Evolve makes their construction challenging. Moreover, issues the multiple aggregation pathways by which the systems can perturbations, the large number of interacting components and complexity arising from the sensitivity of these systems to small bottom-up construction of functional structures is not easy. Nanoscale, assembled molecule by molecule. However, this structures can be built by a bottom-up approach from the such molecular systems. Long-range ordered hierarchical into de assembly, the power of molecules to autonomously assemble methods,7 catalysts to favor one over other possible reaction pathways and a clever combination of sequential noncovalent and covalent reaction steps.

In biological systems, covalent modifications of structures hold by noncovalent interactions are widespread. Examples include the post-translational modifications of protein assemblies.8 Such modifications are covalent reactions that alter the structure, stability, and activity of a protein and hence control its overall function. Chemists are far from being able to mimic such level of control in purely synthetic systems as the understanding of the link between structure dynamics and function is lacking. However, inspired by these natural systems, first steps have been taken to modify supramolecular structures by covalent reactions.

The need for complex functional systems is growing, driven by the interests for device miniaturization, development of energy materials, and efforts to mimic biological processes.1,2 Self-assembly, the power of molecules to autonomously assemble into defined aggregates, is a key player in the construction of such molecular systems. Long-range ordered hierarchical structures can be built by a bottom-up approach from the nanoscale, assembled molecule by molecule. However, this bottom-up construction of functional structures is not easy. Complexity arising from the sensitivity of these systems to small perturbations, the large number of interacting components and the multiple aggregation pathways by which the systems can evolve makes their construction challenging.5 Moreover, issues on prediction of the assembled states and reproducibility urge the community for solutions. Inspired by total synthesis in organic chemistry, a paradigm shift from one-step self-assembly to multistep noncovalent synthesis4,5 was proposed.8 Instead of assembling multiple components in a single step by mixing, several steps are performed one after another until the complex structure is reached. Thus, novel synthetic strategies in the molecular scientists’ toolbox are needed to develop this stepwise approach. These tools include orthogonal directed-assembly methods,7 catalysts to favor one over other possible reaction pathways and a clever combination of sequential noncovalent and covalent reaction steps.

In biological systems, covalent modifications of structures hold by noncovalent interactions are widespread. Examples include the post-translational modifications of protein assemblies.8 Such modifications are covalent reactions that alter the
over radical generation yields polymers with defined molecular weight and dispersity, to make materials with unprecedented properties. In comparison with the plethora of supramolecular assemblies known, only a limited number of examples are reported that apply covalent reactions to supramolecular structures. One reason is that supramolecular structures are difficult substrates for organic reactions. This is due to the weak noncovalent interactions that hold the supramolecular assemblies together (Scheme 1). Typical noncovalent forces are the hydrophobic interactions that hold the supramolecular assemblies together for organic reactions. This is due to the weak noncovalent interactions and hydrogen bonds (Scheme 1b, 1−25 kcal/mol) and metal coordination (Scheme 1c, 10−100 kcal/mol). They drive the formation of ordered supramolecular aggregates of various forms depending on the constitution and the conformational preference of the interacting building blocks. As a result, these structures are highly dynamic making them a challenging target for covalent reactions. The continuous dynamic exchange of building blocks accounts for a high sensitivity to environmental changes. Variation of solvent, pH, concentration, and temperature or the presence of additives can lead to disassembly of a structure. Moreover, the methods commonly used to purify organic compounds disassemble supramolecular products. Thus, typical conditions for organic synthesis, the use of catalysts, incomplete reactions or formation of side-products are often incompatible with specific assembly conditions of supramolecular structures.

These characteristics imply that a covalent reaction has to yield the product quantitatively and with high chemoselectivity at conditions dictated by the assembly, which dramatically limits the repertoire of applicable covalent reactions. However, in the past years, recent progress has revealed the importance of combining covalent and noncovalent reactions to reach enhanced complexity and advanced function.

