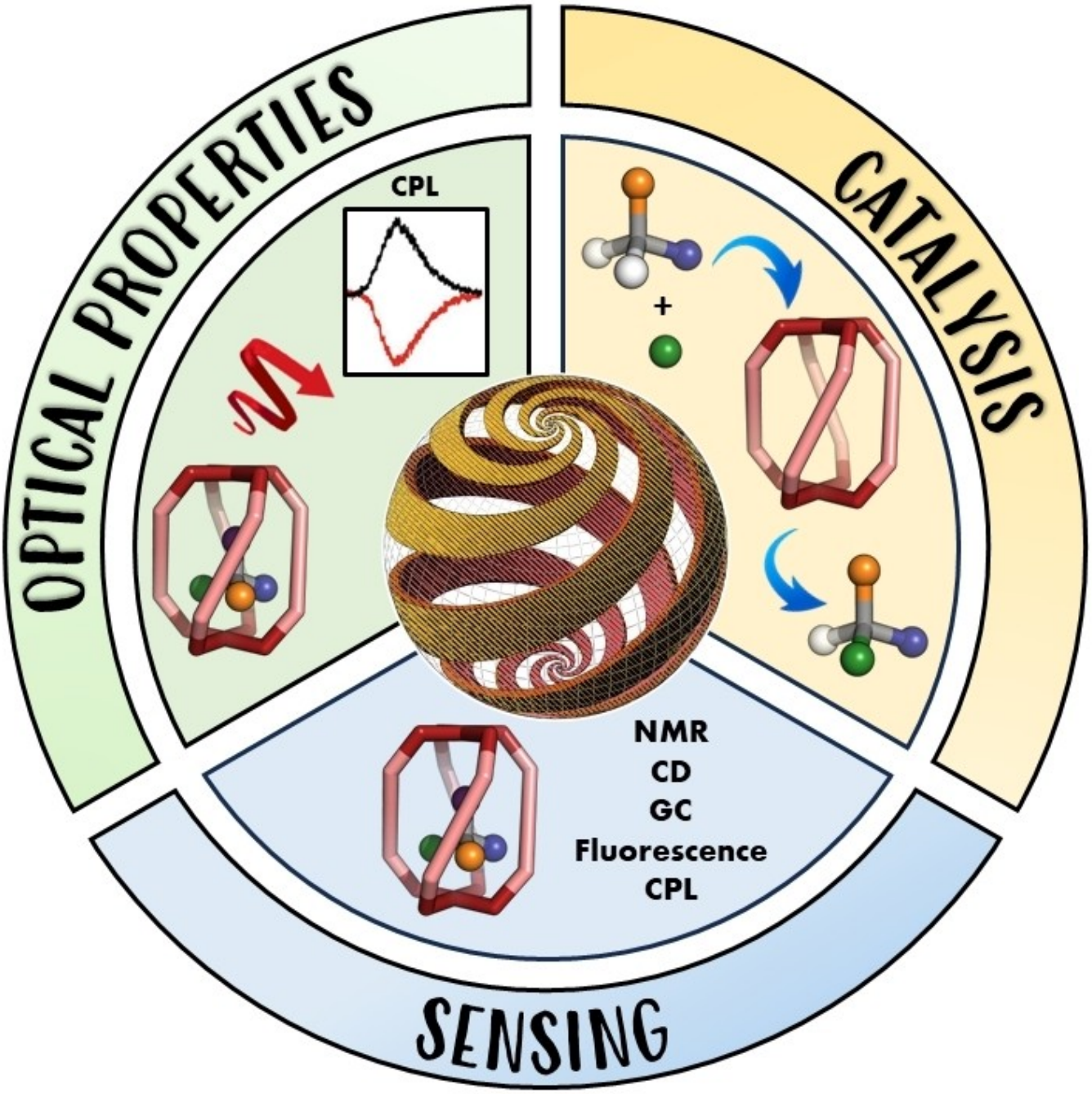
How to cite: *Angew. Chem. Int. Ed.* **2023**, e202311153
doi.org/10.1002/anie.202311153

Supramolecular Chemistry

Exploiting Chirality in Confined Nanospaces

*Federico Begato, Giulia Licini, and Cristiano Zonta**



Abstract: Spatial organization using confinement has been of great interest since the early ages of supramolecular chemistry. Application such as sensing, catalysis and delivery are continuously emerging. This minireview highlights the evolution of chiral supramolecular cages (CSC) applications in the fields of catalysis, sensing and chiroptical properties. More in detail, beside the description of the strategies adopted for the preparation of chiral supramolecular cages, either of purely organic supramolecular architectures or prepared using metal-ligand coordination bonds, recent findings on their applications, with particular attention to stereodynamic systems, are presented to highlight the recent scientific interests and the future opportunities.

1. Introduction

Since the seminal reports of Cram and Lehn,[1,2] control of confined nanospaces has been one of the pillars in the journey of supramolecular chemistry.[3] The possibility to exploit molecular recognition events within organic molecules owning permanent and accessible cavities has continuously contributed to novel applications in catalysis and molecular recognition.[4] Recently, novel synthetic methodologies, mainly based on the use of reticular and/or imine chemistry, have allowed a boost in the development of the field. Structures with increased size, novel topologies, practical applications, and unexpected properties are continuously emerging and raising the bar of innovation in supramolecular chemistry.[5] Within this context, chirality has played a major role in the flourishment of the field.[6] While the initial purposes of chiral confined architectures were only directed to asymmetric guest recognition, exploitation for synthetic transformations and novel chiroptical properties are emerging more intensively in the recent years.[7] This review will cover the impact that confinement in chiral nanospaces, in particular in chiral supramolecular cages (CSC), had in chiral related applications. While the first part is briefly dedicated to the methodologies which have been used to prepare these architectures, in the second part, selected examples in asymmetric catalysis, sensing, and chiroptical activity are reported.

