

**Network-Supported, Metal-Mediated Catalysis: Progress and Perspective**

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## Network-Supported, Metal-Mediated Catalysis: Progress and Perspective

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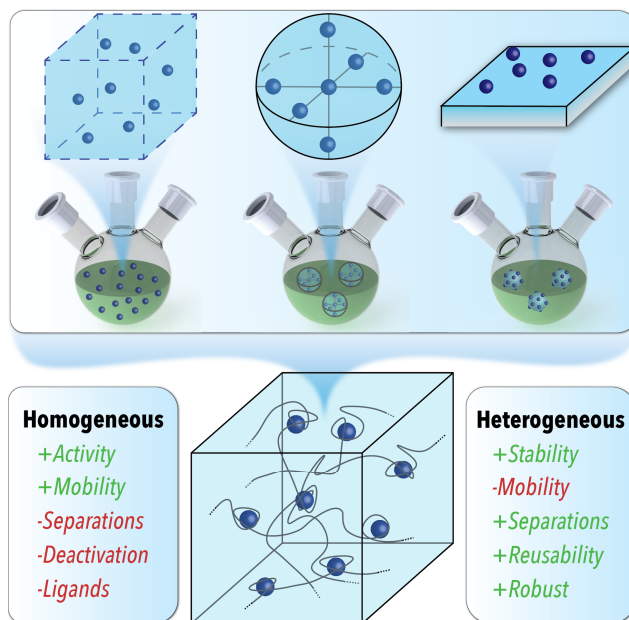
Metal-mediated chemical reactions have been a vital area of research for over a century. Recently, there has been increasing effort to improve the performance of metal-mediated catalysis by optimizing the structure and chemical environment of active catalytic species towards process intensification and sustainability. Network-supported catalysts use a solid (rigid or flexible) support with embedded metal catalysts, ideally allowing for efficient precursor access to the catalytic sites and simultaneously not requiring a catalyst separation step following the reaction with minimal catalyst leaching. This minireview focuses on recent developments of network-supported catalysts to improve the performance of a wide range of metal-mediated catalytic reactions. We discuss in detail the different strategies to realize the combined benefits of homogeneous and heterogeneous catalysis in a metal catalyst support. We outline the unique versatility, tunability, properties, and activity of such hybrid catalysts in batch and continuous flow configurations. Furthermore, we present potential future directions to address some of the challenges and shortcomings of current flexible network-supported catalysts.

### 1.0 Introduction

Chemical transformations are of utmost importance for organic synthesis from fine and commodity chemicals to the active ingredients in pharmaceuticals.<sup>1,2</sup> A wide range of chemical reactions (*e.g.*, cross-coupling reactions) can be mediated through the use of metal-based catalysts.<sup>3–10</sup> The catalysis community constantly seeks to find novel catalytic systems (both homogeneous and heterogeneous) that enable the synthesis of new chemical compounds as well as ones that can improve the performance of existing chemical reactions, either through increased sustainability, catalyst reusability, or reducing the overall cost of the chemical synthesis (*e.g.*, lowering energy requirements for a chemical reaction or by utilizing a more cost-effective metal candidate).<sup>11</sup> Novel network-based catalyst supports have been developed that allow precise control over the structural and chemical environment of catalytic systems and improve the overall performance of metal-mediated catalytic reactions.<sup>12–15</sup> Such network-supported catalysts exhibit significant improvements in catalytic activity, selectivity, accessibility, recyclability, and robustness compared to conventional catalysis strategies.<sup>16</sup>

Historically, catalytic reactions have been classified as either homogeneous (in solution phase with no concentration gradients) or heterogeneous (immobilized on a usually inert and impermeable solid support).<sup>14</sup> Both approaches possess their

unique advantages and disadvantages. Homogeneous, metal-mediated catalysis generally provides higher activity due to maximizing the contact of the catalytic sites with the reaction media, while avoiding concentration gradients produced by phase-specific catalytic activity and mass transport of the reagents to those phases.<sup>7</sup> However, this class of catalysis generally suffers from rapid deactivation and precipitation, uses expensive air-sensitive ligands with complex multistep syntheses, and also requires the removal of the catalyst from



**Fig. 1** Flexible Network-Supported catalysts draw inspiration from the benefits of both heterogeneous and homogeneous catalysis as well as rigid porous networks like metal-organic frameworks (MOFs).

