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RESEARCH ARTICLE

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Facile Fabrication of Bio- and Dual-Functional Poly(2-oxazoline) Bottle-Brush Brush Surfaces

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Abstract: Poly(2-oxazoline)s (POx) bottle-brush brushes have excellent bioniert and lubricious properties, which are promising for the functionalization of surfaces for biomedical devices. Here, we report a facile synthesis of POx based bottle-brush brushes (BBBs) on solid substrates. Initially, backbone brushes of poly(2-*iso*-propenyl-2-oxazoline) (PIPOx) were fabricated *via* surface initiated Cu(0) plate-mediated controlled radical polymerization (SI-CuCRP). Poly(2-methyl-2-oxazoline) (PMeOx) side chains were subsequently grafted from the PIPOx backbone *via* living cationic ring opening polymerization (LCROP), which result in ~ 100 % increase in brush thickness (from 58 to 110 nm). The resultant BBBs shows tunable thickness up to 300 nm and high grafting density (σ) with 0.42 chains/nm^2. The synthetic procedure of POx BBBs can be further simplified by using SI-CuCRP with POx molecular brush as macromonomer (M_n = 536 g/mol, *PDI* = 1.10), which results in BBBs surface up to 60 nm with well-defined molecular structure. Both procedures are significantly superior to the state of art approaches for the synthesis of POx BBBs, which are promising to design bio-functional surfaces.

Introduction

Polymer brushes with low protein adsorption and cell adhesion are receiving extensive attention since they are suitable for highly sensitive *in vitro* diagnostics and clean *in vivo* applications such as biomedical implants.[1] So far, poly-(ethylene glycol) (PEG) is one of the most widely utilized polymers for biomedical applications since it is bioinert and protein-repellent.[1a, 2] However, it has been reported that the PEGs can undergo oxidative degradation and cause antibodies against PEGs *in vivo*.[3] Recently, poly(2-oxazoline)s (POx)s have been established as a promising alternative material due to their good biocompatibility and durability.[4] The reported POx brushes on surfaces that are composed of a linear back bone and densely grafted side chains are termed as bottle-brush brushes (BBBs) due to their cylindrical appearances.[4a] A key advantage of the POx BBBs is dual-functionality that enables to tune surface properties through the functionalization of the backbone as well as side chains.[4a, 4d] As such, POx BBB surfaces have been used in many biomedical applications such as recognition sites for cells, non-fouling coatings against undesirable proteins and surface lubrications.[4e, 4g, 5]

Previously, we reported the synthesis of well-defined POx BBBs *via* self-initiated photografting and photopolymerization (SIPGP) and living cationic ring opening polymerization (LCROP).[4a, 5b] Firstly, poly (2-*iso*-propenyl-2-oxazoline) (PIPOx) backbone brushes from bulk IPOx monomers were synthesized *via* SIPGP by UV-light irradiation (λ_{max} = 350 nm). The side chains were consecutively grafted from the PIPOx backbone brushes *via* LCROP using different 2-alky-oxazoline monomers (**Figure 1a**).[4a, 5b] The SIPGP requires long reaction time (up to 40 h) and comparably large amount monomers (2 mL bulk monomer for each sample). Another challenge is that the already grafted POx brushes can be partially crosslinked by long-term UV irradiation during SIPGP process.[6] Therefore, a more controllable and reliable technique is highly needed.

The recently emerged SI-CuCRP is a very effective and versatile technique to fabricate polymer brushes on planar substrates.[7] The brush growth rate was found among the highest for surface-initiated controlled radical polymerization reported to date.[7h, 8] More importantly, the SI-CuCRP is oxygen tolerant and requires very limited amount of monomers (µL), and therefore can be used to prepare polymer brushes with low cost.[7a, 7j] In addition, by simply variation of the distance (D) between the copper plate and the initiating surface, various structured polymer brushes can be prepared.[7a, 7c, 7g, 7i]

Here, we report the synthesis of well-defined POx BBBs *via* a combination of SI-CuCRP and LCROP. Initially, the PIPOx backbone brushes of up to ~ 130 nm thickness were prepared by SI-CuCRP at ambient conditions. Afterwards, the side group of PIPOx was extended *via* LCROP with 2-methyl-2-oxazoline (MeOx) monomers and resulting in PIPOx-*g*-PMeOx BBBs with thickness up to ~ 300 nm and high grafting density (σ = 0.42 chains/nm^2). The synthetic procedure towards POx BBBs can be further simplified by using SI-CuCRP with POx molecular brush as macromonomer (M_n = 536 g/mol, *PDI* = 1.10), which results in BBBs surface in one grafting process with 60 nm thickness and well-defined molecular structure. Both procedures improve the state of art approaches for the synthesis of well-defined POxs BBBs, which are promising to design bio-functional surfaces.

