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ADVANCES IN HETEROGENIZATION OF CATALYSTS FOR FINE ORGANIC SYNTHESIS *VIA* CATALYTIC OXIDATION IN LIQUID MEDIUM: A REVIEW

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Abstract. Heterogenization of catalysts offers numerous advantages over homogeneous systems, including enhanced stability, reusability, and fine-tuning of properties. This approach is particularly relevant for developing environmentally friendly and sustainable catalytic processes. Microgels, with their unique properties, emerge as promising platforms for catalyst heterogenization. These crosslinked polymer networks exhibit tunable size, porosity, and responsiveness to external stimuli, making them ideal for encapsulating and stabilizing catalytic species. The integration of Se-containing functional groups into the microgel structure further enhances their catalytic potential, leveraging the redox properties of selenium for oxidation reactions. This bioinspired approach offers a novel route for catalyst design and contributes to the development of environmentally friendly and efficient processes.

Keywords: catalysis, heterogenization, heterogeneous catalysts, microgel catalysts, oxidation.

1. Introduction

In response to the critical crisis caused by the depletion of energy and natural resources, as well as environmental degradation due to rapid industrialization, humanity is actively working to implement advanced technologies to ensure sustainable development.[1] One of the key tools in this process is catalysis,[2] which plays a crucial role in reducing air pollution by promoting the development of environmentally friendly technologies. Such technologies provide efficient and selective reactions, minimize emissions of harmful substances, and contribute to wastewater treatment, making a significant contribution to the concept of "green chemistry" and environmental protection.[3]

In this context, the creation of active, selective and energy-efficient catalytic systems is becoming a critical task as they contribute to the transition to carbon-neutral technologies. One of the promising applications of such catalytic systems is the production of high-value organic compounds by catalytic oxidation.[4] In particular, aromatic acids obtained in this way are indispensable precursors for the production of many expensive medical and industrial substances, which emphasizes the importance of further development of these technologies.[5] From an industrial point of view, gas-phase oxidation is more attractive because the lack of solvent simplifies product collection. However, given that fine chemicals are characterized by thermal instability, this process must be carried out in the liquid phase at medium temperatures, which requires the use of special catalysts with high activity, as well as chemoselectivity, regio- and stereoselectivity. To achieve this, many effective methods have been developed, but most of them require the use of stoichiometric oxidants, such as chlorites, chromates, chromium(VI), potassium permanganate, hypochlorite, heavy metals, and organic peroxides. These oxidants are known for their toxicity, corrosiveness, and high cost, and lead to the formation of a significant amount of by-products, which negatively affects the economic efficiency of the process.[6–8] In addition, such processes are impossible without the use of large quantities of organic solvents, such as acetonitrile, dichloromethane, cyclohexane, formic acid, or benzene. Although these methods have significant drawbacks, some of them continue to be widely used in the chemical industry. However, as environmental awareness increases, there is a growing demand for more efficient and environmentally friendly oxidation methods that are in line with the principles of green chemistry.[9,10]

Modern research in the field of selective oxidative catalysis is aimed at developing environmentally friendly technologies that allow reactions to be carried out under mild conditions with minimal environmental impact. For this purpose, reaction systems use "green" oxidants, such as hydrogen peroxide or oxygen from the air, as well as safe solvents, among which water occupies a special

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place.[11,12] The use of hydrogen peroxide as an efficient and environmentally friendly source of oxygen is in line with the principles of green chemistry, allowing for high efficiency and selectivity of reactions while minimizing harmful waste and energy consumption.

Catalytic oxidation in the liquid phase is particularly promising due to the ability to carry out reactions under mild conditions. At the same time, the choice of solvent has a significant impact on the reaction mechanism: organic solvents favor the radical mechanism, while water activates the ionic mechanism, providing additional safety and environmental friendliness, making it preferable from an industrial point of view.

In this context, the choice of catalytic system plays a key role. Heterogeneous catalysts are widely used in industrial processes due to their advantages, such as ease of separation of reaction products, regeneration, and reusability. These characteristics contribute to the implementation of environmentally sustainable and cost-effective synthesis methods.[13–15]

However, to maintain economic viability, a suitable heterogeneous system should not only minimize waste generation but also have activity and selectivity that would be on par with or exceed the existing homogeneous approach. To achieve high efficiency and selectivity of oxidation processes, considerable attention is paid to homogeneous catalysis, which provides high availability of catalytically active centers. However, homogeneous catalysis has several significant limitations, namely corrosivity, toxicity, difficulty in separating the catalyst from the reaction products, difficulties with its recovery and regeneration, as well as high cost.[16]

One of the promising ways to solve this problem is to "heterogenize" homogeneous catalysts by immobilizing them on solid insoluble bases.[17,18] This method allows to preserve the catalytic properties of homogeneous analogs while providing them with the advantages characteristic of heterogeneous systems, including the possibility of recycling and regeneration. This approach allows the combination of the high efficiency and selectivity of homogeneous catalysts with the ease of separation, regeneration, and reuse characteristic of heterogeneous catalysis, which opens up new opportunities for environmentally friendly chemical processes.[19]

Many heterogenized catalysts exist, including metal complexes immobilized on solid carriers such as molecular sieves, ion exchange resins, polymer membranes, zeolites, and organic nanotubes.[20–22] However, immobilization often reduces the reactivity of such catalytic systems compared to homogeneous catalysts due to the limited availability of active sites during reactions.

In this context, the work is aimed to systematize modern scientific achievements in the field of selective oxidative catalysis to develop a highly efficient, environmentally friendly, and reusable catalyst capable of combining the advantages of homogeneous and heterogeneous systems.

2. Overview of Different Types of Heterogenized Catalytic Systems

Heterogenization is the process of transforming a homogeneous catalyst, which dissolves in the reaction medium, into a heterogeneous catalyst, which exists as a separate phase. This offers several advantages, including easier catalyst recovery and reuse, improved stability, and potential for continuous flow processes. Common methods for heterogenization include immobilization of the catalyst onto a solid support like silica, alumina, or carbon materials through various techniques like covalent bonding, encapsulation, or physical adsorption; integrating the catalyst into layered structures like metal-organic frameworks or nanosheets; encapsulation of the catalyst within a polymer matrix, either by polymerization around the catalyst or by incorporating the catalyst into the polymer during synthesis (Fig. 1).

Each method has its own strengths and weaknesses, and the choice depends on the specific catalyst and reaction conditions. Let us review some relevant examples with different reaction systems.

