The various levels of integration of chemo- and bio-catalysis towards hybrid catalysis

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Intimate integration of biological and chemical catalysts has only recently emerged. The first examples of *"Hybrid catalysis"* can be found in the literature from the early 2000's. Since that, the number of studies has progressively increased, but is still modest compared to the quantity of processes that involve one single type of catalyst. This is mainly due to the difficulty for biologists and chemists to communicate and bring together the skills involved in such sophisticated combinations. In this paper, we show and sort the advantages of the catalytic systems and of their variants of integration so as to pave the way for better rationalized development.

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The various levels of integration of chemo- and bio-catalysis towards hybrid catalysis

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Combining catalysts is not a recent concept. For several decades, it has enabled the development of processes that are more economical in terms of solvents, energy, and carbon emissions. This strategy leads the way in current catalytic research aiming to reduce the impact of the chemical industry on the environment and replace synthetic routes based on petroleum with those based on biomass. In particular, hybrid catalysis, consisting of the integrated combination of several catalysts of different types, often a chemical and bio-catalyst, represents one of the most promising innovations in the field, especially when the two catalysts are combined in a single multicatalytic material. Several examples of such achievements have already been reported; however, these are rare compared to single-type catalyst combinations. It is important to understand the issues that govern hybrid catalysis to overcome the obstacles affecting its implementation, starting with the difficulties of communication between scientists of different fields. To surmount this barrier, this article proposes a new naming system for multicatalytic processes and reactions to unify common terms describing the same concepts. This system allows for the comparison of multicatalytic systems developed in both chemistry and biology and highlights their differences, similarities, and limitations. Hybrid catalysis is a rapidly expanding interdisciplinary field that builds on the developments from both the field of catalysis and materials science. Although the number of synthetic examples is limited, they are growing exponentially using the latest innovative materials for the production of multicatalytic materials for use in optimized "one-pot/one-step" processes.

Introduction

The development of more eco-compatible chemical processes is now a priority. The scarcity of fossil fuels coupled with climate change necessitates that we restructure our consumption habits and production models. Since the formalization of the concept of *Green Chemistry* by Anastas and Warner,[1] chemists have been searching for more efficient alternatives to conventional syntheses that are less energy-consuming, more economically sustainable, and more environmental-friendly. Catalytic processes fulfill most of these requirements but traditionally employ a single chemical or biological catalyst for a given reaction step. Individual catalysts are only capable of performing a limited number of reactions, and both chemists and biologists have sought to increase the catalytic reaction scope by combining multiple catalysts. The use of catalyst combinations has therefore increased in recent years mainly due to this reason, but the growing need to find viable alternatives to petroleum as a carbon source may nowadays also play an important role in this development. Biomass is one of Earth's most important and renewable resources; however, it is composed of a much broader molecules diversity than hydrocarbons, making it necessary to identify a range of catalytic pathways to achieve its complete valorization. The primary advantage of combining multiple catalysts is the possibility of diversifying the synthetic routes, and thus the substrates that can be converted, as well as the chemical functions that can be generated. This explains why multicatalytic reactions have become integral to the synthetic strategies of both chemical and biological catalysis research. These systems use and extend the intrinsic qualities of the catalysts and, in general, lead to significant energy savings and higher yields in less time.

Depending on the objective, the different catalysts can be combined in distinct ways with respect to both the process and the reaction sequence. Each of these processes, whether performed in the same reaction "pot" or in one or more stages, offers a range of advantages, but also has disadvantages that limit their application. The "*one-pot/one-step*" process appears to be the most promising for reducing energy consumption, increasing atom economy, and optimizing catalytic efficiency. "*one-pot/one-step*" processes

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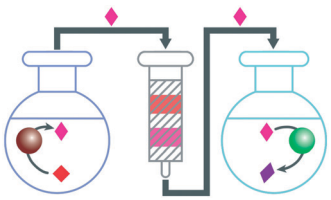
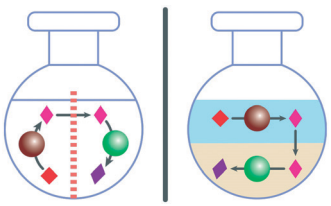
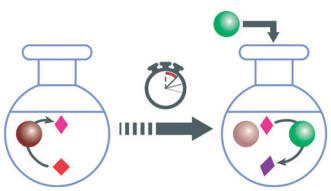
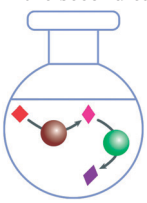
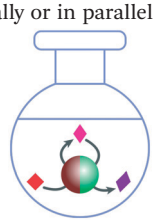
combine two or more catalysts working together in the same reaction, which eliminates the need for purification between each step and, as it occurs within a single reactor, is both cost- and energy-efficient. Furthermore, optimized "*one-pot/one-step*" processes often involve synergistic effects between the catalytic centers, which can shift the reaction balance. This is particularly observed when the catalysts are used not in their isolated forms but as a single multicatalytic material (MCM). The active sites in MCMs are optimally arranged to allow maximum interaction with the substrates and products of the various chemical reactions. Among the various catalyst combinations, "*hybrid*" catalysis, which combines both a chemical and biological catalyst, is the most recent and, undoubtedly, the most complex to implement, but also benefits most from these synergistic effects. However, there are relatively few examples of hybrid catalysis, and those carried out as a "*one-pot/one-step*" process rarely involve an MCM. Although the development of "*hybrid*" MCMs is increasing, the incorporation of a wide range of enzymes, chemical catalysts, and immobilization carriers remains challenging.

To understand the rules and constraints governing the combining of catalysts more fully, it is first necessary to identify the reaction classes that use such combinations. We start by providing a general description of the different possible multicatalyst arrangements along with their respective advantages and disadvantages. To this end, we propose a new general terminology for grouping the elements described in the literature, concentrating on the similarities and differences between chemical and biocatalysis to achieve a more faithful and thorough representation of the two fields. The resultant naming

Table 1 Summary of the different multicatalytic processes

Process type	Advantages	Disadvantages	Process scheme
Two-pots/two-steps 2P2S	→ Flexible processes → Ease of combining catalysts → Fine and independent adjustment of reaction conditions	→ High energy consumption → Poor atom economy	
⇒ The two catalysts are used sequentially in two different reaction compartments			
Two-pots/one-step 2P1S	→ Energy saving → High yields due to synergy (thermodynamics) → Different reaction conditions for the two catalysts	→ Complex implementation → Problem of reagent circulation between compartments	
⇒ The two catalysts are in two separate compartments but are connected to each other and work in parallel			
One-pot/two-steps 1P2S	→ Energy saving → Simple implementation	→ Reaction equilibrium shift not possible → Action required during the process → Longer reaction time	
⇒ At the end of the first catalytic reaction, a second catalyst is added to the same reaction medium to perform the second catalytic step			
One-pot/one-step 1P1S	→ Energy saving → High yields due to synergy (thermodynamics) → Unique set of reaction conditions → Simple implementation	→ Less flexibility → Risk of incompatibility between catalysts	
⇒ The two catalysts are introduced into the reaction medium as the reaction is initiated and work sequentially or in parallel			
Multicatalytic materials (MCMs)	→ Advantages of 1P1S with greater synergy between the catalytic sites and greater ease of implementation	→ Disadvantages of 1P1S	
⇒ The different catalytic centers are grouped together on the same material to simplify and optimize the implementation of 1P1S processes			

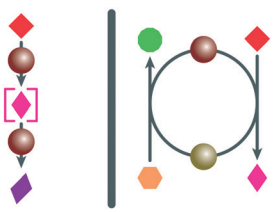
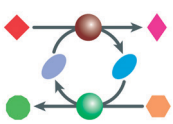
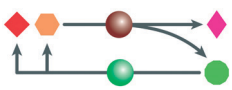
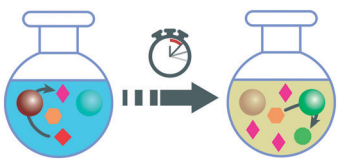
system will allow for a clear description of multicatalytic materials and, more particularly, hybrid materials, and is divided into two sub-parts. The first part describes the different techniques used for multicatalytic processes and the second part details the various reactions that can be performed by combining catalysts. The naming system and different advantages and disadvantages of each process and reaction type are summarized in Tables 1 and 2. To simplify the discussion, only concepts involving the combination of two catalysts are detailed in this review, as systems combining a greater number of catalysts merely involve an additional combination step. After establishing the terminology, we proceed with an evaluation of the multicatalytic systems developed in chemistry and biology by observing their abundance in their respective fields, as well as their key advantages and disadvantages. This enables us to highlight the main challenges limiting the development of so-called "*hybrid*" catalysis, whether it is a combination of two distinct catalysts of different natures or their combination in a single MCM. We conclude this section with the current lines of development and routes that require further exploration.