2. Synthesis of Chiral Supramolecular Cages

CSC can be prepared following two different synthetic strategies. The most straightforward approach is based on the use of building blocks containing at least one stereogenic element (Figure 1a). However, even if achiral building blocks are used, chirality can emerge from the novel elements of symmetry arising in the final architectures (Figure 1b). In the latter methodology, racemic mixtures are usually obtained, and resolution can allow the recovery of the optically pure systems. Within these two synthetic approaches, a particular mention should be given to systems which own interconverting stereogenic elements (Figure 1c-1d).[8] These stereodynamic CSC are usually present in solution as enantiomers, or diastereoisomers, in equilibrium among the different forms. Depending on the energy barrier the interconversion can be fast or not possible.

2.1. Synthesis from Chiral Building Blocks

The initial methodology applied for the synthesis of CSC was based on the use of chiral building blocks. One of the early examples was reported by Collet in 1981 where the formation of a D_3 symmetric chiral cryptophane **1** was achieved joining two chiral cyclotriveratrylene units (Figure 2).[9] While other examples of covalent CSC obtained by direct synthesis were reported,[10] the increase on the overall yield, and somehow the complexity of the architectures, was achieved with the use of dynamic covalent chemistry (DCC) and,[11] among the possible reversible bonds, imine conden-

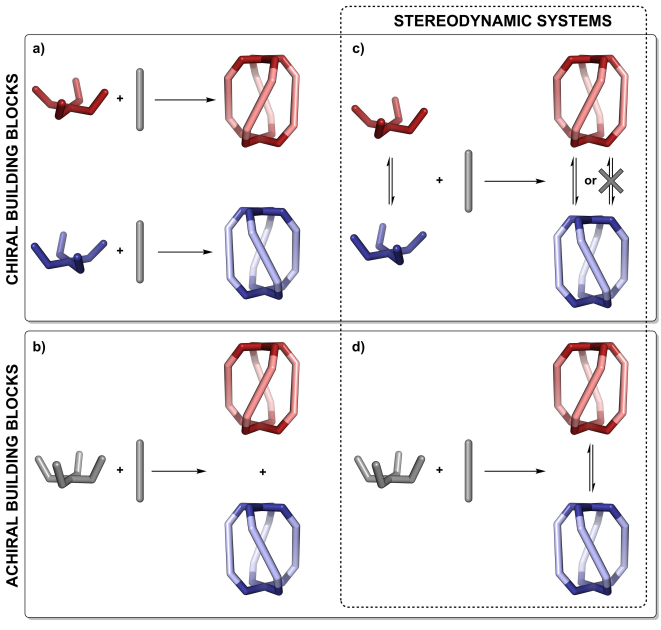


Figure 1. CSC can be obtained starting from subunits: a) containing stereogenic elements, or b) from achiral subunits. Within these two classes: c) the starting building block can also be stereodynamic, thus chiral and in equilibria among the two enantiomers or d) stereodynamic in the final assembly starting from achiral subunits.

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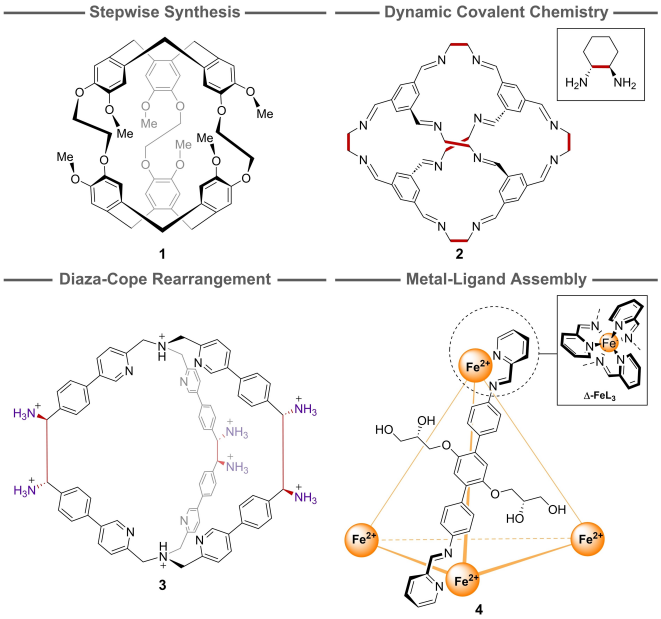

Figure 2. Examples of CSC obtained starting from chiral building blocks.

sation has been the dominant choice.[12] Taking inspiration from the Collett structure, Warmuth reported the first DCC synthesis, an [8:12] nanocube obtained in excellent yields, using an enantiopure triformyl cyclotriveratrylene derivative with a series of dianilines.[13] After this seminal work, several CSC resulting from [2:3],[14] [3:6],[15] [4:6] (**2**),[16] and [8:2][17] condensations have been reported giving rise to a variety of structures and functions (Figure 2). Similarly, we recently combined DCC imine chemistry, together with the possibility to synthetize chiral hydrolytically stable structures with a [3,3]-Diaza-Cope sigmatropic rearrangement to obtain CSC **3** (Figure 2).[18] This strategy allows to combine quantitative yields typical of DCC, together with the stability advantages offered by earlier structures arising from step-by-step synthesis.

Another largely exploited strategy takes advantage of metal-ligand coordination bonds. In these CSC, chirality can be imparted by chiral auxiliaries surrounding the metal at the vertex of the polyhedron (vertice directed), by the linear (edge directed) or planar (face directed) ligands connecting the metals.[19–21] Stang presented the first example of this assembly, preparing M_6L_4-type CSC where the six Pd(II) or Pt(II), that are positioned at the corners of the octahedron, were surrounded by enantiopure **BINAP** as auxiliary which dictated the formation of a *T*-symmetrical structure.[22] Edge directed synthesis was used later by Nitschke for the synthesis of tetrahedral water soluble CSC **4** by self-assembly of enantiopure diaminoterphenylene ligands (Figure 2).[23] In this case, the stereochemistry of the glyceryl groups dictated the handedness of the ligands around the Fe(II) centers. Using these strategies tetrahedral, octahedral, and more complex chiral polyhedra have been obtained.[6] While in initial examples equivalent bridging ligands were connecting the metal centers, more recently mixed ligands have been used to prepare chiral selectively heteroleptic molecular cages.[24]

From the synthetic point of view, it is also worth of interest to consider the cases in which the synthesis is performed using racemic building blocks. In these chiral self-sorting experiments, a distribution among the narcissistic (*viz.* same enantiomer) and the social (*viz.* both

