Tetrahedron Letters 105 (2022) 154052

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Digest paper

Photocatalytic molecular containers enable unique reactivity modes in confinement

Senuri G. Jayawardana, Ella C. Madura, Víctor García-López *

Department of Chemistry, Louisiana State University, Baton Rouge, LA 70806, United States

ARTICLE INFO

Article history:
Received 29 May 2022
Revised 19 July 2022
Accepted 26 July 2022
Available online 29 July 2022

Keywords:
Photocatalytic molecular containers
Confinement
Photoinduced electron transfer
Energy transfer

ABSTRACT

Photocatalytic molecular containers are discrete molecules with photosensitizers or photoredox units in their framework for the indirect light activation of the guest molecules in their cavity. Thus, such containers can carry out unique chemical reactions with high reaction rates, efficient energy or electron transfer, and distinctive regio- and stereoselectivity due to the confinement effects, making them great prospects for organic synthesis. Hence, this digest describes the general considerations for designing and studying photocatalytic molecular containers and showcases their potential by discussing the most representative examples. We forecast new paradigms in organic chemistry and photochemistry will originate from this relatively young field deeply rooted in supramolecular chemistry and photochemistry.

Contents

Introduction

Molecular containers (MCs) [1], such as cages, cavitands, hemicarcerands, cyclodextrins, cucurbiturils, and cyclophanes, are molecules of nanoscopic dimensions with a permanent and intrinsic cavity for the binding or complexation of smaller molecules. Moreover, the confined guests can exhibit different chemical, optoelectronic, and physical properties than in isotropic solutions [2–5]. For instance, confinement accelerates reactivity, enhances or inverts regio- and stereoselectivity, and sometimes enables new reactions [5–11]. This occurs because guest molecules can orient in specific ways or fold into unusual shapes adopting energy-demanding conformations to fit inside the cavity, favoring rearrangements through unique intra- or intermolecular interactions and increasing the effective substrate concentration by several orders of magnitude. Also, confinement can stabilize reactive intermediates or transition states with short lifetimes in the bulk solution [5,12–16].

Accordingly, a tremendous area of opportunity is using light to drive reactions in confinement. For example, the seminal works of Cram [17,18], Kim [19], Ramamurthy [20,21], Sivaguru [22], Macartney [23], Turro [24], Inoue [25–28], Fujita [29–31], Raymond [32], and others have provided extraordinary insights into the fundamental understanding of the light-driven generation and reactivity of the guests' excited states (G^*) and radicals ($G^{\bullet+}$ or $G^{\bullet-}$) inside different MCs. However, widespread use of such systems in chemical synthesis is limited by the need for direct excitation of the guest molecules with harsh short-wavelength

---

* Corresponding author.
E-mail address: vglopez@lsu.edu (V. García-López).

https://doi.org/10.1016/j.tetlet.2022.154052
0040-4039/

irradiation (~254 nm), which could lead to poor selectivity and undesired side reactions. In some instances, longer wavelengths ($\leq$350 nm) could be used, but this is restricted to guest molecules that absorb at that wavelength, limiting the scope of the reaction.

However, such limitations can be overcome by developing photocatalytic molecular containers that in addition to providing the confined space, act as photoredox catalysts or photosensitizers for the indirect generation of the guest's reactive species (G^*, $G^{\bullet+}$ or $G^{\bullet-}$) at longer wavelengths, commonly visible light. The confinement can enhance the efficiency of the photoinduced electron (PET) or energy transfer (*EnT*) process, and modulate the lifetime, reactivity, and selectivity of the guest (G^*, $G^{\bullet+}$ or $G^{\bullet-}$), enabling unique reactivity modes not observed with traditional methods.

Yet, the photochemical generation of the guest's reactive species is just the first step in the catalytic process. The formed radical ($G^{\bullet+}$ or $G^{\bullet-}$) or excited state (G^*) should then participate in an intra- or intermolecular reaction within the cavity to form the desired product. Finally, a guest exchange must occur between the product and a new guest molecule. This step is very important for catalytic turnover and preventing product inhibition. Thus, it is critical to determine and understand the kinetics and thermodynamics of molecular binding, guest exchange, and photocatalysis when working with photocatalytic molecular containers. Also, in some cases, it is important to interpret the role of multiple photoactive units around a single cavity. So, there is still a need for extensive mechanistic studies and deep fundamental understanding to accelerate this field so it can become a practical tool in organic synthesis.

Accordingly, MCs are ideal systems for mechanistic investigations in homogenous solutions; they are discrete structures with well-defined cavities and can be soluble. Such properties facilitate their purification by standard procedures like recrystallization and chromatography and mechanistic studies with conventional solution-based nuclear magnetic resonance (NMR) spectroscopy, UV–vis, fluorescence, and transient absorption (TA) spectroscopies. Moreover, the guests in the cavities of molecular containers exhibit minimal disorder for single-crystal X-ray diffraction (SC-XRD) studies. In combination, all these techniques make it possible to elucidate the guest's conformation, orientation, interactions with the container, and structure/property transitions. Furthermore, the synthetic flexibility of photocatalytic molecular containers allows fine-tuning the cavity size, shape, and stereo- and optoelectronic properties, providing a diversity of confined spaces to achieve extraordinary chemical transformations [33].

This perspective highlights the potential of photocatalytic molecular containers to promote and control the generation, reactivity, and selectivity of highly reactive species and enable distinctive reactivity modes; it presents current and merging strategies for designing and studying new photocatalytic MCs. So, this digest focuses on MCs that enable chemical transformations in their cavities through a PET or *EnT* process between the guest and the container and does not aim to cover all other photoactive MCs designed for other applications. Although, the latter could be repurposed to carry out photochemical transformations.

Likewise, other photocatalytic porous materials, such as metal–organic frameworks (MOFs), covalent organic frameworks (COFs), and mesoporous inorganic solids (e.g., zeolites and mesoporous silica), are out of the scope of this digest. Such systems are insoluble extended tridimensional networks and behave as solid phases. In some cases, they can suffer from crystallographic disorder caused by the disorganization of the guest molecules inside the frameworks [34]. Other systems such as micelles, lipid bilayers, and some polymers with less defined cavities and pores are not discussed either. Nevertheless, these larger assemblies are promising materials for heterogeneous catalysis, gas adsorption, and other applications [35].

General considerations for designing photocatalytic molecular containers

Although photoredox catalysis or photoinduced electron transfer (PET) has been widely investigated in solution [36–38], there are very few examples of MCs displaying truly intra-cavity photoredox catalysis. On the other hand, energy transfer (*EnT*) photocatalysis or photosensitization remains relatively underdeveloped in bulk solutions and even less in confinement, besides having recently emerged as a promising approach to access highly reactive triplet states with unprecedented reactivity [39,40]. Nevertheless, most of the concepts and analytical techniques used for studies in bulk solutions provide valuable insights for designing photocatalytic molecular containers and investigating and elucidating their mechanistic schemes.

When designing MCs to accomplish the desired reactivity, the properties of the photocatalytic units in both the excited and ground states must be considered, specifically, the energies, lifetimes, and quantum yields of the excited states. Also, it is essential to assess the cavity properties (i.e., shape and size) and the thermodynamic and kinetic features of both the photocatalytic process and the container-guest/product interactions (i.e., binding affinity, guest exchange, etc.).

