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# The nucleophilic, phosphine-catalyzed thiol–ene click reaction and convergent star synthesis with RAFT-prepared homopolymers

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ABSTRACT

The synthesis of 3-arm star polymers from reversible addition–fragmentation chain transfer (RAFT)-prepared precursor homopolymers in combination with thiol–ene click chemistry is described. Homopolymers of *n*-butyl acrylate and *N*,*N*-diethylacrylamide were prepared with 1-cyano-1-methylethyl dithiobenzoate and 2,2′-azobis(2-methylpropionitrile) yielding materials with polydispersity indices ($M_w/M_n$) ≤ 1.18 and controlled molecular weights as determined by a combination of NMR spectroscopy, size exclusion chromatography (SEC), and matrix assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS). Subsequent one-pot reaction of homopolymer, hexylamine (HexAM), dimethylphenylphosphine (DMPP), and trimethylolpropane triacrylate (TMPTA) results in cleavage of the thiocarbonylthiol end-group (by HexAM) of the homopolymer yielding a macromolecular thiol that undergoes DMPP-initiated thiol-Michael addition to TMPTA yielding 3-arm star polymers. The presence of DMPP is demonstrated to serve an important second role in effectively suppressing the presence of any polymeric disulfide as determined by SEC. Such phosphine-mediated thiol–ene reactions are shown to be extremely rapid, as verified by a combination of FTIR and NMR spectroscopies, with complete consumption of the C=C bonds occurring in a matter of min. MALDI-TOF MS and SEC were used to verify the formation of 3-arm stars. A broadening in the molecular weight distribution ($M_w/M_n$ ~ 1.35) was observed by SEC that was attributed to the presence of residual homopolymer and possibly 2-arm stars formed from trimethylolpropane diacrylate impurity. Interestingly, the MALDI analysis also indicated the presence of 1- and 2-arm species most likely formed from the fragmentation of the parent 3-arm star during analysis. Finally, a control experiment verified that the consumption of C=C bonds does not occur via a radical pathway.



## 1. Introduction

The thiol–ene reaction is, simply, the hydrothiolation of a C=C bond whose origins can be traced to the turn of the 20th century. Importantly, from a synthetic standpoint, one key advantage of the thiol–ene reaction is its broad applicability and wide range of experimental conditions under which it can be conducted. For example, such reactions can be performed under radical [1], nucleophilic catalyzed [2], and amino acid catalyzed [3], conditions in a regioselective manner to yield *exclusively* Markovnikov or anti-Markovnikov products with virtually ***any*** ene substrate. Historically, the thiol–ene reaction has been evaluated primarily as a means of preparing perfect networks. For example, commercially available tri and tetra functional thiols polymerize with multifunctional enes via a two-step radical step-growth process to yield high density networks [1,4–9]. These radical polymerization reactions proceed readily in the presence of water and/or oxygen, and the final networks have very narrow glass transition regions, on the range of 10–15 °C full width at half maximum, and thus are ideal for tuning their tan $\delta$ damping absorption maxima to ensure high energy absorption upon high energy impact [6,7]. Since radical thiol–ene reactions take place rapidly and proceed to high conversion using essentially any terminal electron rich or electron poor ene there is tremendous latitude in designing systems for applications ranging from holographic diffraction gratings [8] to dental restoratives [9], the latter benefitting from low volume shrinkage and stress buildup during network formation.

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The term 'click chemistry', or 'click reaction', was coined by Sharpless and co-workers in 2001 to describe an approach to building complex molecules from a few, straightforward, thermodynamically favorable reactions, commonly involving the construction of carbon atom–heteroatom linkages [10]. To be classified as a click reaction Sharpless et al. outlined simple criteria that a reaction must meet. For example, the reaction must be modular, broad in scope, give (near) quantitative yields, generate inoffensive byproducts, and be stereospecific [10]. Examples of reactions that fulfill these criteria include the Cu(I) catalyzed reaction between an alkyne and an azide, Diels–Alder reactions in general, C=C bond additions, non-Aldol carbonyl chemistry, and nucleophilic ring opening reactions, especially involving epoxides. Currently, the accepted 'gold standard' of such reactions, the Cu(I)-mediated reaction between an alkyne and azide has been exploited in applications ranging from small molecule organic synthesis, drug discovery, and materials science [11–13]. Recent examples include the ATRP of 3-azidopropyl methacrylate followed by post-polymerization reaction of the pendent azide groups with a variety of functional alkynes [14], the "click" polymerization of monomers bearing both azide and alkyne groups [15], the synthesis of layer-by-layer dendritic films [16], and the preparation of 3-miktoarm stars and 1st generation dendritic copolymers employing a combination of ATRP and alkyne/azide click chemistry. Recently the thiol–ene reaction has been evaluated as a click reaction in alternative areas of materials synthesis. For example, Killops, Campos and Hawker [17] reported the synthesis of 4th-generation thioether-based dendrimers in which a key building step was the radical mediated click thiol–ene reaction between 1-thioglycerol and the starting 2,4,6-triallyloxy-1,3,5-triazone core followed by additional reactions between 1-thioglycerol and ene bonds introduced via the esterification of peripheral OH groups with 4-pentenoic anhydride. Such reactions were shown to be extremely high yielding and facile. Gress, Völkel, and Schlaad [18] described the synthesis and controlled cationic isomerization polymerization of 2-(3-butenyl)-2-oxazoline to yield well-defined (co)polymers with pendent ene functionality. Subsequently, the ene groups were reacted by a thiol-click process, quantitatively, under radical conditions with a range of small molecular thiols including methyl-3-mercaptopropionate, 1-thiolglycerol, and the protected sugar 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranose to yield the corresponding side-chain modified (co)polymers.

