The Power of Thiol-ene Chemistry

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ABSTRACT: As a tribute to Professor Charlie Hoyle, we take the opportunity to review the impact of thiol-ene chemistry on polymer and materials science over the past 5 years. During this time, a renaissance in thiol-ene chemistry has occurred with recent progress demonstrating its unique advantages when compared with traditional coupling and functionalization strategies. Additionally, the robust nature of thiol-ene chemistry allows for the preparation of well-defined materials with few structural limitations and synthetic requirements. To illustrate these features, the utility of thiol-ene reactions for network formation, polymer functionalization, dendrimer synthesis, and the decoration of three-dimensional objects is discussed. Also, the development of the closely related thiol-yne chemistry is described. © 2010 Wiley Periodicals, Inc. J Polym Sci Part A: Polym Chem 48: 743–750, 2010

KEYWORDS: click chemistry; crosslinking; synthesis; thin films; thiol-ene

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INTRODUCTION A defining aspect of polymer science is the efficient construction of materials with useful properties from readily available starting materials. The world of polymer science recently lost a champion of this philosophy when Professor Charles Hoyle passed away on September 7, 2009. A respected leader in the fields of polymer photochemistry and photophysics, Professor Hoyle authored over 160 refereed publications and his work has influenced numerous researchers around the world. On a more personal note, Charlie was one of the guiding lights and inspirations for our group's embrace of thiol-ene chemistry as a robust, efficient, and orthogonal reaction in the construction of polymeric materials. Over the past two decades, Hoyle enjoyed great success researching and promoting the use of thiol-ene chemistry in polymer and materials science. The success of these efforts is evidenced by the recent explosion in popularity of thiol-ene coupling, and thus a perspective article highlighting the recent advancements in this area of research since his 2004 review[1] is a fitting tribute to Professor Hoyle.

The reactions of sulfur containing compounds with alkenes are certainly not a recent discovery. The vulcanization of natural rubber (poly(*cis*-isoprene)) by sulfur, credited to Charles Goodyear, was patented in the mid-19th century.[2] This process was the birth of classical thiol-ene chemistry—the radical addition of thiols across nonactivated carbon–carbon double bonds (Scheme 1). Most authors today use the term thiol-ene to describe the reaction of thiols with a wide variety of unsaturated functional groups, such as maleimides, acrylates, and norbornenes, in addition to unactivated carbon–carbon double bonds. In some of these cases, reaction can take place by a mixed mechanism, including the classical radical addition but also Michael-type nucleophilic addition. Discovered over a century ago, thiol-ene chemistry was used extensively in the middle part of the 20th century as a method for making crosslinked networks.[3,4] Although thiol-ene networks showed remarkable properties, which allowed them to find their way into a variety of commercial products, the process fell out of favor, replaced in many cases by high molecular weight polymers that were not covalently crosslinked. Resurgence over the past decades has occurred in response to the many benefits thiol-ene coupling presents for polymer synthesis: tolerance to many different reaction conditions/solvents, clearly defined reaction pathways/products, and facile synthetic strategies from a range of easily obtained starting materials.[1] These qualities, mostly resulting from the high efficiency and orthogonality of the reaction, have led to thiol-ene chemistry being used increasingly in polymer functionalization and macromolecular synthesis, as well as more traditional applications ranging from crosslinked networks to functionalized biomaterials.[5,6]