Mechanistically, the first stage of the process consists of generating the guest reactive species ($G^{\bullet+}$, $G^{\bullet-}$ or G^*). In an ideal scenario, the photoredox catalyst (PC) in the container absorbs light in the visible region and reaches the excited state (PC^*), with unique redox properties; then, it participates in a single electron transfer (PET) process with the encapsulated guest (G) (Fig. 1**A**), generating the radical intermediate ($G^{\bullet+}$ or $G^{\bullet-}$). The guest radicals can react with another molecule (X) in the cavity and generate the desired product (P) or could escape the cage and undesirably react outside the cavity. Then, the catalyst turnover involves the oxidation or reduction of the catalyst radical ($PC^{\bullet+}$ or $PC^{\bullet-}$) by either a guest molecule, an intermediate, or an external redox-active molecule commonly referred to as sacrificial electron donor (D) or acceptor (A). However, there is a chance that the radical intermediates ($G^{\bullet+}/G^{\bullet-}$ and $PC^{\bullet+}/PC^{\bullet-}$) participate in a fast charge recombination reaction and regenerate the corresponding ground states without producing the desired photocatalysis. A good indication of the feasibility of a photoredox transformation can be provided by calculating the Gibbs energy of photoinduced electron transfer (ΔG_{PET}) [38].

On the other hand, molecular containers using energy transfer (*EnT*) photocatalysis follow the Dexter mechanism; the photocatalyst (PC) or photosensitizer is excited to its singlet excited state ($^1PC^*$), then undergoes intersystem crossing (ISC) to its triplet excited state ($^3PC^*$), which transfers one electron to the LUMO of the guest while simultaneously receiving a HOMO electron from the guest. Such a process generates the excited triplet state of the guest ($^3G^*$) through the transfer of excited-state energy and spin multiplicity (Fig. 1**B**) [40]. The formed $^3G^*$ can react in the cavity or escape the confinement and undesirably react outside in the solution.

The feasibility of *EnT* can be predicted by evaluating the thermodynamic driving force. Thus, the photocatalyst must have a higher triplet excited-state energy (E_T) than the guest. Such E_T values can be obtained from the emission spectra, sensitization experiments, or computational studies. Furthermore, the photosensitizer should have a high absorption cross-section at the desired wavelength, efficient intersystem crossing (ISC) to its triplet state, and a sufficiently long excited triplet state lifetime (τ_T) [39,40].

Considering all the different processes and mechanisms involved, deep mechanistic investigations to fully elucidate the

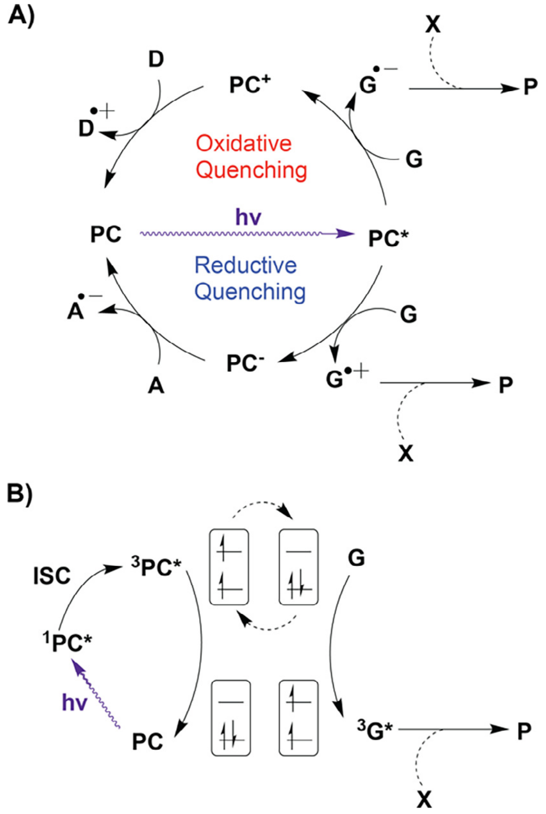

Fig. 1. General mechanisms for photocatalysis. A) Photoredox catalysis (PET) adapted from reference [41] with permission from Royal Society of Chemistry and B) Photosensitization (*EnT*) adapated from reference [40] with permission from Elsevier. PC = Photocatalyst, A = Acceptor, D = Donor, G = Guest, P = Product, X = Could be a second guest molecule, or an external molecule.

photocatalytic pathway are crucial. This is particularly important because, in some cases, the containers could follow different pathways (i.e., chain process or formation of charge transfer complexes or exciplexes) and still form the desired product [38,42]. Thus, UV–vis, transient absorption, actinometry, and steady-state and time-resolved fluorescence and phosphorescence measurements can provide valuable insights.

Assuming the reaction occurs in the cavity and not in the bulk solution, the second stage in the process consists of a guest exchange, where the product is released, and a new substrate molecule occupies the cavity either through a concerted process (an associative mechanism) or a dissociative mechanism [43]. Therefore, it is paramount that the binding affinity of the reactive guest (G) substrate is more significant or at least comparable to the binding affinity of the product (P) to prevent product inhibition during the catalytic processes. Fig. 2 shows the ideal scenarios of unimolecular and bimolecular transformations involving 1:1 and 1:2 MC-G complexes as previously described by Sivaguru [22]. However, there are containers that can encapsulate more than two guests or follow different mechanisms. Consequently, careful thought should be given to tuning the non-covalent interactions and elucidating the thermodynamics and kinetics of the guest exchange. In this regard, methods such as fluorescence titrations, isothermal calorimetric titrations (ITC), NMR, and stopped-flow measurements are beneficial.

Likewise, it is vital to demonstrate that the reaction occurs in the cavity and not outside. Observing a higher reaction yield, regio- or stereoselectivity does not automatically indicate the reaction took place in the cavity. This could occur in some cases because the photocatalyst has enhanced photocatalytic properties while fixated in the cage frame than as a free molecule in bulk solution. Thus, appropriate control experiments are required; for example, one approach can be blocking the cage with “inert” guests with higher binding affinities than the guest substrate, so the reaction occurs exclusively outside the cavity. A different control experiment could be using bulky substrates that do not fit in the cavity but can participate in the reaction outside.

Examples of photocatalytic molecular containers

Only a few examples of molecular containers incorporate external or intrinsic photocatalysts in their framework and have been evaluated to carry out reactions in their cavity. Many other cavitands [44–46], cyclodextrins [47,48], cyclophanes [49], and cages [50–55] that have the potential for photocatalytic activity but have not been studied in that context are not discussed here; however, they have been used as fluorescent sensors or model systems to study interchromophore electronic communication or electron and energy transfer to the bound guests without carrying a chemical transformation.

For simplicity, photocatalytic molecular containers can be broadly divided into two main classes: coordination metal–organic containers and covalently linked molecular containers. The preparation of the former requires fewer synthetic steps due to favorable self-assembly rather than covalently connecting every bond and can produce a variety of polyhedral molecules with distinctive shapes and sizes [56].

Metal-organic molecular containers

Fujita and coworkers reported one of the first photocatalytic metal–organic molecular cages composed of electron-deficient tri-

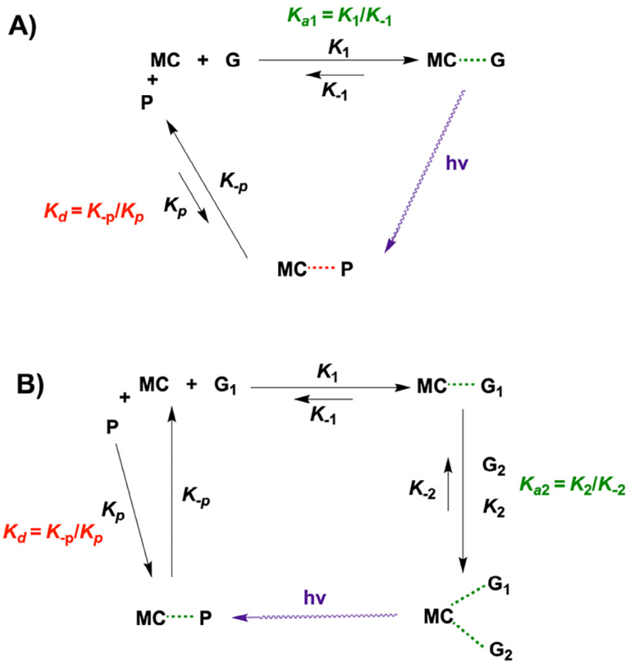

Fig. 2. Paradigms for photocatalytic molecular containers described by Sivaguru. Modified from reference [22] with permission from Royal Society of Chemistry. Photocatalysis involving: A) 1:1 MC-Guest complex and B) 1:2 MC-Guest complex. MC = Molecular container, G, G$_1$, G$_2$ = Guest molecules, P = product, K_a =-thermodynamic binding affinity of the guest with the molecular container for the MC-G complex formation steps, K_d = dissociation constant of the product from the MC, K_1, K_{-1}, K_2, K_{-2} = forward and reverse rate constant for the individual steps for the MC-G formation, K_p and K_{-p} = rate constants for the product association and dissociation with the MC.

