

# Reproducible Green Syntheses Using Hybrid Sol-Gel Catalysts

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Referring to selected examples of reproducible green syntheses using hybrid sol-gel catalysts of the SiliaCat series from different doctoral theses and research works published between 2015 and early 2024, this study briefly illustrates how said catalysts have been applied in a number of green synthetic methods of significant industrial relevance. This shows evidence that the nanochemistry “bottom-up” sol-gel approach based on catalytic species entrapped in organically modified silicas as effective and versatile heterogeneous catalysts developed between the

late 1990s and 2010 has succeeded. Subsequent developments will show how the use of said materials in automated syntheses, supplying data to machine learning algorithms actually leads to faster and cheaper optimization of the reaction conditions. Said progress ultimately will further accelerate industrial uptake of heterogeneous catalysis under flow in the fine chemical industry whose reluctance to change processes was due to the need to replace financially amortized (and expensive) production plants.

## 1. Introduction

Highlighting the technology, environmental and societal megatrends reshaping the chemical industry, a study in 2019 forecast that chemical productions would shift towards catalyzed processes under continuous flow, with oil-derived feedstocks increasingly replaced by feedstocks derived from biological resources.<sup>[1]</sup> This shift would intrinsically lead to decentralized, smaller production plants in which chemicals are flexibly produced with little by-product (waste) formation and no need to stockpile unsold product. The fine chemical industry, on the other hand, conventionally carries out its productions in the versatile (and expensive) multipurpose and multi-product plant (MPP).<sup>[2]</sup> The latter consists of stirred stainless-steel and glass-lined batch reactors equipped with reflux condensers, feed systems, equipment for separation and purification, and storage and effluent treatment facilities.

Fine chemical productions in the MPP usually result in a large amount of unwanted by-products, including spent catalysts and solvent (E factor, mass of waste/mass of product, of 25–200),<sup>[3]</sup> whose disposal adds substantial cost to the overall process production costs.

Regardless of plentiful new green synthetic routes based on catalysis developed by intense academic research work going back to the mid 1990s,<sup>[4]</sup> the main catalytic routes adopted by the fine chemical industry up to the early 2010s were biocatalysis and homogeneous catalysis.<sup>[5]</sup> Except for hydrogenations, in which the lack of a solid catalyst requires unfeasible reaction temperature, fine chemical companies were reluctant to uptake heterogeneous catalysis over supported metal catalysts.<sup>[6]</sup>

In 2021, though, a study provided arguments for which heterogeneous catalysis under continuous flow conditions will become ubiquitous the 21<sup>st</sup> century fine and specialty chemical industries.<sup>[7]</sup> The introduction of new generation stable and highly selective solid catalysts based on heterogenized metal nanoparticles, metal complexes, single-atoms, organocatalysts or enzymes, we highlighted therein, allows to scale-up intensified productions under flow providing substantial economic and technical advantages.

Chiefly due to the need to replace existing expensive equipment already financially amortized, reluctance of industry to uptake continuous manufacturing has been prolonged by widespread shortage of chemists and chemical engineers educated in the field.<sup>[8]</sup> Heterogeneously catalyzed productions under flow substantially reduce production costs, because both addends in Eq.1, namely the intrinsic production cost to produce the desired product ( $C_i$ ) and the cost of producing (and disposing of) unwanted by-products (price of non-conformity, PONC) are lower than in productions using homogeneous catalysts:<sup>[5,7]</sup>

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

When compared to homogeneously catalyzed productions, either in batch or flow reactors, production of fine chemicals via heterogeneously catalyzed reactions using leach-proof catalysts further eliminates waste and reduces production times, because it does not require expensive product purification processes,

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and saves the catalyst that can be reused at length prior to be discharged and replaced with a new catalyst batch.<sup>[7]</sup>

In the following, we use selected examples from doctoral theses and research articles published between 2013 and early 2024 to illustrate how hybrid (organic-inorganic) sol-gel catalysts of the SiliaCat (a tradename of SiliCyle, Canada) series have been applied for the green synthesis of fine chemicals and active pharmaceutical ingredients (APIs). Comprised of organically modified silicates (ORMOSILs) functionalized with different active species, these catalysts belong to the vast class of sol-gel entrapped catalysts.<sup>[9]</sup> The SiliaCat materials in particular show broad applicability to widely different reactions such as hydrogenation, cross-coupling, oxidation, hydrogenation, hydrogenolysis, hydrosilylation, debenzoylation, borylation and more.<sup>[10]</sup> Details on their structure and reasons of their broad, versatile activity can be readily found in the literature.<sup>[10]</sup> Suffice it here to mention that they consist of mesoporous amorphous organosilicas of huge surface area and large specific pore volume whose inner mesoporosity is readily accessed by external reactants. Imparted with high mechanical strength typical of glass, both sol-gel silica and sol-gel ORMOSIL microparticles immersed in water or organic solvent do not swell, and are ideally suited for use in continuous flow reactors.<sup>[11,12]</sup>

