

# Practical Aspects Concerning Catalysis with Molecularly Doped Metals\*\*

Rosaria Ciriminna,<sup>\*[a]</sup> Matteo Formenti,<sup>[b]</sup> Mario Pagliaro,<sup>[a]</sup> and Cristina Della Pina<sup>\*[b]</sup>

Ranging from silver-entrapped dyes and gold-entrapped enzymes through palladium-entrapped graphene oxide, molecularly doped metals (or metal organic alloys, MORALS) are active, stable and uniquely versatile catalysts in a number of reactions of relevance to the chemical industry. Reactions successfully catalyzed by MORALS concern both industry's main sectors,

producing bulk and fine chemicals. Though first reported in 2005, and clearly holding a great applicative potential, their use in catalysis is still surprisingly limited. This study investigates a number of practical aspects concerning molecularly doped metals as heterogeneous catalysts.

## 1. Introduction

Invented by Avnir in 2002,<sup>[1]</sup> molecularly doped metals found their first application in catalysis in 2005 when Behar-Levy and Avnir reported that the Nafion polymer entrapped within Ag (Nafion@Ag) readily mediates the pinacol-pinacolone rearrangement and the dehydration of 2-phenylethanol to styrene with high yield (80% and 90%, respectively).<sup>[2]</sup> In the subsequent two decades the research field of metal-organic alloys (MORALS)<sup>[3]</sup> continued to grow, though at a lower rate than one would expect from the scope and possibilities opened by this new class of materials merging the properties of metals with those of organic molecules.<sup>[4,5]</sup>

Generally obtained as a metal powder efficiently produced from a metal salt precursor, a MORAL is typically produced via a single reduction process followed by entrapment, aggregation and precipitation succinctly summarized by Eq. 1.<sup>[1,4]</sup>



The resulting MORAL generally consists of an aggregate of metal crystallites (with typical particle sizes on the order of 100  $\mu\text{m}$ ) and interstitial porosity, with much of the dopant

molecules residing on the metal crystallite surface in closed interstitial pores formed by the metal crystallite aggregation.<sup>[1]</sup> Crucially important for MORAL chemical applications, the entrapped molecules are accessible to external reactants, as shown since the very first study in which entrapped Congo Red (CR) could be readily reduced with aqueous  $\text{Na}_2\text{S}_2\text{O}_4$ .<sup>[1]</sup>

Ranging from gold-entrapped enzymes<sup>[6]</sup> through palladium-entrapped graphene oxide,<sup>[7]</sup> MORALS are also active and selective catalysts in a number of reactions of relevance to both major segments of the chemical industry, wherein bulk and fine chemicals in nearly each case are produced through catalyzed chemical reactions.

Practice-oriented knowledge is instrumental in ensuring the successful transfer of new catalysis technology to industry.<sup>[8]</sup> Chemical companies, for instance, are interested in acquiring early-stage evaluation of a new catalyst manufacturing (and utilization) cost.<sup>[9]</sup> This study therefore investigates a number of practical aspects concerning the use of molecularly doped metals as heterogeneous catalysts.

## 2. Results and discussion

In general, MORALS are obtained as mechanically robust metallic powders in which the metal crystallites embed the entrapped organic molecules. Such soft metal powder can be easily processed in the catalyst shapes most frequently used in industry, including (see below) compact disks obtained by simple compressing the powders subsequently used as highly selective cathodes for electrocatalytic asymmetric hydrogenations.<sup>[10]</sup>

As put it by Kennema, the co-inventor of a new 3D printing catalyst technology at a large chemical company and catalyst manufacturer based in Germany,<sup>[11]</sup> the shape of the catalyst very often is the main dictator of the overall performance of a catalyst in a commercial reactor.<sup>[12]</sup>

A catalytic MORAL powder, for example, can be readily used to produce a hydroalcoholic ink and the latter used to deposit the ink on widely different catalyst supports. Besides being obtainable in various catalyst shapes, however, the key factor

[a] Dr. R. Ciriminna, Dr. M. Pagliaro  
Istituto per lo Studio dei Materiali Nanostrutturati, CNR  
via U. La Malfa 153  
90146 Palermo (Italy)  
E-mail: rosaria.ciriminna@cnr.it

[b] M. Formenti, Prof. Dr. C. Della Pina  
Dipartimento di Chimica  
Università degli Studi di Milano  
via Golgi 19  
20133 Milano (Italy)  
E-mail: cristina.dellapina@unimi.it

\*\*] A previous version of this manuscript has been deposited on a preprint server (<https://doi.org/10.26434/chemrxiv-2023-2g0d8>).

© 2023 The Authors. ChemCatChem published by Wiley-VCH GmbH. This is an open access article under the terms of the Creative Commons Attribution Non-Commercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

that will determine industry's willingness to uptake a new catalyst is cost. Unless a new catalyst dramatically reduces the cost of an existing process (in which case industry will build a new plant running the newly enabled process), the replacement of an existing catalyst with a new one results in moderate financial savings due to reduced production costs.<sup>[13]</sup> In the latter case, the chemical industry will opt to use the new catalyst only if it is suitable as a "drop-in" solution, without having to invest in new chemical reactors or other new plant components.<sup>[13]</sup>

Being a metal powder efficiently produced from a metal salt precursor, the cost of a MORAL catalyst is practically equivalent to the cost of its metal and organic species precursors in Eq. 1.<sup>[1,4]</sup>

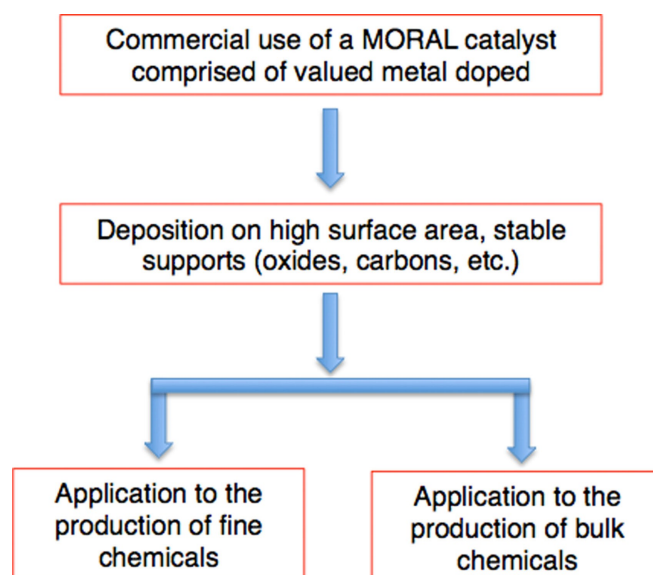
A simple, yet powerful step-based method to assess a catalyst manufacturing cost suggests that an estimate of catalyst manufacturing cost is given by adding together the raw materials and synthesis step costs as a subtotal.<sup>[9]</sup> For example, the cost of a conventional Pt/C catalyst produced on small scale (1 t/day) prepared by wet impregnation of an activated carbon support with chloroplatinic acid ( $\text{H}_2\text{PtCl}_6$ ) is around \$ 35/kg and the estimated market price \$ 60/kg.<sup>[14]</sup> The cost is obtained adding overhead costs consisting of general and administrative costs (G&A calculated as 5% of the aforementioned subtotal), and sales, administrative, research, and distribution costs (SARD, computed as 5% of [subtotal + G&A], plus a selling margin calculated as 50% of [subtotal + G&A + SARD]).<sup>[14]</sup>

Applying the same step-based method to the calculation of the manufacturing cost of a catalyst such CR@Ag (Congo Red in silver, used to selectively mediate the partial oxidation of methanol with air's oxygen)<sup>[15]</sup> or GO@Pd (GrafeOPlad, graphene oxide in palladium usable to synthesize aniline)<sup>[7]</sup> would afford an exceedingly higher catalyst production cost, as the current (early 2023) prices for silver and palladium are, respectively, 760 \$/kg and 45,910 \$/kg.