In this outlook, we analyze the literature on multistep synthesis involving covalent and noncovalent transformations and the ongoing challenges. We first reflect on the synergy between organic and supramolecular chemistry. Then, we discuss seminal examples of organic reactions that have been realized in combination with supramolecular systems. Most of these syntheses are limited to a two-step process. We classify them in covalent reaction steps that are either used for (a) in situ generation of a building block that subsequently assembles or (b) covalent postassembly modification of a robust structure. We conclude that mild, quantitative, and highly chemoselective reactions are compatible with dynamic supramolecular polymers, while particularly robust supramolecular assemblies with limited-dynamicity enable more sophisticated chemical reactions. Finally, considering the huge progress in synthetic chemistry in the past decade, we highlight the enormous, yet unexplored, potential for combined covalent and noncovalent synthesis of complex molecular systems.

### SYNERGY BETWEEN ORGANIC AND SUPRAMOLECULAR CHEMISTRY

Supramolecular chemistry and organic synthesis are sibling disciplines that benefit from each other in their perspectives on, for example, reactivity and self-organization. First, supramolecular interactions are commonly used in organic synthesis to tune the reactivity of substrates and induce selectivity in reactions. One of the multiple examples is the approach of a nucleophile onto a carbonyl electrophile in a defined ∼107° angle (Bürgi–Dunitz angle). This trajectory arises from the favored electrostatic interaction defined by maximal HOMO–LUMO overlap of nucleophile and electrophile (Figure 1a). This supramolecular interaction predicts the stereoselectivity of nucleophilic addition reactions (e.g., aldol reactions) and demonstrates how weak noncovalent interactions can direct the 

![Figure 1](https://dx.doi.org/10.1021/acscentsci.0c00974)
selection of a reaction path to a product. More sophisticated examples that harness supramolecular interactions are catalytic transformations. Here, the catalyst interacts noncovalently with the substrate—it forms a supramolecular assembly—and selectively activates the substrate. A subsequent covalent reaction step affords products with high chemico- and stereo-selectivity. Among countless examples, we like to give one personal highlight reported by Miller and co-workers in which they developed small peptidic catalysts for the site-selective functionalization of erythromycin A. Because of noncovalent interactions between peptide and substrate, site-selective acylation of one out of five possible hydroxy groups was achieved.

Reciprocally, the field of supramolecular chemistry benefits from organic synthesis: the serendipitous covalent synthesis of dibenzo-18-crown-6 by Pedersen introduced the use of noncovalent interactions to drive the formation of a supramolecular product. In a Williamson ether synthesis between catechol and bis(2-chloroethyl)ether with alkali base, the templation of the reactants by the alkali cations via ion-dipole interactions directs the covalent formation of crown-ethers from organic synthesis: the serendipitous covalent synthesis of dibenzo-18-crown-6 by Pedersen introduced the use of noncovalent interactions to drive the formation of a supramolecular product. In a Williamson ether synthesis between catechol and bis(2-chloroethyl)ether with alkali base, the templation of the reactants by the alkali cations via ion-dipole interactions directs the covalent formation of crown-ethers instead of polymers (Figure 1b). Complexation leads to an increase in the statistical proximity of the termini and a decrease in conformational entropy. Therefore, the entropy loss for the cyclization is much less for the complexed than for the noncomplexed species. The growing field of mechanically interlocked molecules, which was initiated by Sauvage and Stoddart, utilizes supramolecular recognition for the covalent synthesis of otherwise very unlikely molecular structures. The supramolecular preorganization of reactive organic substrates by metallosupramolecular, donor—acceptor interactions, or radical templation is used to efficiently construct interlocked structures. This stepping stone has led to the understanding that molecules can recognize each other selectively and assemble into hierarchically structured products with emergent functions greater than the simple sum of the components.

