4	60	97
7	1-phenyl-1-propanol	0.4	180	95 <sup>[c]</sup>
8	3-NO <sub>2</sub>	0.4	90	100
9	3-MeO	7.8	16 h	96 <sup>[d]</sup>
10	4-MeO	8.2	16 h	99 <sup>[d]</sup>
11	piperonal	10	20 h	100 <sup>[d]</sup>

<sup>[a]</sup> Conversion (%) determined by GC/MS.

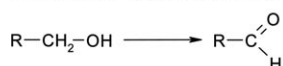
<sup>[b]</sup> 0.05 equiv. of Aliquat 336 were used as phase-transfer agent.

<sup>[c]</sup> Conversion [%] determined by <sup>1</sup>H NMR (300 MHz).

<sup>[d]</sup> Reaction conditions: I<sub>2</sub> (1.8 equiv.), aqueous NaHCO<sub>3</sub>, pH 8, toluene, 22 °C.

**Scheme 2.** Production of benzaldehyde over SiliaCat TEMPO.

### Oxidation of alcohols into aldehydes



#### Stoichiometric reactions

Collins or Sarret reagent : CrO<sub>3</sub>/pyridine

Corey reagent : CrO<sub>3</sub>/pyridine/HCl (PCC)

Swern : oxalyl chloride/DMSO

Corey-Kim : DiMethylSulfide/N-Chloro-Succinimide

Dess-Martin periodinane (DMP)

Others : SO<sub>3</sub>/pyridine, KMnO<sub>4</sub>, MnO<sub>2</sub>, RuO<sub>4</sub>

#### Catalytic dehydrogenation

Copper chromite (gas phase, high temperatures)

Others: Ni Raney, Pd(OAc)<sub>2</sub>...

**Scheme 3.** Traditional oxidation processes employed in industry to obtain fragrances generally made use hazardous and toxic reactants.

stability in performance of the catalyst, that could be reused with practically no loss in activity in all 10 consecutive reaction runs in which it was employed in very small amount (1 mol%).<sup>[38]</sup>

So advanced is the level of the technology that the same reaction can be carried out in water with *no chemical primary* oxidant by applying only a small voltage to a benzyl alcohol solution, and using as catalyst a sol-gel molecular electrode made of organosili-

**Table 5.** Results for reaction in Scheme 2 with different amounts of SiliaCat TEMPO. (Reproduced from ref.<sup>[38]</sup>, with permission).

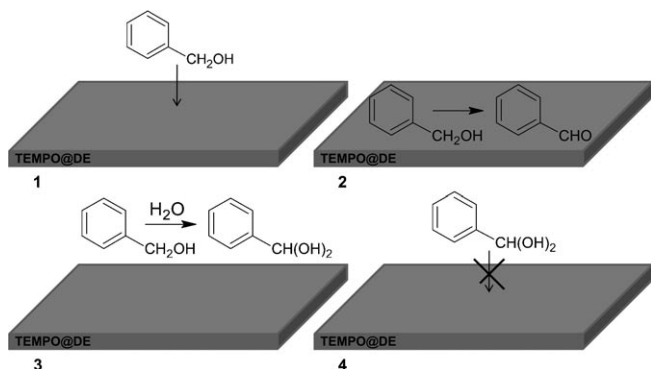
Entry	mol%	Time	Yield	Si
1	0.1	1 h	95%	–
2	0.02	2 h	96%	–
3	0.02	3 h	100%	2 ppm
4	0.01	2 h	83%	3 ppm
5	0.01	3 h	95%	1.6 ppm
6	0.01	4 h	96.5%	1.5 ppm

**Table 6.** Results of consecutive reaction runs in Scheme 2 with 1 mol% SiliaCat TEMPO. (Reproduced from ref.<sup>[38]</sup>, with permission).

