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Substrate Selectivity Imparted by Self-Assembled Molecular Containers and Catalysts

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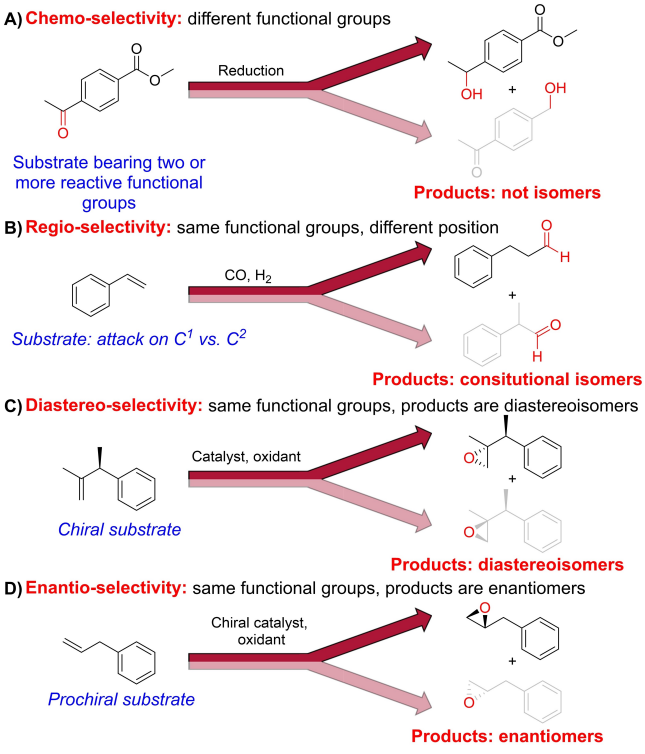
Recent trends in catalysis are devoted to mimicking some peculiar features of enzymes like site selectivity, through functional group recognition, and substrate selectivity, through recognition of the entire surface of the substrate. The latter is a specific feature of enzymes that is seldomly present in homogeneous catalysis. Supramolecular catalysis, thanks to the self-assembly of simple subunits, enables the creation of cavities and surfaces whose confinement effects drive the preferential binding of a substrate among others with consequent substrate selectivity. The topic is an emerging field that exploits recognition phenomena to discriminate the reagents based on their size and shape. This review deals this cutting-edge field of research covering examples of supramolecular self-assembled molecular containers and catalysts operating in organic as well as aqueous media, with special emphasis for catalytic systems dealing with direct competitive experiments involving two or more substrates.

1. Introduction

Selectivity in chemical reactions is considered extremely important, sometimes even more important than substrate conversion since possible substrate recycling ensures overall sufficient product yield. Several are the examples of large scale industrial chemical processes operating under such conditions. For instance, ethylene oxide can be produced by oxidation of ethylene using Ag on ultrapure Al_2O_3 as heterogeneous catalyst with substrate conversion of 7–15% and 80–90% selectivity for the desired epoxide.[1] Similarly, in the Alphabutol® process[2] the dimerization of ethylene to 1-butene is carried out at 50–55 °C and 25 bar using Ziegler-Natta Ti(IV) catalysts with $Al(Et)_3$ as co-catalyst with ethylene conversion of about 50% and 95% selectivity towards 1-butene. A further example is the dehydrogenation of C_6-C_{19} alkanes to the corresponding alkenes in the Pacol-Olex process[3] using fixed bed Pt catalyst on Al_2O_3 at 400–600 °C and 3 bar with conversion as low as 10% obtaining 96% by weight of the corresponding mono-alkenes. As a consequence, catalysts are developed with the aim to largely decrease the activation energy for a specific reaction pathway favoring a certain desired product and, at the same time, avoiding as much as possible by-products formation whose activation energy barriers should remain high. Selectivity is in fact largely considered as preferential formation of the desired product over the other possible ones.

Looking at the right side of a chemical reaction involving a catalyst, the latter is considered chemo-selective if it ensures proper functionalization of one out of two or more functional groups (Scheme 1A). Moreover, a reaction whose product can further react could lead to decreased chemo-selectivity; it is more difficult to selectively stop the reaction to intermediate products like in the oxidation of alcohols to aldehydes avoiding over-oxidation to carboxylic acids, or in the semi-hydrogenation of alkynes to alkenes avoiding alkanes.

A further level of product selectivity is considered when the direction of bond making or breaking occurs preferentially over all other possible directions. In this case the reaction leads to the formation of the same final functional group but installed into different positions of the original moiety. As an example, hydroformylation of terminal alkenes provides linear aldehyde if the reaction occurs on C^1 or branched aldehydes if it takes place on C^2 (Scheme 1B). A further level of selectivity is observed for reactions that provide the same functional group in the same position of the molecule but with different spatial arrangement, which means different stereoisomers. For instance the oxidation reaction on the alkene present on a chiral substrate leads to the formation of diastereoisomers due to the creation of a new stereocenter, properly describing the reaction as diastereoselective (Scheme 1C). A more specific example of stereoselective reactions, specifically called enantioselective, occurs for prochiral substrates in the presence of chiral catalyst leading to the



Scheme 1. Examples of product selectivity typical of homogeneous catalysis; A) chemo-selectivity, B) regio-selectivity, C) diastereo-selectivity, D) enantio-selectivity. Dark red and light red arrows represent reactions leading to higher selectivity/high yield and lower selectivity/low yield, respectively.

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preferential formation of one enantiomer over the other (Scheme 1D).

In all the above reported examples, two important aspects need to be underlined: i) selectivity is imparted frequently by repulsive steric interactions and/or weak attractive intermolecular interactions between the catalyst and the substrate requiring a close proximity between the two species in the rate determining step of the reaction, ii) the surface contact area between catalyst and substrate is limited to a portion of the reagent. In particular, the latter aspect is rather different to what occurs in enzymes.

In the natural catalysts the real catalytic event that dictates the rate of the reaction and consequently the product selectivity is preceded by a supramolecular recognition event in which the substrate is bound with the active site of the enzyme, matching in size, shape, and weak attractive interactions. The specific orientation ensures the occurrence of the reaction on a specific portion of the substrate. This leads to site selectivity properties of enzymes which is an example of the ability to differentiate among reaction sites having in common the same kind of functional group.[4] Frequently, site selectivity and regioselectivity are interchangeably defined in synthetic organic chemistry. For instance, the oxidation of squalene to form squalene oxide by the enzyme squalene monooxygenase occurs exclusively on the terminal double bond among three possible trisubstituted alkene moieties present in the molecule. Another impressive example is the site selective oxidation of cholic acid catalyzed by 12a-hydroxysteroid dehydrogenase with selective formation of the 12-keto product by oxidation of the sterically most hindered secondary alcohol, a result that is not possible using chemical reagents unless through complicate protection-deprotection steps. With the advent of directed evolution, it is possible to engineer existing enzymes with enhanced site-selectivity to suit the needs of organic chemists.[5] Site-selectivity has also been explored with man-made catalysts, for instance for Pd mediated C–H bond functionalization.[6] In particular three approaches are possible, for instance with the use of directing groups present on the substrate, exploiting specific electronically activated positions on the substrates, or through a catalyst-based control. A very interesting example of

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site selectivity in the acetonylation of base-unpaired guanosines in oligonucleotides[7] was recently reported mediated by rhodium(I)-carbene catalysis.

