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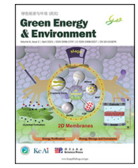

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Viewpoint

Heterogeneous catalysis under flow for the 21st century fine chemical industry

Rosaria Ciriminna [a], Mario Pagliaro [a,*], Rafael Luque [b,c,*]

[a] Istituto per lo Studio dei Materiali Nanostruturati, CNR, via U. La Malfa 153, 90146, Palermo, Italy

[b] Departamento de Química Orgánica, Universidad de Córdoba, Campus de Rabanales, Edificio Marie Curie (C-3), Ctra Nnal IV-A, km 396, Cordoba, 14014, Spain

[c] Peoples Friendship University of Russia (RUDN University), 6 Miklukho Maklaya St., 117198, Moscow, Russia

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Abstract

Due to metal leaching and poor catalyst stability, the chemical industry's fine chemical and pharmaceutical sectors have been historically reluctant to use supported transition metal catalysts to manufacture fine chemicals and active pharmaceutical ingredients. With the advent of new generation supported metal catalysts and flow chemistry, we argue in this study, this situation is poised to quickly change. Alongside heterogenized metal nanoparticles, both single-site molecular and single-atom catalyst will become ubiquitous. This study offers a critical outlook taking into account both technical and economic aspects.

Keywords: Fine chemical; Heterogeneous catalysis; Single atom catalysis; Green chemistry; Chemical industry

1. Introduction

At the end of 2015, a seminal study was published aiming to explain why the pharmaceutical industry does not use immobilized transition metal complexes as catalysts to manufacture active pharmaceutical ingredients (APIs) [1]. Most if not all immobilized transition metal catalysts suffer from poor stability which generally translates into metal leaching, metal contamination of the product, as well as into reaction rate and selectivity generally lower than under homogeneous conditions. Under these circumstances, the authors concluded, there is “no reason to incur the extra added cost in immobilizing the homogeneous catalysts” [1].

This picture was somehow in contrast to what reported in Kirschining's book devoted to the topic in 2004, when industry's researchers at a leading specialty chemical company presented a number of commercially available immobilized catalysts including FibreCat, LigandNet, and EnCat catalysts [2].

In the subsequent fifteen years, several new immobilized solid catalysts have been commercialized. Examples include polystyrene-supported equivalent of tetrakis (triphenylphosphine) palladium (0) PS-PPh_3-Pd, affording high yields of cross-coupling reaction products [3]; the silica-supported FixCat for cross and ring closing olefin metathesis allowing to reduce residual Ru levels below 10 ppm, recyclable

* Corresponding authors.
E-mail addresses: mario.pagliaro@cnr.it (M. Pagliaro), rafael.luque@uco.es (R. Luque).

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for up to 23 runs and efficiently used in continuous flow processes [4]; the Silia*Cat* catalyst series of multipurpose sol–gel entrapped catalysts [5]; and Phos-Cat4 acid catalyst replacing traditional homogeneous acids used in esterification, elimination, rearrangement, cyclisation and hydrolysis reactions [6].

The fine chemical industry is usually identified as an ensemble of contract manufacturing organizations (CMOs) producing APIs for large pharmaceutical firms. This outlook is reductive, as fine and specialty chemical companies supply valued products to a number of large industrial sectors [7]. One is the flavor and fragrance industry with the global demand for flavors, perfumes, and fragrances forecasted to grow 4.9% per year, reaching $36 billion in 2022 [8]. Another is the food and beverage industry. All these large industrial sectors are being reshaped by a global societal megatrend driving the demand of "naturals" [9], which inevitably leads to enhanced demand of green production processes, and thus of catalysis.

To access the valued functional compounds of this strategically important industry in the next few years of the 21st century, we argue in this study, all catalysis methodologies will be involved, well beyond conventional homogeneous catalysis via transition metal complexes and heterogeneous catalysis via supported metals: photocatalysis, biocatalysis, organocatalysis and electrocatalysis.

Catalysts will be successfully immobilized and used under intensified, continuous-flow conditions to afford the multiple functional products increasingly required by advanced and developing economies.

Whatever the catalytic species immobilized – metal nanoparticles, molecular metal complexes, organic molecules, enzymes or single-atoms – if the catalytic material affords stable catalytic activity then the technical, economic, and environmental advantages are so numerous that industrial application under continuous flow can be expected to take place rapidly.

