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Continuous Flow Single-Atom Catalysis: A Viable Organic Process Technology?*

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This article is dedicated to Professor Laura M. Ilharco on the occasion of her recent retirement from University of Lisboa's Instituto Superior Técnico.

Heterogeneous catalysis under continuous flow conditions is increasingly used by the chemical industry to synthesize fine chemicals. Is single-atom catalysis under flow a technically and economically viable organic process technology? Early results

suggest valuable insight *en route* to the industrial uptake of single-atom catalysis in the production of fine and specialty chemicals.

1. Introduction

Called in 2019 the foundation of a “forthcoming revolution in chemistry”,^[1] single-atom catalysis (SAC) merges the advantages of homogeneous catalysis employing organometallic complexes (high selective activity) with those of heterogeneous catalysis (no need for catalyst separation and stable performance of the catalyst during prolonged use). In the decade following its inception in 2011,^[2] plentiful studies have shed light on the reaction mechanisms, including the influence of the reaction environment and SAC deactivation pathways.^[3]

Investigating the technical viability of SAC with Karimi and Luque, some of us recently concluded that the industrial uptake of SAC for chemical productions and for hydrogen fuel cells and water electrolyzers will be rapid, once single-atom catalysts of sufficient metal load and prolonged stability will be developed.^[4]

Heterogeneous catalysis under flow conditions using leach-proof solid catalysts provides so numerous economic and technical benefits that it will become the key enabling technology of the 21st century fine and specialty chemical industries.^[5] The advent of new generation leach-proof and

highly selective supported metal catalysts and flow chemistry indeed addresses the fine chemical industry's historic reluctance to use supported transition metal catalysts.^[6]

Any new chemical technology “is ultimately evaluated in terms of profitability”.^[7] On the other hand, technology valuation based on technical and financial aspects is rarely taught to chemists.^[7] We agree with Cannon and Bree: research chemists should be competent in basic financial analyses and the language necessary to communicate with the chemical industry.^[7]

Filling this educational gap is particularly urgent today when the chemical industry is undergoing a profound transformation in which chemical productions shifting towards advanced catalysis technologies under continuous flow that intrinsically lead to decentralized, smaller production plants for the manufacture of low-volume, high-value chemicals with limited by-product (waste) formation.^[8]

Closing a cycle of techno-economic studies in heterogeneous catalysis,^[4,5,8] in this study we aim to provide an answer to the question: is continuous flow single-atom catalysis a viable organic process technology?

Early results suggest valuable insight in the transition of SAC from a fundamental research topic to an issue of practical relevance for the fine chemical industry.

Heterogeneous catalysis under flow using heterogenized metal nanoparticles, metal complexes, organocatalysts or enzymes fulfills the grand objective to make the production of valued fine chemicals in flexible tonne-scale production plants similar to Taiichi Ohno's lean manufacturing of goods.^[9] The additional advantage of using SACs under flow in catalytic microreactors is, as shown in the following, of synergistic nature.

2. SAC under Continuous Flow Conditions

The first main requirement to be addressed *en route* to practical uptake of SACs is to synthesize catalytic materials of high metal load. From synchronous pyrolysis-deposition through mechano-chemical “precursor-dilution” strategy, several methods have

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been developed to produce SACs of sufficient metal load.^[4] One such method involves the use of mesoporous graphitic carbon nitride obtained via copolymerization,^[10] followed by simple stirring of the as synthesized mp gC_3N_4 (400 mg) in the presence of a relatively large amount of $CuCl_2 \cdot 2H_2O$ dissolved in ethanol under prolonged stirring at 80 °C.^[11] It is enough to heat the resulting doped solid at 500 °C for 2 h under Ar flow to obtain an atomically dispersed copper catalyst in which Cu is uniformly distributed across the mesoporous carbon nitride crystals in the form of Cu(I) coordinated to four N atoms at a distance of 1.9 Å and four C atoms at a distance of 2.7 Å.

