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A Dynamic Duo: Pairing Click Chemistry and Postpolymerization Modification To Design Complex Surfaces

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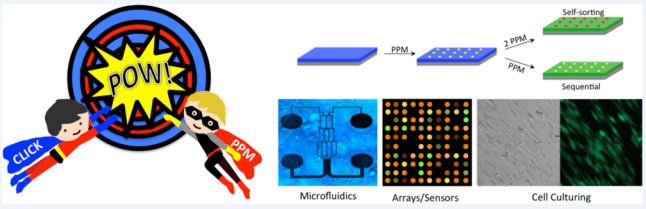
CONSPECTUS: Advances in key 21st century technologies such as biosensors, biomedical implants, and organic light-emitting diodes rely heavily on our ability to imagine, design, and understand spatially complex interfaces. Polymer-based thin films provide many advantages in this regard, but the direct synthesis of polymers with incompatible functional groups is extremely difficult. Using postpolymerization modification in conjunction with click chemistry can circumvent this limitation and result in multicomponent surfaces that are otherwise unattainable.



The two methods used to form polymer thin films include physisorption and chemisorption. Physisorbed polymers suffer from instability because of the weak intermolecular forces between the film and the substrate, which can lead to dewetting, delamination, desorption, or displacement. Covalent immobilization of polymers to surfaces through either a "grafting to" or "grafting from" approach provides thin films that are more robust and less prone to degradation. The grafting to technique consists of adsorbing a polymer containing at least one reactive group along the backbone to form a covalent bond with a complementary surface functionality. Grafting from involves polymerization directly from the surface, in which the polymer chains deviate from their native conformation in solution and stretch away from the surface because of the high density of chains. Postpolymerization modification (PPM) is a strategy used by our groups over the past several years to immobilize two or more different chemical functionalities onto substrates that contain covalently grafted polymer films. PPM exploits monomers with reactive pendant groups that are stable under the polymerization conditions but are readily modified via covalent attachment of the desired functionality. "Click-like" reactions are the most common type of reactions used for PPM because they are orthogonal, high-yielding, and rapid. Some of these reactions include thiol-based additions, activated ester coupling, azide−alkyne cycloadditions, some Diels−Alder reactions, and non-aldol carbonyl chemistry such as oxime, hydrazone, and amide formation. In this Account, we highlight our research combining PPM and click chemistry to generate complexity in polymer thin films. For the purpose of this Account, we define a complex coating as a polymer film grafted to a planar surface that acts as a template for the patterning of two or more discrete chemical functionalities using PPM. After a brief introduction to grafting, the rest of the review is arranged in terms of the sequence in which PPM is performed. First, we describe sequential functionalization using iterations of the same click-type reaction. Next, we discuss the use of two or more different click-like reactions performed consecutively, and we conclude with examples of self-sorting reactions involving orthogonal chemistries used for one-pot surface patterning.

1. INTRODUCTION

As thin-film technology continues to advance, the demand for chemical complexity on two- and three-dimensional surfaces with well-defined spatial control has significantly increased. This is especially true for new technologies such as sensors and diagnostic arrays, microfluidic devices, membranes with selective permeability, and mediation of interactions at the solid−biological interface. The ability to tune the interfacial properties such as wetting, surface energy, and adhesion allows one to control the interactions between the substrate and the surrounding environment. Polymer-based thin films containing reactive functionality offer significant advantages for the intricate design of complex coatings in terms of both structure and morphology.[1−4] Postpolymerization modification (PPM) using a variety of orthogonal coupling chemistries, also known as click reactions, is a strategy that has gained considerable attention because of their high reaction rates, chemical orthogonality, and mild reaction conditions, which are of critical importance when using delicate components such as biomacromolecules or nanostructures.[3,5,6] Multicomponent surfaces can be generated either through sequential click reactions or in a self-sorting manner, in which multiple modifications are performed in one-pot.

Polymer thin films are formed in two ways, by tethering of polymer chains to a surface either physically (physisorption) or

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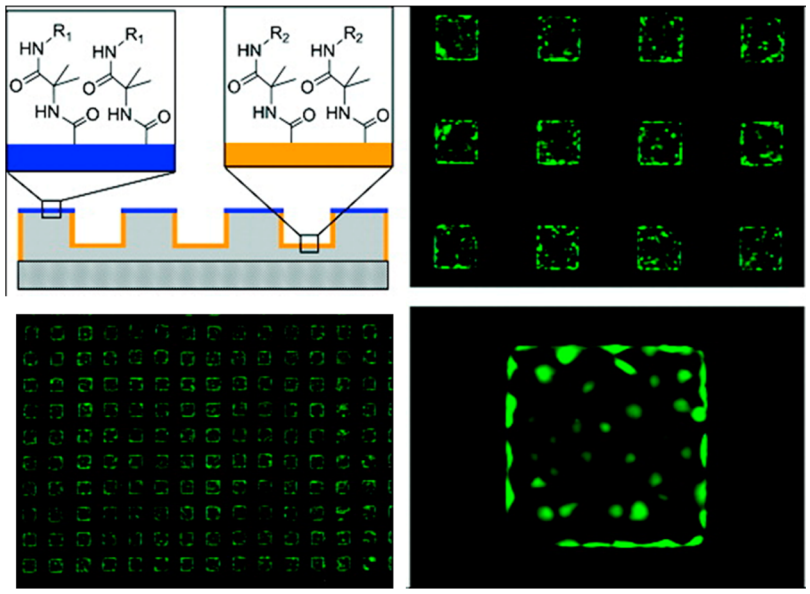

Figure 1. Schematic illustration of microwell modification and fluorescence imaging of kidney fibroblast cells at various magnifications. The microwells are 300 μm × 300 μm. (Adapted from ref 27. Copyright 2011 American Chemical Society.)

