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Design Strategies for Structurally Controlled Polymer Surfaces via Cyclophane-Based CVD Polymerization and Post-CVD Fabrication

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Molecular structuring of soft matter with precise arrangements over multiple hierarchical levels, especially on polymer surfaces, and enabling their post-synthetic modulation has tremendous potential for application in molecular engineering and interfacial science. Here, recent research and developments in design strategies for structurally controlled polymer surfaces via cyclophane-based chemical vapor deposition (CVD) polymerization with precise control over chemical functionalities and post-CVD fabrication via orthogonal surface functionalization that facilitates the formation of designable biointerfaces are summarized. Particular discussion about innovative approaches for the templated synthesis of shape-controlled CVD polymers, ranging from 1D to 3D architecture, including inside confined nanochannels, nanofibers/nanowires synthesis into an anisotropic media such as liquid crystals, and CVD polymer nanohelices via hierarchical chirality transfer across multiple length scales is provided. Aiming at multifunctional polymer surfaces via CVD copolymerization of multiple precursors, the structural and functional design of the fundamental [2.2]paracyclophane (PCP) precursor molecules, that is, functional CVD monomer chemistry is also described. Technologically advanced and innovative surface deposition techniques toward topological micro- and nanostructuring, including microcontact printing, photopatterning, photomask, and lithographic techniques such as dip-pen nanolithography, showcasing research from the authors' laboratories as well as other's relevant important findings in this evolving field are highlighted that have introduced new programmable CVD polymerization capabilities. Perspectives, current limitations, and future considerations are provided.

1. General Overview of Cyclophane-Based CVD Polymerization

Chemical vapor deposition (CVD) polymerization is a widely used technology that provides a substrate-independent surface functionalization platform where reactive species from chemical precursors are preformed in vapor phase and spontaneously polymerize into conformal homogeneous polymer surfaces.[1] CVD polymerization encompasses a variety of deposition techniques, including plasma-enhanced CVD, photon-initiated CVD, and atomic layer deposition. The CVD polymerization process does not require any solvents or initiators, and additionally, the absence of side products and quantitative conversion makes it a sustainable and popular process for surface functionalization particularly suited for biointerfaces.[2] CVD polymers, because of their high purity, flexibility, mechanical strength, and chemical inertness, offer enormous potential in various research fields ranging from microelectronics to photovoltaics, development of sensors, microelectrochemical materials, drug-delivery systems, and have

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demonstrated technological utility as antimicrobial coatings of industrial products, for example, clinically used biomaterials and biomedical devices.[3] CVD polymerization and its applications have been a subject of extensive research.[4] Current challenges, and opportunities in cyclophane-based CVD techniques used for coating materials and microelectromechanical systems are summarized in several focused reviews.[5] This report highlight recent trends and developments in innovative design strategies, patterning/topographic micro- and nanostructuring techniques, implementation of spatial arrangements, and post-CVD fabrication to create bioinstructive surfaces for widespread application possibilities. A discussion about the molecular structuring of reactive parylenes via structural and functional design of the [2.2]paracyclophane (PCP) monomers is provided. The recent findings and some landmark results discussed herein for templated-CVD polymerization (ranging from 1D to 3D nanoarchitecture), including CVD inside confined nanochannels, nanofibers/nanowires synthesis that are chiral or achiral in nature, and surfaces decorated with enantiomorphically pure polymer nanohelices via hierarchical chirality transfer across multiple length scales, would be particularly appealing for researchers aiming to work at the interface of synthetic chemistry, material science, polymers, and biointerfaces. This outlook would trigger collaborations and inspire interdisciplinary research exploring advanced materials.

1.1. Fundamentals of Poly(*para*-xylylene)s Formation via Cyclophane-Based CVD Polymerization

Poly(*p*-xylylene) (PPX) films and their functionalized forms, generally referred to with their trade name "Parylenes," are prepared via a range of polymerization modes, including a reaction pathway using PCP as precursor molecule (Gorham process) that William Gorham first described at Union Carbide in 1966.[6] The cyclophane-based CVD polymerization process can be categorized into three stages: 1) thermal treatment and sublimation of the PCP precursor at 150–200 °C under vacuum (0.2–0.3 Torr), 2) pyrolysis at 550–650 °C where the PCP precursor is cracked in the vapor phase in a custom-built CVD device setup generating two 1,4-quinodimethane radicals (*p*-xylylene) while preserving the functional groups and last, 3) transport of the preformed radicals using an inert gas like argon onto a deposition chamber at lower temperatures (between −40 and 40 °C) where the substrate is placed there by forming parylene polymers or copolymers (**Figure 1**). In general, the substrate independence of the CVD process allows for generic surface engineering protocols. The reactants diffuse through the gas phase and deposit on the surface. They are then adsorbed onto the substrate, with volatile species being desorbed again, and last undergo a chemical reaction. The versatility of the CVD method makes it possible to achieve functional parylene coatings with variable thickness, spatial and temporal compositions, and multilayer formats. This method allows sequential deposition of different precursor components, random copolymers, gradients, microstructuring, and post-CVD surface engineering via orthogonal transformation without altering the polymer skeletal composition.[7]

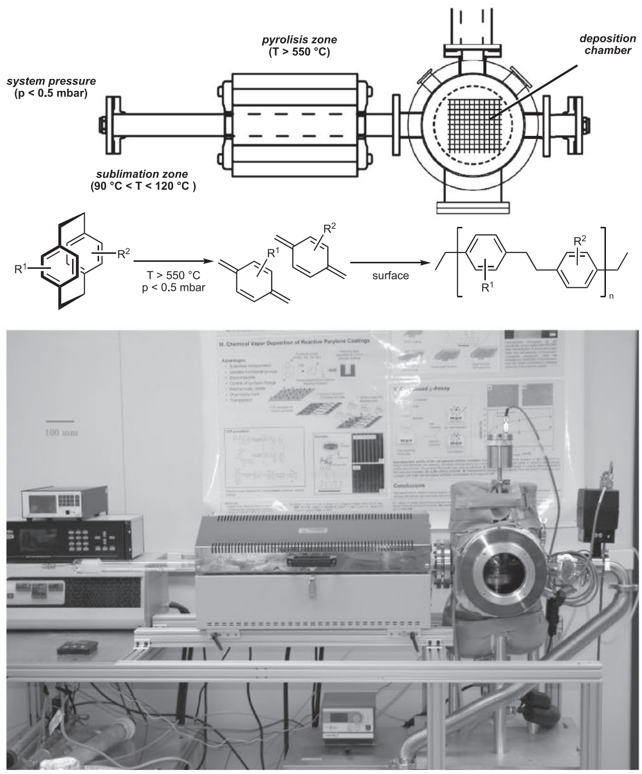


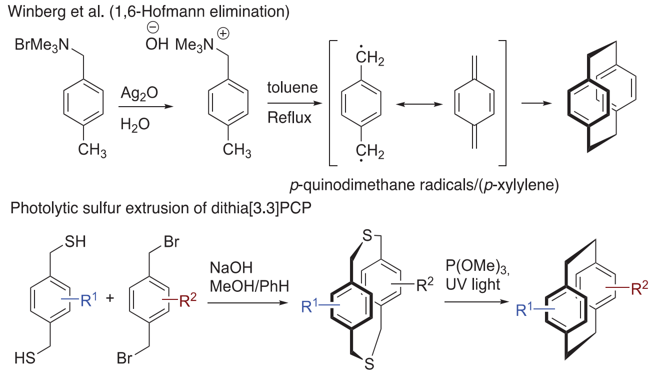
Figure 1. Concept of the Gorham process for PCP-based CVD polymerization into poly(*p*-xylylene)s thin film coating (top) and a digital image of a custom-built CVD device setup (bottom). Figure: Reproduced with permission.[12] Copyright 2011, American Chemical Society.

CVD polymerization of the functionalized PCPs combines several physicochemical steps during deposition at the surface. The experimental device setup for CVD polymerization is designed to control several parameters, for instance, pyrolysis temperature, pressure, rate of carrier gas flux, and substrate temperature.[8] Considering that each step can be controlled, optimizing every CVD process is essential to determine the rate-limiting step. In the pyrolysis zone, the PCP is homolytically cleaved into two *p*-quinodimethane radicals (*p*-xylylene), which can exist in singlet or triplet states. Due to the low energy difference between these two states (8–9 kcal mol^{-1}),[9] it is extremely reactive and condenses at lower temperatures form CVD polymer. During this vaporization process, temperature control is important when optimizing the CVD process for different substituted precursors. The presence of bulky substituents on PCP or those with temperature-sensitive functionalities can interfere with the formation of *p*-quinodimethanes. The reaction kinetics and equilibria are dependent on the partial pressures of the reactants in either phase or the temperature of the gas phase or the surface. If the formation of solid polymer films is desired, it is vital to enhance the surface reaction while simultaneously inhibiting gas-phase reactions lead to powdery deposits on the surface. In the deposition chamber, factors such as deposition temperature, monomer ratio, and deposition rate play an important role in determining the properties of the polymer deposited. The deposition temperature and rate directly influence the polymer formation, which affects properties such as barrier behavior, impacting its use in diverse applications. Lower deposition temperature correlates to a higher growth rate and a higher-molecular-weight polymer deposited, showing superior thermal stability. Although certain trends can be established, exact models for the deposition mechanism of functionalized parylenes are still the subject of ongoing studies. A study of *p*-xylylenes polymerization kinetics employing multiple heating rate differential scanning calorimeter measurements revealed the heat effect and the temperature range of polymerization on the surface morphology.[10] The PPX polymerized at a high heating rate have a granular morphology with high surface roughness, whereas PPX polymerized at a low heating rate have a smoother surface. A broad description of the growth, methods, and existing characterization techniques can be found in earlier reports.[11,12]

1.2. Structural and Functional Design of the [2.2]Paracyclophane Precursors for CVD (Co)Polymerization: Access to Reactive Parylene (Co)Polymers

To achieve materials modulation at a molecular level with precise control over properties and functions, the synthetic design of their customized building blocks is of utmost relevance that bring desired functions once incorporated into materials.[13] In a similar way, for structuring parylenes (skeleton composition) at the molecular level, and enabling post-CVD-surface engineering, the synthetic design of the PCP precursor components is vital to determine its application sphere. PCP was first discovered by Brown and Farthing in 1949 by the gas-phase pyrolysis of *para*-xylylene under low pressure,[14] is a prevalent cofacially stacked scaffold of intriguing structural and electronic properties,[15] which is widely investigated as planar chiral ligands in metal complexes,[16] catalysts in asymmetric synthesis,[17] as well as in chiroptical and optoelectronic materials.[18] PCP derivatives have been introduced in polymer chemistry for preparing π-stacked conjugated polymers via transition-metal-catalyzed coupling, electrochemical, and various polycondensation approaches.[19] Material applications of PCP-derived systems dealing with their stereochemical features (planar chirality) and transannular through-space conjugation have been the subject of excellent reviews.[20] However, in contrast, the planar chirality and cofacially stacked structure of the PCP are lost during the CVD process. At high-temperature PCP core is cracked homolytically at the ethylene bridges.

PCP and certain derivatives can be prepared based on the 1,6-Hofmann elimination of ammonium bromide as described by Winberg in 1960.[21] By the addition of silver(I) oxide to the ammonium salt, the corresponding ammonium hydroxide intermediate is generated in situ. Upon heating, *p*-xylylene is formed that dimerizes into PCP. This route is quite low-yielding (17%). One of the known synthesis methods of the functionalized PCP is using dithia[3.3]paracyclophane derivatives (annulated from 1,4-bis(mercaptomethyl)benzene and 2,5-dibromo-*p*-xylene analogs), which on photolytic sulfur-extrusion affords the corresponding PCP derivatives (**Scheme 1**).[21b]



Scheme 1. Synthesis of PCP via 1,6-Hofmann elimination and general access to unsymmetrically substituted PCPs via photolytic sulfur extrusion.

Using carefully chosen reaction parameters and transformation steps, the PCP core allows different functional groups to be selectively positioned at either only one or both benzene rings or the bridge positions.[22] PCP with various functional groups can be synthesized by electrophilic aromatic substitution, and then quenching the lithio-derivative with electrophiles can incorporate desired functional moieties. A wide variety of chemical functionalities, for instance, alkyne, thiol, hydroxyl, carbonyl, fluorinated groups, amino, ester, and anhydride components that are compatible under the CVD polymerization conditions can be grafted to the PCP scaffold, which after the CVD polymerization can serve as anchoring sites in post-CVD fabrication strategies for tailoring of the polymer surfaces with multiple functions (**Figure 2**).[23–25]

Regioselective functionalization of PCP and resolution strategies pose certain synthetic challenges and can be a tedious endeavor due to the unusual reactivity, especially when larger quantities of enantiomerically pure PCPs are needed which is often viewed as limiting steps in expanding this class of monomers. Although this report is not intended to be an exhaustive display of comprehensive synthesis strategies and to concisely cover every PCP ever synthesized. Some representative modular PCPs optimized for CVD polymerization and post-CVD surface modifications are summarized in **Figure 3** which shall be a valuable resource for a CVD technologist who wishes to increase know-how of the precursor cyclophane chemistry or chemists who wish to explore the chemical space and learn more about CVD process technology.