Previously, the most common use of thiol-ene chemistry was for the formation of crosslinked networks, though this concept has now been extended from bulk materials to hydrogels, thin films, and lithographic applications where a wide variety of novel studies have recently been reported.[5,7–14] In demonstrating the unique attributes of thiol-ene chemistry for network formation, Hoyle has published an impressive body of work regarding the use of thiol-ene chemistry to prepare crosslinked networks with improved physical and mechanical properties.[14–23] These studies addressed the energetics[17] and kinetics[24] of crosslinking, and the effects of alkene,[15,18] thiol,[25] and photoinitiator structure[25,26] on the mechanical properties of networks formed by thiol-ene chemistry. Significantly, the lack of oxygen sensitivity for these radical systems was found to give networks with unique properties. One particularly important contribution by Hoyle and coworkers has been the use of tan δ to characterize the homogeneity of networks (Fig. 1).[1,15] This data has consistently shown that networks formed by thiol-ene chemistry have more regular structures than those formed by standard free-radical polymerization of diacrylates. Exploiting these improvements in mechanical properties and the insensitivity of thiol-ene reactions to water and oxygen, Hawker, Stucky and coworkers developed robust and modular platforms for soft lithography with varied mechanical and adhesive properties (Fig. 2).[12] Excellent pattern transfer was achieved thanks to the ability to easily alter the stiffness and wetability of the networks. In a subsequent publication, the resulting photonic crystals were used to improve light extraction from GaN LEDs in the growth area of energy efficient solid-state lighting devices (Fig. 3).[27]

The inherent versatility of thiol-ene chemistry leading to the preparation of crosslinked, degradable networks in a facile and highly efficient manner has also been exploited by the Anseth and Bowman groups in biomedical applications.[8–11,28–33] Biodegradable PEG-based gels could be formed in the presence of sensitive biological systems and used to encapsulate cells for studying the effect of network structure and chemical modification on cell-materials interactions (Scheme 2).[8,10,33] This work clearly demonstrates the mild reaction conditions associated with thiol-ene chemistry and the compatibility of the process with sensitive functional groups and biological processes.

It was these pioneering efforts by Hoyle and Bowman in demonstrating the robustness of thiol-ene coupling in the network formation, which led our group to the realization that the same chemistry could lead to discreet molecular transformations with a high degree of efficiency and orthogonality. In fact, many of the design features of click
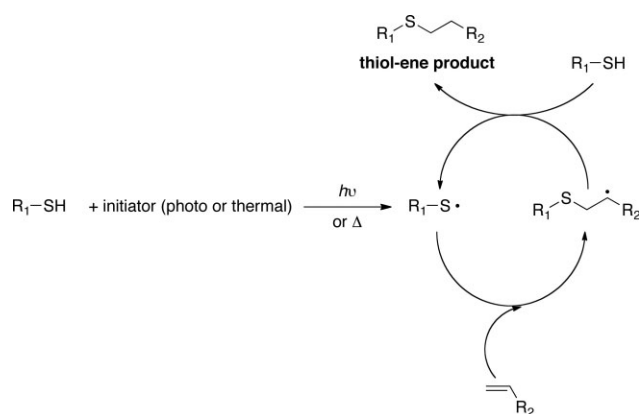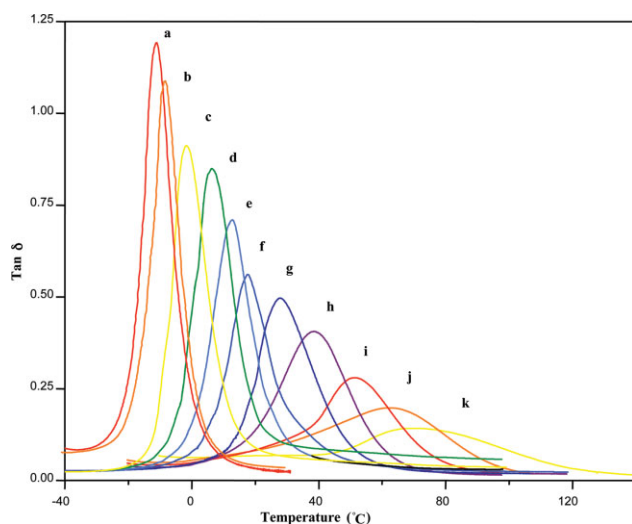

SCHEME 1 Mechanism of radical thiol-ene coupling.