Recycle	Time	Yield
1st	30 min	100%
2nd	30 min	100%
3rd	30 min	100%
4th	30 min	100%
5th	30 min	100%
6th	30 min	100%
7th	30/60 min	88/96%
8th	30/60 min	95/100%
9th	30/60 min	97/100%
10th	30/60 min	90/100%

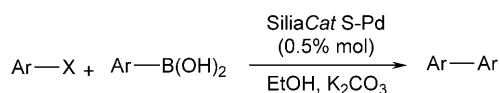
ca doped with the nitroxyl radical TEMPO electrodeposited on the surface of an ITO-coated glass (Figure 4).<sup>[39]</sup>

All the aldehyde formed separates from the reactant solution due to its low water solubility, and no

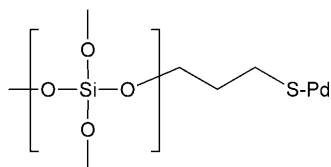


**Scheme 4.** Alcohols are oxidized at the inner surface of TEMPO@DE (1→2) but not so the hydrophilic hydrated aldehydes (3→4) which cannot enter the pores due to the HLB of the material (see text). (Reproduced from ref.<sup>[39]</sup>, with permission).

over-oxidation to benzoic acid takes place thanks to the hydrophobicity of the ORMOSIL surface which prevents diffusion of the hydrated aldehyde molecules (*gem*-diol, Scheme 4).



**Scheme 5.** Suzuki coupling using SiliaCat S-Pd.



**Figure 5.** With applications in Suzuki and Sonogashira reactions, typical SiliaCat S-Pd particulates have a 0.3–0.4 mmol g<sup>−1</sup> load and particle size 63–150 μm. (Reproduced from ref.<sup>[40]</sup>, with permission).

Such an electrochemical synthesis in water starting from benzyl alcohol is highly desirable for the fragrance and pharmaceutical industries where this aromatic aldehyde (obtained by as a by-product in the oxidation of toluene) is employed in large amounts as an intermediate in the manufacture of flavours, perfumery and pharmaceuticals.

## 5 Entrapped Pd Catalysts for Carbon-Carbon Bond Formation

Two new catalysts of the SiliaCat series doped with Pd are now commercially available for Sonogashira and Suzuki coupling reactions (Scheme 5).<sup>[40]</sup> Hence, for example, the material SiliaCat S-Pd (Figure 5) affords high yields of coupled reaction products with different substrates, including deactivated ones such as in entry 2 in Table 7.

Palladium-catalyzed Suzuki<sup>[41]</sup> and Sonogashira<sup>[42]</sup> cross-coupling reactions are powerful methods for carbon-carbon bond formation, and are widely employed in fine chemicals syntheses. In general, a homogeneous palladium catalyst and a ligand are required for these reactions. In the former case, the reaction that has become a standard method takes place between a phenylboronic acid and vinyl or aryl halides; whereas in the Sonogashira coupling reaction, carbon-carbon bond formation occurs on reacting terminal alkynes with aryl or vinyl halides. In both cases, the reaction is catalyzed by Pd(0) formed *in situ* and the presence of a base is required to neutralize the hydrogen halide produced as the by-product.

However, cross-coupling reactions with homogeneous palladium have several shortcomings such as limited reusability, which impacts cost and palladium contamination in the product. Removing residual palladium provides a challenging task for chemists in the pharmaceutical industry to reduce its content to a

**Table 7.** SiliaCat S-Pd Suzuki coupling. (Reproduced from ref.<sup>[40]</sup>, with permission).

Aryl halide	Boronic acid	Time	Product	Yield
		1 h		97%
		16 h		95%
		1 h		98%
		2 h		97%
		2 h		88%



level that meets the demanding requirements of drug regulators. Indeed, despite commercial success, Suzuki coupling still poses many challenges. For example, catalyst costs remain high with some of the newer, more active catalysts being too expensive.<sup>[43]</sup> Clearly, the use of heterogeneous catalysis, enabling straightforward recovery and reuse of the catalyst from the reaction mixture by simple filtration is highly desirable and a major objective of many research efforts.

