

Covalent Organic Frameworks: Organic Chemistry Extended into Two and Three Dimensions

Steven J. Lyle,^{1,2,3,4} Peter J. Waller,^{1,2,3,4} and Omar M. Yaghi^{1,2,3,4,5,*}

Covalent organic frameworks are constructed by covalently linking organic molecules into crystalline 2D and 3D networks. Their architectural and chemical stability, coupled with their porosity, has allowed them to be used as starting materials and products of molecular organic reactions. Increasingly sophisticated structural and chemical design strategies have enabled the synthesis of complex 3D, 2D, and 1D (weaving) structures from geometrically predefined building blocks. Like small molecules, these materials allow for precise spatial organization of chemical functionalities but do so at length scales ranging from a few angstroms to several microns.

Extending Organic Chemistry into Two and Three Dimensions

Covalent organic frameworks (COFs) are porous, crystalline, extended solids that are constructed from molecular organic building units composed of light elements and joined by covalent bonds. Their development has been enabled by their attainment as crystalline solids with permanent porosity – features that allow organic reactions to be carried out on these frameworks without loss of these properties. In other words, the precision known in organic chemistry applied to discrete molecules can now be implemented in 2D and 3D by virtue of these unique features of COF chemistry: (i) the designed synthesis of these frameworks is achieved by the use of geometrically well-defined molecules that retain their shape during COF formation and an understanding of how these molecules are covalently linked and crystallized; (ii) effective crystallization is realized by the choice of linkage and balance of thermodynamic and kinetic control of COF formation through careful consideration of reaction conditions; and (iii) COF crystallinity and porosity facilitate chemical transformation of the frameworks and characterization of the reactants and products of these reactions.

While these concepts serve as the foundation of COF chemistry, and previous reviews have addressed them, recent developments have further extended this new regime of solid-state organic synthesis [1–4]. In this review, we focus on these new developments, highlighting the increasing complexity of novel 2D and 3D COFs, as well as the emergence of molecular weaving as a method of creating ordered networks from the mechanical interlacing of covalently linked 1D threads [5–8]. We demonstrate that COF synthesis no longer relies exclusively on functionally reversible linkages, and how synthetic strategies for COFs that are formed from readily reversible linkages have been refined to produce materials of increasing **crystallinity** (see [Glossary](#)) and **domain size**, for the first time opening up COFs to structural solution by **single-crystal X-ray diffraction** (SXRD) [9]. Furthermore, we show that the chemical transformations of COFs, until recently limited to a handful of pore-modification reactions, now also include direct chemical modification of linkages, resulting in materials inaccessible by *de novo*

Highlights

Covalent organic framework (COF) synthesis has achieved a new level of design through topological, geometric, and chemical control.

2D and 3D COF crystallinity no longer relies entirely on reversible linkage dynamics due to extensive development in the control of stacking interactions, highly directional bonding motifs, *in situ* tautomerization and cyclization strategies, and postsynthetic linkage modifications.

The precision of molecular organic chemistry and the power of single-crystal X-ray diffraction of molecules are extended to 2D and 3D COFs, thereby expanding the scope of organic chemistry and its advantages beyond discrete molecules.

The fact that COFs can be made as architecturally and chemically stable structures allows for chemical reactions to be carried out within their pores, creating structures that are molecularly precise in their functionality and metrics.

¹Department of Chemistry, University of California-Berkeley, Berkeley, CA 94720, USA

²Kavli Energy NanoSciences Institute at Berkeley, Berkeley, CA 94720, USA

³Berkeley Global Science Institute, Berkeley, CA 94720, USA

⁴Materials Sciences Division, Lawrence Berkeley National Laboratory, Berkeley, CA 94720, USA

⁵King Abdulaziz City for Science and Technology, Riyadh 11442, Saudi Arabia

*Correspondence: yaghi@berkeley.edu (O.M. Yaghi).

synthesis [10–15]. These developments extend the chemical and structural control well established in molecular synthesis to ordered 2D and 3D solids, which we view as an integral part of organic chemistry.

From Molecular Geometry to COFs and Molecular Weaving

One of the useful aspects of COF chemistry is the ability to predict a structure based on its building units, or linkers. This structural predictability relies fundamentally on the fact that for a given set of linkers, there is often a single or small number of crystalline structures that are likely to emerge from their linkage. Because many chemically distinct COFs can possess the same structure type, for example, eclipsed hexagonal layers [16], topology has been used as a language to describe COFs based on their connectivity. This topology is described by a set of **vertices** and the **edges** that link them, creating a robust model of an extended structure independent of chemical identity, geometry, or metrics, so long as the underlying connectivity of the structure being described remains constant (Box 1) [17]. These topologies are denoted by a three-letter lowercase bolded symbol, which sometimes corresponds to a prototypical solid-state structure with this topology, while in other cases the designation is arbitrary.

