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# Spatial compartmentalisation effects for multifunctionality catalysis: From dual sites to cascade reactions

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**Abstract:** Catalysis plays a key role in the production of fuels, industrial chemicals and the chemical transformation of fine chemicals. As society faces increasing environmental pollution and energy crises, tandem catalysis has attracted increasing attention as an outstanding model due to its sustainability and environmental friendliness. Compared with traditional stepwise synthesis methods, tandem catalysis not only can couple several different reactions together, but also does not require the separation of intermediates, which provides new ideas for improving reaction activity, regulating product selectivity and developing new methods for catalysis. In order to catalyse cascade reactions efficiently, it is crucial to design suitable multifunctional catalysts, which should contain at least two active sites and achieve spatial separation. Here, we introduce the realisation and application of spatial segregation of metal, acidic and basic sites with examples to provide further insight into the indispensable role of active site compartmentalisation effects in tandem catalysis. In addition, this study highlights the challenges and issues associated with such catalysts, emphasising the importance of effective catalyst enhancement and environmentally sustainable catalytic transformations. The results of the study are intended to provide guidance for the development of rational and efficient catalysts.

**Keywords:** Tandem catalysis; highly efficient catalysis; active site; compartmentalisation effect

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## 1. Introduction

Tandem catalysis is defined as a process in which reactants are transformed to complex products through two or more consecutive catalytic reactions in a single reactor [1-3]. In fact, tandem catalysis is widely found in nature, such as photosynthesis in plants, where carbon dioxide and water are converted into complex organisms through a series of successive reactions catalysed by different enzymes. In recent years, tandem catalysis has received extensive research attention due to the following advantages. (1) Simplifying or even eliminating the isolation, purification, storage, and transport of intermediates, with the attendant loss of time and materials, is more efficient, economically beneficial, and environmentally friendly, especially for processes involving unstable or toxic intermediates[4,5]; (2) In terms of reaction kinetics, according to Le Chatelier's law, tandem catalysis can facilitate the next reaction by consuming its product in situ as a reactant for the of the previous reaction[6]. (3) Tandem catalysis can alter the reaction pathway by unstable intermediates to make it more thermodynamically favourable.

Compared with the traditional stepwise synthesis method, tandem catalysis has been developed as a promising catalytic technology as it provides new ideas to improve the reaction activity, regulate the product selectivity and develop new methods of catalysis. To drive tandem reactions, multiple active sites in one catalyst, mainly consisting of acid, base and metal sites, are emerging and promising approaches. Nanoimmobilization technology allows the combination of different catalytic sites in a single catalyst, and the assembly and spatial distribution of multiple catalytic active sites on a carrier is the key to achieve efficient coupling of different reactions. Spatially isolating different active sites, avoiding interactions, bringing them close together and shortening the diffusion pathways of intermediates to achieve efficient tandem catalysis in line with the current concept of "green and sustainable chemistry". The replacement of conventional step catalysts with multifunctional catalysts for tandem catalysis is expected to be an inevitable trend in the future development of catalytic science and industrial catalytic applications.

Here, we provide an overview of strategies to achieve spatial segregation of multiple active sites on a single catalyst and show examples of each method in application. Herein, we present application examples of spatial partitioning of acidic sites with basic sites, acidic sites with metal sites, basic sites with metal sites, and different metal sites on a single catalyst, and investigate the mechanism of efficient cascade catalysis, which can precisely regulate the distribution of active sites, improve the selectivity of reactants, and realise the targeted synthesis of target products. In addition, we present the prospects and challenges of efficient cascade catalysis through active site partitioning and sincerely hope to contribute to the development of highly selective catalysts.

## 2. Acid site/metal site

With the depletion of fossil energy sources, the catalytic conversion of biomass into fine chemicals offers an alternative sustainable development strategy. The high-yield conversion of cellulose to 1,2-propanediol (1,2-PG) is of great industrial value because the process is atomically economical, carbon-neutral, and produces 1,2-PG for which there is a huge market demand. However, in the cascade reaction for the one-pot conversion of cellulose to 1,2-propanediol, the β-1,4-glycosidic bond of cellulose is first broken to glucose in an acidic environment, and glucose can be isomerised to fructose at either the basic or Lewis acid sites. Subsequent hydrogenolysis of fructose produces the C3 intermediates dihydroxyacetone and ethanol, which are hydrogenated to 1,2-PG. Glucose can also be cleaved to erythrulose and acetaldehyde, which are then hydrogenated to ethylene glycol (EG). Sugars (e.g., glucose and fructose) can be hydrogenated to hexitol, which is an inert hydrogenolyte on most transition metals (e.g., Ru), in a hydrogenation to diols process. Glucose can also be dehydrated to 5-hydroxymethylfurfural (HMF) and further degraded to acetylpropionic acid and formic acid, as well as polymerised to humic acid at acidic sites on the catalyst surface. The whole process has many reaction steps with high reactivity and poor stability of intermediates and target products, resulting in low yields of 1,2-PG. Whereas the current catalytic system containing metal and acid sites can balance the transaldol condensation and hydrogenation reactions towards the target product 1,2-PG, however, the yield and selectivity remain low. The reason for the low intrinsic selectivity is the ambiguous conformation/morphology of the current catalysts, resulting in the metal and acid sites being located in the same plane. Isomerisation of glucose to fructose at the acid site and simultaneous hydrogenation to hexanol at the metal site is inevitable. The selectivity of this multifunctional catalyst is also hampered to some extent due to the encapsulation or poisoning of metal nanoparticles by the proximate acidic groups. Therefore, the development of site-isolated metal-acid multifunctional catalysts for the preparation of high yields of 1,2-PG by controlled hydrogenolysis of cellulose is urgent.