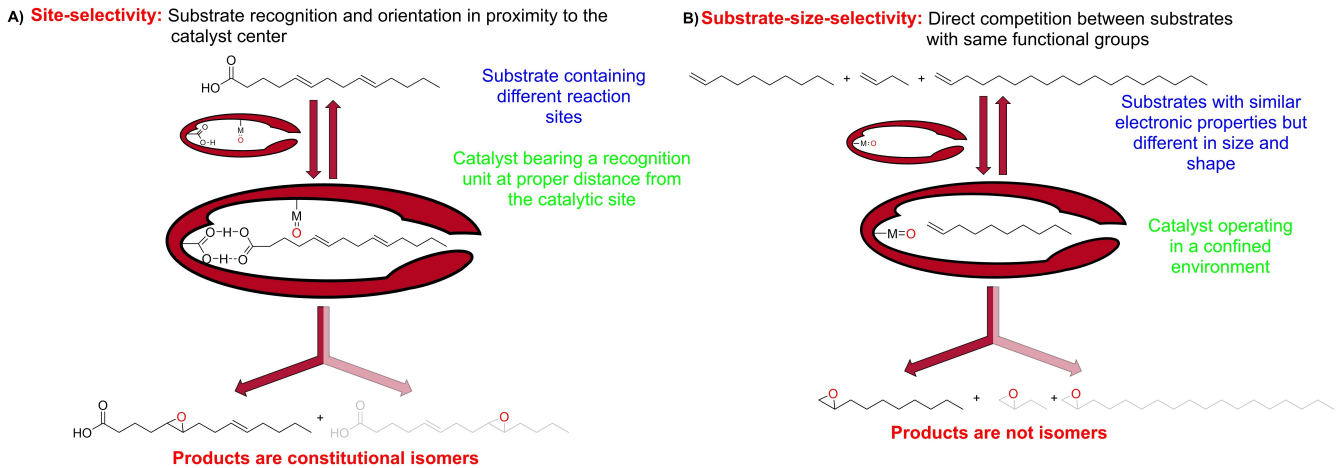
With the aim of achieving site selectivity properties, a common approach consists in the proper design of known catalysts endowed with recognition units. Upon binding of the substrate, one specific portion of the latter is juxtaposed in front of the reactive center. Examples of this approach are most frequently based on completely covalent catalysts. Worth to mention are the site-selective C–H oxidation catalysts developed by Di Olivo, Di Stefano and Costas[8] and more recently by Tiefenbacher[9] in which substrate recognition and positioning occurs via binding of an ammonium terminal unit with crown ethers or cucurbiturils, respectively. Examples of specific site selectivity are interpreted as the consequence of the space and the environment inside the nanometric container. This class of site-specific reactions driven by binding within unimolecular open ended molecular containers or self-assembled capsules has been recently clearly reviewed.[10] An important achievement in the field is for instance the site-selective reduction of a polyenol by a Rh(I) catalyst when operating within the metal-ligand tetrahedral coordination capsule developed by Bergman, Raymond and Toste, while in the absence of the host the fully hydrogenated product was observed.[11] Another outstanding example disclosed by Fujita is the functionalization of linear diterpenoids through U-shaped folding in a confined metal-ligand octahedral coordination cage. The molecular container leads to protection of the central double bond and steers the electrophilic addition or epoxidation exclusively on the terminal one.[12]

Another kind of selectivity of typical of enzymes but seldomly present, or sought, in man-made catalysts is the ability to select one reagent among many others present in the cellular medium (Scheme 2).

Substrate selectivity is variable among enzymes. Some are substrate specific like urease, lactase, glucokinase and do not convert any other substrate containing similar functional groups. Others show relative[13] or broad substrate selectivity with different degrees of efficiency towards non-native substrates.[14] Examples of substrate selectivity in enzymes are countless[15] and this property is frequently analyzed by comparing the Michaelis-Menten constant K_M values for different substrates. Indeed, substrate binding by the enzymes is a key prerequisite for substrate selectivity. This was recently demonstrated for the acylation reaction carried out by *N*-myristoyltransferases. For this enzyme, k_{cat}/K_M values are similar for acetylation with Acetyl-CoA and myristylation with myristyl-CoA, indicating that the rates of the reactions are similar at very low concentration of the substrates, when the enzyme is mostly in the unbound state. On the other hand, the specificity of the enzyme for the transfer of the myristyl moiety becomes evident in competitive experiment, where the K_M (dissociation constant) for myristyl-CoA is four order of magnitude smaller than for acetyl-CoA and the reaction rate was proportionally larger.[16]

It is important to mention that many chiral man-made catalysts can operate like enzymes when considering kinetic resolution of racemic mixtures. In such substrate selective reactions, the two competitive substrates are enantiomers and the chirality of the catalyst, or the enzyme, selectively promotes the favorable conversion into product of one of the two mirror image substrates. In this case the selectivity is directly dictated by matching and mismatching of the stereochemical properties of the two enantiomeric substrates in close proximity with the chiral catalytically active center.

Substrate selection involving size and shape selectivity is more commonly encountered in heterogeneous catalysts, in particular for systems with well-defined cavities[17] such as zeolites[18] or MOFs,[19] while common homogeneous catalysts are generally less selective in competitive experiments using very similar substrates. Examples of substrate selectivity displayed by homogeneous catalysts are still few, frequently based on combinations of substrates in which one among the others is endowed with a specific unit or functional group that is recognized by the catalyst. Worth of mention examples of unimolecular catalysts are the seminal work of Breslow[20] in which coordination of the preferred substrate on a metal center



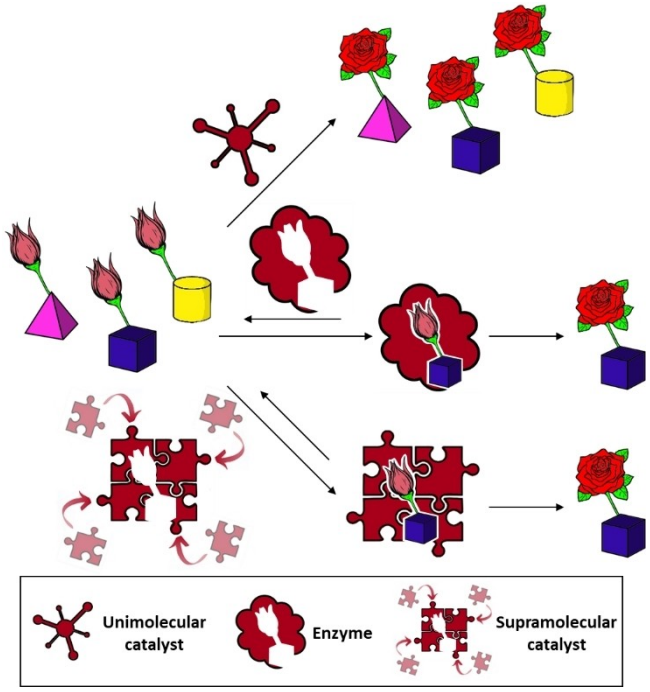
Scheme 2. A) Example of site-selectivity for substrates endowed with recognition units; B) examples of substrate-selectivity among reagents with similar electronic properties but different size and shape.

is the driving force for the substrate selectivity observed. In a recent contribution by Olivo, Di Stefano and Costas the recognition occurs between an ammonium terminal portion of the substrate and a crown ether side chain of the catalyst.[21] Other examples based on ionic interactions with charged substrates are the azide-alkyne cycloaddition[22] mediated by gold nanoparticles endowed with positively charged thiols, or the self-assembled $M_{12}L_{24}$ nanosphere developed by Reek and collaborators, bearing guanidinium units to bind anionic substrates.[23]

Moreover, substrate selectivity is in fact not much considered in catalysis because reagents are frequently very pure, and impurities are different compared to the substrate with respect to functional group composition. In order to observe high substrate selectivity, catalysts need to be endowed with substrate recognition features. The subject started to raise interest with the development of supramolecular catalysis and the implementation of some substrate recognition units in proximity to the catalytic systems. Substrate selectivity can vary considerably depending on the specific size and shape of the competing substrates under investigation. In particular, one difficult substrate selectivity to achieve is between substrates with basically identical electronic and steric properties in close proximity to the functional group that is transformed in the catalytic reaction, but that differ in size and shape in the rest of the molecular structure far away from the point where the reaction takes place.[24] In order to achieve this target, the catalyst needs to completely solvate the substrates to be able to show a certain level of substrate selectivity. This requires complex and extended molecular structures to ensure substrate recognition, which means time consuming synthesis of elaborate promoters. To avoid this drawback and ensure a large contact surface with the substrate, self-assembled supramolecular catalysts[25,26] have also been investigated. Several examples of supramolecular catalysts[27,28,29,30] have been introduced in the recent years[31,32,33] where the catalytic host is designed to bind substrates and accelerate reactions with positive effects on selectivity thanks to confinement effects.[34,35,36,37] The supramolecular interaction between simple and available subunits leads to the formation of well-defined cavities, which are able to activate substrates and stabilize intermediate species through weak non-covalent interactions.[38] While product selectivity has been one of the main targets of supramolecular catalysis, the investigation of the substrate selectivity properties of self-assembled catalysts is still an under investigated field of research.