**IN SITU GENERATION OF SUPRAMOLECULAR BUILDING BLOCKS**

Although covalent and noncovalent interactions go hand in hand in many processes, defined covalent modification on supramolecular assemblies are sparse. Most recent syntheses that combine covalent and noncovalent reactions are realized in situ. As described previously, supramolecular assemblies only form under optimized conditions and are sensitive to external stimuli. As a result, generating the assembling building block in situ is convenient to avoid intermediate separation and purification steps. However, more importantly, generating supramolecular building blocks in situ allows reaching out-of-equilibrium self-assembly. In many examples, assembled building blocks generated in situ are unstable under the chosen reaction conditions and spontaneously degrade, giving a transient assembly state. Understanding how the dynamics of the noncovalent interactions changes over the course of a covalent reaction is studied in depth in the field of systems chemistry. Moreover, it provides a guide for potential reactions and reagents that can be combined with a supramolecular assembly of interest.

Photochemical, Acid/Base, Redox, and Metal Complexation Reactions. Light, pH, electrons, and metal cations are commonly used as stimuli to control supramolecular structures by impacting the covalent framework of the building blocks. Light is noninvasive and therefore a powerful stimulus to perform a chemical reaction on an assembly. Photochemical reactions have been used to trigger assembling via (E)/(Z)-isomerizations of diazo compounds or molecular motors (Scheme 2a) or molecular motors (Scheme 2b), photochemical sigmatropic rearrangement (Scheme 2c) and photodeprotections (Scheme 2d). Since these reactions occur intramolecularly, the reaction rate is concentration-independent, enabling transformations leading to assemblies that require low concentrations. Photochemical reactions have been coupled in both polar and apolar solvents, to perform a chemical reaction on an assembly. Although covalent and noncovalent interactions go hand in hand in many processes, defined covalent modification on supramolecular assemblies are sparse. Most recent syntheses that combine covalent and noncovalent reactions are realized in situ. As described previously, supramolecular assemblies only form under optimized conditions and are sensitive to external stimuli. As a result, generating the assembling building block in situ is convenient to avoid intermediate separation and purification steps. However, more importantly, generating supramolecular building blocks in situ allows reaching out-of-equilibrium self-assembly. In many examples, assembled building blocks generated in situ are unstable under the chosen reaction conditions and spontaneously degrade, giving a transient assembly state. Understanding how the dynamics of the noncovalent interactions changes over the course of a covalent reaction is studied in depth in the field of systems chemistry. Moreover, it provides a guide for potential reactions and reagents that can be combined with a supramolecular assembly of interest.

**Scheme 2. Photochemical, Acid/Base Redox, and Metal Complexation Reactions That Have Been Used in Combination with Supramolecular Assemblies**

For examples where these transformations were applied to supramolecular building blocks, see (a) ref 36; (b) ref 37; (c) refs 38, 39, 43 (d) ref 40; (e) refs 20, 44–46; (f) refs 47–49; (g) refs 50–53 (h) refs 54, 55.
The shape and size of the coordination cages could be modulated by light and translated into switching of the network topology.

Changes of the pH, specifically addition of acid that disrupts hydrogen bonds, is a typical mean to disassemble supramolecular systems. Yet, only a limited number of assemblies have been designed that assemble only in a well-defined pH window.44,45 One example has been reported by Besenius and co-workers in which β-sheet forming peptide sequences with either lysine or glutamic acid residues are attached to BTA units (Scheme 2e).44 Attraction between carboxylate and ammonium groups leads to formation of helical stacks in neutral aqueous environment. Under acidic or basic conditions, protonation or deprotonation of one of the charged species occurs, respectively, leading to disassembly of the stacks. Besides triggering assembly/disassembly by protonation/deprotonation, addition of base has also been used to change the stereochemistry in supramolecular structures.20 In solution, the racemization of phenylglycine units is observed upon addition of base.46 When integrated into a supramolecular BTA helical structure, this racemization of the phenylglycine units results in racemization of the BTA helices with cooperativity effects on the reaction kinetics.20

