

Review

Gold metallacages: Design principles and applications

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THE BIGGER PICTURE Using coordination-driven self-assembly, organic ligands and metal centers can form metallacages, namely porous discrete structures with defined size, shape, and functionality. These three-dimensional structures allow the creation of multifunctional platforms that integrate the properties of their organic and inorganic components and the benefits of supramolecular encapsulation. Gold derivatives have fascinating chemistry, particularly regarding their catalytic and medicinal potential. The integration of this noble metal in metallacages holds huge potential for the generation of functional platforms, but also presents design challenges. This review analyzes the advances in the synthesis of gold-based metallacages and discusses the developments, open questions, and opportunities in applying them.

SUMMARY

Metallacages (MCgs) are three-dimensional (3D)-supramolecular coordination complexes (SCCs) obtained by the self-assembly of metal ions with donor ligands, which are arranged to delimit a cavity. Recently, the number of structural studies using gold ions in the construction of metallacages and the first efforts to design these systems for diverse applications have shed light on the potential of gold MCgs to become useful supramolecular systems in sensing and separation, catalysis, and medicine. This work critically revises the design principles of gold MCgs and their early applications, highlighting the main challenges and opportunities for developing functional assemblies.

INTRODUCTION

Metallacages (MCgs), also named metal-organic cages (MOCs), are structures assembled by metal-ligand bonds with a defined three-dimensional (3D) void.^{1,2} These assemblies belong to the broad family of coordination-driven self-assembled (CDSA) structures known as supramolecular coordination complexes (SCCs)—coordination being used for simplicity, including also organometallic bonds—as well as several related discrete metal-containing systems such as macrocycles, helicates, entangled molecules, etc.^{3–5}

Significant attention has been devoted to developing MCgs, with tailored cavity properties and functions. The possibility to synthesize ligands (Lewis bases) with diverse functionality and directionality, combined with the well-defined coordination geometries of metal ions (Lewis acids) that act as nodes, can create a whole new domain in the chemical space consisting of virtually unlimited structures.^{6–10} To date, a significant part of the reported MCgs portray square planar (Pd(II), Pt(II)),^{11–15} or octahedral metal centers (Fe(III), Ga(III), Co(II), Zn(II), Ni(II), Cu(II), Ru(II),

etc.),^{16–19} bonded to multitopic ligands commonly based on N or O donors.^{17,18,20–22} The choice of the metal-ligand couple depends on both the structural design and the intended use. Diverse applications have arisen thanks to the modular, multi-component nature of these assemblies.^{2,5,7–10,23} For example, many of these metal nodes are catalytically active, suggesting that these 3D structures can be used as nanoreactors benefiting from their host-guest chemistry. Indeed, several of the available MCgs have been projected for applications related to catalysis.^{24,25} However, applications in separation²⁶ and medicine have also been proposed.^{27–29}

Gold is a unique element, presenting large relativistic effects, increased ionization energies, and high redox potential. It typically forms cations in oxidation states +1 and +3, with the former featuring a d^{10} electronic configuration, adopting a linear two-coordinate geometry, while Au(III) complexes prefer a four-coordinated square planar sphere induced by the d^8 configuration.^{30,31} According to Pearson's hard and soft acid-base (HSAB) theory,³² Au(I) is a "soft" Lewis acid, meaning it can form favorable interactions with soft Lewis bases such as S,



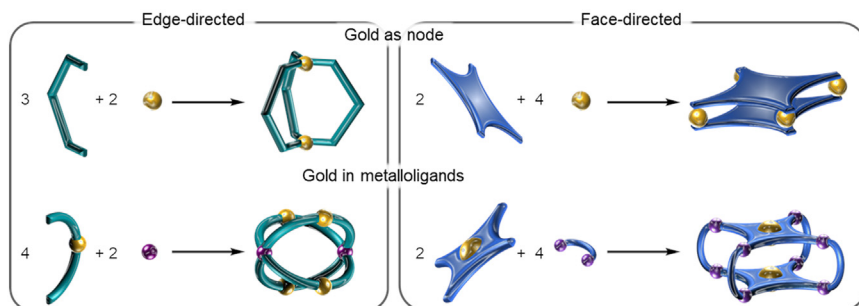


Figure 1. General strategies for the inclusion of gold cations in the structure of MCgs

Multidentate ligands of different topicity can self-assemble by coordination to gold-based nodes (golden spheres), but also gold-containing metalloligands can be assembled by coordination to additional metal centers (magenta spheres). Both approaches can be adapted to edge-directed and face-directed self-assembly principles.

Se, C, and P, whereas Au(III) is more densely charged and so favors “harder” donors such as N, O, and F. Steric factors allowing, Au(I) compounds also have a marked tendency to interact with neighboring Au(I) centers to establish short Au...Au interactions. The exploration of these interactions, named *aurophilic* by Schmidbaur,^{33,34} and the posterior observation of related heterometallic metallophilic (Au...M) and Au...L interactions^{35–40} have revealed important implications in the properties of gold-based materials,⁴¹ opening a vast area of research and producing fascinating structural motifs with enhanced optical properties,^{42–46} as well as intriguing catalytic activity.^{47–49} Of note, due to its open shell configuration, reduced relativistic influence, and higher steric hindrance, *aurophilic* interactions are essentially absent in Au(III) complexes.⁵⁰

The redox potentials of the Au^{III}/Au⁰, Au^I/Au⁰, and Au^{III}/Au^I redox couples in standard conditions are significantly higher (1.52, 1.83, and 1.36 V, respectively) than those observed for platinum or palladium (Pd^{II}/Pd⁰ 0.91 V and Pt^{II}/Pt⁰ 1.19 V).⁵⁰ Consequently, gold is more easily reduced to either Au(I) or the metallic state than palladium or platinum. In catalysis, this may pose the challenge of rapid reduction of the gold complex prior to its catalytic function. Moreover, the higher ionization energy of Au vs. Ag or Cu potentially limits key steps in the gold redox cycle, such as oxidative addition. These features also affect the biological applications of Au(I)/Au(III) compounds, whose uncontrolled metal speciation—i.e., fast ligand-exchange reactions, eventually leading to reduction to Au(0)—is favored in aqueous environment and in the presence of biologically relevant nucleophiles. To provide stability against reduction, the appropriate selection of ligands, in particular chelating bi- and tridentate ones able to form direct metal–carbon bonds, can modify the redox potentials. For example, in the case of Au(III), ligands enabling cyclometallation are of great importance⁵¹ and have enabled applications of Au(III) compounds in catalysis and medicine.^{50,52}

The interest in the supramolecular chemistry of gold compounds began at the end of the last century with the seminal observations of the tendency of Au(I) centers to establish the aforementioned *aurophilic* interactions.^{53,54} Due to the propensity of gold compounds to associate via these non-covalent interactions, many supramolecular structures have been reported, mainly polymers^{55,56} and oligomers,⁵⁷ but also in more complex structures with potential functionality, such as catenanes.⁵⁸ Some of these oligomers were perhaps the first self-assembled MCgs and metallacycles, although they were not immediately

identified as such at that time.³¹ More recently, further examples of gold-based metallacycles⁵⁹ and the first extended 2D and 3D networks, including porous metal-organic frameworks (MOFs), have been reported.^{60–62} The interest in gold-based heterometallic systems fueled the development of “metalloligands”—i.e., gold compounds with available ligand atoms that can coordinate to additional metal centers—which in some cases also produced SCCs.⁶³ In most of these instances, such architectures were observed in the solid state, and their existence in solution was not always proven. Only recently, the rational design of gold-containing MCgs (**AuMCgs**) has yielded the first systems designed for different applications.

This work summarizes the developments in the construction of **AuMCgs**, highlighting some related SCCs, and explores the applications proposed for the reported systems. Purely cage-like metallic clusters are not considered in the scope of this review since they are not formed by metal-ligand coordination and thus fall out of the definition of SCCs. However, we refer the reader to other reviews on that topic.^{64,65} This manuscript is organized as follows: the first section focuses on the structural design strategies adopted for the obtainment of **AuMCgs** (section “*design principles and structural studies*”). Then, the possible applications have been used to categorize **AuMCgs** into systems for supramolecular recognition, luminescence and sensing (section “*supramolecular recognition, luminescence, and sensing*”), catalysis (section “*catalysis*”), or medicine (section “*medicinal applications*”). Finally, the present challenges and opportunities are highlighted in a final outlook and perspectives section.

DESIGN AND APPLICATIONS OF AuMCgs

Design principles and structural studies

Two main CDSA strategies have been exploited to form MCgs, i.e., edge-directed or face-directed (Figure 1).^{4,66} Both are based on the use of directionally oriented multitopic ligands in conjunction with metal nodes of determined geometry. In the edge-directed CDSA, bridging ligands connect to metal centers to generate the cage grid, and in the face-directed approach, ligands of higher topicity, typically planar, are connected by the metal nodes. These approaches are applicable to constructing **AuMCgs**, whereby the gold cations can constitute the nodes of the SCC or be included in a metalloligand either in the main scaffold or as pendant functionalization. In the first case, the use of Au(I) is convenient as its common linear coordination

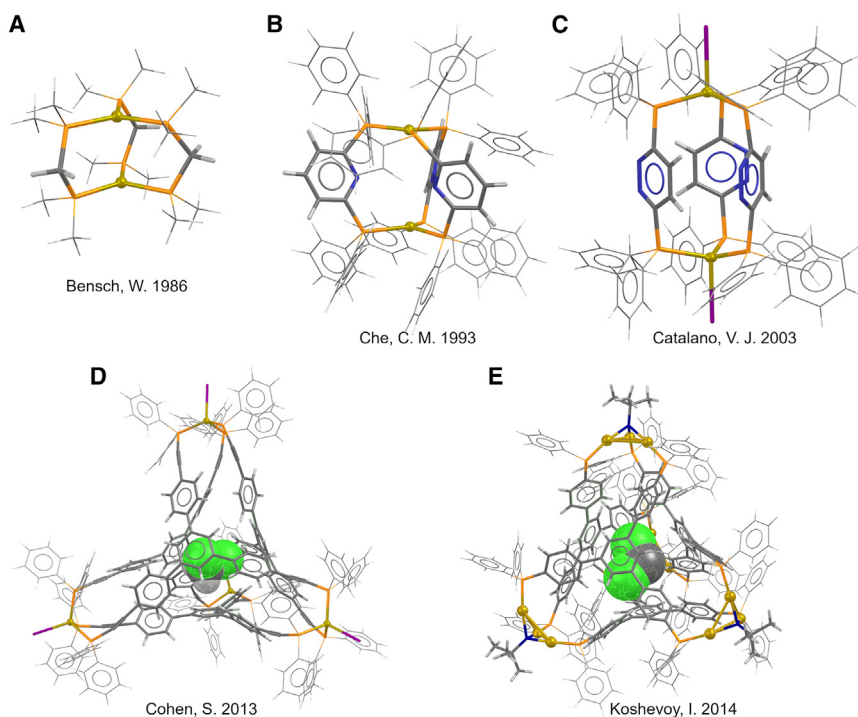


Figure 2. Single-crystal X-ray diffraction (SCXRD) structures of different phosphine-based MCgs with trigonal or tetrahedral Au nodes

(A) First edge-directed cage-like structure $[\text{Au}_2(\mu\text{-dmpm})_3]$ (CCDC 1147298).⁷⁰
(B) Edge-directed Au_2L_3 cage displaying an accessible cavity (CCDC 1288410).⁷¹
(C) $[(\text{AuI})_2\text{L}_3]$ cage displaying tetra-coordinated Au(I) centers (CCDC 208141).⁷²
(D) Face-directed tetrahedral cage built by tritopic panels bound to Au(I) tetrahedral nodes able to encapsulate dichloromethane molecules in the crystal (CCDC 911638).⁷⁹
(E) Face-directed tetrahedral cage with trigonal panels and azanediide-capped tri-Au(I) clusters, including a host dichloromethane molecule (CCDC 794075).⁸⁰ Color code is as follows: H, white; C, gray; N, blue; Cl, green; P, orange; Au, gold; I, purple. The structures were generated using Mercury.⁸¹

allows the construction of extended edges. By contrast, the use of Au-metalloligands for face-directed assembly is less explored, with only a few examples using multinuclear Au(I) planar scaffolds⁶⁷ or Au(III) chelated structures (e.g., in porphyrins).⁶⁸ In any case, different auxiliary metal nodes can be coordinated to the Au-metalloligands to form the assemblies. Within these sections, the type of approach followed for the construction of the different **AuMCgs** is highlighted, i.e., edge- or face-directed (with gold either as a node or in a metalloligand). Of note, despite the rareness of examples in some instances, the different assembly strategies can be applied to achieve both coordination and organometallic systems, the latter featuring a direct Au–C bond. If the carbon donor is part of the edge-node connection, i.e., forming the organometallic bond to the metal node, the so-called supramolecular organometallic complexes (SOCs) are formed.⁶⁹ The different structural and electronic properties of the different families of **AuMCgs** are of relevance for the potential applications discussed in the following sections.