Indeed two major commercial heterogeneous catalysts have been lately introduced for Suzuki coupling reactions: the *PdEnCat*<sup>[44]</sup> catalyst made of Pd encapsulated in a polyurea framework, and *Pd-Smopex-III*<sup>[45]</sup> made of a metal-scavenging styryl thiol-grafted polyolefin fiber treated with palladium acetate. Table 8 and Table 9 show that *SiliaCat* S-Pd employed in the Suzuki and Sonogashira coupling reactions of

Scheme 6 and Scheme 7 is considerably more reactive than other commercial supported catalysts.<sup>[41]</sup>

## 6 Economic Insights

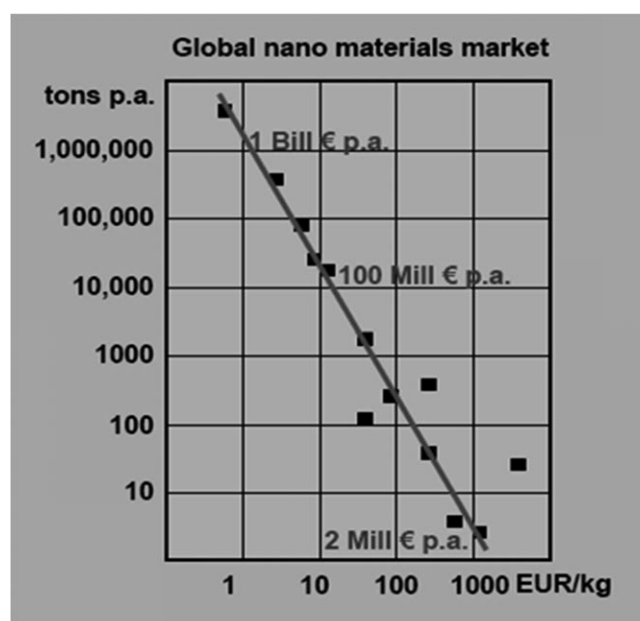
Nanochemistry technologies are slowly reaching the market place as innovative functional materials.<sup>[46]</sup> As put by Hilarius, the major business trap of chemistry-enabled nanotechnologies is the low market volume of the products (Figure 6).<sup>[47]</sup> In other words, the global market for nanomaterials is orders of magnitude smaller than for common chemicals. Catalytic sol-gel silicates for fine chemicals are no exception. All value creation resides in the application whereas

**Table 8.** Comparative test in Suzuki coupling using *SiliaCat*® S-Pd and other commercial catalysts (Reproduced from ref.<sup>[40]</sup>, with permission).

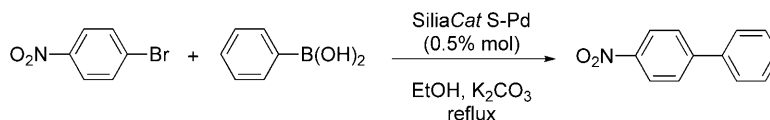
Catalyst	Time	Conversion	Yield
<i>SiliaCat</i> S-Pd	1 h	100%	98%
Pd(OAc) <sub>2</sub>	1 h	100%	98%
Pd EnCat	1 h	50%	–
Pd FibreCat	1 h	30%	–

**Table 9.** Comparative test in Sonogashira coupling using *SiliaCat*® S-Pd and other commercial catalysts (Reproduced from Ref.<sup>[40]</sup>, with permission).

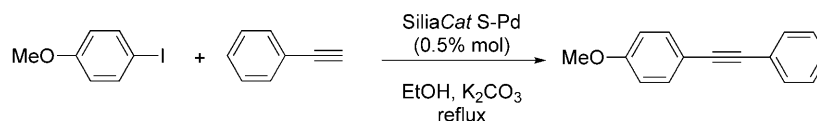
Catalyst	Time	Conversion
<i>SiliaCat</i> S-Pd	4 h	100%
Pd(OAc) <sub>2</sub>	4 h	70%
Pd EnCat	4 h	72%
Pd FibreCat	4 h	66%



**Figure 6.** “Nano materials = nano business?” The global market for nanomaterials is orders of magnitude smaller than for common chemicals. All value resides in the application. (Reproduced from ref.<sup>[47]</sup>, with permission).



