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REVIEW

Thiol-ene "click" reactions and recent applications in polymer and materials synthesis: A first update

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This contribution serves as an update to a previous review (*Polymer Chemistry* 2010, **1**, 17-36) and highlights recent applications of thiol-ene 'click' chemistry as an efficient tool for both polymer/materials synthesis as well as modification. This current contribution covers examples from the literature published up to ca. mid 2013. It is not intended to be exhaustive but rather serves to highlight many of the new and exciting applications where researchers have applied thiol-ene chemistry in advanced macromolecular engineering and materials chemistry.

1. Introduction

The application of a now-established suite of highly efficient chemistries as both synthesis and conjugation tools continues to attract the attention of researchers in the polymer science community. This toolbox of reactions includes, but is not limited to, the catalysed and non-catalysed coupling between an alkyne and an azide,[1-3] indeed cycloaddition reactions in general,[4] as well as a family of thiol-based chemistries[5-7] such as the thiol-ene,[8-12] thiol-yne,[9, 13-15] thiol-isocyanate[16] and thiol-halo reactions.[17, 18] While the Cu(I) catalysed alkyne-azide (CuAAC) reaction is still the preeminent 'click' reaction the thiol-ene reaction, as well as its sister thiol-yne reaction, does in many instances, also meet the relevant criteria to accurately described as such and accounts, to a large extent, for the current renewed interest in this old chemistry. For more detailed information regarding these thiol-based reactions and specific applications readers are directed to several excellent reviews[6, 8, 13, 19-23] as well as a book from the RSC titled *Thiol-X Chemistries in Polymer and Materials Science* edited by Andrew B. Lowe and Christopher N. Bowman.[24]

Since the first review there has been impressive growth in the use of the thiol-ene reaction in polymer synthesis and modification with many new and exciting applications having been detailed that will be highlighted below, Figure 1. In the previous article the applications of thiol-ene chemistry were detailed based on a mechanistic classification, i.e. radical thiol-ene vs thiol-Michael-type reactions.[8] However, an examination of the literature since late 2009 indicates that the majority of the reported studies since this time have focussed on the radical-mediated variant of this reaction. As such, recently reported literature will be summarized based on general application. Basic advances for effecting the thiol-ene reaction will first be detailed followed by summaries describing its use in network syntheses/applications, monomer synthesis and side chain/end-group modification, preparation of various types of branched macromolecules, the preparation of inorganic-organic composites, nanoparticle modification, surface modification, bio-related uses and finally a section covering miscellaneous applications.

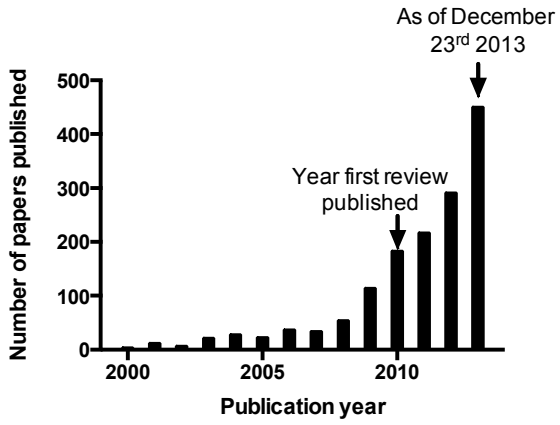


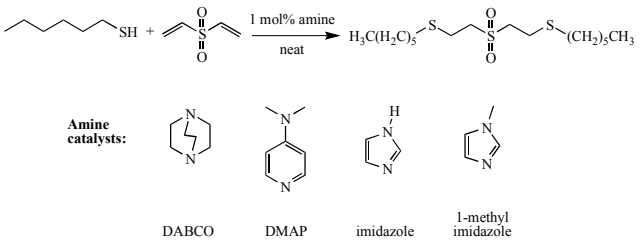
Figure 1 Annual number of papers published on thiol-ene chemistry since 2000. Data generated using SciFinder and "thiol-ene" as a search term.

2. New Practical Considerations

It is well known that the radical thiol-ene reaction can be initiated by a variety of techniques including under traditional thermal conditions with common azo species such as 2,2'-azobis(isobutyronitrile) (AIBN) or via photochemical methods, with or without added photoinitiator, with the latter being the most commonly employed. Recently, the scope of initiation for such reactions was extended when Skinner, Whiffin and Price[25] detailed the room temperature sonochemical initiation of thiol-ene reactions. 1-Butanethiol (in toluene) or cysteamine hydrochloride (in water) were evaluated in their reaction with a series of alkenes including norbornene, *N*-isopropylacrylamide (NIPAM), butyl vinyl ether (BVE), 1-heptene and allylamine. In the case of 1-butanethiol, acceptable, but not quantitative, yields of the thioether adduct were formed sonochemically in the presence of AIBN (20 k Hz ultrasound, 17 W cm^{-2}, [AIBN] = 20 mM, RT) but yields were significantly lower than those obtained in reactions performed under purely thermal initiation ([AIBN] = 20 mM, 50°C, 2h). However, it was noted by the authors that thioethers are susceptible to sonolysis and as such yields may have been limited by undesirable lysis reactions of the thioether adducts yielding radical species that may also have undergone side reactions. Low or negligible yields were obtained for other alkenes under similar conditions. However, conversions could be improved in the sonochemical reactions by increasing ultrasound power, increasing [AIBN], extending the reaction time and or increasing the number of thiol equivalents. For example, the authors noted that in the case of BVE, the yield of hydrothiolation product could be increased from 30% to 88% by conducting the reaction for 4 h in the presence of 60 mM AIBN and 5 equivalents of 1-butanethiol with an ultrasound intensity of 21 W cm^{-2}. While sonochemical initiation appeared to offer little benefit over thermal initiation reactions in organic media, reactions performed under an air atmosphere in water with potassium persulfate serving as the source of primary radicals exhibited more promise. Reactions were performed under similar conditions ($[K_2S_2O_8]$ = 1.75 mM, ultrasound intensity = 17 W cm^{-2}, conversions reported after 1 h). In the case of several alkenes, including 4-pentenoic acid and allyl alcohol, quantitative formation of the thioether adducts was observed for both the sonochemical and thermal systems. Reactions with polymerisable species such as NIPAM and acrylamide did suffer from limited formation of the thioether product due to their propensity towards radical polymerization under the sonochemical and thermal conditions. This is consistent with previous reports of the radical-mediated thiol-ene reaction with polymerisable alkene as substrates.

There have been several papers recently that have described fundamental aspects of the thiol-Michael variant of the general thiol-ene reaction. The thiol-Michael reaction can be initiated by any of the common methods applicable to conjugate addition reactions.[26] This includes base catalysed addition as well as nucleophile-initiation. Of these two general methods the nucleophile-mediated reactions have been previously demonstrated to possess certain advantages compared to the more traditional base-catalysed processes. For example, Chan *et al*.[10] detailed a classical study evaluating the effect of thiol, ene and catalyst/initiator on the kinetics and efficacy of the thiol-Michael reaction. With respect to catalysts/initiators the authors demonstrated that certain tertiary phosphines such as tributylphosphine (TBP) and dimethylphenylphosphine (DMPP) could be employed at extremely low levels while still giving quantitative yields of the thioether adducts. After the phosphines, simple alkyl primary amines such as hexylamine were the next most effective species followed by, in general, secondary and tertiary amines such as triethylamine (TEA), with the latter being comparatively ineffective in such reactions although TEA is still used routinely as an organobase by many researchers for mediating such addition reactions.[18]

Bowman and co-workers[27] detailed an additional group of N-centred nucleophiles as initiators for thiol-Michael addition. In a study of the conjugate addition of 1-hexanethiol to divinylsulfone (DVS) the authors evaluated the catalytic activity of 1,4-diazabicyclo[2.2.2]octane (DABCO), 4-dimethylaminopyridine (DMAP), imidazole and 1-methylimidazole, Scheme 1.

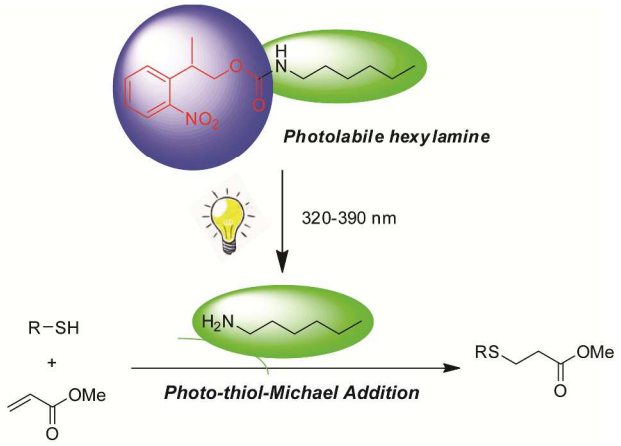


Scheme 1 Thiol-Michael addition of 1-hexanethiol to divinylsulfone mediated by N-centred initiators.

Interestingly, both DABCO and DMAP gave quantitative yields of product in as little as 5 min. Imidazole and 1-methyl imidazole were also extremely effective initiators for this reaction giving 90 % (15 min reaction time) and 96% conversion (5 min reaction time) respectively as determined by real time FTIR spectroscopy. Additionally, all four of these N-centred species were demonstrated to be superior to hexylamine, diethylamine and TEA. However, it is noted that the opposite is true for thiol-acrylate Michael additions, but does nicely highlight how appropriate pairing of catalyst/initiator with thiol and ene is an important consideration in such conjugate addition reactions. Employing theoretical quantum level calculations the authors also demonstrated that the nucleophilic initiation pathway, vs the base catalysed process, was the thermodynamically favoured process in these reactions. Finally, the authors demonstrated that these catalysts were effective in thiol-ene polymerizations between DVS and the 4-functional thiol 2,2-bis(((3-mercaptopropanoyl)oxy)methyl)propane-1,3-diyl bis(3-mercaptopropanoate) (PETMP). In a more recent contribution, Chatani, Nair and Bowman[28] reported a straightforward study comparing the reactivity and selectivity of hexyl acrylate and ethyl vinyl sulfone in thiol-Michael reactions with 1-

hexanethiol mediated by TEA, dimethylphenylphosphine (DMPP) or methyldiphenylphosphine (MDPP). Under typical conditions (1:1 thiol:ene, 0.05 wt% DMPP catalyst for example) ethyl vinyl sulfone was consistently more reactive than hexyl acrylate with a rate of reaction approximately 7x higher than the acrylic species. The enhanced reactivity was attributed to the more electron deficient nature of the vinyl sulfone vs the acrylate. In a mixture of thiol, ethyl vinyl sulfone and hexyl acrylate, in a molar ratio of 1:1:1, it was shown that the thiol Michael reaction, mediated by MDPP, exhibits a high selectivity for ethyl vinyl sulfone. For example, after 20 minutes ~80% of the vinyl sulfone was consumed with no apparent consumption of the acrylate. Increasing the molar ratios to 2:1:1 resulted in the complete consumption of ethyl vinyl sulfone in under 10 minutes with less than 10% of the hexyl acrylate reacting in the same time frame. These results very nicely demonstrated that even though both ethyl vinyl sulfone and hexyl acrylate exhibit a high reactivity in thiol-Michael reactions it is possible to achieve a high degree of selectivity in mixtures of both vinylic species.

Bowman's group have also reported two additional novel initiation processes for the thiol-ene reaction. Cole, Jankousky and Bowman[29] performed a thorough evaluation of the redox-initiated thiol-ene reaction with an emphasis on the formation of networks. The authors demonstrated that redox initiation is, indeed, a viable process with, for example, resulting networks being little different from those prepared via more traditional photoinitiation processes. However, the redox process has the added benefits of facile and quantitative network formation being achieved without regard to sample thickness or pigmentation.



Scheme 2 Photoinitiated thiol-Michael addition of thiols to methyl acrylate employing a masked primary amine. Professor Christopher N. Bowman is kindly thanked for supplying the original image. Reproduced from W. Xi, M. Krieger, C.J. Kloxin and C. N. Bowman *Chem. Commun*. 2013, **49**, 4504-4506.

Xi and coworkers[30] reported a novel amine catalysed thiol-Michael reaction via a photoclick reaction involving a caged primary amine, Scheme 2. The authors first prepared a novel photolabile, protected primary amine, namely 2-(2-nitrophenyl)propyloxycarbonyl (NPPOC)-hexylamine. When irradiated at 320-390 nm in the presence of a thiol and activated substrate, NPPOC-hexylamine cleaves liberating hexylamine that serves as the initiating species for the ensuing thiol-Michael reaction. The authors evaluated the reaction of a series of thiols including simple mercaptoesters, 2-mercaptoethanol and thiophenol with methyl acrylate and demonstrated that a catalyst loading of 5 mol% gave greater than 90% yields of the thiol-Michael adduct after an irradiation time of 60 min. The approach also proved successful in network formation for the reaction between examples of tetrathiols and diacrylates.

As reported previously, and highlighted in the prior mini-review, internal C=C bonds, i.e. 1,2-disubstituted alkenes, exhibit diminished reactivity in radical thiol-ene reactions compared to terminal alkene bonds.[5, 8] This is due, in part, to a competing *cis*/*trans* isomerization process that is very efficiently mediated by thiyl radicals via an addition-isomerization-elimination pathway. This was further highlighted by Claudino, Johansson and Jonsson[31] in their studies of radical thiol-ene coupling between the trifunctional thiol trimethylolpropane tris(3-mercaptopropionate) (**TMPTP**) and the two 1,2-disubstituted alkenes methyl oleate (**MO**) and methyl elaidate (**ME**), Figure 2.

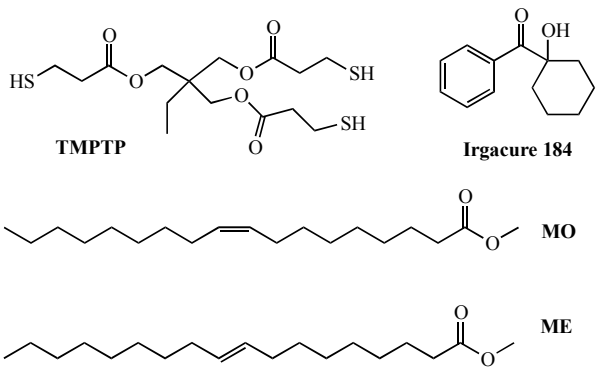
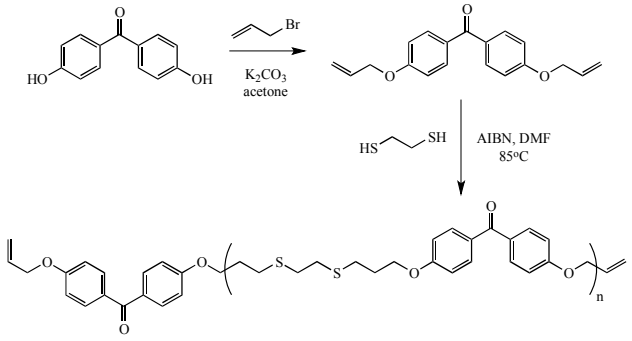


Figure 2 Chemical structures of trimethylolpropane tris(3-mercaptopropionate) (**TMPTP**), the photoinitiator Irgacure 184, methyl oleate (**MO**) and methyl elaidate (**ME**).

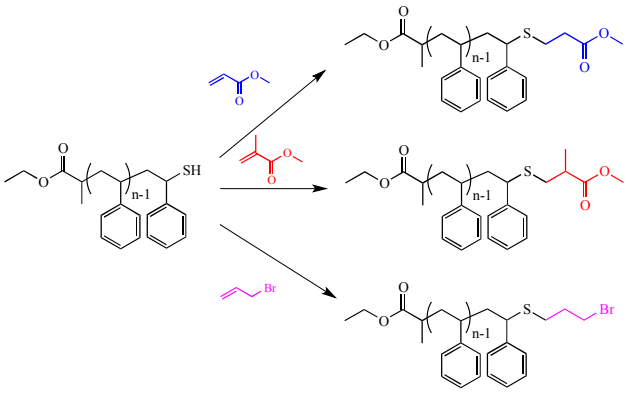
The authors demonstrated that thiol-ene coupling can proceed to high conversions under bulk conditions with an equimolar ratio of functional groups. Consistent with previous studies and reports, the internal *cis* species, **MO**, was shown to undergo an immediate isomerization reaction to the corresponding *trans* species with the *cis/trans* isomerization process significantly affecting the rate of thioether product formation. The authors showed that the *cis*-to-*trans* isomerization was faster than the *cis*-to-thioether reaction whereas the *trans*-to-thioether reaction was faster than the *trans*-to-*cis* isomerization. However, high yields were obtained with no apparent significant side reactions indicating that the use of internal 1,2-disubstituted enes should be possible in network-forming reactions.

Irradiation, with or without added photoinitiator, is the most common method for initiating radical thiol-ene reactions. Given this, it is of interest to prepare new and novel photoinitiators. Temel, Karaca and Arsu[32] described the synthesis of a main chain polymeric benzophenone photoinitiator via radical thiol-ene chemistry and evaluated it in the free radical polymerization of hexanediol diacrylate (HDDA). The polymeric initiator was prepared as outlined in Scheme 3. Reaction of bis(4-hydroxyphenyl)methanone with allyl bromide under weakly basic conditions gave the bis allyl derivative bis(4-allyloxy)phenyl)methanone. Reaction of this difunctional ene with ethanedithiol under thermal conditions in the presence of AIBN gave the polymeric benzophenone-based photoinitiator. Interestingly, the polymeric species exhibited excellent absorption characteristics compared to benzophenone and was shown to have higher initiator efficiency in the subsequent polymerization of HDDA. In a similar vein, Xie *et al.*[33, 34] reported two examples of benzophenone-based polymeric photoinitiators based on hyperbranched poly(ester-amine) and poly(ester/ether) (P1000). In both instances the preparation of the polymeric photoinitiators involved a thiol-Michael reaction between appropriate functional species. Both species were subsequently evaluated in the photopolymerisation of HDDA. In both cases the photopolymerisation rate was determined to be 2x higher than with analogous small molecule benzophenone photoinitiation.



Scheme 3 Outline for the thiol-ene synthesis of a polymeric benzophenone photoinitiator.

Uygun, Tasdelen and Yagci[35] described a comparative study on the type of initiation used in radical thiol ene reactions between thiol-end capped polystyrene, prepared via ATRP followed by end-group transformation, and a series of enes including methyl acrylate (MA), methyl methacrylate (MMA) and allylbromide as well as the reaction of allyl-α-functionalized polystyrene with 3-mercaptopropionic acid. The hydrothiolation reactions were conducted using a range of Type I (2,2-dimethoxy-2-phenyl acetophenone (DMPA) and (2,4,6-trimethylbenzoyl) diphenylphosphine oxide (TMDPO)) and Type II (benzophenone (BP), thioxanthone (TX) and camphorquinone (CQ)) initiators at room temperature by irradiation with a UV lamp emitting at 350 nm as well as



thermal initiation employing AIBN at 80°C. In all instances, reactions were performed at a 1:10 ratio of thiol:ene, Scheme 4.

Scheme 4 Radical thiol-ene coupling between a thiol-terminated polystyrene and MA, MMA and allylbromide.

In all instances, and after purification (note: the (meth)acrylic species inevitably undergo some degree of radical homopolymerization under radical thiol-ene conditions and this impurity needs to be removed for efficient characterization). The end-modified species were obtained in near quantitative yields (85-100%0 with the thermal, AIBN-initiated, reactions giving the lowest yields for all the three enes, where the Type I photoinitiators (DMPA and TMDPO) gave the highest efficiencies. The reverse reaction with allyl-functional polystyrene and 3-mercaptopropionic acid followed a similar trend in terms of yields and efficiencies. This study reaffirms why the majority of radical thiol-ene reactions are best conducted via a photoinitiation process (as opposed to thermal) and that Type I, and especially DMPA, tend to be the preferred photoinitiators.

In addition to advances strictly pertaining to polymer/materials synthesis or functionalisation, there have also been advances reported in small molecule hydrothiolations that have the potential to be expanded into the polymer science field.

In a computational study, Northrop and Coffey[36] evaluated the effect of alkene functionality on the energetics and kinetics of the radical thiol-ene reaction between methanethiol and a series of 12 alkenes, Figure 3 and Figure 4. The authors found that changing the reaction conditions (thiol and ene concentration or rates of photoinitiation and termination) had, as expected, an influence on the overall reaction kinetics for each thiol-ene pair. However, the overall order of reactivity for the alkenes remained unchanged across different system variables. The calculated order of ene reactivity (norbornene > vinyl silane > methyl allyl ether > methyl vinyl ether > dimethyl fumarate > propene > maleimide > methyl acrylate > methyl crotonate > styrene > acrylonitrile > butadiene) is in reasonable agreement with experimentally determined orders of reactivity.[5]

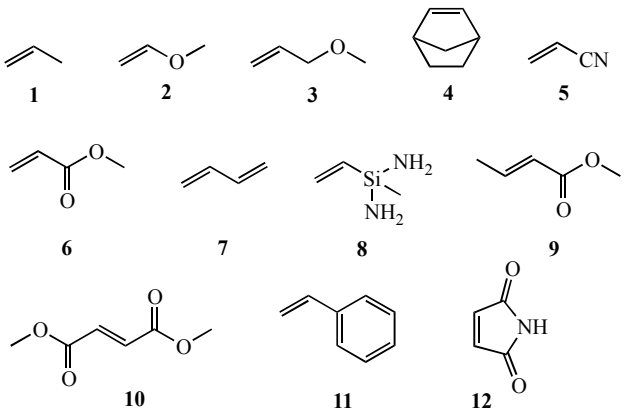


Figure 3 Chemical structures of alkenes evaluated in the theoretical radical thiol-ene reaction with methanethiol: propene (**1**), methyl vinyl ether (**2**), methyl allyl ether (**3**), norbornene (**4**), acrylonitrile (**5**), methyl acrylate (**6**), butadiene (**7**), methyl(vinyl)silanediamine (**8**), methyl crotonate (**9**), dimethyl fumarate (**10**), styrene (**11**) and maleimide (**12**).

Several groups have highlighted the application of transition metals as mediating species for effecting hydrothiolations, including a mini-review by Castarlenas *et al.*[37] Tyson, Ament and Yoon[38] detailed the anti-Markovnikov hydrothiolation of a range of enes with a library of thiols employing the visible light absorbing transition metal photocatalyst ($Ru(bpz)_3^{2+}$) with isolated yields of thioether adducts in the range 73-99%, Scheme 5.

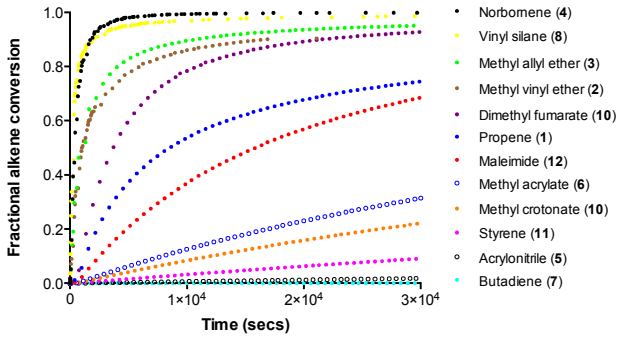
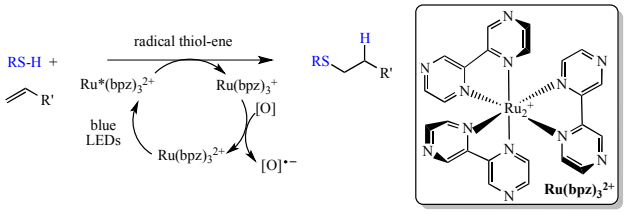


Figure 4 Kinetically modelled conversion vs time curves for the radical reactions between methanethiol and enes **1-12**. Dr. Brian Northrop is kindly thanked for supplying the raw data used to generate Figure 4.



Scheme 5 Radical-mediated anti-Markovnikov hydrothiolation via a visible light absorbing Ru complex.

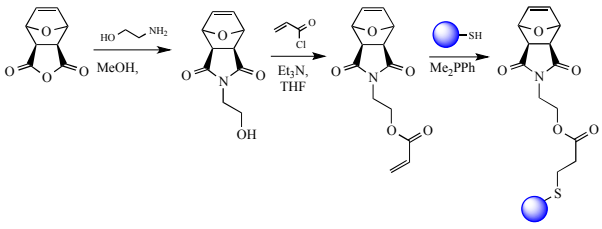
It is perhaps worth reiterating at this point that all of the so-called 'click' reactions, or highly efficient coupling chemistries, are not without their drawbacks and this is equally true of thiol-ene chemistry.[39] For example, Koo and co-workers[40] highlighted perhaps the major limitation of this chemistry, namely employing the radical thiol-ene reaction as a polymer-polymer conjugation tool. While it is an efficient process for small molecule modification of preformed polymers, the coupling of two appropriately functional polymer chains to give AB diblock copolymers, or more advanced species such as star polymers, is generally not efficient even when one component is used in excess.

3. Monomer Synthesis and Polymer Side and End Chain Modification

The thiol-ene reaction has been employed as a synthetic tool in the synthesis of new thioether-based monomers that are susceptible to (co)polymerisation by a range of established methods as well as a valuable method for the modification of suitable side- or end-groups on pre-prepared (co)polymers. Here we will begin by highlighting examples of thiol-ene chemistry that have been employed in novel monomer syntheses and subsequent (co)polymerisations, and then we will discuss examples of thiol-ene reactions on preformed (co)polymers obtained by an equally large, and impressive, number of polymerisation techniques.

Monomer syntheses

Liu and co-workers[41] detailed the synthesis of a library of mono- and multi-functional thioether based *exo*-7-oxanorbornenes and subsequently evaluated their polymerization behaviour via ring-opening metathesis polymerization (ROMP). The thioether monomers were prepared as outlined in Scheme 6.



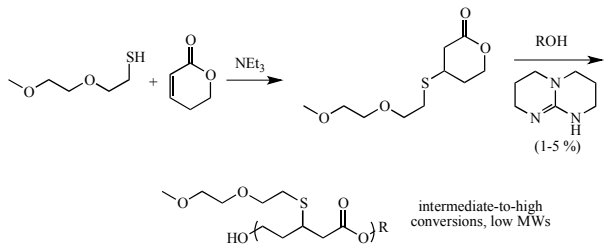
Scheme 6 The synthesis of thioether-based *exo*-7-oxanorbornenes via sequential imidisation, acylation and thiol-Michael addition reactions.

Reaction of commercially available (3a*R*,7a*S*)-3a,4,7,7a-tetrahydro-4,7-epoxyisobenzofuran-1,3-dione with 2-amino-ethanol gave the intermediate OH-functional imide that was readily acylated with acryloyl chloride to give 2-((3a*R*,7a*S*)-

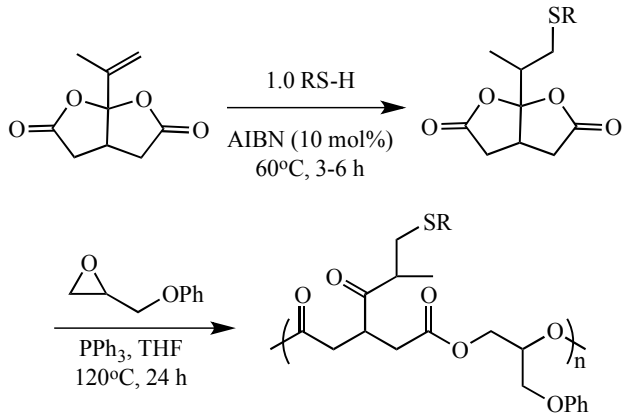
1,3-dioxo-3a,4,7,7a-tetrahydro-1*H*-4,7-epoxyisoindol-2(3*H*)-yl)ethyl acrylate. This was the key intermediate – a potentially ROMPable substrate that contains an activated acrylic side group that is susceptible to thiol-Michael addition (note – the internal, ROMP-active C=C bond, being non-activated, is not able to undergo conjugate addition reactions). The norbornene-acrylate was then treated with a series of thiols including simple mercaptoesters and alcohols, a thiosugar, fluorinated species and a POSS derivative to give a library of functional ROMPable thioethers. In general, all thioether substrates could be readily (co)polymerised with the Grubbs' 1st or 3rd generation catalysts to give well-defined (co)polymers. Extending this preliminary work, the same group described the synthesis and (co)polymerisation of difunctional *exo*-7-oxanorbornenes obtained from the reaction of the above norbornene-acrylate with a series of dithiols.[42] Direct ROMP (co)polymerisation gave novel hyperbranched polymers in which the measured conversions of C=C bonds was significantly higher than that obtained by any other polymerization technique previously employed in the preparation of hyperbranched species via the direct polymerization of a difunctional monomer.

Kim *et al.*[43] have described the straightforward base catalyzed thiol-Michael synthesis and subsequent (co)polymerization of functionalized lactones, Scheme 7. In addition to the formally hydrophilic species shown below hydrophobic species are also readily accessible via the conjugate addition of benzyl mercaptan. (Co)Polymerizations of the thioether monomers in solvents such as toluene, while effective, generally gave low yields whereas bulk polymerizations gave improved conversions. It was also shown that the thioether lactones could be readily copolymerized with other monomers such as ε-caprolactone. These polymerizations were both more rapid and reached higher final conversions.

In a similar vein, Ohsawa *et al.*[44] described the synthesis of thioether based bicyclic bis(γ-butyrolactone) monomers from a common precursor, 6a-(prop-1-en-2-yl)dihydrofuro[2,3-*b*]furan-2,5(3*H*,6a*H*)-dione, Scheme 8.



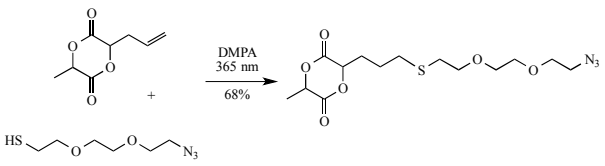
Scheme 7 Thiol-Michael addition of 2-(2-methoxyethoxy) ethanethiol to 5,6-dihydro-2*H*-pyran-2-one and its subsequent homopolymerization.



Scheme 8 Synthesis and (co)polymerisation of thioether-based monomers derived from 6a-(prop-1-en-2-yl)dihydrofuro[2,3-*b*]furan-2,5(3*H*,6a*H*)-dione.

Reaction of the bicyclic bislactone substrate with dodecanethiol, cyclohexylmercaptan and benzylmercaptan gave target thioether products with conversions of 78-97%. Hydrothiolation with thiophenol proved largely unsuccessful (6% conversion). Interestingly, the thioether adducts could be readily copolymerized with glycidyl phenylether to give alternating copolymers whose thermal properties were dependent on the nature of the copolymer side chain functionality. Extending this, the authors also demonstrated that reaction of the precursor ene with 1,6-hexanedithiol gave the analogous difunctional initiator that was employed to give network polymers via the anionic copolymerization with bisphenol A diglycidylether for example.

More recently, Borchmann, Brummelhuis and Weck[45] reported the synthesis of a novel azido-tri(ethylene glycol) lactide derivative that was prepared via a photoinitiated thiol-ene reaction between 3-allyl-6-methyl-1,4-dioxane-2,5-dione and 2-(2-(2-azidoethoxy)ethoxy)ethane-1-thiol, Scheme 9. This monomer was readily polymerized in dry toluene with benzyl alcohol as initiator and $Sn(Oct)_2$ as the catalyst to give a low molecular weight species with a corresponding dispersity ($Đ_M = \bar{M}_w/\bar{M}_n$) of 1.6. The azido-functional polymer was subsequently modified with triarylphosphine modified GRGDS via Staudinger ligation. The overall synthetic strategy is shown in Figure 5.



Scheme 9 Synthesis of 3-(3-((2-(2-(2-azidoethoxy)ethoxy)ethyl)thio)propyl)-6-methyl-1,4-dioxane-2,5-dione via a photoinitiated thiol-ene coupling reaction.

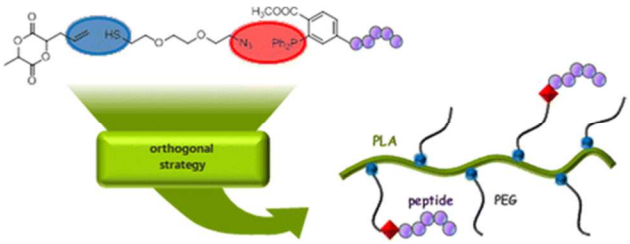
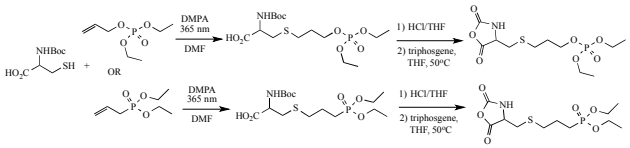


Figure 5 Overall orthogonal ligation strategies for the preparation of novel poly(ethylene glycol)/peptide/polylactide conjugates. Professor Marcus Weck is thanked for supplying the original image. Reproduced with permission from D. E. Borchmann, N. t. Brummelhuis, M. Weck *Macromolecules* 2013, **46**, 4426-4431. Copyright 2013, American Chemical Society.

The targeted product was isolated in high purity with, on average, each polymer chain containing 2-peptide species corresponding to an average degree of modification of 14% (20% was the targeted degree of functionalisation).

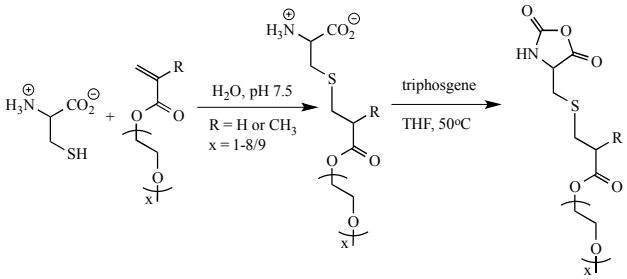
The synthesis, and subsequent polymerisation, of novel thioether-based functional *N*-carboxyanhydride (NCA) monomers has been reported by Das, Kar and Gupta[46] and Fu *et al.*[47] with the former group employing radical thiol-ene coupling and the latter thiol-Michael chemistry. In the work of Das, Kar and Gupta, (*tert*-butoxycarbonyl)cysteine was initially reacted with allyl diethyl phosphate or diethyl allylphosphonate in DMF in the presence of DMPA to give the thiol-ene adducts in high yields (actual values were not given). Conversion of the thioether adducts to the NCA monomers was then accomplished by initial removal of the Boc protecting group followed by cyclisation with triphosgene, Scheme 10.



Scheme 10 Synthesis of NCA monomers 3-(((2,5-dioxooxazolidin-4-yl)methyl)thio)propyl diethyl phosphate and diethyl (3-(((2,5-dioxooxazolidin-4-yl)methyl)thio)propyl) phosphonate via sequential radical thiol-ene coupling, deprotection and cyclisation reactions.

The monomers were polymerised with propargylamine or an azido-poly(ethylene glycol)-NH_2 species as initiators to give low-to-medium molecular weight polymers with low $Đ_M$ values. Fully water-soluble polypeptides were obtained via hydrolysis of the pendent phosphoester groups with iodotrimethylsilane followed by methanolysis. In the case of Fu and co-workers, L-cysteine was reacted directly with a series of oligo(ethylene glycol) (meth)acrylates in water at pH 7.5 (thiol-Michael reaction) to give the intermediate thioether adducts in yields ranging from 88-96%, Scheme 11. Cyclisation with triphosgene in THF at 50°C gave the NCA monomers in 65-80% yield.

Scheme 11 Synthesis of oligo(ethylene glycol)-NCA



monomers via sequential thiol-Michael addition/cyclisation reactions.