Combinations of linear, trigonal, tetrahedral, square, hexagonal, and other more complex linkers have led to an exceptional diversity of COF structures, even when not considering the linkages and linkers used to construct them. In 2D, **hcb** (honeycomb) [16], **sql** (square lattice) [18], **kgm** (kagome) [19], **hxl** (hexagonal) [20], **fxt** [21], **kgd** (kagome-dual) [22], and **bex** [23] topologies have been accessed. In 3D, structures with **dia** (diamond) [24], **ctn** (cubic-C₃N₄) [25], **bor** (boracite) [25], **pts** (platinum sulfide) [26,27], **lon** (lonsdaleite) [9], **srs** (strontium silicide) [28], **rra** [29], and **ffc** [30] topologies have been synthesized [31]. For the majority of combinations of linkers, there are often numerous topologies possible from their combination. At first glance, it would appear difficult to predict the topology formed by a given set of linkers; however, in practice two heuristics have emerged that reliably reduce the number of likely possibilities. First, topologies in their highest symmetry containing only one kind of edge are preferred over those with multiple edges. Second, layered structures with 2D connectivity are preferred when possible. While still useful, recent discoveries have demonstrated the shortcomings of such heuristics. Recently, a **lon** topology COF was synthesized from two tetrahedral building units, a combination that could also have formed a **dia** topology [9]. This is despite the fact that the **lon** topology possesses two types of edge, and **dia** only one. Similarly, an **ffc** topology COF was synthesized from trigonal and square planar linkers, despite twisted boracite (**tbo**) or platinum oxide (**pto**) topologies being expected [30]. New methods of structural prediction will become necessary as more complex COF structures continue to be synthesized [17,31].

All COFs are 3D materials, but their covalent connectivity can be 3D, 2D, or even 1D (Figure 1). In COFs whose connectivity extends in 3D, the crystallinity of the system is almost exclusively a result of the order imposed by the linkage. In layered materials where covalent connectivity extends only in 2D, however, noncovalent interactions play a key role. Because no covalent bonds restrict the position of layers with respect to each other, these systems often exhibit stacking disorder. This disorder is minimized through noncovalent interactions, such as π -stacking or dipole interactions between linkers in adjacent layers. COFs can even be formed from the ordered weaving of 1D threads into an extended 3D network. Much like macroscopic weaving, these threads are held together through their entanglement while still possessing numerous degrees of freedom. Such structures are formed using linkers that contain temporary connections (templates) for the locations in the final extended solid where the 1D threads will cross. The templates can later be removed, after which these crossing points are mechanically,

Glossary

Condensation reaction: a chemical coupling involving the generation of water as a byproduct.

Crystallinity: the regular ordering of atoms in a solid with translational symmetry.

Domain size: the length scale on which a material exhibits translational symmetry.

Dynamic error correction: a process by which linkages that do not contribute to the thermodynamically preferred crystalline phase of a COF are either exchanged or broken and remade to obtain the appropriate connectivity.

Edge: a unit of a COF that links two vertices.

Electron diffraction: an analytical technique conceptually similar to SXRD, but using an electron beam and capable of analysis of submicron crystallites too small for analysis with SXRD.

Reticulate: to link geometrically well-defined building units into an ordered 2D or 3D network.

Single-crystal X-ray diffraction: an analytical technique that uses the diffraction of incident X-rays to determine the structure of a crystal with atomic precision.

Solvothermal reaction: a reaction taking place in a closed system, in which the solvents are heated above their atmospheric pressure boiling points. This is often useful in COF synthesis, as byproducts of condensation reactions are kept in the system, maintaining the reversibility of the linkage.

Tautomerization: a chemical reaction interconverting two constitutional isomers.

Vertex: a unit of a COF that contains at least three points of extension. This is usually an individual linker, but can also be a linkage moiety for linkages that involve cyclotrimerization.

Box 1. Isoreticular Expansion and Desymmetrization

In addition to expressing control over the topology of a COF, there are two additional avenues of synthetic structural control that exist independent of chemical identity. The first of these is the concept of isoreticular expansion and contraction. If the linkers used to make a COF are increased or decreased in size without altering their mode of connectivity, they can reliably be used to synthesize a COF of identical geometry and topology, but with different metrics (Figure I). The major exception to this heuristic is in the case of topologies that can interpenetrate. Interpenetration is observed for topologies in which the unoccupied space possesses the same structure as the occupied space, allowing one or more copies of a structure to regularly interleave. For these topologies, of which **dia** is a common example, increasing linker size leads to higher degrees of interpenetration [9,24,49,78]. It is also possible for the unoccupied space of a topology to be a different structure, in which case two different topology structures could interpenetrate. Nonetheless, a COF based on this principle has yet to be synthesized.

Another avenue of structural control is in the idea of structure desymmetrization. Because topology is only a description of connectivity, edge lengths and the angles between them can be altered from their highest possible symmetry without the topology changing (Figure I). For example, the symmetry of a COF can be reduced by increasing or decreasing the lengths of some, but not all of the linkers. This strategy was used in a series of **hcb** and **sql** topology boronate ester-linked COFs in which either hexahydroxytriphenylene or octahydroxyphthalocyanine was condensed with combinations of two or three linear diboronic acids of differing length. Using 10 different linear linkers, this strategy yielded a library of 220 **hcb** and 55 **sql** topology COFs, of which 53 were chosen at random and synthesized [79]. Desymmetrization by changing extension lengths within an individual linker rather than using multiple linkers has also been employed, allowing for the synthesis of structures with multiple pore sizes [80,81]. Structures can also be desymmetrized by changing angles between points of extension without altering connectivity [82].

The combined tools of isoreticular expansion and desymmetrization allow for readily accessible structural diversity and control over pore shape and size. This can be seen as an additional aspect of structural control upon which synthetic organic chemistry is layered.