Further advantages over conventional solid catalysts consisting of catalytic species 2D-heterogenized at the outer surface of the support include largely enhanced chemical and physical stabilization of the 3D-entrapped catalytic species,<sup>[13]</sup> that in its turn ensure prolonged stability of the sol-gel hybrid catalyst. The catalytic ORMOSIL, in brief, act as molecular sponges that adsorb and concentrate reactants in the sol-gel cages.<sup>[13]</sup>

Referring to selected examples of reproducible green syntheses using hybrid sol-gel catalysts of the SiliaCat series from different doctoral theses and research works published between 2015 and early 2024, this study briefly illustrates how said catalysts have been applied in a number of green synthetic methods. This, *inter alia*, shows evidence that the nanochemistry “bottom-up” sol-gel approach based on catalytic species entrapped in organically modified silicas as effective and versatile heterogeneous catalysts developed between the late 1990s and 2010 has succeeded.<sup>[14,15]</sup>

The green synthetic methods, furthermore, are highly reproducible and amenable to applications using artificial intelligence (machine learning) algorithms for the quick, economic optimization of the reaction conditions, which is particularly important in heterogeneously catalyzed processes when small changes in the process parameters can lead to substantial (and unwanted) changes in the heterogeneously catalyzed process. Subsequent developments since around the late 2010s will show how the use of said materials in automated syntheses,<sup>[16]</sup> supplying data to machine learning algorithms actually leads to faster and cheaper optimization of the reaction conditions (see below). This, ultimately, will further accelerate industrial uptake of heterogeneous catalysis under flow in the fine chemical industry whose reluctance to change processes was due to the need to replace financially amortized (and expensive) production plants.

## 2. Selected Examples

### 2.1. Selective Oxidations

Made from an organoceramic amorphous matrix, SiliaCat TEMPO an organosilica-immobilized TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl) catalyst widely used in the selective Anelli-Montanari oxidation of alcohols to carbonyl compounds,<sup>[17]</sup> or for the selective oxidation of polysaccharide nanofibers.<sup>[18]</sup> Working in Switzerland, in 2013 Aellig graduated from at Zürich's Polytechnic (ETH) with a thesis describing the metal-free oxidation of alcohols using sub-stoichiometric amounts of HNO<sub>3</sub> in combination with the ion-exchange resin Amberlyst-15 in protonic form, or under continuous flow using SiliaCat TEMPO with oxygen as primary oxidant in the presence of a catalytic amount of nitric acid.<sup>[19]</sup>

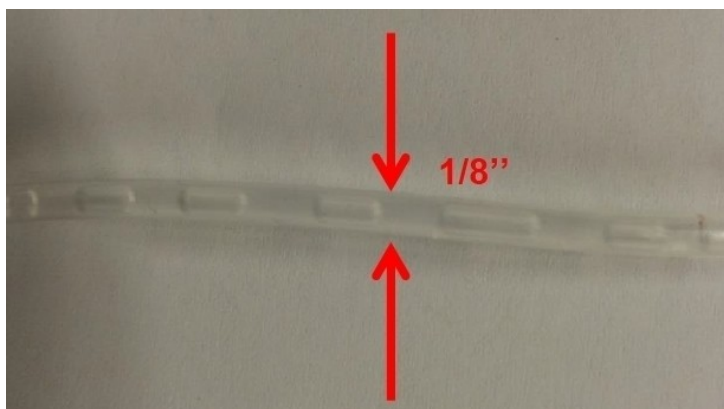
The thesis introduced the use of the hybrid sol-gel catalyst in combination with catalytic amounts of HNO<sub>3</sub> as a NO<sub>x</sub> source and oxygen as primary oxidant under continuous three-phase flow conditions. First the stability of the catalyst was evaluated with benzyl alcohol and the reaction parameters were optimized. Subsequently different substrates were tested, focusing on the oxidation of renewable substrates like lactic acid and 5-hydroxymethylfurfural (HMF).