azine derivatives in four walls and six Pd^{II} complexes in the vertices (**MC-1**). This cage can carry out several transformations in the cavity through a photoredox mechanism (Fig. 3**A**) [29]. For instance, irradiation with UV light led to the regioselective oxidation of encapsulated alkanes (Fig. 3**B**). It was demonstrated that the observed reactivity is due to the confinement effects, as no reaction was observed for open cavities or large guests that cannot be accommodated inside the cage. Moreover, spectroscopic experiments confirmed the photoinduced electron transfer from the guest to the cage resulting in the formation of the radical guest cation ($G^{\bullet+}$) and the cage anion ($MC^{\bullet-}$). Similarly, **MC-1** photocatalyzed the anti-Markovnikov hydration of internal arylalkynes to give benzyl ketones through a photoinduced electron transfer from the guest to the cage (Fig. 3**C**) [30].

Later, **MC-1** was also used for the photoredox demethylation of cyclopropanes, forming the corresponding radicals $G^{\bullet+}$ and $MC^{\bullet-}$ (Fig. 3**D**). It was suggested that the formed strained cyclopropane radical cation ($G^{\bullet+}$) opens accompanied by a nucleophilic attack of a nitrate anion (cage's counter anion). Then, fragmentation occurs to give the product and a nitrite radical. The latter receives one electron from $MC^{\bullet-}$ to restart the catalytic cycle. Also, it was observed that in some cases, the product was obtained as a mixture of *cis* and *trans* isomers even if using the single isomer of the guest substrate, which is explained by the photoisomerization of the product [31].

Dalton and co-workers synthesized a water soluble $Ga_4L_6^{12-}$ cage (**MC-2**) consisting of six diaminonaphthalene biscatecholamide photosensitizing walls and four gallium metal ions (Fig. 4**A**) [32]. The highly anionic cage encapsulates certain linear cinnamylammonium cations that upon excitation with UVA light, experience an allylic 1,3-rearrangement instead of a [2 + 2] cyclization (Fig. 4**B**). The reaction only occurs for guests with strong binding affinity, highlighting the effect of confinement to achieve new reactivity modes and generate the thermodynamically disfavored branched isomer.

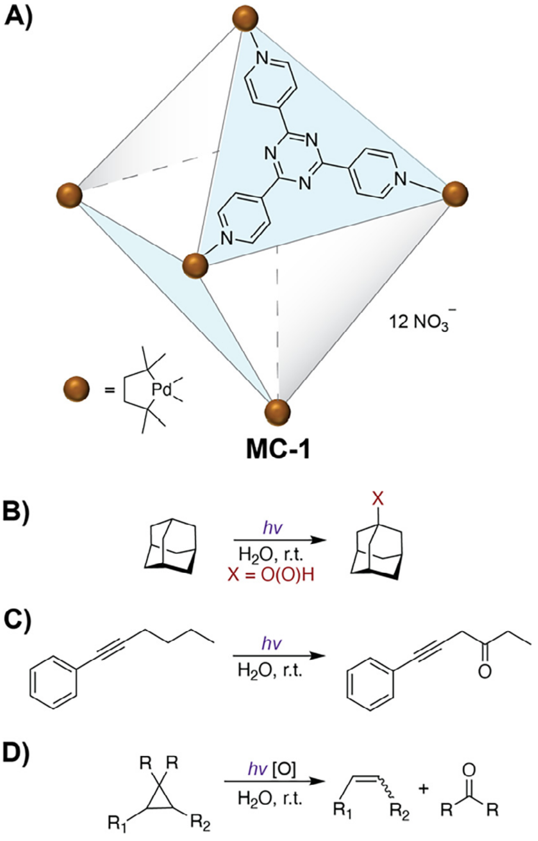

Fig. 3. Fujita's photocatalytic metal–organic molecular cage **MC-1** and the reactions carried out in its cavity. A) Representation of the octahedral cage of the M_6L_4 type. B) Regioselective oxidation of alkanes [29]. C) anti-Markovnikov hydration of internal arylalkynes [30]. D) Demethylation of cyclopropanes [31].

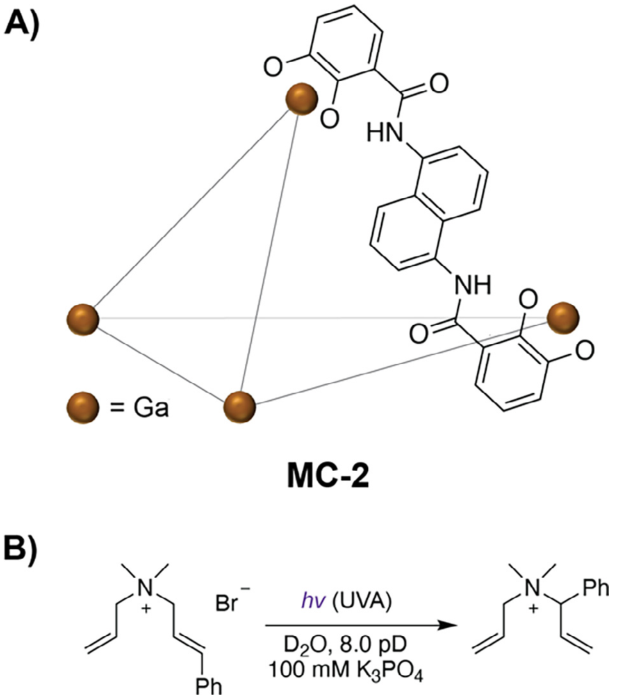

Fig. 4. Dalton's and Raymond's water soluble $Ga_4L_6^{12-}$ cage [32]. A) Representation of the tetrahedral cage. B) Photoredox allylic 1,3-rearrangement of cinnamylammonium cations in the cavity of **MC-2**.

Mechanistic studies demonstrated that the rearrangement occurs via a photoredox mechanism and not through energy transfer photosensitization. Specifically, upon light irradiation, the excited state cage transfers an electron to the guest, which undergoes a C—N bond cleavage, then there is a back electron transfer to the cage and recombination of the two guest fragments. Although UVA light was used, this cage clearly shows the potential of photocatalytic molecular containers.

Pullen and co-workers developed an acridone-based interpenetrated double cage with three small cavities filled with BF_4^- counter anions [57]. Moreover, the BF_4^- counter anions can be replaced by small chloride anions, which generate a larger inner cavity capable of encapsulating guest molecules such as benzene, cyclohexane, norbornadiene, and other bridged derivatives through the formation of London dispersion interactions (Fig. 5**A**). Thus, the cage was used to generate singlet oxygen for the [2 + 4] cycloaddition with 1,3-cyclohexadiene, giving the corresponding endoperoxide as the main product and the hydroperoxide as a side product (Fig. 5**B**). Moreover, control experiments showed that both O_2 and the cage are necessary for this process, as the reaction did not occur when using free acridone or in anaerobic conditions. However, it was demonstrated that the hetero-Diels-Alder reaction can occur outside the cavity, so unbound substrates can also be converted to the peroxide.

