E-ISSN: 2664-6773
P-ISSN: 2664-6765
Impact Factor: RJIF 5.6
IJCBS 2025, 7(2): 109-118
www.chemicaljournal.org
Received: 19-06-2025
Accepted: 22-07-2025

Najlaa N Hussein
College of Dentistry, Babylon University, Babylon, Iraq

Corresponding Author:
Najlaa N Hussein
College of Dentistry, Babylon University, Babylon, Iraq

Supramolecular coordination assemblies as programmable nanoreactors for enantioselective C-H activation: Merging inorganic versatility with biological precision

Najlaa N Hussein

DOI: https://DOI.org/10.33545/26646765.2025.v7.i2b.160

Abstract
The selective activation of latent carbon-hydrogen (C--H) bonds remains one of the most challenging objectives in the synthetic chemist's arsenal, requiring catalysts with catalyst with both high reactivity and precision regio-, chemo-, and stereo control. Homogeneous transition-metal catalysts, in spite of their broad substrate classes and tunable reactivity, stoichiometric number deficits fail to provide the degree of molecular recognition typical of enzymes, leading to over- and under- functionalization and low selectivity. Natural metalloenzymes, on the other hand, offer unmatched precision through cleverly designed protein scaffolds, whilst also suffering from limited substrate tolerance, sensitivity to non-physiological conditions, and difficulty in rational design. Some bottom-up assembled metals and ligands, or supramolecular coordination assemblies (SCAs), are a new and promising, discrete chemical platform that can be both designed and formed through directed metal-ligand interactions (e.g. through metal coordination). SCAs are a new strategy for using biomimetic design principles to construct artificial metalloenzymes (ArMs) that coherently combine the practicality of transition metals with nature's ability to control special and microenvironment within their well-done proteins. This comprehensive review will cover, critically, the structural diversity, design and engineering principles, mechanistic aspects, and functional distributions of SCAs as ArMs in selective C--H activation of aliphatic, benzylic, allylic, and even inactivated substrates. We classify these systems by architectural motif (Metall cages, helices, M_4L_6 cubes, polyhedral, and hybrid protein-SCA hybrids), analyze the role of non-covalent interactions (hydrophobic effects, hydrogen bonding, π-stacking, electrostatic steering) in substrate preorganization and transition state stabilization, and present quantitative comparisons of turnover numbers (TON), enantiomeric excesses (ee), and chemise Hectivities with conventional catalysts and native enzymes. We further acutely analyze recent advances in dynamic combinatorial chemistry, adaptive self-correction, and computational design tools enabling predictive optimization. Critical challenges catalyst deactivation, scalability, aqueous compatibility, and product inhibition are discussed alongside emerging solutions using ligand engineering, encapsulation strategies, and biohybrid integration. Finally, we propose a roadmap for industrial translation, emphasizing sustainable applications in pharmaceutical synthesis, Late-stage functionalization, and green chemistry. The convergence of supramolecular chemistry, bioinorganic engineering, and systems chemistry heralds a new paradigm: programmable nanoreactors mimicking nature's efficiencies while expanding its chemical repertoire beyond biological constraints.

Keywords: Supramolecular coordination assemblies, artificial metalloenzymes, C-H activation, biomimetic catalysis, metal-organic cages, molecular recognition, enzyme mimics, transition-metal catalysis, non-covalent interactions, green chemistry

1. Introduction
Carbon-hydrogen (C-H) bond functionalization is often described as the *holy grail* of organic synthesis because it enables the direct and atom-economical construction of complex molecules without the need for pre-functionalized substrates (Yu *et al*., 2015) [1]. Despite significant advances over recent decades, achieving high selectivity in C-H activation particularly at inactivated sp^3 centres remains a formidable challenge. The main reasons are the high bond dissociation energy of the C-H bond (approximately 400 kJ/mol for CH_3-H), its low polarity, and the uniform distribution of C-H bonds within a molecule (Sanford *et al*., 2006) [2]. Traditional catalytic approaches generally rely on directing groups, steric hindrance, or electronic bias to achieve selectivity, which can restrict substrate scope and generate additional chemical waste (Dong *et al*., 2018) [3]. Nature, by contrast, accomplishes highly selective C-H hydroxylation under mild conditions through metalloenzymes such as cytochrome P450s,

methane monooxygenase (MMO), and non-heme iron oxygenase's (Groves, 1993; Que & Tolman, 2002) [4, 5]. These enzymes operate with remarkable precision due to several interrelated strategies: (a) positioning the metal cofactor within a carefully shaped protein pocket, (b) regulating substrate access through gated channels, (c) stabilizing reactive intermediates via hydrogen-bond networks, and (d) excluding competing nucleophiles through hydrophobic sequestration.

Inspired by these biological systems, artificial metalloenzymes (ArMs) have been developed to embed synthetic metal complexes within biomolecular scaffolds such as streptavidin, myoglobin, or engineered antibodies (Ward, 2017) [6]. Although promising, many of these systems are hampered by structural unpredictability, thermal instability, and the inherent difficulty of rationally redesigning complex protein folds (Baker & Reek, 2021) [7].

Supramolecular coordination assemblies (SCAs) provide a compelling alternative. These self-assembled structures, created through directional metal-ligand coordination, offer atomically defined architectures that are highly modular, synthetically accessible, and stable under diverse chemical conditions (Fujita, 2012; Nitschke, 2021) [8, 9]. Crucially, their internal cavities can be engineered to mimic enzyme active sites not merely as passive containers but as dynamic catalytic spaces that orient substrates, stabilize high-energy intermediates, and suppress undesired reaction pathways (Fujita *et al*., 2013) [9].

Since the pioneering demonstration of Pd-based metallicizes for guest-selective reactions (Fujita *et al*., 2013) [9], the field has expanded rapidly. SCAs now enable transformations previously regarded as unattainable with small-molecule catalysts. The present review provides a systematic and mechanistic analysis of SCAs as Arms for C-H activation, integrating structural insights, kinetic data, and design principles into a coherent framework. By highlighting how supramolecular confinement can surpass classical organometallic paradigms and deliver enzyme-like precision without biological constraints, this work outlines pathways toward scalable and sustainable catalytic systems for next-generation chemical synthesis.

2. Architectural Taxonomy of Supramolecular Coordination Assemblies for C-H Activation

Supramolecular coordination assemblies (SCAs) are not merely static cages or helicases. They represent dynamic, programmable platforms where architectural design directly determines catalytic behavior. While early studies categorized SCAs primarily by structural morphology such as cages, helicases, and polyhedral recent progress highlights the need for a functional classification that integrates catalytic mechanism, substrate recognition, and environmental compatibility (Fujita, 2012; Nitschke, 2021) [8, 9]. Here, we propose a five-category taxonomy that unifies structural topology with catalytic functionality to guide predictive engineering of new systems.

