

Making fine chemicals, nanomaterials and pharmaceutical ingredients over SiliaCat catalysts

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ARTICLE INFO

Article history:

Received 20 March 2020

Revised 1 April 2020

Accepted 5 April 2020

Keywords:

Green chemistry

Sol-gel

Heterogeneous catalysis

ORMOSIL

Chemistry education

ABSTRACT

Referring to selected independent research achievements using sol-gel organosilica catalysts of the SiliaCat series to make fine chemicals, nanomaterials and active pharmaceutical ingredients, we suggest avenues to incorporate these and related sol-gel catalytic materials in green chemistry courses aimed to foster innovation and practical uptake of heterogeneous catalysis as a key green chemistry technology.

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1. Introduction

A large number of new solid catalysts have been introduced in the last two decades to mediate the green synthesis of fine chemicals. From graphene-supported photocatalysts for highly selective photoredox conversions [1] to advanced polymeric catalytic systems [2], in general these new catalysts are stable and highly selective. Amid them, mesoporous solid catalysts comprised of sol-gel nanostructured hybrid silicas including periodic mesoporous organosilicas (PMOs) [3], functionalized silica-based materials obtained by grafting [4], and organically modified silicas (ORMOSILs) [5] functionalized with different catalytic species have been investigated for use in synthetic organic chemistry.

The unique advantages offered by the latter materials include the possibility to entrap enzymes, and even whole cells, retaining the original activity of enzymes in solution, and in certain cases even magnifying it as it happens with ORMOSIL-entrapped lipases discovered by Reetz and co-workers in the mid 1990s [6]; which shortly afterwards became the first sol-gel catalysts to find industrial utilization [7].

The sol-gel nanostructured organosilicas immobilizing and stabilizing organocatalytic species and unstable metallic nanoparticles of the SiliaCat series are successfully applied in widely different synthetic routes relevant to the production of fine chemicals and

active pharmaceutical ingredients (APIs) [8]. The unique features of these sol-gel catalysts, compared to other widely known catalysts, stem from the possibility to finely tune the hydrophilic-lipophilic balance (HLB) of the ORMOSIL ceramic matrix encapsulating the catalytic species in the sol-gel cages [9]. This allows to minimize leaching in the case of physically doped catalysts encapsulating noble metal nanoparticles, and to maximize reactant adsorption and concentration at the cage surface of the inner porosity [10].

Furthermore, the open mesoporosity and large surface area coupled to the high mechanical strength of sol-gel glasses makes them ideally suited for applications under continuous flow [11], affording all the advantages of reactions in flow over synthetic processes in batch reactors [12].

In 2016, we expected that over the next two decades, the pharmaceutical and fine chemicals industries would rely on heterogeneously catalyzed processes carried out in flow reactors located in industrial plants 20 or 30 times smaller than today's batch plants using molecular, metallic and enzymatic catalysts with little or no waste generation and minimal use of energy and resource [11].

In the following we review selected processes using the SiliaCat catalysts for making fine chemicals, nanomaterials and APIs via different chemical reactions. The outcomes of said review two decades after the inception of the green chemistry principles [13] suggest important findings of relevance to both industry's researchers and academic scholars working towards practical uptake of green chemistry technology.

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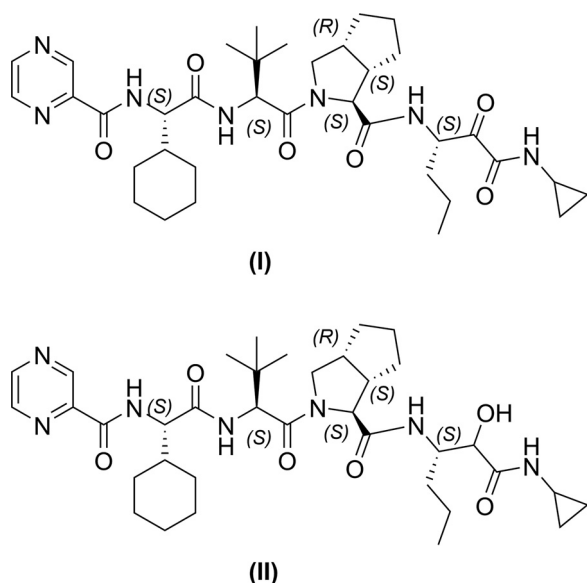


Fig. 1. The industrial synthesis of telaprevir of formula (I) requires the oxidation of the compound of formula (II) to telaprevir. [Structures kindly retrieved from Ref.16].