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Results and Discussion

The preparations of poly (2-oxazoline) bottle-brush brushes (POx BBBs) are outlined in **Figure 1b**. The PIPOx backbone brush was synthesized *via* SI-CuCRP, where a copper plate was sandwiched with an ATRP initiator-modified SiO_2 substrate at a typical distance of 0.5 mm and submerged in a reaction mixture containing 0.5 mL monomer (IPOx), 20 µL ligand (1,1,4,7,7-pentamethyldiethylentriamin, PMDETA) and 1.5 mL solvent (water-methanol, 2:1, v/v).[7a, 7i] Afterwards, the oxazoline groups of PIPOx backbones were converted under inert conditions (argon) using methyl triflate at -35 °C in dry acetonitrile (ACN) to the cationic macroinitiator poly(2-*iso*-propenyl-2-oxazolinium triflate). Then, side chain was prepared *via* LCROP at 80 °C for 4 h using 2-methyl-2-oxazoline (MeOx) as monomer to form PIPOx-*g*-PMeOx BBBs. Comparing to classical SIPGP approach, the SI-CuCRP is more efficient, controllable and requires only minor amount of chemicals (µL), since the reaction is confined between the copper plate and initiating-substrate.[7a].

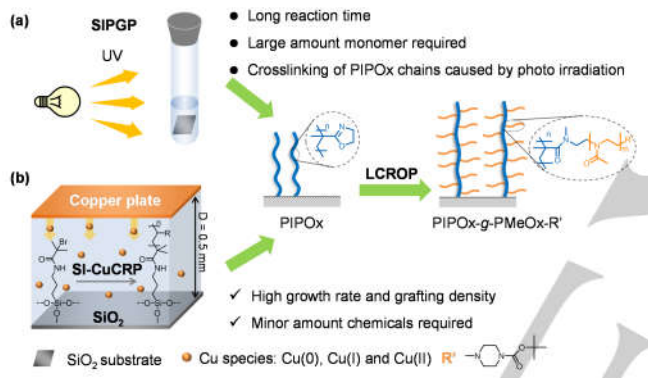

Figure 1. Schematic illustration of the synthesis of POx BBBs. **(a)** Conventional two-step synthesis *via* SIPGP and SI-CuCRP; **(b)** Two-step synthesis *via* SI-CuCRP and LCROP in this work. R = functional groups of different monomers. R' = terminating reagent for LCROP, N-*tert*-butoxycarbonyl piperazine (N-Boc-piperazine). D = distance between copper plate and initiating-substrate.