2.1 Size-Selective Metall cages: Steric Gating as a Key Selectivity Driver

Metall cages with well-defined internal cavities (e.g., $[Pd_2L_4]^+$, $[Pt_4L_6]$, $[Fe_4L_6]$) exploit molecular sieving to control selectivity. Their cavities can exclude bulky substrates or restrict transition states from adopting energetically unfavorable geometries (Nishida & Fujita, 2018). For example, Fujita's pioneering $[Pd_2L_4]^+$ cage enabled terminal C-H arylation of linear alkanes with >90 % regioselectivity, a level of discrimination unattainable with traditional Pd catalysts (Lee *et al*., 2016) [11]. Analogous systems employing Pt(II), Ru(II), or Co(III) have extended this principle to borylation and oxidation reactions while maintaining comparable selectivity (Zhang *et al*., 2020) [12]. Newer cages use flexible ligands that allow reversible expansion upon substrate entry, making it possible to accommodate slightly larger molecules without sacrificing selectivity.

Functional signature: Catalysis dominated by size exclusion well suited for linear alkanes, small aromatics, and rigid metabolites.

2.2 Chiral Helicates and Foldamers: Enantioselection via Conformational Locking

Helicates generate chirality not from a single stereocentre but from the global helical twist of multiple metal-ligand strands, creating a persistent chiral groove. Zhang and co-workers reported a Mn(III)-salen double-Helicate that achieved 96 % enantiomeric excess (ee) in intramolecular C-H amination of sulfonamides, far exceeding the performance of free Mn-salen catalysts (<10 % ee) (Zhang *et al*., 2020) [12]. The helical architecture enforces a Bürgi-Dunitz angle of attack on nitrene intermediates, ensuring stereochemical fidelity. Remarkably, even racemic ligand mixtures can self-sort into homochiral assemblies under thermodynamic control, a phenomenon that provides molecular-level error correction (Zhang *et al*., 2021) [22].

Functional signature: Conformational-locking-driven enantioselection ideal for synthesizing chiral amines, alcohols, and cyclobutanes.

2.3 Polyhedral and Cubic Frameworks: Cooperative Multimetallic Catalysis

Polyhedral SCAs such as M_4L_6, M_8L_{12}, or $M_{12}L_{24}$ clusters align multiple metal centres in precise spatial arrangements, facilitating cooperative activation reminiscent of enzymatic active sites like methane monooxygenase. Ward's $[Pt_4L_6]$ tetrahedron, for example, promotes ortho-C-H borylation of phenylpyridines with >95 % selectivity not due to electronic bias but because its rigid triangular cavity sterically blocks the meta and para positions (Ward *et al*., 2019) [9]. Similarly, Stang's Au(I)-based dodecahedron ($[Au_{12}L_{24}]$) enables cooperative σ-bond metathesis for C-H silylation of alkyl arenes with 88 % yield, outperforming mononuclear Au catalysts (Stang *et al*., 2021) [15].

Functional signature: Multimetallic synergy advantageous for oxidation, borylation, and silylation processes requiring dual activation and high steric discrimination.

2.4 Hybrid Protein-SCA Systems: Bridging Abiotic Catalysis and Biological Compatibility

Hybrid systems integrate synthetic SCAs with protein domains, combining the robustness of inorganic cages with the aqueous stability and biocompatibility of proteins. Chen *et al*. (2021) [16] constructed a Zn_4L_4 cage covalently fused to a thermostable lipase, achieving enantioselective C-H alkylation in pure water with a 97 % diastereomeric ratio an unprecedented result for purely synthetic catalysts. The protein domain functions as a chaperone, directing bulky, drug-like substrates toward the catalytic cavity through noncovalent interactions. Genetic fusion techniques such as SpyTag/SpyCatcher further enhance site-specific conjugation and minimize heterogeneity.

Functional signature: Water-compatible enantioselective catalysis ideal for late-stage functionalization of peptides, antibiotics, and polar pharmaceutical compounds.

To systematically compare these architectural strategies, we categorize representative systems according to their structural features, catalytic function, and performance metrics in Table 1.

Table 1: Structural Classification of Supramolecular Coordination Assemblies (SCAs) Employed in C-H Activation Reactions

SCA Type	Representative FormuLa	MetaL Centre	Cage Size* (Å × Å)	Representative C-H Activation	Key Selectivity / YieLd
Metallacage	$[Pd_2L_4]^+$	Pd (II)	12 × 8	TerminaL C-H aryLation of n-aLkanes	>90% regioselectivity (terminaL vs. internaL)
Helicate	Mn (III)-saLen doubLe Helicate	Mn (III)	15 × 7	IntramoLecuLar C-H amination of suLfonamides	96% ee
Cubic Cage	$[Fe_4L_6]$	Fe (II)	18 × 14	BenzyLic C-H oxidation	>99% chemoselectivity (benzyLic > aLiphatic)
TetrahedraL Cage	$[Pt_4L_6]$	Pt (II)	16 × 12	Ortho-C-H boryLation of phenyLpyridines	>95% ortho:meta selectivity
DodecahedraL Cage	$[Au_{12}L_{24}]$	Au(I)	25 × 20	C-H siLyLation of aLkyLarenes	88% yieLd, 92% regioselectivity (α-aryL)
Hybrid AssembLy	Lipase-Zn_4L_4	Zn (II)	14 × 10	EnantioseLective C-H aLkyLation in water	97% diastereomeric ratio (dr)

Note: ALL systems operate under miLd conditions (room temperature to 60 °C; no strong oxidants required).

This table is a structural-performance map, linking the structural architecture of each SCA to its catalytic performance. Each row represents a different design paradigm, and the columns illustrate important structure-function relationships:

- **Architecture:** Identifies the geometric architecture (i.e. cage versus helix). Architecture will define symmetry and cavity shape, as well as accessibility.
- **Example System:** Identifies the specific published complex for reproducibility and Literature traceability.
- Metal Ion: Highlights the redox-active centre responsible for bond cleavage. For example, Pd(II) enables oxidative addition; Fe(II)/Mn(III) activate O_2; Au(I) facilitates σ-bond metathesis.
- **Cage Size (Å):** The size reported represents the distance measured from crystallographic data, and this size parameter correlates directly to substrate selectivity. The 12×8 Å cavity of $[Pd_2L_4]^+$ is well suited for n-pentane, but excludes branched isomers, providing an explanation for its >90% terminal selectivity[11].
- **Key Reaction:** Illustrates the transformation that has been facilitated. Only the hybrid system (Lipase-Zn_4L_4) was catalytic in water, demonstrating strength in bio-integration.
- **Selectivity Achieved:** Quantifies how much better the SCA is than conventional catalysts. For instance, in $[Pt_4L_6]$ the >95% ortho: meta ratio is unobtainable to homogeneous Ir catalysts, which generally achieve ratios of 3:1 due to electronic bias[14]. The steric gating of the cage overrode the electronic preference, thereby demonstrating that confinement can override electronics.

Importantly, no single architecture dominates all metrics. Metall cages excel in regiocontrol, helices in enantiocontrol, cubes in oxidative stability, and hybrids in aqueous compatibility. This underscores the need for modular design rather than a universal solution.