chemically (chemisorption). Physisorbed polymer films utilize weak intermolecular forces such as hydrogen bonding, electrostatic interactions, and hydrophilic/hydrophobic interactions to adhere to the substrate. These types of films suffer from the major disadvantages of desorption, dewetting, displacement, or delamination, all of which ultimately lead to failure.[7] Applications requiring thin films that are robust and more stable utilize chemisorbed polymers that are covalently immobilized on a surface. The preparation of covalently attached polymers can be completed through either a "grafting to" or a "grafting from" approach. Both techniques have advantages and disadvantages, which depend on the final application of the film and the desirable characteristics that are required. In the grafting to technique, a polymer containing one reactive end group or several reactive groups along the backbone adsorbs and forms a covalent bond with a complementary functionality on the surface. One major advantage of this method is that the polymer can be fully characterized (molecular weight, dispersity, etc.) before grafting. However, this process is self-limiting both thermodynamically and kinetically and results in films that are less than ∼15 nm in thickness.[7] On the other hand, the grafting from approach, which involves polymerization directly from a densely packed self-assembled monolayer of initiators, results in polymer chains that stretch away from the surface because of excluded volume and steric constraints. The resulting films generally have a high grafting density and are known as polymer brushes. Benefits of this technique include thicker films, a greater volume of functional groups, and unique interfacial properties that are a consequence of the polymer chain conformation.

Whether radical- or metal-mediated, the polymerization conditions required to make polymers have limitations in terms of functional group tolerance. For example, many polymerizations require organic solvents, UV light, or high temperatures, which can denature biomacromolecules or degrade other highly reactive functionalities. In these cases, PPM can be utilized to generate polymers with sophisticated chemical functionality that would otherwise be difficult to produce. With PPM, a monomer containing a reactive group is first polymerized, and this is followed by a second reaction to covalently attach the desired functionality. Many of the reactions used for PPM are "click-like" reactions, which are defined as being modular, wide in scope, high-yielding, and rapid.[8−10] Examples of these reactions include thiol-based additions, activated ester coupling, azide−alkyne cycloadditions, some Diels−Alder reactions, and non-aldol carbonyl chemistry such as oxime, hydrazone, and amide formation.[8]

This Account focuses on the generation of complex surfaces in which multiple functionalities are attached to a surface through PPM. For the purpose of this Account, we define a complex coating as a polymer film covalently grafted to a solid, planar surface that acts as a template or platform on which two or more discrete chemical functionalities can be patterned through PPM. The rest of this Account is arranged in terms of the PPM sequence used to obtain these patterns. First, we describe different categories of click-type reactions that are performed sequentially, including some of the advantages and limitations that each type of reactive functionality possesses. Next, we discuss the use of two or more different click-like reactions that are performed consecutively. Finally, we review self-sorting reactions that involve the patterning of orthogonal chemical functionalities in one pot.

2. PATTERNING WITH CONSECUTIVE FUNCTIONALIZATIONS OF THE SAME CLICK-TYPE REACTION

2.1. Active Esters

Generally, polymers with alkyl ester pendant groups are not reactive toward nucleophiles because of the lack of electrophilicity at the carbonyl carbon. However, when the alkoxy group is strongly electron-withdrawing, the enhanced reactivity of the carbonyl group makes it susceptible to attack by strong nucleophiles. These compounds are called activated esters, and when the nucleophile is an amine, this reaction is known as aminolysis. Polymer backbones containing activated esters are probably the most common substrates for PPM.[11] This is

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particularly true for biological conjugation because of the numerous free amines present in proteins from either lysine residues or the N-terminus of the peptide.[12] One disadvantage of this immobilization chemistry is the potential lack of orientation control with a substrate that contains many reactive amino groups. With activated esters, high yields can be obtained under very mild reaction conditions, providing excellent biocompatibility.[13] Several different active esters are used in surface PPM, the most common being azlactones,[14−17] *N*-hydroxysuccinimide (NHS) esters,[4,18−21] and pentafluorophenyl (PFP) esters.[22−26]

Azlactones are a special type of cyclic activated ester that can be ring-opened and do not produce a leaving group fragment when subjected to aminolysis.[14] They generally have lower reaction rates than NHS and PFP activated esters. Patterning of azlactone-based polymers, in conjunction with microwell arrays, has been used to improve cell confinement and growth.[27] Broderick et al.[27] used layer-by-layer assembly to generate polymer thin films containing multilayers of poly(2-vinyl-4,4-dimethylazlactone) (PVDMA) and branched polyethylenimine onto polyurethane microwell arrays. Patterning was achieved by placing the microwell topside down onto an aqueous solution of D-glucamine that was spread over a glass slide. The glucamine provided cell-resistant surfaces surrounding the wells that still contained reactive azlactones coating their interior. The entire microwell surface was then subjected to a solution of kidney fibroblast cells. After 1 day, staining was used to determine viability and the position of cell attachment. Fluorescence images showed viable cells within the wells but no cells on the surfaces functionalized with glucamine, unlike the control, where cell attachment occurred over the entire substrate (Figure 1). Cell confinement and proliferation were observed to last for up to 28 days.

Katz et al.[28] utilized an *o*-nitrobenzyl ester photoprotecting group (ONB PPG) in conjunction with activated esters to pattern two different proteins onto oxide surfaces. Poly(acrylic acid) (PAA) was absorbed onto self-assembled monolayers of 3-aminopropyltriethoxysilane, which left acrylic acid residues available for conjugation with biotin-amine using 1-ethyl-3-(dimethylaminopropyl)carbodiimide (EDC) activation. Terpolymers of methyl methacrylate, *o*-nitrobenzyl methacrylate, and poly(ethylene glycol) (PEG) methacrylate were prepared by free radical polymerization (FRP) to afford water-soluble comb copolymers with short PEG side chains. These terpolymers were spin-coated on top of the biotinylated surface and used as a negative photoresist. Shadow masks were placed on the substrate during UV irradiation, resulting in cleavage of the ONB PPG in the exposed areas. After deprotection, hydrogen bonding between methacrylic acid and PEG caused the exposed areas to become insoluble in water. After the terpolymer that was shielded by the shadow mask was rinsed away, the biotinylated surface was exposed and reacted with Alexa Fluor 647-conjugated streptavidin. Upon simple rinsing of the substrate with a buffered solution of a specific pH, the once insoluble terpolymer dissolved, exposing the unreacted biotin groups. A Texas Red-conjugated streptavidin was then reacted with the remaining biotin, providing distinct areas of chemical functionality. By adjusting the ratio of the three components in the comb copolymer, the pH at which dissolution of the UV-exposed polymer occurs could be specifically tuned.