Commercial parylenes include parylene-N; the most common form is prepared from nonfunctionalized PCP, parylene-C (prepared from mono-chloro-PCP), and parylene-D (prepared from di-chloro-PCP).[26] Parylene-HT or AF4 formed via CVD (from tetra-fluoro-PCP) represent novel polymers with high thermal and chemical stabilities.[27] A diversity-oriented synthesis of perfluoro- and brominated tetrafluoro-PCPs as CVD precursors has also been developed.[28] Using sulfur-extrusion of dithia[3.3]paracyclophane derivatives approach, 4,5,7,8-tetrafluoro- and 4,5,7,8,12,13,15,16-octafluoro-PCP can be prepared with fluoro substitution at either one or both benzene rings of the PCP core.[29] Various substituted PCPs bearing trifluoroacetyl, maleimide, anhydride,[30] pentafluorophenol ester group,[31] and other different functionalized

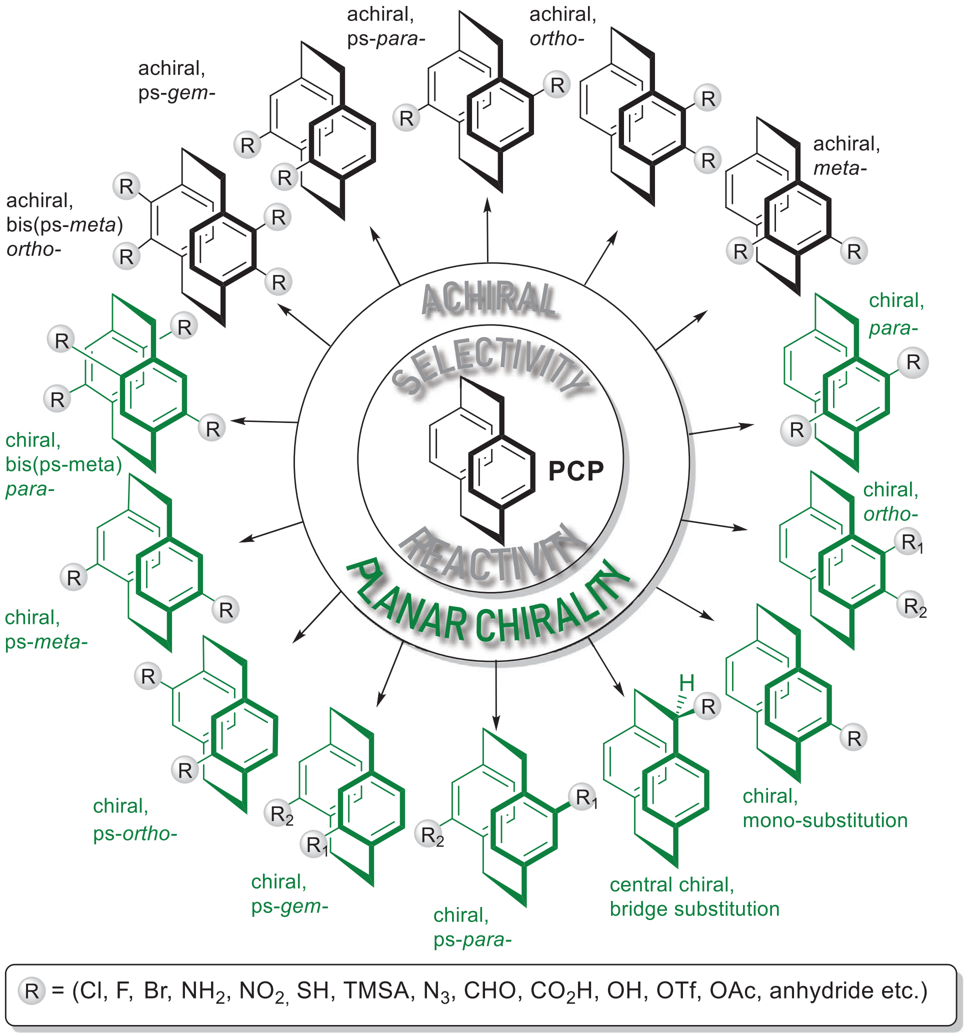


Figure 2. Common substitution of mono-, di-, and tetrafunctionalized PCP with stereochemical descriptions (however, in the CVD process, the stacked structure and planar chirality are lost as PCP is cracked at the ethylene bridges).

PCP monomers have been optimized for CVD (co)polymerization.[32] Improved synthesis of PCPs functionalized with hydroxyl, amine, and aldehyde as useful monomers have been developed that could be utilized in CVD for bioactive coatings.[33] Incorporating the element of stereochemistry and preparing chiral PCPs bearing a stereogenic center in the side-group are promising precursor components that could generate chiral architecture via the CVD process. For the enantiomerically pure cyclophanyl components, the formation of enantiomerically pure PCP-derivatives has been crucial.[34] The polymerization of [2.2]paracyclophanediene monomers (bearing donor–acceptor defined-sequence within the PCP core) have also been recently reported.[35] Functionalized pyridinophanes replacing one of the benzene rings with heteroaromatic consisting of two varying constituent units were synthesized as a useful CVD precursor component.[36] CVD (co)polymerization and post-CVD fabrication strategies using modular PCPs precursor components are discussed in the upcoming sections.

2. Functional Control of Polymer Surfaces and Post-CVD Fabrication Strategies to Bioinstructive Interfaces

Technologically advanced and innovative deposition techniques toward topological and chemically designable surfaces have brought new CVD polymerization capabilities.[37] Cyclophane-based CVD polymerization is compatible with patterning/topographic micro- and nanostructuring strategies. The patterning on functional surfaces can be accomplished using microcontact printing, photopatterning, photomask, or lithographic techniques such as dip-pen nanolithography (DPN).[38] The chemical composition of a parylene polymer can be varied at the molecular level by altering the polymer backbone itself or the functional moieties grafted as side-groups to tune their chemical, physical, and mechanical properties. Chemical modification of poly(*p*-xylylene)s surface by grafting specific functional moieties allows tuning surface properties such as adhesion, wettability, and biocompatibility while preserving the inherent polymeric

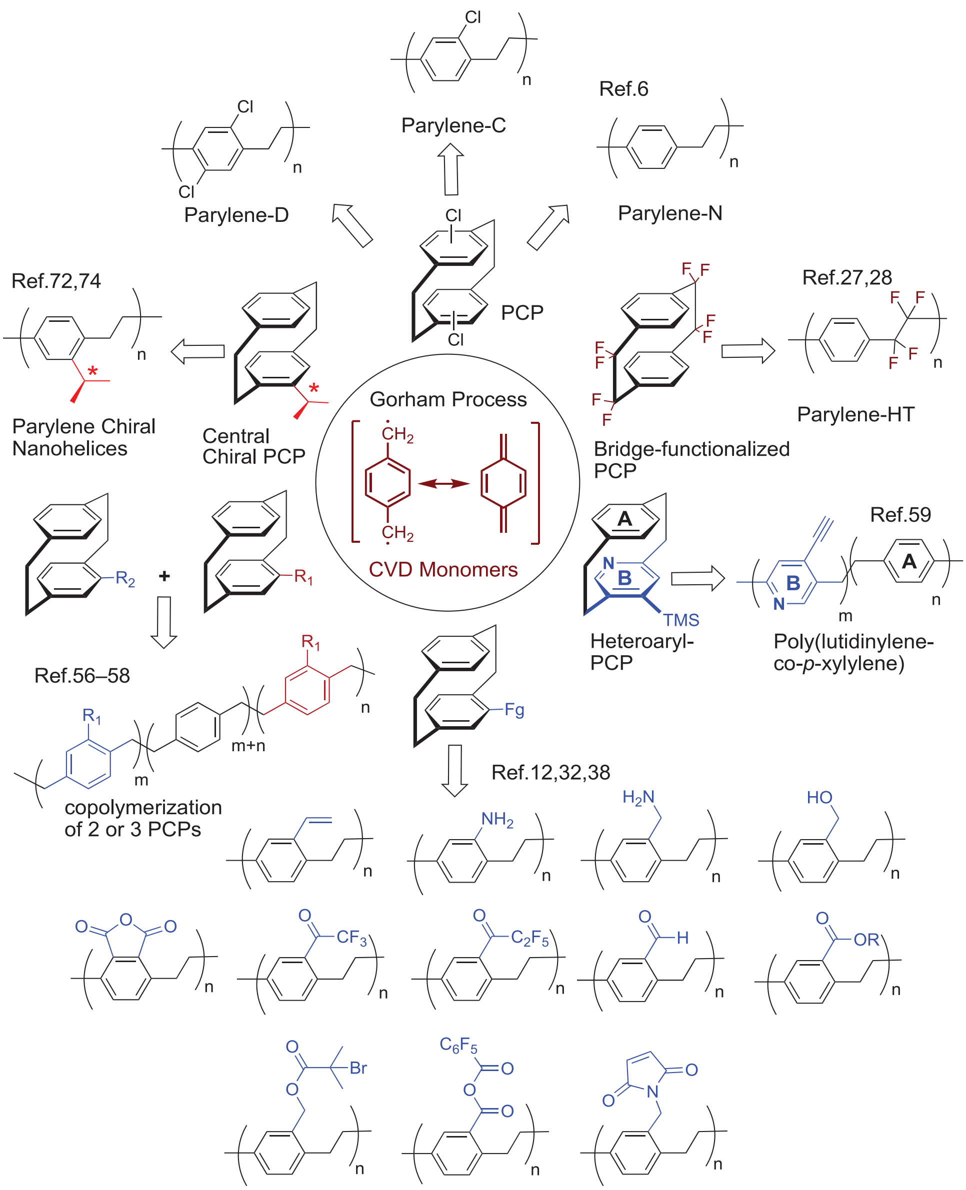


Figure 3. Generalized structural and functional design of the reactive poly(*p*-xylylene)s by CVD polymerization and PCP monomers library.

features. Such reactive surfaces can serve as a versatile platform for diversifying specific application requirements.[39]

2.1. Post-CVD Fabrication Strategies to Multifunctional Surfaces

Poly(*p*-xylylene) surfaces grafted with anchoring sites can be realized by employing predesigned PCP monomers in CVD polymerization, which subsequent to polymerization can be used in post-CVD surface engineering for tailored surface properties and biointerfaces. This includes attachment of a broad range of biomolecules, proteins, antibodies, fluorescent moieties, inorganic nanoparticles, and quantum dots, hence presenting designable biointerfaces with precise control of immobilization chemistries as well as spatial arrangements.[40] Various approaches for structurally controlled polymer surfaces and post-synthetic fabrication strategies have been envisioned. These include azide–alkyne "click" reaction, light-induced thiol–ene/thiol–yne reactions, aldehydes/ketones with hydrazides or alkoxyamines, and surface-initiated atom transfer radical polymerization (SI-ATRP) that have been achieved for applications in (bio)technologies.[41] Alkyne-groups "click" with azide-derivatives via 1,3-dipolar cycloaddition forming stable 1,2,3-triazole linkages efficiently and has been successfully applied in polymer chemistry, materials science, and biotechnology.[42] The possibilities of post-CVD surface modifications via click reaction seed from the PCP monomers prefunctionalized with alkyne-groups. Click chemistry allows spatially controlled immobilization of diverse biocomponents to the alkyne-modified PPXs in a reliable way, creating bioinstructive interfaces.[43] By using a two-source CVD system, copolymers coatings which comprise of reactive surface composition