**Scheme 6.** Suzuki coupling using *SiliaCat* S-Pd.



**Scheme 7.** Sonogashira coupling using *SiliaCat* S-Pd.

the value of the chemicals itself becomes unimportant. Thus, what is essential for a company manufacturing nanochemistry-based sol-gel catalysts is forward integration within the value chain, namely being closer to the customer to which the company manufacturing the catalyst is actually selling a service – their tailored function – rather than a generic chemical.

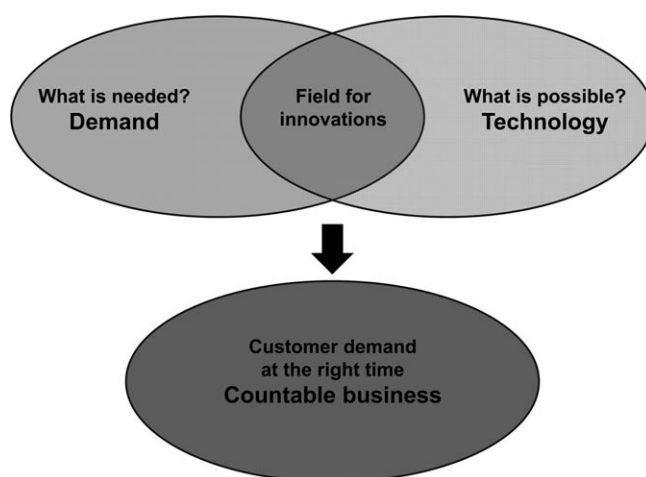
Now, despite the cost, customer pharmaceutical companies conducting catalytic syntheses do not want to reuse catalysts because even slight changes in performance can change the profile or stability of a process. As put by the head of research of one such company:<sup>[48]</sup> “Immobilized catalysts can be very good... but few are available commercially, and producing new high-performing ones is time-consuming. When you have a new chemical entity, where you need a new process and the time window is quite small, you can’t spend time screening homogeneous catalysts to hopefully find one and then immobilize it and not be guaranteed that you’ll get the same performance.”

“We try to optimize for once-through catalyst use, and removing trace metals will probably be an issue no matter what catalyst is used. Thus, catalyst separation is seldom a reason for not using a catalytic process. It’s the price you have to pay”.

In addition, in a regulated industry where products and processes must be validated prior to receiving marketing approval, it is much more difficult to change the process post-launch: by the time of product launch, the pharmaceutical industry aims to have already applied green chemistry practices wherever possible and “reap the benefits of that process from day one of the launch”.<sup>[49]</sup>

Given these premises, it is perhaps of no surprise that only few sol-gel entrapped catalysts were commercialized until 2005. Similarly, even if in 2005 Schüth and co-workers could already write a long review<sup>[50]</sup> on the employment of ordered mesoporous materials in catalysis,<sup>[51]</sup> to the best of our knowledge also these materials have found only limited practical applications.<sup>[52]</sup> The demand for heterogeneous catalysts for fine chemicals, including sol-gel entrapped catalysts, only arose when health and safety standards in the USA and in Europe were made stricter in the late 1990s. The toxic nature of transition metals used as catalysts in many fundamental reactions such as coupling reactions, oxidation and hydrogenation has led to the reduction of tolerated residual concentrations in active pharmaceutical ingredients to single digit ppm levels (Table 2).

This change in legislation is what, in practice, has given place to a countable business (Figure 7) not only for new silica-based catalysts, but also for silica-based metal scavengers made of functionalized sol-gel silicas for the purification of the APIs from remaining metal in place of traditional methods (chromatogra-



**Figure 7.** Technology and innovation. (Reproduced from ref.<sup>[47]</sup>, with permission).

phy, activated carbon, distillation, recrystallization, ultrafiltration, or reverse osmosis) that often lead to problems such as high costs, time consumption, low efficiency, and API losses.

