Solid Single-Atom Catalysts in Tandem Catalysis: Lookout, Opportunities and Challenges

Tania Rodenas[a] and Gonzalo Prieto*[a]

Tandem catalysis stands out as a major instrument towards the intensification of existing and future chemical processes. Initially formulated in the field of homogeneous catalysis, the concept relies on the single-pot integration of two (or more) catalysts showing high specificity for mechanistically decoupled reactions, while being operational and compatible under a single set of operation conditions. Isolated metal atoms stabilized on solid carriers in single-atom catalysts (SACs) hold the potential to reconcile the high reaction specificities of mononuclear sites in molecular catalysts with an intrinsic catalyst compartmentalization on inorganic matrices. Understandably, SACs have started to be considered as platforms in tandem catalysis. Tandem (electro)catalytic processes based on SACs have been showcased recently. While this sets excellent prospects for the expansion of this research subarea, challenges are faced, particularly as to the verification of the tandem nature of the processes.

Background

Process intensification is considered a crucial stepping-stone towards reducing the carbon footprint and improving the sustainability of existing chemical processes and those yet-to-be-developed. Intensification embraces concepts of reaction and materials engineering, process design, and energy management, collectively geared at improving the safety and efficiency, and diminishing the installed size and environmental impact of chemical processes.[1,2] Single-pot catalysis can play a central role in process intensification by: (1) superseding intermediate workup unitary operations for isolation of intermediate products, avoiding energy- and cost-intensive separations; (2) improving the selectivity and safety of the overall transformation if very reactive or unstable intermediate products are produced in a first reaction step, which can be instantly processed in a subsequent reaction, reducing their residence time in the reaction medium and lowering the probability for undesired side-reactions or decomposition; and (3) overcoming thermodynamic equilibrium bounds to the global yield by driving reversible reactions to completion, e.g. via the *in situ* engagement of a reaction product in a subsequent irreversible catalytic step.

Tandem catalysis represents a major subset of single-pot transformations.[3] In recent years, a less systematic application of the term, to refer to a wide variety of catalytic transformations wherein different active centers cooperate to achieve a certain transformation, has become increasingly extended. However, revisiting its origins in the field of homogeneous catalysis with molecular catalysts in solution, *tandem*, from Latin "at length" (one after the other) was coined to refer to a specific subclass of single-pot reactions wherein a single catalyst (auto-tandem) or, most often, different catalysts (concurrent tandem catalysis) steer two (or more) mechanistically decoupled reactions to attain a sequential conversion. In the latter, which shall be the focus of our concept article, the individual reactions take place sequentially at a microscopic scale, however, they occur concomitantly from a macroscopic standpoint, and all catalysts involved are present in the reaction medium from the onset of the reaction.

As it originates in the realm of homogeneous catalysis, hence involving molecular catalysts operating in an ideally gradientless, well-mixed liquid reaction medium, the concept of tandem catalysis is also strongly connected to the notion of catalyst compartmentalization. Compartmentalization encompasses strategies geared at isolating different catalysts, disabling their direct interaction, while permitting the transport and exchange of reactants and intermediate products between their active centers.[4] Avoiding direct interaction of two molecular catalysts integrated in tandem is instrumental to prevent undesired phenomena, e.g. ligand exchange, aggregation or mutual "titration", which shall modify, often deteriorate, the active sites on at least one of the catalysts. The compartmentalization of molecular catalysts for tandem conversion processes dates back to the concept of "*Wolf and Lamb*" reactions introduced by Cohen and coworkers in the early 1980s.[5] Ever since, different approaches have been put forth to compartmentalize molecular catalysts operating in tandem in liquid media. Examples include catalyst encapsulation in

[a] Dr. T. Rodenas, Dr. G. Prieto
ITQ Instituto de Tecnología Química
Universitat Politècnica de València-Consejo Superior de Investigaciones
Científicas (UPV-CSIC)
Av. Los Naranjos s/n
46022 Valencia (Spain)
E-mail: prieto@itq.upv.es