The monomers were polymerised employing TEA as an initiating species to give a series of functional polypeptides with relatively low molecular weights. After isolation and purification the authors evaluated the thermoresponsive properties of the materials in water demonstrating that selected materials exhibited LCST-properties.

Cortez and Grayson[48] described the synthesis and polymerisation of several functionalised 2-oxazolines obtained from the thiol-Michael addition of thiophenol, methyl thioglycolate and *N*-(*tert*-butoxycarbonyl)-L-cysteine methyl ester to a common precursor, 2-isopropenyl-2-oxazoline, employing a butylamine-supported catalyst. Thioether adducts were generally obtained in near-quantitative yields. All functional monomers could be readily polymerised to give polymers with measured molecular weights in range 3,000-8,000 and reasonably low $Đ_M$ values. There has also been significant interest in the thiol-ene modification of preformed (co)polymers and these works will be discussed below.

One area in which there has been significant research activity is the synthesis of novel thioether based monomers derived from renewable natural products and their use to prepare novel polyesters, polyurethanes and polyamides.[49, 50] Firdaus, de Espinosa and Meier[51] reported an extensive study on the synthesis and condensation polymerisation of thioether-functional terpene-based monomers, Figure 6. The authors demonstrated that the addition of alcohol and ester functional mercaptans to terpenes occurs readily at room temperature in the absence of added radical initiator in a regioselective, and diastereoselective, fashion and could be controlled to give mono-, di- and mixed thioether adducts. Homo- and co-polymerisation of these terpene-based monomers with short chain diols gave oligomeric polyesters. In contrast, copolymerisation with long chain fatty acid-based diesters and diols gave polyesters with measured molecular weights up to 25,000.

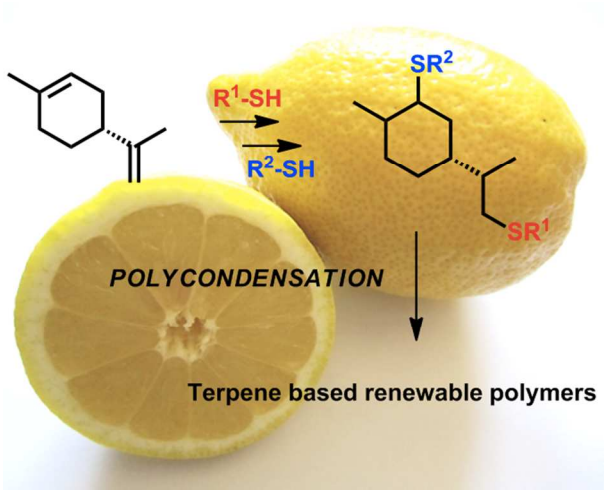


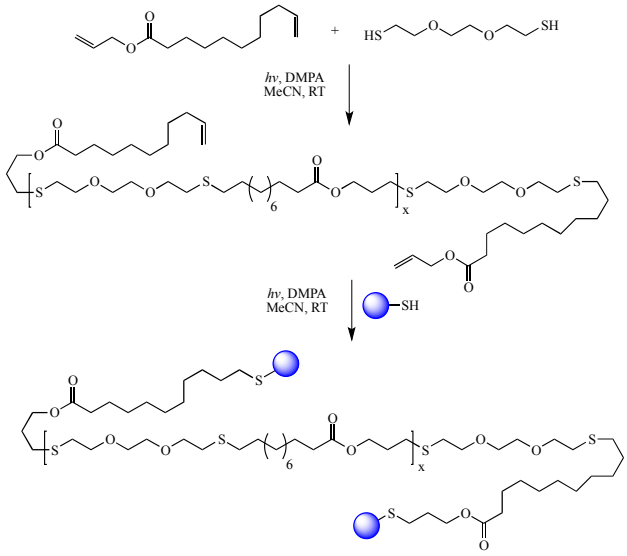
Figure 6 Radical thiol-ene functionalisation of naturally occurring terpenes and their subsequent polycondensation. Professor Michael Meier is kindly thanked for supplying the image. Reproduced with permission from M. Firdaus, L. M. de Espinosa, M. A. R. Meier *Macromolecules* 2011, **44**, 7253-7263. Copyright 2011, American Chemical Society.

In fact, the same group has reported extensively on the use of radical thiol-ene chemistry as a means of preparing novel monomers and polymers via condensation processes from plant oil precursors[52] and have also published a recent review on the topic.[53]

Other research groups have also been active in this area. For example, Desroches and coworkers[54] evaluated the model reaction of 2-mercaptoethanol with oleic acid under radical conditions and the synthesis of a polyol from the reaction of the thiol with rapeseed oil. In the case of reactions with oleic acid the authors identified optimized conditions for avoiding unwanted side reactions/products (disulfides, esterification products and double bond isomerization for example). When applied to rapeseed oil this gave a polyol with an average OH functionality of 3.6 that was used to prepare biobased polyurethanes by reaction with 1,6-hexamethylene diisocyanate and diphenyl-4,4'-diisocyanate.

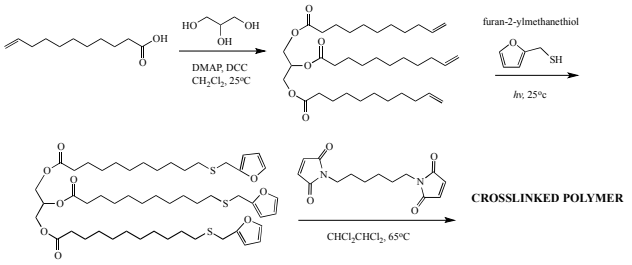
More *et al.*[55] detailed the synthesis of AB self-condensable monomers containing alcohol and acyl azide functional groups based on methyl oleate and methyl 10-undecenoate. The first step in the multi-stage syntheses of these monomers involved the radical thiol-ene addition of 2-mercaptoethanol across the C=C bonds in the starting materials as a means of introducing the required OH functionality. The target α-OH, ω-acyl azide monomers could be readily (co)polymerized to give novel polyurethanes. The approach was also extended to giving diol monomers that were used for polyurethane and polyester syntheses.

Lluch *et al.*[56, 57] reported the synthesis of biobased oligomeric telechelics and their use as building blocks in the preparation of thermoplastic polyurethanes. In the initial report,[56] an excess of the difunctional ene allyl 10-undecenoate was reacted with 3,6-dioxa-1,8-octanedithiol in the presence of DMPA as a photoinitiator to give the oligomeric ene-end functional oligoesters, Scheme 12, with target molecular weights in the range 1,000-3,000, achieved by varying the stoichiometry. Subsequently these were converted in a series of functional telechelic species by the radical reaction of the terminal enes with three different thiols namely 2-mercaptoethanol, 3-mercaptopropionic acid and 3-mercaptopropyltrimethoxysilane.



Scheme 12 Synthesis of telechelic polyester oligomers via sequential radical thiol-ene coupling.

In a follow up report, the authors employed the oligomeric diols, obtained as above from 2-mercaptoethanol to prepare a series of polyurethanes.[57] The structures of the polyurethanes were confirmed using standard methods and the authors also fully characterized the products with respect to their thermal and hydrolytic properties.



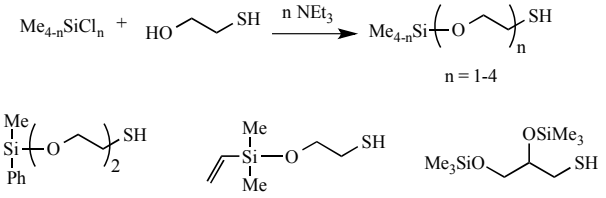
Scheme 13 Synthesis of a trifunctional furan monomer via radical thiol-ene addition to a precursor triene, and its subsequent use in a Diels-Alder polymerisation with a bismaleimide to give a crosslinked polymer.

In an interesting variant of the above condensation chemistries, Vilela, Silvestre and Gandini[58] reported the synthesis of a series of trifunctional monomers that were subsequently polymerised via Diels-Alder reactions between

complimentary furan and maleimide functional groups. As a representative example, undec-10-enoic acid was first reacted with propane-1,2,3-triol in a carbodiimide coupling to give the trifunctional ene propane-1,2,3-triyl tris(undec-10-enoate). In a subsequent step, the triene was treated with furan-2-ylmethanethiol in a radical thiol-ene reaction to give the three-functional furan derivative propane-1,2,3-triyl tris(11-((furan-2-ylmethyl)thio)undecanoate), an A_3 monomer, Scheme 13. This A_3 monomer was copolymerised with the difunctional maleimide derivative 1,1'-(hexane-1,6-diyl)bis(1*H*-pyrrole-2,5-dione) (an A_2 monomer) to give a crosslinked material. Interestingly, the authors also reported the synthesis of asymmetric monomers containing, for example, 2 furan and one protected maleimide (protected A_2B) or one furan with two protected maleimides (protected AB_2) that when polymerized gave hyperbranched polymers.

In an interesting example, Stemmelen *et al*.[59] reported the synthesis and self-assembly of amphiphilic copolymers based on vegetable oils and poly(2-methyl-2-oxazoline). UV-initiated thiol-ene coupling of mercaptoethanol to methyl oleate or grapeseed oil gave the OH functional vegetable oils. The OH groups were then converted to an appropriate initiating group for the cationic ring-opening polymerisation of 2-methyl-2-oxazoline. The resulting amphiphiles were shown, by dynamic light scattering, to undergo self-assembly in aqueous media forming well-defined nanoparticles.

In the general field of thiol-ene chemistry, its application in network syntheses employing multifunctional thiols continues to represent an important area of study. Since multifunctional thiols can be considered monomeric building blocks in step-growth polymerisations the preparation of new multifunctional thiols is also of interest. Recently, Jennings and Son[60] reported the highly selective reaction of simple mercaptoalcohols with chlorosilanes in which reaction occurs exclusively at the OH group yielding a series of novel multifunctional thiols, Scheme 14.



Scheme 14 Synthesis of (multi)functional thiols from the reaction of mercaptoethanol with chlorosilanes.

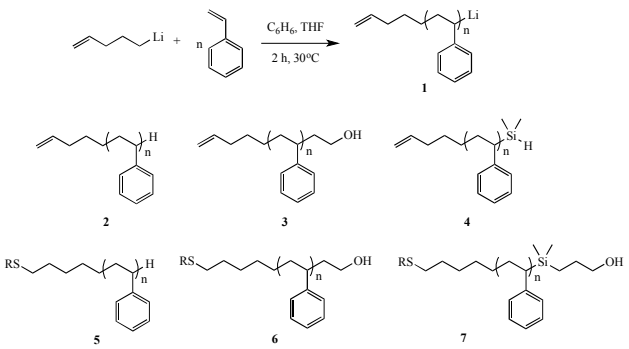
The impressive versatility of this reaction was highlighted by noting that a large library of chlorosilanes are readily available from hydrosilylation reactions of alkenes.

Esquivel and co-workers[61] reported the synthesis of a novel thiol functionalized bis siloxy species as a precursor to the first 100% thiol functionalized periodic mesoporous organosilica. Key to this synthesis was the DMPA-mediated addition of ethanethioic *S*-acid to (*E*)-4,4,7,7-tetraethoxy-3,8-dioxa-4,7-disiladec-5-ene followed by reaction with *n*-propylamine to give the target thiol 4,4,7,7-tetraethoxy-3,8-dioxa-4,7-disiladecane-5-thiol. Employing Pluronic P123 as a template under acidic conditions the thiol-functional periodic mesoporous organosilica was prepared.

The majority of reports in recent years describing the use of thiol-ene chemistry have detailed its application for backbone, end-group and side chain modification of preformed (co)polymers. A wide variety of techniques have been employed in the synthesis of the precursor materials including anionic polymerisation,[62-65] pseudoliving cationic polymerisation,[66] atom transfer radical polymerisation (ATRP),[67-70] single electron transfer living radical polymerisation (SET–LRP),[71] reversible addition-fragmentation chain transfer (RAFT) radical polymerisation,[72-80] catalytic chain transfer polymerisation (CCTP),[81] coordination polymerization and ring-opening polymerisation,[77, 82-91] ROMP and acyclic diene metathesis (co)polymerisation (ADMET),[92-96] modification of preformed naturally occurring polymers[97] as well as conventional radical polymerisation.[98] We will systematically highlight examples of these reports based on the polymerisation technique as listed above.

Classical anionic polymerisation

In a detailed study, Li and co-workers[64] prepared a series of mono- and heterotelechelic polystyrenes employing combinations of anionic polymerisation, chain-end-functionalisation, thiol-ene chemistry and hydrosilylation, Scheme 15. Styrene was initially homopolymerised with 4-pentenyllithium as the initiator to give living polystyryl with an ene functional group at the α-chain end (**1**). The living chains were selectively terminated with CH_3OH to give (**2**), ethylene oxide/CH_3OH to give (**3**) and chlorodimethylsilane to give (**4**). With the ene groups still in tact, these reactive precursors were further functionalised with mercaptoacetic acid, 2-aminoethanethiol hydrochloride and 1*H*,1*H*,2*H*,2*H*-perfluoro-1-decanethiol in the presence of DMPA to give the thioether derivatives **5**-**7**, Scheme 15 (NB – **4** was converted to **7** via an OH functional intermediate obtained from the reaction of **4** with allyl alcohol in the presence of Karstedt's catalyst). The functional polymers were characterised via a combination of $^1H/^{13}C$ NMR spectroscopy, FT-IR spectroscopy, SEC and MALDI-TOF mass spectrometry and confirmed, in each case, 100% functionalisation of the chain ends.



Scheme 15 Synthesis of α-thioether functionalised polystyrenes via ene-functional precursors and radical thiol-ene coupling.

Kienberger and co-workers[63] reported the functionalisation of anionically polymerised isoprene with cysteamine in toluene with AIBN at 80°C for 20h. This process resulted in a brittle white solid with approximately 20% of the polyisoprene ene groups being successfully modified to give an amine-modified polymer. Subsequent protonation or exhaustive alkylation with butyl iodide yielded cationically charged polymers that exhibited biocidal activity against *L. monocytogenes, E. coli, S. aureus* and *P. fluorescens*.

Silverstein *et al*.[65] described the post-polymerisation modification of polystyrene-*block*-poly(1,2-butadiene) (PS-PB) diblock and PS-PB-PS triblock copolymers via radical thiol-ene chemistry with a series of five functional thiols. Initially the authors evaluated the effect of block copolymer molecular weight on dispersity and effective degree of functionalisation. For example, reactions of BOC-cysteamine with the pendent vinyl groups in the butadiene repeat units proceeded to give between 50 and 90% functionalised product with the lowest molecular weight species and 70-90% functional copolymer for higher molecular weight precursors. The less than quantitative degree of modification is not unexpected and is due to undesirable side reactions such as cyclisation and/or crosslinking and has been highlighted previously.[8] In general, a larger excess of thiol resulted in products with narrower molecular weight distributions. For example, in a PS(8,500 MW)-PB(8,000 MW) block copolymer the $Đ_M$ decreased from 1.45 to 1.12 (compared to 1.08 for the parent material) when the thiol:ene ratio was increased from 1 to 10. After optimisation, a range of functional materials was prepared with different thiols with degrees of functionalisation in the range 70-90%. The only exception to this was attempted reactions with thiosalicyclic acid, which failed to react due to steric constraints around the thiol group. The authors subsequently evaluated the thermal properties of the modified materials via differential scanning calorimetry and found that the glass transition temperatures increased after modification. Finally, thin film processing of the parent and modified polymers was examined. For example, in the case of the PS(63,000 MW)-*b*-PB(33,500 MW) parent copolymer disordered cylindrical nanostructures were observed via atomic force microscopy for a thin film cast from CH_2Cl_2, Figure 7A. Similar cylindrical patterned nanostructures were observed for many of the modified block copolymers such as the BOC-cysteamine and thioglycolic acid modified species, Figure 7B and 7C.

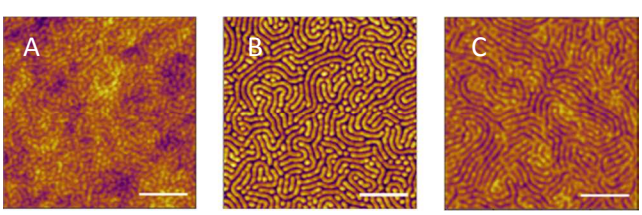


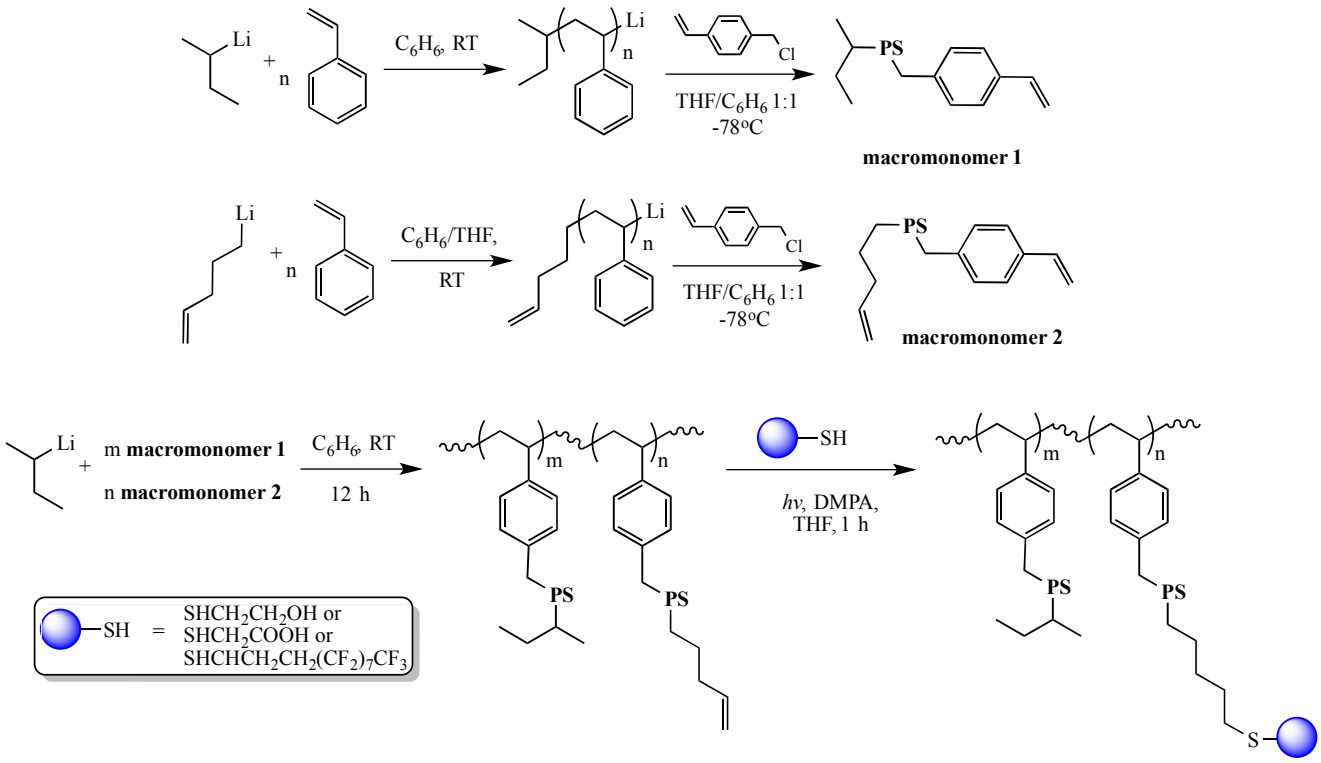
Figure 7 Atomic force microscopy images for a PS-b-PB copolymer: (A) the parent block copolymer, film cast from CH_2Cl_2; (B) BOC-cysteamine modified block copolymer, film cast from DMF; (C) thioglycolic acid modified copolymer, film cast from DMF. Scale bars are 500 nm. Professor Peter Kofinas is thanked for supplying the original image. Reproduced with permission from J. S. Silverstein, B. J. Casey, M. E. Natoli, B. J. Dair, P. Kofinas *Macromolecules* 2012, **45**, 3161-3167. Copyright 2012, American Chemical Society.

In elaborate syntheses, Liu *et al*.[99] reported the preparation of ω-branched, end-functionalised polystyrenes via a combination of living anionic polymerisation and radical thiol-ene coupling. The full synthetic procedure is given in Scheme 16. Initially, two ω-(*p*-vinylbenzyl)polystyrene macromonomers were prepared (macromonomers 1 and 2, Scheme 16) via termination of living polystyryl chains with 4-vinylbenzylchloride. In the case of macromonomer 2, the parent polystyrene chain was prepared via initiation with 4-pentenyllithium which, after end-capping, gave a macromonomer with free ene groups at both the α and ω termini. Subsequent copolymerisation of macromonomers 1 and 2, initiated by *sec*-butyllithium, gave the target comb copolymers with measured molecular weights close to the theoretical values and narrow molecular weight distributions. Importantly, since copolymerisation of macromonomer 2 proceeds exclusively through the ω-(*p*-vinylbenzyl) group the product comb polymers contain pendent enes (derived from the initiator employed for the preparation of the parent polystyrene) that are available for further radical thiol-ene reactions. In this instance these groups were reacted with three commercially available thiols: 2-mercaptoethanol, mercaptoacetic acid and 1*H*,1*H*,2*H*,2*H*-perfluoro-1-decanethiol employing a ~4 fold excess of thiol relative to ene groups and in the presence of a photoinitiator. Employing a combination of ^{1}H, ^{13}C and ^{19}F NMR spectroscopy the authors demonstrated the complete reaction of the pendent ene groups with no evidence of any undesirable side reactions.

Shao, Ni and Shen[62] reported the preparation of amphiphilic graft copolymers with a polyisoprene backbone and pendant PEG chains obtained via a combination of radical thiol-ene coupling with 2-mercaptoethanol to the backbone ene groups followed by an alcohol-isocyanate coupling with an isocyanate functional PEG species. The structure of the final amphiphilic graft copolymer was confirmed using a combination of SEC and ^{1}H NMR and FTIR spectroscopies.

Dimitriou *et al*.[100] reported the anionic/oxyanionic polymerisation synthesis of block copolymers of styrene with ethylene oxide and allyl glycidyl ether. After successful copolymerisation the pendent allylic groups were reacted (quantitatively) with 1*H*,1*H*,2*H*,2*H*-perfluorooctanethiol under UV irradiation in chlorobenzene yielding the fluorinated thioether species. The foul-releasing properties of the resulting materials were also demonstrated.

Pseudoliving Cationic Polymerisation



Scheme 16 Living anionic polymerisation of styrene to generate macromonomers and their subsequent copolymerisation and thiol-ene modification.

To date there has been relatively little on the combination of pseudoliving cationic polymerisation with thiol-ene modification. While there are a few older reports describing the post-modification of ene-end functional oligoisobutenes yields of the thioether products were average and often required extended reaction times.[101] However, more recently, Magenau *et al.*[66] reported the facile and essentially quantitative functionalization of *exo*-olefin polyisobutylene with a range of functional thiols. Near-monodisperse, low molecular weight mono- and difunctional *exo*-olefin polyisobutylenes were prepared via standard procedures and obtained with near-quantitative chain end functionality. The ene end groups were subsequently treated with a range of thiols including 1-chloro-3-mercaptopropane, cysteamine, Boc-protected cysteamine, mercaptoacetic acid and 5-mercapto-1-pentanol, Figure 8. Several points are worth noting. Firstly, as a general observation, essentially quantitative modification of the terminal enes was possible in 3.5-8 min especially if the reaction temperature was maintained below 15°C. A reaction with free cysteamine, and its HCl salt, proved unsuccessful and was attributed to formation of the thiolate species that was unable to undergo radical addition. However, Boc-protected cysteamine reacted rapidly and quantitatively. Finally, the authors demonstrated the ability to conduct a one-pot, two-step process involving radical thiol-ene addition of Boc-cysteamine to the *exo*-olefin followed by removal of the Boc protecting group via the direct addition of 50 vol% trifluoroacetic acid. After workup no by-products were detected and ^{1}H NMR and FTIR spectroscopies confirmed isolation of the target polyisobutylene-NH_2 species. The same group[102] also reported a complimentary approach to the above work, detailing the synthesis of α,ω-difunctional thiol-terminated polyisobutylene, Figure 9. α,ω-Bis bromo functionalised polyisobutylene was initially prepared via the direct quenching of a pseudoliving polyisobutylene to give α,ω-bis[4-(3-bromopropoxy) phenyl]polyisobutylene. The primary bromo groups were then converted to the corresponding thiols by reaction with thiourea followed by base hydrolysis and acidification. Such macromolecular dithiols now have the potential to be used as reagents in any of the broad range of chemistries associated with the mercapto functional group.

In this particular case the authors demonstrated three potential uses for the thiol polyisobutylene telechelics. Reactions of the thiol groups with propargyl acrylate via a thiol-Michael reaction under phosphine initiation yielded the corresponding alkyne telechelic species quantitatively. The yne groups were then subjected to a thiol-yne coupling reaction with a two-fold excess of 6-mercapto-1-hexanol in the presence of DMPA.

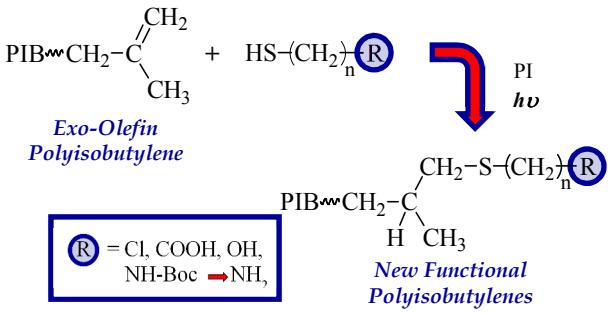


Figure 8 Chemical modifications of *exo*-olefins in polyisobutylene prepared by pseudoliving cationic polymerisation. Professor Robson Storey is thanked for supplying the original image. Reproduced from A. J. D. Magenau, J. W. Chan, C. E. Hoyle, R. F. Storey, *Polym. Chem.*, 2010, **1**, 831.

This gave the 1,2-addition product, as expected. Such two stage thiol-ene (thiol-Michael)/thiol-yne reactions with propargyl acrylate have been previously reported although with RAFT-prepared homopolymers.[103]

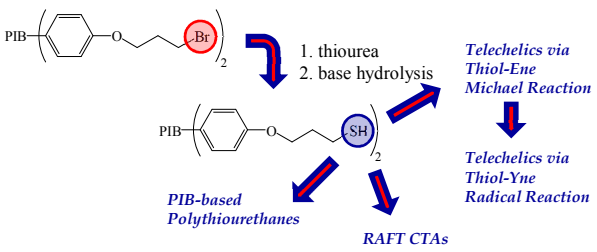
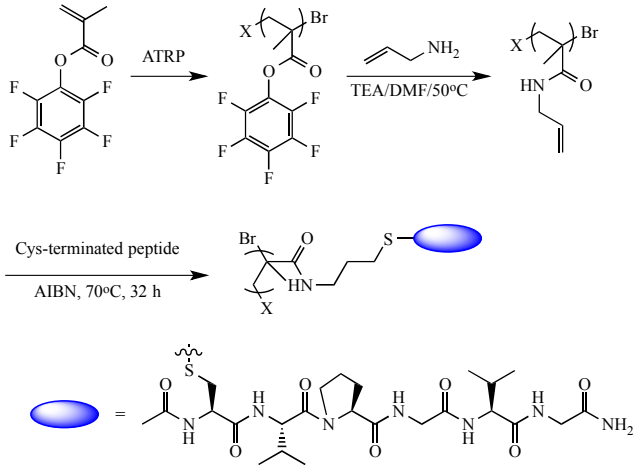


Figure 9 Synthesis of α,ω-thiol functional polyisobutylene and its subsequent use in a series of further chemical transformations. Professor Robson Storey is thanked for supplying the original image.

Additionally, the authors converted the terminal thiol groups into trithiocarbonates that have the potential to serve as macro chain transfer agents in RAFT radical polymerisation. Reaction with carbon disulfide followed by a straightforward alkylation with 2-bromopropionic acid yielded the telechelic polyisobutylene trithiocarbonates. Such straightforward and well-established chemistry clearly offers the potential to produce a range of novel RAFT mediating agents and hybrid polymeric materials. Unfortunately, their subsequent use as RAFT mediating agents was not evaluated. Finally, the authors highlighted the reaction of the telechelic thiols with isocyanates to give α,ω-functional polyisobutylene thiocarbamates, obtained from the reaction with phenyl isocyanate, as well as polythiourethanes.

Atom Transfer Radical Polymerisation (ATRP) and Single Electron Transfer Living Radical Polymerisation (SET-LRP)

Singha *et al.*[67] reported the synthesis of polymer-peptide conjugates via a combination of ATRP and radical thiol-ene chemistries. Pentafluorophenyl methacrylate (PFPMA) was initially polymerized to give homopolymers of low molecular weight (ca. 6.7-8.2K) and reasonably narrow molecular weight distributions ($Đ_M \leq 1.30$ as determined by size exclusion chromatography), Scheme 17. The homopolymers were then treated with allylamine in an acyl substitution reaction converting the pentafluorophenyl esters into the corresponding allyl-amide species giving, formally, poly(allyl methacrylamide) (PAMA). ^{1}H NMR analysis indicated 82% allyl side chain functionalisation. PAMA was then used as the reactive substrate in a radical thiol-ene reaction with the peptide CVPGVG, engineered to have a single cysteine residue. After prolonged heating a hydrophilic polymer was isolated with approximately 50mol% of the allylic groups successfully modified. Attempts to increase the degree of addition/modification were unsuccessful. Non-quantitative modification of ene side groups is not uncommon and has been observed previously and may be attributed to both steric effects and undesirable, competing, radical cyclisation reactions.

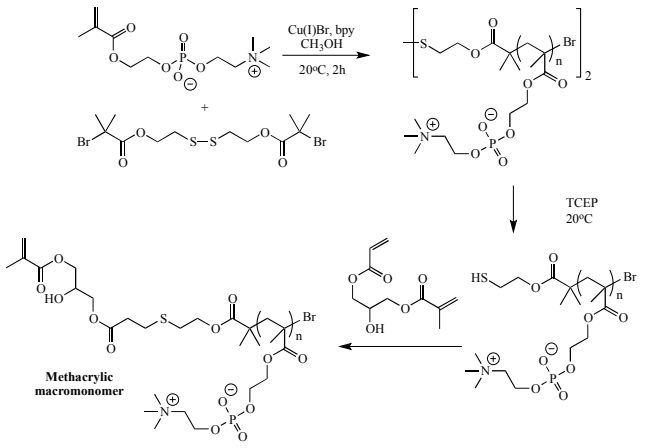


Scheme 17 ATRP-based synthesis of polymer-peptide conjugates via a combination of activated ester chemistry and thiol-ene click reactions.

Warren and co-workers[68] described the synthesis of methacrylic macromonomers based on 2-(methacryloyloxy)ethyl phosphorylcholine (MPC) employing a combination of ATRP and thiol-Michael coupling chemistry and evaluated their subsequent use as polymeric stabilisers in aqueous emulsions. MPC was initially homopolymerised with the difunctional, disulfide-containing initiator disulfanediylbis(ethane-2,1-diyl) bis(2-bromo-2-methylpropanoate), Scheme 18. Cleavage of the disulfide bridges with tris(carboxyethyl)phosphine (TCEP) gave the thiol-terminated polyMPC with molecular weights in the range 14,800-22,000 and corresponding $Đ_M$ values of 1.22-1.36. These thiol-terminated MPC homopolymers were then reacted with 3-(acryloyloxy)-2-hydroxypropyl methacrylate – a

difunctional species containing both acrylic and methacrylic groups. It is known that acrylic groups are far more reactive towards thiol-Michael addition than methacrylic species[10] and thus the conjugate addition reactions proceeded exclusively at the acrylic end to give the corresponding polyMPC methacrylic macromonomers. The structure of the methacrylic macromonomer species was confirmed by NMR spectroscopy.

With the MPC-based macromonomers in hand the authors then evaluated their use, along with the precursor homopolymers, as polymeric stabilisers in the emulsion polymerisation of styrene. For the poly MPC-methacrylate, MPC-thiol and MPC-disulfide, >90% conversions of styrene were achieved with the resulting lattices being near-monodisperse with average diameters < 200 nm as determined by dynamic light scattering and scanning electron microscopy, Figure 10.



Scheme 18 Outline for the synthesis of a polyMPC methacrylic macromonomer by sequential ATRP, disulfide cleavage and thiol-Michael conjugate addition reactions.

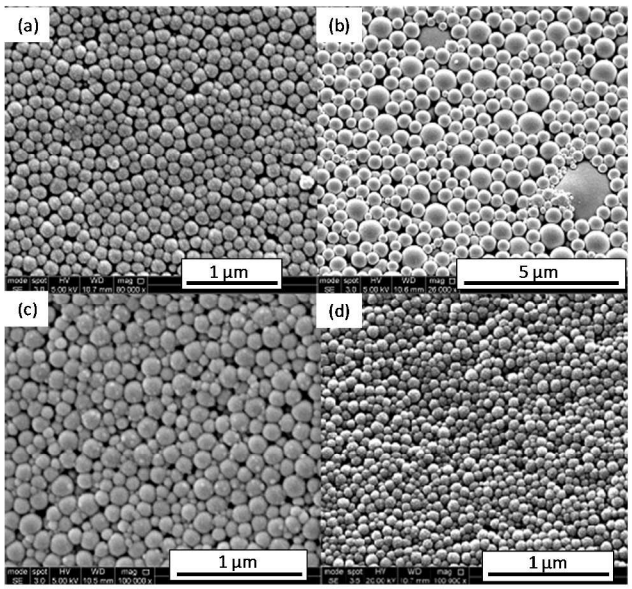


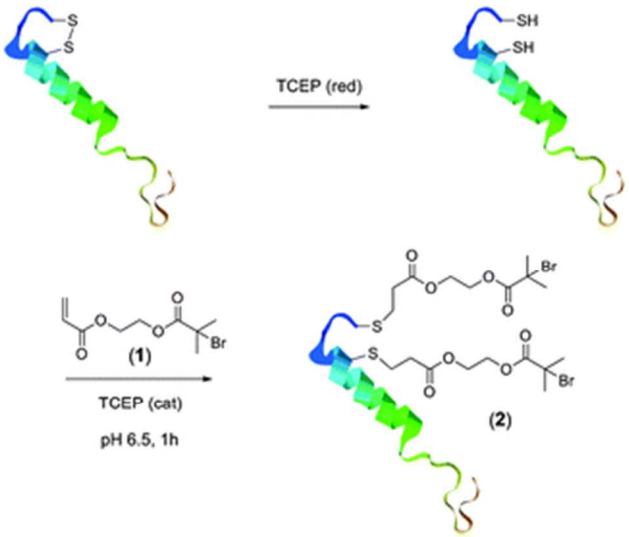
Figure 10 SEM images of polystyrene latexes prepared via aqueous emulsion polymerisation using a $PMPC_{30}$ macromonomer (a), no PMPC stabiliser (b), the $PMPC_{30}$ disulfide precursor (c), and the $PMPC_{30}$-SH species. Professor Steven P. Armes is thanked for supplying the original SEM images. Reproduced with permission from N. J. Warren, C. Muise, A. Stephens, S. P. Armes, A. L. Lewis *Langmuir* 2012, **28**, 2928-2936. Copyright 2012, American Chemical Society.