Homogeneous POx BBB surfaces: The successful grafting of the PIPOx backbone brushes and further side-chain extension with PMeOx are confirmed by water contact angle (θ) and Fourier-transform infrared spectroscopy (FTIR). The FTIR spectra of PIPOx brushes show strong bands at 1660 and 1030 cm^{-1} assigned to the (C=N) and (C-O) stretching modes of oxazoline rings. After LCROP, the band around 1625 cm^{-1} refers to the (C=O) stretching mode of the amide function (amide I band) of PMeOx side chains. In addition, the band around 1425 cm^{-1} is assigned to CH_x deformation modes of backbones and side chains of POx BBBs (**Figure S1**). The water contact angle (θ) of α-bromoisobutyryl bromide (BiBB) initiator-functionalized SiO_2 substrate is 69 ± 2°. However, after first step SI-CuCRP, the θ decreases to 53 ± 2°, which is a typical value for PIPOx brushes as reported previously.[5b] After the second step LCROP, the θ changed slightly to 47 ± 1° due to more hydrophilic PMeOx side chains. The dry thickness (h_{dry}) of the PIPOx backbone brushes and PIPOx-*g*-PMeOx BBBs were measured by ellipsometry and AFM, respectively. As shown in **Figure 2**, the SI-CuCRP at room temperature (RT) resulted in homogeneous PIPOx brushes with h_{dry} = 58 ± 2 nm within 2 h. After 4 h LCROP, the h_{dry} of the resultant BBB increased to 110 ± 4 nm. As reported previously, the highly crowded side chains lead to stretching of the bottle-brush backbones and result in a layer height increase up to ~100 %.[5b] The resultant PIPOx brush and POx BBB show homogeneous surface morphologies with low roughness (Rms) of 1.8 and 1.2 nm, respectively, as investigated by AFM (Figure S2b and S2f). The swollen thickness ($h_{swollen}$ = 155 ± 6 nm) of the BBBs in water was determined by liquid AFM. As such, the BBB grafting density, as estimated through the swelling ratio (S_r (%) = 100 ($h_{swollen}$ - h_{dry})/h_{dry}), is calculated to 0.42 chains/nm^2 (**Figure 2b** and **Table S1**).[7h, 9] In comparison, only 15 ± 1 nm PIPOx layer was obtained in 24 h SIPGP. After LCROP, the resultant PIPOx-*g*-PMeOx BBBs shows only 23 ± 2 nm in thickness and 0.13 chains/nm^2 in grafting density (**Figure S3**). Therefore, the SI-CuCRP approach enables POx BBBs with significantly higher growth rate, thickness and grafting density than classical SIPGP approach.

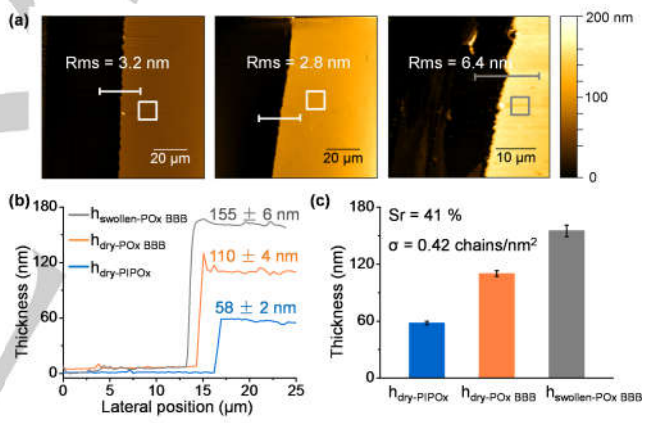

Figure 2. (a) AFM topographic scans of PIPOx backbone brushes *via* SI-CuCRP (left), PIPOx-*g*-PMeOx BBBs after LCROP (middle) and swollen PIPOx-*g*-PMeOx BBBs in H_2O (right), *Rms* = surface roughness. **(b)** Corresponding height profiles taken at scratches of the polymer layer. **(c)** Thickness column plot of POx brushes from (a). S_r = swelling ratio, σ = grafting density.

Grafting kinetics: The thickness variations of PIPOx backbone brushes as a function of SI-CuCRP reaction time was further studied. As shown in **Figure 3a**, PIPOx backbone brushes were synthesized through SI-CuCRP and samples were taken out at different reaction times (i.e. 0.5, 1, 2, 3, and 4 h) and characterized by ellipsometry. As a result, the thickness of PIPOx brushes were 28 ± 1, 34 ± 1, 50 ± 4, 69 ± 7, 78 ± 10 nm, respectively (**Figure 3a, Table S2**). The PIPOx brush thickness reached to 50 ± 4 nm in 2 h SI-CuCRP. With longer reaction time, the growth rate decreased due to the reduced monomer concentration within the confined reaction set-up. After second step LCROP, the dry thickness of resulted BBBs increased to 39

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± 2, 63 ± 4, 88 ± 9, 111 ± 10, 134 ± 7 nm, respectively. (**Figure 3b**, **Table S2)**.