Nevertheless, one of the most remarkable photocatalytic containers is the heterometallic $Pd_6(RuL_3)_8$ (L = 2-(pyridine-3-yl)-1H-imidazo[4,5-f][1,10]-phenanthroline) cage (**MC-4**) developed by the group of Su that can work both as a photoredox catalyst (PET) or as a photosensitizer (*EnT*) (Fig. 6**A**). The photocatalyst RuL_3 is in the walls, and Pd^{II} ions are in the vertices forming a trun-

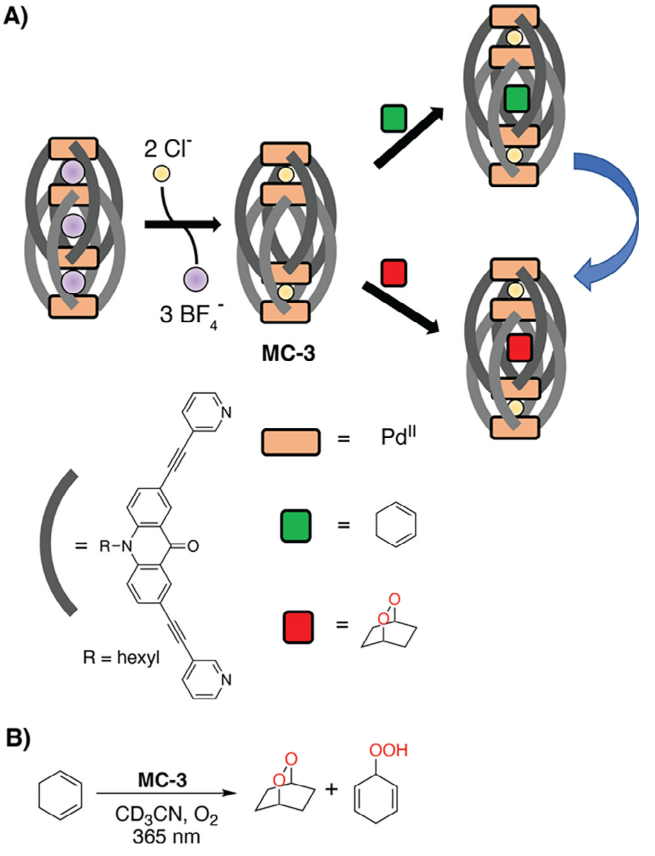

Fig. 5. Pullen's acridone-based, interpenetrated double cage **MC-3**. Adapted from reference [57] A) Chloride anions replace BF$_4$ counter anions inducing the formation of a larger inner cavity for the encapsulation of guest molecules. B) [2 + 4] Hetero-Diels-Alder reaction of 1,3 cyclohexadiene and singlet O$_2$ generated by **MC-3**.

cated octahedron with an open box-like cavity of 1.0 1.4 nm size. Initially, the ***rac*-MC-4** cage was used for the unusual photoinduced dimerization of encapsulated naphthol molecules affording the 1,4-coupling product instead of the usual 1,1-coupling dimer (Fig. 6**B**) [58]. It was found that the cage can encapsulate up to 10 guests in the cavity and can be reused without a noticeable loss of activity or decomposition. Outstandingly, when the homochiral cages -**MC-4** were evaluated separately, opposite enantioselectivity was observed due to the chirality of the confined coordination space enabling chiral recognition and stereocontrol of the dimerization transition state. Enantiopure - and -**MC-4** cages were obtained by the self-assembly of the pre-resolved - or -RuL$_3$ ligands. Thus, -**MC-4** has eight -Ru-centers, while -**MC-4** has eight -RuL$_3$ centers. This was confirmed by single-crystal structure analysis, circular dichroism (CD), NMR, and computational studies [59].

Furthermore, it was demonstrated that the reaction occurs through a photoredox process. First, the excited state *RuL$_3^{II}$ is converted to RuL$_3^{III}$ either by O$_2$ or a charge transfer electron transfer to a Pd center, then the RuL$_3^{III}$ oxidizes the naphthol by a single-electron transfer producing the corresponding radical, which dimerizes via an intermediate naphthalene-1,2-dione (see Fig. 6B).

Later, **MC-4** was also used for visible-light [2 + 2] cycloadditions through triplet sensitization (triplet energy transfer from the Ru^{II} -photosensitizer to the guest molecules). Specifically, **MC-4** induced the stereo-, regio-, and enantioselective [2 + 2] cycloaddition of an acenaphthylene derivative (Fig. 6**C** [60]), and the synthesis of cyclobutanes with high diastereoselectivity by the homo- and heterocoupling [2 + 2] cycloaddition of α,β-unsaturated carbonyl compounds (Fig. 6**D**) [61]. Spectroscopic experiments and evaluation of control molecules proved the host–guest interactions and the critical role of confinement for the observed reactivity. Moreover, the cages showed a minimum decrease in catalytic performance after several cycles, indicating they could be recycled.

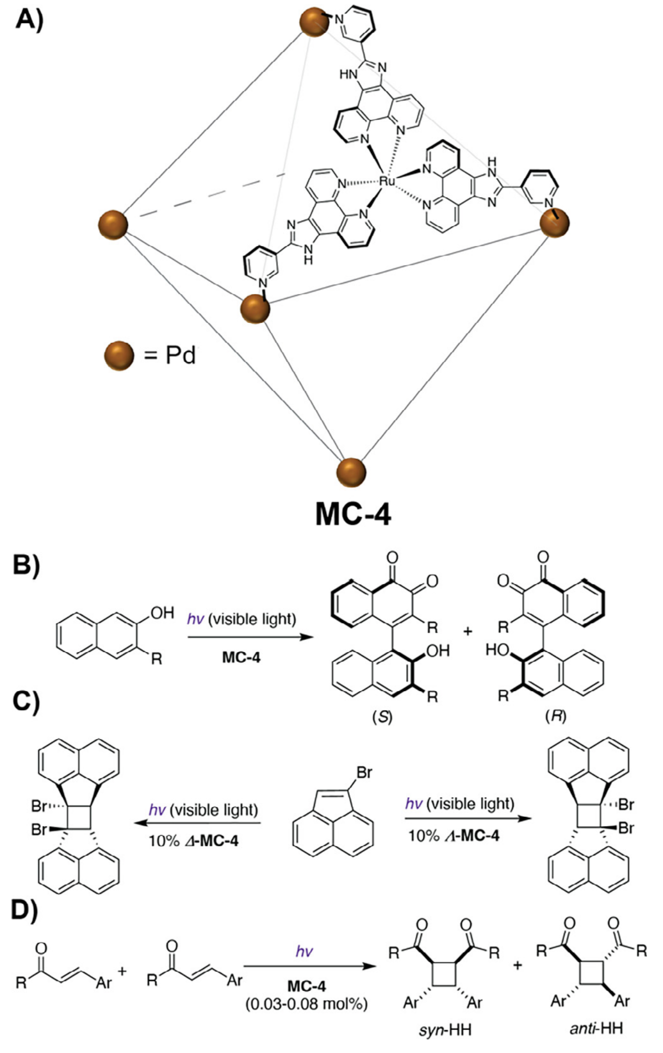

Fig. 6. Su' photocatalytic ruthenium/palladium heterometallic coordination cage. A) Representation of the octahedral cage of the M$_6$L$_8$ type. B) Regiospecific 1,4-coupling of naphthol derivatives in the cavity of **MC-4** through a photoredox mechanism [58]. C) Asymmetric [2 + 2] cycloaddition of acenaphthylene derivatives in the cavity of **MC-4** through an energy transfer mechanism [60]. D) Intermolecular [2 + 2] cycloaddition for α,β-unsaturated carbonyl compounds in the cavity of **MC-4** through an energy transfer mechanism [61].

Another example of a cage for the synthesis of cylobutanes by [2 + 2] cycloadditions was reported by Jin and coworkers (see Fig. 7A) [62]. The reported D$_{4h}$ symmetric cage **MC-5** has a tetragonal structure with a large hydrophobic cavity formed by eight photoactive anthraquinone dicarboxylate linkers in the edges and four 4 tertbutylsulfonylcalixarene capped tetrametallic clusters in the vertices. The large internal volume ($\sim$1516 Å) allows 50.7 % of the cavity for guest encapsulation, and it was assumed that the reaction proceeded via an energy-transfer mechanism (see Fig. 7B).