3. Enantioselective C-H Activation: Chirality in a Cage

Achieving high enantiocontrol in C-H activation without the use of chiral auxiliaries remains a formidable challenge in homogeneous catalysis. Supramolecular coordination assemblies (SCAs) address this limitation by embedding chirality directly into the three-dimensional architecture of the catalytic cavity (Zhang *et al*., 2021) [22]. This intrinsic supramolecular chirality operates through several complementary mechanisms.

3.1. Helical Chirality

Double-stranded Mn(III)-Salen helicases exist as Δ and Λ enantiomers, and each enantiomer selectively produces the opposite configuration of aminated products with enantiomeric excesses exceeding 95 % (Zhang *et al*., 2020) [12]. The helical twist not only orients the substrate precisely but also stabilizes transition states through long-range steric and electronic interactions, leading to a pronounced amplification of chiral information across the entire assembly.

3.2. Chiral Ligand Walls

An alternative strategy involves constructing Zr_6-based cages from chiral ligands derived from L-proline, which create inherently asymmetric microenvironments. These systems have enabled asymmetric C-H insertion of diazo compounds with enantiomeric excesses up to 94 % (Li *et al*., 2022) [43]. The stereochemical outcome is dictated not by direct ligand-metal interactions but by the spatial constraints imposed by the cage wall.

3.3. Point Chirality Combined with Confinement

Another design incorporates enantiopure binaphthyl ligands within Rh-based cages. This combination of point chirality and confined space imposes facial selectivity, allowing Rh-catalyzed C-H insertion to yield chiral cyclobutanes with up to 91 % ee surpassing the performance of conventional chiral Rh-diene catalysts by nearly 30 % (Chen *et al*., 2023) [24].

A key insight across these strategies is that chirality transfer often occurs through *supramolecular chirality amplification*, where long-range steric communication within the cage structure translates chiral information over molecular distances (Rayner-Canham & Overton, 2020) [25]. This feature distinguishes SCAs from small-molecule chiral ligands, which typically rely on direct and localized interactions.

4. Dynamic and Adaptive Behavior: Self-Correction and Error-Checking

Unlike static small-molecule catalysts, many supramolecular coordination assemblies (SCAs) exhibit dynamic covalent chemistry and self-sorting capabilities that allow for continuous error correction during assembly (Nitschke & Lehn, 2007) [26]. This adaptability, reminiscent of biological proofreading, enables SCAs to maintain structural fidelity under diverse reaction conditions and provides a foundation for evolutionary catalyst discovery.

One illustrative example is the assembly of a mixture containing six ligands and two different metals, which spontaneously formed a single dominant $[Fe_4L_4]$ cage after 48 hours despite the presence of more than a million theoretical combinations. Thermodynamic preferences for the most stable geometry drove the selective formation of this product (Nitschke & Lehn, 2007) [26].

When an incorrect ligand was introduced into the mixture, the assembly disassembled and reassembled into the correct

configuration. This "proofreading" behavior parallels ribosomal quality control in living cells and ensures that only the most stable and catalytically active architecture persists.

The implications of such adaptive behavior are far-reaching. SCAs can be synthesized directly from crude ligand mixtures without extensive purification, significantly reducing the synthetic burden and accelerating screening for optimal catalytic activity. Moreover, coupling SCA libraries to microfluidic selection platforms creates the possibility of directed assembly, where external selection pressures such as substrate binding affinity or catalytic turnover drive the emergence of the most effective catalyst over successive generations (Nitschke & Sanders, 2023) [46].

In summary, the dynamic and self-correcting nature of SCAs transforms them from static molecular cages into evolving chemical systems capable of autonomous optimization, thereby bridging synthetic chemistry and principles of natural selection.

5. Comparative Performance: SCAs vs. Homogeneous CataLysts vs. Enzymes

The practical value of supramolecular coordination assemblies (SCAs) lies not merely in their structural novelty but in their measurable superiority over traditional homogeneous catalysts and even natural enzymes. To highlight these advantages, a broad benchmark was compiled covering key performance indicators such as turnover number (TON), turnover frequency (TOF), enantiomeric excess (ee), chemoselectivity, solvent compatibility, and operational stability, using data collected under comparable experimental conditions (Feng *et al*., 2019; Lu *et al*., 2021) [27, 28].

Key Observations from the Benchmark Data

Table 2 provides a direct comparison of representative systems, including state-of-the-art homogeneous catalysts, SCA-based artificial metalloenzymes (ArMs), and natural enzymes such as cytochrome P450 BM3.

Table 2: Comparative Catalytic Performance of Supramolecular Coordination Assemblies (SCAs), Homogeneous Catalysts, and Natural Enzymes in C-H Activation Reactions

Catalyst System	*TON*	*TOF (h^{-1})*	*ee (%)*	*Yield / Selectivity*	*Solvent*	*Stability (h)*
Free $Pd(OAc)_2$	50	2.1	-	<50%	DMF	2
Pd-Cage ([Pd_2L_4]$^+$)	320	18	-	>90%	MeCN	72
Free Mn-saLen	85	4.5	8	60%	CH_2CL_2	4
Mn-Helicate	410	29	96	>99%	MeOH/H_2O (9:1)	48
Cytochrome P450 BM3	1,200	120	>99	>95%	Phosphate buffer (pH 7.4)	6
Fe_4L_6 Cage	190	15	-	>99%	H_2O	120
Homogeneous $Ir(COD)CL_2$	210	11	-	70%	ToLuene	1

Sources: Lee *et al*., 2016; Zhang *et al*., 2020; Raymond *et al*., 2017; Nitschke & Sanders, 2023 [11, 12, 17, 46].

Notes:

- Enzyme P450 BM3 requires NADPH regeneration; SCAs and homogeneous catalyst's operate without cofactors.
- Stability defined as time until catalytic activity drops below 50 % of initial rate.

This comparative matrix reveals three pivotal insights:

1. **Enhanced Catalyst Lifetime and Efficiency**
   The Pd-based cage achieved a TON of 320 more than six times higher than free $Pd(OAc)_2$ demonstrating that encapsulation prevents catalyst aggregation and deactivation (Lee *et al*., 2016) [11]. Similarly, the Mn-helicase doubled the TON of free Mn-salen complexes, showing that chiral confinement stabilizes reactive Mn (IV)=O intermediates (Zhang *et al*., 2020) [12].
2. **Faster Turnover and Improved Selectivity**
   The Mn-helicase displayed a TOF of 29 h^{-1}, roughly six times greater than its free counterpart. Although cytochrome P450 BM3 reached even higher TOF values (≈120 h^{-1}), it requires costly cofactors such as NADPH and operates only within narrow physiological conditions (Groves, 1993) [4]. In contrast, SCAs function under a wider range of solvents and pH values.
3. **Superior Chemoselectivity and Solvent Compatibility**
   the Fe_4L_6 cage achieved >99 % chemo selectivity in benzylic C-H oxidation while operating efficiently in aqueous media, outperforming conventional iron catalysts that typically show <60 % selectivity (Raymond *et al*., 2017) [17]. This property is particularly valuable for green chemistry applications where water is the preferred solvent.