However, in both the production of bulk or fine chemicals, the MORAL catalysts comprised of valued metals entrapping organic molecules would find employment by further deposition of the MORAL microparticles (or nanoparticles) on stable, large surface area catalyst supports such as metal oxides, and activated carbons (Scheme 1).

This has been shown in 2013 by Avnir and co-workers reporting the outcomes of methanol oxidation to formaldehyde over 10–30 nm CR@Ag nanoparticles doped with 1.67 wt.% of CR deposited on  $\text{TiO}_2$  nanofibers.<sup>[16]</sup> The supported MORAL catalyst largely exceeded the catalytic performance of both conventional silver catalyst used in industry (Ag in gauze shape) and of unsupported CR@Ag with respect to all the parameters of the oxidation of methanol to formaldehyde.

Owing to the uniform spreading of the CR@Ag nanoparticles over the porous  $\text{TiO}_2$  nanofibers, which results in higher porosity, larger surface area, and lower sinterability of the separated MORAL particles, the CR@Ag/ $\text{TiO}_2$ -nf catalyst had 18 times higher weight hourly space velocity and 10 times higher space time yield when compared to unsupported submicronic CR@Ag particles. Whereas the latter material was stable only for one reaction run,<sup>[15]</sup> the catalyst comprised of

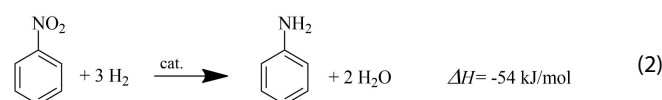


Scheme 1. MORAL catalysts consisting of valued metals to be employed in the production of chemicals.

Cr@Ag nanoparticles supported on  $\text{TiO}_2$  nanofibers was remarkably stable and reusable, with even higher conversion rate (98%) and selectivity (85%) observed after the second reaction run.<sup>[16]</sup>

Formaldehyde is a bulk chemical produced yearly at > 13 million t/a rate chiefly via the partial oxidation of methanol with air in the presence of a 25–30 mm thick bed of Ag crystals, steam, and excess methanol at 650–720 °C affording nearly quantitative conversion to aldehyde, or over a silver catalyst in gauze shape at 600–650 °C affording lower product yield followed by recycling of the unreacted methanol.<sup>[17]</sup>

Another important bulk chemical used as a valuable intermediate for polyurethanes, dyes, pharmaceuticals, phytochemicals, and explosives is aniline which is commercially produced via nitrobenzene hydrogenation (Eq. 2), usually in > 99% yield, in very large amount (over 6.8 million t/a in 2021).<sup>[18]</sup>



To mitigate safety risks, the vapor phase hydrogenation is carried out with a high molar excess of hydrogen (up to 1:200 NB/ $\text{H}_2$  molar ratio) to avoid large partial nitrobenzene pressures leading to overheating of the reaction mixture due to the largely exothermic nature of the hydrogenation process ( $\Delta H = -54 \text{ kJ/mol}$ ).<sup>[19]</sup> The process is carried out mostly in vapor-phase over *i*) Cu/ $\text{SiO}_2$  (promoted with chromium, zinc, and barium) at 250–300 °C and in the presence of excess  $\text{H}_2$  at 4–10 atm, or over *ii*) a Pd/C (promoted with lead to reduce aromatic ring hydrogenation) at 1–7 atm pressure of excess hydrogen.<sup>[20]</sup> Certain companies conduct the hydrogenation in liquid-phase over a *iii*) Pd–Pt/C catalyst (with iron as modifier) at 90 °C under

1 atm H<sub>2</sub>, or over *iv*) Ni/SiO<sub>2</sub> at 200 °C and 6 atm pressurized H<sub>2</sub>.<sup>[20]</sup>

The noble metal Pd–Pt/C catalyst is the most expensive amid the catalysts commercially used, but the process is carried out in liquid phase at 90 °C only, with nitrobenzene conversion to aniline nearing 100% in a single pass. Accordingly, the reactor effluent is virtually free of nitrobenzene, while the H<sub>2</sub> excess is readily separated from the reactor effluent and the liquid product directed to the dehydration column.<sup>[21]</sup>

Improving nitrobenzene reduction in liquid phase by improving the supported Pd catalyst would further contribute to lower aniline manufacturing cost, and lower the environmental “footprint” of its production. Indeed, the 2015 study of Jackson and co-workers from a platinum-group metal (PGM) catalyst manufacturer identifying the hydrogenation mechanism,<sup>[22]</sup> was aimed to improve both catalyst and reactor design. The reaction takes place by coupling the readily formed surface intermediate Ph–N(OH) reacting with itself to eliminate water and produce azoxybenzene, followed by quick hydrogenation and formation of aniline,<sup>[22]</sup> and not through formation of nitrosobenzene as suggested by Haber in 1898.

It is therefore promising the recent discovery that aniline can be readily obtained by reduction of nitrobenzene at room temperature with hydrazine over GO@Pd (GrafeoPlad) nanoparticles.<sup>[7]</sup> The latter will be deposited on a large surface area support and the resulting catalyst evaluated in terms of cost and durability in comparison to the aforementioned bimetallic Pd–Pt/C catalyst. Should its performance turn out to be superior to Pd–Pt/C using H<sub>2</sub> as reductant (and not with expensive hydrazine), the supported GrafeoPlad catalyst would be available as the “drop-in” replacement sought after by the chemical industry for most of the newly developed heterogeneous catalysts.<sup>[13]</sup>

## 2.1 Advantages and disadvantages

Table 1 lists the key advantages along with the main current disadvantages of MORALS as heterogeneous catalysts.