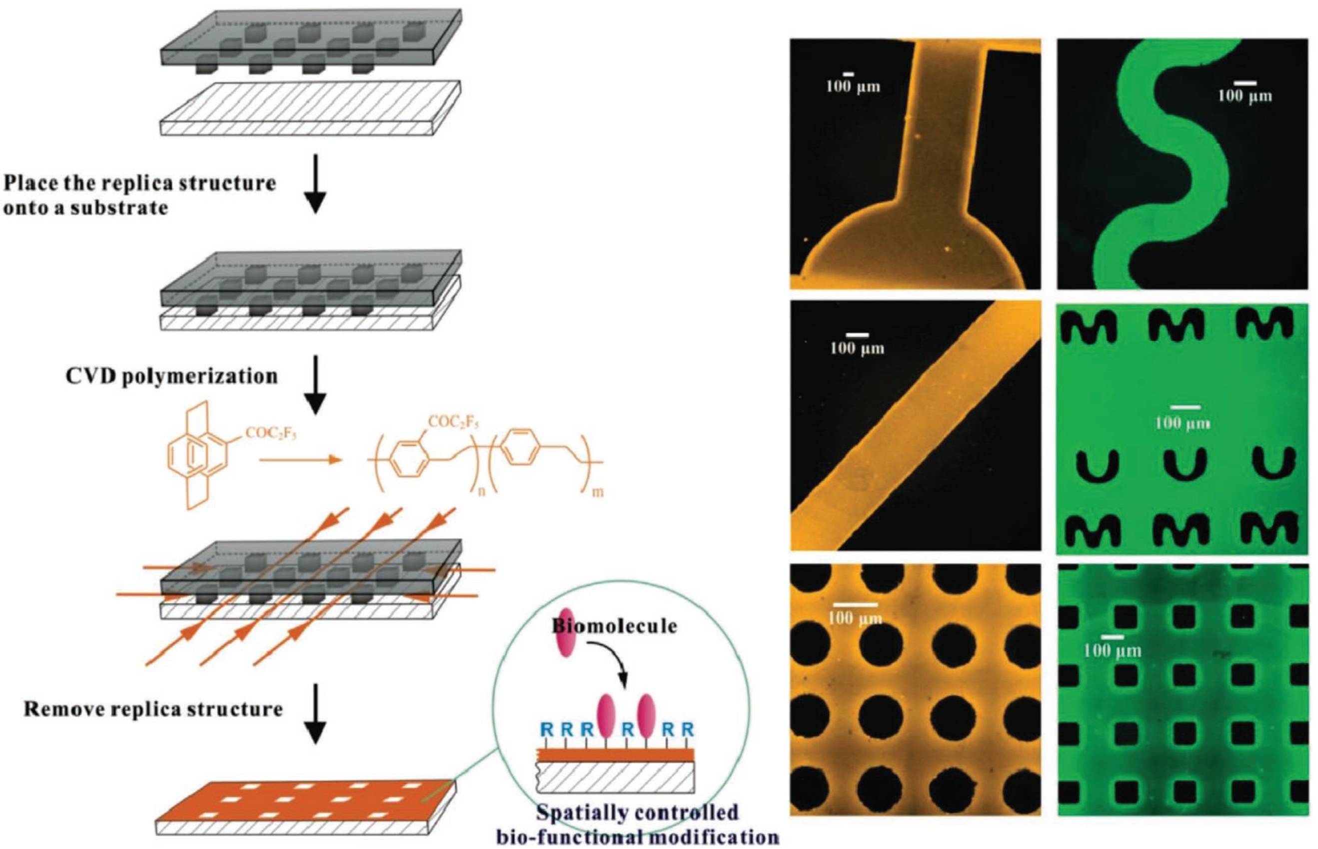


Figure 4. Process of vapor-assisted micropatterning in replica structures (VAMPIR). Fluorescence microscopy images showing the immobilization of QD and fluorescence-labeled biomolecules onto patterned surfaces. All parts: Reproduced with permission.[45] Copyright 2007, Wiley-VCH.

gradients have been fabricated.[44] This enables to selectively immobilize fluoresce-labeled ligands onto the reactive polymer gradients, making CVD-based gradient surfaces a flexible platform for fabricating biomolecular substrates. Topologically and chemically designable surfaces via vapor-assisted micropatterning in replica to generate reactive surface patterns of poly(4-pentafluoropropionyl-*p*-xylylene-*co*-*p*-xylylene) polymer films have been demonstrated.[45] The process relies on masking during CVD polymerization and depositing the reactive coatings within the exposed areas to create desirable geometries. Hydrazide-derived biotin was immobilized onto the functionalized polymer films. To examine the immobilization of biotin ligands within the patterns, both rhodamine (TRITC) conjugated streptavidin and streptavidin-conjugated CdSe quantum dots (Qdot 525) were used for visualization of surface-immobilized biotin that reflect a homogenous binding throughout the surface-modified areas of different predesigned patterns. Some of the representing patterning and topographic micro- and nanostructuring strategies are summarized in **Figure 4**.

CVD polymerization of [2.2]paracyclophane-4-methyl-2-bromoisobutyrate on different substrates creates a novel polymeric initiator coating bearing the bromoisobutyrate side groups that could be post-fabricated via SI-ATRP on treatment with oligo(ethylene glycol) methyl ether methacrylate (**Figure 5**).[46] Similarly, spatially controlled deposition of the initiator coatings using vapor-assisted microstructuring in replica structures resulted in the fabrication of spatially confined microstructures. The CVD polymerization can be also applied to colloid particles and form high-definition microstructured curve surfaces that rival their flat counterparts concerning pattern precision and quality (**Figure 6**).[47]

Employing 4-phenyl-acetyl-PCP monomer, novel photodefinable reactive PPXs coating and its compatibility with capillary force lithography by preparing stable micrometer-sized PEG hydrogel has also been achieved.[48] This concept combines the advantages of a CVD polymer with the ability to conduct photochemical immobilization. Spatially directed nanostructuring with excellent conformity using DPN of biotinylated azide molecules onto poly(4-ethynyl-*p*-xylylene-*co*-*p*-xylylene)-coated on six different substrates without the need for reconfiguring the underlying printing technology has been demonstrated.[49] Functional groups, for instance, alkyne-tagging of ethynyl-presenting polymer, poly(4-ethynyl-*p*-xylylene-*co*-*p*-xylylene)s, enable spatially directed click chemistry, reflecting its potential for biotechnological applications.

2.2. Structuring Multifunctional Surfaces via CVD Copolymerization

Different PCP precursor molecules, each functionalized with moieties of different chemical reactivity, can be employed

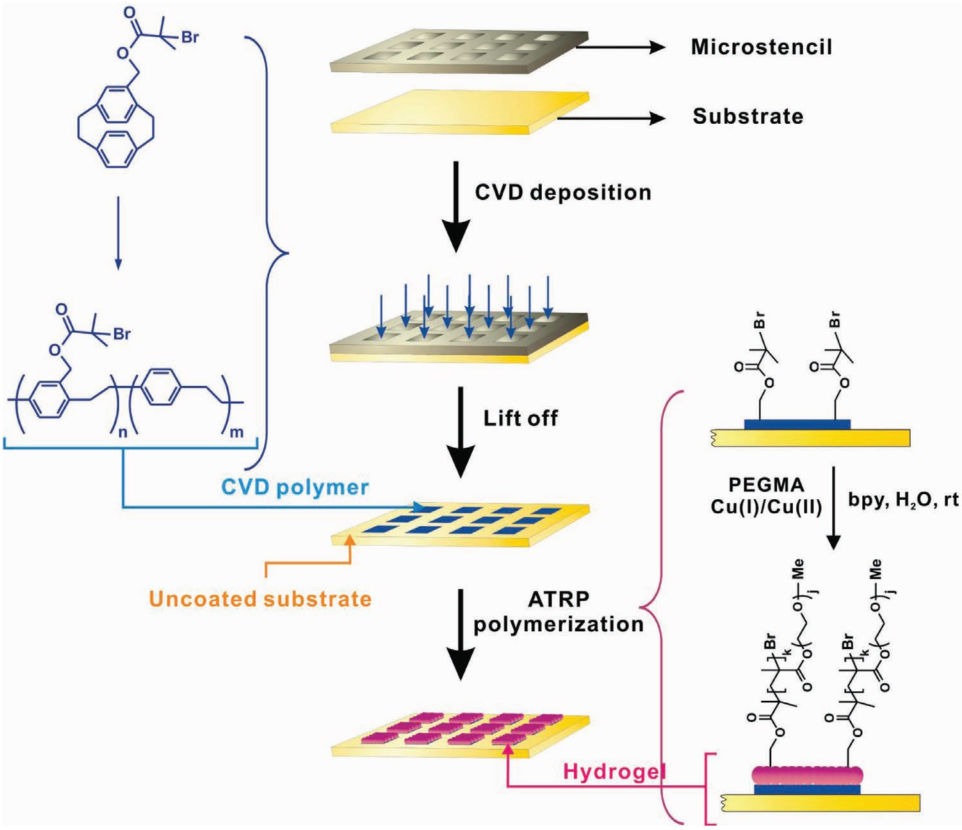


Figure 5. CVD polymerization approach to preparing the vapor-based initiator coating for poly(OEGMA) modification via ATRP. During CVD polymerization, microstencils were used to direct the reactive initiator coating to defined surface areas. Using surface-initiated ATRP, a poly(OEGMA) film is then selectively prepared at areas where the initiator coating has been deposited. Figure: Reproduced with permission.[46] Copyright 2008, Wiley-VCH.

during the CVD copolymerization process to fabricate reactive coatings grafted with multifunctional anchoring sites. Functionalized PCPs bearing alkynes, amino groups, carbonyls, esters, and maleic derivatives have been investigated under CVD copolymerization. We initially adopted a two-component copolymerization strategy with the aim of subsequent post-CVD bio-orthogonal "double-click" chemistry to selectively immobilize desired molecular entities on defined areas of the same surface by utilizing the different chemical reactivity of the anchoring sites.[50] Activated groups (with the first immobilization step being catalyst-free) and nonactivated alkynyl groups (the second step requires CuI as a catalyst) were combined via copolymerization strategy (**Figure 7**).

A multifunctional coating with controlled ratio of alkyne and pentafluorophenyl ester groups was fabricated via CVD copolymerization. Pentafluorophenyl ester and alkyne groups were aimed for simultaneous click reaction and active ester chemistry to achieve copresentation of epidermal growth factor and cyclic arginine–glycine–aspartic acid (cRGD) adhesion peptide.[51] Cell studies with human umbilical vein endothelial cells (HUVECs) and A431 cell lines demonstrate the biological activity of the co-immobilized biomolecules. A more generic and largely applicable strategy by copolymerizing differently substituted two PCP monomer species of 4-formyl-PCP and 4-ethynyl-PCP has been developed to control various biomolecules' co-immobilization.[52] Heparin-binding growth factor (basic fibroblast growth factor in this study) was selectively immobilized through interaction with heparin, which was covalently attached to the CVD polymer surfaces through an aldehyde-hydrazide coupling. An alkyne–azide click reaction was used to co-immobilize the second biomolecule of azido-functionalized adhesion peptides. The details and sequence for co-immobilization of the adhesion peptide and the heparin-binding growth factor are depicted in **Figure 8**.

This strategy was further extended to generate dual-functional bioinstructive polymer coatings poly(4-aminomethyl-*p*-xylylene-*co*-4-ethynyl-*p*-xylylene-*co*-*p*-xylylene) via CVD copolymerization (4-aminomethyl-PCP and 4-alkyne-PCP) for the orthogonal immobilization of two biomolecules (notch ligand delta-like-1 (DLL1) and an RGD-peptide) that govern the fate of hematopoietic stem and progenitor cells.[53] A custom-built setup equipped with two inlet sources was used for the deposition of the copolymer. A quartz crystal microbalance, located in the deposition chamber, was used to monitor the deposition rate. The RGD-peptide, carrying a PEG spacer at the amino terminus of the lysine and an azide moiety at the PEG terminus (sequence RGDSK–PEG–azide), was immobilized on the surfaces via copper-catalyzed alkyne–azide cycloaddition (**Figure 9**). In this proof-of-principle stem cell culture study, polymer surfaces showed cytocompatibility and the proliferation of the hematopoietic stem and progenitor cells is predominantly influenced by the surface concentration of immobilized DLL1.

