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# Recent applications of macrocycles in supramolecular catalysis[☆]

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ABSTRACT

Numerous supramolecular macrocycles have been utilized for developing catalysts by exploiting their specific molecular recognition and ability to form inclusion complexes through noncovalent interactions. The cyclic structure and modified functional groups of these macrocycles can influence substrate and transition state stability, as well as reaction selectivity. The inner cavities of these macrocycles are particularly beneficial, as they enable substrates to adopt preorganized arrangements and serve as versatile platforms for highly efficient supramolecular catalytic systems. This minireview provides an overview of recent advancements in supramolecular catalysis using various macrocycles, such as crown ethers, cyclodextrins, calixarenes, pillararenes, cucurbiturils, and other novel macrocycles.

## 1. Introduction

Inspired by natural enzyme catalysis, many cavity-containing macrocycles have been synthesized and applied in the fields of drug delivery, transmembrance channels, catalysis, separation process, sensors, nanomaterials, and information encryption *etc.* [1–6]. Especially, catalysis is a well-investigated and fast-growing area. Supramolecular catalysis aims to control the chemical reactions through noncovalent interactions. Generally, supramolecular macrocycles catalyze the reactions in two manners, including accelerating and inhibiting reaction rate or altering the reaction path through various supramolecular interactions [7]. These interactions between macrocycles and substrates, such as $\pi-\pi$ stacking, hydrogen bonding, hydrophobic interactions, and electrostatic interactions, could be used to form host–guest complexes with high affinity. The complexation allows substrates to adopt preorganized configurations in the cavities of macrocycles and could stabilize the transition state, which is favorable to catalyze reactions [8]. Primarily, the cavities of macrocycles could increase the collision frequency of the reactants to accelerate the reaction. On the other hand, the cavity could also encapsulate the substrates, avoiding the attack of active species to inhibit reaction rate [9]. In addition, the supramolecular interactions could also change the activation barrier and provide the possibility to develop new reaction [10]. Modified macrocycles with functional groups could enhance the selectivity of supramolecular interactions and then further increase regio- or stereoselectivities, which leads the related reaction into a dominant version.

The interactions serve as the basis for macrocycle-mediated supramolecular catalysis. Given the growing body of literature on supramolecular catalysis, this minireview delves into the various applications of crown ethers, cyclodextrins, calixarenes, pillararenes, cucurbiturils, and other innovative macrocycles within the realm of supramolecular catalysis.

## 2. Macrocycles-based supramolecular catalysis

With the development of supramolecular chemistry, macrocyclic compounds are used as efficient tools to enhance the reactivity and selectivity of specific reactions with their unique affinity to the specific substrates [11–13] and the cyclic structure plays a crucial role in the catalysis [14]. Compared with their monomeric analogues, macrocycles often induce higher catalytic activities. Macrocycles possess the ability to catalyze a diverse range of reactions, such as asymmetric hydrogenation and hydroformylation, polymerization, photooxygenation, photodimerization, chemical bond cleavage, hydrolysis, cycloaddition, isomerization, and degradation. The exploration of macrocycle-catalyzed reactions not only aids in comprehending natural enzyme functions but also offers valuable insights for the development of sophisticated catalytic systems.

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[☆] This paper is dedicated to the memory of Prof. Jiang Wei.

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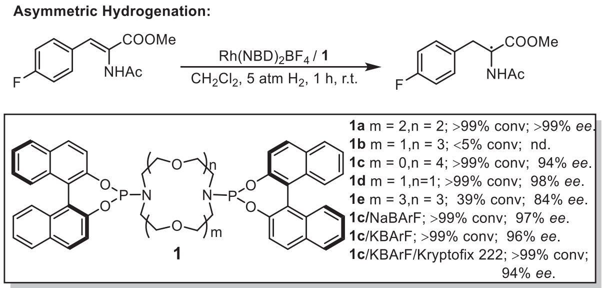


**Fig. 1.** Asymmetric hydrogenation of $\alpha$-dehydroamino acid ester catalyzed by chiral diphosphoramidite ligands **1** and $Rh(NBD)_2BF_4$ [26].

### 2.1. The applications of crown ethers in supramolecular catalysis

Crown ethers exhibit a distinct characteristic of recognizing and forming complexes with alkali metal ions and ammoniums, which serves as the fundamental principle of crown ether-based supramolecular catalysis [15–18]. The host-guest interactions between crown ethers and alkali metal ions enable crown ethers to function as common phase transfer catalysts. By leveraging the robust binding affinity between amine groups and crown ethers, site-selective C–H oxygenation of the methylene unit in aliphatic ammonium salts has been successfully achieved [19]. In recent years, crown ether-based catalysis has predominantly focused on metal ion recognition as its mechanism.

Chiral phosphoric acid derivatized from binaphthol is a class of very useful catalyst [20–22]. The combination of crown ether and chiral phosphoric acid has emerged as an attractive field of supramolecular catalysis. Fan's group has been focusing on the supramolecular catalytic systems based on (aza-)crown ethers and their counterparts [23–25]. They prepared a small library of diaza-crown ether-bridged chiral diphosphoramidite ligands **1** for rhodium-catalyzed asymmetric hydrogenation and hydroformylation reactions [26]. These crown ether-based chiral phosphoric acids ligands exhibited distinct catalytic properties and **1a** showed superior catalytic performance (Fig. 1). Interestingly, catalytic outcomes varied after adding alkali metal salts. The *ee* value fallen back to initial value after adding a compound with stronger binding affinity to alkali metal cations, which confirmed the supramolecular recognition between the alkali metal cation and the diaza-crown ether could affect the catalytic property.

Another example of alkali metal guest tuned asymmetric catalysis was recently achieved by Li's group [27]. They employed 3,3′-bis(aza-crown ether)-derived chiral phosphoric acids **2** as catalyst for the asymmetric acetalization reaction (Fig. 2). The addition of $LiPF_6$ could greatly improve catalytic activity and shorten the reaction time, while the yield decreased from >99% to 59% without the addition of $LiPF_6$. They also utilized aza-crown ether derived chiral BINOL catalyst in the asymmetric Michael addition of alkenyl boronic acids to $\alpha,\beta$-unsaturated ketones [28]. The catalyst demonstrated enhanced enantioselectivity, with no additional enhancement observed from alkali ions in terms of catalytic efficiency.

Due to the unique secondary structure, good biocompatibility and degradability, polypeptides have been widely exploited in the field of biomedicine. Ring-opening polymerization of *N*-carboxyanhydrides is a traditional method for well-defined polypeptide materials, suffering from various side reactions and the need of the long reaction time to finish the polymerization. Cheng and co-workers [29] reported the fast polymerization of *N*-carboxyanhydrides from primary amine initiators with the addition of crown ether in solvents with low polarity and hydrogen-bonding ability (Fig. 3). The addition of crown ether could successfully finish the polymerization with shorter time and inhibit side reactions. The favorable interactions between amino groups and *N*-carboxyanhydrides monomers resulted in the lower activation energy for the ring-opening reaction. Furthermore, they tested the catalytic activity of crown ethers with different size or polymeric analogs and found **3** (18C6) exhibited the highest catalytic activity. Besides, the polymerization could also be achieved in a dichloromethane/water biphasic system with non-purified monomers, which highlighted the utilization of crown ether-catalyzed polymerizations.