## 7 Outlook and Conclusions

Sol-gel catalysts made of doped silicates are heterogeneous materials employing solid-liquid interphases, that offer a number of clear advantages over homogeneous catalysts, including ease of production and scalability (Table 10). In brief, sol-gel entrapped catalysts enhance yields, abate waste and enable full recovery and re-use of the valued catalyst thus resulting in drastically enhanced profitability.

We have briefly described the technology potential using two new powerful commercial catalysts for two fundamental organic reactions, namely selective alcohol oxidation and carbon-carbon coupling.

So what do we need to do to assist the widespread adoption of sol-gel entrapped catalysts? To paraphrase Ozin,<sup>[53]</sup> we need young wise, educated scientists able to cross borders among fields and explaining their advantages and potential to industry’s manage-

**Table 10.** Advantages of sol-gel entrapped catalytic silicates.

Advantages over Homogenous	
–	Purity
–	Enhanced selectivity
–	Reactivity (high turnover)
Easy to Use	
Scalable	
–	Mechanical and thermal stabilities
Economic (green chemistry)	
–	Recyclable
–	Less waste (solvent, metals etc.)

ment. For example, another innovative chemical technology of relevance here is solid-phase synthesis either in batch<sup>[54]</sup> (for drug discovery and process development), or in microreactors<sup>[55]</sup> for carrying out kilogram-scale syntheses in a continuous mode. Future chemical syntheses will be carried out in flow, as now happens with the construction of a car on a production line, by performing catalytic reactions safely, one after another, in continuous microreactors minimizing the consumption of energy and production of waste.

Solid sol-gel catalysts made of porous silicates are ideal candidates for meeting the stringent demands in terms of performance and economic viability of this technology. In this sense, we argue in conclusion, 3<sup>rd</sup> generation sol-gel silicates developed for continuous processes will likely require the development of uniform microparticles<sup>[56]</sup> in place of xerogel particulates, in a process that is analogous to other advances that have occurred in the science and technology of sol-gel materials.

## Acknowledgements

We thank Professors Sandro Campestrini (Padova), Joël Moreau and Michel Wong Ho Chi Man (Montpellier), and David Avnir (Jerusalem) for rewarding collaboration.