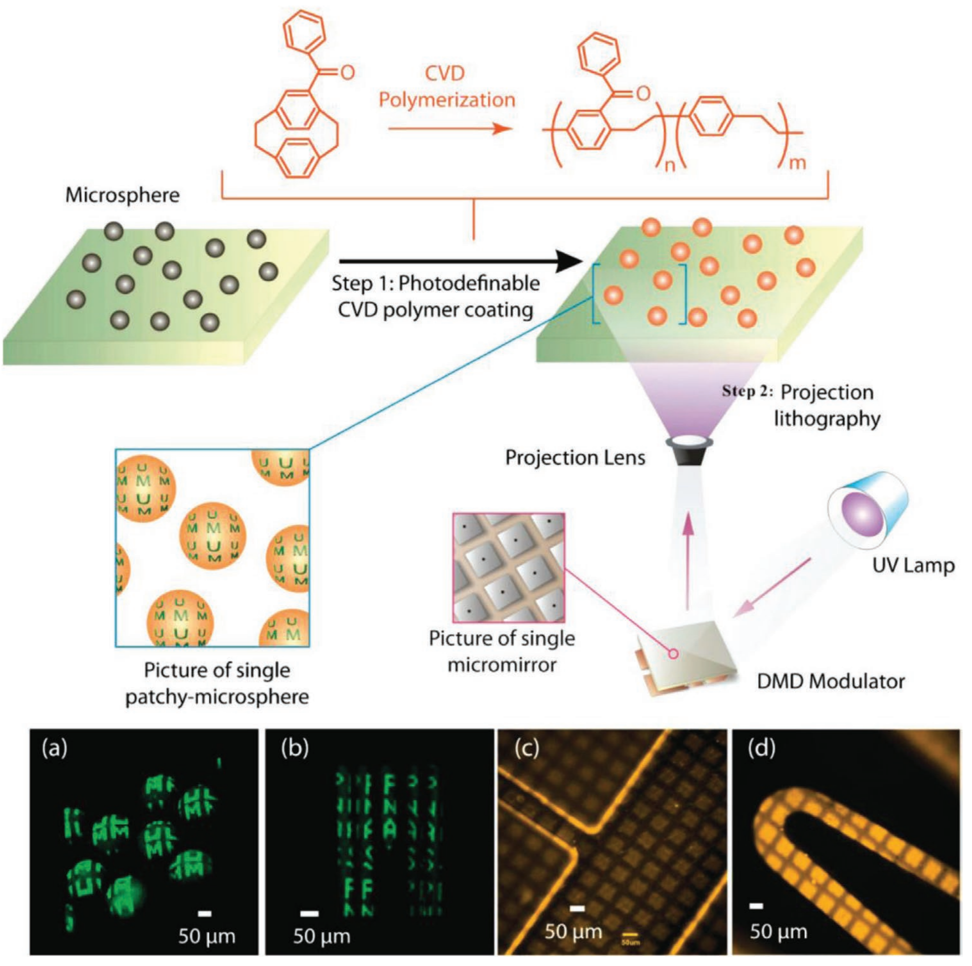


Figure 6. Schematic description of the 3D microstructuring technique. The method comprises two process steps: deposition of the photodefinable CVD coating (step 1) and subsequent projection lithographic rendering of the polymer-coated colloids (step 2). The fluorescence microscopy images in (a–d) show that this technique can be applied to 3D and complex surfaces. All parts: Reproduced with permission.[47] Copyright 2007, National Academy of Sciences of the USA.

Co-immobilization of biomolecules on ultrathin CVD coatings using a combination of coupling chemistries, namely Huisgen cycloaddition and carbonyl-hydrazide coupling, has also been demonstrated on patterned surfaces via vapor-assisted micropatterning in replica structures.[54] Dibromomaleimide-functionalized CVD polymers poly[4-(3,4-dibromomaleimide)-*p*-xylylene-*co*-*p*-xylylene] using 4-(3,4-dibromomaleimide)-PCP precursor were reported demonstrating selective and reversible binding of thiol-containing biomolecules of cysteine-modified peptides.[55] After validating the chemical composition of polymers on different substrate surfaces, including calcium fluoride, prisms, gold, silicon, copper, and glass coverslips, a fluorescent-labeled protein (streptavidin–TRITC) was immobilized onto microengineered surfaces with the help of a thiol-terminated biotin linker (biotin–PEG–thiol). The binding of dibromomaleimides and thiols occurs under physiological conditions. Polymer coatings that could introduce dibromomaleimide groups to a broad range of solid surfaces would thus be desirable for a number of biomedical and biotechnological applications in which specific binding and release of target analytes are desired.

Chen and co-workers have contributed to the development of more diversified vapor-based copolymerization approaches that envision multifunctional polymer surfaces grafted with tunable anchoring sites for orthogonal immobilization. Using a one-step process of CVD copolymerization generates multicomponent coating of poly[(4-*N*-maleimidomethyl-*p*-xylylene)-*co*-(4-methyl-propiolate-*p*-xylylene)-*co*-(*p*-xylylene)] using 4-*N*-maleimidomethyl-PCP and 4-methyl-propiolate-PCP components. Methyl propiolate and maleimide grafted to the CVD polymer enable click reactions with azide-terminated biomolecules, and Michael-type thiol coupling reactions with maleimides. (**Figure 10**).[56] Alexa Fluor-555 azides and fluorescein-labeled cysteines were selected as model substrates for the coupling reactions.

The concept of three-component CVD copolymerization was demonstrated that generate polymer surfaces grafted with trifunctional moieties, namely, acetylene, maleimide, and ketone (using 4-ethynyl-PCP, 4-*N*-maleimidomethyl-PCP, and trifluoroacetyl-PCP in a 1:1:1 molar ratio). Trifunctional polymer surfaces enable specific conjugation of Alexa Fluor-555 azide, fluorescein-labeled cysteine, and Alexa Fluor-350 hydrazide,

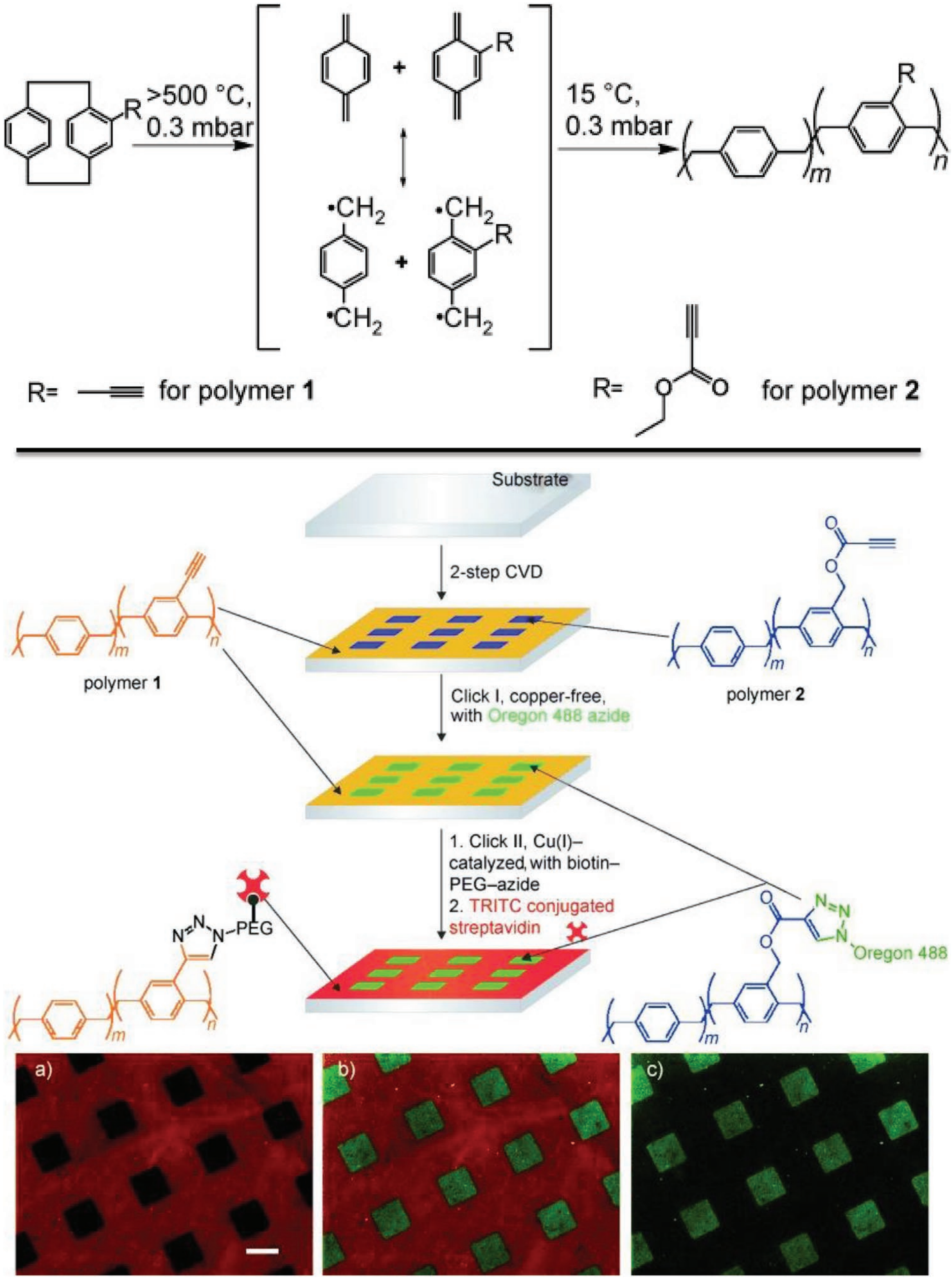


Figure 7. Top: CVD polymerization process of polymers with nonactivated (**1**) and activated alkyne groups (**2**). Bottom: Representation of copolymerization and bio-orthogonal fabrication on the surfaces for sequential immobilization of biocomponents by utilizing different reactivity of activated and nonactivated alkynyl groups toward azide groups. a,c) Fluorescence images of samples prepared as shown in the schematic representation. b) Overlay image of green and red channels shown in (a) and (c). Scale bar: 200 µm. All parts: Reproduced with permission.[50] Copyright 2011, Wiley-VCH.

respectively, as model reporter molecules (**Figure 11**).[57] This concept was further used for preparing trifunctional nanoparticles based on CVD copolymerization with controllable dimensions and confined surface fabrication via alkyne–azide, maleimide–thiol, and atom transfer radical polymerization.[58]

Cyclophane-derived CVD polymers, reported so far, are widely restricted to simple all-carbon backbones. By replacing one or both benzene rings with heteroaromatics in the precursor scaffold, skeletally novel copolymers consisting of two varying constituent units could be achieved. Realizing this concept, an entirely new class of functionalized polymers by CVD polymerization referred to as polylutidines was developed employing pyridinophane derivatives (**Figure 12**). Nitrogen-containing pyridinophanes can introduce different polarities into the polylutidine polymer backbone resulting in surfaces that support an increased adhesion of primary HUVEC compared to the more hydrophobic parylenes.[59]

CVD copolymerization using noncyclophanyl scaffolds of cyclic ketene acetal (5,6-benzo-2-methylene-1,3-dioxepane; BDMO) in combination with PCP that generate degradable

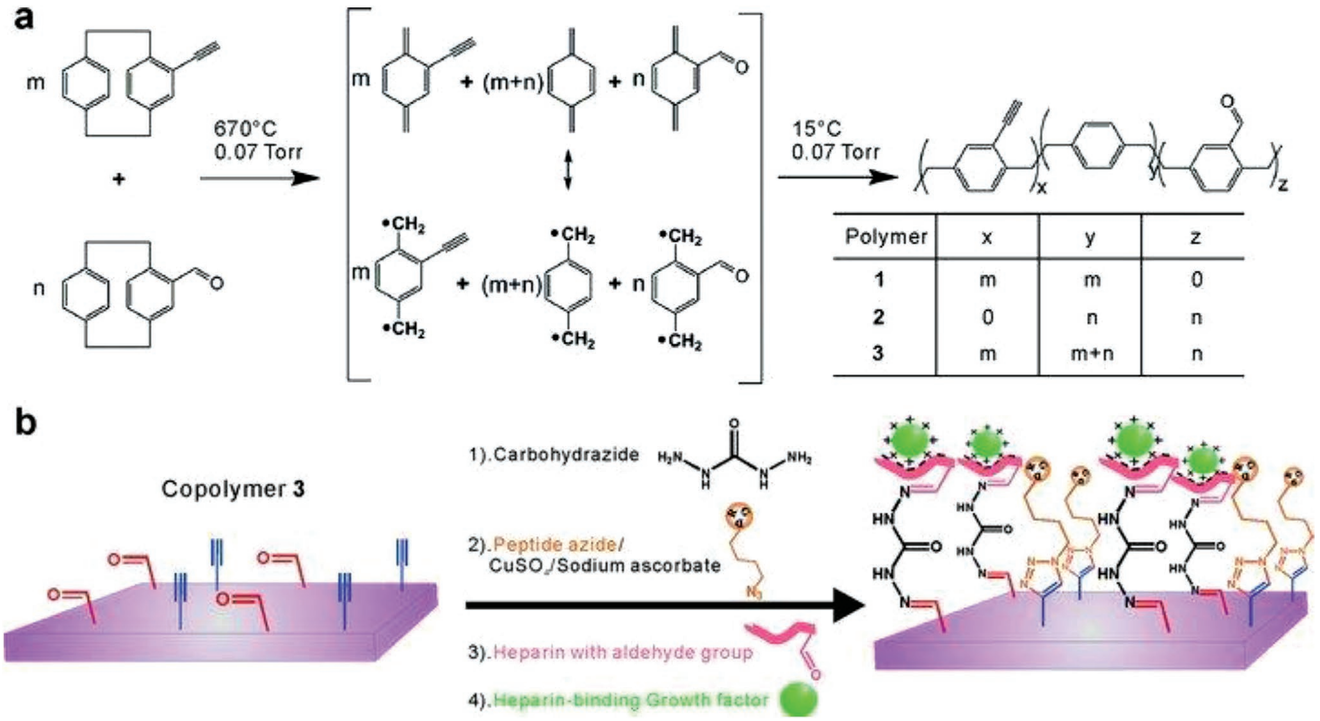


Figure 8. a) CVD copolymerization of PCP bearing aldehyde and alkyne groups. $m = n$ for the copolymer 3 discussed herein. Polymer 1 and 2 are used as controls. b) Co-immobilization for heparin-binding growth factor and adhesion peptide on the copolymer 3. a,b) Reproduced with permission.[52] Copyright 2012, Wiley-VCH.