Performed in transparent Teflon tubes in a continuous flow system including a fixed-bed reactor embedding the solid catalyst, a gas, and a liquid reservoir, the reactions used low vaporization enthalpy 1,2-dichloroethane (DCE) as substrate and product solvent to ease solvent recovery via a phase separator. An HPLC pump was used to pump the liquid phase (solvent, alcohol, HNO<sub>3</sub> and biphenyl standard). It is combined with the O<sub>2</sub> gas flow in a T-mixer, which generates a gas-liquid slug flow (Figure 1). Such segmented flows efficiently promote gas-liquid mass transfer.<sup>[20]</sup>

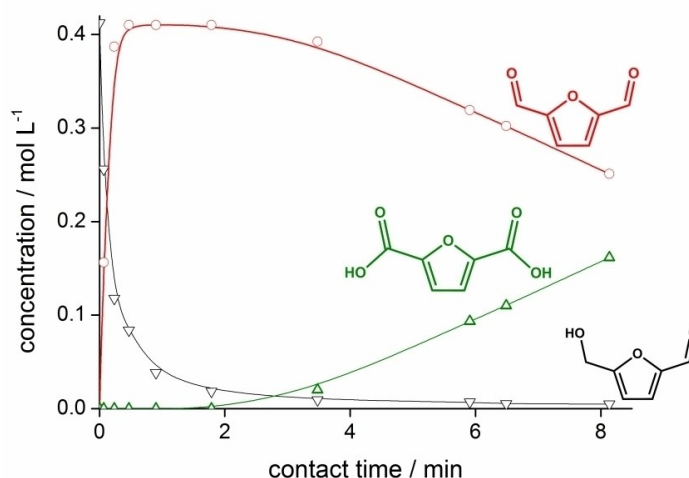
The system pressure was set by a back-pressure regulator at 5 bar to keep a stable segmented flow. The gas-liquid feed enters a packed-bed reactor filled with SiliaCat TEMPO glassy microparticles. The conclusions of this work are amid the most important achievements in green chemistry dedicated to the selective oxidation of alcohols. For example, the selective oxidation of HMF to 2,5-diformylfuran (DFF) was performed with the organosilica-immobilized TEMPO system at 55 °C, 5 bar O<sub>2</sub> and 5 mol% of HNO<sub>3</sub>. With a contact time of 2 min, 97% conversion in HMF could be achieved with 98% selectivity towards DFF (Figure 2).

If obtained from abundant and cheap glucose contained in molasses, DFF is a suitable platform chemical for the synthesis of numerous functional polymers and materials.<sup>[21]</sup> When the contact time was increased, over-oxidation of DFF to 2,5-furandicarboxylic acid (FDCA) was observed (Figure 2). In other words, the use of SiliaCat TEMPO under flow using the aerobic and mild conditions developed by Aellig, allows to oxidise HMF either to DFF or to FDCA, depending on the reaction conditions.

FDCA is the monomer used in the production of polyethylene furanoate (PEF), a polyester copolymer of ethylene glycol and FDCA. Having far better mechanical and gas barrier



**Figure 1.** Slug flow could be observed in the mixing zone before the reactor but also in the fixed bed reactor itself. [Reproduced from Ref.19, In Copyright - Non-Commercial Use Permitted].



**Figure 2.** Concentration vs. time-on-stream for HMF at 55 °C and different contact times (solvent: DCE,  $[HMF]_0 = 0.41$  M,  $[HNO_3]_0 = 5$  mol%, 5 bar  $O_2$ ). In the case of FDCA, contact times higher than 6 min result in the crystallization of FDCA, due to low solubility in DCE. In this case it is enough to working in a different solvent to obtain the same high yields of FDCA. [Reproduced from Ref.19, In Copyright - Non-Commercial Use Permitted].

properties compared to polyethylene terephthalate, PEF can be used for the production of water bottles, food packaging, sports apparel, and footwear. The first commercial 5,000 t/a PEF plant manufacturing also the FDCA precursor is under construction in the Netherlands and will be operational by late 2024.<sup>[22]</sup>

The system is broadly applicable to primary (1-heptanol), secondary (2-heptanol) aliphatic alcohols, benzyl alcohol as well as delicate alcohols that usually dehydrate under acidic conditions like prenol or isoprenol always achieving high reaction rates, excellent yields and selectivities to the corresponding carbonyls, due to the moderate conditions of only 55 °C and 5 bar  $O_2$ . Similarly, the process can be successfully applied to the conversion of lactic acid to pyruvic acid. The oxidation of lactic acid to pyruvic acid is difficult due to the fast decarboxylation of the substrate under reaction conditions employed in conventional alcohol oxidation processes. Used as intermediate for pharmaceutical applications, pyruvic acid is also used by industry in the production of crop protection agents, polymers, cosmetics and foods.<sup>[23]</sup> Industrially, pyruvic

acid is produced by dehydration and decarboxylation of tartaric acid, in which the acid is distilled from a mixture of tartaric acid and potassium hydrogen sulfates at 220 °C, followed by vacuum distillation. The process high cost, \$8,000–9,000/ton in the early 2000s,<sup>[23]</sup> has limited industrial use of pyruvic acid for decades. Since 1992, this keto-carboxylic acid has been produced also microbially (first in Japan, and more recently in China), even though the recovery of the acid from the microbial broth is expensive,<sup>[24]</sup> and the process is not atom efficient.