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enantiomers) diastereoisomeric architectures can be obtained and, to some extent, biased.[25]

2.2. Synthesis from Achiral Building Blocks

In a second approach, cages are chiral as a consequence of the final arrangement of the self-assembled subcomponents. In most cases, chirality is arising from the twisted arrangement that the achiral components assume upon coordination to a metal center. Both enantiomeric cages are present in solution after the synthesis and resolution is necessary to obtain the enantiopure system.[21] The most common methodology for the resolution of these systems is crystallization in the presence of chiral guests which allows the formation of diastereoisomeric species with different solubilities.[26] As example, tetrahedral CSC **6** were prepared by Raymond from the self-assembly of bis-hydroxamate ligand **5** and Ga(III) metal ions (Figure 3).[27] The synthesis led to the formation of a racemic mixture of homo-configuration tetrahedral clusters (ΛΛΛΛ or ΔΔΔΔ), in which the racemization is prevented, and enantiopure *S*-(+)-N-methylnicotinium cation was used to resolve the ΔΔΔΔ enantiomer.

The use of achiral ligands, followed by resolution, has also been extensively employed to prepare more complex polygons, polyhedra and, prisms.[28]

2.3. Synthesis of Stereodynamic Systems

Whitin these two synthetic strategies, a subclass of CSC is represented by stereodynamic architectures which are chiral systems characterized by the presence of one interconverting stereogenic element in the molecular scaffold. Typical examples are atropoisomeric molecules or metal complexes capable of fast ligand sphere modifications, where the low energy required to cross the inversion barrier allows the racemization to be rapid at room temperature.[8] Warmuth took advantage of stereodynamic nature of C_3-trialkoxy-triformylcyclobenzylene **7** which react with (*R*,*R*)-diamino-cyclohexane (***RR*-CHDA**) furnishing only the imine-based homochiral capsule ***PR*-8** (Figure 4).[13] More in detail, heating at 80 °C allows simultaneously the dynamic resolution of cyclotriveratrylene unit, obtaining the exclusive formation of the *P* enantiomer, together with the formation of the CSC.

While in this case the stereodynamic element is blocked in the final assembly in the lower energy diastereoisomer, other cages have been formed using stereodynamic elements still able to interconvert in the final assembly. As example, we reported a series of tris-2-pyridilmethylamine (**TPMA**) based CSC.[29] **TPMA** metal complexes, which have been largely exploited for their capability to interconvert among two helical configurations, can adopt two enantiomeric forms that differ for the handedness of the arms twist, namely Λ (*M*) and Δ (*P*). This property is maintained in the system and binding of a chiral guest shifts the equilibria toward the most stable diastereoisomer.[30]

Chiral stereodynamic systems can also arise from the use of achiral building blocks. As example, Wang reported an arylthiourea stereodynamic cage which is present in the two enantiomeric forms in the crystal structure when an achiral guest is hosted.[31] In the presence of a chiral guest, the system is shifted toward one preferential form as suggested by CD and DFT calculations. Mukherjee reported a metal-coordinated CSC in which tris-pyridyl donor ligand **9** could self-assemble with a Pd(II) complex **10** for the formation of octahedral nanocapsules **11** (Figure 5).[32] The process led to

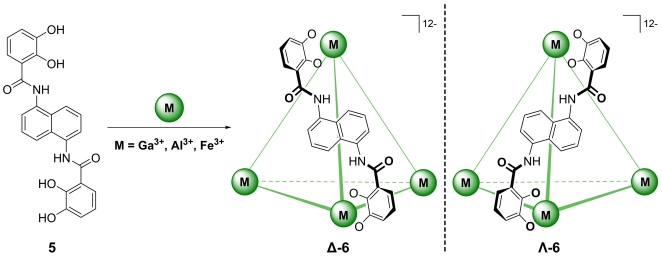

Figure 3. Formation of the racemic mixture of cage **6**.[27]

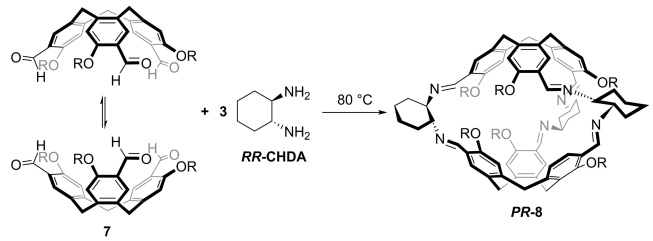

Figure 4. Synthesis of CSC ***PR*-8** starting from stereodynamic component **7**. Enantiopure tris-aldehyde can be recovered from hydrolysis of ***PR*-8**.[13]

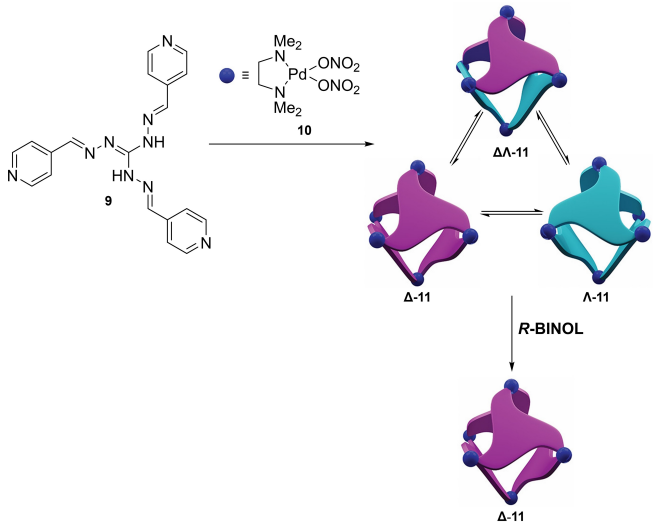

Figure 5. The tris-pyridyl donor ligand **9** in presence of a Pd(II) complex forms a series of octahedral nanocapsules diastereisomers **11**. Resolution is obtained by the addition of ***R*-BINOL**. Adapted with permission from Ref. [32].Copyright 2020 American Chemical Society.

the formation of a complex mixture of interconverting diastereoisomers of the CSC. Addition of ***R*-BINOL** resulted in the encapsulation of the chiral guest through H-bond and the efficient diastereoselective interaction drove the equilibrium selectively toward a single enantiomeric species **Δ-11**.