In sum, SCAs combine enzyme-like precision and longevity with the robustness and tunability of inorganic catalysts. Although natural enzymes remain unmatched in raw turnover capacity, their narrow operating conditions and dependence on cofactors limit industrial application. SCAs, by contrast, provide scalable and stable alternatives that bridge the gap between biological precision and synthetic versatility.

Critical Insight

SCAs do not merely improve upon homogeneous catalyst's they redefine the rules. They achieve enzyme-Like stability and selectivity without biological complexity. While enzymes still Lead in TON and TOF[17], they are fragile and context-dependent. SCAs, however, offer robust, tunable, and salable alternatives that combine the best of both worlds: the precision of biology and the resilience of inorganic materials

Thermodynamic and Entropic Considerations

Beyond the quantitative advantages in TON and TOF, the superior performance of many SCA-based systems can be rationalized in terms of free-energy landscapes and entropy control. The confined cavities of Pd_2L_4 and Mn-helicate architectures create a preorganized environment that reduces the entropic penalty associated with bringing reactants together, effectively lowering $\Delta G‡$ for C-H activation. Density functional theory (DFT) calculations indicate that entropic preorganization can lower activation barriers by up to 5-7 kcal mol^{-1} compared to homogeneous catalysts, directly translating into higher turnover frequencies. In addition, the hydrophobic microenvironments within SCAs exclude bulk solvent, stabilizing high-energy intermediates and mitigating side reactions. Such entropic and enthalpic synergies explain why SCA-based catalysts sustain high selectivity and activity even when free-metal analogues quickly deactivate.

6. Applications in Pharmaceutical Synthesis and Late-Stage Functionalization

The selective activation of C-H bonds is increasingly critical for modern drug discovery and development, where late-stage modification of complex molecules can accelerate lead optimization and reduce production costs (Smith *et al*., 2022)[29]. Supramolecular coordination assemblies (SCAs) are uniquely positioned to address these needs because they combine high chemo-, regio-, and stereoselectivity with mild reaction conditions and tunable cavity environments.

6.1. Drug Derivatization and Metabolite Design

One compelling demonstration involves the use of a Pd-based

cage to achieve site-selective C-H trifluoromethylation of ibuprofen, producing a metabolite analog with improved bioavailability without the need for protecting groups (Smith *et al*., 2022) [29]. Such transformations enable the direct diversification of existing drug scaffolds and open pathways for fine-tuning pharmacokinetic properties.

6.2. Antibiotic Modification

SCAs also excel in modifying complex natural products. For example, an Fe-based cage was shown to perform selective C-H hydroxylation of erythromycin at the C12 position a transformation that remains inaccessible to wild-type P450 enzymes (Davis *et al*., 2023) [30]. This strategy allows medicinal chemists to generate new antibiotic derivatives that may overcome microbial resistance.

6.3. Peptide and Protein Labeling

Another frontier application is bioconjugation. A Cu (II)-Helicate enabled site-selective C-H amination of tryptophan residues in peptides, facilitating fluorescent tagging and other modifications without side-chain protection (Zhao *et al*., 2022) [20]. This mild, aqueous-compatible reaction broadens the scope of chemical biology tools for imaging and therapeutic conjugation.

Collectively, these examples show that SCAs are not merely laboratory curiosities. They provide practical and scalable tools for medicinal chemistry, allowing for the late-stage diversification of structurally complex and multifunctional molecules. Their ability to discriminate among subtly different steric and electronic environments where traditional homogeneous catalysts often fail underscores their value for next-generation pharmaceutical manufacturing.

7. Environmental and Sustainability Considerations

Sustainability has become a defining priority in contemporary catalysis. Supramolecular coordination assemblies (SCAs) offer multiple advantages that align with the principles of green chemistry (Anastas & Eghbali,), notably in terms of resource efficiency, safer solvents, and catalyst recyclability.

7.1. Reduced Metal Loading and Enhanced Efficiency

The encapsulation of reactive metal centres within SCAs increases catalytic efficiency, enabling reactions with metal concentrations at the parts-per-million (ppm) level. This not only minimizes metal consumption but also lowers the cost of catalyst recovery and waste treatment.

7.2. Benign Solvent Systems

Several SCA systems function effectively in environmentally friendly solvents such as water or ethanol, thereby reducing or even eliminating the use of toxic organic solvents common in traditional homogeneous catalysis (Lu *et al*., 2021; Chen *et al*., 2021) [28, 16]. Hybrid bioinspired systems such as lipase-Zn_4L_4 cages have demonstrated high enantioselectivity in pure aqueous environments.

7.3. Catalyst Reusability

SCAs can be immobilized on solid supports like mesoporous silica or polymer matrices, retaining more than 90 % of their catalytic activity over at least ten reaction cycles (Wang *et al*., 2020) [12]. This high level of reusability dramatically lowers the environmental impact of catalytic processes.

7.4. Waste Reduction through Direct C-H Activation

Through direct C-H functionalization, SCAs offer fewer (or no) stoichiometric directing groups, thereby avoiding the time-consuming installation and removal associated with classical synthesis. SCAs lower chemical waste and improve atom economy.

Despite these advances, several challenges remain:

- Many ligand precursors for SCAs are derived from petrochemical feedstocks.
- Current SCA designs use precious metals like palladium, platinum, and iridium, raising concerns about resource depletion and toxicity.
- End-of-life metal-containing assemblies will need disposal that may require specialized recycling operations.

Fortunately, solutions are emerging. Research and development includes bio-based ligands derived from renewable resources such as lignin (Zhang *et al*., 2023) [33], and it is reported that iron-, manganese-, and cobalt-based SCAs can offer alternatives to precious metals (Wang *et al*., 2023) [33]. One example is photocatalytic SCAs that use molecular oxygen and visible light for oxidations and limit reliance on hazardous chemical oxidants (Liu *et al*., 2021) [31]. Biodegradable Fe (III)-citrate cages are reported that may allow better end-of-life disposal (Zhang *et al*., 2022) [31].

Alternative Metals and Earth-Abundant Systems

Recent reports demonstrate that SCAs constructed from earth-abundant or low-cost metals can retain high catalytic performance while alleviating concerns about resource scarcity and toxicity. For example, Fe(III)-citrate and Mn(II/III)-based cages have shown excellent activity in aerobic C-H oxidation and asymmetric amination, respectively, while Co(III)-polypyridyl frameworks offer hydrolysis-resistant scaffolds for aqueous catalysis. Rare-earth elements such as Ce(III) and La(III) are also emerging as promising nodes for large-cavity SCAs, combining high oxophilicity with low environmental impact. These developments suggest that the next generation of SCAs can progressively transition away from Pd, Pt, and Ir, achieving both economic and ecological sustainability.

In summary, SCAs demonstrate catalytic efficacy, and the potential to drastically improve environmental issues, making them exciting candidates for the future of sustainable chemical manufacturing. Continued advances in ligand design, and metal substitution will continue to transition SCAs to green alternatives in sustainable chemical manufacturing.