Reversible addition–fragmentation chain transfer (RAFT) radical polymerization [19–24] is a controlled synthesis technique that employs thiocarbonylthio compounds as degenerative chain transfer agents. Particularly impressive with RAFT is the ease with which it is executed as well as its broad versatility with respect to substrate choice and polymerization conditions. However, in the context of the work reported herein it is important to highlight that (co)polymers prepared via this route bear a single thiocarbonylthio functionality at the chain terminus that is available for post-polymerization reaction. Indeed, such thiocarbonylthio end-groups can be readily reduced to other reactive or non-reactive functionality. For example, Lowe et al. [25] demonstrated the facile $NaBH_4$ cleavage, in aqueous media, of dithioester-terminated (co)polymers to yield the corresponding thiolate terminal materials. When performed in the presence of a gold sol, such reactions resulted in sequential dithioester end-group cleavage followed by covalent attachment/stabilization of the gold sol. Such a sequence of reactions has also been employed for the modification of planar gold surfaces [26] and gold nanorods [27]. Indeed, this facile approach has been adopted by numerous research groups using both $NaBH_4$ [28] as well as other hydride reducing agents. Scales, Convertine and McCormick reported the synthesis of fluorescently tagged poly(*N*-isopropylacrylamide) via sequential $NaBH_4$ cleavage of the trithiocarbonate end-group followed by a 24 h treatment of tris-carboxyethyl phosphine prior to reaction with *N*-(1-pyrenyl)-maleimide [29]. Alternatively, the thiocarbonylthio functionality is known to be easily cleaved using primary and secondary amines to yield thiols, and has been employed in the thioacylation of proteins [30–33]. The treatment of thiocarbonylthio groups with amines has also been examined in the materials arena, especially with RAFT-prepared (co)polymers. Qiu, Tanaka and Winnik recently described the aqueous phase behavior of cyclic poly(*N*-isopropylacrylamide)s that were prepared in a multi-step process, one step of which involved the cleavage of trithiocarbonate end-groups with butylamine [34]. Li and co-workers [35] reported the synthesis of functional telechelics based on RAFT-prepared poly(*N*-isopropylacrylamide) in which the trithiocarbonate end-group was cleaved to a thiol using 2-ethanolamine yielding the free thiol functional species that was subsequently employed in additional modification reactions.

Star (co)polymers are the simplest examples of branched polymers with all branches (arms) extending from a single point. Star (co)polymers can be prepared via one of three general routes: 1) the arm first (convergent) approach, 2) employing a multifunctional initiator (divergent approach), and 3) the microgel approach in which a small amount of multifunctional cross-linking agent is added at the end of a polymerization process. Each of these approaches has associated advantages and disadvantages. The convergent approach allows for a thorough characterization of the arms prior to star formation aiding in the subsequent characterization of the star materials. However, to favor star formation an excess of 'arms' is often required which will exist as an impurity in the final product. Additionally, extended reaction times are often needed to achieve acceptable yields. The divergent approach requires that all initiation sites possess the same reactivity and that all are activated simultaneously, at least if well-defined stars are desired. The microgel approach is the simplest approach to making stars, but it is very difficult to control the number of arms per star. Recently, we reported our initial results regarding the use of a RAFT-prepared homopolymer of *N*,*N*-diethylacrylamide (DEAm) that served as a masked macromolecular secondary thiol in the convergent synthesis of 3-arm star polymers via a macromolecular thiol–ene reaction [36]. The sequential hexylamine-mediated cleavage of the dithioester end-group followed by dimethylphenylphosphine-catalyzed thiol-Michael addition to trimethylolpropane triacrylate resulted in a rapid convergent synthesis of 3-arm star polymers. It should be noted that while star polymers have been previously prepared via RAFT by all three of the methods noted above [37–43], the convergent approach we described had not previously been employed. Indeed, such an approach specifically takes advantage of RAFT-prepared (co)polymers and the click nature of the thiol–ene reaction. Expanding on this initial disclosure we describe herein a more detailed investigation of such convergent star syntheses, further highlighting the versatility of the method for star polymer synthesis and reiterating the synthetic utility of the nucleophilic thiol–ene reaction in polymer/materials chemistry.

## 2. Experimental

All reagents were purchased from the Aldrich Chemical Company at the highest available purity and used as received unless noted otherwise. Trimethylolpropane triacrylate (TMPTA) (>83% pure) was donated by Sartomer. *N*,*N*-Diethylacrylamide was purchased from PolySciences and purified by vacuum distillation. *n*-Butyl acrylate was purified by passage over a column of basic alumina. 1-Cyano-1-methylethyl dithiobenzoate (CPDB) was prepared according to a literature procedure [44]. 2,2′-Azobis(2-

methylpropionitrile) (AIBN) was recrystallized from methanol and stored in a freezer prior to use.

### 2.1. RAFT homopolymerization of N,N-diethylacrylamide (DEAm)

A mixture of DEAm (11.0 g, 86.5 mmol), CPDB (569 mg, 2.57 mmol), AIBN (84.4 mg, 0.514 mmol), and DMF (11.0 g) was added to a Schlenk flask equipped with a magnetic stirring bar. The mixture was stirred for at least 30 min in an ice bath to ensure complete dissolution of all components. The flask was then purged by repeatedly evacuating and refilling with $N_2$ at least 3 times and subsequently immersed in a preheated oil bath at 70 °C. After 11 h the reaction was quenched by rapid cooling in liquid $N_2$ and exposure to air. The polymer was isolated by precipitation into a large excess of hexanes. The polymer was then dissolved in water and isolated by lyophilization yielding 9.53 g of polymer.