2.2. Thiol-Based Click Reactions

Thiol-based click reactions (thiol−yne, thiol−ene, thiol−isocyanate, thiol-Michael addition) are extremely versatile and robust.[29] Unlike other PPM reactions, thiols can couple with various types of functional groups with high efficiency in the presence of water and oxygen.[30] These reactions occur rapidly at room temperature and are metal-free,[31] making thiol-click reactions good candidates for PPM in biological systems. Another added benefit to using thiol-click reactions is the number and diversity of commercially available thiols. This class of reactions provides a large toolbox that can be used to tune the interfacial properties of surfaces without the need for lengthy synthetic schemes, although modification of biological substrates often requires reduction of disulfides to fully access the reactive thiol group.

Our groups, along with others, have exploited several thiol-mediated reactions as a modular PPM approach to fabricate spatially and temporally patterned polymer brush surfaces.[31−34] We first reported the combination of surface-initiated FRP (SI-FRP) and radical-mediated thiol−alkyne PPM.[31] In this approach, SI-FRP and subsequent deprotection of trimethylsilyl-protected propargyl methacrylate (PgMA) provided polymer brushes with pendant terminal alkyne functionality. These alkyne-functionalized polymer brushes were then modified using photochemically induced thiol−yne reactions with a variety of thiols that resulted in pendant dithioether adducts along the polymer backbone. The versatility of the thiol−yne approach was demonstrated using a library of eight thiols, including hydrophilic (i.e., mercaptopropionic acid, MPA), hydrophobic (i.e., 1-dodecanethiol, DDT), and biorelated (i.e., thiocholesterol) functionalities. PPM with low-molecular-weight thiols was observed to be quantitative within minutes, while higher-molecular-weight thiols resulted only in partial conversion to the 1,2-dithioether adducts because of steric congestion within the system. The modularity of the thiol−alkyne platform was further illustrated through sequential and site-selective photopatterning to produce multicomponent hydrophobic/hydrophilic (DDT/MPA) surfaces (Figure 2), both in the lab and outdoors using sunlight as an irradiation source. In 2011, we also reported a related thiol−isocyanate click approach involving SI-FRP and PPM patterning of poly(2-isocyanatoethyl methacrylate) (NCO) platforms with a library of thiols through reactive microcapillary printing (R-μCaP).[33]

2.3. Azide−Alkyne Cycloaddition

Copper-catalyzed azide−alkyne cycloaddition (CuAAC) is a common way to couple molecules to surfaces, but in systems involving live cells, such as the azlactone example above, the copper catalyst can prove cytotoxic.[35] Because of this issue, strain-promoted azide−alkyne cycloaddition (SPAAC), a metal-free click reaction between cyclic alkynes and azides, has been developed, although these reactions are orders of magnitude slower than CuAAC. We have employed poly(*N*-hydroxysuccinimide 4-vinylbenzoate) [poly(NHS4VB)] active ester platforms for PPM with a cyclopropenone-masked dibenzocyclooctyne (DIBO) (Scheme 1).[19] The cyclopropenone moiety, which is unreactive toward azides, undergoes rapid decarbonylation when exposed to UV irradiation (350 nm). The resulting unmasked dibenzocyclooctyne is then available for catalyst-free click chemistry with azides. Exposure of these photoprotecting groups in the presence of a shadow mask provided distinct areas of reactive alkynes while leaving cyclopropenone-protected DIBO in the areas shielded from

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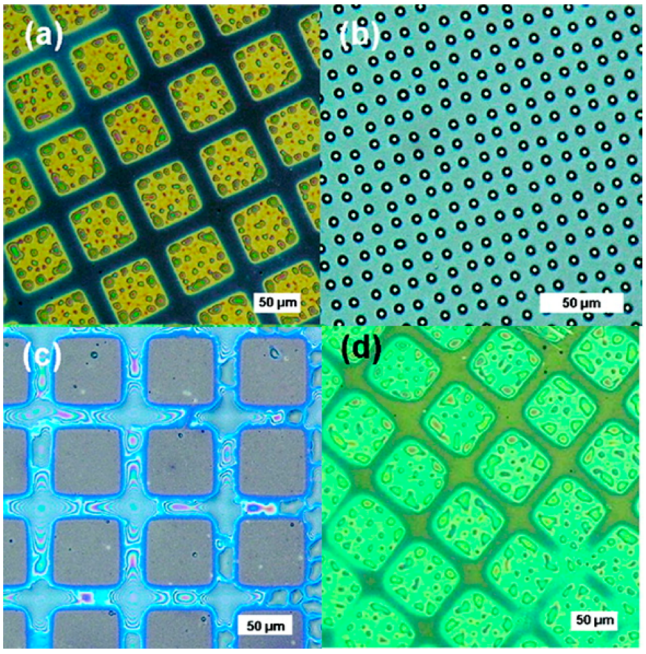


Figure 2. Condensation images of sequential thiol−yne micropatterned brushes showing selective nucleation of water droplets on the hydrophilic MPA areas. (a) MPA/DDT (squares/bars), 300 mesh. (b) MPA/DDT (squares/bars), 2000 mesh. (c) Inverse DDT/MPA (squares/bars), 300 mesh. (d) Sunlight MPA/DDT (squares/bars). The color variations result from thin-film interference under humid conditions. (Adapted from ref 31. Copyright 2009 American Chemical Society.)

photoconversion. Initial cycloaddition with an azide-containing dye was complete in 20 min, after which the substrate was flood-irradiated to release the remaining cyclopropenones. This was followed by a second SPAAC reaction with a different azido dye that yielded patterned chemical functionality.