1. Terminology of multicatalytic processes

1.1. "*Two-pots/two-steps*" processes (2P2S)

Before defining reaction arrangements involving the interaction of two catalysts, it is essential to describe the general processes that utilize multiple catalysts. The first and simplest process consists of two separate catalytic stages and corresponds to the "*multi-stage*" synthesis employed in organic chemistry since its advent. The first catalyst is introduced with its substrates into the first container (flask, reactor, *etc.*) and the reaction is carried out. The products are then purified to serve as substrates for the second catalytic step. The main disadvantage of this "*two-pots/two-steps*" (2P2S) process lies in the need for an intermediate purification step, which is often costly with respect to energy and solvent consumption or infrastructure (Fig. 1). To minimize these costs, the purification step can be limited to the removal of the first catalyst from the reaction medium, with the second reaction occurring directly in the reaction crude. This method is more respectful of the principles of *green chemistry* but is far from optimal. Although 2P2S

Table 2 Summary of the different multicatalytic reactions involved in "*one-pot/one-step*" processes

Type of reaction	Common terminology in chemical catalysis	Common terminology in biocatalysis	Reaction scheme
Domino/cascade	Domino/cascade (identical mechanism) & auto-tandem/assisted tandem (different mechanisms)[2,13]	Fusion enzyme (multiple catalytic sites)[4]	
⇒ A single catalyst with one or more catalytic mechanisms			
Combined tandem	Cooperative reaction[14]	Enzyme and cofactor	
⇒ Two catalysts acting together to transform a single substrate			
Sequential tandem	Orthogonal tandem,[2,13] concurrent cascade,[15,16] relay reaction (1P1S),[14] domino reactions[17]	Linear cascade[4,18–22]	
⇒ Two catalysts operating successively with the product of one being the substrate of the other			
Parallel tandem	Cooperative cascade,[15,16] relay reaction (1P1S)[14]	Parallel cascade[18–22]	
⇒ Two catalysts working in parallel with a reaction intermediate consumed by one and then regenerated by the other. The two pairs of substrates do not interact			
Cyclic tandem	Cooperative cascade,[15,16] relay reaction (1P1S)[14]	Cyclic cascade[18–22]	
⇒ The second catalyst regenerates the substrate of the first from one of the products formed by the first reaction			
Activated tandem	Sequential cascade[15,16]	—	
⇒ Modification of the reaction medium by the first catalytic reaction, leading to the activation of the second catalyst. It is a pseudo-1P1S as the two catalysts are not active at the same time			

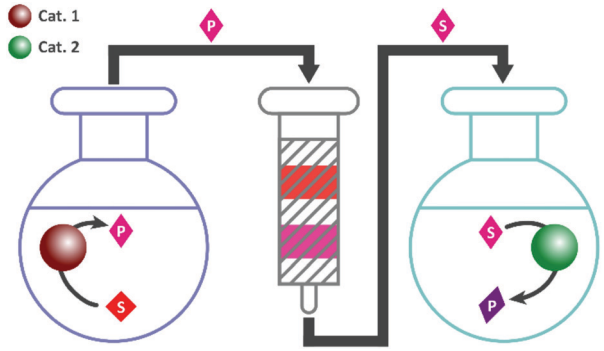


Fig. 1 2P2S multicatalytic reaction process. The product (P) from the first reaction is purified before serving as a substrate (S) for the second reaction. Cat: catalyst.

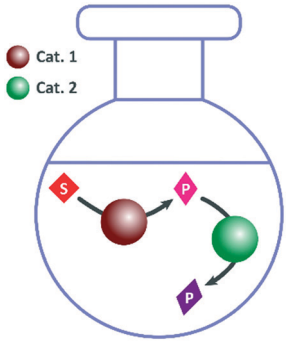


Fig. 2 1P1S multicatalytic reaction process. The two catalysts (cat.) are present from the start of the reaction and work together to achieve the final product (P), often with the implementation of synergistic effects. S: substrate.

processes allow for easy control of the efficiency of the individual catalysts owing to the independent reaction conditions, it is the least efficient concerning catalyst combinations, as the catalysts can only work in sequence without cooperating to achieve better yields or greater product diversity.

Chemists and biologists quickly realized that ideal multicatalytic processes should be performed in a single container, or "*one-pot*", to capitalize on the synergy between two catalysts (displacement of thermodynamic equilibrium, mutual activation, cofactor/cosubstrate recycling, mutual protection against the solvent, *etc.*). These reactions provide an additional advantage over 2P2S by eliminating the purification step and reducing energy and atom consumptions by carrying out several steps concomitantly.

1.2. "*One-pot/one-step*" and "*one-pot/two-steps*" (1P1S & 1P2S) processes

Although many studies have focused on the development of "*one-pot*" reactions, the majority of these reports use this term without specifying either the number of steps performed within this "*pot*" or how they were arranged. These features should be specified to prevent confusion, as a variable number of independent or non-independent steps can be carried out within the same container. Strictly speaking, this terminology should correspond to reactions known as "*one-pot/one-step*" (1P1S), as it describes a process in which all the substrates and catalysts are present in a single container from the outset of the reaction (Fig. 2).[2] However, the vast majority of reactions referred to as "*one-pot*" often describe reactions in which the first catalytic step is carried out using the first catalyst alone, followed by the addition of a second catalyst, with or without an additional substrate, at a given time to achieve the second step of the process. The total reaction is therefore carried out in a single container, in "*one-pot*", but in "*two-steps*" (Fig. 3). This distinction is important because 1P1S reactions have several significant advantages over the "*one-pot/two-steps*" process (1P2S). In addition to the simplified logistics of implementing the 1P1S reaction (true batch reaction without further addition), this process enables synergy between the catalysts, particularly in terms of shifting the reaction equilibrium. For example, by combining a thermodynamically irreversible reaction with a balanced reaction in a single step, the general equilibrium is shifted in favor of the desired product, resulting in greater yields than for the same reaction carried out in two successive steps.

1.3. "*Two-pots/one-step*" (2P1S) processes

The 1P1S processes are ideal for researchers studying multicatalytic systems and are a prime objective when combining catalysts. Unfortunately, the development of these processes is more complex due to the need to make two catalysts cohabitate, which often requires notably different operating conditions and, in certain cases, leads to inactivation of the catalysts. These problems explain the lower proportion of 1P1S reactions in the literature. This difficulty is exacerbated when the combined catalysts are of very different types; *e.g.*, homogeneous and heterogeneous catalysts or chemical catalysts with biocatalysts. To overcome these limitations, researchers often use compartmentalization strategies, confining each catalyst in

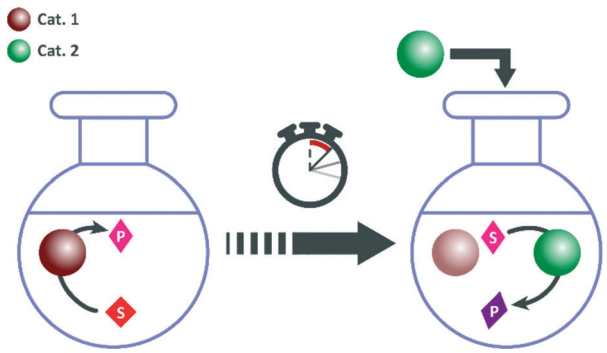


Fig. 3 1P2S multicatalytic reaction process. The second catalyst (cat. 2) is added at a given time after the first catalyst (cat. 1) has completed the first reaction. S: substrate; P: product.

an environment under defined operating conditions. One such strategy separates the catalysts using a physical barrier,[3–5] such as PVDF membranes, cell walls, micelles, *etc.* It is also possible to use a liquid interfaces that functions as a chemical barrier, selecting the compounds that can pass from one compartment to another.[6] These processes can be described as "*two-pots/one-step*" (2P1S) and provide an elegant way of making two separate catalysts coexist (Fig. 4). The 2P1S system retains several advantages, including allowing the thermodynamic equilibrium shifting and eliminating the need for purification between steps. However, these processes also display similar disadvantages to the 2P2S processes, such as the absence of synergy between the catalytic sites, mutual protection against the reaction medium, or mutual activation.

1.4. Processes based on multicatalytic materials (MCMs)

An even more elegant strategy involves co-immobilization of the two catalysts within the same matrix, resulting in a single catalytic material exhibiting two different catalytic properties. These MCMs offer the possibility of an actual 1P1S process while benefiting from compartmentalization effects (Fig. 5).

Several immobilization strategies and supports have already been developed, including mesoporous silicas, zeolites, bimetallic nanoparticles, various polymers, nanoflowers, "*metal–organic frameworks*" (MOFs), "*covalent organic frameworks*" (COFs), "*cross-linked enzyme aggregates*" (CLEAs), hydrogels, lamellar double hydroxides (LDH) or, more simply, fixation on solid supports.[7–12] Each of these supports and techniques has its own set of advantages and disadvantages. The selection of the support and technique generates different outcomes regarding the arrangement of the catalytic sites with respect to one another, which affects the ability of these systems to function in the preparation of a specific catalytic material. The optimal catalytic systems allow exceptionally fine control of the localization of active sites, thus offering the possibility of maximizing synergies between the catalysts by protecting them within microchannels with a particular physicochemical environment or by reducing the distance between substrates/products and the catalytic sites. The challenges associated with the development of these MCMs and, more particularly, those allowing for combinations between enzymes and heterogeneous chemical catalysts, as well as an understanding of the physicochemical mechanisms that govern these systems will be discussed in more detail.

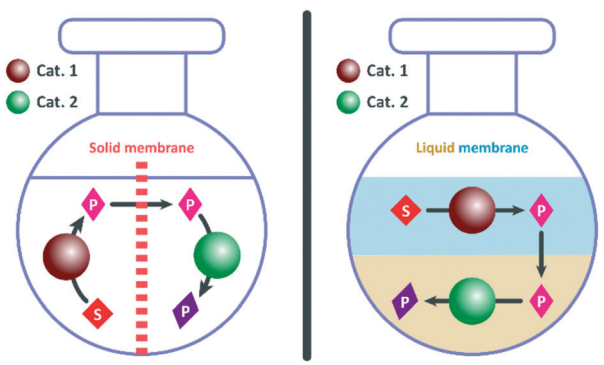


Fig. 4 2P1S multicatalytic reaction process. Left: The two catalysts are separated by a solid membrane (polymer, micelle, cell wall, *etc.*). Right: The two catalysts are separated by a liquid interface (multiphase mixtures, reactors separated by a liquid bridge, *etc.*). Cat.: catalyst; S: substrate, P: product.