A few examples utilize redox reactions to assemble/disassemble molecular systems. The groups of Hermans and George studied in water the stepwise reduction of perylenediimide (PDI)47 and naphthalenediimide (NDI)48,49, respectively, with dithionite and subsequent oxidation with oxygen (Scheme 2f). The uncharged diimides form helical stacks, while reduction to the diionic specie suffers from Coulombic repulsions leading to disassembling (PDI2−) or assembling into a different morphology (nanosheets; NDI2−). A bioinspired redox process is the irreversible formation of disulfides (Scheme 2g), which has found numerous applications in supramolecular systems.50–53 Especially, Otto and co-workers explored disulfide formation in aqueous solution to generate dynamic self-replicating aromatic stacks.50–52 Most of their systems are based on 1,3-phenyl-dithiols or 2,6-naphthalenedithiols attached to amino acids or peptide sequences that drive the formation of defined disulfide macrocycles.

Metal complexation for templated synthesis has already been established in the early days of supramolecular chemistry.32 Yet, besides templation, metal complexation can also be used to induce conformational changes or oligomerization of a molecule leading to different assemblies properties. For example, early work by Nolte and co-workers showed that imidazole amphiphile bilayers form closed vesicles upon dimerization with CuII (Scheme 2h).54 Recently, the group of Sleiman exploited metal complexation for the construction of DNA assemblies.55 DNA double helices with metal enabled coordination of different metal ions in DNA loops or defined interlocking of two DNA double helix strands. This strategy provided access to unprecedented DNA architectures, which can, for example, be used as molecular wires for electron transport.

Overall, photochemical, acid/base, redox and metal complexation reactions have been utilized to tune the assembly state of supramolecular structures. These reactions are often compatible with supramolecular assemblies because they are quantitative and typically do not generate side-products. Yet, these reactions are comparatively simple and provide only limited access to building blocks with new functional groups.

Condensation and Addition Reactions. In the past decade, condensation or addition reactions were exploited to introduce new functional groups into supramolecular systems (Scheme 3). Most examples require additional reagents/catalysts to activate substrates or trap side products. These reagents have to be carefully chosen to not interfere with the supramolecular system. Reported reactions that change the assembly properties of a building block in situ are limited to transformations on carboxylic acid derivatives56−62 (Scheme 3a−d), carbonyl compounds63−69 (Scheme 3e−g), diols70 (Scheme 3h), and alkenes71 (Scheme 3i).

Transformations on carboxylic acid derivatives are an obvious retrosynthetic choice to alter the assembly properties of, for example, peptides, lipids, or aromatic amides/imides (BTAs, NDIs, PDIs). Examples range from in situ formation of esters,56,57 anhydrides,58,59 amides60,61 to orthoesters62 (Scheme 3a−d) to trigger assembly/disassembly. Boekhoven and co-workers extensively studied dissipative cycles based on ester or anhydride formation/hydrolysis in water (Scheme 3a,b).58,59 The coupling reagent EDC is used as a fuel to activate the carboxylic acid. Reactions were coupled to formation/ disaggregation of peptidic hydrogels, lipid-based droplets or nanoparticle aggregates.58,59 The group of Das studied amide bond formations using native chemical ligation (NCL) (Scheme 3c).60,61 Small peptide fragments with C-terminal ester and N-terminal cysteine residues were ligated affording small hydrogelating peptides in water. Von Delius and co-workers took advantage of the dynamic nature of orthoesters to selectively form cryptants in organic solvents (Scheme 3d).62 Exchange of the alcohols moieties of the orthoester and templation with a
metal ion yield cryptands with the thermodynamically most favored cavity size.

Carbonyl compounds show high reactivity with nucleophiles, which make them an extensively used target to generate building blocks with emerging assembly properties (Scheme 3e–g).