Syrett, Jones and Haddleton reported a similar approach for the synthesis of end-functionalised poly(methyl acrylate) via SET-LRP.[71] Methyl acrylate was homopolymerised employing the same disulfide-containing initiator highlighted above for the ATRP of MPC. In a subsequent one-pot process, the disulfide groups were reduced with dimethylphenylphosphine in the presence of an excess of an electron deficient ene resulting, ultimately, in the formation of end-functionalised poly(methyl acrylate) via a thiol-Michael conjugate addition process. The in situ-generated poly(methyl acrylate)-thiol was successfully conjugated to propargyl acrylate, trifluoroethyl methacrylate, methacrylamide and (2-(methacryloyloxy)ethyl)phosphonic acid. Successful conjugation was confirmed using a combination of MALDI-TOF MS and NMR spectroscopy.

Jones and coworkers[104] reported the synthesis of thermoresponsive polymer-protein conjugates employing a combination of nucleophilic thiol-Michael coupling and SET-LRP and the 'grafting from' approach. Salmon calcitonin (sCT) was first treated with TCEP to cleave a disulfide bridge followed by reaction with 2-((2-bromo-2-methylpropanoyl)oxy)ethyl acrylate in a thiol-Michael addition reaction to give the sCT-SET-LRP macroinitiator. This was then employed in the (co)polymerisation of two oligoethylene glycol methacrylates (diethylene glycol methyl ether methacrylate (DEGMEMA) and triethylene glycol methyl ether methacrylate (TEGMEMA)) to give the target polymer-protein conjugates, Scheme 19. Formation of the polymer-protein conjugates was confirmed using SEC. Homopolymers of DEGMEMA and TEGMEMA exhibit lower critical solution temperatures (LCSTs) in aqueous media of 26 and 52°C respectively.[105, 106] With the polymer-protein conjugates in hand the authors evaluated their thermoresponsive properties using a combination of turbidity and dynamic light scattering experiments. Interestingly, the DEGMEMA- and TEGMEMA-sCT conjugates exhibited LCSTs of 24 and 51°C – essentially identical to those reported for the corresponding homopolymers. Finally, the authors demonstrated that the LCST could be tuned simply by preparing a 1:1 DEGMEMEA:TEGMEMA-sCT conjugate via the straightforward statistical copolymerization of the two monomers with the sCT macroinitiator. The obtained copolymer-protein conjugate exhibited an LCST of 37°C – roughly intermediate that of the corresponding homopolymers.

Candan *et al*. reported rather elaborate syntheses involving ATRP of a parent styrene homopolymer followed by quadruple click reactions for the synthesis of cysteine-terminated multiblock copolymers.[70] This is shown schematically in Figure

11. The parent homopolymer was prepared with allyl 2-bromo-2-methylpropanoate as the ATRP initiator giving a well-defined low molecular weight homopolymer (M_n = 5,500; $Đ_M$ = 1.08 as determined by SEC) with an allyl group at the α terminus and the expected bromo group at the ω chain end. The bromo group was then converted to an azido functional group by reaction with sodium azide followed by reaction of the allylic group with *N*-acetyl-L-cysteine methyl ester under radical conditions to give the thiol-ene adduct forming α-cysteine-ω-azide terminated polystyrene (the first click step). The second click process involved reaction of the ω-azide functional group on the polystyrene with an α-anthracene-ω-alkyne poly(ε-caprolactone) via a Cu-catalysed alkyne-azide coupling. This gave an AB diblock copolymer of polystyrene with ε-caprolactone with α-cysteine and ω-anthracene functional groups in which the two blocks are joined by a triazole (cysteine-PS-*b*-PCL-anthracene). This AB diblock copolymer was subsequently reacted with either α-furan protected maleimide-ω-halide-poly(methyl methacrylate) or poly(*tert*-butyl acrylate) via a Diels-Alder coupling reaction. Upon heating the reaction mixture, free maleimide poly(meth)acrylate is liberated via a retro Diels Alder reaction with then undergoes a normal Diels-Alder reaction with the anthracene functionality in cysteine-PS-*b*-PCL-anthracene. This gives a triblock copolymer of PS-PCL-poly(meth)acrylate with cysteine α functionality and halo (Cl or Br) ω functionality. In a final step this triblock copolymer was reacted with a TEMPO-α-functional poly(ethylene glycol) in a nitroxide radical coupling (NRC) click reaction to give the final tetrablock copolymer of PS-*b*-PCL-*b*-poly(meth)acrylate-*b*-PEG. At each coupling step the purity and efficiency of the reaction was confirmed using a combination of NMR spectroscopy and SEC.



Scheme 19 SET-LRP of thermoresponsive sCT-polymer conjugates. Reproduced from M. W. Jones, M. I. Gibson, G. Mantovani, D. M. Haddleton *Polym. Chem*., 2011, **2**, 572-574.

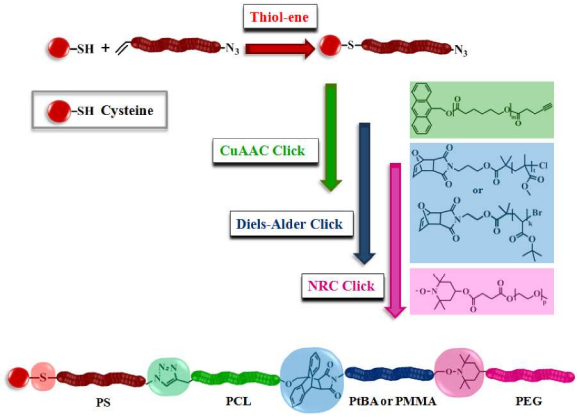


Figure 11 The synthesis of a tetrablock copolymer via four distinct, sequential click coupling reactions of preformed (co)polymers. Professor Ümit Tunca is kindly thanked for supplying the original image. Reproduced with permission from O. A. Candan, H. Durmaz, G. Hizal, U. Tunca *J. Polym. Sci., Part A: Polym. Chem*. 2012, **50**, 2863-2870. Copyright 2012, Wiley Periodicals, Inc.

For example, Figure 12 shows the SEC eluograms for each of the four polymeric species and demonstrates the relatively well-defined nature of each species and attests to the efficiency of each conjugation process.

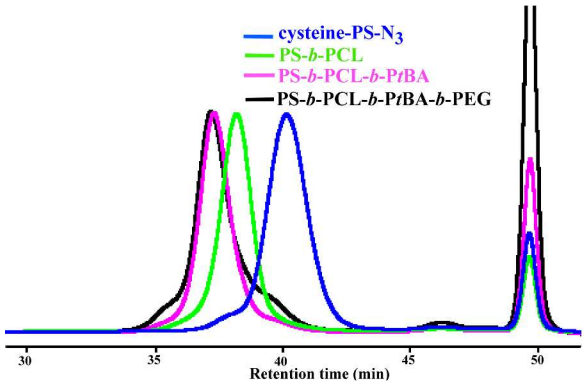
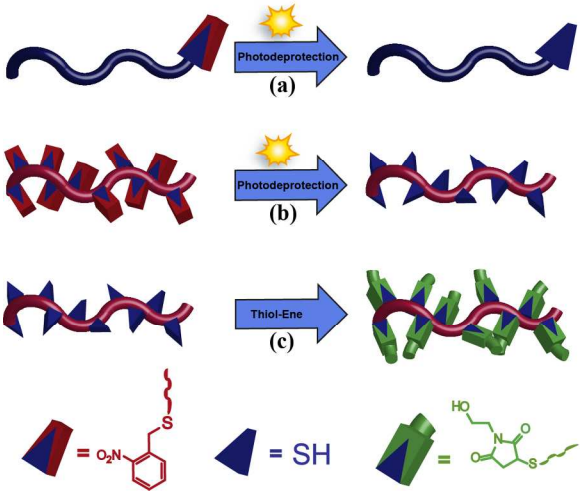


Figure 12 SEC traces of the starting homopolymer, final tetrablock copolymer and intermediate di- and tri-block species prepared via sequential click reactions. Professor Ümit Tunca is kindly thanked for supplying the original image. Reproduced with permission from O. A. Candan, H. Durmaz, G. Hizal, U. Tunca *J. Polym. Sci., Part A: Polym. Chem*. 2012, **50**, 2863-2870. Copyright 2012, Wiley Periodicals Inc.

In recent years there has been some interest in the use of protected or masked thiols, often, but not exclusively, incorporated in a monomer, including examples of photo-liberated species. For example, Pauloehrl *et al.*[107] described the facile, light-triggered release of thiols at ambient temperature that could be used as a methodology for end and side-chain

functionalisation. The general approach is shown schematically in Scheme 20. Key to this approach is the use of species containing the photolabile 2-nitrobenzyl thioether moiety. For example, the novel monomer 2-((3-((2-nitrobenzyl)thio)propanoyl)oxy)ethyl methacrylate was prepared and polymerised by ATRP to give well-defined homopolymers with number average molecular weights between 4,700 and 20,000 and $Đ_M$ values between 1.29 and 1.40. Irradiation (λ_{max} = 320 nm) liberated free thiols along the polymer chain and was conveniently monitored by following the increase in the concentration of released *o*-nitrosobenzaldehyde species by UV-Vis spectroscopy at 345 nm. The data suggested complete photodeprotection after 16 h. This, of course, yields a polythiol that can be further exploited as a reactive scaffold in a range of chemical transformations. In this instance the authors reported the in situ modification of the pendant mercapto groups with 1-(2-hydroxyethyl)-1*H*-pyrrole-2,5-dione in a base catalysed thiol-Michael reaction. NMR spectroscopy indicated a degree of successful backbone modification in excess of 90%.



Scheme 20 Idealised deprotection of photolabile protecting groups located at polymeric end groups and side groups generating macromolecular thiols and their subsequent thiol-Michael coupling with a maleimide. Professor Christopher Barner-Kowollik is kindly thanked for supplying the original image. Reproduced from T. Pauloehrl, G. Delaittre, M. Bastmeyer, C. Barner-Kowollik *Polym. Chem.,* 2012, **3**, 1740-1749.

Recently, Rahimian-Bajgiran and co-workers[108] reported a new approach to tuning the LCST behaviour of poly(oligo ethylene glycol) methacrylate copolymers via the conversion of pendant disulfides to thiols followed by thiol-Michael addition. Precursor copolymers were prepared by ATRP with varying amounts of the hydrophobic, disulfide containing comonomer. Cleavage of the pendant disulfide bonds with dithiothreitol gave the free thiol species and was accompanied by an increase in the LCST compared to the parent polymer. Subsequent reaction of the thiol groups with *tert*-butyl acrylate, catalysed with *n*-butylamine, gave the corresponding Michael adduct and resulted in a lowering of the LCST to a value intermediate of the parent and free-thiol polymers.

Reversible Addition-Fragmentation Chain Transfer (RAFT) Radical Polymerisation

Since the current popularity of thiol-based conjugation chemistries in polymer synthesis and modification can, to a large extent, be traced to novel applications associated with RAFT radical polymerisation (by virtue of the fact that (co)polymers prepared by this technique can be considered as masked macromolecular thiols), it is perhaps not surprising that there continues to be significant interest in combining this particular synthesis technique with a variety of thiol-based chemistries as a means to prepare novel and interesting new materials.

In an interesting variant of instilling end-groups in RAFT-prepared (co)polymers via thiol-ene chemistry (most commonly done at the ω-terminus and exploiting the masked thiol associated with the thiocarbonylthio group[20, 21, 109]), Stamenović *et al*.[79] described the synthesis and application of a series of R-group functional RAFT chain transfer agents that contained norbornenyl groups as part of the R-group fragment (thus instilling thiol-ene reactive functionality at the **α**-termini). This included dithioester, xanthate and trithiocarbonate derivatives, Figure 13. Such RAFT agents are attractive since it is well-documented that norbornenes represent the most reactive substrates towards radical thiol-ene addition reactions.[5, 110]

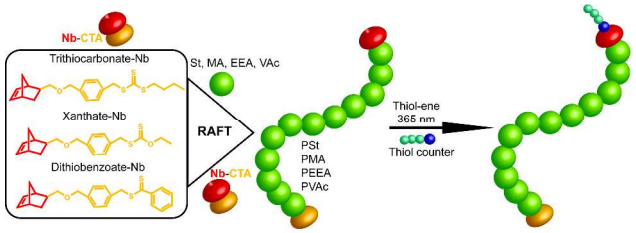


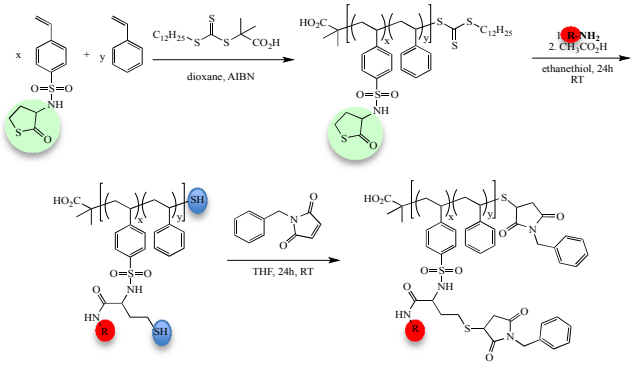
Figure 13 Chemical structures of norbornenyl-functional RAFT chain transfer agents, their use as mediating agents in RAFT homopolymerisations and finally their availability for radical thiol-ene conjugations post-polymerisation. Professor Filip du Prez is thanked for supplying the original image. Reproduced with permission from M. M. Stamenović, P. Espeel, W. V. Camp, F. E. Du Prez *Macromolecules* 2011, **44**, 5619-5630. Copyright 2011, American Chemical Society.

This new family of RAFT agents were effective in mediating the controlled polymerisation of acrylates, styrene and vinyl acetate without undesirable participation of the norbornenyl functional groups albeit under rather specific conditions (limited conversions, controlled polymerisation temperature, and high monomer-to-CTA ratio). Subsequent radical thiol-ene reactions with the norbornenyl functionality was demonstrated to be rapid and generally high yielding although dodecanethiol and benzyl mercaptan required the use of a 5x excess of thiol

(relative to ene) to achieve high conversions to the thioether adducts.

Ho and coworkers[111] reported the synthesis of novel oxazolone ω-functional poly(*N*-isopropylacrylamide) via the hexylamine-mediated aminolysis of the trithiocarbonate end-groups in the parent polymer followed by dimethylphenylphosphine catalysed thiol-Michael addition of the macromolecular thiol with 2-vinyl-4,4-dimethylazlactone (VDMA). NMR analysis confirmed quantitative formation of the azlactone end-functional polymer. Azlactone groups are extremely useful reactive handles and react readily with a range of nucleophiles including thiols, alcohols and amines. The ability to further modify the azlactone functional polymer was demonstrated in its reaction with 4-fluorobenzylamine, which was shown to quantitatively ring open and add to the azlactone species.

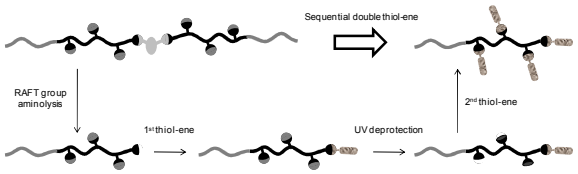
Espeel and co-workers reported a novel approach for simultaneous functionalisation of the ω-chain end and side chain moieties in polystyrene-based copolymers.[112] This approach is complimentary to that detailed above by Pauloehrl *et al.*[107] as a method for introducing free side chain thiol groups. Key to success in this work was the synthesis of the novel thiolactone-containing styrenic derivative *N*-(2-oxotetrahydrothiophen-3-yl)-4-vinylbenzenesulfonamide which was shown to readily copolymerize, employing a trithiocarbonate CTA, with styrene to give well-defined copolymers of intermediate molecular weights and narrow molecular weight distributions, Scheme 21. Importantly, the thiolactone ring can be readily opened by reaction with primary amines giving a free thiol and a new functionality, R, the structure of which is dependent on the primary amine employed in the ring-opening reaction. However, it is also noted that since the parent copolymer was prepared by RAFT, reaction with a primary amine will also cleave the trithiocarbonate end-groups additionally liberating a free thiol at the ω-chain end. In the above example, the authors reacted the precursor copolymer with four different amines: benzylamine, a Jeffamine, 2-aminoethanol and propylamine in the presence of ethanethiol as a reducing agent to give the ring-opened/end group cleaved product and copolymers containing new amine-derived groups in the side chain, Scheme 21.



Scheme 21 Synthesis of styrenic-based polythiols and their simultaneous end- and side-group functionalisation via thiol-Michael coupling with a functional maleimide.

In a second step, the free thiol groups (on the side chain and end group) were reacted with *N*-benzylmaleimide under basic conditions in a thiol-Michael coupling reaction. SEC and NMR spectroscopic analysis indicated near-quantitative modification and retention of the narrow unimodal molecular weight distributions. Finally, the authors extended the process to copolymers of *N*-(2-oxotetrahydrothiophen-3-yl)-4-vinylbenzenesulfonamide with methyl methacrylate. The same group have also reported a similar approach for the modification of statistical copolymers of poly(*N*-isopropylacrylamide) with the thiolactone comonomer *N*-(2-oxotetrahydrothiophen-3-yl)acrylamide.[113]

Previously, we noted that Pauloehrl *et al.*[107] reported the synthesis of a novel methacrylic monomer with a photolabile protecting group as a means of introducing pendent thiol groups in ATRP syntheses. The same group have extended this concept to (meth)acrylamido-based polymeric derivatives employing the corresponding (meth)acrylamide derivatives *N*-(2-((2-nitrobenzyl)thio)ethyl) acrylamide and *N*-(2-((2-nitrobenzyl)thio)ethyl) methacrylamide in RAFT (co)polymerisations.[74] In a manner similar to the previous work these new monomers were employed to facilitate post-polymerisation modification by thiol-ene chemistry but also end-group functionalisation by virtue of the synthesis technique and the availability of a thiol from the thiocarbonylthio-mediating agent. The general synthetic approach is shown in Scheme 22. While the RAFT homopolymerisation of *N*-(2-((2-nitrobenzyl)thio)ethyl) acrylamide was possible, yields were low and polymerisations slow, possibly due to the nitrobenzyl species acting as a retarder. However, it was possible to prepare statistical copolymers or amphiphilic block copolymers via the use of *N,N*-dimethylacrylamide and/or NIPAM as comonomers.

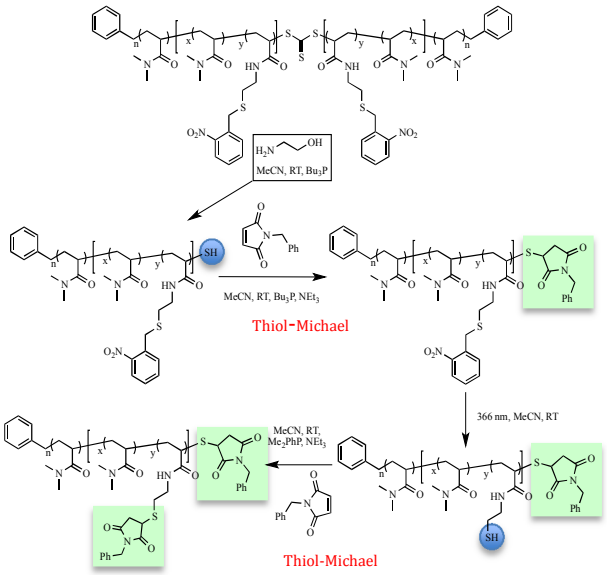


Scheme 22 General synthetic approach to the preparation of thiol-ene end- and side-chain modified (co)polymers via sequential deprotection/coupling strategies. Professor Christopher Barner-Kowollik is kindly thanked for supplying the original image. Reproduced with permission from G. Delaittre, T. Pauloehrl, M. Bastmeyer, C. Barner-Kowollik *Macromolecules* 2012, **45**, 1792-1802. Copyright 2012, American Chemical Society.

Scheme 23 highlights the preparation of one such copolymer and the subsequent deprotection and conjugation reactions involving sequential thiol-Michael reactions. It is important to note that while the authors chose to perform sequential thiol

Michael reactions with *N*-benzylmaleimide this is by no means limiting and alternative Michael acceptors or thiol-based reactions could have been conducted. For example a chain end thiol-Michael reaction could easily be followed by a side chain radical thiol-ene, thiol-isocyanate or thiol-halo conjugation as a means of introducing desired functionality.

The use of thiolactone and nitrobenzyl functional species as masked or protected thiols are not the only groups that can be used to introduce free thiol species into the side chains of RAFT-prepared (co)polymers. An alternative based on acetyl protected thiols was recently reported by Hrsic and co-workers.[114] Block copolymers of poly(ethylene glycol) methyl ether methacrylate with 6-acetylthiohexyl acrylate were readily prepared by dithioester mediated RAFT polymerisation to give well defined macromolecules with narrow molecular weight distributions in high yield with measured molecular weights of ca. 20,000. Such amphiphilic species self-assembled in aqueous media to give polymeric micelles with 6-acetylthiohexyl acrylate forming the hydrophobic core and hydrodynamic radii in the range 12-130 nm depending on the composition. Removal of the acetyl protecting groups, and dithioester end groups, was achieved by treatment with *n*-propylamine to give the analogous free thiol species that were still able to undergo self-assembly in aqueous media. While the authors did not exploit these mercapto groups in thiol-ene reactions they did demonstrate the ability to core crosslink the micelles via simple aerial oxidation of the thiols to disulfides.

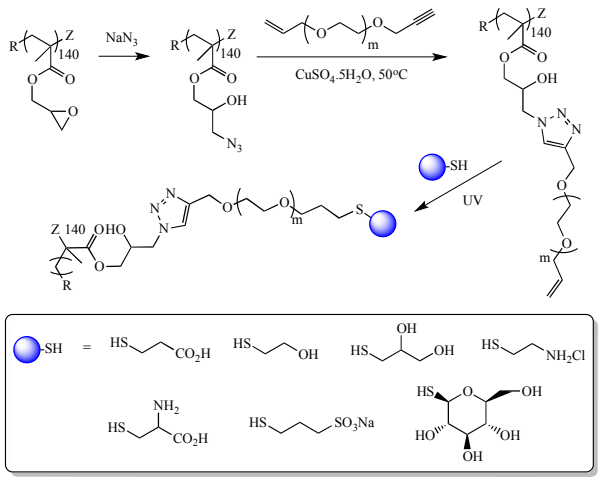


Scheme 23 End and side chain modification of an *N,N*-dimethylacrylamide-*N*-(2-((2-nitrobenzyl)thio)ethyl) acrylamide based block copolymer via sequential aminolysis, thiol-Michael, photodeprotection and thiol-Michael reactions.

Yhaya *et al.*[72] described the RAFT homo- and co-polymerization of vinyl methacrylate to give a series of polymers containing pendent vinyl ester functionality. Novozyme 435 was then employed as an enzymatic catalyst for the addition of a range of thiols, in DMF at 50°C for 72 hours, to the pendent ene bonds. While certain small, primary thiols such as butanethiol gave quantitative thioether products under these conditions, larger, bulkier thiols such as 11-mercapto-1-undecanol (5% conversion) or mono(6-deoxy-6-mercapto)-β-cyclodextrin (35% conversion) resulted in incomplete reactions, perhaps highlighting a limitation of the enzymatic route for effective thioether formation.

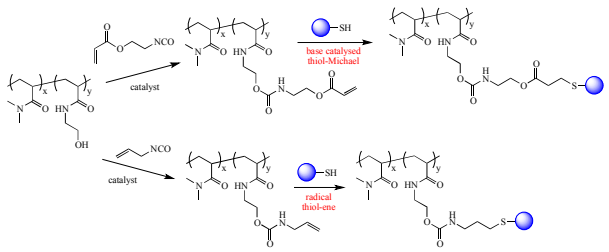
Additional examples of RAFT copolymers with ene functionality in the side chains that have been exploited in post-polymerisation thiol-ene reactions include the work of Jia *et al.*[73] and Wang and co-workers.[115] In the case of the former, 2-vinyloxyethyl methacrylate was prepared and polymerised to give branched polymers (due to some inevitable copolymerisation of the vinyloxy functional group which gives pendant methacrylate reactive groups). However, free ene groups in the branched polymers could be reacted with thiols such as 2-mercaptoethanol and 3-mercaptopropionic acid to give the corresponding thioether functional branched materials. In the case of the latter, AB diblock copolymers of 3-*O*-methacryloyl-1,2:5,6-di-*O*-isopropylidene-D-glucofuranose with 2-hydroxyethyl methacrylate (HEMA) were first prepared and then reacted with acryloyl chloride to acylate the pendent OH groups in the HEMA repeat units thus introducing activated enes into the copolymer side chains. The isopropylidene protecting groups were then removed to give the free sugar repeat units followed by a thiol-Michael coupling of the activated enes with reduced L-glutathione to give comb-shaped glycopolymer/peptide bioconjugates. These species were able to undergo self-directed assembly in aqueous media to give glycopolymer-stabilised micelles that were shown to have a specific interaction with Concanavalin A.

Zou *et al.*[116] prepared a novel ene containing homopolymer derived from poly(glycidyl methacrylate) via sequential NaN_3 ring-opening and Cu-catalysed coupling of the newly introduced azido groups with the yne functionality in an α-allyl-ω-propargyl PEG derivative, Scheme 24. The resulting allyl functional homopolymer was then reacted with a series of small molecule thiols under UV-initiated radical conditions to give a new family of thioether-based functional homopolymers. The authors claimed >99% functionalisation for all thiols provided a 10x excess of thiol was employed relative to ene and reactions were performed for 4 h.



Scheme 24 Synthesis of a novel ene containing methacrylic homopolymer derived from poly(glycidyl methacrylate) and its radical thiol-ene modification with a series of thiols to give novel thioether products.

Flores and co-workers[117] described the side chain modification of parent block copolymers of *N,N*-dimethylacrylamide and *N*-(2-hydroxyethyl)acrylamide via sequential alcohol-isocyanate and hydrothiolation reactions. Both radical thiol-ene and base-catalysed thiol-Michael reactions were employed, Scheme 25. The OH side groups in the parent block copolymer was first reacted with 2-isocyanatoethyl acrylate or allyl isocyanate in the presence of dibutyltin dilaurate at 40°C in the presence of a radical inhibitor to give the corresponding acrylate and allyl side-chain functional block copolymers. The authors reported quantitative modification as determined by NMR spectroscopy and qualitatively by FTIR spectroscopy. These ene functional materials were then subjected to hydrothiolations employing a range of thiols (including the majority of those previously listed in other works) employing base catalysed thiol-Michael addition for the acrylate functional copolymers and thermal radical thiol-ene reactions initiated by 2,2'-azobis(2,4-dimethylvaleronitrile) for the allyl functional species. In the case of the thiol-Michael conjugate additions, hydrothiolation conversions >99% were reported for all thiols employing a slight excess of thiol relative to ene. The exception was *tert*-butylmercaptan that required a 5-fold excess to achieve near-quantitative modification. Also, it is noted that thiols containing acidic functionality required a greater than equimolar concentration of NEt_3 as catalyst (relative to ene) to achieve high conversions. The radical thiol-ene reactions were overall less widely applicable even with a 10x excess of thiol. While quantitative degrees of hydrothiolation were reported for some simple thiols such as propanethiol, *tert*-butylmercaptan, 2-mercaptoethanol and 3-mercaptopropionic acid lower (or zero) conversions were reported for thiophenol, thioglycerol, cysteamine hydrochloride and 2-mercaptosuccinic acid.



Scheme 25 Modification of a poly(*N,N*-dimethylacrylamide)-*block*-poly[*N*-(2-hydroxyethyl)acrylamide] copolymer via sequential alcohol-isocyanate and thiol-Michael/thiol-ene conjugations.

In a complimentary approach employing mask maleimides, Yilmaz, Arslan and Sanyal reported the synthesis of styrenic-based (co)polymers that contain side-chain functional groups susceptible to thiol-Michael and radical thiol-ene conjugation reactions, including examples prepared by RAFT radical polymerisation.[118]

Vandenbergh and Junkers[119] detailed a facile process for obtaining end-modified, RAFT-prepared poly(*n*-butyl acrylate) via the use of a continuous-flow microreactor – a process that has the potential to readily facilitate the large scale production of such materials in an essentially quantitative and ready-to-use manner. However, in this particular report the authors limited themselves to milligram scale reactions at ambient temperature. In a typical reaction, the low molecular weight poly(*n*-butyl acrylate) ($\bar{M}_n$ = 3,800 and $Đ_M$ = 1.10) was initially mixed with 10 eq. of the target acrylic Michael acceptor, e.g. isobornyl acrylate, Figure 14. The reaction was started via the mixing in the reactor of this polymer/acrylate solution with the second solution – a mixture of THF with 10 eq. of hexylamine. The reaction was monitored by ESI mass spectrometry. After a reaction time of only 5 min a significant amount of the conjugate addition product is observed while after 10 min. it represents the most abundant species in the ESI mass spectrum. With virtually complete consumption of the starting materials. Essentially complete conversion to the target product is seen after 20 min. Similar observations were made for other monofunctional acrylates as well as the tetrafunctional species pentaerythritol tetraacrylate although in the case of the latter impurities were also observed that were attributed to the relatively low purity of the parent 4-functional acrylate.

Bian, Xiao and Lang reported the elaborate synthesis of 4-arm star amphiphilic block copolymers employing a combination of ring opening polymerisation of ε-caprolactone with a tetrafunctional initiator, conversion of the resulting OH end-groups to trithiocarbonate species followed by RAFT copolymerisation of *N*-isopropylacrylamide with *N,N*-dimethylacrylamide to give an A-*block*-(B-*co*-C) co-polymer. The trithiocarbonate end groups were then cleaved in the presence of 2-hydroxyethyl acrylate and Bu_3P to reintroduce terminal OH functionality via a thiol-Michael

conjugate addition process and finally these OH groups were reacted with biotin in a carbodiimide-mediated coupling of the star block copolymer, Scheme 26.[77] Products and intermediate polymeric species were characterized by a combination of UV-Vis spectroscopy, SEC and NMR spectroscopy to confirm formation of the desired species and retention of the well-defined molecular characteristics. Each of the star copolymer species are inherently amphiphilic with the poly(ε-caprolactone) segments being hydrophobic. As such, the authors monitored the self-assembly of the star block copolymers in aqueous media employing NMR and fluorescence spectroscopies with pyrene as a hydrophobic fluorescence probe molecule. The nature of the end-groups in the star block copolymers (trithiocarbonate vs. OH vs. biotin) was demonstrated to have an effect on the critical micelle concentration (CMC), hydrodynamic diameter of the self-assembled species, and the LCST. Finally, the authors noted the ability of the biotin-functional micelles to selectively bind avidin as monitored by dynamic light scattering and UV-Vis spectroscopy. Given that avidin has four available binding sites for biotin, interaction of the polymeric micelles with avidin resulted in the formation of interconnected, crosslinked micelles, Scheme 26.

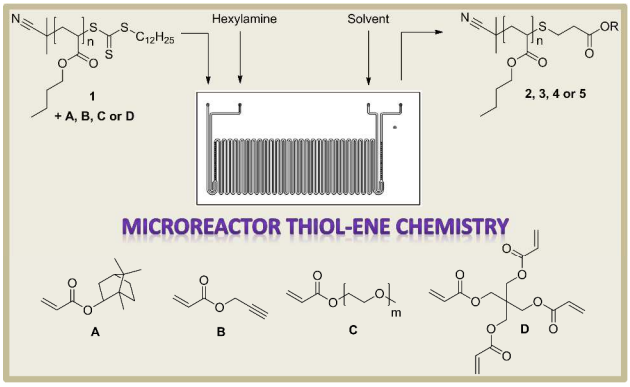
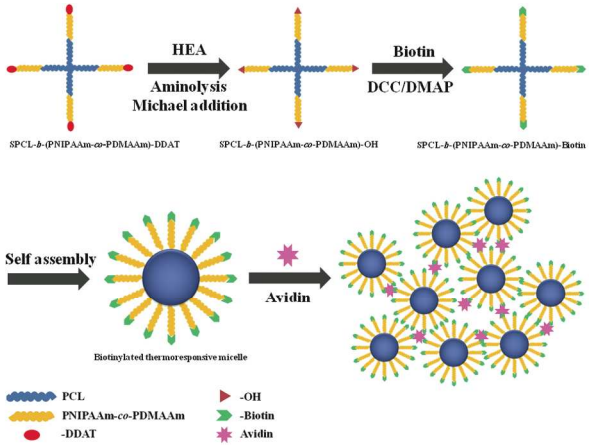


Figure 14 Micro-flow reactor set up for the thiol-Michael end-group modification of a low molecular weight parent poly(*n*-butyl acrylate). Professor Thomas Junkers is thanked for supplying the original Figure. Reproduced with permission from J. Vandenbergh, T. Junkers *Polym. Chem.* 2012, **3**, 2739-2742. Copyright 2012, RSC Publications.



Scheme 26 Preparation of 4-arm star copolymers employing a combination of ring-opening polymerisation and reversible addition fragmentation chain transfer polymerisation followed by end group cleavage in the presence of 2-hydroxyethyl acrylate and finally carbodiimide coupling with biotin. Dr. Yan Xiao is thanked for supplying the original image. Reproduced with permission from Q. Bian, Y. Xiao, M. Lang *Polymer* 2012, **53**, 1684-1693. Copyright 2012, Elsevier Ltd.

In another example of fairly elaborate syntheses in which thiol-Michael coupling plays an important role was reported by Yin and co-workers.[75] Isoprene was initially polymerised by living anionic polymerisation, functionalised at the ω-terminus with ethylene oxide and then hydrogenated (>99%) to give a poly(ethylene-alt-propylene)-OH (PEP-OH) functional material of low molecular weight (3,200) and narrow molecular weight distribution ($Đ_M$ = 1.05). The PEP-OH was then esterified with a trithiocarbonate chain transfer agent to give a novel macro CTA. This was then employed in the gradient copolymerisation of *N,N*-dimethylacrylamide with α-2-deoxy-2-methacrylamido-1,3,4,6-tetra(*O*-trimethylsilyl)-D-glucopyranose with varying target molar incorporations. Following facile removal of the trimethylsilyl protecting groups (>99% at 25°C after 2 min via acid catalysed methanolysis) the trithiocarbonate end group was removed via aminolysis with *n*-butylamine followed by reaction with either methyl or 2-hydroxyethyl acrylate to give the thiol-Michael adduct. This final step was performed to remove the long C12 alkyl chain associated with the macro-CTA to avoid any interference in subsequent self-assembly studies in aqueous media. The chemical structure of the final copolymers is given in Figure 15. Such terpolymers are inherently amphiphilic and undergo self-directed assembly in aqueous media to form spherical micelles with measured hydrodynamic radii of ca. 15.0 nm. However, it is noted that sample preparation was a crucial factor in obtaining low dispersity micellar solutions especially for samples with higher sugar contents. The micellar solutions were thoroughly characterised by dynamic light scattering and cryogenic transmission electron microscopy. Finally, the stability of the glucose functionalised polymeric micelles were evaluated in four biologically relevant media namely PBS (with physiological salts), Opti-MEM (with physiological salts and other small molecule nutrients), DMEM + 10% FBS (partial serum) and 100% FBS (full serum). As a general observation, the glucose functionalised nanoparticles resisted serum protein absorption over an extended period of time (>12 h) demonstrating the potential utility of such nanoassemblies as *in vivo* drug delivery vehicles, Figure 16.