### 2.2. RAFT homopolymerization of n-butyl acrylate

The homopolymerization of *n*-butyl acrylate was accomplished following the procedure detailed above except that the reaction was left for 22.5 h at 70 °C. The residual *n*-butyl acrylate monomer was removed in vacuo at ~1 mbar.

### 2.3. Model reaction between ethyl-2-mercaptopropionate and TMPTA

Ethyl-2-mercaptopropionate (1.8 μL, $1.4 \times 10^{-5}$ moles, 1.5 molar excess based on acrylate functional groups) was added to a scintillation vial (20 mL capacity) along with 0.5 g THF. To this solution were then added TMPTA (2.5 μL, $8.3 \times 10^{-6}$ moles) and dimethylphenylphosphine (DMPP) (10.0 μL, 0.11 M). The reaction was allowed to proceed for 5 min prior to NMR analysis.

### 2.4. Preparation of 3-arm stars (1.5:1 molar ratio of –SH:ene) with poly(n-butyl acrylate) or poly(N,N-diethylacrylamide)

Dithioester-terminated poly(*n*-butyl acrylate) (0.15 g, $1.4 \times 10^{-5}$ moles, molar mass ~ 3700, ~1.5 molar excess based on acrylate functional groups) was dissolved in 0.5 g of THF in a scintillation vial (20 mL capacity). To this solution were added TMPTA (2.5 μL, $8.3 \times 10^{-6}$ moles), dimethylphenylphosphine (10.0 μL, 0.11 M), and hexylamine (20.0 μL, 0.35 M, 4× excess based on [SH] groups). The solution was allowed to react for 5 min prior to analysis by NMR spectroscopy. Dithioester-terminated poly(*N*,*N*-diethylacrylamide) (0.78 g) was dissolved in THF (2.0 g) in a scintillation vial. After dissolution,14 μL of TMPTA was added followed by 29 μL of DMPP. The solution was stirred under nitrogen for 5 min to ensure complete homogeneity. Hexylamine (35 μL) was then added to this solution and the mixture allowed to stir overnight. The polymer was subsequently purified by precipitation into hexanes, followed by drying in vacuo overnight.

### 2.5. Reaction of TMPTA, dimethylphenylphosphine, and hexylamine

This control experiment was performed to confirm that the phosphine was ***not*** catalyzing the addition of the primary amine across the ene double bonds, i.e. catalyzing an aza-Michael addition reaction.

TMPTA (2.5 μL, $8.3 \times 10^{-6}$ moles) was dissolved in 0.5 g of THF in a scintillation vial (20 mL capacity). To this were added dimethylphenylphosphine (10 μL, 0.11 M) and hexylamine (20 μL, 0.35 M). The reaction was allowed to proceed for 5 min prior to NMR analysis.

### 2.6. Reaction of TMPTA, dithioester-terminated polymer, dimethylphenylphosphine, hexylamine in the presence of TEMPO

This control experiment was conducted to verify that the consumption of ene was ***not*** proceeding via a free radical pathway.

Dithioester-terminated poly(*n*-butyl acrylate) ($1.4 \times 10$–5 moles, $M_w$ ~ 3500, ~1.5 molar excess based on ene functional groups) was dissolved in 0.5 g of THF in a scintillation vial (20 mL capacity). TEMPO (0.01 g, 2 wt%) was then added to the solution. To this solution were added TMPTA (2.5 μL, $8.3 \times 10^{-6}$ moles), dimethylphenylphosphine (10.0 μL, 0.11 M), and hexylamine (20.0 μL, 0.35 M, 4× excess based on [SH] groups). The solution was allowed to react for 5 min prior to analysis by NMR spectroscopy.

### 2.7. Instrumentation

MALDI-TOF mass spectrometry (MALDI-TOF MS) was performed on a Bruker Reflex III Instrument equipped with a 337 nm $N_2$ laser in the reflector mode and 20 kV acceleration voltage. α-Cyano-4-hydroxycinnamic acid (CHCA) was used as a matrix for molecular weight determination of the poly(*N*,*N*-diethylacrylamide) polymers before and after star formation.

NMR spectra were recorded on either a 300 (Bruker 300 53 mm) or 500 MHz NMR spectrometer. Specifically, in the case of the 500 MHz spectrometer:

*$^{13}C$ NMR characterization*: All spectra were acquired on a Varian $^{UNITY}$INOVA spectrometer operating at a frequency of 125 MHz for carbon and using a standard 5 mm two channel probe. A 90° pulse-width of 5.75 μs was used. The acquisition time was 1.5 s with no recycle delay, making the time between scans 1.5 s. Proton decoupling was implemented during data acquisition to remove $^{1}H$–$^{13}C$ scalar coupling. Samples were dissolved in THF, with sealed capillaries filled with DMSO-$d_6$ used for deuterium shimming and locking.

*$^{1}H$ NMR characterization*: All spectra were acquired on a Varian $^{UNITY}$INOVA spectrometer operating at a frequency of 499.8 MHz for proton and using a standard 5 mm two channel probe. A 90° pulse-width of 15.25 μs and acquisition time of 1.9 s were used. Typically 64–96 scans were acquired for each sample, with a recycle delay of 4.1 s making the overall time between scans 6 s. Samples were dissolved in $D_2O$ or directly in non-deuterated THF with sealed capillaries filled with DMSO-$d_6$ used for deuterium shimming and locking.