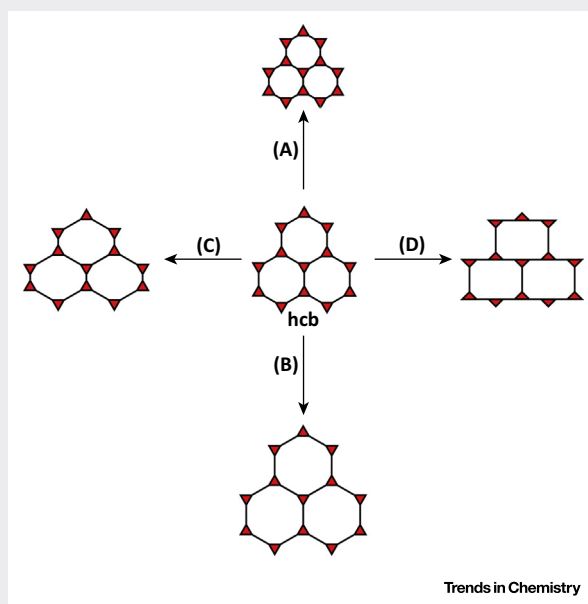


Figure I Honeycomb (**hcb**) Topology under Various Modifications. (A) Isoreticular contraction. (B) Isoreticular expansion. (C) Desymmetrization by changing edge lengths. (D) Desymmetrization by changing vertex angles.

rather than chemically, bound. This was first achieved in COF-505, in which aldehyde-functionalized copper(I)-bisphenanthroline templates were linked through imine **condensation** with benzidine into a crystalline 3D solid. The Cu(I) ions were subsequently removed by treatment with potassium cyanide, increasing the elasticity of the resulting mechanically

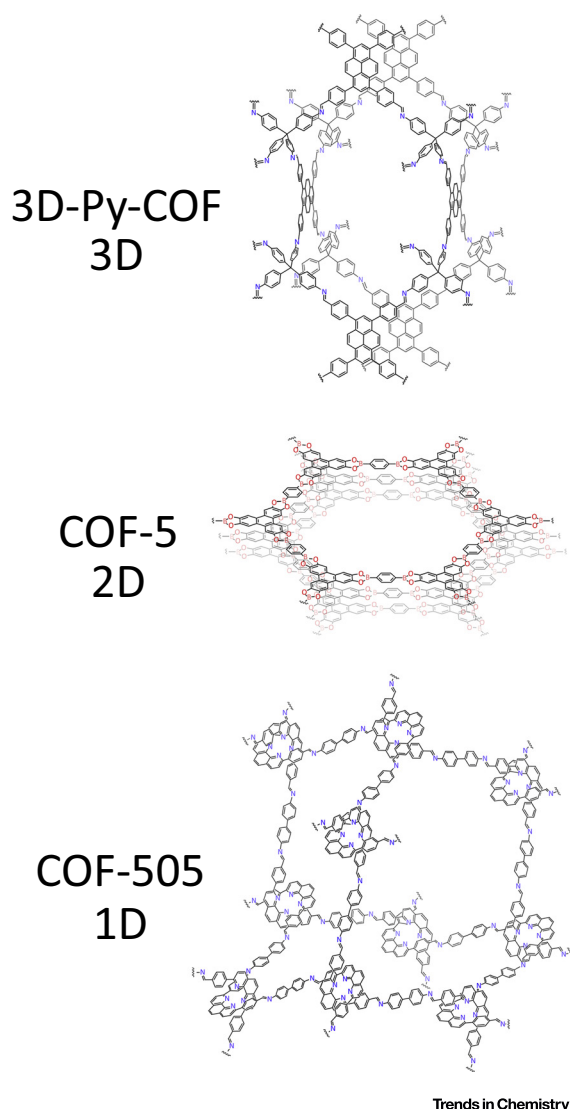


Figure 1. Examples of COFs Built from Covalently Linked 3D, 2D, and 1D (Weaving) Objects. From top to bottom, 3D-Py-COF, COF-5, and COF-505 [5,16,26]. Interpenetration in 3D-Py-COF and COF-505 has been omitted for clarity. Abbreviation: COF, covalent organic framework.

entangled structure tenfold [5]. Recently, a similar copper(I)-bisphenanthroline template was used to synthesize a weaving COF built from the interlocking of 1D square ribbons [7]. Templates necessary for the formation of weaving structures can also be formed *in situ*, as exemplified by COF-112 [6]. In this material, 2,6-pyridinedicarboxaldehyde and singly boc-protected *p*-phenylenediamine were condensed in the presence of Co(II) and trifluoroacetic acid to form a weaving structure. The robust flexibility possessed by weaving COFs allows for frameworks to change their local conformation to accommodate guests that are larger than the natural pores of the material. This adaptive inclusion occurs without changing the connectivity of the parent framework, something not possible in more conformationally inflexible porous materials [8].

