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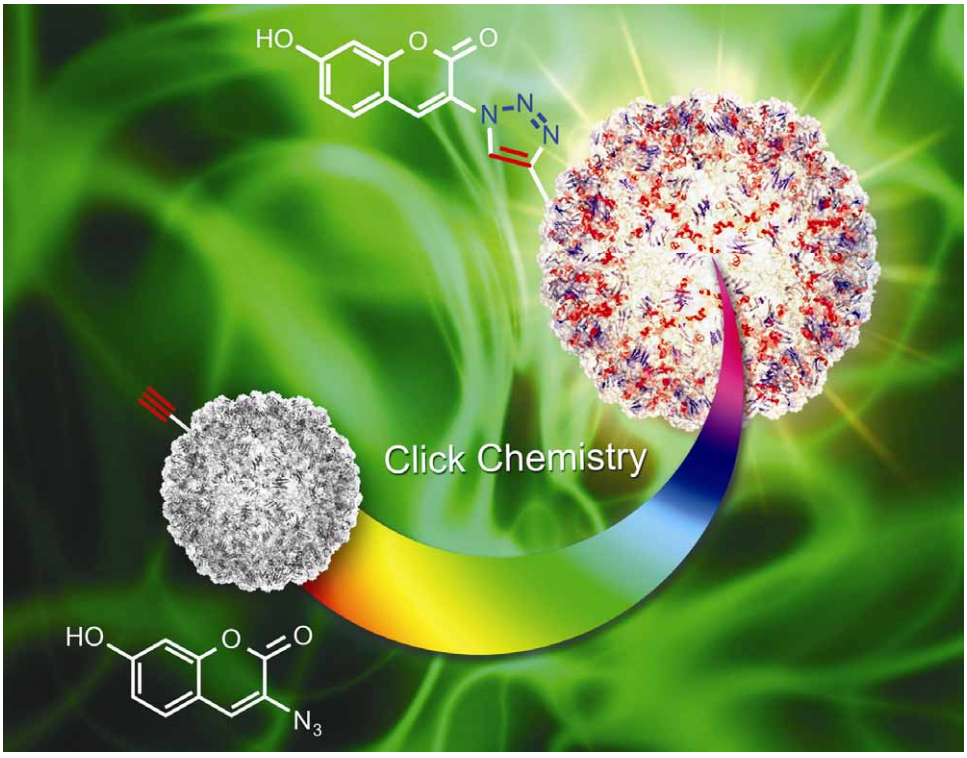

Thiol-click chemistry: a multifaceted toolbox for small molecule and polymer synthesis†‡

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The merits of thiol-click chemistry and its potential for making new forays into chemical synthesis and materials applications are described. Since thiols react to high yields under benign conditions with a vast range of chemical species, their utility extends to a large number of applications in the chemical, biological, physical, materials and engineering fields. This *critical review* provides insight into emerging venues for application as well as new mechanistic understanding of this exceptional chemistry in its many forms (81 references).

1. Introduction

The concept of click chemistry[1] was born from the realization that in order for chemical reactions to be most effective in adapting to a wide range of processes and demands, reactions should be simple, efficient, regioselective, stereoselective where applicable, yield a single product, and be amendable to occurring at ambient temperature and atmospheric conditions, and in benign solvents or neat. Additionally, reactions should require simple or no clean up, and be selective, *i.e.* orthogonal, in their selection of a chemical substrate. One other important feature of click chemistries which should not be ignored is the ability to translate such facile reactions so that they are readily performed by researchers and development personnel across all of the basic disciplines of science and engineering from physicists, biologists, and chemists to chemical, biomedical, electrical, computer, civil, aeronautical, and mechanical engineers. Finally, the reaction should be readily adaptable to work in the field as well as in production facilities and clinics. By taking a critical look at the feedstock of chemical reactions that have been discovered/developed and perfected over the past two centuries, it is certainly possible to come up with a list of chemical reactions that fit many of the assets inherent to "good" click reactions.

In their original click article, Kolb *et al.*[1] considered a range of reactions with considerable emphasis on nucleophilic epoxy–aziridine ring-opening spring-like reactions and [3 + 2] alkyne–azide cycloadditions. The orthogonality and performance of these reactions, especially the alkyne–azide Huisgen reaction, is difficult to achieve with other chemistries. Nevertheless, other chemistries, including the thiol reactions described herein, have many attributes that incorporate the click concept, in part or in whole, and have been referred to in many circumstances as click reactions.

We have adapted the click reaction nomenclature here to refer to various thiol-click reactions where the thiol-click reactions are known to have certain inherent benefits and pitfalls as compared to other click-type reactions. In particular, the assignment of the thiol reactions as click reactions is done recognizing that one of the relative advantages of the thiol-click reactions, the breadth of substrates that are capable of reacting with the thiol due to its high reactivity, also represents one critical disadvantage in that their orthogonality is compromised. Thiols are prone to react either *via* radical or catalyzed processes under very mild conditions with a multitude of substrates. In other words, what makes them so reactive and efficient also makes them susceptible to multiple simultaneous reactions. It is learning to control, or in essence

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† This manuscript is dedicated to the memory of Charles Hoyle who passed away following its original submission. His enthusiasm for and implementation of thiol-click chemistry was unbounded and truly advanced the field in a manner unlike any other.

‡ Part of a themed issue reviewing the latest applications of click chemistry.

Charles E. Hoyle

Charles E. Hoyle received a BS (Baylor), Masters and Doctorate degrees (Northwestern) in Chemistry. After post-docing at the University of Toronto, he joined Armstrong World Industries, and then in 1983, he came to the University of Southern Mississippi. During his 25+ years at USM, he focused on all aspects of polymer photochemistry and photophysics, particularly photopolymerizations. He worked with outstanding colleagues at USM and around the world in this community. Sadly, Professor Charles Hoyle passed away on September 7, 2009, while this article, for which he was the primary driver, was under review. His contributions to his students, colleagues, and the professional community will long be remembered.

hide, the high potential reactivity of thiols in a given environment, and then inducing the selective reaction with a particular substrate by a control signal which is both the challenge, and the opportunity, for thiol-click chemistry as it applies to the chemical, biological, physical and engineering fields. The reactivity of the thiol gives rise to a second relative advantage of the thiol-click reactions in that they proceed, under appropriate conditions, more rapidly than many other click chemistries, with reaction times necessary to achieve high conversions frequently being less than 1–10 seconds. In addition to the relative advantages and disadvantages of the thiol with regard to reactivity, a primary distinguishing feature of the thiol-click reactions is the ability to trigger these reactions, either through photolatent base generators or through radical photoinitiating systems, by exposure to light. For substitution reactions on biological substrates, *in vivo* biomaterials applications, surface modification and photolithographic patterning as well as simply an enhanced level of control, the ability to manipulate the click reactions described here both spatially and temporally through simple control of light exposure represents a largely untapped opportunity for click reactions. Finally, significant relative disadvantages of the thiol-click reactions relative to other reactions in the click family include the prevalent thiol odor, particularly for low molecular weight materials, as well as a lack of shelf stability for many formulations. While these disadvantages are overcome through appropriate handling, stabilizer selection and substrate selection, they do limit the applicability and implementation of thiol-click chemistry in several applications where it would otherwise be appropriate.

Exploring thiols with regard to their materials aspects, it is first noted that sulfur, primarily in the context of vulcanization using natural sources of sulfur, has always been important in macromolecular chemistry and in fact played a key role in the development of polymeric materials at the onset of the industrial revolution. Under suitable conditions and with the use of appropriate catalysts and processing aids, sulfur can be used to crosslink a large number of otherwise thermoplastic polymers. Based upon the success of sulfur in providing critical physical and mechanical properties to a wide array of materials, it is not at all surprising that thiols, traditionally referred to in the literature as mercaptans due to their original use as mercury scavenging agents, are highly reactive molecules that readily participate in a broad scope of chemical and materials processes.[2–12] Chemically, because of the combination of d-orbitals and the inherent electron density associated with sulfur, thiols are classified as soft nucleophiles compared to their alcohol and amine counterparts,[2] and typically exhibit high reactivity with substrates prone to reaction with strong nucleophiles.[2] The related nucleophilic thiolate anions and electrophilic thiyl radicals are highly "motivated" species that have been utilized in a wide range of processes that take advantage of their ability to participate in high yield (many are essentially quantitative) reactions under relatively benign conditions. While the lower molecular weight monofunctional thiols are certainly odiferous and in some cases toxic, when controlled, they are capable of being extremely useful in the facile synthesis of molecular species with uses in the materials, electronics/optical, biological and engineering fields.

What is sometimes overlooked, but absolutely essential in dealing with thiol-based chemistry, is the clear recognition that all thiols are not created equal. In essence, there are four basic types of thiol structures typically encountered (Fig. 1): alkyl thiols, thiolpropionate thiols, thiolacetate (*i.e.* thiol glycolate) thiols and aromatic thiols. In addition to the base thiol structures, the corresponding thiolates and thiyl radicals are also shown in Fig. 1. Arrows indicate the corresponding direction of increasing pK_a of the conjugate acids, hydrogen abstractability (by radicals), nucleophilicity (thiolates) and electrophilicity (thiyl radicals). Each thiol type in Fig. 1 is different with respect to participation in radical and Michael addition reactions.[2,5] The nature of the basic thiol group and the corresponding thiyl and thiolate species provides for an interesting scenario: the highly efficient thiol-based reactions occur with a variety of very useful and readily available organic substrates. Specifically, electron rich enes (radical), alkynes (radical), electron poor enes (Michael addition), isocyanates (carbonyl addition), epoxies (S_N2 ring opening), and halogens (S_N2 nucleophilic substitution) all readily react with thiols, thus constituting a literal *toolbox* of efficient chemical reactions as

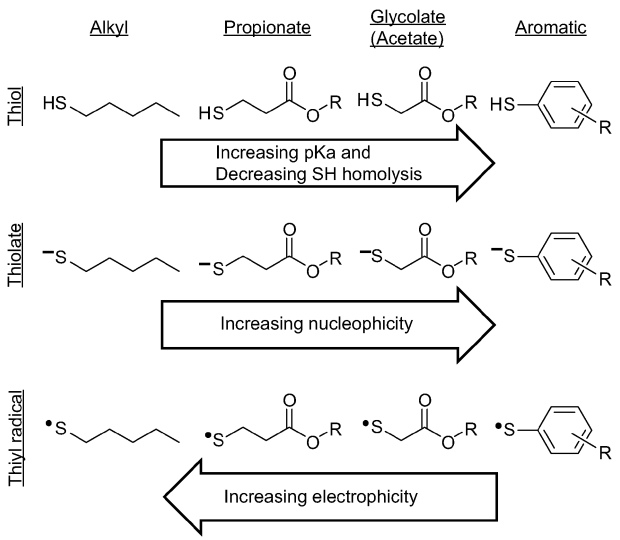
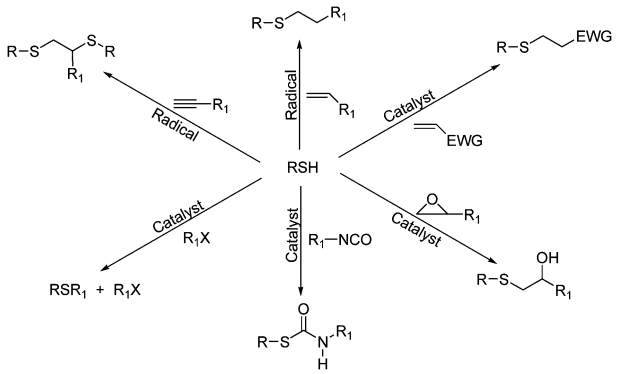


Fig. 1 Structures of various thiol, thiolate and thiyl radical types.



Scheme 1 Toolbox of thiol-click reactions. EWG = electron withdrawing group. X = Br, I and R_1 = aliphatic or aromatic organic/bioorganic groups.

depicted in Scheme 1. Each of the reactions in this thiol-based *toolbox* has many of the aspects of click chemistry, namely they are rapid, proceed to high conversions under mild reaction conditions, react either neat or in benign solvents, where applicable are regioselective, and generally lead to one product that requires either little or no purification. This behavior allows for taking a series of thiols and creating/functionalizing/modifying an exceptional range of molecules and materials with physical, mechanical and chemical properties that can be altered to meet an extensive scope of requirements.

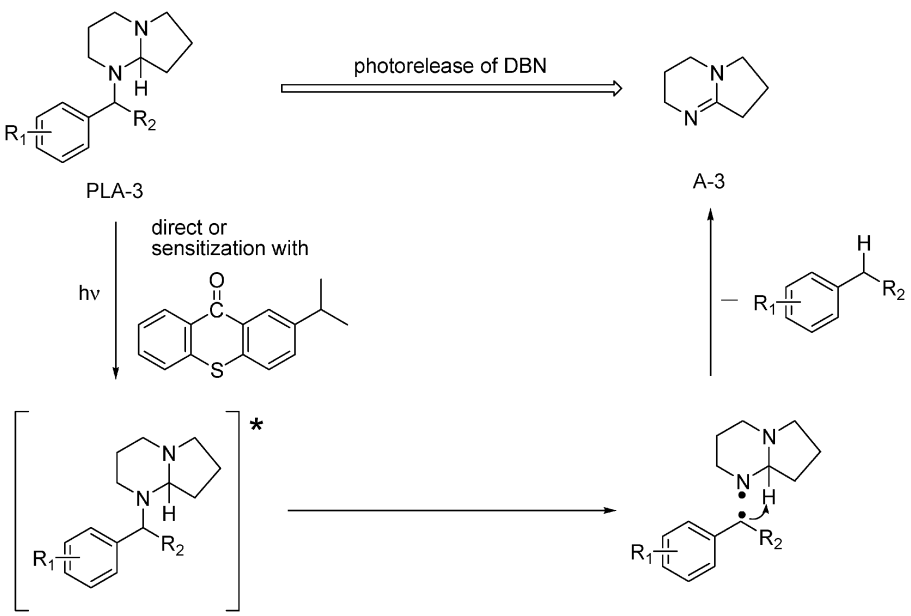
In each of the sections in this review, the basics of each type of thiol-click chemistry are presented along with selected examples that provide a conduit for accessing the appropriate literature. No attempt is made at comprehensively reviewing the literature or history for each of these reactions. In particular, the focus is on selecting representative recent examples of implementations of the thiol-click reaction family, and readers are referred to other reviews that provide older or more comprehensive discussions of individual subtopics.[2–12] A final section of this review focuses on the concept of sequential or simultaneous reactions that involve multiple thiol-click reactions or sequences where at least one of the reactions is a thiol-click reaction. The involvement of multiple click reactions is in the true spirit of the rationale set forth in the original click concept[1] of providing a chemical reaction platform for synthesis of a wide range of chemicals and advanced materials rapidly under benign conditions from readily available starting compounds. As described in the Introduction, there are two basic types of chemistries that comprise the thiol-click chemistry set, those proceeding by radical chain processes and those proceeding by nucleophilic reactions. The radical thiol–ene and thiol–yne reactions have many of the same attributes as the thiol–epoxy, thiol–isocyanate, and thiol–halogen nucleophilic substitution reactions. The basic features of these thiol-click reactions are discussed in terms of their attributes and how they can most effectively be implemented.

2. Nucleophilic thiol-click chemistries

Thiol-click reactions that depend upon the nucleophilicity of the thiol component proceed with a wide range of rates according to the substrate and its propensity for nucleophilic attack by either thiols or thiolate anions. The details of the reactions in this section will provide a clear picture of the driving force behind these types of thiol-based reactions, and their propensity to achieve rapid rates and high conversions provided that appropriate catalysts are selected. The potential for new applications of the nucleophilic thiol-click reactions will be described in terms of chemical reactivity and selectivity. The nucleophilic reactions associated with the thiol–epoxy, thiol–isocyanate, and thiol-Michael addition reactions are initiated by strong bases (some of which are also nucleophiles) which may be added separately as a catalyst or produced in catalytic amounts by efficient photolatent bases that serve as photoinitiators for these reactions, several examples of which are shown in Scheme 2, as recently introduced by Dietliker *et al.*[13] For these photolatent bases, the ability to *turn on* the thiol–nucleophile reaction at a selected time and/or limit the reaction to only exposed regions using patterned light exposure makes thiol-click processes a particularly important, and distinguishing, addition to the click family of reactions.

2.1 Thiol–epoxy click reactions

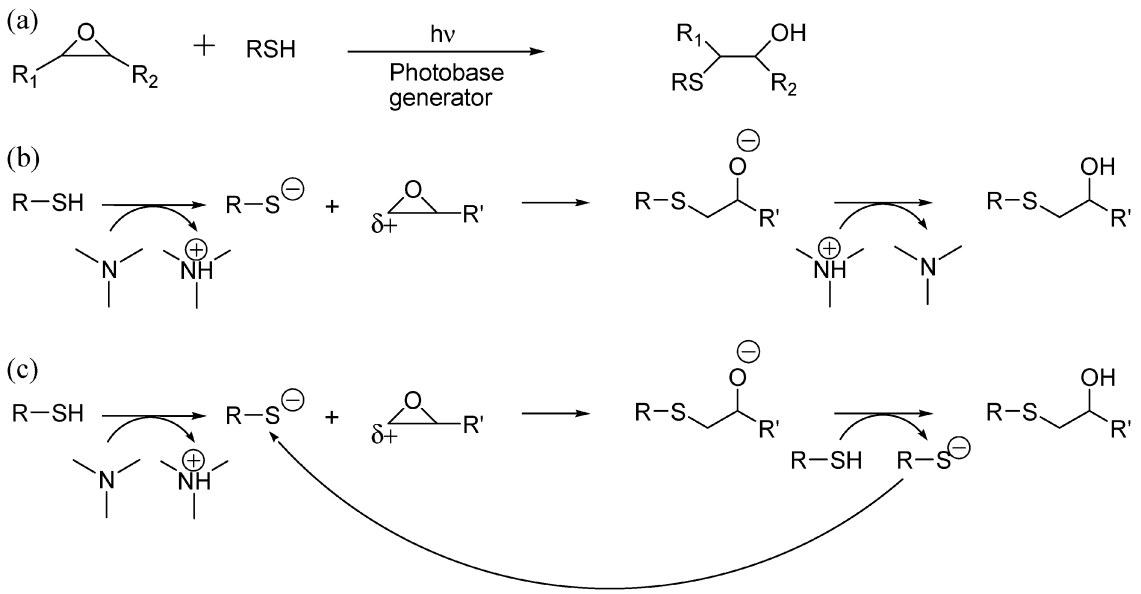
In accordance with the importance of spring loaded oxirane and aziridine ring-opening click reactions in the original article defining click chemistries,[1] we limit our brief discussion to the thiol–epoxide reaction (Scheme 3a). As chronicled in a recent detailed review by Fringuelli, Vacarro and co-workers,[14] the thiol–epoxide reaction is implemented in many important biosynthetic and biomedical applications, and the catalyzed reactions in water and in solvent-free conditions are high yield, commensurate with the click paradigm. The basic thiol–epoxy



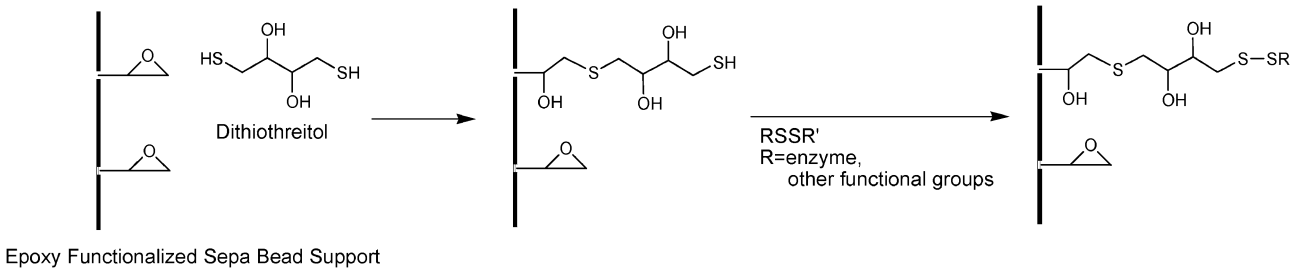
Scheme 2 Photobase generator photolysis mechanisms for both direct and sensitized photolysis.

reaction mechanism is reputedly[15] a simple nucleophilic ring-opening reaction by the thiolate anion followed by protonation of the alcolate anion *via* the quaternary ammonium, originally formed *via* reaction of the base catalyst and thiol to generate the initial thiolate, as depicted in Scheme 3b. The reaction is catalyzed by a variety of strong bases through deprotonation of the thiol. One cannot rule out some level of contribution from the reaction in Scheme 3c involving deprotonation of the thiol in the second step to regenerate the thiolate and complete a two-step anionic chain propagation process. Details of the base-catalyzed thiol–epoxy mechanism remain to be verified, along with details of how the thiol pK_a and thiolate nucleophilicity (see Fig. 1) affect the reaction kinetics. Other catalysts, *i.e.*, $InCl_3$ and Lewis acids, which weaken the carbon oxygen bond and stabilize the alcolate anion upon direct attack by the nucleophilic thiol, are also effective for carrying out thiol–epoxy reactions in bulk.[16] For details on the applications of thiol–epoxy reactions in bulk or water and the corresponding kinetics, yields, stereochemistry and regioselectivity as well as a critical evaluation of catalysts and mechanistic aspects of the reaction, one is directed to Fringuelli's work and references therein as a lead into the literature on this subject.[14,16] Indeed, depending on the reaction conditions and the nature of the thiol structure (see Fig. 1 for various types of thiols), thiol–epoxy reactions approach near quantitative yields when appropriate catalysts are used. While there are certainly some hindrances, when the right types of catalysts and conditions are employed essentially quantitative yields are rapidly achieved. Thiol–epoxy reactions will no doubt continue to develop at a rapid pace for applications in drug synthesis, biologically active components and processes, and the synthesis of numerous organic synthons useful in a variety of synthetic procedures. An excellent example of the use of the thiol–epoxy reaction shown in Scheme 4 indicates how efficiently an epoxy supported bead surface is readily functionalized by an epoxy reaction with dithiothreitol to give a bifunctional support surface that is capable of selective immobilization of model enzymes.[17]

In addition to the clear importance of thiol–epoxy reactions in traditional synthetic arenas and biological/pharmaceutical applications, the ring-opening reaction involving thiols and epoxides is important industrially and involved in the formation of adhesives, high performance coatings and composites and accounts for one of the two major industrial uses of multifunctional thiols, the other being thiol–isocyanate reactions with applications for thiol–ene radical processes



Scheme 3 Catalyzed thiol–epoxy ring-opening coupling reaction. Literature mechanism for the thiol–epoxy reaction sequence.



Scheme 4 Functionalization of support beads *via* initial thiol–epoxy reaction followed by a thiol–disulfide exchange reaction. Enzymes were effectively attached to the surface, however, the process is amenable to attachment of other species *via* the thiol–disulfide exchange reaction. Scheme adapted from ref. 17.