Recently, Herrmans and co-workers developed an assembly/disassembly system based on a reversible nucleophilic addition of sulfite to a benzyaldehyde derivative (Scheme 3g): disassembly of a saccharide benzaldehyde hydrogel is triggered by formation of a hydroxysulfite. Transfer of the sulfite moiety to in situ formed formaldehyde forces regeneration of the benzyaldehyde derivative and regulation of the system.

Particular attention has been drawn to the reversible formation of imines and hydrazones for the synthesis of supramolecular structures (Scheme 3e,f). Imines and acylhydrazones spontaneously form in neutral or acidic aqueous environment between aldehydes and primary amines or hydrazides, respectively, in high yield with only water as a side product. The in situ formation of imines and acylhydrazones has been combined with a broad range of different assemblies (e.g., vesicles, gel, surface-decorated nanoparticles, aromatic helical stacks, or hydrogen-bonded supramolecular polymers) (Scheme 3e–f).

Especially, acylhydrazone-derived systems have been extensively studied by the group of Van Esch and Eelkema. In situ-generated 1,3,5-cyclohexanehydrazones in the presence or absence of aniline catalysts assemble into fibers to form hydrogels in multicomponent systems or as functional materials for drug delivery. 

In particular, the reversibility of the imine bond is a valuable tool. Lehn and co-workers showed that in a library of interconverting acylhydrazones, the selection of the acylhydrazone forming the strongest G-quadruplex hydrogel shifts the reaction equilibrium to its formation— an example of adaptation under the pressure of self-organization. A similar principle was used by Sakai and Matile to develop polyimines as phase-sensitive membrane probes.

The reversible polymerization of fluorene building blocks into polyelectrolytes with interesting optical properties occurs in ordered phases but not in disordered phases of vesicular membranes. Hence, the polyimine formation can be used to sense the organization of a lipid bilayer membrane.

Also, 1,2-diols have been targeted in the synthesis of supramolecular building blocks. The high affinity of boronic acids to cis-1,2-diols were utilized by the group of Das to form amphiphilic sugar nucleobase building blocks (Scheme 3h).

The guanidine building blocks assemble in aqueous salt solutions to G-quadruplex hydrogels.

Olefinic compounds are chemically inert under most conditions but are selectively activated by transition metal catalysts, for example. Recently, the Fletcher group utilized the Ru-catalyzed alkene metathesis to build up carbohydrate amphiphiles in situ for vesicle formation (Scheme 3i). Key for this system is the high chemoselectivity and robustness of the Ru-Grubbs catalyst. The catalyst does not interfere with the assembly and retains its activity even in the presence of stoichiometric amounts of sugar-functionalized olefins in a biphasic system of water and $^3$BuOH.

From the perspective of an organic chemist, it is clear that the covalent reactions employed to generate in situ supramolecular structures (Scheme 3) are textbook examples of basic organic chemistry and pale in comparison with the recent progress in organic synthesis. However, those reactions are first steps to build-up systems with increasing complexity and to understand the fundamental interplay of covalent and non-covalent reaction steps.

**Enzyme-Catalyzed Reactions.** As outlined in the previous paragraph, most combinations of covalent and noncovalent chemistry have been performed in aqueous environment. The reactions require either highly reactive substrates or an activating agent/catalyst. The catalytic efficacy of enzymes is unmatched by synthetic catalyst. Enzymes perform reactions in water, are highly reactive and chemoselective and thus can be combined with various supramolecular assemblies. Especially the group of Ulijn pioneered the biocatalytic synthesis of peptide gelators. The group showed among others that enzymes are versatile catalysts to form and hydrolyze carboxylic acid esters, amides, and phosphoesters (Scheme 4a–c).

The power of redox active enzymes has been harvested by Besenius and co-workers. They showed that the disassembly of BTA-peptide conjugates can be coupled to enzyme-catalyzed methionine oxidation (Scheme 4d). The group of George on the other hand used enzymes to convert redox active viologen-based amphiphiles (Scheme 4e). Reversible oxidation of the viologen dication to the corresponding radical monocation is coupled to a switch from vesicle to sheet-type structures.