To this end, Yang et al. [7] developed a highly selective metal-acid catalyst (Ru/NC@void@MC-$SO_3H$) that isolates metal-acid sites by layer-by-layer assembly prior to chemical transformation. For the difficulties of hydrolysis and hydrogenolysis, sulfonic acid functionalized mesoporous carbon shells based on resorcinol-formaldehyde resin were designed for the hydrolysis of cellulose, while Ru clusters (1.4 nm) were constructed on N-doped carbon cores derived from Ru-containing ZIF-8 for the anti-hydroxyl aldol condensation with the promotion of basic N dopants (**Figure 1**a). In the rationally designed nanoreactor, not only multiple functions were integrated, but also spatial separation of metal and acid sites was achieved. The spatial separation of metal and acid sites not only promotes metal-acid synergy in hydrolysis, isomerization/hydrogenolysis and hydrogenation cascade reactions, prevents metal-acid rejection to reduce side reactions, but also provides designated diffusion pathways that favor the reacting species. All these favor the selectivity of the target intermediate reactions and thus the yield of 1,2-PG. Several catalysts were also comparatively screened in order to investigate the role of Ru and SO3H in the cellulose hydrogenolysis process (**Figure 1**b).

In-depth studies have shown that cellulose hydrolysis is highly dependent on sulphonic acids and that the Ru-Nx-Lewis acid-base pair facilitates the isomerisation of glucose and subsequent hydrolysis of fructose, which is then hydrogenated to 1,2-PG at the metal Ru site. However, the high density of the Ru site is prone to interactions with the neighbouring -$SO_3H$ moiety leading to an accelerated side-reaction, in particular the hydrolysis of cellulose at the $SO_3H$ site to glucose, which in turn is rapidly hydrogenated to sorbitol by the neighbouring Ru sites. Based on this, a possible reaction pathway for the hydrogenolysis of cellulose to 1,2-PG was proposed. As shown in Figure 1c, the hydrolysis of β-1,4-glycosidic bonds in cellulose is facilitated by sulfonic acid on the cellulose shell. The generated glucose can diffuse into the cavity and isomerise to fructose in the presence of pyridinic-N and Lewis acids in the inner core, which also promotes the subsequent hydrogenolysis of fructose to dihydroxyacetone and acetol intermediates, which are rapidly hydrogenated to 1,2-PG at the metal Ru site. The presence of Lewis acidic and basic sites in the Ru-Nx accelerates the isomerisation of glucose to fructose, which is essential for the generation of more 1,2-PG rather than EG. Due to the spatial segregation of the Ru and $SO_3H$ sites, glucose isomerisation predominates over hydrogenation to C6 polyols. The Ru/NC@void@MC-$SO_3H$ site-separated catalysts prepared by integrating isolated Ru and -$SO_3H$ active sites into the yolk-shell nanostructures showed significantly improved metal-acid synergistic interactions, and the yields and selectivities of the cellulose hydrogenation were enhanced, which were two to three orders of magnitude higher than those of cellulose hydrogenation using other Ru-containing catalysts, and were better than those of the state-of-the-art metal-acid catalysts(Figure1d). This work provides a new strategy for the construction of multilevel catalytic structures with different active sites spatially organised on the nanoscale, which will promote the further development of multifunctional catalysts.

Furfural (FA) is an important platform compound that can be produced on a large scale by acid-catalyzed hydrolysis and dehydration of lignocellulosic biomass [8]. Due to the presence of various functional groups, furfural can be converted to various high value-added chemicals under different reaction conditions, among which, the catalytic conversion of furfural to cyclopentanone is an energy-efficient and green synthetic process, and cyclopentanone has a wide range of applications in the food and chemical industries as a multifunctional chemical, making this process of great research importance. The synergistic catalytic reaction of furfural aqueous phase hydrogenation to cyclopentanone usually employs a bifunctional catalyst consisting of metal nanoparticles that are capable of dissociating $H_2$ molecules into H atoms for the subsequent hydrogenation reaction and acid sites for the protonation and dehydration reactions. Thus, the nature of the active ingredient and the carrier plays a decisive role in the direction of the reductive conversion of furfural, accompanied by the distribution of the product. Due to the complex reaction sequence and variable catalyst surface structure, the rational design and construction of effective catalytic structures for furfural conversion remains a challenge, limited by the unclear reaction mechanism. It has been shown that $CeO_2$ loaded Pt catalysts have 98% selectivity for furfuryl alcohols during furfural hydrogenation, however, the poor acidity of $CeO_2$ is not favorable for acid-catalyzed furan ring rearrangement to convert furfural to cyclopentanone [9]. For the active site of bifunctional catalysts for furfural hydrogenation ring rearrangement, the usual assumption is that the reaction occurs at the interface between the metal and the carrier. Therefore, the design of ideal catalysts requires fine tuning of the metal and acid sites in the nano-space to facilitate the activation of the carbonyl group, improve the availability of the acid sites, and promote intermediate diffusion between the two active sites.

Yuan et al. [10] constructed a hierarchical catalytic structure with spatial separation of Pd and acid sites by a multi-step deposition strategy, in which Pd is confined to defective $CeO_2$ nanoclusters, which are dispersed on highly acidic $SiO_2$ with high surface area. In the $Pd/CeO_2/SiO_2$ hierarchical catalytic structure, the intimacy of Pd with the acid sites can be adjusted by adjusting the $CeO_2$ content so that the aqueous phase hydrogenation of furfural follows a unique three-site mechanism. Furfural is vertically adsorbed on the $Pd/CeO_2$ oxygen-rich vacancy, the carbonyl group is selectively hydrogenated, and the furfuryl alcohol formed undergoes acid-catalyzed furan ring rearrangement on $SiO_2$ through the synergistic effect of the acid site and hydrogen spillover to generate cyclopentanone. Meanwhile, the asynchronous catalysis effectively hinders the furan ring hydrogenation to produce tetrahydrofuran alcohol by spatially separating Pd from the $SiO_2$ surface. the $Pd/CeO_2/SiO_2$-10 catalyst has excellent catalytic performance with 93% furfural conversion and 84% cyclopentanone selectivity.