The present review[39] aims at underlying the achievements in substrate selectivity catalyzed reactions focusing the examples to systems in which the true catalytic unit operates within self-assembled confined spaces[34–37] (Scheme 3) and preferentially discussing direct competitive experiments.[40,41]

The choice to focus on this class of self-assembled nanocontainers and catalysts is related to the generally high synthetic effort that is instead requested for the preparation of fully covalent confined catalysts. Moreover, self-assembly provides a wide range of defined nano-environments, some of which are also well investigated in terms of molecular



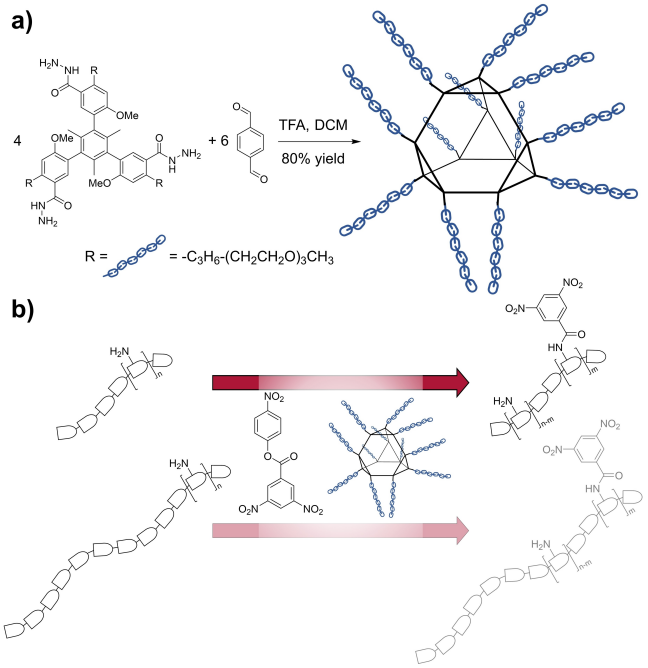
Scheme 3. Substrate selectivity in competitive reactions performed by traditional homogeneous unimolecular catalysts, enzymes, and self-assembled supramolecular catalysts.

recognition phenomena, that facilitate their employment in substrate selective catalysis. The literature covered is mainly related to the last ten years, with a major classification based on the reaction medium: either in organic media with examples of dynamic covalent assemblies, H-bonded and metal-ligand coordination cages,[42] or in water with examples related to metal-ligand capsules and micelles made by surfactants units self-assembled through the hydrophobic effect.

2. Substrate Selectivity in Organic Media

2.1. Dynamic Covalent Nanoreactor

Self-assembly of nanocatalysts can be achieved through the formation of typical dynamic covalent bonds. A very interesting example has been reported based on a self-assembled supramolecular hydrazone-linked tetrahedral organocatalyst bearing triglyme catalytic functional groups. The organocatalyst demonstrated size-selectivity applied to post-synthetic functionalization of polydisperse mixtures of amine-functionalized poly(isobutylene-alt-*n*-octyl maleamide) (Scheme 4).[43] Thanks to the presence of fixed openings, the well-defined cavity of the organocatalyst acted as size selector, allowing preferential accommodation of shorter oligomers. The supramolecular catalyst was crucial to unfold the polymer aggregates enabling the selective functionalization of shorter oligomers through reaction of the amino groups with the active esters to form the corresponding amide derivatives. It is also very important to underline that control experiments carried out with molecules



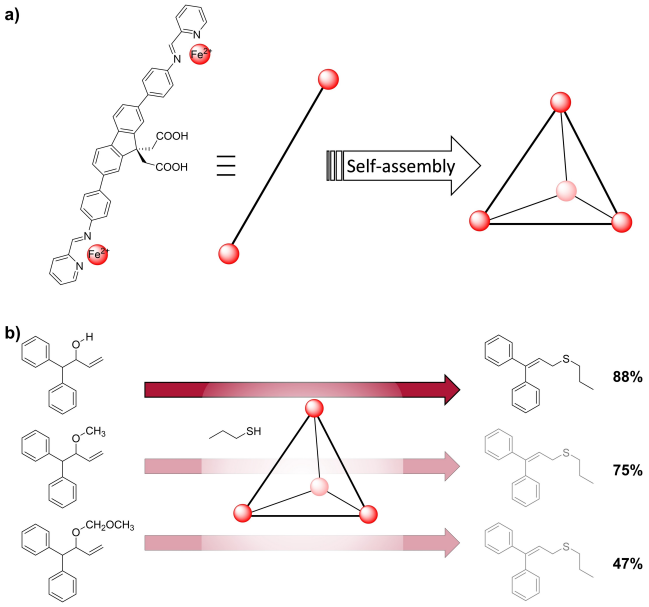
Scheme 4. Supramolecular hydrazone-based tetrahedral organocatalyst bearing triglyme catalytic units (a) and its application towards size-selective preferential functionalization of shorter polymers via amide bond formation of side chain amino groups (b).

resembling one edge of the tetrahedron did not perform nearly as efficiently as the full tetrahedron, demonstrating the importance of the cavity of the supramolecular catalyst with the role to unfold and allow threading of the polymer thus favoring the close proximity of the amino groups of the polymer to the catalytic triglyme units on the tetrahedron. Although the longer chains of the polymer bonded better than the shorter ones, the second uncoiled faster, leading to a kinetic size selection of the substrate from the complex mixture. This approach opened new pathways, in which the presence of a tunable catalyst that displays size-selectivity is crucial to achieve selective functionalization of molecules, as the selective polymers obtained in this example.

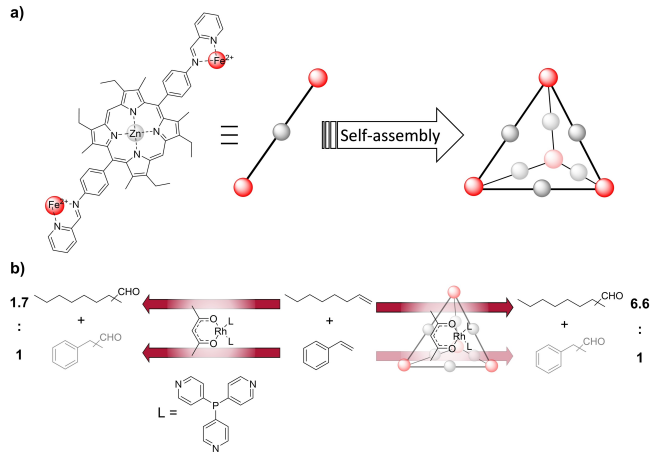
2.2. Coordination cages

Metallosupramolecular architectures represent a large family of structures characterized by well-defined sizes, shapes, and volumes. They have been exploited for many applications such as catalysis, acting as synthetic machinery,[44] as well to mimic properties of biological enzymes.[45] Focusing on direct competitive experiments between very similar substrates bearing the same functional groups, one interesting example involving metal-ligand capsules operating in organic solvent has been reported, based on a self-assembled tetrahedral Fe_4L_6 cage bearing inwardly oriented carboxylic acid functions. The acidic functionalities promoted a variety of acid-mediated dissociative nucleophilic substitution reactions in acetonitrile, proceeding via oxocarbenium ion or carbocation intermediates. The recognition properties of the cavity in which the catalytic functions were present led to marked differences in terms of activity and substrate selectivity with respect to analogous free carboxylic acid surrogates (Scheme 5).[46] It is also interesting to note that small electrophiles showed low reactivity and minimal size selectivity, while optimally sized substrates showed a large, up to 1000-fold, rate increase with respect to control experiments with acid surrogates, displaying also much better substrate selectivity in the thioetherification reaction of vinyldiphenylmethanol. Specifically, for the reaction reported in Scheme 5b, while the supramolecular catalyst favored the conversion of the smaller substrates into products, when simple camphor sulfonic acid was employed the yields were in the opposite order (82%, >98% and >98% respectively for the products in increasing order of molecular weight).