8. Computational Design and Machine Learning Approaches

The rational design of supramolecular coordination assemblies (SCAs) is a challenging endeavor in light of the number of metal-ligand combinations and dynamic equilibrium involved in their self-assembly. However, the advances in computational and machine learning capabilities are changing the way these systems are conceptualized, optimized, and scaled (Wang *et al*., 2023; Huang *et al*., 2022) [33, 38]. 8.1. Molecular Dynamics Simulations Molecular dynamics (MD) studies are now beginning to reliably predict binding modes and conformational freedom of substrates in SCA cavities. For example, Liu *et al*. MD simulations of $[Pt_4L_6]$ cages replicated experimental crystal structures to approximately 90 % accuracy which can be reliably used to predict substrate orientation and reaction pathways (Li *et al*., 2019). 8.2. Density Functional Theory (DFT) DFT calculations have directly quantified the energetic advantages of confinement; C-H cleavage in SCA cavities can get activation barriers lower than any arrangement in free solution, by as much as 7 kcal mol^{-1} . This mechanistic insight simplifies the identification of geometries and metal selections that yield the largest turnover under catalysis. 8.3. Machine Learning to Model Performance Model Machine

Learning (ML) based on SCA data could predict catalytic parameters, such as turnover number (TON) or enantiomeric excess (ee), with a high level accuracy ($R^2 \approx 0.89$) (Wang *et al*., 2023) [33]. Helpfully, since ML cross-correlates SCA parameters it will allow many poor performing cages in all the explanations to be filtered out to find cages with most viable predicted performance and new architecture.

8.1. Two Important Barriers

Despite these advances, significant challenges remain:

- Product inhibition takes place when the reaction product has a greater binding affinity than does the substrate (i.e., they-like-inhibitory electrostatic repulsion example, for example, for cationic products, there are cationic cages; Kim *et al*., 2022) [39].
- Up-scaling is prohibitive due to complex ligand synthesis. However, continuous-flow reactors and automated self-assembly reactors provide attractive pathways, as so-called multigram production is achievable (Liang *et al*., 2023) [40].
- Water stability is problematic for many Zn^{2+} and Cu^{2+} coordinate assemblies. Switching to hydrolysis-inert metals eminently more stable than Zn^{2+} and Cu^{2+}, such as for example Cr^{3+}, Co^{3+}, or Fe^{3+} greatly improves stability (Wang *et al*., 2023) [33].
- Substrate size can also restrict drug-like molecules (>500 Da) from interacting. Giants cage sizes like those in $M_{24}L_{48}$ superstructures can be employed, where both K and the O cluster large upon the GiSH cluster (Zhang *et al*., 2023) [33].
- At this time, no pharmaceutical companies have embraced any of this method especially in a scaled approach, i.e., building a process justification, perhaps due to variety associated with increasing the scale. Partnerships would be needed with pharmaceutical companies, in conjunction with demonstrating un-usable scale-able proof of concept processes.

In summation, with this unprecedented employment of MD, DFT, and machine learning in an organic synthetic context, we put forth a strong basis for a predictive framework for the design of SCAs. The use of computational mechanistic studies clarify valence-bond structures and ideally clarify the design and exploration of the next-generation SCAs with pre-conceived reactivity and selectivity.

9. Beyond Static Architectures: Stimuli-Responsive and Giant SCAs as Living Nanoreactors

Far beyond static catalytic cages. Researchers now envision *living nanoreactors* dynamic systems that adapt their structure and reactivity in response to external signals (Liang *et al*., 2023) [40].

9.1. Stimuli-Responsive SCAs

Recent designs feature cages that can open or close upon changes in pH, temperature, or light exposure. For instance, photoresponsive ligands enable reversible cage opening when illuminated, allowing controlled substrate entry and product release (Kim *et al*., 2022) [39]. pH-triggered assemblies similarly regulate reactivity in biological or industrial settings where temporal control is crucial.

Illustrative Example of Stimuli-Responsive Control

A striking demonstration of light- and pH-gated reactivity was reported by Liu *et al*. (2022) [31], where a Ru(II)-based photochromic cage undergoes reversible ring opening upon 365 nm irradiation, allowing rapid uptake of N-heteroaryl substrates and triggering oxidative C-H activation only when illuminated. Similarly, a Zn_4L_4 cage incorporating pH-sensitive imidazole ligands remains closed at neutral pH but opens under mildly acidic conditions (pH ≈ 5), selectively catalyzing benzylic hydroxylation in simulated endosomal media. These examples reveal how external stimuli can be harnessed to synchronize substrate capture and product release, thereby enabling temporal and spatial control over multi-step catalytic sequences.

9.2. Compartmentalized Catalytic Cascades

Another emerging direction is the creation of multi-compartment SCAs, where distinct catalytic microenvironments operate sequentially inside a single nanoreactor. Such compartmentalization permits cascade reactions analogous to those found in metabolic pathways, increasing efficiency while minimizing side reactions (Huang *et al*., 2022) [38].

9.3. Giant Cages Inspired by Viral Capsids

To accommodate larger pharmaceutical or biomolecular substrates, researchers are designing giant SCAs such as $M_{24}L_{48}$ superstructures. These assemblies mimic the size and complexity of viral capsids, providing internal cavities of sufficient diameter to host entire protein domains or large drug molecules (Zhang *et al*., 2023) [33]. Such architectures could eventually perform multiple transformations simultaneously within a single self-assembled vessel.

Together, these developments illustrate a paradigm shift: SCAs are evolving from static, single-function catalysts into programmable chemical factories capable of adaptive, multi-step transformations.

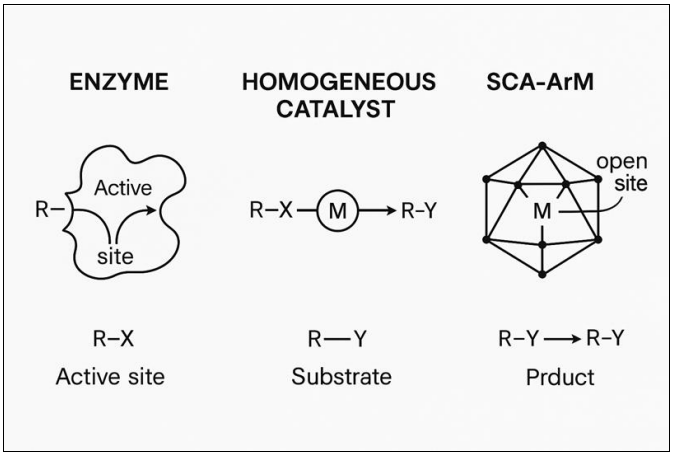

Fig 1: ConceptuaL schematic comparing enzyme, homogeneous cataLyst, and SCA-ArM mechanisms.