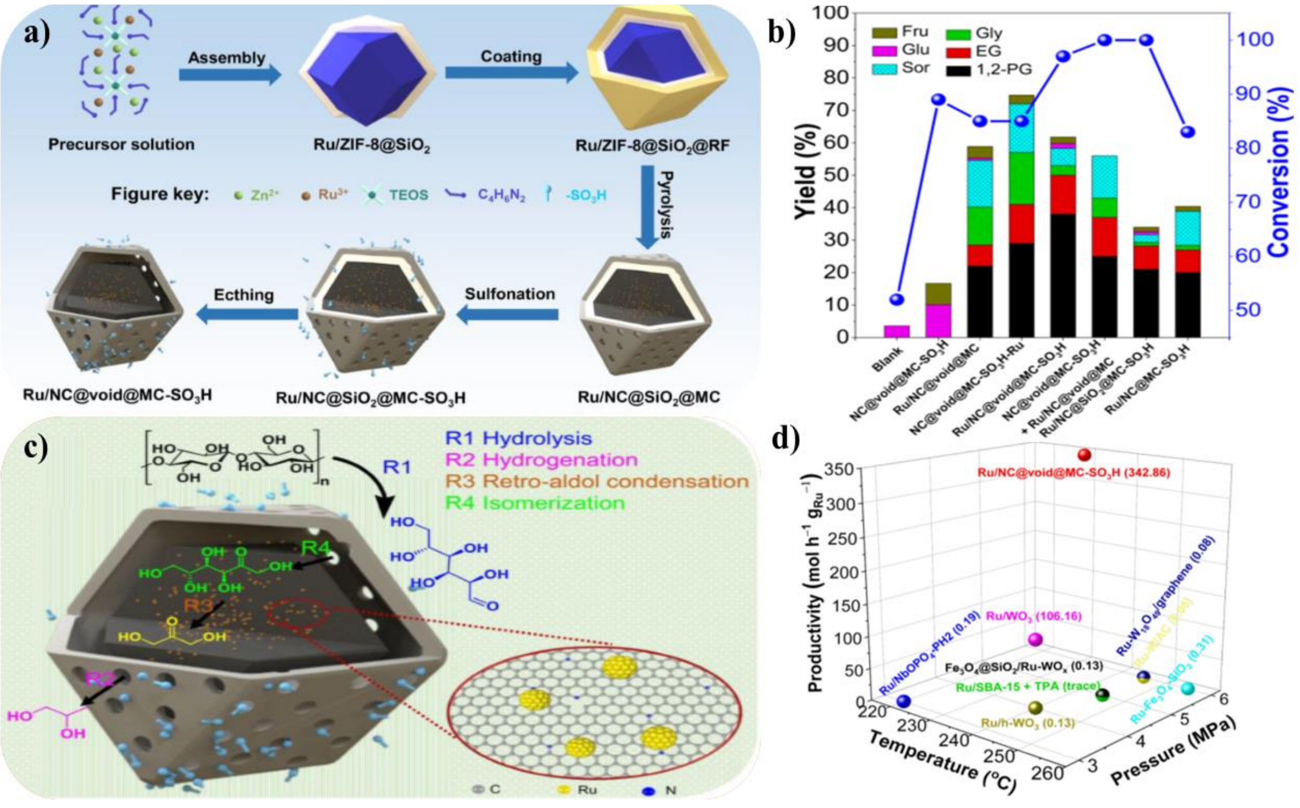

**Figure 1. a)** Schematic description of the synthetic process for Ru/NC@void@MC-$SO_3H$. **b)** Cellulose conversion and yields of main products. Gly, Sor, Glu and Fru represent glycerol, sorbitol, glucose and fructose, respectively. Reaction conditions: cellulose 0.20 g, catalyst 0.06 g, $H_2O$ 20 mL, $H_2$ 6 MPa, 230°C and 5 h. **c)** Possible reaction pathways for cellulose hydrogenolysis to 1,2-PG on Ru/NC@void@MC-$SO_3H$. **d)** Comparison of the productivity of 1,2-PG over different Ru-containing acidic catalysts. [7]