FIGURE 1 Representative plots of tan δ as function of temperature. The low maximum and broad distribution for sample k, which is polymeric diacrylate, shows the heterogeneous nature of the gel and uneven crosslink density. Pure thiol-ene networks, such as, sample a are in contrast very regularly structured. Blending the two (b–j) allows tuning of the mechanical properties. All samples were cured in atmospheric conditions, and data was obtained at a scan rate 2 °C/min.[15]

chemistry as proposed by Sharpless and coworkers[34] are also presented with the thiol-ene reaction. The synthesis of dendrimers serves as an excellent platform to demonstrate the specificity and reliability of this chemistry due to their symmetrical nature and monodispersity. By taking advantage of the high yields and simplified purification requirements of thiol-ene coupling, Killops et al. demonstrated the synthesis of high purity dendrimers using an accelerated procedure without the need for chromatographic purification or protecting groups (Fig. 4).[35] Following this work, Rissing and Son synthesized carbosilane–thioether dendrimers using a combination of thiol-ene chemistry and traditional Grignard-based growth steps for carbosilanes, again demonstrating that thiol-ene coupling is an ideal reaction despite the high synthetic demands of dendritic systems.[36]

The efficiency of thiol-ene coupling has also allowed the chemistry to be used for polymer functionalization, and the orthogonality of the process has permitted a range of starting materials from commodity polymers, such as polybutadiene homopolymers, copolymers, and block copolymers, to
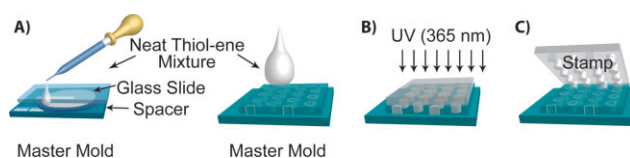

FIGURE 2 Process for stamp fabrication: (A) Cast liquid thiol-ene mixture onto a patterned master mold, (B) cure the material with UV light for 2 min at ambient conditions, and (C) peel the patterned polymeric stamp.[12]
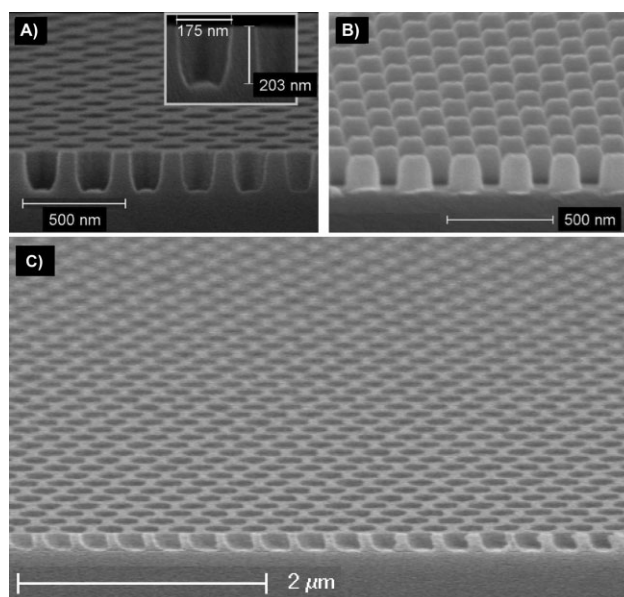

FIGURE 3 SEM images of: (A) The hard master (holes: width ~175, height ~200 nm, period ca. 250 nm), (B) the soft stamp cast on the master mold composed of a crosslinked thiol-ene mixture (posts: height ~200 nm, width ~170 nm, period ~250 nm), and (C) image of calcined titania patterned by soft thiol-ene stamp showing long-range reproduction of master.[12]