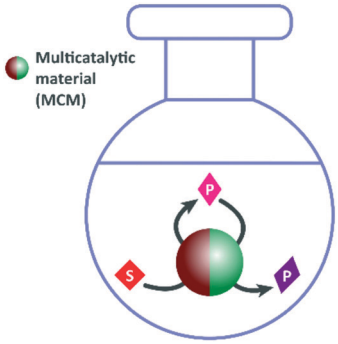


Fig. 5 1P1S multicatalytic reaction process involving a "*multicatalytic material*" (MCM) that combines the active sites of different catalysts. S: substrate, P: product.

2. Naming system for the different reactions involved in multicatalytic processes

In addition to the processes (1P1S, 1P2S, 2P1S, or 2P2S), it is also necessary to classify the multicatalytic reactions using different terminologies based on the arrangement of the catalytic stages. Two catalysts for the same process can be arranged very differently in terms of reaction order, with each arrangement having a dedicated objective for the synthesis. Reports involving catalyst combinations have described reactions using the terms "*cascade*", "*tandem*", "*domino*", "*multi-stage*", "*orthogonal*", "*parallel*", "*cyclic*", *etc.* These terms are used in radically different ways between the studies, and these differences become even more pronounced when comparing chemical and biocatalytic reactions. Although multiple authors have proposed precise terminological classifications, these were generally not adopted, and new classifications emerged every two to three years.[2,4,13–16,18–26] The first and often most widely used classification system in chemistry was proposed by Fogg and Dos Santos; however, it is not optimal for biological systems and requires some adjustment.[26] For clarity within this work, we have proposed a brief terminological classification in combination based this common one and completed with the concepts and terms used in biocatalysis.

2.1. "*Domino*" or "*cascade*" reactions

The first and simplest multicatalytic reaction involves a single catalyst carrying out several successive molecular transformations (Fig. 6). This type of arrangement is often

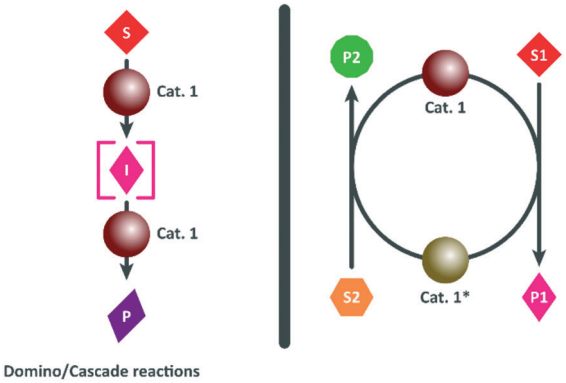


Fig. 6 Multicatalytic "*domino*" or "*cascade*" reactions. Left: The catalyst is not modified and reacts consecutively with different molecules. Right: The catalyst is modified by the first reaction with the first substrate/product pair and regenerated through its reaction with the second substrate/product pair. Cat.: catalyst; S: substrate, P: product.

classified as "*domino*", but the term catalytic "*cascade*" is also used, referring to the fact that the second operation follows directly from the previous one, with the intermediate species generally being unstable.[24,27–29] Contrary to the proposal of Fogg and Dos Santos, we include reactions catalyzed by a single catalyst performing a succession of different catalytic mechanisms under this term, as well as those changing their catalytic mechanism during the reaction following "*activation*" by an external parameter. These two types of reactions are grouped by Fogg and Dos Santos under the term "*auto-tandem*" and "*assisted tandem*", but these terms can be confusing when they are applied to reactions carried out jointly by two separate catalysts. Furthermore, their classification does not differentiate this type of catalyst from multicatalytic materials, which is a key focus of this work. It should be noted that, although "*domino*" reactions generally involve catalytic cycles in which the catalyst is regenerated, this is not the only possible mechanism. This type of reaction is not discussed further since it does not involve catalyst combinations, as the reaction activities are directly dependent on a single catalyst.

Still, it has to be mentioned that some authors proposed very different definitions, involving several catalysts under this terminology. Tietze describes "*domino reactions*" as a "*process involving two or more bond-forming transformations (usually C–C bonds) which take place under the same reaction conditions without adding additional reagents or catalysts, and in which the subsequent reactions result as a consequence of the functionality formed in the previous step*".[17] Far from Fogg and Dos Santos' definition, this latter one refers more to the types of reaction that will be described hereafter as "*sequential tandem*" reactions, and show perfectly how the same terminology can be used to describe very different concepts.

2.2. "*Combined tandem*" reactions

We have grouped all reactions involving several species or catalytic sites under the term "*tandem*" reaction. This idea derives from the fact that while each catalyst can work alone, their combination offers one or more advantages, such as a diversification of the catalyzed reactions, a shifting of the thermodynamic equilibrium, or the activation of one of the catalysts by the other. However, it should be noted that in biocatalysis, this term is often replaced by the term "*cascade*" reaction, which introduces an additional level of confusion between the fields. Having established this prerequisite, the "*tandem*" reactions can be sub-divided into several categories. The first category, which closely resembles "*domino*" reactions, describes reactions that involve a combination of two different catalytic species to enable a single catalytic step and are referred to as "*combined tandem*" reactions (Fig. 7). This should not be confused with a 1P1S process involving an MCM as it involves a single catalytic step leading to a single product. The best examples of this type of reaction are enzymes, some of which require an exogenous chemical species (pyridoxal phosphate, thiamine pyrophosphate, hemes, and other porphyrins) for catalysis. These can be split into two groups depending on their binding strength with the enzyme. The strongly bound ones are usually called "*prosthetic groups*", while the others can have different terminologies.[30] Both can be involved in "*combined tandem*" as long as they exhibit a catalytic activity and are therefore regenerated at the end of the reaction. Note that this type of system was also developed early in chemistry, with elegant examples combining catalysts of the same[31] or different types.[32,33] These examples suggest the extent to which combining catalysts enables the diversification of reactions that can be catalyzed.

2.3. "*Sequential tandem*" reactions

Come next the reactions that involve two separate catalysts and active sites. The first and most widespread type consists of reactions that involve several sequential catalytic stages, leading to the formation of one or more products from one or more substrates by generating stable or unstable intermediates between each step.[4,5,21] These will be called "*sequential tandem*" reactions, as the product(s) from each

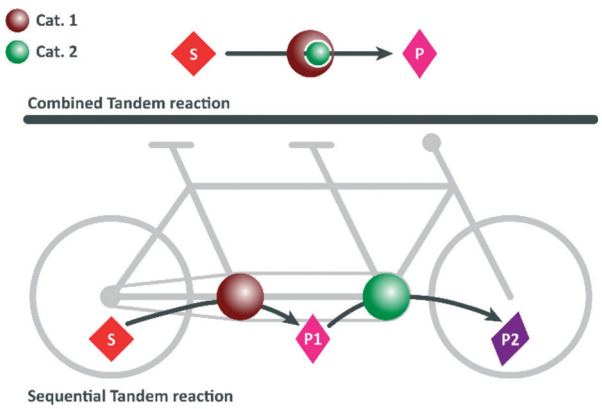


Fig. 7 Multicatalytic "*combined tandem*" (top) and "*sequential tandem*" (bottom) reactions. Cat.: catalyst; S: substrate, P: product.

step serve as the substrate(s) for the next one (Fig. 7). This is the reaction type that is the closest to Tietze's definition, and that is most often qualified as "*catalytic cascade*" in biocatalysis. Due to the successive action of the next catalyst on the product of the previous one, "*sequential tandems*" represent the most promising reaction type for diversification of the synthetic pathways, combining catalysts selectivities, and opening at each step new chemical functions to act onto.

2.4. "*Parallel tandem*" reactions

It is also possible to have reactions involving different catalysts working together without following a precise order. They will be referred to here as "*parallel tandem*" reactions (Fig. 8). They are unique in that they involve two reaction species that are both the substrate of one reaction and the product of the other. These compounds, which can be described as intermediates, are often used in catalytic amounts because they are cyclically generated by the two catalytic reactions. One of the most significant examples of this reaction involves the regeneration of cofactors, such as NAD/NADH and FAD/$FADH_2$ pairs, in biocatalysis. These pairs act as intermediates between two enzymes to enable the transformations that they catalyze. It should be noted that according to the principles of enzymology, these types of compounds should not be considered cofactors but cosubstrates since they are not regenerated by the enzyme during the biocatalytic stage.

The main advantage of "*parallel tandem*" reactions in synthesis is the ability to use small quantities of the intermediates owing to their continuous regeneration. Reducing the quantities of these intermediates can minimize costs and avoid potential inhibition of a catalyst by one of the intermediates. However, as each transformation does not influence the outcome of the other, this type of reaction does not generally expand the range of possible transformations and has limited use for the purposes described here.

2.5. "*Cyclic tandem*" reactions

One variant of the "*parallel tandem*" reaction involves two separate catalysts, one of which transforms a product of the other to restore the substrates of the previous reaction. These reactions, which can be described as "*cyclic tandem*", do not involve an intermediate, but directly use the substrates and products of the accompanying reaction, making them

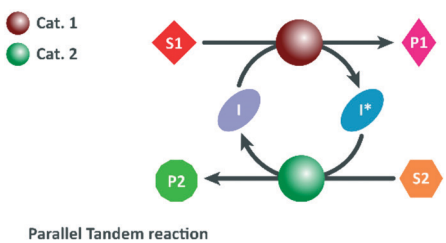


Fig. 8 Multicatalytic "*parallel tandem*" reaction. Cat.: catalyst; S: substrate, I: intermediate; P: product.