Obviously, these reported examples of enzymatic in situ generation of monomers are comparatively simple transformations and could also be achieved with synthetic catalysts. Yet, these fundamental studies show that complex catalysts such as enzymes can be combined with supramolecular systems. We anticipate that the recent breakthrough in the field of directed evolution will in the future enable more sophisticated reactions on supramolecular building blocks and thereby provide sheer unlimited opportunities to construct complex systems.

**COVALENT POST-MODIFICATION OF SUPRAMOLECULAR ASSEMBLIES**

Stable supramolecular assemblies can be modified by covalent reactions without causing their disassembly. The morphology, the dynamics and the overall properties of the architectures can be transformed by performing a covalent reaction on a selective site of the assembly. This strategy not only results in stabilization, diversification, and functionalization of the initial
structures but also in products that could simply not be formed in a single assembly step. Such postassembly modifications are common mechanisms constantly taking place with natural polymers during their formation, folding, or degradation. For example, collagen assembly of triple helices is stabilized by formation of interstrand disulfide bridges. Inspired by this system, Raines and co-workers studied the optimal disulfide bridges and linkers required to enhance the triple helix stability (Scheme 5a). Such disulfide bridged collagen model peptides with “sticky ends” were shown to assemble into >400 nm long fibrils. Alternatively, the group of Wennemers developed oxime-based covalent cross-linkers of collagen triple helices. The strength of the oxime ligation results in an hyperstability of the triple helices conformation. Such strategies to increase the stability of synthetic biomaterials will play a crucial role in regenerative medicine.

Before the concept of covalent postmodification of supramolecular assemblies emerged, the use of noncovalent assemblies as a template for covalent polymerization was widespread, both in material and life sciences. Polymerization of preassembled monomers is a common tool to form polymeric structures with well-defined architectures (Scheme 5b). Rindersdorff pioneered the work on ordered membranes with the formation of polymerized liposomes. Lipids containing diacetylene polymerizable units are oriented into monolayers and then photopolymerized in situ to yield the stabilized liposomes.

Light is a preferential stimulus to induce this polymerization remotely with spatiotemporal control. Likewise, Broer and co-workers showed that thermotropic liquid crystals functionalized with acrylate units can be cross-linked in their liquid crystalline phase and give oriented glassy liquid crystal networks with useful optical and mechanical properties.

Following similar principles, the group of Meijer explored the photopolymerization of hydrogen-bonded supramolecular aggregates decorated with sorbyl moieties in solution. The postassembly covalent polymerization not only stabilizes the supramolecular structures but also transfers chiral information from the supramolecular stack to the polymer backbone formed. A similar strategy was also applied with natural building blocks. For example, the group of Ulijn showed that the tyrosine amino-acid present in assembled tripeptides can undergo oxidative polymerization and form tunable polymeric pigments (Scheme 5c). The sequence of the tripeptides encodes the supramolecular order of the assembly and the efficiency of the polymerization process, leading to polymeric peptides of variable colors.

Also on a peptide assembly, the group of Stupp studied the synergistic noncovalent and covalent polymerizations of peptidic building blocks yielding cylindrical fibers, with a morphology not observed when the noncovalent and covalent polymers are formed independently (Scheme 6). These few insights are only a gleam of the multitude studies on postassembly polymerization. They highlight the benefit of this strategy to translate the well-ordered structures of supramolecular assemblies into polymeric materials with interesting properties.