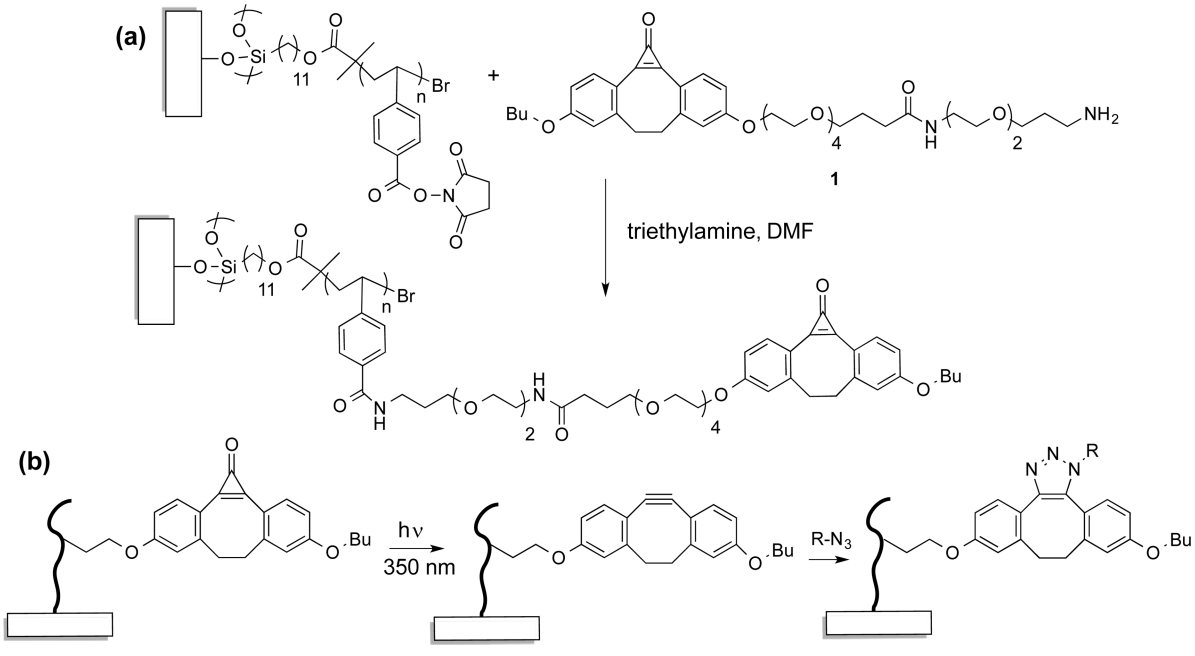
2.4. Diels−Alder Reactions

More recently, we have studied photogenerated 2-naphthoquinone-3-methides (oNQMs) that undergo a hetero-Diels−Alder reaction with vinyl ethers for multicomponent patterning.[36] First, aminolysis of a poly(NHS4VB) film with the oNQM chemical precursor 8-(2-(2-(2-aminoethoxy)ethoxy)ethoxy-3-(hydroxymethyl)naphthalene-2-ol (NH_2-TEG-NQMP) was performed. Photodehydration of NQMP under exposure to 300 or 350 nm light results in the formation of oNQM, which undergoes very rapid ($k > 10^4$ M^{-1} s^{-1}) hetero-Diels−Alder addition to vinyl ethers.[34] The unreacted oNQM moieties add water to regenerate the starting material within 100 ms. NQMP is unreactive toward vinyl ethers in the dark, which allows for photolithographic modification in the presence of a shadow mask (Figure 3).[37] Flood irradiation with a second vinyl ether can be performed without harming the newly formed naphthopyran linker, which is photochemically stable. The poly(NQMP-4VB) brush itself also can be used as a new platform for concurrent click reactions because the photo-Diels−Alder reaction is orthogonal to many other modifications described herein. To demonstrate this orthogonality, a propargyl vinyl ether, an azido vinyl ether, and a vinyl ether−biotin conjugate underwent photoligation with poly(NQMP-4VB) in the presence of a shadow mask to provide patterned areas of alkyne, azide, and biotin functionalities, respectively. The azide patterns were subjected to SPAAC with an alkyne-containing red fluorescent dye, while CuAAC of the alkyne patterns was performed with an azido-green fluorescent dye and FITC-Avidin was conjugated with the biotinylated surface; all of these reactions proved to be efficient. In each case, the poly(NQMP-4VB) surface showed little to no cross-contamination in the unexposed areas.

2.5. Aldehydes

A common strategy to attach carbohydrates and other glycoproteins to surfaces involves aldehyde−hydrazide coupling.[38−41] While this conjugation has been used thoroughly in

Scheme 1. (a) Attachment of Cyclopropenone 1 to Poly(NHS4VB) Brushes; (b) Subsequent Photoactivation and Functionalization of the Polymer Brush Pendant Groups with Azide-Derived Fluorescent Dyes[19]



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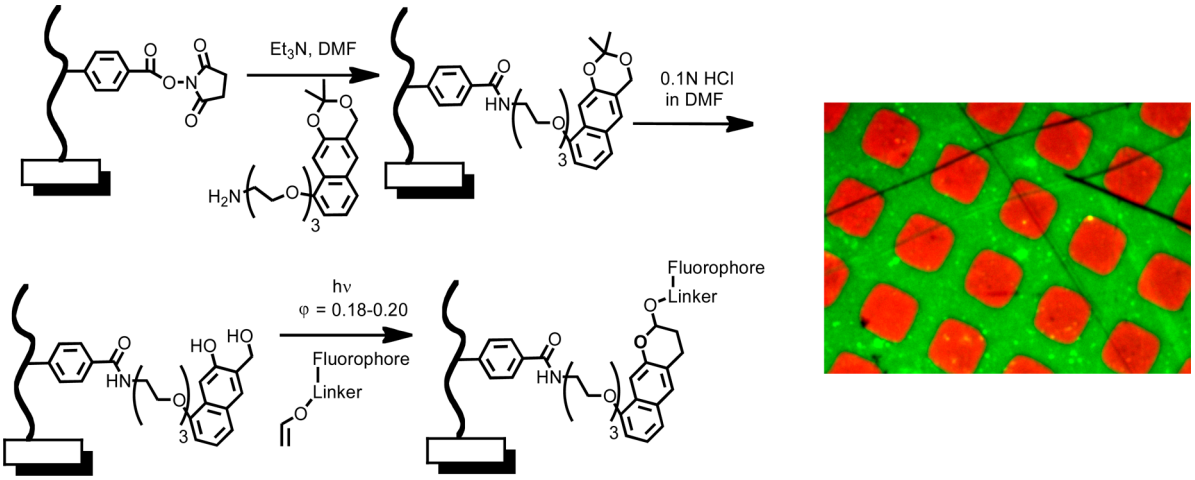

