Mild and Selective C–H Activation of COC Microfluidic Channels Allowing Covalent Multifunctional Coatings

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ABSTRACT: Plastics, such as cyclic olefin copolymer (COC), are becoming an increasingly popular material for microfluidics. COC is used, in part, because of its (bio)-chemical resistance. However, its inertness and hydrophobicity can be a major downside for many bioapplications. In this paper, we show the first example of a surface-bound selective C–H activation of COC into alcohol C–OH moieties under mild aqueous conditions at room temperature. The nucleophilic COC–OH surface allows for subsequent covalent attachments, such as of a H-terminated silane. The resulting hybrid material (COC–Si–H) was then modified via a photolithographic hydroxysilylation in the presence of ω-functionalized 1-alkenes to form a new highly stable, solvent-resistant hybrid surface.

KEYWORDS: cyclic olefin copolymer, mild oxidation, hydroxysilylation, microfluidics, photolithography, hybrid surface

INTRODUCTION

Cyclic olefin copolymers (COCs) are emerging as an increasingly popular substrate material for microfluidics. This is mostly due to their optical transparency, chemical resistance, low water absorption properties, and good biocompatibility. However, COC being quite inert toward chemical modification, of course, hinders the ability to covalently functionalize the surface. A series of methods have been investigated that endow functionalities to COC, as well as reducing its hydrophobicity, (static water contact angles of COC are typically >95°). For instance, covalent coupling of a silane in plasma conditions can be a major downside for many bioapplications. In this paper, we show the first example of a surface-bound selective C–H activation of COC into alcohol C–OH moieties under mild aqueous conditions at room temperature. The nucleophilic COC–OH surface allows for subsequent covalent attachments, such as of a H-terminated silane. The resulting hybrid material (COC–Si–H) was then modified via a photolithographic hydroxysilylation in the presence of ω-functionalized 1-alkenes to form a new highly stable, solvent-resistant hybrid surface.

Supporting Information

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attachment of a silane, as this allows photochemical patterning at a later stage.

We have recently reported on the deposition of a hydrogen-terminated silane on glass (H-glass) and subsequent UV irradiation (302 nm) in the presence of terminal alkenes. We then improved this approach by incorporating a radical-stabilizing substituent (H-Φ-glass), thus reducing the activation energy threshold to light with a wavelength of 328 nm. This allowed the direct attachment of an NHS-containing alkene and subsequent localized DNA attachment. Now typically commercial microfluidic devices are manufactured (and functionalyzed) in parts and then later bonded together. However, many (bio)chemical functions that can be introduced locally with our method are not compatible with the use of the high temperatures needed for bonding. Additionally, such thermal treatments result in a loss of imbued hydrophilicity (by plasma or otherwise) due to surficial polymer reorganization. There are two ways to approach this problem, either to find a method that allows for low-temperature bonding of high-Tg COC (while keeping the COC-surface chemistry unchanged), or to develop a method to modify COC posterior to the bonding procedure. Our paper addresses the latter approach.

In this paper, we therefore show that this approach can be adapted to modify COC substrates into a new hybrid material, hydrogen-terminated-(phenyl)-silanized COC (H-Φ-Si-COC), by modifying COC=OH with a mixture of trichlorosilane and phenylidichlorosilane (5:1 molar ratio). This modification of COC allows for a mild photolithographic covalent attachment (λ = 328 nm) of terminal alkenes onto COC surfaces, including enclosed surfaces such as the inside of microfluidic channels (Scheme 1).

Scheme 1. Scheme for (i) the Modification of COC into a Nucleophilic Surface, COC−OH, via (ii) Copper-Catalyzed Peroxidative Oxidation Followed by a Mild Reductive Washing Step; (iii) Subsequent Silanization with HSiCl3/HSiPhCl3 (5:1 molar ratio) Yields the COC-Φ-Si-H3 Hybrid Material; (iv) This Hybrid Material Is Then Used for Mild Light-Induced Hydrosilylation with a Terminal Alkene

### EXPERIMENTAL SECTION

Acetone (Aldrich, semiconductor grade VLSI PUNARAL Honeywell 17617), dichloromethane (DCM, Sigma-Aldrich) and n-hexane (Merck Millipore) were used for cleaning before modification. All other chemicals were purchased from Sigma-Aldrich and used as received. 10-Trifluoro-acetamide-1-decene (TFAAD) was synthesized based on literature methods. COC 6013 was purchased from TOPAS.