2. Reactivity within Chiral Systems

Taking inspiration by natural cleft within proteins, catalysis has been the ideal playground for the functional exploitation of CSC.[33] Many different types of reactivity have been investigated (e.g. pericyclic reactions,[34] hydroformylations,[35] oxidative biaryl couplings,[36] ring closure,[37] …) with enantiomeric excess (*ee*) ranging from modest to very high. Initial reactivities where mainly taking advantage of the chiral preorganization of the reactants within the cavity, subsequently the incorporation of catalytic sites, either embedded or hosted within confined systems, has been also exploited. While more exhaustive information on these approaches can be find in other reviews,[38,39] two recent examples have shown novel aspects, namely investigation of the role of flexibility in catalysis and stereochemical information transfer, that can open this field to novel opportunities. Raymond, in collaboration with Toste and Bergman, have extensively studied in the recent years the capabilities of a series of chiral Ga(III), Al(III), and In(III)-based tetrahedral CSC to catalyze enantioselective Prins cyclization,[40] aza-Cope rearrangement,[41] and aza-Darzens reactivity.[42] The latter reaction has been recently deeply investigated with a particular attention to the role of the host flexibility. In particular, a series of M(III)-based enantiopure supramolecular assemblies **12** differing in the external chiral amide were prepared and the reaction outcome, in term of enantioselectivity, has shown to correlate with the flexibility of the host measured as kinetics of exchange of a model cationic guest (Figure 6).[42] Somehow this represent the first example in which flexibility is investigated in catalysis, suggesting that this parameter should be taken into account in the development of other catalytic CSC.

In another recent example, Nitschke used CSC **13** built using a chiral formylpyridine which dictated chemo-, regio- and stereo-selective Diels–Alder reactions of the edges of the cage with $\mathbf{C_{60}}$.[43] The subsequent disassembly allows to obtain fullerenes structures with specific functionalization patterns in highly enantioenriched form (Figure 7).

While the "masking" strategy has been primarily studied to obtain regioselective transformations,[44] in this case is the CSC itself which reacts with the guest opening the functional design approach to a novel strategy.

3. Novel Optical Properties

CSC intrinsically offer a facile approach to get well-ordered chromophores able to display novel chiroptical functions. This feature has been studied to obtain system owning enhanced Circular Dichroism (CD) and/or Circularly Polarized Luminescence (CPL).[7,45] While CD properties have been extensively studied in sensing,[46–48] which will be described in the next paragraph, CPL has recently attracted the attention due to the capability of CSC to: induce chromophores cooperative effects, prevent aggregation phenomena, finely tune their distance either by design or by the use of different guests, and to have mixed interacting chromophores.[45,49]

Initial examples have been directed to the emissive properties of lanthanide-based CSC.[50] Yan developed an enantiopure Eu(III) tetrahedral CSC using of ***S*-BINAPO** as ancillary ligand. This strategy allowed the formation of one helical configuration around the metal ion which allowed strong CPL signals ($|g_{lum}|$ up to 0.20), accompanied with an outstanding luminescence quantum yield ($\Phi_{overall}$ = 81 %), which was unprecedent for a lanthanide-based complex.[51] Other emissive Eu systems have been prepared using either chiral ligands in the assembly ($|g_{lum}|$ up to 0.16),[52] a chiral template guest formation ($|g_{lum}|$ up to 0.125),[53] or as in the case reported by Rancan, the formation of a interconverting stereodynamic cage which can be biased toward one preferential diastereoisomer by chiral guest encapsulation ($|g_{lum}|$ up to 0.064).[54]

Studies have been also performed using organic emitting chromophores as building block for CSC. Clever reported a

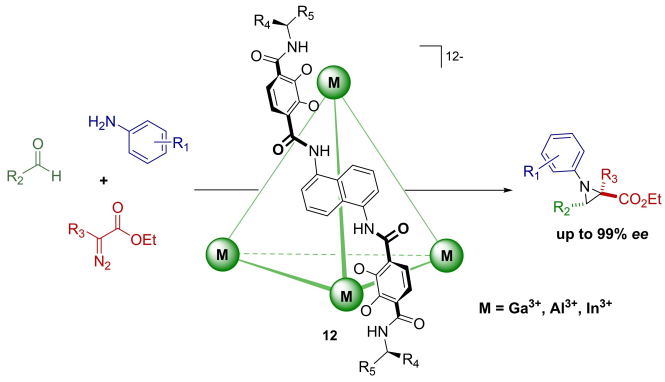

Figure 6. Aza-Darzens condensation catalyzed by enantiopure host **12**.[42]

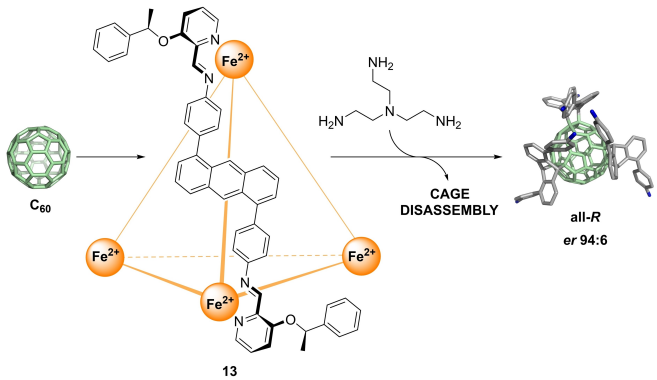

Figure 7. Stereoselective reaction of enantiopure CSC **13** with $\mathbf{C_{60}}$.[43]

Pd_2L_4 CSC, based on chiral helicene ligand and a fluorenone based emissive ligand ($|g_{lum}|$ up to 0.0025).[55,56] Interestingly, the flexibility of **16** upon encapsulation of anionic molecules, an achiral bis-sulfonate guest **17**, provided a changing in CPL output, leading to a bathochromic shift and signal amplification (4 fold increase of $|g_{lum}|$) (Figure 8). This example showed that only the combination of three elements, imparted chirality from ligand **15**, emissive properties from ligand **14**, and Pd cations to create the void cavity, could contribute to achieve novel properties that could not otherwise be obtained with the single components.