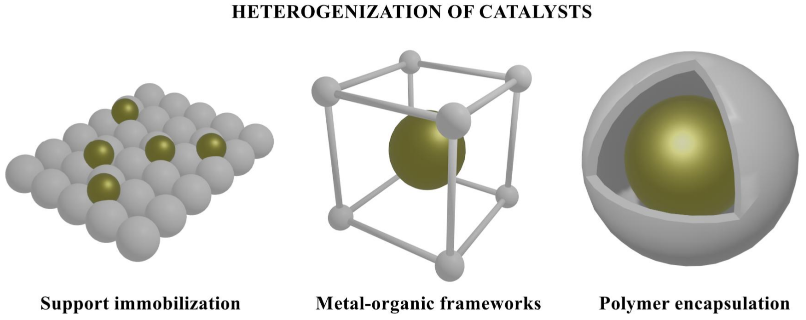

Fig. 1. Common types of heterogenized catalysts

The aldolization reaction is a key enantioselective transformation for the synthesis of β-hydroxycarbonyl compounds, which is naturally catalyzed by aldolases in aqueous medium with high selectivity.[23] However, synthetic proline-based organocatalytic systems usually require organic solvents, as an all-aqueous environment often causes lower yields and loss of selectivity. Although water-active proline catalysts, such as the Shoji[24] and Barbas[25] systems, show improved selectivity, they do not allow for reusability. The heterogenization of proline on solid carriers (nanodiamonds, polymers, mesoporous materials, carbon nanotubes) partially solves this problem by providing recycling of catalysts but is often accompanied by a decrease in efficiency, which requires further optimization.[26,27]

An effective solution was proposed by Demeese *et al.* by creating a nanohybrid catalytic system based on the supramolecular assembly of proline amphiphiles on carbon nanotubes. This system demonstrates high efficiency in enantioselective aldolization reactions in aqueous medium as a single solvent, achieving yields of up to 99% and enantiomeric excess of up to 98%.[28] The catalyst operates at low loading (5 mol%), room temperature, and is reusable without loss of performance. However, the industrial implementation of this system is complicated by the high costs and complexity of scaling up the synthesis of nanohybrids, as well as the sensitivity of the catalyst to reaction conditions. In addition, the efficiency is limited to certain types of substrates, which requires additional optimization to expand applications.

Another variant of heterogenization was proposed by Kumar *et al.* who developed stable polydiacetylene (PDA) micelles capable of complexation with copper, which were obtained by self-organization, polymerization, and loading of Cu into amino-triazole-based amphiphiles.[29] These hybrid micelles proved to be highly efficient nanoreactors for the catalytic Huisgen cycloaddition due to the nanoreactor effect inherent in the micellar environment, which ensures the dispersion of reagents and their concentration near active copper centers. The process in aqueous medium demonstrated high efficiency for a wide range of substrates at low catalyst loadings, with or without ascorbate, under mild reaction conditions that did not require heating or a controlled atmosphere, which emphasizes the significant potential of the micellar system in terms of both efficiency and environmental friendliness of the process. Despite the successful work in the laboratory, the introduction of this catalyst on an industrial scale has certain limitations. In particular, the lack of data on the long-term stability and activity of the catalyst in continuous production and its high cost due to the use of specific materials complicate its use. The processes of catalyst regeneration and extraction from the reaction mixture are energy-intensive and technically complex. In addition, the synthesis of amino-triazole-based amphiphiles and the formation of stable copper-loaded PDA micelles is a multi-stage and costly process, which also complicates the scaling of the developed system.

An alternative solution was proposed by Farah *et al.* who developed a specific microreactor system loaded with a hybrid nanocatalyst consisting of gold nanoparticles (AuNPs) on carbon nanotubes (CNTs),[30] combining metal nanoparticles with microreactors for continuous flow. The optimization of such nanocatalysts is based on ensuring the effective fixation of nanoparticles in a microfluidic device with a carrier that not only stabilizes the catalyst but also facilitates the access of reagents to the active sites and improves catalytic transformations. For this purpose, carbon nanotube-based platforms were chosen as the basis for anchoring gold nanoparticles. The integration of the nanohybrid into microfluidic channels allowed the formation of a porous layer due to the interwoven structure of the nanotubes, which in turn is a carrier for gold nanoparticles. This system has been tested in the selective aerobic oxidation of silanes to the corresponding silanols. The developed microreactor based on carbon nanotubes provided efficient oxidation of silanes in a flow mode, demonstrating the high selectivity and environmental friendliness of the process. The system has been successfully applied to the oxidation of silanes, showing several advantages over traditional batch processes, including continuous production, ease of use, reusability, high level of reaction control, and increased safety. However, the creation of CNT-Au nanohybrids is a multi-stage and expensive process and the use of gold as a key catalyst component increases costs, which limits economic feasibility on a large scale. Lack of detailed data on the long-term stability and activity of the system in continuous production, as well as mechanical wear of the nanotubes and loss of gold nanoparticles, can affect the efficiency and increase the cost of catalyst recovery. The technical complexities associated with the design and operation of microreactors, along with potential difficulties in product recovery and system cleaning, further complicate its implementation. In addition, while the system demonstrates high efficiency for the oxidation of silanes, its applicability to other industrially important reactions requires further research and validation.

In the work of Ziccarelli *et al.* for the first time, it was possible to heterogenize the classical PdI_4^{2-} catalyst for carbonylation, obtaining new heterogeneous materials (PdI_4@MWCNT-imi-X, where X = Br, I), which can be widely used not only in carbonylation reactions but also in other processes catalyzed by Pd(II).[31] The heterogenization was successfully realized in two simple steps by fixing the PdI_4^{2-} anion on functionalized multiwalled carbon nanotubes (MWCNTs) modified with an imidazolium mesh. The new catalysts demonstrated high efficiency in a model reaction of oxidative amino carbonylation of terminal alkynes with secondary amines, providing 2-inamide products in good amounts (50-84%) for various substrates. The main advantages are the simplicity of synthesis, the possibility of reusing the catalyst (retention of activity for up to four cycles), and the low level of product contamination with metals, confirmed by ICP-MS analysis. However, the main limitations for industrial implementation are the gradual deactivation of the catalyst due to the formation of inactive Pd(0) species, as shown by XPS analysis, as well as the need for optimization to ensure stability and activity under conditions of long-term use.