The Formation Chemistry of COFs and the Importance of Linkages

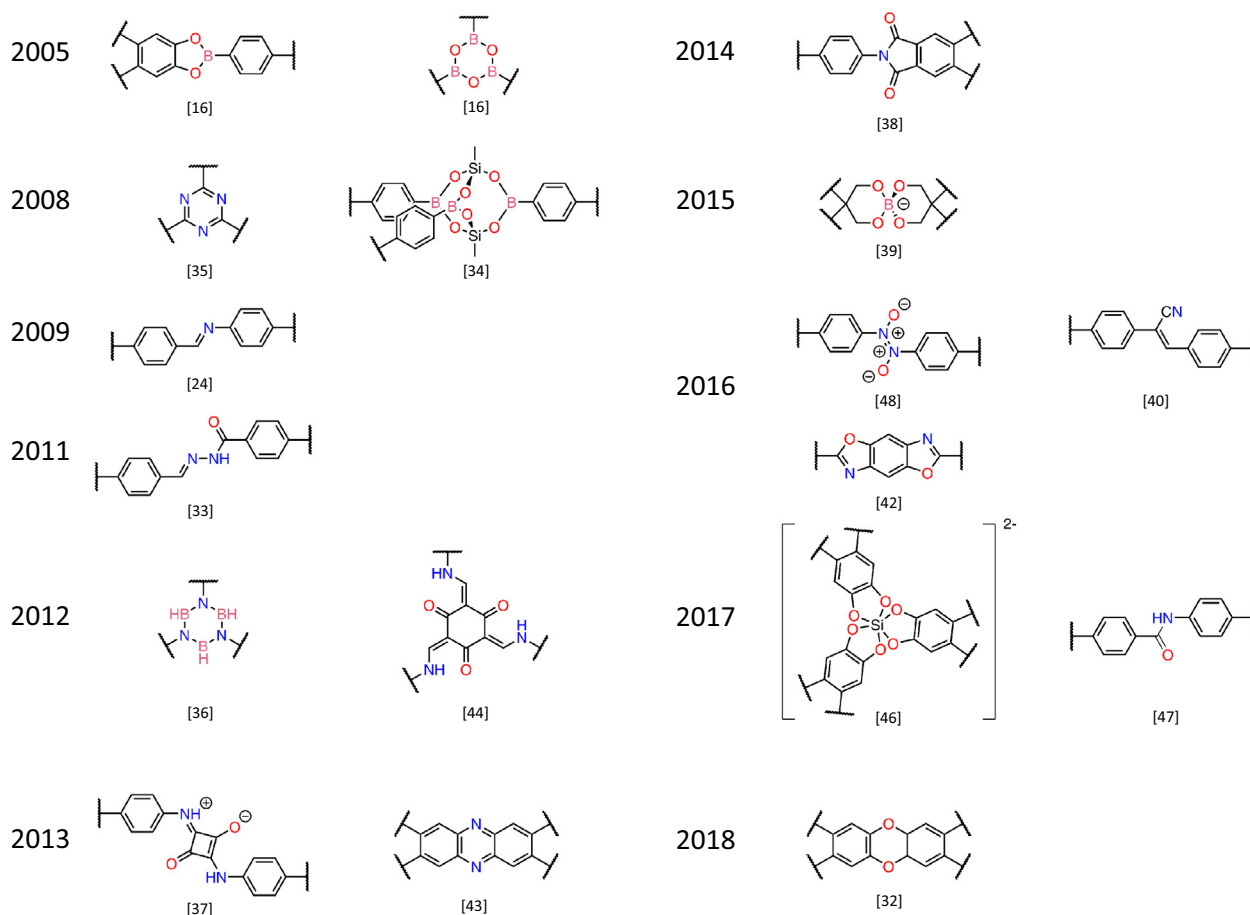
The use of directional and reversible bonding to construct well-ordered macromolecules has been the hallmark of dynamic covalent chemistry, and it was upon this backdrop that the first COFs were synthesized. Boronate ester and imine condensation were among the first reactions to be used in the synthesis of COFs, both of which possessed sufficient dynamic reversibility to form well-ordered crystalline networks under appropriate solvothermal conditions [16,24]. The difficulty in identifying reaction conditions under which a set of linkers will **reticulate** into an ordered network is referred to as the 'crystallization problem'. The synthetic difficulty in achieving new linkages initially led to a reliance on highly reversible condensation reactions such as boroxine anhydride and boronate ester formation in which there was a trade-off between the degree of crystallinity and the chemical stability of the resultant material under hydrolytic conditions, thus limiting their material applications [16]. Since then, numerous new linkage chemistries have been developed and the stability–crystallinity trade-off in COFs synthesized *de novo* upended (Figure 2) [16,32–48]. Even more recently, developments in COF synthesis have enabled the formation of morphologically well-defined COF single crystals of tens of microns in size, amenable to analysis of their structures by SXRD [9]. It has previously been possible to make 1–2- μm -sized COF crystals which were characterized by **electron diffraction** [5–7,49].

It has been our observation in COF chemistry that the more readily reversible a linkage chemistry, the more crystalline the structures formed from it will be. These more reversible chemistries provide additional **dynamic error correction**, making the thermodynamic minimum of that system more accessible. Viewed alone, this establishes an inverse relationship between ease of crystallization and the chemical stability of the resultant material. However, recent developments such as the tuning of noncovalent stacking interactions in 2D COFs (Box 2), the combination of highly reversible condensation reactions with *in situ* **tautomerization** or cyclization, and highly directional linkage motifs have all led to general improvements in COF chemical stability without sacrificing crystallinity.

The first of these strategies, exemplified through triazine-linked COFs, is that of using harsh, high-temperature crystallization conditions. The first triazine-linked COF was synthesized through the nitrile cyclotrimerization of 1,4-dicyanobenzene at 400 °C in molten ZnCl_2 [35]. These conditions allowed for sufficient reversibility of the triazine linkage but precluded the incorporation of any additional functional groups on the linkers that would possess reactivity under those conditions.