Table 1. Advantages and disadvantages of MORALS to be employed as heterogeneous catalysts.	
Advantages	Disadvantages
High and tuneable selective activity	A certain amount of valued metal atoms in catalyst particles not accessible to external reactants
Highly reproducible and easily scaled-up preparation via solution chemistry	No published studies on scaled-up processes mediated by MORALS
High physical and chemical stability	Need for further deposition on porous, stable support to lower operational costs
In principle, applicable to either bulk and fine chemical production processes as drop-in technologies	Limited number of published studies, regardless of excellent early achievements
Easily applicable to continuous-flow processes	Lack of studies demonstrating technical viability even at 100 g product scale

### 2.1.1 Advantages

The first key advantage of MORALS lies in their high and uniquely tuneable selective activity due to wide variety of organic molecules that can be entrapped within the metal lattice, from enzymes<sup>[6]</sup> through catalytic metal complexes<sup>[23]</sup> and polymers.<sup>[2]</sup> The entrapment process allows to finely tune the original activity of the bare metal by altering the metal work function in the range of 1 eV, due to the charge transfer interactions between the dopant molecule and the surrounding 3D metallic inter-crystallite cage.<sup>[24]</sup>

Showing the exceptional versatility of catalytic MORALS, for example, is the case of an oxidizing Ir pincer complex entrapped in Ag or in Pd and a reducing Rh complex entrapped in Ag applied in a multistep process with opposing oxidations and reductions.<sup>[25]</sup>

The second key advantage is the pronounced physical and chemical stability of MORALS: the entrapped molecules indeed are protected from harsh environmental conditions and have a much better stability and concentration than corresponding metals on whose surface the organic molecules are two-dimensionally physically or chemically adsorbed.<sup>[1,4,5]</sup> For example, L-asparaginase entrapped in Au remains alive at the extreme pH of 13, which normally kills the enzyme instantly, whereas collagenase and laccase entrapped in the same noble metal show excellent recyclability for eight cycles (Figure 1).<sup>[26]</sup>

The high physical (mechanical and thermal) and chemical (lack of leaching in most solvents except strong solvents such as DMSO)<sup>[27]</sup> stability makes catalytic MORALS easily applicable to continuous processes carried out under flow, as well as applicable to either bulk and fine chemical production processes as “drop-in” technologies.

Finally, likewise the sol-gel process used to produce new generation heterogeneous entrapped catalysts,<sup>[28]</sup> the synthesis of MORALS takes place in liquid phase, mixing aqueous solutions of the precursors, thereby making the material synthetic route displayed in Eq. 1 both highly reproducible and scalable, with virtually no metal loss and by-product formation.

### 2.1.2 Disadvantages

A MORAL consists of metal powder with a relatively small weight percent of entrapped organic molecules. A certain amount of valued metal atoms “buried” in the inner surface of catalyst particles will thus not be accessible to external reactants. In addition, practical utilization in heterogeneous catalysis requires further deposition of the catalyst micro- or nanoparticles on a porous, stable support to widen the catalyst porosity and surface area, and lower sinterability of the doped metal particles deposited.<sup>[16]</sup> This adds one step to the catalyst preparation, requiring proper selection of the most suitable catalyst support and deposition method.

Perhaps the most important difficulty towards MORAL practical application is due to the limited number of studies devoted in two decades (2002–2022) to these fascinating and highly promising catalytic materials (Table 2). For instance, a

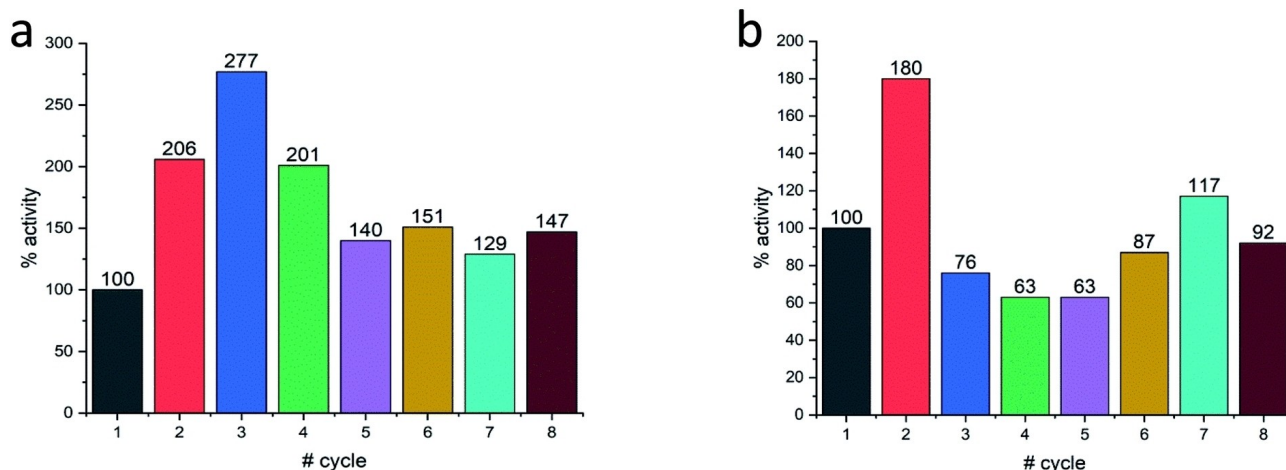


Figure 1. Recyclability of (a) Col@Au and of (b) Lac@Au. [reproduced from Ref.26, CC-BY Creative Commons License].

Table 2. Selected research papers reporting the use of catalytic MORALS, year of publication, and main achievement.