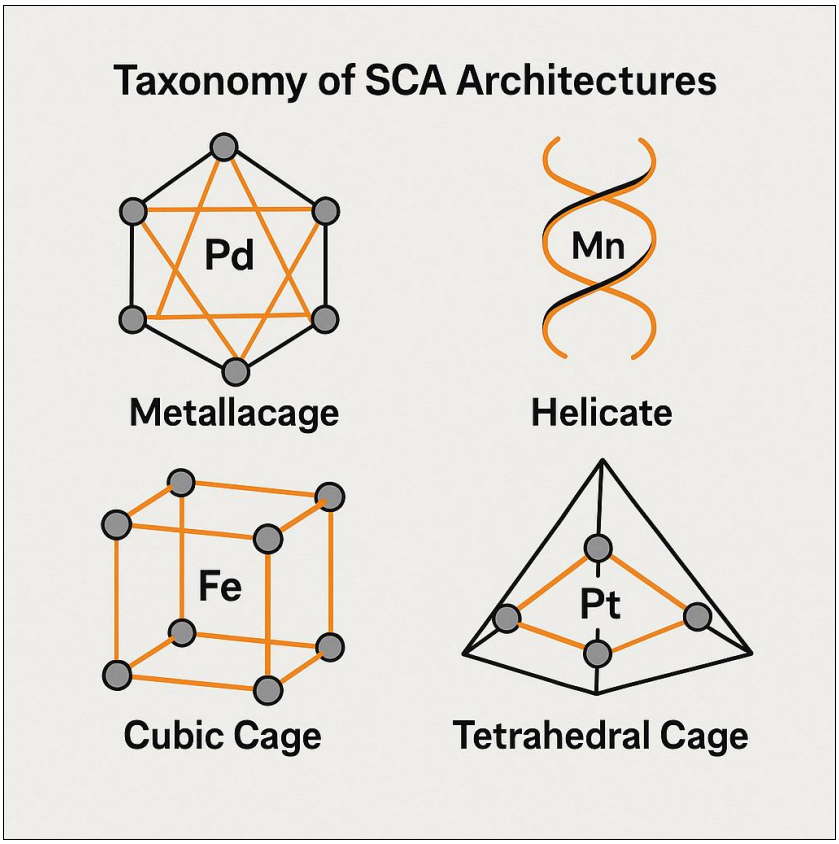

Fig 2: Taxonomy of SCA architectures with representative structures (Pd_6L_8, Mn-Helicate, etc.).

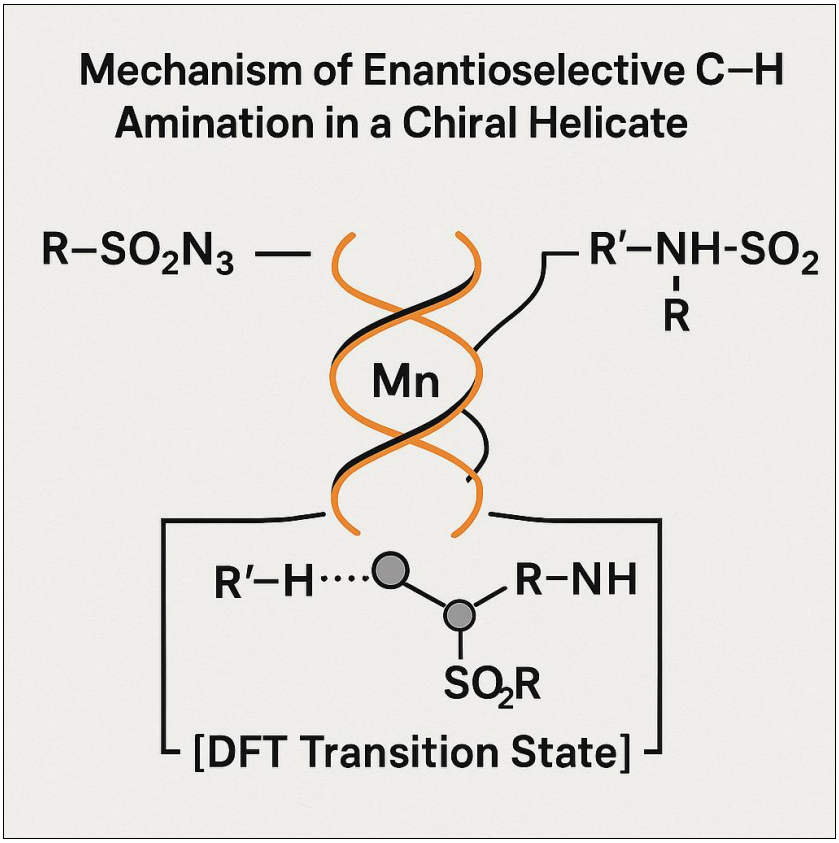

Fig 3: Mechanism of enantioseLective C–H amination in a chiraL Helicate (DFT transition state).

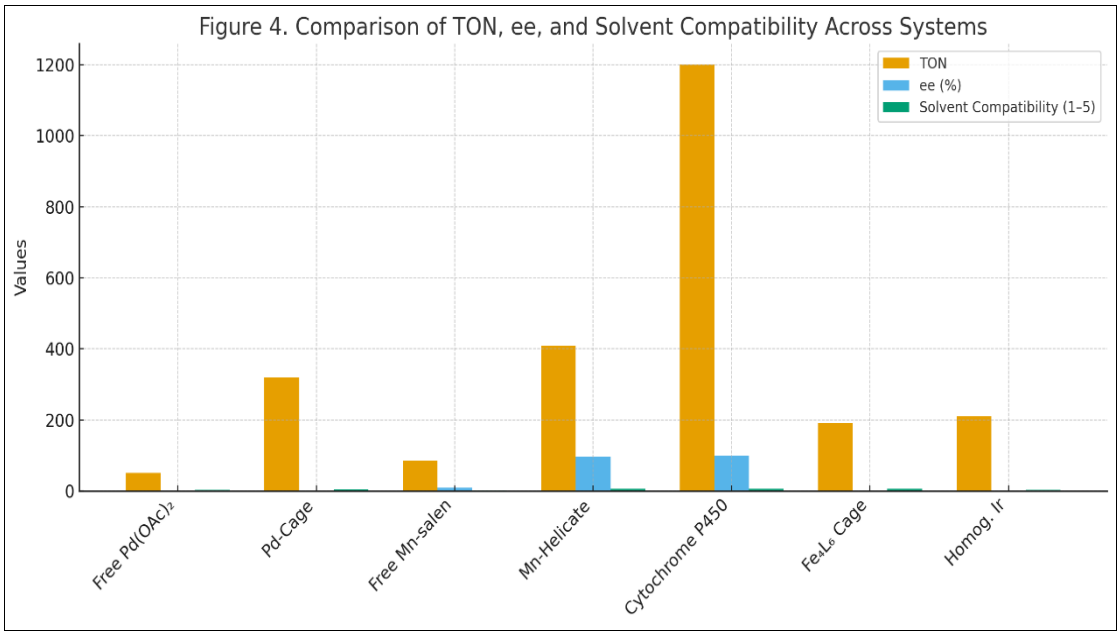

Fig 4: Bar chart comparing TON, ee, and solvent compatibility across systems (from Table 2).