Coordination AuMCgs

Perhaps, the first structure reminiscent of a **AuMCg** was reported in 1986 by Bensch et al. and featured an edge-directed Au_2L_3 -type of assembly, namely $[\text{Au}_2(\mu\text{-dmpm})_3]^{2+}$ (Figure 2A, L = dmpm = dimethylphosphinomethane).⁷⁰ In this case, given the short bridging groups in the ligands, correspondingly short Au···Au contacts (3.05 Å) were observed between the 3-coordinated trigonal planar Au(I) nodes, resulting in a 3D structure lacking a cavity. Nevertheless, the design principle was established, and, using this type of edge(ligand)-directed self-assembly, another Au_2L_3 (L = 2,6-bis(diphenylphosphino)pyridine) cage example was formed with a longer linker, enabling a larger cavity and impairing the Au···Au contacts (Figure 2B).⁷¹ In these

first two examples, unusual three-coordinated Au(I) centers were obtained as nodes due to the use of weakly coordinating anions. By contrast, the presence of coordinating anions such as halides results in tetra-coordinate tetrahedral Au(I) centers giving $\text{Au}_2\text{X}_2\text{L}_3$ systems (where L = diphosphine and X = halogen, Figure 2C), and diverse diphosphines have been shown to produce this type of edge-directed arrangements.^{72–74} The $\text{Au}_2\text{X}_2\text{L}_3$ structures obtained using diphosphines functionalized with additional inner donor atoms were demonstrated to act as cryptands, encapsulating cations,^{74–77} and also enabled the obtaining of heterometallic AuML_3 systems (M = Pd(0) or Pt(0)).⁷⁸

Tetra-coordinated Au(I) centers and trigonal tridentate phosphines have been assembled to achieve face-directed tetrahedral structures.⁸² Similarly to the case of the edge-directed systems, the first reported structures $[\text{Au}_4(\text{tppeb})_4]^{4+}$ (tppeb = 1,3,5-tris((diphenylphosphino)ethynyl)benzene) lacked hosting capabilities due to limited cavity size.⁸² However, the use of an extended ligand (1,3,5-tris(4-((diphenylphosphino)ethynyl)phenyl)benzene, (Figure 2D) increased the cavity size, rendering the cage capable of hosting small solvent molecules.⁷⁹

Given the Au(I) center's preference for di-coordinated linear geometries and their tendency to form auriphilic contacts,³⁰ Au(I) cations can cluster around a single non-metal (e.g., O, S, and C), giving multi-aurated centers that display auriphilic contacts.^{33,83} As metallophilic contacts are weaker in other metal centers,⁸⁴ this is a unique feature of gold that can originate highly directional multinuclear nodes, and the formation of this type of cluster has been used to produce both edge-directed and face-directed assemblies. In the first case, a pair of capping hyper-coordinated μ^4 -benzoylmethylidyne Au_4 clusters ($^{\text{R}}\text{CAu}_4$) were bridged by diphosphines (PP), yielding cages with the general formula $[(^{\text{R}}\text{CAu}_4)_2(\mu\text{-PP})_4]$. Interestingly, these systems were spontaneously formed by the reaction of 1 equiv of the bridged dinuclear Au(I) compound bearing ethynylbenzene (CCPh) as

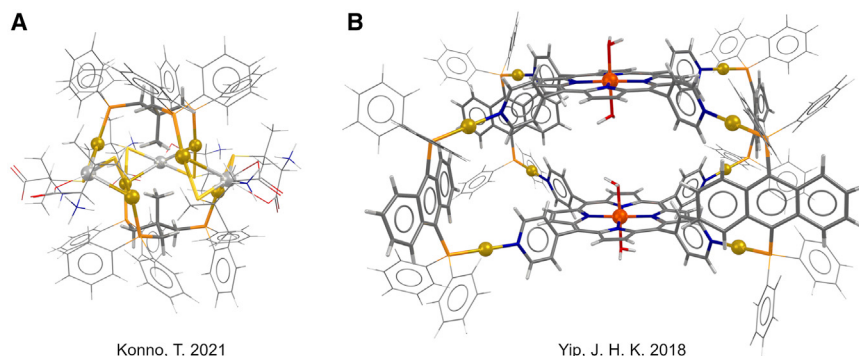


Figure 3. Heterometallic coordination AuMCgs

(A) SCXRD of a heterometallic Ag/Au cage-like structure (CCDC 2024986).⁸⁸ (B) SCXRD of the cofacial porphyrin prism assembled using a digold clip, the coordination of iron to the porphyrin renders the system heterometallic (CCDC 1556461).⁸⁹ Color code is as follows: H, white; C, gray; N, blue; O, red; P, orange; Fe, scarlet; Ag, silver; Au, gold. The structures were generated using Mercury.⁸¹

anionic ligand $[\text{Au}_2(\text{CCPh})_2(\text{m-PP})]$ and 3 equiv of the cationic compound $[\text{Au}_2(\text{THT})_2(\text{m-PP})]^+$ (THT = tetrahydrothiophene) in acetone in the presence of water and triethylamine (Et_3N).⁸⁵ In a similar approach, trimetallic azanediide-capped Au(I) clusters have been assembled with both bridging 1,4-bis(diphenylphosphine)benzene and 1,3,5-tris(4-(diphenylphosphino)phenyl)benzene ligands, generating edge-directed trigonal prisms or face-directed tetrahedral arrays, respectively.⁸⁰ The inclusion of dichloromethane (DCM) has also been observed in the X-ray structure of the tetrahedral system (Figure 2E). More recently, similar small $[\text{Au}_3(\mu^3\text{-S})]^+$ clusters were assembled together with 2,6-bis(diphenylphosphino)-1,1'-biphenyl (dppbp),⁸⁶ and in this case, due to the ligand design, the clusters are oriented toward the cage cavity, giving $[(\text{Au}_3\text{S})_8(\text{dppbp})_{12}]^{8+}$ cages displaying anion-dependent structural changes between cubic and rhombic prism structures. The dynamic nature of the systems was also studied, showing the possibility of thermally converting the cubic structures to $[(\text{Au}_3\text{S})_6(\text{dppbp})_9]^{6+}$ trigonal prisms. The prevalence of either type of cage was found to be related to the solvent polarity.⁸⁶

Since Au(I) is a soft acid, it forms especially stable bonds with soft-donor ligands, from which it is hardly displaced, and it scarcely competes with hard metal ions for nitrogen or oxygen-based donors. This well-defined coordination chemistry allows the use of Au(I) metalloligands as building blocks tolerating the presence of harder Pearson's acids to achieve heterometallic MCgs by CDSA. For example, $[\text{Au}_3(\text{o-phen})_3(\text{triphos})]$ (triphos = 1,1,1-tris(diphenylphosphinomethyl)ethane, D-H2pen = D-penicillamine) has been used to coordinate the o-phen donor atoms to Co(II),⁸⁷ Ag(I), and Cu(II)⁸⁸ metal ions, not only generating a cage-like heteronuclear edge-directed assembly $[(\text{Au}_6\text{M}_3(\text{tdme})_2(\text{o-pen})_6)]^{3+}$ ($\text{M} = \text{Co(II)}, \text{Cu(I)}, \text{or Ag(I)}$, tdme = 1,1,1-tris(diphenylphosphinomethyl)ethane, Figure 3A) but also producing a supramolecular mesoporous solid structure by the assembly of these units in an extended crystal lattice.

Prismatic MCgs built by the cofacial face-directed assembly of planar multitopic ligands with linear pillars are common in the field. Using this principle, *gold-clip* pillars were employed to link ferroporphyrin panels, generating square prisms (Figure 3B).⁸⁹ The so-called "gold-clip" consisted of Au(I) centers bridged by 9,10-bis(diphenylphosphino)anthracene (dppAn), which were generated upon the abstraction of the chloride ligand from $[\text{Au}_2\text{Cl}_2(\mu^2\text{-dppAn})]$ with silver triflate. The gold atoms were then coordinated

to Fe(III)-containing tetra(4-pyridyl)porphyrin (TPyP) from the compounds $[\text{Fe}(\text{H}_2\text{O})_2(\text{TPyP})]\text{OTf}$ (OTf = trifluoromethyl sulfonate) and $[(\text{FeTPyP})_2(\mu\text{-O})]$ in DCM/methanol (MeOH). The two generated systems were related and could be interconverted by acid/base stimuli.⁸⁹ As in this case, the use of metallocporphyrins as ligands is a way of generating heterometallic SCCs.

The examples discussed until this point deal with the use of phosphines as the main building blocks coordinating Au(I), with the participation of other ligands, including pyridines and thiolates, as secondary ligands. The chemistry of phosphine Au(I) compounds presents the advantage of requiring mild formation conditions to yield compounds with good chemical stability, particularly in the case of linear di-coordinated Au(I). However, the introduction of additional ligands in the media can significantly compromise the prevalence of the structures observed in the solid state due to the dynamic nature of Au–P bonds in solution.^{90–93} This is, perhaps, the reason why most of these structures have not been extensively exploited in the typical applications of MCgs based on other metals—such as catalysis, separation, or medicine—requiring the systems to be stable in complex solution mixtures.

More recently, ligands other than phosphines have been applied to build **AuMCgs**. For example, the group of Severin achieved the assembly of $(\text{Au(I)})_3(\text{pyrazole})_3$ panels to form prismatic and tetrahedral face-directed imine-linked cages with differential π -basic cavities (section "supramolecular recognition, luminescence, and sensing").⁹⁴ More recently, they have adapted these synthons to obtain complex heterotrimetallic MCgs,⁶⁷ and in this case, boronate ester-capped clathrochelate Fe(II) complexes bearing pyrazole and pyridine groups were used to form $\text{Au}_3(\text{pyrazolate})_3$ heterobimetallic ligands. The obtained ditopic and tritopic donor ligands were then assembled by coordination to Pd(II), giving, respectively, Pd_2L_4 and Pd_6L_8 MCgs.⁶⁷ These systems are among the first examples of heterotrimetallic MCgs and the first example containing gold. In a different approach, we recently proposed the use of Au(III) porphyrins as metalloligands in CDSA. In particular, we used the Ru-clip approach to link porphyrin-Au(III) panels in an **AuMCg** with interesting biomedical properties (section "medicinal applications").⁶⁸

Nevertheless, integrating gold in coordination MCgs is still challenging. On the one hand, while using kinetically labile, reversible coordination bonds, such as Au(I)-phosphine or Pd(II)-pyridine as building motifs, great assembly precision can