methacrylate- and styrenic-based systems and poly(ethylene glycol) to be used. A recent example of polymer functionalization by thiol-ene addition from Schlaad and coworkers took advantage of a poly(oxazoline) derivative with alkene side groups prepared by cationic ring opening polymerization.[37] The authors demonstrated the ability to attach a wide array of thiols onto the polymer backbone. Similarly, David and Kornfield developed a synthetic protocol for the preparation of a variety of functionalized polybutadienes (PB) (Scheme 3).[38] Moving away from backbone functionalization, Campos et al. reported the synthesis of styrenic, methacrylic, and caprolactone monomers, each bearing alkene-functionalities that could be combined with functional initiators and postpolymerization modifications to further increase the range and architectural position of orthogonal groups that can be built into macromolecular systems and accessed through thiol-ene addition.[39–41] Both photochemical and thermal radical conditions were tested to explore the efficiency of the thiol-ene reaction, and it was found that using photochemical conditions leads to faster and, in many cases, quantitative reaction. The authors also verified the orthogonality of thiol-ene with copper catalyzed azide-alkyne cycloaddition (CuAAC).[43–45] Ma et al. studied a series of monomers containing alkenes and their usage for the synthesis of homopolymers, block copolymers, and random copolymers.[46] By tuning the block length/composition of these materials, incorporating reactive fluorinated styrenic monomers, and maleic anhydride, they demonstrated the synthesis of highly functionalizable systems capable of nanoscale organization into macromolecular assemblies. These materials provide an
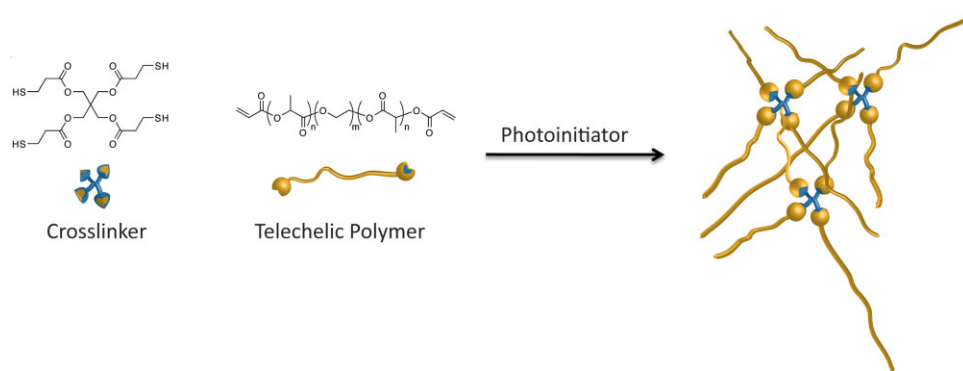
SCHEME 2 Network structures formed from polyfunctional thiol crosslinkers have well-defined and easily modified crosslink density. The network depicted here includes blocks of poly(lactic acid), which allows tuning of the degradation profile.

excellent example of the modular nature of thiol-ene chemistry and its inherent synthetic versatility when combined with other chemistries. In illustrating this potential, the authors allowed the maleic anhydride units to undergo functionalization with an amine, whereas the alkene functional units remain available for functionalization by thiol-ene reaction.

Nucleophilic thiol-ene coupling via Michael addition has also been used to create and decorate more complex polymeric architectures and three-dimensional nano-objects.[13] An excellent illustration from Hoyle and Lowe is the formation of three-arm star polymers by a coupling-to convergent method.[47] Thiols liberated from thiocarbonylthio RAFT endgroups by aminolysis could be used to couple poly(N,N-diethylacrylamide) (pDEAm) to a triacrylate core with the assistance of a phosphine-based catalyst. A variety of analytical techniques indicated the successful and high yielding formation of star polymers. Similarly, Schlaad and coworkers have published several papers demonstrating the use of thiol-ene modification of PB to create macromolecular structure on a larger length scale. In a 2006 publication, the PB segment of PB-poly(ethylene oxide) (PEO) block copolymers were modified with hydrophobic cysteine-containing oligopeptides.[48] The change in volume fraction of the hydrophobic segment of the amphiphile imparted morphological change during assembly in water toward lower curvature structures, such as, vesicles. A follow-up to this work showed the modification of PB with hydrophilic thiols, giving direct access to polymer amphiphiles, which assembled into lamellar vesicles similar to liposomes.[49] This ability to functionalize nanoscale objects was also addressed by Anseth and coworkers in 2008.[50,51] In this publication, CuAAC was chosen as the initial crosslinking reaction for its efficiency in forming networks and its orthogonality with alkenes. The orthogonality between CuAAC and thiol-ene coupling allowed for the introduction of unreacted alkenes throughout the resulting hydrogel. The alkenes were subsequently functionalized by photochemical thiol-ene reaction, enabling photopatterning of the material using a variety of thiols. In particular, fluorescent tags were used to visualize the patterning of the hydrogel, and further demonstrated the excellent resolution of this strategy. This concept was extended in a subsequent publication through the use of strain-promoted azide-alkyne coupling (SPAAC),