**Oxidation of the COC Surface.** For monolayer formation on flat substrates, cyclic olefin copolymer, COC 6013 (TOPAS), was milled into 1 × 1 cm pieces and sonicated for 30 min in ethanol/acetone (1:1), subsequently dried with argon, and placed under vacuum for 1 h at room temperature. Surface modifications were conducted directly afterward.

COC is quite inert and lacks nucleophilic groups on the surface. These groups act as covalent anchoring points for the intended subsequent silanization steps. Two oxidation methodologies were thus studied. A simple way of oxidizing the COC substrate is by using an air plasma for 30 s. This method is not compatible with bonded microfluidic channels. Solution-based oxidation of COC was performed via peroxidative oxidation of the COC surface for 20 min. The surface was immersed and sonicated (37 kHz, RT) immediately after mixing a 5 mL solution of Cu(OAc)2 (73 mg, c1 20 mM) in 15 mL of 30% H2O2 (c2 22.5% (v/v)), rinsed with ethanol, and blow-dried with N2 flow to remove surfacial water, followed by sonication in a methanolic solution of NaBH4 (112 mM) for 5 min. Sonication prevents nucleation of gas bubbles on the COC surface, which hinder the surface modification. Freshness of the hydrogen peroxide, and thus its high concentration, is necessary for a proper oxidation of the surface.

Oxidation inside a microfluidic channel was performed by flushing the above-mentioned solution for 20 min at a 50 μL/min flow rate (channel dimensions: width 300 μm, height 150 μm).

**Formation of Hydrogen-Terminated Si-COC (H-SiCOC).** Gas phase modification of COC with HSiCl3 was performed as previously described.

**Formation of Hydrogen-Terminated (Phenyl)-Si-COC (H-Φ-SiCOC).** A 1:5 molar mixture of Cl2PhSi-H and Cl3Si-H was added to semiconductor grade aceton under bubbling N2. The oxidized COC surfaces (1 × 1 cm) were immersed for 20 min. Afterward, the substrates were washed copiously with ethanol, dried under argon and stored in an opaque container. For the microfluidic chip, the solution was flushed and allowed to react for 20 min. After which, aceton was copiously flushed through.

**Photochemical Surface Modification.** A drop of TFAAD was placed on a H-SiCOC or H-Φ-SiCOC slide in a glovebox. An appropriate cutoff filter (295 or 320 nm) was placed on the drop and gently pressed against the first slide, homogeneously spreading the alkene, mimicking a closed glass microfluidic channel while blocking the reaction from undesirable high energy emissions. The surfaces were then illuminated with a pen lamp (pen lamp 302 or 328 nm, Jenlab Inc., Irvine, CA, USA), which was placed approximately 1 cm above the surface. A cutoff filter is necessary due to a strong presence of higher energy wavelengths (Figures S1 and S2). The entire setup (lamp and substrate) was covered in aluminum foil, and the sample irradiated for 16 h. After irradiation, the substrates were rinsed with aceton, sonicated in ethanol/aceton for 5 min and quickly dried under argon. The surfaces were directly used for surface characterization or stored under air.

**Photolithography.** Photolithography was performed with a pen lamp, as in the aforementioned setup, in combination with a gold electron microscope grid (SEM F1, Gilder Grids, Figure S3). This photolithographic mask was placed on top of the H-SiCOC or H-Φ-SiCOC slide with a drop of TFAAD. After spreading of the liquid, a cutoff filter was placed on top of the mask as a cover, above which the pen lamp was placed (ca. 1 cm distance). Samples were irradiated for 16 h, removed from the glovebox, and cleaned as described above. The patterns were examined with optical microscopy, scanning electron microscopy (SEM).

Photolithography on the microfluidic devices were performed by first flushing TFAAD, followed by irradiation under the same conditions as described above (the light-induced reaction was carried out on a stopped-flow). The photomask used was a thick aluminum photomask (1 cm) placed on top of the H-SiCOC or H-Φ-SiCOC slide with a drop of TFAAD. After spreading of the liquid, a cutoff filter was placed on top of the mask as a cover, above which the pen lamp was placed (ca. 1 cm distance). Samples were irradiated for 16 h, removed from the glovebox, and cleaned as described above. The patterns were examined with optical microscopy, scanning electron microscopy (SEM).
value is the average of at least five droplets of at least three different samples.