Covalently linked molecular containers

In 2019 Feng and coworkers reported two chiral imine cages based on perylene diimides (PDIs) as photoactive units for energy and electron transfer processes (**MC-6**, Fig. 8**A**) [63]. The cages have a large cavity (ca. 1.5 0.9 0.8 nm^3) formed by four PDIs units on the edges connected by two tetraphenylethene (TFBE) units on opposite faces. Specifically, the (*RRRR*)-PDI-TFBE and (*SSSS*)-PDI-TFBE enantiomeric cages were synthesized, but only the former was investigated in detail. Fluorescence studies and computational molecular modeling suggest that the (*RRRR*)-PDI-TFBE cage can encapsulate several molecules of polycyclic aromatic hydrocarbons (PAHs) through favourable π–π interactions and quench their fluorescence through an energy transfer mechanism. The number of encapsulated molecules ranges from 8 to 22, depending on the size of the guests. Moreover, the authors utilized the cages as photocatalysts for the Smile rearrangement of 2 aryloxybenzoic acids to aryl salicylates (Fig. 8**B**). It was proposed that the rearrangement occurs by a photoinduced single electron transfer. However, it is unclear if the reaction occurs exclusively within the confinement of the cage.

Later, Liu and co-workers reported an enantiomeric tubular organic cage (**MC-7**) with three porphyrin walls connected through cyclohexanediimine groups (Fig. 9**A**) [64]. The individual cages (**MC- 7**) have an intrinsic cavity and a length of 3.3 nm. However, they can pack into a porous three-dimensional supramolecular framework in the solid state. Particularly, the porphyrin units in the cages showed a triplet lifetime almost twice longer than the individual monomer, ensuring high efficiency for the generation of singlet oxygen. Thus, the cages were used for the oxidative coupling of benzylamine into *N*-benzylidenebenzylamine in homogenous solutions (Fig. 9**B**). Additionally, the supramolecular framework was used for the heterogeneous oxidative coupling of different primary amines into imines, which occurs 2–5 times faster than the porphyrin monomer and known metal–organic frameworks (MOFs). Although N_2 sorption experiments demonstrated the permanent porosity of the supramolecular framework in the solid state, it is unclear if the reactions occurred exclusively inside the cavities.

Following a similar approach, Sun and co-workers synthesized an organic cage with a tubular structure of 2.4 nm in length and an intrinsic cavity formed by three photocatalytic 1,6 pyrene walls and six cyclohexadiimine groups linked by twelve imine bonds (**MC-8**, Fig. 10**A**) [65]. Remarkably, this cage can also self-assemble in the solid state through intercage C—H… interactions forming a supramolecular network with intercage cavities of 1.1 nm. This intercage packing shifts the absorption of the pyrene-based photocatalyst to the visible region. Also, the cage has a high reduction potential [-1.60 vs SHE], so it was tested as a photoredox catalyst for the aerobic-hydroxylation of benzeneboronic acid derivatives, showing good stability and 99 % conversion (Fig. 10**B**). However, similar to **MC-7**, it is not clear if the reaction takes place exclusively in the intrinsic or intercage cavities.

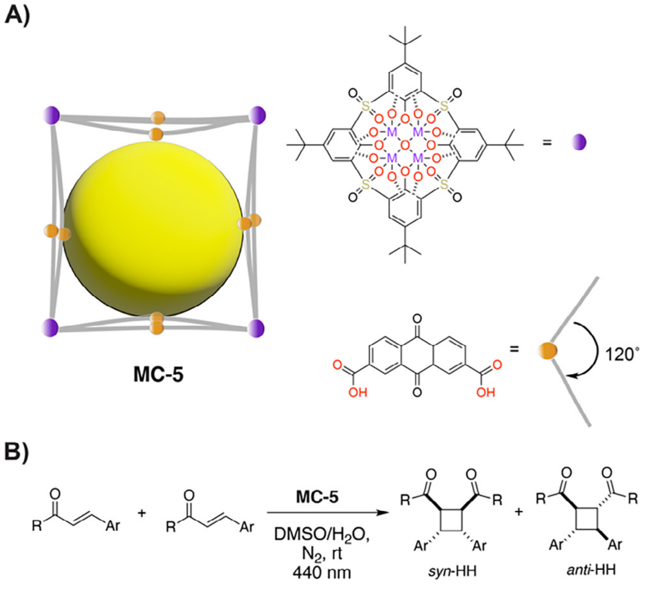

Fig. 7. Anthraquinone-based metal–organic molecular container. Adapted from reference [62] with permission from Royal Society of Chemistry (https://pubs.rsc.org/en/content/articlelanding/2021/DT/D1DT00652E). A) Representation of the D_{4h} symmetric cage MC-5. B) Intermolecular [2 + 2] cycloaddition for α,β-unsaturated carbonyl compounds in the cavity of **MC-5** through an energy transfer mechanism.

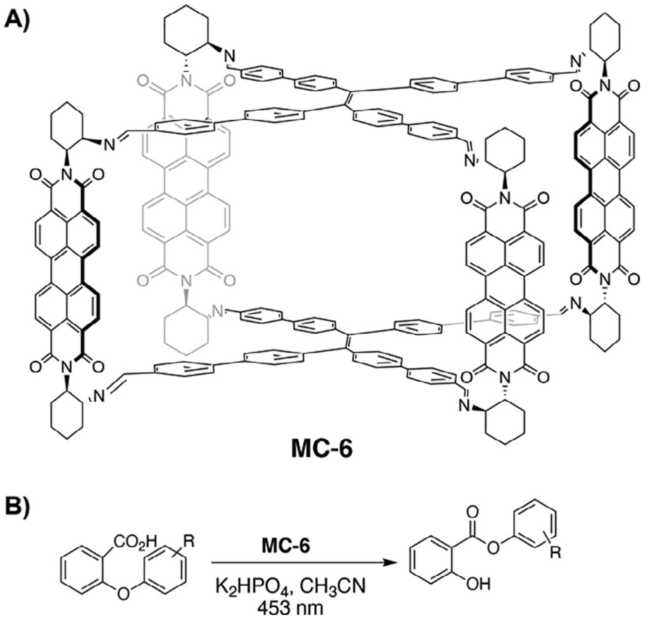

Fig. 8. Feng's perylene diimide-based organic cage [63]. A) Representation of the cubic **MC-6** cage. B) Smile rearrangement of 2 aryloxybenzoic acids induced by **MC-6** cage.

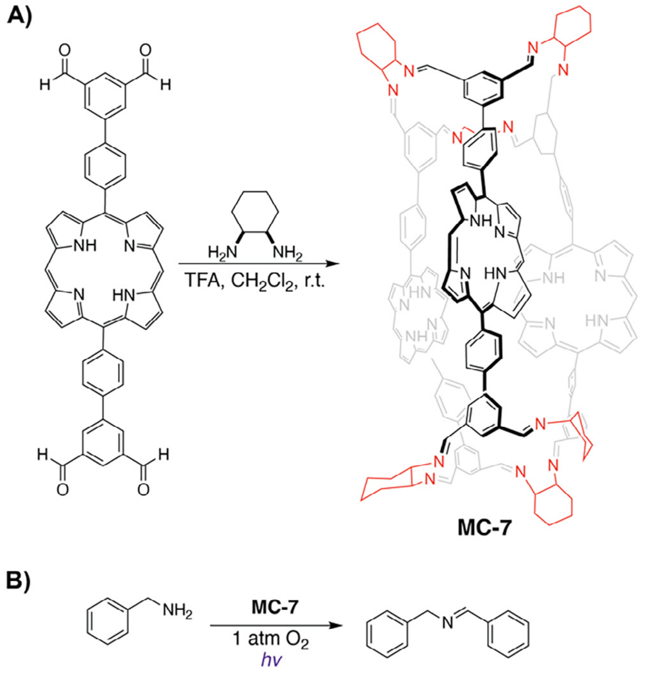

Fig. 9. Liu's covalently linked molecular cage [64]. A) Synthesis of tubular porphyrin-based organic cage **MC-7**. B) Oxidative coupling of benzylamine into *N*-benzylidenebenzylamine by **MC-7** in homogenous solutions.