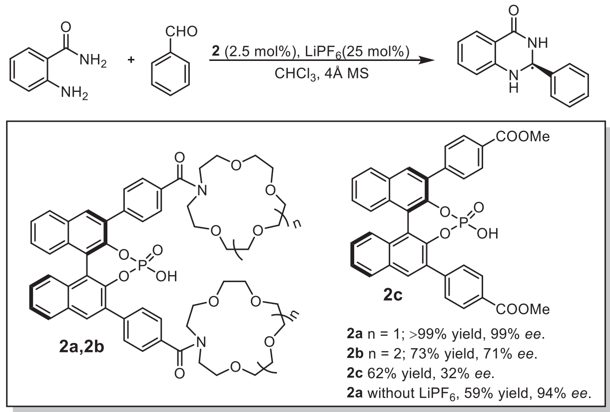


**Fig. 2.** Asymmetric acetalization reaction catalyzed by chiral phosphoric acids **2** [27].

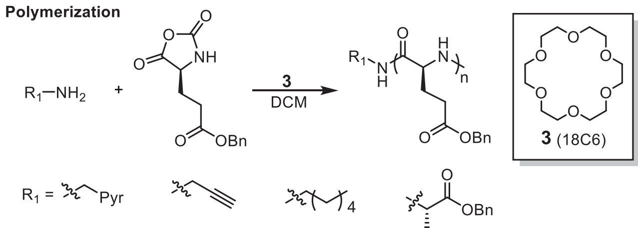


**Fig. 3.** 18C6-catalyzed polymerization of *N*-carboxyanhydrides from small-molecular amine initiators [29].

These examples have demonstrated that crown ether not only could directly act as catalysis to accelerate the reaction process, but also could be used as a host for alkali metal ions to tune the reactivity and enantioselectivity. Moreover, the size of the crown ether ring and the solvent also affected the reactions, leading to the change the reactivity and enantioselectivity. The catalytic capabilities of crown ethers have been demonstrated, however, the mechanism responsible for these unique supramolecular effects need to be fully elucidated. It is imperative to devote efforts towards unraveling the reaction mechanisms and extending the application of crown ether-based supramolecular catalysts to encompass other asymmetric reactions. Such endeavors are crucial for advancing the field of supramolecular catalysis.

### 2.2. The applications of cyclodextrins in supramolecular catalysis

Cyclodextrins (CDs) are cyclic oligosaccharides consist of glucose units linked by $\alpha$-1,4-glycosidic bonds [30]. The number of glucose units for $\alpha$, $\beta$, and $\gamma$-CD is 6, 7, and 8, respectively [31]. CDs possess the hydrophilic external surface and hydrophobic cavity, leading to the excellent water-solubility and the ability to encapsulate hydrophobic molecules [32]. Therefore, CDs are suitable to catalyze reactions performing in aqueous media. Gill's group [33] reported $\beta$-CD catalyzed the synthesis of 2-amino-4*H*-pyranoquinolines in an aqueous medium under ultrasound irra-

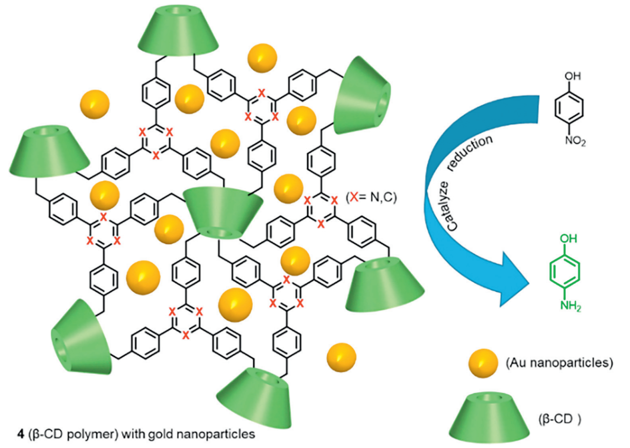


**Fig. 4.** The synthetic routes of $\beta$-CD polymer networks and the catalyzed reduction reaction [35].

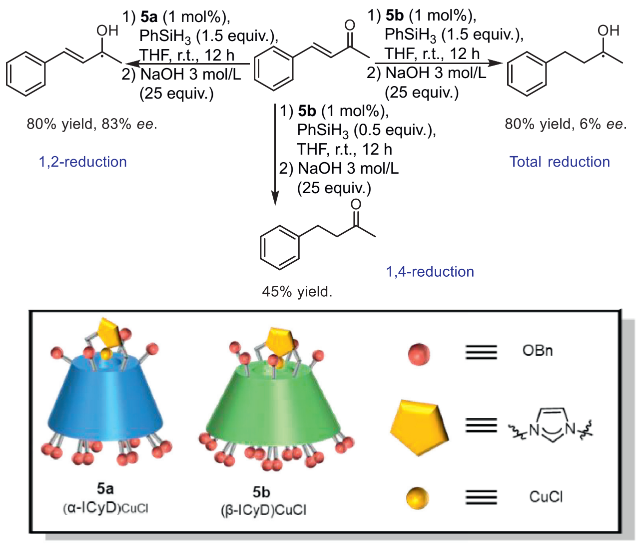


**Fig. 5.** Chemo-selective hydrosilylation of $\alpha,\beta$-unsaturated ketones with CD complexes **5** [36].

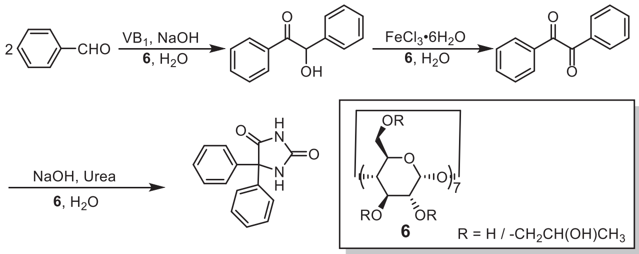


**Fig. 6.** Synthesis of phenytoin catalyzed by **6** in water [38].

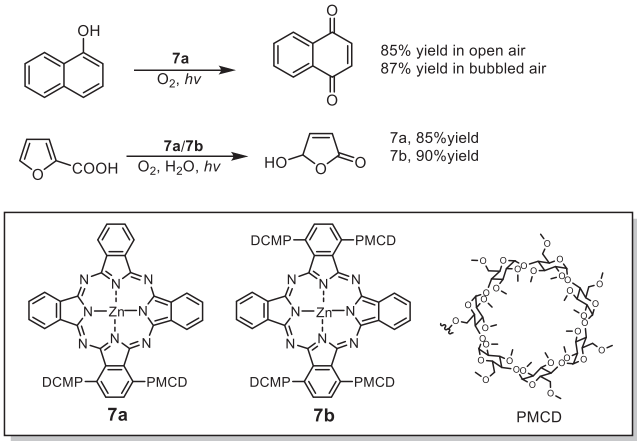


**Fig. 7.** Photooxygenation of 1-naphthol and 2-furoic acid using **7** as the photosensitiser [39].

diation. Manet and co-workers [34] obtained CD-based polymer which could encapsulate and solubilize reactants efficiently resulting in the photooxygenation could be performed in homogeneous aqueous environment. Ding and co-workers [35] utilized $\beta$-CD polymeric networks **4** as the supporting material to immobilize Au nanoparticles to catalyze the reduction of 4-nitrophenol (Fig. 4). The hydroxyl groups and nitrogen atoms in polymer networks played a synergistic role to refine the small size of Au nanoparticles, leading to the excellent dispersity in water and the high catalytic efficiency through host-guest interactions.

The hydroxyl groups on both rims can either form complexes with substrates or modify functional groups. Modified CDs with functional groups could significantly enhance the ability to catalyze the specific reactions. Sollogoub and co-workers [36] introduced an *N*-heterocyclic carbene to $\alpha,\beta$-CDs, which allowed CDs to encapsulate copper within the cavity and selectivly catalyzed the hydrosilylation of $\alpha,\beta$-unsaturated ketones (Fig. 5). The cavity size of **5** could control the chemoselective of copper-catalyzed hydrosilylation. As shown, **5a** with smaller cavity induced the 1,2-addition, while **5b** produced the fully reduced product. Victor's group [37] synthesized thioglycolic ester modified $\beta$-CD. After adding Pd(II) source, the CD-based supramolecular catalytic system displayed more efficient catalytic activity for Suzuki-Miyaura C–C coupling reaction.