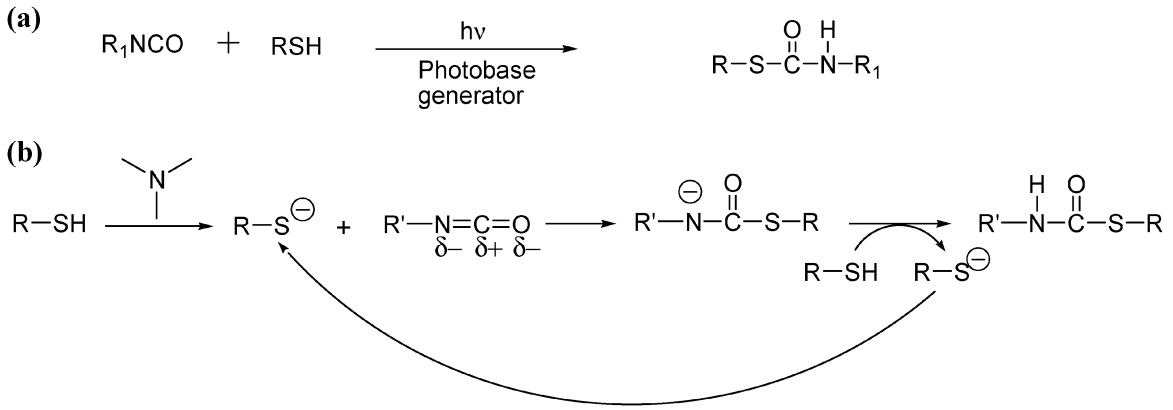
expanding in the high performance coatings and optical fields. The industrial success of thiol–epoxy and thiol–isocyanate reaction chemistries indicates that most objections due to odor or handling of multifunctional thiols can be readily overcome, *e.g.*, the road for expansion of other thiol-click chemistries will not be limited by this restrictive barrier. One particularly important new use of thiol–epoxide click chemistry is its use as a two component "self-healing agent" that, when included in a traditional epoxy matrix *via* a microencapsulating process, readily reacts when a crack is inflicted on the material to initiate a healing process that allows the material to nearly fully recover mechanically attesting to the high efficiency of the thiol–epoxy reaction even under highly restrictive matrix conditions.[18]

While these commercial applications of epoxy–thiol reactions have been well established for decades, taking a lead from the well-known use of a variety of base catalysts for thiol–epoxy reactions, a relatively new concept using light to generate trialkyl amine base catalysts[19] and even stronger bases such as diazabicyclo[4.3.0]none-5-ene (DBN in Scheme 2)[13] has emerged as an efficient process in the catalysis of thiol–epoxy reactions. Photobase generators produce catalysts essentially on demand and hence can be used much as radical- and acid-based photogenerators have been traditionally used to initiate radical chain and cationic chain polymerization processes, respectively. In the case of multi-functional epoxides and thiols, essentially quantitative conversion is attained in bulk assuming the correct combination of photobase generator catalyst, temperature and light exposure is employed. The use of photobase generators is especially appropriate since it introduces a new option for spatially and temporally controllable photochemically initiated processes that are currently being touted for use in polymerization reactions for coatings, adhesives and composite applications. This presents significant potential for expansion to other more traditional roles of thiol–epoxide reactions in organic synthesis and biological applications. Finally, these photoinduced thiol–epoxy reactions have the potential for being combined with radical and cationic polymerization processes, either in tandem or in sequence, thus opening up several exciting possibilities for future development including extension to water-based systems which is particularly intriguing for applications in a number of fields.

2.2 Thiol–isocyanate click reactions

Polyurethanes comprise one of the commodity classes of polymeric materials that have extremely high versatility. Due to their elasticity and ability to respond to impact, stretching and other physical manipulations, polyurethanes have, in addition to a wide range of industrial materials applications as coatings, adhesives, elastomers and foams, been adapted to the fabrication of biomedical, electronic and optical devices. Polythiourethanes, the sulfur analog of polyurethanes, have not received the same level of attention. However, because of the ability to form thiourethane linkages by an efficient, high-yield click process with no byproducts, there is every reason to believe that the future of the chemistry of multifunctional thiols and isocyanates to generate polythiourethanes and the related reaction of monofunctional thiols and isocyanates will see significant growth reminiscent of the recent expansion of thiol–ene chemistry. For this reason, it is important to consider the basics of thiol–isocyanate chemistry in the context of its historical development.

While the facile addition of thiols to isocyanates to give thiourethanes was known by the early 1940s, it was not until 1960 that Dyer *et al.*[20] reported the rapid and efficient formation of a single alkyl thiourethane product in solution (Scheme 5a) with no side products for the base-catalyzed thiol–isocyanate coupling reaction. The efficiency and absence of byproducts typically found for alcohol–isocyanate reactions have been confirmed for the case of both small molecule thiourethane and polythiourethane synthesis.[21,22] The kinetics of the base-catalyzed reaction of primary and secondary thiols with phenylisocyanate indicate a rapid reaction, with non-aromatic isocyanates proceeding at much lower rates. The anionic sequential chain-growth–step-growth process depicted in Scheme 5b, essentially identical to the alternating chain transfer and propagation two-step process in thiol–ene radical polymerization as described in ref. 4, 5, 7 and 8 and discussed in Section 3.1, is consistent with all of the kinetic data reported to date. The proton abstraction depicted in the second step to regenerate the thiolate anion readily occurs in keeping with the relatively low pK_a values of thiols relative to other typical organic protic species. This accounts for the observation that the thiol–isocyanate reaction proceeds rapidly and without side products in the presence of water, alcohols, and amines.

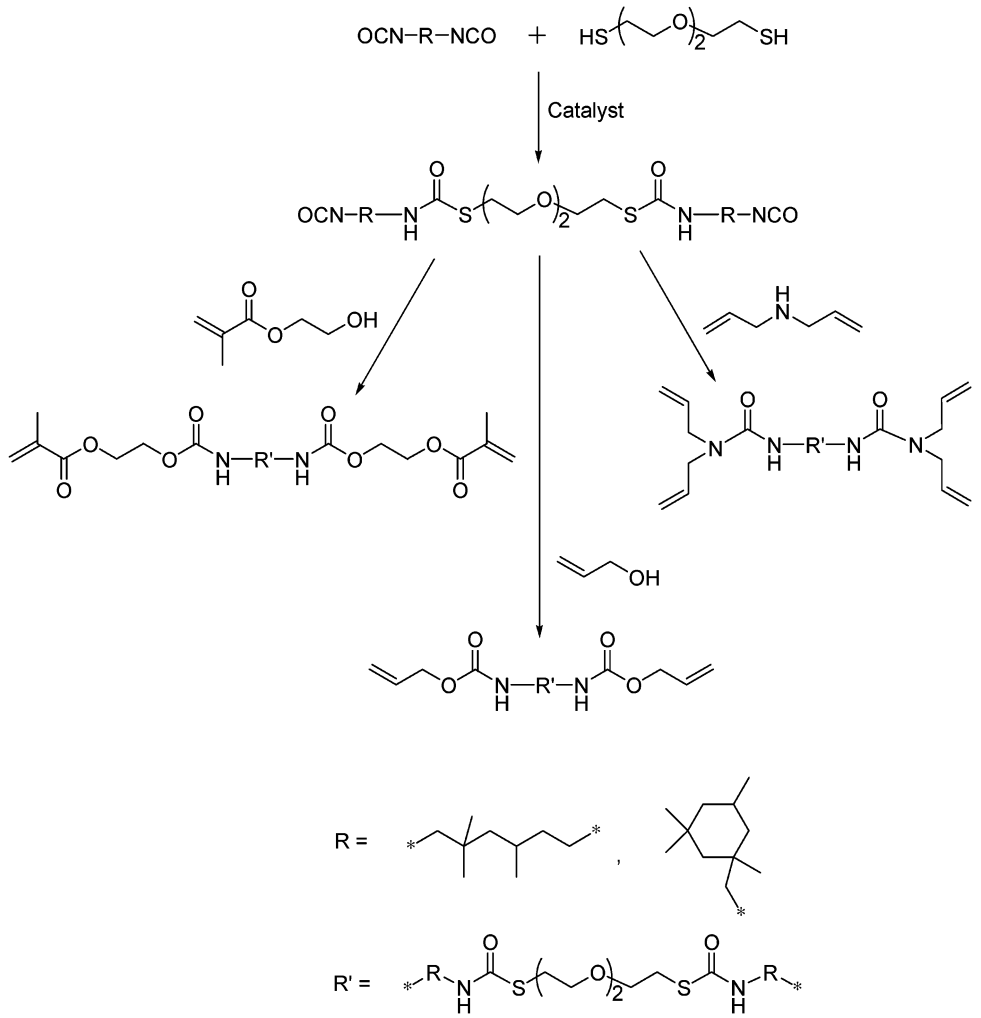


Scheme 5 (a) Tertiary amine catalyzed thiol–isocyanate coupling reaction. (b) Feasible mechanism for the thiol–isocyanate reaction sequence.

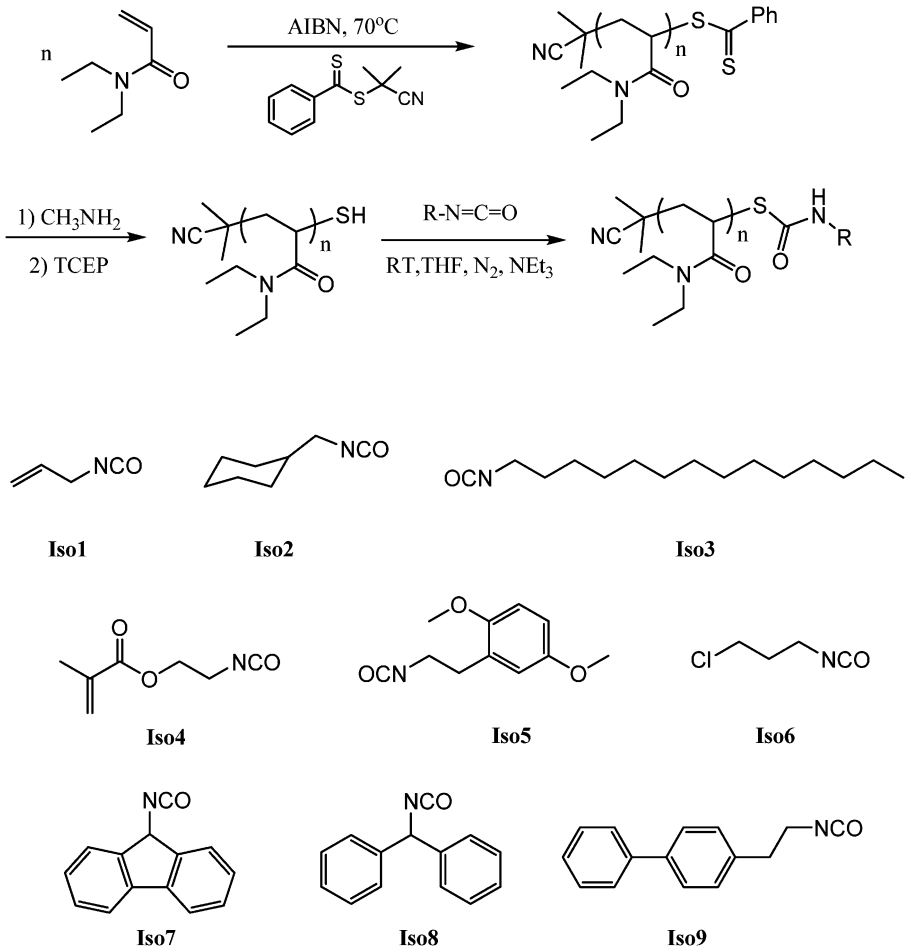
Despite the much higher efficiency of thiol–isocyanate reactions using mild catalysts at low concentrations compared to alcohol–isocyanate reactions, interest from the chemical community was minimal for almost a half century. Beginning in the mid to late 1980s and continuing until today, amine (and other) catalyzed synthesis of a range of polythiourethanes *via* the reaction of difunctional thiols and diisocyanates, primarily for application as high refractive index materials, has emerged.[23–25] This activity has continued to expand due to successful industrial and commercial applications that have opened up for polythiourethane-based optical materials.

As the use of polythiourethanes in optical applications expanded, new chemical strategies for thiol–isocyanate chemistry were developed, and better catalyst systems began to emerge. To illustrate the potential of thiol–isocyanate click reactions, three examples from the literature are discussed here to illustrate their utility. In the first example, diisocyanate terminated thiourethane oligomers of high purity were synthesized and subsequently functionalized by reacting with ene-functionalized alcohols, such as allyl alcohol, 2-(hydroxyethyl)methacrylate, and diallylamine.[22] The resulting di- and tetrafunctional vinyl-terminated telechelic oligomeric monomers are shown in Scheme 6. These vinyl-terminated species and similar types of multifunctional monomers with highly refractive thiourethane linking units form a class of reactive monomers suitable for use in a wide range of optical materials applications. In yet another example, difunctional methacrylates with thiourethane backbone groups and sulfide links were formed by a thiol–isocyanate click reaction. When polymerized, the resultant films produced highly refractive, scratch resistant coatings on polythiourethane and polycarbonate optical plastic lens materials.[25] Finally, thiol–isocyanate reactions have been used to functionalize the end groups of RAFT-based polymers. For example, as shown in Scheme 7, RAFT polymers with thiol chain ends readily react with isocyanates bearing a wide variety of attached functional groups where the thiol-click reaction is a triethylamine catalyzed thiol–isocyanate click reaction.[26] These three examples among many illustrate the importance of the thiol–isocyanate reaction in polymer materials applications.

Since many of the industrial uses of multifunctional thiol–isocyanate click chemistry involve the formation of highly refractive crosslinked polythiourethane materials, it is essential to establish the physical and mechanical nature of the films as they relate to their polyurethane counterparts. It was recently demonstrated that such networks[27] have much higher



Scheme 6 Synthesis of isocyanate terminated oligomers and reactive telomers.



Scheme 7 Synthesis of thiocarbamate end-functionalized poly(*N*,*N*-dimethylacrylamides) by thiol–isocyanate click reactions.

refractive index values than comparable polyurethanes, but exhibit enhanced uniformity as attested to by the narrow peak of the tan δ *versus* temperature plot (see Fig. 2). The narrow mechanical transition is a direct result of the click nature of the thiol–isocyanate reaction that leads to a single thiourethane product with little-to-no side products,[20–22] resulting in high conversions with network uniformity typically associated with thiol–enes.[5,7] All of this performance is achieved without sacrificing the high degree of hydrogen bonding usually associated with polyurethanes. Thus, not only are these crosslinked polythiourethane networks highly refractive, but due to their uniformity they can dissipate impact energy with the efficiency only rivaled by thiol–ene networks at their respective glass transitions.[5,7]

Before concluding this section on thiol–isocyanate chemistry, it is important to point out just how rapid the thiol–isocyanate reactions are when appropriate catalysts are used. In investigations by many industrial and academic labs, it has become apparent that strong bases are essential for initial production of the thiolate anion and effecting rapid thiol–isocyanate coupling processes, *i.e.*, bases with higher conjugate acid pK_a values, are the most efficient catalysts. Hence, the basic order of catalytic reactivity is DBN > trialkyl amine > aromatic amine. These catalysts, depending upon concentration and the exact structures of the reactive components, proceed at reaction rates comparable to or faster than for primary amine–isocyanate reactions to form ureas! We have found that even low concentrations of DBN result in essentially quantitative conversions on the scale of minutes or less. Interestingly, one of the most efficient catalysts for thiol–isocyanate reactions involves the use of low concentrations of trialkylphosphines in combination with acrylates.[28] The coupling reaction of a typical 1 : 1 molar thiol–isocyanate pair is complete in very short times with no byproducts when a tributylphosphine–acrylate co-catalyst system is used. The reaction is much faster than if a strong base is used under identical conditions and catalyst concentrations. The resulting carbon-centered bases produced by the addition of trialkyl phosphine nucleophiles to acrylates catalyze thiol–isocyanate reactions that proceed to near 100% conversion in bulk in a few seconds, most likely by the mechanism in Scheme 5b.

Finally, it is important to realize that thiol–isocyanate chemistry as a highly efficient click tool for organic and polymer synthesis is just beginning to emerge. Perhaps it will be most important when used in combination with other thiol and non-thiol-click chemistries. A specific example of the application of thiol–isocyanate chemistry in a sequential thiol-Michael/thiol–isocyanate process is highlighted in Section 4.

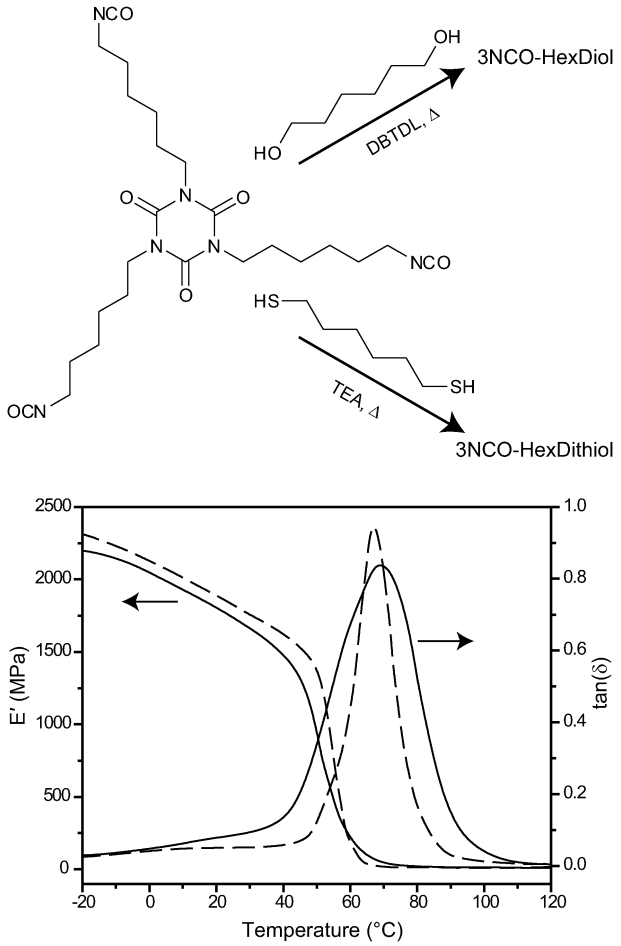


Fig. 2 Dynamic mechanical analysis plots of storage modulus (E') *versus* temperature and tan δ *versus* temperature for polyurethane and polythiourethane networks.

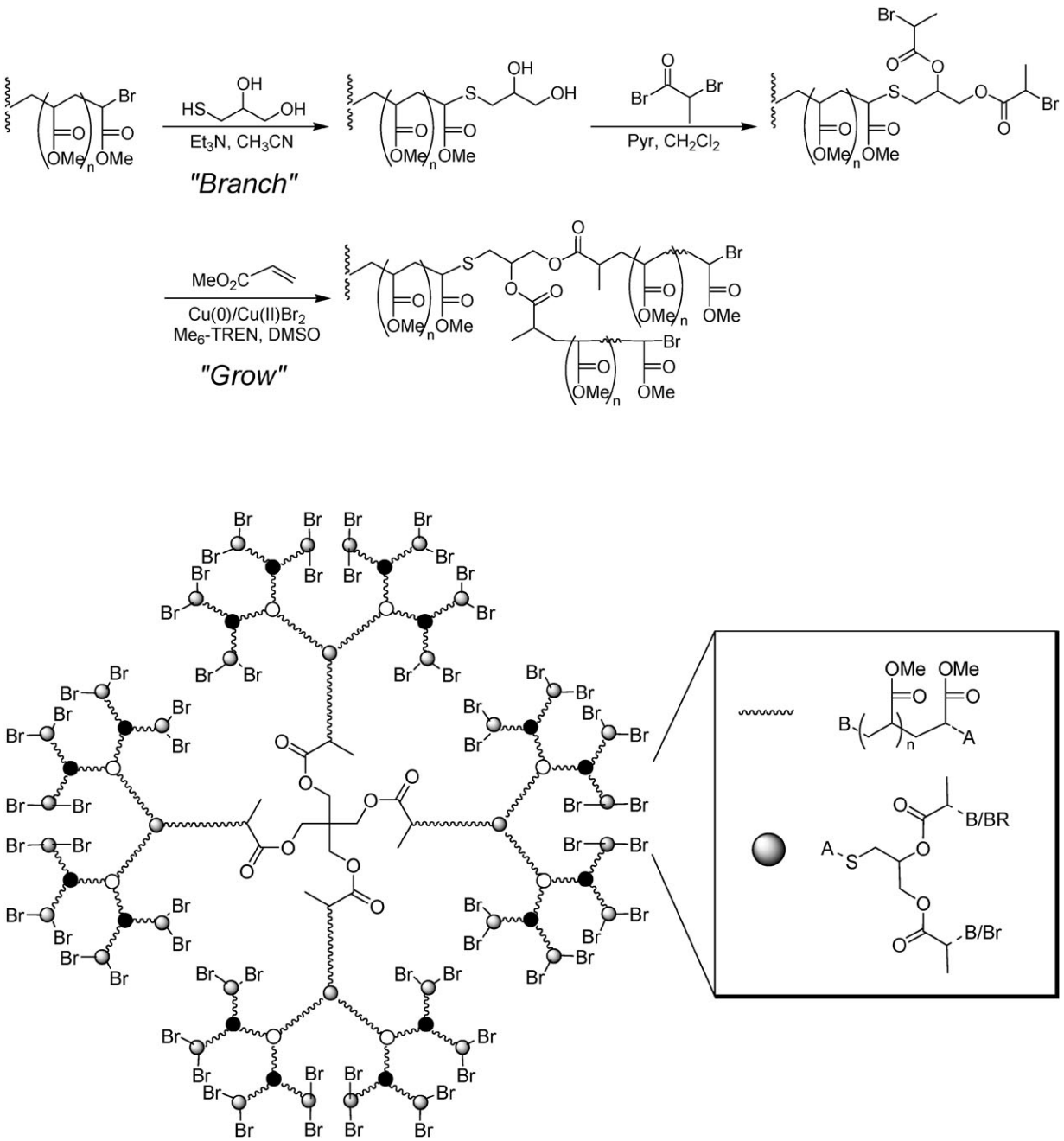
2.3 Thiol–halogen nucleophilic substitution click reactions. The ability of thiols, which are prototypical soft nucleophiles, to participate in rapid and efficient substitution reactions with reactive substrates bearing readily displaceable leaving groups, *e.g.* halogens, has resulted in the thiol–halogen nucleophilic reactions being touted as efficient click chemistry.[29–31] The halogenated salts produced by the thiol–halogen nucleophilic displacement reaction in the presence of relatively mild organic bases such as trialkyl amines are readily removed as precipitants in a very simple and effective clean up procedure. While thiol–halogen nucleophilic reactions are not pure *fusion* processes as specified by Kolb *et al.* [1] Percec's laboratory[29] recently demonstrated that the displacement reaction rate of the S_N2 nucleophilic substitution of reactive bromine groups by a wide range of thiols warrants its consideration as a click reaction. Particularly noteworthy, was their observation[29] that, due to its high relative nucleophilicity compared to alcohols, the thiol functionality of 2-mercaptoethanol and other aliphatic thiol–dialcohol species added exclusively to halogen end-functionalized polymers and other halogenated species. This result provides a powerful conduit for selective end functionalization of polymer chain ends and attests to the orthogonality of the thiol–halogen click reaction, *i.e.*, the halogen is displaced by thiol even in the presence of a large excess concentration of alcohol groups. We also interject that the thiol displacement should also be favored in systems containing aliphatic amines. Percec and his colleagues[29] employed the triethylamine catalyzed thiol–halogen reaction, referred to as thio–bromo click chemistry, in combination with an efficient acylation reaction with 2-bromopropionyl bromide. It was demonstrated that the thiol–halogen reactions could be effectively used to make two types of dendrimers, the first (not shown) being multiarm dendrimer macroinitiators with arms ranging from 4 to 32, and the second as shown in Scheme 8 multiarm dendritic polymers with polyacrylate units connecting each of the branch units. Since the thio–bromo click reaction is amenable to all types of thiol-functional groups, it was envisioned by the authors that the dendrimer periphery could be functionalized to enhance self-organization as well as initiating controlled radical polymerizations.

