

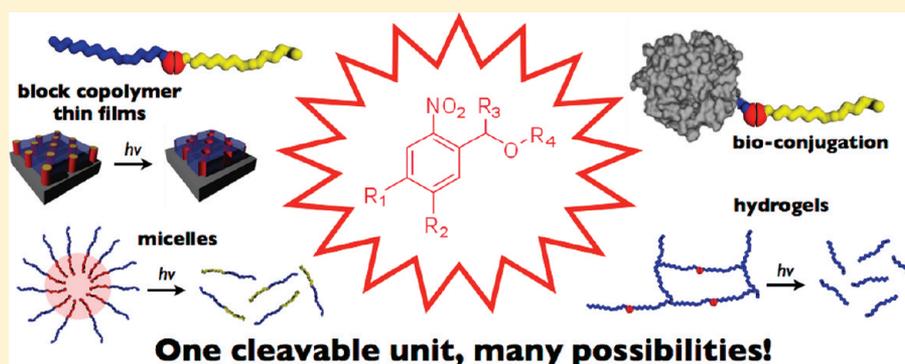
o-Nitrobenzyl Alcohol Derivatives: Opportunities in Polymer and Materials Science

Hui Zhao,^{†,⊥} Elizabeth S. Sterner,[‡] E. Bryan Coughlin,^{*,‡} and Patrick Theato^{*,†,§,⊥}

[†]Institute for Technical and Macromolecular Chemistry, University of Hamburg, Bundesstrasse 45, D-20146 Hamburg, Germany

[‡]Department of Polymer Science & Engineering, University of Massachusetts, 120 Governors Drive, Amherst, Massachusetts 01003-4530, United States

[§]World Class University (WCU) program of Chemical Convergence for Energy & Environment (C₂E₂), School of Chemical and Biological Engineering, College of Engineering, Seoul National University (SNU), Seoul, Korea



ABSTRACT: Polymers featuring photolabile groups are the subject of intense research because they allow the alteration of polymer properties simply by irradiation. In particular, the *o*-nitrobenzyl group (*o*-NB) is utilized frequently in polymer and materials science. This Perspective pays particular attention to the increasing utilization of this chemical group in polymer chemistry. It covers the use of (i) *o*-NB-based cross-linkers for photodegradable hydrogels, (ii) *o*-NB side chain functionalization in (block) copolymers, (iii) *o*-NB side chain functionalization for thin film patterning, (iv) *o*-NB for self-assembled monolayers, (v) photocleavable block copolymers, and (vi) photocleavable bioconjugates. We conclude with an outlook on new research directions in this rapidly expanding area.

1. INTRODUCTION

Photolabile groups have been used extensively in synthetic organic chemistry and have found numerous applications in academia and industry. While organic synthesis engaged the use of photolabile protecting groups as a tool for orthogonal deprotection, the development of photoacid generators, which act as H⁺ sources upon irradiation, and acid-sensitive photoresists have enabled the production of photosensitive materials employed in the microelectronic¹ and coatings industries.² Bochet has previously summarized the various photolabile groups that find intensive application in synthetic chemistry.³

Among the many photolabile groups that have been studied, *o*-nitrobenzyl (*o*-NB) alcohol derivatives have gained tremendous attention in the area of synthetic organic chemistry and beyond. First described by Schofield and co-workers,⁴ the chemistry was not widely recognized until Woodward and co-workers utilized what has become one of the most popular photolabile protecting groups.⁵ It is based on the photoisomerization of an *o*-nitrobenzyl alcohol derivative into a corresponding *o*-nitrosobenzaldehyde upon irradiation with UV light (Scheme 1), simultaneously releasing a free carboxylic acid. This mechanism has been investigated in detail, most recently by Wirz and co-workers.^{6,7}

The photodeprotection of *o*-NB esters usually yields carboxylic acids, accompanied by an *o*-nitrosobenzaldehyde.¹⁰ Fréchet and co-workers demonstrated that the concept could be expanded to yielding organic bases by employing *o*-nitrobenzyl carbamates of amines and diamines, which then result in the release of the respective alkylamines.¹¹ Logically, this chemistry was extended to *o*-NB variants used for alcohol deprotection¹² and peptide deprotection.¹³ 2-Nitrobenzylidene acetals have also been utilized, releasing 1,2-dihydroxy compounds after photolysis and subsequent ester hydrolysis.¹⁴ This chemistry has recently been extended to an *o*-nitrobenzyl triazole linker, prepared by the [2 + 3] Huisgen cycloaddition or “click” reaction of alkynes and azides, releasing a free 1,2,3-triazole leaving group.¹⁵ Recent developments have focused on the design of *o*-NB-based protecting groups with a red-shifted absorption to allow photolysis to occur using two-photon excitation techniques.¹⁶

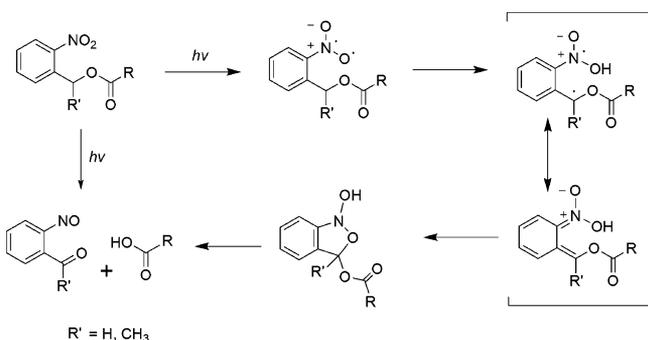
Linkers and protecting groups based on *o*-NB chemistry can usually be cleaved in minutes when exposed to 300–365 nm

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Scheme 1. Photoisomerization Mechanism of *o*-Nitrobenzyl Alcohol Derivatives into an *o*-Nitrosobenzaldehyde, Releasing a Carboxylic Acid^{3,8,9}



light, with times varying from several hours with a low-intensity 1.3 mW/cm² 365 nm source¹⁵ to 5 min or less when applying light intensities of 20–40 mW/cm².^{2,17} Photocleavage efficiency tends to improve when wavelengths near 300 nm are used, as the *o*-NB linker itself displays an absorption maximum at or near this wavelength.⁶ Studies have also shown that including substituents on the aromatic ring or at the benzyl position of the linker can shift the photocleavage wavelength¹⁸ or prevent the formation of photodimerized byproducts.¹⁹

Other advances in photocleavable junction structure and application include *o*-NB thioxanthone derivatives, which act as intramolecular sensitizers,²⁰ and the 2-(2-nitrophenyl)-propoxycarbonyl (NPPOC) photolabile protecting group, which was developed to address possible issues with photocleavage byproduct photodimerization.^{21–24} Its photocleavage proceeds via a β -elimination mechanism, resulting in a styrenic product that protects against the formation of the expected *o*-nitrosobenzaldehyde. Other studies focused on the integration of an orthogonal photolysis of different photoprotecting groups, e.g., 3',5'-dimethoxybenzoin, in conjunction with *o*-NB derivatives.^{3,25,26}

The application of photolabile molecules, especially *o*-NB derivatives, is not limited to organic synthesis as can be seen by recent developments in biological applications of such photolabile compounds.²⁷ Photoactivated bioagents, so-called “caged compounds”, are an important tool for studying cell signaling events.⁷ Consequently, reversible photoswitches have also been investigated. As an example, Chang and co-workers presented a “caged peroxide generator” based on photolysis of an *o*-NB-protected 1,2,4-trihydroxybenzene. This linker can be triggered on demand and was shown to produce H₂O₂ by reducing molecular oxygen via a superoxide intermediate.²⁸ Reviews by Heckel, Xing, Zhang, and their respective co-workers have summarized the various applications of caged and light-switchable small molecules (e.g., neuroactive amino acids, steroid hormones, lipids, and cellular signaling molecules), proteins, and nucleic acids.^{29–31}

Recently, Katz and Burdick have reviewed developments in the area of light-responsive biomaterials, which include the use of the *o*-NB functionality.³² Besides its focus on biological complexes, it represents the first summary of synthetic polymers that contain *o*-NB moieties. Even though *o*-NB esters have been investigated in polymer science since 1977,^{33,34} it has not been until very recently that studies appeared that take full advantage of this photolabile group in polymer and materials science applications.