Figure 3. (left) Scheme showing the PPM process: poly(NHS4VB) to poly(NQMP-4VB) to simultaneous production of oNQM and functionalization with a Diels–Alder reaction. (right) Fluorescence image of a patterned substrate after sequential immobilization of rhodamine B (red) and fluorescein (green) vinyl ethers.

biological applications for labeling,[12] its use in patterning with polymer brushes and PPM is rare. This reaction is especially significant for immobilizing carbohydrates because the reducing end of sugars contains an aldehyde functional group in the ring-opened form. The aldehyde can directly be used either for reversible (imine formation) or permanent (reductive amination) immobilization without the need for further chemical derivatization.[42]

Chemical vapor deposition (CVD) polymerization has been used by Lahann and co-workers as a method to generate biomimetic surfaces based on aldehyde–hydrazide coupling.[38] This solvent-free polymerization technique is useful for making complex surfaces because polymer films can be generated on various substrates such as gold, silica, and polydimethylsiloxane (PDMS).[38] This technique generates cross-linked polymer networks and affords excellent control over the film thickness. An aldehyde-containing monomer, 4-formyl[2,2]-paracyclophane, was polymerized via CVD to generate poly[(4-formyl-*p*-xylylene)-*co*-(*p*-xylylene)] on the surface of various substrates. Reactive microcontact printing (R-μCP) was used to stamp adipic dihydrazide, a small molecule containing two hydrazide groups, one to react with aldehydes present within the polymer film and the other to react with the reducing end of a sugar.[38] 2-α-Mannobiose was then attached to the surface only in areas containing adipic dihydrazide and was visualized using a rhodamine-conjugated mannose-specific lectin. Although not demonstrated in this work, the latent aldehydes present after R-μCP are still available for further conjugation. With respect to this approach, further experimentation is required to determine the reduction of reactive groups and extent of cross-linking that occurs when a dihydrazide linker is used.

In a more recent study, aldehydes in patterned polymer films were used for protein micropatterning.[39] Surface-initiated atom transfer radical polymerization was used to generate brushes of poly{*N*-[(2,2-dimethyl-1,3-dioxolane)methyl]acrylamide}, a polymer containing acetal-protected diols that were deprotected postpolymerization to yield poly[*N*-(2,3-dihydroxypropyl)acrylamide] (PDHPA). By means of a combination of photo- and wet chemical lithography, a photoresist was used to mask areas of the PDHPA substrate, and the remaining exposed areas were then subjected to mild oxidation using sodium periodate. After removal of the remaining photoresist, the resulting surface contained patterns of aldehydes and diols. The PDHPA areas were found to be nonfouling because of their inherent neutrality and hydrophilicity, which prevented hydrophobic interactions that would lead to nonspecific absorption.[43] The regions containing aldehydes were used to immobilize proteins onto the substrate. A rhodamine–streptavidin solution was initially used for imine formation, and the imines were then reduced to the amines using sodium cyanoborohydride. After the streptavidin functionalization, the antifouling PDHPA areas either remained as is or could be further oxidized to pattern multiple proteins. To demonstrate this, oxidation of latent diols followed by conjugation with FITC-BSA yielded a multiprotein-micropatterned surface.

3. PATTERNING WITH CONSECUTIVE FUNCTIONALIZATIONS USING MULTIPLE CLICK-TYPE REACTIONS

As described above, many surface PPMs have utilized the same click reaction performed sequentially using either photolithography or microprinting. In some cases, however, using different click reactions to pattern the same surface[19,22,23,36,44−47] provides many advantages in terms of orthogonality, functional group compatibility, and site isolation, which acts to minimize nonspecific immobilization.

3.1. Radical/Base-Catalyzed Thiol Reactions

The previous examples of thiol-mediated PPM utilized the reaction of thiol modifiers in solution with alkyne or isocyanate moieties immobilized on the brush surface.[31,33,34] Conversely, immobilization of pendant thiols as reactive moieties on the brush surface enables postmodification processes using a wide selection of functional acrylates and maleimides via thiol-Michael addition or functional isocyanates via thiol–isocyanate reactions. Unfortunately, the highly reactive nature of unprotected thiols precludes their use as pendant functional groups in radical-mediated polymerizations because of their large chain-transfer constants and facile oxidation to disulfides. To circumvent these issues, we recently employed PPGs, including ONB and *p*-methoxyphenacyl (PMP) thioethers, as latent thiol functionalities along the polymer brush backbone.[32]

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Addressing the PPGs with UV light facilitated efficient deprotection of the ONB or PMP groups while simultaneously yielding the reactive thiol for additional postmodification with isocyanates and maleimides. Micropatterns of multiple functionalities with sharp lateral resolution across the brush surface were obtained using a combination of photolithography and sequential orthogonal thiol-click reactions. After cleavage of the PPGs in distinct areas of the brush using a shadow mask and UV light, a base-catalyzed thiol−isocyanate reaction was performed to couple fluorescein isothiocyanate to the surface. Flood irradiation removed the PPGs initially preserved by the shadow mask, providing reactive thiols for the immobilization of Texas Red C2 maleimide via a thiol-Michael addition. We extended this concept to block copolymer brush architectures where ONB-protected thiols were present in either the buried or exposed block, enabling selective modification of chemical functionality vertically throughout the brush.