We provide a critical outlook taking into account technology, economic and industrial aspects that are rarely taken into account together in the chemistry literature. The outcomes will be useful to practitioners of innovation in catalysis and in chemistry in industry and in academia.

2. Immobilized catalysts under flow

According to the vice-president of chemical development at a pharmaceutical company talking in 2017:

> «Two areas of technology have emerged in recent years as particularly important for API manufacturing: flow chemistry and catalysis as both can be applied to a broad scope of APIs. Catalysis provides shorter/more atom-economical, more cost-effective, and greener processes, while also providing novel reactivities that were not accessible before. Flow chemistry is another green technology that expands the horizon of the types of chemistry that can be used for making bulk APIs» [10].

Indeed industrial applications of flow chemistry − enabling processes that are more efficient, faster, safer, cleaner and much cheaper than productions in batch – are already numerous [11].

Heterogeneously catalyzed processes under flow in small reactors are particularly convenient, since liquid and gas reagents flowing across the solid catalyst sense high local concentration of the catalytic species which, combined with short diffusion paths and superior mixing, affords quicker reaction without downstream work-up and purification steps [12].

Originally confined to the manufacture of bulk chemicals where it has been used since the early days of the chemical industry, the use of heterogeneous catalysis started to expand to the production of fine chemicals since the early 2000s. For example, as reported by Bonrath in 2014, in the manufacture of vitamins, carotenoids, flavoring and fragrance compounds, wherein industry is finally replacing former stoichiometric processes with heterogeneously catalyzed syntheses [13].

This trend it is now gaining further relevance with the commercialization of the first catalytic production processes under flow with large catalyst manufacturers advertising new heterogeneous catalysts capable "to meet the increased interest in continuous processing in pharmaceutical and fine chemical applications" [14].

3. Profit-driven process innovation

Referring to the rapidly declining return on investment in pharmaceutical research and development (R&D) activities, a manager at a large pharmaceutical company recently suggested [15] that the main reasons for this quick decline include slower development of new drugs due to rising clinical trial costs in a more stringent regulatory environment, and increasing competition from generic manufacturers producing much cheaper versions of existing drugs after the original patents have expired.

Usually referred to as "generics" to identify formerly patented molecules with pharmaceutical activity such cheaper drugs are ultimately produced thanks to API manufacturing at fine chemical companies according to current good manufacturing practice (cGMP) mostly in China and in India. To enhance profit margins, therefore, these companies need to lower production costs via enhanced production processes.

This reverses the approach to innovation in fine chemical companies working as CMOs producing APIs from product to process innovation.

In 2013, Ciriminna and Pagliaro extended to chemistry Crosby's approach to quality in manufacturing based on the "price of nonconformity" (PONC) as a simple, yet highly effective financial measure of quality [16].

According to this approach, quality is achieved through prevention, rather than by control, because removing errors, omissions, and superfluous work from manufacturing processes does not add cost, but rather reduces cost.

Seen from this perspective, the large amount of waste testified by the 25−200 E factor (mass of waste/mass of product for assessing the environmental impact of manufacturing processes) [17] typical of the fine chemical and pharmaceutical industry processes, stands as a hallmark of poor process quality, adding unwanted cost (Fig. 1) that a company should rather eliminate from its overall PONC.

To reduce cost, industry's managers will therefore undertake action to eliminate the PONC cost of producing unwanted byproducts from the overall cost of the process (C) in eq. (1), and also to lower the intrinsic cost (C_i) of the current manufacturing process:

$$C = C_i + PONC \quad (1)$$

Now, when a new catalyst suitable for an existing industrial synthetic process is introduced, industry will generally opt for one of two options (Fig. 2) [18].

In brief, if the return on investment (ROI, the ratio between the net profit and cost of investment resulting from the investment) offered by the new catalyst and catalytic process is large and prolonged in time, a completely new plant will be built whose economics outperform the older process/plant by such an extent to make the investment economically sound.

If, instead, the economic advantages offered by the new catalyst do not lead to a ROI value large enough to justify a switch to a new chemical plant or process, industry will only use the new catalyst if it can directly replace the catalyst currently employed in the existing process/plant (drop-in solution).