Article title	Year	Reference/Main achievement
Silver doped with acidic/basic polymers: novel, reactive metallic composites	2005	Ref.2/ Nafion@Ag) readily mediates the pinacol-pinacolone rearrangement and the dehydration of 2-phenylethanol to styrene with high yield.
Organically doped metals – a new approach to metal catalysis: enhanced Ag-catalyzed oxidation of methanol	2007	Ref.15/Nafion@Ag catalyzes the methanol partial oxidation to formaldehyde lowering the temperature needed for maximal conversion by 100 °C, the temperature to reach the maximal selectivity by 200 °C, and doubling the maximal space velocity.
Bioactive enzyme-metal composites: The entrapment of acid phosphatase within gold and silver	2009	Ref.6/Acid phosphatase is entrapped in Au and successfully hydrolysis of <i>p</i> -nitrophenyl phosphate by the new MORAL demonstrated.
Organically doped silver nanoparticles deposited on titania nanofibers: enhanced catalytic methanol oxidation	2013	Ref.16/CR@Ag supported on titania nanofibers catalyst affording methanol partial oxidation to formaldehyde with 18 times higher weight hourly space velocity and 10 times higher space time yield when compared to unsupported submicronic CR@Ag particles. Catalyst is recyclable.
Dual catalytic activity of palladium doped with a Rhodium complex in a one-pot, four step process	2015	Ref.23/Wilkinson Rh catalyst entrapped in Pd mediating both hydroformylation and hydrogenation with a ratio that depends on H <sub>2</sub> and CO pressures applied to a one-pot, four step sequence, including hydroformylations of phenyl acetylenes, reduction of nitrobenzene to aniline, carbonyl-amine condensations forming imines, and imine reductions.
Copper encapsulated alkaloids composite: An effective heterogeneous catalyst for electrocatalytic asymmetric hydrogenation	2016	Ref.10/Cinchonidine@Cu powder compacted into coin subsequently used as cathode for for electrocatalytic asymmetric hydrogenation of ketones using water as only hydrogen source under ultramild conditions. Catalyst reusable at will.
Catalyst@metal hybrids in a one-pot multistep opposing oxidation and reduction reaction sequence	2017	Ref.25/Oxidation and reduction combined in a multistep process that also involves a condensation reaction, thanks to the combination of an oxidizing Ir complex entrapped in Ag ([Ir]@Ag) and a reducing Rh complex entrapped in Ag ([Rh]@Ag), and [Ir]@Pd, in which [Ir] acts as the oxidizing catalyst, and Pd is the reducing catalyst.
Composite materials with combined electronic and ionic properties	2019	Ref.31/FAA-3@Ag employed as a ion and electron conductive cathode of anion exchange membrane fuel cell preserves both ionic and electronic conductivities and exhibits enhanced electrocatalytic activity with a significant improvement in cell performance.
Graphene oxide in palladium nanoparticle (GrafeoPlad): a new class of catalytic materials for heterogeneous catalysis	2023	Ref.7/Graphene oxide entrapped in palladium nanoparticles (GO@nPd) establishes a new class of catalytic materials for heterogeneous catalysis, first demonstrated with nitrobenzene reduction to aniline with hydrazine under ultramild conditions.
Confinement of ionomers for electrocatalytic CO <sub>2</sub> reduction reaction via efficient mass transfer pathways	2023	Ref.32/PiperION@Ag anion exchange resin entrapped in Ag nanoparticles affords a ink that further deposited on gas diffusion electrode exhibits low cell voltages in the electrocatalytic reduction of CO <sub>2</sub> . Electrode operates stably for over 220 h with cell voltage at 300 mA cm <sup>-2</sup> nearly unvaried.

simple search carried out on a research database using the queries “molecularly doped metals” and “catalysis” by early April 2023 returned only 27 articles.<sup>[29]</sup> This is even more surprising considering that all studies devoted to MORALS in catalysis also by research groups in countries beyond Israel (the

country hosting Avnir’s research team), reported highly promising results, including crucially important catalyst stability, even though no real long-term stability test is available (many technical heterogeneous catalysts are used over hundreds or even thousands of hours).

For example, Wang and Lu in China in 2016 reported the highly successful use of alkaloid@Cu as cathode for the electrocatalytic asymmetric hydrogenation of aromatic ketones using water as a green, safe and free hydrogen source under very mild conditions (Scheme A in Figure 2).<sup>[10]</sup> The catalyst, cinchonidine@Cu (CD@Cu, 2.25 wt% in CD) in powder form, was easily compacted into “coin” disk shape and subsequently used as cathode for electrolysis under ultramild conditions (see below). A typical hydrogenation was carried out in a mixture of 50 mM substrate, 0.1 M tetraethylammonium iodide in a 20 mL solvent mixture MeCN/H<sub>2</sub>O=9/1, with a CD@Cu cathode and a Mg anode, affording in each case high yields of asymmetric alcohols for all 7 different substrates tested.

The bars in Figure 2D graph, furthermore, shows that the electrocatalytic MORAL cathode fully retained its high enantioselective activity in the 10 consecutive reaction runs in which it was tested in the asymmetric hydrogenation of methyl benzoylformate used as model substrate, constantly affording optically active *R*-methyl mandelate with a 78% enantiomeric excess (ee) and a 94% yield (and no by-product).<sup>[10]</sup>

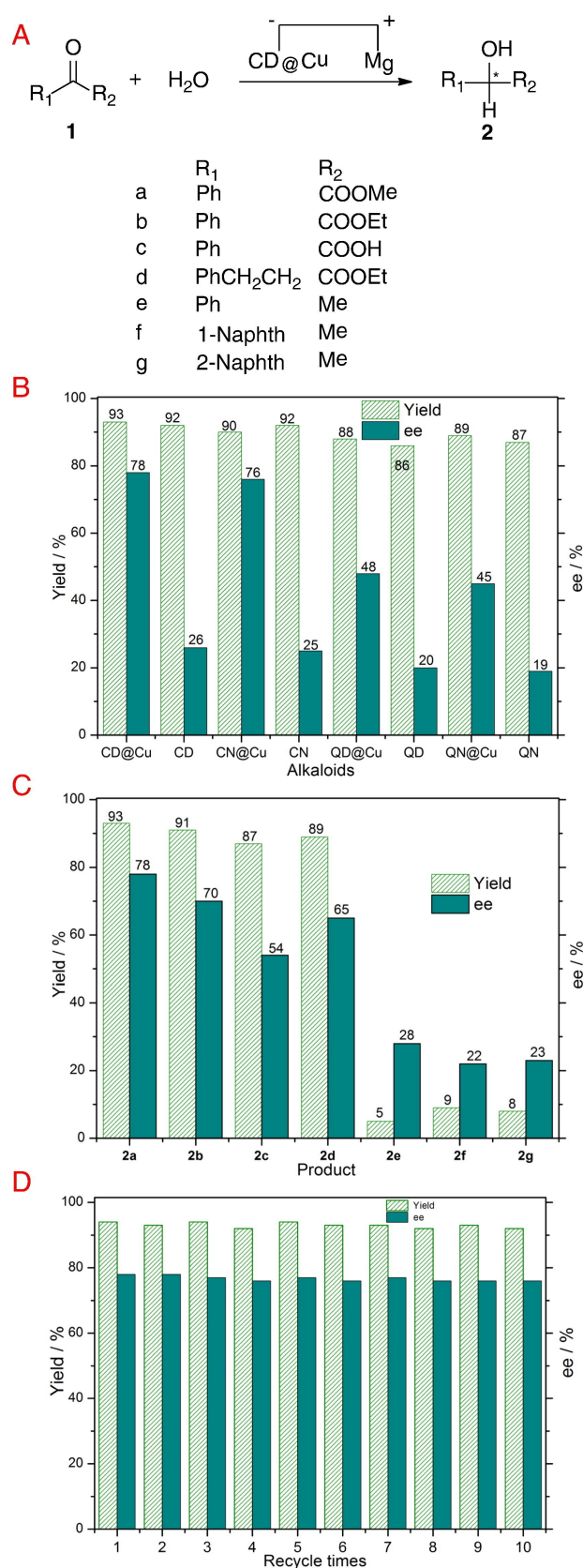
A 78% ee for the asymmetric hydrogenation of a carbonyl function is rather poor and not economically viable when compared to a typical homogeneously catalyzed reaction, but the study offers a relevant proof of concept. After each reaction run no other cathode treatment was employed besides washing the cathode with acetonitrile prior to reuse it in a subsequent reaction run under the same conditions with fresh reagents.

The SEM images (Figure 3) and XRD patterns of the catalyst prior and after 10 consecutive reactions clearly indicated no change in morphology and crystal structure of the catalyst, with all original CD dopant remaining entrapped in the Cu lattice.