Masteri-Farahani's study developed two heterogeneous catalysts, MnTIPP@SBA-16 and MnTBPP@SBA-16, by encapsulating manganese porphyrins (MnTIPP and MnTBPP) in nanocells of the mesoporous material SBA-16.[32] The uniqueness of the method lies in the fact that porphyrins remain mobile inside the mesopores without interacting with the silica walls, but at the same time cannot leave the pores due to their reduced size after silylation. This ensures high catalytic activity and stability of the catalysts, allowing them to combine the properties of both homogeneous and heterogeneous systems. The catalysts demonstrate high selectivity and efficiency in the mild olefin epoxidation reactions using sodium hypochlorite as an oxidant and remain active after at least five cycles of use. The main advantages are their stability, high catalytic efficiency, regenerability, and ability to process small substrates. However, for industrial implementation, the disadvantages may be the complexity and cost of synthesis, as well as limitations in working with larger molecules due to the size of the pores.

In the study by Andreu *et al.* heterogeneous catalytic systems based on proline dipeptides were developed, which demonstrate high efficiency in aldol condensation reactions. It has been found that the addition of zinc or sodium acetate significantly improves the activity and stereoselectivity of catalysts, which in the form of trifluoroacetate salts have low conversion.[33] It was found that the absolute configuration of the aldol product depends solely on the chirality of the N-terminal proline, while the stereoselectivity is determined by the chirality of both amino acids in the dipeptide and reaches its maximum values for the enantiomeric pair ReS, SeR. The best results were observed when neutral essential primary amino acids were used as the second component. The advantages of these catalysts are their high stereoselectivity, improved activity in the presence of co-catalysts, and the ability to work effectively at low temperatures. However, for industrial implementation, limitations can be high sensitivity to reaction conditions, dependence on additional components such as zinc salts, and the complexity of system optimization for large-scale synthesis.

In particular, one of the most promising areas of research in nanoscience is the synthesis of active magnetic nanoparticles that can be easily removed and recycled from reaction systems using an external magnet. Magnetoresponsive nanoparticles have been widely used in many catalytic reactions, in particular in oxidation processes. Among all magnetic materials, transition metal ferrites with the general formula MFe_2O_4 (M = Cu, Co, Ni) are distinguished. One of the existing transition metal ferrites is copper ferrite ($CuFe_2O_4$), where copper and iron can be used as a magnetically reduced catalyst.

Afnan Al-Hunaiti *et al.* have developed an environmentally friendly method for the synthesis of magnetic $CuFe_2O_4$ nanoparticles. The resulting nanoparticles with an average size of 19.7 nm were used as an effective catalyst for the oxidation of various arylalkanes in moderate to high yields under solvent-free conditions. The key advantages of this method are the ease of preparation of a heterogeneous catalytic system, recyclability, and favorable reaction conditions, which provide high yields and selectivity to acids in the range of 42 to 87%.[34] The disadvantages of this catalyst include limited recyclability. In addition, its mechanism of action is not yet fully understood, which makes it difficult to optimize and predict its behavior under different conditions. The possible leaching of metal ions, in particular copper and iron, during prolonged reactions can reduce activity and create contamination risks. The catalyst demonstrates moderate reaction speed and selectivity: variations in yields for different toluene derivatives indicate that its efficiency is not universal for all substrates. These limitations indicate that, despite its promise, the catalyst requires further optimization to improve its durability, stability, and industrial-scale applicability.

Many chromium compounds have found applications as catalysts for the selective oxidation of various organic substrates. Chromium compounds oxidize almost all organic functional groups in a homogeneous environment, with major disadvantages such as separation and toxicity.[35] Cr-containing molecular sieves of great catalytic value, such as CrS-1, Cr-β, CrAPSO-5, CrAPSO-11, and CrAPSO-34, with pore sizes ranging from microporous to small channel sizes, do not allow for the retention of large organic molecules. Mesoporous silica MCM-41, which has a pore size of 2-50 nm, is widely used due to its ordered arrangement and high specific surface area; due to the above properties, these materials have found wide application in the field of catalysis. Among the disadvantages of MCM-41 are its weak acidity and lack of the required redox capacity. To improve the catalytic and functionalized properties, Kaur *et al.* synthesized the Cr-MCM-41 catalyst by the in situ method at a Cr/Si ratio of 0.033, which provides a conversion of toluene to benzaldehyde at 97.19% in 18 hours, which is significantly higher than that of chromium oxide nanoparticles, which reached 85.2% conversion in 36 hours. Cr-MCM-41, obtained by the wet impregnation method, also showed high efficiency - 95% conversion of toluene to benzaldehyde, but it took 36 hours to achieve this result.[36] Among the disadvantages of such catalytic systems are the high concentration of chromium, which can contribute to pore blockage and reduce catalytic activity, and the long reaction time (18 hours) is impractical for industry. In addition, Cr(VI)-based catalysts have limited stability and can leach, posing environmental and toxicological risks.

Zinc oxide (ZnO) nanomaterials are promising due to their high selectivity, stability, low cost, environmental safety, and high excited-state binding energy (60 meV). ZnO can be synthesized in various forms, but doping with transition metal elements allows for adjusting their physical and chemical properties. Carbon nanotubes (CNTs) are often used as a carrier for metal nanoparticles, which enhance their oxidative properties by slowing down electron-hole recombination. However, the complex structure of CNTs makes them difficult to solubilize and uniformly coat with nanoparticles. To overcome these difficulties, Sadiq *et al.* developed a catalyst in the form of zinc-manganese oxide (Zn-Mn) nanoparticles deposited on functionalized multiwalled carbon nanotubes using co-deposition and condensation methods. The developed catalyst allows to achieve the conversion of cinnamic alcohol to cinnamic aldehyde in water at 60 °C the level of 97.2%.[37] However, the use of carbon nanotubes as a carrier has a number of limitations that make it impossible to use them in industry, including poor solubility, difficulties with functionalization, tendency to aggregation, toxicity, and high production costs, which complicates their widespread use.

As an alternative to carbon nanotubes, metal-organic frameworks (MOFs), which combine the characteristics of micro- and mesoporous materials constructed by self-assembly of organic ligands and metal ions, are attracting interest, as heterogeneous catalysts or carriers for a wide range of organic transformations, not only due to the highly ordered arrangement of catalytically active centers, but also because of their advantages in liquid phase separation and recycling. MOFs are a type of coordination polymers that have many advantages, including high specific surface area, high energy capacity, and adjustable pore size.[38]

In their study, Sheng-Chun Chen reported the synthesis of a copper catalyst on a metal-organic framework that can be easily regenerated and reused several times without significant loss of catalytic activity or structural deterioration.[39] Of particular importance in this context is the relatively low thermal and chemical stability of metal-organic frameworks, especially in comparison with inorganic porous solids. MOFs remain very sensitive to moisture and unstable in the open air: they can undergo hydrolysis, amorphization, or phase transformation even at room temperature.