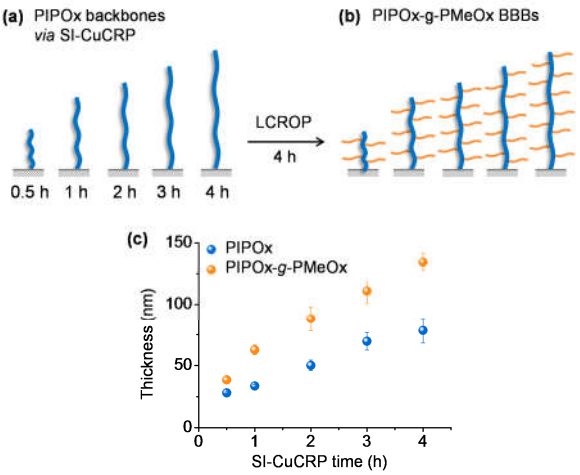

Figure 3. (a) Schematic of thickness variations of PIPOx backbone brushes as a function of SI-CuCRP reaction time. **(b)** Resultant POx BBBs from (a). **(c)** Thickness plots of time-thickness dependency of PIPOx backbones *via* SI-CuCRP (blue) and resultant PIPOx-*g*-PMeOx BBBs after LCROP (orange).

Structured POx BBB surfaces: Patterned POx BBB surfaces are of great interest because they can be used to spatially controlling protein adsorption, cell adhesion and molecular sensing.[10] In the case of SI-CuCRP approach, since the polymerization employs a self-assembled monolayer (SAM) of surface-anchored initiators, the patterned polymer brushes are simply accessible with patterned initiator-SAMs, which are prepared by UV irradiation through a photomask (**Figure 4a**).[11] As shown in **Figure 4b**, the PIPOx backbone brushes were selectively formed on initiator-covered areas in SI-CuCRP and then lead to patterned PIPOx-*g*-PMeOx BBBs after second step LCROP (**Figure 4c**).

One of the most important characteristics of POx BBBs are the dual-functionalities from backbones and side chains. In order to study the accessibility to such dual-functionalities, two fluorescencent dyes were used to label the PIPOx backbones and the PMeOx side chains, respectively. Specifically, we employed dansyl chloride (maximal λ_{em} ~ 525 nm)[12] to label the PIPOx backbones, which can react with secondary amine groups and form stable sulfonamide. As shown in **Figure 4c**, the fluorescent emission of PIPOx-grafted areas presented a selective and fully functionalization of the PIPOx brushes. In order to prove the dansyl chloride is not physically adsorbed, the active group of this compound was protected by N-tert-Boc and then reacted with the PIPOx patterns. As expected, no fluorescence emission was observed *via* epifluorescence microscopy (**Figure S5**). Afterwards, the PMeOx side chains were labelled by Cy5-NHS-ester (maximal λ_{em} ~ 670 nm), which is a reactive dye for the labeling of amino-groups.[13] Thus, the Boc end group on side chains had to be deprotected using trifluoroacetic acid and then the deprotected BBBs were allowed to react with excess Cy5-NHS-ester in dry dimethylformamide with trimethylamine as a base for 24 h. After extensive cleaning to remove the excessive non-reacted dye, the sample was investigated using epifluorescence microscopy, as shown in **Figure 4b**, the fluorescent emission of labelled BBB side chains was presented. Therefore, the respective labelling of the backbones and side chains of POx BBBs with fluorescencent dyes demonstrate the dual-functionalities of the POx BBB surfaces.

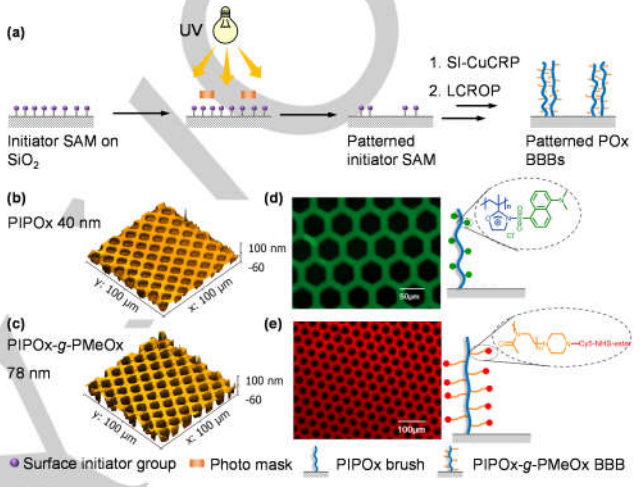

Figure 4. (a) Schematic illustration of the preparation of patterned polymer brushes. Structures can be introduced by UV light through a photo mask by removing uncovered initiator-SAMs. **(b)** 3D AFM topographic scan of patterned PIPOx backbone brushes after 1.5 h SI-CuCRP; **(c)** 3D AFM topographic scan of patterned PIPOx-*g*-PMeOx BBBs after 4 h LCROP. **(d)** Schematic illustration of coupling of the dansyl chloride with the PIPOx backbones (right) and epifluorescence microscopy image (left) (λ_{ex} = 440-470 nm). **(e)** Schematic illustration of coupling of the Cy5-NHS-ester with the PMeOx side chains (right) and epifluorescence microscopy image (left) (λ_{ex} = 525-550 nm).