The large surface area (several hundreds $m^2 g^{-1}$) and mesoporous nature of graphitic C_3N_4 synthesized via the copolymerization method,^[10] ensure that the resulting powdered catalyst ($Cu_1@mpgC_3N_4$) has a large metal load of 1.2 wt%, while retaining large surface area ($\sim 200 m^2 g^{-1}$) and pore specific volume ($\sim 0.7 cm^3 g^{-1}$).^[11]

The latter catalyst was recently dip-coated alongside an alumina-based wash-coat layer onto a 3D printed oxide dubbed "catalytic static mixer" (CSM) quickly and reproducibly manufactured at low cost by three-dimensional (3D) printing via an electron beam melting method developed in Australia by Hornung and co-workers.^[12] The resulting coated catalyst is then placed inside a tubular stainless steel microreactor and used for continuous catalytic conversions.^[12] Providing low pressure drop, the structured and regular shape of the 3D-printed CSM oxide minimizes flow maldistribution, while the steel tube ensures enhanced heat transfer and controlled reaction conditions.

Employed to mediate the continuous-flow heterogeneous hydrogenation of benzaldehyde and furfural with H_2 gas, the resulting CSM coated with $Cu_1@mpgC_3N_4$ achieved very high turnover frequency values, 551 h^{-1} for benzaldehyde and 1563 h^{-1} for furfural, under the relatively harsh conditions (24 bar and 120 °C) affording the highest yields of the corresponding alcohols.^[11] Running the furfural hydrogenation for 150 min at steady state, no drop in the formation of furfuryl alcohol was observed (Figure 1).

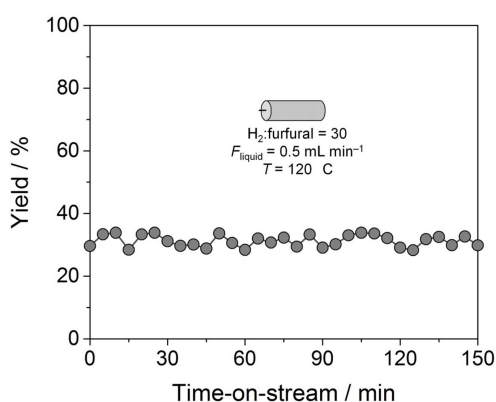


Figure 1. Hydrogenation of furfural over CSMs coated with $Cu_1@mpgC_3N_4$. Reproduced from Ref. [11], under a Creative Commons Attribution 4.0 International License.

Carrying out the reaction both in Australia and in Italy using the same CSM over seven months for a total accumulative reaction time/time-on-stream beyond 200 h,^[11] the catalyst remained stable and active. Its weight before the first hydrogenation (7.458 g) and after seven months of use (7.461 g) nearly did not change.

The catalyst was found to be leach-proof since the amount of Cu concentration (and also of other metals contained in the stainless-steel scaffold, such as Cr, Fe, Ni, and Mo) detected by ICP-MS was below the detection limit regardless of the relatively harsh reaction conditions (24 bar and 120 °C).

Considering possible industrial uptake, the reaction conditions are harsh, the yield in alcohol is low (31 %), and the flow rate (30 $mL h^{-1}$) slow, but the work established the needed proof of concept that SACs employed under flow are as stable as when employed under batch conditions,^[13] while the reaction rate is *several orders of magnitude higher* when compared to turnover frequency (TOF) values for similar aldehyde reductions mediated under batch conditions by electroplated CSMs incorporating Pd(0), Pt(0) or Ni(0) nanoparticles, having TOFs between 0.1 and 40 h^{-1} .^[14]

Now that at least two major methods exist for the large-scale fabrication of SACs with high metal loadings, namely the solvent-free mechanochemical synthesis^[15] and the two-step adsorption of metal complexes with 1,10-phenanthroline onto commercial carbon black followed by pyrolysis,^[16] several other leach-proof SACs will be employed under flow.