Wang and coworkers [38] reported the synthesis of benzoins in water catalyzed by vitamin $B_1$ ($VB_1$) and **6** (2-hydroxypropyl-$\beta$-CD) (Fig. 6). The substrates were well dissolved using **6** as co-catalyst, which accelerated the reactions and increased the reaction efficiencies. The role of **6** acted as a phase-transfer catalyst, facilitating the solubilization of benzaldehyde in water. This green synthetic method avoided the use of metals, hazardous organic solvents, and base, leading to a promising strategy for the drug synthesis.

Phthalocyanines are commonly used as photosensitizers for photooxygenation reactions, which are usually carried out in organic solvents due to their limited water solubility. Ng's group [39] prepared the permethylated $\beta$-CD-conjugated zinc(II) phthalocyanines **7** as efficient sensitizers for photooxygenation of 1-naphthol and 2-furoic acid (Fig. 7). $\beta$-CD not only could suppress the aggregation and increase the hydrophilicity of the phthalocyanine core, therefore, the photooxygenation could be furnished in aqueous media, but also immobilize phthalocyanines on the surface of adamantane-modified silica nanoparticles through host–guest interactions to enhance the photostability and facilitate the recycling of the CD-based sensitizers.

The hydrophobic cavities of CDs could entrapment hydrophobic molecules to alter their solubility in aqueous solution and providie a chiral environment for guest molecular to control the enantioselectivity of various chemical reactions. These features allow CDs to be frequently used as supramolecular chiral catalysts. Photodimerization of anthracenecarboxylic acid is an intensively investigated model photoreaction, which could produce four *anti*/*syn*- and head-to-tail (HT)/head-to-head (HH) isomeric cyclodimers. Yang's group [40] investigated the effect of pH on [4+ 4] photodimerization of anthracenecarboxylic acid mediated by the native and modified $\gamma$-CDs **8** (Fig. 8). $\gamma$-CD could form 1:2

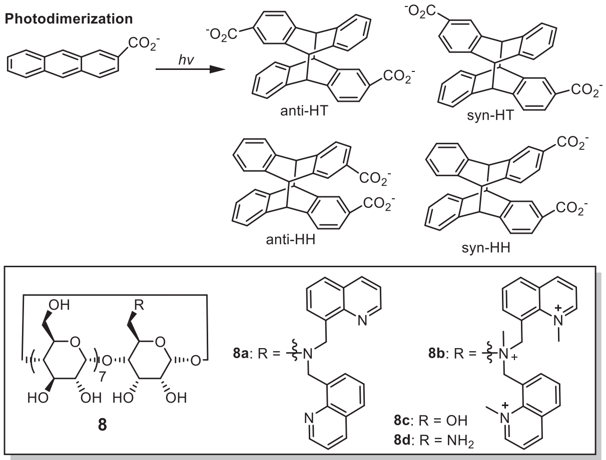


**Fig. 8.** Photodimerization of 2-anthracenecarboxylic acid to give four cyclodimers and chemical structure of **8** [40].

host-guest complex with anthracenecarboxylic acid to accelerate the photodimerization. Compared with the native $\gamma$-CD, the modified CD derivatives improved the stereoselectivity significantly. In the acidic pH range, HH orientation in the cavity of CDs was more favorable, resulting in the decreased *ee* value of HT cyclodimer. Subsequently, the manipulating selectivity of products mediated by native and modified $\beta$-CD derivatives under different pH conditions was also achieved by the same group [41]. They also introduced the carboxylate group into anthracenecarboxylic acid to enhance the performance of photodimerization through the increase of steric and electrostatic interactions [42]. In spite of the advantages mentioned above, CDs still suffer a prominent disadvantage that the antipodal chiral cavities are not readily available. To address this issue, Yang's group [43] synthesized and successfully separated diastereomeric pairs of tri-cavity chiral host composed of one pillar[5]arene sandwiched by two $\beta$-CDs. With bulky substituents on pillar[5]arenes, $\beta$-CDs could block the interconversion of the enantiomeric conformers, so that diastereomeric pairs could be isolated. The conjugation positions of $\beta$-CD and the absolute configuration of the central pillar[5]arene could essentially affect the stereoselectivity of the photodimerization of anthracenecarboxylic acid.

CDs can also coordinate with alkali metal ions to form a stable extended structure. Stoddart and coworkers [44] reported the solid-state metal-organic framework **9** assembled from chiral $\gamma$-CD building blocks and alkali metal ion ($K^+$) for the selective photodimerization of 1-anthracenecarboxylate (Fig. 9). The unique porous tunnels of metal organic framework could encapsulate 1-anthracenecarboxylate by exchanging with $OH^-$ anions residing in the porous cavities of the frameworks, which reduce the unfavorite effect, resulting from the electrostatic repulsion between the two carboxylate anions in the pre-organized anthracene dimer, which led to the anti-HH as the major enantiomer upon photodimerization.

Recently, Liu and coworkers [45] utilize $\gamma$-CD metal-organic framework as working electrode to catalyze ammonia synthesis and achieved a maximum rate of $NH_3$ production up to 4.66 mg h$^{-1}$ cm$^{-2}$ and high Faradaic efficiency of 79.3% (Fig. 10). The hydroxyl groups in $\gamma$-CD could coordinate $K^+$ ions to form extended 3D $\gamma$-CD-$K^+$ frameworks with six CDs. On the other hand, the uncoordinated hydroxyl groups in $\gamma$-CD were dominant catalytic sites, which would effectively absorb and activate nitrate through hydrogen-bonding interaction to induce $NO_3^-$ reduction reaction. Additionally, the uncoordinated hydroxyl group had an affinity for anionic nitrate *via* hydrogen-bonding interaction, while

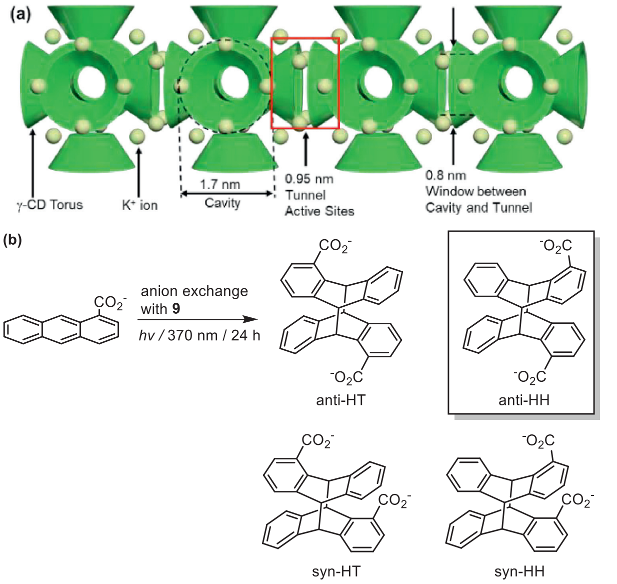


**Fig. 9.** (a) The structure of $\gamma$-CD metal-organic framework **9**. (b) Selective photodimerization of 1-anthracenecarboxylate in $\gamma$-CD metal organic framework [44].

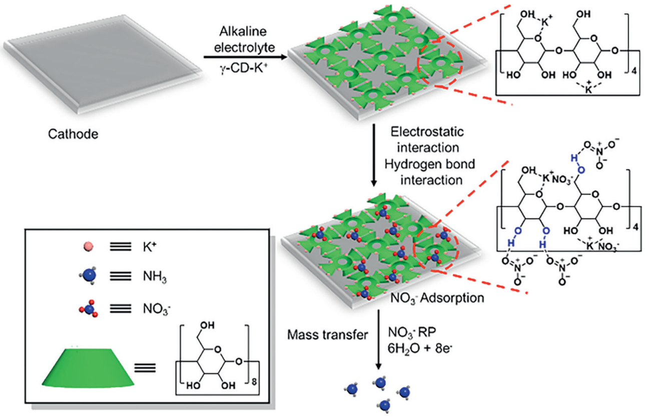


**Fig. 10.** The electrochemical nitrate reduction process catalyzed by $\gamma$-CD-$K^+$. Copied with permission [45]. Copyright 2022, American Chemical Society.

the coordinated $K^+$ ions had an affinity for $NO_3^-$ *via* electrostatic interaction, which were contributed to the enrichment effect of $NO_3^-$ ions and further improved the performance of electroreduction over the electrode.