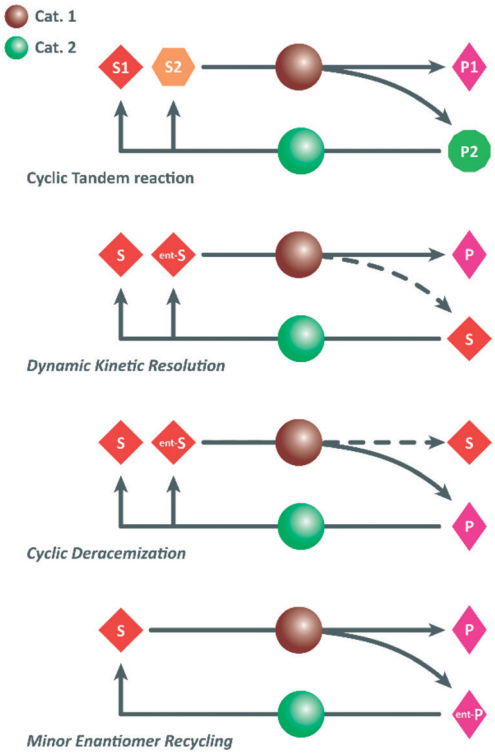


Fig. 9 Multicatalytic "*cyclic*" reactions. Dynamic kinetic resolution (bottom) is a variant of the "*cyclic tandem*" reaction (top) in which the substrates are in a racemic mixture. One of the two enantiomers is transformed by the first catalyst, while the other enantiomer is racemized by the second to result in a racemic mixture. This dynamic kinetic resolution reaction is the oldest type of cascade reaction developed by combining a chemical and bio-catalyst. Cat.: catalyst; S: substrate, P: product.

interdependent. A common good example of this reaction type is "*dynamic kinetic resolution*" (DKR), which simultaneously involves a racemization and stereoselective step (Fig. 9).

In DKR, one of the substrate enantiomers is constantly racemized by one of the catalysts to generate the other enantiomer, that will then be converted by the other catalyst. A variation, called "*cyclic deracemization*", describes a "*cyclic tandem*" reaction where the second catalyst does not act on the remaining substrate enantiomer, but on the product of the first catalytic step, often an achiral molecule.[34–36] This methodology helps to effectively deracemize the substrate racemate, releasing one pure substrate enantiomer in the end of the process, instead of a new enantiomeric pure product. Therefore, it does not help diversifying the catalytic pathways, but is very useful to be used as the last step of a process involving achiral catalysts that would not result in only the desired enantiomer production. Additionally, unlike DKR, this second type of "*cyclic tandem*" reaction is more in line with the concept of multicatalytic reactions proposed by Tietze. A third variation of this strategy, named as "*minor enantiomer recycling*" (MER), was proposed by Moberg and describes "*cyclic tandem*" reactions involving this time the conversion of an achiral substrate in a mixture of

enantiomers.[37,38] Following this first step, the undesired enantiomer product, the so called "*minor enantiomer*", is then reconverted into the achiral substrate. This strategy benefits from its coupling with thermodynamically favorable side-reactions that enable equilibrium shifting. These reactions can then be performed as "*parallel tandems*" in even more complex multicatalytic systems. Moreover, while the two first strategies are aiming to increase chirality in systems where it is already present, this third one additionally introduces new chiral centers, which makes it particularly suitable for several applications such as pharmacology, where the biological activity of the molecules is often based on their three-dimensional structure and space orientation. To conclude with "*cyclic tandem*" reactions, as will be described later, DKR and its variations are one of the first realisations of the combination of several catalysts in an integrated and efficient manner using a chemical catalyst with a biocatalyst. Still, similar to "*parallel tandem*" reactions, these reactions do not diversify reaction pathways. But they are particularly effective for introducing chirality into asymmetric syntheses, and their application generally remains limited to this function.

2.6. "*Activated tandem*" reactions

One final reaction type involves a catalyst, the product of which activates the medium for a subsequent catalytic step. These "*activated tandem*" reactions differ from "*domino*" reactions as they involve two distinct catalytic species; however, these reactions do not involve true, simultaneous catalytic steps, as the product of one results in the progression of the other without necessarily being its substrate (Fig. 10).

These reactions are of great interest for the implementation of autonomous 1P2S systems (not requiring the addition of a catalyst or substrate at a given time) and can be described as pseudo-1P1S; however, they are not optimal since the yields are often limited by the change in reaction conditions. We, therefore, prefer "*real*" 1P1S systems that can be operated continuously.

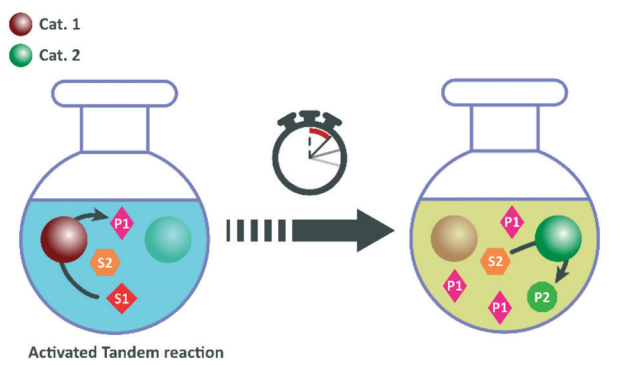


Fig. 10 Multicatalytic "*activated tandem*" reaction. Cat.: catalyst; S: substrate, P: product.

2.7. Combining several tandem reactions for obtaining synergistic effects

It is possible to combine several of the previously mentioned reactions types to form self-regenerating catalytic systems. One of the most elegant examples in biocatalysis is the system developed by the Kroutil group using an alcohol dehydrogenase (ADH) and a transaminase (Cv-TA) sequentially to convert linear hydroxylated compounds into their corresponding diamines *via* a 4-step "*sequential tandem*" reaction combined with a "*parallel tandem*" reaction to regenerate the cofactors and amine donors (Fig. 11).[39] This process uses alanine dehydrogenase (AlaDH) to regenerate the NADH consumed by ADH and the alanine consumed by Cv-TA from the co-products of these two enzymes and ammonia solution. It allowed the efficient generation of linear diamines with 8, 9, and 10 carbons, which are advantageous for the synthesis of polymers, such as nylon.

As efficiently described by this example, all the aforementioned types of multicatalytic reactions can be combined together to increase the diversity of the reactional pathways that are available for chemicals synthesis. Another layer complexity can then be added on top of this with the combination of the different process categories (*n*P*n*S), greatly introducing chemical diversity into research and provide tools for an industry searching for new solutions. However, each of these combinations has its own restrictions, limiting its use within industrial processes, particularly in the field of chemical catalysis. This partially explains why such multicatalytic systems are not more often described, and understanding precisely these limitations is therefore a crucial step toward their development.

3. Multicatalytic systems in chemistry and biology: abundance and limits

Having established the terminology, it is possible to perform the state-of-the-art of multicatalytic systems in chemistry and biology, in order to identify the obstacles that remain for developing such systems. As we have already specified, the

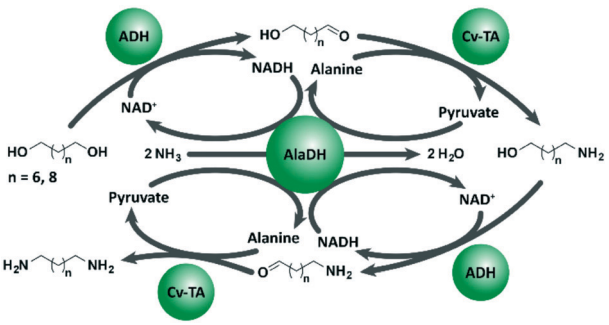


Fig. 11 Multicatalytic concept combining four "*parallel tandem*" reactions to form a "*sequential tandem*" reaction in which the cofactors and amine donors are regenerated from the ammonia solution (Sattler *et al.*, 2012).[39] ADH-hT: alcohol dehydrogenase, AlaDH: alanine dehydrogenase, CV-ωTA: transaminase.

type of process most sought after in multicatalytic synthesis is 1P1S due to the many advantages it offers in terms of reaction diversity and synergy between catalysts.

3.1. Added-value of developing multicatalytic systems

Before proceeding, we briefly summarize the general reasons that are given throughout literature to justify the development of multicatalytic systems, although these do not fully reflect the actual added value of these processes. Interestingly, 1P1S processes are overwhelmingly regarded as useful for the synthesis of asymmetric compounds,[40,41] which often have high value-added properties (cosmetics and pharmaceuticals). It is true that this process, regardless of the reaction arrangement, allows for the introduction of one or more asymmetric centers, as well as new chemical functionalities, owing to the combination of one or more stereoselective catalysts. However, reactions that do not lead to chiral molecules are also of great importance as these are responsible for the production of a wide range of widely used materials (polymers, paints, small molecules used within the chemical industry, *etc.*). Although the reactions responsible for these products are rarely cited as benefits of the 1P1S processes, their very high volumetry more efficiently exploits the advantages of this system. The 1P1S process eliminates the need for purification and significantly minimizes infrastructure requirements. Moreover, combining *n* catalysts within the same pot minimizes the need to heat *n* pots, each potentially requiring substantial energy to catalyze the reaction. These principles also apply to high value-added molecules, but their importance is inversely proportional to the compound value: we are less concerned with the energy used for the synthesis of an expensive anticancer drug produced in limited quantity than with the energy needed to produce plastics used worldwide and sold for a few euros per ton.