ester-linkages inserted into the PPXs backbone has been demonstrated.[60] BMDO features a seven-membered cyclic ketene acetal ring that undergoes quantitative rearrangement, which makes it suitable for CVD copolymerization (**Figure 13**). Using this concept, alkyne-functionalized surfaces (prepared by copolymerization of alkyne-functionalized 4-ethynyl-PCP) can be further exploited via click reaction. The degradation kinetics are dependent on the ratio of ketene acetals to PCP. This concept combines interfacial multifunctionality with hydrolytic degradability in CVD polymers, opening up new application possibilities for PPXs.

3. 1D to 3D Spatial Architectures by Templated CVD Polymerization

Structuring materials by a dimensional organizing principle, for instance, molecular arrangements in chain polymers and controlled molecular arrangements in second and third dimensions to construct complex architectures, has been the subject of extensive research.[61] Challenges and opportunities arise depending on the system's dimensionality; in particular, the key issue in materials modulation is preserving morphology and inheriting distinct features, for instance, stereochemistry, chirality, or responsiveness that are crucial for certain practical material applications. In this context, integrating the CVD polymerization process with a template-driven approach can significantly advance the molecularly controlled structuring of parylenes with tailored shapes, dimensions, and chemical features. Greiner and co-workers has reported the preparation of high surface-to-volume microstructures such as tubules by vapor deposition techniques.[62] They describe the use of poly(L-lactide) or PLA fibers formed by electrospinning (0.3–3.5 µm) as templates to coat PPX polymer over it by CVD polymerization. This PPX-PLA core–shell was then easily transformed into PPX microtubes by annealing the PLA fiber core at 280 °C under vacuum, a temperature at which the PPX polymer remains stable. Using this method, PPX porous microtubes in the order of 100 µm long, 0.05–3.5 µm inner diameter, and 0.1–1 µm wall thickness could form. Broer and co-workers have studied the penetration of *p*-xylylene vapors into small rectangular channels indirectly by measuring the thickness of the resulting polymer films in those channels as a function of the penetration distance.[63] By studying various process conditions such as monomer, residual vapor pressure, and monomer deposition rate, two conclusions were reported: 1) a valid flow model could be derived for depositions at low monomer and gas pressures showing large penetration distances and a decrease in the film thickness, and 2) by increasing the monomer pressure and deposition rate, a viscous type flow leading to accumulation of the polymer at the entrance of the channel was observed. However, replacing the less reactive *p*-xylylene with chloro-*p*-xylylene showed a controlled flow through the entire channel. As an implication of the above described report would be the accessibility of microporous channels for CVD polymer coatings. Lahann and team have demonstrated the ability to coat nonfunctional and functional PPX polymers in confined microgeometries leading to homogenous surface coverages with a high aspect ratio highlights the usefulness of the cyclophane-based CVD coatings for potential applications in

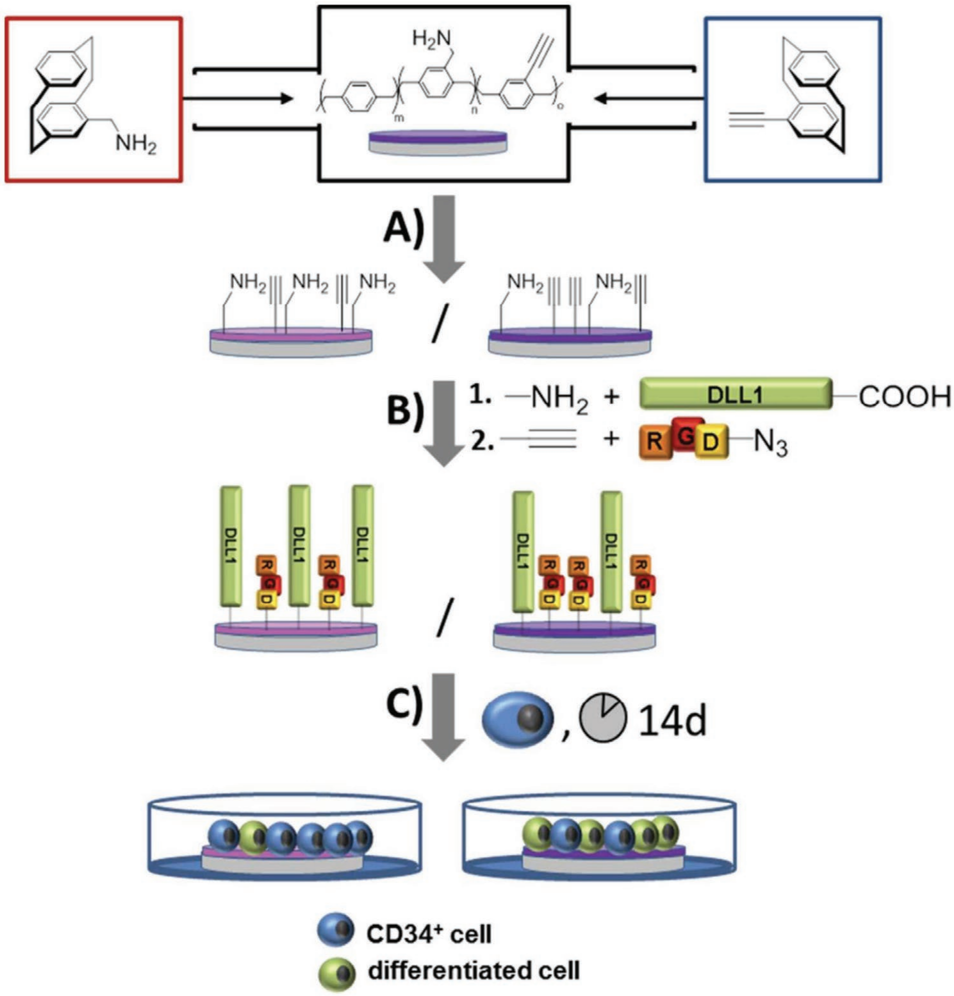


Figure 9. Schematic representation of the presented biomaterial concept comprising three steps: a) CVD polymerization of copolymers with varying composition, b) biofunctionalization, c) HSPC cultivation. All parts: Reproduced with permission.[53] Copyright 2017, American Chemical Society.

micro/nanofluidics.[64] Both straight (1600 µm long) and curving (2800 µm long) poly(dimethylsiloxane) microchannels of the dimension 75 µm high × 100 µm wide were coated with PPX containing reactive functional groups such as amines, activated carboxylic acids, and anhydrides for chemical binding of biologically relevant ligands. PPX functionalized with $-COCF_3$, $-COC_2F_5$, $-Cl$ groups, and the nonfunctional variant all show deposition degrees of >80% and >40% for the straight and curving geometries, respectively, with deposition thickness of 113 and 74 nm (PPX-$COCF_3$), 57 and 33 nm (PPX-COC_2F_5), 46 and 24 nm (PPX-Cl), and 33 and 16 nm (PPX) for the straight and curving channels of the corresponding four PPX polymers. It was shown that such coated microchannels could immobilize biotin. PPX-$COCF_3$ coating in the microchannel was reacted with modified streptavidin followed by streptavidin–biotin conjugation with homogenous distribution. In an attempt to make smaller microstructures on surfaces, Lahann and team have explored the formation of dense polymer brushes on surfaces using a grafting-from approach on patterned surfaces that ultimately resemble the fabrication of microstructures.[65] By patterning hydroxyl-functionalized PPX polymer on substrate, the −OH groups can be used to grow poly(ε-caprolactone) or PCL polymer brushes by a surface-initiated ring-opening polymerization whose spatial resolution was defined by the patterned base hydroxyl-PPX layer. Keeping in mind that the area of nanostructures on 2D substrates has been studied for a long time, the current focus of research is shifting toward the fabrication of free-standing nanomaterials such as nanoparticles and nanotubes, nanowires, using polymers as soft matter. A popular choice for preparing such materials is lithography or masking techniques. Demirel and co-workers have used CVD polymerization as the standalone technique to prepare highly porous PPX films containing free-standing, parallel columns made up of nanowires.[66] They demonstrate the formation of 50 µm thick PPX films comprised of 50–100 nm diameter nanowires with unprecedented aspect ratios simply by placing the substrate at an angle (<10°) to the vapor influx.

3D materials tend to exhibit high porosity making them ultralight that have been used in absorbers, insulators, and diverse others applications.[67] Ultraporous 3D sponges are made from polymer fibers, and find applications in a larger sphere, especially tissue engineering, cell culture, and other