2. Syntheses of APIs and fine chemicals

2.1. Selected syntheses over SiliaCat TEMPO

Telaprevir of formula (I) (Fig. 1) is a viral protease inhibitor widely used as the active pharmaceutical ingredient in commercial antiviral drugs for the treatment of hepatitis C [14]. Its synthesis includes a key alcohol oxidation step of the compound of formula (II) to telaprevir (Fig. 1) using Dess-Martin Periodinane or via the biphasic Anelli-Montanari protocol involving TEMPO (2,2,6,6-tetramethylpiperidine *N*-oxyl) dissolved in dichloromethane (DCM) with NaClO and a catalytic amount of bromide in the aqueous phase.

Even though remaining in the finished product in small amounts, the presence of genotoxic TEMPO in a drug is highly undesirable [15] (genotoxic impurities in API at the end of the synthesis process must be absent), whereas the safer Dess-Martin Periodinane reagent is both expensive and a high molecular weight compound, which limits its industrial utilization.

In 2013, researchers from a pharmaceutical company based in Italy reported the successful synthesis of the telaprevir with a yield of 90%, a chemical purity exceeding 99%, and a telaprevir diastereoisomer content lower than 0.10% by replacing homogeneous TEMPO with heterogeneous SiliaCat TEMPO [16].

Consisting of a methyl-modified silica matrix functionalized with the TEMPO moiety chemically bound to the organosilica matrix, SiliaCat TEMPO is a versatile alcohol oxidation catalyst [17].

In detail, SiliaCat TEMPO (55 mg) is added to a solution of intermediate II in Fig. 1 (250 mg, 1 eq) in DCM (1.25 mL) kept at 0 °C in contact with water (1 mL) at buffered pH thanks to the presence of 1.5 eq of NaHCO₃ containing also 0.5 eq NaBr. It is enough to slowly add the mixture kept under vigorous stirring with a small excess (1.1 eq) of aqueous NaClO (12.4% w/w, 0.202 mL) to quickly obtain and then isolate the desired telaprevir with the aforementioned high yield and selectivity while quantitatively recovering the SiliaCat TEMPO catalyst (55 mg) [16].

According to the industry research scientists, the process is industrially scalable due to the use of a cheaper, safer, and easier to handle oxidation system under mild reaction conditions providing high yields of the product. As required by API mandatory manufac-

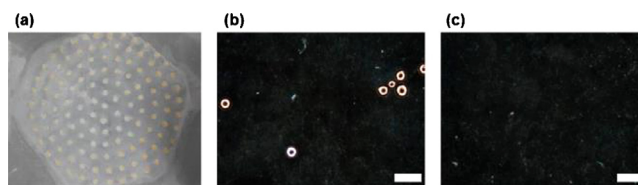


Fig. 2. (a) SiliaCat TEMPO beads on the 50 μm nylon mesh after the oxidation reaction; (b) suspension containing SiliaCat TEMPO, NaOCl and bacterial cellulose solution; (c) the suspension in (b) after filtration. Scale bar = 300 μm . [Reproduced from Ref.19 under kind Creative Commons Attribution License].

turing regulation concerning genotoxic impurities, for example, no trace of TEMPO was found to contaminate the isolated API in the reaction mediated by SiliaCat TEMPO.

Though using a recyclable solid catalyst which leaving no impurities, the use of DCM, which is far from being a green solvent, in the aforementioned oxidation reaction will be replaced by an alternative green solvent, including esters such as EtOAc, MeOAc, and MTBE now routinely used for bleach oxidation of alcohols catalyzed by stable *N*-oxy radicals [18].

The versatility of SiliaCat TEMPO was recently been exploited by industry research scientists from a household and health care chemical company based in South Korea. Indeed, the team has shown how the surface oxidation of bacterial cellulose over SiliaCat TEMPO rapidly affords TEMPO-oxidized cellulose nanofiber (CNF) devoid of TEMPO contaminant species, and easily separated from the reaction mixture [19].