Aellig found that with a contact time of only 15 s, 98% conversion of lactic acid (0.5 M) in lactic acid and over 98% selectivity towards pyruvic acid could be obtained employing the mild reaction conditions mentioned above. Besides the high reaction rates, and the small amount (5 mol%) of  $HNO_3$  required as co-oxidant, and the “greenness” of the process due to the use  $O_2$  as primary oxidant, what makes the catalyst and the process amenable for industrial uptake is the fact that the catalyst remained stable over several h making the process attractive, compared to transition metal-catalyzed systems that

very often suffer from deactivation and/or low activities. In detail, no decomposition of the catalyst could be observed at 55 °C for over 8 h, and the electron paramagnetic resonance (EPR) signals retained the same magnitude and shape after reaction (Figure 3), pointing to the fact that at this temperature the catalyst did not decompose even after 2 hours on stream.

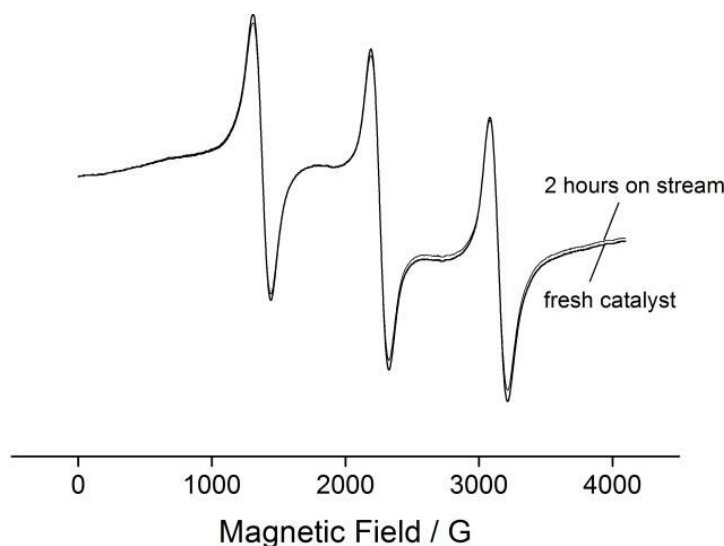
"This system", Aellig concluded, "offers a promising alternative to state-of-the-art stoichiometric oxidants or transition metal catalysts for the environmentally benign and economical oxidation of alcohols".<sup>[19]</sup>

## 2.2. Selective Hydrogenations

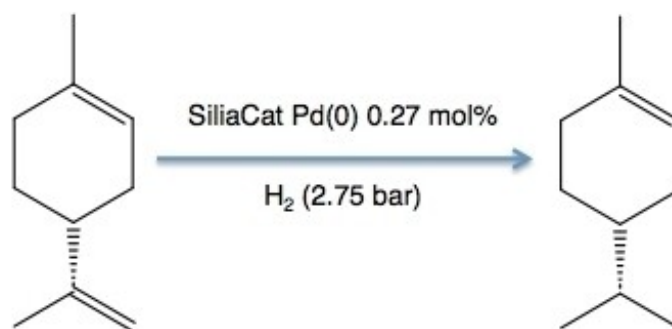
Comprised of 6–8 nm Pd nanoparticles entrapped in a mesoporous organosilica xerogel, SiliaCat Pd(0) is a highly active and selective hydrogenation catalyst. The material for example smoothly mediates the solvent-free of limonene to menthene (*p*-1-menthene) at room temperature under a modest (2.75 bar) H<sub>2</sub> pressure (Scheme 1).<sup>[25]</sup>

In detail, it is enough to add limonene with 0.27 mol% of SiliaCat Pd(0), pressurize the mixture with only 2.75 bar H<sub>2</sub> and stir the mixture at room temperature to observe nearly full conversion of limonene to menthene (96%) in 6 h, with just a minor amount (2%) of *p*-cymene as by-product. This selectivity should be compared to that of conventional Pd/C catalyst that employed in similar hydrogenation under 3 bar H<sub>2</sub> at 30 °C non selectively catalyzes the hydrogenation of limonene to *p*-1-menthene, *p*-menthane and also the isomerization of *p*-1-menthene to *p*-2-menthene and *p*-3-menthene, as well as to the formation of bicyclic compounds.<sup>[26]</sup> It also relevant, in light of forthcoming practical applications, that the sol-gel hybrid catalyst, contrary to most commercial palladium and platinum supported catalysts, is *not* pyrophoric and can be safely used in the presence of H<sub>2</sub> without risks of fire and flame formation.<sup>[27]</sup>

Limonene-derived menthene is the starting material for the synthesis of poly(menthene carbonate) (PMenC), namely a high glass transition temperature transparent polycarbonate analogous to poly(limonene carbonate) (PLimC) but without the terminal double bonds of limonene. In other words, PMenC is



**Figure 3.** EPR spectra of the initial catalyst and of the used catalyst 2 hours time-on-stream at 55 °C. (solvent: DCE, [PhCH<sub>2</sub>OH]<sub>0</sub> = 500 mM, [HNO<sub>3</sub>]<sub>0</sub> = 5 mol%, 5 bar O<sub>2</sub>) [Reproduced from Ref.19, In Copyright - Non-Commercial Use Permitted].