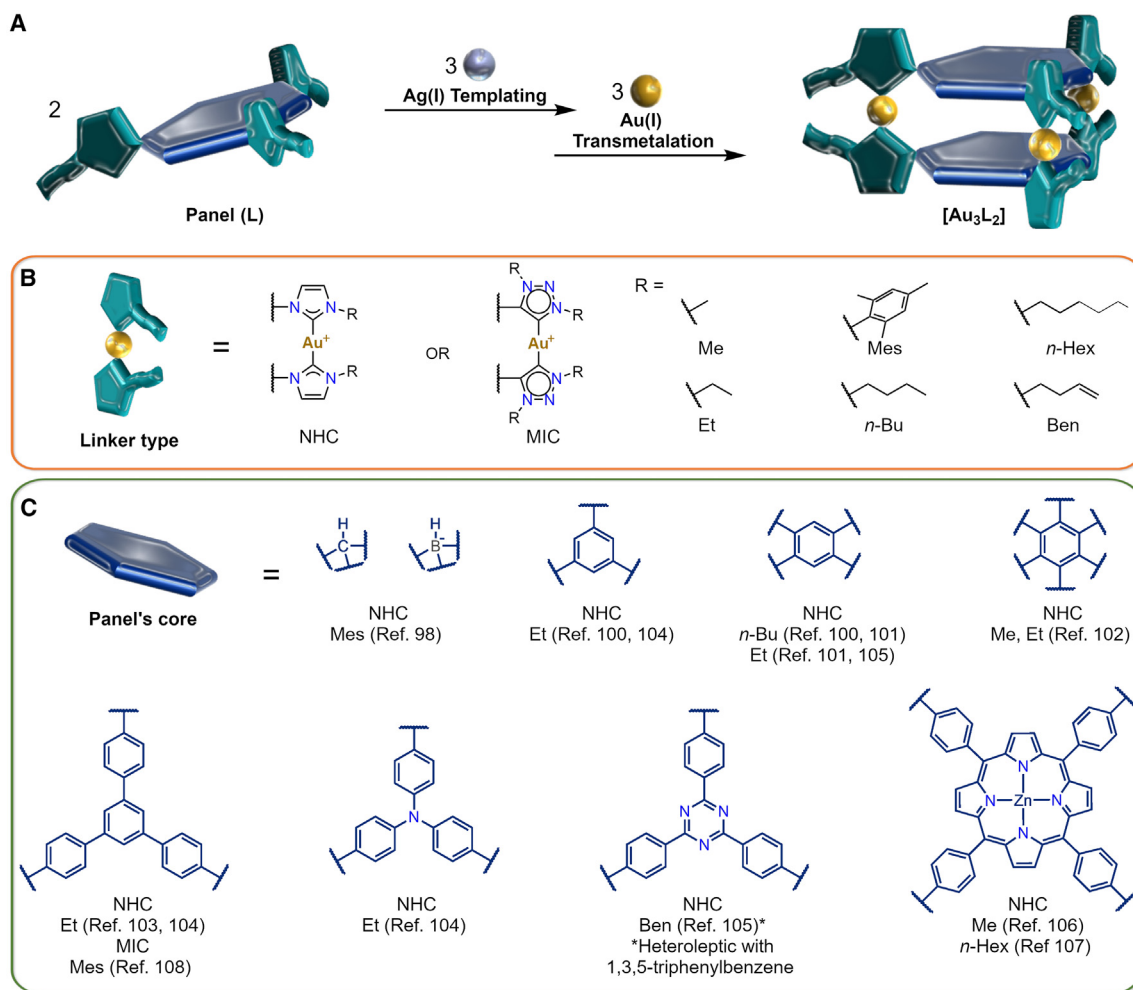


Figure 4. Face-directed self-assembly of bis-carbene Au(I)MCgs

(A) To form bis-carbene Au(I)MCgs, isostructural Ag(I) cages are first assembled, templating the structures that are further transmetalated to the final gold-containing cages. This design has allowed the obtaining of **AuMCgs** of different sizes, as well as the inclusion of functional modifications in the NHC wingtips. (B) Different scaffolds reported in the literature. Bis-NHC (or MIC) Au(I) moieties can link planar multitopic panels, and this is achieved by including imidazolium or triazolium moieties in the peripheric positions of different cores.

(C) The panels used in the reported examples so far are trisubstituted tetrahedral atoms,⁸⁹ multi-substituted benzenes,^{90–92,94,95} triphenylbenzene,^{93,94,98} triphenylamine,⁹⁴ triphenyltriazine,⁹⁵ and porphyrin panels.^{96,97}

be obtained, and it can also compromise the stability of the systems in application-relevant conditions. On the other hand, using kinetically inert coordination bonds such as Au(I)–nitrene or Pt(II)–pyridine can increase kinetic stability; however, it can also diminish the self-corrective nature of the self-assembly process, giving rise to kinetically trapped, unwanted by-products, and requiring harsher reaction conditions under longer times (unless microwave heating can be used)⁶⁸ to yield the desired products.

Organometallic AuMCgs

The use of organometallic building blocks in the construction of MCgs and other SOCs is dominated by half sandwich and metal carbonyl nodes, in which the organometallic ligands often provide directionality to the node but do not participate in the assembly main framework.^{95,96} Organometallic bonds as building motifs are less common.⁶⁹ However, some examples are known,

particularly using multitopic N-heterocyclic carbenes (NHCs), which form stable compounds with late transition metals. In this area, while diverse metals can form 90° nodes with adequate protecting ligands (i.e., Pt(II), Ir(II), Ni(II)), Au(I) ions allow fine control toward the formation of face-directed assemblies thanks to their preferred linear geometry.⁹⁷ The area of 3D organometallic Au(I) structures featuring Au–C bonds is a growing field due to the increased stability in solution compared with the coordination-based analogs mentioned above. However, there are only a limited number of well-defined examples with distinct ligand scaffolds. The synthetic strategy that has dominated the production of organometallic **Au(I)MCgs** uses carbenes as ligands in the face-directed assembly of panels to give cofacial structures of the SOCs family (Figure 4). One of the first examples of such systems was reported in 2008 by Tubaro and coworkers,⁹⁸

whereby scorpionate-type tris-imidazolylborate precursors [HB(RImH)₃]Br₂ (R = Mes = mesityl and *t*-Bu = *tert*-butyl, Figure 4) were activated with silver oxide to assemble AgMCGs bearing two NHC carbene ligands and three Ag(I) centers, followed by transmetalation to form the corresponding AuMCGs.⁹⁸ In this work, the precursor AgMCGs were effective catalysts for Sonogashira reactions, but no further studies were carried out with the corresponding AuMCGs. As transmetalation from Ag(I) adducts is the more extended strategy to generate carbene-gold scaffolds, most of the cage structures of this type are reported together with their silver analogs. However, to keep the focus of the review, we center the discussion on the final gold-based organometallic cages, which are more stable compared with the silver assemblies⁹⁹ and, thus, present a broader scope in terms of possible applications.

In this area, the group of Hahn pioneered the formation of bis-NHC Au(I) pillars for the assembly of cofacial structures (Figure 4).¹⁰⁰ Their denominated cylinders were first assembled using benzene scaffolds. In detail, 1,2,3-tri- or 1,2,4,5-tetra-halobenzene was reacted with imidazole, followed by alkylation of the remaining imines. Generation of the tri- and tetra-Ag(I) NHC complexes yielded cofacially linked structures, which could be transmetalated to produce Au(I) MCGs.^{100,101} The concept was further expanded to generate hexametallic assemblies with dodecacarbene structures when 1,2,3,4,5,6-hexakis(*N*-alkylimidazolium)benzene NHC ligands were bridged by gold centers.¹⁰² Despite their novelty, the applications of these MCGs as host systems remained limited due to the small cavity for the inclusion of guest molecules.

Therefore, in order to increase the cavity size, the 1,3,5-trisubstituted benzene NHC backbone was substituted with 1,3,5-triphenylbenzene (Figure 4).¹⁰³ Considering a pseudo-triangular-prismatic structure, the internal volume of the cavity was predicted to be approximately 5-fold greater than the tri-Au(I) cylinders previously synthesized.^{100,101} An X-ray structure of the AuMCGs revealed a triangular prism arrangement linked by Au(I) atoms with π - π interactions between the two central phenyl rings of the tri-NHC ligands, adopting a nearly coplanar orientation.¹⁰³ However, due to the π - π interactions between the central phenyl rings, the cavity volume remained limited, with no hosting capabilities reported.

In more recent work, Hahn and coworkers demonstrated the ability of three tris-NHC ligands with different spacers—but similar topology—to react with Ag(I) to obtain exclusively three homoleptic MCGs (Figure 4). This revealed, for the first time, a highly selective narcissistic self-sorting assembly in which the homoleptic nature was preserved upon transmetalation with Au(I).¹⁰⁴ In addition, this work was further extended to form heteroleptic AuMCGs upon social self-sorting of tris-NHC ligands featuring a central electron-deficient triazine and an electron-rich benzene.¹⁰⁵ Besides the use of benzene-like cores, Richeter and coworkers first reported NHC-functionalized meso-tetraphenyl porphyrins linked by Au(I) pillars forming prismatic cages.^{106,107} In general, the use of single bis-NHC Au(I) pillars to link coplanar panels can generate interesting systems. Still, the obtained cavities are often too constrained to host even small molecules.

Not only NHCs but other types of carbene donors can be applied to generate gold assemblies. A design similar to that

described above using triphenylbenzene panels was applied to obtain homoleptic 1,2,3-triazole mesoionic carbene (MIC)-based Ag(I) and Au(I)MCGs (Figure 4). Although the host-guest chemistry was not explored, the combination with similar NHC ligands enabled the obtainment of unique heteroleptic AgMCGs with a cylindrical shape.¹⁰⁸ However, this was not extended to the Au analogs. Finally, Ibáñez and Peris¹⁰⁹ designed a rigid trigonal-prismatic MCg using triphenylene-tris(imidazolylidene) Au(I) moieties as panels, which are then clipped by carbazoyl-bis(alkynyl) as linkers, generating face-directed cages with a selective cavity for the inclusion of coronene (section “supramolecular recognition, luminescence, and sensing”; Figure 6).¹⁰⁹

While the strategy to form organogold cages discussed in the examples above includes the implementation of a carbon donor in the capping ligands of the Au(I) nodes used for the self-assembly to generate SOC, an alternative approach includes Au-C bonds in the cage's panels or edges. In this case, the organometallic bond influences the edge and face stability, geometry, and overall properties but only indirectly affects the self-assembly, which is again determined by classical coordination chemistry (either edge- or face-directed). As for the classical coordination systems, these types of heterometallic SOC are achievable thanks to the improved stability of Au-C bonds and the low affinity of the gold center for the auxiliary ligands used in the self-assembly. For example, Nitschke et al. exploited the concept of “subcomponent self-assembly”²³ and combined dianiline NHC-Au(I) complexes with picolinaldehyde to form Schiff-base organogold ligands *in situ*. The latter could produce edge-directed M₄L₆ tetrahedral cages by CDSA (M = Zn(II) and Cd(II), Figure 5A).¹¹⁰ Interestingly, the cages could disassemble and form AuNPs by further addition of Au(I).¹¹⁰ Additionally, Han and coworkers explored the use of NHC-Au metalloligands for the edge-directed assembly of homo- and heteroleptic cages using cyclopentadienyl Zr(IV)-based trimetallic clusters as nodes, and the structures showed interesting dynamic ligand-exchange behavior, which has proven useful in the generation of heteroleptic assemblies.¹¹¹ In 2021, a Au(I) metalloligand [Au₃(4-Py)₃(μ^3 -triphosph)] (triphosph = 1,3,5-tris(diphenylphosphino)benzene; 4-Py = 4-pyridylidene) was used as an organogold(I) building block to generate edge-directed heterometallic cages by coordinating the pyridine residues to cis-protected Pd(II) or Pt(II) nodes (Figure 5B). In this example, the synthesis from a boronated precursor of the organometallic Au(I) metalloligand, where the metal center is attached directly to the pyridine donor fragment, and subsequent cage assembly were described. While no X-ray structure was obtained, the assemblies were characterized in solution by NMR spectroscopy and mass spectrometry.¹¹²

Supramolecular recognition, luminescence, and sensing

The porous nature of MCGs is one of their more attractive features.^{1,10,113,114} The possibility of acting as hosts for small molecules holds the potential for MCGs to develop applications in separation and sensing.^{26,115,116} The opportunity to create guest-tailored size and shape cavities by CDSA is an essential advantage of MCGs compared with other host systems, i.e., macrocycles, although the number of successful applications of MCGs

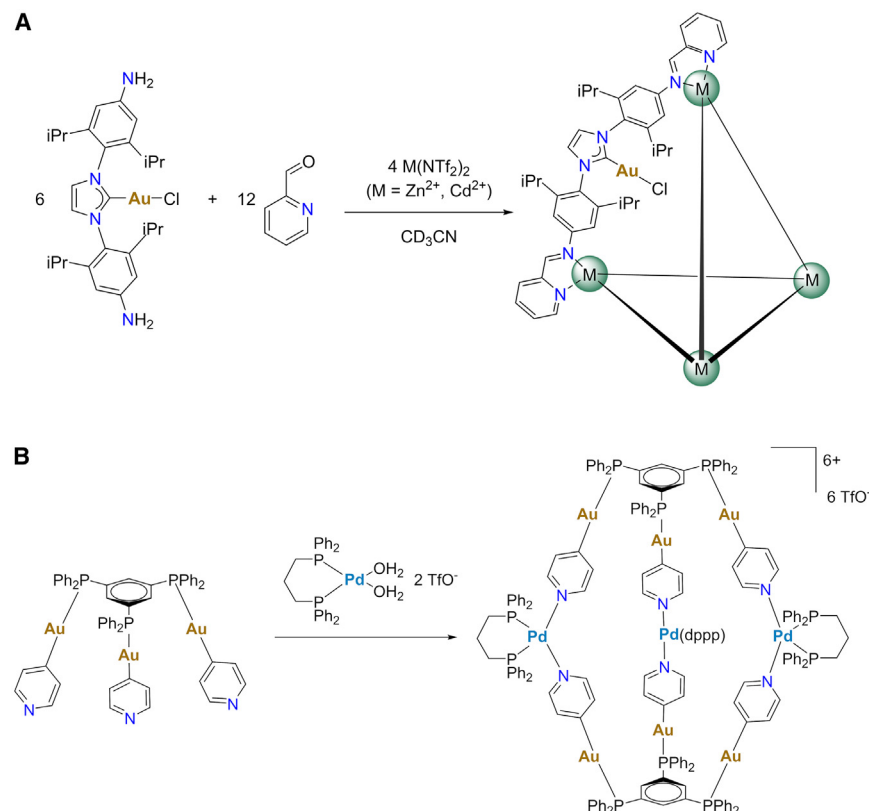


Figure 5. Heterometallic organometallic AuMCgs

(A) Subcomponent self-assembly of NHC-Au metalloligands to form tetrahedral edge-directed MCgs.¹¹⁰

(B) Self-assembly of Pd₃L₂ edge-directed MCg using an Au-containing metalloligand.¹¹²

that, if not yet applied for sensing on the whole, set a necessary foundation for developing functional sensors. It should also be noted that examples of both coordination and organometallic **AuMCgs** are shown below, highlighting the great potential of these systems for such applications.