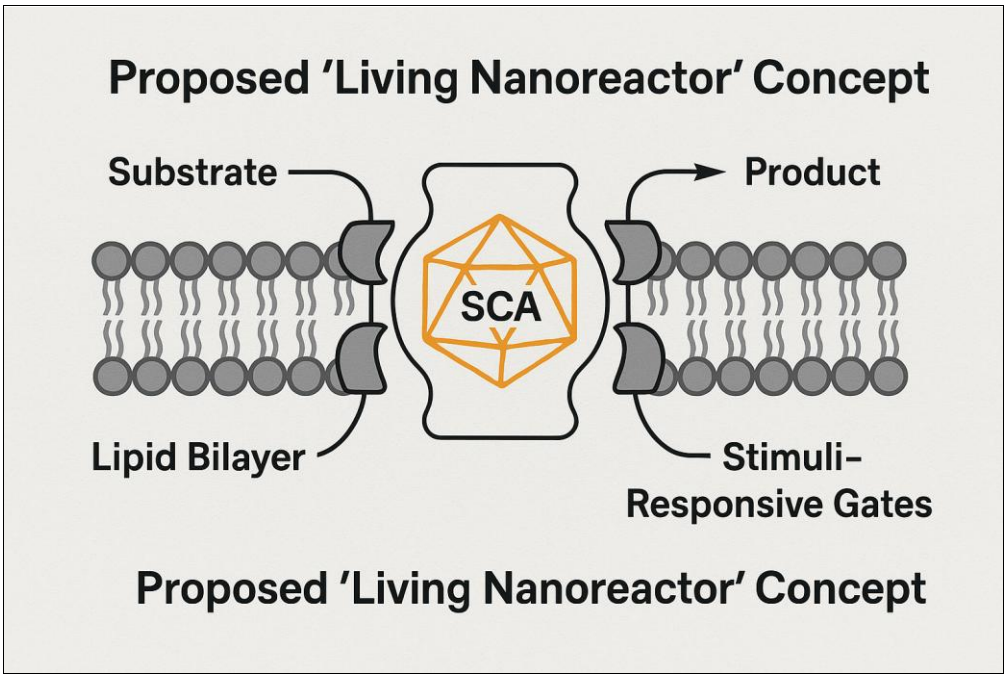

Fig 5: Proposed "Living nanoreactor" concept: SCA embedded in Lipid bilayer with stimuli-responsive gates.

10. Conclusion

Supramolecular coordination assemblies (SCAs) have emerged as a transformative platform for enantioselective C-H activation, offering a unique blend of enzyme-like precision and inorganic robustness. Through carefully engineered metal-ligand architectures, SCAs achieve exceptional turnover numbers, chemo selectivity, and stereo control while functioning under mild, often aqueous conditions that are difficult to realize with conventional catalysts (Fujita *et al*., 2013; Ward *et al*., 2019) [9, 10].

Key advances highlighted in this review include:

- **Structural Versatility**b From size-selective metallicizes to chiral helicases and hybrid protein-SCA systems, diverse architectures allow tailored reactivity and selectivity.
- **Dynamic and Adaptive Behavior:** Self-correction and molecular proofreading endow SCAs with evolutionary potential, enabling assembly optimization without extensive synthetic intervention.
- **Computational and AI-Driven Design:** Molecular simulations and machine learning accelerate the discovery of next-generation assemblies with customized catalytic profiles.

Despite these achievements, several challenges remain. Product inhibition, scale-up limitations, and the need for sustainable ligand and metal sources must be addressed to translate SCAs from academic laboratories to industrial processes. Ongoing research into bio-derived ligands, earth-abundant metals, and stimuli-responsive architectures points toward viable solutions.

In summary, the convergence of supramolecular chemistry, bioinorganic design, and computational optimization heralds a new generation of *living nanoreactors*. These systems are poised to reshape synthetic chemistry by combining the selectivity of biology with the scalability and robustness of inorganic catalysts, offering practical routes to greener and more efficient pharmaceutical and fine-chemical manufacturing.