The supramolecular assemblies can operate also as nanoreactors in which a common metal catalyst can be embedded to impart substrate selectivity properties. In an interesting recent work, Reek and collaborators presented the first example of size-selective hydroformylation of terminal alkenes exploiting a rhodium complex encapsulated in a metal-organic cage operating in acetonitrile. The catalyst was bound to the cage exploiting the interactions of the *tris*-pyridylphosphine ligands coordinated to the rhodium center with the zinc(II)-porphyrin complexes that constitute the framework of the supramolecular self-assembly (Scheme 6a).[47] The metal-ligand cage operated as a second coordination sphere for the catalyst, steering substrate selectivity. The gap on the walls of the cage decreases upon binding of the catalytically active species (from 7.9 Å to 5.0 Å), affording the crucial effect of a slower diffusion of larger substrates into the cage. Therefore, the encapsulated catalyst displayed clear preference for smaller substrates, leading to



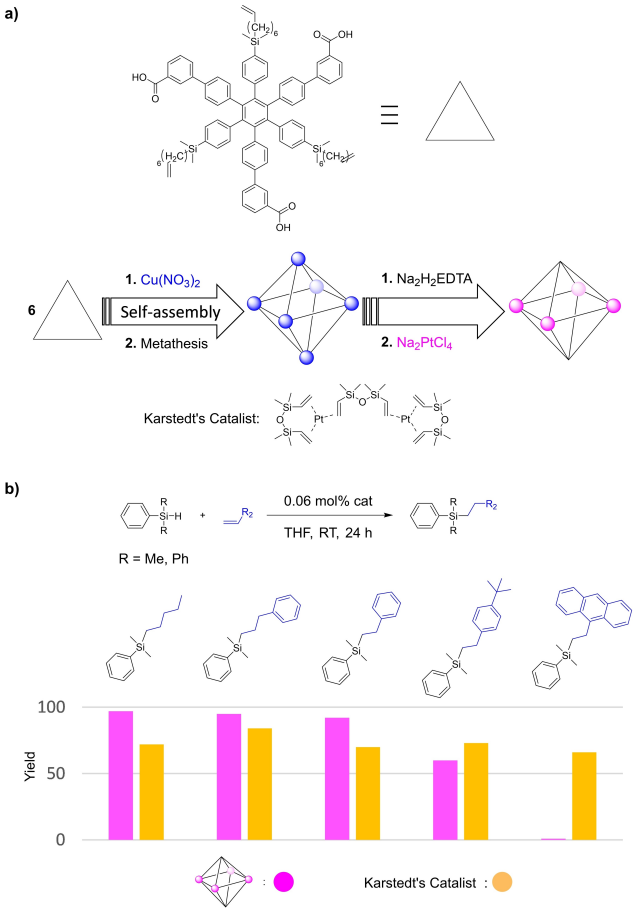
Scheme 5. Tetrahedral Fe(II) metallo-organic cage bearing inwardly oriented catalytic carboxylic acid units (a) and substrate selective thioetherification reaction of vinyldiphenylmethanol derivatives favoring smaller substrates (b).



Scheme 6. Tetrahedral metallocage bearing porphyrin units for binding of a Rh(I) catalyst within the supramolecular assembly (a) and its application in the competitive selective hydroformylation of 1-octene over vinylbenzene, while the Rh(I) catalyst showed only modest substrate selectivity in the absence of metallocage assembly (b).

selectivity that was not observed in bulk tests without metal-organic framework to act as host. In competitive experiments between 1-octene and vinyl-benzene, the free Rh(I) catalyst showed a 1.7:1 preference for the aliphatic alkene while the nested catalyst improved the substrate selectivity for the same substrate up to 6.6:1 (Scheme 6b).

Complex self-assembled structures can be achieved combining metal-ligand coordination and simple rapid stabilization of the structures via catalytic macrocyclization. In a recent remarkable example, the creation of the catalytic nano-environment suitable for substrate selective properties was obtained by self-assembly through metal coordination of organic aromatic hexaphenylbenzene panels, further cross-linked through ring closing metathesis. The obtained metal-ligand truncated octahedral cage was modified removing the Cu(II) ions initially used to template the structure and inserting four Pt(II) metal centers as true catalytic sites in a 1.8 nm pore size (Scheme 7a).[48] The confinement of the catalyst enhanced both the activity and the selectivity of the platinum complex. Comparison with the dinuclear Pt(II) Karstedt's catalyst towards hydrosilylation reactions displayed activities ten times higher with the extra advantage of being recyclable. What is really impressive is both the performance in terms of size- and site-selectivity when substrates differing steric hindrance or in functional group composition were employed. For substrate selectivity, when unhindered substrates were tested the caged Pt metal centers displayed higher catalytic activity than the reference Karstedt's catalyst. The activity of the supramolecular catalyst was paired and surpassed when larger substrates were employed. In fact, in the reaction between phenyl dimethylsilane and the series of terminal alkenes reported in Scheme 7b, the reaction mediated by Karstedt's catalyst yielded the corresponding products in the range 66–84%, while the caged Pt catalyst afforded decreasing amounts of products with increasing size of the alkene. As mentioned above, the catalyst served as a highly site-selective hydrosilylation catalyst for



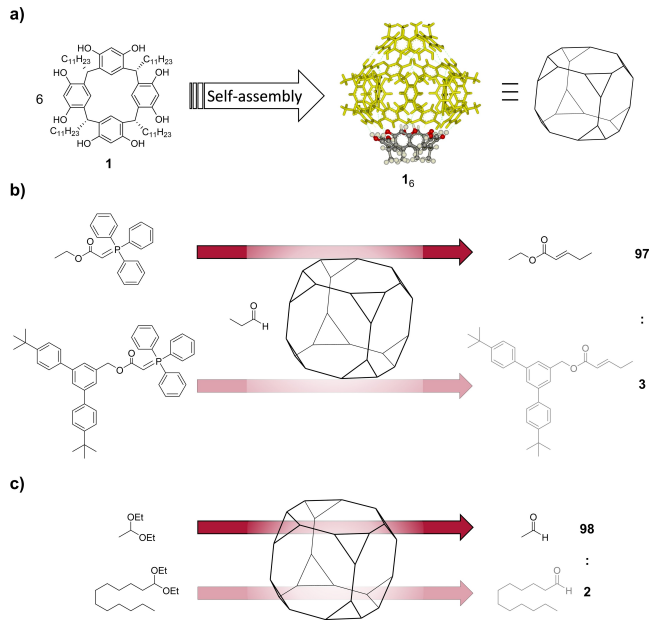
Scheme 7. Synthesis of the self-assembled metallo-organic cage through coordination of hexaphenylbenzene panels to Cu(II), ring closing metathesis and metal exchange with Pt(II) and structure of the Karstedt's catalyst (a); substrate selectivity displayed by the nanostructured catalyst in the hydrosilylation of different-size silanes showing preference for smaller substrates, while as reference free Karstedt's catalyst did not demonstrate substantial substrate selectivity (b).

substrates with multiple functional groups, further mimicking other features typical for enzymes.

2.3. Hydrogen-Bonded Nanoreactors

Among hydrogen bonded supramolecular capsules, the resorcin[4]arene hexameric capsule (Scheme 8) has received great attention by the scientific community in the recent years thanks to its simple synthesis, well-understood binding properties and in particular to its large cavity, that enables to accommodate different combinations of substrates and catalysts.[49,50,51] The capsule has been investigated as a catalyst and as a nanoreactor able to host metal and organocatalysts, in some cases investigating also the substrate selectivity induced by the size and shape of its cavity, that is pseudo-spherical with a diameter of about 1.4 nm.