Within this Perspective, we focus on the incorporation of *o*-NB-based photolabile groups in polymer materials. We pay particular attention to the increasing utilization of this chemical group in polymer chemistry in the past few years. We cover the use of (i) *o*-NB-based cross-linkers for photo-degradable hydrogels, (ii) *o*-NB side chain functionalization in (block) copolymers, (iii) *o*-NB side chain functionalization for thin film patterning, (iv) *o*-NB for self-assembled monolayers, (v) photocleavable block copolymers, and (vi) photocleavable bioconjugates, and we conclude with an outlook on this rapidly expanding area.

2. *O*-NB-BASED CROSS-LINKERS FOR PHOTODEGRADABLE HYDROGELS AND NETWORKS

While research directions in biochemistry and biomaterials have focused on “caged compounds”,³¹ the first breakthrough applications of *o*-NB-based photolabile linkers in polymer science have been achieved in the preparation of cross-linked networks.³⁵ Motivated by biological applications, the scientific community has found these photodegradable hydrogels to be of great interest. For example, *o*-NB-based cross-linkers have been used in the cross-linking of hydrophilic poly(ethylene glycol) chains, resulting in hydrogels which are commonly used as scaffolds in tissue engineering and drug delivery. Torro and co-workers reported a first example of model cross-linked networks based on *o*-NB linkers in 2007.³⁶ Their synthesis can be summarized in two steps: First, a four-armed star polymer containing *o*-NB linkers and terminal azides was prepared by atom transfer radical polymerization (ATRP) of *tert*-butyl acrylate followed by a simple postmodification of the terminal bromide into azide. In the second step, cross-linking was achieved by adding a bifunctional alkyne under copper(I) catalysis conditions, resulting in the CuAAC formation of 1,2,3-triazole linkages. An alternative route used a bifunctional *o*-NB linker and a tetrafunctional unit for the CuAAC cross-linking reaction (Scheme 2). Further, they demonstrated that a photodegradable four-arm star polymer with terminal azides can be prepared by a one-pot CuAAC/ATRP reaction. The insoluble network could be degraded to linear polymers with a defined molecular weight by exposure to UV light.

Similarly, Kasko and co-workers also used a cross-linking system based on *o*-NB (Figure 1, upper).¹⁷ However, they combined the efficient light degradable property of *o*-NB esters with the biocompatibility of PEO, resulting in a photocleavable hydrogel.^{37–39} This laid the foundation to trap living cells in the hydrogels, which may be released upon irradiation with light in a highly controlled manner (Figure 1a). Using two-photon photolithography, 3D channels for the migration of cells can successfully be obtained (Figure 1b). This “smart hydrogel” takes advantage of *o*-NB-based cross-links and thus opens an exciting application area for hydrogels.^{40,41} More recently, Kasko and co-workers have extended the application of photodegradable hydrogels based on *o*-NB cross-links to negative and positive patterning strategies. Furthermore, conjugating the *o*-NB unit to a coumarin dye in the photodegradable macromer enabled the two-photon degradation of the *o*-NB group as well as fluorescence visualization of the hydrogel.⁴²

Similarly, Kros and co-workers prepared photodegradable hydrogels based on dextran.⁴³ By utilizing the acrylate–thiol Michael addition of dithiolated PEG to dextran functionalized with acrylate-modified *o*-NB moieties, they were able to form

Scheme 2. Cross-Linking Network Based on *o*-NB Linker (Reprinted with Permission from Ref 36. Copyright 2007 American Chemical Society)

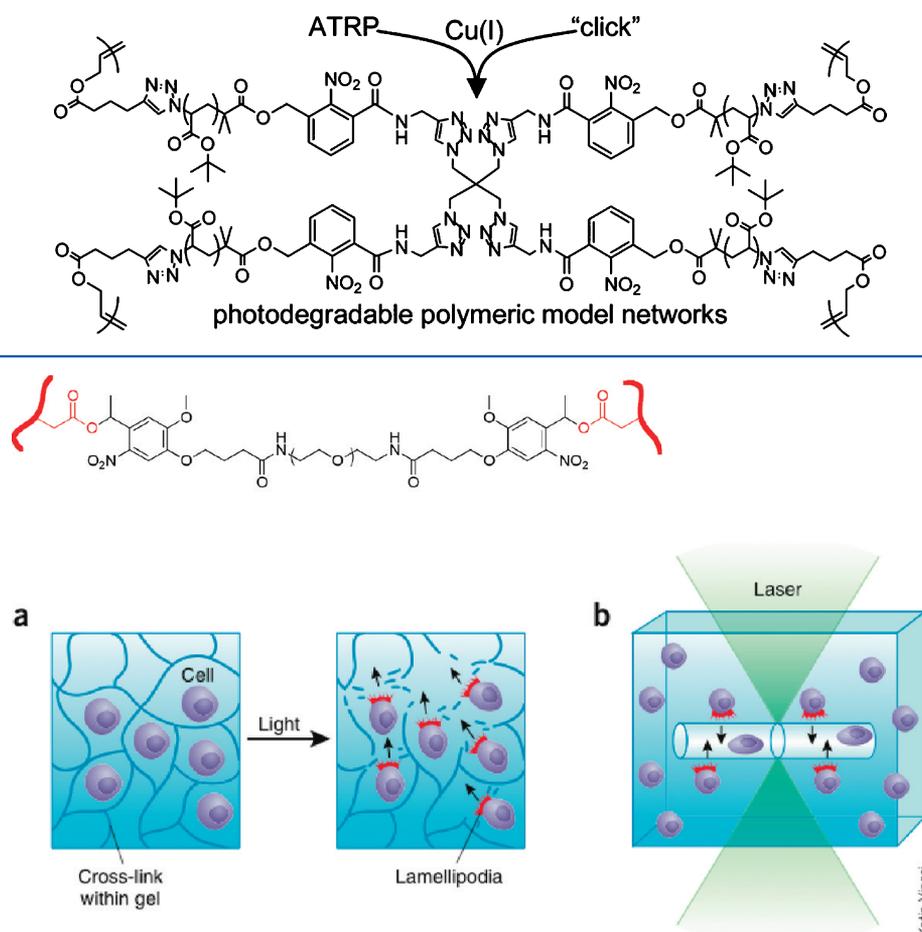


Figure 1. Chemical structure of a photodegradable hydrogel based on an *o*-NB linker (upper) (redrawn after ref 17) and light-induced migration of entrapped cells (lower).³⁷

biocompatible hydrogels. Photodegradation of the hydrogels was achieved by UV irradiation at 365 nm for 72 h, releasing green fluorescent protein from the hydrogel. They also demonstrated that the photodegradation was possible via a two-photon excitation using a pulsed near-infrared laser. Shoichet and co-workers have extended these photolabile chemistries to agarose- and hyaluronan-based materials,⁴⁴ producing three-dimensional structured materials with applications to tissue scaffolding⁴⁵ and using the unmasking of photolabile moieties to anchor biomolecules to hydrogel surfaces to allow these materials to control cell growth and mobility.⁴⁶ Recently, Anseth and co-worker showed that thiol-ene click chemistry as well as strain-promoted azide-alkyne cycloaddition in combination with *o*-NB-based localized degradation allows fabrication of 3D cytocompatible hydrogels.⁴⁷ Kasko and co-workers could also demonstrate that *o*-nitrobenzyl ether linkers allows the photorelease of potential drugs within hydrogels.⁴⁸

Further, Burdick and co-workers showed that thin film poly(hydroxyethyl methacrylate)-based hydrogels could be spatially altered when copolymerized with *o*-NB acrylate and subsequently irradiated, resulting in dramatic swelling in the irradiated areas,⁴⁹ thereby controlling spatially and temporally material properties and cellular interactions. The spatial and temporal manipulation of mechanical properties of hydrogels

plays an important factor in cell growth, which was investigated by Wang and co-worker, who studied the photoinduced softening of *o*-NB cross-linked polyacrylamide hydrogels.⁵⁰

Besides macroscopic gels and networks, Landfester and Klinger recently demonstrated the successful use of *o*-NB-based cross-linkers for the fabrication of photodegradable PMMA microgels. Utilizing miniemulsion techniques, particles in the range of 140–200 nm were prepared. Of particular note is the wavelength-controlled selective degradation of these hydrogels, achieved by using carbonate and carbamate *o*-NB cross-linkers.⁵¹