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dendrimer molecules,[6] encaging in polymersome vesicles or micelles,[7] or tethering onto polymers.[5]

Key to the successful realization of a tandem catalysis process is a high reaction specificity and selectivity of the integrated catalysts. While these are inherent characteristics of molecular catalysts such as enzymes and organometallic complexes, all-inorganic solid catalysts typically expose a broader diversity of active centers on their surface, which often steer more than one reaction path. In recent years a significant deal of scientific attention has been placed on the concept of single-atom catalysts (SACs), as a notion which holds the potential to bridge the fields of homogeneous and heterogeneous catalysis.[8–10] In SACs, isolated metal centers are typically stabilized through M–O or M–N bonds onto solid carriers, lacking additional metal atoms in their most direct coordination spheres. These sites may be regarded as proxies for ligand-stabilized monoatomic centers, which are ubiquitous in molecular catalysts. Moreover, their stabilization onto a carrier, typically oxide- or carbon-based materials, endows them with those technical advantages inherent to solid inorganic catalysts, i.e. uncomplicated handling, high mechanical and chemical stability, and easy recovery from reactants and products.

It is therefore not out of surprise that single-atom catalysts have started to be considered as platforms for tandem catalysis. Figure 1 provides an overview on the evolution of scientific activities – using the number of scientific publications as a metrics therefor – on tandem catalysis and single-atom catalysis, respectively. Both areas have seen a significant increment in the volume of scientific work. Particularly remarkable is the surge experienced by research on SACs in less than a decade back from now. Hitherto, few scientific publications have discussed results at the touching point of both research areas. However, it is already apparent that the application of single-atom catalysts in tandem catalysis is a sub-field expected to develop with high momentum in the coming years.
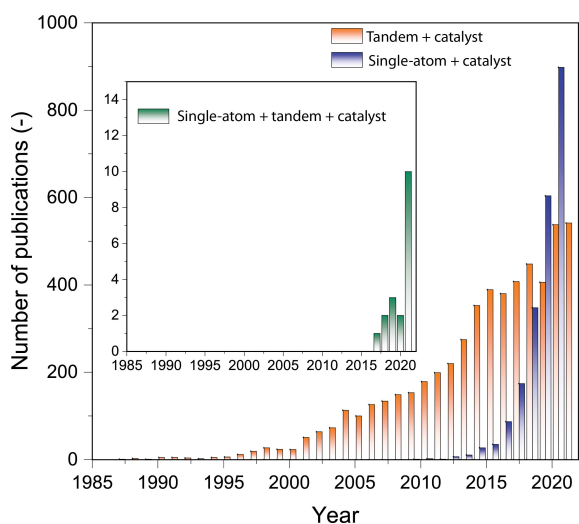
In this concept article, different manners single-atom solid catalysts may be integrated in tandem processes are presented and showcased with selected examples from the recent scientific literature. Emphasis is placed on those challenges faced not only to realize a successful tandem process based on SACs, but additionally to unequivocally demonstrate the tandem nature of the conversion. Moreover, some misconceptions are discussed, which in the opinion of the authors should be carefully considered to ensure that this emerging scientific sub-area develops in the most rigorous manner to realize its full potential.

Design of Tandem Catalysis Systems Based on Single-Atom Catalysts

As discussed above, the origins of tandem catalysis are strongly entangled to the application of compartmentalized molecular catalysts in a liquid reaction medium. Figure 2a illustrates the case of two organometallic catalysts encapsulated in micelle compartments. As exemplified in Figure 2b, the integration of two SACs provides a conceptually similar compartmentalization of two different mononuclear metal catalysts in non-contacting solid matrices, enabling them to cooperate in the same reaction medium while preventing direct inter-catalyst interactions.