Using a different approach, Liu reported hexahedral CSC **19** able to encapsulate achiral emitting dyes.[57] More in detail, a chiral assembly of an enantiopure biphenyl based ligands and Pd(II) cations lead to the formation of a Pd_6L_{12} structure which, after the addition of potassium sulfonate boron-dipyrromethene (**BODIPY**) dye **20** resulted in the complete encapsulation of the guest inside the cavity of the host. In particular, 1:2 stoichiometry was obtained, and it was accompanied to the rise of a broad CPL band around 550 nm, that was not observed with both the free cage and guests (due to the aggregation-caused quenching of the dyes), with $|g_{lum}|$ values around 10^{-3}–10^{-4}, that were increased by one order of magnitude in crystalline state (Figure 9). The obtained results highlighted that only encapsulation of the **BODIPY** into the hollow host, allowed to avoid the aggregation of the dye and induce a chirality in both ground and excited state.

4. Molecular Recognition for Sensing Applications

Confined nanospaces have been also applied for the selective detection of different analytes.[58] Depending on the resulting inclusion complexes different techniques ranging from chiroptical spectroscopies to NMR, Gas Chromatography (GC), and Fluorescence have been used.

4.1. NMR Spectroscopy

CSC have been extensively used as chiral solvating agents (CSA) for the distinction, through the formation of diastereomeric species, of chiral analytes. Starting from the pioneering work of Collet on chiral cryptophanes able to bind enantioenriched CHFClBr,[59] different works have reported the capability of chiral structures to distinguish enantiomers by ^{1}H NMR spectroscopy. Cryptophanes and derivatives have been studied for their chiral recognition towards chiral oxiranes, amino alcohols, ammonium ions, epichlorohydrin.[60,61] As example, Martinez reported a chiral hemi-cryptophane **21** which displayed notable enantioselec-

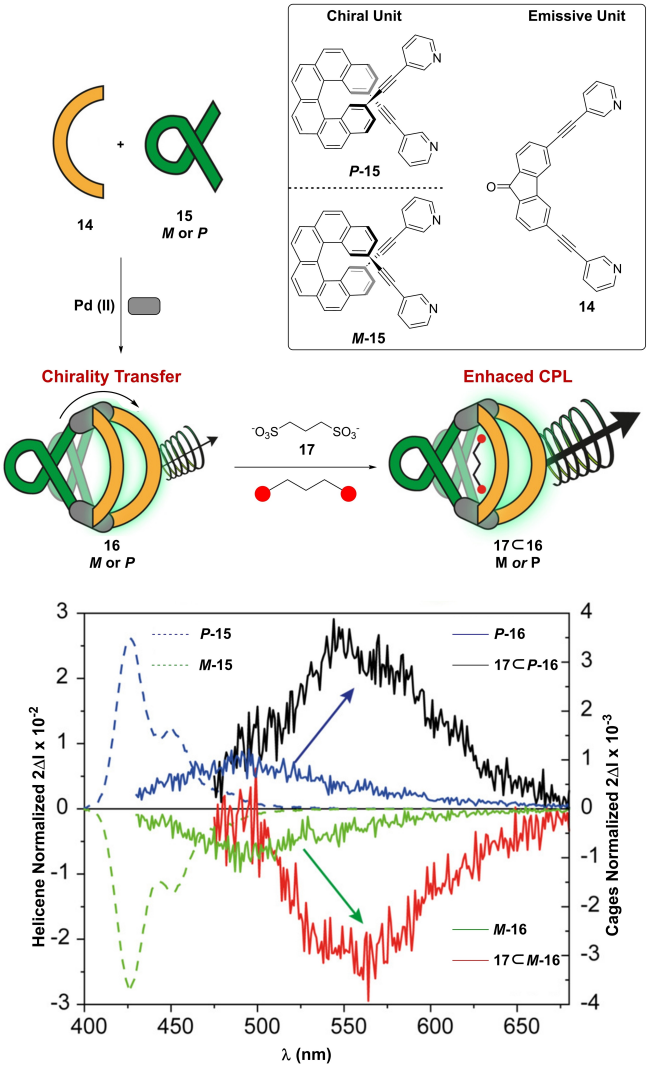

Figure 8. CPL modulation upon encapsulation of guest **17** in the chiral host **16**. Adapted from Ref. [55].

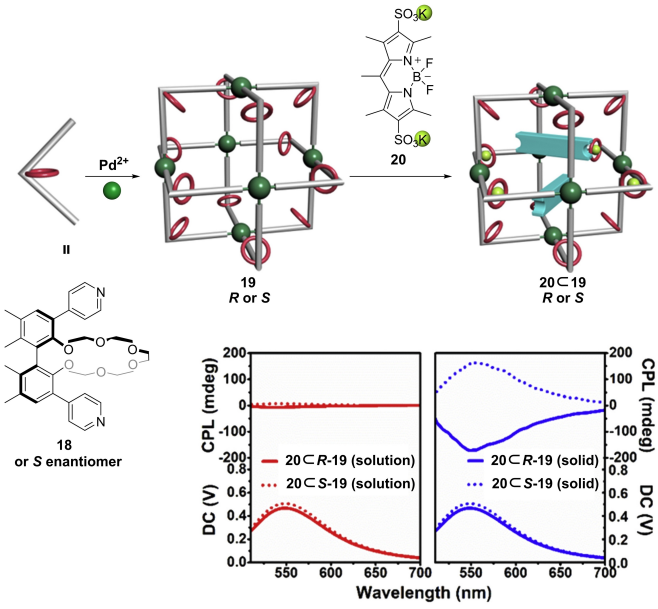

Figure 9. Induced CPL in solution and solid state upon encapsulation of guest **20** in the chiral host **19**. Adapted with permission from Ref. [57]. Copyright (2021), Elsevier.

tive recognition properties toward a wide range of sugars that were studied using NMR.[62] Interestingly, switching the chirality of the host allowed a changing in the substrate selectivity. In particular, the ***M*-21** enantiomer was **Oct-*β*-glucose** selective while the ***P*-21** enantiomer displayed a **Oct-*β*-mannose** preference (Figure 10). The change in the substrate discrimination could be attributed to different interactions of the substrates with the inner asymmetric cavity of the host.