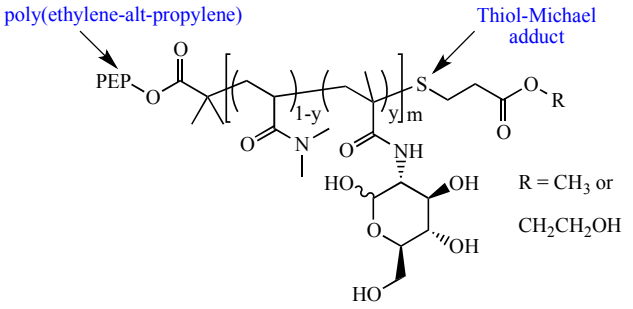


Figure 15 Chemical structure of poly(ethylene-*alt*-propylene)-*block*-poly[(*N,N*-dimethylacrylamide)-*grad*-(2-methacrylamido glucopyranose)].

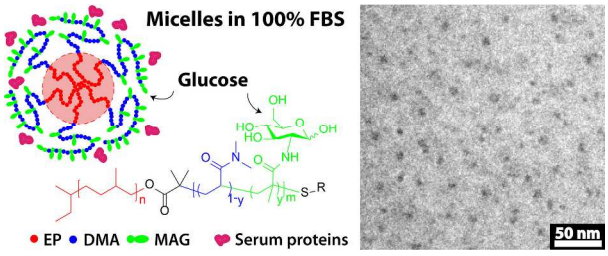
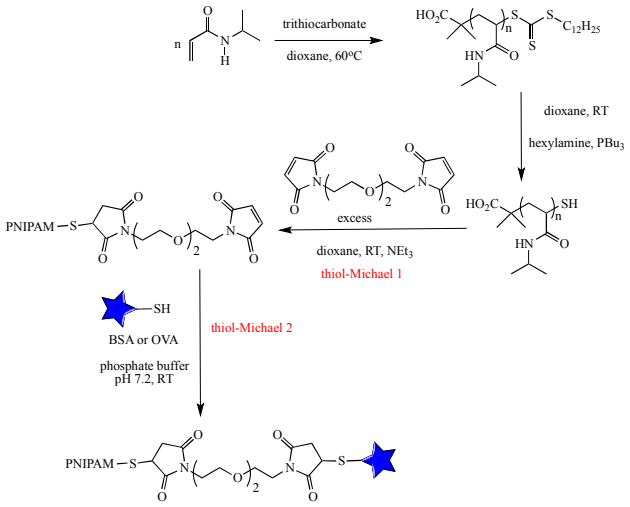


Figure 16 Chemical structure of the idealized terpolymer, its self-assembled, micellar state and a TEM image highlighting the spherical nature of the polymeric self-assemblies. Professor Marc A. Hillmyer is thanked for supplying the original image. Reproduced with permission from L. Yin, M. C. Dalsin, A. Sizovs, T. M. Reineke, M. A. Hillmyer *Macromolecules* 2012, **45**, 4322-4332. Copyright 2012, American Chemical Society.

Given that many biologically relevant molecules including examples of pharmaceutics, proteins and peptides contain free sulfhydryl groups it is perhaps not surprising that researchers have explored thiol-ene chemistry as a means of preparing polymer/bio-relevant conjugates. For example, Li and co-workers[120] reported the conjugation of bovine serum albumin (BSA) or ovalbumin (OVA) to well-defined, RAFT-prepared, poly(*N*-isopropylacrylamide) via two sequential thiol-Michael coupling reactions, Scheme 27. Preparation of a poly(*N*-isopropylacrylamide) homopolymer was followed by a thiocarbonylthio end-group aminolysis with hexylamine in the presence of PBu_3 to give the corresponding macromolecular thiol. In the first thiol-Michael coupling, this macromolecular thiol was reacted with 1,8-bismaleimidodiethyleneglycol under basic conditions yielding the maleimide end functional poly(*N*-isopropylacrylamide). In a second thiol-Michael reaction, the free maleimide group was reacted with BSA or OVA to give the target polymer-protein conjugates. Successful formation of the polymer-protein conjugates was confirmed using a combination of SDS-PAGE and SEC.



Scheme 27 Outline for the synthesis of polymer-protein conjugates of RAFT-prepared poly(*N*-isopropylacrylamide) with bovine serum albumin or ovalbumin via two sequential thiol-Michael reactions.

For example, Figure 17 shows the SDS-PAGE results for the poly(*N*-isopropylacrylamide)-BSA (left) / OVA conjugates (right). In both instances lanes **a** are molecular weight markers (MWs span the range 30-200 KDa), lanes **b** are the native proteins, **c** the unpurified polymer-protein conjugates and lanes **d** the conjugates after purification by gel filtration. In both instances conjugation was clearly successful and pure polymer-protein conjugates were readily obtained. The activity of the poly(*N*-isopropylacrylamide)-BSA conjugate was subsequently evaluated in the hydrolysis of 4-nitrophenyl acetate. At 25°C the conjugate exhibited identical hydrolytic activity to native BSA confirming that conjugation to poly(*N*-isopropylacrylamide) had little-to-no effect on the activity of BSA.

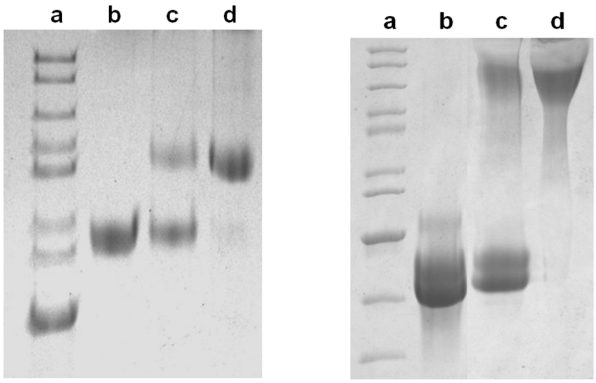


Figure 17 SDS-PAGE results for poly(*N*-isopropylacrylamide)-BSA (left) and poly(*N*-isopropylacrylamide)-OVA (right) polymer-protein conjugates. Associate Professor Brent S. Sumerlin is thanked for supplying the original image files.

Reproduced from M. Li, P. De, H. Li, B. S. Sumerlin *Polym. Chem.* 2010, **1**, 854-859.

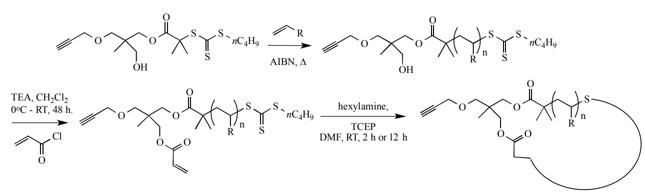
A novel one-pot approach to doxorubicin-conjugated, PEGylated reversibly crosslinked polymeric particles was reported by Wong, Kavallaris and Bulmus.[121] A parent reactive scaffold of poly(pyridyl disulfide ethyl methacrylate) ($\overline{M}_n$ = 8,900; $Đ_M$ = 1.18) was reacted with doxorubicin and PEG, each of which was functionalised with a maleimide group (in the case of doxorubicin the molecule also contained an acid labile hydrazine functionality), in the presence of a disulfide reducing agent. Conjugation was accomplished via thiol-Michael coupling. Approximately 50% of the available pyridyl disulfide groups were reacted with near equimolar amounts of the doxorubicin and PEG species. This amphiphilic species was readily dispersed in water giving particles with a dynamic light scattering measured hydrodynamic diameter of ~ 192 nm. The pH-dependent release of doxorubicin from the PEGylated polymeric particles was demonstrated HPLC using a visible light detector at 490 nm. At pH 5.0 ca. 80% of conjugated doxorubicin was released after 70 hr.

In a related report, Pan *et al.*[80] reported the synthesis of *N*-(2-hydroxypropy)methacrylamide (HPMA) homopolymers and copolymers of HPMA with *N*-methacryloylglycyl-phenylalanylleucylglycyl-doxorubicin (a doxorubicin containing methacrylamido derivative) employing a difunctional RAFT chain transfer agent containing an enzymatically degradable oligopeptide sequence (the same sequence as in the doxorubicin monomer). RAFT polymerisation yielded the linear copolymer with a doxorubicin content of 7 wt% and $\overline{M}_w$ of 27,800 and a corresponding $Đ_M$ of 1.19. The thiocarbonylthio end groups were then cleaved via *n*-butylamine-mediated aminolysis to give the macromolecular dithiol. This well-defined precursor was then chain extended in a step-growth reaction with a PEG-bismaleimide (thiol-Michael polymerisation) to give a material with a broad distribution of molecular weights (note: the sample was fractionated and mono-, di-, tetra-, and octa-block species clearly identified). The enzymatic degradability of the polymer backbone and release of doxorubicin was evaluated by incubation with cathepsin B and papain ($\overline{M}_w$ of polymer evaluated: 227,700). Analyses indicated that the polymeric backbone was cleaved within 30 min while the release of doxorubicin increased with incubation time.

Roy and co-workers[122] reported the synthesis of polymer-trimannoside derivatives via a combination of RAFT and radical thiol-ene chemistry. A precursor statistical (co)polymer of allyl methacrylate and HPMA were prepared by dithioester-mediated RAFT to give a material containing approximately 20 mol% allyl methacrylate with an SEC-measured $\overline{M}_n$ of 6,300 and $Đ_M$ = 1.23. The pendent allylic groups were then reacted with 1.4 equivalents (based on pendant ene groups) of a thiolated trimannoside, namely [(2-(2-(2-mercaptoethoxy)ethoxy)ethyl-α-D-trimannoside, in the presence of DMPA as a photoinitiator for 2h. The reaction resulted in approximately 87% consumption of ene bonds as judged by ^{1}H NMR spectroscopy. As expected, the trimannoside polymer conjugates were also able to efficiently bind Con A as determined by UV-visible spectroscopy.

Two groups have recently reported the synthesis of cyclic polymers from linear precursors employing a thiol-ene reaction in the cyclisation step. Lu, Jia and Monteiro[123] reported the cyclisation of RAFT-prepared homopolymers of styrene, *tert*-butyl acrylate, *N*-isopropylacrylamide and *N,N*-dimethylacrylamide. The overall process is outlined in Scheme 28.

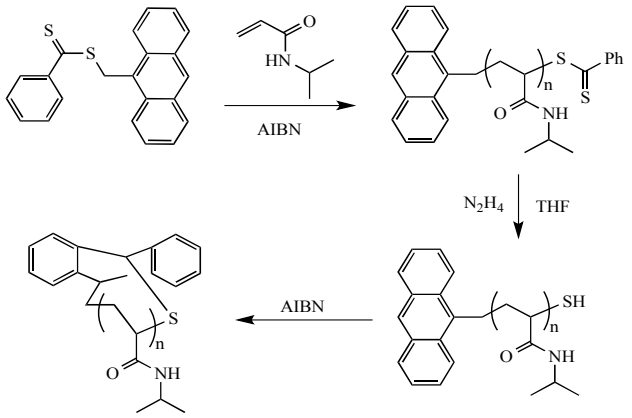
The multi-functional RAFT CTA, 3-hydroxy-2-methyl-2-((prop-2-yn-1-yloxy)methyl)propyl 2-(((butylthio)carbon-thioyl)thio)-2- methylpropanoate, containing reactive OH and yne functionality, was employed in the homopolymerisation of the above listed monomers to give low molecular species with $\overline{M}_n$'s in the range of ca. 3,500-4,000 and $Đ_M$ values of 1.08-1.13. The OH groups at the α-terminus were then acylated, with acryloyl chloride, to give the α−□□□□□□□□□□□□□□□□□□□□□□□□□□□□□□□□□□ Subsequent treatment of the homopolymers with hexylamine in the presence of TCEP resulted in a two-step process involving first aminolysis of the ω-trithiocarbonate giving the macromolecular thiols followed by an intramolecular thiol-Michael addition at the α-chain end to give the cyclic polymers. Optimization of the reaction conditions facilitated the preparation of cyclic materials in upto an 80% yield.



Scheme 28 Synthesis of cyclic homopolymers via sequential acylation, aminolysis and thiol-Michael reactions.

This particular approach gave cyclic polymers that still contained reactive yne functional groups available for further reactions. The authors demonstrated that these were readily reacted with (1-azidoethyl)benzene in a Cu-catalysed alkyne/azide coupling. All materials were thoroughly characterized using a combination of MALDI-TOF MS, NMR spectroscopy and SEC.

In related work, Liu *et al.*[124] reported the RAFT-based synthesis of cyclic poly(*N*-isopropylacrylamide) via a radical-based cyclisation involving the reaction of the macromolecular thiol with the α-anthracene group, Scheme 29.

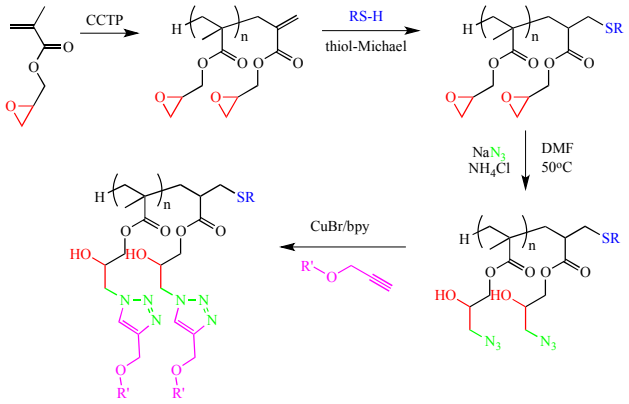


Scheme 29 Synthesis of cyclic poly(*N*-isopropylacrylamide) via sequential hydrazinolysis and radical thiol-ene reactions.

Successful cyclisation was verified using SEC, UV-vis spectroscopy and NMR spectroscopy. The cloud points of the linear and cyclic polymers were determined and it was found that the cyclic species possessed a cloud point 1°C lower than the linear analogue at a polymer concentration of 2.0 gL^{-1}.

Catalytic Chain Transfer Polymerisation (CCTP)

CCTP is a very efficient Co(II)-mediated radical polymerisation technique that facilitates the straightforward synthesis of methacrylic macromonomers. Since the macromonomers contain ω-activated ene functionality they are perfectly suited as substrates in thiol-Michael coupling reactions. The bulk of the reported literature combining CCTP with thiol-ene chemistry has been reported by Haddleton and co-workers.[81, 125-127] For example, Zhang *et al.*[81] described the synthesis of a range of end-functionalised glycopolymers employing a combination of thiol-Michael coupling, ring-opening chemistry and Cu-catalysed alkyne-azide side-chain modification, Scheme 30, in a complimentary approach to a previous report.[128] Glycidyl methacrylate was first polymerised in the presence of CoBF and AIBN to give the corresponding macromonomers with average degrees of polymerisation of 11 and 30. The methacrylic end-groups were then reacted with benzyl or propyl mercaptan in the presence of dimethylphenylphosphine yielding the corresponding thiol-Michael adducts. In a subsequent ring-opening reaction, the pendent epoxy functional groups were reacted with sodium azide as a means of introducing side-chain azido functionality. In a final conjugation step, the newly introduced azide species were reacted with functional alkynes including di(ethylene glycol) methyl ether, mannose and fucose derivatives giving, for example, sugar derivatives in readily accessible gram quantities. In a similar report,[125] the authors polymerised glycidyl methacrylate to give the macromonomer and then conducted a thiol-Michael reaction at the chain end with benzyl mercaptan mediated by dimethylphenylphosphine. As with the chemistry outlined in Scheme 28 this leaves the pendent epoxy rings in tact and available for other chemical reactions. Here the authors ring-opened the epoxy groups with 1° and 2° amines (*n*-propylamine and diethylamine). Successful thiol-Michael adduct formation and ring-opening was confirmed by a combination of ^{1}H NMR spectroscopy, SEC and MALDI-TOF mass spectrometry.



Scheme 30 Sequential CCTP, thiol-Michael end-group modification, side chain ring-opening of an epoxide and Cu-catalysed alkyne-azide coupling as a route to highly functional materials.

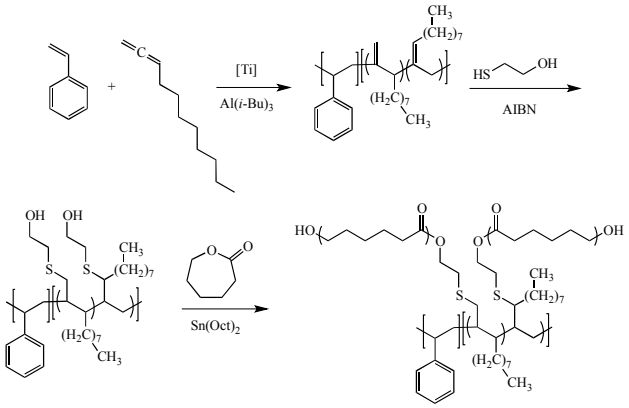
Slavin, Khoshdel and Haddleton[126] reported the surface modification of α-keratin with copolymers of oligo(ethylene glycol) methyl ether methacrylates and allyl methacrylate (typical resulting $\bar{M}_n$ = 1,600-4,400 as determined by NMR spectroscopy). Disulfide bonds were reduced with ammonium thioglycolate or TCEP followed by thiol-Michael addition to the activated ω-chain ends to give the polymer-protein adducts. Successful modification was confirmed by differential scanning calorimetry (DSC) by measuring the denaturation temperature of the unfolding protein in α-keratin. Successful conjugation is expected to raise this characteristic temperature as was found to be the case. Confirmation of polymer conjugation was also achieved by hydrothiolation of the pendent allylic groups in the conjugated copolymer with a fluorescent, coumarin-based probe. Subsequent imaging with a fluorescent microscope demonstrated good surface coverage.

Coordination Polymerisation

Within the last several years there has been some interest in the straightforward preparation of functional polyethylene and its copolymers. For example, Mazzolini *et al.*[129] described the synthesis of essentially quantitatively functionalised vinyl-terminated polyethylene employing the P,O-chelated species [Ni($Ph_2PC(CO_2Et)$=$C(C_6H_5)O$)$Ph(PPh_3)$] as the polymerisation catalyst, yielding a homopolymer with a measured $\bar{M}_n$ of 1,440 (as determined by high temperature SEC) and $Đ_M$ of 1.80. Initial investigations of the radical reaction between the vinyl-end groups and thioglycolic acid indicated that 10 equivalents of thiol was necessary to achieve near quantitative degrees of thioether adduct formation (95%) and minimise undesirable side-reactions. The end-group modification was extended to

other thiols including 2-mercaptoethanol, thioglycerol, 3-chloropropanethiol and methyl thioglycolate to give the corresponding thioether-poly(ethylene)s with degrees of functionalisation of ≥ 93.0%.

Hong and co-workers[89] detailed the copolymerisation of ethylene with 5-vinyl-2-norbornene, 5-ethylidene-2-norbornene and dicyclopentadiene mediated by $[PhNC(CF_3)CHCO(Ph)]_2TiCl_2$ and MMAO to give high molecular weight materials with up to 30 mol% incorporation of the bicyclic comonomer. These reactive scaffolds were then subjected to radical thiol-ene modification, with DMPA as a photoinitiator, with a library of thiols including 2-mercaptoethanol, thioglycerol, methyl thioglycolate and mercaptopropionic acid. With the exception of 2-mercaptoethylamine, degrees of functionalisation in excess of 94% were readily achieved giving highly functional polyethylene derivatives that retained the well-defined characteristics of the precursor materials. Employing a combination of coordination copolymerization and ring-opening polymerisation Ni, Zhu and Shen[82] reported the preparation and characterisation of novel graft copolymers with a poly(*n*-octylallene-*co*-styrene) backbone and poly(ε-caprolactone) side chains, Scheme 31. Key to the successful preparation of these novel graft copolymers is the hydrothiolation of the exo-methylene bonds in the precursor poly(*n*-octylallene-*co*-styrene) material. The authors claim quantitative addition as judged by NMR and FTIR spectroscopies.



Scheme 31 Synthesis of novel graft copolymers via sequential Ti-mediated copolymerisation of styrene and octylallene, radical thiol-ene backbone modification with 2-mercaptoethanol followed by Sn-mediated ring-opening polymerisation of ε-caprolactone.

Li *et al*.[130] reported the synthesis of AB diblock copolymers of isotactic polystyrene with poly(ethylene glycol) and subsequently studied their crystallisation driven self assembly in DMF. Styrene was homopolymerized with 1,4-dithiabutandiyl-2,2'-bis(6-*tert*-butyl-4-methylphenoxy) titanium dichloride and methylaluminoxane as the catalyst/co-catalyst pair in the presence of 1,7-octadiene as a chain transfer agent to give highly isotactic polystyrene with ene end-groups (typical measured molecular weight: ~10,000 with a $Đ_M$ of 1.65).

Ring-Opening Polymerisations

There has also been significant interest in the application of ring-opening polymerisation, often in combination with a second polymerisation technique, *vide supra*, as a means of preparing reactive (co)polymers amenable to further thiol-ene modification. In an elegant example, Shao et al.[88] described the synthesis and characterisation of amphiphilic diblock copolymers comprised of poly(ε-caprolactone) and a polyphosphoester bearing a range of functional side-groups. OH-terminal poly(ε-caprolactone) was first prepared via standard ring-opening of ε-caprolactone with benzyl alcohol as the initiator in the presence of $Sn(Oct)_2$. This was subsequently chain extended with an acrylate functional cyclic phosphoester, prepared from the reaction of 2-chloro-2oxo-1,3,2-dioxaphospholane with 2-hydroxyethyl acrylate giving copolymers with the general structure shown in Figure 17. Importantly, this gives block copolymers with pendent acrylic functionality that can be utilised in subsequent thiol-Michael reactions. Modification with four different thiols in DMF with pyridine as the catalyst gave the conjugate addition adducts in quantitative yield with the exception of 3-mercaptopropionic acid. Such straightforward chemistry gave a family of materials with very different surface properties, as judged by contact angle measurements on thin-film casts, as well as materials capable of undergoing self-directed assembly to give polymeric micelles in aqueous media that could be used for drug loading and delivery. Specifically, it was shown that the amphiphilic, self-assembled, micelles could be loaded with doxorubicin and used as delivery vehicles to inhibit the proliferation of KB cells.

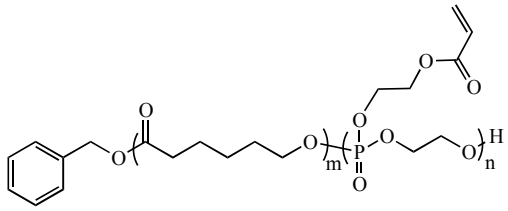
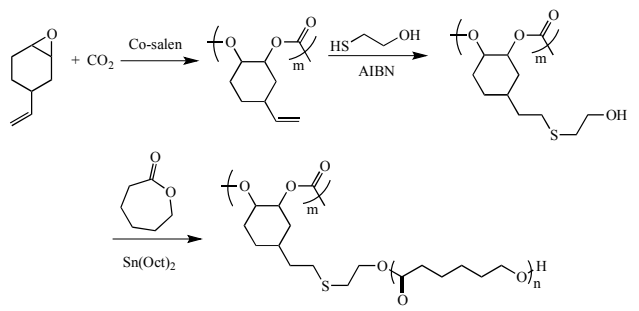


Figure 17 Chemical structure of poly(ε-caprolactone)-*block*-poly(2-((2-oxido-1,3,2-dioxaphospholan-2-yl)oxy)ethyl acrylate) copolymers prepared by ring-opening polymerisation.

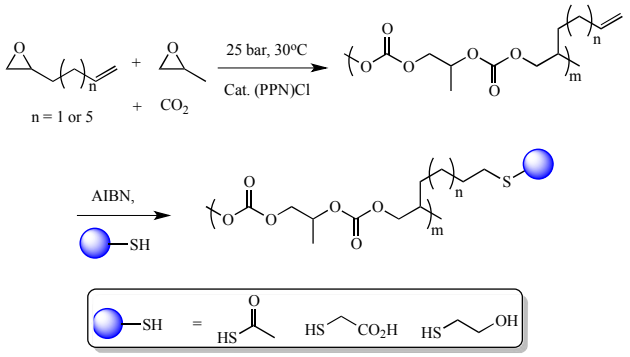
Zhang *et al*. described the synthesis of well-defined graft copolymers via a combination of living CO_2/epoxide copolymerisation, radical thiol-ene coupling and the ring opening polymerisation of ε-caprolactone. 3-Vinyl-7-oxabicyclo[4.1.0]heptane was initially copolymerised with CO_2 with a Co-salen complex to give well-defined polycarbonate species with pendent alkenes with an average degree of polymerisation of 40, Scheme 32.



Scheme 32 Synthesis of polycarbonate-*graft*-polyester polymers via sequential ring-opening copolymerisation of an epoxide with CO_2, radical thiol-ene coupling, and Sn-mediated ring-opening polymerisation of ε-caprolactone.

The precursor was then reacted with a 40 fold excess of 2-mercaptoethanol (to avoid possible crosslinking reactions) in THF with AIBN at 70°C which, after repeated precipitations to remove the excess thiol) gave the corresponding OH functional material which could serve as a macro-initiator in the final synthesis step. Somewhat fortuitously, the OH-functional macroinitiator was soluble in ε-caprolactone at room temperature and therefore the graft copolymers were readily prepared by simple heating to 120°C in the presence of $Sn(Oct)_2$. A series of graft copolymers with degrees of polymerisation for the ε-caprolactone ranging from 8-87 were prepared with the graft polymerisation proceeding in a relatively well-defined manner as judged by SEC. The authors also briefly examined the crystallisation and melting behaviour of these novel graft copolymers with the crystallisation temperature, melting temperature and degree of crystallinity increasing with increasing length of the grafted poly(ε-caprolactone) side chains.

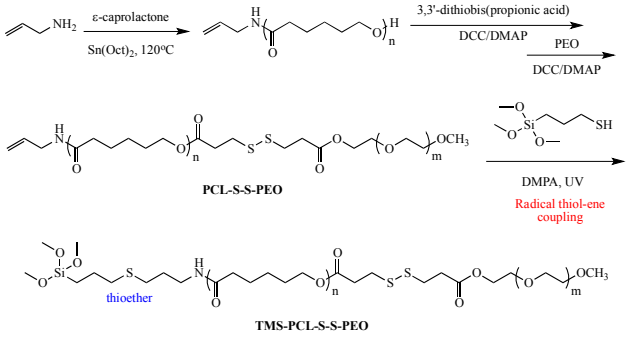
In closely related work, Geschwind, Wurm and Frey[131] recently reported the synthesis of terpolymers of varying molar composition obtained from the ring-opening copolymerisation of 1,2,-epoxy-5-hexene or 1,2-epoxy-9-decene, propylene oxide and CO_2. After purification, a series of polymers with molecular weights ranging from 10,000-32,000 and $Đ_M \leq 1.38$ were obtained, Scheme 33. These parent copolymers were subsequently modified via an AIBN-mediated radical thiol-ene reaction with a series of thiols such as ethanethioic *S*-acid, 2-mercaptoacetic acid and 2-mercaptoethanol. Conversions in all cases were reported to be >99%. In the case of ethanethioic *S*-acid, base hydrolysis of the thiol-ene adduct yielded the free-thiol analogous copolymers although it was noted that care must be taken to avoid undesirable hydrolysis of the polycarbonate backbone given the relatively harsh conditions required. Side chain modification with 2-mercaptoethanol gave materials with pendent OH groups and thus could serve as a multifunctional macroinitiator for the ring opening polymerisation of L-lactide. The grafting-from polymerisations were performed in toluene at 90°C with $Sn(Oct)_2$ as the catalyst. Successful grafting-from was confirmed using standard SEC and ^{1}H NMR spectroscopic methods.



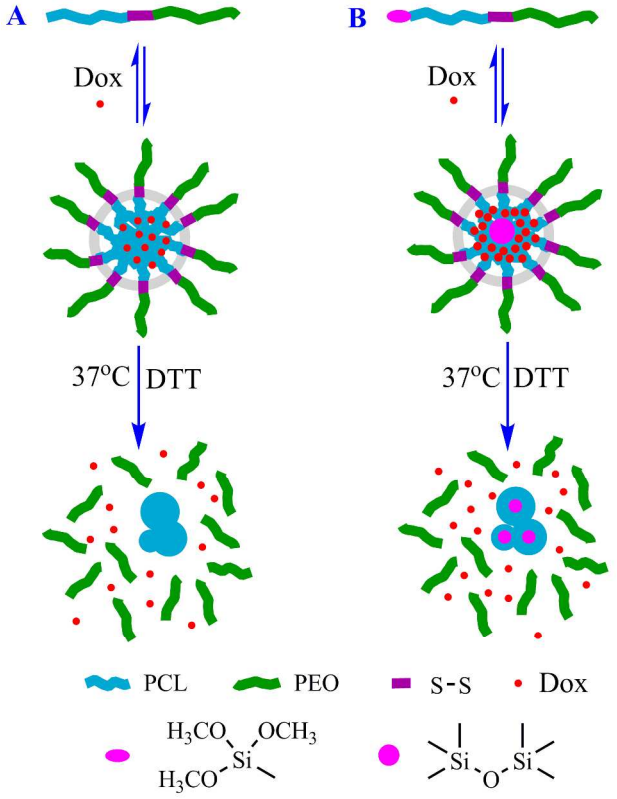
Scheme 33 Synthesis of novel polycarbonates containing pendent terminal ene functionality and their subsequent hydrothiolation via radical thiol-ene coupling chemistry.

Yue and co-workers[85] described the synthesis of end- and side-chain functionalised polyesters obtained from precursor (co)polymers of allyoxyl poly(ethylene glycol)-*block*-poly(L-lactide) and methoxy poly(ethylene glycol)-*block*-poly(L-lactide-*co*-2-methyl-2-allyloxycarbonyl propylene carbonate). The polymers were prepared via standard techniques and the thiol-ene modifications were accomplished under radical conditions with UV irradiation without any added photoinitiator. Successful conjugation was achieved with three common thiols namely thioglycerol, 3-mercaptopropionic acid and Boc-protected mercaptoethylamine.

Wang and Dong[90] reported the synthesis of bioreducible and core-crosslinked micelles derived from α-trimethoxysilyl poly(ε-caprolactone)-S-S-poly(ethylene oxide) AB diblock copolymers. The synthesis of the block copolymers is shown in Scheme 34.



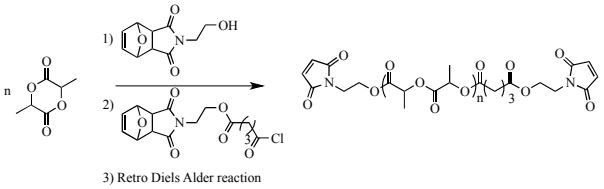
Scheme 34 Synthesis of α-trimethoxysilyl poly(ε-caprolactone)-S-S-poly(ethylene oxide) AB diblock copolymers via ring opening polymerisation of ε-caprolactone, followed by two sequential carbodiimide couplings and finally a radical thiol-ene reaction with 3-mercaptopropyltrimethoxysilane to the α-terminal ene.



Scheme 35 Self-assembly and doxorubicin loading of polymeric micelles derived from poly(ε-caprolactone)-S-S-poly(ethylene glycol) with (B) and without (A) trimethoxysilane end groups and reducing agent-induced release of doxorubicin from the aggregate cores. Professor Chang-Ming Dong is thanked for supplying the original colour image used in this Scheme.

Allylamine initiated, $Sn(Oct)_2$ catalysed ring-opening polymerisation of ε-caprolactone gave an allyl α-functional poly(ε-caprolactone) with an NMR-determined molecular weight of 4,500 and $Đ_M$ of 1.47. Subsequent sequential carbodiimide couplings, firstly with 3,3'-dithiobis(propionic acid) (to introduce the reducible disulfide linkage) and then with poly(ethylene oxide) gave the allyl-terminal poly(ε-caprolactone)-S-S-poly(ethylene oxide) AB diblock. In the final modification step, the α-allylic group was reacted with 3-mercaptopropyltrismethoxysilane employing DMPA as the catalyst and irradiation at 365 nm to give the thioether adduct quantitatively and a final NMR determined molecular weight of 19,680 for the modified block copolymer. Both the allyl-terminated block copolymer and the final trimethoxysilane analogue are inherently amphiphilic and undergo self-assembly in an aqueous environment. In the case of the trimethoxysilane derivative, core-crosslinking also occurs due to a sol-gel reaction. The self-assembly process and size of the resulting aggregates was monitored using a combination of UV-Vis spectroscopy (to determine the critical micelle concentration), dynamic light scattering and transmission electron microscopy. The ability to 'degrade' the micelles with 1,4-dithiothreitol under biologically relevant conditions was also demonstrated. Loading of both core crosslinked and uncrosslinked micelles with doxorubicin was also achieved (note: the core crosslinked micelles were able to sequester double the amount of doxorubicin compared to the non-crosslinked species) and the release kinetics monitored in the presence and absence of 1,4-dithiothreitol. Release of doxorubicin was significantly slower in the case of the core crosslinked species and, not surprisingly, increased dramatically in the presence of the reducing agent due to degradation of the aggregate species. This process is shown schematically in Scheme 35. Similar α-functional poly(ε-caprolactones) have been reported by Darcos *et al*.[132] AIBN-mediated radical thiol-ene reaction of the pendent ene groups with 2-(Boc-amino)ethanethiol followed by removal of the Boc protecting group yielded the primary amine-functionalized polyesters. Subsequent reaction with fluorescein isothiocyanate gave the corresponding thiocarbamate-linked fluorescently tagged (co)polymers.

The synthesis of stereoregular cyclic poly(lactide)s was reported by Stanford, Pflughaupt and Dove.[84] α,ω-Maleimide functional poly(lactide)s were first prepared as outlined in Scheme 36.



Scheme 36 Synthesis of bismaleimido-functional polyesters via the use of furan-protected initiators and terminating agents.

Homopolymerisation was initiated by an OH bearing 7-oxanorbornene derivative and quenched by the oxanorbornene derivative pentanedioyl chloride mono[2-(3,5-dioxo-10-oxa-4-azatricyclo[5.2.1.$0^{2,6}$]dec-8-en-4-yl)ethyl] ester. Finally, heating under vacuum at 100°C for 24h induced a [4+2] cycloreversion, liberating furan and the target bismaleimido functional polylactide. Subsequent reaction with 1,2-ethanedithiol under reducing and dilute conditions in the presence of NEt_3 gave the target cyclic polylactide. The structure of the cyclic species was confirmed using a combination of size exclusion chromatography and MALDI-TOF MS. For example, Figure 18 shows the MALDI-TOF MS spectra for a linear (a) and the corresponding cyclic homopolymer (b). A consistent increase in the molecular weight distribution of 94Da confirmed that addition of a single 1,2-ethanedithiol to each polymer chain while an apparent *decrease* in the molecular weight as determined by size exclusion chromatography confirmed efficient cyclisation – the latter being due to the more compact hydrodynamic volume of the cyclic species vs the linear counterpart.

Silvers, Chang and Emrick[133] reported the synthesis and TBD (1,5,7-triazabicyclo[4.4.0]dec-5-ene) initiated

polymerisation of ene and yne functional lactones to give homopolymers and copolymers of controlled molecular weights and narrow molecular weight distributions amenable to radical thiol-ene/yne and/or alkyne azide coupling chemistries. As a representative example, AB diblock copolymers of α-allyl-δ-valerolactone and α-propargyl-δ-valerolactone were reacted with 5.0 equivalents of dodecanethiol (based on total number of ene and yne functionalities) in DMF at 80°C in the presence of AIBN as a radical initiator, Scheme 37. After a period of 3 h, conversion to the thioether adducts was essentially complete as evidenced by the complete disappearance of the ene and yne signals in the NMR spectrum. SEC analysis of the products showed an increase in the molecular weight from 13,900 for the parent copolymer to 22,800 for the product while still retaining the original narrow molecular weight distribution.