## 3. Acid site/base site

It is well known that the integration of acid and base sites in a single catalyst is still not easy, either in biological or artificial structures. There are very rare examples of precise spatial distribution sequences of acid and base metal sites within a single catalyst for tandem reactions. Since acid-base bifunctional catalysts are prone to mutual destruction of active sites during one-pot synthesis, it is desirable to spatially isolate the antagonistic functions to coexist on a single catalyst in order to overcome the problem of neutralization of incompatible groups. For example, Helms et al. [11] used a star-shaped polymer as a support to separate the acid and base groups. Kaneda et al. used two layered clays, $Ti^{4+}$ exchange montmorillonite and Mg-Al hydrotalcite, as bifunctional catalysts. Li et al. [12] prepared shell cross-linked micelles (SCMs) with acidic sites in the shell layer and basic sites in the core layer from amphiphilic poly(2-oxazoline) triblock copolymers. A typical acid-base bifunctional tandem dealkyl-nitroformaldehyde reaction was carried out using this material as a dual-chamber nanoreactor, which exhibited good catalytic activity. The sites of the acid and base during this reaction are located in different regions of the micelles, allowing the two steps in the reaction sequence to proceed essentially in separate compartments, similar to the compartmentalization that occurs in biological systems. With the formation of the yolk shell, the problem of mutual acid-base neutralization is further well resolved to some extent. Moreover, the core or shell contains precisely different active sites. For example, Yang et al. [13] reported the positioning of a basic core ($-NH_2$) and an acidic shell ($-SO_3H$) in an egg yolk shell nanoreactor by an organosilicon assisted selective etching method, showing high catalytic activity in the Henry cascade reaction of single site deacetylation. Furthermore, Song et al. [14] reported another yolk-shell nanosphere with an acidic core and a basic shell, leading to further activity and selectivity due to the rational spatial order of the acid-base sites in the cascade reaction sequence. However, so far, the acidic sites in acid-base bisulfonic acid catalysts have been mainly provided by acidic organic compounds in the acid-base cascade reaction. The disadvantage of these materials is the relatively weak strength of the acid at a certain alkalinity, i.e., the interactions of the acid-base pairs are not perfectly matched over a catalyst.

To further regulate the interaction and ensure the spatial segregation of acid-base pairs, You et al. [15] designed bilayer hollow mesoporous silica nanospheres (HMS-Al@MS-$NH_2$) by a two-step condensation method, in which the acidic site -Al was introduced into the inner shell and $-NH_2$ was bound to the outer shell, and the bilayer shell structure achieved the spatial segregation of acidic and basic sites, and the mesopores inside the shell promoted the mass internal to the hollow transfer (**Figure 2**a). As a spatially separated acid-base bifunctional catalyst, HMS-Al@MS-$NH_2$ demonstrated its high catalytic performance in the Knoevenagel cascade reaction. During catalysis, the reactant (benzaldehyde dimethyl acetal) can pass through the hollow space to the inner shell, where it is converted to the intermediate (benzaldehyde) by a decondensation reaction. In the outer layer, the intermediate (B) diffuses from the inner shell and can be further catalytically generated into the target product (benzyl ethyl cyanoacetate) (**Figure 2**b). Under optimized conditions, the conversion of benzaldehyde dimethyl acetal at 110 °C for 2 h was close to 100 %, and the selectivity to the target product benzyl cyanoacetate was 100 %. This is mainly attributed to the spatially isolated basic and acidic sites, as well as the voids and mesopores in the shell that favor mass transfer. Moreover, Yang et al. [16] constructed the material MIL-101(Cr)@MOF-867 with a core-shell structure by growing MOF-867 on super-stable MIL-101(Cr). The obtained MIL-101(Cr)@MOF-867 with both acid and base sites showed ultra-high conversion in the deacetalization-Knoevenagel tandem reaction, thanks to the Lewis acid sites catalytic deacetalization reaction provided by Cr and Zr clusters and the Brönsted base sites to catalyze Knoevenagel reaction provided by pyridine (**Figure 2**c). Moreover, the catalyst has excellent stability. There was almost no decrease in catalytic activity after 5 repeated uses (**Figure 2**d).

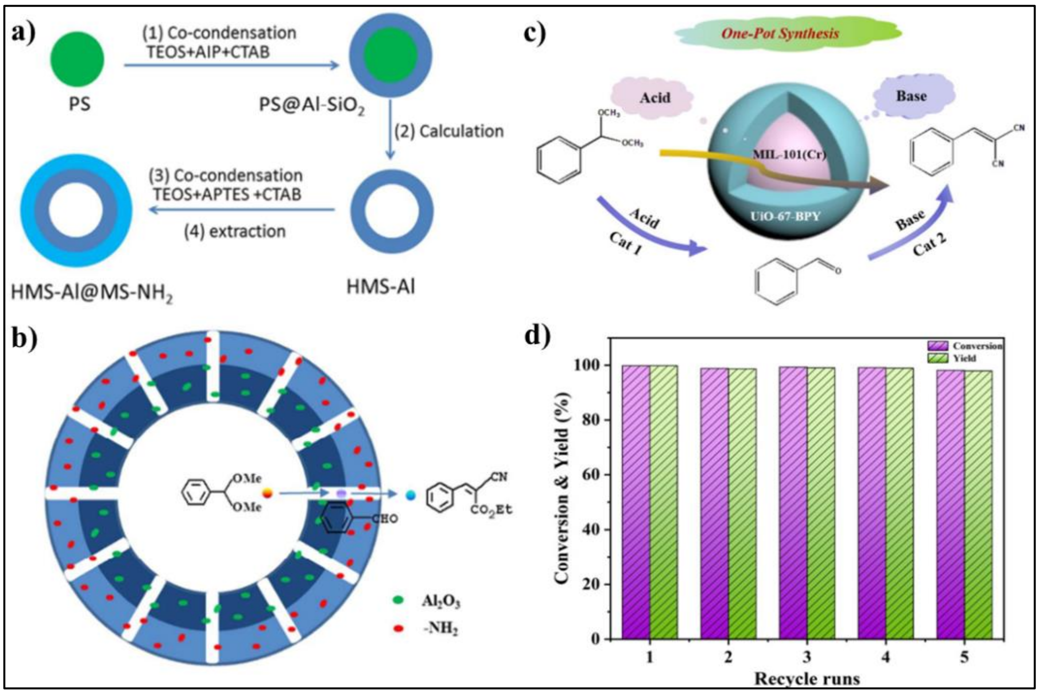

**Figure 2. a)** Scheme for the preparation of double-shelled mesoporous HMS-Al@MS-$NH_2$. **b)** Schematic reaction flow of the two-step cascade reaction sequences on the double–shelled structured bifunctional catalyst HMS-Al@MS-$NH_2$. **c)** Efficient bifunctional core-shell MIL-101(Cr)@MOF - 867 composites catalyse deacetyl- Knoevenagel tandem reactions. **d)** Recycle tests of MIL-101(Cr)@MOF-867 for deacetalization-Knoevenagel tandem reaction [15].