**Scheme 1.** Solvent-free selective hydrogenation of (+)-limonene to (+)-*p*-1-menthene mediated by SiliaCat Pd(0) at room temperature. [Adapted from Ref.25, CC BY 4.0 Creative Commons License].

the saturated version of PLimC affording a polycarbonate of better thermal processability via extrusion and injection moulding, and a prolonged ultraviolet stability.<sup>[28]</sup> In the case of PMenC, indeed, no cross-linking or undesired oxidation reactions at high temperature can occur which is particularly important in light of forthcoming practical applications of these versatile biobased polycarbonates.<sup>[29]</sup>

As noted by Mohan and Mejia in study devoted to green organic chemistry laboratory in undergraduate education, hydrogenation reactions are typically atom economical, but often require high temperatures and pressures.<sup>[30]</sup> On the other hand, SiliaCat Pd(0) is so active and selective in the hydrogenation of alkenes and alkynes, that even the safe reaction in a hydrogen balloon at room temperature can be used to teach students green organic synthesis. As shown by O'Connor and co-workers, under said ultramild conditions the catalyst selectively mediates the hydrogenation of a wide variety of alkenes and alkynes with experimental yields ranging from 60–95% (Scheme 2).<sup>[31]</sup>

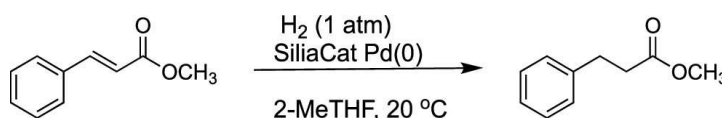
The ability to reuse the easily recoverable biobased solvent 2-methyltetrahydrofuran (MeTHF) obtained from sugars via furfural or levulinic acid, significantly less toxic than THF,<sup>[32]</sup> the catalyst prolonged reusability, and the fact that no byproducts form, show evidence of the true sustainability of hydrogenations mediated by said hybrid sol-gel catalyst.<sup>[30,31]</sup>

### 2.3. Selective Hydrogenolysis

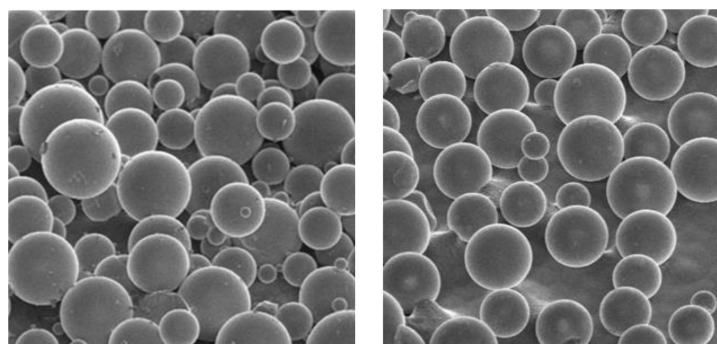
Metal-catalyzed cleavage of C–O, C=O, and C–OH bonds with hydrogen (hydrogenolysis) in alcohol, ester, and carbonyl compounds is an important reaction both in synthetic organic chemistry and in the emerging biorefinery where it allows to access directly valuable platform chemicals.<sup>[33]</sup> Working at Laval University (Canada), Pandarus in 2019 reported in her thesis the

introduction of a new generation version of the SiliaCat catalysts comprised of spherical hybrid microparticles.<sup>[34]</sup> In other words, the spherical version of SiliaCat Pd(0) selectively mediates the hydrogenolysis of aromatic alcohols, aldehydes, and ketones by using a low amount of palladium under mild reaction conditions.<sup>[35]</sup> In detail, the full hydrogenolysis of benzyl alcohol to toluene on a 375 mmol scale in a 500 mL reactor was achieved using a modest catalytic amount (0.1 mol% Pd) at 70 °C under 3 bar H<sub>2</sub>. Under these optimal conditions, the SiliaCat Pd(0) was vastly superior to a number of different commercial solid palladium catalysts including Pd/C, the ROYER catalyst (3 wt% Pd<sup>0</sup>/polyethylenimine/SiO<sub>2</sub>), and Pd Escat 1351 (5 wt% Pd<sup>0</sup>/SiO<sub>2</sub>). The catalyst is stable and does not display any morphology change before the 1st and after the 8th reaction run (Figure 4).