Organic SEC was conducted on a Waters system comprised of a Waters 515 HPLC pump, Waters 2487 Dual λ absorbance detector, Waters 2410 RI detector with a PolymerLabs PLgel 5 μm guard column and a PolymerLabs PLgel 5 μm MIXED-C column, in THF stabilized with 281 ppm BHT at a flow rate of 1.0 mL/min. The column was calibrated with a series of narrow molecular mass distribution poly(methyl methacrylate) standards.

FTIR spectra were recorded using a modified Bruker 88 spectrometer equipped, with an MCT detector, over the range 4000–400 $cm^{-1}$ at a resolution of 4.0 $cm^{-1}$. Samples were sandwiched between two sodium chloride salt plates at a thickness of ~20 μm. Each spectrum was collected over 32 scans. The data were analyzed with the Bruker OPUS/IR Version 4.0 software.

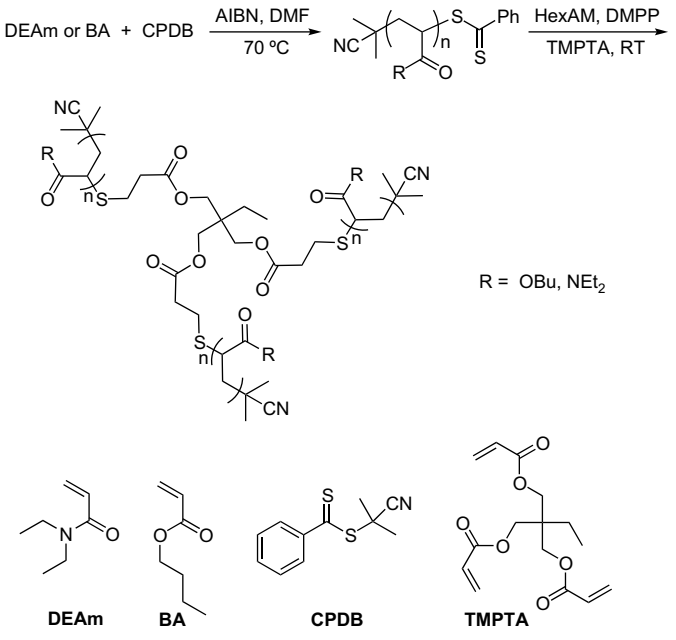
## 3. Results and discussion

RAFT-prepared (co)polymers serve as convenient precursors to reactive thiol/thiolate-terminal materials that can be used for subsequent post-polymerization reactions. Given the current, and growing, interest in click chemistry we examined the application of RAFT-synthesized homopolymers of *N*,*N*-diethylacrylamide (DEAm) and *n*-butyl acrylate (BA) as dithioester-terminal precursors in the

convergent synthesis of 3-arm star polymers via a nucleophilic, phosphine-catalyzed macromolecular thiol–ene reaction with the trifunctional coupling agent trimethylolpropane triacrylate (TMPTA). The general synthetic approach is outlined in Scheme 1.

Precursor homopolymers of polyDEAm (PDEAm) and polyBA (PBA) were prepared under typical RAFT conditions employing 1-cyano-1-methylethyl dithiobenzoate (CPDB, Scheme 1) as the RAFT chain transfer agent (CTA) in conjunction with AIBN as the source of primary radicals, at 70 °C in DMF. Table 1 summarizes the molecular characteristics of the resulting homopolymers ($M_{n,theory}$, $M_{n,exptGPC}$, $M_{n,exptNMR}$, $M_p$ (the peak maximum molecular weight, see Discussion later in manuscript), and $M_w/M_n$).

Entirely consistent with homopolymers prepared by RAFT, the resulting materials possess narrow molecular mass distributions with the polydispersity indices ($M_w/M_n$) being ≤1.18. The observed difference in the measured $M_n$ by SEC and the theoretical $M_n$ is a direct result of the fact that the SEC instrument was calibrated with narrow molecular mass distribution poly(methyl methacrylate) standards which are not ideal standards for the synthesized homopolymers. However, the $M_n$ as determined by via end-group analysis using $^1$H NMR spectroscopy is entirely consistent with the targeted $M_n$ based on the degree of conversion. As a representative example, Fig. 1 shows the $^1$H NMR spectrum, SEC trace (RI signal – shown inset) and MALDI-TOF MS trace for the PDEAm1 homopolymer (similar information for the PDEAm2 homopolymer is available in our recent communication [36]). Several points are worth noting. Given the low-targeted $M_n$ of the PDEAm and PBA homopolymers of 4500 at quantitative conversion their absolute molecular mass can be readily determined by end-group analysis using NMR spectroscopy. Fig. 1A shows the $^1$H NMR spectrum of the PDEAm1 homopolymer recorded in $D_2O$. The protons associated with the phenyl end-group group are clearly visible at ~7.6–7.8 ppm and are labeled b. A simple ratio of the integrals associated with b versus the resonance labeled a, which is assigned to the methylene protons directly bonded to the nitrogen atom of the amide side-group, yields a calculated absolute $M_n$ of 3800. In contrast, the $M_n$ determined by SEC was 2800 (see inset). Supporting the end-group calculations is




**Scheme 1.** Synthetic outline for the convergent approach to 3-arm star polymers under nucleophilic phosphine-catalyzed conditions using RAFT-prepared precursor homopolymers.