**Germanium Attenuated Total Reflection Fourier Transform Infrared Spectroscopy (GATR-FTIR).** GATR-FTIR spectra were recorded with a Bruker Tensor 27 FT-IR spectrometer, using a commercial variable-angle reflection unit (Auto Seagull, Harrick Scientific). A Harrick grid polarizer was installed in front of the detector and was used for measuring spectra with p-polarized radiation with respect to the plane of incidence at the sample surface. Single channel transmittance spectra were collected at an angle of 25° using a spectral resolution of 4 cm⁻¹ and 1024 scans while flushing with dry N₂. Obtained spectra were referenced with a clean siliconized COC substrate (silanized COC substrates were referenced with oxidized COC).

**X-ray Photoelectron Spectroscopy (XPS).** XPS spectra were recorded on a JPS-9200 photoelectron spectrometer (JEOL, Japan). The analysis was performed under ultrahigh vacuum conditions using a monochromatic Al Kα source at 12 kV and 20 mA, and an analyzer pass energy of 10 eV. A takeoff angle of 80° was used, with a precision of ±1°. All XPS spectra were analyzed with Casa XPS software (version 2.3.15). The binding energies were calibrated on the hydrocarbon (CH₂) peak with a binding energy of 285.0 eV. Because of the electrostatic charging of the surface during the measurements, a charge compensation was used with an accelerating voltage of 2.8 eV and a filament current of 4.80 A.

**Atomic Force Microscopy (AFM).** AFM imaging was performed under air using both a Digital Instruments NanoScope V Multimode Scanning Probe Microscope (Bruker, MA) and a JSPM-S400 (JEOL, Japan) Scanning Probe Microscope in AC-AFM ("tapping") mode with a noncontact silicon nitride cantilever with a stiffness of 0.8-8 N/m (Veeco Metrology, Santa Barbara, CA) at a scan speed of 1 μm/s, in the Scan-assist imaging mode. Images were flattened with a second-order flattening procedure using Nanoscope Analysis software (v1.5) and WinSPM software (v5.0).

**Scanning Electron Microscopy/Scanning Auger Microscopy (SEM/SAM).** Morphologies of TFAAD micropatterns were analyzed by SEM. Measurements were performed at room temperature with a scanning Auger electron spectroscopy system (JEOL Ltd. JAMP-9500F field emission scanning Auger microscope). SEM images were acquired with a primary beam of 0.8 keV. The takeoff angle of the instrument was 3°.

## RESULTS AND DISCUSSION

In order to be able to covalently silanize a COC substrate, the surface first needs to be activated. Activation of a COC surface into a nucleophilic anchor-containing surface can be achieved via oxidation of the alkane surface into C–OH groups (e.g., alcohol or acid). A ubiquitous surface oxidation method makes use of oxygen or air plasma, modifying the C–H terminus into a C-Ox (e.g., alcohol, acid, ketone, aldehyde). This plasma method was evaluated and compared with a mild oxidation based on exposure to an aqueous solution of hydrogen peroxide (22.5% (v/v)) and copper acetate (20 mM) (Figure 1).

An air plasma-based treatment of COC substrates for 10 s gives immediate results. The static water contact angle drops from 100° to <30°, indicating the rapid formation of hydrophilic surface groups. From GATR-FTIR measurements it becomes clear that a variety of surficial carbonyl species are present (Figure 1a), as expected under the harsh oxidation conditions provided by plasma. Wide range XPS data reveal an increase in total oxygen content, while XPS C 1s narrow scans show many peaks to indicate that multiple functional groups are now present on the surface (due to the presence of various oxidized forms of carbon, e.g., (C–OH) 286.9 and 289.3 (C=O). Unfortunately, this surface-modification technique is not able to homogeneously functionalize the inside of intricate COC channels because of plasma-diffusion limitations in microfluidic devices.  

In order to bypass the limitations stated above, we looked into other C–H activation chemistries. Due to the similarities between COC and (cyclo)hexane, we hypothesized that this copper-catalyzed water-based chemistry could also work on a COC surface. To test this, we first exposed COC to 30% (v/v) H₂O₂ and no change in the water contact angle was observed, even after simultaneous sonication for 30 min. However, upon the addition of copper(II) acetate, a contact angle of 83 ± 2° was obtained in just 30 min.