In a particularly clever rendition of the thiol–*p*-fluoro click reaction, recent work by Samaroo *et al.*[30] showed that porphyrinoid macrocyclics with four pentafluorophenyl groups (Scheme 9) undergo rapid and nearly quantitative reactions with a cadre of aromatic and aliphatic thiols with high yields achieved when various mild bases were used. The products in Scheme 9 certainly demonstrate the potential of using such click reactions to effectively modify biologically important cores to enhance solubility, intermolecular binding, aggregation and transport in biological media. By a very similar process, Becer *et al.*[31] prepared glycopolymers (Scheme 10) *via* a nucleophilic substitution of a *p*-fluorine group by a thiol-glucose unit in a pentafluorophenyl side group of a pentafluorostyrene homopolymer and a styrene–pentafluorostyrene block copolymer. ^{19}F NMR kinetics indicated that under mild conditions with a trialkyl amine base present, the one product substitution reactions were essentially quantitative on the order of a little over one hour. In addition to potential use as bioorganic materials with stimuli-responsive blocks, it was speculated that the metal-free thiol–fluorine click displacement reaction could be utilized to produce functionalized nanoparticles for coating material components for body implants. Other thiols with different attached groups could be reacted in a like manner to provide a host of different functional polymers.

In summary of the results in this section, the work depicted in Schemes 8–10 is indicative of the potential, especially in the dendrimer and bioorganic arena, for extending thiol-click chemistry to a wide range of new and exciting applications.

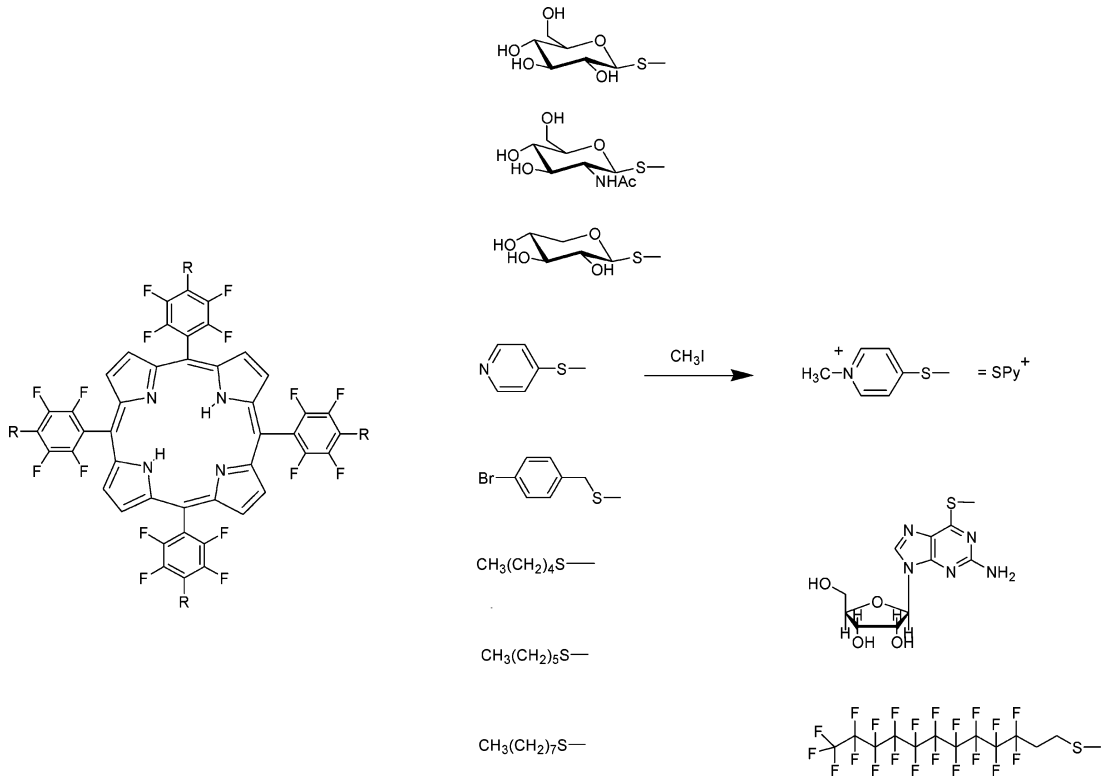
2.4 Thiol-Michael addition reactions

The conjugate, or Michael, addition of thiols, or thiolate anions, to electron deficient C=C bonds has been studied since at least the 1940s[32] and continues to receive attention today with significant efforts devoted to the development of novel catalytic systems often with the aim of achieving facile, green syntheses.[33–36] From a more traditional, or fundamental, standpoint the hydrothiolation of an activated C=C bond is readily accomplished under base catalysis with reagents such as sodium methoxide, benzyltrimethylammonium hydroxide, and even relatively weak organobases such as NEt_3.

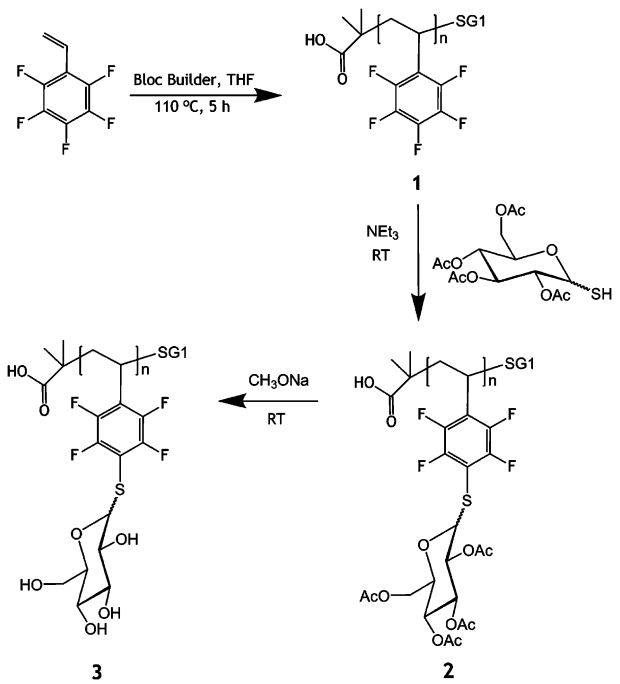


Scheme 8 Synthesis of bromo-terminated macromolecular dendrimers *via* thio–bromo click and acylation reactions. Scheme adapted from ref. 29.

The accepted mechanism for such reactions is given in Scheme 11. The base, B, abstracts a proton from the thiol generating the thiolate anion, RS^-, and the conjugate acid BH^+. The potent nucleophilic thiolate anion attacks the electrophilic β-carbon of the C=C bond, generating the intermediate carbon-centered anion, itself a very strong base, that abstracts a proton from the conjugate acid, BH^+, yielding the thiol-Michael addition product with concomitant regeneration of the base catalyst. After initiation, this two-step anionic propagation process, similar to the insertion–abstraction propagation sequence of thiol–ene radical reactions, is very rapid due to the relative availability of the thiol proton, and proceeds without interference from other proton sources (water, alcohol) in contrast to anionic polymerization chain processes for example. While it is impossible to review all the features of this general base mechanism and its literature applications here, it is worth mentioning that the overall rate and yield of such reactions can be influenced by factors such as solvent polarity and pH (in the case of solution reactions), base catalyst strength, pK_a of the thiol (see Fig. 1), steric bulk of the thiol, and the nature of the electron withdrawing group (EWG) on the C=C bond. For a detailed review the interested reader is directed to a recent publication by Long *et al.*[37] However, the important point to reiterate is that the

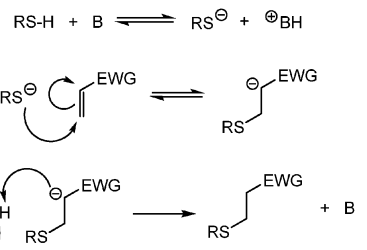


Scheme 9 Synthesis of tetra-substituted porphyrinoids by the halogen-nucleophilic displacement click reaction of pentafluorophenyl groups. Scheme adapted from ref. 30.



Scheme 10 Synthesis of glycol polymers using a thiol–halogen nucleophilic displacement click reaction of pentafluorophenyl side groups. Scheme adapted from ref. 31.

traditional base-mediated thiol-Michael reaction is without doubt a versatile and important synthetic tool that continues to find wide spread use in polymer and organic chemistry, as exemplified by the work highlighted below.



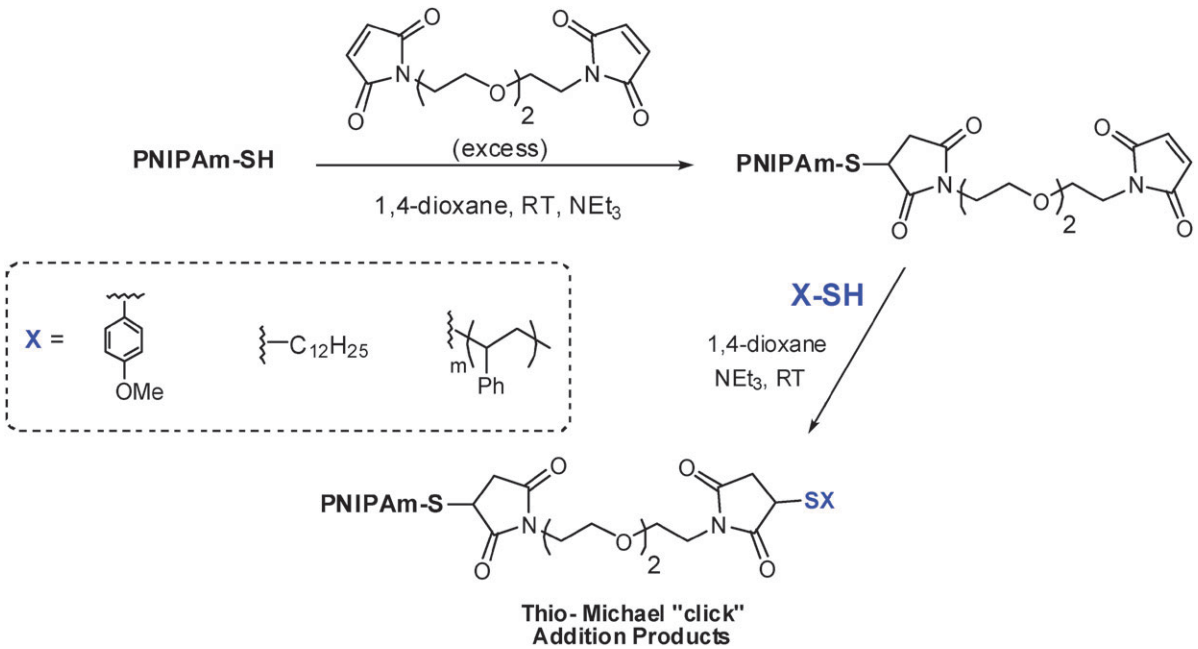
Scheme 11 The base catalysed hydrothiolation of an activated C=C bond.

One important area in which the traditional base-mediated thiol-Michael reaction has found extensive application in recent years is in the preparation of α- and ω-functional (co)polymers commonly, but not exclusively, derived from (co)polymers synthesized by RAFT. For example, Sumerlin and co-workers[38] recently described the preparation of ω-functional poly(*N*-isopropylacrylamide) (PNIPAm) homopolymers *via* sequential base-catalyzed thiol-Michael reactions with a bis-maleimide. Cleavage of the trithiocarbonate end group on PNIPAm was accomplished *via* an aminolysis reaction in the presence of the reducing agent tributylphosphine to yield the corresponding thiol-terminated homopolymer. Subsequent reaction with an excess of bis-maleimidodiethyleneglycol at ambient temperature in the presence of a catalytic amount of NEt_3 yielded the maleimide-end-functional homopolymer (Scheme 12). This approach introduces a reactive handle, the maleimide group, which can be further modified with other thiol-bearing reagents. For example, subsequent

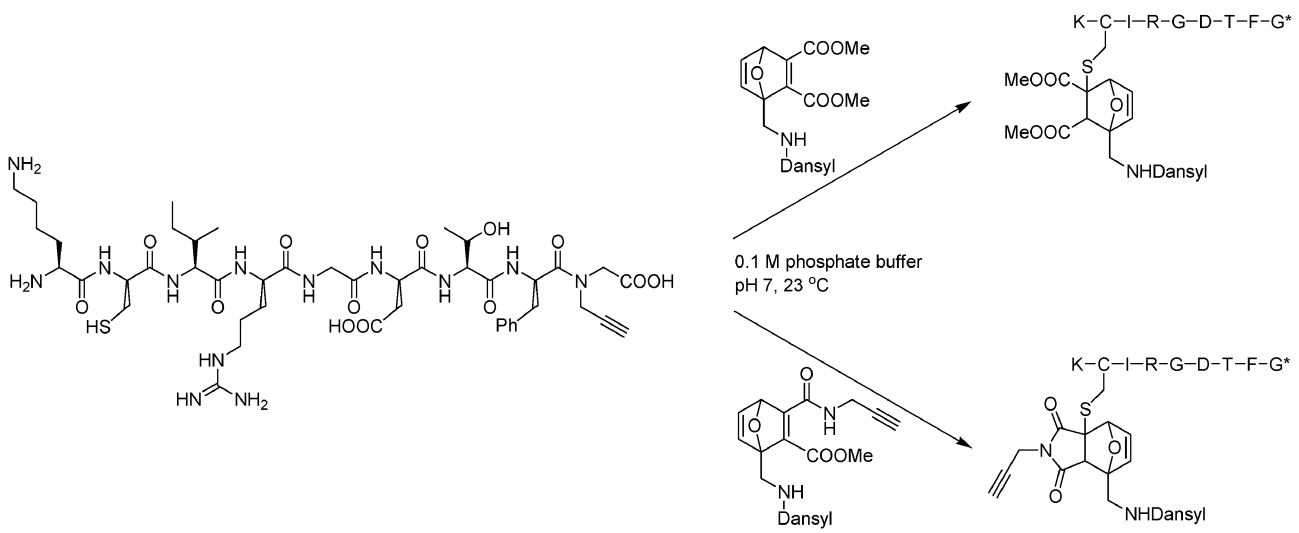
reaction with 4-mercaptoanisole or dodecanthiol yielded the hydrophobically modified PNIPAms while reaction with thiol-terminated polystyrene highlighted the approach as a facile modular route to AB diblock copolymers.

In a recent novel application in the field of bioorganic chemistry, Hong *et al*. described the base-mediated thiol-Michael reaction for the synthesis of fluorescent molecules based on 7-oxanorbornadienes (Scheme 13).[39] Dansyl-labeled 7-oxanorbornadienes were prepared by a Diels–Alder reaction between a dansyl-functional furan and alkyne-diesters of general formula $RO_2CC{\equiv}CCO_2R$ in moderate-to-high yield. These non-fluorescent species could be "turned-on" by treating the norbornadiene with a thiol, under iPr$_2$NEt base catalysis, resulting in thiol-Michael addition across the highly activated, tetra-substituted C=C bond. The high efficacy of this reaction was demonstrated with simple small molecule thiols such as 2-mercaptoethanol and ethyl-3-mercaptoproprionate as well as with much more complex molecules including the nonapeptide shown in Scheme 13 and thiolated BSA. Importantly, it is worth noting that this base-catalyzed thiol-Michael reactive pair represents one of the most efficient of all Michael donor–acceptor systems and will, no doubt, receive further attention in the bioorganic and polymer/materials fields.

As stated above, it is impossible to review all the recent literature pertaining to the synthetic applications of the base-mediated thiol-Michael reaction. However, we hope that with these two recent examples alone, covering both synthetic



Scheme 12 Sequential, base-catalyzed macromolecular thiol–maleimide/thiol–maleimide reactions as a route to ω-functional poly(*N*-isopropylacrylamide) and as a modular approach to AB diblock copolymers. Scheme adapted from ref. 38.



Scheme 13 Peptide modification of activated 7-oxanorbornadienes *via* thiol-Michael coupling. Scheme adapted from ref. 39.

polymer and bioorganic chemistry will serve to highlight that traditional base-catalyzed thiol-Michael reactions are "alive-and-well" and have impressive potential in a broad range of fields and applications and will no doubt continue to receive attention in the synthesis of ever-more complex and functional small and macromolecules.

While the traditional base-catalyzed thiol-Michael reaction is a highly versatile process, significant efforts have been, and are being expended on the development of novel catalytic systems that efficiently and cleanly effect such thiol-Michael addition reactions. One important area that has recently garnered attention as a powerful catalytic approach is that of *nucleophilic catalysis* employing simple primary/secondary amines as well as certain tertiary phosphines for such reactions.[37,40,41] Indeed, under appropriate conditions, nucleophile-mediated conjugate additions do proceed with exceptional click characteristics as exemplified by recent reports from Lowe, Hoyle and co-workers[42–45] in the convergent synthesis of star polymers, the preparation of branched thioethers, and in the straightforward preparation of ω-functional homopolymers prepared by RAFT.

To demonstrate the potency of nucleophilic catalysis for thiol-Michael reactions, consider a recent study by Chan *et al.*[46] on the bulk reaction of hexanethiol (5 mmol) with hexyl acrylate (5 mmol) in the presence of 0.43 M hexylamine ($HexNH_2$), *n*-dipropylamine (nPr_2NH), and NEt_3 under ambient conditions (presence of oxygen, moisture, RT). Fig. 3 shows the experimentally determined kinetic profiles obtained by following the disappearance of thiol-functional groups by real-time FTIR spectroscopy for the thiol–acrylate reaction in the presence of the three different amine catalysts. In the case of $HexNH_2$ the thiol-Michael reaction is fast, with essentially quantitative conversion being obtained after ~500 s. While it is generally considered that secondary and tertiary amines are more basic than primary amines, the difference in pK_a values for these three catalysts spans only 0.4 pK_a units (pK_a of $HexNH_2$ = 10.6 and pK_a of nPr_2NH = 11.00) and as such the large differences in the kinetic profiles (~3 orders of magnitude for the k_{app} values determined at 30% conversion) would not be expected based simply on these pK_a differences. Indeed, based on the pK_a values alone the predicted effectiveness of these catalysts would be: nPr_2NH > NEt_3 > $HexNH_2$. However, the kinetic profiles are easily rationalized if the amines are serving not as bases, but as nucleophiles. The relative nucleophilicity for such alkylamines, considering only steric factors which is valid in this instance, should follow the order: primary > secondary > tertiary. As such, based on the proposed mechanism, in which the first step is the aza-Michael addition to an activated ene, the proposed reactivity order would be primary amine > secondary amine ≫ tertiary amine, exactly as observed in the kinetic profiles. Finally, note that the rate is significantly increased by simply raising the catalyst concentration (Fig. 3) from 0.43 M to 0.75 M allowing quantitative conversion in ~120 s.

While primary and secondary amines are highly efficient nucleophilic catalysts for thiol-Michael reactions, certain phosphines exhibit exceptional catalytic properties. Phosphines are well-known to serve as efficient organocatalysts in a variety of fundamental organic reactions and are less basic but more nucleophilic compared to amines of an identical substitution pattern.[47] Given the impressive nucleophilic catalytic activity of simple 1°/2° alkylamines, one would predict that phosphines would also serve as potent catalysts. Indeed, this hypothesis proves to be true. Fig. 4 shows the kinetic profiles for the reaction between hexyl acrylate (2.0 M) and hexanethiol (2.0 M) in 45 wt% benzene (to slow the rate and allow real-time IR measurement) in the presence of four different phosphines (P-*n*-Pr_3, PMe_2Ph, $PMePh_2$, and PPh_3) at a concentration of only 0.003 M.[46] Aryl substitution results in a drastic drop in rate as expected, *i.e.*, in terms of catalytic activity: P-*n*-Pr_3 > PMe_2Ph > $PMePh_2$ > PPh_3.

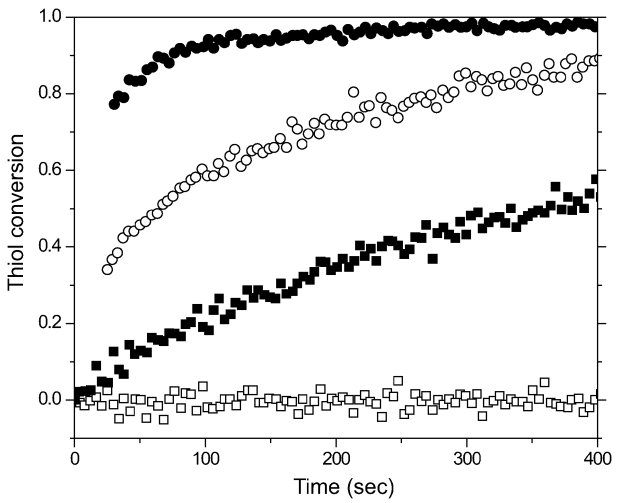


Fig. 3 Kinetic profiles for the reaction of hexyl acrylate (5.0 mmol) and hexanethiol (5.0 mmol) in the presence of 0.43 M triethylamine (open squares), 0.43 M dipropylamine (filled squares), 0.43 hexylamine (open circles), and 0.75 M hexylamine (filled circles). Figure adapted from ref. 46.