Mesoporous molecular sieves with transition metals integrated into their crystal lattice are of considerable interest due to their catalytic activity in the processes of hydrocarbon oxidation under mild conditions. Due to their special electronic configurations and variable valence state, transition metal oxides, in particular manganese oxides, are known to exhibit high catalytic activity in the selective oxidation of hydrocarbons. Mahdavi and his colleagues synthesized a catalytic system where manganese oxide (MnO) was deposited on mesoporous silica SBA-15. Mn-SBA-15 was synthesized by the controlled atomic layer deposition (ALD) method.[40] This system proved to be an effective catalyst for the oxidation of benzyl alcohol in the liquid phase, providing 70% conversion of benzyl alcohol and 100% selectivity to benzaldehyde. Manganese oxide-based catalysts supported on SBA-15 (Mn-SBA-15) have some limitations that make them less suitable for industrial applications. The atomic layer deposition (ALD) method is expensive and difficult for large-scale production and requires specific aprotic solvents and alkyl peroxides, which are expensive and require special safety measures. In addition, the thermal stability of the catalytically active phase is limited, and there may be a loss of activity with repeated use. Ensuring and maintaining the mesoporous structure of SBA-15 with the required uniformity is a challenge in large-scale production. Although Mn-SBA-15 demonstrates high selectivity in the laboratory, deviations in performance and selectivity are possible in industrial conditions, which increases the risk of by-products and additional purification costs. These factors, together with possible environmental risks, make this catalyst less suitable for industrial use.

Deng and other researchers reported the synthesis of manganese oxide-based octahedral molecular sieves (OMS-2), which exhibit significantly higher catalytic activity in the liquid-phase oxidation of p-chlorotoluene compared to other manganese oxides (MnO_2, Mn_3O_4, $Mn(OAc)_2$), as well as transition metal oxides such as Co_2O_3, V_2O_5 and Fe_2O_3. This catalyst provides 86.0% conversion of p-chlorotoluene and 68.7% selectivity of p-chlorobenzaldehyde formation.[41] OMS-2 is easily recovered by centrifugation and can be reused, and after four reaction cycles, its main characteristics remain stable, as confirmed by X-ray diffraction and N_2 adsorption/desorption analysis. According to the results of temperature-programmed desorption and thermogravimetric analysis, the high catalytic activity of OMS-2 is due to the large amount and mobility of lattice oxygen. Despite their promising activity and selectivity in the laboratory, catalytic systems based on octahedral manganese oxide molecular sieves (OMS-2) have limitations for industrial use. Although OMS-2 can be reused, the stability and durability of these catalysts in industrial conditions remain questionable, as partial loss of activity is possible over time, which increases costs. The proposed free radical mechanism can lead to side reactions, causing the formation of undesirable products, complicating purification. In addition, leaching of manganese ions in the liquid phase is possible, which can contaminate the product and create environmental risks.

Among the various methods of heterogenization of homogeneous catalysts, immobilization on polymeric carriers attracts special attention, as they have a number of advantages over other materials. Insoluble polymers provide easy separation of the catalyst from the reaction mixture, simplifying purification procedures and reducing costs.[42] In addition, they allow the catalyst to be reused without losing its activity, promote the stability of catalytic centers, and provide controlled selectivity in chemical transformations. For example, polymer-supported reagents demonstrate the acceleration of reactions due to the effect of the local concentration of active groups in the polymer matrix, which is an important advantage for organic synthesis, especially in an aqueous environment.

Recently, Masaki *et al.* synthesized polymeric dicyanoctene acetal by copolymerizing monomeric dicyanoketene acetal (DCKA) with ethylene glycol dimethacrylate.[43] The location of the catalytically active DCKA groups in the polymer makes it easier for substrates to interact with the catalyst, which significantly increases the reaction rate, especially in aqueous medium. The aqueous environment promotes the efficient diffusion of lipophilic substrates to the active sites of the polymer and the rapid removal of hydrophilic products, preventing their accumulation. This ensures a continuous reaction, increases its efficiency, and reduces costs due to the repeated use of the catalyst.

Summarizing the above, heterogenization offers several advantages over traditional homogeneous catalysis. Using nanoparticles allows for easy separation from the reaction mixture, making purification simpler and more cost-effective. Carbon nanotubes enhance the oxidative properties of catalysts, while metal-organic frameworks offer high specific surface areas, adjustable pore sizes, and ease of recycling. Polymer-supported catalysts are particularly appealing due to their ability to promote the stability of catalytic centers, provide controlled selectivity in chemical transformations, and accelerate reactions due to the effect of local concentration of active groups in the polymer matrix. This local concentration effect is especially beneficial in aqueous environments, where it facilitates the diffusion of lipophilic substrates to the active sites of the polymer and the rapid removal of hydrophilic products.

The key advantage of polymeric materials is their structural diversity. Depending on the needs, polymers can be crosslinked, branched, or linear. Cross-linked polymers are characterized by their ability to retain active ingredients, such as metal nanoparticles or drugs, for a long time. Polymer gels are networks crosslinked by cross-links that can expand in a compatible solvent.[44] Among polymer gels, those that can swell in water are called hydrogels. The cross-linked polymer structure of gels can be classified into three types: macrogels, which are characterized by a significant cross-linked structure with a diameter of more than 1 micron; microgels, consisting of three-dimensional cross-linked colloidal particles dispersed in a solvent with a diameter of 1 micron to 100 nm; nanogels with a three-dimensional cross-linked structure, whose diameter varies from 1 nm to 100 nm.[45] Microgels and nanogels have advantages over macrogels due to their smaller size and larger surface area. In addition, microgels demonstrate increased adsorption capacity compared to nanogels due to their more developed porous structure and increased specific surface area, which makes them suitable supports for catalyst heterogenization.

3. Microgels as a Promising Supports for Heterogenization of Catalysts

Microgels are unique systems that differ significantly from traditional colloidal structures, such as rigid nanoparticles, micelles, or vesicles. Due to the presence of cross-linking agents, microgels retain their structural integrity, which allows for precise control of their properties, from "colloidal" to "macromolecular". The crosslinked polymer network provides stability of inorganic particles against aggregation and adds stimulus-sensitive functionality to the system. Recently, "smart" microgels have gained significant importance due to their sensitivity to external stimuli such as temperature, pH, and ionic strength.[46–48] Due to these features, microgels are widely used in selective catalysis and nanoreactors and are particularly suited as a support for the heterogenization of catalysts.

The peculiarity of microgels is their ability to maintain stability and swelling in both water and organic solvents, which allows the use of a wide range of chemical methods for modification. This is especially important for creating catalysts with selectively located reactive groups that actively interact with substrates. In addition, their sensitivity to external stimuli (temperature, pH, light, ionic strength) opens up opportunities for tuning physicochemical properties and increasing the efficiency of catalytic processes.