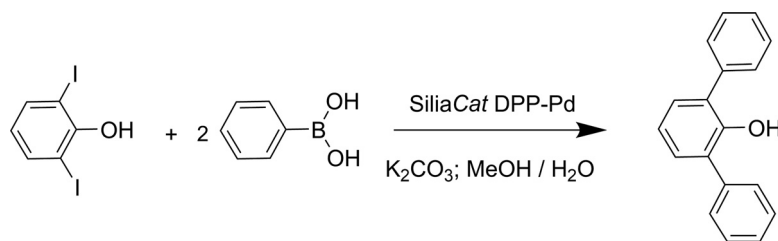
In closer detail, the one-pot synthesis of CNF was carried out overnight at room temperature (25 °C) by treating 20 g of a bacterial cellulose sheet previously cut into small pieces suspended in 500 mL water containing NaOCl and SiliaCat TEMPO. The pH was kept unvaried at 10 by an automatic titrator charged with 0.5 M NaOH.

Upon completion, the reaction was quenched by adding ethanol to the suspension and the catalyst was easily separated from the CNF product by a simple filtration through a nylon mesh leaving no catalyst residues on the valued CNF product suitable for cosmetic and personal care applications. The large size difference between the organosilica beads (63–250 μm) and the CNF (80 nm), enables quick filtration through a nylon mesh (pore size: 50 μm) using a vacuum decompression device. Only the cellulose nanofibers in solution pass through the nylon mesh porosity while the solid SiliaCat TEMPO remains on the filter from where it is easily recovered for reuse, allowing a pure nanofiber solution to be obtained (Fig. 2) [19].

On the other hand, the repetitive centrifugal separation for removing the TEMPO catalyst from the cellulose nanofibers obtained via conventional homogeneously catalyzed process (the de Nooy's process for the selective oxidation of polysaccharides with NaOCl/NaBr/TEMPO [20]) was not suitable for scale-up due to centrifuge's equipment not supporting continuous processing with a large amount of reactant.

Showing evidence that the cellulose fibers are not penetrated by the heterogenized TEMPO moieties at the surface of the catalyst, when the oxidation is carried out over SiliaCat TEMPO the original 100 nm average diameter of the bacterial cellulose nanofibers decreases to only 80 nm, whereas the cellulose nanofiber diameter decreases more than half (up to 30–50 nm) during the conventional homogeneously catalyzed process [20].

This outcome is of significant relevance in light of the anticipated broad-scope applications of TEMPO-oxidized CNF in a number of different industrial sectors, well beyond health and personal care [21].



Scheme 1. The Suzuki Miyaura reaction of phenyl boronic acid and 2,6-diiodophenol mediated by SiliaCat DPP-Pd affords of 2,6-diphenylphenol of high purity. [Adapted from Ref.23, with kind permission].

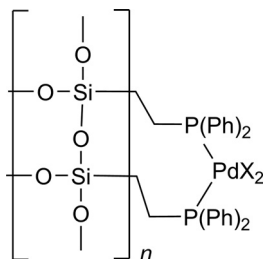


Fig. 3. Frequently portrayed chemical structure of SiliaCat DPP-Pd.

2.2. Selected syntheses over SiliaCat DPP-Pd

Consisting of an organosilica matrix functionalized with diphenylphosphine ligands bound to Pd(II), SiliaCat DPP-Pd is used for a wide range of Pd-catalyzed cross-coupling reactions. Often represented with the chemical structure shown in Fig. 3, the catalyst actually is not a SiO₂ xerogel, but rather a fully alkylated organosilica matrix in which every Si atom is bound to the C atom of a methyl group [22]. The latter aspect has uniquely important consequences extensively investigated with Ilharco and Fidalgo in several fundamental studies in sol-gel science [9].

The catalyst shows high leaching resistance and this stability can be exploited for making a variety of fine chemicals under flow. One example is the process (Scheme 1) developed by an industrial researcher in the Netherlands for preparing 2,6-substituted phenols, and in particular 2,6-diphenylphenol, consisting of a double coupling of a boronic acid and a 2,6-dihalogenphenol in a Suzuki-Miyaura reaction on sterically hindered *ortho* positions [23].