3. *o*-NB SIDE CHAIN FUNCTIONALIZATION IN POLYMERS AND BLOCK COPOLYMERS TO PHOTOTRIGGER MICELLE DISRUPTION

Responsive micelles formed from environmentally (pH, redox, light, temperature, etc.) sensitive block copolymers in solution have attracted great attention since they find potential applications in targeted drug delivery, cosmetics, and many other fields.⁵² In particular, light is an intriguing external stimulus because it is efficient and convenient and can be applied in a targeted and specific manner via a variety of focusing or lithographic techniques. Consequently, light responsive block copolymer micelles have been explored for entrapping dyes and drugs with the intention of releasing them at a defined time

and location. For recent reviews on photoresponsive block copolymers, see publications by Gohy and co-workers and Zhao.^{53,54} *o*-NB esters are a good candidate for constructing light responsive materials since they are efficiently cleavable upon UV exposure. Early works by Zhao and co-workers explored the use of pyrenylmethyl esters, which can be cleaved upon UV irradiation to yield 1-pyrenylmethanol and the corresponding carboxylic acid.⁵⁵ Later, Zhao and co-workers turned their focus to *o*-NB and nicely demonstrated its use as a side chain functionality within amphiphilic block copolymers to prepare light responsive micelles (Figure 2).⁵⁶ In this aspect, Gohy and

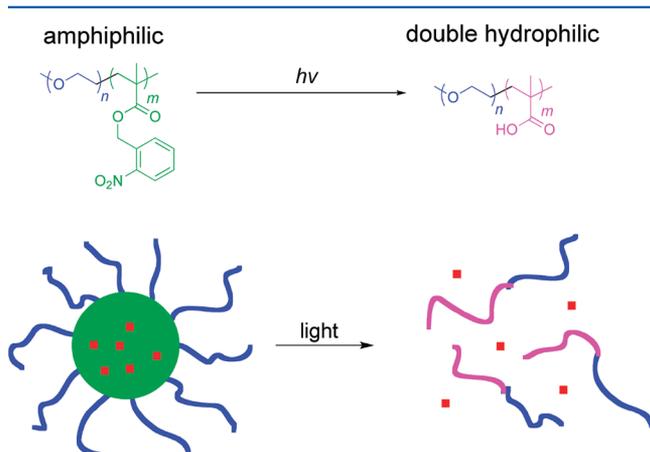


Figure 2. Chemical structure and photolysis of *o*-NB-containing amphiphilic block copolymers and their use for photocontrolled drug release (redrawn after ref 56).

co-workers conducted a fundamental study on the possibilities of polymerizing 2-nitrobenzyl methacrylate under various controlled radical polymerization conditions.⁵⁷ It was discovered that 2-nitrobenzyl acrylate cannot be polymerized under conditions suitable for ATRP, nitroxide-mediated polymerization (NMP), or reversible addition–fragmentation chain transfer (RAFT) polymerization. In contrast, 2-nitrobenzyl methacrylate can be polymerized under RAFT conditions with some degree of control and under ATRP with better control as long as conversions are kept below 30%.

Accordingly, Zhao and co-workers synthesized an amphiphilic block copolymer composed of poly(ethylene oxide) (PEO) and poly(2-nitrobenzyl methacrylate) (PNBM) by ATRP starting from a PEO macroinitiator. Because of the *o*-NB group, this amphiphilic block copolymer can be turned into a double hydrophilic block copolymer upon irradiation, i.e., photocleavage of the ONB ester yielding essentially a poly(methacrylic acid) block. Consequently, Zhao and co-workers demonstrated that this results in the destruction of the micelles, as demonstrated by the controlled release of Nile Red—previously trapped inside the hydrophobic core of the micelle—upon irradiation (Figure 2). Thus, it is one of the first examples showing the potential application of *o*-NB linkers in drug delivery and phototherapeutics.

Zhao and co-workers extended this concept by adding a thermosensitive material, yielding multiresponsive (temperature and light) micelles based on *o*-NB.⁵⁸ They synthesized a thermal- and light-sensitive diblock copolymer composed of a hydrophilic poly(ethylene oxide) (PEO) block and a temperature- and light-sensitive poly(ethoxytri(ethylene glycol)-acrylate-*co*-*o*-nitrobenzyl acrylate) (P(TEGEA-*co*-NBA)) block by ATRP (Figure 3). Above the lower critical solution

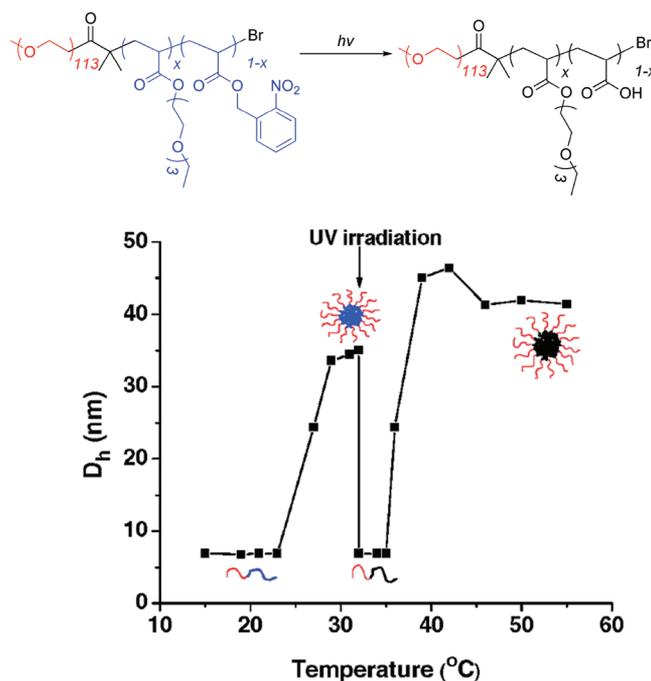


Figure 3. Thermo- and light-sensitive micelles based on *o*-NB-containing copolymer and their hydrodynamic diameter (D_h) response to temperature changes and UV irradiation. (Reprinted with permission from ref 58. Copyright 2008 American Chemical Society.)

temperature (LCST) of the thermosensitive poly(ethoxytri(ethylene glycol)) block, the block copolymer is amphiphilic and self-assembles into micelles. After UV irradiation, the LCST of the block copolymers shifted from 25 to 36 °C due to the change of hydrophilicity from the deprotection of the *o*-nitrobenzyl acrylate comonomer to acrylic acid (Figure 3). Nile Red is known to fluoresce in hydrophobic environments, but this fluorescence is negligible in aqueous solution and was used to probe the micelle formation. Before irradiation, micelles were formed of the photoprotected block copolymer that had Nile Red in their core, resulting in high fluorescence. After irradiation, the fluorescence dropped sharply, indicating release of the dye and disintegration of the micelles. Raising the temperature further caused the now-deprotected copolymer to again form micelles, sequestering the Red Nile and restoring the system's fluorescence (Figure 3).

It was later shown that a 20 wt % solution of PEO-*b*-P(TEGEA-*co*-NBA) forms micelles upon heating above the LCST, resulting in an optically isotropic gel that can withstand finite yield stress. Upon UV irradiation the *o*-NB ester is cleaved resulting in dissociated micelles, leading to a transformation from a gel to a free-flowing liquid.⁵⁹ Similar effects have been observed for the thermo- and light-sensitive triblock copolymer P(TEGEA-*co*-NBA)-*b*-PEO-*b*-P(TEGEA-*co*-NBA), in which the temperature-induced sol–gel transition originates from the formation of a 3D network of hydrophobic cores of dehydrated P(TEGEA-*co*-NBA) blocks bridged by hydrophilic PEO chains.⁶⁰

In efforts to accelerate the degradation time, Zhao and co-workers designed an amphiphilic triblock copolymer with multiple photocleavable moieties positioned repeatedly along the hydrophobic middle block.⁶¹ PEO chains were attached as hydrophilic blocks to a hydrophobic polyurethane containing *o*-NB groups. The block copolymer micelles showed fast