Sophisticated organic syntheses have been applied to rotaxane and catenate assemblies in the field of molecular machines. Cascades of covalent and noncovalent reactions bring these molecular machines into action. Rotaxanes and catenanes are locked supramolecular structures that cannot be disassembled with common stimuli. Therefore, it has been demonstrated that they can withstand very well organic synthesis conditions. A remarkable example was proposed by Leigh and colleagues who reported on artificial small-molecule machine able to synthesize a peptide in a sequence-specific manner. The molecular machine is a rotaxane containing a ring on which the peptide is synthesized and a thread with reactive sites. The ring slides on the thread and reacts with amino-ester building blocks via a sequence of native chemical ligation steps from the strand. The peptide sequence is controlled by stepwise reactions performed between the ring and the thread.

Only robust assemblies (i.e., metal-architectures) have been combined with multistep covalent reactions. A common strategy is to perform “click” reactions on the noncovalent substrate because of the high efficiency and selectivity of these reactions under mild conditions. For example, the group of von Delius employed Sonogashira and copper-catalyzed azide–alkyne “click” reactions to tune the dynamics and degradability of orthoester cryptands. Similar strategies have been applied by the group of Nitschke to decorate metallo-supramolecular cages.

Scheme 5. (a) Covalent Modification of Collagen Model Peptides Leading to Stabilization of the Triple Helical Assembly; (b) Polymerization of Pre-Assembled Lipid Bilayers Functionalized with Diacetylenes; (c) Polymerization of Assembled Tripeptides into Polymeric Pigments

https://dx.doi.org/10.1021/acscentsci.0c00974
ACS Cent. Sci. 2020, 6, 2060–2070
and span the molecular complexity achievable with these structures.22 Recently, they demonstrated that postassembly modification of a tetrazine-edged coordination cage can lead to multiple structural transformations of the structure (Scheme 7).21 An inverse electron-demand Diels–Alder reaction between cyclooctyne and the tetrazine ligands forming the edges of the cage led to the formation of three different cyclooctylpyridazine-edged architectures. Those three architectures were interconverted by combining the covalent post-assembly modification with subcomponent exchange and anion template in a sequence-dependent manner. This example shows how covalent reactions can introduce controlled instability in supramolecular structures. It requires a fine balance of reactivities to perform the covalent transformation without disassembling the supramolecular structure. Similarly, post-assembly modification reactions have been used to control host–guest interactions in triphenyl phosphine-paneled coordination complexes.102 Their studies also highlight that side products formed during postmodification reactions can lead to cage decomposition, forcing them to carefully optimize the system.

Because of the high stability of cage assemblies, not only the cage scaffold but also host molecules trapped inside the cage can be covalently modified. Recently, this has been showcased, for example, in the selective modification of fullerenes. Depending on the shape of the cage, different sites of the fullerene can be accessed from the exterior allowing for regioselective cyclopropanation or 1,3-dipolar cycloadditions.103–105 MOFs exhibit a remarkable chemical robustness, which makes them targets for covalent postassembly modification.23,106 The group of Yaghi presented the covalent incorporation of tripeptides within the pores of multivariate MOF by seven postsynthetic reactions performed in tandem.107 They showed that the MOFs keep their porosity properties after postassembly modification, while developing catalytic activity. Their study also confirmed the importance of having highly reactive functionalities (i.e., primary amines) to perform high-yielding postsynthetic reactions.

■ CONCLUSIONS AND FUTURE DIRECTIONS

Recent work in supramolecular chemistry stimulated the idea that complex molecular systems are obtained in a stepwise process of covalent and noncovalent reactions. While such a synthesis has so far not been achieved, progress toward this goal is ongoing. We classified the existing strategies in two categories: (1) covalent in situ generation of supramolecular building blocks guiding assembly/disassembly, and (2) covalent postassembly modifications on robust supramolecular structures. These examples demonstrate how covalent reactions performed on assemblies can induce stabilization and functionalization of ordered structures. But beyond functionalization, covalent reactions in combination with supramolecular structures can also be used as competitive forces to drive adaptation in the constitution and the dynamics of an entire system, something very common in biology. Hence, integrating covalent reactions with noncovalent structures leads to superior systems with emerging properties, such as oscillations47 and chemically fueled molecular motion.100 The covalent reactions act as a trigger to store and release metabolic energy and therefore to develop dynamic structures reminiscent of living systems.