Xuan and coworkers [46] utilized hydrogen bonding and van der Waals contacts between polyoxometalate and $\alpha$-CD to construct organic-inorganic hybrid framework. The supramolecular polyoxometalate-CD framework displayed 1D rod-like shape and opened channels along with the a- and c-axes. The porous structure facilitated the selective oxidation of sulfides to sulfoxides at room temperature with high selectivity up to 99%.

The complex responding to external stimuli could be used to design supramolecular system with regulated catalytic activity. Liu's group [47] reported a photo-controllable supramolecular catalytic system of polycationic $\alpha$-CD **10** and Au nanoparticles (Fig. 11). Azobenzene-modified diphenylalanine guest molecule was used to regulate the catalytic activity. After exposing to UV irradiation, guest molecule underwent the *trans-cis* isomerization and exited from the $\alpha$-CD cavity, triggering the catalytic activity of Au nanoparticles to selectively oxidize glucose.

CDs exhibited many unique properties, such as excellent water solubility, inherent chirality, spectrally transparent, low toxic-

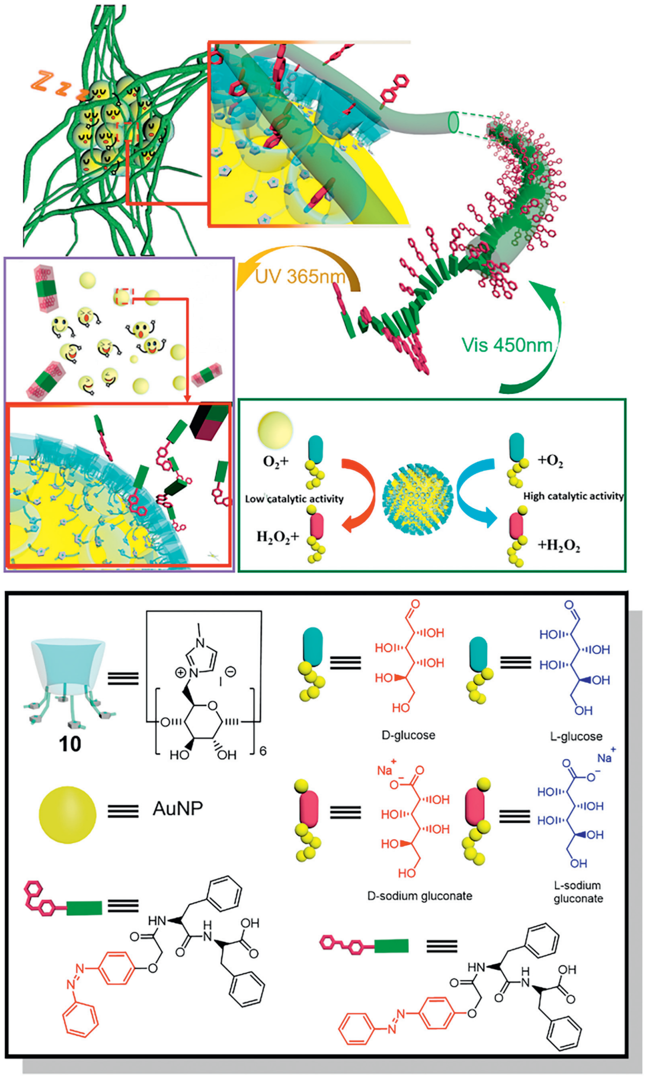


**Fig. 11.** Photo-control of the catalytic activity of polycationic $\alpha$-CD/Au nanoparticles assemblies and chiral recognition catalytic process. Copied with permission [47]. Copyright 2021, Wiley-VCH GmbH.

ity, biocompatibility, and biodegradable. The hydrophobic cavities of CDs can accommodate a wide range of substrates *via* hydrophobic interactions. Therefore, CDs are ideal carriers for hydrophobic organic molecules and catalyze reactions in water for the green synthesis. Moreover, the chiral cavities of CDs provide the chiral microenvironment for guest molecules to control the regional and stereoselectivity. However, CDs are susceptible to degradation in the presence of strong acids, making them ineffective as catalysts under low pH conditions.

### *2.3. The applications of calixarenes in supramolecular catalysis*

Calixarenes with a cup-like structure are synthesized from the condensation of *p*-alkylphenols and formaldehyde under basic conditions [48]. The lower and upper rims of calixarenes are relatively easy to modify, which could enhance the affinity for neutral and charged species and be employed as a supramolecular catalytic system [49].

Li and co-workers [50] synthesized calix[4]arene derivatives **11** decorated with bis-squaramide at the upper rim to catalyze a serial of asymmetric Michael addition of 1,3-dicarbonyl compounds (Fig. 12). Calix[4]arene cavity and squaramide catalytic centers promoted the asymmetric Michael addition reactions synergistically. Subsequently, Arduini and co-workers [10] synthesized a versatile calix[6]arene derivatives modified with trifluoromethylsulfonamide at the upper rim to catalyze Michael addition of indoles under *pseudo*-physiological reaction conditions. The hydrogen bonding interactions between trifluorosulfonamide moieties and nitro groups could lower activation barrier, promoting the nucleophilic attack of the indoles.

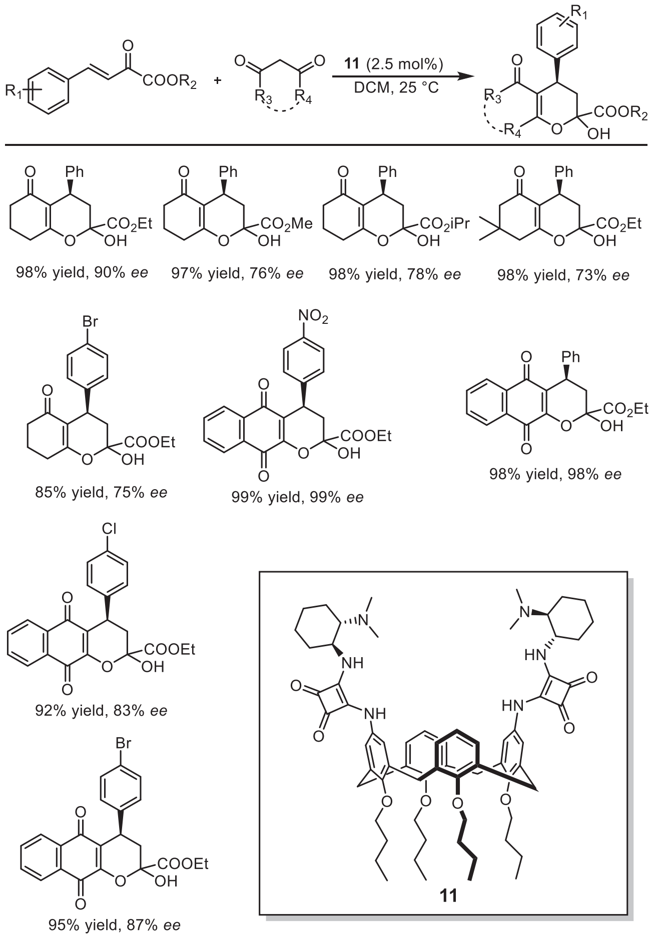


**Fig. 12.** The asymmetric Michael addition reaction of $\beta$-unsaturated $\alpha$-keto esters and 1,3-dicarbonyl compounds [50].