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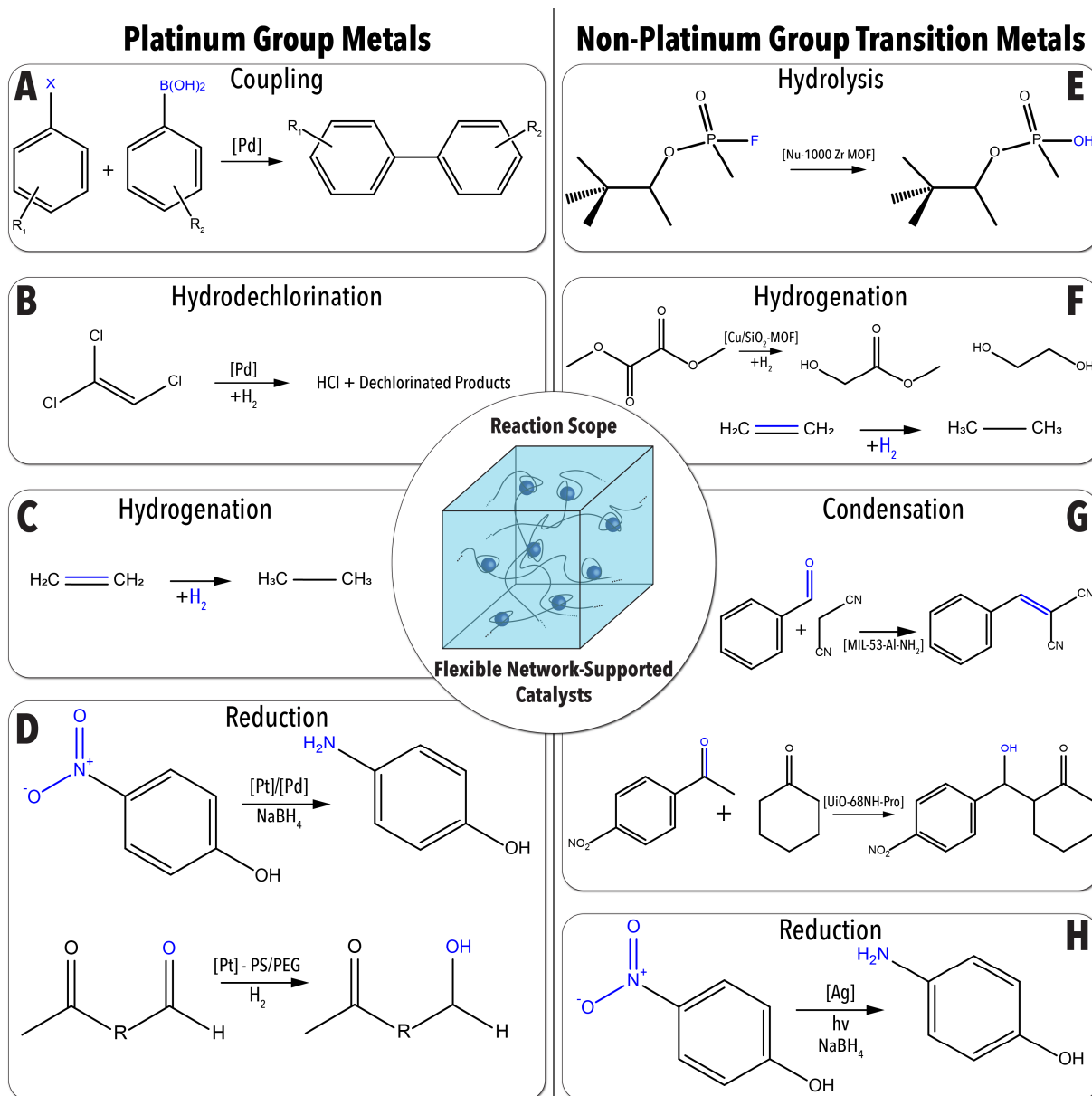
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the final product. Heterogeneous metal-mediated catalysis, on the other hand, suffers a loss of activity compared to homogeneous systems in exchange for the ability to readily isolate the product from the catalyst. In addition, many heterogeneous catalysts require complex multistep surface modifications to immobilize the reactive sites.<sup>17</sup> Recent efforts have attempted to utilize the best properties from each class of catalysis by using robust, flexible, and permeable networks for tunable confinement of active catalytic species (Fig. 1).<sup>18–20</sup> Such novel catalytic systems increase catalyst accessibility to reactive species, and thereby overall activity through precise control over network flexibility, mobility, and permeability

while maintaining the physical or chemical interactions required to successfully confine either the active functional groups or catalytic sites. Network mechanical integrity is also necessary for post-reaction steps such as catalyst separation, recovery, and recycling.

Flexible network and metal-organic-framework (MOF)-based catalytic strategies have been successfully employed to promote a broad range of metal-mediated chemical reactions, including cross-couplings, condensation reactions, functional group modifications, and decompositions using both classic platinum group metals (*e.g.*, palladium (Pd), platinum (Pt), ruthenium (Ru)) as well as other transition metals (*e.g.*, silver



**Fig. 2** Exemplary reactions recently conducted using network-based catalysts, including (A) Pd-catalyzed carbon-carbon cross-coupling reaction,<sup>13–15</sup> (B) decomposition by hydrodechlorination,<sup>17</sup> (C) alkene hydrogenations,<sup>6</sup> (D) reduction of nitro- and aldehyde functional groups,<sup>26,27</sup> (E) decomposition via hydrolysis,<sup>31</sup> (F) copper-catalyzed hydrogenations,<sup>32</sup> (G) condensation reactions,<sup>33</sup> (H) Non PGM reduction of nitro-functional groups.<sup>27</sup>

(Ag), copper (Cu), zirconium (Zr), iron (Fe), nickel (Ni), cobalt (Co)), shown in Fig. 2. Specifically, polymer-based networks<sup>12</sup> offer the ability to create a vast library of catalyst scaffolds and handles to fine-tune catalytic performance by varying the chemical composition of the network. This unique fine-tuning characteristic allows for precise control over bulk polymer network properties such as stiffness, permeability, and affinity for reactive species, which can be leveraged to further optimize the desired metal-mediated catalytic reaction. Furthermore, the polymer-based scaffolds are mainly compatible with green solvents (*e.g.*, water), also promoting chemical process sustainability. Cross-coupling reactions (Fig. 2A)<sup>5,13-15,21</sup>, due to their vast application in chemical synthesis, represent the most common class of metal-mediated catalytic reactions studied using network-based catalysts. The network-based catalysts allow ligand-free cross-coupling reactions in aqueous<sup>13,14,22,23</sup> or organic<sup>25,26</sup> reaction media while sequestering the active metal species for facile catalyst recovery and reuse. The network-supported catalysts have also found use in the degradation of impurities and contaminants (Fig. 2B).<sup>17</sup> Additionally, a wide range of chemical transformations for various oxidations and reductions of critical functional groups (Fig. 2 C, D), including alkenes,<sup>6</sup> aldehydes,<sup>26</sup> as well as nitro and azide containing compounds<sup>27</sup> have been investigated. As the Pt group metals often involve a significant expense due to required large metal loadings, many researchers have explored the possibility of developing network-based catalysts using other, less-expensive transition metals.<sup>23,27-30</sup> For example, network-supported catalysts containing standard transition metals (*e.g.*, Zr) have been successfully utilized to pacify harmful agents (Fig. 2E).<sup>31</sup> A wide range of standard transition metal network-based catalysts are currently being developed as an alternative to Pt group metals for a standard suite of chemical reactions (*e.g.*, hydrogenations, Fig. 2F),<sup>32</sup> couplings and condensations (Fig. 2G),<sup>33</sup> and functional group modifications (Fig. 2H).<sup>27</sup> Network-based catalytic systems allow for a wide variety of application-guided immobilization strategies that can be tailored to specific metals, precursors, products, or solvents, depending on the challenge being addressed. As the network-based catalysts involve confinement of active sites, it becomes feasible to operate chemical reactions in either batch<sup>14,27,34</sup> or continuous flow mode<sup>13,14,26</sup> with the network-supported catalytic particles in a reaction vessel or immobilized in a packed bed, respectively (Fig. 3). The batch operation allows for simple experimental setups for rapid testing of a relatively low number of reaction conditions without advanced material handling strategies. Continuous flow operation can allow high-throughput, scalable reactions with the ability to incorporate automatic reaction condition screening as well as online analysis that could be coupled to process control strategies.<sup>35</sup> Although the network-supported catalysts are robust, continuous flow operation may be limited at higher flowrates if a monolithic reactor has small pores or a particle packed bed reactor has a low void volume.