A similar strategy was recently used by Nitschke in the recognition of steroids employing enantiopure Fe_4L_4 CSC obtained through the self-assembly of triazatruxene trialdehyde and chiral amine subcomponents.[63] The binding process between the cage and the guests was studied using NMR, showing remarkably enantioselectivities and diastereoselectivities. Notably, it was observed that one CSC enantiomer binds one equivalent of canrenone, while two molecules of the same guest were encapsulated in the other stereoisomer, unrevealing an unprecedent binding phenomena.

We also recently reported imine based CSC able to self-assemble in the presence of complex mixtures like wine or fruit juices.[64] Taking advantage of templating dicarboxylic acids naturally present in these mixtures it was possible to report composition of (a)chiral dicarboxylic acids in fruit juices and wines using ^{1}H NMR, and employing the enantiopure CSC **22**, determine the *ee* of tartaric and malic acids present in these matrixes (Figure 11).

4.2. Circular Dichroism

CD has been employed in combination with CSC for the sensing of several analytes such as: choline derivatives,[54,65,66] achiral molecules,[67] chiral drugs,[68] binaphthol,[32] binaphthyl-disufonate,[69] and chiral molecules in water.[70] The interest has recently moved in the possibility to have these systems working in complex mixtures. In these media, the selectivity and specificity of CSC find their peculiar application. As example, Davis developed an achiral cage-like receptor **23** with outstanding selectivity for glucose, able to translate the binding event in a chiroptical signal.[71] Cage **23** was composed by two triethylmesitylene units held together by bis-ureidobenzenecarboxamido scaffolds functionalized with nonacarboxylate moieties in order to maintain the water solubility (Figure 12). CD was found to be an efficient technique to study glucose sensing in biological matrices, due to the absence of chromophores in the scaffold of the chiral analyte, thus the influence on the receptor could be easily monitored. The high selectivity for glucose, that was achieved exploiting the specific interactions that this molecule establish inside the void cavity of the host, implies that the presence of other interferents (for example L-glucose) could be negligible. This chiroptical probe was thus applied for the determination of the D-glucose content

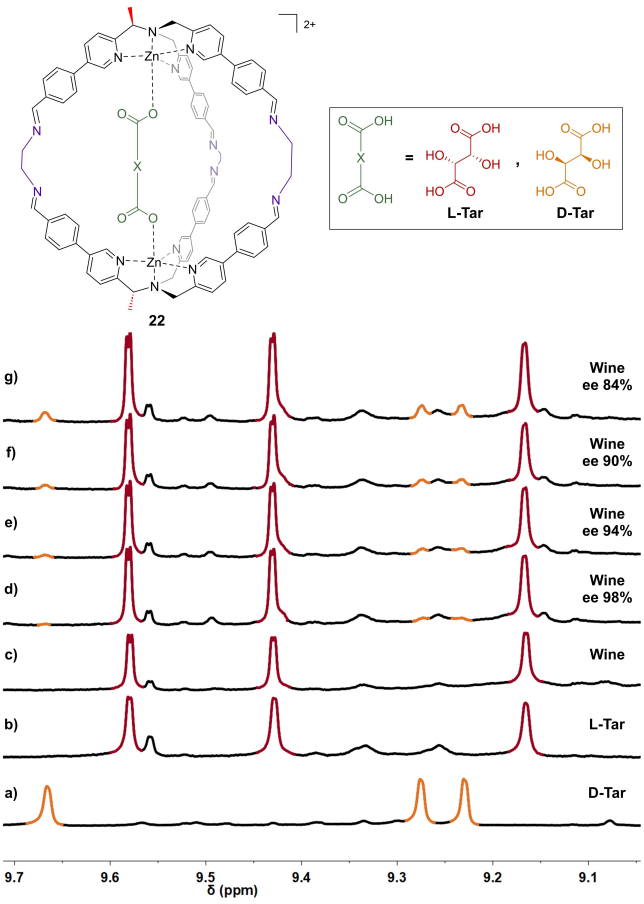

Figure 11. Determination of tartaric acid *ee* via ^{1}H NMR using enantiopure **22** as chiral solvating agent. Partial ^{1}H NMR spectra of the α-pyridine protons region of the CSC **22** formed adding a) **D-Tar** acid, b) **L-Tar** acid, and Valpolicella wine with **L-Tar** c) pure, d) *ee* 98%, e) *ee* 94%, f) *ee* 90%, g) *ee* 84%. Reproduced from Ref. [64] with permission from the Royal Society of Chemistry.

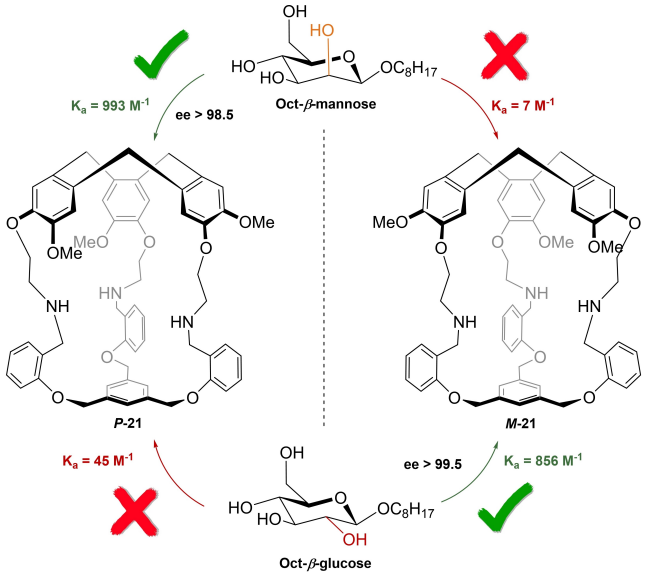

Figure 10. Schematic representation of the selectivity of both enantiomers of receptors **21** toward the sugar guests **Oct-*β*-glucose** and **Oct-*β*-mannose**.[62]