Salvio and co-workers [51] synthesized amphiphilic calix[4]arenes **12**, which have four guanidine or arginine units at the upper rim to cleavage the phosphodiester bond of DNA or RNA model compounds efficiently (Fig. 13). In their work, the long alkyl chains of **12** at the lower rim could block the cone conformation and the amphiphilic chains led to spontaneous aggregation and improved the reaction rate in solution.

Würthner's group [52] synthesized oligo(ethylene glycol)-functionalized axial calix[4]arene ligands for light-driven catalytic water oxidation. The ethylene glycol chains could provide sufficient water solubility for catalytic water oxidation. Moreover, the water-soluble calix[4]arene-based cyclic dinuclear ruthenium complex showed the outstanding catalytic activity of photocatalytic water oxidation with a turnover frequency of 15.5 $s^{-1}$.

The modification of calixarenes with specific functional groups can have a significant influence on molecular recognition and catalytic activity. Among them, sulfonic acid group allow for the macrocycles to mediate acid-catalyzed reactions. Ethylene glycol chains could enhance the water-solubility. Charged groups can promote the electrostatic interactions and induce spontaneous aggre-

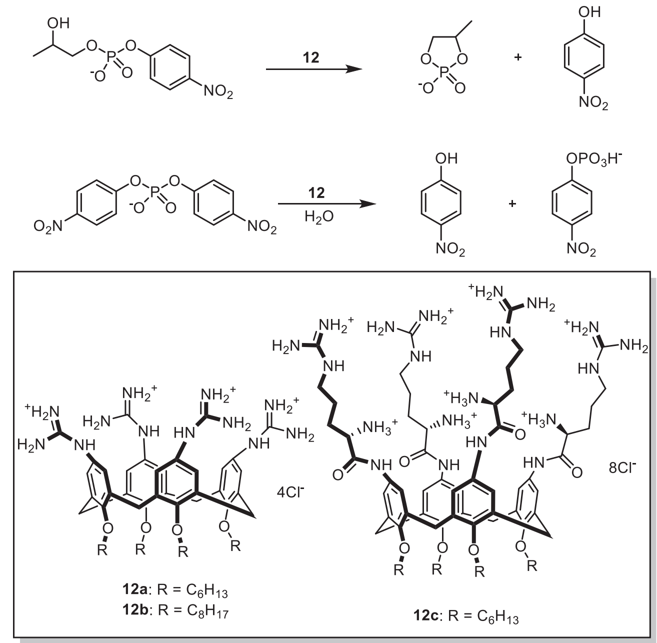


**Fig. 13.** The amphiphilic calix[4]arenes catalyzed phosphodiester cleavage [51].

gation. Additionally, the combination of calixarene cavities and catalytic centers elicits a synergistic effect, resulting in exceptional catalytic performance. These distinguishing characteristics position calixarene as a superior framework for supramolecular catalysis.

### 2.4. The applications of pillararenes in supramolecular catalysis

Pillararenes are pillar-shaped macrocycles connected by -$CH_2$- in para position, which was firstly reported by Ogoshi and coworkers [53]. Compared with the macrocycles discussed before, pillararenes also possess hydrophobic cavities to accommodate organic reactants or stabilize the forming transition state [54]. Moreover, the modification at both rims is also easy to achieve. Notably, the structure of pillararenes is relatively rigid and the conformations are well-defined, which make pillararenes as the highly-studied scaffolds in supramolecular chemistry [55].

Carboxylated pillararenes could form stable host-guest complex with cationic guest, such as molecule with trimethylammonium group. Sashuk's group [56] found the electrostatic interaction between carboxylic groups in pillararenes and trimethylammonium group in hydrazones is crucial for the hydrolysis of hydrazones in water. Wang and coworkers [57] utilized carboxylated pillar[5]arene **13** and photosensitizer with ammonium terminal group to construct stable supramolecular nanoparticles in aqueous solution (Fig. 14). The aggregation behavior of photosensitizer induced by pillar[5]arene could enhance fluorescence significantly. Moreover, the obtained nanoparticles exhibited the excellent ability to generate singlet oxygen, which could be used as nanoreactors to oxidize dopamine to polydopamine. Encapsulating catalase or adamantane derivative (AMPPD) could increase the $^1O_2$ generation efficiency. Simultaneously, carboxylated pillar[5]arene was utilized to construct highly efficient artificial light-harvesting systems by the same group [58]. Pillar[5]arene could lower the critical aggregation concentration of salicylaldehydeazine derivative and enhance its aggregation-induced emission effect in aqueous solution. The nanoparticles formed *in-situ* could transfer energy to the entrapped dyes such as Eosin Y and Nile Red for further chemical transformations. The antenna effect of the artificial light-harvesting systems reached 30.1 at donor/acceptor ratio of 200/1. Due to the capability of excitation free radical, these supramolecular systems were applied for the photocatalytic dehalogenation reaction of $\alpha$-bromoacetophenone in higher yields than that with dyes due to the minimizing photobleaching effect.

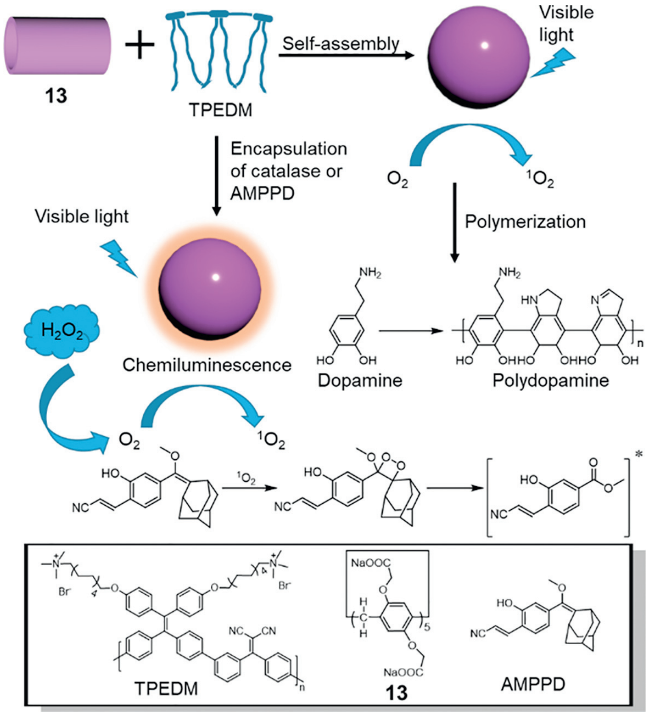


**Fig. 14.** The system of singlet oxygen generation based on carboxylated pillar[5]arene. Copied with permission [57]. Copyright 2020, Elsevier B.V.

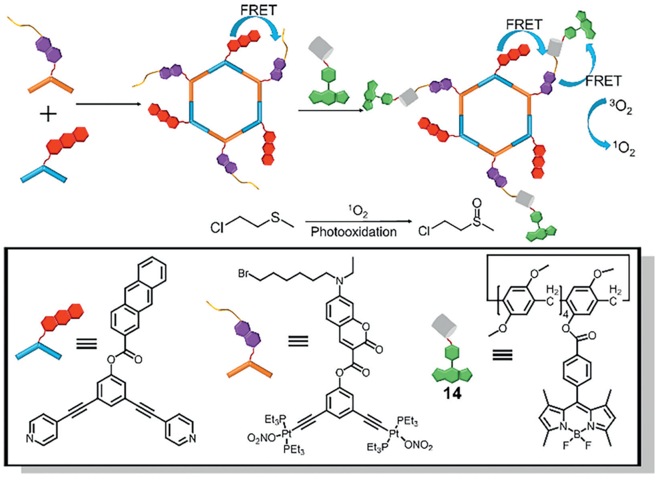


**Fig. 15.** The photooxidation reaction of pillar[5]arene-based energy transfer supramolecular system [59].

Yang and co-workers [59] reported pillar[5]arene-based energy transfer supramolecular system for photosensitized oxidation of sulfide (Fig. 15). The energy transfer depends on the donor-acceptor distance. The metal-ligand coordination between dipyridyl building block labeled with anthracene and coumarin-containing diplatinum(II) building block, and the host-guest interactions between dipyrromethene boron difluoride-containing pillar[5]arene building block **14** and the long-chain alkyl bromide moieties in coumarin building block, could control the distance and the number of fluorophores precisely. In addition, the two-step fluorescence-resonance energy transfer system exhibited 1.5-fold higher $^1O_2$ generation efficiency and 1.2-fold higher photoox-