This was the case, to exemplify the concept, of a new ring closing metathesis (RCM) catalyst affording an antiviral molecule with the use of 0.05 mol% homogeneous Ru catalyst load, affording the RCM product (a macrocycle intermediate) via a new process reducing the *E*-factor from 370 to 52 kg/kg [19]. “The new RCM process” the authors from a pharmaceutical company concluded “could be readily accommodated in the existing standard multipurpose reactors in chemical production, and the need for a multimillion dollar capital investment was averted” [19].

For decades heterogeneous catalysis in the fine chemical industry has remained confined to hydrogenation processes which, in the absence of a metal catalyst to mediate the reaction between hydrogen and organic compounds, require high (> 400 °C) and technically unfeasible reaction temperatures.

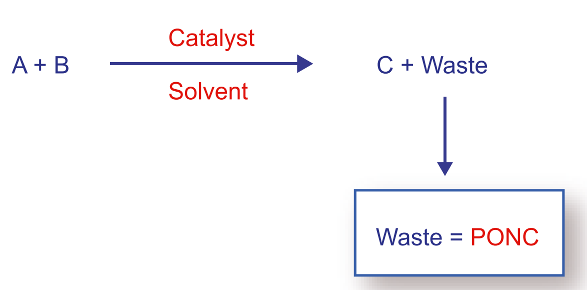

Fig. 1. Any waste in a chemical reaction used by industry to afford the desired product (C) adds to the overall price of nonconformity (PONC) paid by the company.

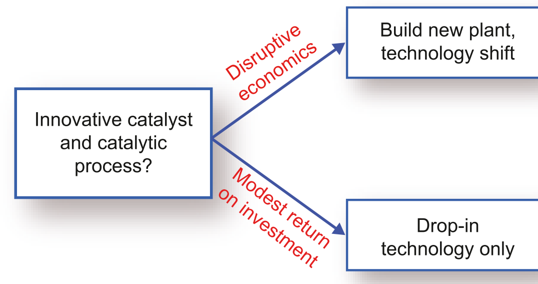

Fig. 2. When a new catalyst is developed a new plant is built only if it affords disruptive economics. Otherwise, the catalyst will be used only if it can be applied as a drop-in replacement for the old catalyst.

The shift from batch-wise to manufacturing under flow in industry has started from heterogeneously catalyzed hydrogenation reactions.

The reactants, namely the substrate dissolved in liquid phase and H_2 gas, are continuously passed through the small reactor containing the packed solid catalyst. Mass and heat transfer capability under flow in such flow reactor are significantly higher and it is instructive to notice the interest for such intensified production processes at India's largest pharmaceutical company [20].

Amid the three major impacts of intensification on manufacturing operations, production process and production facility, the manager responsible for Operations at the aforementioned India-based firm, emphasizes how the new production under flow under tightly controlled conditions in small reactors results “in much smaller, safer and cheaper production units” [20].

This reduces the barrier to entry the fine chemical industry market.

Now, fine chemical manufacturers may flexibly and quickly produce only the amount of functional products required by the customer when it is required, truly becoming demand-driven companies in which manufacturing takes place similarly to what happens at plants of world's class good manufacturers using intensified, “lean” production methods [21].

This innovation trend may explain the spur in demand of practical innovation in catalysis and flow chemistry mentioned in 2017 by another pharmaceutical industry's innovation manager [10], with professional development courses “featuring top speakers from academia and industry” currently being routinely organized to “provide industrial chemists with an unparalleled opportunity to explore how catalysis can change the landscape of process chemistry” [22].

Under these circumstances, the basic reason for the “high reproducibility because of GMP” argument typically objected to catalysis and flow chemistry innovation in API and fine chemical manufacturing loses its value. Most innovation in catalysis, indeed, ends up finding no practical application due to insufficient ROI generation potential.

This is the commonly found case of pharmaceutical and fine chemical production processes which, no matter if catalytic or stoichiometric, usually take place in batch under homogeneous conditions with all the reaction components combined and held under controlled conditions until reaction is complete with reaction typically taking hours, and the product isolated at the end of the process cycle carrying out purification and crystallization on the entire batch with fine control of unit operations as required by cGMP protocols [23].