Employed in the hydrogenolysis of 4-carboxybenzaldehyde (4-CBA) the catalyst effectively mediates the full conversion of 4-CBA to *p*-toluic acid at 100 °C under 3 bar H<sub>2</sub> in five consecutive cycles without a decrease in catalytic activity. Obtained as a by-product during the purified terephthalic acid (PTA) industrial synthesis, 4-CBA is removed from PTA via hydrogenolysis over a fixed bed catalyst of Pd/C.<sup>[36]</sup> However, the hydrogenolysis conditions are much harsher than those demonstrated on laboratory scale using SiliaCat Pd(0).<sup>[35]</sup> In detail, in industry the crude TA feed is combined with water to approximately 15 wt% concentration and dissolved at 290 °C under 14 bar H<sub>2</sub> pressure in excess of water vapor pressure at this temperature. This solution is then flowed over the Pd/C catalyst in the fixed bed. The resulting recrystallized PTA is very pure and contains less than 25 ppm 4-CBA.



**Scheme 2.** Hydrogenation of methylcinnamate mediated by SiliaCat Pd(0) in a hydrogen balloon. [Adapted from Ref.30, Copyright (2020), with permission from American Chemical Society].



**Figure 4.** SEM images at 100 x magnification of SiliaCat Pd(0), D50 = 100 μm, in reusability test before reaction (left) and after 8 consecutive cycles (right). [Reproduced from Ref.35, CC BY-NC-ND 4.0 Creative Commons License].

## 2.4. Cross Coupling Reactions

Consisting of an organosilica-entrapped Pd(II) catalyst obtained by sol-gel hydrolytic polycondensation to methyltrimethoxysilane and diphenylphosphine functionalized silane, SiliaCat DPP–Pd, is a highly stable and active catalyst for nearly all cross-coupling reactions.<sup>[37]</sup> Having large surface area and specific pore volume (suffering thus no pressure drop), and being mechanically and chemically robust like all the glassy catalysts of the SiliaCat series, the material is particularly well suited for use under continuous flow in microreactors.<sup>[38]</sup>

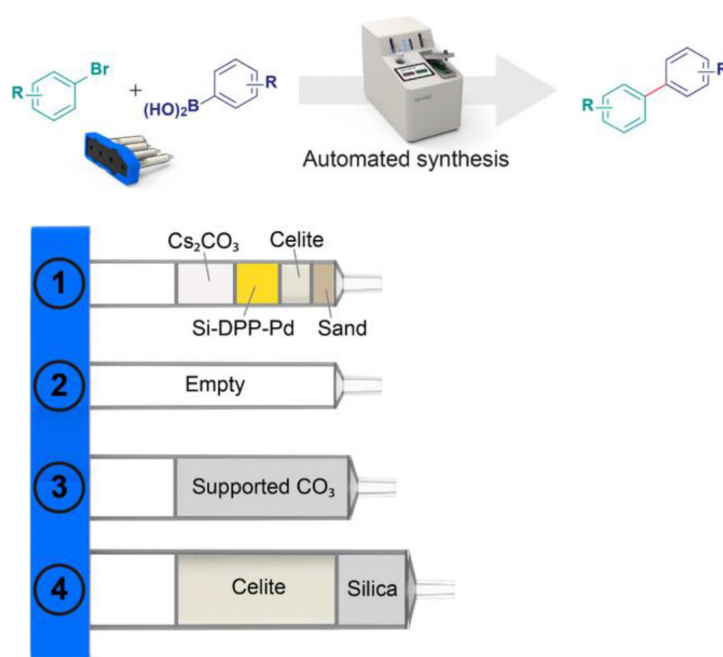
Graduating from Massachusetts Institute of Technology (USA), Aroh reported in the doctoral thesis in which reported a new optimization algorithm for the determination of optimal conditions and kinetic rate parameters in continuous flow systems with dynamic inputs.<sup>[39]</sup> Amid many other reactions investigated, the scholar optimized the conditions for the Suzuki-Miyaura cross-coupling reaction using 3-bromopyridine and phenylboronic acid as model substrates for the reaction under continuous flow mediated by with SiliaCat DPP–Pd in a packed-bed reactor.