3.2. Multicatalytic systems in biocatalysis

A review of the literature revealed that 1P1S processes are more prevalent in biocatalysis than in chemical catalysis. More than a dozen journals covered the topic of enzyme tandem reaction development in 2019, most of which carried out within the same reaction medium.[5,42–44] Tandems reactions have become almost unavoidable when using enzymes, including for their cofactors and cosubstrates regeneration capabilities, and they are now almost considered as being catalysts in their own right, with their own properties and substrate spectrum. Some research teams have even specialized in producing fused enzymes to combine their activities.[45] If the techniques for combining enzymes are so highly developed, it is likely due to the ability of multiple enzymes to function under similar conditions (in water, at moderate temperatures, and a pH close to 7). Of course, the reaction parameters (concentrations, pH, temperature, cofactors, activators/inhibitors) must be precisely adjusted for each reaction to obtain the optimal conditions for the different enzymes, leading to the production of diverse enzymatic cascades. This is crucial since the extreme sensitivity of enzymes to the environment can lead to a significant decrease in their activity in response to even minor changes. This optimization requires extended enzymology skills to identify the enzyme that will provide the greatest potential under the desired conditions. In addition, if an enzyme is not available for a given application or condition, an extraordinary panel of tools is now available for engineering enzymes possessing the desired properties (Fig. 12).[46–54]

Alternatively, it is possible to explore biodiversity to identify new enzymes displaying the desired properties. Nature provides an incredible reservoir of enzymatic diversity, and a rapid search for a limited number of candidates with defined properties (thermostability, pH resistance, substrate promiscuity, *etc.*) is now possible due to the development of high-speed tools. This work benefits from the long evolution of these catalysts in organisms that have colonized every environment under extremely varied physicochemical conditions. These constraints generated enzymes exhibiting a wide range of properties that can now be exploited for synthesis. Combining high-throughput screening tools with streamlined enzymatic testing will allow for the discovery of catalysts capable of functioning in 1P1S systems (Fig. 13). Finally, as previously mentioned, the direct environment of the enzyme can be manipulated to improve or alter its properties, for example, by immobilization or compartmentalization into various structures (cells, micelles, *etc.*).[42] The compilation of these tools now permits a growing number of enzyme combinations. However, as few industrial processes currently use enzymes, this is not the ideal solution to the synthesis of most chemical compounds. The industrial use of enzymes is limited due to the fragility of these biomolecules and the difficulty of purifying them without subsequent deactivation, particularly when they have not been immobilized on a solid carrier. It is therefore difficult

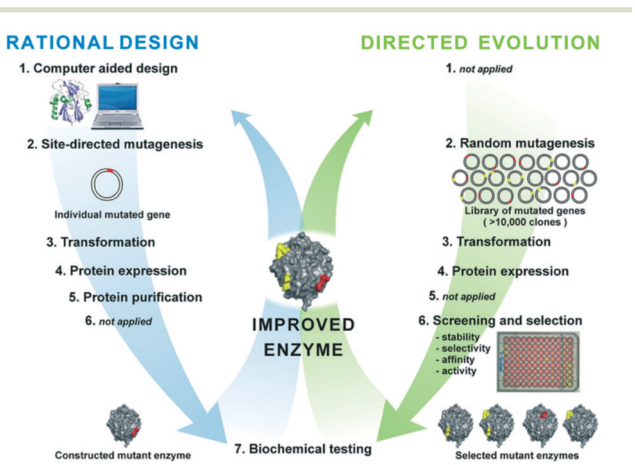


Fig. 12 Comparison of rational design and directed evolution strategies for the development of new enzymes (Dvorak, 2007)[55] (©Zbyněk Prokop and Jiří Damborský, Loschmidt Laboratories, Masaryk University, Brno, Czech Republic).

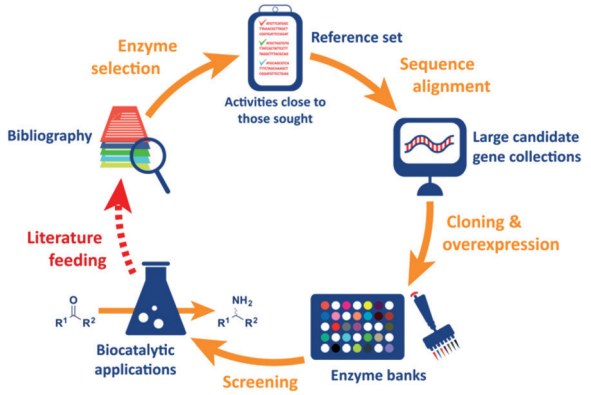


Fig. 13 General strategy for the identification of new enzymes through a genomic exploration of biodiversity.

to recycle these catalysts, and their high production cost limits their consideration by manufacturers. Moreover, purification constitutes an important additional cost factor. The same is true for immobilization, especially for high value/low volume processes, such as pharmaceutical production, leading to no economical advantage of immobilising an enzyme. All these factors restrain most industrial biocatalytic processes to the use of cells or only partly purified enzymes. Therefore, the development of enzymatic biocatalysts that can be easily and cheaply purified, immobilized and recycled remains a key challenge regarding their use in industry.

3.3. Multicatalytic systems in chemistry

3.3.1. Reasons for the lower abundance of multicatalytic systems in chemistry. Surprisingly, the majority of journals dealing with multicatalytic reactions describe this chemical field as being largely inspired by natural systems (enzyme tandem reactions, cells),[2,13,28,41,56–60] with some authors even claiming that it directly derives from nature.[23] Biological systems are generally considered to be at a particularly advanced stage of optimization with a far greater degree of complexity than artificial chemical catalysts. For example, N-heterocyclic carbenes (NHC) use a simplified version of the transketolases mechanism, enzymes that use thiamine pyrophosphate (TPP) as a natural NHC cofactor for the formation of carbon–carbon bonds.[28]

The living cell could be considered the most sophisticated and first 1P1S multicatalytic system ever developed. Hundreds of catalysts having different forms, mechanisms, physicochemical properties, and reaction conditions are combined within it, interacting synergistically by establishing finely regulated thermodynamic equilibria. Cell organization is an important source of inspiration for the compartmentalization of catalysts. Cells have different organelles compartmentalizing each of the families of particular catalysts. For example, mitochondria and chloroplasts, which specialize in generating cellular energy, deploy perfectly arranged systems of immobilized catalysts to optimize electronic exchanges between them. The importance of multicatalytic processes in biocatalysis research could be derived from the complexity of cellular catalysts. This transposition of the natural environment into artificial, chemical, and biocatalytic processes justifies the need for close collaboration between chemists and biologists. This gave rise to the development of innovative systems bridging the two disciplines by incorporating chemical catalysts directly into biological structures, such as catalytic peptides and artificial enzymes.[34,61–68]

Despite this strong source of inspiration, there remain far fewer examples of multicatalytic reactions in chemical catalysis than in biocatalysis. This is even more evident for 1P1S reactions. However, chemistry does not lack diversity in the range of developed catalysts: the panel of homogeneous and heterogeneous chemical catalysts currently available in synthesis is significantly higher than the range of currently known and usable enzymes. Although a combinatorial approach has quickly imposed itself in order to generate diversity in biocatalysis, given that the tools allowing the creation or research of new enzymes have only appeared relatively recently, chemists have very early on benefited from the many elements of the periodic table and in particular from the transition metals, but also from the great variety of structures and assemblies that can be created with them. It is precisely this diversity of chemical catalysts and their operating conditions that make them difficult to combine into in a 1P1S process. Consequently, many industrial processes are nowadays effective using only one well-optimized chemical catalyst, thus limiting even more the need for combining two catalysts.[2] In addition, chemical catalysts often have simpler structures compared to catalytic systems derived from living organisms, making the catalytic sites harder to protect from inhibition by other species, such as substrates, parallel reaction products, or other catalysts. It is not uncommon to find secondary reactions that lead to catalyst poisoning, deactivation, parasitization, or dimerization when two chemical catalysts are combined.[2]

3.3.2. Types of immobilized chemical catalysts and their combination for developing multicatalytic systems. To respond to these difficulties and benefit from the diversity of chemical catalysts through multicatalytic systems, chemists use numerous compartmentalization and immobilization techniques to limit inhibition, as described above. This strategy gave rise to the widely explored field of heterogeneous catalysis, which allows chemists to develop very efficient processes that can easily recycle the catalysts. We can classify heterogeneous catalytic materials into three main families according to their type (Fig. 14):[13]

- Organic catalytic materials. This family regroups all organic heterogeneous entities, excluding those that use transition metals fixed on organic supports. The main materials of this type are catalytic polymers functionalized with organic catalysts through covalent or weak bonds. Dendrimers are a prime example of this class and have already been used in Michael additions and nitroaldolic condensations;

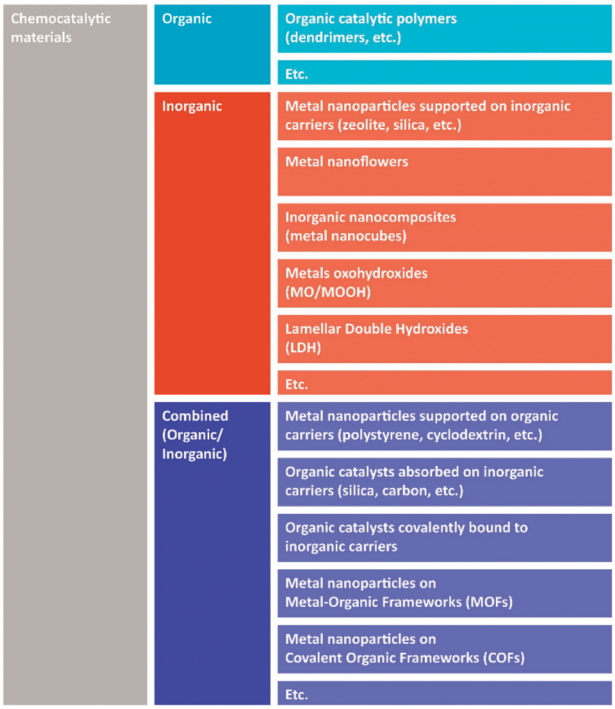


Fig. 14 Overview and examples of families of chemical catalytic materials.