As a catalyst, the resorcinarene capsule showed interesting size selectivity properties, as reported by Tiefenbacher in the reaction involving two different Wittig ylides characterized by



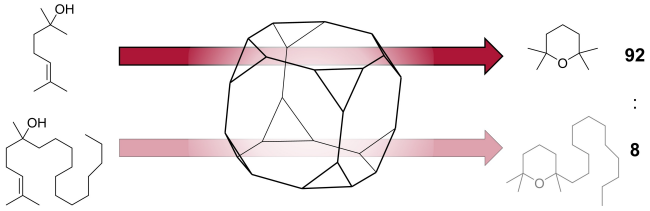
Scheme 8. Schematic representation of the self-assembly of resorcinarene units forming the hexameric hydrogen bonded capsule (a) and its performances in the Wittig reaction of propionaldehyde with two ylides characterized by different steric hindrance (b) and in the hydrolysis of different chain length acetals (c).

rather different size (Scheme 8b).[52] Results showed that in the presence of the capsule the two alkene products were obtained in a 3:97 ratio in favor of the larger alkene product, whereas in the same experiment performed in the absence of the capsule the ratio between the two products was only 53:47 with basically no differentiation between the two ylides.

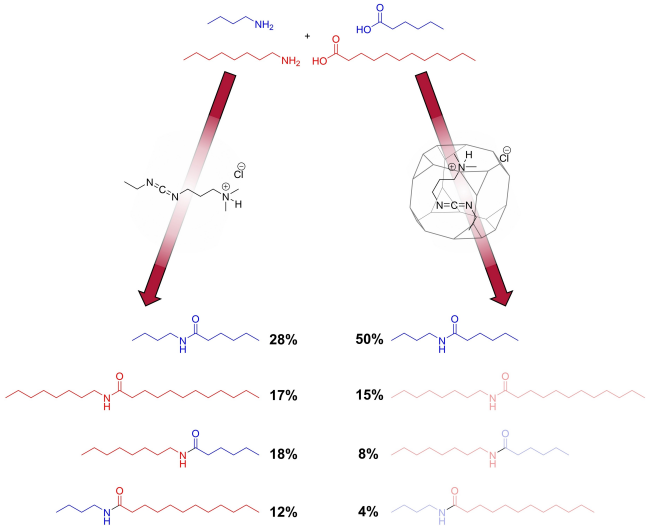
Similarly, the resorcinarene capsule exhibited interesting selectivity properties towards the hydrolysis of acetals (Scheme 8c). By changing the alkyl group of various lengths acetals, it was possible to observe a considerably slower reaction rate with longer substrates. The only evincible correlation between the reaction rate and the length of the acetals was the different encapsulation rate of these molecules. Smaller substrates can, in fact, be accommodated in the capsule faster that bigger ones, thus achieving higher conversions. This interesting behavior was even more fruitful when it was exploited to selectively hydrolyze one acetal in the presence of another. After 60 minutes, an equimolar mixture of 1,1-diethoxyethane and 1,1-diethoxydodecane in the presence of the capsule showed a 98:2 selectivity in favor of the smaller aldehyde product, with an 85% combined conversion. Besides, the control experiment performed using TFA as acid catalyst, afforded a 65% of combined conversion, with a 37:63 ratio of products favoring the longer chain product. These experiments strongly highlight the important characteristic of the resorcinarene capsule of enabling reactions under mild conditions, that is achievable through stabilization of cationic intermediates and transition states.

Another example of application of the resorcinarene hexamer involving size-selectivity behavior was demonstrated for the intramolecular hydroalkoxylation of unsaturated alcohols to the corresponding cyclic ethers (Scheme 9).[53] At optimized conditions, the reaction of 2,6-dimethylhept-5-en-2-ol achieved full conversion after 3.5 days at 30 °C, affording selective formation of the cyclic ether. In direct competitive experiments with pairs of substrates like 2,6-dimethylhept-5-en-2-ol and 2,6-dimethyloctadec-2-en-6-ol, 53% overall conversion with a 92:8 ratio between the shorter and the longer products was observed after 64 h . Differently, using triflic acid as simple Brønsted acid, overall substrate conversion was 67% in 7 h, but the ratio between the two products was 46:54, indicating negligible substrate selectivity in the absence of a confined space able to discriminate the substrates.

The resorcinarene capsule has been exploited also as a nanoreactor, rather than a catalyst itself. An example is the condensation reaction between aliphatic carboxylic acids and amines with the cationic reagent 1-ethyl-3-(-3-dimethylaminopropyl) carbodiimide hydrochloride as condensing agent, which was selectively hosted in the cavity of the capsule. Differently from the reaction occurring free in solution, the confined space available for the reagents in the nanometric reaction chamber efficiently allowed to steer the substrate selectivity, observing in many competitive experiments the preferred consumption of the shorter substrates. In Scheme 10 is specifically described the substrate selectivity imparted by



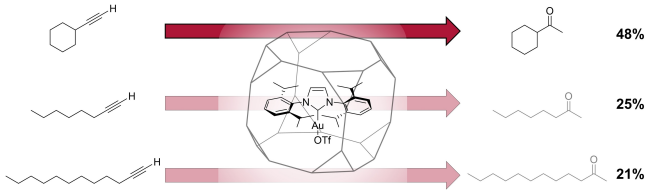
Scheme 9. Schematic representation of the performances of the capsule towards the intramolecular hydroalkoxylation of unsaturated alcohols to the corresponding cyclic ethers.



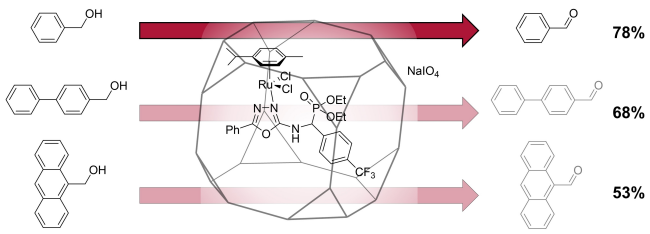
Scheme 10. Comparison of the performances in the substrate selective amide coupling between different chain length amines and carboxylic acids performed by the carbodiimide condensing agent free in solution and hosted within the resorcinarene capsule.

the capsule in an experiment comprising two amines with two acids leading to overall four possible different amide products with different lengths.[54] While in the absence of the capsule the yield for the amide products was in the range 28 to 12%, with the capsule it was much higher (from 50 to 4%) with the shorter amide obtained preferentially.

The hosting properties of the resorcinarene capsule enabled the confinement of organometallic complexes[55] as well as catalysts known for their product selectivity properties, thus also imparting some degree of substrate selectivity. In particular, the hexameric capsule was used to encapsulate cationic carbene-gold catalyst that was tested in competitive hydration reaction of terminal alkynes. (Scheme 11).[56] In fact, when a mixture of ethynylcyclohexane, 1-octyne and 1-dodecyne was hydrated in the presence of the hosted catalyst system, the three alkynes showed a 48%, 25% and 21% conversion respectively. This was due to the different shape of the cyclic substrate compared to the linear ones. In fact, those compounds need to partially fold in order to fit into the cavity left by the catalyst, thus decreasing their reactivity. Moreover, the ratio of the initial rate for the three substrate was 3.4:1.3:1.0 respectively, while using the free Au(I) catalyst, the normalized rates resulted 1.5:1.0:1.0. The shape selectivity displayed by the cavity of the capsule favored more compact substrates. This was interpreted considering that to be accommodated within the residual space available in the cavity, flexible and long substrates need to fold assuming high energy conformations that hamper their binding by the capsule. Newsworthy results were also obtained employing rigid aromatic terminal alkynes like phenylacetylene, *p*-methyl-phenylacetylene and *p*-(*t*-butyl)-phenylacetylene. For this set of competitive substrates, the observed normalized relative initial rates were 1.0:1.4:1.5 respectively in the hydration reaction using the free Au(I) catalyst in solution. Conversely, for the encapsulated catalyst, a reversed order of reactivity was observed due to preferential binding of the shorter rigid substrate, observing a relative normalized rate of 1.6:1.3:1.0 for phenylacetylene, to *p*-methyl-phenylacetylene and *p*-(*t*-butyl)-phenylacetylene.



Scheme 11. Schematic representation of the performances of the catalytic system comprising the NHC–Au(I) catalyst encapsulated inside the resorcinarene self-assembly towards the hydration of aliphatic alkynes characterized by different length and hindrance of the carbon chain.



Scheme 12. The encapsulation of the neutral Ru(II) catalyst within the resorcinarene hexameric capsule steers substrate selectivity in the oxidation of alcohols to the corresponding aromatic aldehydes, with preference for less hindered alcohols compared to larger ones.