Temperature significantly affects the hydrodynamic radius (HR) of microgels, showing an inverse relationship between temperature and particle size. With increasing temperature, the hydrodynamic radius of microgels decreases, while with decreasing temperature it increases. This phenomenon is explained by changes in the interactions between the polar parts of microgels and water molecules. At low temperatures, these interactions are strong, which contributes to the swelling of microgels. However, as the temperature increases, polar interactions weaken, while hydrophobic interactions increase, leading to the release of water molecules from the microgel structure and its collapse.[49]

This dependence was confirmed by Lu *et al.* who showed that with an increase in temperature from 20 °C to 50 °C, the hydrodynamic radius of microgels decreased from 980 nm to 502 nm. Thus, the temperature sensitivity of microgels allows for the adjustment of their size and properties, which is important for their use in various industries.[50]

Microgels based on poly(N-vinylcaprolactam) (PVCL) have attracted particular attention due to their chemical stability, biocompatibility, and sensitivity to external stimuli. PVCL is a well-studied thermosensitive polymer that is second only to poly(N-isopropyl acrylamide) (PNIPAAm) in terms of its prevalence. Both polymers have a similar lower critical solution temperature (LCST) in water - about 30-32 °C, at which microgels based on them go from swelling to collapse. Aqueous microgels based on PVCL are usually spherical, forming stable dispersions in solution, their key characteristics being crosslinking density and swelling degree.[51,52] Below LCST, microgels swell by absorbing solvent molecules. With increasing temperature, the interaction of the polymer with the solvent weakens, which contributes to the collapse of the structure: the polymer chains come closer together, displacing most of the water from the interchain spaces. PVCL's biocompatibility is an important advantage for its use in biomedical and environmental applications, making microgels based on it promising for creating functional materials in areas such as drug delivery, water purification, and catalytic processes.[53]

The following methods are used to prepare PVCL-based microgels: dispersion polymerization, precipitation polymerization, and reverse microemulsion polymerization. It should be noted that to obtain thermosensitive microgels in an aqueous medium, polymerization must occur at temperatures above the final temperature below the critical solubility. Under such conditions, the water-soluble monomer reacts to form an insoluble polymer at a given polymerization temperature. Emulsion polymerization is a versatile technique that produces particles with a narrow size distribution. It can be carried out both with and without the presence of an added surfactant (emulsion polymerization without surfactant). This method allows to obtain very small microgel particles (*e.g.*, with a particle diameter of less than 150 nm), but it is difficult to completely remove the residual surfactant.[54]

A considerable amount of research has been devoted to the use of microgels as microreactors for the fabrication and stabilization of metal nanoparticles (NPs). As mentioned above, metal nanoparticles have a wide range of applications in various fields, but appropriate stabilization systems are required to maintain their size and stability. Various materials are used to stabilize nanoparticles, such as surfactants, dendrimers, and polymers, including polymeric microgels. Among these stabilizers, polymeric microgels have proven to be extremely effective in providing long-term stability of nanoparticles. Microgels play an important role in improving the performance of metal nanoparticles by ensuring their stability and protection against aggregation. For example, a study by Arif *et al.* demonstrated that aggregation of gold nanoparticles (Au NPs) did not occur in core-shell microgels even after three months, which emphasizes their high stability.[55] Chang *et al.* synthesized Au NPs-based hybrid microgels with a similar structure, which demonstrated higher catalytic activity compared to individual gold nanoparticles.[56] These results indicate that microgels are promising candidates for the production and stabilization of metal nanoparticles in various applications.

In addition to their sensitivity to stimuli, the use of crosslinked PNIPAM microgels as microreactors for embedding various metals (*e.g.*, silver, gold, iron) and semiconductor nanoparticles (quantum dots), creating microgel-nanoparticle hybrids, is of considerable interest. Embedding nanoparticles in microgel matrices can improve their long-term stability. In addition, the optical and catalytic properties of nanoparticles can be modulated by stimulus-sensitive parameters, which opens up numerous applications.[57]

Pany *et al.* have developed a method for the synthesis of silver nanoparticles, PNIPAM-Ag and PNIPAM-co-AAc-Ag hybrids, and their immobilization into a polymerized hydrogel matrix. The catalytic tests in the reduction of 4-nitrophenol to 4-aminophenol showed that the polymerized hydrogel with immobilized anionic hybrid microgels (MG(A)-Ag) demonstrates the highest catalytic activity with a short induction period of 3 minutes, outperforming nanoparticles in suspension.[58] The results indicate that the proposed material can be effectively used as a reusable catalyst with high activity. In addition, the proposed methodology can be adapted to immobilize other nanoparticle hybrids in a hydrogel matrix for a variety of applications. However, for the introduction of this catalyst into the industry, significant improvements are needed to improve stability, reduce sensitivity to conditions, and optimize the synthesis process for large-scale production.

The work of Biffis *et al.* demonstrated the possibility of extending the method of microgel synthesis to stabilize metal nanoclusters and obtain gold (Au) nanoparticles with controlled sizes.[59] The use of vinylpyridine as a functional monomer allowed to obtain small Au nanoclusters with a narrow size distribution, which showed high catalytic activity in the reactions of aerobic oxidation of primary and secondary alcohols in an aqueous medium. It was found that the catalytic activity depends on the open surface of the nanoparticles and the affinity of the substrate for the aqueous medium. For secondary alcohols, the reaction was completely selective to ketones, while for primary alcohols, carboxylic acids were formed, sometimes with a small yield of esters, due to the more efficient oxidation of hydrated aldehydes in water using gold catalysts. However, the synthesis process of this catalyst is complex and requires precise control of nanoparticle size, which increases the cost of scaling up and complicates production. In addition, the activity of the catalyst depends on the affinity of the substrate for the aqueous medium, which limits the versatility of its use for various chemical reactions. In addition, in the case of primary alcohols, the formation of by-products such as esters may require additional purification steps, increasing the cost of the process. The catalyst's service life and stability in long cycles also remain poorly understood.