## 4. Acid site/base site/ metal site

Among the most important fine chemicals, aryl amines are of great significance since they serve as precursors in the production of dyes, pigments, pharmaceuticals, and agricultural chemicals. The synthesis of aryl amines involves multistep reactions usually Csingle bondC bond formation followed by reduction of nitro group. Recently, heterogeneous bi/multifunctional catalysts have drawn increasing interest owing to their ability to catalyze these multistep reactions in one pot domino/cascade processes. Several solid bifunctional catalysts have been used for sequential Csingle bondC bond forming reactions. For instance, Puthiaraj et al. [17] prepared a dual functionalized porous organic polymer (CBAP-1(EDA-$SO_3H$)) for cascade deacetylation-Knoevenagel reaction and deacetylation-Henry reaction. Among other examples, Shinde et al. [18] developed bifunctional (acid/base) catalytic sites in the crystalline organocatalytic porous COF (2,3-DhaTph) for cascade Deacetalization-Knoevenagel reaction. Xu et al. [19] synthesized a multilamellar organic–inorganic hybrid zeolite and used for tandem Deacetalization-Knoevenagel reaction, Toyao et al. [20] prepared an amino-functionalized metal–organic framework (MIL-101(Al)-$NH_2$) and applied it for one-pot sequential Deacetalization–Knoevenagel condensation reaction. Zhang et al. [21] reported bifunctional lanthanide cluster based metal–organic frameworks (MOFs) for tandem Deacetalization−Knoevenagel reaction. A few reports in the literature also demonstrate the development of Pd immobilized and amino functionalized materials for the Csingle bondC bond formation and subsequent reduction of nitro group or alkene in domino processes. For example, Puthiaraj et al. [22] developed an aromatic porous polymer functionalized with basic amine sites and Pd nanoparticles (Pd/DETA-APP) for Knoevenagel condensation-chemoselective transfer hydrogenation. Zhao et al. [23] reported a core shell Pd nanoparticles @ metal organic frameworks (Pd@IRMOF-3) as a multifunctional catalyst for cascade Knoevenagel- selective hydrogenation, Jiang et al. [24] prepared a polymer bound and Pd nanoparticles loaded metal organic framework (Pd@PDEAEMA-g-UiO-66) for biphasic cascade reaction. Verde-Sesto et al. [25] demonstrated the post-functionalization of porous polymeric Aromatic frameworks with an organocatalyst and a transition metal catalyst for tandem condensation–hydrogenation reactions. Montolio et al. [26] reported dual catalyst based on AuNP-Polymeric Ionic Liquid composite for the Knoevenagel/hydrogenation single-pot tandem reaction. However, these examples reveal that the design and application of bifunctional catalysts in domino reactions is limited to a maximum of two steps. In another study, Biradar et al. [27] reported a mesoporous silica-based trifunctional catalyst (Pd-$SO_3H$-$NH_2$-SBA-15) for the cascade Deacetylation-Henry-hydrogenation reaction. Trifunctional group catalysts show high efficiency in one-pot, three-step reactions and four different chemical transformations.

However, the instability of alkaline solutions on the surface of silica-based materials and the limited number of functional sites limit their application in tandem catalysis. Ke et al. [28] successfully combined a stable multifunctional catalyst with antagonistic acid, base and anchoring metal sites by employing a stepwise anchoring strategy. Through fine tuning, the achievable acid, base and anchoring metal sites can be regulated and controlled in a highly ordered position, thus ensuring efficient communication between the three functional catalytic sites while synergistically facilitating the tandem conversion process. The results showed that the multifunctional monocatalyst exhibited excellent catalytic performance in a one-pot, three-step Deacetaldehyde- Knoevenagel - Hydrogenation (D-K-H) model reaction with a benzonitrile yield higher than 99%. Yao et al. [29] proposed a simple and step-by-step approach to construct acidic (phosphotungstic acid (HPW)), basic (amines) and metallic (palladium nanoparticles (NPs)) trifunctional integrated catalysts with spatial affinity using nanoscale HP-UiO-66-$NH_2$ synthesised in a modified DMF/acetic acid (Ace)/water system as a carrier. Specifically, by finely controlling the ratio of immobilised HPW to amines, the acid-base properties can be tuned and robust bifunctional catalysts with accessible acid-base sites can be obtained. Then, Pd precursors were introduced by impregnation and further reduced in $H_2$ to obtain trifunctional Pd@HPW@HP-UiO-66-$NH_2$ (**Figure 3**a). The surface morphology of the hierarchical catalysts was characterised by SEM analysis. As shown in Figure 3b, the SEM image of HP-UiO-66-$NH_2$ clearly shows the inter-particle mesoporous network formed by the aggregation of microcrystalline UiO-66-$NH_2$ particles (with an average particle size of 15 nm). The inter-particle mesoporous network remained unchanged after the introduction of HPW molecules and Pd NPs (**Figure 3**c). The microstructure of Pd@HPW@HP-UiO-66-$NH_2$ was further investigated by transmission electron microscopy (**Figure 3**d and e). By focusing the thin portion of 0.86 wt% Pd@HPW@HP-UiO-66-$NH_2$, mesoporous voids (~13-20 nm) between the NPs can be observed in the TEM images, which are in good agreement with the results of the pore size distribution (**Figure 3**d). The high-resolution TEM images show that highly dispersed PdNPs around 3 nm are immobilised within HP-UiO-66-$NH_2$ (**Figure 3**e). The TEM elemental mapping maps also show that the Pd, N, W and P elements are uniformly distributed on the sample (**Figure 3**f and g). Similarly, excellent catalytic activity and yield (>97%) were achieved for the one-pot three-step Deacetylation-Knoevenagel-Hydrogenation (D-K-H) catalytic reaction.