3.2. Oxime/CuAAC

Oximes, which are formed through the condensation of aldehydes or ketones with hydroxylamine, have also recently been used for complex surface modification.[45] The Maynard group used electron-beam lithography to selectively cross-link eight-armed star polymers of PEG containing terminal aminooxy and alkyne functional groups. Oxomyoglobin and azidoubiquitin were then patterned sequentially through oxime and CuAAC reactions, respectively, followed by conjugation with protein-specific antibody tags. Areas between the micro-protein patterns showed excellent nonspecific binding due to the high density of PEG realized through the star polymer geometry as well as the absence of cross-contamination between protein zones. Vertical multilayer click protein patterns were also demonstrated using consecutive electron-beam lithography and protein conjugation steps.

3.3. Aldehyde/CuAAC

Lahann recently developed a new type of CVD polymerization, vapor-assisted micropatterning in replica structures (VAMPIR), that has been used for the deposition of patterned polymer thin films.[44] Two functionalized *p*-xylylene precursor monomers, one having an aldehyde functionality and one containing an alkyne, were polymerized sequentially with a PDMS mold placed directly onto the substrate before the second polymerization. The aldehydes present on the resulting patterned film were modified with adipic dihydrazide in order to attach mannobiose to the surface. CuAAC was used to react an azidogalactose with the free alkynes, providing regions of different sugars (Figure 4). Lectins specific for mannobiose and β-galactose were conjugated to the surface in order to visualize the well-defined pattern.

3.4. Acyl Ketene/TAAC

Copolymers containing both alkyne and azide residues have been used by Hawker to generate cross-linked polymer networks with residual reactive groups available for further functionalization.[47] Styrene, vinylbenzyl azide, and a TMS-protected propargyloxystyrene were copolymerized using FRP conditions. After deprotection of the alkyne, the copolymer was spin-coated onto a hydrophobic surface and heated to cross-link the film via thermal azide−alkyne cycloaddition (TAAC). The concentration of reactive moieties remaining after cross-linking was easily tuned by adjusting the annealing temperature, controlling the mobility of the polymer chains and ultimately the density of cross-linking. Thermal microcontact printing was

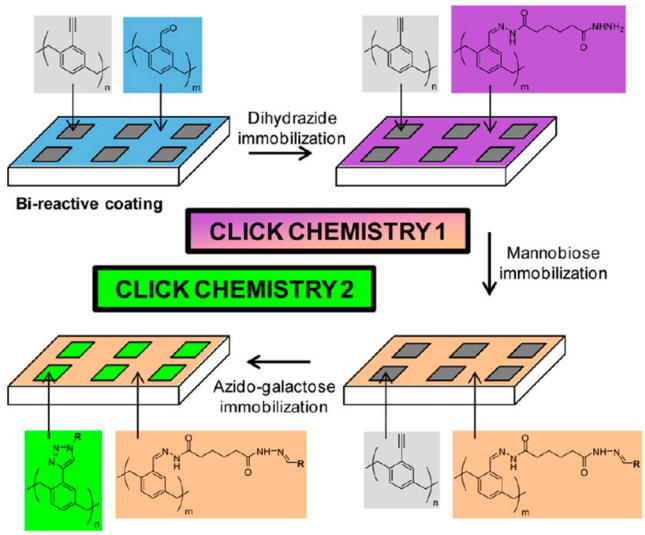

Figure 4. Schematic illustration of the strategy used for successive immobilization of two saccharides on microstructured CVD coatings. (Reproduced from ref 44. Copyright 2013 American Chemical Society.)

used to introduce new functionalities in combination with azide−alkyne cycloaddition. A third type of monomer, 2,2,6-trimethyl-5-(4-vinylbenzyl)-4*H*-1,3-dioxin-4-one, an acyl ketene precursor, was added to the copolymer to demonstrate the orthogonality of TAAC with other reactive chemistries. The acyl ketene precursor undergoes thermolysis at much higher temperatures to generate the corresponding ketene, which is an excellent electrophile that is reactive toward a variety of nucleophiles. After spin-coating of the copolymer containing the three reactive groups, the film was cross-linked at 90 °C by way of TAAC. Micropatterning of the surface-bound alkynes and azides was also performed at 90 °C. The substrate was then heated to 150 °C in order to activate the ketene in the presence of a red amine dye to produce a trifunctional surface (Figure 5). The high temperatures required for activation are a potential disadvantage and can limit the types of molecules available for patterning.

4. PATTERNING WITH MULTIPLE CLICK-LIKE REACTIONS IN ONE POT

Self-sorting is defined as the ability to distinguish between self and nonself within a complex mixture. This is a cornerstone of supramolecular chemistry in biology but far less common in synthetic systems.[48] Creating self-sorting surfaces, or surfaces that contain reaction sites for two or more types of orthogonal chemistries, is a method that can be used to generate complex functionality through one-pot PPM reactions.[22,23,46] These relations result in the ability to perform multiple PPM reactions simultaneously, which minimizes the number of synthetic steps, protecting groups, and workup procedures that occur in many of the patterning examples described above.

4.1. CuAAC/Aminolysis

Gleason has fabricated self-sorting surfaces through a combination of capillary force lithography (CFL), plasma-enhanced chemical vapor deposition (PECVD), and initiated chemical vapor deposition (iCVD).[46] A polymer bilayer consisting of cross-linked poly(allylamine) (PAAm) and non-cross-linked poly(propargyl methacrylate) (PPMA) was synthesized using consecutive PECVD and iCVD, respectively.