The first examples of **AuMCgs** applied as hosting systems involve the chelation of metal centers via ligand-metal coordination within the cage cavity. By the placement of donor atoms within the small cavity of Au(I)-based cages, cations can be included: in particular, the groups of Noll and Catalano reported diverse systems in which, in the solid state, Na(I), Tl(I), or even Hg(0) can be cryptated (Figure 6A).^{72,75–78}

With the increase of cavity size by the expansion of linkers on **AuMCgs**, the inclusion of solvent molecules was often

observed in the solid state (see examples mentioned in section “design principles and structural studies”). The potential of these coordination systems for functional hosting has been scarcely explored. For example, the use of different diphosphines modulates the cavity size in [(^RCAu₄)₂(μ-PP)₄] cages and allows the inclusion of DCM or carbon disulfide (CS₂) when the μ-PP ligand is 1,3-bis(bis(diphenylphosphino)ethynyl)benzene.⁸⁵

In NHC or MIC-based organometallic systems, the extended use of a single Au(I) center as a linking motif of coplanar panels significantly limits the effective cavity volume, with the C-C distance in the C-Au-C pillar being roughly 4 Å.¹⁰⁰ This limiting factor constrains the cavity, preventing the effective inclusion of guest molecules. An option to circumvent this limitation is to geometrically modify the linking between the NHC and the facial ligands to provide further spacing between them. In this sense, Han and collaborators¹²³ first introduced imidazo[1,5-*a*]pyridine-based NHCs attached to either benzene or triphenylbenzene. The geometry of the ligand places the donor carbon away from the ligand's core plane, increasing the interfacial distance to 7 Å (Figure 6B).¹²³ Further modification of these scaffolds by exchanging the triphenylbenzene core to 2,4,6-triphenyl-1,3,5-triazine allows an additional span in the cavity size by increasing the planarity of the face ligand. This, in turn, permits efficient π-stacking among the ligands, which was exploited to generate the first gold-based mechanically interlocked cages.¹²⁴ In the case of porphyrin panels, while the first report linking the NHC directly to the porphyrin via the

for sensing are still limited.¹¹⁵ The superior stability and the interesting photophysical properties of gold, which can be used to generate intrinsically luminescent assemblies, set it as an attractive building block. As seen in the precedent section, many of the fundamental studies dealing with **AuMCgs** showed limited porosity, preventing the formation of inclusion complexes and giving an important space for innovation. To achieve functionality, the cavity sizes should be tuned to achieve voids adequate for hosting not only small molecules of interest (i.e., CO, CO₂, NO_x, and NH₃) but also larger compounds (e.g., drugs, pollutants, and biomarkers). Besides the favorable coordination geometries of Au(I) and Au(III) ions included in MCgs, the high electron affinity and Lewis acidity of gold cations can modify the electronic distribution within the organic cage scaffolds,^{68,117} as well as the overall charge; therefore, the hosting capabilities of **AuMCgs** would be expectedly distinct from non-regious systems. Furthermore, for supramolecular sensing applications, the host capabilities should be coupled to reporting modalities, particularly stimuli-responsive luminescence and electrochemical signals, which are attractive features.^{116,118–120} Using gold within the structures could be advantageous, for example, to enhance the triplet-harvesting capabilities of the MCgs due to the heavy-atom effect.¹²¹ Which, when non-radiative paths are suppressed, can enhance the luminescence of AuCgs.¹²² As discussed ahead in this section, exploratory studies of the host-guest properties of **AuMCgs** have appeared, and the first examples of functionalization with fluorescent labels have arisen, and some **AuMCgs** have already been applied to generate stimuli-responsive host-guest systems

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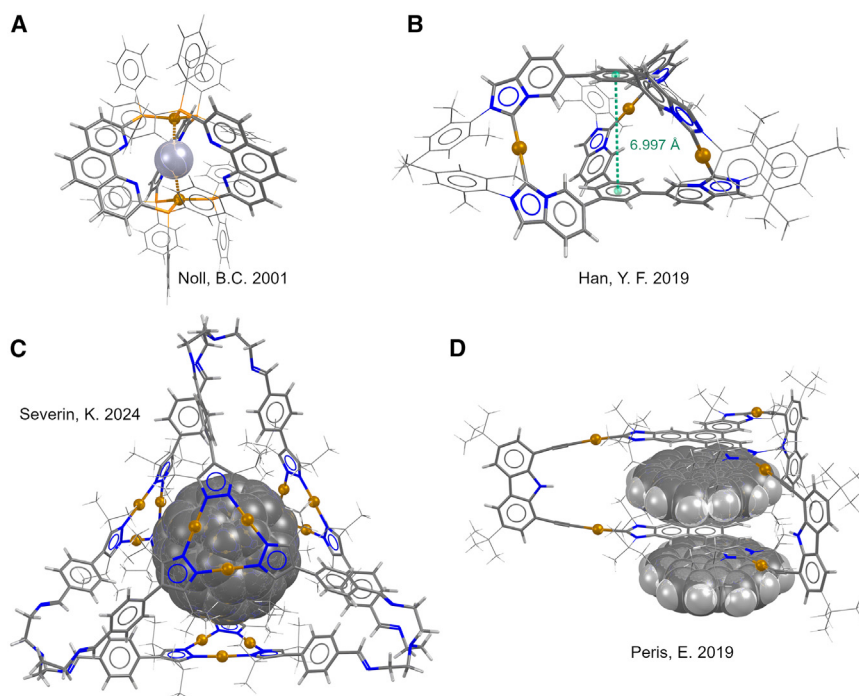


Figure 6. AuMCgs tailored for the hosting of different species

(A) Cryptand-like cage trapping Hg(0) (CCDC 156335).⁷⁵ (B) BisNHC Au(I) cage with an expanded cavity, meant to improve the void accessibility observed in these kinds of systems (CCDC 1885047).¹²³ (C) Au₃(pyrazolate)₃-based tetrahedral cage encapsulating C₆₀ (CCDC 2309725).⁹⁴ (D) NHC-clipped hexa-Au(I)MCg binding coronene both in and out of the cavity (CCDC 1899766).¹⁰⁹ The structures were generated using Mercury.⁸¹

wingtips could not include guest molecules,¹⁰⁶ following work demonstrated that the addition of a methylene spacer between the porphyrin scaffold and the NHC increased the system flexibility, allowing the enlargement of the cavity to encapsulate 1,4-diazabicyclo[2.2.2]octane (DABCO).¹⁰⁷

Besides the cavity size and shape, another critical factor to tune when designing versatile MCg hosts is the cavity's nature. Recently, Au₃(pyrazolate)₃ panels have been used to form cages displaying π -basic cavities.⁹⁴ Prismatic coordination cages with those panels, linked via imide bridging, were shown to enable capturing octafluoronaphthalene, a π -acidic system. On the other hand, the affinity of the Au₃(pyrazolate)₃ panels for the surface of C₆₀, demonstrated by previously reported co-crystallization, suggested that a larger cavity could allow the inclusion of C₆₀ as a guest, which was effectively observed in a tetrahedral cage (Figure 6C).⁹⁴

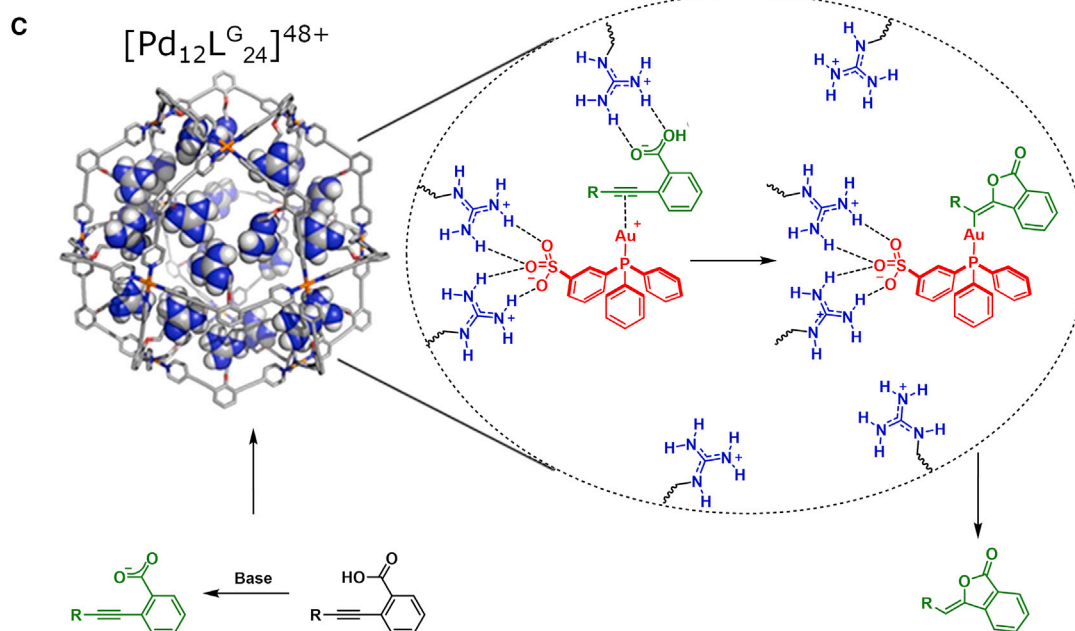
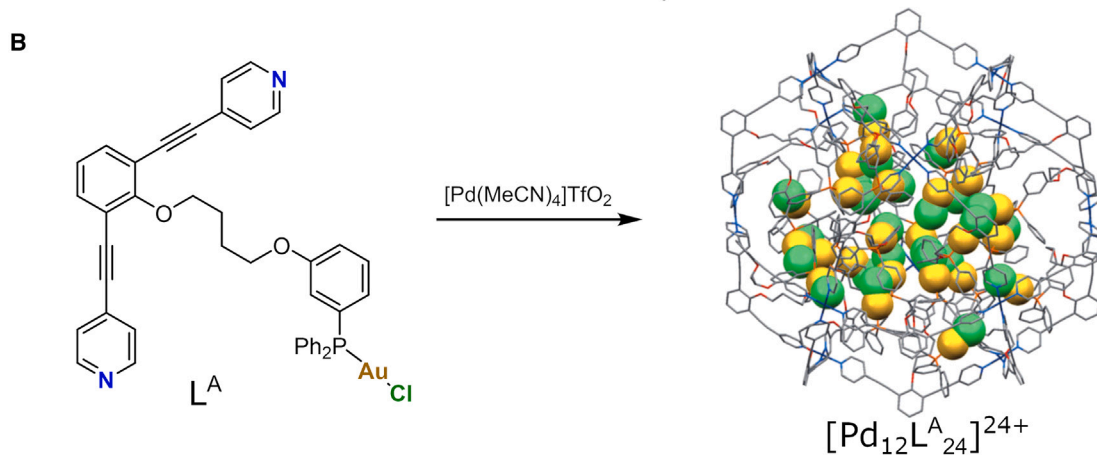
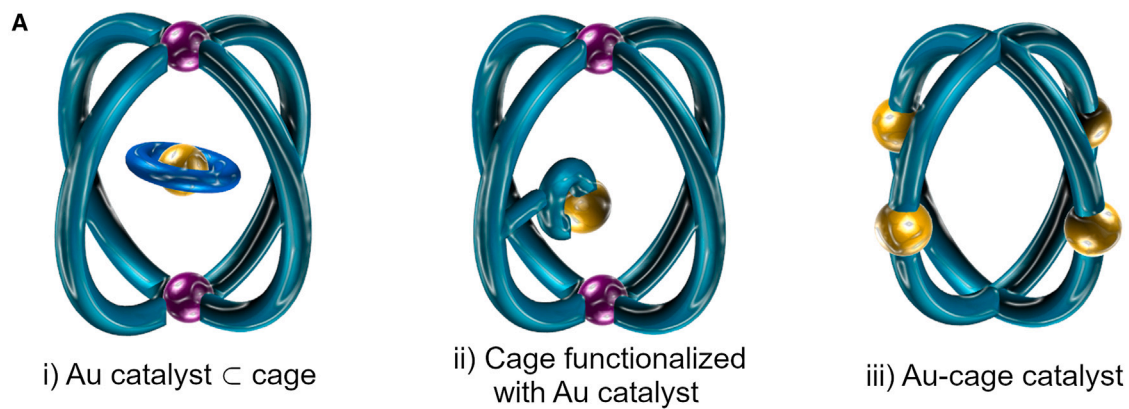
Furthermore, the introduction of readable signals is of great relevance to exploit the potential of **AuMCgs** in sensing, and luminescent readouts are probably the most popular modality in supramolecular sensor design.¹¹⁹ Creating photoactive **AuMCgs** is appealing not only for sensing purposes but also for other applications (i.e., imaging, photocatalysis, etc.). The group of Mukherjee used 1,4-dihydropyrrolo[3,2-b]pyrrole NHC-derivatives as ligands for the formation of **Au(I)MCgs**. The ligand's aggregation-induced emission (AIE) was activated due to linkage-induced restriction of molecular rotation in the assembled cages.¹²⁵ However, as in other systems, the cavity space is reduced; therefore, the use of these systems as host-guest-based sensors is limited. Other AIE-based luminescent **AuMCgs** have been recently proposed for cell imaging (section "medicinal applications").¹²⁶ Besides intrinsic luminescence, functionalization with fluorophores is a straightforward way to