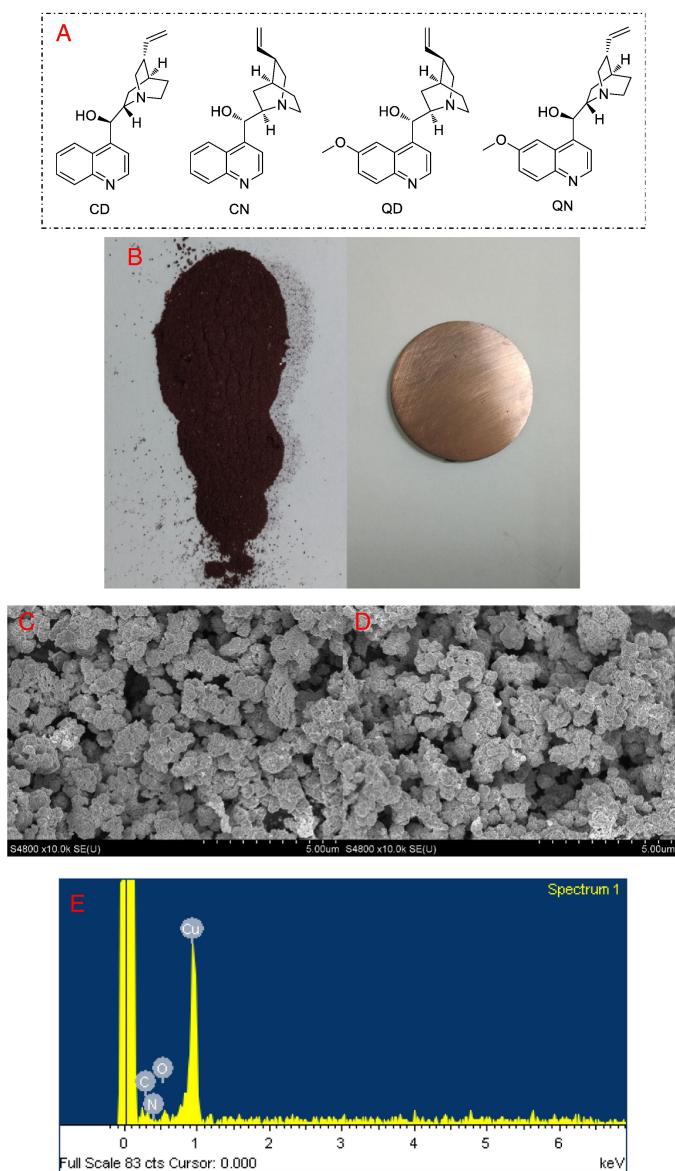
The SEM microscopy images also illustrate that the morphology of MORAL catalysts does not differ from that of metal catalysts comprised of undoped metal microparticles. The same is true also for MORAL nanoparticle catalysts. For example, a similar exceptional catalytic stability to that of the CD@Cu electrocatalyst (and even more striking due to the harsh reaction conditions), is shown by the aforementioned supported CR@Ag/TiO<sub>2</sub>-nf catalyst in methanol selective oxidation to formaldehyde.<sup>[16]</sup>

The nanometric silver crystallites doped with CR in the preheated 1.00%CR@Ag/TiO<sub>2</sub>-nf catalyst (Figure 4b) after the second reaction run retain their size and morphology with a few large (in the range of hundreds of nm) faceted Ag particles (Figure 4c,d). Employed in three consecutive reaction runs, the latter catalyst showed increased conversion compared to undoped Ag/TiO<sub>2</sub>-nf (from 60 to 80% at 400 °C, from 70 to 90% at 500 °C, and from 75 to 95% at 550 °C).<sup>[16]</sup> We remind that in industrially catalyzed processes, for example in the synthesis of bulk chemicals like methanol, catalyst removal and additions are common to obviate to the deterioration of reactor performance in terms of conversion of reactants or selectivity of desired products as the catalyst ages.<sup>[30]</sup>

In brief, even though MORAL catalysts do not differ in morphology from undoped metal catalysts, they deeply differ in chemical structure, with the catalyst structure dramatically affecting catalyst performance.



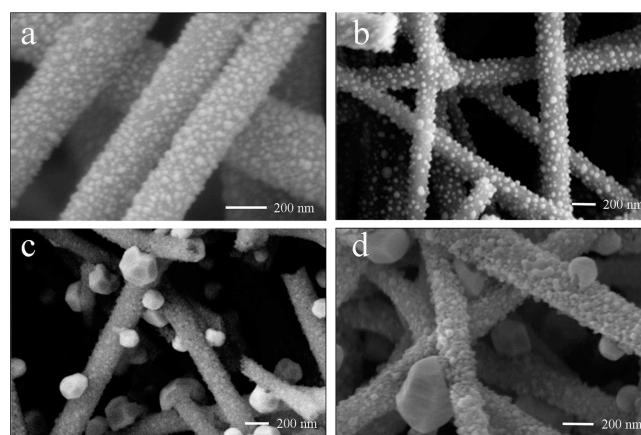
**Figure 2.** A: reaction scheme; B: comparison of entrapped and non-entrapped alkaloid catalysts using methyl benzoylformate as substrate; C: asymmetric hydrogenation with different substrates at CD@Cu cathode; D: reuse test of CD@Cu using methyl benzoylformate as substrate in ten consecutive reactions. [Copyright Elsevier, 2016. Reproduced from Ref. [10], with kind permission].



**Figure 3.** A: Molecular structure of alkaloids; B: CD@Cu composite before (left) and after press (right); FE-SEM patterns of CD@Cu before (C) and after using (D); E: EDX spectra of CD@Cu. [Copyright Elsevier, 2016. Reproduced from Ref. [10], with kind permission].

For instance, more recently, Dekel and Avnir reported the discovery of an ionomer@Ag comprised of FAA-3 anion-conducting ionomer (a widely used ion-conducting material in fuel cells) entrapped in silver combining enhanced electrocatalysis and the ionomer properties in an anion-exchange membrane fuel cell, conventionally dealt with separately.<sup>[31]</sup> We briefly remind that the membrane electrode assembly (MEA) cell configuration based on gas diffusion electrodes (GDEs) eliminates the use of cathode electrolyte, lowers the overall fuel cell resistance, and overcomes the mass transfer limitations in the H-cell configuration.

The FAA-3@Ag MORAL employed as a ion and electron conductive electrode in anion exchange membrane fuel cell preserved *both* ionic and electronic conductivities and exhibited



**Figure 4.** Morphology of 1.00%CR@Ag/TiO<sub>2</sub>-nf catalyst: (a) initial morphology; (b) after preheating at 300 °C under N<sub>2</sub>; (c, d) after the second partial methanol oxidation process run. [Copyright American Chemical Society, 2013. Reproduced from Ref. [16], with kind permission].

enhanced electrocatalytic activity and a significant improvement in cell performance. In detail, the peak power density value of  $\sim 200 \text{ mW cm}^{-2}$  reached by the ionomer@Ag was more than one order of magnitude higher than the  $\sim 12 \text{ mW cm}^{-2}$  peak power density obtained with the pure Ag cathode.