Conclusions and perspectives

The examples discussed here highlight the potential of photocatalytic containers to carry out unique chemical transformations

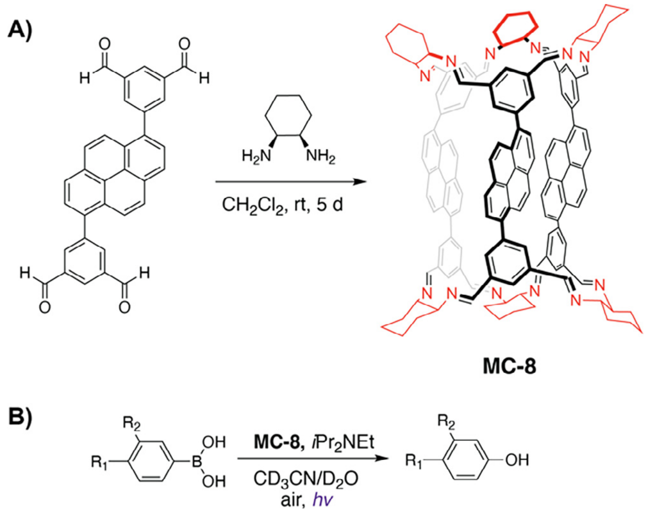

Fig. 10. Pyrene-based organic cage. A) Synthesis of tubular pyrene-based organic cage **MC-8** [65]. B) Hydroxylation of benzeneboronic acid derivatives by **MC-8**.

not accessible by individual photocatalysts in bulk solution or by non-photoactive molecular containers. Nevertheless, the lack of unified paradigms that merge photocatalysis (indirect excitation) and host–guest chemistry is slowing down this field to become a common tool in organic synthesis. Thus, there is a need for thorough mechanistic studies that provide fundamental understanding and insights into the design of efficient photocatalytic molecular containers. For instance, machine learning and other computational tools could help accelerate the field and guide the design of photocatalytic units with specific optoelectronic properties and how to incorporate them in molecular containers to achieve the required shape, size, chirality, and specific non-covalent interactions with the target guests [66–68]. Likewise, the concepts and methods from supramolecular chemistry and photochemistry provide the foundation for experimental investigation. Particularly, because there are numerous reported molecular containers with photoactive units that could carry out chemical transformations in their cavities through PET or *EnT* but have not been investigated in this setting. So, although still a young field, photocatalytic molecular containers will bloom in the coming years and deliver new paradigms in organic chemistry through interdisciplinary collaborations.

Data availability

No data was used for the research described in the article.

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.

Acknowledgments

Víctor García-López, Ph.D., holds a Career Award at the Scientific Interface from the Burroughs Wellcome Fund. Also, this material is based upon work supported by the National Science Foundation under Award No. OIA-1946231; any opinions, findings, and conclusions or recommendations expressed in this material are those of the author(s) and do not necessarily reflect the views of the National Science Foundation.

References

[1] D.J. Cram, Molecular container compounds, Nature 356 (1992) 29–36, https://doi.org/10.1038/356029a0.
[2] F.S. Santos, E. Ramasamy, V. Ramamurthy, F.S. Rodembusch, Confinement effect on the photophysics of ESIPT fluorophores, J. Mater. Chem. C 4 (2016) 2820–2827, https://doi.org/10.1039/C5TC03245H.
[3] C.J. Otolski, A.M. Raj, V. Ramamurthy, C.G. Elles, Ultrafast dynamics of encapsulated molecules reveals new insight on the photoisomerization mechanism for azobenzenes, J. Phys. Chem. Lett. 10 (2019) 121–127, https://doi.org/10.1021/acs.jpclett.8b03070.
[4] C.J. Otolski, A.M. Raj, V. Ramamurthy, C.G. Elles, Spatial confinement alters the ultrafast photoisomerization dynamics of azobenzenes, Chem. Sci. 11 (2020) 9513–9523, https://doi.org/10.1039/D0SC03955A.
[5] A.B. Grommet, M. Feller, R. Klajn, Chemical reactivity under nanoconfinement, Nat. Nanotechnol. 15 (2020) 256–271, https://doi.org/10.1038/s41565-020-0652-2.
[6] M. Morimoto, S.M. Bierschenk, K.T. Xia, R.G. Bergman, K.N. Raymond, F.D. Toste, Advances in supramolecular host-mediated reactivity, Nat. Catal. 3 (2020) 969–984, https://doi.org/10.1038/s41929-020-00528-3.
[7] Y. Xue, X. Hang, J. Ding, B. Li, R. Zhu, H. Pang, Q. Xu, Catalysis within coordination cages, Coord. Chem. Rev. 430 (2021), https://doi.org/10.1016/j.ccr.2020.213656 213656.
[8] Y. Fang, J.A. Powell, E. Li, Q. Wang, Z. Perry, A. Kirchon, X. Yang, Z. Xiao, C. Zhu, L. Zhang, F. Huang, H.-C. Zhou, Catalytic reactions within the cavity of coordination cages, Chem. Soc. Rev. 48 (2019) 4707–4730, https://doi.org/10.1039/C9CS00091G.
[9] Y. Okamoto, T.R. Ward, Supramolecular Enzyme Mimics. In Comprehensive Supramolecular Chemistry II; Elsevier, 2017; pp 459–510. doi: 10.1016/B978-0-12-409547-2.12551-X.
[10] V. Ramamurthy, J. Sivaguru, Supramolecular photochemistry as a potential synthetic tool: photocycloaddition, Chem. Rev. 116 (2016) 9914–9993, https://doi.org/10.1021/acs.chemrev.6b00040.
[11] K. Wang, J.H. Jordan, X. Hu, L. Wang, Supramolecular strategies for controlling reactivity within confined nanospaces, Angew. Chem. Int. Ed. 59 (2020) 13712–13721, https://doi.org/10.1002/anie.202000045.
[12] A.S. Sunny, V. Ramamurthy, An organic capsule as a matrix to capture and store reactive molecules at room temperature in aqueous solution: 7- *Cis* -β-ionone †, Photochem. Photobiol. 97 (2021) 1365–1375, https://doi.org/10.1111/php.13473.
[13] D. Micheroni, Z. Lin, Y.-S. Chen, W. Lin, Luminescence enhancement of *Cis* -[Ru (Bpy)$_2$ (Py)$_2$] 2+ via confinement within a metal-organic framework, Inorg. Chem. 58 (2019) 7645–7648, https://doi.org/10.1021/acs.inorgchem.9b00396.
[14] B. Chatelet, H. Gornitzka, V. Dufaud, E. Jeanneau, J.-P. Dutasta, A. Martinez, Superbases in confined space: control of the basicity and reactivity of the proton transfer, J. Am. Chem. Soc. 135 (2013) 18659–18664, https://doi.org/10.1021/ja409444s.
[15] R. Warmuth, O-Benzyne: strained alkyne or cumulene?—NMR characterization in a molecular container, Angew. Chem. Int. Ed. Engl. 36 (1997) 1347–1350, https://doi.org/10.1002/anie.199713471.
[16] A. Galan, P. Ballester, Stabilization of reactive species by supramolecular encapsulation, Chem. Soc. Rev. 45 (2016) 1720–1737, https://doi.org/10.1039/C5CS00861A.
[17] D.J. Cram, M.E. Tanner, R. Thomas, The taming of cyclobutadiene, Angew. Chem. Int. Ed. Engl. 30 (1991) 1024–1027, https://doi.org/10.1002/anie.199110241.
[18] D.J. Cram, The design of molecular hosts, guests, and their complexes (nobel lecture), Angew. Chem. Int. Ed. Engl. 27 (1988) 1009–1020, https://doi.org/10.1002/anie.198810093.
[19] S.Y. Jon, Y.H. Ko, S.H. Park, H.-J. Kim, K. Kim, A facile, stereoselective [2 + 2] photoreaction mediated by cucurbit[8]uril, Chem. Commun. 19 (2001) 1938–1939, https://doi.org/10.1039/b105153a.
[20] M.V.S.N. Maddipatla, L.S. Kaanumalle, A. Natarajan, M. Pattabiraman, V. Ramamurthy, Preorientation of olefins toward a single photodimer: cucurbituril-mediated photodimerization of protonated azastilbenes in water, Langmuir 23 (2007) 7545–7554, https://doi.org/10.1021/la700803k.
[21] R. Kaliappan, L.S. Kaanumalle, A. Natarajan, V. Ramamurthy, Templating photodimerization of stilbazoles with water-soluble calixarenes, Photochem. Photobiol. Sci. 5 (2006) 925, https://doi.org/10.1039/b606658e.
[22] N. Vallavoju, J. Sivaguru, Supramolecular photocatalysis: combining confinement and non-covalent interactions to control light initiated reactions, Chem. Soc. Rev. 43 (2014) 4084, https://doi.org/10.1039/c3cs60471c.
[23] R. Wang, L. Yuan, D.H. Macartney, Cucurbit[7]uril mediates the stereoselective [4+4] photodimerization of 2-aminopyridine hydrochloride in aqueous solution, J. Org. Chem. 71 (2006) 1237–1239, https://doi.org/10.1021/jo052136r.
[24] W.S. Chung, N.J. Turro, J. Silver, W.J. Le Noble, Modification of face selectivity by inclusion in cyclodextrins, J. Am. Chem. Soc. 112 (1990) 1202–1205, https://doi.org/10.1021/ja00159a048.
[25] A. Nakamura, Y. Inoue, Supramolecular catalysis of the enantiodifferentiating [4 + 4] photocyclodimerization of 2-anthracenecarboxylate by γ-cyclodextrin, J. Am. Chem. Soc. 125 (2003) 966–972, https://doi.org/10.1021/ja016238k.