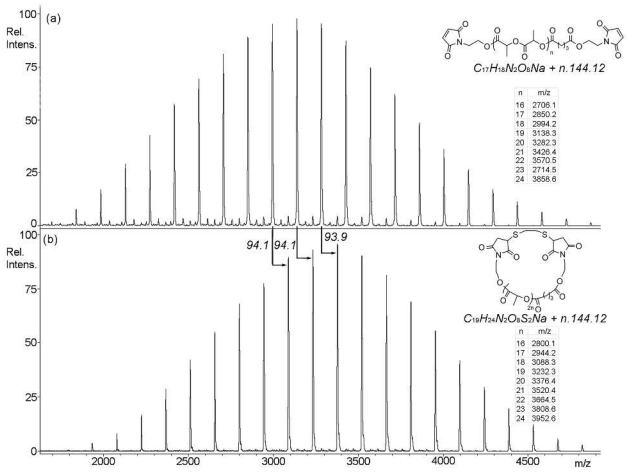
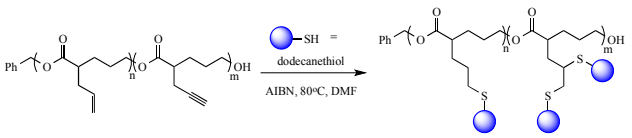
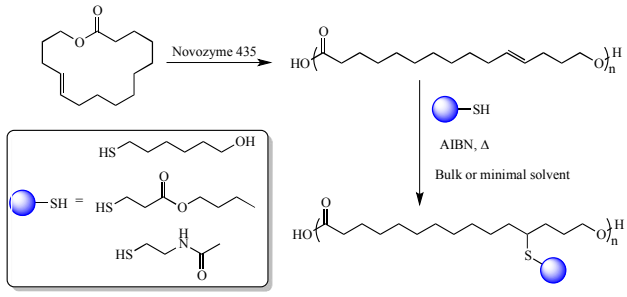


Figure 18 MALDI-TOF MS spectra for a linear polylactide (a) and the corresponding cyclic species (b). Associate Professor Andrew P. Dove is thanked for supplying the original image file. Reproduced with permission from M. J. Stanford, R. L. Pflughaupt, A. P. Dove *Macromolecules* 2010, **43**, 6538-6541. Copyright 2010, American Chemical Society.



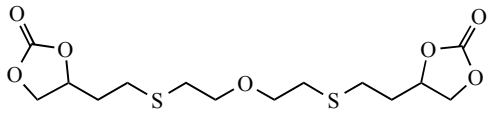
Scheme 37 Simultaneous radical thiol-ene and thiol-yne reactions with dodecanethiol along the backbone of a novel polyester containing both allylic and propargylic functional side groups.

Ates, Thornton and Heise[134] detailed the backbone radical thiol-ene modification of unsaturated polyesters obtained from the ring opening polymerisation of the macrolactone globalide, Scheme 38. Due to the low ring strain associated with globalide, effective homopolymerization could only be achieved via an enzymatic process, in this case with Novozym 435, to give a homopolymer with an average measured molecular weight of 16,000 and corresponding $Đ_M$ of 2.5. Importantly, however, polymerisation of globalide gives a polymer with C=C bonds in the backbone that are available for further, post-polymerisation, modification. However, it is noted that these are internal C=C bonds and as such are less reactive.[8] In an initial screening, the polyglobalide was reacted with butyl 3-mercaptopropionate with AIBN as the source of initiating radicals, and gave a product in which >75% of the backbone C=C bonds were consumed. In the case of *N*-acetylcysteamine and 6-mercaptohexanol, degrees of modification >95% were obtained with optimisation of the reaction conditions.

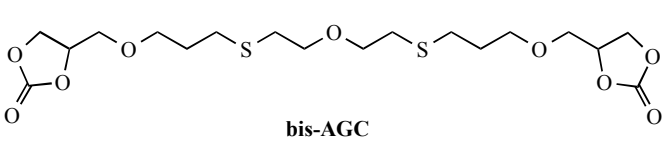


Scheme 38 Enzyme catalysed ring opening polymerisation of globalide and subsequent backbone modification via radical thiol-ene coupling.

The preparation of isocyanate-free polyhydroxyurethanes was reported by Benyahya *et al.*[135] The ene functional cyclocarbonates 4-(prop-2-en-1-yloxy)methyl]-1,3-dioxolan-2-one (AGC) and 4-ethenyl-1,3-dioxolan-2-one (AC) were initially prepared prior to reaction with 2,2'-oxybis(ethane-1-thiol) via initiator-free UV irradiation to give the thioether-functional biscyclocarbonates, Figure 19.



bis-AC



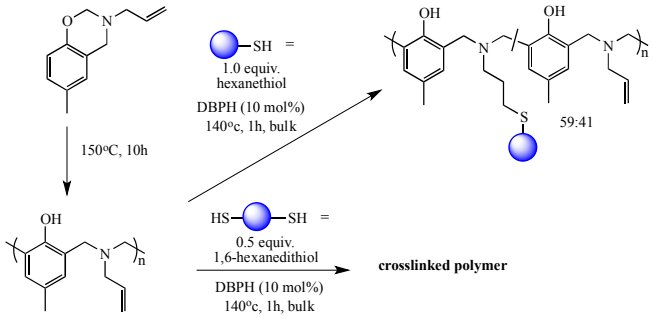
bis-AGC

Figure 19 Chemical structures of the biscyclocarbonates 4,4'-(((oxybis(ethane-2,1-diyl))bis(sulfanediyl))bis(ethane-2,1-diyl))bis(1,3-dioxolan-2-one) (**bis-AC**) and 4,4'-(2,9,16-trioxa-6,12-dithiaheptadecane-1,17-diyl)bis(1,3-dioxolan-2-one) (**bis-AGC**).

Step growth polymerisation of **bis-AG** and **bis-AGC** was then performed with decane-1,10-diamine as comonomer, yielding the target polyhydroxyurethanes with measured $\overline{M}_n$'s of 7,000 and 9,000 and $Đ_M$'s of 1.5 and 3.2 for the **bis-AC** and **bis-AGC**

derivatives respectively. As with other polyurethanes these novel materials exhibited good thermal stability.

While the bulk of the thiol-ene work associated with ring opening polymerisation has been conducted with polyester and polycarbonate materials these are not the only substrates that can be used. Oie, Sudo and Endo[136] reported the synthesis and post-polymerisation modification of a polybenzoxazine bearing an allylic side group (obtained from the polymerisation of *N*-allyl-benzoxazine), Scheme 39.

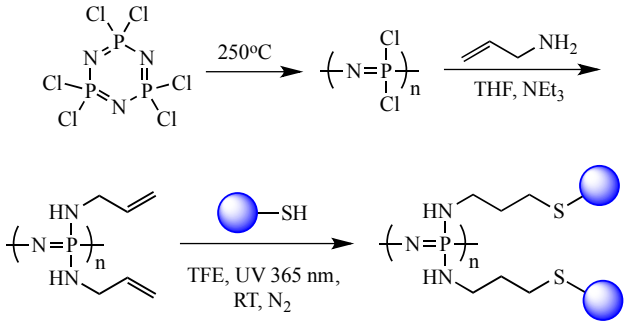


Scheme 39 Ring opening polymerisation of *N*-allyl-benzoxazine and its subsequent radical thiol-ene modification with hexanethiol and 1,6-hexanedithiol.

Reaction of the pendent allylic groups with 1.0 equivalent of hexanethiol gave the corresponding thioether adduct in which ~60% of the allyl groups had reacted, as determined by ^{1}H NMR spectroscopy. Similarly, reaction with 0.5 equivalents of 1,6-hexanedithiol yielded an insoluble crosslinked polymer.

The synthesis and post-modification of synthetic polypeptides was reported by Sun and Schlaad.[83] *N*-Allylglycine-*N*-carboxyanhydride was prepared and polymerised using primary amines as initiators including PEG-NH_2 to give novel AB diblock copolymers of low molecular weight and narrow molecular weight distributions. Addition of methyl 3-mercaptopropionate to the pendent allyl groups in the homo- and block copolymers was then evaluated employing both thermal- and photochemical-initiated reaction conditions. Interestingly, while the thermal route (AIBN, DMF, 70°C, 1 day) afforded quantitatively modified (co)polymers that retained the well-defined characteristics of the parent (co)polymers (suggesting the absence of any significant side reactions) the photochemical route generally resulted in lower degrees of modification (75-85% depending on conditions and light source). Attempted glycosylation of the polypeptides with 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranose under both initiation conditions was largely limited to low-to-intermediate degrees of functionalisation (10-50%) and was attributed to poor solvent quality. However, the use of TFA as a solvent and the use of the unprotected sugar 1-thio-β-D-glucopyranose facilitated the photoinitiated addition reaction to proceed to ca. 50% for the homopolymer while quantitative modification was observed for the block copolymer after 2 days.

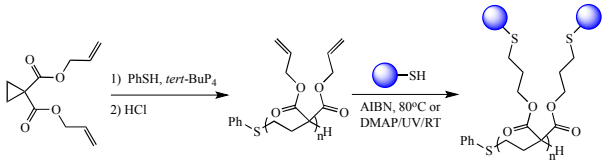
Thermal ring-opening polymerisation of hexachlorocyclotriphosphazene to polydichlorophosphazene followed by nucleophilic substitution of the chloro groups by allylamine gives the bis allylic derivative poly(bis(allylamine)phosphazene) as reported by Qian *et al.*, Scheme 40.[137] The structure of the allylic derivative was confirmed using ^{1}H and ^{31}P NMR spectroscopy. The polymer was subsequently reacted with a twofold excess of four thiols: pentanethiol, 3-mercaptopropionic acid, thioglycerol and 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranose. Reactions were performed in TFE at room temperature in the presence of DMPA as a photoinitiator and irradiation at 365 nm. All four mercaptans were reported to add quantitatively to the polyphosphazene backbone allyl groups with 100% conversion being achieved in <60 min for the first three listed thiols while longer reaction times were required for achieve high levels of modification of the sugar derivative.



Scheme 40 general synthetic procedures for the synthesis of thioether-based polyphosphazene derivatives via radical mediated hydrothiolation of a bisallylic derivative.

Another type of polymer bearing two allylic side groups per repeat unit that were subjected by radical thiol-ene couplings were reported by Illy and co-workers.[87] The functional monomer diallyl cyclopropane-1,1-dicarboxylate was prepared in two steps involving acylation and cyclisation steps. The monomer was then homo- and co-polymerised employing thiophenol as an initiator in conjunction with the phosphazene base *tert*-BuP_4. (Co)Polymerisations proceeded to very high/quantitative conversions giving materials of variable molecular weights and low dispersities ($Đ_M \leq 1.23$). The general polymerisation and modification of a homopolymer is shown in Scheme 41. Benzyl mercaptan was initially evaluated as a model thiol in the radical thiol-ene reaction with the allylic side groups employing AIBN at 80°C as a thermal azo initiator and DMPA as a room temperature photoinitiator. With a 10 fold excess of thiol relative to enes and at an allyl concentration of ca. 200 mM quantitative thioether formation was achieved after only 20 min irradiation as confirmed by NMR spectroscopy. There was no evidence of undesirable side reactions such as cyclisation. In contrast, thermally initiated AIBN-mediated reactions under the same conditions resulted in limited conversions of ca. 80% even at very long reaction times. The difference was attributed to the occurrence of

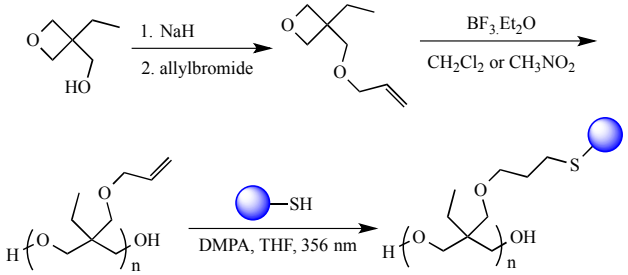
intramolecular cyclisation in the thermal systems as a result of a preference for cyclisation vs H-atom abstraction at elevated temperatures.



Scheme 41 Anionic ring opening polymerisation of diallyl cyclopropane-1,1-dicarboxylate and subsequent thiol-ene modification of the pendent allylic functional groups.

Given the observed difference between the thermal and photochemical processes subsequent thiol-ene modifications with 2-mercaptoethanol, 11-mercaptoundecanol, 3-mercaptopropionic acid and 2,2-dimethyl-1,3-dioxolan-4-yl methanethiol were conducted photochemically. In all instances, ^{1}H NMR spectroscopy indicated conversions to the thioether adducts >99%.

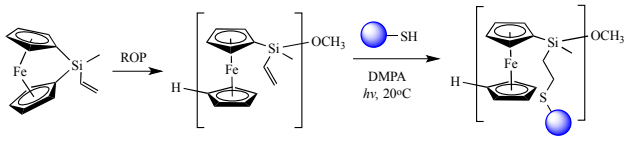
Schulte *et al.*[138] reported the synthesis, cationic ring opening polymerisation and subsequent modification of polymers obtained from 3-allyloxymethyl-3-ethyloxetane, Scheme 42.



Scheme 42 Synthesis and cationic ring opening polymerisation of 3-allyloxymethyl-3-ethyloxetane and its subsequent photoinitiated radical thiol-ene modification with *N*-acetyl-L-cysteine methyl ester and 3-mercaptopropionic acid.

Homopolymers with molecular weights ranging from 41,500-131,500 and corresponding $Đ_M \geq 2.0$ were prepared (although cyclic oligomers were also detected as undesirable side-products). In addition to detailed characterisation of the polymerisation products the authors demonstrated how the obtained allyl-functional polymers could be quantitatively modified via photoinitiated thiol-ene reactions with *N*-acetyl-L-cysteine methyl ester and 3-mercaptopropionic acid. While it is generally assumed that the anti-Markovnikov addition product is the sole (or primary) addition product, in this report the authors were able to identify 11 and 9%, respectively, Markovnikov addition species.

The controlled, photo-mediated, ring-opening (co)polymerisation of strained methylvinylsila[1]ferrocenophanes has been reported by Manners and co-workers, Scheme 43.[139, 140]



Scheme 43 Ring-opening polymerisation of methylvinylsila-[1]ferrocenophane with subsequent photoinitiated radical thiol-ene modification of the pendent ene groups.

In initial screening experiments, poly(ferrocenylmethylvinyl-silane) (PFMVS) homopolymers, with $\bar{M}_n$'s of 10,000 and 25,800 and corresponding $Đ_M$'s of 1.02 and 1.03, were reacted with a series of thiols (1-hexanethiol, 1-nonanethiol, 1-docecanethiol, 1-octadecanethiol, methyl-2-mercaptoacetate and the HCl salt of 2-(diethylamino)ethane-1-thiol) with DMPA as a photoinitiator. In all reactions an excess of thiol was employed (typically 1.3-1.8 equivalents). Analysis of the purified products via NMR spectroscopy indicated that in all instances the pendent vinyl groups were completely consumed within 30 min (24 h in the case of the amino derivative), while SEC analysis indicated that the modified polymers retained the narrow molecular weight distributions observed for the parent homopolymers. The authors extended their studies to include an AB diblock copolymer poly(ferrocenyldimethylsilane) with PFMVS. This was subsequently modified with the dodecyl and octadecyl-thiols under conditions to afford quantitatively modified copolymer as well as examples with fractional degrees of modification.

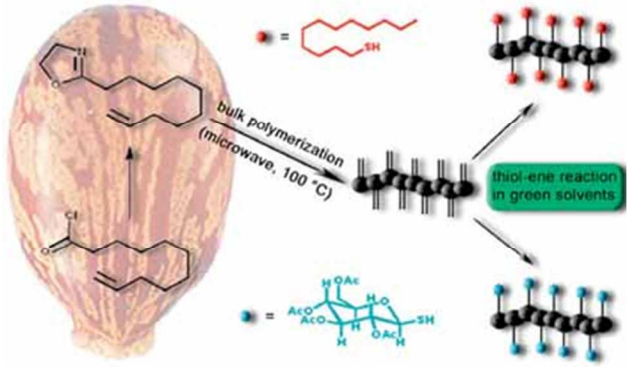


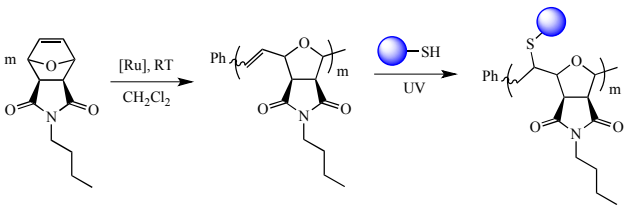
Figure 20 Synthesis, bulk polymerisation, and thiol-ene modification of 2-(dec-9-enyl)-2-oxazoline. Reproduced with permission from K. Kempe, R. Hoogenboom, U. S. Schubert *Macromol. Rapid Commun* 2011, **32**, 1484-1489. Copyright 2011, Wiley publications.

In a final example of the side chain modification of an ene functional (co)polymer obtained by a ring-opening polymerisation process, Kempe, Hoogenboom and Schubert[111] detailed the synthesis and bulk cationic ring-opening (co)polymerisation of the novel monomer 2-(dec-9-enyl)-2-oxazoline, Figure 20, to give (co)polymers of controlled molecular weight and low $Đ_M$'s. With (co)polymers in-hand the authors employed green solvents (2-methyl-THF and methyl

laurate) in subsequent UV-initiated thiol-ene reactions (without added photoinitiator) with 1-dodecanethiol and 2,3,4,6-tetra-*O*-acetyl-1-thioglycolpranose. Full conversion of the pendent ene bonds to the corresponding thioether adducts was confirmed via ^{1}H NMR spectroscopy.

Ring-opening Metathesis and Acyclic Diene Metathesis Polymerisations

Ring-opening metathesis polymerisation (ROMP) and acyclic diene metathesis polymerisation (ADMET) are transition-metal mediated processes that yield, directly, (co)polymers with unsaturation in the (co)polymer backbone. We highlighted above how Liu *et al.*[41, 42] prepared, using thiol-Michael coupling, and (co)polymerised a series of mono and multifunctional *exo*-7-oxanorbornene monomers obtained from the common precursor 2-((3a*R*,7a*S*)-1,3-dioxo-3a,4,7,7a-tetrahydro-1*H*-4,7-epoxyiso- indol-2(3*H*)-yl)ethyl acrylate. Aside from offering a facile route to functional ROMPable monomers this demonstrated that the thioether functional group was inherently compatible with the metathesis process. Exploiting the unsaturation in ROMP polymer backbones, van Hensbergen, Burford and Lowe[92] recently detailed the post-polymerisation modification of the backbone bonds in a ROMP homopolymer derived from (3*aR*,7*aS*)-2-butyl-3a,4,7,7a-tetrahydro-1*H*-4,7-epoxyisoindole-1,3-(2*H*)-dione, Scheme 44, with a library of 16 different thiols including benzyl mercaptan, 2-mercaptoethanol, thioglycerol, PEG-thiol, 3-(triethoxysilyl)propane-1-thiol, 9*H*-fluorene-9-thiol, 11-(1*H*-pyrrol-1-yl)undecane-1-thiol, and the sugar (2*S*,3*S*,4*R*,5*S*,6*R*)-2-(acetoxymethyl)-6-mercaptotetrahydro-2*H*-pyran-3,4,5-triyl triacetate under radical mediated conditions. In all instances a 2-fold excess of thiol (based on C=C bonds) was used along with DMPA as a photoinitiator.



Scheme 44 ROMP of (3*aR*,7*aS*)-2-butyl-3a,4,7,7a-tetrahydro-1*H*-4,7-epoxyisoindole-1,3-(2*H*)-dione and subsequent radical hydrothiolation of the backbone C=C bonds.

In general, the hydrothiolation reactions proceeded to give essentially quantitative formation of the thioether adducts facilitating the straightforward introduction of a range of interesting functionality. However, in several instances addition was observed to be incomplete and/or accompanied by undesirable side reactions. For example, in the case of 9*H*-fluorene-9-thiol and thiophenol degrees of modification of only ca. 55% were achieved under conditions optimized for many of the other thiol substrates. Similarly, degrees of modification of ~85% were observed for 4,5-dihydrothiazole-2-thiol and benzo[*d*]oxazole-2-thiol.

Wolfberger *et al.*[141] described the preparation of poly(norbornene)-based films and aggregates that were photochemically crosslinked with a tetrafunctional thiol, Figure 21.

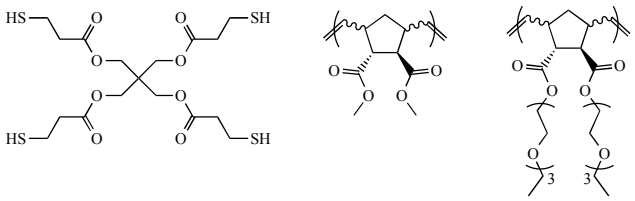
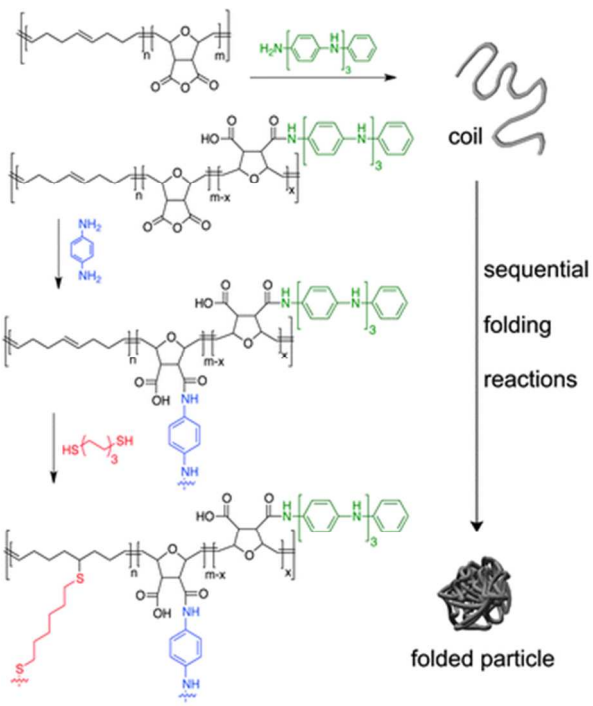


Figure 21 Chemical structures of the tetrathiols and examples of the norbornene-based homopolymers employed in the crosslinking reactions.

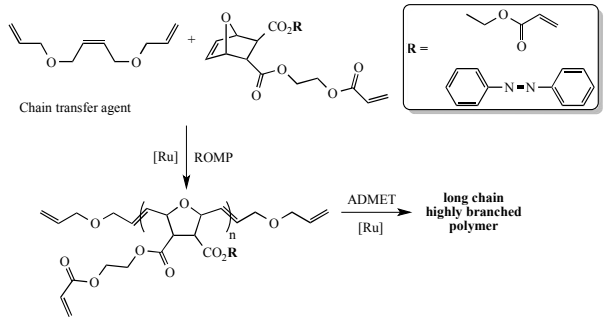
For example, transparent polymer films of the dimethyl ester polymer were prepared by spin casting from a CH_2Cl_2 solution also containing 10 wt% of the photoinitiator Lucirin TPO and 37.7 wt% of the tetrafunctional thiol. Subsequent irradiation with UV light resulted in the expected crosslinking. The approach was also extended to self-assembled AB diblock copolymers in a selective solvent, i.e. crosslinking of polymeric micelles as well as in the preparation of photo patterned thin films. This preliminary disclosure was further expanded by Griesser and co-workers.[142]



Scheme 45 Controlled chain folding in a novel ROMP-prepared copolymer via sequential ring-opening and thiol-ene reactions. Reproduced with permission from D. Chao, X. Jia, B. Tuten, C. Wang, E. B. Berda, *Chem. Commun.* 2013, **49**, 4178-4180. Copyright 2013, RSC publications.

Chao *et al*.[143] recently described the controlled folding of a novel electroactive polymer from a random coil to a folded particle employing sequential covalent and non-covalent intra-chain interactions, Scheme 45. The process was based on their previous findings on reversible chain aggregation in an oxidation-reduction process.[144] A parent copolymer of poly(oxanorbornene anhydride-*co*-cyclooctadiene) was prepared by ROMP employing Grubbs' 3rd generation catalyst. In the first step an aniline tetramer was reacted with 50% of the pendent anhydride groups, introducing the electroactive chemical groups as well as beginning the folding process. The remaining anhydride groups were then reacted with *p*-aminoaniline, forming the first round of covalent intramolecular crosslinks. This was followed by a radical thiol ene reaction of 1,6-dimercaptohexane with the backbone ene functional groups forming the second intramolecular covalent chain interactions (Note: all steps were performed at a concentration below *c** to avoid *inter*molecular chain crosslinking). The expected increase in molecular weight was observed after each modification step, as evidenced by SEC-MALLS while DLS confirmed the decrease in hydrodynamic radii after each step.

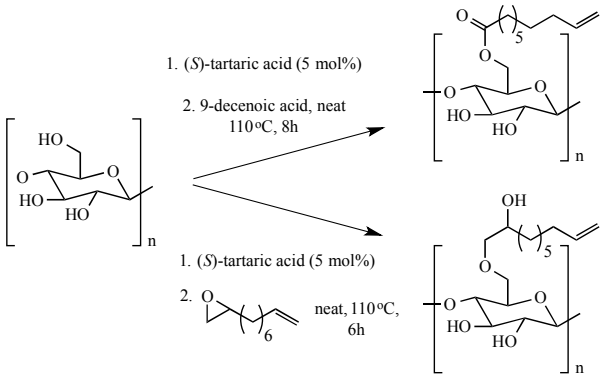
Ding and co-workers[145, 146] reported the synthesis of crosslinked, functional nanoparticles employing a combination of tandem ROMP and acyclic diene metathesis (ADMET) polymerisations followed by thiol-Michael-based crosslinking, Scheme 46. Ruthenium-mediated ROMP of a functional 7-oxanorbornene monomer containing either one or two pendent acrylate groups in the presence of the chain transfer agent (*Z*)-1,4-bis(allyloxy)but-2-ene yielded a bis-allyloxy telechelic polymer with pendent acrylic side groups. Subsequent ADMET of the telechelic macromonomers yielded a series of long chain highly branched polymers with reactive acrylate groups and molecular weights in the range 8.5-47.9 kDa. These branched polymers were converted to crosslinked, thiol-functional polymeric nanoparticles in an *intramolecular*, 1-dodecylamine-mediated, thiol-Michael reaction with 1,4-butanedithiol executed under dilute conditions. Successful formation of the nanoparticles was confirmed using a combination of SEC and FTIR spectroscopy.



Scheme 46 Sequential ROMP and ADMET yielding branched (co)polymers with pendent acrylic functionality susceptible to thiol-Michael crosslinking.

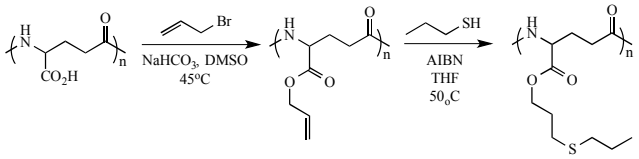
Modification of Naturally Occurring Polymers

In addition to the extensive studies focusing on the synthesis and modification of synthetic macromolecules there has been some interest in the thiol-ene modification of naturally occurring polymers. Zhao and co-workers[147] reported the heterogeneous photochemical thiol-ene modification of cellulose that had initially been modified to introduce appropriate ene functional groups, Scheme 47. Initially, the 9-decenoic acid modified cellulose was treated with benzyl mercaptan in the presence of 1 wt% DMPA and irradiated with a UV lamp for 1h. Successful conjugation was confirmed via fluorescence – the precursor cellulose did not fluoresce while the benzyl mercaptan treated substrate did. Base hydrolysis of the ester side chains yielded a material that like the precursor functional cellulose exhibited no fluorescence confirming the observed fluorescent behaviour was due to the benzyl



mercaptan hydrothiolation reaction. Several additional thiols were also examined and basic physical properties elucidated.

Scheme 47 Chemical modification of cellulose to introduce pendent ene functionality susceptible to radical thiol-ene



addition.

Pacini *et al*.[148] reported the chemical modification of poly(γ-glutamic acid)s (PGA) including the introduction of pendent allyl ester functionality, Scheme 48.

Scheme 48 Chemical modification of poly(γ-glutamic acid) with allyl bromide and subsequent radical-mediated thiol-ene addition with1-propanethiol.

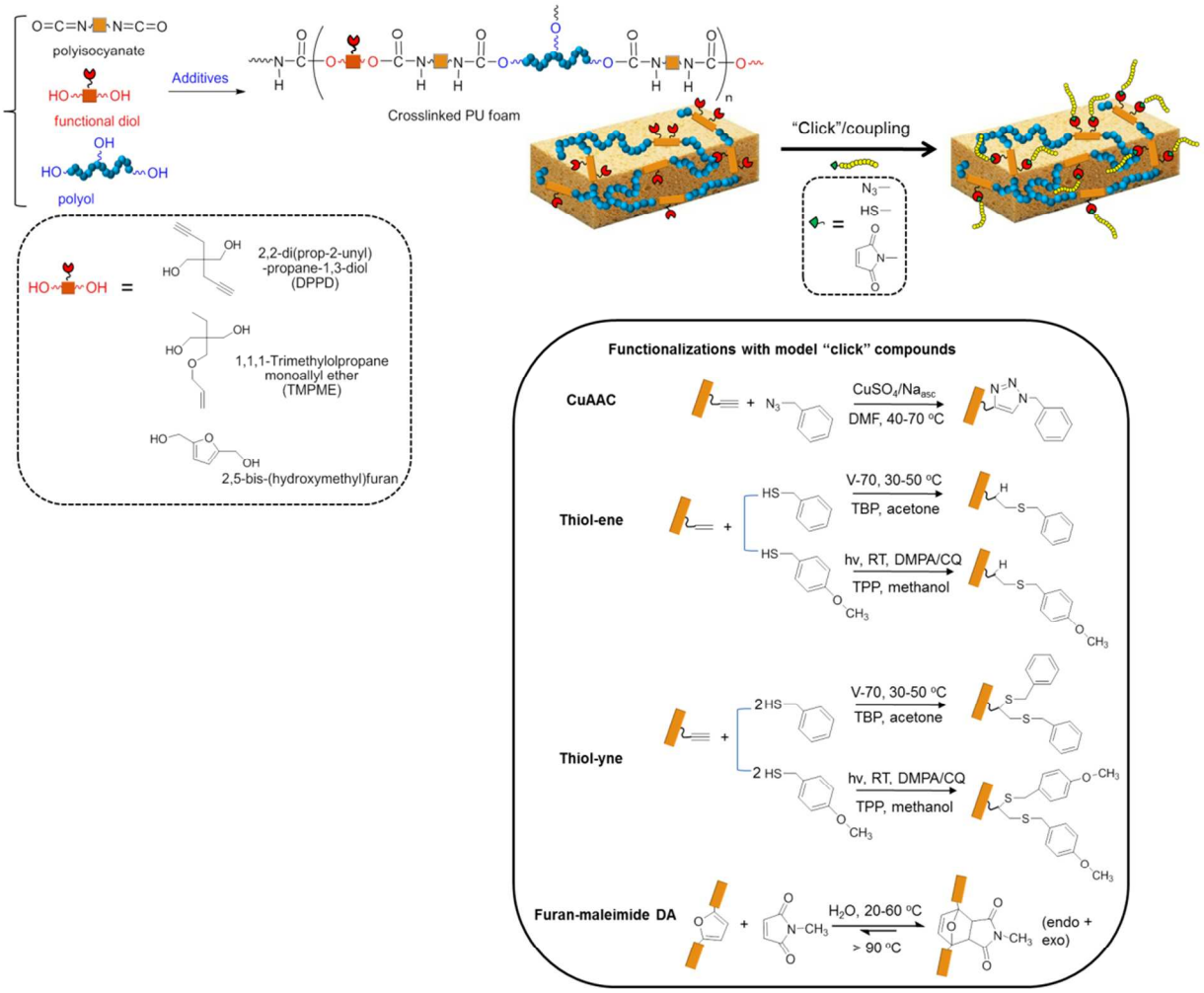
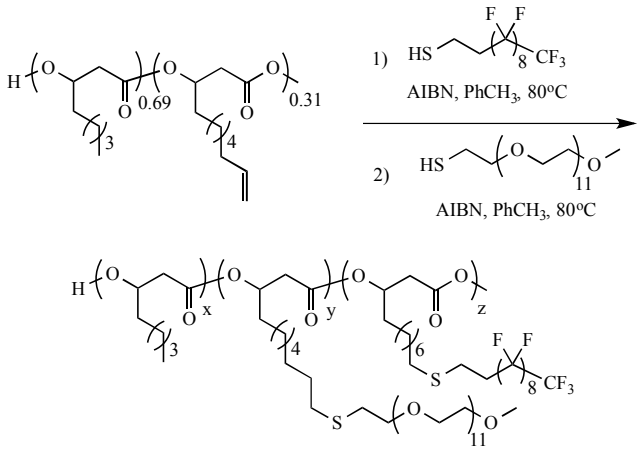


Figure 22 Outline for the synthesis of functional polyurethane foams, their subsequent modification via "click" or highly efficient coupling chemistries and a Scheme (inset) highlighting the coupling chemistries employed. Professor Filip Du Prez is thanked for supplying the original image. Reproduced with permission from L.-T. T. Nguyen, J. Devroede, K. Plasschaert, L. Jonckheere, N. Haucourt, F. E. Du Prez *Polym. Chem.* 2013, **4**, 1546-1556. Copyright 2013, RSC publications.

Reaction of the parent PGA with allyl bromide in the presence of $NaHCO_3$ gave the corresponding allyl ester functional PGA (note – the degree of modification could be tuned and complete functionalisation required several esterification reactions to be performed). In the literature example, the authors reacted a statistical copolymer containing allylester and *n*-hexylester side groups (with 56 mol% allylic groups) with 1-propanethiol in the presence of AIBN at 50°C to give the hydrothiolated product quantitatively as judged by ^{1}H NMR spectroscopy with the disappearance of the vinylic resonances.

Poly(3-hydroxyalkanoates) are naturally occurring polyesters synthesized and produced by many bacteria and used, when needed, as a source of energy. Babinot *et al.*[149] recently described the synthesis of multicompartment micelles based on poly(3-hydroxyoctanoate-*co*-3-hydroxyundecenoate) with a molar ratio of 69:31. Sequential grafting of 2-perfluorooctyl-1-ethanethiol and thiol-functionalised poly(ethylene glycol) monomethyl ether oligomers via AIBN-mediated radical mediated reactions gave the target thioether polymers, Scheme 49.



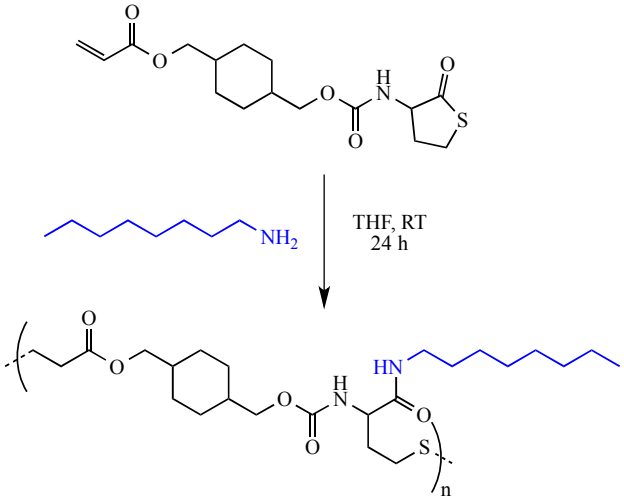
Scheme 49 Sequential, radical thiol-ene modification of poly(3-hydroxyoctanoate-*co*-3-hydroxyundecenoate) with fluorinated and PEG-based functional thiols.