**Table 1**
Summary of homopolymer characteristics.

| Homopolymer | $M_n$ theory[a] | $M_n$ by SEC[b] | $M_n$ by NMR | $M_p$ by SEC | $M_w/M_n$[b] |
|---|---|---|---|---|---|
| PDEAm1 | 4500 | 2800 | 3800 | 3400 | 1.15 |
| PDEAm2 | 4500 | 2900 | 4400 | 3600 | 1.18 |
| PnBA | 4500 | 3600 | 3300 | 4300 | 1.18 |

[a] At quantitative conversion.
[b] Determined in THF, relative to poly(methyl methacrylate) standards.

the MALDI-TOF MS data. Fig. 1B shows the MALDI-TOF MS trace for the PDEAm1 homopolymer along with an expansion between 3000 and 4000 a.m.u. shown inset. The major distribution is centered at ca. 3800 a.m.u., a value identical to that calculated by end-group analysis. The difference in atomic mass between the major peaks is 127.86 a.m.u., very close to the atomic mass of the DEAm monomer of 127.10 a.m.u. Similar data were obtained for the PBA homopolymer. For example, Fig. 2 shows the $^1$H NMR spectrum of the PBA homopolymer, again demonstrating the ability to perform accurate end-group analysis.

With the well-defined homopolymers in-hand the convergent synthesis of 3-arm star polymers via a macromolecular thiol–ene

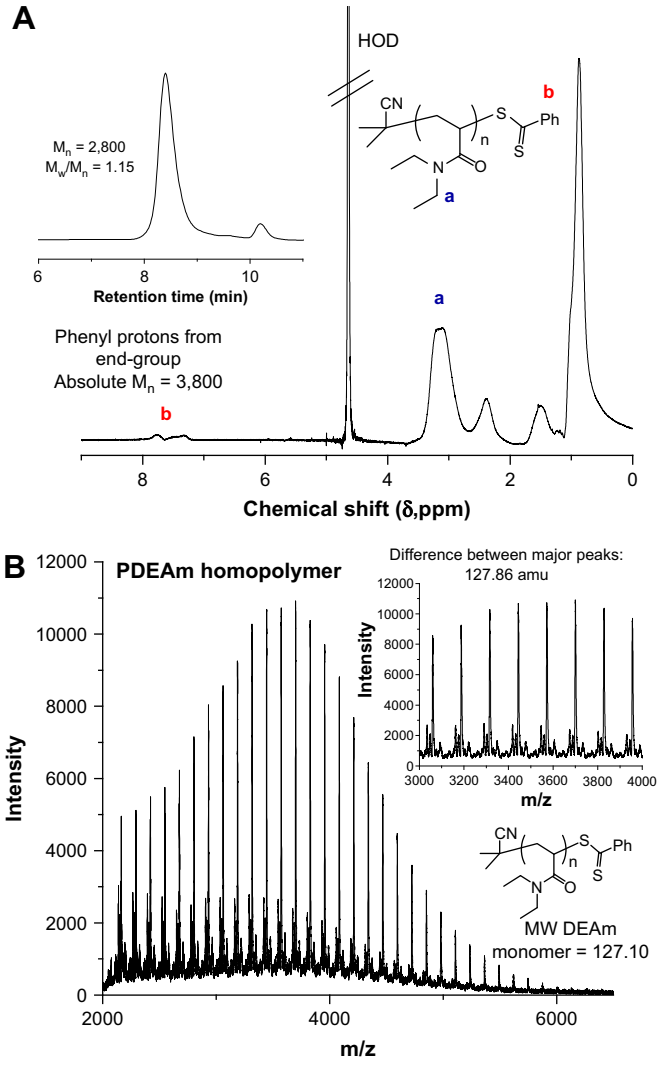



**Fig. 1.** (A) $^1$H NMR spectrum, recorded in $D_2O$, of PDEAm2 demonstrating the ability to conduct end-group analysis with the SEC trace (RI signal) shown inset, and (B) the MALDI-TOF MS trace of the same homopolymer with an expansion between 3000 and 4000 a.m.u. shown inset.

click reaction employing trimethylolpropane triacrylate (TMPTA) as the coupling reagent under phosphine-catalyzed conditions was examined in greater detail. To reiterate, the nucleophile catalyzed thiol-Michael reaction can be conducted using a primary or secondary amine although, as noted recently [36], dimethylphenylphosphine (DMPP) serves as an extremely potent catalyst for such reactions. The convergent star synthesis was accomplished by employing a combination of primary amine (hexylamine (HexAM)) and DMPP. The HexAM was added to specifically serve as the cleaving agent of the dithioester end-groups on the PDEAm/PBA homopolymers while the DMPP was employed to catalyze the subsequent macromolecular thiol–ene reaction. Previously, it was noted [36] that the presence of the phosphine, aside from serving as an extremely effective catalyst for the thiol-Michael reaction, served an equally important role in eliminating the presence of disulfide, formed from the reaction between the reduced RAFT homopolymers, a reaction that can occur readily in the presence of *only* amine. The application of phosphines as reducing agents for *disulfides* is well documented. For example, Scales et al. reported the treatment of PNIPAm, containing significant polymeric disulfide after $NaBH_4$ end-group reduction, with triscarboxyethyl phosphine [29]. However, in this report the authors reported the need for extended reaction times (24 h) and the use of a large excess of phosphine (150 molar excess based on thiol functionality) to achieve the desired reduction. In contrast, performing the dithioester end-group reduction in the *presence* of phosphine serves the same function, although such extended reaction times or high concentrations are not required [36]. To further highlight this beneficial effect, Fig. 3 shows the MALDI-TOF MS traces for the PBA homopolymer (absolute $M_n$ of 3300 as determined by $^1H$ NMR end-group analysis) in which the dithioester group was cleaved with HexAM in the absence (Fig. 3A) and presence of DMPP (Fig. 3B). When the cleavage reaction is performed with only HexAM under a normal air atmosphere, the MALDI-TOF MS trace clearly shows that in addition to the desired thiol-terminated product, the reaction also results in the formation of the corresponding disulfide as evidenced by the presence of a second distribution centered at about ca. 6700 a.m.u. In contrast, when the reaction is performed with the HexAM/DMPP combination, the MALDI-TOF MS trace indicates the absence of any disulfide. Clearly, such an approach is more convenient than the sequential approach reported previously for obtaining thiol-terminated RAFT-prepared (co)polymers. The exact role of the DMPP is not, however, clear and its exact mode of action has not been elucidated at this time. However, it is presumably acting in one of two possible ways. Disulfide formation is a direct result of the aerial oxidation of the thiol-terminated homopolymers. Therefore, DMPP is either inhibiting the aerial oxidation process or, as reported previously, is serving as a reducing agent for disulfide that may be formed during the end-group reduction.