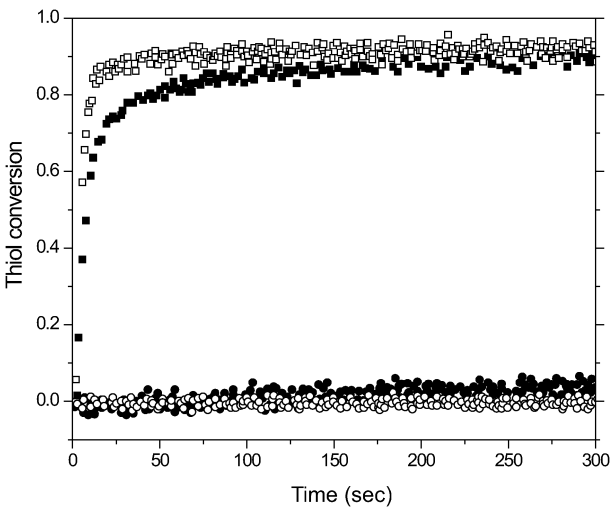
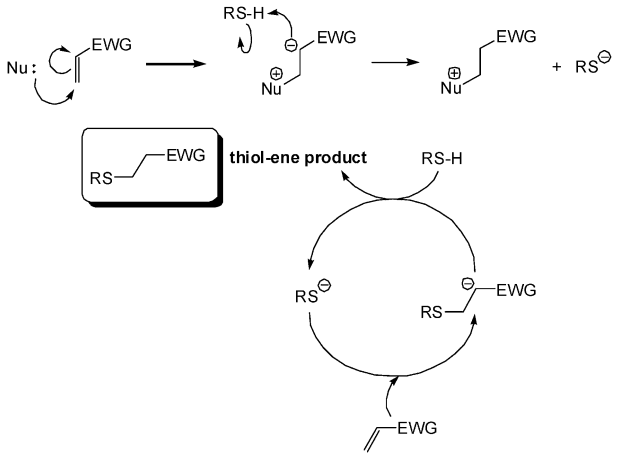


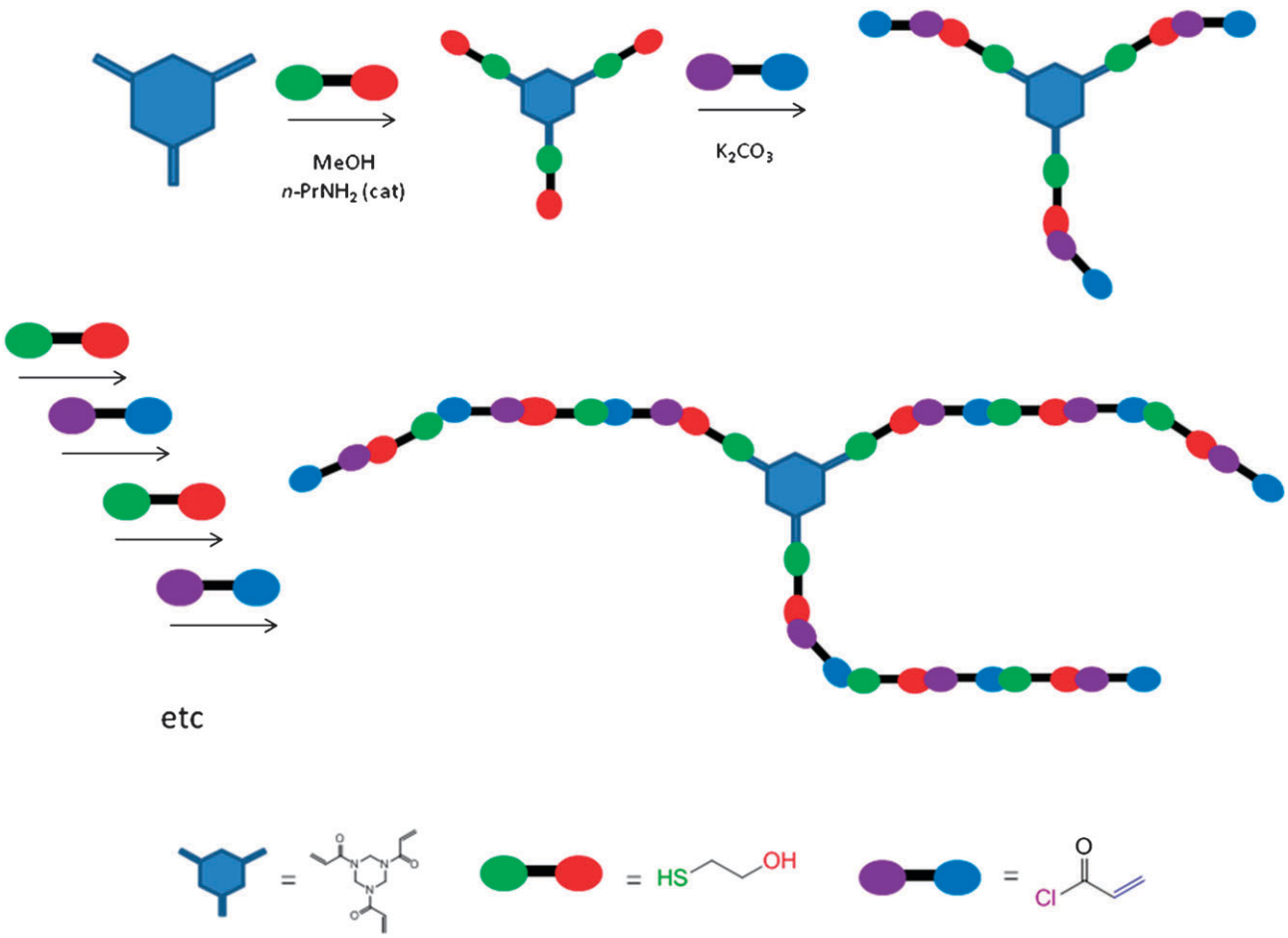
Fig. 4 Kinetic profiles for the reaction of hexyl acrylate (2.0 M) with hexanethiol (2.0 M) in 45 wt% benzene in the presence of 0.003 M tri-*n*-propylphosphine (P-*n*-Pr_3) (open squares), dimethylphenylphosphine (PMe_2Ph) (filled squares), methyldiphenylphosphine ($PMePh_2$) (filled circles), and triphenylphosphine (PPh_3) (open circles). Figure adapted from ref. 47.

What is important to note is that the *tertiary* trialkyl phosphine, even at the very low concentration of 0.003 M, has a k_{app} ~2 orders of magnitude *greater* than the primary amine, $HexNH_2$, which was employed under bulk conditions and at a concentration ~2 orders of magnitude higher than the phosphines, thus demonstrating the enhanced nucleophilic catalytic behavior of phosphines *versus* amines. Since phosphines are much poorer bases than alkylamines, it is clear that a base-catalyzed process is not in effect. Based on these observations, a proposed mechanism for such nucleophile-mediated thiol-Michael addition reactions is given in Scheme 14, whereby the nucleophile (amine or phosphine) undergoes conjugate addition to the activated C=C bond generating the strong intermediate carbanion, that deprotonates the thiol, generating a thiolate anion that then enters an anionic chain process in which the thiolate anion undergoes direct thiol-Michael addition, regenerating the strong carbanion that deprotonates more thiol with concomitant generation of the thiol-Michael product.



Scheme 14 Proposed mechanism for the nucleophile-mediated hydrothiolation of an activated C=C bond.

In another recent example demonstrating the potency of nucleophilic primary amine catalysis and the thiol-Michael reaction, Rissing and Son[48] described the facile and highly efficient synthesis of star-shaped oligomers constructed from a triazine core (Scheme 15). Reaction of 1,1′,1′′-(1,3,5-triazinane-1,3,5-triyl)triprop-2-en-1-one with 2-mercaptoethanol in the presence of *n*-$PrNH_2$ results in a quantitative thiol-Michael addition across the amide bonds. Subsequent acylation with acryloyl chloride reintroduces activated C=C bonds that undergo another *n*-$PrNH_2$-catalyzed thiol-Michael reaction



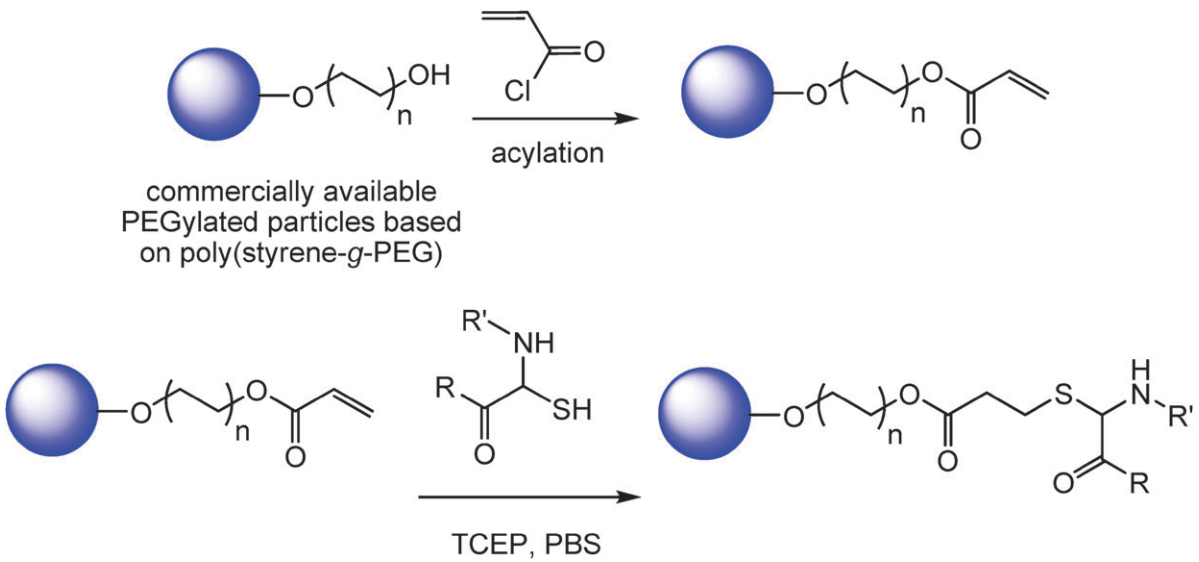
Scheme 15 Cartoon highlighting the synthetic route to 3-arm star thioether oligomers *via* sequential thiol–ene/acylation reactions. Scheme adapted from ref. 48.

with additional 2-mercaptoethanol. Repeating this sequence of reactions results in forming the target branched oligomeric structures.

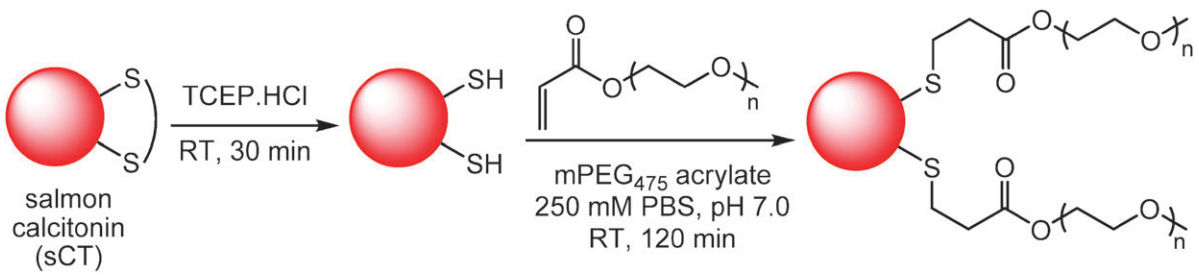
In addition to polymer modification and the synthesis of oligomeric molecules, the nucleophile-mediated thiol-Michael reaction has been employed extensively in the field of bio-conjugation as exemplified by the work of Hubbell and co-workers. For example, Heggli *et al.*[49] described a facile approach for the surface modification of commercially available PEGylated particles based on poly(styrene-*graft*-poly(ethylene glycol)) (Scheme 16). Acylation, with acryloyl chloride, of surface hydroxyl groups yielded the corresponding acrylate-functional particles. Subsequent thiol-Michael reaction with cysteine, in the presence of TCEP and PBS, yielded the corresponding cysteine-functional particles.

Further highlighting the effectiveness of phosphines, or 1°/2° amines as highly effective nucleophilic catalysts for thiol-Michael reactions, Haddleton and co-workers recently described the one-pot, organophosphine catalyzed synthesis of polymer–protein bioconjugates, Scheme 17.[50] Treatment of salmon calcitonin (sCT) with TCEP under ambient conditions for 30 min results in the TCEP-mediated reduction of a Cys^1–Cys^7 disulfide bridge yielding the corresponding free thiols. Subsequent addition of poly(monomethoxy ethylene glycol) (meth)acrylates to this reduced solution results in the TCEP-catalyzed thiol-Michael addition yielding the target polymer–protein conjugates rapidly and with extremely high efficiency. The effectiveness of phosphines as organocatalysts for thiol-Michael reactions will be further highlighted in Section 4, where examples of sequential thiol-click reactions are presented.

When any type of thiol-Michael addition reaction is anticipated, whether initiated by traditional base catalysts, Lewis acids, metal catalysts, or primary amine/phosphine catalysts, it is essential to take into account that both thiol and ene structures are also important factors that also have a measurable effect on the kinetics of such thiol-Michael reactions. Hexanethiol was employed in these studies since it is one of the *least* reactive thiols and thus slowed the reaction kinetics to a point that they could be accurately measured. Significantly faster rates, for any of the catalytic systems, can be attained by substituting hexanethiol (or any other alkylthiol) with mercaptoglycolates or mercaptoproprionates, both of which have lower thiol pK_a's (see Fig. 1). Additionally, the structure of the activated ene plays an equally important role. The more electron deficient the C=C bond the more reactive it is towards Michael addition. For example, in terms of C=C bond reactivity, maleimides > fumarates > maleates > acrylates/acrylamides > acrylonitrile > crotonate > cinnamate > methacrylates/methacrylamides.



Scheme 16 Thiol-Michael modification of acrylic-functional particles as a route to amino acid modified surfaces. Scheme adapted from ref. 49.

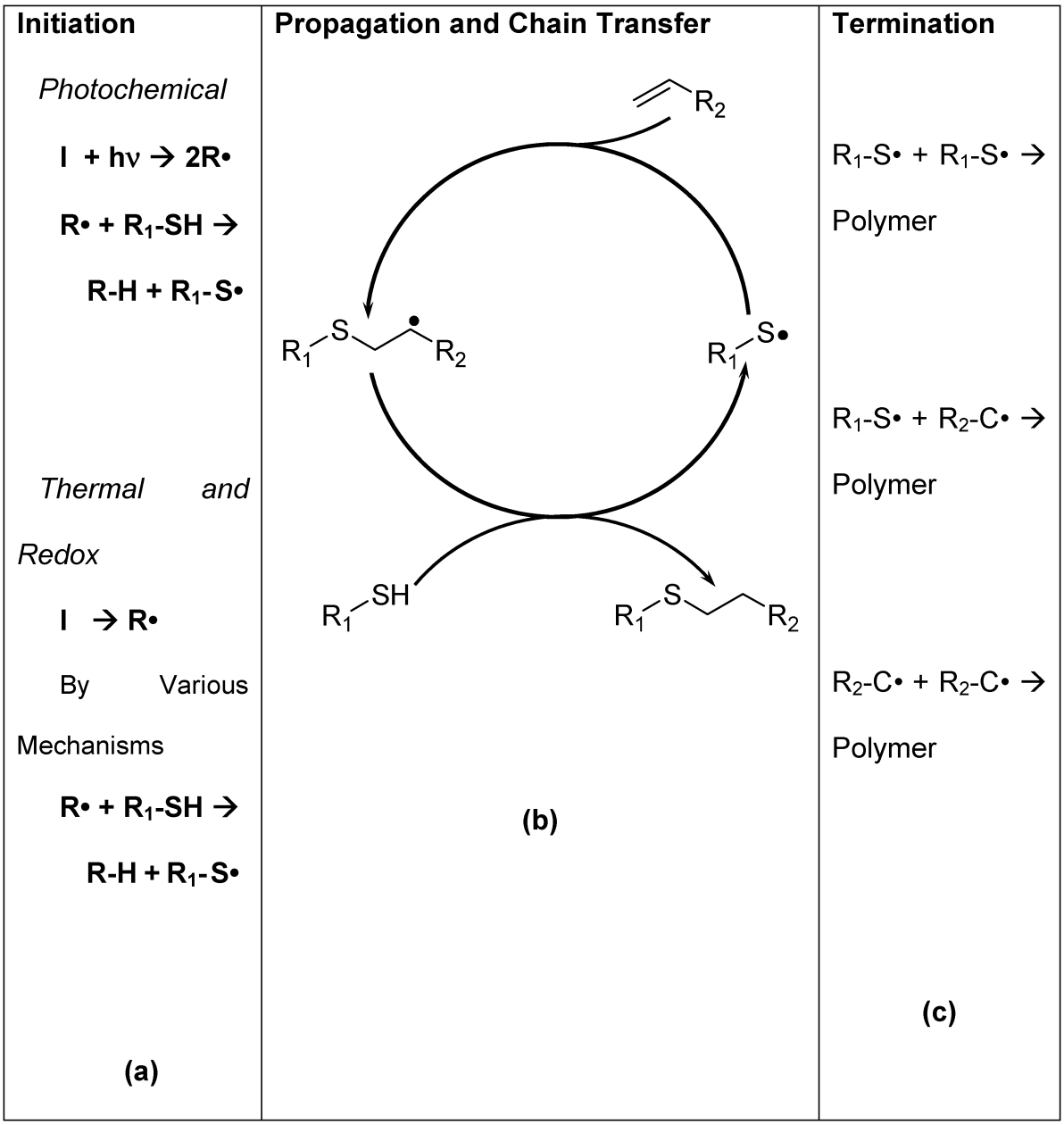


Scheme 17 The synthesis of polymer–protein bioconjugates derived from salmon calcitonin and poly(monomethoxy ethylene glycol) (meth)acrylates constructed *via* phosphine catalyzed thiol-Michael addition. Scheme adapted from ref. 50.

In summary, nucleophile-mediated thiol-Michael reactions, as well as traditional base-catalyzed reactions, proceed with the hallmark characteristics of a click reaction, *i.e.* they are extremely rapid, proceed under bulk conditions in the presence of air and moisture, give quantitative yields, require no clean up and are regiospecific. Primary alkylamines are extremely potent nucleophilic catalysts for such reactions although enhanced catalytic activity can be attained in the case of trialkylphosphines such as P-*n*-Pr_3 although similar catalytic activity is observed for the easier to handle PMe_2Ph.

3. Thiol-radical click chemistries

In 2007 Schlaad and co-workers[51] first identified the radical-mediated thiol–ene reaction as a click reaction. Their classification was recognition of the simple, highly efficient, robust nature of the reaction whether used for small molecule derivatization or for polymerization. In fact, there are two distinct radical-mediated thiol-click processes, the thiol–ene and thiol–yne reactions.[2–12] Both of these radical-mediated processes achieve rapid reaction rates, high degrees of amplification wherein a single radical causes hundreds to tens



Scheme 18 The radical-mediated thiol–ene reaction mechanism. The radical generation, *i.e.* initiation, steps shown in (a) are generally performed by photoinitiation though thermal and redox methodologies have been employed for radical generation. Initiators are not necessary as the polymerization can be photochemically initiated in the absence of a distinct initiator species. The click nature of the reaction is derived from the coupled chain transfer and propagation reactions presented in (b) while the termination process involving bimolecular radical reactions between radicals of various types is presented in (c).

of thousands of chemical reaction events to occur, and high extents of reaction all typically associated as benefits of chain-growth free radical polymerization processes. However, these two reactions are among the only such processes, the thiol-Michael reactions that proceed *via* an anionic chain process as discussed in Section 2.4 being the other, that simultaneously incorporate the benefits of a step-growth mechanism with regard to polymer molecular weight evolution and the capacity for reacting large numbers of functional groups for each reactive intermediate, *i.e.*, radical, generated. This potent combination of two reaction motifs, generally considered to be mutually exclusive, is a powerful tool that in the case of multifunctional thiols and multifunctional enes has been utilized for several decades to induce some of the most efficient polymerization processes in the polymer materials field with applications in fields as diverse as optical lenses, rapid sealing optical adhesives, overprint varnishes, and protective high performance coatings, to name but a few. Because of this synergistic attribute combination, these radical-mediated thiol–ene and thiol–yne reactions are also powerful tools in small molecule, biomolecule and polymer functionalization. Recently, radical thiol–ene chemistry has also been translated into many applications in the electronics, optics, and biological fields, and combined with its twin sister the highly efficient thiol–yne chemistry, purports to be a strong candidate for revolutionizing the production of a wide array of advanced materials. The salient features of both radical-mediated processes are detailed here along with a limited discussion of recent work in these areas.

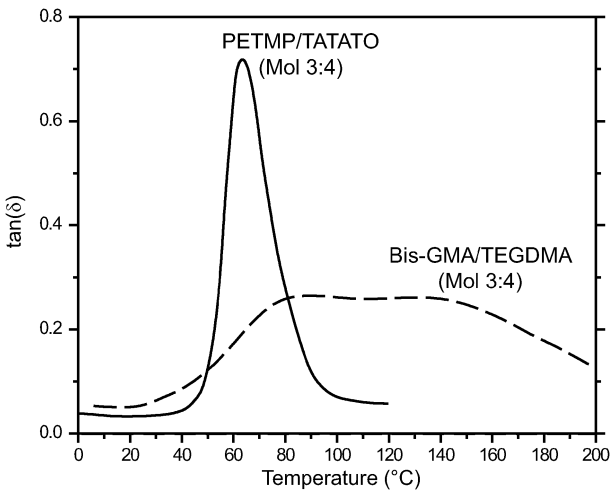


Fig. 5 Varying heterogeneity of traditional (meth)acrylate copolymers and thiol–ene networks. Here, the loss tangent as measured by dynamic mechanical analysis is plotted as a function of temperature for two networks: a mixture of bisphenol-A dimethacrylate (bis-GMA) and triethylene glycol dimethacrylate (TEGDMA) (70/30 by weight) and a stoichiometric mixture of pentaerythritol tetra(3-mercaptopropionate) (PETMP) and triallyl-1,3,5-triazine-2,4,6-trione (TATATO). The thiol–ene sample has a half-width of approximately 20 °C, indicative of a uniform network structure while the dimethacrylate network has a glass transition temperature half-width of greater than 100 °C, indicative of a highly heterogeneous structure.