It is also useful to remind that the catalysis industry has another source of revenues in the regeneration of spent catalysts obtained from its customer chemical companies. Supported noble metal catalysts used for hydrogenation, for example, are typically sent back to the manufacturer after use for refining and re-manufacturing with typical losses at refining for Platinum Group Metals (PGMs) used varying between 2–5% for Pd and Pt, 5–10% for Rh and 10–15% for Ru during refining [24].

4. An industry in transition

Han, a renown green chemistry scholar based in China, is often approached by companies "wondering whether we could provide or recommend some green technologies to them" [25].

> «Many company operators come to me to talk about their factories … They are eager to make their production processes green and to meet the government's requirements. But once we came to the stage of industrialization, there exists the problem of cost and profit. No matter how green the process of a technology is, it could not be considered as a real 'green technology' as long as it is too expensive and cannot be industrialized. So, we have to create more highly effective and economically viable technologies to authentically promote the development of green industries» [25].

The development and commercialization of the "economically viable" catalysis technologies mentioned by Han will no longer be restricted to conventional catalyst companies, but is likely to involve soon several new players, often academic spin-offs.

Selected examples may include the company established to commercialize immobilized ruthenium complexes using Grela's ammonium-tagged NHC ligands as an anchor for immobilization [26]; and the company relying on Perez-Ramirez's single-atom catalysts comprised of noble metal single-atoms anchored to graphitic carbon nitride exfoliated sheets [27], already able to offer platinum group metal-based single-atom heterogeneous catalysts on the kilogram scale [28].

Supported by the Foundation for Polish Science, Professor Grela's team is working towards the commercialization of his catalysts for fine chemical manufacturing [29]. Asked to comment, he remarked: "Our catalyst makes chemical production via versatile olefin metathesis more environmentally-friendly, more selective, and easily scalable under flow. So, I think that it is just matter of time to see some first applications in pharma too" [30].

Along with most of the world's fine chemical industrial plants, China and India host also advanced school of chemistry, with numerous Indian and Chinese scholars contributing key advances in catalysis, including single-atom catalysis in which China clearly excels [31]. It is therefore likely that China- and India-based innovative catalysis companies will shortly emerge supplying new generation solid catalysts to fine chemical manufacturers.

The same can be expected to take place shortly in Russia, Iran and Brazil. Russia's fine chemical industry is currently undergoing modernization with new production facilities, as well as modernization of existing ones by both Russia-based companies as well as foreign companies investing in new production sites within the world's largest country [32].

Plentiful innovation in catalysis is available at Russia's academic institutions. For example, in the last five years Ananikov's team in Moscow has developed a number of advanced new solid catalysts suitable for immediate commercialization. Enough is to cite here the new Pd/C catalyst made *in situ* in less than 5 min via direct deposition of Pd^0 nanoparticles onto the highly accessible surface area and the avoidance of ill-defined Pd^{II}/Pd^0 states [33].

Today, catalysis companies supply the fine chemical and pharmaceutical industries mainly with catalysts used to accomplish conventional hydrogenation, asymmetric hydrogenation, cross coupling and ring closing metathesis reactions. Underlining the societal relevance of catalysis, all the aforementioned processes were recognized with the Nobel prize: Sabatier (along with Grignard) in 1912 for his studies on the direct hydrogenation of organic molecules on powdered nickel [34]; Knowles (alongside Noyori and Sharpless) in 2001 for the discovery that rhodium coordinated by chiral phosphine ligands performs asymmetric catalytic hydrogenation [35]; Schrock for catalytic metathesis reactions in 2005 [36]; Suzuki, Heck, and Negishi in 2010 for palladium-mediated cross-coupling reactions [37].

In almost each case of the aforementioned reactions, fine chemical companies, including the CMO suppliers of pharmaceutical firms, are supplied with homogeneous catalysts or chiral ligands; whereas catalysis via stable nitroxyl radicals coupled to inorganic oxidant (NaClO, $Cu(I)/O_2$, etc.) is increasingly replacing toxic inorganic oxidants such as Mn(VI) and Cr(VI) previously used in overstoichiometric amount for the selective oxidation of alcohols to aldehydes and ketones [38].

All above processes can be carried out under flow with significant advantages, and industry has already started to replace conventional batch processes with reactions under flow. For instance, a large pharmaceutical company in 2015 switched from batch to flow-chemistry the Anelli-Montanari oxidation to convert an alcohol to an aldehyde in the course of manufacturing an API [39].