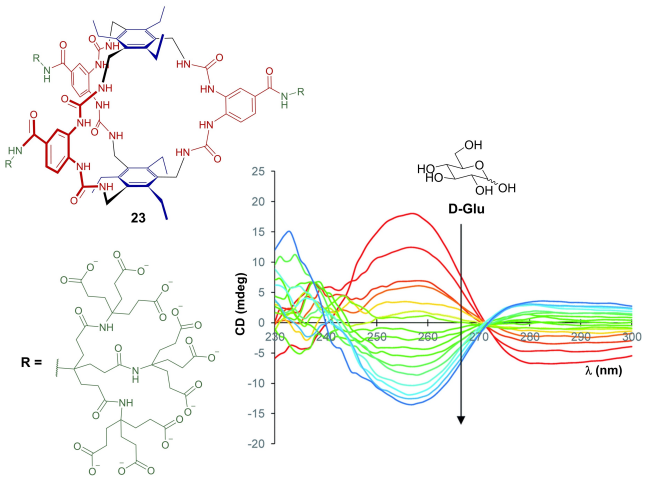

Figure 12. CD spectra from the titration of D-glucose into filtered, diluted, glucose-free human serum, in the presence of L-glucose (2 mM) and cage **23** (0.25 mM). Reproduced from Ref. [71] with permission from the Royal Society of Chemistry.

in human serum, that closely match standard biochemical procedures.

Another example in which a CSC could act as chiroptical sensor for an achiral guest was reported by Pasini and Amendola.[72] CSC **24** detected perrhenate (ReO_4^-) using CD in aqueous media (Figure 13). Due to the similar features, perrhenate is usually used as surrogate of the hazardous pollutant pertechnate TcO_4^- for binding studies, thus the development of sensors for this species have received considerable attention. Upon addition, the binding of perrhenate was translated in a significant variation in the chiroptical output of the host. Interestingly, the chiroptical probe was effective also in the presence of complex matrixes like fruit juices.

As reported earlier for NMR, we also recently reported the use of **TPMA**-based stereodynamic cage able to self-assemble in the presence of a complex mixture like wine or fruit juices and selectively encapsulate dicarboxylic acids present in the matrixes.[73] The CSC can allow the quantification of tartaric acid in complex mixtures using also CD. This is due to the preferential enhancement of the dichroic signal for tartaric acid which is more than one order of magnitude higher than the structural closest system malic acid.

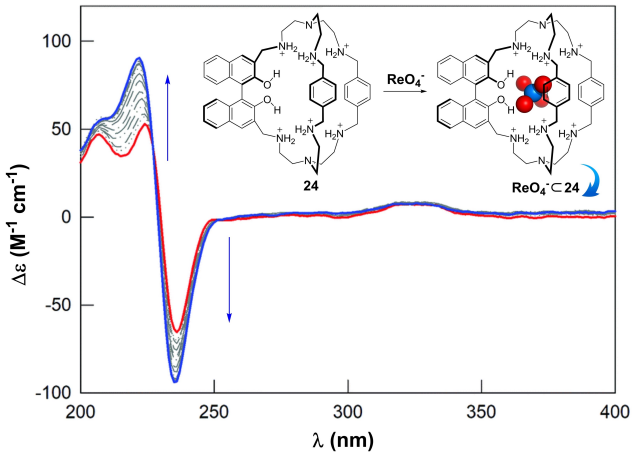

Figure 13. CD titration of cage **24** (0.1 mM in 0.05 M CF_3SO_3Na, pH 2) with $NaReO_4$ (red and blue lines: initial and final spectra, respectively). Reproduced from Ref. [72] with permission from the Royal Society of Chemistry.

4.3. Gas Chromatography

The possibility of supramolecular cages to form porous organic materials, have been extensively studied.[16] These Porous Organic Cages (POCs) have become a suitable alternative to the more common cyclodextrins, showing promising commercial applicability as stationary phases for chiral separation in GC.[74] Cooper reported the use of imine-based CSC **2** that could be coated inside a standard capillary column for chiral GC separation.[75] The tetrahedral CSC was synthetized through imine-condensation between 1,3,5-triformylbenzene and ***RR*-CHDA** and showed an high level of permanent microporosity. Cage **2** was then coated to a capillary column and employed for the separation of racemic mixtures, demonstrating high selectivity for linear 2-hydroxy alkanes. The same structure was also employed by the group of Yuang in a wider analyte scope.[76]

4.4. Fluorescence and Circularly Polarized Luminescence

While several examples of achiral supramolecular cages are reported as fluorescent sensors,[77] less examples of CSC are present in literature. Cui reported fluorescent CSC able to perform enantioselective enhancement of luminescence for amino acids and saccharides recognition mixing Zinc(II) and enantiopure pyridyl-functionalized salan ligands.[78,79] Another approach, which allows the *ee* of the analyte, is the use of CPL properties of stereodynamic systems.[54,80,81] The most common approach involves the use of helicates or tetrahedral systems, in which the presence of the chiral analytes drive the systems toward the formation of the most stable diastereoisomer. This bias, which is directly related to the *ee*, can be measured using either CD or CPL.

5. Other Applications

5.1. Chiral Resolution

In this paragraph are reported two examples in which the stereochemical information is transferred from a chiral guest to the cage, or vice versa. While these can be seen as other cases of chiral resolution, the peculiarity is either in the resolution process or in the way it has been monitored.

Clever reported an example of chirality induction on an embedded dithienylethene unit in a palladium based cage triggered by encapsulation of a chiral guest and irradiation with light.[82] This photochromic component display an helical arrangement of the chromophores, and upon irradi-

ation can reversibly interconvert between the open and the closed forms. In the absence of a chiral input and after irradiation, a racemic mixture of the close isomer is produced. On the other side, in the presence of an enantiopure chiral guest (a camphor sulfonate) encapsulated in the inner cavity of the structure, a preferential helix conformation in the chromophore units was observed, and upon irradiation, a stereoselective closure was obtained (up to 25 % of *ee*).