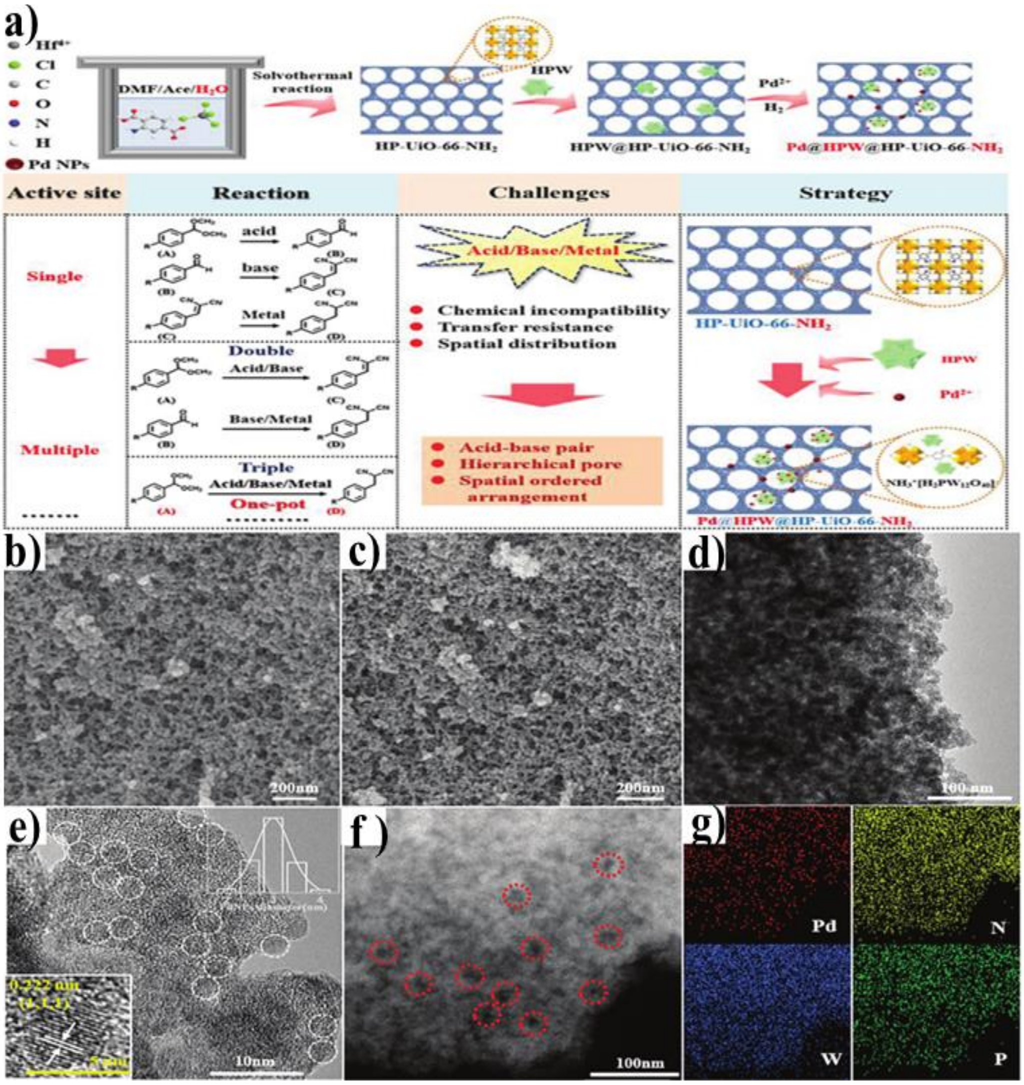

**Figure 3. a)** Schematic illustration of the synthesis of Pd@HPW@HP-UiO-66-NH2; the exclusive role of acid/base/metal sites in the D–K–H tandem reactions, the challenges and proposed design strategy for the construction of a trifunctional catalyst; SEM images of **b)** HP-UiO-66-NH2 and **c)** 0.86 wt% Pd@HPW@HP-UiO-66-NH2; **d)** TEM image of 0.86 wt% Pd@HPW@ HP-UiO-66-NH2; **e)** HRTEM (high-resolution transmission electron microscopy) image and **f)** HAADF (high-angle annular dark field)-STEM image of 0.86 wt%Pd@HPW@HP-UiO-66-NH2; **g)** corresponding EDX elemental mapping [29].

## 5. Different metal sites

Loaded metal catalysts are at the heart of multiphase catalysis [30-32]. Dual metal-involved catalysts are necessary to achieve high catalytic efficiency, because they can respectively catalyze one step of the sequential hydrogenation aforementioned. The positioning of spatially separated multiple metal nanoparticles (NPs) on a single carrier is currently at the forefront of designing loaded metal catalysts, as such catalysts are able to efficiently cascade multi-step reactions [6,33]. Their significant advantages are the shortened diffusion distances of reaction intermediates and the realization of different metal NPs synergistic catalysis between them, both of which improve reaction efficiency and tunable selectivity [33,34]. The ideal loaded multimetallic cascade catalysts should have the following characteristics: (i) the ability to spatially isolate different metal NPs in close proximity; (ii) have short nanochannels to connect different metal NPs, thus ensuring efficient molecular transport between them; and (iii) achieve positive synergistic catalysis.