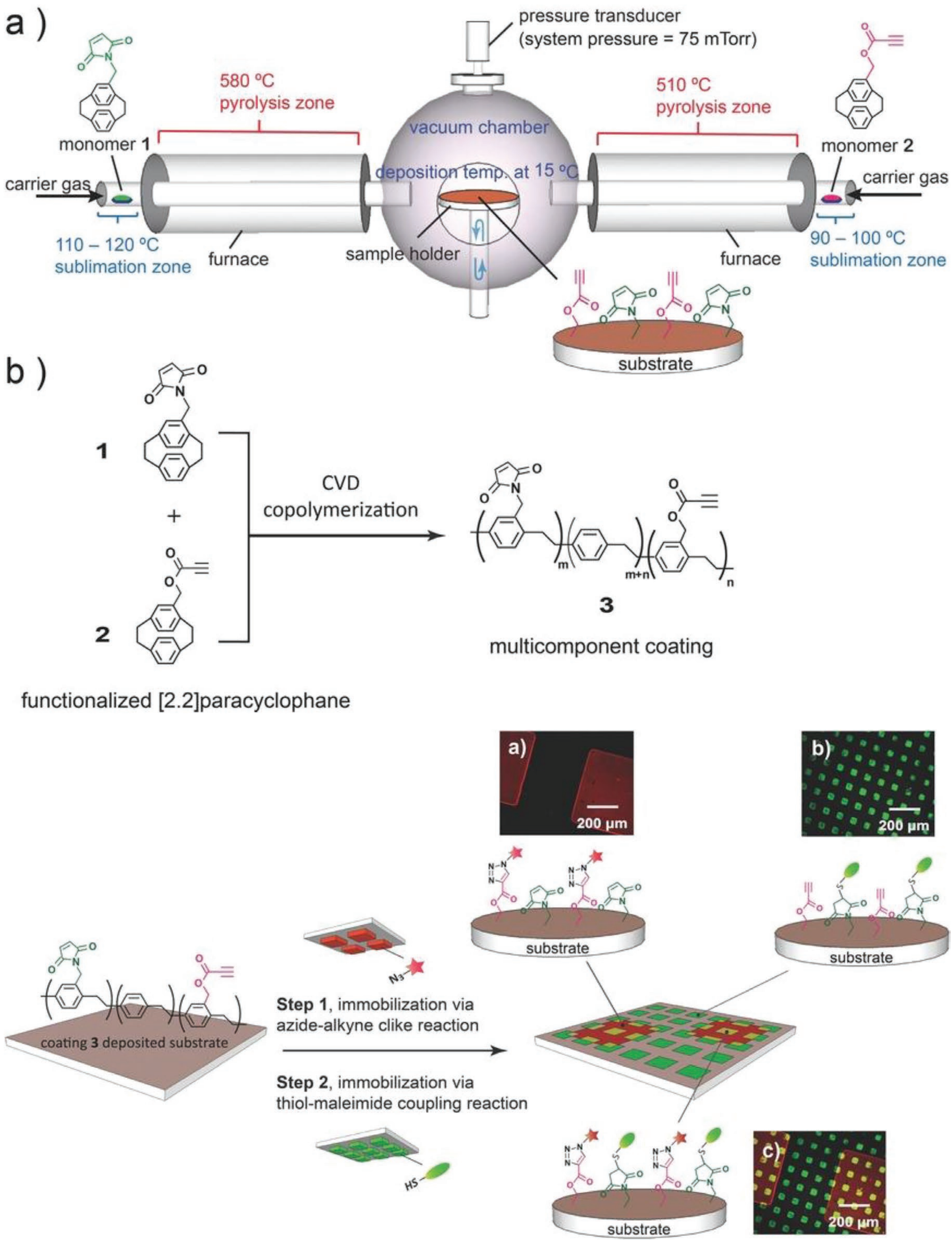


Figure 10. Top: a) Schematic illustration of a two-sourced CVD copolymerization used to prepare the multicomponent coating. b) CVD copolymerization of a 1:1 molar ratio of 4-(*N*-maleimidomethyl)-PCP (**1**) and 4-methyl-propiolate-PCP (**2**) to form poly[(4-*N*-maleimidomethyl-*p*-xylylene)-*co*-(4-methyl-propiolate-*p*-xylylene)-*co*-(*p*-xylylene)] (multicomponent coating) (**3**) (m:n = 1:1). Bottom: Schematic illustration of multicomponent coating and immobilization of multiple biomolecules by biorthogonal approach. An azide–alkyne click immobilized the Alexa Fluor-555 azides, and a thiol–maleimide coupling was used to immobilize fluorescein-labeled cysteines. The process of µCP was used to confine specific conjugation to selected areas. a) The red-channeled fluorescence microscopy image illustrates the immobilization of the Alexa Fluor-555 azides. b) The green-channeled fluorescence microscopy image reveals the immobilization of the fluorescein-cysteines. c) Overlaid images of (a) and (b). All parts: Reproduced with permission.[56] Copyright 2014, Wiley-VCH.

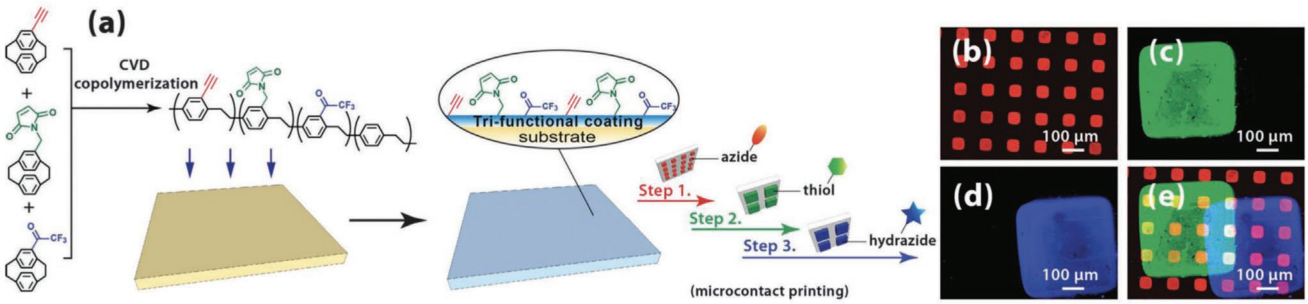


Figure 11. a) Trifunctional coating homogeneously deposited via CVD copolymerization. b–e) Fluorescence microscopy images showing the immobilized molecules of Alexa Fluor-555 azides (red channel) (b), fluorescein-labeled cysteines (green channel) (c), Alexa Fluor-350 hydrazides (blue channel) (d), and overlaying images (e). The µCP process was used to confine specific conjugation at selected areas. All parts: Reproduced with permission.[57] Copyright 2013, Royal Society of Chemistry.

similar biological applications.[68] Duan and co-workers prepared ultralight polyacrylate sponges from electrospun fibers of poly(methacrylate-*b*-methyl methacrylate-*b*-4-methacryloyloxybenzophenone) and polyacrylonitrile blends, which on further coating with defined PPX polymer by CVD polymerization were capable of exhibiting tunable density, mechanical property, solvent resistance, and hydrophobicity.[69] In a report by Greiner and co-workers, they made 3D foam structures using a template-assisted approach, wherein expanded polystyrene and sugar cubes were used as template foams.[70] PPX polymer was then coated on these foams, and subsequently, the template foam structure was dissolved to obtain inverse foam structures. In this particular case, inverse foam structures made up of parylene polymers gave insight into the actual foam structure and properties and, at the same time, showed interesting wetting behavior and thermal properties that can be exploited for use in various applications.

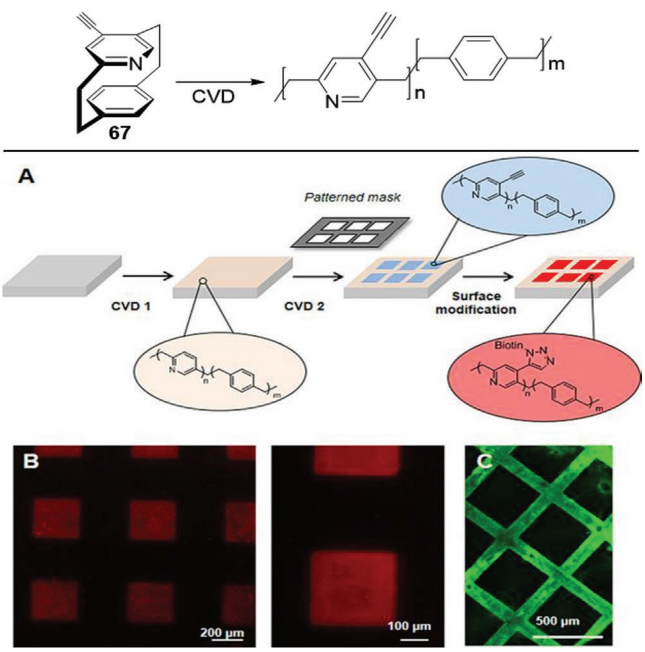


Figure 12. Top: Formation of functional polylutidine-*co*-parylene polymers. Bottom: A) Schematic representation of the protocol for biotin immobilization on the functional coating. B) Fluorescence images after streptavidin incubation and c) fluorescence image after azido-PEG microcontact printing on polymer 10 coating (PEG is located on a square pattern in this case) and BSA-FITC incubation. All parts: Reproduced with permission.[59] Copyright 2017, Wiley-VCH.

Scaling down from micro- to nanostructures, templating techniques are commonly used to prepare nanomaterials that are smaller than 1 µm. For example, lithography, direct laser writing, and DNA origami are some templating approaches for the fabrication of polymeric nanomaterials. These bottom-up and top-down approaches both allow for extremely precise and small nanostructures as small as 5 nm. Taking a closer look at this range, it is inevitable that molecular ordering of certain materials can serve as templates to prepare a range of nanomaterials. Liquid crystals (LCs) are an excellent choice as templates for confined polymerization, leading to tailored nanoarchitectures and further into macroscopic arrangements.[71] Properties of LCs make them attractive such as the intrinsic property of order over diverse length scales, local manipulation of the template, anisotropy, complex pattern formation, and optically attractive birefringence properties. Lahann and co-workers have investigated an LC-templated CVD approach to prepare nanohelices of chiral parylene polymers on surfaces with tunable length, pitch, and higher-order mesoscale morphologies by varying the chirality of the template.[72] Initially they investigated the CVD polymerization of various achiral PCP precursors into nematic and cholesteric LCs templates, emphasizing the role of the template in dictating the morphology of the nanofibers. By using nematic LCs, straight fibers were obtained, while blue-phase LCs yielded nanostructures with pores of around 500 nm in diameter (**Figure 14**). By using cholesteric LCs, the helical chirality could be transferred to the obtained nanofiber in the form of a spiraling of the fiber in the µm range. Most notably, the morphology and structural regularity of the template is strictly preserved, even upon removal of the LCs template.

Taking a step further, by employing PCP precursors bearing a stereogenic chiral center in CVD polymerization into supported films of LCs enable the formation of superhierarchical arrays of nanohelices. Chiral PCP precursors bearing a stereogenic center in the side-group enable surfaces formation decorated with enantiomorphically pure polymer nanohelices across multiple length scales, a phenomenon often observed in nature.[73] The chiral information was directly encoded into the

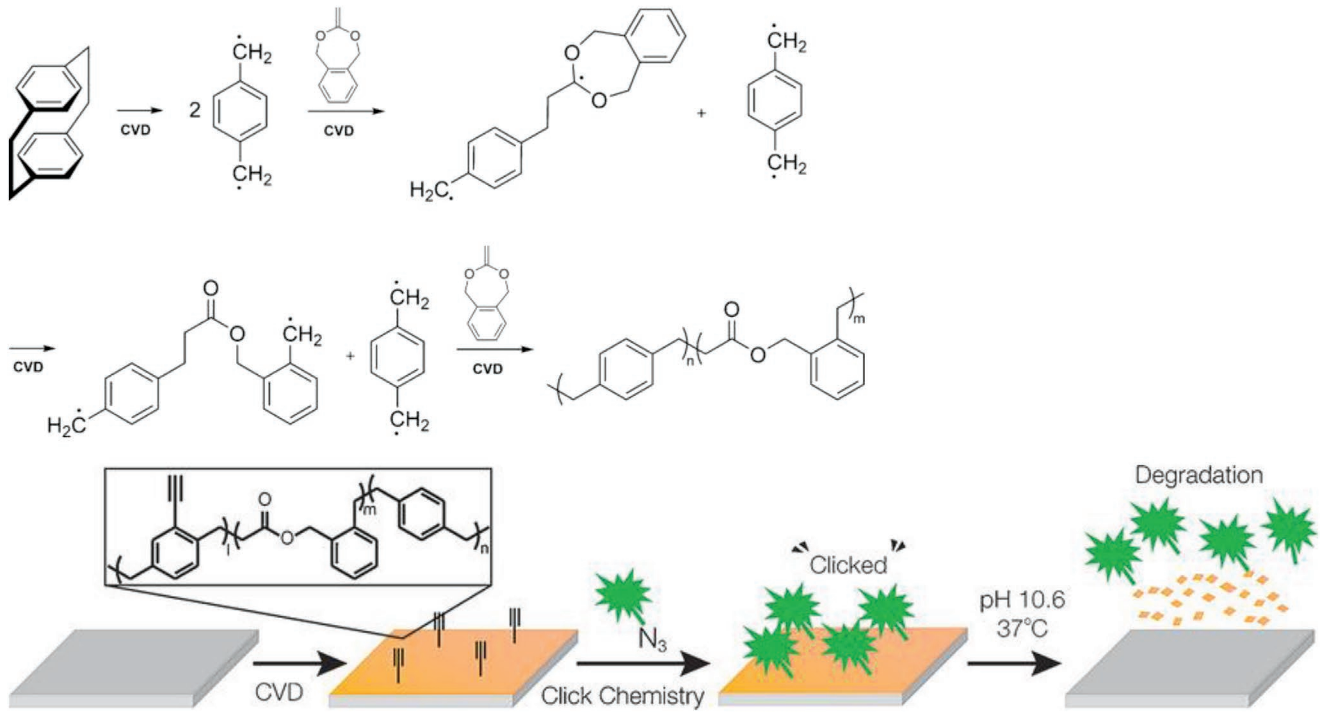


Figure 13. Proposed mechanism of the CVD synthesis of backbone-degradable polymers. A cyclic ketene acetal, was copolymerized with radicals generated by the pyrolysis of PCP. BMDO polymerized following a ring-opening radical polymerization mechanism, while undergoing a rearrangement into a polyester. Figure: Reproduced with permission.[60] Copyright 2017, Wiley-VCH.