In the study by Jiang *et al.* a glucose detection system based on Fe/GOx microgel with a stable cascade channel for intermediates was developed, which provides accurate and sensitive analysis.[60] The microgel with coordination of iron (Fe) and glucose oxidase (GOx) formed a tubular structure through the use of acrylamide, acrylic acid, and chitosan, which provided a high specific surface area and stability in the aqueous medium. This tubular channel improves the transport of H_2O_2 and the efficiency of catalysis *via* the Fenton reaction. The system demonstrates high activity, reusability, and stability after five catalytic cycles. The Fe/GOx microgel can be used to detect free radicals using light and electrochemical signals, opening up new prospects for an accurate biosensor in medical diagnostics. However, despite the high sensitivity in the detection of glucose, performance may be limited in the oxidation reactions of other substrates due to the specificity of the structure and mechanism of H_2O_2 transport. The tubular structure provides stability in aqueous medium, but its efficiency may decrease in other solvents. Creating a microgel with iron coordination is a complex and resource-intensive process, which makes it difficult to scale up for industrial use.

In the work of Ma *et al.* hydrophobically modified chitosan microgels (h-CSMs) with different crosslinking densities were developed using sodium phytate as a crosslinking agent.[61] A detailed study of the influence of crosslinking density on their rheological properties, adsorption kinetics, viscoelasticity, and behavior at the interface between organic and aqueous phases was carried out. It has been found that with an increase in the crosslinking density, microgels transition from a polymer-like state to ultra-soft structures with an increased elastic modulus. This property makes it possible to form stable interface layers with a high modulus of viscoelasticity due to the interaction between the microgel nuclei, which helps to reduce interfacial tension and increase the efficiency of emulsification and catalytic processes. The use of sodium phytate ensured uniform particle size, improved rheological characteristics, and opened up opportunities for controlling properties by adjusting the crosslinking density. However, despite their unique properties, the developed microgels face several limitations that complicate their implementation in the industry. Among the main drawbacks is the complexity of synthesis, especially ensuring a homogeneous particle structure on a large scale, as well as the high cost of production due to the use of specialized components such as sodium phytate. In addition, their dependence on external conditions such as pH and temperature limits their stability and versatility in industrial applications. The lack of scalability of the synthesis methods also makes it difficult to produce in the volumes required for commercial use. Therefore, although these microgels show high potential for applications in emulsifiers, catalytic systems, and controlled release of active substances, further research should focus on reducing the cost of synthesis, improving material stability, and developing scalable technologies that would allow the introduction of these materials into industrial processes.

4. Organoselenium Catalysts

While there are numerous effective oxidation methods, most of them have significant drawbacks. Many of these methods require stoichiometric amounts of toxic, hazardous, or expensive oxidants (such as potassium permanganate, chromates, and chlorites) and organic solvents (such as benzene, formic acid, and methylene chloride), which creates significant environmental and safety concerns.

Hydrogen peroxide is an environmentally friendly alternative, as it produces only water and oxygen when it decomposes. It is commercially available, inexpensive, easy to use, and has a high content of active oxygen.[62] However, even though the oxidation of organic substrates with H_2O_2 as the final oxidant is usually thermodynamically advantageous, the insufficient reaction rate limits its practical use. To solve this problem, hydrogen peroxide-activating catalysts are used to provide the required rate of the targeted transformation. Efficient activation of H_2O_2 is often achieved through the use of metal-based catalysts such as vanadium, titanium, molybdenum, and others.[63]

Organoselenium compounds act as an alternative to metal-based catalysts for the catalytic activation of peroxides in oxidation reactions.[64,65] Organoselenium compounds are extremely important and valuable reagents in synthetic chemistry due to their widespread use in organic synthesis. Due to the unique chemical properties of selenium, organoselenium catalysis has attracted considerable attention as a potential alternative to reactions catalyzed by transition metals. In addition, selenium is much cheaper than noble metals, has a high abundance, is easily transported, and can be stored for a long time without changing its chemical properties. Organoselenium catalysts are used in mild and neutral conditions using environmentally friendly methods that do not require ligands or additives. Thus, research in the field of organoselenium catalysis opens up new opportunities for the development of innovative environmentally friendly synthesis methods with industrial potential.

Selenium compounds, particularly diselenides, are effective catalysts in oxidation reactions with peroxides due to their ability to form selenic and perselenic acids. Perselenic acid, produced by the reaction of diselenides with H_2O_2, acts as a powerful oxygen transfer agent, making it a key component in oxidation processes (Fig. 2). The activity of diselenides depends on the structure of substituents: coordination groups (amines, alcohols, amides) and longer carbon chains significantly enhance their catalytic efficiency.

Glutathione peroxidase (GPx), a natural enzyme with a selenol group in its active site, catalyzes the breakdown of peroxides into water or alcohols through a redox cycle involving selenium (II) and (IV) states (Fig. 3a). This mechanism has inspired the development of synthetic GPx mimetics (Fig. 3b), such as ebselen, which exhibits high activity in thiol oxidation and protection against oxidative stress. Thus, synthetic organoselenium compounds hold great promise for applications in chemistry and biomedicine.[66–69]

Over the past decades, diselenide-based reagents together with H_2O_2 have successfully proven to be efficient and practical catalysts in many useful transformations, such as the dehydration of aldoximes to nitriles, oxidation of isatin, epoxidation of alkenes, Bayer-Williger oxidation of α,β-unsaturated ketones to vinyl esters, oxidation of amines, and dihydroxylation of cyclohexene to trans-1,2-cyclohexanediol. These processes are characterized by mild reaction conditions, high tolerance to various functional groups, and excellent regioselectivity.