POx BBB gradients: Gradient polymer brushes are interesting anisotropic platforms to control the chemical, physical or morphological properties gradually across the surface.[14] In conventional surface-initiated polymerization (SIP) techniques, polymer brush gradients can be prepared by controlling polymerization time or initiator densities gradually along the surface.[15] However, both strategies require tedious reaction steps and/or instruments, and consume a large amount of monomers. In the case of SI-CuCRP, PIPOx brush gradients can be prepared straightforward using a tilted Cu-plate (**Figure 5a**). Because the gradual variation of the distance (D) between the Cu source and initiating-substrate allows gradually changed polymerization rate and thus leads to polymer brush gradients.[7c] Even after side chain grafting, the gradient conformation was retained, but their thickness were systematically increased. For example, SI-CuCRP with 3 h results in PIPOx brushes with gradient thickness ranging from 9 to 130 nm (**Figure 5d**). The consecutive LCROP for 4 h enhances the gradient range to 14 - 320 nm as measured by AFM and ellipsometry (**Figure 5e&Table S4**). It is worth to note that the polymer layers at edge

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are thicker (with 11 - 28%) than that of middle positions (Figure S7). This is mainly due to the diffusion of monomer from outside to the reaction "chamber" (between copper plate and initiator substrate), which leaded to gradient concentrations of monomer along Y-direction from edge to middle, and thus resulted in varied polymerization rate and brush thickness. The gradient brush thickness also results in gradual wetting properties as revealed by water contact angle measurements (**Figure S6b**). Furthermore, we show that the POx BBBs can also be prepared through a one-step SI-CuCRP of beforehand prepared POx macromonomer. The methacrylic acid (MAA) terminated $P(MeOx)_7$ macromomers (M_n = 536 g/mol, *PDI* = 1.10) were synthesized according to Kobayashi *et al*.[16] (**Figure S8**) and characterized by gel permeation chromatography (GPC) and proton nuclear magnetic resonance (^{1}H NMR).[16] After 4 h SI-CuCRP with tilted copper plate, the yield brush shows gradient thickness ranging from 6 to 60 nm (**Table S4&Figure S8**). The grafting density of the resultant POx BBB was determined by liquid AFM as 0.19 chains/nm^2 (**Figure S9**). Comparing to the two-step synthesis described above, the brush thickness and grafting density of the POx BBB from one-step approach are much lower due to the steric repulsion among macromonomer chains.[17]