These amphiphilic copolymers were then self-assembled via the nanoprecipitation technique into water to give spherical micelles as determined by TEM. Finally, their in vitro cytocompatibility was demonstrated

Miscellaneous polymer synthesis and modification

There has also been recent interest in novel syntheses and modifications of polyurethanes with the group of Du Prez paying particular attention to this research area. For example, Nguyen *et al.*[150] recently detailed a kinetic comparison for a series of click and efficient coupling chemistries employed in the surface modification of polyurethane foams, Figure 22. This included thermal and photochemical initiated thiol-ene reactions, Cu-mediated alkyne-azide reactions, thiol-yne coupling and Diels Alder reactions between furan and maleimide substrates. The polyurethane foams were prepared by the reaction between a polyisocyanate and a diol bearing the desired "clickable" functionality and a trithiol. The efficiency of the subsequent coupling reactions was monitored *in situ* by real time FTIR or by the withdrawal of aliquots and subsequent analysis by NMR spectroscopy. In all instances reduced rates and conversions were observed for the coupling reactions, compared to homogeneous modification protocols, an effect ascribed to diffusional limitations and highlighted the need for rather specific reaction conditions to optimize rates and yields. With specific reference to the thiol-ene reactions, these were found to be somewhat more sensitive to the diffusional limitations resulting in a narrower range of necessary experimental conditions to achieve acceptable rates of reaction and degrees of modification. However, the ability to perform such reactions at ambient temperature via photoinitiation was highlighted as an advantage of such chemistry especially in potential biological applications.

Espeel *et al.*[151] highlighted an isocyanate-free method for the preparation of polyurethanes via a two step amine-mediated ring-opening of a thiolactone with a subsequent thiol-Michael addition reaction. Key to success was the preparation of a substrate containing both an acrylic functional group and a thiolactone species. As an example, the authors reported the difunctional species, (4-((((2-oxotetrahydrothiophen-3-yl)carbamoyl)oxy) methyl)cyclohexyl)methyl acrylate, shown in Scheme 50.



Scheme 50 Chemical structure of (4-((((2-oxotetrahydrothiophen-3-yl)carbamoyl)oxy)methyl) cyclohexyl) methyl acrylate and its amine-initiated homopolymerisation to give a polyurethane.

Treatment of the acrylic thiolactone with octylamine (1.1 equivalents in 0.5 M THF at RT) results in the formation of a linear polyurethane with a measured $\bar{M}_n$ of 12,000 and corresponding $Đ_M$ of 1.69. Polymer is formed, presumably, by a two-step process. Firstly, the octylamine attacks the thiolactone in a ring opening reaction liberating a free thiol. The thiol then undergoes a thiol-Michael reaction at an acrylic bond to give the thioether adduct. Provided these sequential processes occur intermolecularly then a polymer is formed. Importantly, the slight excess of amine employed will also served as the catalyst for the thiol-Michael addition reaction. An important feature of this approach is the ability to introduce side chain functionality simply by appropriate choice of primary amine. The authors nicely demonstrated the wide range of possibilities by employing allylamine, propargylamine, furfurylamine, *N,N*-dimethylethylenediamine, 3-morpholinepropylamine, as well as mixtures of amines, as the polymerisation initiators. The authors noted that a polymer obtained from allylamine could be post-modified in a radical thiol-ene reaction with 1-octanethiol.

Wang and co-workers[152] reported the synthesis and modification of a series of novel polyamides prepared via the Passerini reaction. Within their library of materials they reported the preparation of two ene-bearing polyamides that were readily converted to the thioether adducts in an AIBN-mediated reaction with 1-dodecanethiol.

4. Dendrimers, Hyperbranched and Star Polymers

Branched (co)polymers are non-linear macromolecules that may be classified based on the number of branching points, resulting topology and or uniformity of the branching characteristics. Common examples include star polymers (formally defined as branched polymers in which the arms emanate from a single branching point), hyperbranched (co)polymers and dendrimers, although more 'exotic' types of materials also exist. Two recent reviews highlight the use of various thiol-X chemistries employed in the synthesis and modification of branched (co)polymers and as such we will only highlight a limited number of examples here and interested readers are directed to these other contributions.[153, 154]

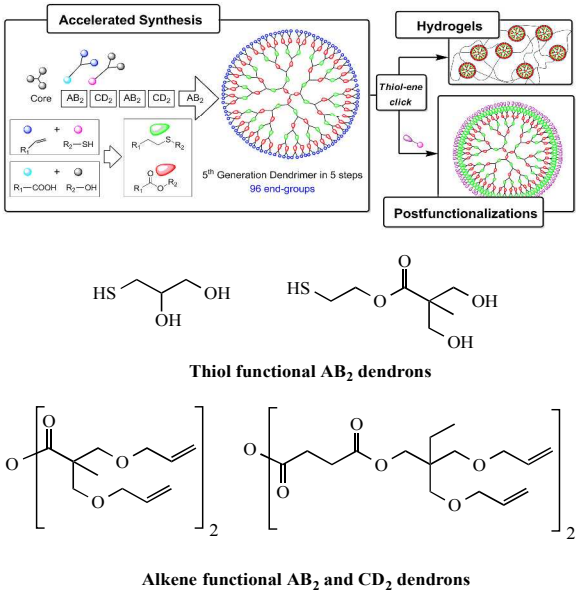


Figure 23 General approach for the preparation of 5th generation dendrimers using a combination of thiol-ene and esterification chemistries and chemical structures of the thiol and ene functional dendrons employed in their synthesis. Associate Professor Michael Malkoch is kindly thanked for supplying the original image file. Reproduced with permission from M. I. Montañez, L. M. Campos, P. Antoni, Y. Hed, M. V. Walter, B. T. Krull, A. Khan, A. Hult, C. J. Hawker, M. Malkoch *Macromolecules* 2010, **43**, 6004-6013. Copyright 2010, American Chemical Society.

As noted in the first mini-review, the potential of thiol-ene chemistry in the synthesis of branched polymers was recognized very early and has continued to attract attention. Montañez *et al.*[155] detailed the rapid synthesis of 5th generation dendrimers employing a combination of thiol-ene and esterification chemistries using **AB$_2$** and **CD$_2$** monomers. The general approach is outlined in Figure 23. As a representative example, the core molecule triallyl isocyanurate was initially reacted with the thio functional **AB$_2$** dendron 2-mercaptoethyl 3-hydroxy-2-(hydroxymethyl)-2-methylpropanoate in MeOH in the presence of the photoinitiator DMPA. This gave a 1st generation, six functional OH dendrimer. DCC/pyridine mediated esterification of the OH groups with the **CD$_2$** dendron 3-(allyloxy)-2-((allyloxy)methyl)-2-methylpropanoic anhydride to give the 2nd generation dendrimer containing 12 ene functional groups. Up to 4th generation species were readily prepared, via sequential thiol-ene and esterification reactions, in high yield and purity as determined by NMR spectroscopy, SEC and mass spectrometry.

The preparation of other dendrimer species employing different combinations of **AB$_2$** and **CD$_2$** dendrons and trifunctional core molecules were also reported. Postfunctionalisation of appropriate dendrimers was also demonstrated. For example, 2nd and 4th generation dendrimers containing C=C functional groups at their periphery were readily functionalised with small molecule thiols such as 3-mercaptopropionic acid, benzyl mercaptan and (((9*H*-fluoren-9-yl)methoxy)carbonyl)cysteine.

Following this report, Antoni *et al.*[156] detailed a facile and rapid procedure for the synthesis of high molecular weight, well-defined 6th generation dendrimers via sequential radical thiol-ene and Cu-catalysed alkyne-azide coupling reactions, Figure 24. Key to success was the use of the **AB$_2$** (2-((2-mercaptoethoxy)carbonyl)-2-methylpropane-1,3-diyl bis(5-azidopentanoate)) and **CD$_2$** (3-(allyloxy)-2-((allyloxy)methyl)-2-methyl-*N*-(prop-2-yn-1-yl)propanamide) monomers both of which were readily accessible in a few synthetic steps in high overall yield.

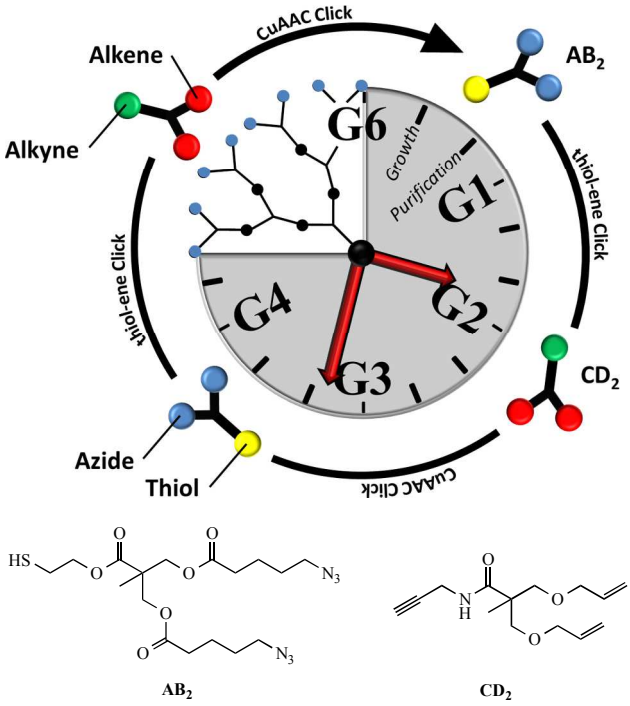
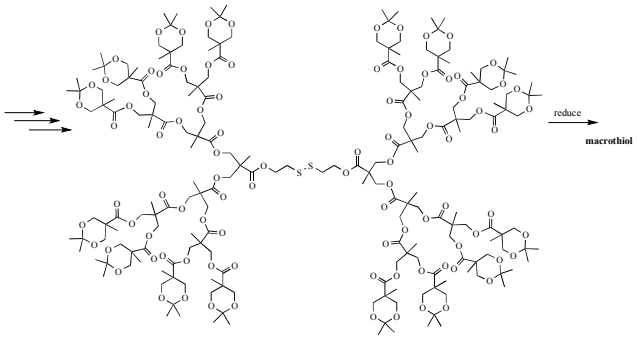


Figure 24 Facile and rapid synthesis of 6th generation dendrimers via sequential thiol-ene and alkyne-azide coupling reactions employing the novel **AB$_2$** and **CD$_2$** monomers shown. Professor Craig J. Hawker is thanked for supplying the original image file.

Employing a 2,4,6-tris(allyloxy)-1,3,5-triazine core, the allylic groups were first reacted with the thiol functional group in the **AB_2** monomer in a photoinitiated thiol-ene reaction to give the 6-functional azido 1st generation dendrimer. Subsequent reaction with the **CD_2** monomer in a Cu-catalysed alkyne azide coupling gave the 12-functional allylic 2nd generation dendrimer. Simply repeating this sequential process gave, ultimately, the 6th generation species with each step requiring approximately 3 hours to accomplish the coupling chemistry and isolation for the next step. To highlight the facile nature of the process, 1st-4th generation species were readily prepared on multigram scales and easily purified by passage through a silica plug. Each generational species was thoroughly characterized employing a combination of FTIR and NMR spectroscopies as well as SEC. Since each dendrimer has peripheral groups that are enes or azido functional groups each generational dendrimer can also be readily functionalized via either thiol-ene of alkyne-azide coupling reactions with small molecules to generate entire new series of functional dendrimers. For example, the 4th generation dendrimer, containing 48 ene chain end groups, was reacted with thioglycerol in a radical thiol-ene reaction to give the corresponding 96-functional OH dendrimer. Examples of coupling reactions to give dendrimers with hydrophilic, hydrophobic and bioactive groups were reported.

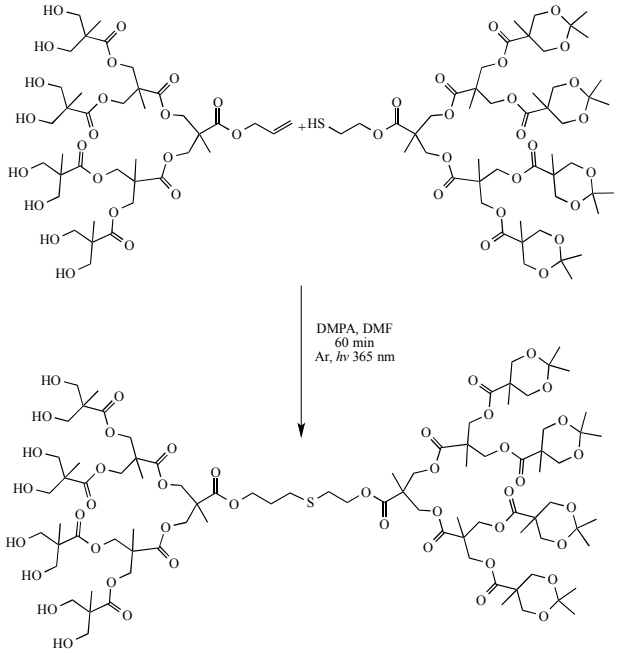
Walter and coworkers[157] reported the synthesis of a series of dendritic-based species using novel macrothiols. An example of the synthesis of such a macrothiol is given in Scheme 51.



Scheme 51 Use of a disulfide functional diol to generate dendritic structures that can be subsequently reduced to macro-thiols.

Esterification of 2,2'-disulfanediylbis(ethan-1-ol) with 2,2,5-trimethyl-1,3-dioxane-5-carboxylic anhydride followed by acid-mediated deprotection of the acetals gives disulfanediylbis(ethane-2,1-diyl) bis(3-hydroxy-2-(hydroxymethyl)-2-methylpropanoate). Repeated esterification, hydrolysis and esterification steps gives the 16-functional acetal disulfide which, after reduction of the linking disulfide bond gives a novel macrothiol. Reaction of this macrothiol dendron with the triene 2-((hept-6-enoyloxy)methyl)-2-methylpropane-1,3-diyl bis(hept-6-enoate) in the presence of DMPA and with irradiation at 365 nm followed by acidic deprotection of the acetals yields a generation 4 dendrimer, isolated in a 58% yield, with 48 OH end groups. Bifunctional, or asymmetric dendrimers were also readily obtained via the coupling of two dendrons employing thiol-ene coupling, Scheme 52. In this particular instance, a 5:1 molar ratio of thiol:ene was employed and pure bifunctional product was isolated in 76%. The purity of the product was confirmed via MALDI-TOF mass spectrometry, SEC and NMR spectroscopy. In addition to those dendritic structures highlighted the authors also reported the synthesis of examples of linear-dendritic species.

In another example where thiol-ene and alkyne-azide reactions were combined, Javakhishvili and coworkers[158] described the synthesis of linear-dendritic cholesteryl-poly(ε-caprolactone)-*block*-poly(L-lysine)$_{G2}$ copolymers. Ring-opening polymerisation of ε-caprolactone using 5-hexyn-1-ol as an initiator and $Sn(Oct)_2$ as catalyst gave poly(ε-caprolactone) with a $Đ_M$ of 1.11 and an NMR-determined degree of polymerisation of 20. Following esterification of the OH chain end with 4-pentenoic acid the ω-alkyne group was coupled with a 2nd generation L-lysine dendron bearing Boc protecting groups. Thiocholesterol was then coupled to the α-chain end in a radical thiol-ene reaction initiated by DMAP. Finally, the Boc protecting groups were removed by treatment with TFA to give the target linear-dendritic copolymer. The structure was confirmed by MALDI-TOF mass spectrometry and NMR analyses.



Scheme 52 Synthesis of asymmetric dendrimers via radical thiol-ene coupling of thiol and ene functional dendrons.

As already noted, the thiol-ene reaction, while useful as a 'construction' tool for preparing dendrimers and other dendritic

materials, it is also a convenient modification tool for branched structures that contain terminal ene functional groups. This was nicely demonstrated by Conte *et al.*[159] Using a 4th generation alkene functional dendrimer as a common substrate (with 48 ene functionalities) the peripheral ene groups were coupled with four different sugar thiols (glucose, mannose, lactose and sialic acid derivatives), two PEG thiols and the tripeptide glutathione by irradiation at 365 nm in the presence of DMPA. NMR spectroscopy on the non-purified products showed the complete disappearance of the alkene resonances suggesting complete functionalisation of all 48 groups. Pure products were isolated in high-to-excellent yield with the exception of the tripeptide derivative. MALDI-TOF mass spectrometry was used to verify the structure of the products.

Ortiz *et al.*[160] reported the synthesis of a second-generation thiol-functional dendrimer and its subsequent use in thiol-ene photopolymerisation with the multifunctional enes 1,6-hexanedioldiacrylate, pentaerythritol triacrylate and triallyl triazine. The dendrimer was prepared via a multistep procedure involving an initial photo-mediated thiol ene reaction between 3-allyloxy-1,2-propanediol and pentaerythritol tetrakis mercaptopropionate to give an 8-functional alcohol. Subsequent acid-catalysed esterification of the OH groups with 3-mercaptopropionic acid gave the first generation 8-functional thiol dendrimer. Repeating this sequence of reactions yielded the target second-generation dendrimer.

In convergent dendrimer syntheses it is necessary to have appropriately functionalized dendron building blocks. Recently, Fuentes-Paniagua *et al.*[161] highlighted the thiol-ene synthesis of a range of neutral and cationic carbosilane-based dendrons containing a variety of reactive species including examples with OH, SH and N_3 functional groups, Figure 25.

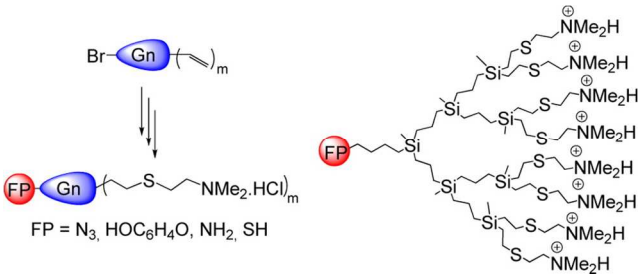
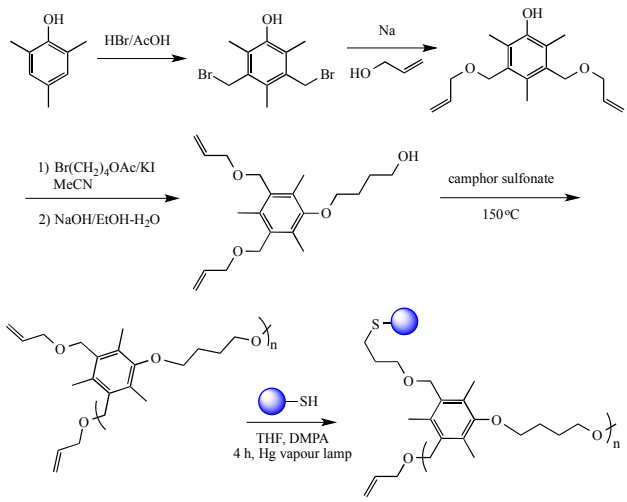


Figure 25 Thiol-ene synthesis of cationic dendrons bearing a range of functional focal point groups. Reproduced with permission from E. Fuentes-Paniagua, C. E. Peña-Gonzáles, M. Galán, R. Gómez, F. Javier de la Mata, J. Sánchez-Nieves *Organometallics* 2013, **32**, 1789-1796. Copyright 2013, American Chemical Society.

Starting from carbosilane dendrons with a Br atom focal point and ene groups at the periphery (these precursors were prepared based on a previous literature report for the synthesis of analogous allyl functional carbosilane dendrons[162]) initial modification focussed on the substitution of the Br atom with other desirable functional groups. Azido and OH groups were introduced directly to the ene functional dendrons whereas primary amine and thiol functionalities were initially installed in a masked form. Subsequently, the terminal vinyl groups on the dendron precursors were reacted with $HS(CH_2)_2NMe_2$•□□□ in the presence of DMPA as a photoinitiator to give, quantitatively, the thioether dendrons.

In addition to dendrimers, thiol-ene chemistry has been employed in the modification of hyperbranched polymers. For example, Yu and co-workers[163] reported the synthesis of novel hyperbranched glycopolymers via a post-polymerisation modification route. Hyperbranched poly(amido amine) was first prepared via the Michael addition polymerisation of *N,N*-methylene bisacrylamide with 1-(2-aminoethyl)piperazine. The resulting hyperbranched polymer contained approximately 24% unreacted enes as determined by ^{1}H NMR spectroscopy. These reactive groups were subsequently exploited in the base-mediated thiol-Michael reaction with 1-thio-β-D-glucose to give the novel glycopolymers. A 2-fold excess of thiosugar ensured complete reaction within 2 h.

Roy and Ramakrishnan[164] detailed the synthesis and acid catalysed melt polymerisation of a novel bis allyloxy, AB_2, monomer to give a hyperbranched polymer. After polymerisation the pendent allylic groups were readily modified with four different thiols under standard radical-mediated conditions to give a series of new derivatised polymers, Scheme 53. ^{1}H NMR spectroscopy indicated complete consumption of the allyl groups.

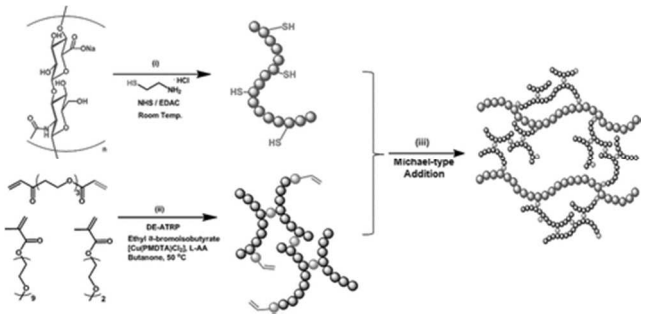


Scheme 53 Synthesis of 3,5-bis((allyloxy)methyl)-2,4,6-trimethylphenol, its acid-mediated melt polymerisation and subsequent post-polymerization radical thiol-ene coupling of the pendent allyl groups.

Foix *et al.*[165] described the synthesis of a new hyperbranched polymer via sequential esterification and radical thiol-ene reactions. 1,1,1-Tris(hydroxymethyl)propane was initially reacted with 10-undecenoyl chloride to give the corresponding trifunctional ene that was then treated with thioglycerol to give the six-functional alcohol. Repeating this

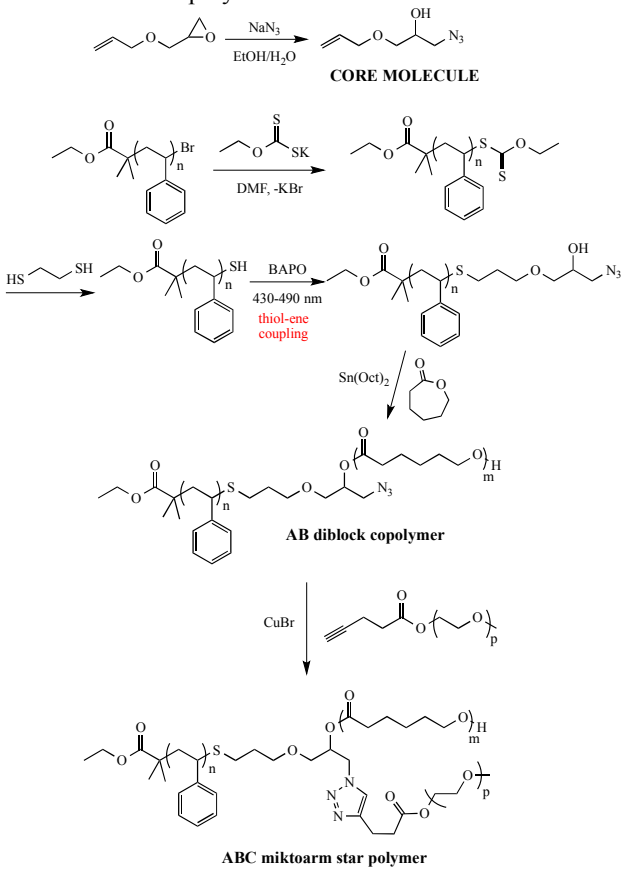
sequence also yielded the 12- and 24-functional alcohols. The authors highlighted how these hyperbranched polymers could serve as dual latent macroinitiators for the curing of cycloaliphatic epoxy resin. Specifically, the thioether groups were initially reacted with a triaryl sulfonium salt (photoinitiator) resulting in the formation of a thermal macroinitiator containing trialkyl sulfonium groups. Subsequent thermal curing of the epoxy resin gave highly crosslinked networks.

Dong *et al.*[166] reported the synthesis of a well-defined poly(ethylene glycol)-based hyperbranched thermoresponsive polymer containing a high content of acrylic groups, Scheme 54, via deactivation enhanced ATRP. Reaction of this hyperbranched polymer with thiol-modified hyaluronan via thiol-Michael addition gave a novel biocompatible hydrogel.



Scheme 54 "One□step" preparation of thiol□ene clickable PEG□based thermoresponsive hyperbranched copolymer for in situ crosslinking hybrid hydrogel. Reproduced with permission from Y. Dong, A. O. Saeed, W. Hassan, C. Keigher, Y. Zheng, H. Tai, A. Pandit, W. Wang *Macromol. Rapid Commun.* 2012, **33**, 120-126. Copyright 2012, John Wiley & Sons.

Star polymers also belong to the family of branched polymers and, not surprisingly, thiol-ene chemistry has also been exploited in this important area of synthesis. Iskin, Yilmaz and Yagci employed a combination of radical thiol-ene coupling, ring-opening polymerisation and Cu-catalysed alkyne-azide to prepare ABC miktoarm star polymers via a combined divergent and convergent approach.[167] The core molecule, 1-(allyloxy)-3-azidopropan-2-ol, was prepared from the straightforward reaction between 2-((allyloxy)methyl)oxirane and sodium azide with the product being obtained in a 96% yield. The first arm, polystyrene containing a ω-SH group, was prepared in a three step process involving ATRP to give the parent Br-terminated polystyrene, nucleophilic substitution of the Br group with the xanthate salt potassium *O*-ethyl carbonodithioate followed by cleavage of the ω-xanthate group with 1,2-ethanedithiol. The polystyrene-SH was then grafted to the core molecule in a radical thiol-ene coupling mediated by bis-(2,4,6-trimethylbenzoyl) phenylphosphine oxide (BAPO) – a visible light absorbing initiator. Successful coupling was confirmed by ^{1}H NMR and FTIR spectroscopies and SEC. This yielded a polystyrene which contained both OH and N_3 functional groups at the ω-terminus. Following this, ε-caprolactone was polymerized utilizing the terminal OH group as the initiator and $Sn(Oct)_2$ as the catalyst to give, formally, an AB diblock copolymer. In the final step, an yne-functional PEG was coupled to the azido group using a Cu(I) catalyst at 60°C. The total synthesis of the ABC miktoarm star polymers is outlined in Scheme 55.



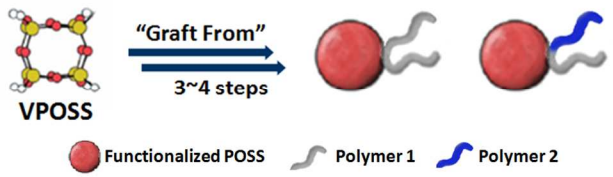
Scheme 55 Synthesis of ABC miktoarm star polymers via a combination of radical thiol-ene coupling of a polystyryl-thiol, ring-opening polymerisation of ε-caprolactone and Cu-catalysed alkyne-azide coupling of an yne functional poly(ethylene glycol).

5. Organic-Inorganic Hybrid Materials

Several research groups have examined the use of thiol-ene chemistry as a means of preparing novel organic-inorganic hybrid materials either as network materials or, most commonly, as new functional derivatives of polyhedral oligomeric silsesquioxanes (POSS),[168] including novel thermo- and pH-responsive species.[169] For example, Rózga-Wijas and Chojnowski[170] described the synthesis of a novel octakis-2([3-(trimethoxysilyl)propyl]thio)ethyl-octasilsesquioxane (POSS-M24) via the radical thiol-ene addition of 3-mercaptopropyltrimethoxysilane to octavinyloctasilsesquioxane (POSS-V8) in the presence of AIBN at 60°C in toluene. Formation of POSS-M24 was verified using a combination of ^{1}H, ^{13}C and ^{29}Si NMR spectroscopies and mass spectrometry.

Li and co-workers[171] described the preparation of a series of POSS-based amphiphiles in which a functionalized POSS species served as the 'head' and contained two symmetric or asymmetric polymeric tails, Scheme 56.

POSS-V8, referred to by the authors as VPOSS, was initially monofunctionalised in a thiol-ene reaction with thioglycerol. This gave a diol functional VPOSS (POSS-V7-$(OH)_2$) with seven free ene groups. This diol was used directly as a difunctional initiator in the ring-opening polymerisation of ε-caprolactone to give a POSS cage with two identical polymeric tethers. Successful synthesis of PCL-VPOSS-PCL was confirmed using a combination of NMR spectroscopy, SEC and MALDI TOF mass spectrometry. The PCL-VPOSS-PCL was further surface modified in a second thiol-ene reaction between the remaining POSS-bound vinyl groups and 2-mercaptoethanol giving a highly hydrophilic POSS-cage. The OH groups were also used to introduce ATRP-initiator functionality by reaction of one or both of the OH groups with 2-bromoisobutyryl bromide. In the case of the difunctional POSS-ATRP initiator, polymerisation of styrene was accomplished with a large excess of monomer and limited to 20% conversion to prevent any undesirable copolymerization of the vinyl groups on the POSS-cage. The product was characterised via standard procedures and also subsequently post-modified in another thiol-ene reaction as noted above. In the case of the heterobifunctional initiator it was noted that while it is in principle possible to perform ring-opening polymerisation of ε-caprolactone followed by ATRP of styrene, or vice-versa, optimal results were obtained when ATRP was performed first. As with the pure polystyrene or poly(ε-caprolactone) tethered POSS species, the hybrid was also subjected to a subsequent surface modification of the remaining vinyl groups on the POSS cage in a thiol-ene reaction with 2-mercaptoethanol.



Scheme 56 Synthesis of symmetric and asymmetric twin-tailed POSS. Professor Stephen Z. D. Cheng is kindly thanked for supplying the original image. Reproduced with permission from Y. Li, X.-H. Dong, K. Guo, Z. Wang, Z. Chen, C. Wesdemiotis, R. P. Quirk, W.-B. Zhang, S. Z. D. Cheng *ACS Macro Lett.* 2012, **1**, 834-839. Copyright 2012, American Chemical Society.

The same group have extended these initial studies to include more exotic examples of such giant POSS-based amphiphiles in which thiol-ene chemistry has played a key role in the syntheses.[172, 173]

In an interesting combination of thiol-ene chemistry with POSS species, Yu *et al.*[174] described the synthesis of hybrid, photocrosslinked polymersomes obtained from the co-assembly of acrylate-functionalised poly(ether amine) and octamercaptopropyl POSS ($POSS(SH)_8$), Figure 26.

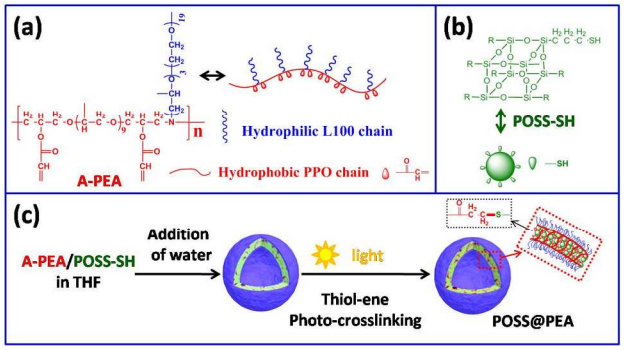


Figure 26 Chemical structures of the amphiphilic poly(ether amine) derivative, octamercaptopropyl POSS and the subsequent mixing, self-assembly and photocrosslinking of the hybrid polymersomes. Professor Xuesong Jiang is thanked for supplying the original image. Reproduced from B. Yu, X. Jiang, N. Qin, J. Yin *Chem. Commun.* 2011, **47**, 12110-12112.

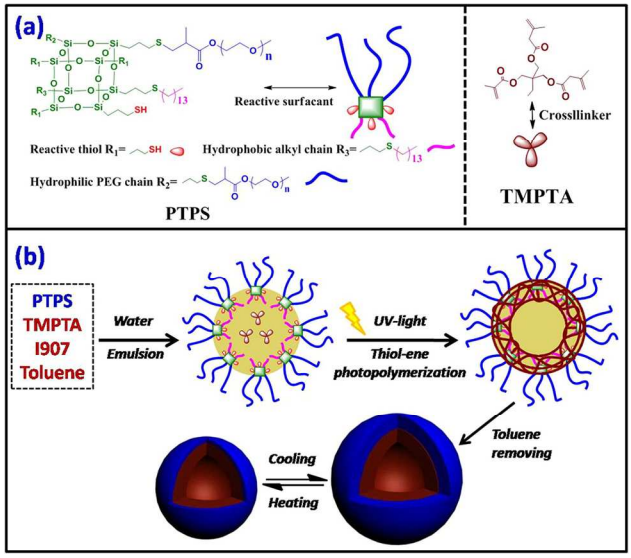


Figure 27 Preparation of microcapsules via a one-pot interfacial thiol-ene photopolymerisation. Reproduced with permission from D. Liu, B. Yu, X. Jiang, J. Yin *Langmuir* 2013, **29**, 5307-5314. Copyright 2013, American Chemical Society.

The amphiphilic poly(ether amine) derivative and $POSS(SH)_8$ were co-assembled via the gradual addition of water to a THF solution of the two components. Assembly resulted in the formation of vesicles in which the hydrophobic domain contained poly(propylene oxide) bearing acrylic groups along with $POSS(SH)_8$. Upon exposure to UV light at 364 nm the hydrophobic domain of the polymersomes was crosslinked via radical mediated thiol-Michael reactions. The authors also demonstrated that it was possible to control the self-assembled size and morphology (micelles vs. vesicles) simply by varying

the ratio of polymer:POSS. The ability of the crosslinked vesicles to serve as dispersing species for both hydrophilic and hydrophobic dyes was also demonstrated. In a related study, Liu and co-workers[175] demonstrated a straightforward and robust approach for the preparation of hybrid microcapsules via a one-step thiol-ene photopolymerisation at the interface between toluene and water, Figure 27. The amphiphilic POSS surfactant (denoted PTPS Figure 27 (a)) is prepared by initially grafting the hydrophilic PEG and hydrophobic alkyl chains to a precursor reactive POSS to give the surfactant with an average ratio of thiol:alkyl chain:PEG of 3:2:3. In an emulsion of toluene in water PTPS resides at the water-toluene interface while the hydrophobic trimethacrylate crosslinker (TMPTA) resides in the hydrophobic toluene phase. Irradiation in the presence of the photoinitiator I907 resulted in thiol-ene polymerisation at/near the surface of the droplets giving the surface crosslinked microcapsules, see Figure 28 for example. The feed ratio of PTPS:TMPTA:toluene was systematically varied and shown to be an important variable in controlling both the microcapsule size and wall thickness. All microcapsules were characterised using a combination of SEM and TEM. Such capsules were also shown to undergo a temperature-induced shrinkage when dispersed in water and was attributed to the gradual desolvation of the coronal PEG chains. As with their previous work noted above on POSS hybrid polymersomes these amphiphilic microcapsules were also shown to be capable of hosting guest molecules such as Nile Red.