Using a state-of-the-art continuous flow laboratory reactor (a Labtrix Start system fitted with a catalyst cartridge), quantitative yield of 2,6-substituted phenols was achieved in far shorter reaction times when compared to reaction under batch. For instance, in the continuous flow system a reaction time of 4.8 min at the reaction temperature of about 100 °C resulted in a yield of 99% by weight in 2,6-diphenylphenol.

The high yield and the high purity of the 2,6-diphenylphenol obtained makes it particularly suitable as precursor for the preparation of poly(2,6-diphenylphenylene oxide) (Tenax), a porous polymer widely used as a column packing material for trapping volatiles from air (VOC) or liquids, the preparation of which requires a purity of 2,6-diphenylphenol of at least 99.9% [24].

SiliaCat DPP-Pd can successfully replace homogeneous Pd catalysts such as in the synthesis of new antimalarial APIs recently developed by a pharmaceutical company for treating, improving or even eradicating the pathology or symptomology of the disease caused by *Plasmodium* parasites (with a recent significant increase in malaria mortality due in part to the fact that *Plasmodium falciparum*, the deadliest parasite, has acquired resistance against most antimalarial drugs, except artemisinin).

The synthesis of said new APIs consisting of heterocyclic compounds having nitrogen as a ring hetero atom, is based on Suzuki-Miyaura cross coupling of the corresponding heterocycle bromide with arylboronic acid (Scheme 2) [25].

The SiliaCat DPP-Pd effectively replaces an homogeneous catalyst such as Pd(dppf)Cl₂ and also enables to carry out the reaction under microwave irradiation. For example, a microwave vial is charged with the appropriate substituted 4-bromophenol and phenyl boronic acid (1 eq.), K₂CO₃ (1.5 eq.) and SiliaCat DPP-Pd (0.1 eq.) in MeOH. The capped vial is submitted to microwave irradiation for 15 min at 120 °C, after which the product in solution, readily separated from the solid catalyst via filtration, is isolated by conventional organic product isolation procedures.

In the field of functional materials, Welch's team in Canada extensively demonstrated how the direct hetero(arylation) (DHA) synthesis of organic dyes for organic photovoltaic solar cells is ideally carried out over SiliaCat DPP-Pd catalyst leading to excellent yields and high-purity molecular materials with negligible Pd-metal contamination [26].

Heterogeneously carried out over the highly active and recyclable sol-gel catalyst SiliaCat DPP-Pd proved to be a highly-effective method to access a number of water-soluble organic dyes developed for printable solar cell applications [27]. Being soluble these semiconductor organic materials (Fig. 4) can be dissolved in a solution and processed on substrates to make, for instance, flexible organic photovoltaic (OPV) solar cells [28].

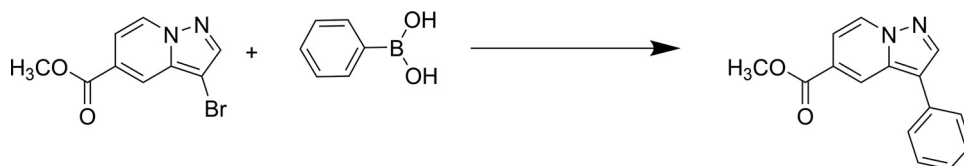
The team successfully extended the heterogeneously catalyzed DHA approach extension to a range of different substrates showing how it operates effectively on milligram to multigram scale reactions using reagent-grade solvents under atmospheric conditions [29].

2.3. Selected syntheses over SiliaCat Pd⁰ and SiliaCat Pt⁰

Consisting of organosilica ceramic matrices physically doped with Pd or Pt nanoparticles, SiliaCat Pd(0) and SiliaCat Pt(0) are highly selective multipurpose catalysts which have been used in a number of different reactions including highly selective hydrogenations, hydrogenolysis, cross-coupling, and hydrosilylation conversions [8].