which avoids the use of cytotoxic copper salts, an important consideration for live cell based platforms.[52] Connal and Caruso also recently took advantage of thiol-ene coupling as a route to manipulating three-dimensional objects.[53] The authors constructed a multilayer coating on the surface of a silica nanoparticle using a layer-by-layer approach by alternating deposition of poly(vinyl pyrrolidone) (PVP) and poly(methacrylic acid) (PMA), the latter containing ~10 mol % of either alkene or thiol functional groups (Scheme 4). The inherent interdigitation between the layers of the assembly allowed for facile crosslinking of the whole assembly using photochemical thiol-ene coupling. The silica core and PVP were then selectively removed, leaving behind a crosslinked PMA capsule. One under-appreciated feature of thiol-ene chemistry is the stability and permanence of unreacted thiol or alkene residues after reaction. As a result, secondary reactions can be performed and in the above example, Connal and Caruso take advantage of residual thiols in the crosslinked multilayer structures by subsequently attaching alkene-terminated PEG chains, thereby changing the surface chemistry and creating protein-resistant particles. This last feature is a major advantage of thiol-ene chemistry, the high tolerance of the reaction allows excess unreacted thiol or alkene units to be involved in secondary thiol-ene reactions.
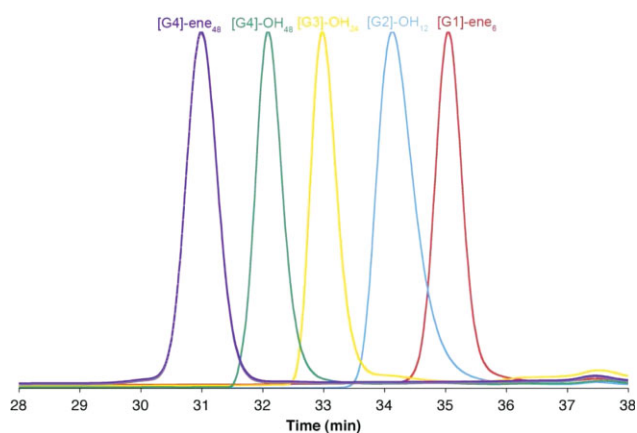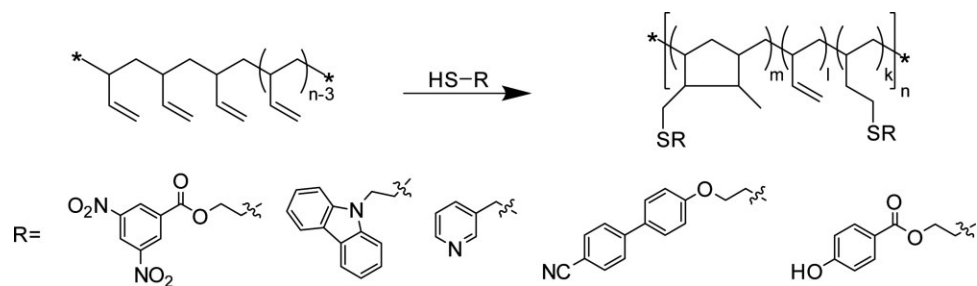

FIGURE 4 Size exclusion chromatography traces of dendrimers made by thiol-ene show regular growth.[35]