In this minireview article, we focus on highlighting recent developments in the emerging area of network-supported catalysis with a strong focus on elastomer and hydrogel-based networks. For discussion of metal-mediated cross-couplings,

## Batch Synthesis

- Simple Setup
- Quick Testing
- Manual Sampling



## Continuous Flow Synthesis

- High Throughput
- Scalable
- Automated Sampling
- Precise Process Control
- Minimize Variation
- Online Reaction Monitoring

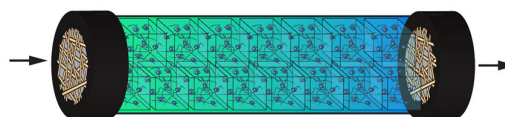


Fig. 3 Schematic illustration of volume-supported catalysis in batch and continuous flow formats.

MOFs, microporous catalyst scaffolds, and properties of elastomers and hydrogels, we direct the reader to recent comprehensive review articles on these topics (cross-coupling,<sup>11</sup> MOFs,<sup>36</sup> microporous catalysts<sup>37</sup>, and properties<sup>38,39</sup>).

## 2.0 Network-Supported Catalysis

Network-supported catalysts are formed by the inclusion of active sites (*e.g.*, functional group, a single atom, nanoparticle) within the confines of a (flexible) disordered network material. These network materials generally allow for the diffusion of solvents and reagents into the bulk as opposed to monolithic materials with mainly impermeable high surface area supports. In this section, we discuss the versatility of network-based catalysts from the choice of host material to the catalyst site morphology. We provide a brief overview of the types of handles available for tuning and optimizing network-based catalysts towards a given application. Furthermore, we discuss the catalytic performance of exemplary flexible polymer-supported catalysts in Pd-catalyzed Suzuki-Miyaura cross-coupling reactions, conducted in flow.

### 2.1 Network Materials and Morphology

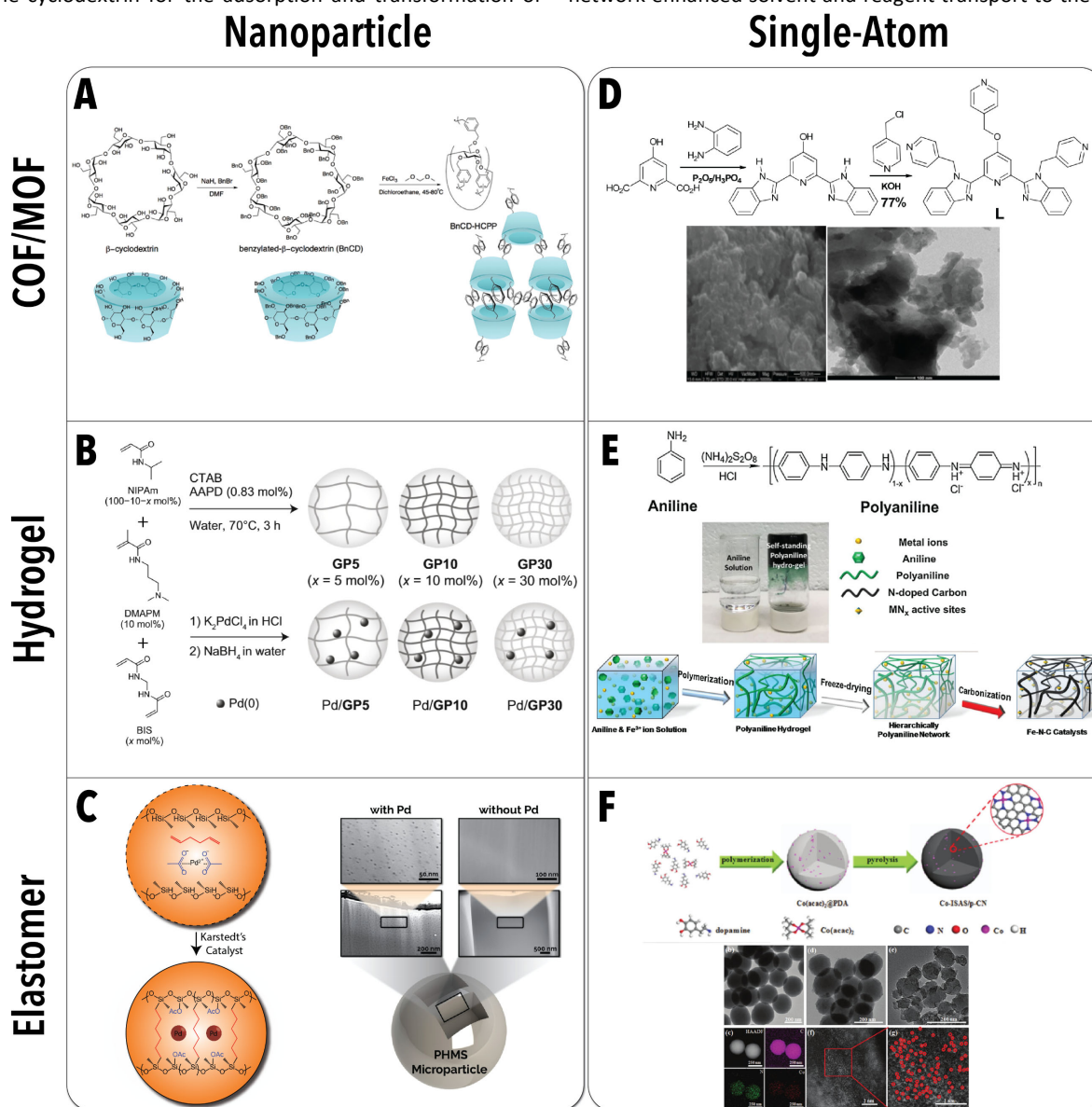
Hybrid network-based catalytic systems are constructed from many different building blocks allowing for the method to be compatible with a wide range of chemical reactions and offer the ability to tune the behavior of the reaction environment and performance of the catalytic reaction. In general, hybrid metal-based catalysts can either incorporate single-atom reaction sites within the network or can confine *in situ*-formed metal nanoparticles to serve as active reaction sites. The most commonly utilized host materials to support the catalyst sites and provide a robust structure are covalent-organic-frameworks (COFs)<sup>40</sup>, MOFs,<sup>36</sup> or flexible polymers.<sup>13-15</sup> Although COFs and MOFs can form strong microporous