Shul’pin reviewed how the addition of additives, such as PPh₃, in the washing/quenching solution can be used to favor the decomposition of the CyOO⁺ species into the alcohol (CyOH) counterparts instead of into ketones or other minor overoxidation products such as esters. However, attempts to use PPh₃ to favor the conversion of COC-OO⁺ to COC–OH did not yield satisfactory results. The PPh₃ oxidation adduct (O═PPh₃) forms a sticky precipitate that whitens the substrates and clogs microfluidic channels. Adding a small amount of nitric acid (20 mM) in the oxidation solution, increased the yield slightly and shows some tuning ability toward the alcohol product is possible; similar results were found in solution. However, we found an easy alternative method by using methanolic NaBH₄ in the washing step (by sonication for 5 min) of the copper-catalyzed oxidized surfaces. This yielded further a reduction in the water static contact angle to 72 ± 2° (Table S1). These values are close to those of other COC–OH substrates found in literature. Our method represents a clear improvement in that it is much milder (no UV required, room temperature, aqueous solution), and leaves far less contaminants on the surface.

To further corroborate this, the surfaces were analyzed by GATR-FTIR (Figure 1b–d). The presence of alcohol (3174 cm⁻¹) and carbonyl groups (1735 cm⁻¹) indicates that the surface has undergone oxidation. Evidently, the intensity of carbonyl-related stretching peaks is reduced compared to what is observed upon air plasma-treatment, suggesting that the aqueous Cu/H₂O₂ oxidation is mild compared to plasma treatment. Of specific interest is the basically flat IR spectrum in the C=O region (Figure 1d) upon NaBH₄ washing. Finally, the formation of C=O and COO⁻ bonds implies a lower amount of surficial CH and CH₃ bonds (compared to the reference background), leading to the inversion of those peaks (i.e., positive peaks around 2850–2950 cm⁻¹).
XPS wide scans show that our peroxidative treatment yields a clear increase of oxygen content when compared to bare COC, and less than for plasma-treated COC (Figure 2(i)). In Figure 2(ii) the C 1s narrow scans indicate a predominance of C−C bonds (285.0 eV) for all substrates, whereas in the oxidized substrates C═O and C≡O are distinctly present (286.8 and 289.3 eV). In Figure 2(iii), the O 1s narrow scans show the presence of C−O−H (532.7 eV − 57.6%) and O−C═O (533.8 eV − 42.4%) for the COC that was subject to plasma treatment; COC that has been subjected to the Cu/H2O2 or Cu/H2O2/HNO3 oxidation show a predominant presence of C O−H (532.4 eV − 56 or 68%) along with the less prevalent C═O (531.4 eV, 17.2 or 11.6%), O−C═O (534.0 eV, 26.5 or 20.1%), and copper oxide (529.9 eV) contaminants due to just washing with water for analysis purposes. COC that was reductive NaBH4 washing step yields a near-quantitative conversion to alcohols, free of Cu oxide contaminants. 33

While traditional plasma activation is a viable and operationally simple option in many instances, the resulting presence of basically only one type of oxidized carbon obtained at room temperature is a major accomplishment by our method compared to air/oxygen plasma methods. 34

As previously mentioned, the ability to generate OH-terminated COC surfaces allows for a wide variety of functionalization chemistries. In the current paper, we present as an example the first of those under current development. Given the increasing use of COC in the fabrication of microfluidic devices, chemistries that allow for plastics photolithography are extremely desirable. 35 In line with our previous work done on borosilicate glass, 23,24 we aimed to modify COC−OH with a 5:1 molar mixture of trichlorosilane and dichlorophenylsilane. With this, we envisioned to fabricate a hybrid material, hydrogen-(phenyl)-terminated silanized COC (COC-Si−Φ1-H3), that would have a similar reactivity as the previously reported H-Φ-glass.

Of specific interest were the findings that H-Φ-glass was shown to be highly stable in air for months, while being smoothly reactive toward alkenes using light of λ ~ 328 nm. 23,24

The hybrid material COC-Si−Φ1-H3 was prepared along these lines and analyzed. Static water contact angles (85° for COC−Si−H and 90° for COC-Si−Φ1-H3) were similar to the ones we reported for analogous silicon-based substrates. 23,24 XPS wide scans (Figure 3a) show the presence of Si at 102 eV, indicating the formation of an ultrathin layer on top of COC. Analysis by GATR-FTIR, while using COC−OH as a reference background—see Figure 1d for its spectrum—confirms the presence of two different Si−H stretching bands, which we attributed to O3Si−H at 2249 cm−1 and to O2ΦSi−H at 2185 cm−1 (Figure 3c).

Having characterized the COC-Si−Φ1-H3 substrates, we proceeded with modifying it further via light-induced hydro-silylation. For this, we chose 10-trifluoro-acetamide-1-decene (TFAAD) as developed by Hamers36−39 as a reactivity probe. This alkene is useful to evaluate attachment, due to the IR-active carbonyl group and three C−F bonds with characteristic XPS C 1s and F 1s signals, and can be easily converted into an amine, upon deprotection.