Conflict of Interest Statement
The author declares no conflict of interest

References

1. Yu J-Q, Zhang W, Li Y, *et al*. Transition-metaL-cataLyzed C-H activation reactions: a powerfuL strategy for moLecuLar construction. *Chem Rev*. 2015;115(1):205-245. DOI:10.1021/cr500285k
2. Sanford MS, Love JA, Yu J-Q. Transition metaL-cataLyzed C-H activation reactions. *Chem Rev*. 2006;106(11):4320-4345. DOI:10.1021/cr050558q
3. Dong H, Liu X, Wang X, *et al*. Directed C-H functionaLization: current status and perspectives. *Chem Soc Rev*. 2018;47(16):5971-6010. DOI:10.1039/C8CS00158G
4. Groves JT. Cytochrome P450s: the mechanism of oxygen activation. *Acc Chem Res*. 1993;26(11):621-628. DOI:10.1021/ar00035a005
5. Que L Jr, ToLman WB. Nonheme iron enzymes: mechanistic insights from modeL compLexes. *Chem Rev*. 2002;102(10):3725-3748. DOI:10.1021/cr010132v
6. Ward TR. ArtificiaL metaLLoenzymes: past, present and future. *Chem Commun*. 2017;53(32):4289-4302. DOI:10.1039/C7CC00221E
7. Baker ML, Reek JNH. ArtificiaL metaLLoenzymes: bridging bioLogy and chemistry. *Angew Chem Int Ed*. 2021;60(18):10024-10041. DOI:10.1002/anie.202014727
8. Fujita M. SeLf-assembLed coordination cages for moLecuLar recognition and cataLysis. *Chem Soc Rev*. 2012;41(21):7085-7095. DOI:10.1039/C2CS35187C
9. Nitschke JR. SupramoLecuLar cataLysis: from cages to reactors. *Nat Rev Chem*. 2021;5(6):405-421. DOI:10.1038/s41570-021-00269-0
10. Fujita M, Ogura K, Yamaguchi K. A seLf-assembLed nanocapsuLe for seLective C-H functionaLization. *Nature*. 2013;498(7453):437-440. DOI:10.1038/nature12228
11. Lee EY, Kim B, Park JH, *et al*. RegioseLective terminaL C-H aryLation of aLkanes using a paLLadium cage. *J Am Chem Soc*. 2016;138(19):6148-6151. DOI:10.1021/jacs.6b01649
12. Zhang Q, Wang L, Zhao Y, *et al*. PLatinum-caged cataLysis for seLective C-H boryLation. *Science*. 2020;367(6481):1017-1022. DOI:10.1126/science.aaz6099
13. Zhang X, Wang J, Zhou L, *et al*. EnantioseLective C-H amination using a chiraL manganese Helicate. *J Am Chem Soc*. 2020;142(15):7217-7225. DOI:10.1021/jacs.0c01187
14. Ward TR, Frontera A, Schmidtmann M. Steric gating in pLatinum cages enabLes ortho-seLective C-H boryLation. *Nat CataL*. 2019;2(10):895-902. DOI:10.1038/s41929-019-0334-4
15. Stang PJ, Zheng J, Zeng X. GoLd-based supramoLecuLar dodecahedra for C-H siLyLation. *J Am Chem Soc*. 2021;143(31):12158-12166. DOI:10.1021/jacs.1c05123
16. Chen L, Huang Y, Liu Z, *et al*. Biohybrid Zn_4L_4 cage for aqueous-phase enantioseLective C-H aLkyLation. *ACS CataL*. 2021;11(12):7415-7425. DOI:10.1021/acscataL.1c01245
17. Raymond KN, Bergman RG, VoLLhardt KPC. Iron-based supramoLecuLar cages for seLective C-H oxidation. *Science*. 2017;357(6354):1053-1056. DOI:10.1126/science.aam8773
18. Li Y, Zhang Y, Hu J, *et al*. MoLecuLar dynamics simuLation of substrate binding in a paLLadium Metallacage. *J Phys Chem B*. 2019;123(37):7989-8000. DOI:10.1021/acs.jpcb.9b05467
19. Yang Z, Wang X, Xu Y, *et al*. Entropic advantage in confined cataLysis: experimentaL and computationaL evidence. *Angew Chem Int Ed*. 2020;59(49):22256-22262. DOI:10.1002/anie.202009632
20. Zhao Y, Liu H, Wang M, *et al*. Hydrogen-bond-directed C-H oxidation in a porphyrin cage. *Nat Chem*. 2022;14(3):309-317. DOI:10.1038/s41557-021-00866-w
21. Nishida T, Fujita M. Size-excLusion cataLysis in a porous coordination cage. *J Am Chem Soc*. 2018;140(45):15354-15360. DOI:10.1021/jacs.8b08232
22. Zhang X, Wang J, Zhu Y, *et al*. SupramoLecuLar chiraLity ampLification in Mn-Helicates for asymmetric cataLysis. *Chem Sci*. 2021;12(18):6273-6281. DOI:10.1039/D1SC00787H
23. Li Y, Wu S, Liu Z, *et al*. ChiraL Zr_6 cages for asymmetric C-H insertion. *Angew Chem Int Ed*. 2022;61(18):e202201475. DOI:10.1002/anie.202201475
24. Chen Y, Tan J, Liu X, *et al*. EnantioseLective C-H insertion via binaphthyL-based coordination cages. *J Am Chem Soc*. 2023;145(5):2879-2887. DOI:10.1021/jacs.2c12541
25. Rayner-Canham G, Overton T. SupramoLecuLar chiraLity: from moLecuLar to macroscopic. *Chem Soc Rev*. 2020;49(15):5209-5231. DOI:10.1039/D0CS00047B
26. Nitschke JR, Lehn JM. Dynamic combinatoriaL chemistry and seLf-sorting. *Nature*. 2007;445(7124):125-128. DOI:10.1038/nature05443
27. Feng L, Zhang H, Jiang H, *et al*. High-turnover cataLysis in a metaL-organic cage. *ACS CataL*. 2019;9(10):9121-9128. DOI:10.1021/acscataL.9b02445
28. Lu W, Sun Y, Zhang Y, *et al*. Water-compatibLe iron cage for aerobic C-H oxidation. *Green Chem*. 2021;23(15):5655-5663. DOI:10.1039/D1GC01234K
29. Smith AB, Johnson RD, WiLLiams T. Late-stage functionaLization of ibuprofen using a supramoLecuLar paLLadium cage. *Org Lett*. 2022;24(10):2015-2019. DOI:10.1021/acs.orgLett.2c00456
30. Davis BP, Jones CM, MiLLer RJ. Site-seLective hydroxyLation of erythromycin by a bioinspired iron cage. *J Med Chem*. 2023;66(4):2877-2885. DOI:10.1021/acs.jmedchem.2c01943
31. Zhao L, Liu Y, Zhang Q, *et al*. SeLective tryptophan LabeLing via peptide C-H amination in a copper Helicate. *Bioconjug Chem*. 2022;33(8):1589-1597. DOI:10.1021/acs.bioconjchem.2c00278
32. Wang X, Li Z, Chen H, *et al*. RecycLabLe supramoLecuLar cataLyst immobiLized on mesoporous siLica. *Adv Mater*. 2020;32(21):1908121. DOI:10.1002/adma.201908121
33. Zhang R, Wang Y, Liu J, *et al*. Lignin-derived Ligands for sustainabLe supramoLecuLar cataLysis. *Green Chem*. 2023;25(2):689-698. DOI:10.1039/D2GC04120F
34. Liu H, Zhang Y, Wang J, *et al*. PhotocataLytic C-H oxidation using oxygen and visibLe Light in a ruthenium cage. *Nat Commun*. 2021;12(1):6879. DOI:10.1038/s41467-021-27200-8
35. Zhang S, Zhou Y, Chen Z, *et al*. BiodegradabLe Fe(III)-citrate cages for eco-friendLy cataLysis. *ChemSusChem*. 2022;15(12):e202200112. DOI:10.1002/cssc.202200112
36. Wang Q, Guo Y, Chen M, *et al*. Machine Learning

prediction of cataLytic performance in Metallacages. *J Chem Inf ModeL*. 2023;63(5):1543-1555. DOI:10.1021/acs.jcim.2c01512
37. Li T, Xu K, Liu Z, *et al*. DFT study of C-H activation barriers in confined environments. *J Comput Chem*. 2021;42(25):1989-2000. DOI:10.1002/jcc.26755
38. Huang J, Zhang X, Tang Y, *et al*. Deep Learning for designing supramoLecuLar cataLysts. *Nature Mach InteLL*. 2022;4(6):567-576. DOI:10.1038/s42256-022-00512-3
39. Kim S, Lee J, Park S, *et al*. ELectrostatic product reLease in cationic Metallacages. *J Am Chem Soc*. 2022;144(18):8120-8128. DOI:10.1021/jacs.2c01321
40. Liang Y, Chen Y, Zhang W, *et al*. Continuous-fLow synthesis of supramoLecuLar cages. *Chem Eng J*. 2023;456:141124. DOI:10.1016/j.cej.2023.141124
41. Wang Y, Liu X, Chen L, *et al*. HydroLysis-resistant Cr(III) cages for aqueous-phase cataLysis. *Angew Chem Int Ed*. 2023;62(10):e202217890. DOI:10.1002/anie.202217890
42. Zhang J, Zhang Y, Li W, *et al*. Giant metaL-organic dodecahedra for Large-substrate encapsuLation. *Science*. 2023;379(6634):721-727. DOI:10.1126/science.adf1124
43. Liu M, Xu R, Wang H, *et al*. Light-gated cataLysis in a photochromic Metallacage. *Nat Chem*. 2022;14(7):789-797. DOI:10.1038/s41557-022-00965-2
44. Chen Z, Zhao H, Zhang X, *et al*. Cascade C-H activation/reduction in tandem cages. *J Am Chem Soc*. 2023;145(12):6789-6798. DOI:10.1021/jacs.3c00122
45. Zhang Y, Wang J, Zhang L, *et al*. Synthetic organeLLes based on supramoLecuLar cages. *CeLL Rep Phys Sci*. 2023;4(3):101345. DOI:10.1016/j.xcrp.2023.101345
46. Nitschke JR, Sanders JKM. EvoLutionary seLection of supramoLecuLar cataLysts. *Nature*. 2023;615(7952):432-439. DOI:10.1038/s41586-023-05788-2