- Inorganic catalytic materials. They regroup catalysts with metallic catalytic centers fixed or compartmentalized on inorganic supports. These include all unorganized/unfaceted inorganic metallic nanoparticles (metals supported on silica, zeolite, *etc.*), as well as more sophisticated structures like metallic nanoflowers or inorganic nanocomposites (*e.g.*, metallic nanocubes). The latter differ from nanoparticles in their fine and differentiated arrangement of inorganic phases, giving them specific mechanical, electrical, thermal, or optical properties.[60,69] Also included in this class are metal oxides and oxohydroxides (MO/MOOH) and lamellar double hydroxides (LDH). The former is expected to aid in the development of multicatalytic materials by concomitantly exposing acidic and basic sites,[10] while the latter has already proven useful for chemical catalysis and enzyme immobilization;[70,71]

- Combination of an inorganic support with an organic catalytic center or *vice versa*. These materials include metallic nanoparticles immobilized on or in polymers. For example, elegant encapsulation of mono- and bimetallic nanoparticles (Au and/or Pd) within polystyrene meshes allows for catalysis of several types of reactions (oxidative amination, oxidative formation of imine or esters, Michael reaction).[72] More recently, cyclodextrins have been developed which can effectively fix metallic nanoparticles and porphyrin groups.[73] Their high solubility makes them of interest for processes in homogeneous catalysis, as well as for biomedical applications where they have been long studied.[74] Conversely, it is possible to fix organic catalysts on inorganic supports, thus taking advantage of the high catalytic activities of organic catalysts, while offering greater stability and recyclability. The first grafting attempts were carried out by simple adsorption of an organic catalyst on an inert core of silica or carbon. Since this approach relies on weak bonds (van der Waals) between the catalyst and its support, significant release (leaching) is often observed, limiting its application. The possibility of linking the two entities using a covalent bond was therefore studied. Recent advances in this field have made it possible to fix several organic catalytic centers to the same support, allowing the streamlined design of multicatalytic materials.[59] A relatively recent member of these families are MOFs, which have proven particularly useful for applications in chemical and biological catalysis. These nanomaterials, formed from the structured arrangement of metal centers linked by organic ligands, have already been widely studied for their ability to immobilize chemical catalysts, in particular transition metals, either by replacing the metal ions of the nanomaterial or by encapsulating the transition metals within their channels.[7,8,13,75–77] COFs are an important counterpart to MOFs lacking the metal centers, with the ligands linked by covalent bonds. Like their metallic counterparts, the channel structure of COFs can be used to immobilize chemical catalysts, and there have been several applications in catalysis.[13,73]

Most of the previously described materials have been used to design multicatalytic systems with varying degrees of success, in terms of their synthesis alone or of their implementation (Table 3).[13] Thus, we can globally group multicatalytic chemical materials into three main families. The first are materials with concomitant Brønsted acidic and basic sites, such as MOOH.[10,13] The next is a combination of Lewis and Brønsted acids, as with the modification of zeolites by isomorphic substitution of silica atoms with tri- or tetravalent metal ions.[10,13,78] In general, this type of material is made from silica or aluminum silicates. Finally, there are Brønsted base/metal combinations, often in the form of metallic nanoparticles or LDH. One example is metal-amide type catalysts that allow the formation of different carbon–carbon bonds depending on the reaction type.[79] It is clear that the most common catalytically active sites in chemistry are acidic, basic, or metallic, which generally function in dehydration/hydrolysis/isomerization, condensation, and hydrogenation/dehydrogenation/oxidation, respectively. Jagadeesan *et al.* (2016) and Climent *et al.* (2014) provide excellent reviews of chemical multicatalytic materials.[13,57]

3.3.3. Summary of multicatalytic systems in both chemical and biocatalysis. The differences and similarities governing the creation and use of multicatalytic materials in biology and chemistry can be summarized as follows. Enzymatic biocatalysis accounts for many 1P1S processes, but is difficult to apply to the industrial field due to the fragility of the catalysts. In contrast, chemical catalysis offers a large diversity of single catalysts, which are difficult to apply to 1P1S processes due to cross inhibition between the catalytic sites. Both fields seek to apply the compartmentalization of catalysts and the rational grouping of several distinct

Table 3 Representative list of advantages and disadvantages of supported chemical catalysts[13]

Type of catalyst	Advantages	Disadvantages
Organic polymer catalysts	Colloidal stability, high activities	Low stability in the face of a chemical attack, difficult control of the arrangement of catalytic sites
Metallic nanoparticles on inorganic supports	High thermal stability, very good separation	Low selectivity, mechanical fragility
Nanoflowers	Very high specific surface area, good separation	Fragile for industrial applications
Inorganic nanocomposites	Rational design possible, many additional non-catalytic properties	Fragile materials based on their composition
Metal oxohydroxides	Easy synthesis, good separation	Fairly low activity
Lamellar double hydroxides	Easy synthesis, great compatibility with metals	Fragile in solution
Metallic nanoparticles on organic supports	Colloidal stability	High release, difficult synthesis
Organic catalysts adsorbed on inorganic supports	High activity, better separation	High release
Organic catalysts bound on inorganic supports	Low release, rational synthesis possible, better separation	Lower activity
Metal–organic frameworks	Very fine control of the catalytic centers, great versatility of structures, good separation	Fragile against hydrolysis at extreme pH and high temperatures
Covalent-organic frameworks	Increased stability, less costly synthesis	Less structural flexibility

catalytic sites as a solution to overcome these obstacles. Combining these two types of catalysis within the same material could represent a viable solution for implementing more efficient and diversified 1P1S processes.[80] This latter concept is often called "*chemobiological catalysis*", but we prefer the term "*hybrid catalysis*" because it better reflects the inter-cooperation of these two very different catalytic species.

4. Review of international research in hybrid catalysis

It is first necessary to specify the particular type of hybrid catalysis being described in this work (Fig. 15). As with chemical and bio-catalysis, hybrid catalysis can be classified according to the types of reaction processes previously described (*nPnS*); although, this classification only refers to hybrid catalysis intended for the synthesis of compounds. It should be noted that there are other factors motivating researchers to combine a biocatalyst with a chemical catalyst. For example, hybrid catalysis is useful for regenerating costly cosubstrates ("*cofactors*") used in biocatalysis, such as NADH and $FADH_2$. This field of research has gained much attention and has been expanding rapidly in recent years.[81–84] However, this review is primarily focused on diversifying synthetic routes and accessibility to new compounds, thus only the former type of hybrid catalysis will be discussed here.

The different hybrid processes can be classified into four categories: 2P2S, 2P1S, 1P2S, and 1P1S. Among the various strategies that can be implemented, we will not consider the work carried out with cells of microorganisms, regardless of their state (whole cells, resting cells, living cells, hybrid fermentation).[78,85,86] Although this field is particularly promising and marked by a current wave of innovation, the

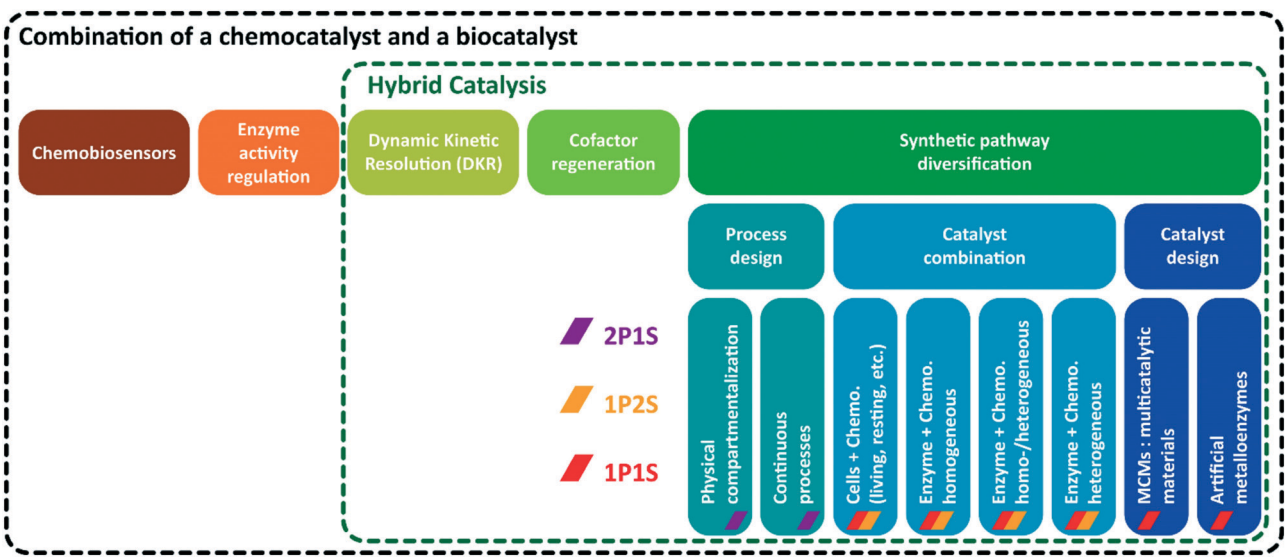


Fig. 15 Different approaches and objectives for combining a chemical and biological catalyst.

challenges governing these biological systems are distinct from those of enzymes and will need to be addressed in a dedicated manner. We will also put aside artificial metalloenzymes[15,34,62,68,84] because they represent a separate and well-studied disciplinary field. The same will apply to continuous hybrid processes that are better described as part of chemical/biological engineering. We will also not deal with hybrid biosensors because, although these do use an enzyme and chemical catalyst, these systems are focused on molecular detection rather than synthesis.[87–91] Finally, although it is a synthetic strategy, we will not discuss DKR or its variations since its goal is not to create a new molecule, but rather to deracemize a mixture of enantiomers more efficiently.[34,37,38,92–97]

It is worth noting, however, that DKR is one of the oldest and most widely used forms of hybrid catalysis. In fact, until 2010, there were fewer than 15 synthetic examples of hybrid catalysis used for chemicals synthesis, and combining chemical and bio-catalysts was almost exclusively limited to DKR reactions. The Bäckvall group is one of the most productive teams in the field of hybrid catalysis and has contributed extensively to the emergence of hybrid catalysis in catalysis research, with the development of MCMs enabling DKR reactions and tandem syntheses.[98,99] DKRs have thus paved the way for combining chemical and bio-catalysts in synthesis.