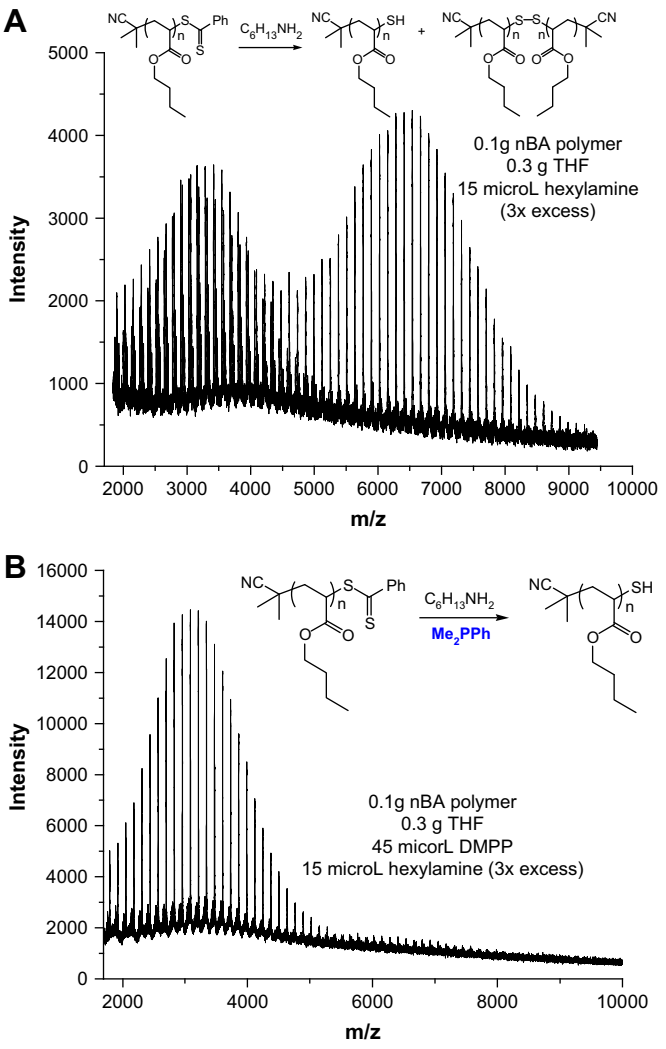



**Fig. 3.** (A) MALDI-TOF MS trace of the products obtained after dithioester end-group reduction of PBA performed in the presence of only hexylamine (0.1 g BA homopolymer in 0.3 g THF with 15 μL of hexylamine), and (B) MALDI-TOF MS trace of the same homopolymer after end-group reduction in the presence of hexylamine and dimethylphenylphosphine (0.1 g BA homopolymer in 0.3 g THF, 45 μL of dimethylphenylphosphine, and 15 μL of hexylamine).

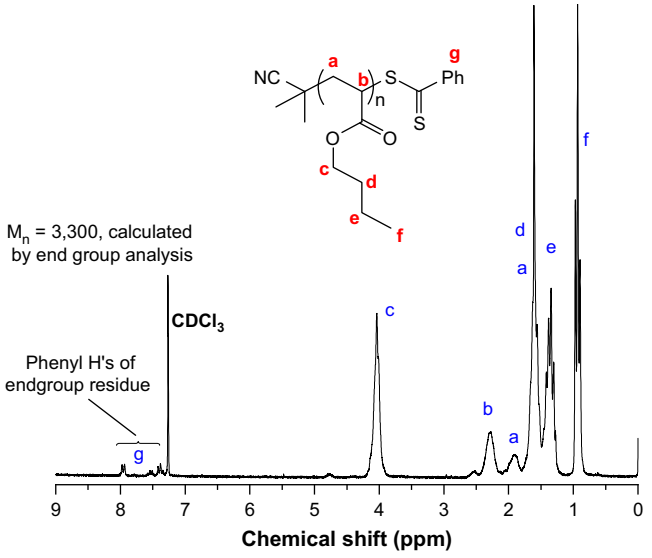



**Fig. 2.** $^1H$ NMR spectrum, recorded in $CDCl_3$, of PBA with end-group analysis.

The beneficial effect of the added DMPP was also verified by SEC. Fig. 4 shows the chromatograms (RI signal) for the PDEAm1 homopolymer after cleavage of the dithioester end-groups performed in the presence and absence of DMPP. When conducted in the absence of DMPP, the SEC trace shows the presence of a higher molecular mass species as evidenced by the bimodal distribution – there is a clear shoulder centered at a retention time of ~8.1 min on the main distribution. In contrast, but entirely consistent with the MALDI-TOF MS results for the PBA homopolymer, when the reduction is performed in the presence of DMPP the resulting distribution is symmetric and unimodal with no evidence of any higher molecular mass species resulting from the formation of disulfide.