Indeed, another SAC-catalyzed chemoselective reduction of nitro compounds to produce multifunctional anilines under flow achieving a high TOF ($> 8000 h^{-1}$) and relatively high productivity (5.8 $g h^{-1}$ of aniline) was recently demonstrated using a Pt_1-MoS_2 -GF catalyst (GF stands for graphite felt), in a bench-top flow cell operated under fast flow condition at high reactant concentration (0.2 M).^[17]

The stability tests conducted at low conversions ($< 10\%$ and $< 30\%$) for a continuous 12 h operation at 70 °C showed no decay in activity, despite minor fluctuations in yield due to temperature fluctuation and GC-MS sampling. Further stability examination conducted in the quantitative conversion regime for 24 h clearly showed the steady production of aniline (Figure 2).

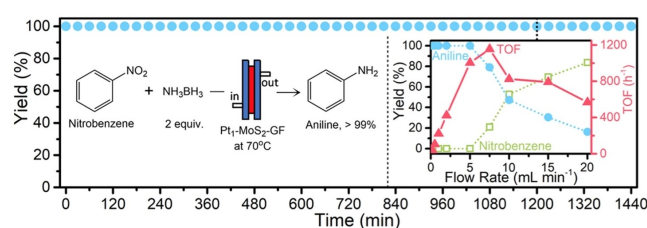


Figure 2. 24 h on-stream demonstration of the Pt_1-MoS_2 -GF catalyst in the quantitative conversion regime of nitrobenzene to aniline under flow. Condition: 0.025 M nitrobenzene with 0.050 M ammonia borane in acetonitrile/ H_2O mixture (5:1, v/v) at a flow rate of 1 $mL min^{-1}$. Yield vs. flow rate test shown in the inset as performed at 20 h. Reproduced from Ref. [17], under a Creative Commons Attribution 4.0 International License.

Showing again evidence of the advantages provided by using the single-atom catalyst under flow, values of 0.02–0.07 g h⁻¹ were reported for the same SAC-mediated reaction under batch conditions.^[18,19]

SAC under flow is also ideally suited to carry out important synthetic organic chemistry reactions that are known to be catalyzed by trace amounts of the catalytic metal species.^[20] Embedding the single-atom species in a stable heterogeneous SAC indeed eliminates the intrinsic uncontrollable nature of trace metal catalysis easily poisoned by impurities in the reaction medium.

This was recently demonstrated by China-based scholars who developed a palladium SAC deposited on large surface area porous organic ligand polymer (POL) showing a remarkably high selective catalytic activity in the hydrosilylation of allenes.^[21]

In detail, the 772,358 turnover number of the Pd₁@POL-5 catalyst was 200 times higher than the state of the art catalyst, whereas the catalyst employed in the continuous flow system full retained its selectivity and activity in 10 consecutive reaction runs affording the reaction product diphenyl(undec-1-en-3-yl)silane without reduction in activity and selectivity (Figure 3).

Even though carried out on small laboratory scale (0.25 mmol allene substrate), the work according to the researchers lays the foundation for the large-scale application of SAC employing trace amount of catalyst in the synthesis of valued molecules including silicones.^[21]