In pursuit of ideal loaded multimetallic cascade catalysts, researchers have explored a variety of nanostructured materials that are essential for achieving spatial localisation of multimetallic NPs. For example, core-shell nanostructures were employed to spatially isolate two metallic NPs in the core or shell for $CO_2$ hydrogenation [36,37]. Similarly, $TiO_2$ nanotubes were reported to position Pt and Ni NPs on their outer or inner surfaces by atomic layer deposition to transfer hydrogenation. Graded porous silica was also used to localise the bimetallic NPs by gradually modifying their pore surfaces to sequentially oxidise cinnamyl alcohol [38].

Despite the great success in constructing cascade catalysts by spatial separation of multiple metal NPs, these existing materials either lack segregated structures to accommodate the outer surfaces of the metal NPs or fail to provide well-defined nanochannels to connect the different metal NPs at the nanoscale [38,39]. The unsatisfactory integration of all the desired features in a single catalyst hinders the efficient co-catalysis to be realisation. Thus, there is a large gap between these reported catalysts and the ideal cascade catalysts. In this context, the development of new nanostructured materials to individually localise multiple metal nanoparticles in close proximity at the nanoscale, thereby exploiting the full potential of cascade catalysts, is a rather challenging task. Zou et al. [40] developed a constrained coating etching strategy to synthesize novel multi-chamber mesoporous organosilicas (MCMOS), which cleverly assembles one metal nanoparticle (Ru) in the surface groove of the material and confines another metal nanoparticle (Pd) in the internal nano-cavity of the material, thus achieving spatial separation of the two metal nanoparticles and maintaining a certain spatial distance at the nanoscale(**Figure 4**b). The TEM images of such a fabricated Ru/Pd/MCMOS show that both Ru and Pd NPs are colocalized within a single particle. In addition, the surface grooves and nanocavities of the material are connected by uniform mesoporous channels. Such nanoscale channels provide an efficient pathway for the transport of intermediates between two metal nanoparticles. Sequential hydrogenation of nitroaromatics is an important conversion process for the production of cycloaliphatic primary amines, which are important intermediates for a wide range of high-value chemicals. The transformation consists of a two-step hydrogenation, i.e. nitrohydrogenation and aromatic ring hydrogenation (**Figure 4**a). It has been shown that Ru NPs are catalytically active for the hydrogenation of aromatic hydrocarbons, whereas Pd NPs are the ideal catalysts for nitro hydrogenation. The Ru/Pd/MCMOS cascade catalyst has been demonstrated to have high catalytic efficiency in the continuous hydrogenation of nitroaromatics to cyclohexylamine, and the final product cyclohexylamine (CA), as well as trace amounts of aniline (AN, intermediate) and ethylcyclohexylamine (ECA, byproduct), were produced in a reaction time of 2.5 h under mild reaction conditions (80°C, 2.0 MPa) with a yield of 99.2%. In order to test the performance of Ru/Pd/MCMOS, a set of catalysts, including monometallic and bimetallic catalysts, were also tested (**Figure 4**b). Under the same reaction conditions, the monometallic Pd/MCMOS catalyst yielded ≥99% of the intermediate aniline (AN), and only trace amounts of the final product CA were detected (**Figure 4**e). Another monometallic Ru/MCMOS catalyst yielded only 11.2% conversion of NB, in which case no product CA was detected (**Figure 4**e). When a physical hybrid catalyst (a mixture of Pd/MCMOS and Ru/ MCMOS) was used, the yield of the final product CA was 15.5% in the same reaction time, although the conversion in the first step reached 99.9% (**Figure 4**e). The CA generation rate of the physical mixed catalyst was only 3.55 h-1, which was 7.72 times lower than that of Ru/Pd/MCMOS (**Figure 4**e). In addition, two other bimetallic catalysts were tested in order to verify the effect of spatial segregation of the active sites on the catalytic performance: the RuPd/DSNs catalyst (without spatial segregation), in which Ru and Pd NPs were coloaded into the same channel of the DSNs, and the PdRu/MCMOS alloy catalyst. The CA yield of Ru-Pd/DSNs was 34.0% at a yield of 7.95 $h^{-1}$, whereas PdRu/MCMOS showed almost no CA-producing activity (**Figure 4**e).