Another strategy used to address this crystallinity–reversibility trade-off is to combine a linkage reversible under mild conditions with a second, functionally irreversible tautomerization or cyclization *in situ*. This allows access to both dynamic error correction through linkage reversibility and a stable final product without reaction conditions that would preclude the incorporation of additional functional groups onto the material. COFs formed through imine condensation followed by tautomerization to β -ketoenamines possess substantially higher hydrolytic stability in aqueous acid and base relative to imine-linked COFs [44,50,51]. This strategy was also employed to synthesize benzoxazole-linked COFs through sequential imine condensation and oxidative cyclization [42,52].

In cases where both the linkers and target linkage are conformationally inflexible, it is possible to synthesize COFs from linkages that are functionally irreversible. This has been demonstrated in the synthesis of phenazine- and dioxin-linked COFs [32,43]. For these systems, it is thought that the limited degrees of freedom of linkers and intermediate oligomers and strong stacking interactions reduce the type and number of defects to an extent that crystalline material can be obtained despite minimal dynamic reversibility.



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Figure 2. Linkages Used to Crystallize COFs *de novo* to Date, Organized by the Year in Which They Were First Demonstrated. See also [16,24,32–40,42–44,46–48]. Abbreviation: COF, covalent organic framework.

One severe limitation of COFs relative to many other solid-state materials is that they are nearly always obtained as aggregated polycrystalline powders with small domain sizes. This creates limitations in both optoelectronic and electrocatalytic applications, where charge mobility depends on well-ordered domains and controllable morphology, and precludes characterization techniques such as SXR [40,53,54]. Two strategies have been developed recently to address this, each related to modifying the crystallization mechanisms observed for imine- and boronate ester-linked COFs under **solvothermal** conditions.

In imine-linked frameworks, COF formation proceeds first through the precipitation of an amorphous polyimine that then transforms into a crystalline network through acid-catalyzed exchange reactions at elevated temperatures [55]. This initial precipitation prevents the formation of defect-free crystallites of sufficient size for analysis by SXR. To address this, a series of COF reactions were performed at room temperature with the addition of a large excess of aniline. In these reactions, aniline acted as a modulator, preventing rapid polyimine precipitation and forcing framework assembly to occur over the course of a month through exchange

Box 2. Design of Stacking Interactions in 2D COFs

Unlike 3D COFs, 2D COFs possess a crystallographic direction along which the structure is ordered only through noncovalent interactions. One early strategy to engineer stacking order within 2D COFs was in the use of linkers with large polycyclic aromatic cores such as porphyrins and phthalocyanines, which have a strong preference to stack in molecular crystals [18,53]. Eclipsed stacking order can be induced through the use of so-called molecular docking sites, in which the out-of-plane conformation of one linker templates the out-of-plane conformation of other linkers within a framework. This was demonstrated for COFs utilizing tetraphenylethylene- and triphenylbenzene-based linkers, which adopt propeller-shaped conformations that force matching conformation of linkers in layers above and below them [83]. These propeller conformations are chiral in the solid state and can be biased through the use of chiral additives. The resulting chiral COFs were shown to provide enantioselectivity in Henry reactions [84]. The design of slipped-stacking and staggered arrangements between layers has also been demonstrated using linkers whose conformations provide directional stacking offsets or the introduction of bulky out-of-plane groups that prevent eclipsed stacking of layers [52,85,86].

Eclipsed stacking order can also be induced through the use of dipole–dipole and arene–perfluoroarene interactions. The former of these was demonstrated in a 2D-COF with a pyrene-4,5-dione-containing linker. An increase in observed surface area for this material relative to a ketone-free analog was attributed to regular alternation of linker dipoles, an arrangement with more favorable stacking energy relative to both parallel dipole stacking and stacking of unfunctionalized pyrene units [87]. The strong stacking interactions of aromatic and perfluorinated aromatic compounds have similarly been utilized to provide more uniform eclipsed stacking arrangements in 2D COFs [88,89].