SCHEME 3 Functionalization of poly(butadiene) using thiols made via thioester intermediates.[38]

In research continuing Hoyle's many contributions to the study of networks, Anseth and Bowman have recently explored thiol-yne chemistry for use in network formation, with the major distinction from thiol-ene chemistry being that the alkyne can react with two thiols (once as an alkyne, and again as a vinyl sulfide), leading to more densely crosslinked networks when compared with standard thiol-ene systems.[54] As the thiol-ene addition is a 1:1 reaction rather than a chain polymerization, chemists must use densely functionalized oligomers, small molecules, or polymers to achieve high cross-link density, thus limiting physical and mechanical properties. In direct contrast, the thiol-yne reaction allows doubling of the crosslink density as compared with thiol-ene systems and polymerization of a trifunctional thiol with difunctional alkyne leads to much higher crosslink density as manifested in a dramatic increase in T_g to 49 °C, as opposed to −22 °C for the polymer formed from the same thiol and the corresponding difunctional alkene. In addition, the alkyne-based material also had a rubbery modulus of 80 MPa, versus 13 MPa for the alkene-based material. Chan et al. also performed a systematic study of crosslinked networks prepared using thiol-yne chemistry.[55] In this report, the effect of alkyne and thiol structure was related to a number of properties, including refractive index, modulus, and glass transition temperature.

Thiol-yne chemistry has also been demonstrated as an effective way to functionalize surfaces in a facile and efficient manner.[56] In a recent publication, Hensarling et al. fabricated an alkyne-rich surface by surface-initiated photo-polymerization of trimethylsilane-protected propargyl methacrylate, followed by basic deprotection. A variety of thiols were then attached to the surface using photo-activated ($\lambda = 365$ nm) thiol-yne coupling. This concept was extended to patterning by using a photomask. In this case, regions of hydrophilicity were patterned with a hydrophobic matrix, and sharp confinement of water droplets to the hydrophilic regions demonstrated the high resolution of the patterning technique. Sunlight was also shown to be an effective light source, showing quantitative conversion of the tethered alkynes in <1 h (Fig. 5).