4.1. History and statistics of hybrid catalysis

The history of hybrid catalysis began in 1980 through the combination of an inorganic heterogeneous catalyst with an enzyme. Makkee *et al.* were the first to combine glucose isomerase with Pt/C for the efficient conversion of D-glucose to D-mannitol.[100] The enzyme is responsible for isomerizing glucose to fructose, which is then hydrogenated to mannitol by the metal. Interestingly, this was also the very first example of a 1P1S reaction, as the two catalysts were used in tandem in solution. To allow the enzyme to function under these reaction conditions, the authors immobilized it in gelatin and cross-linked it with glutaraldehyde to form a "*cross-linked enzyme aggregate*" or "CLEA". The group similarly tested a wide variety of transition metals (Ni, Ru, Rh, Ir, Pd) and found that ruthenium was also usable but was more quickly deactivated by the enzyme. Following this initial success, it was not until the early 2000s that another example of a non-DKR hybrid catalysis was reported. In 2003, Schoevaart *et al.* described the combination of L-proline as a homogeneous organic catalyst and D-galactose oxidase to synthesize derivatives of 4-deoxy-D-glucose from D-galactose using a one-pot/three-step process.[101] A year later, Edin *et al.* described the synthesis of enantiomerically pure acetylated aldols by combining aldolization with acetylation, catalyzed respectively by L-proline and a lipase.[102] Following the prioneering work of Makkee *et al.*, it was not until 2005 that a new 1P1S example appeared[103] and 2007 before another combination of two heterogeneous catalysts was again

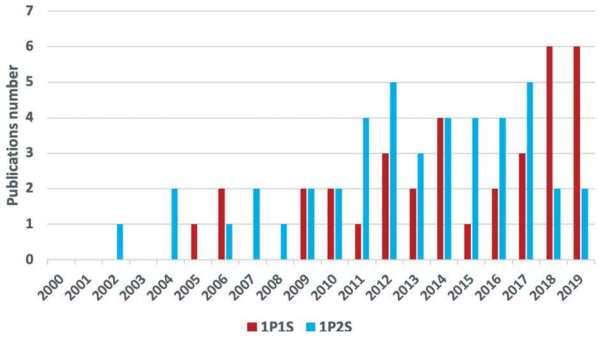


Fig. 16 The number of publications describing hybrid catalysis reactions using 1P1S (red) and 1P2S (blue) processes since 2000.

reported.[104] Therefore, there are only nine examples of 1P2S and six examples of 1P1S hybrid catalysis reported before 2010 (Fig. 16), which explains why this field of research is still in its infancy and why it is of such great interest. Although still relatively small, the number of studies describing the combination of chemical and biological catalysts has increased significantly over the past 10 years, with the variety of new available chemical compounds increasing proportionally.[3,15,60,105–115]

Despite these advances, hybrid processes, similar to biocatalysis, are rarely employed in industrial synthesis owing to the reasons previously described for the fields of chemical and bio-catalysis. However, this type of process is undoubtedly valuable for industry, both in terms of atom economy/energy savings and operational ease. A key issue is the lack of reported examples involving "*real*" 1P1S hybrid catalysis. To date, there are only 36 examples of 1P1S processes in hybrid catalysis (Fig. 17). Of these, only 15 (one-third of these from 2018/2019) describe the use of two immobilized (heterogeneous) catalysts. However, as discussed earlier, immobilization/compartmentalization represents an essential aspect in the development of effective tandem reactions, whether for the protection of reactive species against deactivation, the establishment of synergistic effects, or simply recycling. Finally, there are only 13 MCMs used in 1P1S processes and less than 10 in 1P2S processes. Owing to the enormous advantage provided by this type of hybrid material in developing 1P1S synthetic processes, this underexplored field remains a priority if hybrid catalysis is to

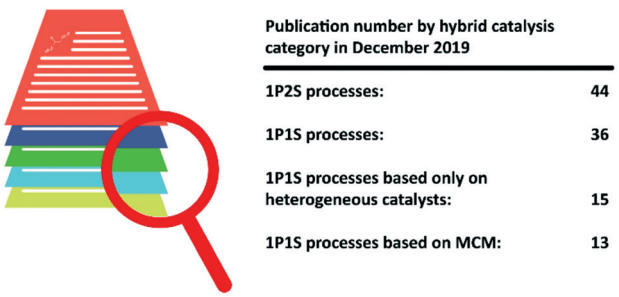


Fig. 17 2019 bibliographic analysis describing examples of 1P1S and 1P2S hybrid catalysis.

be applied to the synthesis of compounds similar to conventional chemical catalysis.

4.2. Challenges for the development of hybrid catalysis

Two main obstacles affect the development of hybrid catalysis processes. The first involves the communication barrier that exists between chemists and biologists, affecting potential collaborations. As with any interdisciplinary field, the implementation of these new processes requires specialized skills from the respective fields (Fig. 18). From chemistry, skills in the synthesis of catalysts (homogeneous and heterogeneous) and a detailed knowledge of their catalytic properties are required to anticipate the reactions that can occur, as well as the species that could inhibit them. These skills must be accompanied by a detailed knowledge of chemical and structural characterization to characterize the synthesized species, both in terms of their composition and their molecular arrangement. On the other hand, the development of such hybrid processes also requires an in-depth knowledge of biological systems to produce and effectively utilize enzymes. These skills include molecular biology and biological engineering for synthesizing enzymes, and enzymology and the immobilization of enzymes for implementing the process. Finally, in addition to this diverse list, knowledge of materials chemistry, which concerns the synthesis of immobilization supports, the study of their physicochemical properties (stability, hydrophobicity/hydrophilicity, acidity, *etc.*), and their structural characterization, is required, especially when it comes to MCMs synthesis. The wide variety of skills required drastically limits the number of teams able to conduct this type of research and requires effective communication between the collaborating researchers, as the language and scientific challenges across the fields are often very different. Additionally, there is often reluctance by chemists and biologists to participate in interdisciplinary projects.

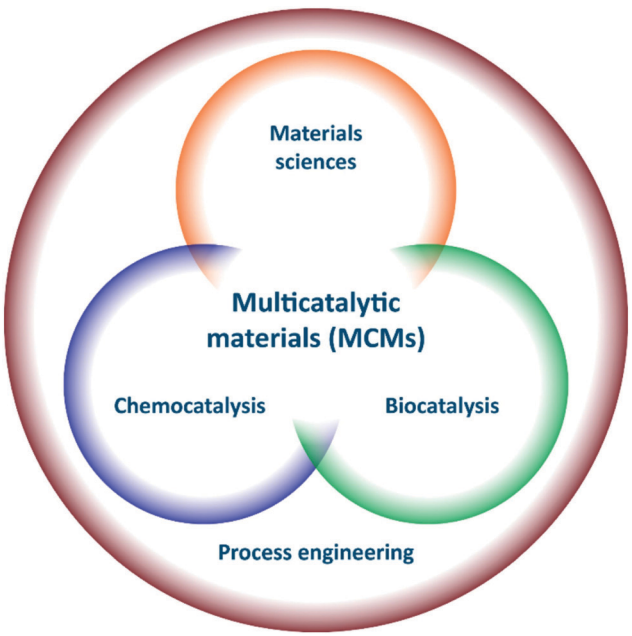


Fig. 18 Scientific fields involved in the development of multicatalytic materials (MCMs).

The second challenge is scientific and is comprised of two parts. The first step is to validate the compatibility of immobilized catalysts on separate supports across a large variety of hybrid catalytic systems before combining them within the same structure. Any cross inhibitions that occur must be considered when choosing the final support to avoid these effects, for example by spatial or physical isolation of the active sites. This groundwork will establish an initial map of compatibility between existing chemical and bio-catalysts. Only a small portion of chemical catalysts can be used in these syntheses since not all will be active in an aqueous medium. The second step involves the development of MCMs to improve catalyst compatibility, extend their reaction conditions, remove inhibition, and create synergy between catalytic sites.[3] Developing a system of catalyst compartmentalization within the same material, which guarantees separable active sites in close proximity, *via* a finely controlled synthesis is a promising solution. However, this research is still in its infancy and many avenues are yet to be explored.

There are a limited number of examples describing 1P1S MCMs, most of which use a lipase as the biocatalyst. These enzymes are particularly resistant to temperature and other operating conditions and are known to be compatible with organic solvents, allowing esterification reactions to be performed in the absence of water. Due to these properties, a large number of commercial and non-commercial lipases have been immobilized on solid supports. These enzymes represent a strong foundation for developing hybrid catalysts and present the fewest challenges for this process. However, it is essential to develop MCMs using other classes of enzymes. There are also a wide variety of chemical catalysts available to study. As previously described, many types of catalysts have been successfully immobilized on a range of support materials, both organic and inorganic. Among them, transition metal-based metallic nanoparticles can be easily synthesized with fine-tuned control of their size. This is important as the size of the particles can affect their activity and their inhibition of the accompanying enzymes.[94,116,117] Metals can catalyze many types of reactions and are active in aqueous medium, making them good candidates for the implementation of hybrid processes with a wide variety of enzymes.[106,118–121]