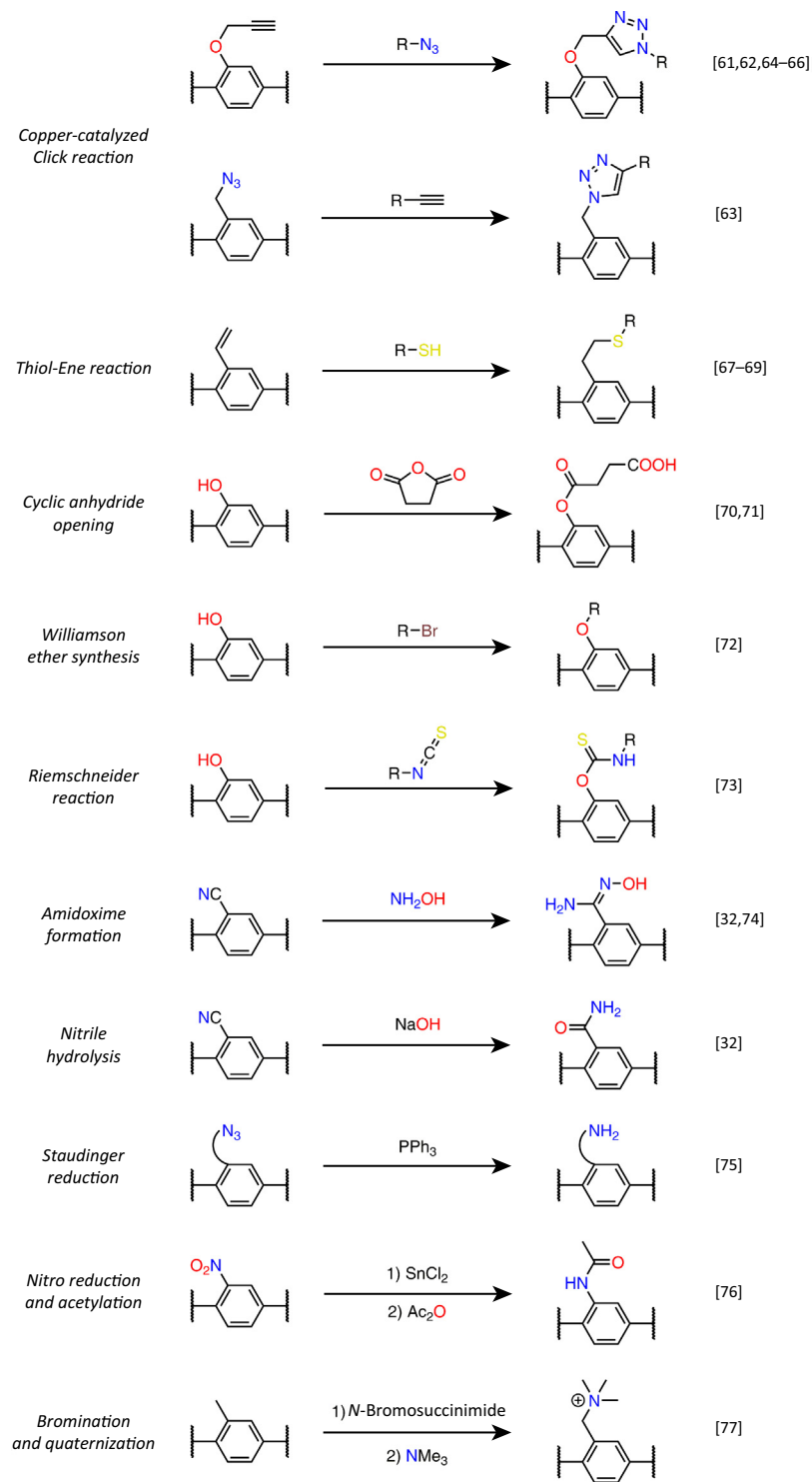
reactions. The highly ordered crystals obtained from this process allowed (for the first time) solution of COF structures by SXRD, with resolution as low as 0.83 Å [9].

2D boronate ester-linked COFs, rather than forming initial precipitates that then crystallize, form nanocrystalline domains in solution that then irreversibly aggregate and precipitate [56]. It was found that by adding acetonitrile to the reaction solution, these nanocrystals could be prevented from aggregating. The colloidal COF nanocrystals were then grown by slow addition of monomers under conditions that inhibit additional nucleation. Using this process, COF crystallites at an initial size of approximately 30 nm in diameter were grown to 1- μm crystallites [57].

COFs as Starting Materials and Products in Organic Synthesis

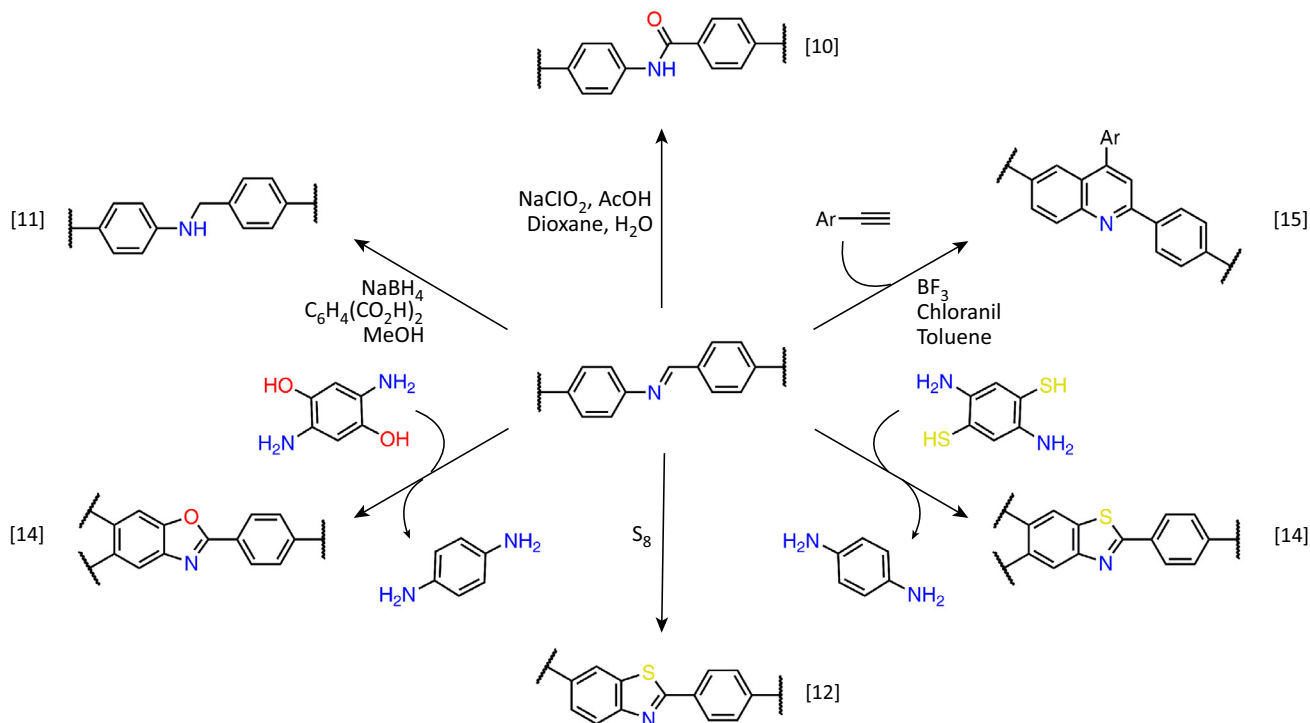
One of the most powerful aspects of COF chemistry is the ability to treat structures as regularly ordered surfaces displaying organic functionalities that can participate in reactivity. This provides extensive flexibility in materials synthesis, because these structures are amenable to further functionalization even after crystallization. This is in contrast to nonporous organic solids, where a lack of accessibility of functional groups and limited or nonexistent mass transport place severe restrictions on the chemical transformations that can be performed. In COFs, pore networks and large internal surfaces make functional groups accessible, enabling quantitative chemical transformations to take place much as they do in solution. It is in this light that COFs serve as ready starting materials for organic synthesis. These transformations include noncovalent inclusion of compounds into COF pores, covalent functionalization of linkers (Figure 3), linkage conversion (Figure 4), and linker exchange.