Figure 1. Yearly evolution of the number of scientific publications on tandem catalysis, single-atom catalysis and single-atom catalysts for tandem catalysis. Data retrieved from searches in Scopus using the combinations of search terms indicated in the legend to the figure.
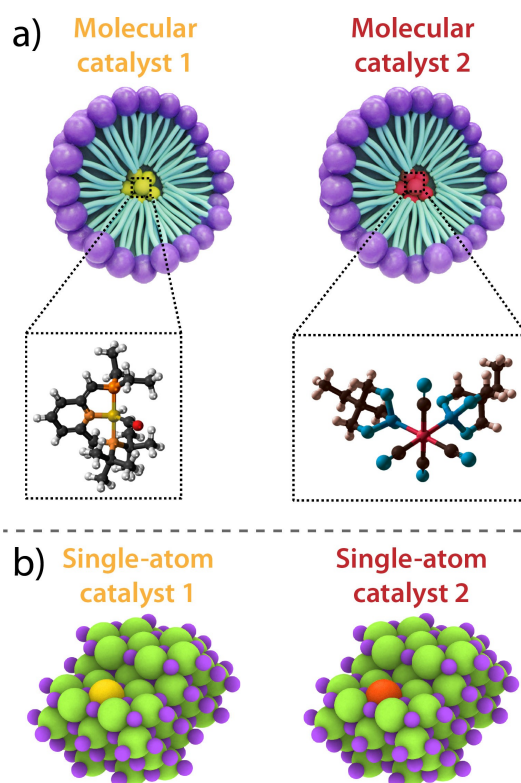

Figure 2. Schematic representation of the analogy between the tandem integration of a) two molecular organometallic catalysts compartmentalized in micelles, and b) two single-atom catalysts compartmentalized via their stabilization on different oxide carrier materials.

Integrating two different SACs in a common reaction medium is arguably the most versatile approach to realize a tandem process, as it facilitates independent optimization of each of the catalysts for their own target reaction. This is the approach pursued by Sarma et al.[11] to realize a tandem olefin isomerization-hydrosilylation process (Figure 3). Applied on α-olefin substrates, Ru1/CeO2 and Rh1/CeO2 single-atom catalysts showed remarkable specificities towards double-bond isomerization and anti-Markovnikov hydrosilylation of terminal olefins, respectively, while avoiding undesired olefin hydrogenation which was promoted by catalysts based on metallic aggregates. The cooperation of Rh- and Ru-based SACs, in a solvent-free liquid medium, resulted in notably higher yields and regioselectivity to terminal organosilane products compared to either of the two catalysts on an individual basis, or a benchmark molecular Pt Karstedt's hydrosilylation catalyst. On the latter technical catalyst, olefin double-bond chain-walking and hydrosilylation reactions were found to compete, at similar rates, on a single active site. This makes olefin on-site residence time less effective and leads to lower overall reaction rates compared to the case where these competing reaction paths are "disentangled" on the surface of two separate catalysts. The tandem system enabled a single-step conversion of industrially relevant mixtures of terminal and internal aliphatic olefins to valuable terminal organosilanes with regioselectivities up to 96%.

In a similar vein, Lin et al[12] integrated two single-atom catalysts to realize a tandem electrocatalytic CO2 reduction (CO2ER) to methane. Cobalt (II) phthalocyanine (Co1Pc) and Zn dispersed on nitrogen-doped carbon (Zn1—N—C), both solids bearing isolated metal atoms stabilized in nitrogen coordination environments, were physically blended with Nafion® as ionomer and casted on carbon paper to realize a bifunctional cathode for CO2ER. Electrocatalytic tests pointed to CO as a key intermediate product in the tandem. Experimental and computational evidence indicated that Zn1—C—N is an excellent catalyst for CO electroreduction. However, direct CO2 electroreduction shows a sluggish kinetics on this catalyst. In contrast, Co1Pc is particularly effective in the partial CO2 electroreduction to CO. Decoupling CO2ER to CO and further COER to CH4 on the two catalysts was proposed to favor higher CO fugacities and thus competitive CO adsorption on the Zn sites, adding to preserve a higher availability of *H on Zn1—N—C and facilitating full CO electroreduction to methane.