3.1 Thiol–ene radical click reactions

While both heat and light have been used to generate radicals that initiate the thiol–ene radical chain process, the use of light has enormous advantages for small molecule synthesis, surface and polymer modification, and polymerization reactions. When photoinitiation is used, the reaction is readily controlled both spatially and temporally with associated benefits accumulating with regard to the ability to manipulate the reaction further by controlling the reaction rate and extent simply by manipulating the light intensity, the dose or the

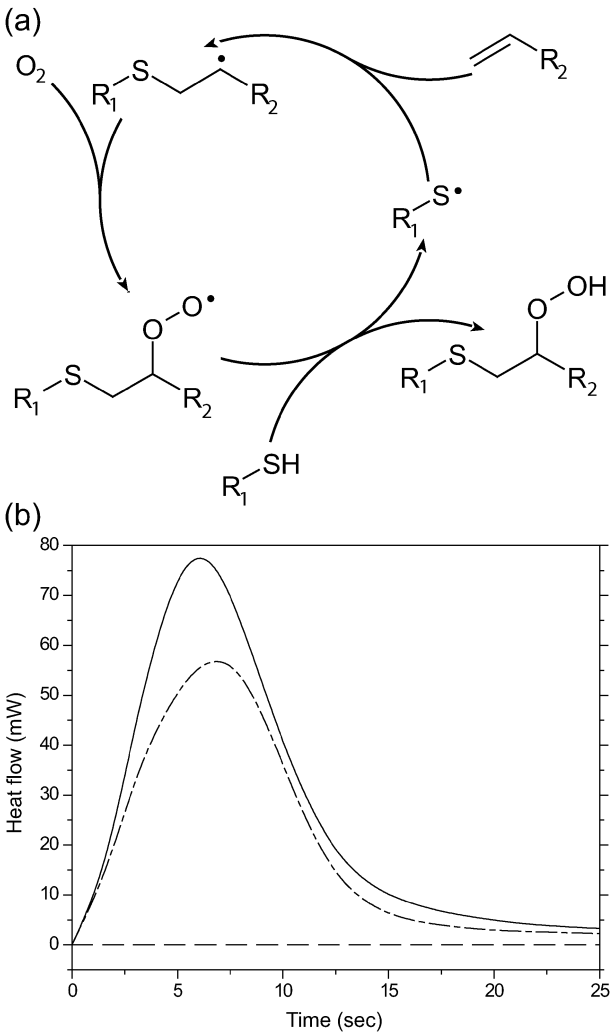


Fig. 6 The capacity for overcoming oxygen inhibition in radical thiol–ene reactions. Generally, oxygen reacts with polymerizing radicals to form inactive peroxy radicals; however, as illustrated in (a) for thiol–ene reactions, the peroxy radical abstracts a hydrogen from the thiol to form an active thiyl radical that restarts the polymerization with little or no observed depression of the polymerization rate. In (b) these effects are observed by comparing the polymerization rate as measured by photo-DSC for polymerizations of tripropylene glycol diacrylate in nitrogen (solid line), air (dashed line), and with 30 mol% trithiol in air (dot-dashed line). Samples contain 1 wt% DMPA and were polymerized at a light intensity of 0.6 mW cm^{-2} using 365 nm light. Here, the presence of the thiol nearly restores the acrylate to its polymerization rate in a purged environment. (Panel b is adapted from ref. 15.)

duration of the exposure. Further control of the reaction is achieved by manipulating the initial stoichiometry of the reactants with complete consumption of the limiting reactant readily achieved and the remainder of the excess reactant available for subsequent modification. The radical-mediated thiol–ene and thiol–yne reactions, along with the base-catalyzed thiol–isocyanate, thiol–epoxide, thiol–halide and thiol-Michael addition reactions described in Section 2, represent particularly attractive combinations of the click reaction chemistry paradigm with the capability to photoinitiate the click reaction. This synergistic combination of capabilities promotes significant advantages and has propelled thiol–ene chemistry to the forefront of novel polymerization and polymer modification reactions in recent years. Herein, we describe the mechanism of the thiol–ene and thiol–yne polymerization reactions and appropriate methodologies for their implementation in polymerizations, polymer and surface modification, molecular synthesis, and bioorganic reaction processes.

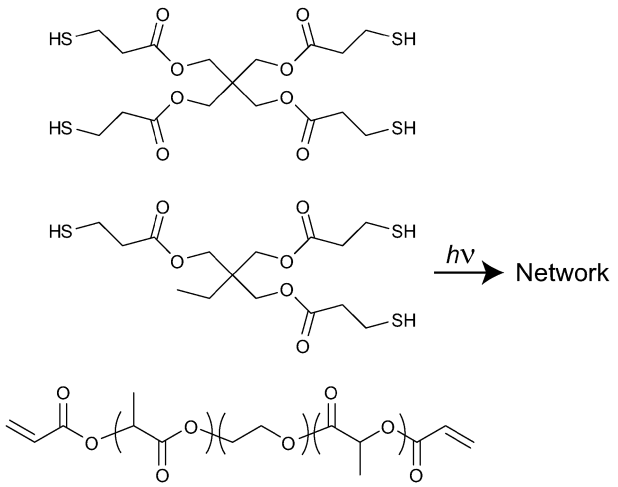


Fig. 7 Structures of components used to fabricate photopolymerized thiol–acrylate hydrogel networks with the ultimate variation in swelling and degradation rate dictated by thiol content.

Table 1 Thiol–acrylate polymers form hydrogels with initial mechanical and degradation properties that are tunable based on the initial thiol content. Here, multiacrylate monomers containing degradable polylactide sequences were copolymerized with trimethylolpropane tris(3-mercaptopropionate). Thiol–acrylate photopolymerizations were complete in less than one minute with 0.1 wt% Irgacure 2959 and 5 mW cm^{-2} UV light, and polymers were formed that were more than 10 cm in thickness (data adapted from ref. 18)

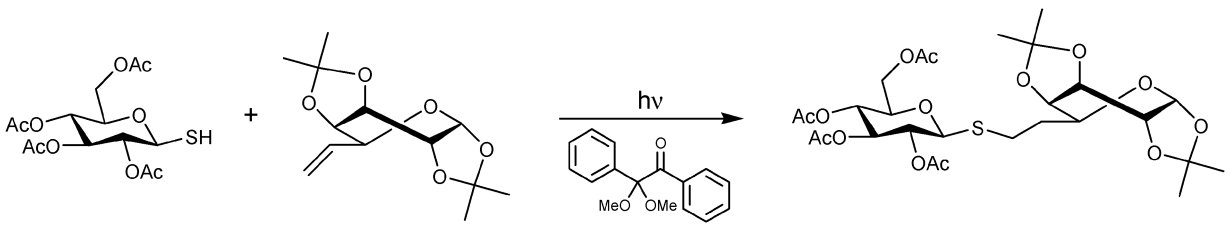
Thiol content/mol%	Time to degrade from 10–90% mass loss/days	Initial compressive modulus/kPa
0	36	3400
5	37	3900
15	31	3400
30	22	3000

While significant interest has recently been focused on the thiol–ene reaction, particularly with the general push to identify and implement click reactions, the reaction itself has been known and studied for quite a long time. Posner[52] was the first to discover the thiol–ene addition reaction in 1905, while Kharasch *et al.*[53] were the first to propose the basic mechanism including reaction steps for the thiol–ene polymerization in 1938. This work transitioned to work by Marvel and Chambers[54] and Morgan *et al.*[55] that was built upon by Jacobine and co-workers and laid the foundation for the more recent work[4,5,56] in thiol–ene reactions and photopolymerizations.

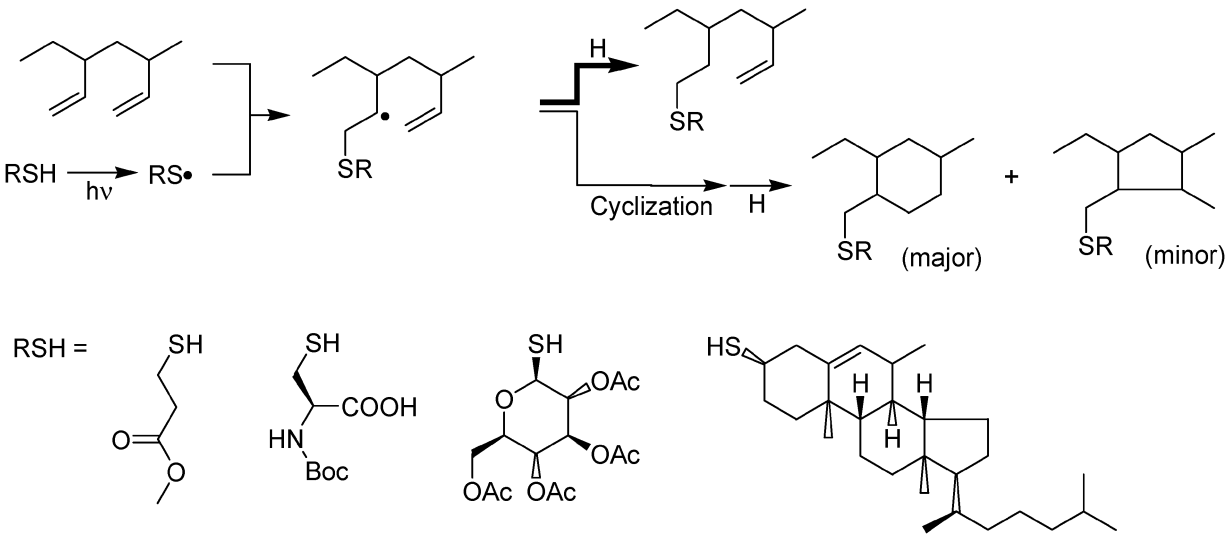
Throughout this time period, a vast array of work has been performed in an effort to understand and implement radical-mediated thiol–ene reactions, primarily focusing on the photo-initiated reactions. This large body of literature is detailed in several review articles[2–7,9–12] wherein a far more detailed explanation and elaboration of the reaction kinetics, mechanisms, and applications is found. Herein, we will attempt to summarize the teachings of that literature with regard to the mechanisms and best practices for performing the radical thiol–ene click reactions, while highlighting a few recent examples of where we believe that radical-mediated thiol–ene chemistry will lead.

As indicated, radical-mediated thiol–ene reactions combine the classical benefits of a very large number of reaction events being catalyzed by the formation of a single radical, *i.e.*, the classical chain reaction process, with the delayed gelation and molecular weight evolution associated with step-growth polymerizations that arise from the *net* addition of a single thiol across a single ene. It is noted that technically thiol–ene addition actively involves the thiyl radical derived from one thiol molecule and the hydrogen of a second thiol. The initiation, coupled chain transfer and propagation, and termination reactions for the radical-mediated process are presented in Scheme 18. As with acrylic, styrenic, and other radical-initiated polymerization and reaction processes, the radical thiol–ene reaction mechanism necessarily encompasses three distinct reaction processes: initiation, the polymerization or coupling reactions, and termination.

In general, the initiation process for the thiol–ene reaction can be simplified such that any appropriate methodology for generating radicals will suffice to initiate the polymerization. Thermal, redox, and photochemical methodologies for



Scheme 19 Photoinitiated coupling of glucosyl thiol with galactose-based ene to generate a sulfide linked disaccharide. Scheme adapted from ref. 64.



Scheme 20 Sunlight initiated reaction of ene groups of 1,2-polybutadiene and several thiol biological components. Scheme adapted from ref. 65.

generating radicals are all appropriate and successful in achieving the desired addition product. In its initial implementation for thiol–ene reactions, photoinitiation was classically performed with the use of benzophenone and other hydrogen abstraction initiators; however, faster, more efficient photoinitiation is achieved with typical Norrish type I cleavage initiators such as dimethoxyphenylacetophenone (for ultraviolet initiation), phosphine oxides (for visible light initiation) and other similar initiators. It is worth noting that some type II initiation systems such as those based on camphorquinone and an amine do not initiate the photopolymerization of thiol–ene polymerizations as efficiently as they initiate conventional (meth)acrylic photopolymerizations. The origin of this interesting observation is still being investigated.

One of the most unique and beneficial aspects of the radical thiol–ene click reaction is its ability to *self-initiate* the polymerization in the presence of ultraviolet light. This "initiatorless" photopolymerization[57] is remarkable, particularly in keeping with the concept of simplicity embodied by the click paradigm—essentially, the monomers themselves act to absorb the light and generate the radicals, eliminating the need for any additional catalyst to be provided and with the small absorption of the monomers being largely eliminated upon polymerization to form an optically transparent material, even at the initiating wavelengths. This initiation methodology has been found to work for nearly all bulk thiol–ene systems. Shorter wavelength ultraviolet light is generally far more effective at initiating a rapid polymerization but can be limited in its ability to penetrate through thicker films depending upon competing absorption reactions whereas the longer wavelength ultraviolet light leads to slower polymerizations but ones that have been carried out to lead to polymers up to 30 cm thick![57]

The use of photoinitiation in thiol–ene polymerizations requires appropriate selections and combinations of light sources and initiating components. While the thiol–ene system is responsive enough to proceed when exposed to low wavelength UV light sources without the addition of photoinitiator, the polymerization is dramatically accelerated when an optimal combination of light source and radical photoinitiator, preferably a type I cleavage initiator, are used. To maximize the thiol–ene reaction rate, one should assure that there is overlap between the emission spectra of the light source and the absorption spectra of the initiator. For optimal reaction the total absorption of the initiating system at the overlapping emission wavelengths should be between 0.1 and 1.0 to assure

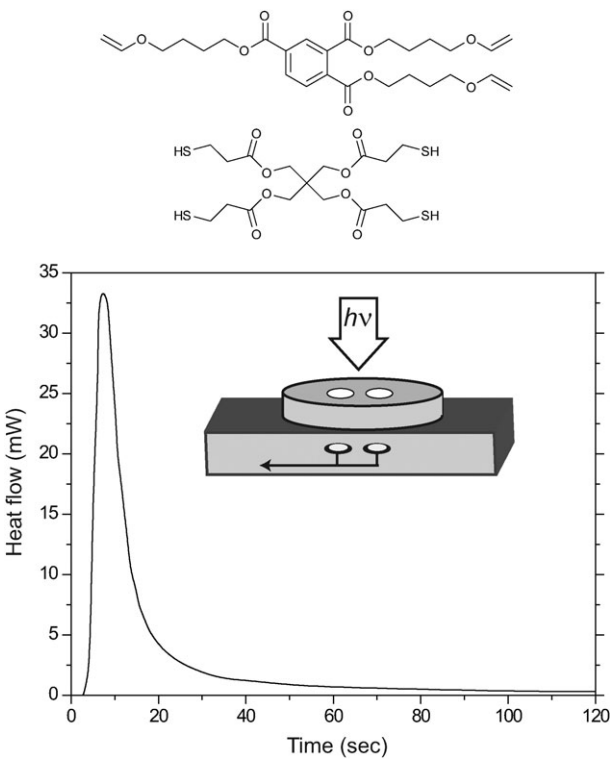
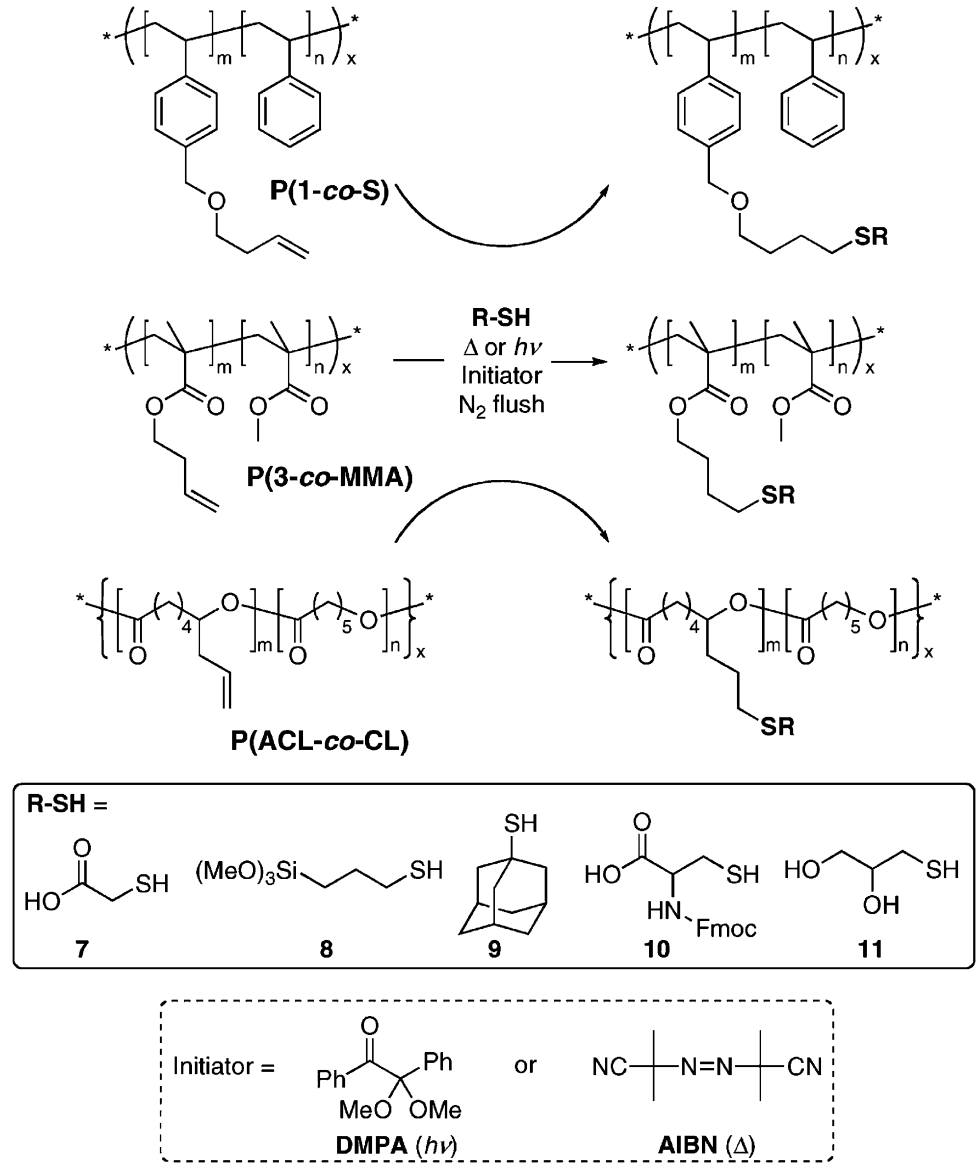


Fig. 8 Photo-DSC of sunlight cure of 1 : 1 molar thiol–ene system (tetrathiol and trivinyl ether structures shown). Photoinitiator 1 wt% 2,2-dimethoxy-2-phenylacetophenone based on total sample weight. The differential scanning calorimeter (DSC) shown in inset allows monitoring of polymerization exotherm upon exposure to sunlight (photo-DSC). Unpublished work.

that there are both sufficient absorbed photons to generate the radicals as well as sufficient penetration of the light to assure reaction throughout the entire thickness of the film. Absorption of less than approximately 0.25 will lead to uniform reaction rates while absorption values beyond that will lead to faster reactions at the incident surface and slower reactions at the opposite side after the light has transversed the reaction medium.

The core of the click methodology embodied by the thiol–ene reaction is encompassed by the alternating propagation and chain transfer cycle that is illustrated in Scheme 18b. The combined propagation and chain transfer reactions, proceeding at exactly equivalent rates in an ideal thiol–ene reaction where no homopolymerization of the ene occurs, lead to the highly efficient formation of a single coupled product in which, in net, one thiol adds across one ene to produce an addition product. The coupled reactions are so rapid and efficient that the cycle will occur up to 100 000 times per radical generated (at very low initiation rates and radical concentrations). Overall rates are at least as fast for thiol–ene systems as for traditional acrylic systems where the acrylic systems are rapid only due to significantly higher radical concentrations associated with diffusion limited termination that is not a factor in thiol–ene polymerizations until very high conversions[56]. For the more common ene functionalities, the relative polymerization rates of the thiol–ene systems are fastest for norbornene and vinyl ether moieties followed by allyl ethers then terminal olefins with internal olefins reacting much more slowly.[5] Similarly, for the thiols, the fastest thiols are typically found to be thiol glycolate or thiol propionate

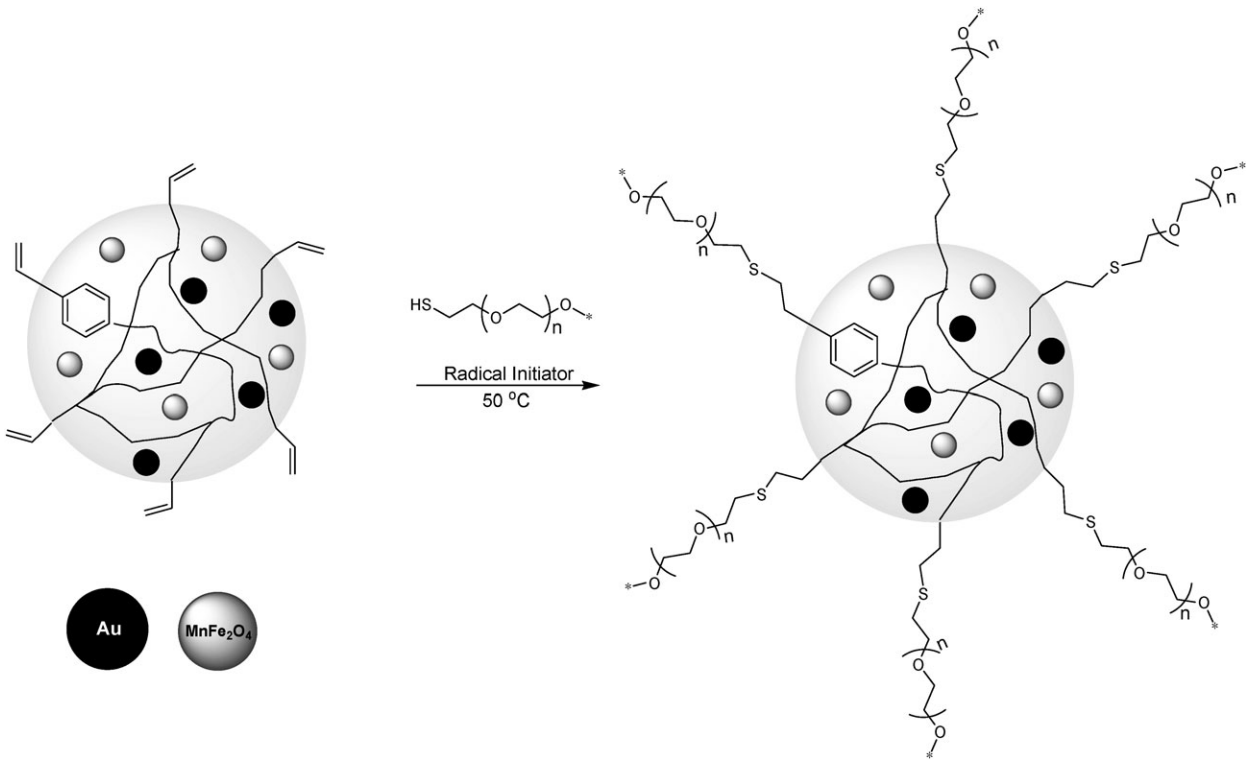


Scheme 21 Approach to thiol–ene polymer modification. Here, Hawker and co-workers developed and evaluated several approaches to side chain polymer functionalization (shown) as well as telechelic and asymmetric end group functionalization (not shown) including the ability to modify schemes for functionalizing polymer sequentially through Huisgen and thiol–ene click reactions, demonstrating the orthogonality of the two approaches. Scheme adapted from ref. 66.