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networks, they generally lack flexibility compare to as cross-linked hydrogels or elastomers.<sup>41–49</sup> Both COFs and MOFs, as well as hydrogels and elastomers, can be employed for either nanoparticle<sup>13,46,50,51</sup> or single atomic site-based catalysis.<sup>23,30,52</sup> Metal nanoparticle encapsulation can either be performed as *in situ* reduction of metal salts in solution or generating the network around pre-existing nanoparticles. Li *et al.*<sup>22</sup> used a hyper-crosslinked  $\beta$ -cyclodextrin scaffold to support gold (Au) nanoparticles in the high pore-volume cages formed by the cyclodextrin for the adsorption and transformation of

organic molecules in aqueous media (Fig 4A). It was found that the scaffold material had a strong impact on adsorbing the organic molecules in aqueous solution resulting in close contact with the active catalyst sites for further transformation or degradation. For hydrogel-based catalysis, Matusmoto *et al.*<sup>51</sup> used a cross-linked poly N-isopropylacrylamide (pNIPAm) as a hydrogel scaffold for the confinement of Pd nanoparticles within the hydrogel network to perform carbon-carbon cross-coupling reactions in aqueous media, where the hydrogel network enhanced solvent and reagent transport to the active

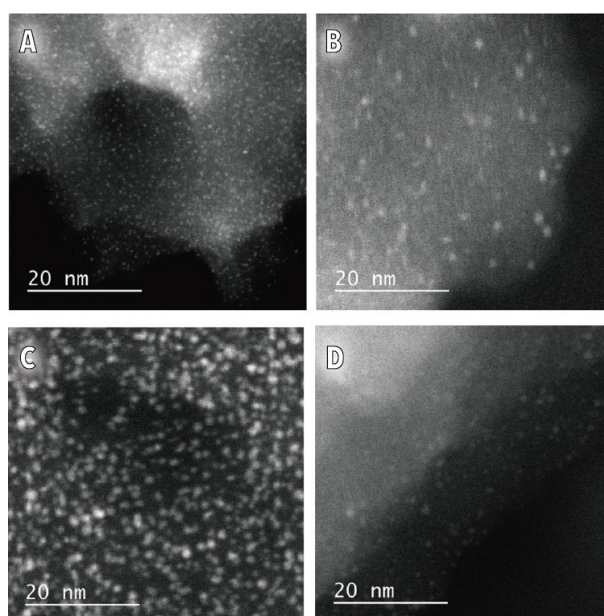


**Fig. 4** (A) Au nanoparticles in cross-linked  $\beta$ -cyclodextrin utilized for the reduction of 4-nitrophenol. Reproduced from ref. 22 with permission from Elsevier. (B) Pd nanoparticles in pNIPAm utilized for Suzuki-Miyaura cross-coupling. Reproduced from ref. 50 with permission from Springer Nature. (C) Pd nanoparticles in cross-linked polyhydromethyl siloxane utilized for carbon-carbon cross-coupling reaction. Reproduced from ref. 13 with permission from Wiley. (D) Pd-based metallogel with nitrogen containing heterocycle linkers utilized for Suzuki-Miyaura cross-coupling. Reproduced from ref. 51 with permission from Elsevier. (E) Atomic iron in a polyaniline network utilized for the oxygen reduction reaction in acidic media. Reproduced from ref. 23 with permission from Elsevier. (F) Cobalt in pyrolyzed polydopamine networks utilized for the oxygen reduction reaction in basic media. Reproduced from ref. 30 with permission from Wiley.

catalytic sites on the Pd clusters (Fig 4B). Bennett *et al.*<sup>13</sup> used a similar system for a Pd-based cross-coupling reaction with a siloxane elastomer instead of a hydrogel to allow increased network tunability and *in situ* reduction of Pd salts while tolerating increased reaction temperatures (Fig 4C). The silyl functionality of the siloxane network served as both a network cross-linking site and a facilitator for the reduction of metal salts with no added reducing agents (*e.g.*, sodium borohydride).