In addition to the combination of two standalone SACs, other configurations are possible to integrate single-atom catalysts in tandem conversion schemes. Figure 4 summarizes schematically some of these plausible configurations. They
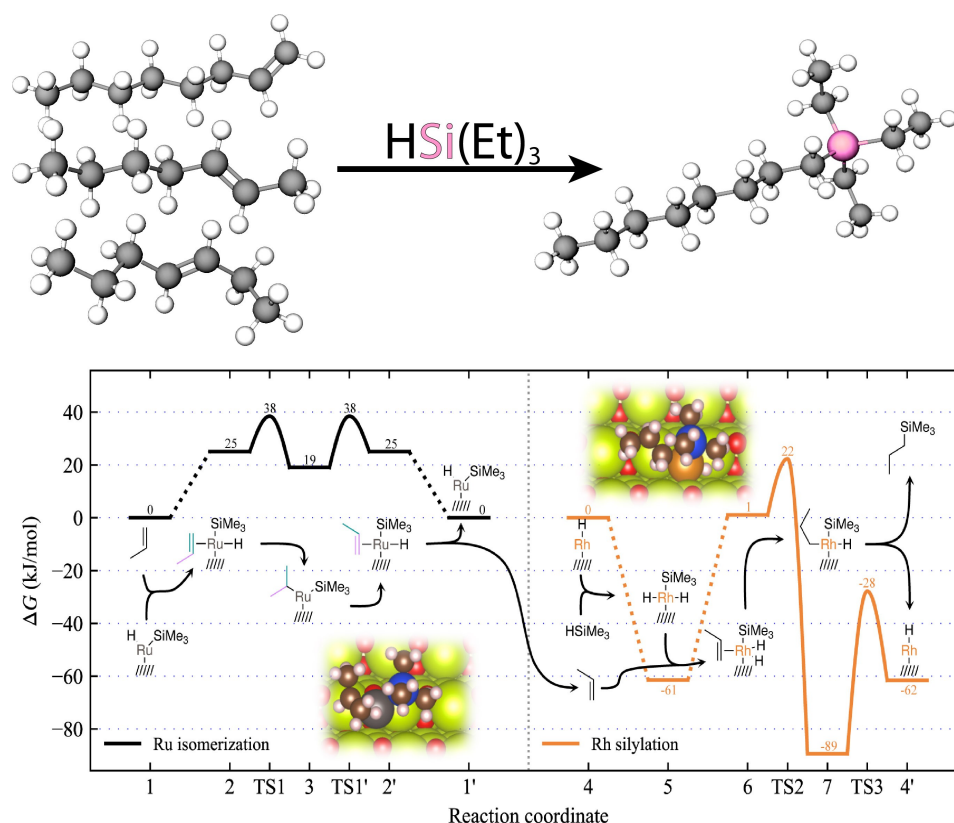