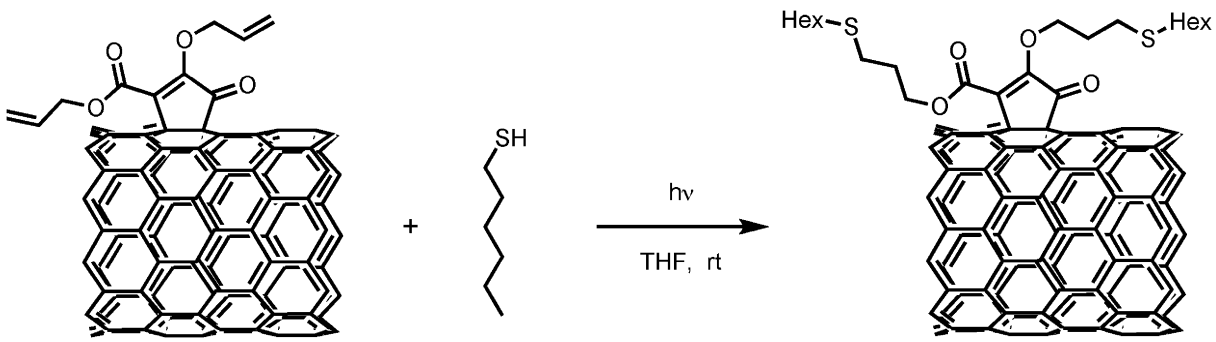
based.[5] The termination reaction in thiol–ene polymerizations occurs through bimolecular reactions between two radicals, although little study has been done to elucidate the details of the termination reaction.

The step-growth nature of the molecular weight evolution in thiol–ene photopolymerizations has dramatic benefits with regard to the material properties that are achievable. First, the crosslinked networks formed as a result of these polymerization reactions are homogeneous and uniform to an extent not achievable by any other type of photopolymerization reaction. The network homogeneity has most traditionally been observed as a narrowing of the loss tangent peak as measured *via* dynamic mechanical analysis. For thiol–ene polymers as compared with polyacrylate networks, the half-width of the tan δ peak is reduced from widths that can be more than 100 °C for acrylic polymers to as little as 10–15 °C for thiol–ene polymers. This dramatic difference in network heterogeneity is illustrated in Fig. 5 where the transition behavior of a conventional methacrylate network and a thiol–ene network are compared.[58] One benefit of this homogeneity is a dramatically increased capacity for mechanical energy absorption in these materials when they are maintained near their glass transition temperatures.[59] The relative ease of controlling the glass transition temperature of these polymers through composition and functionality where higher glass transition temperatures are achieved with higher functionality monomers enables one to tune the temperature at which optimal mechanical energy absorption occurs.

Further, the step-growth nature of the molecular weight evolution also has practical implications on the structural evolution in thiol–ene networks where the gel point conversion is now significantly delayed relative to acrylic polymers.



Scheme 22 Grafting of PEG-terminated thiol onto poly(divinylbenzene)–Au–$MnFe_2O_4$ nanoparticles *via* thiol–ene radical coupling induced by 2,2′-azobis(2-amindinopropane) hydrochloride. Scheme adapted from ref. 67.



Scheme 23 Photolyzed functionalization of a modified single wall carbon nanotube *via* thiol–ene click reaction. Scheme adapted from ref. 68.

Whereas the theoretical gel points in multiacrylate monomer polymerizations are theoretically below 1% conversion and practically less than 5–10% conversion, gel points in thiol–ene polymerizations may occur from 50–80% conversion depending upon the component functionalities. The delay in the formation of a permanent network structure enables the polymerizing system to continue to flow for an extended period of the polymerization, accommodating the shrinkage that is occurring as a result of the polymerization. Ultimately, this behavior results in polymer networks with significantly reduced shrinkage stress as compared to their (meth)acrylic counterparts, making them suitable for an array of coatings and dental materials applications.[58]

As a means for further reducing the stress during polymerization and creating a ''covalent, adaptable network'' that is able to change shape in response to applied stresses and strains, techniques were developed for incorporating allyl sulfides into the thiol–ene networks where the allyl-functional groups reacted with the thiyl radicals present during or after polymerization to induce an addition–fragmentation process.[60,61] The addition–fragmentation process, which is inducible by radical generation was shown to enable stress relaxation, creep recovery, and photoinduced actuation in thiol–ene networks.

One additional advantage of the thiol–ene reaction is its ability to overcome oxygen inhibition and thus be performed in a broader range of atmospheric conditions than conventional radical photopolymerization reactions. Fig. 6 presents the mechanism by which thiol–ene polymerizations are able to overcome oxygen, wherein the peroxy radical abstracts a hydrogen from a thiol to regenerate a thiyl radical which reinitiates polymerization, as well as results demonstrating the very limited reduction in polymerization rate that occurs when thiol–ene polymerizations are performed in the presence of oxygen.[4,5,7,9] The ability to overcome oxygen inhibition is not limited to polymerizations but is also achieved in molecular synthesis and polymer modification reactions that utilize the radical thiol–ene process.

Because of the nature of the radical thiol–ene reaction and the characteristic that each ene group that participates in the reaction forms only a single bond with another thiol in contrast to conventional acrylic photopolymerizations in which each acrylate ends up coupled to two other acrylates, the crosslinking density of ideal thiol–ene systems is limited. While methods have been developed to produce high glass transition temperature polymers from ideal thiol–ene reactions,[62] the synergistic combination of thiol–ene and conventional acrylic photopolymerization reactions has proven to be beneficial in numerous ways. Thiol–acrylate, thiol–methacrylate and thiol–ene–(meth)acrylate systems[7] have all been explored with regard to their kinetics and material properties. The presence of the thiol in each of these reaction systems has been shown to enable initiatorless polymerizations and overcome oxygen inhibition while also leading to the formation of a more uniform polymer network and reducing the stress that arises during the polymerization.[7] One example of a thiol–acrylate polymerization is presented in Fig. 7 where the advantages of radical thiol–ene click reactions

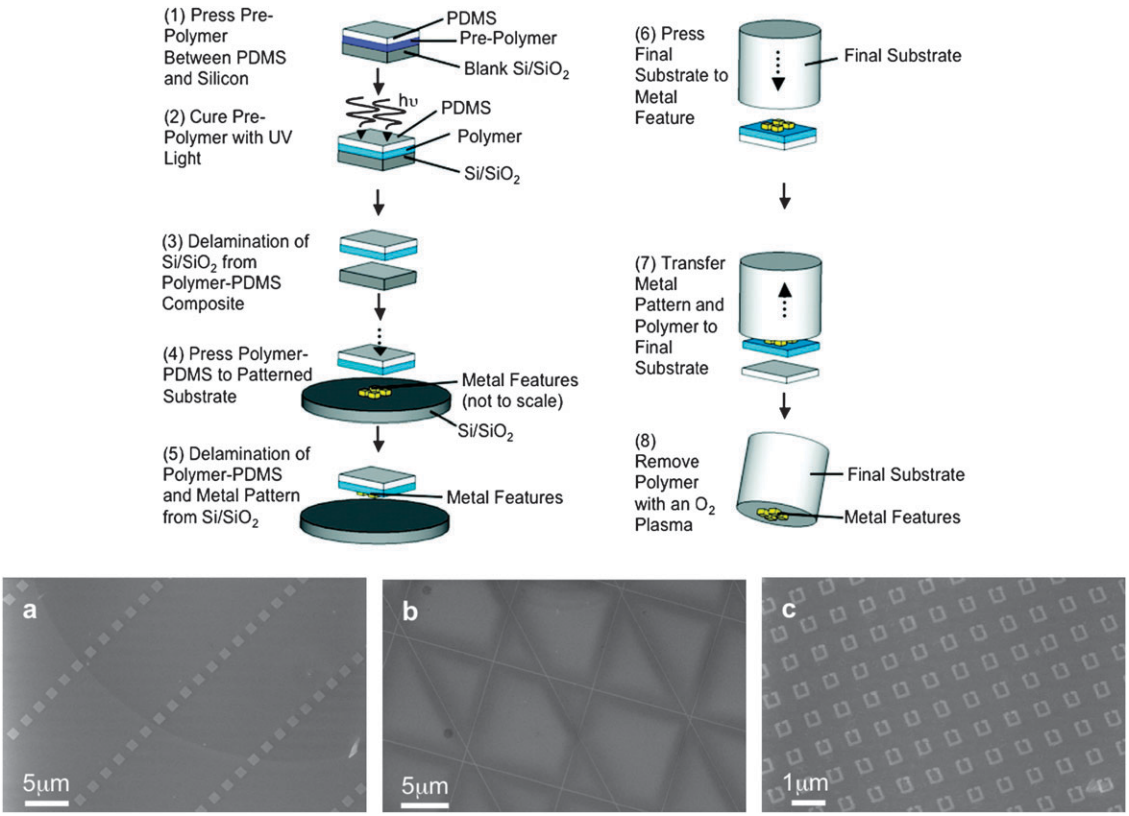
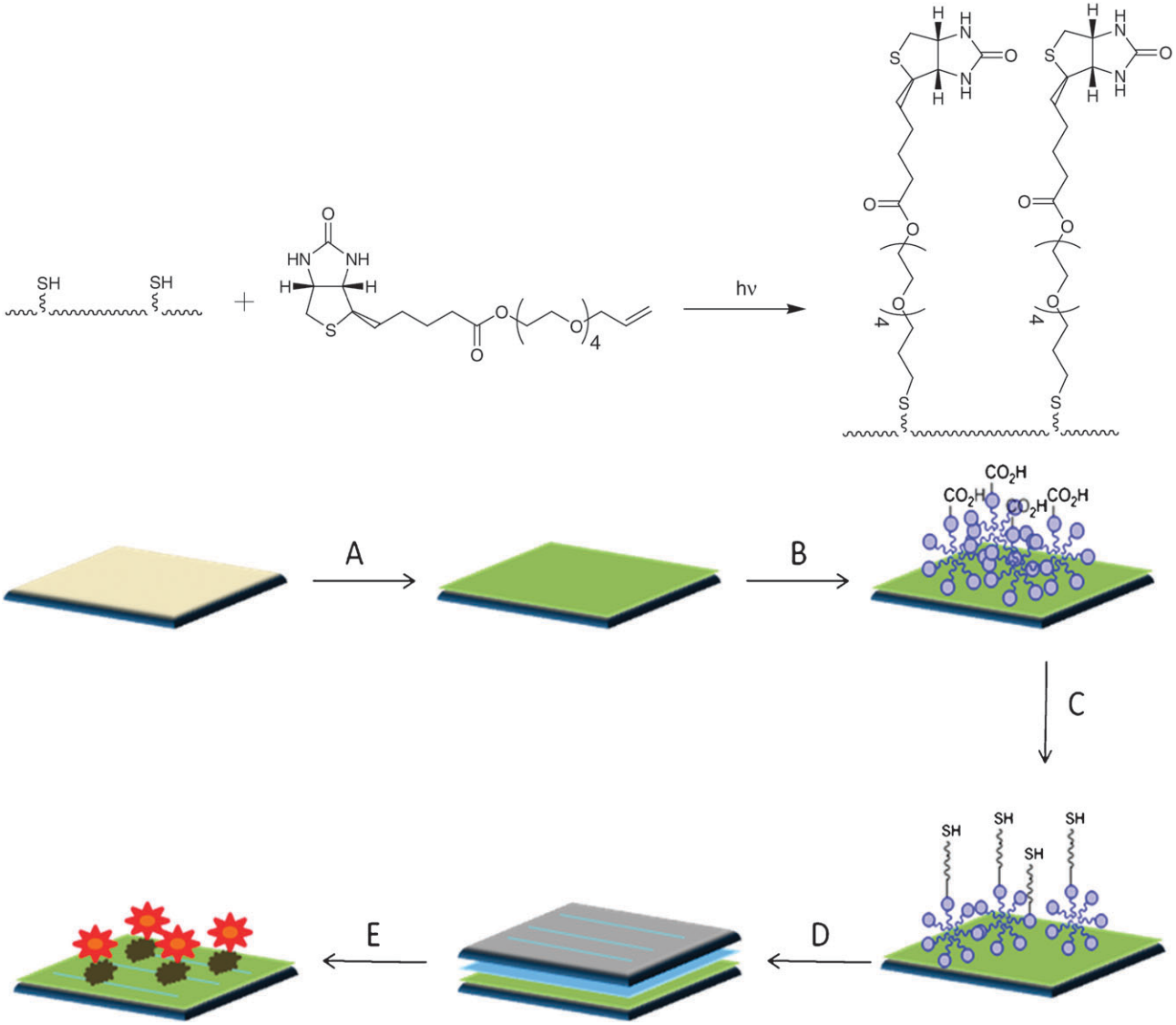


Fig. 9 General procedure employed for transferring metallic nanostructures. SEM of three different types of gold patterns (a, b and c) transferred to optical fiber facets *via* the transfer procedure. Figure is reproduced with permission from ref. 69.

are extended to hydrogels through implementation of a thiol–acrylate photopolymerization.[63] Here, a thiol–acrylate hydrogel is formed where the properties of the hydrogel, including its initial swelling and its degradation rate, are controlled by the thiol concentration in the initial reaction mixture. Increasing thiol concentration reduces the crosslinking density of the material, promoting a higher initial degree of swelling and simultaneously increasing the degradation rate of the material as seen in Table 1.

Due to the simplicity and click nature of the reaction as well as the unprecedented uniformity of the photocured thiol–ene polymers and the insensitivity of the curing process to oxygen, it is possible to obtain materials cured in air, patterned by light, and with ultimate properties ranging from elastomeric materials with low modulus to hard materials capable of sustaining high impact without cracking or fracture.[4,5,7] With the additional capacity of thiols to cure readily with essentially any terminal ene moiety, the resultant choice of comonomers provides the possibility to tune the final physical, thermal, and chemical properties of these finished materials over a range appropriate for an almost infinite array of applications. There is no question that these advantages afforded by thiol–ene curing and the unprecedented physical/mechanical properties of photocured thiol–enes have opened up potential for expansion into new areas in the materials, optics/electronics, and biological/biomedical arenas that include holographic and non-holographic polymer dispersed liquid crystals, nanolithography, nanoparticle functionalization, rapid frontal polymerization, low stress networks, hydrogels, high T_g and hybrid networks, dendrimer and hyperbranched structures, surface modification, microfluidic devices, plasmonic sensors, high mechanical energy absorbing networks,



Scheme 24 (A) Activation of surface by plasma vapor deposition involving silanization; (B) deposition of amino acid linker *via* dendrimers; (C) thiol functionalization of surface; (D) cast and cover ene-functionalized biotin derivative with photomask; (E) photolyze, remove mask, and react patterned biotin derivative with fluorescent labeled streptavidin to generate patterned surface that could be imaged using confocal fluorescence microscopy. The basic thiol–ene reaction in step E involving attachment of the biotin derivative is expanded at the top of the scheme. Scheme adapted from ref. 70.

patterning, dielectric layering, optical lenses and gratings, beam steering devices, step-and-flash imprinting, biomaterials, and bioorganic reaction functionalization. Applications in these areas have been reviewed extensively elsewhere.[5,7,9–12] Herein, for the purposes of illustration we touch on only a few of the recent implementations that portend the future possibilities for radical thiol–ene reactions. These illustrative applications range from small molecule coupling synthesis[64] and functionalization of linear polymers[65,66] and polymer nanocomposites[67] to modification of single wall carbon nanotubes,[68] nanoscale patterning of structural reliefs on non-planar silicon oxide surfaces,[69] surface patterning of thiol-functionalized silicon oxide surfaces by mono-ene-functionalized biomolecules,[70] and a photoinitiated polymerization for patterning of a dithiol–divinyl ether thiol–ene polymerization initiated by thiyl radicals on the surface.[71,72] The final three methods[70–72] can be used creatively in a range of interesting and novel applications that benefit from the high reactivity of the thiol functionality.

Fiore *et al.*[64] exposed a simple mixture of a glucosyl thiol and a galactose-based ene in both protic and non-protic solvents to produce a sulfide linked disaccharide thiol–ene coupled product (Scheme 19). The product was obtained in high yield even under ambient conditions in air. In fact the reaction readily proceeded even upon exposure to unfocused sunlight indicating the tremendous latitude that is afforded by the very rapid and efficient thiol–ene radical reaction sequence. This work is particularly important since it highlights the ability of thiol–ene reactions to proceed even under very mild, ambient processing conditions, opening up the way for future trends of performing efficient thiol–ene click reactions using solar radiation. Yet another example of using sunlight to effect a thiol–ene coupling reaction under mild conditions (Scheme 20) in benign solvents between thiolated biologically active amino acid, sugar and cholesteryl groups and 1,2-polybutadiene was demonstrated by Schlaad's laboratory.[65] The biohybrid polymers produced in short exposure times estimated to have reaction half-lives of one hour or so in sunlight were conducted without photoinitiator. This work, the culmination of a large number of publications dealing with polymer thiol–ene click light induced polymer-functionalization reactions listed in ref. 7 from Schlaad's, along with the work from Dondoni's laboratory,[64] reiterate the fast reaction times that are readily achieved under ambient conditions for either small molecule coupling reactions[64] or polymer modification/functionalization.[65] As a final example of sunlight induced thiol–ene reactions, Fig. 8 shows a reaction exotherm that is complete on the order of seconds for the thiol–ene polymerization of the 1 : 1 functional group mixture of tetrathiol and trivinyl ether monomers with no solvent present. The final cured network film was tack-free in a few seconds upon exposure to sunlight illustrating the unprecedented efficiency of the thiol–ene polymerization reaction. These three examples (Schemes 19, 20 and Fig. 8), which range from biomolecular coupling of small molecules to reactive biofunctionalization of linear hydrophobic polymers to curing of network films with unprecedented uniformity, demonstrate both the efficiency of thiol–ene reactions and their adaptability to being effected under benign conditions with the expenditure of minor amounts of energy, *i.e.*, thiol–ene reactions are perfect candidates for solar radiation processing.

Next, in another example of polymer thiol–ene functionalization (see ref. 4, 7, 9–12 for other polymer-functionalization examples), Hawker and co-workers[66] made a clear and concise comparison of various radical generation methodologies and examined a number of different motifs to define the conditions required for polymer functionalization by thiol–ene reactions. Scheme 21 presents a summary of their approach where they successfully demonstrated that both side chain and terminal alkene-functional groups can be readily reacted with thiols.

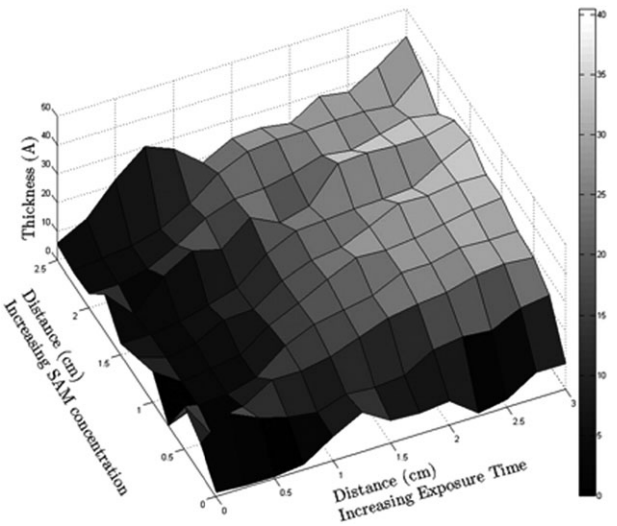
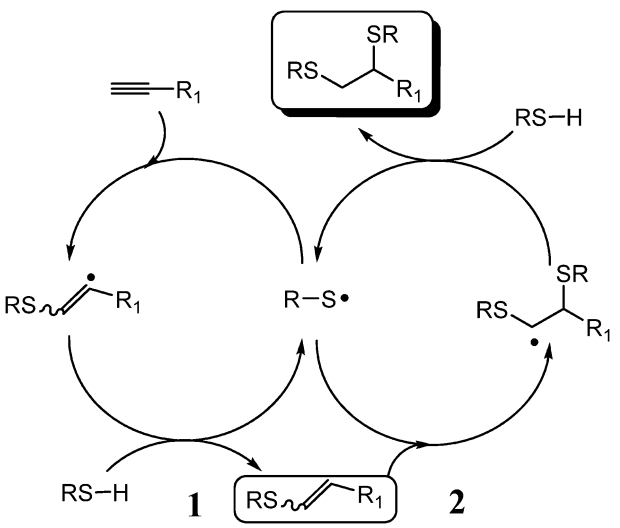


Fig. 10 The formation of a two-dimensional gradient of grafted thiol–ene polymer thickness. The two gradients are established by creating gradients in surface thiol density and light intensity orthogonal to each other where the ultimate film thickness then depends on the orthogonal chain density and molecular weight gradients. A stoichiometric mixture of hexane dithiol and divinyl ether were initiated with 0.1 wt% initiator and 365 nm UV light with at an intensity of 60 mW cm^{-2}. The maximum thickness is 40 Å. Figure is reproduced with permission from ref. 72.