generate luminescent cages. Interestingly, Wang et al. showed the possibility of including AIE-gens by post-assembly modification of NHC-Au(I) cages using copper-catalyzed alkyne-azide cycloaddition (CuAAC).¹²⁷ These results highlight the robustness and versatility of the bis-NHC-Au(I)-based systems for generating platforms with different applications.

Nevertheless, even when the MCgs are not photoactive, the presence of gold can be useful in the design of sensing plat-

forms with stimuli-responsive host-guest behavior, particularly for intrinsically luminescent analytes. As observed by Rodriguez and coworkers, the presence of Au(I) centers in MCgs can promote the activation of triplet emissive states at room temperature in guest molecules, which otherwise would not be observed in solution. This is the case when aromatic fluorophores (methylsalicylate, 8-hydroxyquinoline, and naphthalene) are included in the heterometallic [(triphos)(AuC₆F₄py)₃]₂Ag₃ cage.¹²⁸ The effect was rationalized as a consequence of an external heavy-atom effect, i.e., the triplet state population promoted by spin-orbit coupling facilitated intersystem crossing, acting intermolecularly due to the spatial proximity of the guest with the gold atoms of the cage.

However, as excited-state dynamics are highly variable, different host-guest systems may present different outcomes. The photoactivity of **AuMCgs** can also act in the opposite direction and cause the quenching of the intrinsic fluorescence of guest molecules upon encapsulation. For example, Ibañez and Peris have demonstrated that trigonal-prismatic hexagold organometallic MCgs obtained by face-directed assembly from triphenylene-tris(N-heterocyclic carbene) faces and carbazolyl-bis(alkynyl) clips (Figure 6D) can trap coronene with an association constant of $\beta \approx 4.5$, which was higher than that observed for other aromatic hydrocarbons.¹⁰⁹ This is due to the larger size of coronene, giving an extended π -stacking with the cage panels, which was observed in the single crystal X-ray diffraction structure.¹⁰⁹ In solution, upon encapsulation, the luminescence of coronene is quenched. Although not discussed by the authors, this is probably due to energy transfer processes involving the cage that favor non-radiative relaxation of the excited states,¹²⁹ suggesting the potential of the systems to generate quenching-based sensing platforms. Remarkably,



(legend on next page)

related tetragold metallacycles built from pyrene-bis-imidazolidene NHC ligands and the same clip structures have shown not only to display selectivity for planar polyaromatic hydrocarbons over curved ones,¹³⁰ but also to be able to displace mechanically interlocked guests selectively from the cavity in the presence of coronene.¹³¹ This type of stimuli-responsive behavior is particularly interesting for the creation of selective sensors, and its translation to this context is a promising possibility.

Catalysis

Homogeneous gold catalysis is an ever-growing field, and in this context, Au(I) has become very popular over the last few decades due not only to its strong π -acidity, which allows for the activation of alkynes, allenes, and alkenes,¹³² but also to the more recent discovery of the versatility of gold to generate structures of commercial appeal.^{133,134} Furthermore, Au(I) complexes are mostly air-stable and compatible with physiological conditions, as previously evidenced by examples of their use as bio-orthogonal catalysts in living cells.¹³⁵ However, challenges faced in catalysis involve high catalyst loading, deactivation/poisoning of the catalyst over time, and lack of selectivity. Gold catalysis is known to be highly influenced by the environment and noncovalent interactions,⁴⁹ which has prompted its implementation in supramolecular approaches. The inclusion of the metal catalyst within a supramolecular cage has been proposed as a way to modulate the regio- and chemoselectivity, as well as to improve catalyst stability and activity, resembling the working principle of enzymes.¹³⁶ As gold is a versatile metal catalyst, three main strategies can be envisioned to build MCg-based gold catalysts (Figure 7A): (1) supramolecular encapsulation of a gold catalyst within a MCg, (2) functionalization of a cage structure with gold-based catalysts, and (3) cages including gold as both building block and catalysts. It is important to note that strategy (1) does not constitute a **AuMCg** per se; however, this concept is fundamental to the further application of **AuMCgs** in catalysis and, thus, is featured in this section. Moreover, noncovalent encapsulation of gold catalysts into MCgs is the predominant approach explored so far to improve catalysis via confinement. In addition, no examples of strategy (3) have been reported so far, and this could be partly due to the scarce overall availability of the Au(I) nodes, particularly those engaged in organometallic bonds, to participate in ligand-exchange reactions, which are crucial to the mechanisms of catalysis.

While most of the catalysis involving cages profit only of their confined space, recently, MCgs with catalytic metal nodes have shown activity in metal-mediated catalysis. For example, catalytic Pt₂L₄ systems showed favorable effects related to substrate encapsulation, which can concomitantly help stabilize the cage structure during the catalytic cycle.¹³⁹ Reaching this with **AuMCgs** is still challenging. In the case of more dynamic

AuMCgs based on coordination bonds with phosphines, these may suffer from poor reversibility—i.e., once the cage is disturbed to allow catalytic activity, it cannot be easily regenerated, giving low turnover numbers. Such limitations could be overcome using organogold centers in which the Au–C bonds are tuned to increase the reversibility.¹⁴⁰

As detailed above, MCgs can be tuned to control the shape and size of the cavity and so can allow flexibility to encapsulate a variety of different metal catalysts, including gold (Figure 7A). Furthermore, the MCg design can also allow the size-dependent encapsulation of organic substrates to induce protection of the catalyst from large poisons.^{141–145} Seminal work by Toste, Raymond, and coworkers¹⁴⁶ described the ability of a small tetrahedral [Ga₄L₆]¹² (L = *N,N'*-bis(2,3-dihydroxybenzoyl)-1,5-diaminonaphthalene) cage to encapsulate Au(I) phosphine coordination complexes (Me₃PAuX, where X = halide and Me₃P = trimethylphosphine). When encapsulated, the fully ionized form Me₃PAu⁺ is favored due to the preference of the hydrophobic cavity for cations. The encapsulated Au(I) catalyst ([Au(PMe₃)⁺ ⊂ cage) demonstrated an 8-fold rate increase for the hydroalkoxylation of allenes in water compared with its non-encapsulated precursor, which the authors postulated to be due to the catalyst's decomposition (Table 1, entry 1).¹⁴⁶

This work was further extended to tandem catalysis with a variety of enzymes,¹⁴⁷ performing esterase- and lipase-mediated acetate hydrolysis prior to hydroalkoxylation catalyzed by the [Au(PMe₃)⁺ ⊂ Ga₄L₆ cage complex (Table 1, entry 2). The encapsulation of the Au(I) catalyst is believed to prevent Au(I) from strongly coordinating to the amino acid residues of the enzyme, which the authors proposed to be responsible for the significant decrease in catalytic ability observed for the non-encapsulated complex. The reactions were carried out in tris buffer (pH 8) with 5% organic solvent (DMSO or MeOH) to aid the solubility of the substrate. Moreover, the catalysis could still take place regardless of which catalyzed reaction occurred first.¹⁴⁷ In later work, the selectivity of the [Au(PMe₃)⁺ ⊂ Ga₄L₆ complex was demonstrated during the cyclization of a monoterpene due to water exclusion inside the cage cavity, forming the deprotection product rather than the product of water addition formed with the non-encapsulated Au(I) complex (Table 1, entry 8).¹⁴⁹

Recently, Reek and coworkers¹⁵⁰ explored the ability of the [Au(PMe₃)⁺ ⊂ cage complex reported above to perform catalysis in living cells. In this work, the free [Au(PMe₃)Cl] complex and [Au(PMe₃)⁺ ⊂ Ga₄L₆ cage complex were able to catalyze the intramolecular hydroarylation reaction to produce a fluorescent dye in similar yields. However, in physiologically relevant media, unlike the free catalyst, the [Au(PMe₃)⁺ ⊂ Ga₄L₆ complex retained some catalytic activity, albeit very low yields (Table 1, entry 9), with no catalysis observed for the free complex or cage in the presence of cell culture media. Due to the limited stability in

Figure 7. AuMCgs in catalysis

(A) Strategies for MCg-based gold catalysis: (Ai) noncovalent encapsulation of a gold catalyst within a MCg, (Aii) endo-functionalization of a MCg cavity with Au catalytic center, and (Aiii) a catalytic Au cage. Golden spheres = Au ions magenta spheres = metal nodes.

(B) Synthesis of the Pd₁₂L₂₄^A (L^A = Au-coordinating ligand) presenting the highest local concentration of gold catalyst. Adapted with permission from Gramage-Doria et al.¹³⁷ Copyright 2014 John Wiley and Sons.

(C) Guanidinium endo-functionalized Pt₁₂L₂₄^G cages (L^G = 1-(2-(2,6-bis(4-pyridylethynyl)phenoxy)ethyl)guanidine triflate) which encapsulate sulfonated Au(I) catalysts via hydrogen bonds. Adapted with permission from Gonell and Reek.¹³⁸ Copyright 2019 John Wiley and Sons.

physiologically relevant solutions, the high toxicity of the substrate, and the inability of the $[\text{Au}(\text{PMe}_3)]^+ \subset$ cage complex to cross the cell membrane, further cage and substrate design is required before these systems can be applied *in vivo*.¹⁵⁰

Despite the many advantages of encapsulating gold catalysts within MCgs, there are still some issues to be considered, especially when applying these in aqueous/biological environments. For example, leakage of the catalyst from the cage cavity due to displacement by another substrate. Additionally, the catalyst and substrate must be in the cage at the same time to ensure a good turnover number, and the cage must be optimized to encapsulate the specific catalyst during the catalytic cycle, where it may change size, shape, and charge.⁹

The strategy to functionalize the ligand scaffold of MCgs with gold catalytic centers (Figure 7Aii) involves ligand templating to encapsulate a catalyst by tethering to a ligand, which is then self-assembled into a cage. This design provides a more general approach since the different building blocks can be exchanged to incorporate different catalysts, and the second coordination sphere can be tuned to improve the activity and selectivity of the cages.⁹ Interestingly, the local concentration of the gold catalyst can be modulated by using different ratios of ligands between those that bind gold and those that do not.