## References

- [1] A. Rosenfeld, D. Avnir, J. Blum, *J. Chem. Soc. Chem. Commun.* **1993**, 583.
- [2] R. Ciriminna, M. Pagliaro, *Curr. Org. Chem.* **2004**, *8*, 1851.
- [3] L. von Bertalanffy, *General System Theory – Foundations, Development, Applications*, 13<sup>th</sup> printing of revised edition, George Braziller, New York, **2001**.
- [4] R. Ciriminna, M. Pagliaro, *Chem. Eur. J.* **2003**, *9*, 5067.
- [5] F. Gelman, D. Avnir, H. Schumann, J. Blum, *J. Mol. Catal. A: Chem.* **1999**, *146*, 123.
- [6] R. Zhang, W. Y. Yu, K. Y. Wong, C. M. Che, *J. Org. Chem.* **2001**, *66*, 8145.
- [7] R. Ciriminna, S. Campestrini, M. Pagliaro, *Adv. Synth. Catal.* **2003**, *345*, 1261.
- [8] N. Kim, M. S. Kwon, C. M. Park, J. Park, *Tetrahedron Lett.* **2004**, *45*, 7057.
- [9] A. Adima, J. J. E. Moreau, M. Wong Chi Man, *Chirality* **2000**, *12*, 411.
- [10] M. T. Reetz, A. Zonta, J. Simpelkamp, *Angew. Chem.* **1995**, *107*, 373; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 301.
- [11] IMS Health, IMS forecasts global pharmaceutical market growth of 4–6% in 2010; Predicts 4–7% expansion through 2013, October 7, 2009.
- [12] J. L. LaMattina, *Drug Truths: Dispelling the Myths About Pharma R&D*, Wiley, New York, **2008**.
- [13] B. W. Cue Jr, *Chem. Eng. News* **2005**, *83* (39), 46.
- [14] S. J. Broadwater, S. L. Roth, K. E. Price, M. Kobašlija, D. Tyler McQuade, *Org. Biomol. Chem.* **2005**, *3*, 2899.
- [15] R. Ciriminna, L. M. Ilharco, A. Fidalgo, S. Campestrini, M. Pagliaro, *Soft Matter* **2005**, *1*, 231.
- [16] R. Ciriminna, M. Pagliaro, *Org. Process Res. Dev.* **2006**, *10*, 320.
- [17] A leach-proof and reusable sol-gel catalyst (Na/SiO<sub>2</sub>) for rapid biodiesel synthesis has been recently described and is obtained by mixing NaOH with ethanol and water, followed by calcination at 600 °C: E. Akbar, N. Binitha, Z. Yaakob, S. K. Kamarudina and J. Salimonc, *Green Chem.* **2009**, *11*, 1862–1866.
- [18] Search conducted with the Scopus scientific database as of June 15, 2010.
- [19] P. Anastas, J. T. Warner, *Green Chemistry: Theory and Practice*, Oxford University Press, New York, **2000**.
- [20] Homogeneous catalysts were not commercialized because of difficulties associated with separating the products from the catalyst: D. J. Cole-Hamilton, *Science* **2003**, *299*, 1702.
- [21] A. D. Chandler Jr, *Shaping the Industrial century: The Remarkable Story of the Evolution of the Modern Chemical and Pharmaceutical Industries*, Harvard University Press, **2005**.
- [22] A. Thaler, *Chem. Eng. News* **2005**, *83* (36), 55.
- [23] A detailed account of the research outcomes can be found in the 5 volumes of the series: S. M. Roberts, J. Whittall, (Eds.), *Catalysts for Fine Chemical Synthesis*, Wiley-VCH, Weinheim, **2007**.
- [24] J. M. Thomas, R. Raja, *Acc. Chem. Res.* **2008**, *41*, 708.
- [25] M. R. Pitts, *Platinum Met. Rev.* **2008**, *52*, 64.
- [26] R. Augustine, S. Tanielyan, S. Anderson, H. Yang, *Chem. Commun.* **1999**, 1257–1258.
- [27] For example, Arkema's oxidation catalyst Oxynitrox S100. [http://www.arkema.com/pdf/EN/products/research\\_and\\_development/Oxynitrox/oxynitrox\\_v3\\_presentation.pdf](http://www.arkema.com/pdf/EN/products/research_and_development/Oxynitrox/oxynitrox_v3_presentation.pdf).
- [28] D. Avnir, *Acc. Chem. Res.* **1995**, *28*, 141–145.
- [29] R. A. Sheldon, M. Wallau, I. W. C. E. Arends, U. Schuchardt, *Acc. Chem. Res.* **1998**, *31*, 485.
- [30] R. Ciriminna, C. Bolm, T. Fey, M. Pagliaro, *Adv. Synth. Catal.* **2002**, *344*, 159.
- [31] T. Fey, H. Fischer, S. Bachmann, K. Albert, C. Bolm, *J. Org. Chem.* **2001**, *66*, 8154.
- [32] Z.-L. L. Lu, E. Lindner, H. A. Mayer, *Chem. Rev.* **2002**, *102*, 3543.
- [33] Porous materials are classified into three groups: microporous (pore size < 2 nm), mesoporous (pore size 2–50 nm), and macroporous (> 50 nm). K. S. W. Sing, D. H. Everett, R. A. W. Haul, L. Moscou, R. A. Pierotti, J. Rouquerol, T. Siemieniowska, *Pure Appl. Chem.* **1985**, *57*, 603.
- [34] A. Fidalgo, R. Ciriminna, L. M. Ilharco, M. Pagliaro, *Chem. Mater.* **2005**, *17*, 6686.
- [35] A. Michaud, G. Gingras, M. Morin, F. Béland, R. Ciriminna, D. Avnir, M. Pagliaro, *Org. Process Res. Dev.* **2007**, *11*, 766.
- [36] M. Mifsud, K. V. Parkhomenko, I. W. C. E. Arends, R. A. Sheldon, *Tetrahedron* **2010**, *66*, 1040.
- [37] K. Alfonsi, J. Colberg, P. J. Dunn, T. Fevig, S. Jennings, T. A. Johnson, H. P. Kleine, C. Knight, M. A. Nagy, D. A. Perry, M. Stefaniak, *Green Chem.* **2008**, *10*, 31.