Finally, the material on which to immobilize the catalysts must be considered. Various solid particles can be used to manufacture biohybrid catalysts, ranging from silica to reduced graphene oxide to a polymer matrix composite.[3,15] The Bäckvall group pioneered the synthesis of "*hard*" biohybrid MCMs by incorporating enzymes and metallic nanoparticles in mesoporous silica.[99,122] These supports each have distinct advantages and disadvantages, but unlike soft

materials, solid supports benefit from a fixed structure and act solely as inert supports.[123] Unfortunately, they lack flexibility and adjustability, which are essential factors for regulating catalytic performance. Several flexible supports have also been tested, including the peptide chains of the enzymes themselves, particularly those forming cage-shaped structures that provide a tight space for the growth of metallic nanoparticles.[15] While it has proven effective in several cases, the use of a protein as the only template is often accompanied by nanoparticle aggregation, making it difficult to control their final size and obtain ultra-fine particles.[15] Other types of flexible supports have been developed, such as self-assembled capsules (micelles, *etc.*); however, these do not allow much control over the arrangement of the catalytic sites and are often soluble in water and mechanically soft, making them vulnerable to mechanical actions and difficult to recycle.[123] In general, it is difficult to control the site and distribution of catalyst immobilization on macro-supports, regardless of their "*hardness*", whereas nanostructures offer good regulation of their size, form, structure, chemical functionalities, and the dispersion of the catalysts within them. In addition, to improve the stability and recyclability of multicatalytic materials while offering maximum synergy between the active sites, it is important to employ materials that are macroscopically structured, but allow fine control over the distribution of active sites at the nanometric level. Several new materials appear to be excellent candidates for the development of such catalysts, including MOFs and COFs. MOFs, otherwise known as "*porous coordination polymers*" (PCPs), are synthesized by the self-assembly of metal ions or "*polyoxo-clusters*" (transition metals of the 3d block, metals of the 3p block, or lanthanides) with ditopic or polytopic organic ligands (carboxylates, nitrogen donor groups, sulfonates, or phosphonates) in the form of highly porous crystals (channels).[8] The concept of "*isoreticular synthesis*", introduced in 2002 by O'Keeffe and Yaghi,[8,124] has since governed the synthesis of MOFs, allowing for the creation of new structures with almost unlimited pore sizes, forms, and functions. This great versatility is linked to the wide variety of metals and ligands that can be used in their synthesis and the ability to post-functionalize them both at the metal centers and ligands.[75] Several studies describe the production of multi-metallic and multi-ligand MOFs, although these are difficult to synthesize.[125,126] This structural and synthetic diversity is of particular interest for designing multicatalytic materials (Fig. 19).

While many studies have reported the use of MOFs for designing efficient heterogeneous biocatalysts[9,127] and various chemical catalysts (Fig. 20),[7] studies describing their use in the development of hybrid catalysts are almost nonexistent, with the first example being reported in 2019.[123] The same is true for COFs, which, although more rigid than their metal-center counterparts, offer excellent resistance to solvents as well as good control of their porosity, and thus the dispersion of active sites. Studying these innovative materials should provide new hybrid MCMs that will offer chemists and biologists access to novel, more efficient, less

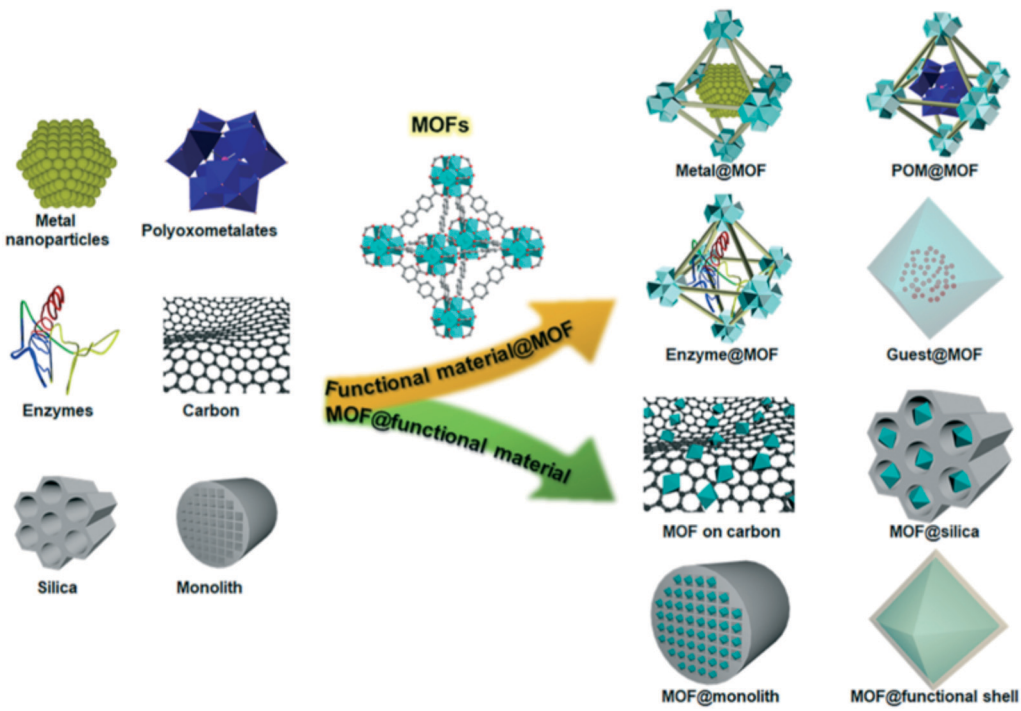


Fig. 19 Diversity of functionalization and incorporation of MOFs for the development of materials with multiple properties, including catalysis (Chen and Xu, 2019).[7] Reprinted from *Matter*, volume 1 issue 1, Chen and Xu, *Metal–Organic Framework Composites for Catalysis*, page 58, Copyright (2020), with permission from Elsevier.

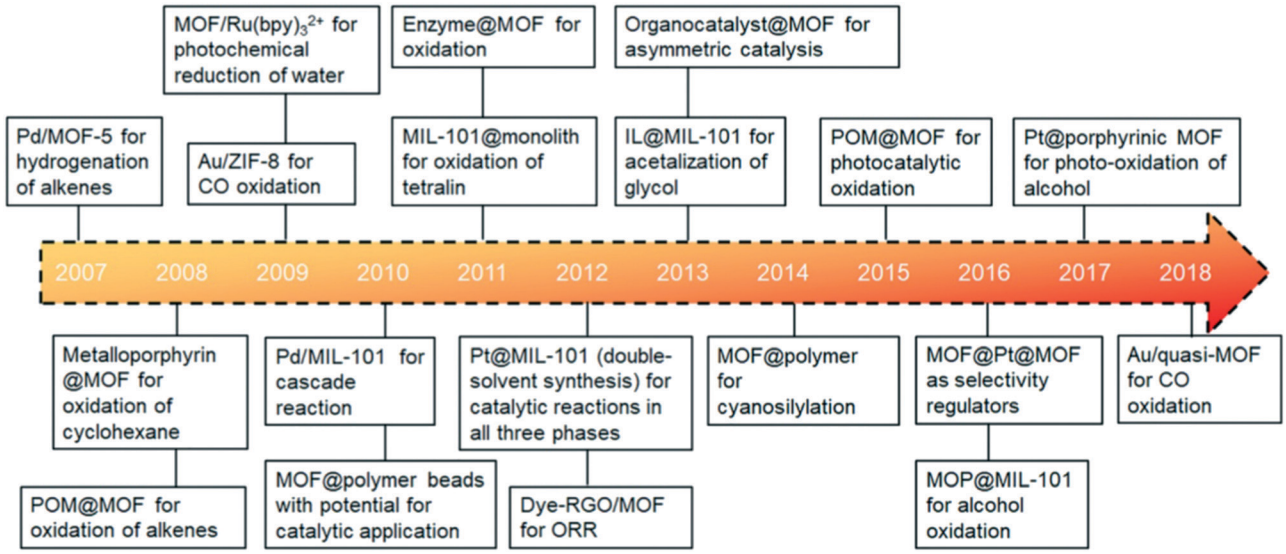


Fig. 20 Timeline of MOF-based catalysis (Chen and Xu, 2019)[7] (MOF: metal–organic framework; POM: polyoxometalate; bpy: 2,2′-bipyridine; GERD: reduced graphene oxide; ORR: oxygen reduction reaction; IL: ionic liquid; MOP: metal–organic polyhedral) reprinted from *Matter*, volume 1 issue 1, Chen and Xu, *Metal–Organic Framework Composites for Catalysis*, page 59, Copyright (2020), with permission from Elsevier.

costly, less energy-consuming, and more diversified reaction paths in the near future.

Conclusions

Combining catalysts is now an integral part of the synthetic strategies of both chemists and biologists, due to its multiple advantages, such as the reduction of energy or infrastructure costs. The diversity of these combinations, both in terms of the process and type of reaction, allows them to overcome a variety of barriers at the catalytic level and to access a growing number of compounds. However, the use of catalyst combinations in the fields of chemical catalysis and biocatalysis is still limited. Although they are highly developed in the field of biocatalysis due to the relative uniformity of the reaction conditions required by enzymes, multi-biocatalytic processes remain difficult to recreate on an industrial scale because of the fragility of the catalysts and the difficulty of using them with high concentrations of substrates and products. Conversely, the extraordinary range of reactions that are accessible through the diversity of chemical catalysts has motivated chemists to develop new formulations rather than explore combined catalytic systems. Optimal reaction conditions are often very different between catalysts, and thus chemists have not progressed much in the development of materials combining several catalysts, with the few teams that do study these primarily inspired by biological systems. Despite these drawbacks, combining catalysts in a single efficient material should provide a foundation for new types of catalysis. In particular, hybrid catalysis, consisting of a highly integrated combination of two different catalysts, often a chemical and bio-catalyst, would greatly benefit from these advances. Multicatalytic materials could be used to advance this young, rapidly expanding field. Many challenges must still be overcome, both in terms of communication between disciplines and individuals and in terms of scientific principles, for the development of new materials that are both robust and structured to allow for the finely controlled dispersion of active sites within them. Currently, new systems are emerging based on metal–organic frameworks and covalent organic frameworks, which should soon allow access to novel catalytic entities.

Conflicts of interest

There are no conflicts of interest to declare.

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