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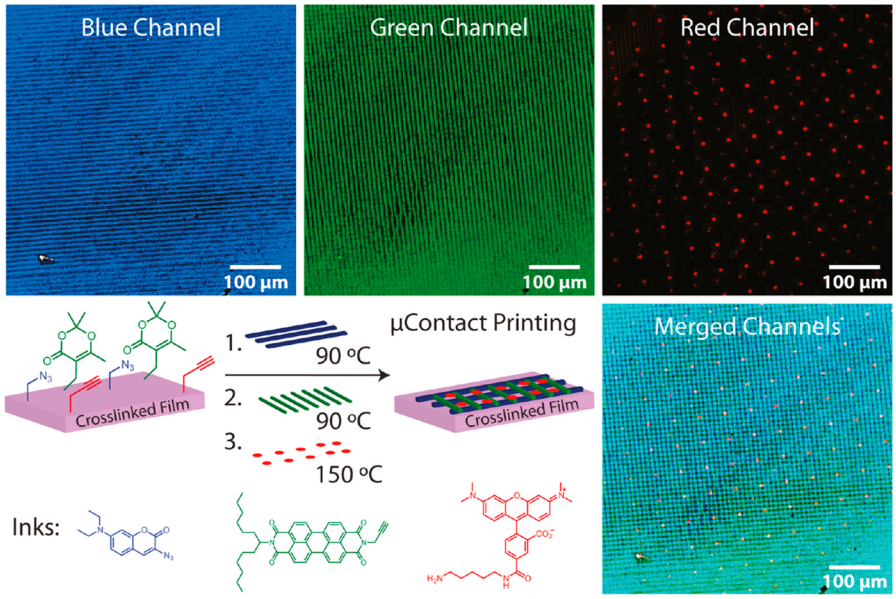

Figure 5. Trifunctional polymer films that were functionalized in a three-step process with blue, green, and red dyes orthogonally using thermal microcontact printing. (Reproduced from ref 47. Copyright 2011 American Chemical Society.)

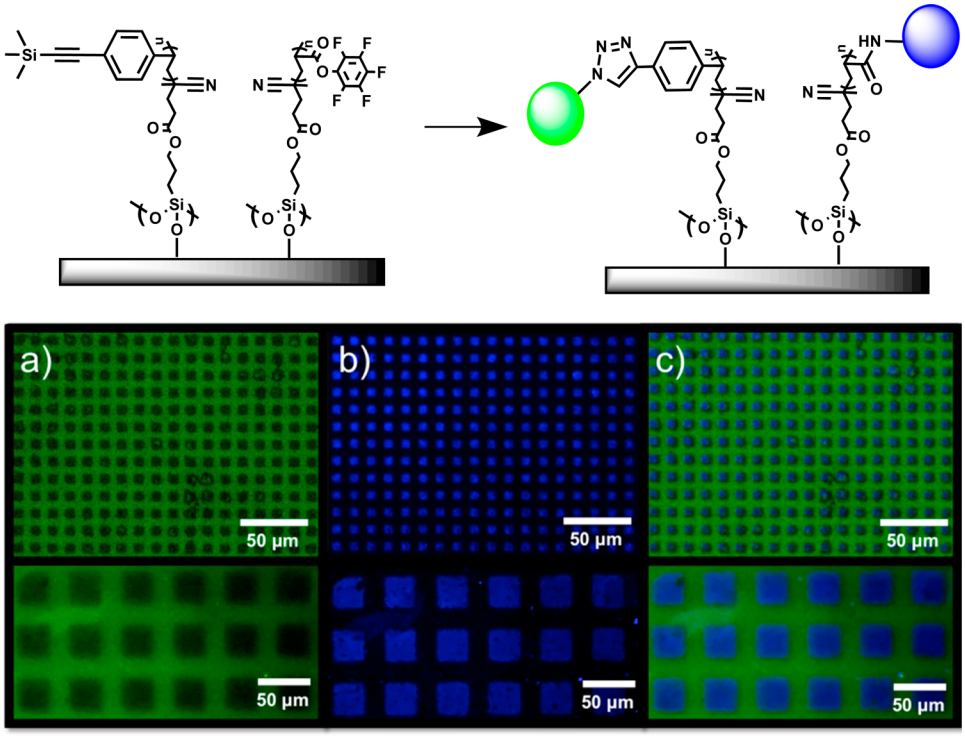

Figure 6. (top) Schematic illustration of one-pot functionalization. (bottom) Fluorescence microscopy images of patterned surfaces fabricated through sequential free radical polymerizations and self-sorting postpolymerization modification. Top row: square grids with a 12.5 μm pitch. Bottom row: square grids with a 62 μm pitch. (a) PFPA functionalized through aminolysis with AMP. (b) TMSES functionalized through CuAAC with AF. (c) Excitation of both dyes. (Adapted with permission from ref 22. Copyright 2013 American Chemical Society.)

During the CFL patterning process, which involved annealing above the glass-transition temperature (T_g) of the non-cross-linked PPMA layer, well-defined areas of PAAm and PPMA were generated. An azidorhodamine dye and an NHS-fluorescein dye were then reacted with the polymer surface from a single solution that contained a mixture of the two dyes. In an orthogonal, self-sorting fashion, the azidorhodamine dye formed triazole linkages with the surface-bound alkynes of PPMA, while the NHS-fluorescein conjugated only with the free amines of the PAAm sections through aminolysis.

We recently developed an activated ester platform based on poly(pentafluorophenyl acrylate) [poly(PFPA)][24] for the generation of self-sorting surfaces because of its increased reactivity toward nucleophiles and excellent aqueous stability.[22,23] In our first report, poly(PFPA) brushes were grafted from oxide surfaces using photoinitiated SI-FRP in the presence