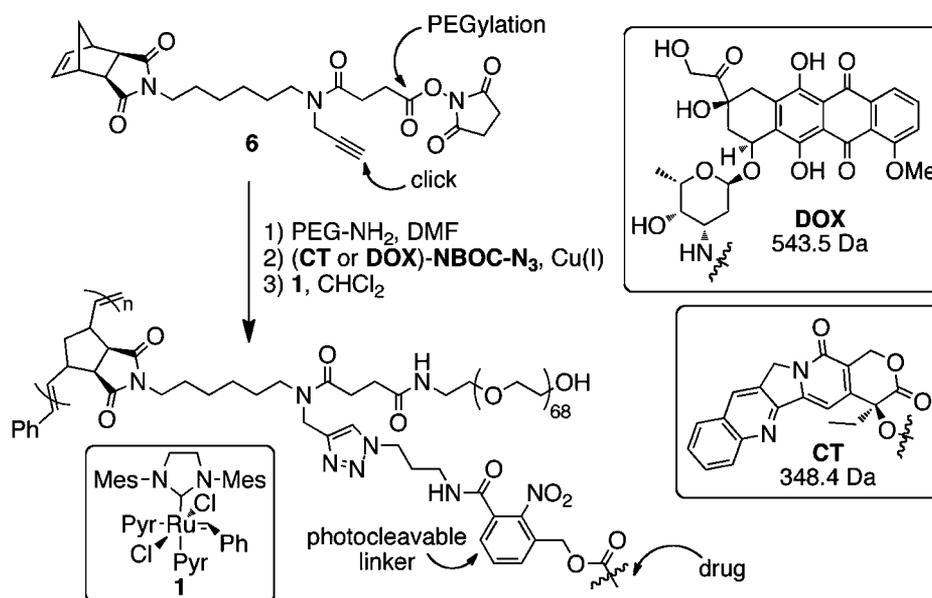


Figure 4. Synthesis and structure of polynorbornene-g-PEO polymers. (Reprinted with permission from ref 65. Copyright 2010 American Chemical Society.)

photocleavage of the micelle core within 180 s, and as a result a burst release of hydrophobic guests was achieved. An alternative approach was reported by Thayumanavan and co-workers, who synthesized photocleavable facially amphiphilic dendrimers that form micelles in water.⁶² Upon irradiation with UV light (365 nm, 200 s) photocleavage of the *o*-NB esters occurred and resulted in a slight change of the hydrophilic–lipophilic balance, which was sufficient to cause dissociation of the micelles and subsequent release of hydrophobic guest molecules. Noteworthy, the cleavage of *o*-NB groups from polymeric side chains results in the release of nitrosaldehyde, which may be toxic or cause other side effects in vivo.

While most approaches focused on micellization in water, Gohy and co-workers synthesized poly(dimethoxynitrobenzyl acrylate)-*block*-polystyrene as a block copolymer with photocleavable side groups in one block.⁶³ Upon UV irradiation in chloroform the resulting hydrophilic poly(acrylic acid) block becomes insoluble, and the block copolymer self-assembles in micelles, which were used to trap dyes into the micelle core. Rather than utilizing *o*-NB esters to alter the solubility properties of a polymer chain, Grubbs, Tirrell, and their respective co-workers have used *o*-NB esters for the photoinduced release of covalently bound drugs from bottle-brush polynorbornene-g-PEO polymers (Figure 4).⁶⁴ UV irradiation released the drug molecules (doxorubicin or camptothecin) from the brush core. Viability tests of MCF-7 human breast cancer cells mixed with the micelles showed at least a 12-fold increase in toxicity after irradiation-induced drug release.⁶⁵

Meijer and co-workers showed that particle aggregation can also be controlled via an intramolecular collapse of a single polymer chain. They designed and synthesized a poly-(norbornene) with 2-ureidopyrimidone (UPy) groups in the side chain, which were protected at the terminal carbonyl site with an *o*-NB ether. As a result, this effectively decreased the strong association of UPy groups. Photodeprotection of the *o*-NB group released the UPy groups, permitting their intramolecular dimerization and resulted in a decrease in hydrodynamic volume. AFM analysis of spin-cast films of these solutions revealed single chain nanoparticles.⁶⁶ In an elegant approach, Almutairi

and co-workers designed light-sensitive polymers based on a self-immolative quinone–methide system.⁶⁷ Photocleavage was possible via one- and two-photon processes. They were able to encapsulate Nile Red as a model guest molecule within polymeric nanoparticles and release the guest upon irradiation. In contrast, Wei and co-workers utilized third-, fourth-, and fifth-generation poly(imidoamine) (PAMAM) dendrimers as nanocarriers and peripherally modified these dendrimers with photocleavable *o*-NB groups.⁶⁸ Salicylic acid and adriamycin could be encapsulated in the core of the dendrimers and released upon UV irradiation (365 nm). They found that the fourth generation dendrimer was best suited to hosting the guest molecules.

4. *O*-NB SIDE CHAIN FUNCTIONALIZATION FOR THIN FILM PATTERNING

There has been one early report on including *o*-NB ethers in the main chain of polyethers, which were prepared by polycondensation of 2-nitro-1,3-xylylenedibromide with 4,4'-isopropylidenediphenol.⁶⁹ It was demonstrated that these polymers decomposed upon UV irradiation and thus suggested these materials for positive-type photoresists. Similar work was conducted by Lee and co-workers, who synthesized a polyimide precursor with *o*-NB ester functionalities in the side chains. They could show that this polyimide became soluble in basic solution after UV irradiation and thus can be used as positive photoresist.⁷⁰ Doh and Irvine designed a terpolymer poly(*o*-nitrobenzyl methacrylate-*co*-methyl methacrylate-*co*-(ethylene glycol) methacrylate) (P(*o*-NBMA-*co*-MMA-*co*-EGMA)) to prepare thin film patterns on the micrometer scale. They demonstrated that for a terpolymer composition of 43 wt % *o*-NBMA, 38 wt % MMA, and 19 wt % EGMA the exposed areas of a thin film could be dissolved by phosphate-buffered saline after UV irradiation (see Figure 5). Conjugation of biotin to the hydroxyl end groups of PEGMA units allowed selective immobilization of streptavidin on the surface and led to multicomponent protein patterning.⁷¹ In follow-up work, Doh and co-workers used an optimized photosensitive terpolymer to pattern arrays composed of several proteins by utilizing

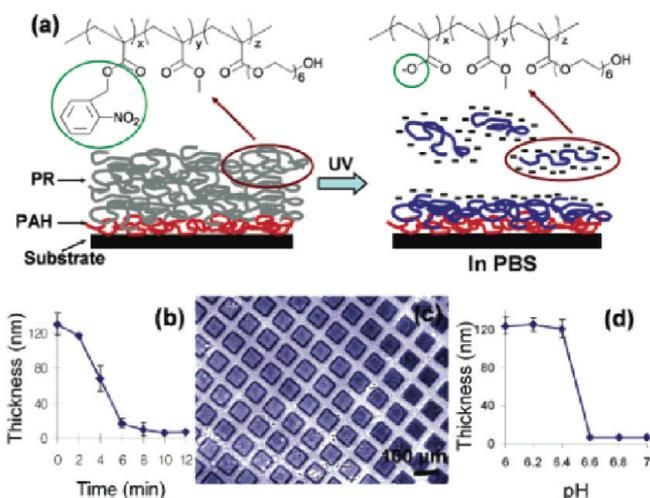


Figure 5. Chemical structure of a photosensitive terpolymer and its mechanism for patterning. (Reprinted with permission from ref 71. Copyright 2004 American Chemical Society.)

microscope projection lithography. They could also extend this approach to the photopatterning of immune cells.⁷²

Batt and co-workers undertook a similar approach. They prepared a photosensitive hydrogel surface composed of acrylamide, methylenebis(acrylamide) and functional group-containing methacrylate (FGM). This FGM could either be 2-nitrobenzyl methacrylate or 2-aminoethyl methacrylate hydrochloride, which after polymerization was used to form the 2-nitrobenzyl-derived carbamate. UV irradiation resulted in cleavage of the *o*-NB group and allowed for local protein immobilization through primary amines available on lysine residues by bis(sulfosuccinimidyl)-suberate or carbodiimide coupling chemistry.⁷³

Another exciting approach was taken by Ionov and Diez, who utilized the combination of thermoresponsive and photoresponsive characteristics for the patterning of thin polymer films. They synthesized a series of copolymers composed of *N*-isopropylacrylamide and *o*-nitrobenzyl acrylate and could show that the LCST of these polymers differed by almost 50 °C before and after UV irradiation. This temperature-dependent solubility behavior was used to pattern spin-coated thin films by patterned UV irradiation. Sequential removal of irradiated and nonirradiated areas could be achieved by washing steps at different temperatures, allowing the patterning of proteins.⁷⁴