[26] Y. Inoue, T. Wada, N. Sugahara, K. Yamamoto, K. Kimura, L.-H. Tong, X.-M. Gao, Z.-J. Hou, Y.u. Liu, Supramolecular photochirogenesis. 2. Enantiodifferentiating photoisomerization of cyclooctene included and sensitized by 6- *O*-modified cyclodextrins, J. Org. Chem. 65 (2000) 8041–8050.

[27] C. Yang, T. Mori, Y. Origane, Y.H. Ko, N. Selvapalam, K. Kim, Y. Inoue, Highly stereoselective photocyclodimerization of α-cyclodextrin-appended anthracene mediated by γ-cyclodextrin and cucurbit[8]uril: a dramatic steric effect operating outside the binding site, J. Am. Chem. Soc. 130 (2008) 8574–8575, https://doi.org/10.1021/ja8032923.

[28] C. Ke, C. Yang, T. Mori, T. Wada, Y. Liu, Y. Inoue, Catalytic enantiodifferentiating photocyclodimerization of 2-anthracenecarboxylic acid mediated by a non-sensitizing chiral metallosupramolecular host, Angew. Chem. Int. Ed. 48 (2009) 6675–6677, https://doi.org/10.1002/anie.200902911.

[29] M. Yoshizawa, S. Miyagi, M. Kawano, K. Ishiguro, M. Fujita, Alkane oxidation via photochemical excitation of a self-assembled molecular cage, J. Am. Chem. Soc. 126 (2004) 9172–9173, https://doi.org/10.1021/ja047612u.

[30] T. Murase, H. Takezawa, M. Fujita, Photo-driven anti-markovnikov alkyne hydration in self-assembled hollow complexes, Chem. Commun. 47 (2011) 10960, https://doi.org/10.1039/c1cc14523a.

[31] W. Cullen, H. Takezawa, M. Fujita, Demethylenation of cyclopropanes via photoinduced guest-to-host electron transfer in an M $_{6\ L}$ 4 cage, Angew. Chem. Int. Ed. 58 (2019) 9171–9173, https://doi.org/10.1002/anie.201904752.

[32] D.M. Dalton, S.R. Ellis, E.M. Nichols, R.A. Mathies, F.D. Toste, R.G. Bergman, K.N. Raymond, Supramolecular Ga $_{4\ L}$ $^{6\ 1}$2– cage photosensitizes 1,3-rearrangement of encapsulated guest via photoinduced electron transfer, J. Am. Chem. Soc. 137 (2015) 10128–10131, https://doi.org/10.1021/jacs.5b06317.

[33] V.A. Azov, F. Diederich, Switching Processes in Cavitands, Containers and Capsules. In Molecular Switches; Feringa, B. L., Browne, W. R., Eds.; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2011; pp 257–300. doi: 10.1002/9783527634408.ch8.

[34] G.A. Leith, C.R. Martin, J.M. Mayers, P. Kittikhunnatham, R.W. Larsen, N.B. Shustova, Confinement-guided photophysics in MOFs, COFs, and cages, Chem. Soc. Rev. 50 (2021) 4382–4410, https://doi.org/10.1039/D0CS01519A.

[35] Y. Li, M. Karimi, Y.-N. Gong, N. Dai, V. Safarifard, H.-L. Jiang, Integration of metal-organic frameworks and covalent organic frameworks: design, synthesis, and applications, Matter 4 (2021) 2230–2265, https://doi.org/10.1016/j.matt.2021.03.022.

[36] J.M.R. Narayanam, C.R.J. Stephenson, Visible light photoredox catalysis: applications in organic synthesis, Chem. Soc. Rev. 40 (2011) 102–113, https://doi.org/10.1039/B913880N.

[37] M.H. Shaw, J. Twilton, D.W.C. MacMillan, Photoredox catalysis in organic chemistry, J. Org. Chem. 81 (2016) 6898–6926, https://doi.org/10.1021/acs.joc.6b01449.

[38] N.A. Romero, D.A. Nicewicz, organic photoredox catalysis, Chem. Rev. 116 (2016) 10075–10166, https://doi.org/10.1021/acs.chemrev.6b00057.

[39] F. Strieth-Kalthoff, M.J. James, M. Teders, L. Pitzer, F. Glorius, Energy transfer catalysis mediated by visible light: principles, applications, directions, Chem. Soc. Rev. 47 (2018) 7190–7202, https://doi.org/10.1039/C8CS00054A.

[40] F. Strieth-Kalthoff, F. Glorius, Triplet energy transfer photocatalysis: unlocking the next level, Chem 6 (2020) 1888–1903, https://doi.org/10.1016/j.chempr.2020.07.010.

[41] Y. Xi, H. Yi, A. Lei, Synthetic applications of photoredox catalysis with visible light, Org. Biomol. Chem. 11 (2013) 2387, https://doi.org/10.1039/c3ob40137e.

[42] M.A. Cismesia, T.P. Yoon, Characterizing chain processes in visible light photoredox catalysis, Chem. Sci. 6 (2015) 5426–5434, https://doi.org/10.1039/C5SC02185E.

[43] M.D. Pluth, K.N. Raymond, Reversible guest exchange mechanisms in supramolecular host-guest assemblies, Chem. Soc. Rev. 36 (2007) 161–171, https://doi.org/10.1039/B603168B.

[44] V. García-López, M. Zalibera, N. Trapp, M. Kuss-Petermann, O.S. Wenger, F. Diederich, Stimuli-responsive resorcin[4]arene cavitands: toward visible-light-activated molecular grippers, Chem. – Eur. J. 26 (2020) 11451–11461, https://doi.org/10.1002/chem.202001788.