Yet, integrating these individual subsystems into a specific target remains a challenge. An example of such a target is an artificial cellular matrix as a multicomponent supramolecular system for the growth of stem cells to organoids.108 This requires performing controlled chemistry in an adaptive material which communicates with living system. Another example of such a target could be molecular systems for artificial photosynthesis. Such a machinery is composed of supramolecular antenna complexes that capture sunlight and transfer the energy to reaction centers.109 The reaction centers can then serve as
catalysts, which use the energy gained to catalyze covalent reactions. In order to synthesize such advanced targets, future directions will focus on applying sophisticated reactions to supramolecular systems to achieve emerging complexity. So far, the majority of reactions utilized in combination with supramolecular assemblies are redox, condensation and addition reactions—chemistry developed more than a century ago. Stereoselective synthesis or domino reactions are still elusive. More recently developed strategies, such as electro- and photochemical or organocatalyzed reactions, have also not been taken into account. This vast number of chemical reactions opens sheer endless opportunities to synthesize systems with emerging complexity. Yet, the high dynamics of supramolecular assemblies dictates the reaction conditions (solvent, pH, concentration, temperature) at which covalent reactions can be applied. It is therefore essential to develop supramolecular structures that assemble in a broad range of solvents, temperatures, and concentrations, enabling conditions typical for covalent reactions. Moreover, cooperative interactions in assemblies often translate small changes into big consequences with sharp phase transitions. Coupled to covalent reactions, these characteristics are also opportunities to explore new insights on chemical reactivity.

Once chemoselective reactions for functionalization of assemblies are identified, a stepwise increase of structural and functional complexity can be achieved. Fundamental structural and kinetic-mechanistic studies on assemblies are inevitable to understand if a reaction occurs on a monomeric or assembled building block—an aspect of pathway selection that ultimately guides the architecture of the assembly. The measurements are complemented with mathematical modeling and theoretical analyses. Key to perform such fundamental studies is the physicochemical characterization of the reaction product and its dynamics. Depending on the reaction conditions, standard techniques for characterization of organic molecules such as nuclear magnetic resonance (NMR) or infrared spectroscopy (IR) or mass spectrometry (MS) might not be applicable. This is based on the detection limits of the methods (e.g., NMR) and samples detection leading to disassembly (MS). We therefore envision that techniques developed to analyze biological systems such as cryo-electron microscopy, super resolution microscopy, or native MS are promising candidates to characterize supramolecular systems.

Finally, purification steps are required to separate the desired reaction product from remaining starting materials, site-products or catalysts. The purification methods for covalent synthesis (e.g., chromatography and precipitation) often decompose the structures obtained. Further development will require noninvasive and carefully tuned separation steps such as, for example, dialysis, extraction, and solid-supported scavenger.

What can supramolecular chemists and synthetic organic chemists learn from each other? Supramolecular chemists would benefit from applying the methodology of organic synthesis: the ability to combine chemical reactivity, fundamental structural, and mechanistic insights with advanced characterization and purification methods in a stepwise approach, following strict protocols with report on purity and yield. Organic chemists could deepen their knowledge on the reactivity of the noncovalent bond and be challenged by supramolecular building blocks as substrates. This roadmap might lead to build up systems with emerging complexity in a multistep approach. Yet, to design multistep noncovalent synthesis, a collaborative effort of synthetic and supramolecular chemists is needed. Hence, in this path of exciting challenges, why not design a supramolecular building block inspired by a motif recently obtained with a new synthetic procedure? Or challenge a newly developed reaction on a supramolecular substrate instead of the total synthesis of a natural product? We believe that the construction of complex molecular systems is not only a vision for supramolecular chemists but also a chance for fruitful collaborations at the interface of supramolecular and synthetic chemistry.
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