The regular pore networks found in COFs facilitate noncovalent inclusion of various species into the pores of those materials, providing a large surface area contact between the guest liquid or solid and the host framework. Significant enhancements of hole and electron photoconductivity in COFs have been achieved through the inclusion of fullerenes, iodine, or tetracyanoquinodimethane into the pores of the material [41,43,48,58]. In each of these cases, the parent framework and its guests serve as electron donor–acceptor pairs. Proton conductivity has also been imparted to COFs through the inclusion of imidazole or triazole proton carriers. The ordered pore networks of COFs were found to be essential, with a compositionally identical



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Figure 3. Postsynthetic Linker Modifications Explored to Date. See also [32,61–77].



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Figure 4. Postsynthetic Linkage Modifications Explored to Date. See also [10–12,14,15].

nonporous polyimine shown to possess a roughly thousand-fold lower conductivity [59]. Using COFs as a host for sulfur in lithium-sulfur batteries has been shown to improve performance by trapping intermediate lithium polysulfides that would otherwise shuttle charge between electrodes internally [60].

Effective covalent postsynthetic modification of COFs has three primary criteria. The first of these is that the linkage must be stable under the conditions of the postsynthetic modification so that the structure remains intact. The second is that the target reaction must be high yielding with minimal side reactions, since unlike in solution-state chemistry, it is not possible to separate out multiple products of a postsynthetic modification. The third criterion, still inadequately addressed in the field, is that of effective characterization. True evaluation of postsynthetic modifications' conversion and yield is best achieved with digested solution-state ^1H NMR or solid-state ^{13}C or ^{15}N NMR spectroscopy, preferably with isotopic labeling at relevant positions.

Azides and terminal alkynes can each be readily incorporated into COFs, allowing for functionalization through Cu(I)-catalyzed azide-alkyne cycloadditions. This reaction has been used to incorporate a variety of functional groups into COF pore structures including chiral pyrrolidine moieties used to catalyze asymmetric Michael additions, thiols for use in selective Hg(II) sequestration, TEMPO radicals, and functional groups such as primary amines and carboxylic acids which would be incompatible with the synthesis of the parent COF [61–66].

Numerous other functionalization reactions have been explored in addition to azide-alkyne cycloadditions. Thiol-ene coupling reactions have been used to functionalize COFs containing

terminal olefins [67–69]. This method has been used to drastically increase framework hydrophobicity through the attachment of perfluoroalkyl groups to the pore wall of an imine-linked COF, leading to enhancement of its resistance to aqueous acid and base [68].

Carboxylic acid groups have been introduced to COFs through the reaction of pendant hydroxyl groups with succinic anhydride, resulting in improved CO₂ uptake [70]. In another system, a material functionalized in this manner was used for the selective uptake of lanthanide ions from water [71]. These hydroxyl groups have also been used to attach tetraalkylammonium species to a framework through ether linkages, resulting in a heterogeneous catalyst for the formation of formamides from secondary amines and CO₂ [72]. Fluorescence labels have been attached to COFs through thiocarbamates formed from the reaction of pendant hydroxyl species with thiocyanates [73].

In addition to attachment of desired functionalities through various chemical linkages, COFs can be modified more directly through chemical manipulation of functional groups on their linkers. A COF containing amidoxime groups formed from the postsynthetic reaction of pendant cyano groups with hydroxylamine was found to be effective in the rapid removal of uranium from contaminated water, reducing concentrations from 1 ppm to less than one three-hundredth of the 30 ppb limit set by the United States Environmental Protection Agency (US EPA) for drinking water [74]. Cyano groups have also been hydrolyzed to amides in dioxin-linked COFs, where the linkage tolerates the strongly basic conditions necessary for the transformation [32]. Likewise, aromatic and aliphatic primary amines have been formed in COF pores through the reduction of aryl nitro and azide groups, respectively [75,76]. Benzylic bromination has also been performed postsynthetically, allowing the subsequent introduction of tetraalkylammonium species by nucleophilic substitution [77].