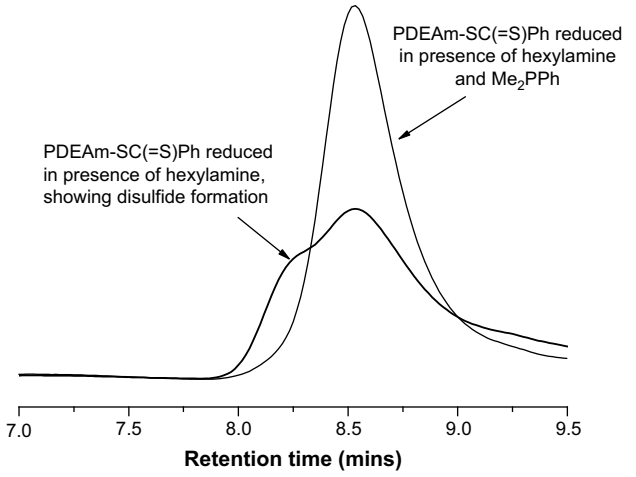



**Fig. 4.** SEC traces (RI signal) of the products obtained after end-group cleavage with hexylamine of PDEAm1 in the presence and absence of dimethylphenylphosphine demonstrating the beneficial effect of phosphine in reducing/eliminating the presence of polymeric disulfide.

Having demonstrated the well-defined nature of the precursor homopolymers and the clearly beneficial nature of the DMPP not only serving as a potent nucleophilic catalyst for the macromolecular thiol–ene reaction but also acting as an effective reagent for preventing/reducing disulfide formation, a more detailed examination of the actual star-forming reaction was conducted.

As demonstrated previously, real-time FTIR [1,5] is an extremely effective means of monitoring thiol–ene reactions. Indeed, for reactions between *small molecule* thiols and enes, absorption bands associated with both functional groups can be monitored readily in real time. Specifically, the ene presents distinct IR bands that can be monitored at ca. 1600 (C═C stretch) and 810 $cm^{-1}$ (the C–H bend in C═C–H), whereas the consumption of the thiol can be followed by following the disappearance of the weak band at 2575 $cm^{-1}$. Unfortunately, given the polymeric nature of the thiol in these convergent star syntheses it was not possible to directly monitor the band associated with the thiol due to its low concentration. However, the consumption of the ene could be readily followed. As a representative example, Fig. 5A shows the IR spectrum, plotted between 900 and 780 $cm^{-1}$, for the reaction of PDEAm1 with TMPTA/DMPP before and 5 min after the addition of HexAM. The band of interest at 810 $cm^{-1}$ (the C–H bend in C═C–H) is clearly visible as a shoulder on the more intense band at ca. 790 $cm^{-1}$ in the spectrum (solid line) of PDEAm1, TMPTA and DMPP. A second spectrum recorded approximately 5 min after the addition of HexAM is also shown in Fig. 5A (dotted line), and indicates close to complete conversion after this short period of time. This highlights the fact that the macromolecular thiol–ene reaction is rapid which while not common for convergent star syntheses is entirely consistent with the thiol–ene reaction in general. Similar observations were made in the case of the PBA homopolymer (Fig. 5B).

The rapid consumption of C═C bonds was also confirmed by $^1$H NMR spectroscopy. Fig. 6A shows the $^1$H NMR spectrum, recorded in THF with a DMSO-$d_6$ inset, plotted between $\delta = 6.5$ and 5.5 ppm for dithioester-terminal PBA and TMPTA highlighting the presence of the vinylic functional groups on TMPTA as evidenced by the resonances at ~6.3, 6.05–6.1, and 5.8 ppm all associated with the hydrogen atoms on the C═C bonds. Following the acquisition of this spectrum, the sample tube was removed from the spectrometer, the required volumes of DMPP and HexAM added, the tube reinserted in the spectrometer, the sample locked/shimmed and a second spectrum recorded, Fig. 6B. Consistent with the FTIR

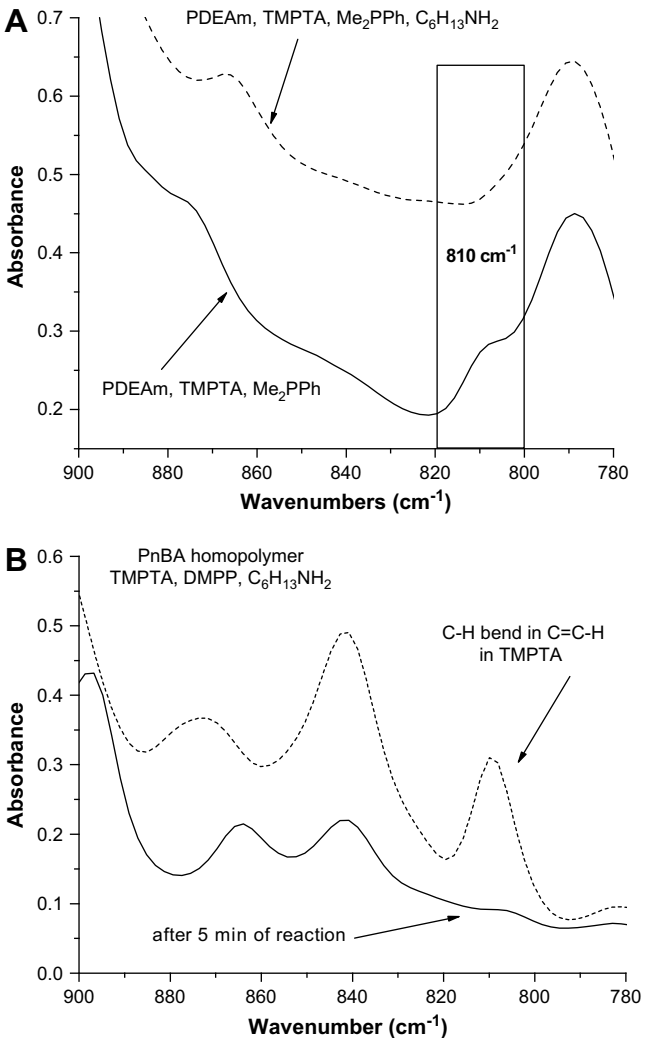



**Fig. 5.** (A) FTIR spectroscopic trace for PDEAm2, TMPTA, and dimethylphenylphosphine before and after the addition of hexylamine highlighting the rapid consumption of C═C bonds as evidenced by the disappearance of the band at 810 $cm^{-1}$ associated with the C–H bend in C═C–H of TMPTA, and (B) same experimental data for the corresponding PBA homopolymer.