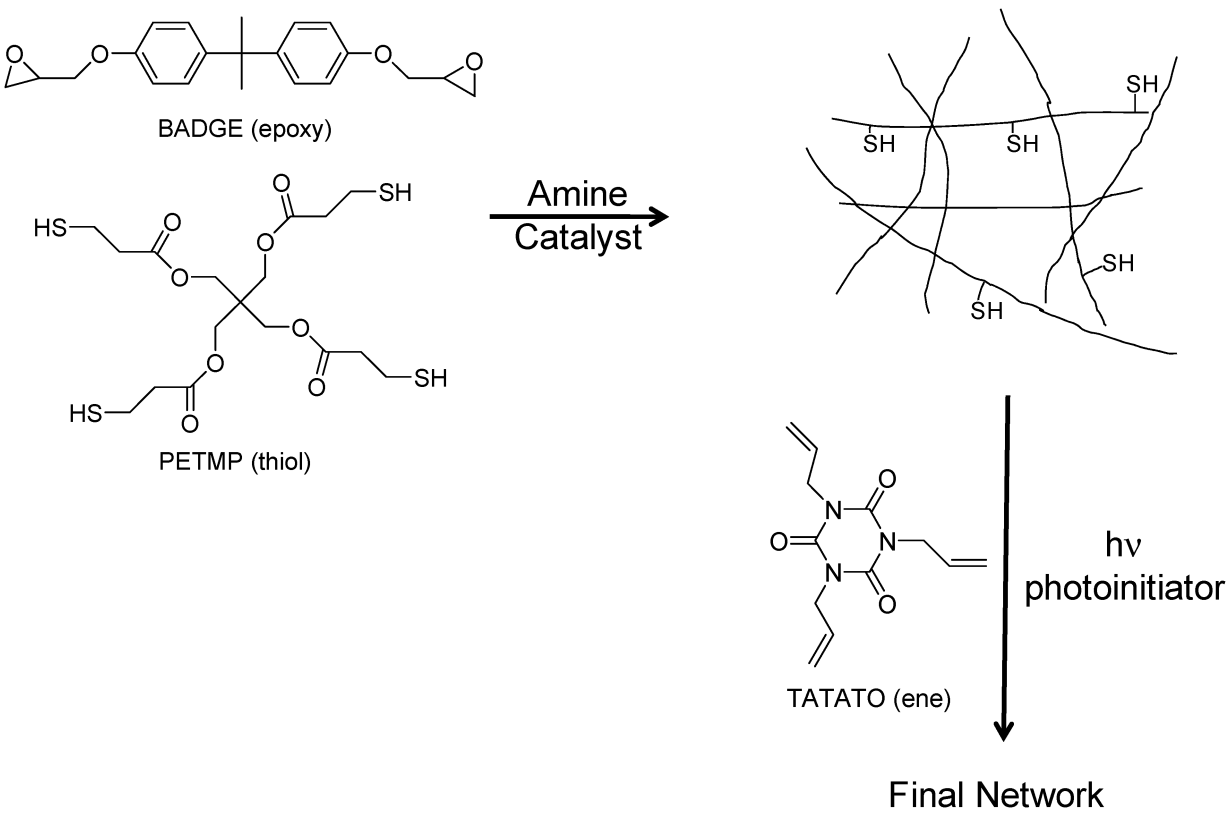


Scheme 25 Proposed mechanism for the double hydrothiolation reaction, under radical conditions, of terminal alkynes.

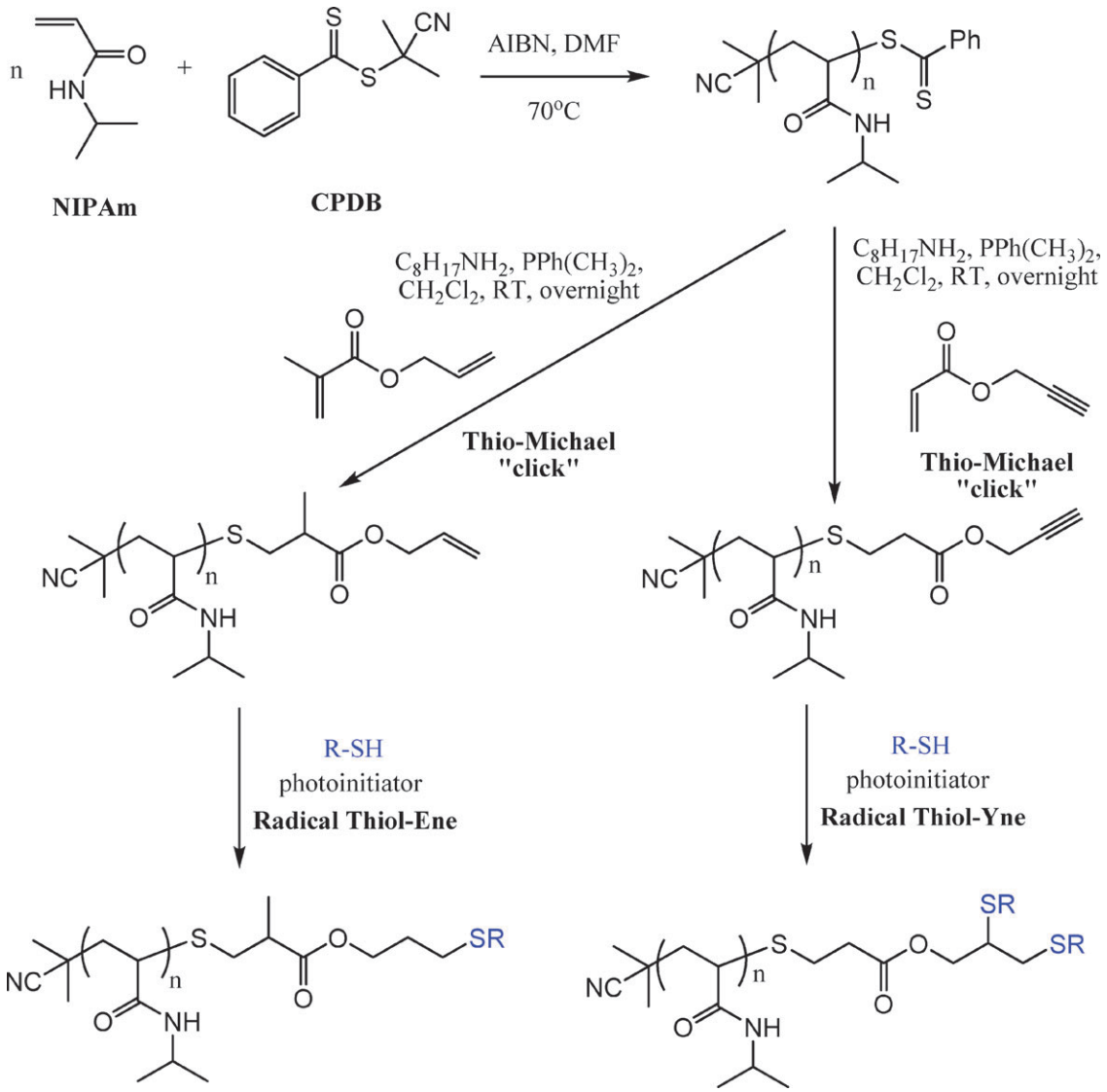
They found that both photochemical and thermally initiated thiol–ene reactions were orthogonal to the presence of azides on the polymer, enabling sequential thiol–ene and Huisgen click reactions. Hawker's group[67] extended the thiol–ene grafting in Scheme 21 applied to linear polymers to magnetic organic–inorganic nanoparticles comprised of polydivinylbenzene and a mixture of gold and $MnFe_2O_4$. The thermally induced grafting of thiol-terminated polyethyleneglycol to the nanoparticles as shown in Scheme 22 resulted in nanoparticles that were easily dispersed with significant reduction in aggregation.

While the road for polymer functionalization has been well established by Schlaad, Hawker, Parent, and others[7,9–12] there are also numerous examples of using thiols to functionalize nanoparticles.[7,9] The recent example[68] shown in Scheme 23 is essentially a cousin of the polymer-functionalization processes in that one can take a structured single walled carbon nanotube (SWCNT) with side group allylic ene groups, which might be envisioned somewhat as an oligomeric aromatic structure with pendant ene groups, and functionalize it with thiols using a photoinitiated thiol–ene radical reaction process at very low temperatures. The potential for extensive functionalization of SWCNTs and related species such as fullerenes with a wide range of thiol-functional species including silicates (*i.e.* POSS), long chain hydrocarbons, perfluorinated chains, acids, esters, and alcohols as well as biointeractive components such as sugars, amino acids, and cholesterol. Essentially any thiol-functionalized chemical species, of which there are a large number currently available or readily synthesized, can be used to carry out the functionalization process.

As detailed elsewhere,[7] the radical-mediated thiol–ene reaction has been used extensively for patterning with a variety of lithographic and stamping methodologies. A particularly informative adaptation of this technology was recently used for metal nanoscale patterning of small non-planar surface structures.[69] As shown in Fig. 9, a thin photopolymerized thiol–ene network was created from a thiol–ene mixture with an excess thiol : ene molar functional group ratio. The excess thiol groups in the flexible 200 nm film readily picked up and transferred gold particles from a silicon surface to non-planar optical fiber facets. Scanning electron micrographs of three gold pattern types that were successfully transferred to the optical fiber substrates were obtained. The transfer method was reputed to give high spatial resolution that could be readily adapted to a large range of patterns. This latest work in patterning complements a large body of literature[5,7] that details the extensive use of thiol–ene networks as media for patterning including use in nano-stamping, step-and-flash lithography, surface patterning, and a wide range of related nano-patterning techniques. Following the use of thiol-functional surfaces as an ideal medium for materials applications, Waldmann *et al.*[70] conducted the simple coupling of silicon surface bound thiols with simple (Scheme 24) hydrophobic alkenes and demonstrated that hydrophobic surfaces are effectively patterned on a microscopic or nanoscopic scale. This demonstration of how chemical patterning of surfaces is readily achieved points out a core of tremendous opportunity for using enes with a wide range of attached chemical species. One can envision patterning with ene-functionalized chemical structures that can impart hydrophilicity, fluorescence,



Scheme 26 Sequential thiol–ene/thiol–epoxy reactions.



Scheme 27 Sequential thiol–ene/thiol–ene and thiol–ene/thiol–yne functionalization of thiol end capped poly(*N*-isopropylacrylamide).

bioactivity, bio and chemical sensors, metal scavengers, and other activities with precision spatial control.

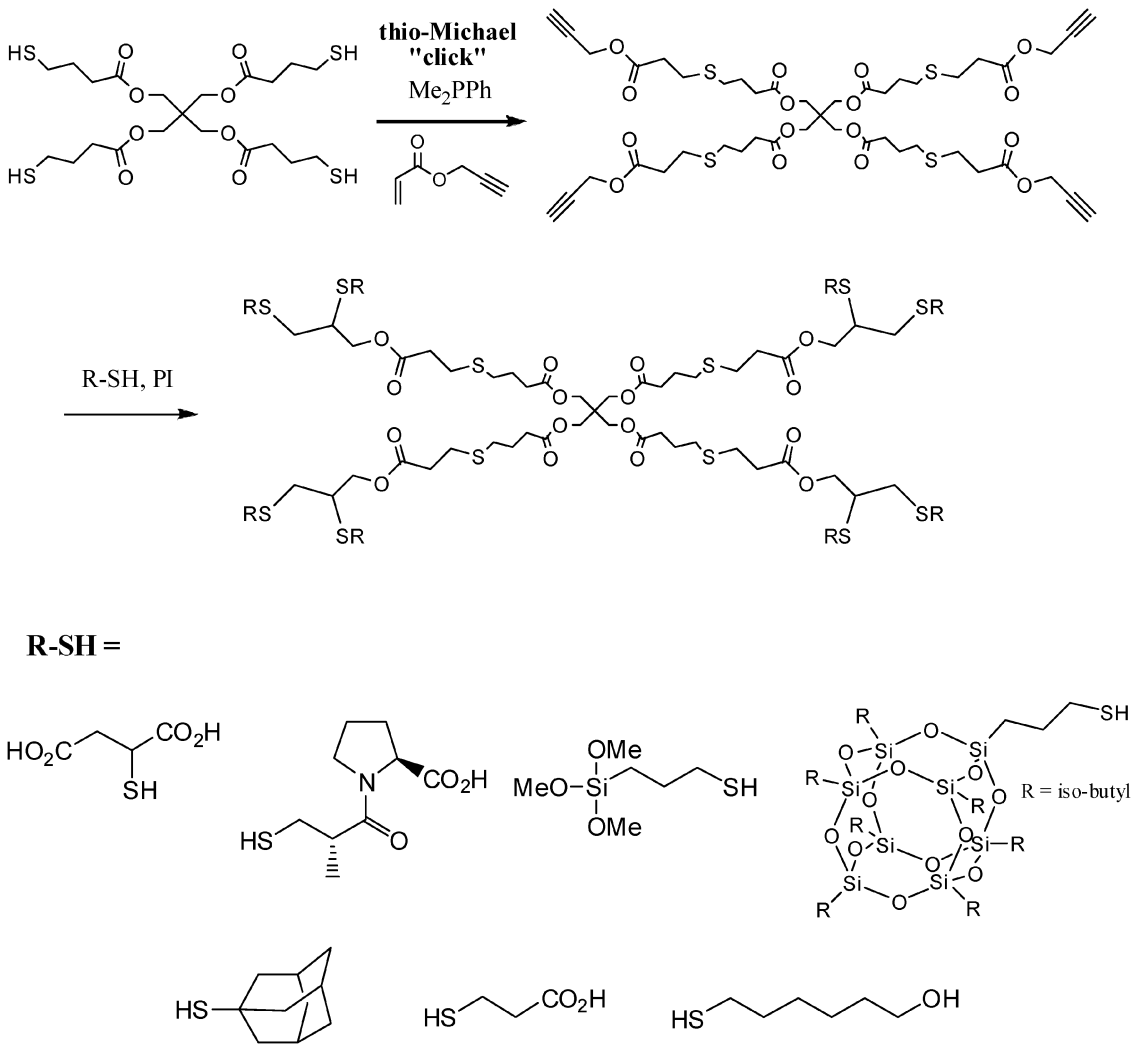
One of the clear advantages of the photoinitiated thiol–ene radical process is the ability to control spatially where the thiol–ene reactions, either simple coupling reactions or radical polymerization, occur. In the case of polymerization, the light exposure time and intensity control the extent of polymerization and hence define the characteristics of the thiol–ene reaction for surface grafting and modification.[71,72] As shown in Fig. 10, Khire *et al.*[72] have recently exploited this advantage to create substrates exposed to gradients of thiols on the surface and/or gradients in light intensity to create patterned surfaces. Here, they used this technique to create orthogonal gradients in polymer molecular weight (by changing the light intensity) and in polymer grafting density (by changing the initial thiol density). Similar surfaces were also modified with a cell-adhesive peptide in a gradient manner and the variation in cell density in response to this gradient was then observed. This work demonstrates the clear value of the thiol–ene reaction in surface modification, biomaterials applications, and creation of materials with gradient or patterned chemical, physical and biological properties. The self-limiting nature of the step-growth thiol–ene polymerization was also exploited by surface grafting a dithiol–diene graft with varying initial stoichiometric ratios of thiol : ene.[71] Here, the ideal step-growth nature of the molecular weight evolution combined with the high yield guaranteed by the click nature of the reaction enabled the graft polymer molecular weight, as correlated directly to the graft-film thickness, to be readily manipulated simply through changes in the initial stoichiometry. Further, the functional groups originally in excess remain as the terminal units of the graft polymer chains, enabling further derivatization to readily occur.

3.2 Thiol–yne radical click reactions

A complementary reaction to the thiol–ene radical reaction described above is the thiol–alkyne (thiol–yne) radical reaction. While thiol addition to ynes has been known for over half a century[8] and originally noted for its high yields and ease of

execution, it is a reaction that has been essentially overlooked in recent years, especially in the synthetic materials and polymer arenas. An important and distinguishing feature of the thiol–yne reaction compared to the thiol–ene reaction is the ability for an yne-bond to react with two equivalents of thiol, *i.e.* form a double addition product with 1,2-regioselectivity. However, mechanistically, the two thiol addition reaction steps each proceed in a similar manner to the radical thiol–ene reaction (Scheme 25).

A thiyl radical is generated from a parent thiol either thermally or photochemically, with an added photoinitiator, and undergoes direct addition to the yne-bond yielding the reactive, intermediate, thioether–vinyl radical that undergoes chain transfer with additional thiol to yield the intermediate vinylthioether as shown in Scheme 25 (part 1).[73] The vinylthioether subsequently undergoes a second thiyl radical addition (formally a thiol–ene reaction) to yield the intermediate carbon-centered radical that undergoes a second chain transfer reaction with thiol yielding the double addition, thiol–yne, product (Scheme 25, part 2) with regeneration of a thiyl radical that reenters the chain process. In a detailed real-time infrared kinetic analysis, Fairbanks *et al.*[73] showed that the subsequent thiol–ene reaction was approximately three times faster, *i.e.*, a rate constant 3× greater than the initial thiol–yne reaction. Aside from the mechanistic similarities to the thiol–ene reaction, from a practical standpoint it also possesses all the benefits associated with the radical thiol–ene reaction and as such should be considered an important addition to the thiol-based click reaction toolbox. While barely examined in polymer/materials synthesis, several applications of this important reaction have been reported in the preparation of high density films/networks,[73] as a means of preparing tunable high refractive index films,[74] as a tool in biomaterials synthesis,[8] and importantly in two demonstrations of tandem thiol–ene/thiol–yne reactions as a means of preparing highly branched thioethers[75] and as a tool for preparing double-ω-functional polymers initially prepared by RAFT.[76] The full potential of the radical thiol–yne click reaction has yet to be realized, but it represents an interesting, and complementary, process to both the thiol–ene and alkyne–azide reactions.

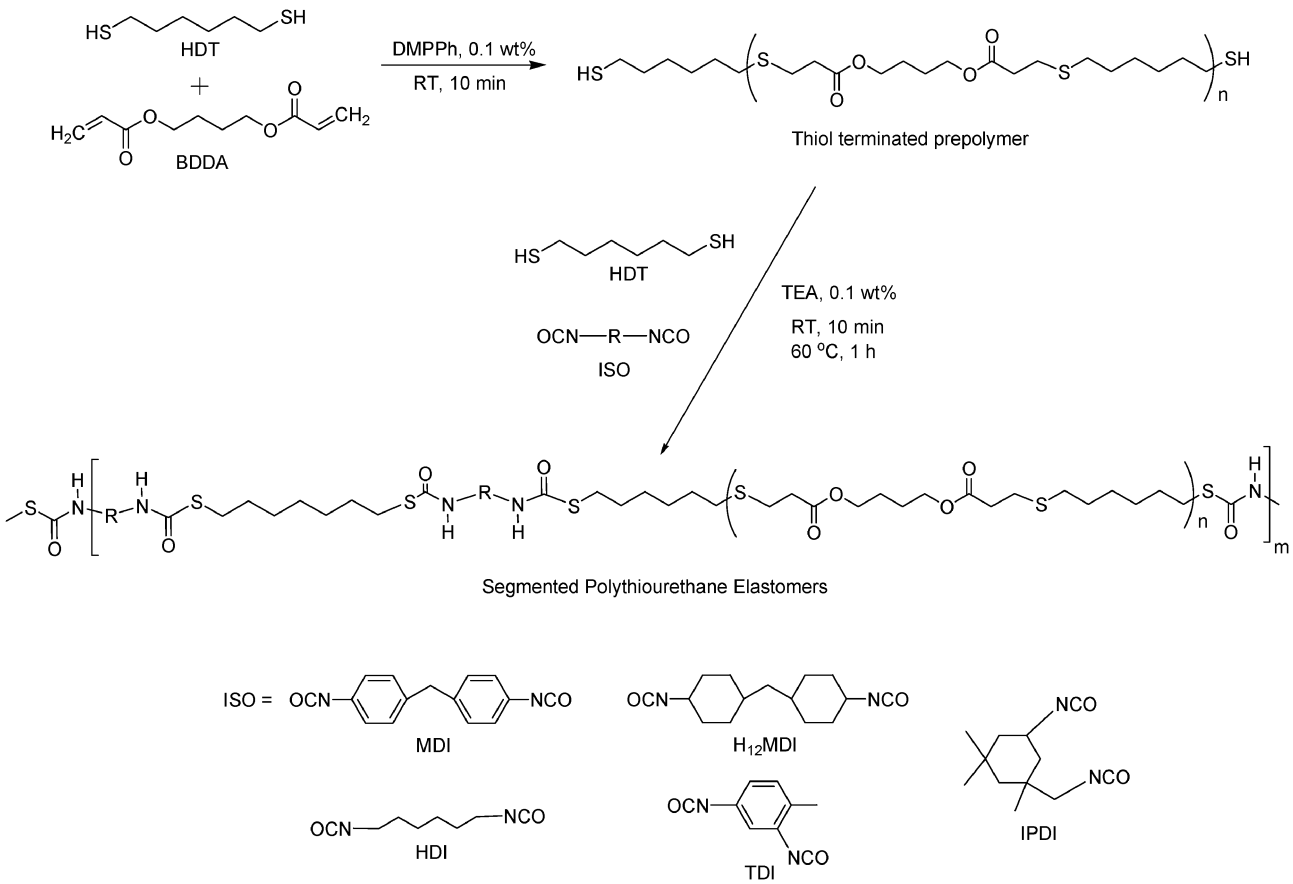


Scheme 28 Phosphine catalyzed thiol-Michael addition of tetrathiol with propargyl acrylate followed by functionalization *via* thiol–yne photochemically mediated reaction.