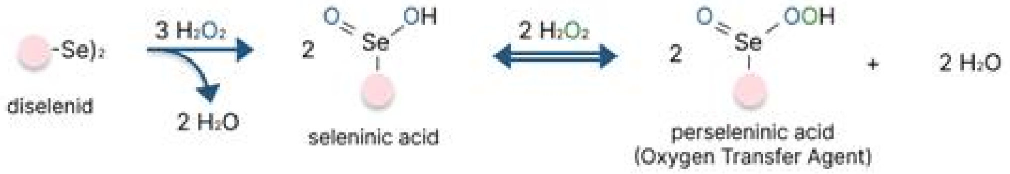

Fig. 2. Preparation of perseleninic acid by reaction of diselenide with H_2O_2

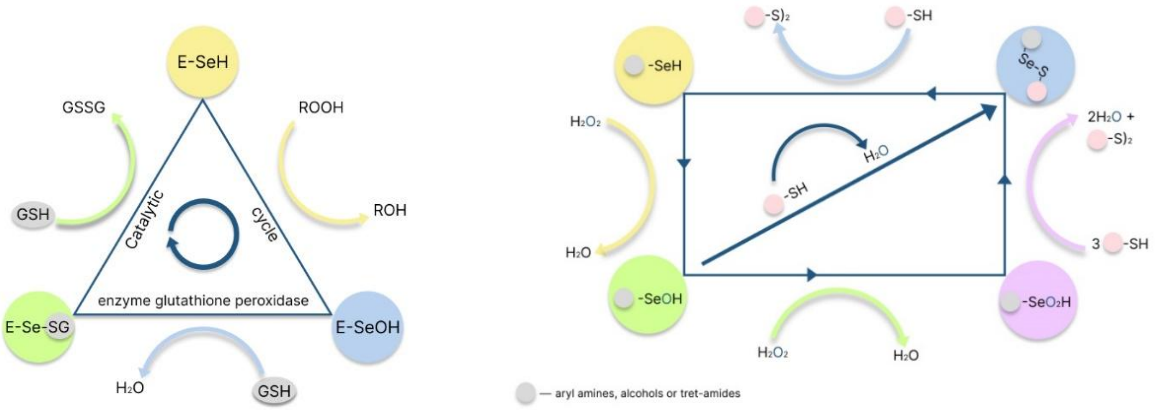

Fig. 3. a) Catalytic cycle of the glutathione peroxidase, b) Catalytic cycle of the glutathione peroxidase mimetics

Methylselenic acid, benzoselenic acid, phenylselenol, and diphenyl diselenide were investigated as catalysts for the oxidation of acrolein with hydrogen peroxide.[70] All catalysts showed activity in the oxidation reaction. The most effective catalyst for the synthesis of acrylic acid is diphenyl diselenide, which achieved a 69 % yield of acrylic acid, and benzoselenic acid for methyl acrylate. It was found that the concentration of hydrogen peroxide (water content) affects the ratio of products (acid/ester), *i.e*., a higher water content leads to an increase in acid yield. However, a lower water content results in a higher methyl acrylate yield as well as a higher overall rate of product formation. Thus, the ratio of products can be controlled by the water content of the reaction mixture. Diphenyl diselenide was also found to be active in the oxidation of other aldehydes, namely methacrolein and crotonic aldehyde, but the yields of methacrylic and crotonic acids were lower than acrylic acid.

Rangraz *et al*. have developed a heterogenenized organoselenium catalyst based on Fe_3O_4 magnetic nanoparticles, which is used for the oxidation of aldehydes to carboxylic acids under mild conditions with hydrogen peroxide as an environmentally friendly and inexpensive oxidant.[71] The developed catalyst allows for achieving a 99 % yield of benzaldehyde oxidation products with hydrogen peroxide. Reusability tests have shown that the organoselenium catalyst immobilized on Fe_3O_4 can be recycled and reused at least four times without significant loss of catalytic activity. In addition, the ease of recovery and high reuse efficiency of the catalyst, as well as the use of inexpensive selenium, make this method economically viable.

To effectively mimic the protein structure, a three-dimensional (3D) porous structure is required to provide anchorage for the active Se groups and create a partitioned environment to facilitate the diffusion of reagents necessary for catalytic reactions. Several polymeric structures containing selenium have been discussed in the literature, including supramolecular micelles, dendrimers, hyperbranched polymers, and nanogels. However, most of the developed systems utilize the redox properties of the selenium atom for drug delivery. The use of functional polymeric structures with selenium modifications as bioinspired catalysts is still insufficiently explored.[72]

The introduction of Se-containing functional groups into the structure of a microgel based on poly(N-vinylcaprolactam) is a promising approach to the creation of effective catalysts suitable for the low-temperature synthesis of unsaturated carboxylic acids by oxidation of the corresponding unsaturated aldehydes. This approach also provides the possibility of catalyst isolation and reuse.

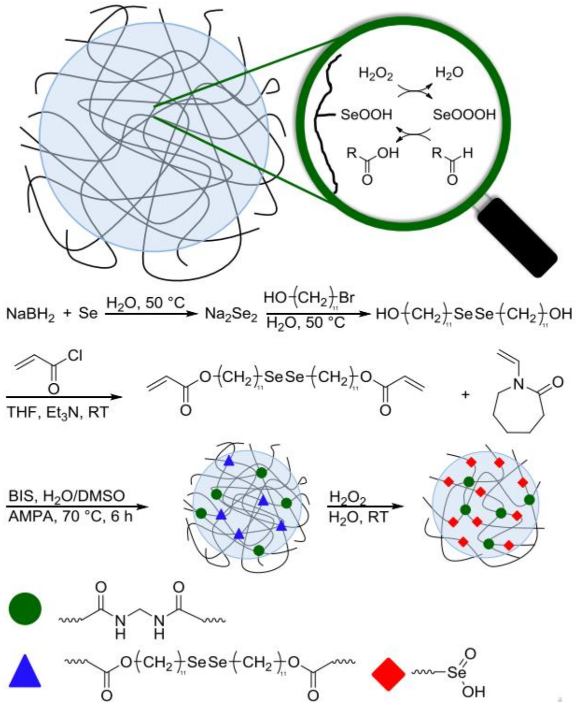

Fig. 4. Selenium-modified microgels as a catalyst for aldehyde oxidation were obtained by synthetic routes of creating a diselenide crosslinker (Se Xlinker) and introducing Se Xlinker into PVCL microgels simultaneously with BIS as a permanent crosslinker. The microgels can be oxidized by H_2O_2, resulting in the conversion of diselenide groups into selenic acid groups. Adapted under permission from the literature.[73]