Researchers at a pharmaceutical company used SiliaCat Pd(0) to synthesize a key intermediate to new APIs useful for the treatment or prevention of bacterial infections, such as urinary tract infection and inflammatory bowel disease. Only the double bond of the pyran ring in the precursor shown in Scheme 3 is hydrogenated [30].

In detail, a solution of 2',7'-dibromospiro[2,5-dihydropyran-6,9'-fluorene] from precursor AG27 (200 mg, 0.510 mmol) in EtOAc (7 mL) is added with SiliaCat Pd⁰ (26 mg, 0.0013 mmol). Hydrogen is then bubbled for 5 min and the reaction is stirred under H₂ atmosphere under ultramild hydrogen balloon conditions for 1



Scheme 2. The general procedures to obtain new antimalarial APIs based on Suzuki-Miyaura cross coupling of heterocycle bromide with arylboronic acid. [Adapted from Ref.25, with kind permission].

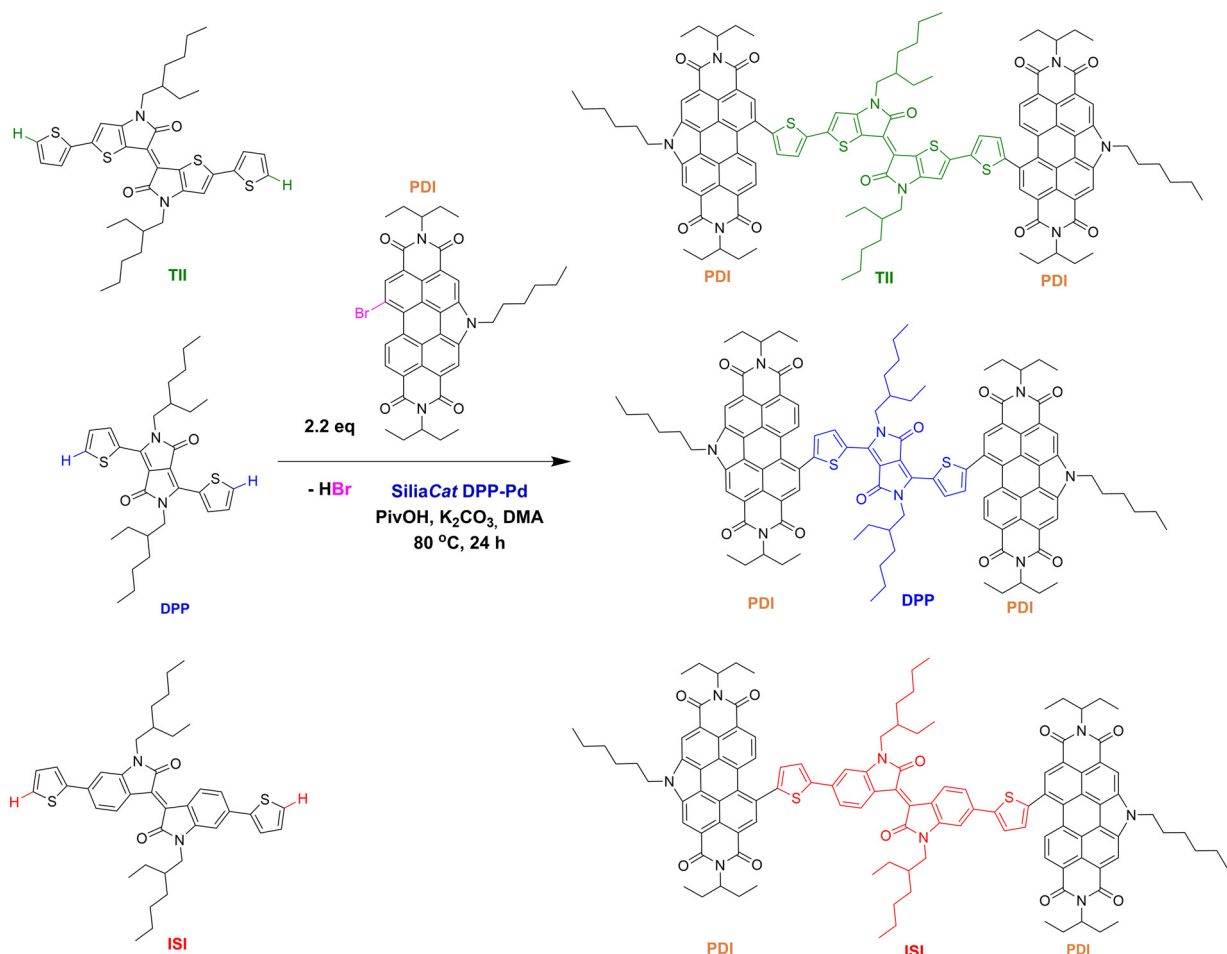


Fig. 4. Soluble organic dyes developed for printable solar cell applications developed using a sol-gel entrapped catalyst at Professor Gregory Welch's Laboratory, University of Calgary. [Adapted from Ref.27, with kind permission].



Scheme 3. Preparation of Intermediate AG29 2,7-Dibromospiro[fluorene-9,2'-tetrahydropyran]. The two bromide groups are required for a subsequent Sonogashira coupling with two mannose-bearing terminal alkynes. [Adapted from Ref.30, with kind permission].

week. After conventional isolation procedures, the title compound is obtained in 60% yield as a pale yellow solid.

It is also remarkable that, compared to palladium on charcoal catalyst, SiliaCat Pd(0) is non pyrophoric [31], which is a very important requirement for the industrial upscale of any hydrogenation process carried out in industry using H₂ as reducing agent.

Researchers at a chemical company in Japan specializing in dental materials and equipment have successfully used SiliaCat Pt(0) as heterogeneous hydrosilylation catalyst to synthesize silane coupling agents having a radical-polymerizable group to make composite organic-inorganic fillers [32]. The catalyst, for instance, mediates the reaction between 2-((undec-10-enyloxy) carbonylamino

ethyl methacrylate and triethoxysilane under mild reaction conditions (35 °C, no need to exclude air). After 12 h the reaction is complete and the SiliaCat Pt⁰ is entirely removed by simple centrifugation, while the solvent (toluene) is recovered by an evaporator.

3. Fostering innovation via renewed education