PCP precursors rather than the templating LCs medium. Two chiral precursors, (S_p,S)-1-(4-[2.2]paracyclophanyl)ethanol and (S_p,R)-1-(4-[2.2]paracyclophanyl)ethanol, on CVD polymerization into a nematic LCs resulted in regular arrays of nanohelices (**Figure 15**).[74] Depending on the molecular chirality of the 1-hydroxyethyl-PCP precursor, extended arrays of enantiomorphic nanohelices were formed from achiral nematic templates. In contrast, templated CVD polymerization of the achiral PCP precursor under identical conditions resulted in straight nanofibers rather than nanohelices. Arrays of chiral nanohelices extend over hundreds of microns and consistently display enantiomorphic micropatterns. Circular dichroism spectroscopy of nanohelical dispersions in methanol indicates mirrored signals at 242 nm of similar magnitude and opposite Cotton effects circular dichroism spectrum of achiral PCP-derived dispersions did not show any discernible signals. This demonstration of the particular role of the stereogenic center in the formation of nanohelices, competing chirality effects by replacing the nematic cyanobiphenyl-based (E7) phase with a cholesteric phase and using surfaces decorated with nanohelices toward detection of the chirality of (1S)-1-(2,5-dimethylphenyl)ethanol might contribute to understanding the nature's concept of multiscale chirality transfer. This approach can significantly advance scientific capabilities for molecularly controlled soft matter surfaces. The scope of suitable chiral PCP monomers can be broadened to evaluate helicity induction.

We further have studied the concept—how molecular size and functional moieties substituted to the PCP precursors influence the fabrication of parylenes with regards to the template morphologies. Crystal-controlled polymerization using a coordination-driven metal–organic framework (MOF)-based confined nanospaces has been an emerging concept for tailoring polymer architectures, functions, and applications.[75] Employing the crystalline 3D HKUST-1 MOF as a sacrificial template, we have demonstrated parylenes particle synthesis with morphology and porosity transcription inside the host 3D framework.[76] The *para*-xylene diradicals formed during CVD polymerization diffuse into confined nanochannels of the crystalline 3D HKUST-1 MOF and spontaneously polymerize to generate parylene@MOF composites. Here, MOF-confined geometries can act as a sacrificial template and, upon dissolution/removal of the coordinating metal ions, facilitate the formation of templated hollow and solid parylene particles with the transcription of the parent crystals HKUST-1 morphology and porosity. Chloro-PCP and nonfunctionalized PCP were tested in initial studies. The templated morphologies depend on subtle changes in the chemical composition of the CVD precursors as indicated by clear morphological differences observed for parylene solid (PPX) and hollow (PPX-Cl) particles synthesized from nonfunctionalized and chloro-substituted PCP precursors relate to the different dynamical behavior of PCP precursors and their diffusion into the MOF nanopores. Crystal shape and cross section of the parylene particles PPX and PPX-Cl before and after the focused ion beam are shown in **Figure 16**. MOF-templated CVD polymerization with the implementation of 3D spatial arrangements establishes a new platform for synthesizing parylene particles with structurally controlled morphologies, where molecularly imprinted structuring is modulated by the choice of both the host template and the CVD precursors. This is an inspiring approach via

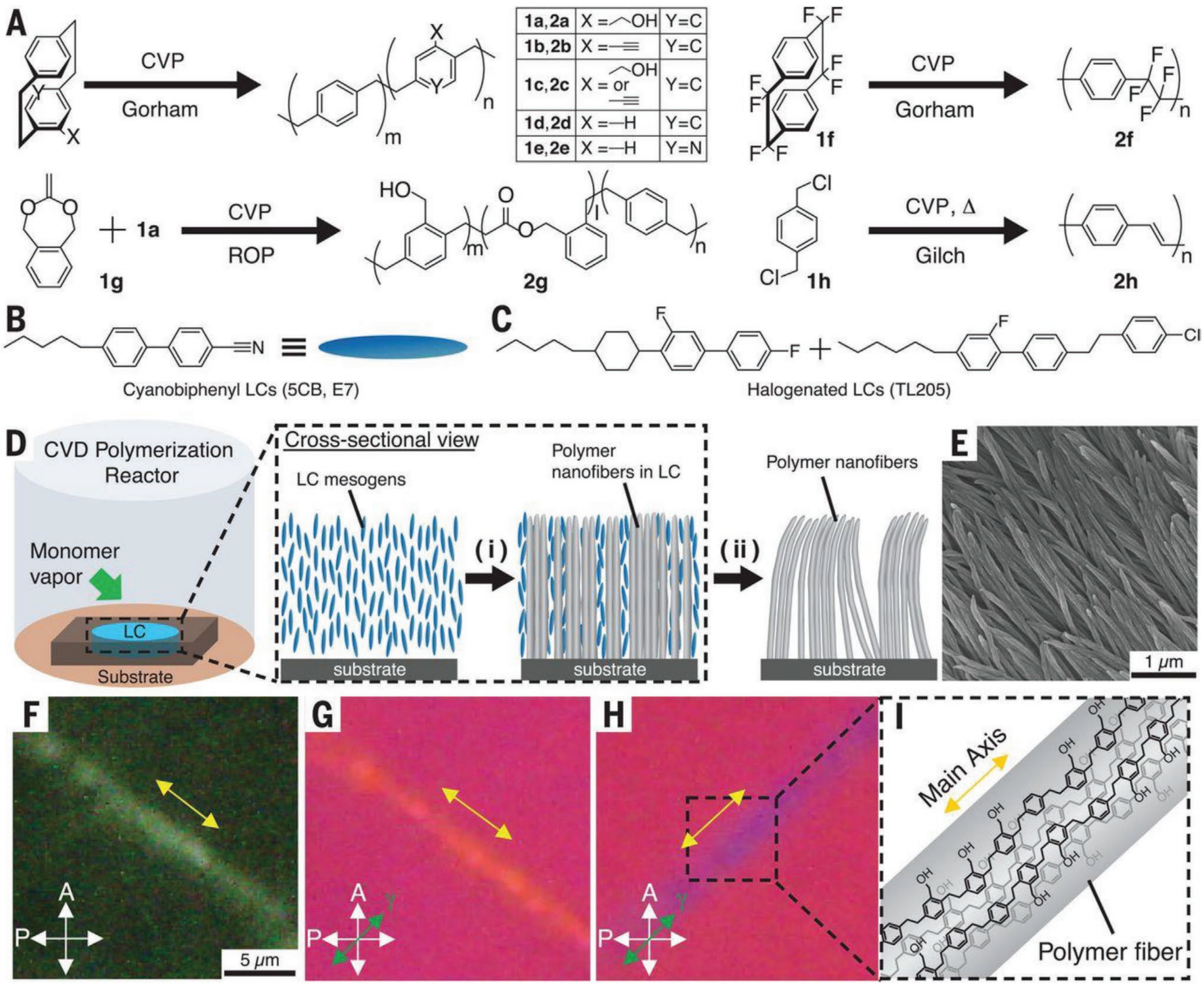


Figure 14. Templated synthesis of nanofiber arrays via CVP into anisotropic media. A) CVP of 1a to 1h yields polymers 2a to 2h. *m*, *n*, and *l*: copolymer repeat units; Δ: 250 °C. B,C) Representative chemical structures of cyanobiphenyl-based (5CB and E7) (b) and halogenated (TL205) (c) LCs. D) Fabrication of polymer nanofibers via CVP into an LC phase aligned perpendicular to the substrate. i) CVP; ii) LC removal. E) Scanning electron microscopy (SEM) images of nanofibers polymerized from 1a (10 mg) in 5CB. After the nanofiber synthesis, the LC template was removed. F) Optical microscopy image (crossed polars) of a nanofiber. Orientations of the analyzer (A) and polarizer (P) are shown in the white double-arrow cross. The yellow double arrow indicates the main axis of the nanofiber. G,H) Microscopy images (crossed polars) of the nanofiber with a quarter-wave plate with its slow axis (G, green double arrow) perpendicular (G) or parallel (H) to the fiber axis; lower-order interference colors (yellow in (G)) indicate a decrease in retardance. I) Analysis of interference colors of the nanofiber in (G) and (H) indicates that the polymer chains are aligned along the fiber axis. A–I) Reproduced with permission.[72] Copyright 2018, The Authors, published by American Association for the Advancement of Science.

exploiting the large diversity of crystalline MOFs networks with variable pores, crystal sizes, and shapes in CVD polymerization could provide a new platform for synthesis of 3D polymer nanostructures via confined CVD. Aiming for certain functions or post-CVD fabrication would need in-depth exploration.

Cyclophane-based multicomponent CVD (co)polymerization on sublimating ice particles as a dynamic template has been recently introduced that produces the corresponding poly(*p*-xylylene) (co)polymer porous 3D particles with hierarchical pore structures down to the nanometer scale, replicating the ice particle template (**Figure 17**).[77] This vapor-phase sublimation and deposition process occurs simultaneously at the dynamic vapor–solid interface, where the deposition of the poly(*p*-xylylene)s occupies the space vacated by the sublimating ice.[78] Ester alkyne and maleimide functionalities grafted to the corresponding functional PPXs surfaces were further conjugated by immobilizing the fluorescence probes, Alexa Fluor 555-labeled azide, and fluorescein-labeled (FITC) cysteine. This concept of vapor-phased fabrication, forming a scaffold matrix consisting of poly(chloro-*p*-xylylene)s, and encapsulating multiple living cells and growth factors into the compartmentalized combinations of controlled geometric dimensions represent a step forward with ample opportunities.[79] The concept of templated CVD opens a new platform for designing PPX with programmable geometry, alignment, and chemistry.

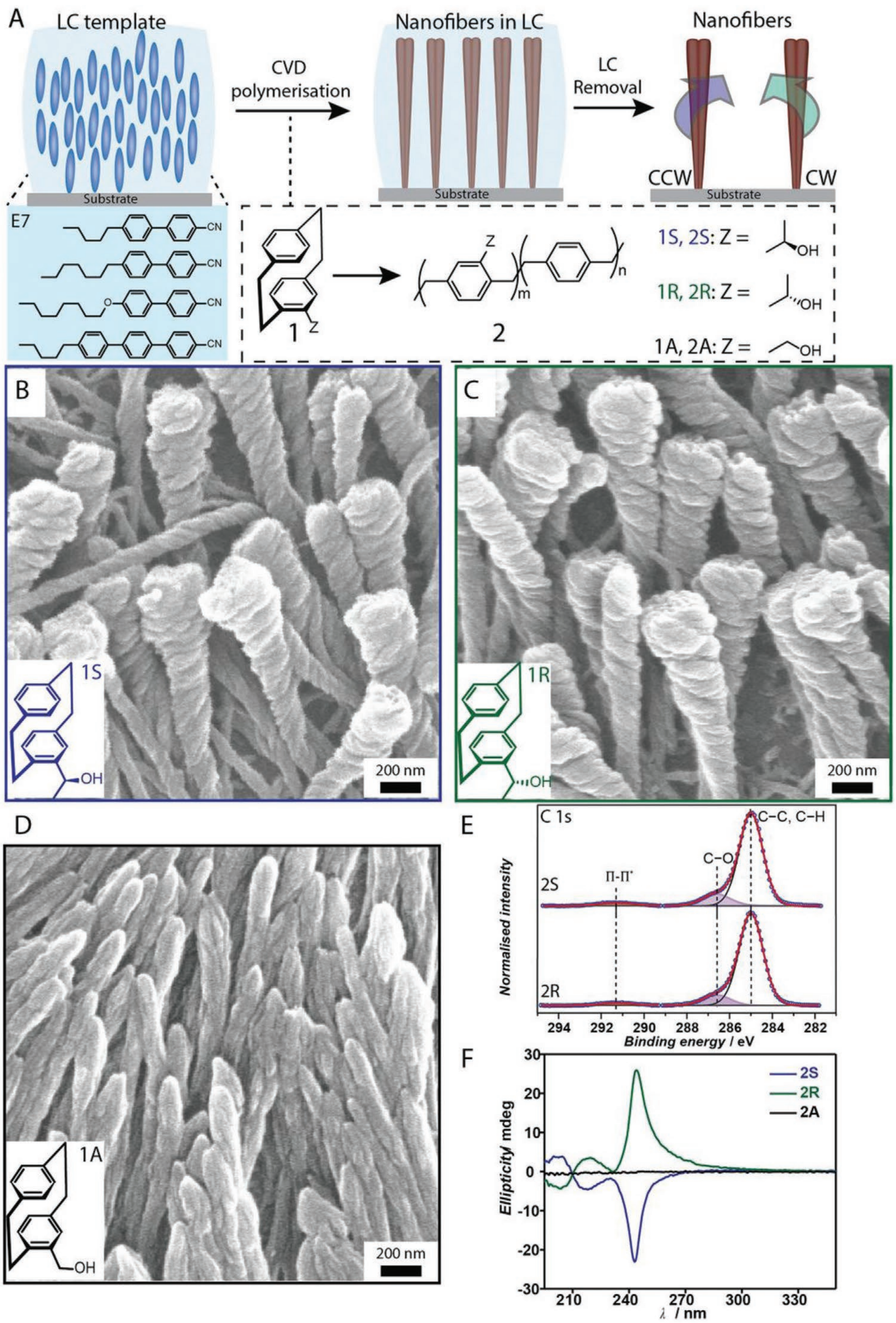


Figure 15. A) Templated synthesis of polymer nanohelices via CVD polymerization into a nematic LC film. Inset: Chemical representation of CVD polymerization of chiral and achiral precursors. B–D) SEM images of nanohelices 2S and 2R and achiral nanofibers 2A prepared by CVD polymerization of 1S (B), 1R (C), and 1A (D), respectively (the LC is homeotropically anchored on a surface before polymerization and was removed prior to SEM). E) High-resolution C1s XPS spectra of 2S and 2R confirming identical chemical composition for nanohelices with opposite handedness; these spectra are identical to the achiral nanofibers. F) Circular dichroism spectra of nanohelices 2S (blue) and 2R (green) and achiral nanofibers 2A (black). A–F) Reproduced with permission.[74] Copyright 2021, The Authors, published by Wiley-VCH.