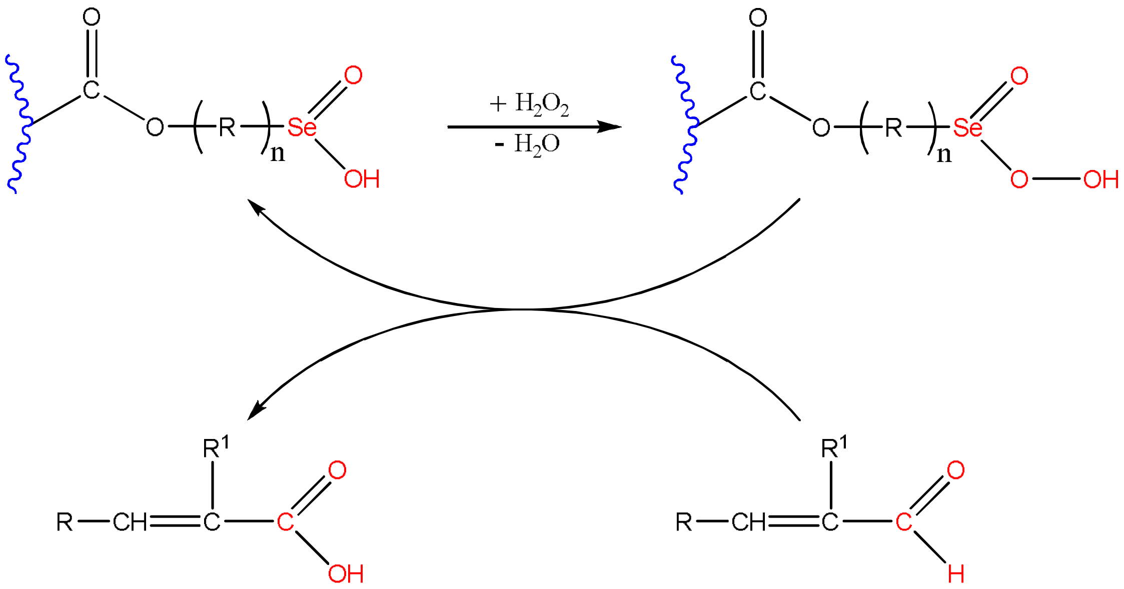

Fig. 5. Model oxidation reaction catalysed by Se-modified microgel

In their study, Tan *et al.* utilized the microenvironment created by the three-dimensional polymeric mesh structure of PVCL-based microgels to introduce selenium functional groups as catalytic centers to achieve GPx-like activity.[73] For this purpose, a three-step synthesis was carried out to obtain a diselenide crosslinker (Fig. 4). The diselenide crosslinker was then integrated into PVCL microgels using conventional precipitation polymerization together with a permanent crosslinker (BIS). After breaking the diselenide bonds under the action of H_2O_2, selenic acid-modified microgels were obtained (Fig. 4). In the model reaction of the oxidation of acrolein to acrylic acid (Fig. 5), the developed catalyst ensures the yield of acrylic acid at the level of 79.1%. It was found that the samples of B1.5 Se1.0 and B1.5 Se2.0 microgels show exceptional catalytic activity compared to the diselenide crosslinker, which indicates the potential use of selenium-modified PVCL microgels as effective catalysts for various oxidation processes.[74] The synthesized selenium-modified microgels are capable of catalyzing oxidation reactions with high activity and selectivity at moderate temperatures, which can significantly reduce energy consumption in technological processes.

Moreover, compared to homogeneous selenium catalysts such as diphenyl diselenide, bis(11-acryloxyundecyl) diselenide, and selenous acid, the heterogenized Se-microgel catalysts demonstrate higher activity in acrolein oxidation reaction in methanol (Fig. 6), which, along with the ease of separation and reuse, makes them perspective for industrial application.

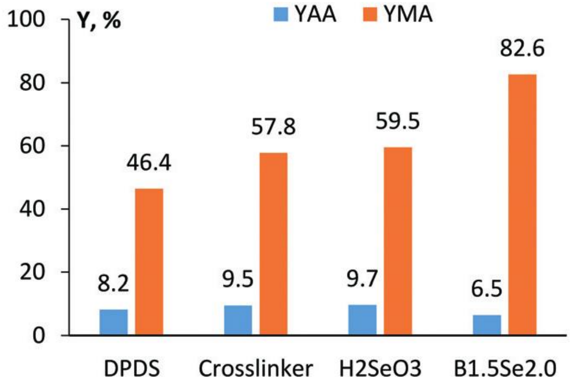

Fig. 6. Comparison of the activity of the different Se-catalysts in acrolein oxidation. YAA and YMA – yields of acrylic acid and methyl acrylate respectively, DPDS – diphenyl diselenide, Crosslinker – bis(11-acryloxyundecyl) diselenide, H_2SeO_3 – selenous acid, B1.5Se2.0 – heterogenized Se-modified microgel. Adapted under permission from the literature.[74]

5. Conclusions and Perspectives

Heterogenization of catalysts has emerged as a crucial strategy in modern catalysis, offering numerous advantages over homogeneous systems. Immobilizing catalysts onto solid supports not only facilitates their separation and reuse but also enhances their stability and allows for fine-tuning of their properties. This approach has paved the way for the development of more efficient, environmentally friendly, and sustainable catalytic processes. The use of solid supports, such as metal oxides, zeolites, and polymers, has enabled the development of robust and reusable catalysts, reducing waste generation and minimizing environmental impact.

Microgels, with their unique combination of properties, are a promising platform for catalyst heterogenization. These crosslinked polymer networks exhibit tunable size, porosity, and responsiveness to external stimuli, making them ideal for encapsulating and stabilizing catalytic species. The porous nature of microgels allows for efficient diffusion of reactants and products, while their responsiveness to external stimuli enables controlled release and activity modulation. The integration of Se-containing functional groups into the microgel structure further enhances their catalytic potential. The redox properties of selenium, as observed in the glutathione peroxidase enzyme, can be harnessed to catalyze oxidation reactions. This bioinspired approach not only offers a novel route for catalyst design but also contributes to the development of environmentally friendly and efficient processes.

Future research should focus on exploring the synthesis and characterization of Se-modified functional microgels with varying crosslinking densities and Se-containing functionalities. Investigating the catalytic activity of these microgels in various oxidation reactions, including the synthesis of unsaturated carboxylic acids, is crucial. Optimizing the reaction conditions, such as temperature, pH, and solvent selection, will be essential for maximizing catalytic efficiency and selectivity.

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ДОСЯГНЕННЯ В ГЕТЕРОГЕНІЗАЦІЇ КАТАЛІЗАТОРІВ ТОНКОГО ОРГАНІЧНОГО СИНТЕЗУ КАТАЛІТИЧНИМ ОКИСНЕННЯМ У РІДКОМУ СЕРЕДОВИЩІ: ОГЛЯД

Анотація. *Гетерогенізація каталізаторів має численні переваги порівняно з гомогенними системами, зокрема підвищену стабільність, можливість багаторазового використання та тонкого налаштування властивостей. Цей підхід є особливо актуальним для розробки екологічно чистих і сталих каталітичних процесів. Мікрогелі з їхніми унікальними властивостями є перспективними платформами для гетерогенізації каталізаторів. Ці зшиті полімерні мережі демонструють регульований розмір, пористість і чутливість до зовнішніх стимулів, що робить їх ідеальними для інкапсуляції та стабілізації каталізаторів. Інтеграція Se-вмісних функціональних груп у структуру мікрогелю ще більше підвищує їхній каталітичний потенціал, використовуючи окисно-відновні властивості селену для реакцій окиснення. Цей біологічно натхненний підхід пропонує новий шлях для дизайну каталізаторів і сприяє розвитку екологічно чистих та ефективних процесів.*

Ключові слова: *каталіз, гетерогенізація, гетерогенні каталізатори, мікрогелеві каталізатори, окиснення.*