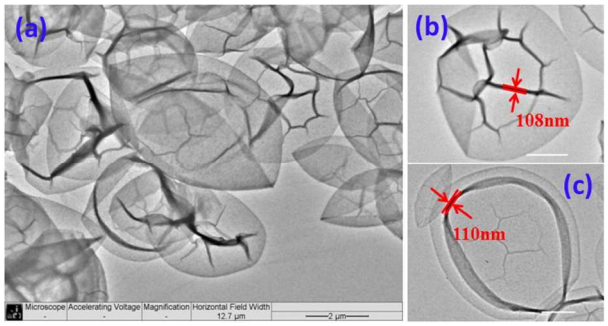


Figure 28 Representative TEM images of microcapsules produced via a one-pot interfacial thiol-ene photopolymerisation at a ratio of 1:0.85:48 PTPS:TMPTA:toluene. Reproduced with permission from D. Liu, B. Yu, X. Jiang, J. Yin *Langmuir* 2013, **29**, 5307-5314. Copyright 2013, American Chemical Society.

The same group reported the synthesis of hybrid materials based on mercapto-bearing POSS and a triacrylate derivative of castor oil and performed detailed kinetic, thermal and physical characterisation of the composite materials.[176]

Alves, Scholder and Nischang[177] reported the synthesis and functionalisation of highly porous organic-inorganic hybrid materials obtained from the free radical initiated polymerisation of vinyl-substituted POSS species (obtained as a mixture of different cage-sized species) in the presence of PEG200 (nominal molecular weight 200 g/mol^{-1}) as a porogen. Particular attention was paid to the effect of initiator concentration as well as the ratio of porogenic solvent mixture (PEG200:THF) on the dry state surface area and porosity of the resulting materials, with detailed characterization studies performed. In the context of this review, however, it is important to note that the direct polymerisation of such vinyl POSS derivatives results in a significant number of unreacted vinyl groups yielding, therefore, materials susceptible to subsequent modification. In this report, crosslinked material was suspended in $CHCl_3$ in the presence of DMPA and thioglycolic acid and subsequently irradiated at 22°C. FTIR analysis indicated a rapid reaction with significant hydrothiolation occurring within 60 s and near quantitative addition within 10 min, Figure 29.

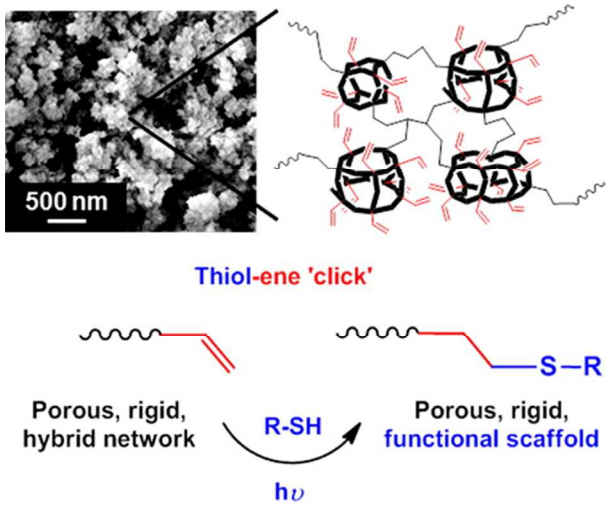


Figure 29 Thiol-ene modification of vinyl-functional POSS-based networks. Reproduced with permission from F. Alves, P. Scholder, I. Nischang *ACS Appl. Mater. Interfaces* 2013, **5**, 2517-2526. Copyright 2013, American Chemical Society.

Additional examples in which thiol-ene chemistry has been utilized in hybrid materials syntheses include the work of Kim *et al.*[178] and the preparation of novel insulating materials with high dielectric constants, and Sparks and co-workers[179] report of thiol-ene network materials containing cyclic tetravinylsiloxanetetrols. In fact, a significant number of the hybrid materials reported are either networks or coatings.

Colucci *et al.*[180] detailed the preparation of hybrid silicate/thiol-ene photocured coatings via dispersing a number of different silicates, sepiolite fibres (a complex magnesium silicate) or lamellar kaolin (an aluminium silicate) at a concentration of up to 7.0 wt% in a thiol-ene system comprising trimethylolpropane trismercaptopropionate, allyl pentaerythritol and benzophenone. The added filler had little effect on the radical thiol-ene process but did result in materials with slightly higher T_g's and surface hardness. The same group

have also reported hybrid materials obtained via simultaneous radical thiol-ene and sol-gel processes.[181]

Hybrid materials have also been prepared for chromatographic applications.[182, 183] For example, Chen and co-workers reported the preparation of a biphasic silica hybrid monolithic column, Figure 30. Sulfonate functional (segment A, for online preconcentration) and vinyl functional (segment B, for separation) silica monoliths were prepared simultaneously in a capillary via a sol-gel process. The presence of the vinyl groups in segment B allowed for radical thiol-ene modification to introduce a range of functionality based on separation need – in this particular instance the vinyl groups were coupled with octadecanethiol or 6-mercapto-1-hexanol. The effectiveness of the system was demonstrated in the successful separation of the structurally similar amines *p*-phenylenediamine, aniline, *p*-toluidine, *N*-methylaniline, *N,N'*-dimethylaniline and diphenylamine.[183]

Thiol-ene/clay nanocomposite thin films were recently reported by Bae.[184] Photoinitiated polymerisation of pentaerythritol tetrakis(3-mercaptopropionate) with 1,3,5-triallyl-1,3,5-triazine-2,4,6-trione in the presence of 1 wt% octadecylamine surface modified clay yielded novel, transparent, organic-inorganic hybrid materials in which the clay was homogeneously dispersed in the thiol-ene matrix as confirmed by transmission electron microscopy. These films were evaluated with respect to their gas permeation properties and it was shown that the films possessed excellent oxygen permeability comparable to PET.

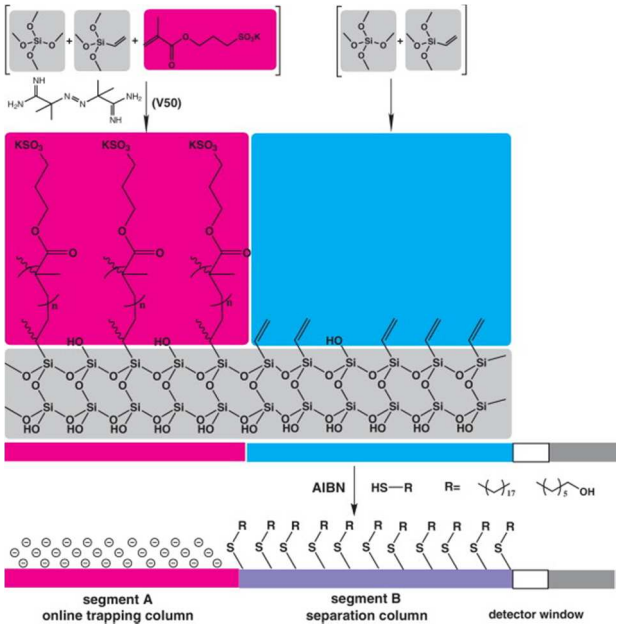
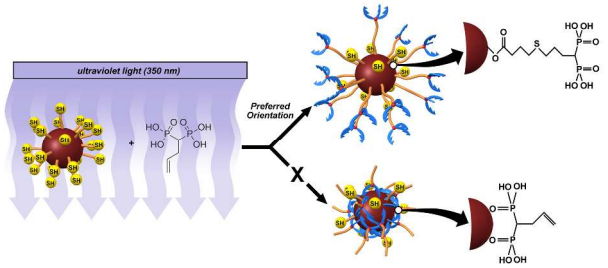


Figure 30 Outline for the preparation of a hybrid biphasic silica monolith containing unreacted ene groups amenable to functionalisation by radical thiol-ene coupling. Reproduced with permission from Y. Chen, K. Wang, H. Yang, Y. Liu, S. Yao, B. Chen, L. Nie, G. Xu *J. Chromatogr. A*, 2011, **1218**, 7982-7988. Copyright 2012, Elsevier.

6. Nanoparticle Modification

There has also been considerable interest in the synthesis of nanoparticles as well as their surface modification with an emphasis on silica and iron-based species although soft polymeric nanoparticles have also been studied. For example, Rutledge *et al.*[185] detailed a straightforward process for preparing diphosphonic acid functionalized iron oxide nanoparticles. Historically this has proven difficult since the phosphonic acid groups have an inherently high affinity for iron oxide surfaces and achieving the desired orientation (free acid groups) on such metal oxide surfaces has been challenging. In this example, the authors first prepared thiol-functionalized iron oxide nanoparticles which were reacted with but-3-ene-1,1-diyldiphosphonic acid under UV irradiation in the presence of a photoinitiator. Successful surface modification, with the desired orientation, i.e. thioether formation via a thiol-ene reaction, was confirmed using a combination of IR, XPS and TGA, Scheme 57.



Scheme 57 UV-initiated modification of thiol-functionalised iron oxide nanoparticles with an allylic bisphosphonic acid ligand. Dr. Marvin Warner is kindly thanked or supplying the original image. Reproduced with permission from R. D. Rutledge, C. L. Warner, J. W. Pittman, R. S. Addleman, M. Engelhard, W. Chouyyok, M. G. Warner, *Langmuir,* 2010**, 26**, 12285. Copyright 2010, American Chemical Society.

Amici and co-workers reported a different approach to obtaining modified iron oxide nanoparticles.[186] Here, Fe_3O_4 particles with an average diameter of ca. 30 nm were treated with vinyltrimethoxysilane as a means of introducing surface vinyl functionality. These were subsequently reacted with PEG-dithiols under UV irradiation to give the PEG-functionalized species. Successful modification was confirmed via FTIR and TGA.

Liang *et al.* reported a method for obtaining Fe_3O_4 nanoparticles with both magnetic and electrochemical properties.[187] Carboxylic acid functionalized Fe_3O_4 nanoparticles were first prepared via standard procedures. These were converted to thiol-functional species via a carbodiimide-mediated amidation reaction with 2-aminoethanethiol. Subsequently, the thiol-functional Fe_3O_4 was reacted with vinylferrocene under initiator-free UV irradiation.

As noted, combining thiol-ene chemistry with silica-based nanoparticles has also attracted attention. Li and co-workers[188] reported a multi-step approach to hairy hollow microspheres employing a combination of distillation-precipitation polymerisation and thiol-ene chemistry, Figure 31. Near monodisperse silica core-poly(*N*-vinylcarbazole) shell (SiO_2@PVK) particles were initially prepared by surface initiated distillation-precipitation polymerisation of *N*-vinylcarbazole, in the presence of divinylbenzene, from SiO_2 nanoparticles prepared by a sol-gel process. This yielded core-shell precursors containing available, reactive ene groups on their surface. RAFT-prepared poly(*N*-isopropylacrylamide) ($\bar{M}_{n,SEC}$ = 11,600 and $Đ_M$ = 1.32) was then grated to the surface of the microspheres via radical thiol-ene coupling following cleavage of the thiocarbonylthio end-groups with $NaBH_4$. Hollow microspheres were obtained by HF etching of the silica cores. These hollow particles were shown to possess fluorescent and thermoresponsive properties. The same group has also reported the synthesis of similar nanospheres via the same general multi-step procedure but in the polymer grafting-to stage employed a combination of alkyne-azide and thiol-ene coupling reactions giving particles containing at least two distinct polymers attached to the particles.[189]

Similar thermo- and pH-responsive silica nanoparticles have been reported by Kotsuchibashi *et al.*[190] Silica nanoparticles were first prepared and then reacted with 3-(trimethoxysilyl) propyl methacrylate to introduce surface methacrylic groups. Poly(*N*-isopropylacrylamide) (thermoresponsive) and poly(2-(diethylamino)ethyl methacrylate) (pH responsive), prepared by RAFT, were converted to their macromolecular thiol forms by treatment with $NaBH_4$ and then reacted, as a mixture, with the ene functional silica nanoparticles under radical conditions to give dually responsive polymer-modified particles.

Shen and co-workers have also employed sol-gel chemistry in combination with thiol-ene coupling to prepare hybrid silica/titania microspheres.[191] Vinyl functional silica nanoparticles were first prepared via a sol-gel reaction with vinyl triethoxysilane in the presence of sodium dodecylbenzene sulfonate. AIBN-mediated thermal radical thiol-ene coupling of the surface ene groups with 3-mercaptopropionic acid gave the acid surface functional silica particles. A second sol-gel reaction with titanium tetrabutoxide and ammonia solution as catalyst in the presence of the silica particles yielded amorphous hybrid SiO_2/TiO_2 core-shell microspheres. Finally, calcination at 500°C for 2 h converted the amorphous TiO2 layer into anatase titania which were shown to exhibit good photocatalytic performance in the degradation of methyl orange.

Novel biofunctional silica nanoparticles have been reported by Ruizendaal *et al.* employing a different approach in the synthesis of the parent nanoparticles, Scheme 58.[192]

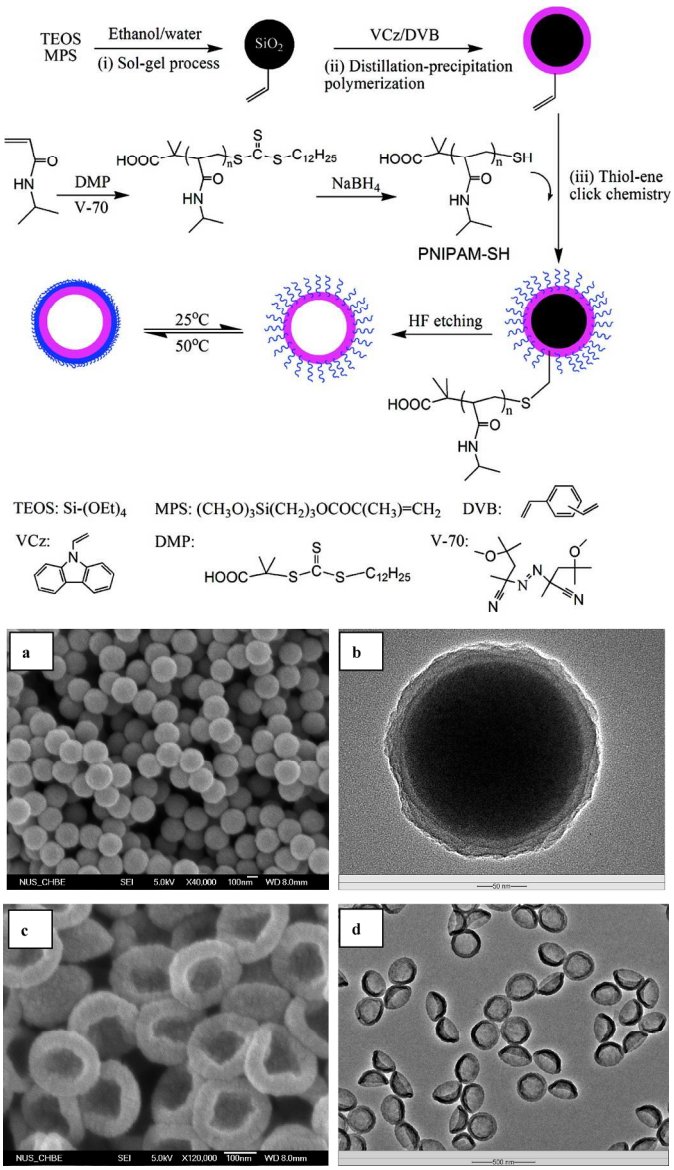
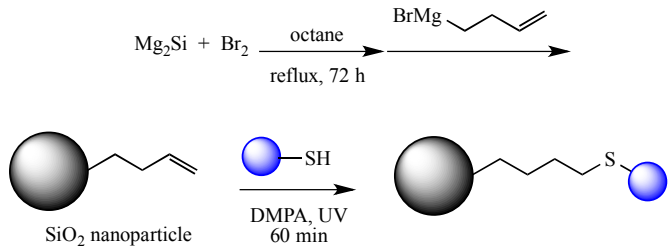


Figure 31 Synthesis of thermoresponsive, hollow, nanoparticles via a combination of sol-gel, distillation-precipitation and thiol-ene click chemistries and representative FESEM (a) and TEM (b) images of the SiO_2@PVK-poly(*N*-isopropylacrylamide) nanoparticles and TEM images (c and d) of the same nanoparticles after HF etching of the silica cores. Reproduced with permission from G. L. Li, L. Q. Xu, X. Tang, K. G. Neoh and E. T. Kang *Macromolecules* 2010, **43**, 5797-5803. Copyright 2010, American Chemical Society.



Scheme 58 Outline for the preparation of thioether-functional silica nanoparticles via the oxidation of Mg_2Si followed by nucleophilic substitution and finally thiol-ene coupling.

Bromine terminated SiO_2 nanoparticles were first obtained via the oxidation of Mg_2Si with bromine. Reaction with 4-butenylmagnesium bromide yielded the corresponding ene-functional species. A variety of small molecule thiols were subsequently coupled to the nanoparticles via the common photoinitiator-mediated or thermal azo-mediated routes. Conjugated thiols included 2-mercaptoethanol, ethyl 2-mercaptoacetate and 2-mercaptoacetic acid. In addition to these straightforward thiol-ene couplings, the authors reported the preparation of biofunctional silica nanoparticles with possible application as biosensors via carbodiimide-mediated coupling of single strand DNA (ssDNA) to acid functional silica nanoparticles (obtained via the thiol-ene coupling of the parent nanoparticles with 2-mercaptoacetic acid). Successful functionalisation was confirmed using a combination of UV-vis and fluorescence spectroscopies.

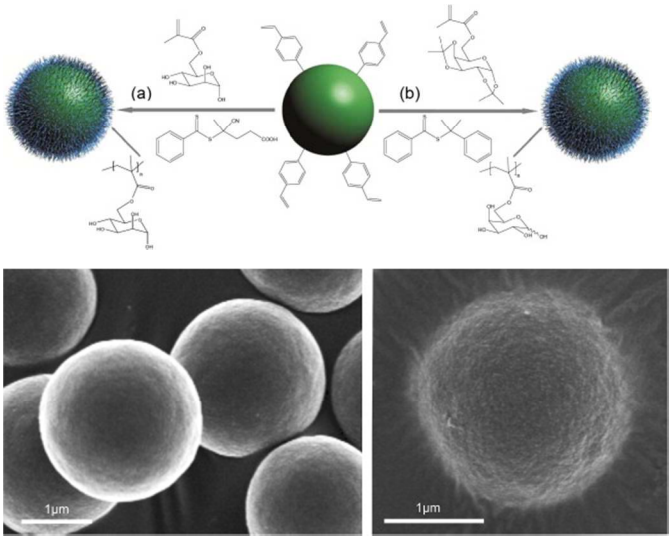


Figure 32 Synthetic outline for the preparation of glycopolymer functional polydivinylbenzene microspheres and SEM images of unmodified microspheres (left) and a poly(6-*O*-methacryloyl mannose) modified microsphere (right). Reproduced with permission from A. Pfaff, L. Barner, A. H. E. Müller and A. M. Granville, *Eur. Polym. J.*, 2011, **47**, 805-815. Copyright 2011, Elsevier.

In addition to the modification of inorganic particles, there has been significant interest on the surface modification of soft, polymeric nanoparticles. For example, Pfaff *et al.*[193] described the synthesis of galactose or mannose functional polydivinylbenzene microspheres, Figure 32, employing a combination of distillation and RAFT polymerisation techniques.

Grafting-from, grafting-through and grafting-to approaches were utilized to obtain the glycopolymer-modified particles. Of relevance here, is the grafting-to approach. As an example, poly(6-*O*-methacryloyl-1,2:3,4-di-*O*-isopropylidene galacto pyranose) was conjugated to the microspheres in the presence of hexylamine to cleave the RAFT-instilled thiocarbonylthio end groups and AIBN in DMF. Removal of the protecting groups gave the free sugar coated particles that were readily dispersed in aqueous media.

Korthals and co-workers[194] described the radical thiol-ene modification of syndiotactic 1,2-polybutadiene nanoparticles (average diameter of ca. 13.0 nm) in an aqueous dispersion. Careful control of the reaction conditions facilitated degrees of functionalisation up to 85% with methyl 3-mercaptopropionate and 3-mercaptopropionic acid. In the case of sodium 3-mercaptopropanesulfonic acid, functionalisation was restricted to surface vinyl groups. Grafting of the tripeptide glutathione was also reported.

The thiol-ene mediated crosslinking of well defined, biodegradable nanoparticles and nanocapsules has been reported by Zou *et al.*, Figure 33.[195] Precursor polymers of lactide with the allyl functional lactide derivative, **1** Figure 33, were prepared by ring opening polymerisation employing two different alcohols as initiators and DMAP as the catalyst. The authors next identified appropriate conditions for preparing transparent miniemulsions of the parent, precursor copolymers in which water was employed as the continuous phase, *n*-butyl acetate as the oil phase and hexadecane as a hydrophobe. Addition of the dithiol 1,4-butanediol bis(3-mercaptopropionate) and photoinitiator DMPA to these miniemulsions results in partioning of these hydrophobic species into the polymeric nanoparticles. Subsequent UV irradiation for 30 min yielded the target crosslinked, biodegradable materials. High conversions of the allyl/dithiol groups to the corresponding thioethers was confirmed by IR spectroscopy.

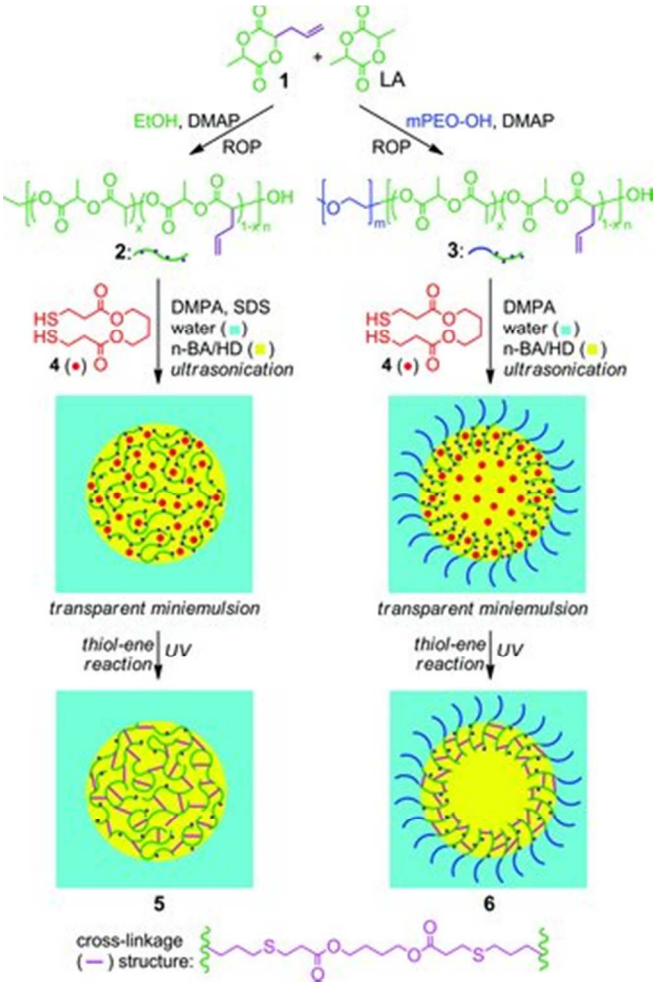


Figure 33 Preparation of polylactide-based biodegradable, crosslinked nanoparticles. Reproduced with permission from J. Zou, C. C. Hew, E. Themistou, Y. Li, C.-K. Chen, P. Alexandridis and C. Cheng *Adv. Mater.* 2011, **23**, 4274-4277. Copyright 2011, John Wiley & Sons.

Recently, Štorha, Mun and Khutoryanskiy[196] described the synthesis of thiolated and acrylic-functional nanoparticles from pentaerythritol tetrakis(3-mercaptopropionate) and pentaerythritol tetraacrylate. The authors reported that when the reactions were performed in DMF that it was possible to obtain macroscopic transparent gels or sols depending on the total concentration and ratio of the tetrathiols to tetraacrylate, with sols being favoured at lower concentrations and less-stoichiometric ratios of reactants although could only be obtained in low yields of 3-16 %. Particles bearing excess thiol groups and previously labelled with fluorescein-5-maleimide were evaluated as potential mucoadhesive species. After being dispersed on a mucosal surface the surface was washed with artificial urine and then examined by fluorescence microscopy. Their binding ability was reported to be similar to that of other thiol-containing (co)polymers being developed as transmucosal drug delivery vehicles.

An interesting approach to hollow polymeric nanocapsules was detailed by Balasubramanian, Han and Chamberlayne.[197] The thiol-ene photopolymerisation of resorcinarene cavitand thiol with 2-, 3- or 4-functional enes yielded hollow nanocapsules of varying thickness and rigidity, the two latter features being controlled by the functionality of the ene, Figure 34.

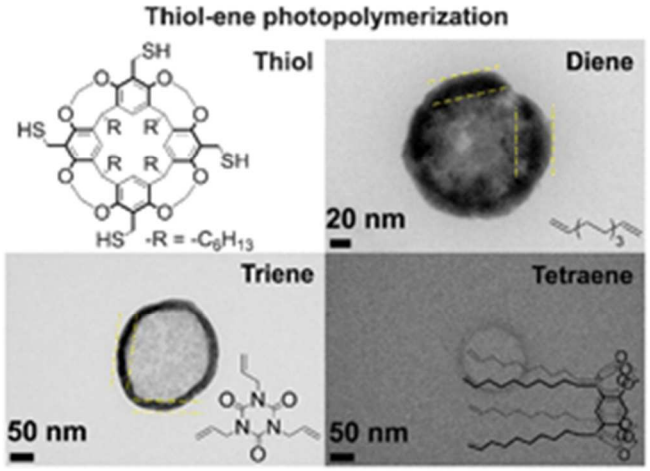


Figure 34 Chemical structures of resorcinarene cavitand thiol and TEM images of the nanocapsules obtained from the thiol-ene photopolymerisation of the thiol with 2-, 3-, and 4-functional enes. Reproduced from R. Balasubramanian, S. Han and C. Chamberlayne, *RSC Adv.*, 2013, **3**, 11525-11528.

Moczko and co-workers[198] reported a novel solid phase approach to the synthesis of core-shell molecularly imprinted polymer nanoparticles, Figure 35, prepared against melamine. The glass bead, melamine template was mixed with the polymerisation mixture consisting of methacrylic acid as the functional monomer, ethylene glycol dimethacrylate and trimethylolpropane trimethacrylate as crosslinking monomers, *N,N*-diethyldithiocarbamic acid benzyl ester as iniferter and pentaerythritol tetrakis(3-mercaptopropionate) as chain transfer agent, in acetonitrile and irradiated with UV. After polymerisation, low temperature washing was employed to remove unreacted monomer and low affinity molecularly imprinted species. High affinity species were recovered by washing at elevated temperature. Reaction of the high affinity nanoparticles, before removal at elevated temperature, with a series of functional series by grafting to strategies, including thiol-ene coupling, further enabled the preparation of functional nanoparticles without adversely affecting recognition properties.

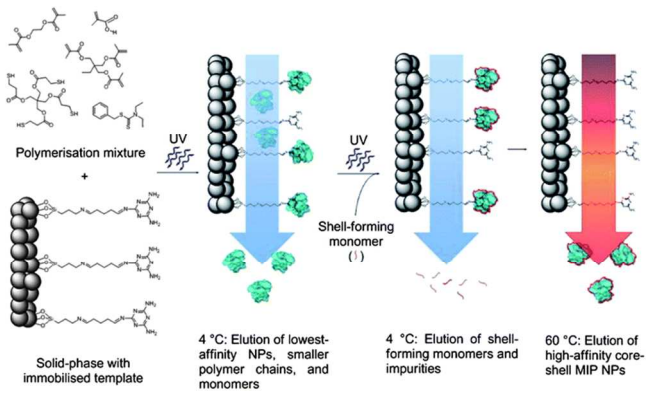


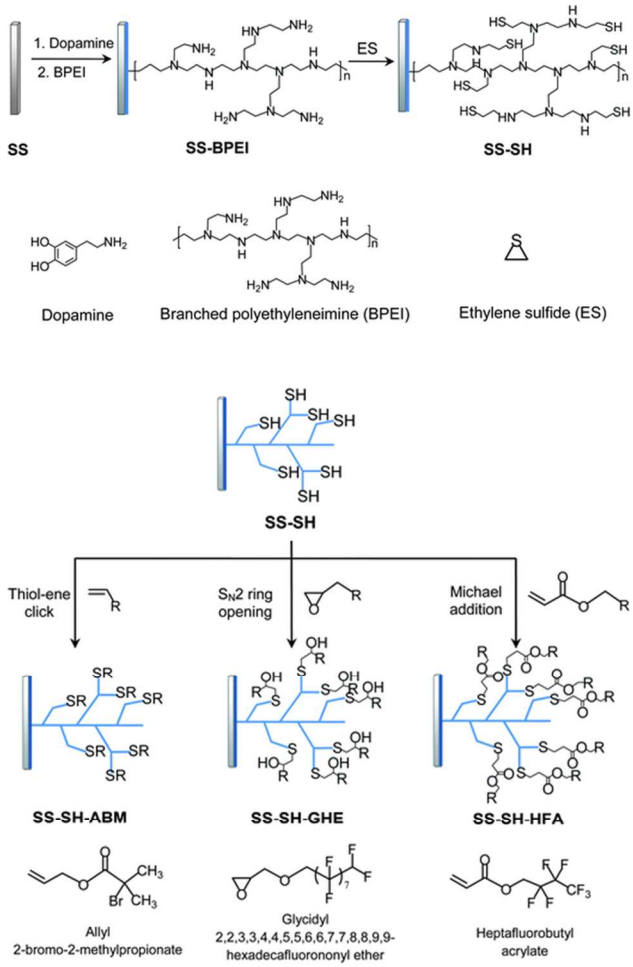
Figure 35 Solid phase synthesis of core shell molecularly imprinted polymer nanoparticles. Reproduced from E. Moczko, A. Poma, A. Guerreiro, I. P. d. V. Sansalvador, S. Caygill, F. Canfarotta, M. J. Whitcombe and S. Piletsky, *Nanoscale*, 2013, **5**, 3733-3741.

7. Surface Modification

The modification of a range of different surfaces is another area that has benefitted significantly from the increased interest in thiol-ene chemistry. Much of the early work in this area has been recently reviewed by Hensarling and Patton[199] and Liang, Shen and Guo,[200] and as such we will only highlight a few more recent examples here.

Yang *et al.*[201] recently reported the modification and functionalisation of stainless steel surfaces. The adopted approach is shown in Scheme 59. Polydopamine was initially coated on the stainless steel surface and served as an anchor for the subsequent coupling of branched polyethyleneimine. The facile reaction of the primary and secondary amine groups in the polyethyleneimine layer was then exploited in the reaction with ethylene sulfide as a means of introducing thiol functional groups. These mercapto groups were then used to further modify the hyperbranched structure employing three different thiol-based chemistries.

As representative examples, the thiol functionalities were reacted with ally 2-bromo-2-methylpropanoate via a radical thiol-ene reaction (this introduces an ATRP initiator to the hyperbranched structure that can, if desired, be further utilized), glycidyl 2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9-hexadecafluorononyl ether via an S_n2 ring-opening reaction to give a highly hydrophobic surface and with heptafluorobutyl acrylate via a hexylamine-mediated thiol-Michael reaction. Water contact angle measurements were made on each of the final and intermediate surface modified species and nicely demonstrated how surface properties could be changed via these simple modification reactions. Additionally, the authors extended their studies to include the modification of the thiol-functional surfaces with biologically relevant (co)polymers. For example, radical thiol ene coupling of an ene α-functional poly(2-hydroxyethyl methacrylate), prepared via ATRP, gave the poly(2-hydroxyethyl methacrylate) functional hyperbranched species. This was subsequently exploited in the block copolymerisation of the sulfobetaine derivative *N*-(3-sulfopropyl)-*N*-(methacryloxyethyl)-*N,N*-dimethyl ammonium betaine. In bacterial adhesion studies using Gram-positive *Staphylococcus epidermidis* (*S. epidermidis*) the sulfobetaine modified surface was shown to exhibit superior antiadhesion characteristics compared to the precursor stainless steel unmodified surface, the thiol-modified surface and the poly(2-hydroxyethyl methacrylate) functional species.



Scheme 59 Surface modification of stainless steel to first introduce thiol functional groups, followed by further functionalisation of the hyperbranched structure via radical thiol-ene, thiol-epoxy and thiol-Michael reactions. Reproduced from W. J. Yang, K.-O. Neoh, E.-Tang Kang, S. L.-M. Teo, D. Rittschof *Polym. Chem.* 2013, **4**, 3105-3115.

Oberleitner *et al.*[202] described a straightforward approach for the preparation of patterned self-assembled monolayers on silicon oxides and in particular glass for cell biology applications. The basic approach involved modification of an ene functional Si surface with thiol-terminated oligoethylene oxide.

Bhairamadgi *et al.*[203] reported a comparative study employing radical, photo-mediated thiol-ene and thiol-yne chemistries for the modification of oxide-free Si(111) surfaces, Figure 36. In both instances extremely high levels of surface coverage were achieved without any oxidation of the Si surface. As expected, the thiol-yne reaction resulted in higher surface coverage due to the ability of two thiols to add to each yne group.

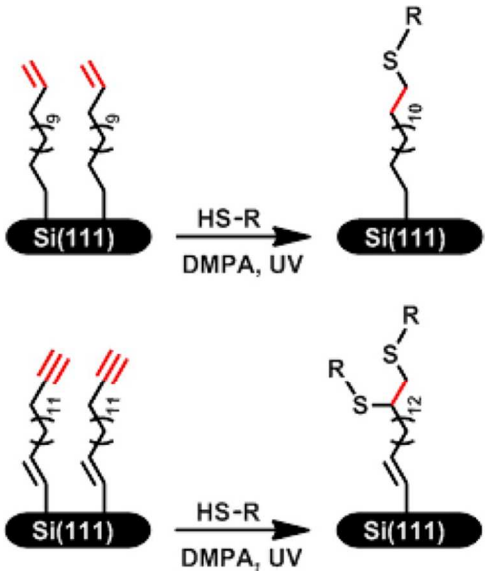


Figure 36 Radical thiol-ene and thiol-yne chemistries as efficient routes for the surface modification of oxide-free Si(111) surfaces. Reproduced with permission from N. S. Bhairamadgi, S. Gangarapu, M. A. Caipa Campos, J. M. Paulusse, C. J. van Rijn and H. Zuilhof, *Langmuir*, 2013, **29**, 4535-4542. Copyright 2013, American Chemical Society.

Cai and co-workers[204] reported the preparation of functional poly(vinylidene fluoride) (PVDF)-based membranes via surface-initiated thiol-ene chemistry, Figure 37.