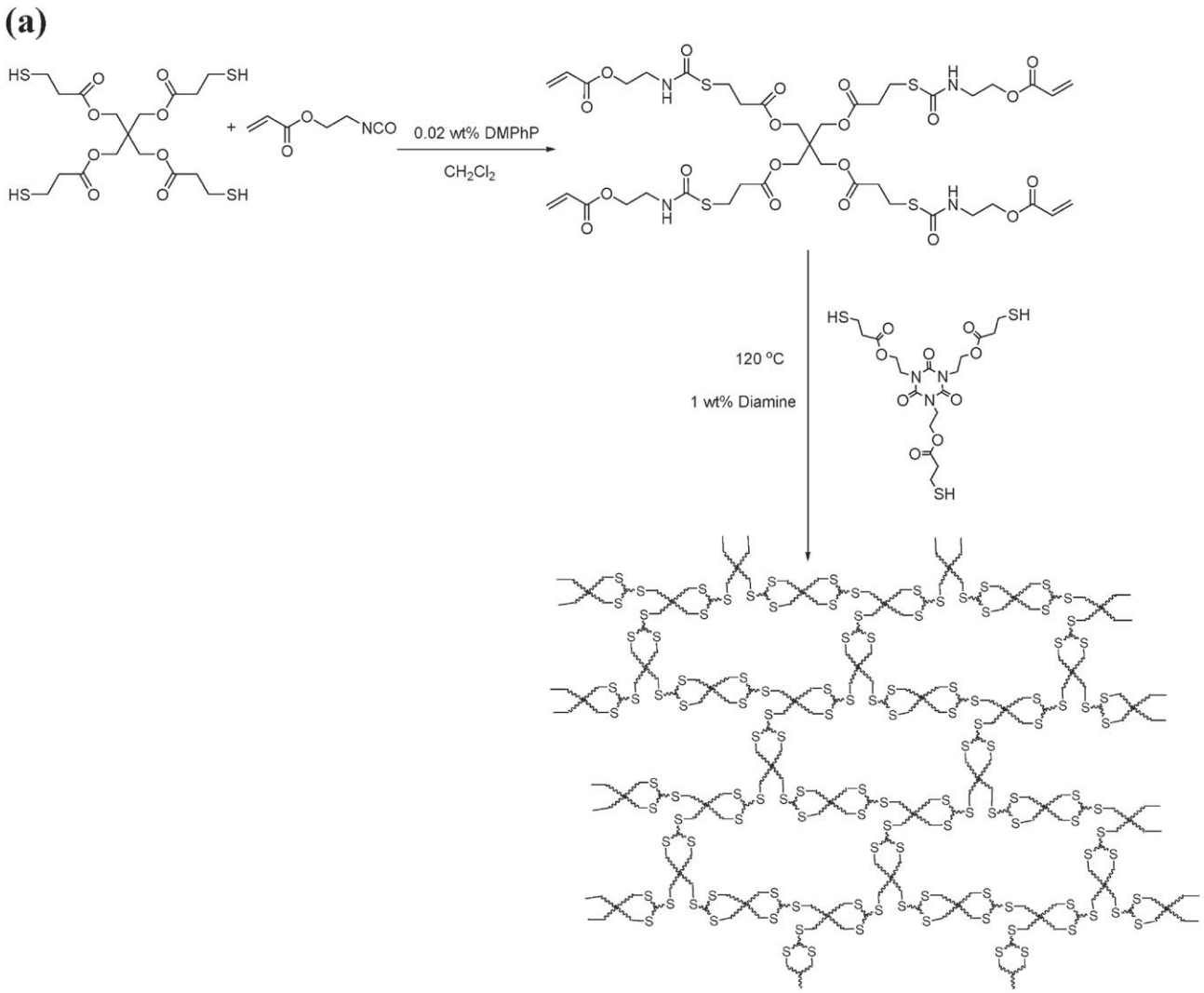
4. Sequential thiol-click reactions

As we have already pointed out, one ultimate goal of click chemistry is the potential of combining multiple click reactions, either performed simultaneously or in tandem, to synthesize complex structures and materials. In recognition of this task, several recent examples of sequential processes involving two thiol reactions of a thiol, or even more interestingly, thiol-click and alkyne–azide click reactions are considered. It is stressed that the reaction sequences highlighted in this section proceed to high conversions, in many cases with quantitative yields, in the presence of air and water. The first dual click sequence considers a combination thiol–ene radical reaction followed by an amine catalyzed thiol–epoxide reaction. Carioscia *et al*. demonstrated that the thiol–ene reaction can be made to proceed prior to the thiol–epoxy reaction or *vice versa* (Scheme 26), depending upon the time delay between adding the amine catalyst for the thiol–epoxy reaction and the light exposure.[15] The thiol–ene(radical)/thiol–epoxy hybrid polymerization processes produce exceptionally high strength materials without the problems typically associated with shrinkage and stress that accompanies the synthesis of other high performance thermoset materials. These materials are particularly important since they possess the distinctive qualities that one expects from materials that are used in the most mechanically demanding applications, such as associated with dental restoratives. As shown in Scheme 27, other sequential thiol-Michael/thiol–yne(radical) or thiol-Michael/thiol–ene(radical) processes have been used to functionalize polymer chain ends, taking advantage of the double addition of thiols to the yne chain ends created by pre-reaction of thiol-functionalized water soluble polymers with propargyl acrylate.[45] Using the same thiol-Michael/thiol–ene(radical) combination in Scheme 27, it was also possible to synthesize the array of multifunctional (either 8 or 16) thioethers shown in Scheme 28.[44] In a slightly different approach, it has been shown that it is possible to synthesize linear thermoplastic urethane type polymers with structures virtually unattainable by other methodologies. A phosphine catalyzed thiol-Michael addition between a dithiol and a diacrylate to form a thiol-terminated linear oligomer followed by a subsequent trialkyl amine catalyzed reaction of the dithiol oligomer with a series of diisocyanates resulted in the first facile and click synthesis of a highly elastic segmented polythiourethane in essentially quantitative yields (Scheme 29).[77] The thiol–ene(radical)/thiol–epoxy,[15] the thiol–ene(radical)/thiol–yne(radical),[45] the thiol-Michael/thiol–yne(radical),[44] and the thiol-Michael/thiol–isocyanate[73] reactions are presented as examples of how thiol-click chemistries can be combined for materials synthesis not easily achieved by other means, and can be used as a guideline for future extensions of thiol-click chemistry.

Two other sequential click reactions are unique in that they involve dual reactive centers on the same monomer unit with

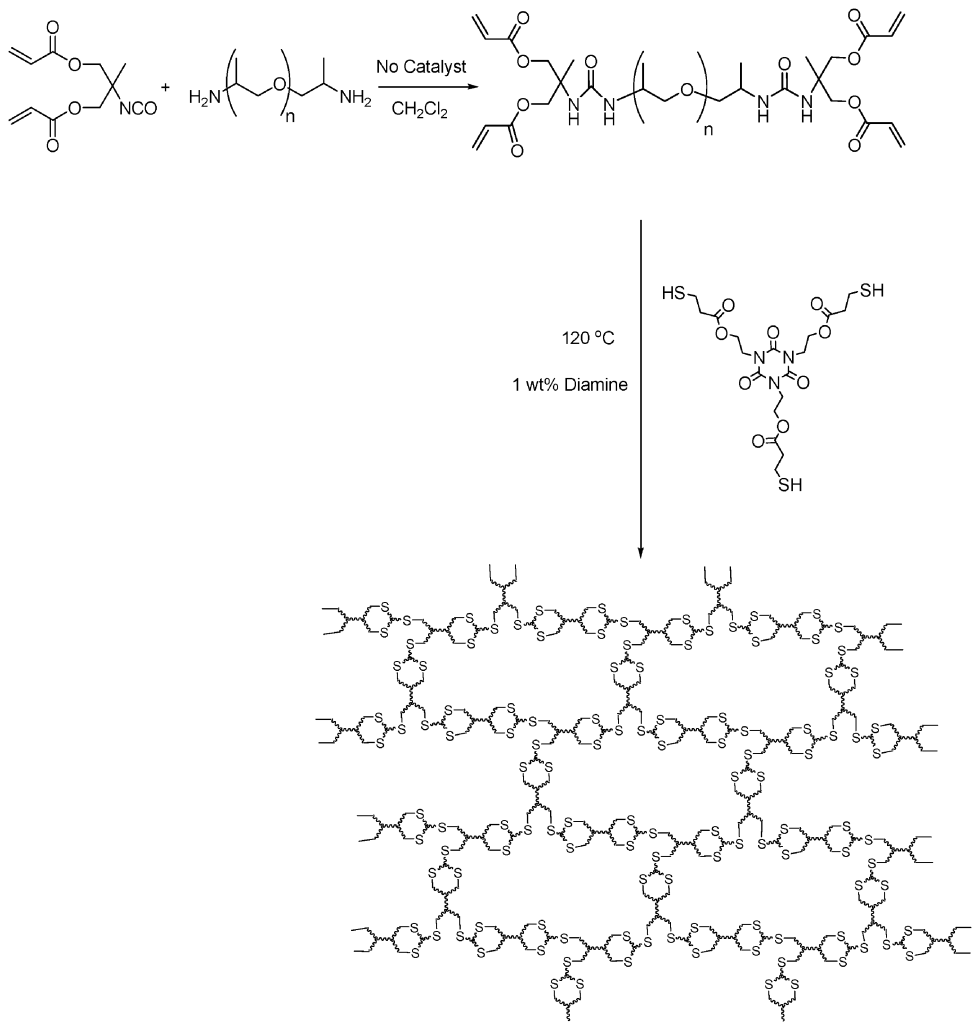


Scheme 29 Synthesis of segmented polythiourethanes by sequential thiol–ene and thiol–isocyanate click reactions. Unpublished work.



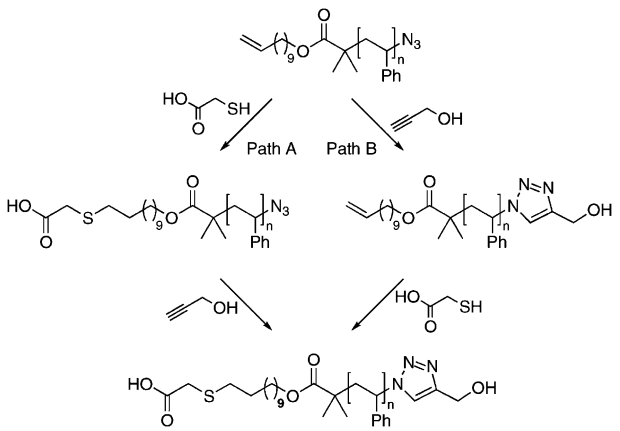
Scheme 30 (a) Sequential phosphine catalyzed thiol–isocyanate and amine catalyzed thiol–acrylate Michael addition reactions for generating ultra uniform crosslinked networks with high refractive index. (b) Real-time IR kinetic plot showing selective thiol–isocyanate conversion for reaction of tetrathiol with isocyanate-functionalized acrylate monomer. Note that the thiol-Michael addition was conducted at 120 °C to ensure high conversion due to the vitrification effect which can restrict conversion when the glass transition temperature exceeds the reaction temperature. Unpublished work.

very different and selective reactivity. This approach allows for one of the reactive centers to add orthogonally to a thiol (in the present case an isocyanate unit) and attain essentially quantitative conversion while preserving the other unit



Scheme 31 Sequential amine–isocyanate and amine catalyzed thiol–acrylate Michael addition reactions for generating ultra uniform crosslinked networks with high glass transition temperatures. Note that the thiol-Michael addition was conducted at 120 °C to ensure high conversion due to the vitrification effect which can restrict conversion when the glass transition temperature exceeds the reaction temperature.

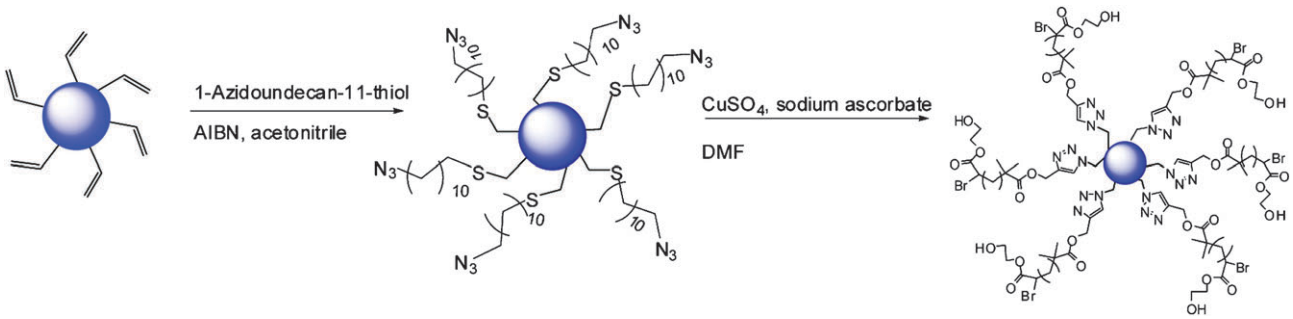
(in the present case an acrylate unit) for participation in a thiol-Michael reaction with a second trithiol in sequential fashion. As shown in Scheme 30a, the thiol–isocyanate reaction between a mixture (prepared to have a 1 : 1 : 1 SH : ene : isocyanate functional group ratio) of a tetrathiol and 2-isocyanatoethyl acrylate in the presence of a phosphine catalyst leads to quantitative conversion (Scheme 30b) and the generation of a pure tetraacrylate (no clean up required) with thiourethane linking groups. The tetraacrylate, after mixing on a 1 : 1 thiol : acrylate functional group ratio with the trithiol whose structure is shown in Scheme 30a, subsequently undergoes an efficient secondary amine catalyzed thiol-Michael addition reaction to produce a hard, highly uniform network (*i.e.* narrow tan δ peaks) with high refractive index. In a closely related example, a catalyst-free amine–isocyanate click reaction occurs exclusively between an oligomeric diamine (Scheme 31) and the isocyanate group of 2-isocyanatoethyl acrylate to generate in quantitative yield a tetraacrylate with urea linking groups with no need for purification. As in the case in Scheme 30, a sequential reaction between the tetraacrylate and trithiol leads to a highly uniform (*i.e.* narrow tan δ peaks), hard film with all of the desirable attributes usually associated with polyureas.



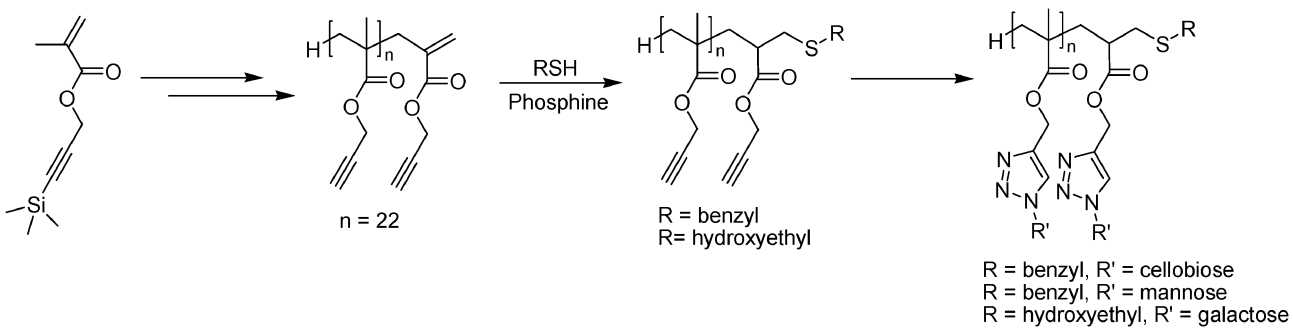
Scheme 32 End group functionalization of polystyrene *via* sequential thiol–ene radical and alkyne–azide click reactions. Scheme adapted from ref. 66.

Finally we close this review by describing what is deemed to be a recombination of multiple alkyne–azide/thiol–ene reactions. While two sequential thiol-click chemistries can be utilized to produce a unique materials platform, the real opportunities lie in combining multiple families of click reactions. This goal has indeed been accomplished in exceptional fashion by recent work by several research groups who have combined thiol–ene radical click chemistry and alkyne–azide click chemistry to produce distinctive, highly functional materials. In the first case,[66] terminal asymmetric telechelic polystyrene was formed by the thiol–ene coupling to a terminal ene on one end of the polystyrene with thiol glycolic acid and the click reaction of a terminal azide on the other end with a hydroxy-functional azide (Scheme 32). The dual functionalization was formed sequentially, with either reaction proceeding first. This example illustrates the power of dual click reactions to rapidly functionalize linear polymers orthogonally with very high yields. Sequential click reactions were also used to functionalize microsphere surfaces as exemplified in Scheme 33.[78] The residual surface vinyl "ene" surface groups on the divinylbenzene microspheres readily react by a photoinitiated thiol–ene radical click process with an end-functionalized azide decane-11-thiol, converting the microspheres into a surface with azide groups that readily react through a second Cu catalyzed click reaction with an yne end-functionalized poly(hydroxyethyl methacrylate). The sequential reaction methodology presented in Scheme 33 is demonstrative of the power of using sequential click reactions, the thiol–ene(radical)/alkyne–azide(Cu catalyzed) reactions, to functionalize with water soluble polymer arms that are effective in controlling the solution properties of the microspheres in aqueous environments. It is obvious that this approach should serve as an extremely powerful process for attaching virtually any type of R groups to the microspheres, provided that the R groups are functionalized with terminal azides. In a very recent example, Nurmi and co-workers[79] showed that sequential alkyne–azide and thiol-Michael addition reactions in sequence could be effectively used to form a series of glycolpolymers as illustrated in Scheme 34 where the poly(propargyl methacrylate) linear polymer was first end functionalized by the dimethylphenylphosphine catalyzed thiol-Michael addition reaction between the methacrylate end group to give terminal benzyl or alcohol groups and followed by the alkyne–azide click reaction between cellobiose, mannose or galactose azides.

As a final illustration of the efficacy of thiol–ene/alkyne–azide sequential click reactions, Anseth's laboratory used the Cu catalyzed reaction of a tetraazide-functionalized PEG with a diacetylene polypeptides to form hydrogels with allylic groups available for further reaction with a second photo-initiated thiol–ene reaction.[80,81] The patternable photo-initiated thiol–ene reaction involved the use of a fluorescently labeled cysteine (with reactive –SH) containing peptide. The result was the unique ability to produce a patterned protein gradient (identifiable by fluorescence). The potential exists for extending this dual click sequence to a wide range of hydrogels, whose structure can be controlled by the PEG azide–diacetylene polypeptide structures that form the basic hydrogel by the initial alkyne–azide click reaction as well as the chemical structure of the cysteine labeled peptide that participates in the second photoinitiated thiol–ene reaction with the allyl ether groups on the hydrogel. Recently, in what

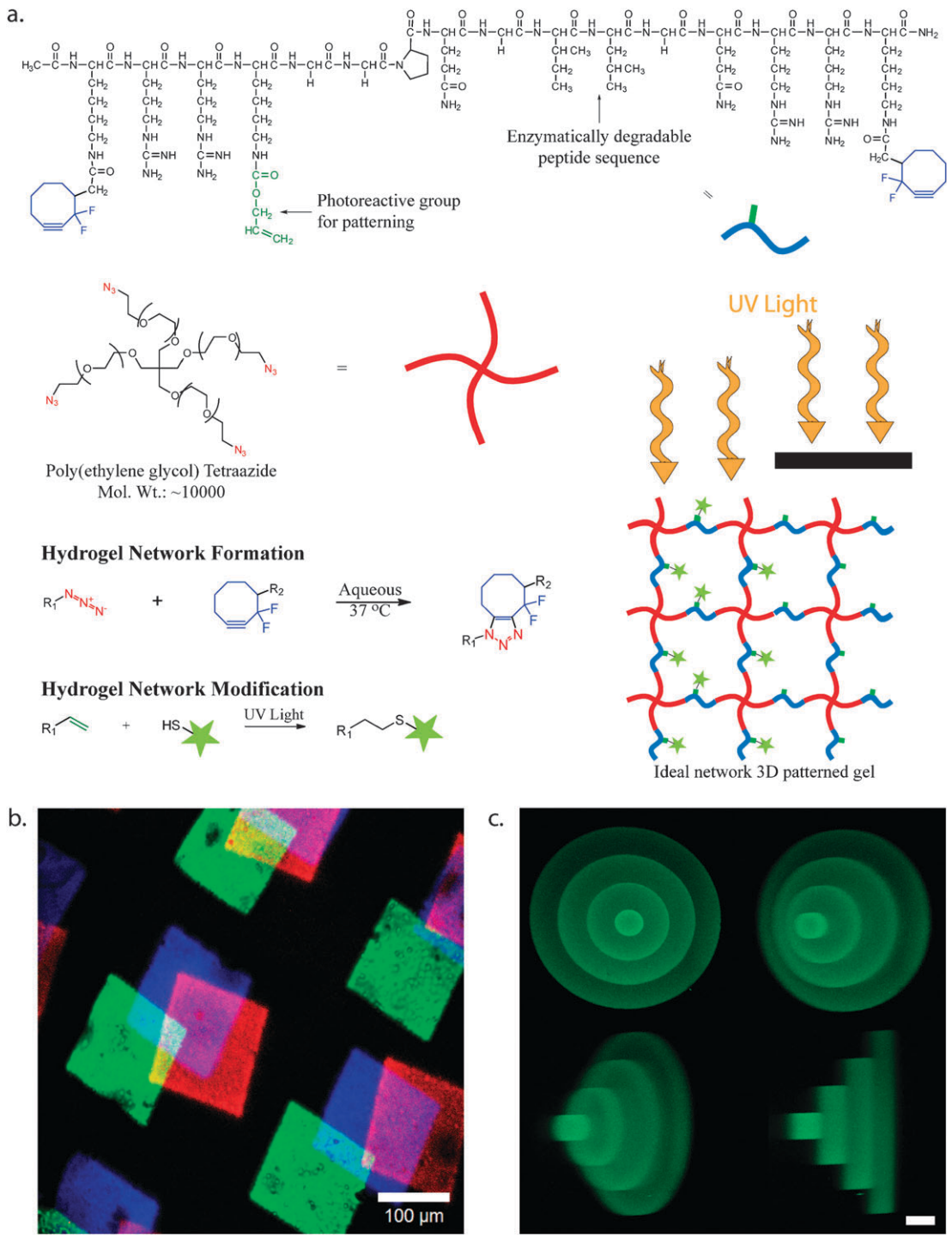


Scheme 33 Functionalization of polydivinylbenzene-based microspheres using sequential thiol–ene and alkyne–azide Huisgen click reactions. Scheme reproduced from ref. 78 with permission.



Scheme 34 Synthesis of functionalized glycopolymers using sequential click reactions. Scheme adapted from ref. 79.

can only be called an *eye to the future* for bioorganic synthesis, Anseth's sequential thiol–ene/alkyne–azide dual click process was extended (see Scheme 35) to a complete metal-free methodology for 3D patterning of cells encapsulated by the click derived hydrogels. As seen in Scheme 35, the initial hydrogel was formed in water by reacting a model peptide with two terminal difluorinated cyclooctynes with the tetraazide derived by functionalizing a four arm PEG—without the need for a Cu metal catalyst. The ideal 3D gel network has a reactive allyl ester ene group for reaction



Scheme 35 (a) Click-functionalized macromolecular precursors first react *via* the [3 + 2] Huisgen cycloaddition to form a 3D ideal network hydrogel through a step-growth polymerization mechanism. On swelling into the material, relevant thiol-containing biomolecules are covalently affixed to the hydrogel network *via* the thiol–ene reaction in the presence of UV light. (b) Photomasks were used to introduce three different fluorescently labeled peptide sequences within the gel, a process that can be repeated at desired times and spatial locations to introduce additional biochemical cues. (c) By controlling the focal point of laser light in 3D using a confocal microscope, micron-scale spatial patterning resolution is achieved. Scale bars = 100 and 50 μm in (b) and (c), respectively. Scheme adapted from ref. 81.

with thiol-functionalized biological signaling probes that respond to changes that may occur in the cellular environment such as protease activity, migration, proliferation, and morphology. This exciting technology is directly amenable to attachment of multiple probes that can simultaneously report a variety of changes in the cell. There is little question that this extraordinary application that combines the latest developments in alkyne–azide and thiol–ene chemistries serves as a vivid pictorial description of the best that both chemistries have to offer for the biological and biochemical fields, and it is fitting that this is the final description of thiol-click chemistry and its marriage with alkyne–azide chemistry—the future will surely benefit from this royal marriage of two quintessential click reactions.

5. Summary and the future of thiol-click chemistry

One focus of chemistry in the 21st century will be the development of custom molecules and materials that are targeted to specific, high value applications. As such, the demand for highly efficient click reaction chemistries that yield high purity, readily accessible products is significant and is likely only to increase in the future. Here, the cadre of thiol-click reactions has been demonstrated to be versatile, highly efficient and applicable to an array of molecular synthesis and materials applications. It is amenable to surface and particle patterning, bioorganic synthesis, polymer modification, imprint nanolithography, fabrication of optical components, hydrogel synthesis, curing of hard protective coatings and many other functions. Uniquely and depending specifically on the catalyst type and methodology employed, the thiol-functional group is capable of participating in a vast range of click reactions with various functional groups including alkyl halides, epoxides, enes, acrylates, ynes, and others. The methodology for employing these chemistries as well as a brief description of their mechanisms and value has been presented here; however, the future portends even greater and richer implementations of these reactions whether in multi-click reactions as highlighted in Section 4 or in a vast range of other synthetic and materials science applications.

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