COC-Si−Φ1-H3 substrates were modified with TFAAD using 328 nm light. The TFAAD-substituted COC-Si−Φ1-H3 substrates were characterized by GATR-FTIR using COC-Si−Φ1-H3 as reference background (see Figure 3c for the spectrum of COC-Si−Φ1-H3 itself). The carbonyl stretching peak from TFAAD was clearly present at 1705 cm−1 (Figure 4c). 23 The reversal of the Si−H peaks at 2249 and 2185 cm−1 indicates that there are less Si−H bonds than before the hydrosilylation, i.e., that the alkene reacted with the hydrogen-terminated surfaces forming Si−C bonds. Wide range XPS scans show the presence of fluorine, while C 1s narrow scans indicate the presence of CF3 groups at 293.5 eV (Figure S4). This further confirms covalent attachment of TFAAD onto the COC-Si−Φ−H3 surfaces.
Similarly to the results obtained on glass, AFM measurements of these surfaces show that the roughness does not change considerably upon modification (RMS roughness from $1.9 \pm 0.5$ nm to $2.0 \pm 0.5$ nm) (Table S2), which is another significant improvement over plasma-based oxidations.21

Photolithography on open substrates was performed by positioning a contact mask (circular TEM grid with circles and spokes, Figure S3) on top of the COC-Si-$\Phi_1$-H$_5$ substrates during the light-induced hydrosilylation reaction. We then planned to visualize the resulting pattern by scanning electron microscopy (SEM) (Figure 5, Table S3).

Interestingly, when cleaning the modified substrate with dichloromethane (DCM) for 5 min to allow for SEM measurements, we observed that the pattern had slowly become visible by naked eye. Further exposure to DCM (30 min) showed clear degradation by the solvent of the nonexposed areas, while the TFAAD-modified areas resisted solvent damage effectively (Figure 5a–d). Overall, the ability to covalently bind an ultrathin, yet highly protective coating that can be further modified27,40 opens the use of these substrates for many applications.

We then finally proceeded to modify the channel of an already bonded COC microreactor (Micronit) into COC-OH by flowing the oxidation solution for 20 min at 50 $\mu$L/min and washing for 5 min (50 $\mu$L/min) with methanolic NaBH$_4$. Silanization was carried out and a fully modified COC-Si-$\Phi_1$-H$_5$ microfluidic channel was photopatterned with TFAAD (see Supporting Information for details). We then tested the ability of the TFAAD patches to protect the device from a prolonged flow of DCM (30 min at 50 $\mu$L/min). As can be seen from Figure 6b, the coating provides significant protection even to harsh solvents such as DCM. In the absence of a protective coating (Figure 6b, c), the polymer swells and cracks, starting as stripe-like cracks at the side of the channel (Figure 6b). In addition, the bonding strength between the COC top and bottom substrates is severely weakened and leakage occurs. Since the TFAAD moiety is by no means optimized for this purpose, functional group optimization will likely provide significant possibilities for further improvement of the protection.

**CONCLUSIONS**

In conclusion, we have demonstrated a mild aqueous C–H activation method to modify the surface of cyclic olefin copolymers (COC). This method can be applied to open plastic substrates as well as to bonded microchannels, and yields highly defined alcohol-terminated COC surfaces without carbonyl-containing moieties. Because of their nucleophilic character, such surface-bound alcohol moieties can be used for a very wide array of surface modifications. When, for example,
reacted with hydroxilanes (such as Cl₂Si–H or Cl₃PhSi–H), this surface yields a hydrogen-terminated Si–COC surface. This new hybrid surface is highly stable in air and photopatternable via a mild light-induced hydrosilylation with terminal alkynes. The TFAAD functional monolayer attached in this fashion enhanced the resistance of the COC to organic solvents (e.g., DCM). In addition, TFAAD is well-known for its ability to undergo further surface modifications for, for example, biological applications.\(^3\)\(^7\)\(^4\)\(^0\)\(^4\)\(^1\)

This research opens a door toward the mild activation of what was considered a highly inert substrate that required harsh modification techniques. This technique is currently transposed to other C–H containing polymer analogues, e.g., polyphenyl ethers/oxides (PPEs/PPOs), and speeding up the process via the photochemical attachment of 1-silanols rather than 1-alkynes, which is ca. 2 orders of magnitude faster on H-terminated Si(111).\(^4\)\(^2\) is also under investigation in our laboratories.

## ASSOCIATED CONTENT



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