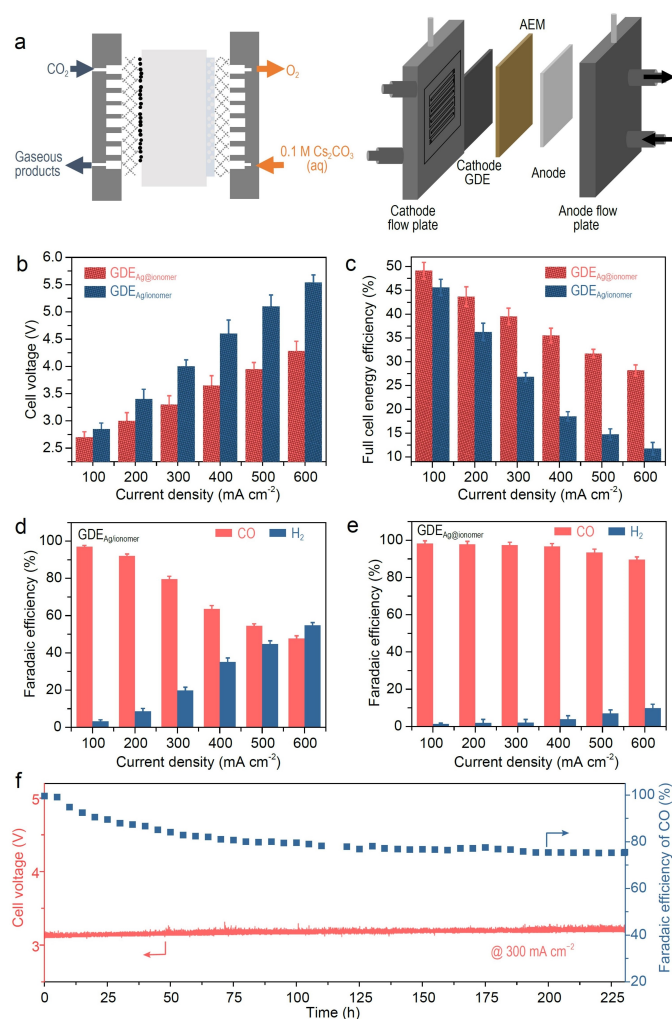
This new ability to impart electronically conducting electrocatalysts with ionic conductivity is of general value because the MORAL synthesis approach may be expanded to other ionomeric materials and other metal electrocatalysts, eventually leading to the introduction of new, less costly hydrogen fuel cells and alkaline electrolyzers.

Indeed more recently, the approach was extended to CO<sub>2</sub> electroreduction by Gong and co-workers in China. The team entrapped the ionomer poly(aryl piperidinium)-based anion exchange resin (PiperION) in Ag nanoparticles (PiperION@Ag) eventually dispersing the resulting MORAL in isopropyl alcohol producing a ink that was further deposited as catalyst layer on the gas diffusion electrode (GDE).<sup>[32]</sup> Used as cathode in a MEA cell (Figure 5), the cathode exhibits low cell voltage ( $\sim 3.3 \text{ V}$  at  $300 \text{ mA cm}^{-2}$ ) in the electrocatalytic reduction of CO<sub>2</sub>.

Contrary to a cathode in which the ionomer has been deposited on Ag nanoparticle surface (GDE Ag/ionomer), the electrode functionalized with the MORAL shows stable cell voltage for over 220 h at a current density of  $300 \text{ mA cm}^{-2}$  and high CO Faradaic efficiency of 90% even at  $600 \text{ mA cm}^{-2}$  current density (Figure 5).

### 3. Perspectives and conclusions

The history of innovation in catalysis for synthetic organic chemistry in the last two decades (2002–2022) has plentiful lessons to teach concerning the attitudes of the fine chemical industry towards new heterogeneous catalytic technologies. Following the successful uptake first of asymmetric hydrogenations via homogeneously catalyzed processes using metal complexes with (often proprietary) chiral ligands and then of



**Figure 5.** (a) 2D and 3D view of the MEA electrolyser. (b and c) cell voltages and full cell energy efficiencies of MEAs with GDE<sub>Ag@ionomer</sub> and GDE<sub>Ag/ionomer</sub> as the GDE at different current densities. Faradaic efficiency for CO and H<sub>2</sub> over (d) GDE<sub>Ag@ionomer</sub> and (e) GDE<sub>Ag/ionomer</sub> in the MEA. (f) Stability test of GDE<sub>Ag@ionomer</sub> at the current density of 300 mA cm<sup>-2</sup>. [Reproduced from Ref. [32], CC BY Creative Commons License].

carbon-carbon cross coupling reactions, the industry (and its main customer, the pharmaceutical industry) has been highly receptive to innovation in homogeneous catalysis.<sup>[33]</sup>

This is not the case for heterogeneous catalysis, with industry generally lamenting the poor stability of supported metal catalysts giving place to metal leaching and product contamination with metal residues.<sup>[34]</sup> The uptake of green chemistry technologies in the fine chemical and pharmaceutical industries has been chiefly driven by increased profitability, with only technologies offering quick return on investment (less than 3, and preferably less than 2 years) eventually considered for commercial uptake.<sup>[35]</sup> A single recent (2019–2021) case of industrial uptake of a new green chemistry process at a fine chemical company in China (where alongside India most of the global production of fine chemicals takes place) shows that this has been indeed the case.

Using a flow reactor system occupying one-tenth the area of the original batch process and requiring 30 fewer operators, said company today manufactures a fine chemical requiring a diazotization and a hydrolysis step in significantly increased yield and with improved profits.<sup>[36]</sup> The payback period for the project's investment was <20 months. Instead of 8 h for diazotization and 4 h for hydrolysis, the flow system requires a few min to afford the product, with a continuously stable production for more than 8,000 h per year. Besides being much safer and producing 75% less solid waste when compared to the abandoned batch process, the new production route has replaced six batch reactors of 3,000 L each and, in the second step, two flow reactors supplanting three batch reactors of 6,000 L. Only in China, the same flow reactor manufacturer has installed another 60 systems in the subsequent two years.<sup>[36]</sup>

In this transition from reactions in batch reactors towards continuous flow catalytic productions, the next step will be the shift from homogeneous to heterogeneous catalysis based on new-generation solid catalysts,<sup>[37]</sup> amid which molecularly doped metals will be one key component of the new catalyst palette available to fine chemical manufacturers. Indeed, reporting in 2021 the under-utilization of heterogeneous catalysis for cross-coupling reactions, researchers at a fine chemical company based in the USA concluded that it has been caused by “under-recognition of its benefits such as catalyst recovery, reusability, and low metal leaching”<sup>[38]</sup> occurring with “more defined and robust new-generation solid catalysts”<sup>[38]</sup>

Rather than relying on what academics write about heterogeneous catalysis in fine chemicals manufacturing, it is instructive to review what industry actually does.