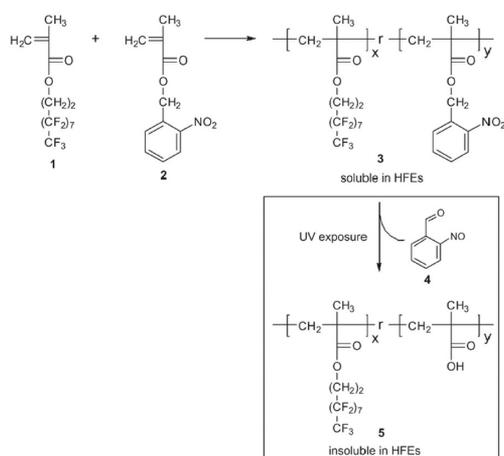


Figure 6. Synthesis of the UV-sensitive acid-stable polymer resist and patterned photoresist SEM images.⁷⁵

o-NB-based photoresists can be employed in the patterning of organic electronics, which was shown by Ober and co-workers. They synthesized a copolymer composed of 3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptafluorodecyl methacrylate and *o*-nitrobenzyl methacrylate and observed that it was soluble in hydrofluoroethers before irradiation and insoluble after irradiation with UV light at 365 nm (Figure 6). Thus, they could demonstrate that this copolymer represents a nonchemically amplified acid-stable resist for submicrometer patterning of PEDOT:PSS.⁷⁵

5. *O*-NB FOR SELF-ASSEMBLED MONOLAYERS (SAMS) TO CONTROL SURFACE PROPERTIES

While applications of photopatternable polymer thin films on the basis of *o*-NB are continuously growing, there have also been studies presented on photocleavable self-assembled monolayers (SAMs). SAMs in general have proven powerful tools to control surface energy, which influences a variety of properties, e.g., adhesion, wetting and flow profiles, or etch resistance. Moore and co-workers have utilized photopatternable SAMs using *o*-NB chemistry to direct liquid flow inside microchannels (Figure 7).⁷⁶ Essentially, the *o*-NB-based SAM was employed in a photolithographic—and thereby contact free—method resulting in patterns of differing surface free energies inside microchannels. This difference in the surface free energies confined aqueous solutions to the irradiated, and thus hydrophilic, regions resulting in control of the flow patterns, as shown in Figure 7.

Rather than merely taking advantage of a change in surface hydrophilicity after UV irradiation of an *o*-NB-derived SAM, several studies have concentrated on utilizing the distinct surface chemistry obtained after photocleavage. Evans and co-workers first studied a SAM containing *o*-NB as a protecting group for COOH and NH₂ groups on gold surfaces. In comparison to photodeprotection by UV irradiation in solution, on gold surfaces a lower chemical yield (<50%) was achieved. This might presumably be due the quenching of excited molecules by the gold or an imine formation in case of protected amines.⁷⁷ However, for *o*-NB-protected carboxylic groups on SAMs, the yield during UV irradiation could be dramatically improved in the presence of acids.⁷⁸ Using HCl/methanol as a catalyst resulted in formation of the methyl ester.

Kikuchi and co-workers prepared a SAM on a glass substrate featuring an *o*-NB group as well as an activated ester group, 1-[3-methoxy-6-nitro-4-(3-trimethoxysilylpropoxy)phenyl]ethyl

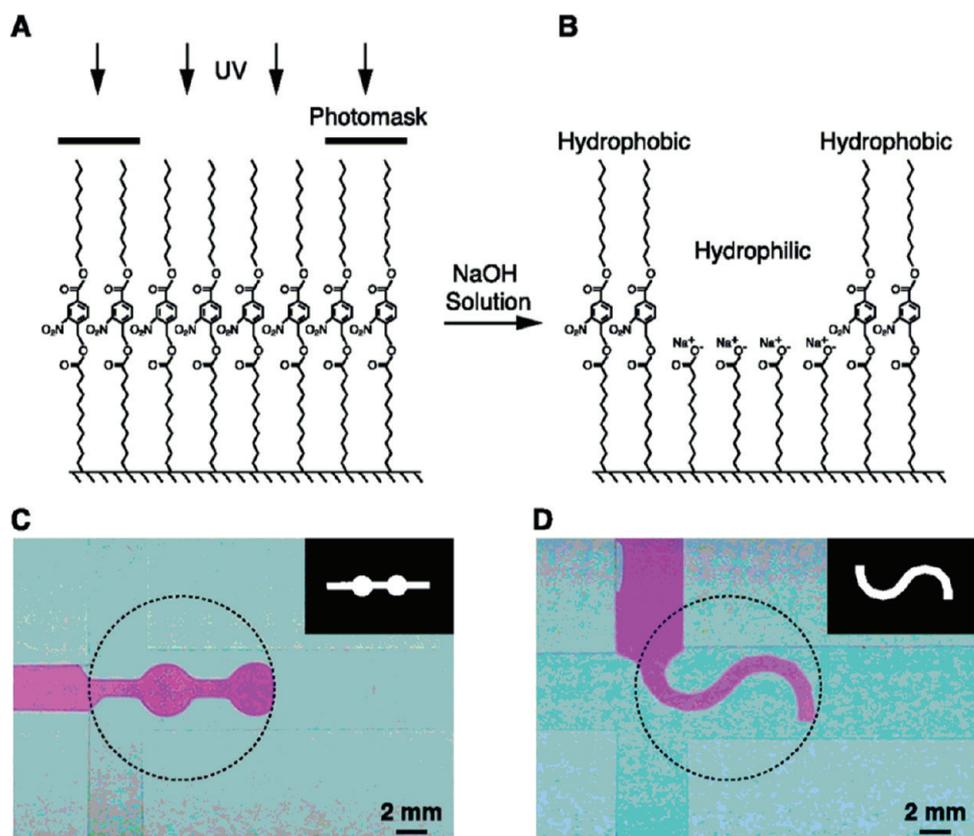


Figure 7. (A, B) Photopatterning by UV light to induce hydrophilic and hydrophobic surface patterns inside microchannels. (C, D) Flow profiles of dilute Rhodamine B aqueous solution inside the surface patterned microchannels.⁷⁶

N-succinimidyl carbonate, that allowed for the attachment of amino-terminated poly(ethylene glycol) (PEG-NH₂), resulting in photopatternable PEG-SAMs.⁷⁹ Upon UV irradiation, it was possible to detach PEG and thus change from a cell nonadhesive to a cell adhesive substrate. In combination with illumination through a photomask, cellular patterns were created.

Jonas and co-workers demonstrated that surface modification based on *o*-NB groups is orthogonal to a benzoin-based photoprotection group. They showed that mixed SAMs of both photocleavable groups can be selectively cleaved by choosing the appropriate irradiation wavelength. The benzoin group is almost quantitatively cleaved by irradiation at 254 nm, while the *o*-NB group remained fully intact under these conditions. Irradiation at 365 nm resulted in the cleavage of not only the *o*-NB but also the benzoin group, likely due to its weak absorbance band at 380 nm. However, irradiation at 411 nm leads to cleavage of the *o*-NB with the benzoin group being stable.⁸⁰ In further studies, they described an optimized *o*-NB-based photoprotection for carboxylic acid groups to be utilized within SAMs on quartz slides, 1-(4,5-dimethoxy-2-nitrophenyl)ethyl 4-(triethoxysilyl)butanoate. Standard deprotection by a single-photon process (UV irradiation at 365 nm) was confirmed in solution and in a monolayer. Additionally, a two-photon deprotection could be achieved with a 780 nm laser, which provided access to near-field induced patterning.⁸¹ They could also induce the photoprotection by localized two-photon induced activation through neighboring enhanced electromagnetic near-fields around metallic nanostructures.⁸²

Zhao and co-workers prepared gold nanoparticles functionalized on the surface with *o*-NB alcohol as well as gold nanoparticles with benzylamine on the surface (Figure 8).⁸³

Taking advantage of the light-triggered “click” reaction of *o*-nitrobenzyl alcohol with benzylamine, which results in the formation of 2-(*N*-benzyl)indazolone, they were able to assemble the gold nanoparticles upon irradiation with UV light. The length of the formed nanochains increased with increasing irradiation time.