4. Current Status, Challenges, and Future Research Directions

The concept of structuring CVD polymer materials are evolving beyond conventional trends. The interest in vapor-deposited materials and modulation at a molecular level via the synthetic design of the precursor components is progressing tremendously.[80] In this report, we provide an overview and highlight a few points in the context of the synthetic design of the CVD monomers, deposition techniques, and post-deposition

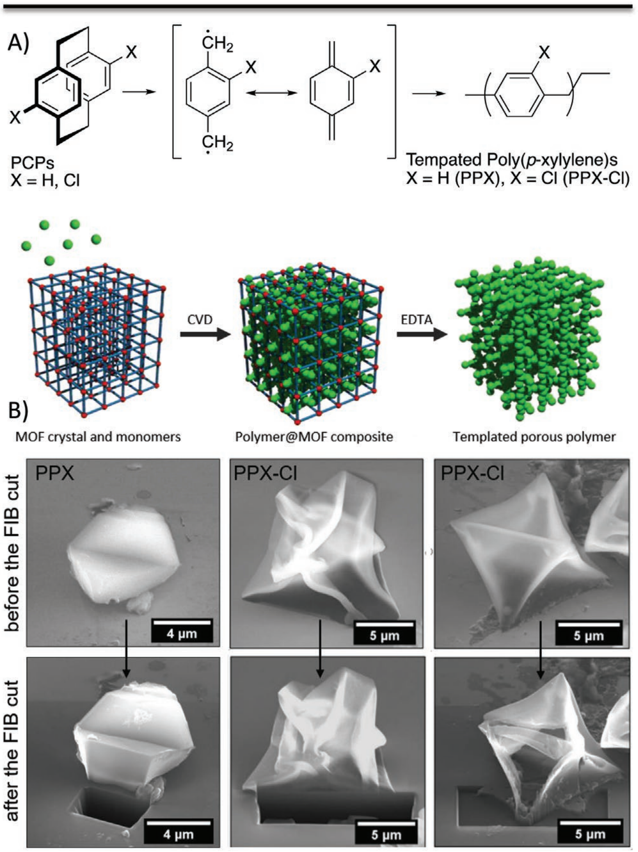


Figure 16. A) Schematic illustration of poly(*p*-xylylene)s polymerization via CVD using MOF crystals as a template; EDTA stands for ethylenediaminetetraacetic acid. B) Crystal shape and cross section of the parylene particles PPX and PPX-Cl before and after the focused ion beam (FIB-cuts). A,B) Reproduced with permission.[76] Copyright 2022, American Chemical Society.

fabrication from the overall application perspectives, particularly in biointerface engineering. We discuss CVD polymerization of PCPs onto surfaces to elucidate the role of molecular reaction control for major structural elements: including the primary sequence of CVD copolymers, topologically defined polymer architectures, and hierarchical controlled chirality in nanofiber-decorated polymer surfaces. Diverse application possibilities and tunable properties of the functional parylenes arise from the judicious design of the CVD monomers, that is, PCP precursor molecules. Incorporating synthetically tunable components into PCPs that are compatible under the CVD conditions and also synthetically tunable through post-CVD fabrications facilitate the formation of multifunctional interfaces. The chemical composition of the parylene polymers can be varied by tuning the polymer backbone or functional moieties grafted as a side-group. For instance, alkyne, thiol, hydroxyl, carbonyl, fluorinated groups, amino, and ester components can be substituted as side groups to the PCP scaffold. These chemical functionalities can be used as anchoring sites for tailoring post-CVD surface engineering without alteration of skeletal formats. Post-CVD fabrication strategies, for instance, azide–alkyne “click” chemistry, light-induced thiol–ene/thiol–yne reactions, aldehydes/ketones with hydrazides or alkoxyamines, and SI-ATRP have been demonstrated.

Beyond the synthetic design of the CVD precursors, employing technologically advanced and innovative deposition techniques for structuring parylenes could bring new capabilities and opportunities in CVD polymerization. Cyclophane-based CVD polymerization is compatible with most of the techniques for micro- and nanostructuring strategies such as microcontact printing, photopatterning, using a photomask, or lithographic techniques such as DPN. In a custom-built device setup, multiple PCP molecules, each functionalized with moieties of different chemical reactivity, can be deposited to generate multifunctional coatings and can be fabricated in a post-deposition process.

Despite the enormous progress in structuring parylenes, challenges remain that offer the opportunity for certain improvements. The precise control of deposition rates during CVD polymerization and continuous polymer film formation can be challenging considering PCP precursors with bulkier moieties because of their sublimation. Although commercial systems for CVD polymerization are available and a wide variety of PPX films can be prepared from PCP monomers, the tedious syntheses, selective derivatization of PCP, resolution, and sublimation of bulkier PCP monomers are often viewed as limiting steps in expanding this class of monomers. Synthesizing functionalized PCPs, in some cases can be a tedious endeavor because regioselective functionalization and resolution strategies pose certain synthetic challenges due to the unusual reactivity of PCP, especially when larger quantities of enantiomerically pure PCPs are needed. Efficient and novel synthesis routes with controlled functionalization of the PCP scaffolds would contribute to a broader platform for molecular surface engineering via CVD polymerization.

By replacing one or both benzene rings with heteroaromatics within the CVD-monomer could generate an entirely new class of skeletally novel polymers. This concept has been demonstrated by incorporating pyridinophanes into the polylutidine polymer backbone. Copolymerization of electron-rich and -poor precursor units could lead to new developments. Furthermore, developing cleavable or backbone-degradable polymers have been an inspiring long-standing research objective. Investing more efforts in developing backbone-degradable PPXs would open up new application possibilities. In general, parylene copolymers have a statistical monomer sequence. For instance, theoretically, employing asymmetrically substituted PCP in CVD polymerization, the repetition units can be connected head-to-head, head-to-tail, and tail-to-tail. Besides the statistical copolymer structures, sequence control during CVD polymerization could result in alternative outcomes, such as alternating copolymer sequences or forming two individual homopolymers. Hence, understating and enabling a strict sequence control would enable structuring of sequence-defined parylenes. Addressing composition control of the primary sequence of CVD copolymers would lead to a predictable (molecular) structure of the functional polymer layers. Molecular precision could directly translate into defined properties and functions and offers the unique opportunity to determine quantitative structure–property relationships.

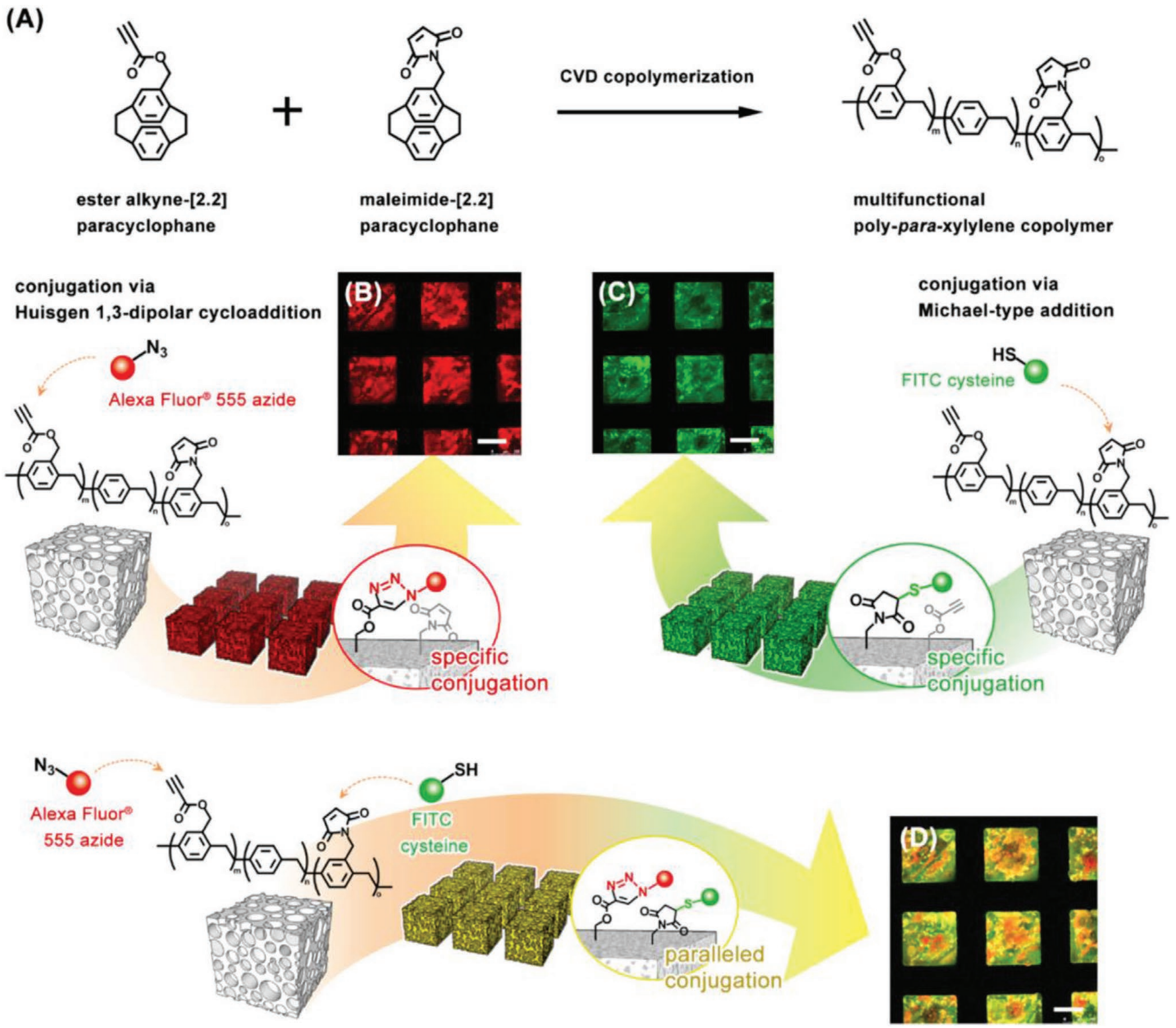


Figure 17. Multifunctional CVD on ice template. A) Reaction scheme using ester alkyne- and maleimide-functionalized *p*-xylylenes for copolymerization and deposition on the same ice template substrate to fabricate a porous and multifunctional poly(*p*-xylylene) material. B) Fluorescence microscopy image showing the specific conjugation of Alexa Fluor 555-azide (red channel) toward the ester alkyne groups on the interface of the porous material. C) Fluorescence microscopy image showing a second and specific conjugation of FITC cysteine (green channel) toward the maleimide groups on the same porous material. D) Paralleled conjugations of the two fluorescence molecules (overlaid image). Scale bars: 250 µm. Figure: Reproduced with permission.[77a] Copyright 2020, American Chemical Society.

The work shown in this report for templated CVD polymerization is focused on the use of nematic and cholesteric LC phases as well as MOF nanochannels. There is a plethora of other LCs phases that exhibit distinct molecular orderings, and in a similar way a large diversity of crystalline MOF networks is available with variable pores, crystal sizes, and shapes that can be examined as confined templates for the synthesis of 3D polymer nanostructures. Copolymerization strategy of multiple components and heteroaromatics-containing PCP precursor components can be combined with the concept of templated-CVD method to create novel class of polymers. We also believe that collaborative efforts combining expertise in organic synthesis, polymers, materials chemistry, and interface engineering will significantly contribute toward molecularly controlled structuring of soft matter with tailored architecture and function.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords

[2.2]paracyclophane monomer designs, biointerfaces, cyclophane-based chemical vapor deposition polymerization, parylenes synthesis, post-chemical-vapor-deposition fabrication, surface engineering

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