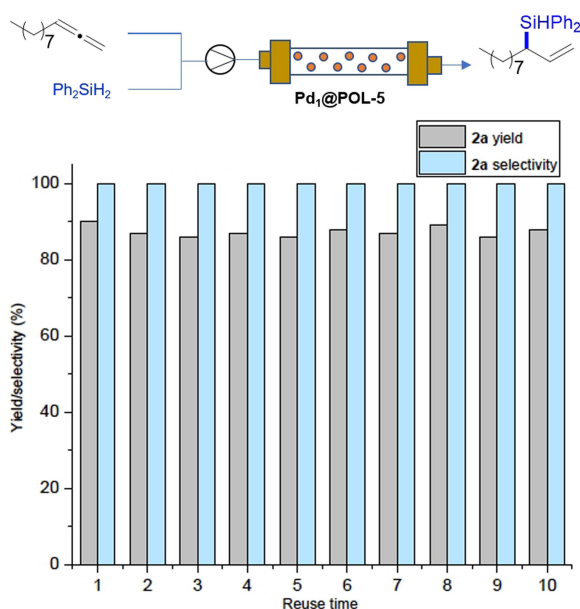


Figure 3. Yield and selectivity in ten consecutive hydrosilylation reactions between allene **1a** (0.25 mmol) and Ph₂SiH₂ (0.275 mmol) mediated by the same Pd₁@POL-5 catalyst. Reproduced from Ref. [21], with kind permission from Tsinghua University Press.

3. Industrial Uptake?

The fine chemical industry, we anticipate in the following, will shortly uptake SACs for the synthesis of many of its valued products under flow conditions. First, a SAC catalyst can replace a conventional metal nanoparticle-based heterogeneous catalysts in a drop-in replacement of the type sought by the chemical industry.^[22]

Second, whether in the form of “catalytic reactors” of tailored geometries in which the catalytic species are coated on the channel wall of the reactor reproducibly made by 3D metal printing, or as large surface area organic, inorganic or organic-inorganic hybrid materials, SACs under flow are ideally suited to further lower production costs due to enhanced stability of the catalyst, and largely enhanced TOF (when compared to reaction under batch conditions).

The real obstacle to the industrial uptake of heterogeneous catalysis in flow reactors to replace homogeneous catalytic processes carried out in batch reactors was and is the need to completely replace the existing (and expensive) batch reactors with the new flow reaction systems. Commenting on the slow but inevitable industrial uptake of heterogeneous catalysis in the fine chemical and pharmaceutical industries, in 2013 some of us concluded that this evolution would “slowly but inevitably” lead to the ultimate objective of green chemistry in this important industry, namely “chemical manufacturing with no waste generation and with minimal energy use”.^[23]

In the subsequent decade several fine chemical companies have shifted the production of valued fine chemicals to new flow systems.^[24] This is a rather unique case of fast uptake of completely new manufacturing technology in an industry that, besides advances in control technology, had never changed its manufacturing basics since its inception in the 1930s.

The reason is simple. Under continuous flow, production costs are lower and product purity (*i.e.*, quality) is better also due to enhanced lot-to-lot consistency.^[25] For example, in fine chemical productions water (32%) and solvents (56%) contribute to ~80% of the typical production process mass intensity.^[26] The use of flow chemistry dramatically reduces the use of solvents and water, directly translating into financial savings. In addition, inventories (including catalyst inventory) are substantially lower, further reducing costs.

As suggested by Kappe, “flow means green”,^[27] but it also means cost-efficiency (*i.e.*, money), because shifting chemical productions from batch to continuous flow reactors maximizes value production, and minimizes waste. In 2013, some of us associated the aforementioned waste, namely the large material waste testified by the 25–200 *E*-factor (Environmental factor, the ratio of waste over product) of the fine chemical and pharmaceutical companies,^[28] to the price of non-conformity (PONC) paid by any manufacturing organization when carrying out activities not required to produce a product meeting its requirements.^[23]

In brief, the overall cost of a production process (*C*), includes the intrinsic production process cost (*C_i*) plus the PONC cost of producing (and disposing of) unwanted by-products [Equation (1)].^[23]

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

In a highly competitive marketplace, successful fine chemical companies are not those that are “greener” but those able to supply customers with products, including pharmaceutical ingredients, at the lowest price, highest purity and best lot-to-lot consistency.^[23] Catalytic processes under flow are significantly greener than conventional processes in batch reactors. Yet, more importantly from a practical viewpoint, catalysis under flow dramatically reduces production costs,^[25] because it reduces the value of both addends in Equation (1), namely the intrinsic production cost to produce the desired product (C_i) and the PONC.