Such surface-immobilized photocleavable groups based on coumarin have recently been used by Zhu and co-workers, who presented a mesoporous silica nanoparticle-based drug delivery system.⁸⁴ Bowman and co-workers immobilized *o*-NB acrylate on silica nanoparticles and used those to grow linear polymer grafts by a thiol–acrylate polyaddition reaction.⁸⁵ Upon exposure to UV light, the grafted polymers were released and analyzed and were found to be similar to polymers formed in bulk.

6. *O*-NB JUNCTIONS TO CLEAVE BLOCK COPOLYMERS

Block copolymers (BCPs) have been studied extensively due to their ability to self-assemble into a range of well-defined, well-ordered structures. Most common are the spherical, cylindrical, gyroidal, and lamellar morphologies found in bulk.⁸⁶ In recent years the interest in block copolymers serving as nanotechnological templates has resulted in a multitude of research efforts. Block copolymer thin films with a morphology oriented perpendicular to the substrate are the current focus of many research groups, with a particular aim of preparing well-ordered, nanoporous thin polymer films. Currently, several challenges have to be addressed to overcome the limitations still present in thin block copolymer films. The first is achieving high lateral order in the morphology, and the second is facile, selective removal of one phase.

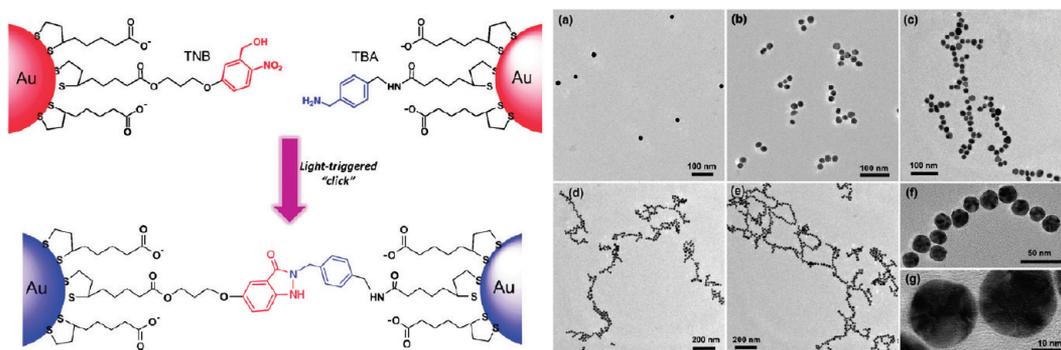


Figure 8. (left) Light-triggered covalent assembly of gold nanoparticles. (right) TEM micrographs of the Au NPs after UV irradiation of increasing time: (a) 0, (b) 5, (c) 10, (d) 15, and (e) 30 min. Images (f) and (g) are the high-resolution TEM characterizations of an obtained Au NPs nanochain.⁸³

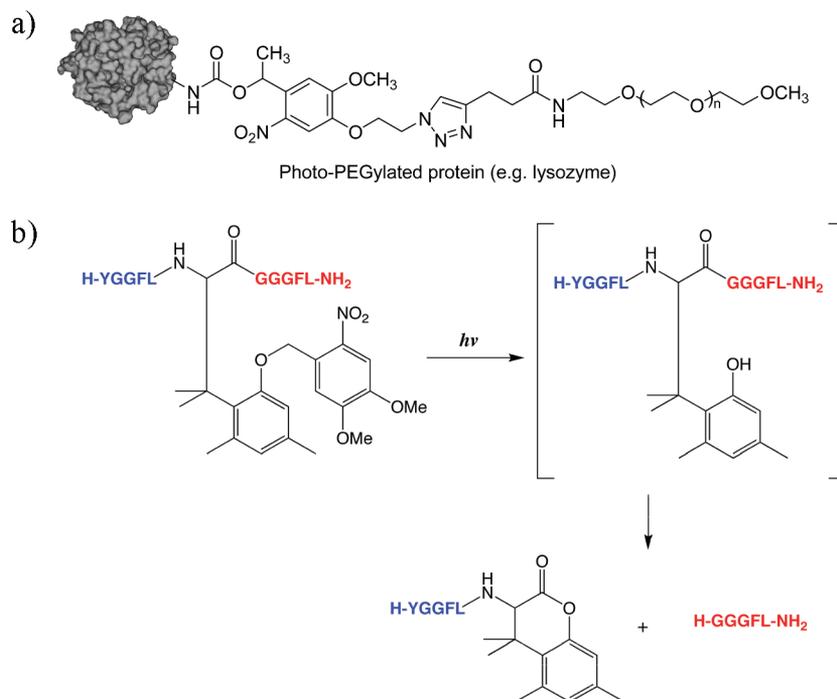


Figure 9. (a) Photocleavable PEGylated lysozyme¹⁰⁵ and (b) schematics of a photoinduced peptide bond cleavage (redrawn after ref 106).

Several methods that allow for selective removal of one domain have been presented in the literature, such as chemical etching, ozonolysis, pH induced hydrolysis, and UV degradation. In particular, block copolymers with a cleavable junction are interesting since they can be used as precursors for generating hollow structures after cleavage and selective removal of one of the blocks. This can have an impact on the formation of hollow micelles and nanoporous polymeric materials.^{87,88}

As *o*-NB is a well-known photocleavable junction, photocleavable block copolymers can be prepared based on this structure. In early work, Penelle and co-workers explored the synthesis of a photolabile initiator for ATRP on the basis of *o*-NB. The polymer obtained by ATRP was then coupled to amine-terminated polystyrene to yield the photocleavable block copolymer, whose photolability was demonstrated by GPC analysis.⁸⁹ However, no thin film characterization was performed, even though the same group presented an alternative approach that utilizes an anthracene dimer as a photocleavable junction point which resulted in PS-*b*-PMMA that showed a cylindrical microdomain morphology.^{90,91} The anthracene

dimer approach suffered from the fact that symmetric dimers as well as nonreacted homopolymer had to be removed by selective solubilization.

Kang and Moon adopted the original idea of Penelle, becoming the first to prepare and characterize photocleavable block copolymer thin films based on *o*-NB.⁹² They prepared the photocleavable diblock copolymer polystyrene-*block*-poly(ethylene oxide) (PS-*hν*-PEO) by ATRP using an *o*-NB-functionalized PEO macroinitiator (Figure 10). The photolysis of PEO-*hν*-PS has been studied by GPC, which showed that the molecular weight of the block copolymer decreased with increasing time of UV exposure. Since PEO-*b*-PS is a well-known block polymer for the generation of well-ordered films, they also used the PEO-*hν*-PS to get ordered nanoporous films by spin-coating. Compared to other cleavable block copolymers (i.e., the acid-cleavable trityl ether junction),⁹³ the *o*-NB-based block copolymer can be cleaved into two blocks under mild conditions. As a result, they demonstrated that a porous polystyrene film can be obtained after irradiating the block

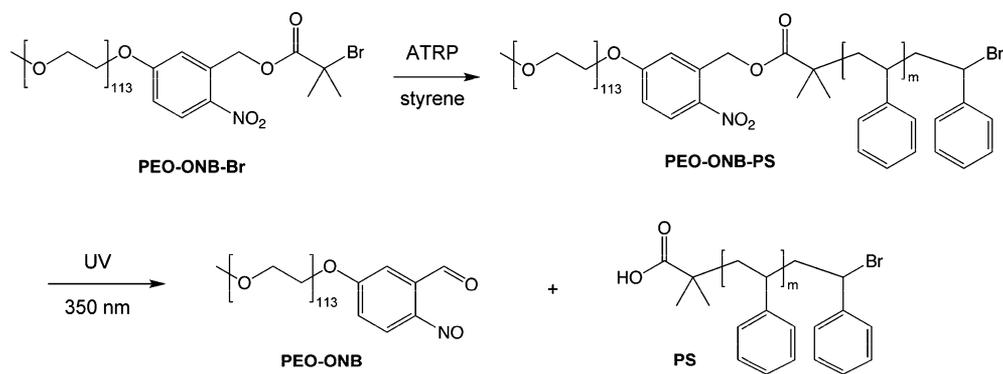


Figure 10. Synthesis and photolysis of PEO- $h\nu$ -PS by ATRP (redrawn after ref 92).