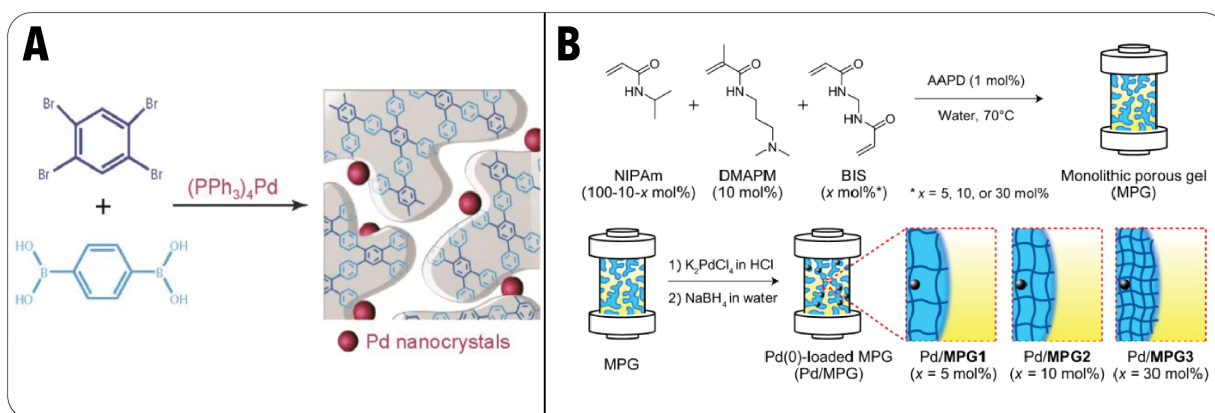
In addition to nanoparticle-based catalysis, single atomic site catalysis has also been successfully demonstrated using the network-based catalysis approach. Ye *et al.*<sup>54</sup> formed a Pd-based metallogel using polydentate linkers containing nitrogen heterocycles that bind to Pd (Fig 4D). It was demonstrated that the network of linkers was connected by atomic Pd species that provided catalytic activity for Suzuki-Miyaura cross-coupling reactions. Hydrogels have also been utilized for single atomic site catalysis using network-based catalysts. Qiao *et al.*<sup>23</sup> used a polyaniline network for immobilization of atomic Fe to be used as the single atomic sites for oxygen reduction in acidic conditions at the cathode of a proton exchange membrane fuel cell (Fig 4E). The polyaniline network displayed enhanced activity and stability as compared to conventional Fe-N-C catalysts, which can show carbon corrosion due to the carbon black support material.<sup>23</sup> In another network-supported catalyst study, Han *et al.*<sup>30</sup> used a polydopamine encapsulation followed by pyrolysis to form nitrogen-doped carbon nanospheres, used as a proof-of-concept demonstration of establishing single-atom catalyst sites from various noble and nonprecious metals (Fig 4F). Although Pd is the most prevalent metal for catalysis in these systems due to its efficacy and wide range of applicability to chemical reactions, other metals have also been demonstrated to be successful in their impregnation in these network supports. For example, Huang *et al.* reduced Ag, Pt, Au, and Rh using the popular method of metal ion diffusion into the network followed by the introduction of the reducing agent NaBH<sub>4</sub> to make the active catalyst nanoparticles (Fig. 5).<sup>55</sup>

Network-supported catalysts confer many of the advantages provided by heterogeneous catalyst systems, with the additional



**Fig. 5** HAADF-STEM images of (A) Ag, (B) Pt (C), Au, and (D) Rh nanoparticles loaded within a cyclodextrin polymer network. Reproduced with permission from Ref. 55.

benefits of volume confinement as opposed to conventional immobilization on solid impermeable surfaces. Confinement of the active catalyst species within the bulk of the material will provide better spatial accessibility and mobility of the catalytic centers relative to immobilizing catalysts on solid impenetrable surfaces. Furthermore, it has been demonstrated that such volume confinement of the active catalyst centers will achieve less leaching compared to a similar heterogeneous catalyst, leading to an improved lifetime and recyclability profile.<sup>14,55</sup> Network-supported catalysis adds a dimension to the reaction compared to surface heterogeneous catalysis. The three-dimensional network support uptakes solvent and reactants ideally acting as a pseudo-homogeneous catalyst with diffusion resistance. Both elastomers and hydrogels can be a viable option for network-based catalysts with the optimal choice for a given system depending



**Fig. 6** (A) Gel synthesis of a solid polyphenylene porous support with catalytically active Pd nanocrystals utilized for Suzuki-Miyaura cross-coupling reaction. Reproduced from ref. 50 with permission from Wiley. (B) Monolithic porous gel synthesis for Pd-embedded hydrogel support for aqueous carbon-carbon cross-coupling reactions in flow. Reproduced from ref. 21 with permission from American Chemical Society.

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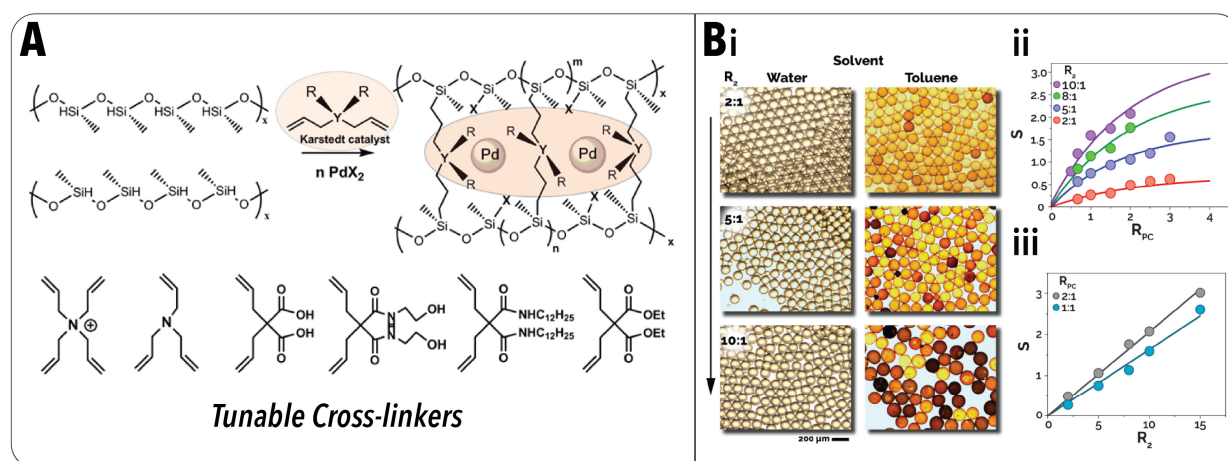
on parameters such as the reacting species, solvent, and reaction temperature. A second consideration for material selection is physical parameters of the network such as convective and diffusive transport properties (both heat and mass), and the overall toughness and durability of the material to processing, handling, and recycling.