The group of Reek has made substantial contributions in this area, applying the ligand-templated strategy on Fujita's polyhedra.¹⁵¹ The first example reported in 2014¹³⁷ describes the edge-directed synthesis of $\text{Pd}_{12}\text{L}_{24}$ polyhedron *endo*-functionalized with phosphine Au(I) and with triflate as counter anions (Figure 7B). The concentration of gold within the sphere can be modulated by mixing the Au-containing metalloligand (L^{A} = chloro(4,4'-((2-(4-(3-(diphenylphosphaneyl)phenoxy)butoxy)-1,3-phenylene)bis(ethyne-2,1-diyl))dipyridine)gold(I)) and the analog with an acetate group instead of the phosphine Au(I) (L^{B} = 2,6-bis(pyridin-4-ylethynyl)phenyl acetate) during the self-assembly process. The ratio of L^{A} and L^{B} was altered to control the local concentration of gold without changing the overall catalyst concentration in solution. The cages were synthesized by reacting the $[\text{Pd}(\text{MeCN})_4](\text{OTf})_2$ precursor with the building blocks L^{A} and L^{B} at 45°C over 12 h. The catalytic ability of the cages was demonstrated for the hydroalkoxylation of an allenol molecule, forming either a 5- or 6-membered ring. The authors found that at the highest local concentration of Au (1.1 M), the 5-membered product could be isolated selectively with the highest yield (Table 1, entry 3). Interestingly, the same reactivity could not be observed with the parent compound, $[\text{Ph}_3\text{PAuCl}]$, even at high concentrations.¹³⁷ Therefore, the authors proposed that the increased activity of the spheres was not only due to the higher Au concentration but was also caused by the $\text{d}^{10}\text{-d}^{10}$ aurophilic interactions formed at higher concentrations. Additionally, in most other cases, the decoordination of the chlorido ligand is required to form the active catalyst; however, in this work, the AuCl species were already active due to their high concentrations within the spheres. Similar high selectivity was observed in the cyclization of a 1,6-enyne, in which again only the 5-membered product was observed (Table 1, entry 10).¹³⁷

In later work, Reek and coworkers replaced Pd(II) with Pt(II) to improve the overall kinetic stability of the MCgs toward sub-

strates with more reactive functional groups and harsher catalytic conditions.¹⁴⁸ In detail, both cages were synthesized using the same neutral Au(I) building block as in previous work (1 equiv) with $[\text{Pd}(\text{MeCN})_4](\text{BF}_4)_2$ or $[\text{Pt}(\text{MeCN})_4](\text{PF}_6)_2$ (0.5 equiv). Interestingly, in this work, a different counter ion was used for the Pd(II) salt (BF_4 anion vs. OTf anion), which resulted in less catalytically active Pd-AuMCgs for the intramolecular hydroalkoxylation of an allenol molecule than the previously reported Pd-AuMCgs with triflate anion (Table 1, entry 4). However, both Pd-AuMCgs outperformed the Pt-AuMCgs for this reaction, with the Au(I) building block alone showing no activity.¹⁴⁸

Furthermore, since it has been well-documented that cationic gold complexes show higher catalytic activity compared with their neutral precursors within these cages, the enhanced stability of the Pt-AuMCg did allow the cationic gold complexes to be introduced post-cage formation with silver salts, which was not possible with the Pd-AuMCgs due to decomposition-caused activity loss. The cationic Pt-AuMCgs showed superior catalytic activity for the [4+2] cycloaddition of 1-(prop-2-yn-1-yloxy)hexane compared with the neutral Pt-AuMCg and Pd-AuMCg, as well as the parent cationic gold building block (Table 1, entry 11).¹⁴⁸ As previously demonstrated with the Pd-AuMCgs, the ratio of Au-functionalized and non-functionalized building blocks (L^{A} and L^{B}) could be easily tuned to increase the local concentration of Au, which, as expected, increased the catalytic activity.¹⁴⁸ Additionally, the reactivity for the cyclization of 1,6-enynes was tested, demonstrating a strong influence of the solvent—in acetonitrile, no conversion was observed, whereas nitromethane yielded full conversion but with lower selectivity (Table 1, entry 12) than previously observed with the Pd analog. Finally, the cage system showed a marked difference in the product distribution, i.e., 5-membered or 6-membered lactones, when evaluating the lactonization of alkynoic acids compared with the free catalyst (Table 1, entry 5).¹⁴⁸

More recently, guanidinium moieties were introduced into the ligands to generate a high local concentration of hydrogen bond donor groups within a similar Pt(II) cage ($[\text{Pt}_{12}\text{L}_{24}^{\text{G}}](\text{TfO})_{48}$, L^{G} = 1-(2-(2,6-bis(4-pyridylethynyl)phenoxy)ethyl)guanidine triflate), which can strongly bind sulfonate-containing guests. Therefore, in this work, $[\text{AuCl}(\text{TPPMS})]$ (TPPMS = triphenylphosphinomonosulfonate) was chosen as the catalytic Au complex and encapsulated into the $\text{Pt}_{12}\text{L}_{24}^{\text{G}}$ MCg via strong hydrogen bonding (Figure 7C).¹³⁸ The guanidinium moieties are also able to bind carboxylate-containing substrates, albeit more weakly, and so can be used to pre-organize the substrate in the Pt-AuMCg. The necessity of the guanidinium to pre-organize the substrates was reflected in the cyclization of 4-hexynoic acid, with 100% conversion of the substrate observed with the lowest local concentration of Au, meaning there are more available guanidinium sites to coordinate the substrate. Additionally, the reaction could not proceed with the cationic Au complex alone and showed low conversion without the presence of the cage. However, in all cases, the 5-membered product was favored (Table 1, entry 6), which contrasts with the result obtained for the same reaction when the gold catalyst was covalently tethered to the MCg. It should also be mentioned that the active cationic Au(I) species was generated *in situ* by the addition of a silver salt, and a base

was required to deprotonate 4-hexynoic acid so it could bind to the guanidinium groups.¹³⁸

Furthermore, the reaction scope was extended to include the cyclization of 2-alkynyl benzoic acid, which can form isocoumarin (6-endo-dig product) or phthalide (5-exo-dig product). Interestingly, the reaction with the cationic $[\text{Au}(\text{TPPMS})]^+$ was very fast, yielding full conversion over 1 h with the isocoumarin formation favored. However, upon the addition of the cage and base, the reaction rate decreased, and the selectivity toward the phthalide was increased (Table 1, entry 7).¹³⁸ Increasing the local concentration of gold decreased the reaction conversion, as observed for the cyclization of 4-hexynoic acid, due to fewer available guanidinium groups; however, the selectivity was also affected, with selectivity toward the isocoumarin favored at higher gold concentration.¹³⁸

Medicinal applications

After the discovery and extended application of cisplatin as an anticancer agent, the development of drugs based on different metals grew rapidly.^{152–154} In this context, gold compounds have been widely investigated as new-generation anticancer drugs,^{52,155–161} acting by targeting different cancer-relevant proteins, including the redox homeostasis-related enzymes thio-redoxin reductase¹⁶² and glutathione reductase,^{163,164} the DNA-repair machinery,^{165–167} and relevant membrane water/glycerol/hydrogen peroxide channels.^{168,169} Furthermore, some organometallic Au(I) compounds based on NHC ligands have recently attracted attention as non-covalent stabilizers for guanine-quadruplexes (G4s), which are non-canonical secondary DNA structures found in oncogenes' promoter and telomeric regions.^{170,171} Based on their unique mechanisms of action, different from classical Pt(II) therapeutics, gold-based drugs are potentially suitable to treat aggressive Pt-resistant cancers.¹⁷² The recent rise in interest in the medical applications of supramolecular chemistry^{29,69} has opened new horizons, and including relevant metal centers, such as gold, in supramolecular architectures is one of the obvious avenues toward the design of bioactive SCCs.^{12,27,69}

Although only a handful of **AuMCgs** have been explored for medical applications, these first examples showcase superior properties with respect to non-regious systems, evidencing the vast potential of **AuMCgs** in this area. The first application of **AuMCgs** in imaging was reported by Han and collaborators,¹²⁶ who based their design on 1,2,3-triazolium-decorated tetraphenylethene (TPE) panels that display AIE. The cage is formed by linking the panels via Au(I) MIC coordination—similar to the NHC-based systems discussed in section “[design principles and structural studies](#)”—yielding the fluorescent MIC organometallic cage $[\text{Au}_4\text{L}_2](\text{OTf})_4$ (Figure 8A, L = 1,2,3-triazolium-decorated TPE). The organometallic assembly features strong green fluorescence from 510 to 520 nm in dilute solutions (Φ_F = 22%–32%) due to restricted rotation-activated emission of the TPE moieties caused by the formation of Au(I)–C_{MIC} bonds. Moreover, these organometallic frameworks demonstrated a remarkable ability to tune their fluorescence wavelength and intensity in response to solvent composition and temperature changes in solution. In the solid state, these structures displayed an interesting phenomenon of pressure-responsive emission

characterized by red-shifting progressive emission intensity decrease upon increased external pressure from 508 nm (ambient conditions) to 590 nm (10.59 GPa).¹²⁶ The organometallic cage $[\text{Au}_4\text{L}_2](\text{OTf})_4$ has also been used in cell imaging due to its bright blue fluorescence (Figure 8B), allowing its visualization via confocal laser scanning microscopy in the cell lines A549 (non-small cell lung cancer), HeLa (cervical cancer), and SMMC-7721 (hepatocellular cancer). In addition, the organometallic cage exhibited anticancer properties, with half maximal effective concentration (EC_{50}) values in the low μM range, demonstrating comparable, if not superior, potency to cisplatin.¹²⁶ Overall, this is a representative example of a supramolecular gold-based platform with well-characterized fluorescent properties for cell imaging. Further studies in this direction must address the critical practical challenges, such as light generation in the red regime, to increase the targeted localization *in vivo*.

Besides the imaging potential of SCCs, their design can be directed to endow them with other interesting properties, including as photosensitizers (PSs) for photodynamic therapy (PDT).²⁷ PDT is a non-invasive therapeutic method that generates reactive oxygen species (ROS) at the cancer site. In general, photoexcitation leads to the excitation of a PS that, via energy transfer to oxygen, generates ROS.¹⁷⁵ The *in situ*-generated ROS causes oxidative stress that can lead to apoptosis in cancer cells.

Recently, our group developed an Au(III) porphyrin-based MCg constructed from the face-directed assembly of two tetra-meso-(4-pyridyl)porphyrin-Au(III) panels linked by four Ru-Clips ($[\text{Ru}_2(\text{p-cymene})_2(\mu^2-1,4\text{-dioxobenzoquinone})]$) used as cage pillars (Figure 8C).⁶⁸ This system was first applied as a PS for the photodynamic treatment of A375 cells (human malignant melanoma) and human gastric parietal cancer cells (HGT-1) *in vitro*, observing increased selective phototoxicity when compared with the parent Au(III) porphyrin complex (Figure 8D). Our studies demonstrated that this effect is due to an increased cellular uptake of the cage compared with the parent Au(III) porphyrin, highlighting the relevance of the 3D assembly to modulate the biological properties. Furthermore, the interaction of the gold porphyrin cage with G4s was studied, revealing intriguing stabilization properties that were not observed in the corresponding apo- or Zn(II) cages.⁶⁸ The stabilization of G4s has been recognized as a potential strategy for regulating transcription and inhibiting telomerase activity, both of which are processes of significant interest in cancer therapeutics.^{176–178} G4s are known to interact preferentially with planar, aromatic, and positively charged molecules.¹⁷¹ Consequently, SCCs that present extended planar ligands have a high propensity to act as G4 binders.¹⁷⁹ The **AuMCg** showed a remarkable stabilization and selective interaction (vs. duplex DNA) with the promoter G4 sequence C-KIT1. Furthermore, a combination of atomistic simulations (metadynamics) and experimental evidence suggested that the selectivity was due to the ability of the **AuMCg** to accommodate an adenosine flanking the G4 structure within its cavity (Figure 8E).⁶⁸ Overall, this study demonstrates not only the potential of **AuMCgs** as multifunctional biomedical entities but also highlights their efficacy, as selective target binders by auxiliary host-guest interactions, a feature previously overlooked in supramolecular systems. Noteworthy, most of the