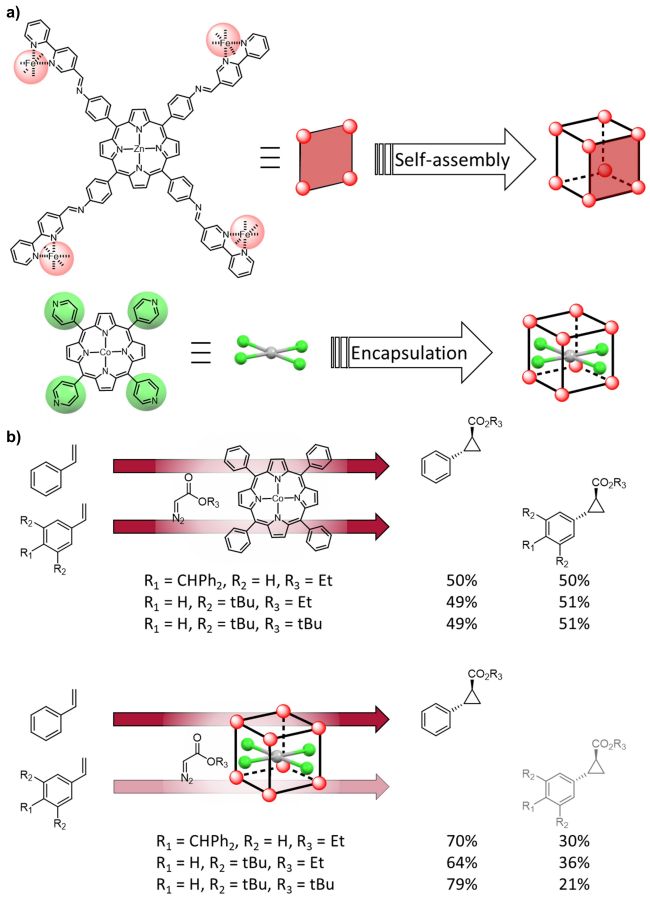
The first example of encapsulation of the neutral (*p*-cymene)-ruthenium(II) catalyst inside a self-assembled hexameric capsule of resorcin[4]arene was recently reported (Scheme 12).[57] The encapsulation of the neutral arene-ruthenium(II) complex was thoroughly confirmed by different analytical techniques, in particular ^{31}P and ^{19}F NMR spectra suggested a mobility behavior of the complex inside the capsule, that was further supported by molecular dynamics calculations, highlighting possible supramolecular interactions between the complex ligands and the inner surface of the capsule. The system was employed for the catalytic oxidation of mixtures of three arylmethyl alcohols to the corresponding aldehydes, using $NaIO_4$ as oxidant. Despite the longer reaction times, if compared to those of the free catalyst in solution, the presence of the resorcinarene host demonstrated a significative degree of size selectivity in the oxidation of benzylic alcohols. Indeed, the final yields of arylaldehydes resulted decreasing according to the increase of the steric hindrance of the aromatic rings, obtaining 78% yield of benzaldehyde, 68% of 4-phenyl-benzaldehyde and 53% of anthracene-9-carbaldehyde, whereas no difference in reactivity between the three alcohols was observed in the reference experiment without the capsule as a host. The results of this work clearly show the potential of neutral complexes hosted in supramolecular aggregates, suggesting many other similar investigations.

3. Substrate Selectivity in Water

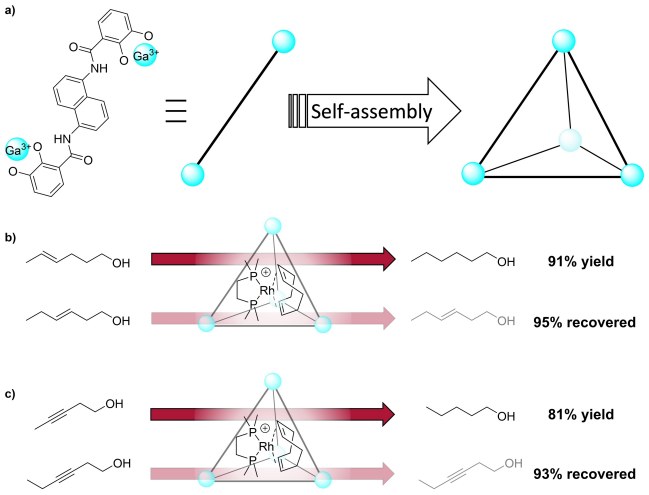
In aqueous media, among other weak intermolecular forces, the hydrophobic effect plays a crucial role in particular for substrate recognition, but also poses some limitations in terms of solubility. Because of this, in supramolecular catalysis self-assembled systems in water need to be highly charged like in the case of coordination cages, or decorated with hydrophilic external units like in the case of micelles.

3.1. Coordination cages

Coordination cages offer different geometries and electronic properties[58] for the development of substrate selective catalysts. An example of size substrate selectivity for cyclopropanation reaction using a caged cobalt–porphyrin catalyst was developed based on a cubic M_8L_6 molecular flask made with zinc-based porphyrin faces held together by iron atoms at the vertexes (Scheme 13).[59] The molecular cube was found to be soluble in various solvents and solvent mixtures, such as water-acetone displaying enhanced catalytic performance with respect to simple organic solvents. The cubic molecular cage acted as a host for catalysts, making the latter selectively accessible to substrates able to migrate through the openings



Scheme 13. Structure of the Co(II)-porphyrin catalyst hosted within a cubic M_8L_6 metal-ligand capsule (a); substrate selective cyclopropanation reaction of styrenes mediated by free or encapsulated Co(II) porphyrin catalysts leading to preferential conversion of smaller substrates in the presence of the cage as confined nano-environment (b).

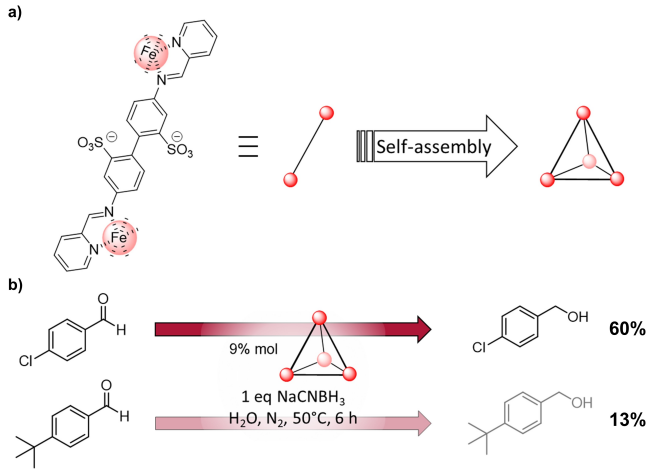


Scheme 14. Schematic representation of the tetrahedral Ga(III) metalloorganic cage as host for the Rh(II) phosphine catalyst (a); substrate selective performance of the encapsulated catalyst in the competitive hydrogenation of (*E*)-hex-4-en-1-ol and (*E*)-hex-3-en-1-ol (b) and pent-3-yn-1-ol and hex-3-yn-1-ol (c).

present on the surface, thus leading to substrate size selection for this ship-in-a-bottle catalyst. As shown in Scheme 13b, while traditional free Co(II) porphyrin complex in solution did not discriminate between pairs of styrene substrates, the encapsulated one led to substrate size selectivity in favor of smaller styrene derivatives that could sneak more easily in the confined cubic nanoreactor. In fact, selectivities as high as 79:21 for the competitive experiment between styrene and 3,5-bis-*tert*-butylstyrene were observed. The size of the diazo reagent was important as well, with reduced size selectivity with ethyl compared to *tert*-butyl diazoacetate (Scheme 13c).