Performed by increasing the HPLC peak of the 3-phenylpyridine relative to the biphenyl internal standard, the optimization was actually made possible by the stability of the catalyst over 5 h of continuous use. The platform used to perform and monitor this and other reactions on the lab scale, indeed, performs the optimization using steady state experimental conditions. One heated packed-bed reactor and 3 pump flow rates are the parameters of the optimization that were varied in order to find the optimal reaction conditions for the Suzuki-Miyaura cross-coupling between 3-bromopyridine and phenylboronic acid mediated by SiliaCat DPP–Pd under

flow. The optimization algorithm developed was an improvement upon traditional adaptive response surface methodology (ARSM) optimization approach leading to highly efficient use of information gained in each experiment to optimize a reaction systems comprised of one or two reactors. This results in decreased time to identify the optimal conditions, and reduced consumption of reactants. The stable heterogeneous catalyst coupled to flow chemistry, thus, enables enhanced chemical manufacturing driven by data supplied by process analytical tools that make ARSM an adaptive technique.<sup>[40]</sup>

The ultralow metal leaching from SiliaCat sol-gel catalysts allows for example their use in the automated Suzuki-Miyaura synthesis of a wide variety of cross-coupling products without the need of tedious workups including catalyst filtration and Pd scavenging.<sup>[16]</sup> In closer detail, collaborating with a former PhD student from his team at Zurich ETH who later established a company manufacturing the cartridge-based automated synthesis system for accelerating discovery organic synthesis, Bode and co-workers developed a four component capsule enabling the aforementioned automated syntheses.

The SiliaCat catalyst is incorporated in the first capsule between one layer of sand and another of Celite to prevent any catalyst loss (Figure 5). Then a third layer consisting of Cs<sub>2</sub>CO<sub>3</sub> is added as optimal base for the cross-coupling reaction. Another compartment of the capsule contains a solid-supported tetraalkyl amine carbonate (“supported CO<sub>3</sub>”) used to remove the excess boronic acid. Finally, a third compartment containing two pads (one of silica combined with another of Celite) eliminates water and water-soluble components. The method was automated and applied to the Suzuki-Miyaura cross coupling of a wide range of aryl bromides (and aryl chlorides) and boronic acids, as well as to the modification of highly



**Figure 5.** Automated Suzuki-Miyaura cross coupling (top), and content of the capsule for the automated Suzuki-Miyaura cross coupling (bottom). [Reproduced from Ref.16, Copyright (2024), with permission from American Chemical Society].

functionalized bioactive molecules.<sup>[16]</sup> In total, more than 50 different cross coupling products were prepared in good to excellent yields demonstrating that the method replacing manual synthesis not only saves time and workforce, but it is also of broad scope.

Only the unreactive aryl bromide or homocoupling side reaction products could not be removed from the crude reaction due to their similarity to the desired diaryl product, requiring for removal the use of flash chromatography to obtain high-purity product (>95%). Showing further evidence of the advantages enabled by sol-gel hybrid catalysts mentioned in the introduction, conventional polystyrene-bound Pd catalyst (PS-PPh<sub>3</sub>-Pd, equivalent to the homogeneous catalyst Pd(PPh<sub>3</sub>)<sub>4</sub>) could not be employed because it partly dissolved in the reaction solvent (2:2:1 DME/EtOH/H<sub>2</sub>O). Non-toxic dimethyl ether (DME) used to promote the solubilization of most aryl bromides, whereas water was beneficial for both the reaction itself and the solubilization of the boronic acid and base.

To check the reproducibility of the complete process and demonstrate that the standardized method was reproducible, the team conducted multiple experiments with two sets of substrates. The outcomes of the experiments (Figure 6) confirmed that the method is indeed consistent, with the consecutive reactions affording comparable yields each time. The team concluded that the method is “extendable to other types of cross couplings or palladium-catalyzed transformations”<sup>[16]</sup> that indeed in the case of the SiliaCat catalysts functionalized with Pd(II) or Pd(0) species include hydrogenation, debenzoylation, hydrogenolysis, and many other reactions.<sup>[10]</sup>

### 3. Outlook and Conclusions

Hybrid organosilica catalysts such as the SiliaCat catalysts briefly illustrated in this account are amid the new generation solid catalysts available to new and existing fine chemical companies to start producing fine chemicals in continuous flow processes.

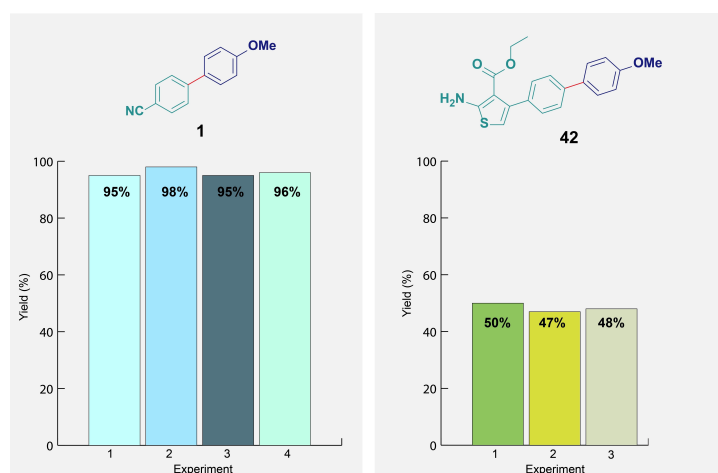
Many others are available on the marketplace, and others (including single-atom catalysts) are about to be commercialized. For example, a flow chemistry systems manufacturer based in Europe offers a comprehensive set of cartridges (“CatCarts”) consisting of a stainless-steel tube packed with a solid catalyst of a specific particle size range ready for use (equipped with a filter system at each end of the tube allowing the solution containing the reactants to pass through the column but prevents catalyst from coming out).<sup>[41]</sup>