## 2.2 Network Control

Although all network-based catalysis efforts have similar goals of creating a highly accessible catalyst without the need for subsequent metal separation, several different catalyst scaffolds have been successful for carrying out metal-mediated chemical reactions. An effective approach used to create active Pd species within a network-based catalyst was to synthesize a solid, porous polymer support with Pd nanocrystals dispersed and trapped in the micropores of the support (Fig. 6A).<sup>53,56</sup> The Pd-loaded polymer support was synthesized by Pd-catalyzed cross-coupling of 1,2,4,5-tetrabromobenzene and benzene-1,4-diboronic acid. The multifunctional benzenes allow for polymerization into a polyphenylene (PPhen) network. The utilized catalyst, Pd triphenylphosphine Pd(PPh<sub>3</sub>)<sub>4</sub>, decomposed at 150°C in dimethylformamide into Pd nanocrystals. Therefore, the simultaneous decomposition of the Pd complex and the *in situ* carbon-carbon cross-coupling polymerization allowed for successful confinement of active Pd nanoparticles within the porous polymer network.<sup>51</sup> The thermal and chemical stability of PPhen is higher than those of most polymers,<sup>51</sup> which makes this approach suitable for a wide range of organic transformations. The micropores allow the reaction environment to remain “solvent-like” for high catalyst accessibility while maintaining the reusability and catalyst affixing that is commonly beneficial to heterogeneous catalysts. Additionally, the favorable interaction of organic reagents with the aromatic backbone of the support network allows for enhanced catalytic performance. This network-based catalytic system demonstrated effectiveness in carrying out Suzuki-

Miyaura cross-coupling reactions with different reactants. The superior performance of this Pd-loaded PPhen catalyst could be attributed to the ease of access to Pd nanocrystals in the micropores and the reagent affinity for the polymer support.

In a different network-based catalytic study, a monolithic porous gel with embedded active Pd nanoparticles was demonstrated to be an effective catalyst for continuous Suzuki-Miyaura cross-coupling reactions in water at 30°C (Fig. 6B).<sup>15</sup> The catalyst support was synthesized by copolymerizing NIPAm, N-(3-dimethylaminopropyl)methacrylamide (DMAPM), and N,N'-methyl-enebisacrylamide (BIS) as the gel matrix, tertiary amine ligand, and crosslinker, respectively. Gels with different network sizes were synthesized using 5, 10, and 30 mol % crosslinker and a fixed DMAPM content of 10 mol %. Pd loading was carried out by gel adsorption of potassium tetrachloropalladate (II) and subsequent reduction to Pd(0) using sodium borohydride. The utilization of NIPAm provided the gels significant hydrogel nature, therefore, promoting the transfer of aqueous mobile phase with feed reactants from the bed capillaries or interspatial pores into the gel walls where the active Pd sites were anchored. The catalytically active Pd nanoparticles, confined within the gel, catalyzed the Suzuki-Miyaura cross-coupling reaction. The reaction products were readily able to diffuse back into the network capillaries and eventually out into the eluent stream. Among different hydrogel network sizes, the Pd-loaded gel with the larger network size (*i.e.*, the least amount of crosslinker) had the highest reaction conversion at all residence (reaction) times tested. The improved catalytic performance of the Pd-loaded gel with the larger network size was not only due to the higher amount of hydrogel NIPAm within the gel, but also the looser network allowed for faster diffusive transport of the reagents to the active catalytic sites within the network. Overall, the hydrogel-based catalytic system was applicable to chemical reactions in water at 30°C, where the catalyst experienced no detectable leaching and remained active after 30 days of use. This hydrogel-based catalyst support trends toward an ideal



**Fig. 7** (A) Cross-linker variance for network functionalization in an elastomer support. Reproduced from ref. 14 with permission from American Chemical Society. (Bi) Brightfield images of PHMS microparticles synthesized at different elastomer:crosslinker ratios ( $R_2$ ) when dispersed in water (left column) and toluene (right column). (Bii) Swelling ratios,  $S$ , of PHMS microparticles in toluene with respect to water at different  $R_2$  and elastomer:catalyst ratios ( $R_{2c}$ ). Reproduced from ref. 13 with permission from Wiley.

catalyst, because it not only experiences no detectable leaching (due to the confinement of the active catalyst species within the network), but it also has a more favorable reaction solvent diffusion within the hydrogel support. Despite the superior continuous performance of this network-supported catalyst, it holds significant limitations, including temperature compatibility issues due to the thermoresponsiveness of pNIPAm gel. At temperatures higher than 30°C, the polymer support experiences significant network collapse, which decreases the reaction substrate diffusivity within the network and, therefore, the reaction conversion.

A common strategy to tune the catalyst scaffold's affinity for reagents is through the addition of functional groups to the chemical crosslinker (Fig 7A).<sup>14</sup> The chemical functionality, length, and amount of the chemical crosslinker can all be precisely tuned within the network to better fit the needs of desired metal-mediated catalytic reactions, further providing another level of tunability for yield and regio/chemo-selectivity optimization. For example, polar and hydrophilic functional groups can increase the swelling of a hydrophobic polymer backbone—utilized as the catalyst scaffold—in an aqueous reaction media, thereby enhancing the accessibility of the catalytic site resulting in an increased reaction yield. An effective way to measure the network-based catalyst affinity for the reaction solvent (or mobile phase) is through swelling characterization (Fig 7B).<sup>20</sup> Swelling of a polymer gel occurs when it uptakes solvent, increasing the volume and effective mesh size of the gel.<sup>57</sup> Swelling is a physical property of a polymeric gel that illustrates the gels affinity for the solvent at a specific temperature. The solvent swelling ratio is considered as one of the most important parameters for flexible network-supported catalysts, which allows for direct tuning of transport into and through the network support.

### 2.3 Polymer-Supported Cross-Coupling Reactions

The versatility of network-supported catalysts can allow for the development and utilization of multiple approaches for the same metal-mediated catalytic reaction depending on the substrate- or process-specific requirements. Matsumoto *et al.* utilized pNIPAm as the scaffold of choice for conducting Suzuki-Miyaura cross-coupling reactions due to the polar nature of the utilized aryl halide, which was more suited to strictly aqueous conditions (Fig. 8Ai).<sup>15</sup> The Pd-loaded pNIPAm catalyst was demonstrated to be a very effective catalyst with minimal leaching (Fig. 8Aii) of the active Pd species while maintaining a reasonable reaction rate and conversion during continuous operation for residence times of up to 3 h (Fig 8Aiii&iv). Bennett *et al.*<sup>13</sup> performed a similar Suzuki-Miyaura cross-coupling reaction in a continuous flow packed-bed microreactor, but with a more hydrophobic aryl halide which required a mixed ethanol and water solvent for a better substrate solubility, as well as a hydrophobic polysiloxane network scaffold to tolerate the reaction solvent and reaction temperature (65°C) (Fig. 8Bi).<sup>13</sup> The elastomer network, similar to the hydrogel scaffold, maintained long-term activity with low Pd leaching. Other network considerations include an affinity for reaction

substrates and desired reaction conditions. As shown in Fig. 8Bii, the Suzuki-Miyaura cross-coupling reaction substrate (4-iodotoluene) had a higher affinity for the network than the internal standard (naphthalene) as it started to elute later for the same initial start time. Fig. 8Biii shows Pd-mediated cross-coupling yields at different residence times in the packed bed reactor, utilizing the polymer-supported catalyst.<sup>13</sup> Network durability also plays a vital role in material selection for the catalyst host in the continuous flow polymer-supported catalysis. The network must be robust enough to withstand reaction temperatures and flow rates without permanent deformation while maintaining good diffusive (batch and flow) and convective (flow) transport properties.