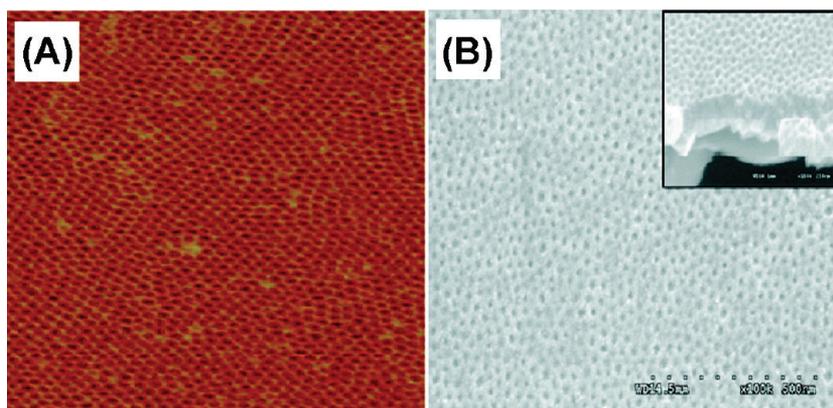


Figure 11. (A) AFM image ($1 \times 1 \mu\text{m}^2$) of PS- $h\nu$ -PEO (23.7-*b*-5.0 K) films (thickness = 43 nm) spin-coated onto silicon wafers and solvent annealed for 2 h (benzene/water). (B) SEM image of the nanoporous PS thin film resulting from photocleavage and selective solvent removal (methanol/water) of PEO phase. A side view (45°) is shown in the inset image. (Reprinted with permission from ref 92. Copyright 2009 American Chemical Society.)

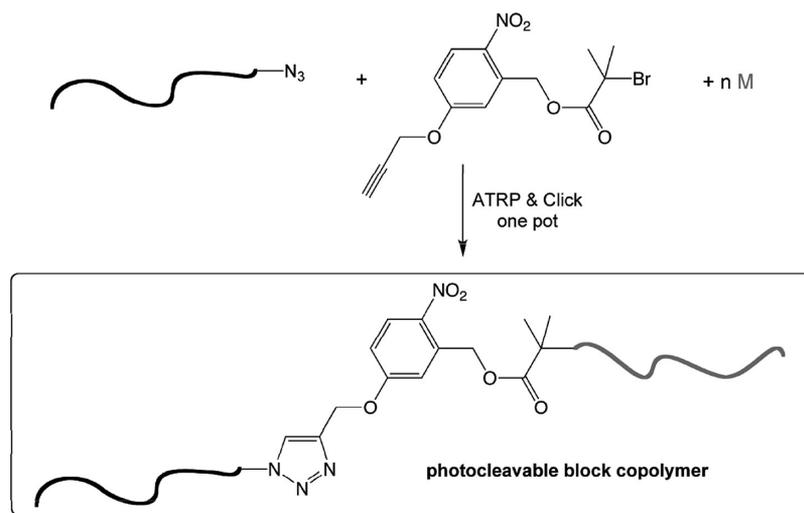


Figure 12. Synthesis of PEO- $h\nu$ -PS by ATRP–CuAAC click reaction (redrawn after ref 95).

copolymer thin film with UV light followed by washing with a water/methanol mixture (Figure 11).

A bifunctional *o*-NB-based ATRP initiator can also be prepared for the synthesis of symmetric homopolymers that can be degraded upon UV irradiation.⁹⁴ Recently, Fustin and co-workers developed a more versatile synthetic route toward photocleavable block copolymers on the basis of an *o*-NB junction.⁹⁵ As copper(I) is known to be a catalyst for both ATRP and azide–alkyne cycloaddition (CuAAC) click reaction,

they performed ATRP and click chemistry in a one-pot synthetic strategy using an ONB ester featuring dual functionality to synthesize several photocleavable block copolymers including PS- $h\nu$ -PEO, which was used in the work of Kang and Moon (Figure 12). An advantage of their work is that their synthesis avoids the preparation of a macroinitiator, (PEO-*o*-NB-Br in Figure 10), which are often more difficult to synthesize than small molecule initiators (Figure 12). Theato, Coughlin, and co-workers extended this approach by combining

RAFT polymerization and a subsequent intermacromolecular azide–alkyne click reaction, providing more flexibility in the synthesis of photocleavable block copolymers.⁹⁶ Highly ordered thin films were prepared, and after photoetching the resulting nanoporous films were used to prepare the first examples of nanostructures from a photocleavable polymer template.

Besides well-ordered nanoporous thin film applications, amphiphilic block copolymers with an *o*-NB junction also find use in the encapsulation/release of objects through, for example, a polymersome–micelle transition. Meier and co-workers synthesized an amphiphilic poly(γ -methyl- ϵ -caprolactone)-*block*-poly(acrylic acid) (PmCL-*o*-NB-PAA) with *o*-NB junction by ring-opening polymerization and ATRP (Figure 13). A dual

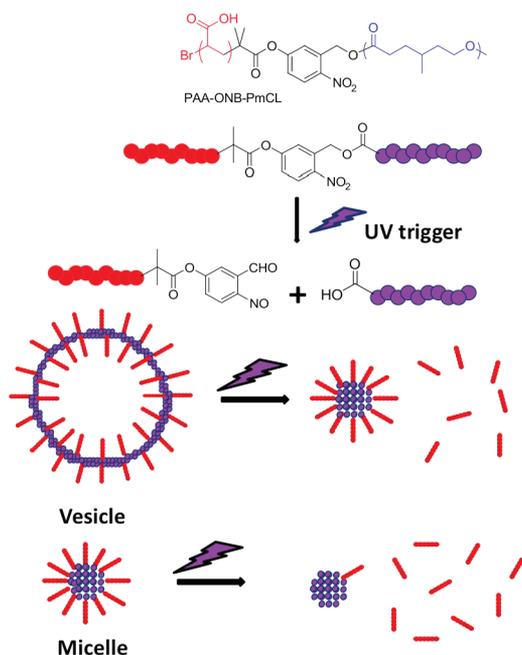


Figure 13. The concept of photocleavable nanocarriers based on amphiphilic block copolymers with *o*-NB junctions (redrawn based on ref 97).

initiator based on *o*-NB was synthesized and used for the sequential ring-opening polymerization of *m*CL and ATRP of *tert*-butyl acrylate (*t*BA).⁹⁷ Afterward, the *Pt*BA block was hydrolyzed, resulting in the amphiphilic diblock copolymer PmCL-*o*-NB-PAA, which forms aggregates in aqueous solution. Those aggregates—proposed to be micelles or polymersomes—can be degraded by light, demonstrated by a decrease in the size of the aggregates after UV irradiation.

An alternative approach was presented by Zhao et al., who utilized a photodegradable polyurethane block (PUNB) in their synthesis of an amphiphilic triblock copolymer, PEO-*b*-PUNB-*b*-PEO. The short polyurethane middle block was composed of multiple *o*-NB units that allowed a fast photodegradation of the micelles in solution.⁶¹

Poly(ϵ -caprolactone)-based block copolymers that feature an *o*-NB photocleavable junction have also been investigated by Nojima and co-workers. They have prepared a polystyrene-*block*-poly(ϵ -caprolactone) diblock copolymer with an *o*-NB-based junction. They demonstrated that this block copolymer possesses a cylindrical morphology and the crystallization behavior of the PCL chains behaves very differently before and after irradiation with light, as a result of the cleavage of the PCL chains.⁹⁸

Klán and co-workers extended the use of photocleavable junctions based on *o*-NB to an orthogonal photocleavable linker, which functionalized the benzylic and phenacyl positions with leaving groups.⁹⁹ The detachment of the groups can be achieved selectively and orthogonally upon irradiation. A very promising alternative to the *o*-NB-based photocleavable junction was reported by Keller and co-workers, who prepared photolabile diblock copolymers with a truxillic acid junction.¹⁰⁰

7. PHOTOCLEAVABLE BIOCONJUGATES

Applications of *o*-NB linkers in conjugating biological and synthetic molecules have increased over the past few years. Hydrophilic *o*-NB-based photocleavable linkers can be cleaved using small UV diodes, which combine several advantages (small, no heat release, narrow emission profile). Such linkers have been described as suitable for supports in chemical proteomics.¹⁰¹ Similarly, biotinylated photocleavable polyethyleneimine has been synthesized and investigated for the controlled release of nucleic acids from solid supports.¹⁰² Nagamune and co-workers have presented a biotinylated photocleavable caging agent on the basis of the 6-bromo-7-hydroxycoumarine-4-ylmethyl group that can be used for site-selective caging of plasmids.¹⁰³ Burke and co-workers demonstrated a multipurpose *o*-NB linker that featured two orthogonal functional groups, *N*-hydroxysuccinimidyl and sulfhydryl, allowing for the selective binding of peptides or other amine-terminated groups and oligonucleotides, which can then be used for nucleic acid selections.¹⁰⁴