Driven by global societal megatrends concerning the environment, health, and energy significant change affects the chemical industry [33], including new customer demand of chemical products devoid of negative impact on human health and on the environment. In this context, flow chemistry increasingly used in fine chemical and API manufacturing to afford product of high and constant purity (quality) [34], becomes also a key lean production methodology in which the production is truly “pulled” by customer demand through flexible flow reactors [35]. With new flow chemistry technology, production can be easily increased or decreased depending on demand, ending API shortages for example, which are frequently causing shortage of low-margin, generic drugs including life-saving drugs including life-saving drugs such as antibiotics across many countries.

Increasing the uptake of heterogeneously catalyzed processes carried out under flow in place of stoichiometric or catalytic homogeneous processes in batch reactors, requires a significantly larger number of young research chemists with a close knowledge of these new synthetic routes. In the words of Wiles, a flow chemistry entrepreneurial scientist, “there is still a long way to go to bridge the skills gap that currently exists, particularly relating to practical experience” [36].

Researchers working in heterogeneous catalysis and in flow chemistry applied to synthetic organic chemistry regularly publish the results of their intense research activities across the world.

This accelerated rate of scientific and technological innovation creates the skills gap found by Wiles *en route* to enable fine chemical, specialty chemical and pharmaceutical manufacturers to benefit from the advantages of continuous flow manufacturing [36].

As suggested by Hofstein, the main goal of chemistry education is to develop chemistry-literate students who will find chemistry studies relevant and applicable [37]. The present brief review of the achievements using sol-gel organosilica catalysts of the SiliaCat series to make fine chemicals, nanomaterials and APIs via different reactions independent of our work shows that these materials can be used during the Organic Chemistry Laboratory education to demonstrate the aforementioned relevance and applicability. This was done for example by scholars in the US using SiliaCat Pd(0) for selective hydrogenation reactions [38].

These materials can be used to effectively transfer new green chemistry concepts and new skills to undergraduate students in the laboratory enabled “to interact *intellectually* as well as *physically*” [39] with the subject of their study, via easily handled materials which are not pyrophoric and do not require to exclude air from reactions as important as cross-coupling reactions as it happens with conventional Pd/C catalysts.