When compared to traditional heterogeneous catalysts, polymer network-supported catalysts often perform better. For example, Huang *et al.* compared a classic Pd/C heterogeneous catalyst to their synthesized cyclodextrin network decorated with active Pd nanoparticles.<sup>55</sup> They discovered that in a hydrogenation reaction, the network-supported Pd catalyst achieved 100% conversion of 4-nitrophenol maintained over 7 cycles with negligible leaching. Although the classical Pd/C catalyst produced comparable catalytic activity and short reaction time, its recyclability was not as optimal as the network-supported catalyst (over 4% of the catalytic activity was lost after 2 cycles).<sup>55</sup>

### 3.0 Summary and Outlook

The network-supported catalysts utilizing flexible and<sup>56</sup> robust host scaffolds, discussed in this minireview article, have been demonstrated to provide an ideal reaction environment for next-generation sustainable, metal-mediated chemical transformations. An ideal network-supported catalyst should provide strong, leaching-free, confinement of the active metal sites while maintaining high activity and substrate transport through the network for catalyst site accessibility. The network-supported catalyst should be easily separated from the reaction mixture or stream and be durable at reaction conditions throughout many catalytic cycles.

Current heterogeneous catalyst systems generally involve complex immobilizations on solid, impermeable supports, which can lead to a decrease in activity in comparison to the confinement within a flexible support network. Additionally, the synthesis of many network-supported catalysts is a simple one-step network formation either around preformed catalyst sites or followed by a simple metal reduction into an active form. Options for network-based catalyst systems range from encapsulated nanoparticle methods to bound single-atom metal sites. Many different support materials have been successfully attempted, including hydrogels (*e.g.*, pNIPAm, polyaniline), elastomers (*e.g.*, polysiloxanes),<sup>18</sup> and COFs (*e.g.*, cross-linked cyclodextrin, nitrogen heterocycle linkers). Although flexible network catalysts have higher diffusion resistance than MOFs, they generally allow for better tuning of both the catalyst and the support. The flexible network materials can be further functionalized either through direct chain functionalization, copolymerization, or the addition of



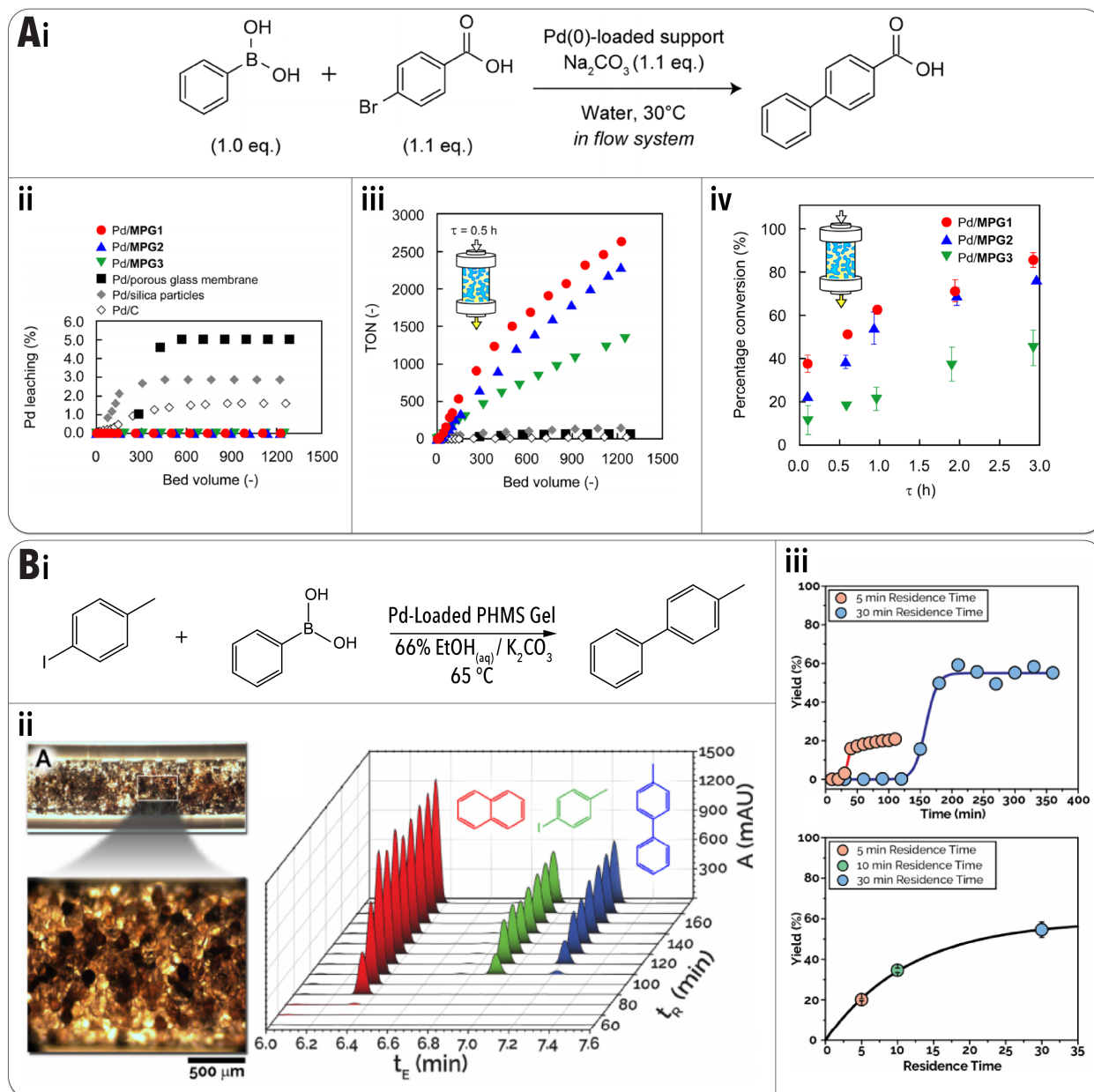
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functional linkers.<sup>59,60</sup> Given the vast array of potential network materials and catalytic sites, network-supported catalysts can be adapted to provide a robust, facile, and tunable candidate for a diverse selection of chemical reactions and reaction conditions. Although network-supported catalysts usually underperform compared to homogeneous catalysts in yield and conversion, the drawbacks of homogeneous catalysis (e.g., multistep ligand synthesis, catalyst sensitivity, catalyst recovery, and deactivation) are significantly improved or eliminated in network-supported catalysts. The network-