Self-assembled tetrahedral metallo-organic cages were also recently employed for the encapsulation of a hydrogenation catalyst to achieve selective olefin hydrogenation. This self-assembled polyhedron, based on the coordination of six bidentate ligands to four Ga(III) ions was able to host a ruthenium catalyst within its cavity (Scheme 14).[60] This system allowed to achieve site-selective hydrogenation of alkenes derivatives, dictated by the steric profile of the substrate. Furthermore, selective monohydrogenation was obtained in the presence of multiple sites of unsaturation (for example, employing linolenic acid as substrate). Newsworthy results were obtained when performing competition experiments between the supramolecular host-guest system and the free catalyst. When (*E*)-hex-4-en-1-ol and (*E*)-hex-3-en-1-ol were left to react in the presence of the catalytic system, only the first was transformed into the saturated derivative (91 % yield), while the latter was recovered almost completely (95 %). Similar results were obtained with a mixture of pent-3-yn-1-ol and hex-3-yn-1-ol: while the first one was converted with the same yield as in the former experiment, the latter was still present after 20 h of reaction with >98 % recovery of substrate. However, the most exciting result was the competition experiment performed to determine the discrimination exerted by the catalytic system between methyl- and ethyl-substituted olefins. Good conversion of methyl-olefin was obtained (81 %), while ethyl-olefin was recovered in high yield (93 %). This example of difference in reactivity between supramolecular supported and free catalyst is certainly promising for selectivity in important processes such as olefin hydrogenation reactions.

In a recent article the peculiar properties of the polyanionic tetrahedral Fe_4L_6 metal-ligand capsule developed by Nitschke were described as a catalyst in the carbonyl reduction employing the very mild reducing agent $NaCNBH_3$ (Scheme 15a).[61] The organometallic cage promoted the reaction by favoring the protonation of the substrate and by stabilizing the oxocarbenium ion in the cavity, while in the absence of the catalyst the reaction occurred only at low pH values. Moreover, the well-defined size and shape of the cavity promoted selective substrate reduction. As shown in Scheme 15b, in the presence of 9 mol% of the catalyst, the substrate conversion was significantly affected by the steric bulkiness, leading to conversion of the smaller *p*-chlorobenzaldehyde up to 60 %, while only the 13 % of the bulkier *p*-*tert*-butylbenzaldehyde was converted. In the control experiment without the catalyst the two benzyl alcohols were produced in low and comparable amounts (7 %).



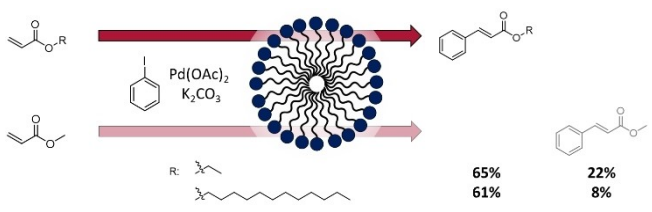
Scheme 15. Structure of the polyanionic tetrahedral metal capsule (a), substrate selective hydride reduction of rigid aromatic aldehydes promoted by the capsule with preferential conversion of the smaller substrate (b).

3.2. Micellar Nanoreactors

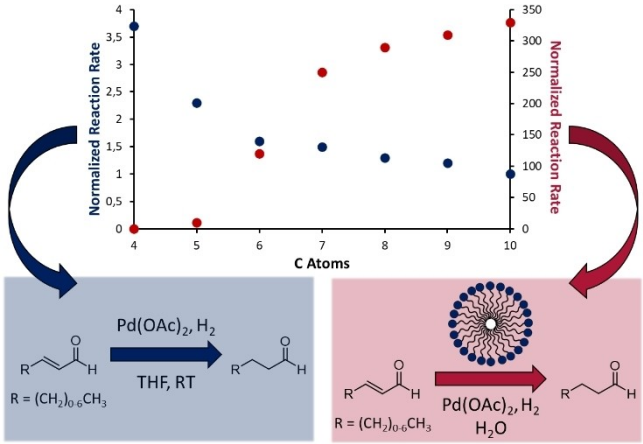
Another strategy that can be efficiently employed to achieve size selectivity in water involves the use of micellar catalytic systems. In a previous work, some of us reported an example of Heck coupling catalyzed by $Pd(OAc)_2$ in which substrate selectivity was imparted by the use of cationic cetyltrimethylammonium bromide surfactant (CTAB) under micellar media conditions (Scheme 16).[62] Using a series of acrylate esters bearing different alkyl side chains, no substrate selectivity was detected in DMF in pairwise competitive experiments between methyl acrylate and the longer acrylates. This clearly indicated that there was neither steric discrimination based on the elongation of the carbon chain, nor an electronic effect on the electrophilicity of the α,β-unsaturated bond. On the other hand, when micelles were employed, a remarkable substrate discrimination was observed, based on the different hydrophobic properties of the reagents. In fact, even between methyl and ethyl acrylate a noticeable difference in reactivity was observed, with 22% and 65% conversion to the corresponding cinnamyl esters. The size selectivity was further increased in a competitive experiment between methyl acrylate with the much more hydrophobic dodecyl acrylate, leading to only 8% yield for the methyl cinnamate and 61% for the dodecyl cinnamate.

Substrate selectivity imparted by micellar environment can reach much higher values by proper combination of the catalytic system and the nature of the surfactant. A landmark example was reported for the palladium catalyzed reduction of α,β-unsaturated aldehydes with hydrogen in water, through the formation of stabilized Pd nanoparticles stabilized by the micellar core with an average diameter of 4.6 nm. In particular, after a long screening, the chemo-selective reduction of unsaturated aldehydes ranging from crotonaldehyde to (*E*)-dec-2-enal to the corresponding aliphatic aldehydes was achieved with hundreds fold selectivity using sodium dodecyl sulfonate (SDSU) as surfactant (Scheme 17).[63] Size selectivity was measured for equimolar mixtures of seven unsaturated aldehydes from C_4 to C_{10}, observing increasing reactivity for longer substrates, with overall a >300 fold preference for the reaction of the longer C_{10} substrate with respect to the shorter C_4, as a consequence of the higher hydrophobic character of the former which leads to higher concentration in proximity of the Pd nanoparticles. It is noteworthy the reversed substrate selectivity for the same reaction for the same series of substrates when operating in tetrahydrofuran where only minimal steric effects are present leading to a ~3.5 higher reactivity for the shorter C_4 substrate compared to the longer C_{10}. This inversion of substrate selectivity clearly states the importance of the hydrophobic effect in recognition and catalysis in aqueous media, providing some hints to mimic enzyme substrate selectivity.

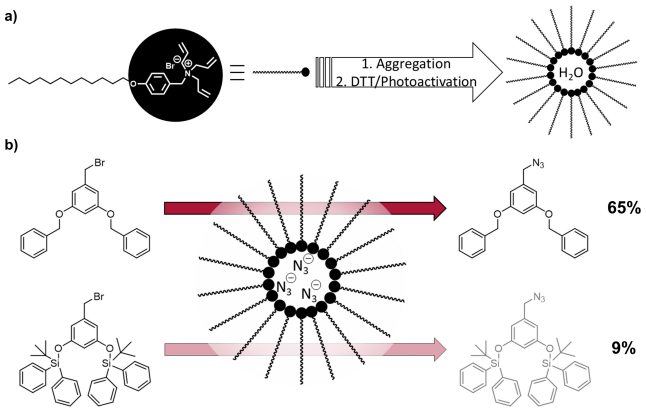
Interfacial cross-linked reverse micelles (ICRMs) can also be effectively employed for substrate selective micellar catalysis. This type of supramolecular host, that assembles from cationic surfactants bearing allyl moieties on the polar ammonium head group, are subjected to covalent cross-linking with dithiothreitol (DTT) and photoactivation via thiol-ene radical chain reaction creating a nano-water phase within an organic solvent. In this water pool the reaction between sodium azide and different benzyl bromide derivatives displayed substrate selectivity which is mainly due to the alkyl density outside the ICRM core. (Scheme 18).[64] Bulkier benzyl bromide substrate derivatives are less likely to react, while a substrate with similar



Scheme 16. Substrate size selectivity on the Heck cross coupling mediated by cationic surfactant micelles in water, favoring the more hydrophobic substrates.