A proxy for industry's activities in the field are publications in the leading organic process journal (*Organic Process Research & Development*). From enzymatic stereoselective reactions with heterogenized enzymes,<sup>[39]</sup> through the acid-catalyzed synthesis of valued dimethyl fumarate over silica-supported propylsulfonic acid,<sup>[40]</sup> researchers from fine chemical, pharmaceutical, and flavor and fragrance companies regularly report findings concerning the use of heterogeneous catalysts to produce valued fine chemicals. Almost invariably, the solid catalysts are used under continuous flow conditions. For example, the dehydrogenation of meta-isobutyl-methylcyclohexene to produce perfumery ingredients mediated by Pd/AIO<sub>x</sub><sup>[41]</sup> through asymmetric Michael addition reactions over polymer-supported *cis*-pyrrolidine.<sup>[42]</sup>

This is in line with Pagliaro's 2019 forecast for which, driven by global societal megatrends concerning the environment, health, and energy, manufacturing processes in the chemical industry will evolve into heterogeneously catalyzed processes carried out under continuous flow in much smaller production units, with little (or no) waste co-production.<sup>[43]</sup>

The development of breakthrough innovation in heterogeneous catalysis, such is the case of molecularly doped metals,<sup>[4,5]</sup> is part of this megatrend nexus which includes also digitization of manufacturing processes. For instance, the new digitally controlled 3D printing catalyst shaping technology lately developed by industry to produce catalysts with an open structure (resulting in a larger surface area and lower pressure

drop across the reactor),<sup>[11]</sup> in principle can be extended to supported MORALS. Another key advantage of these catalytic materials is that their synthetic methodology based on reduction of the precursor metal ions in the presence of organic molecules in solution at room temperature without the need to exclude air (Eq. 1) has substantial sustainability advantages. Metal ion reduction is usually complete, with no loss of valued metal in solution. Also the entrapment of the organic molecules is very effective, with no (or very little) loss of dopant organic molecules remaining non-entrapped in the metal lattice structure of the resulting MORAL. Being generally more active and selective than their metal counterparts, such as in the case of undoped silver compared to Ag doped with organic dye molecules deposited on TiO<sub>2</sub> nanofibers employed in methanol oxidation to formaldehyde,<sup>[16]</sup> reactions mediated by MORALS can be carried out at lower temperature and for shorter reaction time, thereby increasing the sustainability of the catalytic production by a large extent.

Finally, a question raised by eminent colleagues in catalysis science and technology suggests one reason which likely explains the poor number of studies on molecularly doped metals. Commenting on the case of an oxidizing Ir pincer complex entrapped in Ag or in Pd and a reducing Rh complex entrapped in Ag applied in a multistep process with opposing oxidations and reductions,<sup>[25]</sup> the colleague asked: "if the Ir pincer is entrapped in the metal matrix, how does the substrate get to the pincer complex? Pure metals usually have no pores. A sketch of this would be nice".<sup>[44]</sup> Research chemists understand and communicate chemistry concepts through modeling and representation.<sup>[45]</sup> Regardless of many attempts to represent the entrapment of organic molecules by Avnir,<sup>[4,5]</sup> many chemists may have failed to represent the idea of a porous metal structure with interstitial pores accessible to external reactants.<sup>[1]</sup>

As molecularly doped metals hold great applicative potential as new-generation solid catalysts, this study will hopefully foster progress concerning the use of MORALS as new catalysts of practical relevance.

## Acknowledgements

This study is dedicated to Shu Kobayashi, University of Tokyo, for all his team has done for the progress of heterogeneous catalysis under continuous-flow for fine chemical synthesis. We thank Giovanna Bellanti and Salvatore Romeo, Istituto per lo Studio dei Materiali Nanostrutturati, CNR, for providing assistance in administrative tasks during many years of work. This study was carried out within the MICS (Made in Italy – Circular and Sustainable) Extended Partnership, EU Next-GenerationEU (Piano Nazionale di ripresa e resilienza – Missione 4 componente 2, investimento 1.3 - D.D. 1551.11-10-2022, PE00000004).

## Conflict of Interests

The Authors declare no competing financial interest.