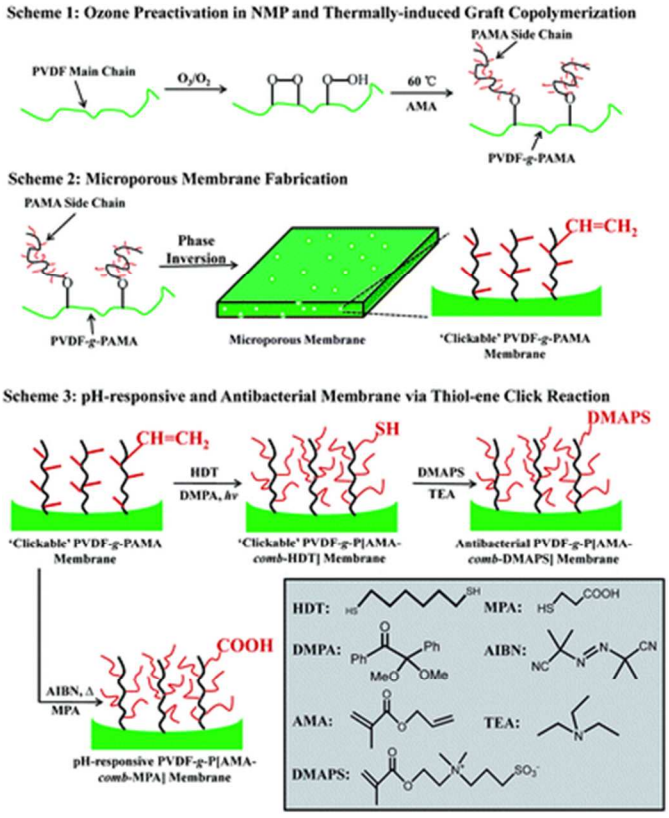


Figure 37 Synthesis of functional poly(vinylidene fluoride) copolymer membranes and surface initiated thiol-ene coupling. Reproduced from T. Cai, R. Wang, K. G. Neoh, E. T. Kang *Polym. Chem.* 2011, **2**, 1849-1858.

Ozone activated poly(vinylidenefluoride) was first reacted with allyl methacrylate to give the corresponding graft copolymer bearing allylic side chains. This was then cast into a microporous membrane via a phase inversion process yielding a substrate with a high concentration of reactive allylic groups on the surface and within the pores. Thermally initiated thiol-ene coupling of the en groups with 3-mercaptopropionic acid gave the corresponding acid functionalized membrane that exhibited interesting pH-dependent permeation behaviour that was most pronounced between pH = 2-4. Alternatively, the authors demonstrated that the allylic groups could be reacted with 1,6-hexanedithiol under photochemical conditions, in the presence of DMPA, to give a thiol-functionalized surface. Base-mediated thiol-Michael reaction of the surface-bound thiols with the zwitterionic sulfobetaine methacrylate 3-((2-(methacryloyloxy)ethyl)dimethylammonio)propane-1-sulfonate yielding the corresponding betaine functional surface that was shown to reduce microbial adhesion in a comparison with the unmodified surface. The ability of betaine-modified surfaces to

resist non-specific adsorption and exhibit antimicrobial properties is known.[205, 206]

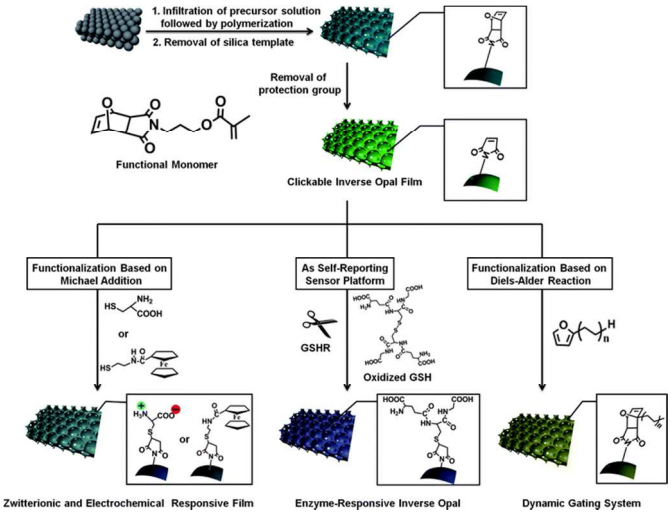


Figure 38 Outline for the preparation of a maleimide functional polymer inverse opal and its subsequent modification via thiol-Michael and Diels-Alder chemistries. Reproduced from H. Yang, X. Li, Y. Lan, T. Tian, J. Cui, T. Zhu, D. SHen and G. Li, *J. Mater. Chem. C.*, 2013, **1**, 6120-6128.

Inverse opals consist of a regular arrangement of spherical void spaces surrounded by solid walls and are useful for their potential application in catalysis, sorption, chromatography and as possible bioactive materials. Yang and co-workers[207] recently described the preparation of maleimide functional polymeric opals. Methyl methacrylate, ethylene glycol dimethacrylate, 2-((3a*R*,7a*S*)-1,3-dioxo-1,3,3a,4,7,7a-hexa-hydro-2*H*-4,7-epoxyisoindol-2-yl)ethyl methacrylate and AIBN in dichloromethane were mixed in the presence of a silica colloidal crystal template. After copolymerisation, HF etching of the silica template and removal of the furan protecting group the maleimide functional inverse opal was obtained, Figure 38. The authors then demonstrated how from this one functional material a series of new and interesting species could be readily obtained. For example, immersion of the maleimide functional film in an appropriate solution containing cysteine or a thiol-functional ferrocene yielded, after washing, the target pH responsive zwitterionic and electroactive inverse opal films. In the case of the zwitterionic modified species, it was shown that the new material could serve as a naked-eye pH detector, with the film exhibiting a distinct green colour at pH 6.0 when the zwitterion is electrically neutral and a red colour above and below the isoelectric point.

Ye *et al*.[208] described the synthesis of siloxane functionalized phosphorylcholine or sulfobetaine-based polymers to serve as surface modifiers of a biodegradable Mg alloy to confer reduced thrombogenicity and corrosion resistance. The polymers were prepared via radical thiol-ene photopolymerisation employing 3-(trimethoxysilyl)propane-1-thiol as the initiator yielding siloxane, α-functional homopolymers. These were then attached to the Mg alloy surface via reaction between the siloxy functionality and surface OH groups. Successful surface attachment was confirmed via x-ray photoelectron spectroscopy. Platelet deposition and activation was markedly reduced for the polymer modified alloy compared to the unmodified species. Both modified species also exhibited improved corrosion resistance.

Zeng and co-workers detailed a novel approach for the immobilisation of a $Ru(bpy')_3^{2+}$ derivative on an electrode to give a solid state electrochemiluminescence sensor.[209] Pentenyl functionalised $Ru(bpy')_3Cl_2$ was initially prepared and then reacted with a thiol functional indium tin oxide substrate obtained from the treatment of the indium tin oxide surface with 3-mercaptopropyl trimethoxysilane. The authors demonstrated that the Ru-modified surface exhibited excellent stability in organic media and exhibited a good electrochemiluminescence response to tri-*n*-propylamine.

Tingaut, Hauert and Zimmermann[210] detailed three highly effective and facile approaches for the functionalisation of cellulose films that are summarized in Figure 39.

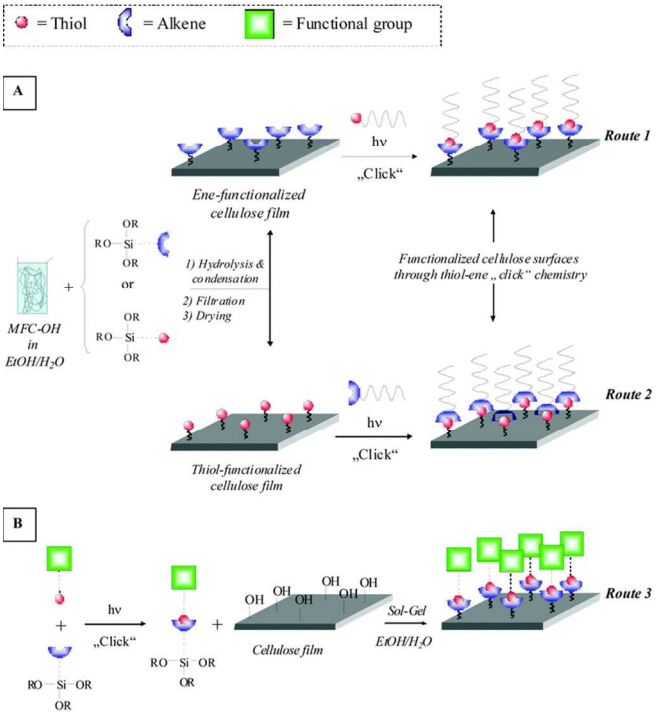


Figure 39 Three possible routes to modified cellulose films employing thiol-ene 'click' chemistry. Reproduced from P. Tingaut, R. Hauert, T. Zimmermann *J. Mater. Chem.* 2011, **21**, 16066-16076.

In the case of the two examples exemplified by Route A, ene and thiol-functional alkoxysilanes were introduced to the cellulose surface via hydrolysis reactions between the surface OH groups and the alkoxysilanes. Vinyl groups were introduced using vinyltrimethoxysilane while SH groups were

obtained from the reaction with 3-mercaptopropyltrimethoxysilane. Successful reaction was confirmed using a combination of IR spectroscopy and XPS analysis. In the case of the ene modified surface, further functionalisation was possible in a solventless photochemical thiol-ene coupling with methyl thioglycolate conducted at room temperature with DMPA as the photoinitiator. Reaction was rapid within the first 5 min. and was attributed to the successful coupling between the thiol and readily accessible surface ene groups. Subsequently the reaction rate dropped but the conversion continued to increase as the less accessible, probably internally localised, ene groups underwent reaction. For the thiol-functional cellulose films the reaction with allyl butyrate was evaluated also under photochemical conditions with DMPA. In this instance little-to-no reaction was observed for the first 30 min. with this being attributed to slow activation of the thiol groups, i.e. their conversion to thiyl radicals. Even after 180 min. the reaction with allyl butyrate appeared to be somewhat limited. In the third approach, the authors initially prepared a thioether functional alkoxysilane from the reaction between vinyltrimethoxysilane and methyl thioglycolate (photochemically, DMPA, room temperature) that was subsequently reacted with the cellulosic OH groups. Not surprisingly, this proved to be an effective method for surface modification but highlighted and broadened the scope for cellulose surface functionalisation.

Wickard *et al.*[211] reported a two step modification of hydrogen-terminated silicon(111) surfaces involving either initial grafting of poly(1,2-butadiene) ($\bar{M}_n$ = 3200-3500) followed by thiol-ene functionalisation, or partial thiol-ene modification of parent poly(1,2-butadiene) in solution followed by subsequent surface grafting. A small series of functional thiols were evaluated and, in general, the targeted degrees of thiol-ene modification agreed very well with those determined by elemental microanalysis. The only exception to this was 11-mercaptoundecanoic acid that gave consistently, and significantly, lower degrees of coupling than targeted. All modified surfaces were characterized using a suite of techniques including contact angle goniometry, spectroscopic ellipsometry, XPS and atomic force microscopy.

In related work, tuning the hydrophilicity of nanoporous crosslinked poly(1,2-butadiene) via photochemical thiol-ene modification with mercaptosuccinnic acid or sodium 2-mercaptoethanesulfonate was reported by Berthold, Sagar and Ndoni.[212] The coupling of both thiols, even in a porous environment, was shown to be essentially quantitative for both species further highlighting the utility of the radical-mediated thiol-ene reaction.

Wu and co-workers reported an interesting approach facilitating both thiol-ene and thiol-yne surface modification with polymers deposited on a variety of substrates including gold, polystyrene, glass, Ti, and polydimethylsiloxane, Figure 40.[213]

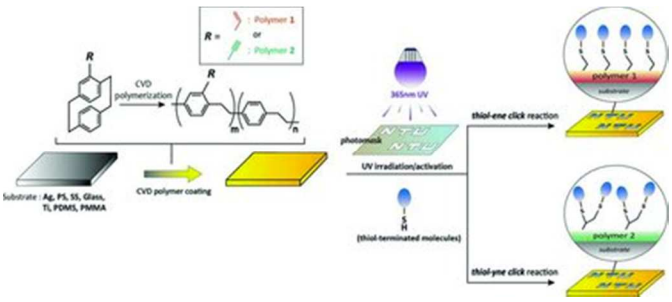
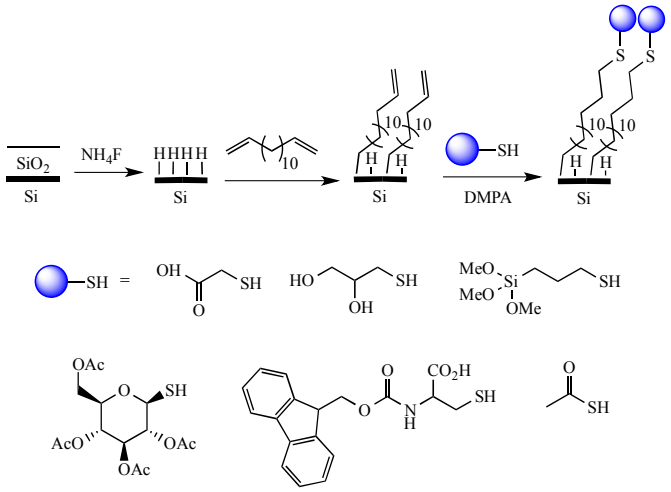


Figure 40 Thiol-ene or thiol-yne modification of polyxylylene-based copolymers deposited on a range of different substrates. Reproduced with permission from J. T. Wu, C. H. Huang, W. C. Liang, Y. L. Wu, J. Yu and H. Y. Chen, *Macromol. Rapid Commun*. 2012, **33**, 922-927. Copyright 2012, John Wiley & Sons.

Ene or yne-functional (co)polymers were prepared on various substrates via the chemical vapour deposition polymerisation (CVDP) of 4-vinyl[2.2]paracyclophane or ethynyl[2.2]paracyclophane respectively. The ene and yne groups were subsequently reacted with a thiol-terminated PEG (exact molecular weight was not given in the manuscript) photochemically in the presence of DMPA. The primary focus of this study was focused on the ability to pattern surfaces using a photomask and to demonstrate regioselective antifouling properties as a result of the selective surface modification with PEG.

Not surprisingly, a significant amount of effort has been devoted to the modification of silicon and silicon oxide surfaces.[214-222] For example, Campos, Paulusse and Zuilhof[215] detailed the use of the photochemical thiol-ene coupling reaction for the facile modification of oxide-free Si(111), Scheme 60.



Scheme 60 Chemical modification of a Si surface via thiol-ene chemistry and the library of thiols employed in the photochemical coupling reactions.

Treatment of SiO_2-free Si(111) with neat 1,13-tetradecadiene at 80°C gave the ene-terminal organic monolayer as confirmed using a combination of contact angle measurements, ATR-IR spectroscopy and XPS. A series of small molecule thiols were subsequently employed to modify the ene functional surfaces via photochemically promoted coupling with DMPA as the photoinitiator. In all cases a high surface coverage was observed, as determined by XPS and IR spectroscopy, with no evidence of any SiO_2 formation.

The modification of metal surfaces such as gold has also attracted some interest.[223, 224] For example, Norberg *et al*.[223] described the modification of polystyrene coated gold surfaces with species presenting ene or yne functionality that were utilized to prepare glycoconjugates via thiol-ene and thiol-yne chemistries, Figure 41.

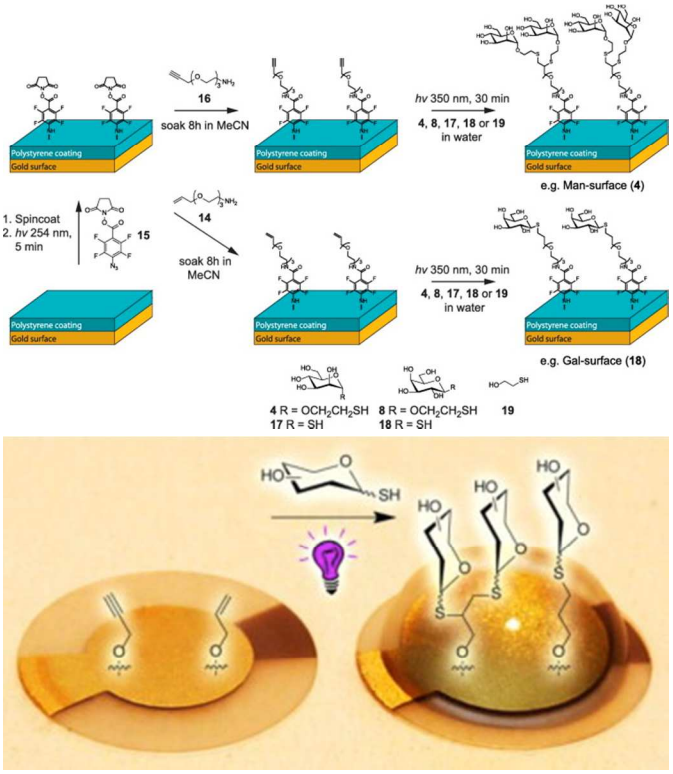


Figure 41 Thiol-ene/yne modification of gold/polystyrene surfaces with appropriately functional sugars to give the corresponding sugar-modified surfaces for biosensor applications. Reproduced with permission from O. Norberg, I. H. Lee, T. Aastrup, M. Yan and O. Ramstrom, *Biosens. Bioelectron.*, 2012, **34**, 51-56. Copyright 2012, Elsevier.

Initial surface functionalisation involved treatment of the polymeric coating with a fluorophenylazide derivative that was followed by nucleophilic acyl substitution reactions to introduce the ene and yne functionality. These groups were then reacted with mannose and galactose-thiols directly in water under irradiation in the absence of added photoinitiator. Reactions were fast, being complete within 30 min and any impurities such as disulfides were readily removed by washing. As expected, the carbohydrate-modified surfaces exhibited good selectivity towards model lectins (Con-A which is specific for α-D-mannosides and RCA-1 which is specific for β-D-galactosides).

8. Polymeric Networks and Crosslinked Materials

Since the current interest in the thiol-ene reaction is due, predominantly, to the pioneering work of Bowman and co-workers and Hoyle *et al*. in highly homogeneous thioether network syntheses it is not surprising that the use of this reaction has continued to attract significant attention in the preparation and application of crosslinked polymers/materials.[225]

Within this broad research field there has been significant interest in the preparation and application of hydrogels,[226-233] the synthesis of crosslinked beads/polymeric nanoparticles,[234, 235] the development of dental restorative materials,[236-239] nanoprint/soft lithography,[240-243] as well as the preparation of porous materials by emulsion templating,[244, 245] the synthesis of novel polyanhydride networks,[246, 247] and gas barrier and transport properties associated with thiol-ene networks.[248-251] Additionally, there have been numerous reports detailing the general synthesis and properties of new thiol-ene-based networks and crosslinked materials[252-271] as well as rather specific applications such as the synthesis of boron-containing materials,[254] the preparation of sucrose polymers,[272, 273] the preparation of high refractive index materials,[274] the effect of organoclays on oxygen inhibition in acrylate and thiol-acrylate photopolymerisations,[275] tuneable networks for Li ion conduction,[276] the synthesis of flame-retardant coatings,[277] and the preparation of shape memory polymers.[278]

Given the broad applicability of the thiol-ene reaction in network materials synthesis, and their associated properties, we will not review all of the above topics here but will rather highlight several examples demonstrating its impressive applicability.

In the field of hydrogels, Shih, Fraser and Lin[226] described a visible-light mediated thiol-ene process for the preparation of multilayer hydrogels employing eosin-Y as a non-cleavage type photoinitiator, Figure 42, building on their previous report of hydrogelation employing eosin-Y.[279] The initial thiol-ene gel was formed from the reaction of a tetrafunctional norbornene-PEG derivative with dithiothreitol under visible light irradiation to give expected well-defined hydrogels (note: high concentrations of eosin-Y can result in non-ideal network formation and significant retention of eosin-Y in the gel). At appropriate levels of eosin-Y, the initially formed gel can be swollen in PBS – a process that results in the leaching of the eosin-Y from the gel material. While this 'leached' initiator is not as effective as 'fresh' initiator it can be employed in the subsequent initiation of additional thiol and ene for interfacial polymerisation. The preparation and immediate immersion of a hydrogel in a second monomer solution (blue microparticles were also added for imaging purposes) resulted in a second-gel

forming around the initial core hydrogel. This approach was readily extended to 3-layer gels.

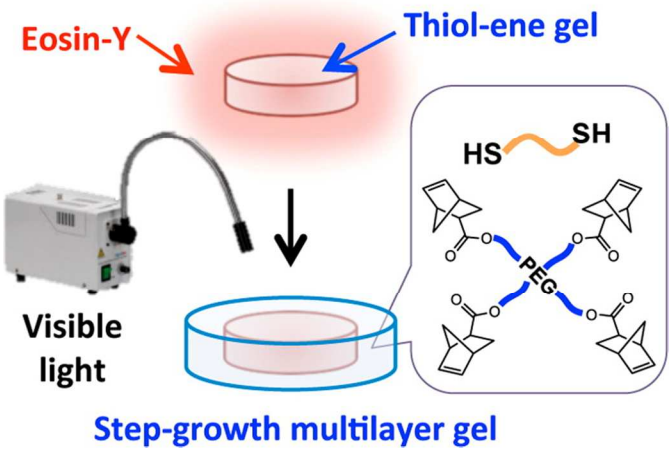


Figure 42 Sequential, multilayer hydrogel formation using a visible light source and eosin-Y as a non-cleavage initiator. Reproduced with permission from H. Shih, A. K. Fraser and C. C. Lin, *ACS Appl. Mater. Interfaces*, 2013, **5**, 1673-1680. Copyright 2013, American Chemical Society.

Also employing tetrafunctional norbornene derivatives as the ene component in hydrogel formulations, Aimetti, Machen and Anseth[227] detailed the preparation of degradable hydrogels based on a PEG-norbornene with a human neutrophil elastase (HNE) sensitive peptide thiol crosslinker, Figure 43.

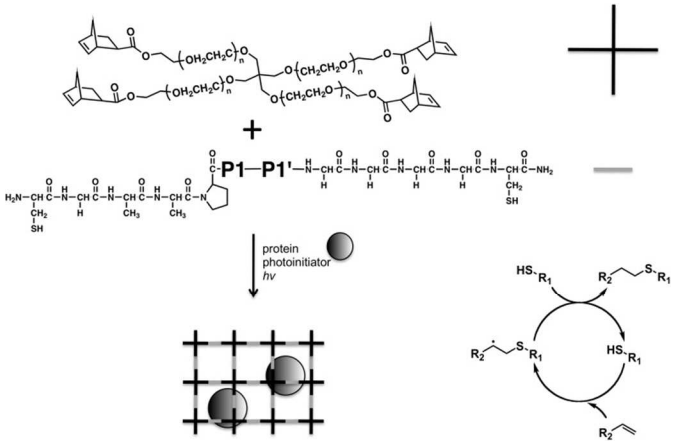


Figure 43 Synthesis of a degradable, human neutrophil elastase-sensitive PEG-based hydrogel. Reproduced with permission from A. A. Aimetti, A. J. Machen and K. S. Anseth, *Biomaterials*, 2009, **30**, 6048-6054. Copyright 2009, Elsevier.

Such HNE sensitivity renders the gel degradable at sites of inflammation. The authors demonstrated that gel degradation was sensitive to the concentration of thiol-crosslinker and the concentration of HNE and noted that mechanistically, gel degradation occurs via a surface erosion process. To highlight the potential use of these HNE sensitive hydrogels as potential delivery platforms, bovine serum albumin (BSA) was encapsulated in the gel and subsequently released upon gel degradation. No release of BSA was observed in the absence of HNE.

Degradable thiol-ene networks based on anhydride functionality have been reported by Shipp and co-workers.[246] Photoinitiated polymerisation of 4-pentenoic anhydride with pentaerythritol tetrakis(3-mercaptopropionate) in the presence of 0.1 wt% 1-hydroxycyclohexyl phenyl ketone as initiator gives the target crosslinked materials. Importantly, these anhydride-containing networks are susceptible to hydrolysis reactions when immersed in aqueous media. For example, Figure 44 shows a series of time-lapsed photographs of highlighting the gradual degradation of such gels after immersion in deionised water.

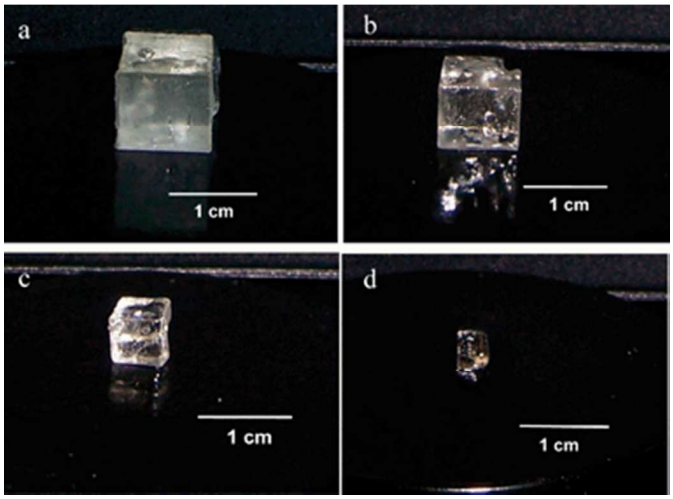


Figure 44 Four digital photos demonstrating the hydrolysis and associated degradation of a gel containing anhydride linkages after 0 h (a), 18 h (b), 48 h (c) and 72 h (d) immersed in deionised water. Reproduced from D. A. Shipp, C. W. McQuinn, B. G. Rutherglen and R. A. McBath, *Chem. Commun.*, 2009, 6415-6417.

The gradual degradation of the anhydride gels is clearly evident and the expected hydrolysis reaction was confirmed by ^{1}H NMR spectroscopy with the identification of the tetrakis carboxylic acid species expected from anhydride cleavage.

In the field of soft lithography, Ashley *et al.*[242] described a robust photopolymerisable thiol-ene formulation for the photolithographic fabrication of microfluidic devices via contact liquid photolithographic polymerisation (CLiPP), Figure 45. In this CLiPP approach, step a involves initial fixing of the glass slide to a chamber base after which a monomer mixture is added to the chamber (pentaerythritol tetra(3-mercaptopropionate) and triallyl-1,3,5-triazine trione for example). In step b an aligned mask is placed on top of the monomer resin, which is then brought in contact with the monomer and lowered to the desired feature height, step c. In step d, the monomer mixture is exposed to collimated 365 nm UV radiation through an aligned mask, after which the mask is

removed from the cured monomer and discarded, step e. This is followed by the removal of unreacted, excess monomer by solvent washing, step f, which ultimately yields the targeted structural features, such as raised cylinders or recessed columns with high feature quality, step g. The authors demonstrated that optimal feature quality and aspect ratio were observed for formulations with the lowest initiator (Irgacure 651 and Irgacure 184) concentrations and for initiator inhibitor (Q1301) ratios spanning the range 1:1 to 1.5:1.

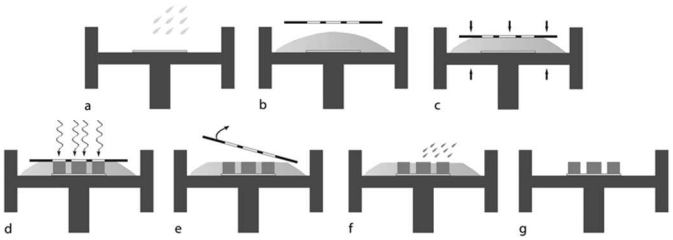


Figure 45 General approach for the preparation of microfluidic features. Reproduced from J. F. Ashley, N. B. Cramer, R. H. Davis and C. N. Bowman, *Lab Chip*, 2011, **11**, 2772-2778.

Highly porous polymeric materials can be readily obtained by thiol-ene/yne network formation via high internal phase emulsion templates as nicely demonstrated by Lovelady *et al*., Figure 46.[244]

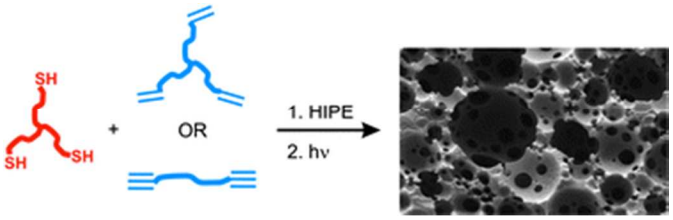


Figure 46 Thiol-ene/yne photopolymerisation syntheses of highly porous polymeric network materials. Reproduced from E. Lovelady, S. D. Kimmins, J. Wu and N. R. Cameron, *Polym. Chem.*, 2011, **2**, 559-562.

In initial experiments, the triacrylate species trimethylolpropane triacrylate and the trithiol trimethylolpropane tris(mercaptopropionate) were employed at a 1:1 molar ratio of thiol to ene functional groups. A high internal phase emulsion (HIPE) was established using 25 vol% organic and 75 vol% aqueous phases employing the polymeric surfactant Hypermer B246. The HIPE was successfully formed and cured without any obvious phase separation. Increasing the aqueous phase content also led to an increase in the material porosity. A brief evaluation of the physical properties of the resulting porous materials was conducted. For example, it was reported that the use of the diyne, octadiyne, in place of the ene gave materials with higher T_g's. This is not unexpected given the higher crosslink density associated with materials prepared by the thiol-yne vs. the thiol-ene reaction. However, this report clearly highlighted the impressive utility of the thiol-ene and thiol-yne reactions for the straightforward preparation of the targeted, highly porous materials.

Finally in this section we would like to highlight the shape memory polymers reported by the Bowman group, Figure 47.[278]

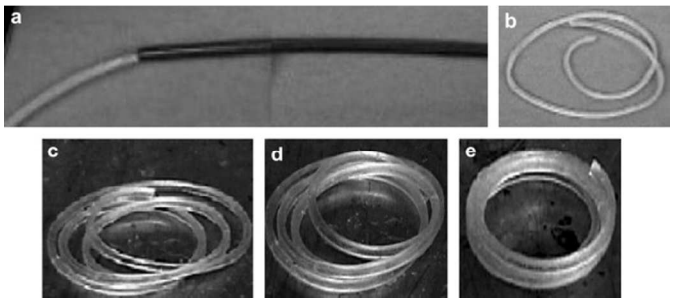


Figure 47 A series of pictures demonstrating shape memory behaviour for materials formed from allyl pentaerythritol and isophorone diurethane thiol. (a) The polymer coils were then heated to 10°C above their T_g and then constrained in tubing. The polymers were cooled below their T_g to −5°C and stored for 1 week in the tubing. (b) The polymers are released from the tubing at ambient temperature, after which they were observed for 4 min. Polymers were then placed in an oven maintained 10°C above their T_g. The time taken for the coils to form was recorded. Coil images were recorded at (c) 4 min, (d) 4.5 min, and (e) 5 min. Reproduced with permission from D. P. Nair, N. B. Cramer, T. F. Scott, C. N. Bowman and R. Shandas, *Polymer*, 2010, **51**, 4383-4389. Copyright 2010, Elsevier.

While shape memory polymers are known, these authors demonstrated how two thiol-ene based combinations have significantly improved properties compared to the more traditional acrylic-based systems. Aside from the 'commonly' accepted advantages of thiol-ene network materials such as the ability to prepare ideal, homogenous networks, low shrinkage stress and little-to-no oxygen inhibition, the thiol-ene materials prepared here were also tough and flexible compared to their acrylic analogues. The authors noted that the thiol-ene polymers exhibited excellent shape fixity as well as a rapid and very distinct shape memory response.

9. Conclusions

This review has, hopefully, given some insight into the remarkable adoption and application of thiol-ene and thiol-Michael chemistries in recent years in a broad range of areas associated with polymer and materials chemistry. Very significant contributions continue to be made in the general, broad field of polymeric networks and crosslinked materials as well as in the use of the thiol-ene and thiol-Michael reactions as tools for monomer synthesis and post-polymerisation modification. The general ease with which such chemistries can be executed, coupled with the often-observed 'click' characteristics are largely responsible for the significant

increase in the application of these reactions. These two features alone suggest that these chemistries will continue to attract significant attention from researchers working on a range of synthetic challenges.

Acknowledgements

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Notes and references

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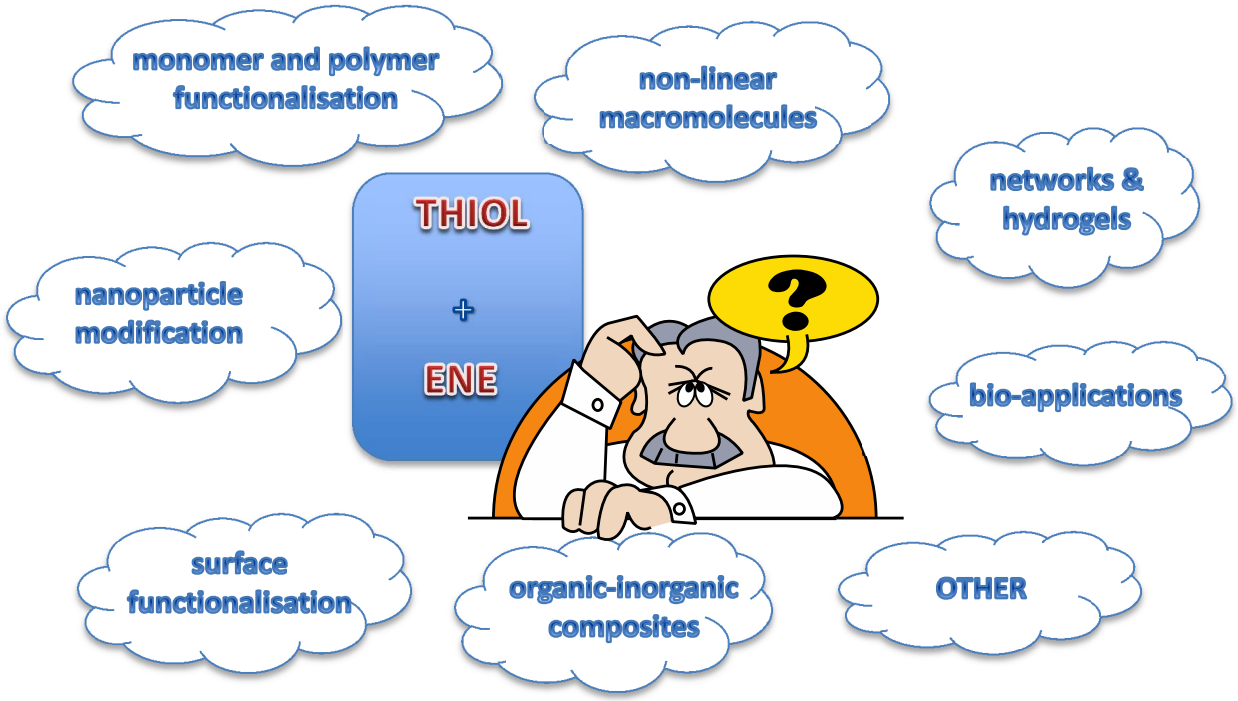
TOC graphic



Biography

Andrew B. Lowe is currently Professor of Polymer Science & Engineering and an ARC Future Fellow in the School of Chemical Engineering at the University of New South Wales (Sydney, Australia) where he is affiliated with the Centre for Advanced Macromolecular Design. He graduated from the University of Sussex with BSc (Hons) (1993), DPhil (1998) and DSc (2009) degrees, completing his DPhil under the supervision of Professors Steven P. Armes and Norman C. Billingham. He spent ~11 years at the University of Southern Mississippi first as a postdoctoral researcher with Professor Charles L. McCormick and then as an Assistant Professor of Organic Chemistry and subsequently as an Associate Professor of Polymer Science & Engineering (with tenure). He has published > 120, peer reviewed papers, book chapters, encyclopaedia articles and is co-inventor on six patents. Professor Lowe is a Fellow of the Royal Society of Chemistry (FRSC) and the Royal Australian Chemical Institute (FRACI). His research interests cover novel applications of thiol-x 'click' chemistries, RAFT radical polymerisation, metathesis-based polymerisations, water-soluble polymers, stimulus-responsive materials and polymer self-assembly in solution.