In the fine chemical industry, homogeneous catalysis has been the dominant technology in the last four decades.^[29] Though clearly underutilized by the industry, such as in the case of heterogeneous catalysis for cross-coupling reactions,^[30] the use of heterogeneous catalysis in continuous productions clearly lowers production costs. As noted by Kobayashi and co-workers, heterogeneously catalyzed processes under flow not requiring purification processes allow flow reactions to be assembled in a multi-step and continuous manner for the synthesis of complex molecules.^[31]

Moreover, reactions taking place in the confined space surrounding the immobilized catalytic species translate into high catalyst concentration allowing to overcome reactivity problems or conversion issues.^[31] Kobayashi's team, for example, recently demonstrated the continuous-flow synthesis of (*R*)-tamsulosin, one of the world's most prescribed drug, using three sequential heterogeneous catalytic reactions under flow without requiring isolation of any intermediates and with only volatile or easily removed by-products.^[32]

Three noble metal heterogeneous catalysts comprised of supported metal nanoparticles were employed: Pt/C, Pd on dimethylpolysilane-modified silica, and Pd on activated carbon/calcium phosphate. The continuous-flow reactions were much more efficient than the batch reactions for the key reductive amination step, and the final deprotection step based on hydrogenolysis could also be performed in continuous-flow. “We believe our heterogeneous catalysis-based multistep continuous-flow synthesis”, concluded the researchers, “provides a benchmark model for future pharmaceutical manufacturing”.^[32]

Whenever a SAC is available to replace a nanoparticle-based heterogeneous catalyst, this will be the case for the manufacturing not only of APIs and vitamins, but also of the wide variety of the fine chemical industry's products, especially considering that from the industrial utilization viewpoint, structured catalytic reactors such as those 3D-printed have several advantages compared with traditional packed-bed reactors.^[11]

4. Perspectives and Conclusions

Reviewing selected examples of the first utilization of SACs under continuous-flow conditions, this study shows evidence

that employed under flow, SACs are not different from state of the art supported metal nanoparticle catalysts^[5] in affording significantly higher TOFs compared to the same catalysts employed in batch reactor conversions.

As shown for example by Vilé and co-workers investigating the hydrogenation of furfural with H_2 mediated by $Cu_1@mpgC_3N_4$ coated on a ceramic support,^[11] new generation, high load (1.2% in this case) SACs under flow conditions are stable and do not rearrange into nanoparticle catalysts via movement on the surface or via the leaching/precipitation mechanisms. This is important because, as suggested by Pérez-Ramírez and co-workers lately reviewing single-atom catalysis for synthetic organic chemistry, loss of SAC stability and the regeneration of SACs so far have received little attention.^[3]

Being generally comprised of customer manufacturing organizations (CMOs), namely companies supplying active ingredients to variety of industrial customers including the pharmaceutical industry, fine chemical enterprises compete on cost, quality and speed of delivery.

Heterogeneously catalyzed processes under flow reduce both the intrinsic production cost to produce the desired product [C_i in Equation (1)] and the cost of producing unwanted by-products, dramatically reducing production costs when compared to traditional production processes carried out in the multi-purpose and multi-product plant (MPP) with stirred tank reactors equipped with reflux condensers (costing in excess of \$30 million) typical of fine chemical companies.^[33]

Production under flow, furthermore, enhances the lot-to-lot consistency and dramatically lowers production times and thus time of customer delivery.

The technology of continuous processing in the manufacture of fine chemicals that a large fine chemical manufacturer found to be “moving from embryonic to maturity” in 2013,^[34] in the late 2010s started to be widely adopted by fine chemical and API manufacturers.^[35] A variety of modular, advanced flow reactors and auxiliaries for commercial manufacturing of excellent productivity (0.6–5 kg/min) are now commercially available from different suppliers. Companies already exist owing multipurpose industrial flow systems installed in API manufacturing plants regularly inspected by the drug regulation authorities.^[36] Furthermore, such flow equipments are portable and readily installable in any plant to develop, scale-up and validate flow chemistry processes under good manufacturing practices (GMPs).