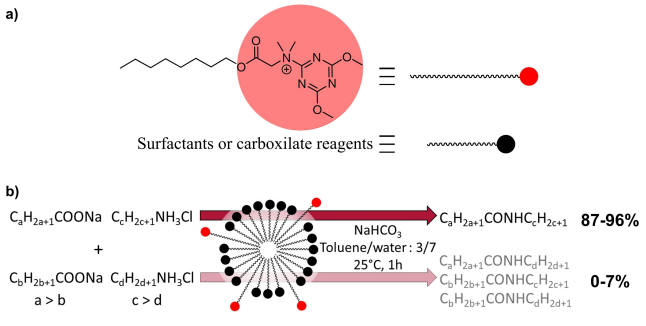
Scheme 17. Plot describing the size selectivity in the $Pd(OAc)_2$ catalyzed hydrogenation of unsaturated aldehydes in organic medium (THF) where the shorted substrates react slightly faster than the longer, while under micellar media the substrate selectivity is reversed with longer more hydrophobic substrates reacting more than three hundreds of times faster than the shorter ones.



Scheme 18. Structure of a single-tail ammonium surfactant for interfacial cross-linker micelles (a); substrate selectivity in the nucleophilic substitution of azide on benzyl bromides favoring the smaller substrates (b).

electronic properties but lower steric hindrance shows much higher conversion. These results were also confirmed in competitive reactions with a selectivity of almost 7:1 in favor of the smaller substrates. The ratio W0 defined as $[H_2O]/[Surfactant]$ turned out to affect the selectivity, with a general decrease of size selectivity with higher W0 values. Moreover, most interesting results concern the comparison of two different types of ICRMs, bearing single-tail and double-tail structure. It was expected that micelles bearing double-tail surfactants would have a higher alkyl density and thus be able to impart a greater "sieving" effect on the substrates with concomitant higher size selectivity. Conversely, surfactants with a single tail gave the best results in terms of selectivity. The authors propose that this result could be due to interparticle aggregation, which is only possible for this class of ICRMs, thus tightening the alkyl shell and increasing substrate selectivity.

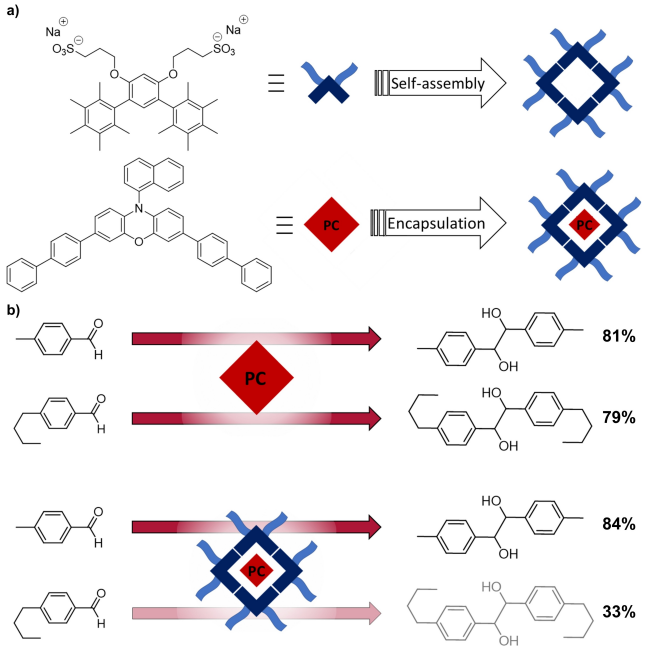
An interesting example of selection of substrates based on the hydrophobic effect was reported in the case of the dehydrative condensation between carboxylic acids and aliphatic amines at emulsion interfaces mediated by an *in situ* formed cationic surfactant bearing a 1,3,5-triazine-based dehydrative condensing unit (Scheme 19a).[65] The latter reagent



Scheme 19. Amide coupling reaction mediated by mixed micelles comprising an amphiphilic ammonium surfactant bearing a 1,3,5-triazine-based dehydrative condensing (a); substrate selective reaction observing preferential conversion of longer combinations of two acids and two amines with respect to the shorter ones forming selectively two out of four possible amide products (b).

operating under micellar conditions favored the reaction of longer and more hydrophobic substrates. Several competitive reactions were carried out with butylamine and two different sodium salts of linear carboxylic acids. In particular, a selectivity ratio of about 25:75 was observed between substrates that differ by only one C atom, and values as high as 1:99 could be achieved when the alkyl chain length differed by 4–5 carbon atoms. The selectivity observed was due to the hydrophobic character of carboxylic acid and it was also possible to predict the results based on their octanol-water partition coefficient logP, especially for difference greater than one. Further experiments showed very interesting results concerning dual selective reactions in which the exclusive formation of the product with the two longest alkyl chains among the four possible ones was observed (Scheme 19b).

As last examples dealing with nano-environments operating in water, it is worthy to mention the development of new V-shaped aromatic rigid surfactants that enable the formation of well-defined capsule-like aggregates in water composed by the self-assembly of few surfactant units. The *bis*-anionic amphiphilic compound reported in Scheme 20a[66] favored the solubilization in water of the photoredox organic catalyst phenoxazine. This compound promoted a series of C–C bond formation reactions through the reductive generation of the C-centered radical species, using visible light irradiation at room temperature in presence of air. In particular, for the pinacol coupling reaction, selective reaction of smaller aromatic aldehydes was achieved due to the nanoconfinement effects imparted by the apolar core of the nano-capsules in water (Scheme 20b). Indeed, it was observed that reactivity was



Scheme 20. Phenoxazine photoredox catalyst hosted within micelles formed by V-shaped rigid amphiphilic surfactants forming well defined capsule-like in water (a); substrate selective pinacol coupling reaction mediated by the micellar catalytic system favoring the shorter aldehyde substrates, while in the absence of surfactant the reagent conversion was almost identical (b).

altered according to the length of the side chains of the *para*-substituted benzaldehydes: substrates with smaller chains showed faster reactivity compared to longer ones. Moreover, catalyst recycling was obtained as well, further evidencing the many advantages that confined catalysts in water provide with respect to organic media reactions.

4. Summary and Outlook

The present article deals with a specific kind of selectivity related to the ability of a catalytic system to select a proper reagent among others. Substrate selectivity is in fact very common for enzymes that select the substrate prior to the catalytic event, while it is much less common with man-made catalysts. To achieve sufficient substrate recognition artificial catalyst needs to host it surrounding most of its surface. This requires artificial catalysts endowed with recognition sites which are frequently highly demanding in terms of synthetic complexity.

A straightforward approach consists in the development of self-assembled catalysts from simple subunits that spontaneously provide large and defined nano-environments, whose size, shape, and peculiar host properties are responsible for substrate binding and consequent transformation into products, imparting substrate selective properties. The present review underlined the most interesting achievements in this specific subject in the recent years, spurring future investigations in this largely unexplored topic in between supramolecular chemistry and homogeneous catalysis, with the aim to further move man-made catalysts towards real enzyme behavior mimics.

In particular, dynamic covalently bonded capsules, hydrogen bonded, and metal-ligand coordination capsules have been developed to operate in organic media, frequently selecting shorter and more compact substrates. Specific examples of metal-ligand capsules have been developed also in water displaying interesting substrate selectivity properties again based on size and shape requirements imparted by the cavity of the nano-catalyst. Differently, self-assembled micelles have been developed with substrate recognition driven mainly by the different hydrophobic properties of the substrates.

A direct collaboration between supramolecular chemistry specifically for molecular recognition and homogeneous catalysis will facilitate the process of mimicking substrate selectivity observed in enzymes. The large variability of self-assembled nanocontainers and nanocatalysts that can be achieved from a limited number of simple organic or metal subunits will certainly spur the investigation of new potentialities of confined catalysis for substrate selectivity. Larger assemblies will also ensure the possibility to accommodate traditional metal or organocatalysts enabling to implement substrate selectivity in catalysts that have been developed so far for their product selectivity properties, achieving substrate selectivity as an extra feature. Moreover, by proper combination between well-established supramolecular receptors, metal centers, metal nanoparticles[67] and catalytic units it is possible to move from homogeneous supramolecular catalysts to heterogeneous one,[68] further widening the possible approaches to substrate selectivity. The latter, still underinvestigated field of research, will certainly become much more popular in the near future, allowing us to make a step forward in enzyme mimics.

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Keywords: Confinement effect · enzyme mimics · molecular recognition · substrate selectivity · supramolecular catalysis

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