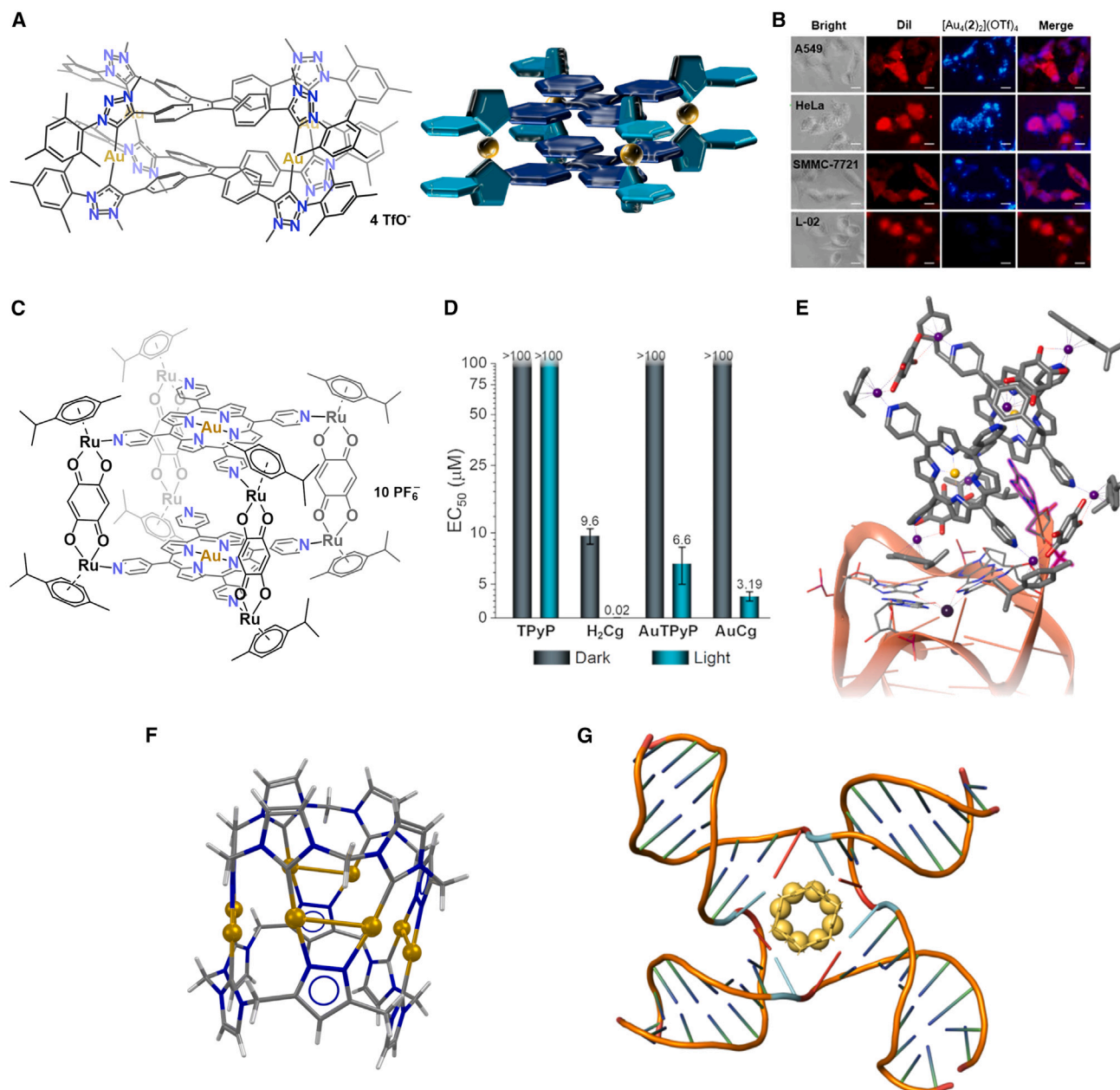


Figure 8. Medicinal applications of AuMCgs

(A) Chemical structure and schematic representation of the **Au(I)MCg** $[\text{Au}_4\text{L}_2](\text{OTf})_4$ ($\text{L} = 1,2,3\text{-triazolium-decorated tetraphenylethene}$) displaying AIE.¹²⁶
(B) Confocal laser scanning microscopy images of different cancer cell lines incubated with $[\text{Au}_4\text{L}_2](\text{OTf})_4$ for 4 h; scale bar, 20 μm . (A) and (B) have been published in CCS Chemistry 2022.¹²⁶
(C) Chemical structure of the Au(III) porphyrin cage.
(D) Increase in the photoinduced toxicity of the gold porphyrin MCg compared with the corresponding free porphyrin.
(E) Interaction of the gold porphyrin MCg with CKIT-1 G4 structure as calculated by metadynamics showing the encapsulation of an adenosine residue (highlighted in purple) that increases its selectivity. (C)–(E) have been published in CCS Chemistry 2024.⁶⁸
(F) SCXRD structure of a Au(I) pillarplex (CCDC 1498661).¹⁷³ Color code is as follows: H, white; C, gray; N, blue; Au, gold. The structure was generated using Mercury.⁸¹
(G) Interaction of the Au(I) pillarplex with a 4WHJ DNA as calculated by molecular dynamics. Adapted with permission from Craig et al.¹⁷⁴ published by the American Chemical Society.

aforementioned favorable properties are due to the presence of gold ions in the MCg scaffold, as shown by comparative experiments with non-aurated analogs. Interestingly, while other metalla-assemblies have shown affinity for G4s, due to their high positive charge, the selectivity of the interactions is often a challenge.^{180–183} Instead, our work showed that the unique electronic effects of gold can improve selectivity.⁶⁸

Despite the few examples of gold cages in medicine, other closely related SOCg have also shown exciting properties, which should fuel further developments in the field. An interesting example is the recent report of gold pillarplexes¹⁷⁴—tubular-shaped SOCg composed of two organic heterocyclic ligands linked by linear two-coordinated Au(I) centers via coordination and organometallic (NHC) bonds forming a pore-like structure¹⁷³ (Figure 8F)—which can interact with DNA 4-way Holliday junctions (4WHJ) and duplex Y-forks. 4WHJ are pivotal to essential biological processes involving DNA, such as insertion, recombination, and repair.¹⁸⁴ These nucleic acid structures exhibit dynamic behavior, transitioning between open and closed conformations, with the former being the biologically active form.¹⁸⁵ Of note, the Au(I) pillarplex is water-soluble thanks to the presence of chloride counter ions, which are exchanged in a biological environment where the solubility of the compound may be challenged. Nevertheless, the interaction between a Au(I) pillarplex and the 4WHJ was studied by gel electrophoresis, evidencing the formation of a nucleic acid species (likely bound to Au) that migrates more slowly than the unbound 4WHJ.¹⁷⁴ Insights from molecular dynamics simulations suggest that the Au(I) pillarplexes selectively interact with the open conformation of the 4WHJ, where the four DNA arms are distinct and not stacked together (Figure 8G). In the absence of the pillarplex, the cavity of the 4WHJ promptly reverts to a closed state. Additionally, the pillarplex was also capable of binding to 3-way junctions. However, due to their substantial size, they induce an opening and expansion of these junctions, thereby disrupting base pairing. This disruption is evidenced by increased hydrodynamic size and decreased thermal stability of the junctions. At higher concentrations, pillarplexes facilitate the reorganization of both 4-way and 3-way junctions into Y-shaped DNA forks, thereby enhancing the availability of junction-like binding sites.¹⁷⁴ The cellular uptake of the gold pillarplex was investigated in A549 cells, and ca. 10% of the amount of gold absorbed was localized in the cell nucleus after 24 h. Overall, the Au(I) pillarplex was only moderately cytotoxic after 72 h incubation.¹⁷⁴ This study presents an intriguing avenue for future in-depth studies to elucidate the cellular impacts of this family of compounds and also reveals the potential held by gold-based SCCs to engage with non-conventional targets of medical relevance. Nevertheless, solubility issues and stability concerns of the Au(I) NHC bonds forming the pillarplexes should be carefully addressed to enhance their anticancer activity and avoid their disassembly prior to reaching the pharmacological targets.

Another family of CDSA systems used for biomedical applications are the Au(I)-based macrocyclic chelators used by the groups of Maia and Spreckelmeyer to chelate M^{3+} metal ions, in particular ^{68}Ga and ^{177}Lu , which can be used in nuclear imaging and therapy, respectively.¹⁸⁶ The metallochelators $[\text{M} \subset \{\text{Au}_3(\text{L}^R)_3\}]$ —where $\text{L}^R = 2,6\text{-dipicolinoylbis}(\text{N,N-diethylthiourea})$ or $2,6\text{-dipicolinoylbis}(\text{N,N-dimorpholythiourea})$ and $\text{M} = \text{Y}^{3+}$,

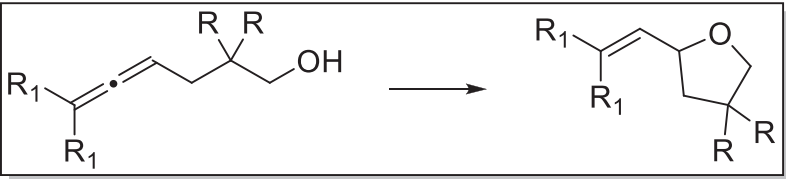
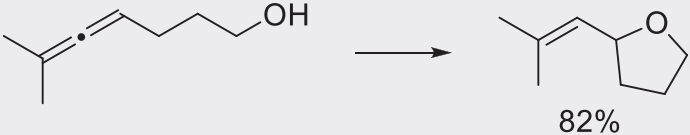
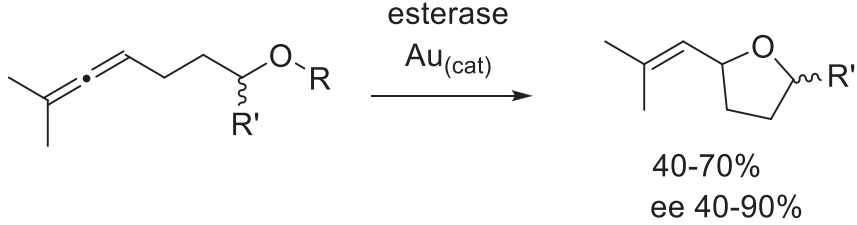
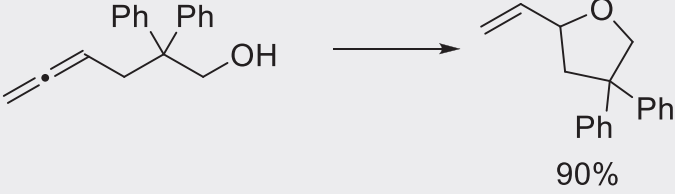
Lu^{3+} , Tb^{3+} , and La^{3+} —feature a molecular structure in which three ligand molecules are arranged in a helical fashion forming a coordination polyhedron around the lanthanide(III) ions, which can be defined as a distorted tricapped trigonal prism. These compounds cannot be categorized as MCg as their structures do not delimit a cavity in the 3D space. Nevertheless, and despite the compounds instability in physiological conditions,¹⁸⁶ the authors suggested the integration of radioactive ^{198}Au as a therapeutic β^- emitter ($t_{1/2} = 2.7$ days, $E_{\beta-\text{max}} = 0.96$ MeV $E_\gamma = 412$ keV) within the coordination compound to generate bimetallic theranostic platforms, i.e., structures carrying two radionuclides for therapy and diagnosis within the same construct.²⁹ Inspired by this work, further exploration of true $^{198}\text{AuMCg}$ s may be relevant for the generation of theranostic supramolecules, which is an emerging topic in radiopharmaceutical design.²⁹

OUTLOOK

The boom of gold chemistry at the end of the last century was fueled by the interesting supramolecular chemistry of this element's compounds—centered on the aurophilic interactions—as well as by the rise of gold catalysis and the exploration of gold chemotherapeutics. Some gold compounds inadvertently sketched the principles of what later would be known as MCg.