Drawing the analogy with the evolution of thiol-ene chemistry, the thiol-yne reaction can also be applied for the defined functionalization of alkyne units. For example, Yu et al. has demonstrated that the thiol-yne reaction is well suited for
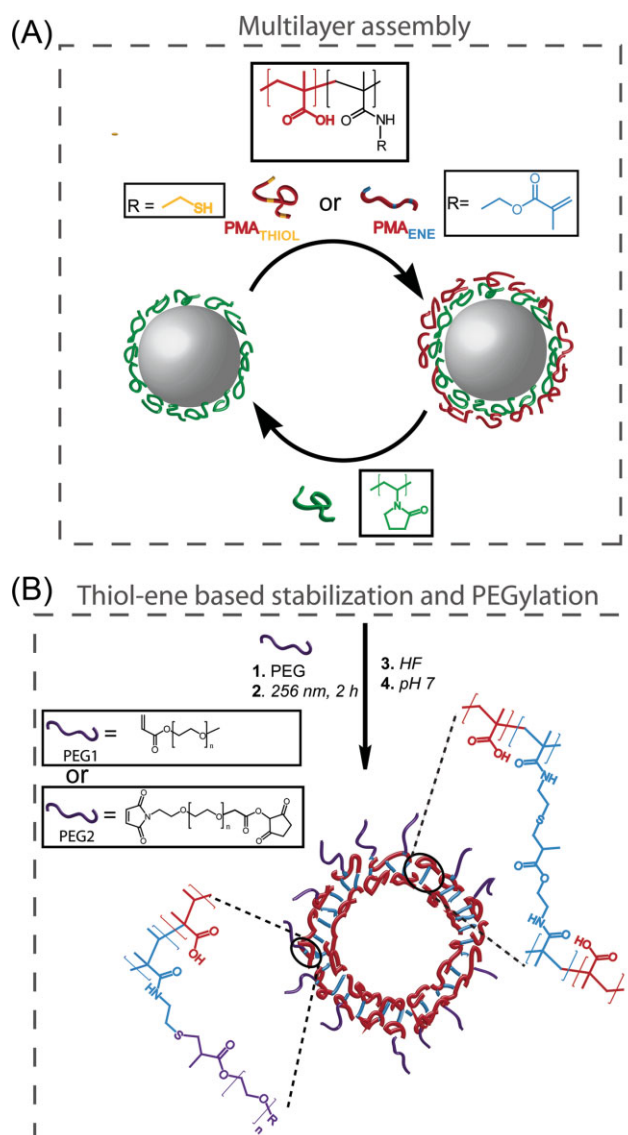
SCHEME 4 (A) A multilayer assembly is grown around a silica particle, with the poly(methyl acrylate) layers alternating between having thiol or alkene incorporation. (B) The PMA portion of the multilayer assembly is crosslinked, whereas the silica template and PVP are removed. Residual thiols are used to attach PEG to the hollow assemblies.[53]
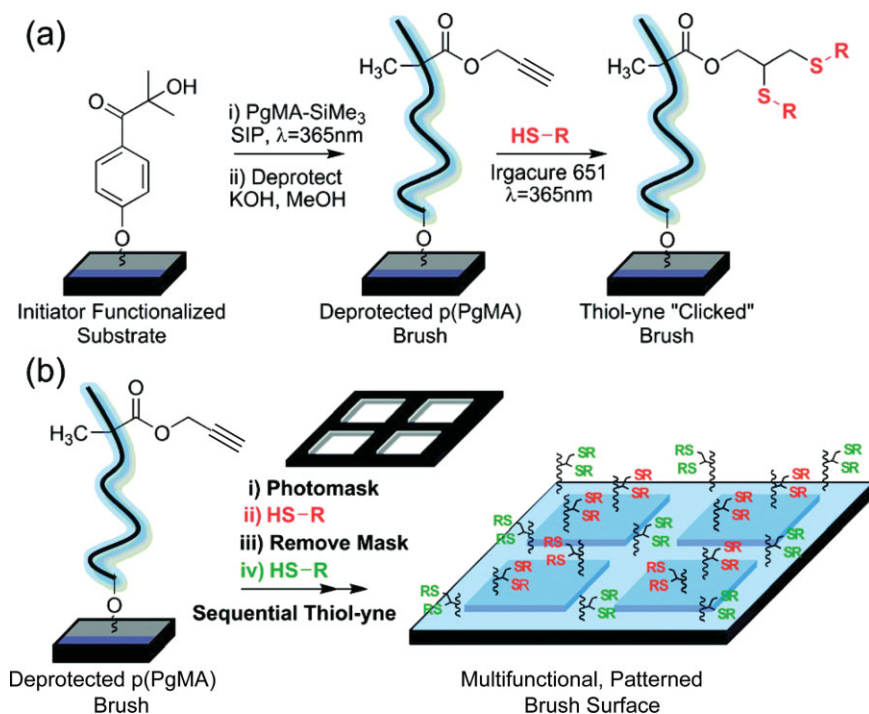
FIGURE 5 Functionalization of an alkyne derivatized surface with different thiols by thiol-yne chemistry. Sunlight was demonstrated to be an effective source of initiation.[56]