While in the previous examples the chiral information was transferred from the chiral guest to the host, chirality transfer from a cage to a perfluorinated dicarboxylic acid was instead reported by our group.[83] We could demonstrate that encapsulation inside a CSC induces a preferential helical twist of the alkyl chain of the guest. Perfluorinated alkanes are known to adopt preferentially helical conformations in solution due to hyperconjugative interactions between the σ_{CC} and σ^*_{CF} orbitals. Inclusion of a perfluorinated dicarboxylic acid within a chiral supramolecular cage resulted in the formation of a preferential chiral configuration. Vibrational CD (VCD) spectroscopy combined with DFT calculations were employed in this case to investigate the chirality induction. It should be noted that VCD can be a very powerful tool for the study of the conformation adopted by CSC.[84]

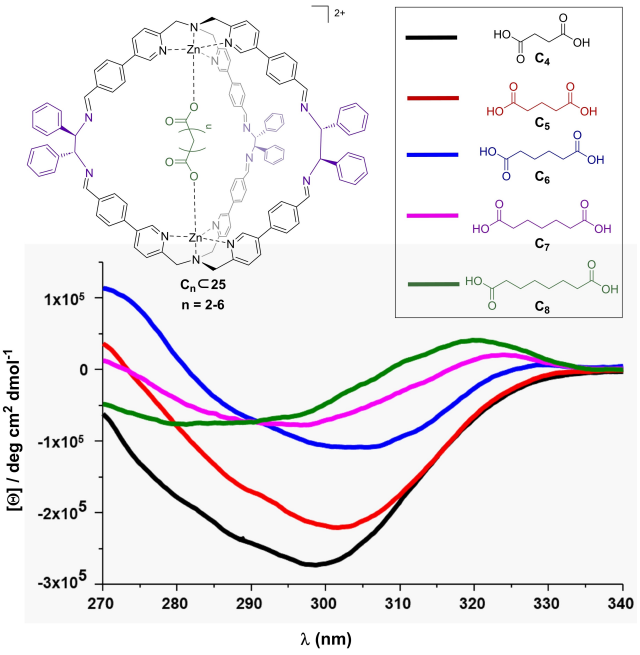

Figure 14. CD signal response of the CSC **25** upon encapsulation of dicarboxylic acids with different chain lengths. Adapted with permission from Ref. [86]. Copyright 2019 American Chemical Society.

5.2. Diastereodynamic Systems

As showed by many examples presented in this review, stereodynamic chiral supramolecular cages have found several applications in sensing. In particular their interaction with a chiral molecule shifts the system toward the more stable diastereoisomer and CD can be effectively used to gather the enantiopurity of the molecules. Switching among different conformational states can also be obtained when a dynamic stereogenic unit is associated with configurationally stable stereogenic elements. In these diastereodynamic systems case, diastereoisomers in dynamic exchange can be biased also by achiral effectors.

As example, Martinez and Dutasta reported a chiral supramolecular cage constituted by an enantiopure hemicryptophane molecules and a dynamic oxidovanadium(V) complexes. The systems exhibited a reversible change in the CD signal uniquely controlled by alternating changes of solvent from $CDCl_3$ to C_6D_6.[85]

Recently we also reported the chiral supramolecular cage **25** that displayed an inversion of the CD signal upon the addition of different achiral dicarboxylic guests.[86] The effect in this case was ascribed to the diastereodynamic nature of the cage which was determined by the two **TPMA** stereodynamic units and the six stereogenic carbon atoms of the three diamine linkers. Theoretical studies demonstrated that the guest length was able to induce the system to move toward opposite configurations, changing the handedness of the helix of the two **TPMA** units together with a variation of the relative orientation of the diamine phenyl rings (Figure 14).

Nitschke reported very recently an example of a diastereodynamic cube formed using enantiopure porphyrin ligand containing four chiral amides which self-assembles with octahedral Zn(II) or Co(II) to produce O-symmetric M_8L_6 CSC.[87] Λ- or Δ-handedness of the metal centers, the dynamic unit, can be controlled by the solvent environment. As example, Λ_8-M_8L_6 is present in acetonitrile, but the opposite handedness Δ_8-M_8L_6 is observed in nitromethane.

5.3. Release and Uptake

While several examples of triggered release or uptake of guests are present for achiral supramolecular cages,[88] one example has been reported by our group for CSC in which selective subcomponent substitution has been used to invert cage chirality.[89] In particular, once a **TPMA**-based imine cage was formed using ***R,R*-CHDA** in the presence of a racemic mixture of L-and D-dibenzoyl tartrate, a preference toward the D-enantiomer ($dr = 17:1$) was observed. Subsequent addition of a quinone led to cage disassemble and release of the guest. Addition at this point of ***S,S*-CHDA** allowed the formation of the cage which selectively bound the L-dibenzoyl tartrate.

5. Conclusions and Perspectives

Dynamic covalent imine and coordination chemistry have in recent years allowed the preparation of chiral confined nanospaces of increasing complexity. This structural evolution has led not only to applications in recognition and

catalysis, but also to the exploitation of these systems in novel contexts. Among them, many results on CPL chiroptical properties and stereodynamic systems have characterized the recent publications. In the future more studies on the role of flexibility and on selective uptake delivery should furnish novel fundamental knowledge to further increase the performances of chiral supramolecular cages.

Acknowledgements

Fondazione CARIPARO (Chiralspace) is acknowledged for funding.

Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords: Chirality · Circular Dichroism · Circular Polarized Luminescence · Stereodynamic Systems · Supramolecular Cages

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Manuscript received: August 2, 2023
Accepted manuscript online: September 4, 2023
Version of record online: ■■, ■■

Minireviews

Supramolecular Chemistry

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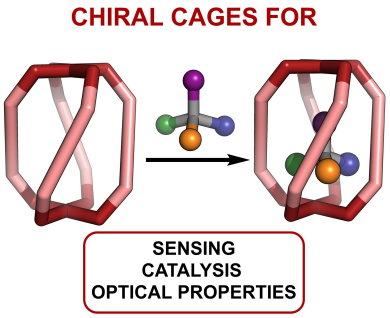
Exploiting Chirality in Confined Nanospaces



The development of novel synthetic strategies for the preparation of chiral supramolecular cages has led in the recent years to a boost on their applications. This minireview highlights some recent examples on the applications that these systems have found in catalysis, sensing and in the development of systems with novel chiral optical activities.