## Data Availability Statement

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

**Keywords:** Molecularly doped metals · Catalyst cost · Green chemistry · Metal organic alloys · MORAL

- [1] H. Behar-Levy, D. Avnir, *Chem. Mater.* **2002**, *14*, 1736–1741.
- [2] H. Behar-Levy, D. Avnir, *Adv. Funct. Mater.* **2005**, *15*, 1141–1146.
- [3] G. Palmisano, V. Augugliaro, R. Ciriminna, M. Pagliaro, *Can. J. Chem.* **2009**, *87*, 673–677.
- [4] D. Avnir, *Acc. Chem. Res.* **2014**, *47*, 579–592.
- [5] D. Avnir, *Adv. Mater.* **2018**, *30*, 1706804.
- [6] R. Ben-Knaz, D. Avnir, *Biomaterials* **2009**, *30*, 1263–1267.
- [7] M. Formenti, M. Pagliaro, C. Della Pina, R. Ciriminna, *ChemRxiv*. **2023**, <https://doi.org/10.26434/chemrxiv-2023-hw1tj>.
- [8] M. Pagliaro, *J. Flow Chem.* **2021**, *11*, 53–58.
- [9] K. M. Van Allsburg, E. C. D. Tan, J. D. Super, J. A. Schaidle, F. G. Baddour, *Nat. Catal.* **2022**, *5*, 342–353.
- [10] H.-P. Yang, Q. Fen, H. Wang, J.-X. Lu, *Electrochem. Commun.* **2016**, *71*, 38–42.
- [11] BASF introduces X3D technology for 3D painting catalysts, *Word of Chemicals*, 7 October 2022. [www.worldofchemicals.com/media/basf-introduces-x3d-technology-for-3d-painting-catalysts/8307.html](http://www.worldofchemicals.com/media/basf-introduces-x3d-technology-for-3d-painting-catalysts/8307.html) (accessed July 3, 2023).
- [12] M. Kennema, Shaping the future of catalysts, *Heterogeneous Catalysts for Sustainable Industry*, Royal Society of Chemistry, Burlington house, London, 25 November 2019. [www.rsc.org/events/download/Document/22aa656d-0217-4196-9a45-5ae20ca03e36](http://www.rsc.org/events/download/Document/22aa656d-0217-4196-9a45-5ae20ca03e36) (accessed July 2023)..
- [13] R. Ciriminna, C. Della Pina, E. Falletta, J. H. Teles, M. Pagliaro, *Angew. Chem. Int. Ed.* **2016**, *55*, 14210–14217.
- [14] The real market price for Pt/C in 2017 was 75 \$/kg, about 20% higher than the estimate. See: F. G. Baddour, L. Snowden-Swan, J. D. Super, K. M. Van Allsburg, *Org. Process Res. Dev.* **2018**, *22*, 1599–1605.
- [15] G. E. Shter, H. Behar-Levy, V. Gelman, G. S. Grader, D. Avnir, *Adv. Funct. Mater.* **2007**, *17*, 913–918.
- [16] Y. Aouat, G. Marom, D. Avnir, V. Gelman, G. E. Shter, G. S. Grader, *J. Phys. Chem. C* **2013**, *117*, 22325–22330.
- [17] A. W. Franz, H. Kronemayer, D. Pfeiffer, R. D. Pilz, G. Reuss, W. Disteldorf, A. O. Gamer, A. Hilt, Formaldehyde, *Ullman's Encyclopedia of Industrial Chemistry*; Wiley: Hoboken (NJ): **2016**.
- [18] S&P Global, Nitrobenzene and Aniline, New York: **2023**. [www.spglobal.com/commodityinsights/en/ci/products/nitrobenzene-and-Aniline-chemical-economics-handbook.html](http://www.spglobal.com/commodityinsights/en/ci/products/nitrobenzene-and-Aniline-chemical-economics-handbook.html) (accessed July 3, 2023).
- [19] M. Gheorghie, S. Dragos-Nicolae, *J. Loss Prev. Process Ind.* **2010**, *23*, 112–126. <https://doi.org/10.1016/j.jlp.2009.06.007>.
- [20] T. Kahl, K.-W. Schröder, F. R. Lawrence, W. J. Marshall, H. Höke, R. Jäckh, Aniline, *Ullman's Encyclopedia of Industrial Chemistry*; Wiley: Hoboken (NJ): **2011**.
- [21] Intratec Solutions, Aniline Production from Nitrobenzene, March 1, 2016. [www.chemengonline.com/aniline-production-nitrobenzene-liquid-phase-intratec-solutions/](http://www.chemengonline.com/aniline-production-nitrobenzene-liquid-phase-intratec-solutions/) (accessed July 3, 2023).
- [22] E. A. Gelder, S. D. Jackson, C. M. Lok, *Chem. Commun.* **2005**, 522–524.
- [23] L. Shapiro, M. Driess, D. Avnir, *ChemCatChem* **2015**, *7*, 2033–2037.
- [24] J. He, L. Iagher, L. Etgar, D. Avnir, *Chem. Commun.* **2018**, *54*, 7203–7206.
- [25] L. Shapiro, D. Avnir, *ChemCatChem* **2017**, *9*, 816–823.
- [26] Y. Baruch-Shpigler, D. Avnir, *Chem. Sci.* **2020**, *11*, 3965–3977.
- [27] O. Sinai, D. Avnir, *Chem. Mater.* **2011**, *23*, 3289–3295.
- [28] M. Pagliaro, *J. Sol-Gel Sci. Technol.* **2020**, *95*, 551–561.
- [29] Search carried out at [www.scholar.google.com](http://www.scholar.google.com) (April 4, 2023).
- [30] G. Sawyer, *Chem. Eng. Prog.* **2019**, *115*, 52–58.
- [31] N. Ralbag, M. Mann-Lahav, E. S. Davydova, U. Ash, R. Galed, M. Handl, R. Hiesgen, E. Magliocca, W. Mustain, J. He, P. Cong, M. Beale, G. S. Grader, D. Avnir, D. R. Dekel, *Matter* **2019**, *1*, 959–975.
- [32] X. Du, P. Zhang, G. Zhang, H. Gao, L. Zhang, M. Zhang, T. Wang, J. Gong, *Nat. Sci. Rev.* **2023**, *nwad149*, DOI: 10.1093/nsr/nwad149.
- [33] See, for example, the following report from a pharmaceutical company: R. T. Ruck, N. A. Strotman, S. W. Krska, *ACS Catal.* **2023**, *13*, 475–503.
- [34] S. Hübner, J. G. de Vries, V. Farina, *Adv. Synth. Catal.* **2015**, *358*, 634–641.
- [35] R. Ciriminna, M. Pagliaro, *Org. Process Res. Dev.* **2013**, *17*, 1479–1484.



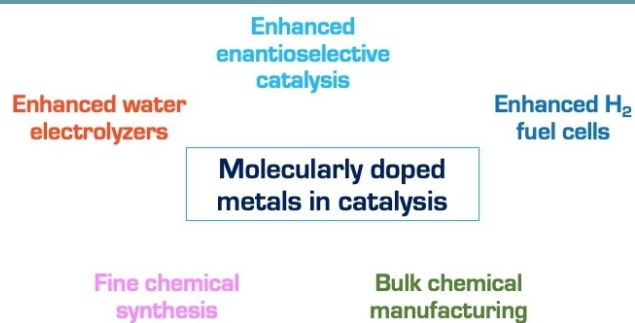
- [36] Y. Jiang, Continuous flow reactors yield multiple benefits, *Chemical Processing*, 9 October 2022. [www.chemicalprocessing.com/processing-equipment/reaction-synthesis/article/21436111/continuous-flow-reactors-yield-multiple-benefits](http://www.chemicalprocessing.com/processing-equipment/reaction-synthesis/article/21436111/continuous-flow-reactors-yield-multiple-benefits) (accessed July 3, 2023).
- [37] R. Ciriminna, M. Pagliaro, R. Luque, *Green Energy Environ.* **2021**, *6*, 161–166.
- [38] S. Vásquez-Céspedes, R. C. Betori, M. A. Cismesia, J. K. Kirsch, Q. Yang, *Org. Process Res. Dev.* **2021**, *25*, 740–753.
- [39] M. Hobisch, P. De Santis, S. Serban, A. Basso, E. Byström, S. Kara, *Org. Process Res. Dev.* **2022**, *26*, 2761–2765.
- [40] F. Dedè, O. Piccolo, D. Vigo, *Org. Process Res. Dev.* **2021**, *25*, 292–299.
- [41] M. A. Lovchik, C.-L. Tse, S. Ellwood, *Org. Process Res. Dev.* **2020**, *24*, 2906–2914.
- [42] H. Ochiai, A. Nishiyama, N. Haraguchi, S. Itsuno, *Org. Process Res. Dev.* **2020**, *24*, 2228–2233.
- [43] M. Pagliaro, *Angew. Chem. Int. Ed.* **2019**, *58*, 11154–11159.
- [44] Question of an anonymous reviewer of the present study, July 2023.
- [45] M. Pagliaro, *Eur. J. Chem.* **2010**, *1*, 276–281.

---

Manuscript received: June 13, 2023  
Revised manuscript received: July 6, 2023  
Version of record online: ■■, ■■

## PERSPECTIVE

---



*Dr. R. Ciriminna\*, M. Formenti,  
Dr. M. Pagliaro, Prof. Dr. C.  
Della Pina\**

1 – 10

**Practical Aspects Concerning  
Catalysis with Molecularly Doped  
Metals**

We investigate a number of practical aspects concerning molecularly doped metals as heterogeneous

catalysts. Regardless of remarkable achievements, their utilization is surprisingly still limited.

---