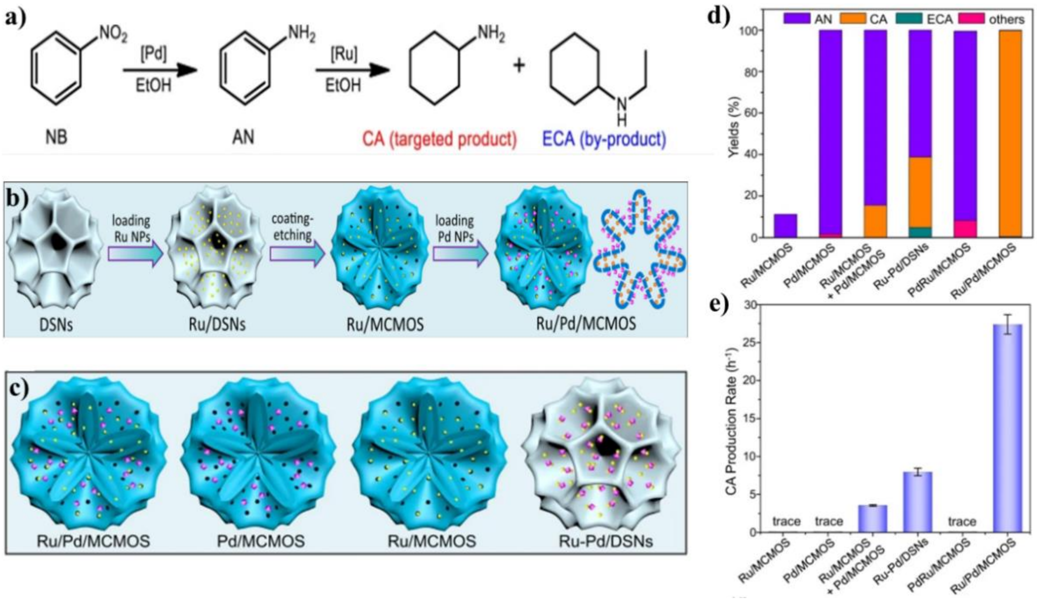

**Figure 4**. **a)** Reaction network of the sequential hydrogenation of nitrobenzene. **b)** Schematic illustration for the fabrication of Ru/Pd/MCMOS. **c)** Schematic illustration of four catalysts including Ru/Pd/MCMOS, Pd/MCMOS, Ru/MCMOS and Ru-Pd/DSNs. d) Product distributions of the sequential hydrogenation over different catalysts. **e)** The CA production rate over different catalysts. The production rate value is estimated according to the CA yield of 20–30% [40].

It is clear that despite containing bimetals, their sequential hydrogenation activity is much lower than that of the cascade catalysts. This can be explained by electronic effects. As can be seen from the TEM image of Ru-Pd/ dsn, in this non-compartmentalised sample, the small Ru and the large Pd NPs are so close that they are in direct contact with each other. The XPS results proved that this situation leads to charge transfer between the two metals (**Figure 5**).This situation leads to a charge transfer between the two metals and, therefore, a decrease in the surface electron density of the Ru NPs, resulting in the inability of the aromatic ring to adsorb and activate [41].

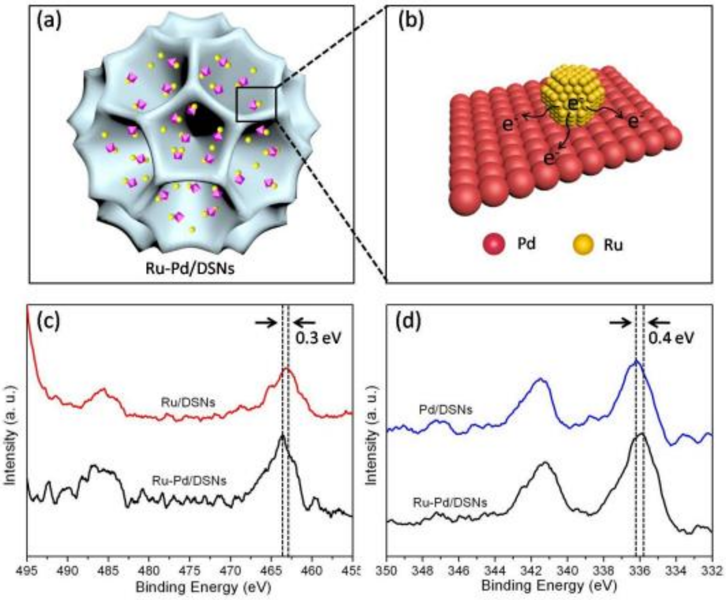

**Figure 5.** Characterization of the Ru-Pd/DSNs catalyst. **a)** Illustration of the Ru-Pd/DSNs catalyst. **b)** Illustration of the possible charge transfer process when the small Ru NPs and the large Pd NPs are jointly loaded in the dendritic channels of DSNs. **c)** Ru 3p XPS spectra of Ru/DSNs and Ru-

Pd/DSNs. **d)** Pd 3d XPS spectra of Pd/DSNs and Ru-Pd/DSNs. Noting: As displayed in Figure 8c, the Ru 3p3/2 binding energy of Ru-Pd/DSNs was obviously blue-shifted from 463.2 eV to 463.5 eV in comparison to that of Ru/DSNs. Meanwhile, compared with the Pd 3d5/2 peak position of Pd/DSNs, the Pd 3d5/2 binding energy of Ru-Pd/DSNs was obviously red-shifted from 336.2 eV to 335.8 eV. Because of the identical conditions for loading metal NPs, the Ru particle size of Ru-Pd/DSNs was as same as that of Ru/DSNs and the Pd particle size of Ru-Pd/DSNs remained in good agreement with that of Pd/DSNs. Since the disturbance of metal particle size could be excluded, such a distinct shift of binding energy in both Ru 3p and Pd 3d XPS spectra provided clear evidences for the charge transfer from Ru to Pd in the Ru-Pd/DSNs catalyst [40].

## 6. Conclusion and Outlook

The spatial segregation of active sites plays a crucial role in improving the catalytic performance of catalysts. In this review, the application of spatial segregation of acid and base sites and metal sites in a single catalyst in improving the catalytic performance is presented respectively, and the basic mechanism of their action is further introduced.

In multiphase catalysis, the active site compartmentalization effect has a significant impact on the cascade reaction. The combination of different catalytic sites in a single catalyst, and the assembly and spatial distribution of multiple catalytic active sites on the carrier is the key to realize the efficient coupling of different reactions. Spatial isolation of different active sites to avoid their interactions and bring them close to each other shortens the diffusion routes of intermediates, thus realizing an efficient cascade catalytic process. The exposure and isolation of the active site may largely influence the interaction with the carrier and is critical to the catalytic performance. Therefore, precise manipulation of these important parameters is essential to demonstrate their relationship with catalytic performance, leading to a significant improvement in catalyst activity and selectivity in practical applications.

## Declaration of Competing Interest

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

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