- [38] A. Michaud, V. Pandarus, L. Tremblay, R. Ciriminna, M. Pagliaro, F. Béland, *Top. Catal.* **2010**, 53, 1110.
- [39] G. Palmisano, R. Ciriminna, M. Pagliaro, *Adv. Synth. Catal.* **2006**, 348, 2033.
- [40] L. Tremblay, *SiliaCat: Highly Reactive and Recyclable Heterogeneous Silica-Based Catalysts*, Informex 2009, San Francisco, January 27th, **2009**.
- [41] A. Suzuki, in: *Handbook of Organopalladium Chemistry for Organic Synthesis*, (Ed.: E.-I. Negishi), Wiley-Interscience, New York, **2002**.
- [42] R. Chinchilla, C. Nájera, *Chem. Rev.* **2007**, 107, 874.
- [43] A. M. Rouhi, *Chem. Eng. News* **2004**, 82 (36), 49.
- [44] See the company's website at the URL: [www.reaxa.com](http://www.reaxa.com).
- [45] X. Jiang, J. Sclafani, K. Prasad, O. Repi, T. J. Blacklock, *Org. Process Res. Dev.* **2007**, 11, 769.
- [46] M. Pagliaro, *Nano-Age*, Wiley-VCH, Weinheim, **2010**.
- [47] V. Hilarius (Merck), *Farbe und Funktion – Von neuen Effekten zu innovativen Produkten*, Nanomat, **2010**. [www.nanomat.de/pdf/hilarius.pdf](http://www.nanomat.de/pdf/hilarius.pdf).
- [48] Personal communication from H.-U. Blaser, chief technology officer of Solvias.
- [49] H. Parsons, *The Greening of Pharma*. PharmaManufacturing.com (**2008**). [www.pharmamanufacturing.com/articles/2008/054.html?page=4](http://www.pharmamanufacturing.com/articles/2008/054.html?page=4).
- [50] A. Taguchi, F. Schüth, *Microporous Mesoporous Mater.* **2005**, 77, 1.
- [51] The above mentioned review has been recently followed by a theme issue of a catalysis journal, see, *Top. Catal.* **2010**, 53, 1–45.
- [52] F. Schüth, “A titanium-modified material synthesized by Avelino Corma has been used commercially by Sumitomo Chemicals, Mobil also claims an application in commercial units of ordered mesoporous materials, but no details have been released”. Correspondence with M. Pagliaro (June 2010).
- [53] G. Ozin, L. Cademartiri, *Nanochemistry*, RSC Publishing, Cambridge, **2005**.
- [54] For example, for complex, multi-step synthesis protocols in a variety of reaction conditions with Mettler Toledo's MIniBlock XT system: S. Bräse, S. Dahmen, J. Heuts, *Tetrahedron Lett.* **1999**, 40, 6201.
- [55] X. Zhang, S. Stefanick, F. J. Villani, *Org. Process Res. Dev.* **2004**, 8, 455.
- [56] C. J. Barbé, L. Kong, K. S. Finnie, S. Calleja, J. V. Hanna, E. Drabarek, D. T. Cassidy, M. G. Blackford, *J. Sol-Gel Sci. Technol.* **2008**, 46, 393.