supported catalysts often outperform heterogeneous catalysts, providing a tunable and stable platform for a wide range of metal-mediated chemical reactions. Further research into network-supported catalysts will allow for better performance and a larger reaction scope to realize the full potential of this category of catalysts.

Despite the advantages of network-supported catalysts (vide supra), these systems face some challenges concerning mechanical strength needed to withstand the forces in a packed bed reactor at relatively high volumetric flowrates, while trying



**Fig. 8.** (Ai) Carbon-carbon cross-coupling reaction performed in the porous pNIPAm monolith reactor loaded with Pd nanoparticles. (Aii) Pd leaching study of pNIPAm support (Aiii) Catalyst activity compared with conventional supported Pd catalysts. (Aiv) Residence time study of cross-coupling reaction conversion. Reproduced from ref. 15 with permission from American Chemical Society. (Bi) Carbon-carbon cross-coupling reaction performed in the packed bed reactor of cross-linked polyhydromethyl siloxane microparticles loaded with Pd nanoparticles. (Bii) Waterfall plot showing start-up phase of reaction. (Biii) Reaction yield at 5, 10, and 30 min residence times. Reproduced from ref. 13 with permission from Wiley.

to maintain a high degree of transport of reagents and solvents throughout the bulk of the network. Attempting to maintain the accessibility and activity of the catalyst while making it durable enough for repeated reactions and recycling is an area of considerable interest in the field. One other limitation that must be considered when selecting a polymer system for a given reaction is that the network may collapse in a given solvent at a given temperature (e.g., PNIPAm in water collapses at temperature > 32°C). This behavior would lead to a dramatic increase in transport resistance.

Another major area of active investigation in the field of network-supported catalysis is determining how the network is interacting with the metal sites for stabilization and confinement. Furthermore, the effect of the network properties and morphology on the interactions with the reaction substrates, intermediates, and products need to be further evaluated for designing the next generation network-supported catalysts. Little is known about the detailed reaction mechanisms within such complex network materials, making them prime targets for further studies. The interactions between network material and reaction species can be strictly bulk interactions such as affinity and transport behavior or chemical interaction with the catalytic cycle (e.g., steric effects, direct participation, or metal coordination). Especially crucial for flexible networks is the need to explore the network-metal interactions through high-resolution characterization techniques, including nuclear magnetic resonance and diffuse X-ray scattering. Another potential area of research in network-based catalysts is extending the library of metals that can be utilized by this unique class of catalysts to either perform metal-mediated catalytic reactions at a lower cost or to widen the reaction scope for novel syntheses.

The heterogeneous nature of the network-supported catalysts and minimal leaching behavior allow for multistep reactions to be conducted in series in a telescopic manner through a continuous flow platform for the streamlined synthesis of complex chemicals. The flow reactors containing the network-based catalysts can take the form of (i) packed beds loaded with particles of the network material, (ii) an *in situ*-formed porous monolithic structure with pores for flowing reaction mixture, or (iii) deposited on the surface of the channel walls.<sup>61</sup>

Once a broad-strokes network-supported catalyst family has been selected for a given application, the versatility of the network support material can be utilized for minor chemical and compositional adjustments to further optimize the catalyst for the unique requirements of each metal-mediated catalytic system. Utilizing the discussed network-supported catalysis strategy in this minireview article, process chemists will have the ability to standardize reactors for better reproducibility, characterization, and reaction development. Opportunities are available to make more versatile, easy to synthesize, robust, and tunable network materials with effective metal catalyst confinement. Polymer-supported gas-liquid catalytic reactions are also a future step for these catalytic systems, opening opportunities for other important catalytic reactions such as carbonylation, amination, hydroformylation, and

hydrogenation. We are confident a significant number of important metal-mediated catalytic reactions can be developed to perform in a network-based catalytic system and receive the unique benefits offered by the tunable network support material.

## Conflicts of interest

There are no conflicts to declare.

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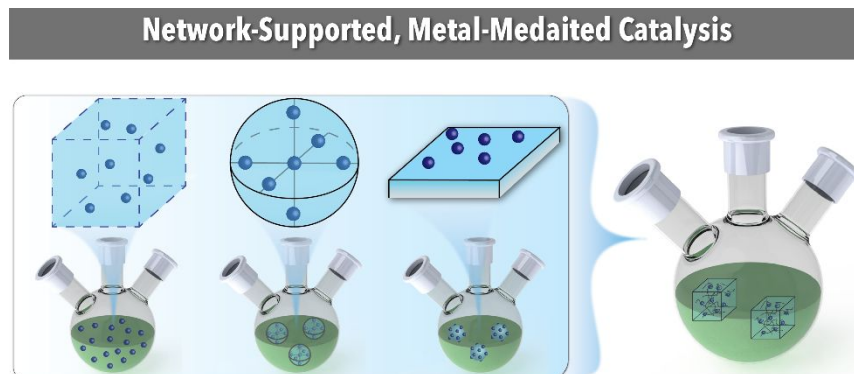
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## MINIREVIEW

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**TOC Graphic:**

This minireview focuses on recent developments of network-supported catalysts to improve the performance of a wide range of metal-mediated catalytic reactions.