Now, the yield to the desired aldehyde product has increased from 75% in the batch reaction to 90% due to limited over-oxidation to carboxylic acid whereas the reaction is now performed using a 15 L h^{-1} meso-reactor at 15 °C rather than at −70 °C as in previous batch process. We remind that the process uses 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) as catalyst and aqueous NaOCl as primary oxidant in a two phase system. Further oxidation to the corresponding carboxylic acid is an undesirable by-product.

Recognizing that several "catalyst systems in which the immobilized system exhibits equal or superior reactivity and/or offers enhanced stability to the homogeneous equivalent" were reported since the early 2000s, recently a team of research chemists at different pharmaceutical companies revisiting key research areas in green chemistry from the industry's viewpoint, concluded that "the immobilization of catalysts remains an exciting area particularly with the growth of interest in continuous manufacturing" [40].

For example, regardless of common misconception that enzymes are unstable and expensive and unsuited for scalable chemical processing, the number of enzyme-mediated reactions performed by industry in a continuous manner over immobilized enzymes is significant and rapidly on the rise [41].

The same will occur in electrocatalysis now that ultrastable sol–gel single-site catalytic electrodes or nanostructured photocatalysts are available to selectively oxidise alcohols using an electric current only [42], or make fine chemicals using visible light generated by new LED-based energy efficient light sources in flow photoreactors [43].

5. Outlook and conclusions

Ever since its inception in 1875 with the first heterogeneously catalyzed industrial process (the Pt-catalyzed conversion of SO_2 to SO_3 to make sulfuric acid), heterogeneous catalysis has been the key enabling technology of the chemical industry.

Catalysis, in general, is used in the production of 80% of industrially important chemicals, namely in more than $10 trillion in goods and services of the global gross domestic product annually, with the global demand on catalysts exceeding $30 billion in 2016 [44].

Heterogeneous catalyst is, by far, the largest type segment of the industrial catalyst market, as solid catalysts enable batch or continuous processes in which reaction products are readily separated from the catalyst, with the catalyst remaining available for subsequent manufacturing steps until losing its activity and becoming "spent" to be replaced with fresh catalyst.

Innovation in catalysis for fine chemicals is coming in the form of new-generation solid catalysts replacing both conventional homogeneous and heterogeneous catalysts, and new organic process technology with conversions under continuous flow replacing chemical processes in batch.

This wave of innovation is due to reshape both manufacturing at fine chemical and pharmaceutical companies and catalyst development and production at catalysis companies, enabling also the industrial uptake of electrocatalysis and photocatalysis which for more than a century have remained confined to a few industrial processes. For example, scholars in China recently reported how polymeric carbon nitride, a cheap and stable photocatalyst, once mixed with glass beads can be easily used in a continuous-flow photoreactor affording high visible light penetration to promote the synthesis of cyclobutanes on gram scale (81% yield) at room temperature in air [45].

Similarly, scholars in Britain, in collaboration with India's largest generics manufacturer, recently employed two NADH-dependent enzymes (lactate dehydrogenase and formate dehydrogenase) heterogenized on carbon mixed with glass beads for the conversion of pyruvate to lactate in a continuous packed bed reactor with concomitant *in situ* cofactor recycling [46]. High conversion and productivity levels were achieved in the flow reactor for more than 30 h, demonstrating that it is now possible to shift many other biotransformations requiring NADH from batch to flow.

Uptake of newly developed heterogeneously catalyzed processes under flow by the existing and new fine chemical companies will be rapid because capital expense is relatively low, and operation costs are dramatically reduced, whereas valued fine chemical ingredients are in increasing demand not only from the pharmaceutical industry but also from food and beverage, flavor and fragrance, cosmetic, personal care, electronic and advanced materials industries.

Eventually, in the renewed fine chemical industry [47], today's production plants embedding stirred tank reactors for batch production processes will be replaced by a network of decentralized smaller and modularized production units in which manufacturing of fine chemicals and APIs will flexibly take place via catalytic processes carried out under flow and under mild reaction conditions, mostly over solid catalysts.

In these processes, little or no waste will be produced thanks to high stability and selectivity of new-generation solid catalysts coupled to finely controlled reaction conditions enabled by the digitally controlled flow microreactor technology [48].

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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