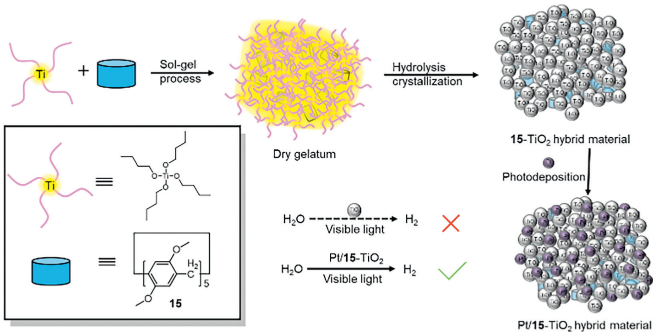


**Fig. 16.** The fabrication of the organic-inorganic hybrid material and photocatalytic water splitting [63].

idation activity than that of its corresponding one-step energy transfer system, which proved that orthogonal self-assembly was an efficient approach to improve catalytic activity. Wen and co-workers [60] reported the conjugated macrocycle polymers with pillar[5]arene struts to catalyze the oxidation of sulfides. Interestingly, the conversion and yields were proportional to the binding strength of pillar[5]arene toward the sulfides, which confirmed the host-guest interactions could induce the different catalytic performance for different substrates.

In addition to forming inclusion complexes with organic molecules within their hydrophobic inner cavity, pillararenes could also be employed to form organic-inorganic hybrid materials. Zhao and co-workers [61] obtained Au nanoparticles with average diameter of 2–3 nm for the catalytic reduction of nitroaromatics. 2D covalent organic framework and macrocyclic host pillar[6]arenes could prevent the nucleation increase of Au, so that the heterogeneous 2D catalyst could show highly catalytic performances. Yao and co-workers [62] prepared hybrid polymeric materials by incorporating Pd nanoparticles into a pillar[5]arene-based supramolecular polymer, which was used as green catalysts to catalyze reductions of toxic nitroaromatics and C—C bond-forming Suzuki—Miyaura reaction in aqueous solution. The acylhydrazone units in supramolecular polymer could control the size of Pd nanoparticles. Finally, ultrafine Pd nanoparticles of nearly 4 nm was synthesized and exhibited desirable catalytic activity. Jia and co-workers [63] prepared organic-inorganic hybrid material with p-dimethoxy pillar[5]arene **15** and titanium dioxide through sol-gel method (Fig. 16). After loading Pt nanoparticles, the supramolecular hybrid material was applied in photocatalytic water splitting with visible light and showed good activity and stability.

Pillararenes tend to encapsulate linear chain molecules within their cavities. Modifying the upper or lower rims of pillararenes can enhance their binding strength, enabling the construction of supramolecular aggregates with specific catalytic activity. The variances in binding constants result in selective binding of guest molecules by macrocyclic hosts, giving rise to pillararene-based catalysts with unique selectivity. Additionally, the rigid and symmetrical structure of pillararenes contributes to the improved stability of these assemblies. These exceptional physical and chemical properties have garnered significant attention and led to extensive studies on pillararenes as supramolecular catalysts.

### 2.5. The applications of cucurbiturils in supramolecular catalysis

Cucurbiturils (CBs) are pumpkin-shaped macrocycle composed of glycoluril units bridged by methylene units [64]. Compared with crown ethers and CDs, the structure of CBs is rather rigid. CBs possess hydrophobic cavity and hydrophilic carbonyl portals, which enabled them to bind substrates or stabilize transition state selectively [65].

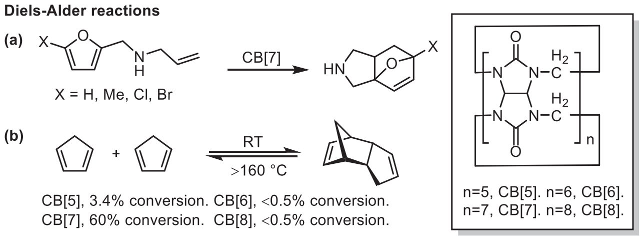


**Fig. 17.** (a, b) Diels—Alder reactions catalyzed by CB[*n*]s [66,67].

The Diels—Alder reaction is a widely utilized molecular transformation for assessing the catalytic efficiency of macrocycles. Rosta's group utilized cucurbit[7]uril (CB[7]) as a macrocyclic container to enhance the Diels-Alder reaction of *N*-allyl-2-furfurylamine derivatives [66]. The presence of CB[7] significantly accelerated the cycloaddition rates (Fig. 17a). Both calculations and experimental findings indicated that the catalytic effects were a result of conformational changes, electrostatic shielding, and $pK_a$ shifts of the ligand. Another study by Nau and co-workers [67] utilized cucurbit[*n*]uril (CB[*n*], $n = 5–8$) as supramolecular catalysts for catalyzing Diels-Alder reactions involving cyclopentadiene (Fig. 17b). Among these variants, only CB[7] exhibited rapid conversion of cyclopentadiene to dicyclopentadiene. This acceleration effect can be attributed to CB[7] effectively confining the substrates, leading to the formation of tightly packed complexes.

The hydrophobic cavities of CB[*n*] play a crucial role in stabilizing reactants or transition states, thereby influencing the reaction process. For instance, Li *et al.* [68] demonstrated that CB[5] can stabilize $NH_3$ molecules at the entrances of the host and widen the forbidden energy gap. This stabilization effect led to a negative shift in both the conduction band and the valence band potentials, thereby enhancing the migration efficiency. Another study by Jiang *et al.* revealed that CB[6] could effectively encapsulate high-energy water, making it a suitable container for this purpose [69]. In Meng's work [70], CB[7] was reported to catalyze Click cycloaddition reactions by stabilizing the reactants, preventing copper(I) oxidation, and accelerating the reaction. Lee *et al.* [71] investigated the thermally activated isomerization reactions of m-xylene and found that CB[6] selectively catalyzed the meta-to-para isomerization by stabilizing the transition state. Ge *et al.* [72] demonstrated a selective pinacol rearrangement of hydrobenzoins mediated by CB[7], where the encapsulation of substrates within the CB[7] cavity led to the formation of ketones as the sole product.

Regarding CB[*n*] ($n$ = 8, 10), the hydrophobic cavity is sufficiently large to accommodate two guests simultaneously, forming a ternary complex. In a study conducted by Niemeyer's group [73], viologen-functionalized water-reducing catalysts and naphthol-functionalized photosensitizers were synthesized (Fig. 18). CB[8] was capable of binding the electron-poor viologen and the electron-rich naphthol units, resulting in the formation of heteroternary 1:1:1 complexes. This arrangement brought the catalyst subcomponents into closer spatial proximity, thereby enhancing the photocatalytic efficiency. Another research team, led by Das [74], employed the CB[8]-stabilized charge-transfer ternary complex of pyrene and viologen derivatives to construct vesicular nanozymes.