Driven by substantially lower production costs, since the early 1990s fine chemical and pharmaceutical companies based in Japan, western Europe and north American countries relocated API production to fine chemical companies based in China and India. Those countries became therefore dependent on imports. Alongside frequent shortage of fundamental drugs, the COVID-19 outbreak revealed the “irresponsible reliance”^[37] for the supply of life-saving APIs.

It may therefore not be surprising to learn that the governments of USA,^[38] European countries,^[39] India, and of several European countries including France are now supporting fine chemical companies manufacturing both APIs and key

starting materials (KSMs) to bring back production in their home countries ("reshoring").

Production of organic molecules via catalytic processes carried out in continuous flow not only minimizes the production and the total installed cost, but it also accelerates the design, construction and installation of the new flow plants. Indeed, commenting on the reshoring efforts of both API and KSM productions from China, the director of India's largest pharmaceutical industry association recently noted how:

"India's National Institutes of Pharmaceuticals Education and Research (NIPER), scientific institutions and companies are working on improved processes to provide cost-efficient options. With advanced technology, there are many drugs that can be produced faster, cheaper and with a smaller environmental footprint."^[40]

The advanced technology mentioned above is flow chemistry, and its cleanest and economically most advantageous version makes use of heterogeneous catalysts. Amid these catalysts, SACs stand out as the ultimate advanced heterogeneous catalysis technology made available by the ingenuity of research chemists. In addition, 3D printing enables cost-efficient manufacturing of flow reactors for heterogeneously catalyzed processes,^[12] with full freedom of design to meet the different process needs for the specific class of chemical reactions (oxidations, hydrogenations, nitration, hydrosilylation, cross-coupling reactions etc.).

Alongside many other heterogeneous catalysts including immobilized enzymes,^[41] high metal load, leach-proof SACs will be regularly used across the world's companies comprising the fine chemical industry.

Driven also by the need to remain competitive the shift to clean fine chemical productions based on continuous processes will inevitably take place also in China where in 2017 more than 40% of the world's API output was produced (until the mid 1990s, western Europe, the USA and Japan produced 90% of the API global output).^[40]

China hosts a huge fine chemical industry that after more two decades of investments in pollution control, especially reduction of wastewater, was recently found to be ready to uptake clean technology oriented to pollution prevention.^[42] The Asian country, where also single-atom catalysis was discovered,^[2] leads by far the world in terms of scientific articles published every year in the field of chemistry.^[43] A large share of said articles reports achievements of research in green chemistry.

Based on the outcomes of the present analysis, we anticipate and forecast that the fine chemical industry will progressively, but inevitably, switch to heterogeneous catalysis under continuous-flow conditions to manufacture most of its valued products. Driven by lower production costs, quicker production times and enhanced lot-to-lot consistency, the technology will make use of a variety of newly developed heterogeneous catalysts, including supported biocatalysts, electrocatalytic species, organocatalysts, metal nanoparticles and also single-atom catalysts.

Compared to other catalytic materials, the latter SACs will progressively replace most other metal catalysts due to their

intrinsic higher stability and lower amount of the heterogenized catalytic species which are often rare and expensive.

In conclusion, as shown by the India's efforts involving National Institutes of Pharmaceuticals Education and Research,^[40] the industrial uptake of new production technology based on heterogeneous catalysts (including SACs) under flow, requires universities to educate and train a significantly larger number of research chemists and chemical engineers skilled in both flow chemistry and heterogeneous catalysis. This, in its turn, requires to enhance education in catalysis founding its teaching and learning of catalysis on a unified approach based on reaction mechanism, visualization and renewed laboratory activities.^[44]

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords: fine chemical industry · flow chemistry · organic process · single-atom catalysis

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