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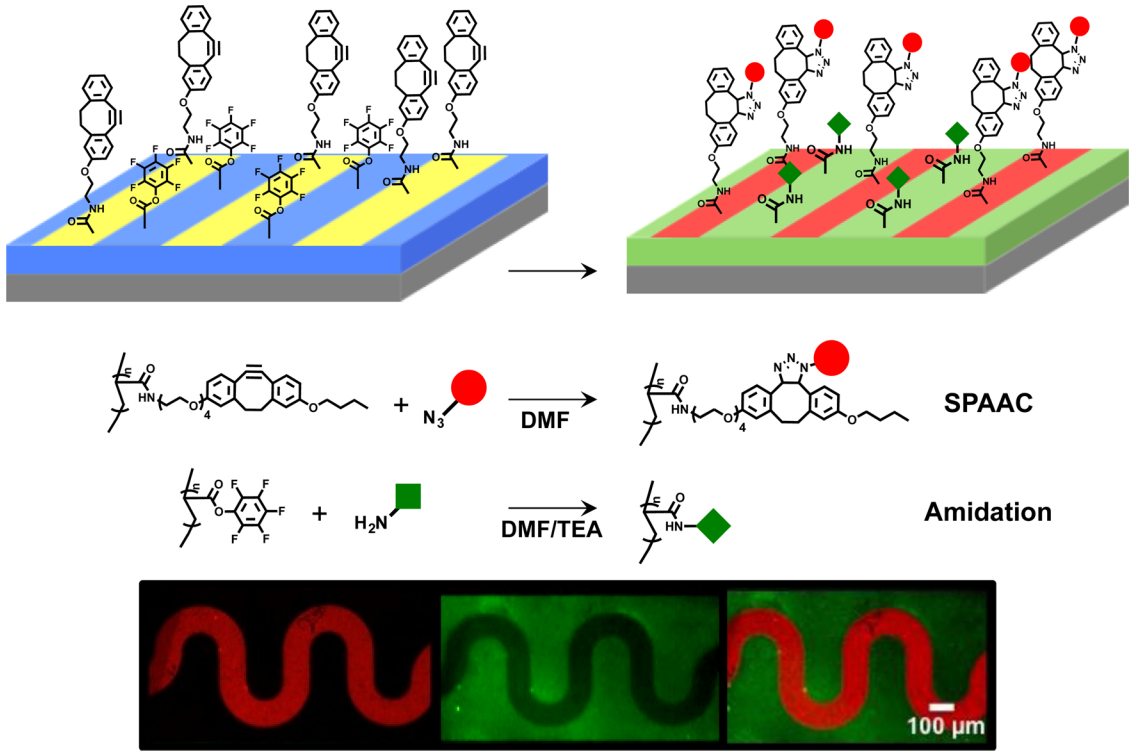

Figure 7. (top) Representative scheme of the one-pot, self-sorting SPAAC/aminolysis reaction on a patterned surface. (bottom) Fluorescence microscopy images of patterned surfaces. (Reproduced with permission from ref 23. Copyright 2013 Royal Society of Chemistry.)

of a shadow mask. This generated patterns of poly(PFPA) and also preserved surface-bound initiators for a subsequent polymerization. 4-(Trimethylsilyl)ethynylstyrene (TMSES) was then polymerized from the remaining initiators with flood UV irradiation. These two monomers undergo modular click reactions, aminolysis and CuAAC,[3] that can be performed in one pot. To demonstrate this, a mixture of 1-aminomethylpyrene (AMP) and 5-azidofluorescein (AF) was used to generate a multicomponent surface with little to no cross-contamination (Figure 6). Deprotection of the alkyne prior to PPM was not required, as heating the solution allowed for dual desilylation/CuAAC through a copper acetylide intermediate.[22,49] While not observed in this report because the polymerizations were run to high conversion, particular care must be taken to destroy all of the radical initiators within the region where the first polymerization occurred to ensure that cross-contamination between the two reactive functionalities does not occur.

4.2. SPAAC/Aminolysis

Because of the inherent limitations of multiple polymerizations, potential for cross-contamination, and monomer restrictions when photoinitiated SI-FRP is used, we recently developed a grafting to method for polymer brush generation using poly(PFPA).[23] This polymer can be prepared on a large scale using conventional FRP and has excellent solubility for subsequent characterization. Because of the high reactivity of the PFP leaving group, we observed that poly(PFPA), when annealed above T_g in an inert atmosphere, can directly conjugate the polymer to the silanol groups on oxide substrates while leaving ample reactive ester functionality for further conjugation by PPM. We also found that thermal annealing under ambient conditions (i.e., water present) caused hydrolysis and the formation of anhydride cross-links, which lead to thicker films. We then used reactive microcapillary printing to functionalize discrete areas of the brush with an amino-DIBO derivative. In a one-pot dual functionalization, the micropatterned substrate was then subjected to aminolysis [poly(PFPA) regions] and SPAAC [poly(DIBO) regions] using amine and azide dyes. Figure 7 shows the high-fidelity patterns with no cross-contamination between regions that were observed with fluorescence microscopy.

5. CONCLUSIONS

In this Account, we have described the recent advances in generating complex surfaces through postpolymerization modification of polymer thin films that are covalently grafted to surfaces. Polymer-based platforms offer an immense number of advantages over other coating technologies because of the special interfacial properties and boundless versatility they provide. PPM and click-like reactions represent a powerful duo—a combination that continues to provide patterned, multifunctional surfaces that serve as enabling technologies in areas ranging from biotechnology to engineering, such as cell proliferation and viability, microfluidics, membranes, sensors, and diagnostic devices.

Currently, the complexity of these surfaces is typically limited to two or three different functionalities, and the challenge of attaining a complete, orthogonal functionalization still remains. All of the work described above is limited to two-dimensional surfaces, and new methodologies must be developed to pattern complex, 3D structures (particles, fibers, and macroscopically rough surfaces) with high fidelity and no cross-contamination. An active research focus is needed in specific areas to better understand the reactivity in surface-based postpolymerization modification, such as the following: (i) elucidating the relationship between sterics and molecular weight of the modifying component; (ii) describing how the reactivity is

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affected by permeability and diffusion into polymer brushes of different grafting densities, particularly when the substrates and species in solution have different phobicities (e.g., hydrophobic brush and hydrophilic solution); and (iii) investigating the influence of reaction rates with respect to charge density, particularly with polyelectrolyte brushes. Identification of new click-like reactions that broaden the modularity and functional group compatibility, enable greater spatial and temporal control, and augment orthogonality are also necessary to expand chemical complexity. This highly interdisciplinary field will do nothing but grow as the demand for complex surfaces rapidly expands.

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Notes

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