Figure 3. Tandem olefin isomerization/hydrosilylation via the single-pot integration of Ru1/CeO2 and Rh1/CeO2 single-atom catalysts. Top: schematics of the direct and regioselective conversion of a mixture of terminal and internal aliphatic olefins to terminal organosilanes. Bottom: Periodic DFT (PBE-D3)-derived free energy diagram for the tandem process. Olefin isomerization is catalyzed by Ru1/CeO2 (left) while subsequent hydrosilylation with HSiMe3 is catalyzed by Rh1/CeO2 (right) single-atom sites. Reactants considered: propene as model olefin, HSiMe3 as silylating agent (Me: methyl). T = 393 K, P = 10 bar. Free energy diagram reproduced from ref. [11] Copyright (2020), with permission from Wiley-VCH.
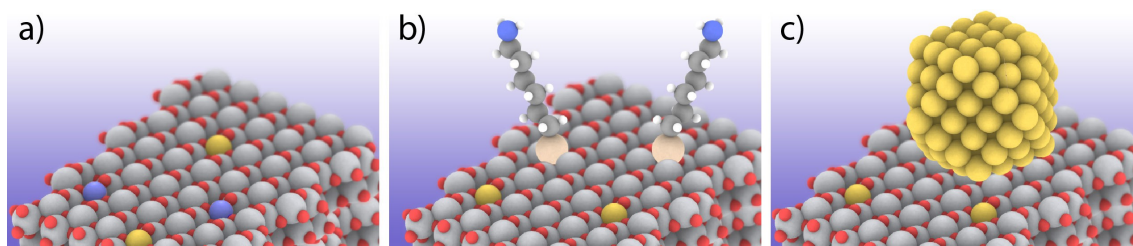
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Figure 4. Schematic representation of different possible configurations for the integration of single-atom catalysts in tandem catalysis processes. a) two different metals atomically dispersed on a common oxide carrier; b) atomically dispersed metal centers combined with surface-tethered organic active sites (basic sites on aminoalkylsilyl moieties as a showcase); and c) isolated metal atoms combined with metal aggregates (nanoparticles) on a common support.

range from different metals atomically dispersed on the surface of a single (oxide) carrier,[13] to supported single-atom sites combined with surface-tethered organocatalysts, to the integration of isolated metal atoms and metal aggregates (e.g. nanoparticles). In all cases, the use of a common carrier poses greater challenges for the individual optimization of each catalyst. As it shall be discussed later, it makes it also more difficult to perform exclusion studies to demonstrate the superiority of the tandem of catalysts.

The higher active site structural simplicity and uniformity in single-atom catalysts offers prospects for high selectivity. However, mononuclear centers find limitations for reactions which require the participation of various centers on extended metal surfaces, particularly those which involve the dissociation of various reactants followed by coupling events. In those cases, metallic nanocrystals are superior, if not exclusive, catalysts. These considerations have motivated studies wherein single-atom catalysts are integrated with metal nanocrystal catalysts in tandem.

An area where such combinations of single-atom and agglomerate metal catalysts have already proven advantageous is the electrocatalytic reduction of CO_2. Intensive research in

this area has shown extended copper surfaces to be the catalyst of choice, essentially in exclusivity, when C–C coupling events are to be promoted to produce C_{2+} products.[14] The reaction is believed to be mediated by CO (or partial hydrogenation products thereof) and a high surface CO coverage (θ_{CO}) has been shown to promote C–C coupling on copper.[14] However, Cu surfaces are only modestly active towards the CO_2ER to CO. These considerations led Li et al.[15] and Meng et al.[16] to investigate the tandem integration of SACs with excellent activity for the electroreduction of CO_2 to CO, namely Fe porphyrins and isolated Ni atoms within polymeric triazine frameworks, respectively, with Cu nanocrystals. Once again, CO was found to be the key intermediate product in the tandem electrocatalytic process. Attenuated Total Reflection Fourier-Transform Infrared (ATR/FTIR) spectroscopy proved a local enrichment in molecular CO on the surface of the copper-based electrocatalyst upon integration with a specific SAC for partial CO_2 reduction. This was shown to foster C–C coupling to multicarbon products, i.e. ethylene in the work by Li et al.[16] and ethanol, with Faradaic efficiency (FE) > 40% and full-cell energy efficiency of up to 13%, in the study by Sargent and coworkers (Figure 5).[15] Building on this concept, very recently
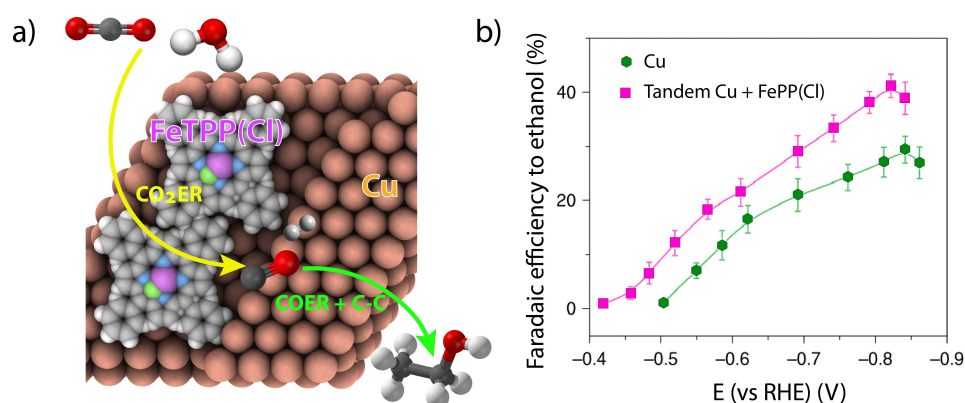