Postsynthetic modification provides a unique opportunity in the screening of COF materials for functional properties such as gas uptake, separations, and catalysis in that the same parent framework can serve as a starting material for a wide array of COFs, each with chemically unique pore environments. In these systems, the crystallization problem needs only to be solved once in order to access a near-infinite variety of functional crystalline, porous materials. This strategy was used to optimize the pore environment of an imine-linked COF for gravimetric CO₂ uptake, allowing for a roughly threefold increase in CO₂ uptake for the best performing system relative to its parent COF [62].

Postsynthetic modification not only provides control over the identity of functional groups attached to COFs, but also their overall density in the framework. Introduction of linkers with and without functionalities necessary for covalent postsynthetic modification allows for synthetic control over the density of those groups in the final product. For systems in which large species are being attached to the framework, limiting the density of attachment sites can prevent pores from becoming inaccessible and restricting those materials' performance in gas sorption, separations, and catalysis applications. In fact, for many postsynthetically modified COFs used in these applications, optimal performance is achieved with mixed functionality, or multivariate systems [62–66].

COFs can be further modified through chemical transformations of their linkages. It has been demonstrated in several cases that linkage modification can take place with preservation of the original material's connective structure and inherent properties of crystallinity and porosity. This provides a means of obtaining COF linkages that would otherwise be difficult or impossible to synthesize *de novo*, because it is not dependent on the reversibility of those linkages. Imines, the most well explored and widely applied of COF linkages, have served as the platform thus far for the exploration of linkage conversion (Figure 4).

In the first report of this strategy, two imine-linked COFs were oxidized quantitatively to amides using a mild Pinnick-type oxidation with sodium chlorite and an acetic acid catalyst. These crystalline, porous, amide-linked materials demonstrated retention of their crystallinity in concentrated aqueous solutions of HCl and NaOH, conditions in which their parent materials did not survive [10]. Linkage transformation has also been demonstrated by reduction of imine-linked COFs to amines with sodium borohydride. The resulting amine-linked COFs were used to enhance both selectivity and Faradaic efficiency for the reduction of CO₂ to CO at a COF-coated silver electrode. The enhancement was attributed in this system to chemisorptive concentration of CO₂ in the amine-linked COF coating [11].

Imine linkages have also been transformed into thiazoles through reaction of the framework with elemental sulfur. The reaction proceeds first through the formation of thioamides, which then cyclize to thiazoles. These materials displayed not only improved chemical resistance, but also enhanced stability under a transmission electron microscopy electron beam, facilitating the direct observation of defect sites and grain boundaries in the material [12].

The reversibility of the imine linkage often limits material stability, but this property can be utilized in postsynthetic modifications. Imine exchange reactions have been used to transform a COF into one of identical topology but reduced pore metrics by replacing benzidine in the structure for shorter but geometrically equivalent *p*-phenylenediamine. This occurred without dissolution of the original material, indicating that the transformation proceeded through exchange rather than recrystallization [21]. Similar reactivity has been used to generate core-shell nanoparticles using an incomplete exchange reaction. Exchange occurred outside-in, with the center of the nanoparticles containing only the original linker [13].

This linker exchange approach has been adapted to access new linkages through postsynthetic modification. *p*-Phenylenediamine linkers in a COF were exchanged with ones bearing pendant hydroxyl or thiol groups, which were then oxidatively cyclized into benzoxazole or benzothiazole linkages, respectively. Unlike the method previously used to synthesize benzoxazole-linked COFs *de novo*, this strategy allowed for a complete decoupling of the initial COF crystallization from the subsequent irreversible cyclization [14].

Imine linkages can also be transformed by aza-Diels–Alder reactions with substituted phenylacetylenes into exceptionally robust aromatic linkages. This reaction not only allowed for the introduction of various functional groups to the structure without the need for prefunctionalization of the linkers, but also afforded materials stable to a wide array of harshly acidic, basic, oxidative, and reductive environments [15].

Concluding Remarks

Organic synthesis is still often thought of primarily as the study and implementation of chemical transformations in the solution state, however, this is no longer the case. Challenges remain (see Outstanding Questions), but COFs represent an extension of synthetic tools thoroughly explored in molecular species to well-ordered covalently linked solid-state materials through a combination of dynamic reversibility, the tailoring of stacking interactions in the solid state, and principles of topological and geometric design. COFs, rather than being the final products of a synthetic pathway, now serve as synthetic intermediates capable of transformation into a near-infinite number of novel and otherwise inaccessible functional materials.

Outstanding Questions

The tendency for COFs to crystallize in high symmetry, single-edge topologies has provided predictive power in COF design, but also restricted the topological diversity of observed COF structures. What predictable methods of breaking from this tendency can be used to open up additional structural control?

What are synthetic methods that can reliably produce single-crystalline COFs in a wide variety of systems? This is essential for continued development in the field, as the majority of COFs thus far produced are insufficiently crystalline and morphologically unsuitable for structural solution by SXRD or electron diffraction techniques.

How can the library of postsynthetic modifications used in COFs be further expanded? Access to a diverse set of chemical tools will allow COF postsynthetic modification to move from a regime of isolated chemical transformations to one of well-understood organic retrosynthesis in the solid state. Unlike in small molecule retrosynthesis performed on zero-dimensional objects in solution, this reticular retrosynthesis will be one performed on three-dimensional solids, and include topological and structural, in addition to chemical design.

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