The idea of selective removal of polymers has also inspired protein scientists. While PEGylation is a common technique to enhance the pharmacokinetic properties of proteins, it abrogates protein activity in many other applications. Deiters and co-workers have taken advantage of this fact and conjugated a photocleavable PEG to lysozyme. This resulted in a completely inactive enzyme whose activity could be recovered after irradiation with UV light ($\lambda = 365$ nm) for 30 min, due to removal of the PEG unmasking the protein (Figure 9a).¹⁰⁵ The concept of alteration of peptides by light was taken further by Shigenaga and co-workers, who designed a photocleavable amino acid that could induce a peptide bond cleavage at the C-terminal position based on the integration of an *o*-nitrobenzyl ether group that triggers a cascade of reactions upon irradiation with either single-photon UV or two-photon near-IR light (Figure 9b).¹⁰⁶

8. OUTLOOK AND CHALLENGES OF PHOTOLABILE GROUPS IN POLYMER CHEMISTRY

We have highlighted active research areas in polymer and materials science that utilize the photolysis of *o*-nitrobenzyl groups. This field is rapidly developing and new reports are published frequently. We have paid particular attention to research achievements in polymer chemistry. Photodegradable hydrogels with *o*-NB-based cross-linkers are being used to construct tailored hydrogels that can be further elaborated by selective photodegradation. These hydrogels are currently studied as three-dimensional matrices to entrap and guide cells, and future applications may include adjustable feature size and novel geometries. Side chain functionalization in block copolymers uses *o*-NB to produce smart materials with tunable hydrophobicity–hydrophilicity and LCST properties, with an overall goal of producing micelles with tunable assembly and

disassembly behavior. Further investigation of these materials may include micelles designed to host guest molecules for photoinduced delivery. Thin film patterning with side chain functionalized *o*-NB materials and *o*-NB-based self-assembled monolayers allows for the tailoring of surface energies and chemistries through photocleavage. Side chain functionalized *o*-NB materials may provide new methods of photolithographic patterning of microscale thin polymer films, while photocleavable self-assembled monolayers may allow the modification of surfaces on the nanoscale, such as those in microfluidic channels or on nanoparticles. This is particularly interesting, as it could be foreseen to use such surface modification techniques to guide liquid flows between two plates without the need for static side walls. Technologically exciting is the utilization of *o*-NB junctions to cleave block copolymers upon irradiation, accessing feature sizes that are difficult to achieve with current lithographic techniques. Herein, the distinct synthetic placement of the photocleavable moiety becomes important. Selective solvent removal of one component generates nanoporous membranes, which can further serve as nanoscopic templates. Finally, bioconjugates based on *o*-NB chemistry lend researchers the ability to use photolysis to trigger the unmasking or release of a biologically active compound, causing a cascade of reactions. The possibility to trigger the photolysis of *o*-NB moieties by one- and two-photon induced absorption have already been applied in a few examples, and further investigations of these chemistries are expected to lead to exciting developments when it comes to localized release of biological moieties. More fundamental investigations to enhance photolysis, via increased kinetics or alteration of photolysis wavelength, will permit faster dynamics and system responses.

While this Perspective has highlighted some of the current developments, there are certainly untold opportunities to combine the orthogonality of photolability with other chemical transformations and techniques for material manipulation. In this respect, the utilization of *o*-NB photocleavable moiety can be regarded as the counterpart to “click chemistry” in polymer science. “Unclicking” chemical bonds selectively and precisely presents a new and rising research area in polymer science and *o*-NB groups will surely play a dominant part in this area.^{107–109} Thus, the synthetic combination of click methods to prepare macromolecules with phototriggered “unclicking” based on *o*-NB groups will result in advancements in macromolecular engineering with high fidelity. Undoubtedly, the careful application of *o*-NB cleavage strategies will continue to facilitate the preparation of macromolecular materials with unprecedented structural control.

Further, insight regarding the limits of the photocleavage reaction of *o*-NB groups is needed. The fact that a nitrosoaldehyde is released after cleavage may be problematic for certain biological applications. However, aldehydes are also suitable candidates to be used in a “reclicking” chemistry with amines, hydrazines, or hydroxyamines.¹¹⁰ This may be utilized to cleave and re-form polymer and block copolymer chains on the molecular level.

All in all, it is fascinating to see that the precise positioning of a single functional group within a polymer chain allows the delicate control of a variety of polymer properties,¹¹¹ ranging from the controlled folding of polymer chains to synthetic routes that may eventually facilitate the synthesis of macromolecules with controlled primary structures.^{112–114} The opportunity to combine this controlled synthesis of macro-

molecules with the cleaving polymer chains in a controlled way by utilizing *o*-NB groups provides myriads of possibilities.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: coughlin@mail.pse.umass.edu (E.B.C.); theato@chemie.uni-hamburg.de (P.T.).

Present Address

[†]Institute for Technical and Macromolecular Chemistry, University of Hamburg, Bundesstr. 45, D-20146 Hamburg, Germany.

Biographies



Hui Zhao received his B.S. in Material Chemistry from Shandong Polytechnic University, China, in 2006. He received a Master's degree in Polymer Chemistry from Zhejiang University, China, in 2010, under the guidance of Prof. J. Z. Sun and Prof. B. Z. Tang. He then joined the group of Prof. P. Theato to pursue a PhD degree in Chemistry. As a visiting student, he spent 6 months in the group of Prof. E. B. Coughlin at the University of Massachusetts, Amherst. His research interest includes synthesis of photocleavable polymers and block copolymers based on *o*-nitrobenzyl derivatives and their application as nanoporous materials.



Elizabeth S. Sterner was born in 1985 in Minneapolis, MN. In 2007, she received her B.S. in chemistry with Honors from Creighton University, where she did undergraduate research with Dr. Stephen S. Gross preparing ionic liquid-polymer composites. She is currently working toward her doctorate in polymer science and engineering at UMass Amherst under the supervision of Prof. E. Bryan Coughlin. Her current research projects focus on applications of photocleavable junctions to complex polymer architectures.



E. Bryan Coughlin studied chemistry at Grinnell College and received his B.A. in 1988. Upon the completion of his Doctorate in Chemistry at the California Institute of Technology in 1993 under the direction of John Bercaw, he joined the Central Research and Development Department of the DuPont Company. He was on the technical staff for nearly 6 years. He is a coinventor of DuPont's Versipol Polyolefin Technology Platform and has over 25 patents to his name. Since 1999, Dr. Coughlin has been on the Faculty of the Polymer Science and Engineering Department at the University of Massachusetts, Amherst, where he is currently a Full Professor. He has won a number of research awards: NSF CAREER award, 3M nontenured faculty award, DuPont Young Faculty award, among others. He has been actively involved in the governance of the Polymer Materials: Science and Engineering Division of the American Chemical Society. His research interests are broad and cover aspects of synthetic polymer chemistry and material characterization studies of polymers for use in fuel cells, lithium ion batteries, light harvesting polymer for organic photovoltaics, functional hybrid materials, and fire-safe polymers.



Patrick Theato studied chemistry at the University of Mainz and the University of Massachusetts, Amherst, and obtained his Ph.D. degree under the supervision of Prof. R. Zentel at the University of Mainz in 2001. Shortly after, he was awarded a Feodor Lynen Postdoctoral Research Fellowship from the Humboldt Foundation and joined the group of Prof. D. Y. Yoon at Seoul National University (Korea), where he worked as a postdoctoral fellow, followed by a short research stay at Stanford University with Prof. C. W. Frank. In 2003, he joined the University of Mainz as a young faculty and completed his Habilitation in 2007. From 2009 to 2011 he held a joint appointment with the School of Chemical and Biological Engineering at Seoul National University within the WCU program. In 2011, he accepted a prize senior lectureship at the University of Sheffield, UK. Shortly after he moved to University of Hamburg, Germany, where he is currently an

associate professor for polymer chemistry. His current research interests include the defined synthesis of reactive polymers, design of multi-stimuli-responsive polymers, versatile functionalization of interfaces, hybrid polymers, polymers for electronics, templating of polymers, and light responsive polymers.

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