Liu and coworkers [75] developed a novel method to create an organic 2D polypseudorotaxane using a naphthol-modified porphyrin (TPP-Np), viologen derivatives (DMV), and CB[8] (Fig. 19). This polypseudorotaxane served as a versatile platform for the synthesis of highly refined Pt nanoparticles. The oxygen atoms present at the periphery of CB[8]'s macrocycle structures played a crucial role in stabilizing the Pt nanoparticles, while the macrocycle struc-

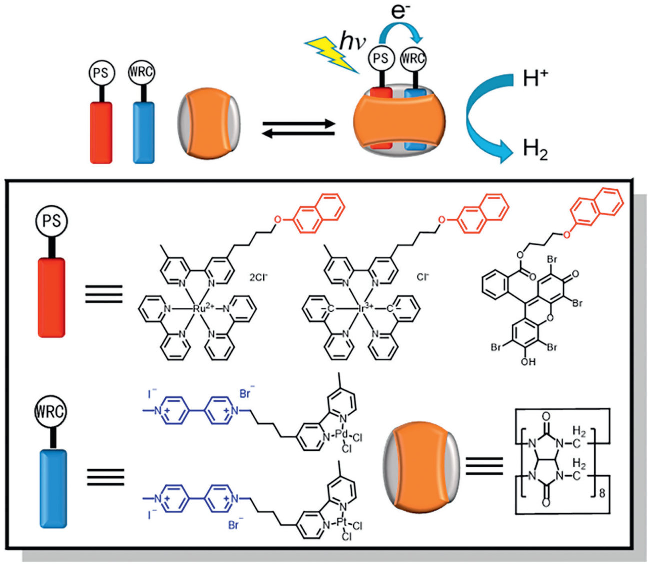


**Fig. 18.** Photocatalysts for hydrogen generation and water reducing catalysts based on hetero-ternary host-guest complexes of CB[8] [73].

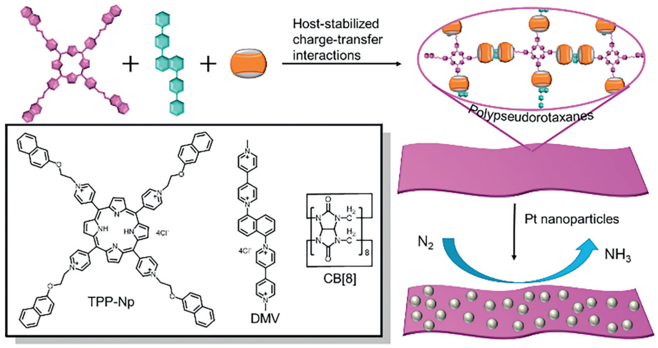


**Fig. 19.** The construction of the 2D polypseudorotaxanes based on CB[8] *via* host-stabilized charge-transfer [75].

tures themselves provided localized hydrophobic sites that inhibited competing reactions. These characteristics were particularly advantageous for enhancing the electrochemical nitrogen reduction reaction.

Li and co-workers [76] attached six styrylpyridinium units to $[Ru(bpy)_3]^{2+}$ cores. CB[8] could not only bind styrylpyridinium units to formed highly stable porous three-dimensional metallo-supramolecular polymer, but also promote [2 + 2] photodimerization of the ethylene units. The photodimeric metallosupramolecular polymer exhibited the higher catalytic activity for visible light photocatalysis of organic transformations as a result of increased stability. Subsequently, Xu and co-workers [77] prepared CB[8]-based supramolecular organic framework for catalyzing aerobic oxidation of aryl boronic acids and thioethers. The tetra-arm monomer containing four *N,N*'-dimethyl 2,5-bis(4-pyridinium)thiazolo[5,4-*d*]thiazole could form stable supramolecular dimer in the cavity of CB[8], which led to the effective concentration of the dimer and improved catalytic performances.

Despite the absence of chiral cavities like CDs, CB[*n*] can still be utilized to regulate the photodimerization of anthracene derivatives. A noteworthy example is the work conducted by Liu's group [78], which investigated the photodimerization of 9-substituted anthracene derivatives within the cavities of CB[8] and CB[10] (Fig. 20). Interestingly, the desired reaction took place when CB[10] was employed as the catalyst, while an unexpected observation of photosolvolysis occurred when CB[8] was used as the catalyst.

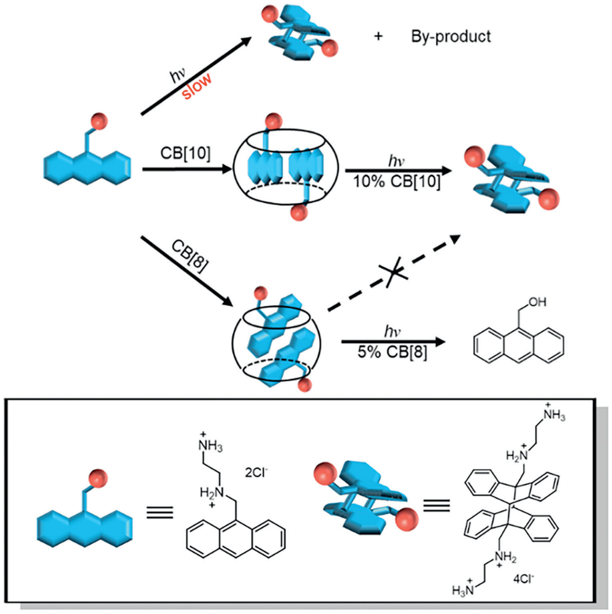


**Fig. 20.** CB[*n*]-mediated photodimerization of 9-substituted anthracene derivative [78].

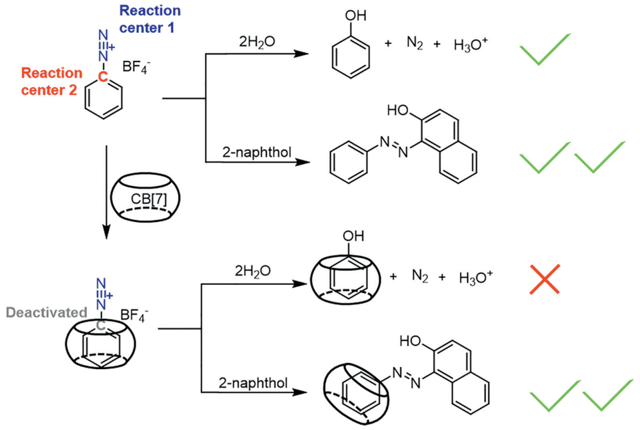
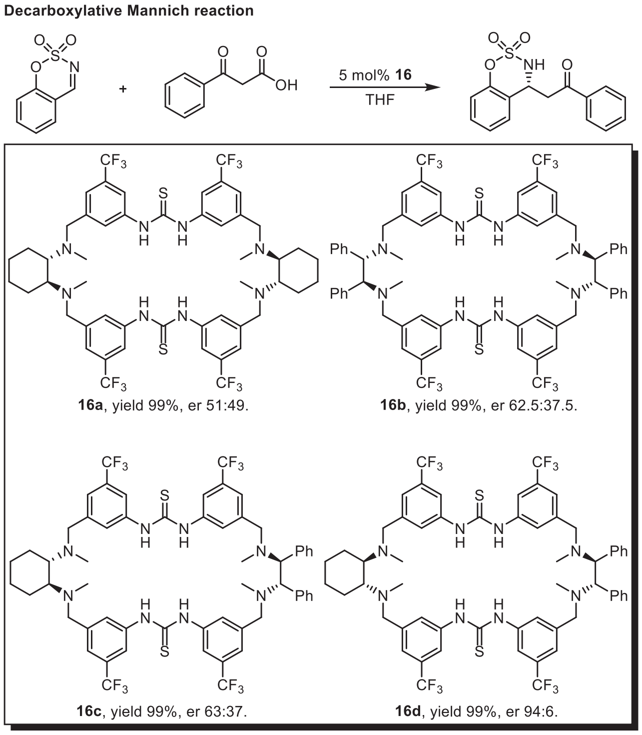


**Fig. 21.** The reaction pathway of phenyl diazonium ions with and without CB[7] [80]. Reactions were performed in aqueous media at 25 °C.