Being mesoporous glassy beads of high mechanical strength, large surface area and high pore volume, these catalysts are well suited for use in flow reactors [11], in which conventional solid reactants are notoriously difficult to handle [40].

Hence, looking to the near future, not only the SiliaCat catalysts but a variety of catalytic materials is used to demonstrate the relevance of combining sol-gel approaches and flow chemistry. The latter include sol-gel catalytic silica aerogels functionalized with enzymes using the recently developed bio-friendly procedure for the entrapment of enzymes retaining both the enzymatic activity and the air-light structure of the aerogel [41]; enzymes covalently immobilized onto macrocellular silica monoliths giving place

in continuous flow to high and truly stable biocatalytic activity to afford high yields of chiral amines [42]; or even whole-cells entrapped within hollow silica microspheres affording even better solid transaminase biocatalysis [43].

4. Outlook and perspectives

Briefly reviewing the use of SiliaCat sol-gel catalysts in synthetic organic chemistry from laboratories independent of ours has several lessons to teach.

In agreement with the early studies dealing with catalytic ORMOSILs showing enhanced performance when compared to homogeneous organocatalyst [44] and enzyme counterparts [6,5], in several reactions of practical relevance these materials give place to better products (higher purity, higher selectivity, less polymer degradation in the case of polymer conversion [5]) through better processes (higher yield, shorter reaction time, reduced by-product formation).

However, even more than the enhanced catalytic performance in terms of selective activity, it is the largely enhanced physical and chemical *stability* of organic molecules (including organometallic complexes and enzymes) entrapped in silica-based materials [10] coupled with the fact that organosilica does not undergo swelling in any solvent that allows for the high operational stability of relevance to industry considering the shift to heterogeneous catalysis [45].

The performance of these materials is the consequence of fundamental structure-activity relationships [9,5], enabling the development of optimized sol-gel heterogeneous catalysts by applying useful mathematical tools such as bioinformatics and experimental design.

For example, scholars in Hungary have lately shown how combining the latter methods allow the identification of the optimal organosilane precursor mixture composition (a ternary composition) affording the best sol-gel ORMOSIL doped with lipase B from *Candida antarctica*, for a number of enantioselective conversions [46], even though each substrate requires individual optimization.

Finally, these materials are a valued educational tool for chemistry education performed in the digital and green chemistry era [47], when the processes for making fine chemicals, nanomaterials and pharmaceutical ingredients are no longer independent of tight requirements in terms of atom economy and material efficiency in resource utilization.

Scholars in Iran for instance lately reported the high activity of SiliaCat Pd(0) employed in low amount (0.5 mol%) in the nitrobenzene reduction to aniline with hydrazine at room temperature noting that due to its stability the catalyst could be reused several times without significant loss of reactivity [48]. The reduction of nitrobenzene with hydrogen is the most convenient route to aniline, though current production methods based on (promoted) nickel or copper fluidized-bed catalysts require high temperatures (300–475 °C) in the presence of a large excess of hydrogen at 1–5 bar, and prolonged reaction times [49].

Recently reviewing 25 years of practice of education in green chemistry, Haack and Hutchison noted amid the unmet needs “the lack of uniform demand or pull for green chemistry from academic and industrial stakeholders” [50]. In the field of heterogeneous catalysis, however, industry and the academy work towards the same aim (demand): developing new materials enabling atom- and energy-efficient syntheses and reaction processes.

The uptake of green heterogeneous catalysis under flow in the fine and specialty industry critically depends on economic drivers and on newly trained chemists, engineers and workforce (human resources) [36]. Said new training invariably goes through effective (green) chemistry education [47]. ORMOSIL sol-gel catalysts provide a true solid “catalyst palette” for combining laboratory exper-

iments and theory in a balanced and purposeful way to offer said expanded chemistry education across countries.

Declaration of Competing Interest

The authors declare no competing interest.

Acknowledgments

This article is dedicated to Professor Gregory Welch, University of Calgary, Canada, for all he has done to advance the field of organic materials for organic electronics and photovoltaics also using sol-gel entrapped catalysts.

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