polymer chain-end difunctionalization (Scheme 5).[57] In this case, polymers with thiol chain ends were prepared by aminolysis of RAFT-grown PNIPAm, and then Michael addition with either allyl or propargyl acrylate gave alkene and alkyne terminated polymers, respectively. Significantly, the Michael addition reaction can be used to selectively target
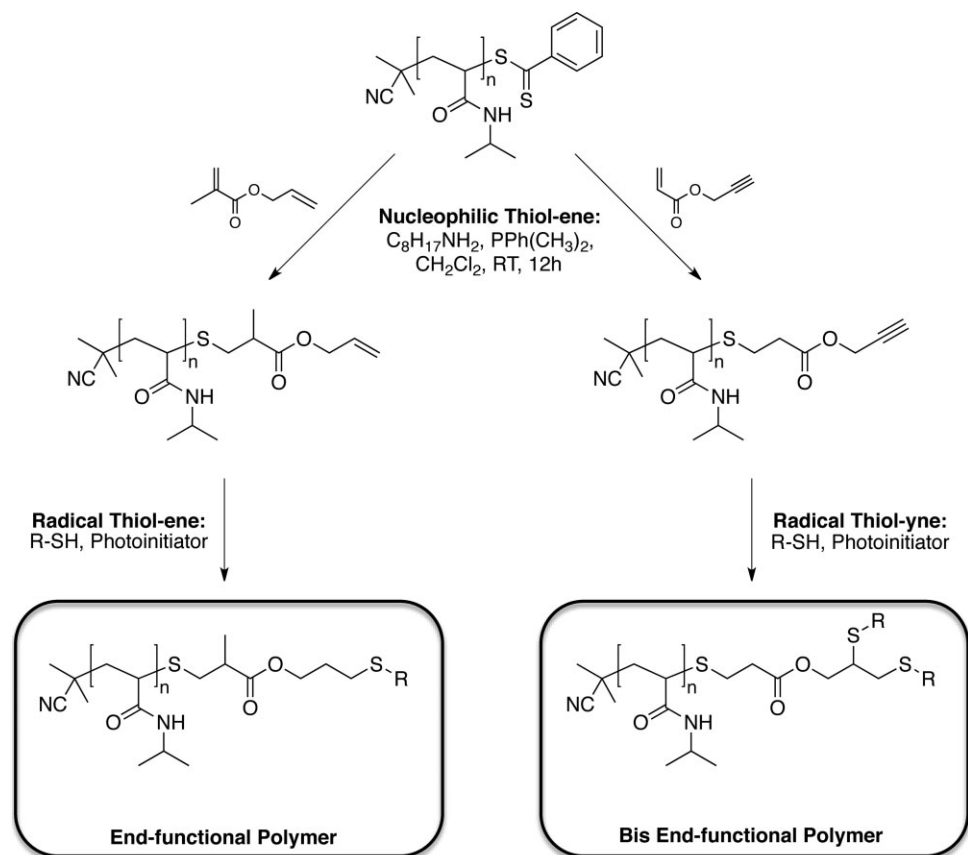
SCHEME 5 Alkene and alkyne polymers, respectively, are made from RAFT polymers by nucleophilic thiol-ene coupling of acrylates to the polymeric thiol afforded by aminolysis of the RAFT group. Thiols are then coupled by thiol-ene or thiol-yne reactions to give end-functional polymer and bis(end-functional) polymer.[57]

the acrylate moiety in the presence of either alkenes or alkynes, greatly simplifying the synthesis of such functional polymers and demonstrates the versatility of thiol chemistry. These polymers were then further functionalized by either thiol-ene or thiol-yne reactions with commercially available thiols, and ^{1}H-NMR spectroscopy showed complete consumption of the allyl or propargyl protons with the concomitant appearance of unique resonances for the added thiols. Integration of these peaks demonstrated that thiol-yne chemistry provided full double functionalizations, whereas thiol-ene provided full stoichiometric conversion.

In looking to the future, the passion of Professor Charlie Hoyle for thiol-ene chemistry is certainly matched by its potential. The increasing complexity in many macromolecular systems mandates high-yielding chemistries that can be performed independently and without interference from atmospheric contaminants or competing functional groups, hence the combined power and promise of thiol-ene chemistry. The ability to use thiol-ene chemistry in combination with other polymerization and functionalization reactions allows increased sophistication in macromolecular structure and compositional complexity without an increase in the synthetic requirements. This opens up new vistas to the greater polymer science community and allows nonexperts access to functional materials through thiol-ene chemistry, a fitting legacy for Professor Charles Hoyle.

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