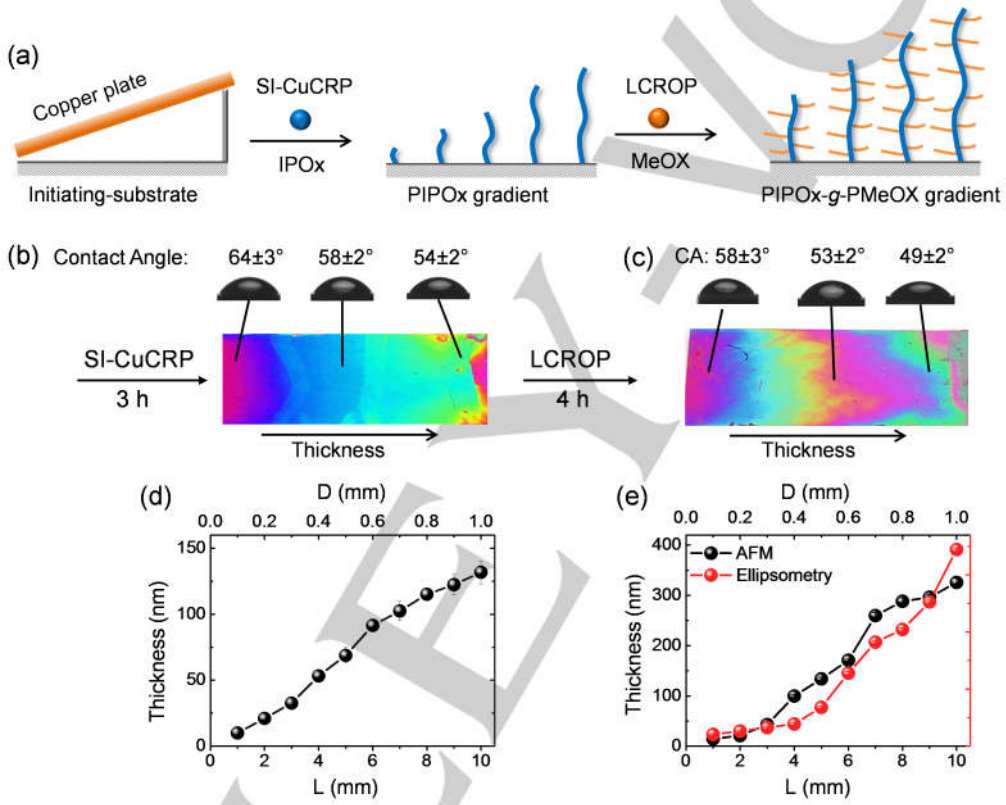

Figure 5. **POx BBB gradient *via* two-step approach. (a)** Schematic illustration of the synthesis of PIPOx-*g*-PMeOx BBB gradient *via* SI-CuCRP and LCROP. **(b)** Optical image and water contact angle data of resultant PIPOx gradient. **(c)** Optical image and water contact angle data of resultant POx BBB gradient. **(d)** Thickness plots of PIPOx backbone gradient as measured by ellipsometry. **(e)** Thickness plots of the POx BBB gradient as measured by AFM and ellipsometry, respectively.

Conclusion

In this work, we report two approaches for the synthesis of well-defined POx BBB surfaces *via* SI-CuCRP. The two-step synthesis consists of successive SI-CuCRP and LCROP polymerizations that enables the fabrication of POx BBBs with high layer thickness (up to ~ 300 nm) and grafting density (σ = 0.42 chains/nm^2). The synthesis of PIPOx backbones *via* SI-CuCRP is more controllable and consumes minimum monomers in comparison to conventional SIPGP approach. The characteristic dual-functionalities of resultant PIPOx-*g*-PMeOx BBBs are demonstrated by respective labelling of backbone and side chain with fluorescence dyes. In addition, the SI-CuCRP also enables a one-step approach to prepare well-defined POx BBBs with PMeOx macromonomers, since the macromonomer (i.e. side chain) can be fully characterized before grafting polymerization. Regarding to the facile fabrication procedures (especially for patterns and gradients), bio- and dual-functionalities, the POx-based BBBs surfaces presented in this work are promising for various biomedical applications, e.g.

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selectively tuning the surface adhesion, protein adsorption and cell behaviors.

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Keywords: polymer brush • bio-functional surfaces • controlled radial polymerization • poly(2-oxazolines) • bottle-brush brushes

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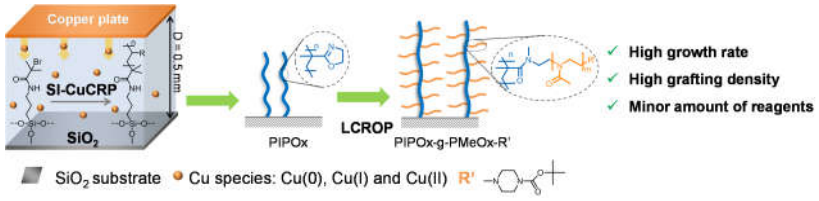

The facile fabrication of POx BBBs with high layer thickness (up to ~ 300 nm) and grafting density (σ = 0.42 chains/nm^2) *via* surface-initiated Cu-mediated controlled radical polymerization (SI-CuCRP) is presented. The patterned and gradient POx BBB surfaces were fabricated in a straightforward manner. The dual-functionalities of POx BBBs were demonstrated by fluorescent labelling.

Yunhao Du, Tao Zhang, Dan Gieseler, Maximilian Schneider, Daniel Hafner, Wenbo Sheng,Wei Li, Fred Lange, Erik Wegener, Ihsan Amin, and Rainer Jordan**

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Facile Fabrication of Bio-and Dual-Functional Poly(2-oxazoline) Bottle-Brush Brush Surfaces

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