Exceeding the 100 threshold, the list of available solid catalysts in “CatCarts” no longer includes only conventional Pd/C or Pt/SiO<sub>2</sub> catalytic materials, but rather many advanced catalysts in which the metal is doped with organic (for example, polyethyleneimine) and inorganic (for example, vanadium) species; or multiple metals are deposited on the same support (for example, 5% Pd - 1% Fe/C); or, called “complex catalysts”, including organosilica SiliaCat or polyurea-encapsulated palladium (Pd EnCat) catalysts.

“Are you wondering how many times can a CatCart be used? The longevity of the catalyst depends on the reaction type and conditions. With careful planning of the reaction and washing the CatCart with pure solvent, it can be used for up to 20–30 times”.<sup>[42]</sup>

In conclusion, the driving factor that will progressively (but inevitably) lead fine chemical companies to uptake flow chemistry productions, is not the will to be “green” or “sustainable”. Chemical companies compete amid themselves to supply customers with their products at the lowest production cost, highest purity and lot-to-lot consistency, and in the shortest possible time. Continuous manufacturing (CM) dramatically improves product purity, consistency of production “campaigns”, and substantially reduces cost.

Indeed, a survey carried out in 2018 by industrial researchers amid 25 fine chemical companies manufacturing APIs and 10 pharmaceutical companies found a first significant increase in the industrial uptake of continuous manufacturing (CM).<sup>[43]</sup> “What caused such a rapid change in the level of adoption of CM technologies among contract manufacturing organizations



**Figure 6.** Suzuki-Miyaura cross coupling reactions performed several times on the “console” for the synthesis of the molecules 1 and 42. [Reproduced from Ref.16, Copyright (2024), with permission from American Chemical Society].

(CMOs)?” asked the academic and industrial researchers editors of a recent journal’s themed issue on flow chemistry:

“The answer is undoubtedly complex, but it certainly includes the manufacturers realizing the benefits of these technologies and increasing CM demand from their clients. The most important benefits of flow have not changed, but CMOs appear to have realized that they must offer CM capabilities or lose clients to competitors”.<sup>[44]</sup>

In the same perspective, this critical account on the use of sol-gel hybrid catalysts in synthetic organic chemistry will hopefully contribute to further inform researchers in green chemistry (and early career researchers in particular) applied to the industrial synthesis of both fine and bulk chemicals that green chemistry in the chemical industry has been and continues to be driven by cost-reduction efforts. This was first shown by Sheldon,<sup>[45]</sup> who had worked in the industry for about 20 years, and has been recently confirmed by Murphy, the inventor of the green synthesis of Ibuprofen. Recounting the early industrial roots of green chemistry during the 1970’s and 1980’s, Murphy has extensively shown how already in the 1970s industry’s managers (and researchers) were aware that economically and technically viable low effluent were so advantageous that they would be adopted.<sup>[46,47]</sup>

Reluctance of industry to adopt CM using heterogeneous catalysts has been due to the necessity to replace existing and already amortized multi-product plants. Now, on the other hand, companies willing to continue with conventional productions in batch carried in MPPs increasingly face competition from companies producing via homogeneously or heterogeneously catalyzed processes carried out in continuous flow at a fraction of the cost and in significantly shorter time. Showing evidence of early signs of change, industry’s researchers lately started to publish pleas for the uptake of heterogeneous catalysis under flow, for example for ubiquitous cross-coupling C–C bond formation reactions.<sup>[48]</sup> Seen from this practical viewpoint in which technologies actually conflict with each other, research chemists specializing in green chemistry and catalysis may lose a certain *naïveté* often common amid academic researchers.

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## Conflict of Interests

The authors declare no conflict of interest.

## Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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Aiming to contribute to eradicate a certain *naïveté* common to many research chemists specializing in green chemistry and catalysis, this study illustrates through selected examples of reproducible green syntheses using hybrid sol-gel

catalysts from doctoral theses and research articles published between 2013 and early 2024, how said catalysts have been applied to a number industrially relevant green synthetic methods.

Dr. R. Ciriminna\*, Prof. R. Luque\*, Dr. M. Pagliaro\*

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**Reproducible Green Syntheses Using Hybrid Sol-Gel Catalysts**