Cucurbiturils could exhibit both catalytic and inhibitory properties, depending on the substrate molecules involved. For instance, Xu's group [9] demonstrated that cucurbit[8]uril (CB[8]) can enhance the Fenton degradation of a perylene diimide dye. CB[8] formed a supramolecular complex with the dye in a 1:1 molar ratio, inhibiting its aggregation in aqueous solutions. This inhibition led to an increased collision frequency between the dye and oxidants, thus accelerating the reaction. Moreover, the oxidation products were released from the CB[8] cavity, enabling the encapsulation of another dye molecule and establishing a catalytic cycle. Aliaga and coworkers [79] reported that CB[7] inhibits the hydrolysis of Schiff bases. This inhibited effect can be attributed to the inclusion of the coumarin scaffold when CB[7] is present in excess, preventing the attack of a water molecule. Lee's group [80] investigated the influence of CB[7] on the reaction pathway of phenyl diazonium ions (Fig. 21). Phenyl diazonium ions possess two electrophilic reaction centers, the $\alpha$-carbon and the diazo group. Through complexation with CB[7], the electrophilic $\alpha$-carbon was deactivated while the diazonium group remains active for diazo coupling. The deactivation of the $\alpha$-carbon site could be



**16a**, yield 99%, er 51:49. **16b**, yield 99%, er 62.5:37.5.

**16c**, yield 99%, er 63:37. **16d**, yield 99%, er 94:6.

**Fig. 22.** Macrocycle-catalyzed decarboxylative Mannich reaction of cyclic aldimine with $\beta$-ketoacid [83].

attributed to electrostatic interactions between the cationic diazonium group and the portal of CB[7].

CB[*n*] serves as highly efficient molecular containers, offering a hydrophobic environment and confined space for guest reactants. By arranging substrates in a preorganized state through noncovalent interactions or stabilizing reaction intermediates, CB[*n*]s exert precise control over the reactivity and selectivity of chemical reactions. With their high association constants towards reactants or intermediates, coupled with weak binding to the resulting product to facilitate efficient catalytic cycles. These distinctive properties make CB[*n*]s exceptional catalysts, finding application in diverse organic reactions. However, it should be noted that modifying CB[*n*]s is more challenging compared to crown ethers, cyclodextrins (CDs), calixarenes, and pillararenes. Additionally, CB[6], CB[8], and CB[10] are almost insoluble in water, with increased solubility achievable only in acidic solutions or by forming host-guest complexes, which may restrict their applicability to some extent.

### *2.6. The applications of other macrocycles in supramolecular catalysis*

The advancement of supramolecular catalysis relies on the progress in creating innovative macrocycles. The pursuit of synthesizing macrocycles with exceptional structure and function has been a central objective for supramolecular chemists. This endeavor holds the potential to enhance the exploration of highly efficient artificial catalytic systems, particularly for catalyzing complex reactions that pose significant challenges [81,82].

Wang's group [83] successfully synthesized tetraamino-bisthiourea chiral macrocycles **16**, which were utilized as catalysts in the decarboxylative Mannich reaction of cyclic aldimines containing a sulfamate heading group (Fig. 22). The crystal structure analysis revealed that the presence of a sulfate anion induced the formation of a sandwich-like complex involving two macrocycles. This substrate-induced dimerization caused the macrocycles to adopt an n extroversive conformation, activating the imine substrate for nucleophilic attack and resulting in high yield and enantioselectivity. Subsequently, they retained the bis-diarylthiourea motifs to ensure high binding affinity towards sulfonate anions. They further modified the chiral moieties to BINOL in order to synthesize chiral bisthiourea macrocycles [84]. These macrocycles exhibited strong binding affinities towards ethanedisulfonate and displayed high *ee* values in the Friedel-Crafts reaction of indoles.

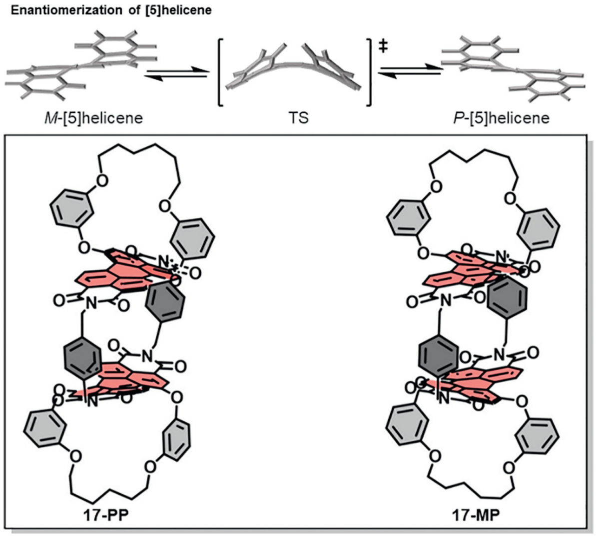


**Fig. 23.** Optimized equilibrium and transition state pertaining to the enantiomerization of [5]helicene. Copied with permission [85]. Copyright 2023, Wiley-VCH GmbH.

Recently, Würthner and colleagues [85] synthesized a chiral perylene bisimide cyclophane **17**, which served as a catalyst for the enantiomerization of [5]helicene (Fig. 23). The unique chiral cavity in the cyclophane facilitated the binding of the [5]helicene enantiomer and stabilized the transition state. Notably, the rate of [5]helicene enantiomerization was remarkably accelerated.

## 3. Conclusions and perspectives

In nature, enzyme catalyzed reactions majorly rely on the selectivity of substrates. Similarly, the specific binding between reactants and macrocycles plays a crucial role to affect the yield and selectivity of reactions. The advantages of macrocycles have been exhibited in different types of reactions, therefore, the following key points must be considered to design a supramolecular catalyst involving macrocycles.

The first factor to consider is the size of the cavity in macrocycles, which plays a crucial role in facilitating supramolecular catalysis. Macrocyclic analogues with varying numbers of repeating units exhibit different bonding constants with the same substrate due to the size-matching effect. For example, crown ethers like 15C5 exhibit a strong affinity for specific alkali metal ions like $Na^+$, while 18C6 shows a similar affinity for $K^+$ and 21C7 for $Cs^+$. Additionally, macrocycles with more repeating units, such as CB[8] and CB[10], accommodate multiple substrates simultaneously. This allows for closer spatial proximity of the reactants, thereby promoting dimerization reactions.

The second crucial aspect is the selection of functional groups that are modified at the periphery of macrocycles or substrates. Macrocycles often possess confined spaces that contribute to stabilizing both the ground state and the transition state through their inner cavities. Incorporating functional groups at the reactive periphery of macrocycles imparts the capability to selectively recognize specific molecules and enhances regio/stereoselectivities. Similarly, modifying substrates with functional groups not only enhances complexation with macrocycles but also imparts responsiveness to external stimuli, such as light, pH, temperature, thereby allowing regulation of catalytic performance.

The last consideration is the synergistic effect between macrocycles and catalytic center. Macrocycles can not only function as catalysts alone, but also incorporate with other catalytic center to enhance the catalytic activity. For example, CDs, calixarenes, and pillararenes modified with positively or negatively charged group could lower the critical aggregation concentration and induce guests to form supramolecular aggregate, which could further enhance aggregation-induced emission effect and increase the effective concentration of the active sites resulting in a better catalytic performance. Metal nanoparticles possess excellent catalytic activity. Macrocycles can stabilize active centers, enhance water solubility, and promote the formation of metal nanoparticles with uniform size to increase catalytic activity.

In the past few decades, various macrocyclic hosts have been developed as supramolecular catalysts to control chemical reactions. However, the tedious synthesis procedure, low yield, and complex conformation pose challenge for the design and development supramolecular macrocyclic catalysts. Despite of the advances in theoretical calculation, which provides explanations for the possible catalytic mechanism, some supramolecular effects in catalytic process remains unknown. Moreover, novel macrocycles may bring us new functions, and even new reactions in catalysis. However, their catalytic properties are poorly explored. Towards these deficiencies, research will continue to enrich the variety of macrocycles and the understanding of supramolecular catalytic mechanism.

## Declaration of competing interest

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

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