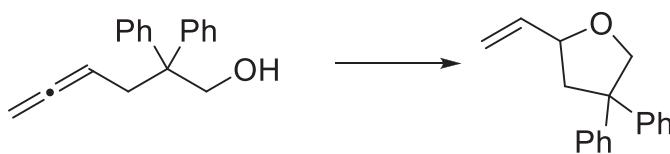
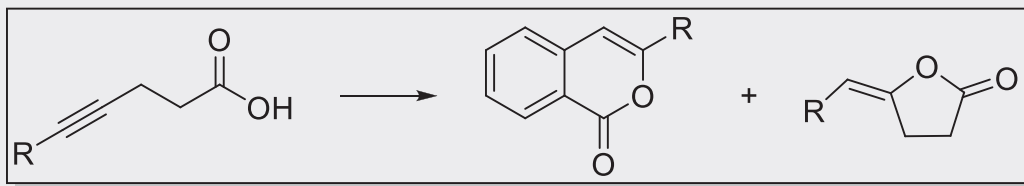
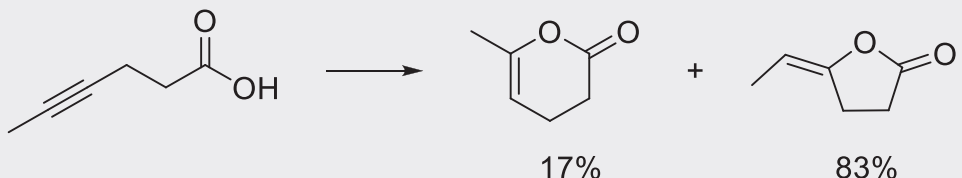
The deliberate design of SCCs has brought new senses to traditional coordination and organometallic gold chemistry. Exploring the structural possibilities of generating **AuMCg**s has dominated the research in the area. More recently, cumulative structural knowledge has driven interest in exploiting the 3D structures of **AuMCg**s for different applications. The inclusion of gold ions in MCg has convened a new dimension to the already fascinating supramolecular, catalytic, and medicinal properties of this precious metal. To date, the vast majority of the available **AuMCg**s are based on Au(I), mainly featuring monodentate ligands. Unfortunately, this design is unable to sufficiently stabilize Au(III) from reduction, while it favors Au(I) metallacycle formation.¹⁸⁷ Thus, although Au(III) prefers a square planar coordination geometry, the known Fujita-type 3D-assemblies (based on Pd(II) and Pt(II) square planar centers) cannot be generated using this metal ion. The only available example of a Au(III) cage uses porphyrin ligands,⁶⁸ suggesting chelation as a strategy to build Au(III)-based panels. Other strategies available to stabilize Au(III) are yet to be explored, such as the use of cyclometalating ligands as building blocks in **AuMCg**s. With respect to catalytic applications, more efforts could be invested in the development of Au(III)-based cages, considering that Au(III) complexes have shown promising catalytic activity toward different transformations (e.g., cross-coupling reactions) when sufficiently stabilized by multidentate ligands and organometallic bonds.^{135,188,189} In general, hybrid designs allowing a compromise between stability and dynamism should be pursued to achieve the use of the gold cages themselves as catalysts. Not only organometallic catalysis but also photo- and electrocatalysis options have yet to be exploited, profiting from the broad photo- and electrochemistry of gold compounds.^{190,191} In fact, gold-based photocatalysis has recently shown important progress, and thus, the use of **AuMCg**s for photo-driven electron transfer processes holds important promise.¹⁹⁰

Table 1. Gold catalysis in MCgs

Entry	Catalyzed reactions	Catalyst	Ref.
Hydroalkoxylation of allenols			
			
1	 82%	$[\text{Au}(\text{PMe}_3)]^+$ $\subset \text{Ga}_4\text{L}_6$ cage	Wang et al. ¹⁴⁶
2	 40-70% ee 40-90%	$[\text{Au}(\text{PMe}_3)]^+$ $\subset \text{Ga}_4\text{L}_6$ cage	Wang et al. ¹⁴⁷
3	 90%	$[\text{Pd}_{12}$ $\text{L}_{24}^{\text{A}}](\text{TrfO})_{24}$	Gramage- Doria et al. ¹³⁷

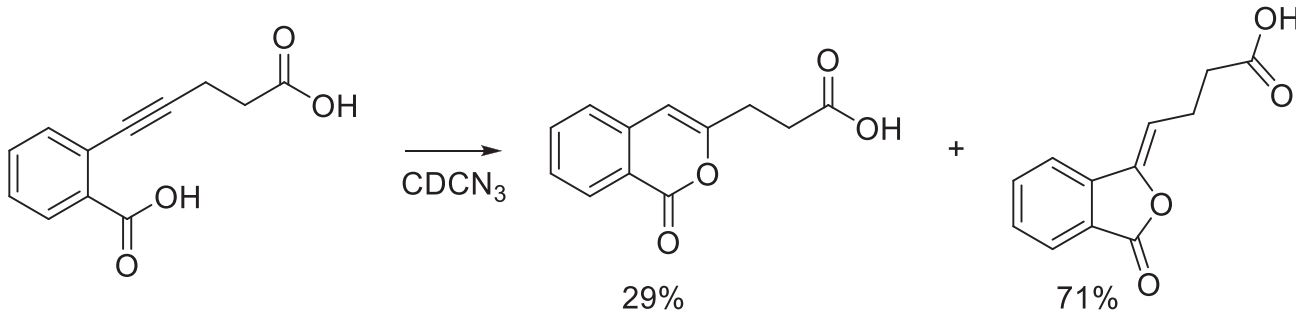
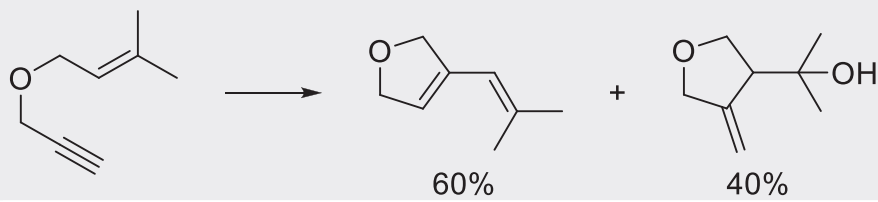
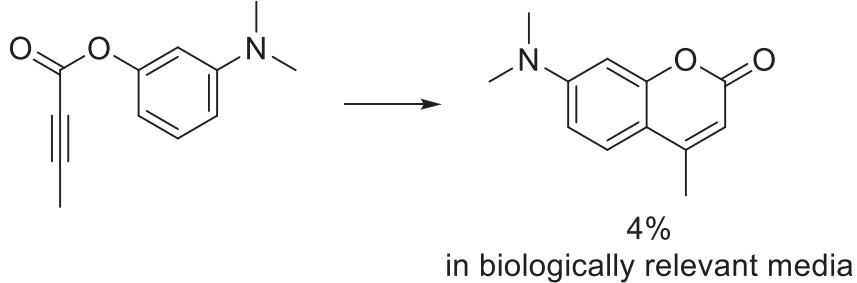
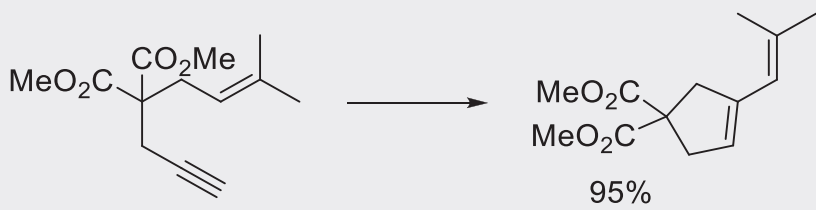
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Table 1. Continued

Entry	Catalyzed reactions	Catalyst	Ref.
4	 83% (M = Pd, X = BF₄) 68% (M = Pt, X = PF₆)	[M ₁₂ L ^A ₂₄](X) ₂₄	Leenders et al. ¹⁴⁸
Cyclization of alkanoic acids			
5	 67% 33%	[Pt ₁₂ L ^A ₂₄] (PF ₆) ₂₄	Leenders et al. ¹⁴⁸
6	 17% 83%	[Au(TPPMS)] ⁺ ⊂ [Pt ₁₂ L ^G ₂₄] (TfO) ₄₈ + Et ₃ N	Gonell and Reek ¹³⁸

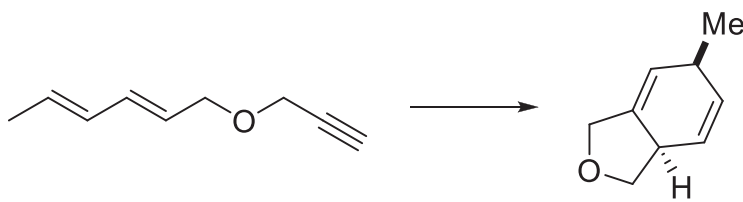
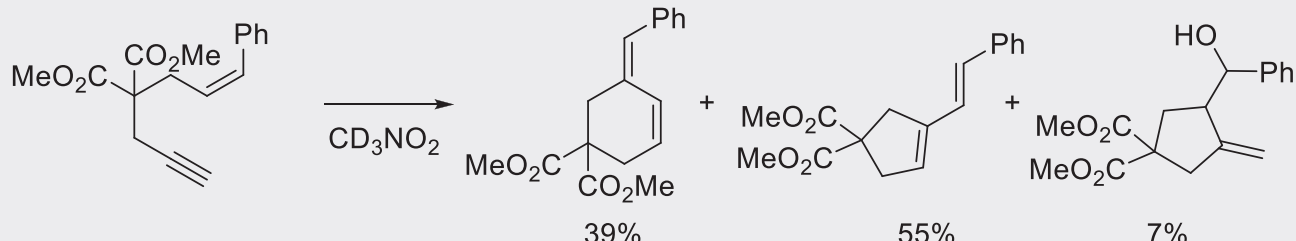
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Table 1. Continued

Entry	Catalyzed reactions	Catalyst	Ref.
7		$[\text{Au}(\text{TPPMS})]^+$ $\subset [\text{Pt}_{12}\text{L}_{24}]$ $(\text{TfO})_{48} + \text{Et}_3\text{N}$	Gonell and Reek ¹³⁸
Other cyclization reactions			
8		$[\text{Au}(\text{PMe}_3)]^+$ $\subset \text{Ga}_4\text{L}_6$ cage	Hart-Cooper et al. ¹⁴⁹
9		$[\text{Au}(\text{PMe}_3)]^+$ $\subset \text{Ga}_4\text{L}_6$ cage	James et al. ¹⁵⁰
10		$[\text{Pd}_{12}\text{L}_{24}]$ $(\text{TfO})_{24}$	Gramage-Doria et al. ¹³⁷

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Table 1. Continued

Entry	Catalyzed reactions	Catalyst	Ref.
11	 3% (M = Pd, X = BF ₄) 17% (M = Pd, X = BF ₄) + AgPF ₆ 15% (M = Pt, X = PF ₆) 97% (M = Pt, X = PF ₆) + AgPF ₆	[M ₁₂ L ^A ₂₄](X) ₂₄	Leenders et al. ¹⁴⁸
12	 39% 55% 7%	[Pt ₁₂ L ^A ₂₄] (PF ₆) ₂₄	Leenders et al. ¹⁴⁸

L^A = chloro(4,4'-((2-(4-(3-(diphenylphosphaneyl)phenoxy)butoxy)-1,3-phenylene)bis(ethyne-2,1-diyl))dipyridine)gold(I).

L^G = 1-(2-(2,6-bis(4-pyridylethynyl)phenoxy)ethyl)guanidine.

L = *N,N'*-bis(2,3-dihydroxybenzoyl)-1,5-diaminonaphthalene.

The achievement of systems with both accessible cavities and proven stability is still challenging for the successful production of **AuMCgs** as carriers that can be used later in sensing and separation operations, and profiting from the heavy-atom effect and other interesting photophysical properties of gold is yet to be used in the construction of intrinsically luminescent **AuMCgs**.

For biomedical applications, some common challenges of SCCs, i.e., lack of targeting capabilities and poor solubility, can be overcome relatively easily with some of the **AuMCg** designs already available. For instance, the functionalization of wingtips in NHC-based systems is a straightforward alternative to adding hydrophilic character,^{192,193} and eventually active targeting.¹⁹⁴ The study of interactions of gold-based MCgs with clinically relevant targets is still in its infancy and should also be extended. Moreover, the virtual applications of this kind of system are not limited to those listed herein, and much more is yet to come. For example, metal particles templated under confinement,¹⁹⁵ profiting from the pre-organization of gold centers in the MCg structure, can be a way to create atomically precise metallic nanoparticles with a double purpose of the cage as a template and gold source. The use of gold-based structures for the construction of functional systems such as molecular machines is also to be progressed.¹⁹⁶ Overall, the current research in **AuMCgs** has generated promising and startling results that should incentivize the design and creation of new functional structures that will progressively incorporate the different facets of the fascinating chemistry of gold.

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AUTHOR CONTRIBUTIONS

Investigation, S.R.T., N.W., and G.M.-A.; visualization, G.M.-A.; writing – original draft, S.R.T., N.W., and G.M.-A.; and writing – review and editing, S.R.T., A.C., and G.M.-A.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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