Figure 5. a) Schematic illustration of the heterogeneization of a molecular FeTTP(Cl) single-atom molecular catalyst onto a Cu crystal. The extended metallic surface and the Fe-based SAC cooperate in a tandem CO_2ER with high Faradaic efficiency (EF) to direct ethanol production. A locally high concentration of the intermediate product CO, promoted by the faster CO_2 electrocatalytic reduction to CO provided by the FeTTP(Cl) SAC, favors C–C coupling and the production of ethanol by COER on the bare Cu surface. On the catalyst model, Cu atoms are depicted in ochre, Fe in purple, Cl in light green, N in blue, C in dark gray and H in light gray. b) Ethanol Faradaic efficiency over the applied potentials for the bare Cu catalyst and the tandem of FeTTP(Cl) + Cu catalysts. RHE: reversible hydrogen electrode; FeTTP(Cl): 5,10,15,20-tetraphenyl-21H,23H-porphine iron (III). Experiments performed in a gas diffusion electrode-based flow cell using 1 M $KHCO_3$ as electrolyte. Panel b adapted from ref. [15] Copyright (2019), with permission from Springer Nature.

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Zhang et al.[17] have devised segmented gas-diffusion electrodes for CO_2ER, wherein layers of the CO-producing SAC and the C–C coupling Cu-based nanocrystal catalyst are alternated. The arrangement of the two catalysts is designed to manage spatial variations in the fugacity profile for the CO intermediate product in the electrolyte. The underlaying goal is to ensure as high as possible θ_{CO} on those electrode sections corresponding to the copper-based catalyst, to sustain high rates for C–C coupling events. An overall FE of 90% from CO_2 to C_{2+} products, namely ethylene, ethanol and acetate compounds, was demonstrated under optimized conditions.

Opportunities and Challenges

The above selected examples, and other pieces of research in the recent scientific literature, showcase the potential of single-atom catalysts in the area of tandem catalysis. In view of the expansion possibilities held by both tandem catalysis and SACs independently (Figure 1), the above works likely form just the foundation of a thriving research sub-area at the boundary of these two catalysis disciplines. The tandem approach seems particularly promising to decouple e.g. reactions for the activation of recalcitrant, small molecules from reactions involving subsequent chain propagation (towards higher added-value condense products) on two different catalysts.[18] The former steps typically require surmounting higher activation energies, hence applying a single catalyst to drive both reactions may often result in suboptimal performances. Excellent examples are the achievements reviewed above on the CO_2 electrocatalytic reduction to multicarbon products, by the tandem integration of CO_2-activating SACs with further CO-mediated C–C coupling on metal aggregate catalysts.

Also of importance is to consider that the optimal formulation for two catalysts in a tandem process may differ significantly from that of a benchmark single catalyst, which may exist for the same overall conversion. In tandem catalysis, a high reaction specificity by the catalysts is essential, in order to achieve the highest possible control over the rates of the integrated reactions. This is exemplified in the work from our group on the tandem olefin isomerization/hydrosilylation. While Pt-based catalysts would be a conventional choice for both reactions, it is the tandem integration of Ru- and Rh-based SACs, which independently show higher reaction specificities, what results in an optimal performance by preventing the two reaction paths to compete on a single active site.