[45] S.D. Starnes, D.M. Rudkevich, J. Rebek, A cavitand–porphyrin hybrid, Org. Lett. 2 (2000) 1995–1998, https://doi.org/10.1021/ol0000859.

[46] S.D. Starnes, D.M. Rudkevich, J. Rebek, Cavitand–porphyrins, J. Am. Chem. Soc. 123 (2001) 4659–4669, https://doi.org/10.1021/ja010038r.

[47] A. Nakamura, S. Okutsu, Y. Oda, A. Ueno, F. Toda, Synthesis of a rhenium complex appending a cyclodextrin unit on a ligand, Tetrahedron Lett. 35 (1994) 7241–7244, https://doi.org/10.1016/0040-4039(94)85371-1.

[48] I. Tabushi, K. Fujita, L.C. Yuan, Specific host-guest energy transfer by use of β-cyclodextrin, Tetrahedron Lett. 18 (1977) 2503–2506, https://doi.org/10.1016/S0040-4039(01)83804-1.

[49] S.T.J. Ryan, R.M. Young, J.J. Henkelis, N. Hafezi, N.A. Vermeulen, A. Hennig, E.J. Dale, Y. Wu, M.D. Krzyaniak, A. Fox, W.M. Nau, M.R. Wasielewski, J.F. Stoddart, O.A. Scherman, Energy and electron transfer dynamics within a series of perylene diimide/cyclophane systems, J. Am. Chem. Soc. 137 (2015) 15299–15307, https://doi.org/10.1021/jacs.5b10329.

[50] F. Iizuka, H. Ube, H. Sato, T. Nakamura, M. Shionoya, Self-assembled porphyrin-based cage complexes, M $_{11\ L}$ 6 (M = Z^{n} II, Cd ^{I}I), with inner coordination sites in their crystal structure, Chem. Lett. 49 (2020) 323–326, https://doi.org/10.1246/cl.190943.

[51] S. Hong, M.R. Rohman, J. Jia, Y. Kim, D. Moon, Y. Kim, Y.H. Ko, E. Lee, K. Kim, Porphyrin boxes: rationally designed porous organic cages, Angew. Chem. Int. Ed. 54 (2015) 13241–13244, https://doi.org/10.1002/anie.201505531.

[52] X. Jing, C. He, L. Zhao, C. Duan, Photochemical properties of host-guest supramolecular systems with structurally confined metal-organic capsules, Acc. Chem. Res. 52 (2019) 100–109, https://doi.org/10.1021/acs.accounts.8b00463.

[53] P.P. Neelakandan, A. Jiménez, J.D. Thoburn, J.R. Nitschke, An autocatalytic system of photooxidation-driven substitution reactions on a Fe ^{II} $_{4\ L}$ 6 cage framework, Angew. Chem. 127 (2015) 14586–14590, https://doi.org/10.1002/ange.201507045.

[54] A.J. Musser, P.P. Neelakandan, J.M. Richter, H. Mori, R.H. Friend, J.R. Nitschke, Excitation energy delocalization and transfer to guests within M ^{II} $_{4\ L}$ 6 cage frameworks, J. Am. Chem. Soc. 139 (2017) 12050–12059, https://doi.org/10.1021/jacs.7b06709.

[55] I. Regeni, B. Chen, M. Frank, A. Baksi, J.J. Holstein, G.H. Clever, Coal-tar dye-based coordination cages and helicates, Angew. Chem. Int. Ed. 60 (2021) 5673–5678, https://doi.org/10.1002/anie.202015246.

[56] M. Pan, K. Wu, J.-H. Zhang, C.-Y. Su, Chiral metal-organic cages/containers (MOCs): from structural and stereochemical design to applications, Coord. Chem. Rev. 378 (2019) 333–349, https://doi.org/10.1016/j.ccr.2017.10.031.

[57] S. Pullen, S. Löffler, A. Platzek, J.J. Holstein, G.H. Clever, Substrate and product binding inside a stimuli-responsive coordination cage acting as a singlet oxygen photosensitizer, Dalton Trans. 49 (2020) 9404–9410, https://doi.org/10.1039/D0DT01674H.

[58] J. Guo, Y.-W. Xu, K. Li, L.-M. Xiao, S. Chen, K. Wu, X.-D. Chen, Y.-Z. Fan, J.-M. Liu, C.-Y. Su, Regio- and enantioselective photodimerization within the confined space of a homochiral ruthenium/palladium heterometallic coordination cage, Angew. Chem. Int. Ed. 56 (2017) 3852–3856, https://doi.org/10.1002/anie.201611875.

[59] K. Wu, K. Li, Y.-J. Hou, M. Pan, L.-Y. Zhang, L. Chen, C.-Y. Su, Homochiral D4-symmetric metal-organic cages from stereogenic ru(ii) metalloligands for effective enantioseparation of atropisomeric molecules, Nat. Commun. 7 (2016) 10487, https://doi.org/10.1038/ncomms10487.

[60] J. Guo, Y. Fan, Y. Lu, S. Zheng, C. Su, Visible-light photocatalysis of asymmetric [2+2] cycloaddition in cage-confined nanospace merging chirality with triplet-state photosensitization, Angew. Chem. Int. Ed. 59 (2020) 8661–8669, https://doi.org/10.1002/anie.201916722.

[61] J.-S. Wang, K. Wu, C. Yin, K. Li, Y. Huang, J. Ruan, X. Feng, P. Hu, C.-Y. Su, Cage-confined photocatalysis for wide-scope unusually selective [2 + 2] cycloaddition through visible-light triplet sensitization, Nat. Commun. 11 (2020) 4675, https://doi.org/10.1038/s41467-020-18487-5.

[62] Y. Jin, H. Jiang, X. Tang, W. Zhang, Y. Liu, Y. Cui, Coordination-driven self-assembly of anthraquinone-based metal-organic cages for photocatalytic selective [2 + 2] cycloaddition, Dalton Trans. 50 (2021) 8533–8539, https://doi.org/10.1039/D1DT00652E.

[63] X. Feng, P. Liao, J. Jiang, J. Shi, Z. Ke, J. Zhang, Perylene diimide based imine cages for inclusion of aromatic guest molecules and visible-light photocatalysis, ChemPhotoChem 3 (2019) 1014–1019, https://doi.org/10.1002/cptc.201900058.

[64] C. Liu, K. Liu, C. Wang, H. Liu, H. Wang, H. Su, X. Li, B. Chen, J. Jiang, Elucidating heterogeneous photocatalytic superiority of microporous porphyrin organic cage, Nat. Commun. 11 (2020) 1047, https://doi.org/10.1038/s41467-020-14831-x.

[65] N. Sun, D. Qi, Y. Jin, H. Wang, C. Wang, C. Qu, J. Liu, Y. Jin, W. Zhang, J. Jiang, Porous Pyrene Organic Cage with Unusual Absorption Bathochromic-Shift Enables Visible Light Photocatalysis. CCS Chem. 2021, 2917–2925. doi: 10.31635/ccschem.021.202101202.

[66] S. Bennett, A. Tarzia, M.A. Zwijnenburg, K.E. Jelfs, Chapter 12. Artificial Intelligence Applied to the Prediction of Organic Materials. In Theoretical and Computational Chemistry Series; Cartwright, H. M., Ed.; Royal Society of Chemistry: Cambridge, 2020; pp 280–310. doi: 10.1039/9781839160233-00280.

[67] T.K. Piskorz, V. Martí-Centelles, T.A. Young, P.J. Lusby, F. Duarte, Computational modeling of supramolecular metallo-organic cages-challenges and opportunities, ACS Catal. (2022) 5806–5826, https://doi.org/10.1021/acscatal.2c00837.

[68] A. Tarzia, K.E. Jelfs, Unlocking the computational design of metal-organic cages, Chem. Commun. 58 (2022) 3717–3730, https://doi.org/10.1039/D2CC00532H.