Plenty of opportunities emerge in the horizon. However, several challenges are also faced and it behooves scientists to ponder a number of considerations to ensure that this research area develops on solid grounds.

By the earliest definition of *tandem catalysis*, the requirement for the sequential reactions to be mechanistically independent excludes processes wherein various sites participate along a single reaction mechanism. The cooperation of various types of surface atoms in a single reaction mechanism, e.g. metal nanoparticles and peripheral support sites,[19] is pervasive in heterogenous catalysis. Most notably on SACs,

which lack metal-metal direct coordination, various vicinal species, e.g. lattice oxygen or hydroxyl groups on oxide supports, oxygen vacancies and other types of defects, etc are oftentimes required to cooperate with the isolated metal atom for a given reaction mechanism to complete a *turnover*. By the same token, bifunctional processes mediated by fleeting, non-isolable intermediates, e.g. adsorbed species which migrate between two neighboring sites via spillover phenomena, should not be considered tandem catalysis *strict sensa*.

Perhaps as significant as realizing novel tandem catalysis processes based on single-atom catalysts is to substantiate the tandem nature of the process. A first approach in this direction is to identify key intermediate products and carefully assess the performance of each individual catalyst on both the starting reactants as well as the intermediate products. This exercise requires, however, to be able to isolate and test each of the two catalysts separately. This may be notably challenging when dealing, e.g. with two types of single-atom catalysts on a common carrier oxide, or a continuous metallic structure in so-called single-atom alloys.[20] The latter is another versatile platform to isolate single metal atoms of two different "guest" metals within a single "host" metallic matrix.

The integration of single-atoms and metal aggregates is considered a particularly versatile catalyst design strategy for tandem processes. The co-existence of single-atoms and metal clusters is frequently observed as a result of synthesis procedures targeting specifically SACs, at metal loadings beyond the capacity of the support to stabilize isolated atoms/cations. Firstly, it is important to consider that exposure particularly to reductive reaction conditions establishes a driving force for Ostwald ripening phenomena[21] which, if not outweighed by the binding strength of the isolated atoms to the support, may lead to metal redistribution during operation, eventually depleting isolated atoms in favor of the growth of the metal aggregates. The assessment of site stability is of central significance in single-atom catalysis at broad, and it calls for extensive *operando*, at least post-reaction, analysis of metal nuclearity. This matter is of even greater concern when isolated metal atoms and metal aggregates are concomitantly present on the catalyst surface. Secondly, this catalyst configuration may prove particularly demanding when it comes to developing reference catalyst materials containing exclusively one of the two catalytic species. This is necessary for exclusion tests geared at studying individual catalytic performances and establishing rigorous comparisons to the tandem. It is often not easy to produce comparison materials which contain small metal clusters free from atomically dispersed species. The use of conventional reference catalysts, with comparatively larger metal nanoparticles may prove inadequate in cases where reaction structure sensitivity phenomena enforce vastly different reactivity on very small clusters and on larger nanocrystals. An alternative approach to deconvolute the bifunctional system is the application of chemical treatments designed to selectively etch one type of metal species from the catalyst surface. However, it should be bear in mind that such treatments may introduce modifications on the remaining metal or the support itself (redispersion/agglomeration, poisoning, promotion by

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leftovers, etc) with unpredictable catalytic consequences. In view of these considerations, a preferred scenario is the development of individual catalysts as different materials. This enables their tandem integration by co-slurrying in liquid reaction media, or conformation of intimate composites for gas-solid catalysis processes, while enabling independent control and assessment of their individual physicochemical and catalytic properties.

Our growing capacity to tune, characterize and utilize metals atomically dispersed on inorganic solids ensures a fertile ground for the development of new electro-, photo- and thermally driven tandem conversion processes which draw on the unconventional features of single-atom catalysts.

Conflict of Interest

The authors declare no conflict of interest.

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