spectroscopic results, the C═C bonds are *completely* consumed within this short period of time with absolutely no evidence of any vinylic H's present in the $^1$H NMR spectrum.

While both the FTIR and $^1$H NMR spectroscopic data demonstrate that the C═C bonds are consumed extremely rapidly in the presence of dithioester-terminal polymer, HexAM and DMPP, neither technique proves unequivocally that the consumption of ene bonds is due to the desired thiol–ene reaction. In an attempt to verify that the disappearance of the C═C bonds was due to the macromolecular thiol-Michael reaction $^{13}$C NMR spectroscopy was used to identify the original vinylic carbon atoms after reaction with the macromolecular thiols. To aid with structural verification a small molecule model reaction was first conducted. Specifically, the DMPP catalyzed reaction between ethyl-2-mercaptopropanoate, a small molecule model for the polymeric ester/amide, and TMPTA was conducted and the product characterized with respect to specifically identifying the chemical shifts of the saturated carbon atoms labeled a and b in Fig. 7A, i.e., those that were originally the vinylic carbon atoms of TMPTA. In this small molecule model reaction the key resonances were clearly visible at $\delta = 34.59$ (carbon atom alpha to the C═O group) and 26.52 (carbon atom

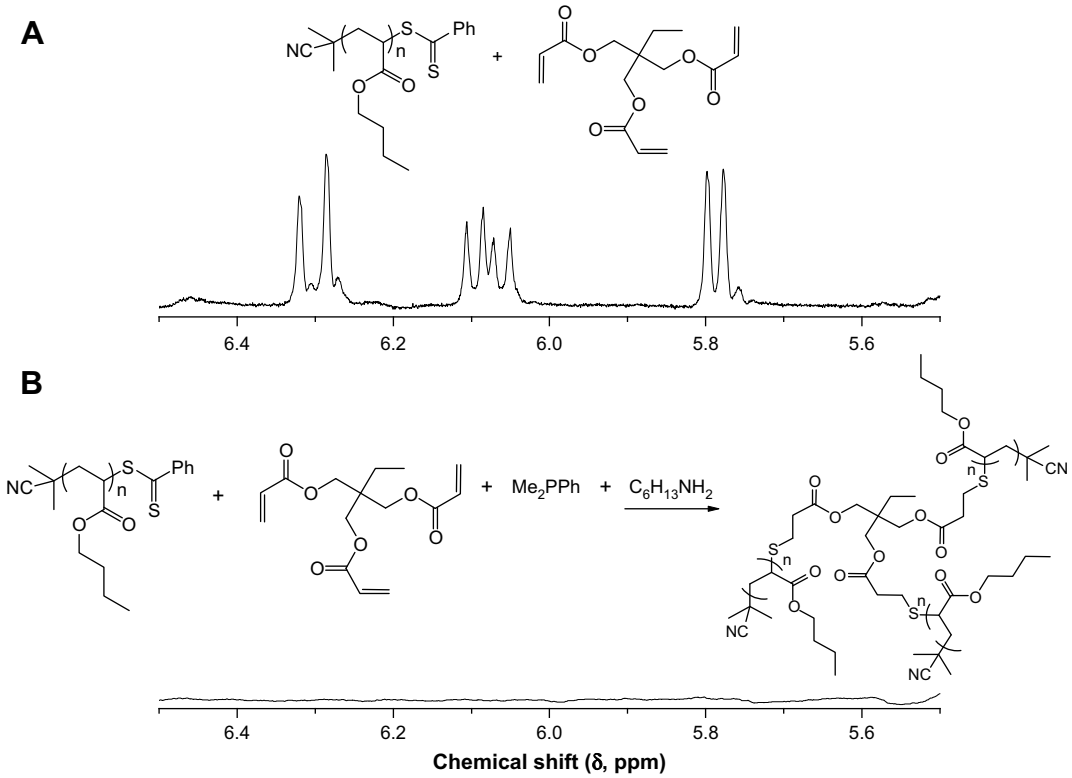



**Fig. 6.** (A) $^{1}$H NMR spectrum of PBA + TMPTA, recorded in $CDCl_3$, highlighting the presence of the vinylic hydrogens in TMPTA, and (B) the $^{1}$H NMR spectrum of the same solution recorded approximately 5 min after the addition of hexylamine and dimethylphenylphosphine highlighting the complete absence of C=C bonds (NB – y scale ranges are identical).

directly bonded to S) ppm. Having successfully identified the region and resonances of interest the same analysis was performed on the polymeric star products. Fig. 7B shows the $^{13}$C NMR spectrum, plotted between $\delta = 35$ and 26 ppm for the reaction between PDEAm1 and TMPTA with DMPP as catalyst and HexAM as end-group cleaving agent. Obviously, such $^{13}$C NMR analysis on a moderate-to-high molecular mass 3-arm star polymer is not as straightforward; however the resonances of interest are observed at $\delta = 34.59$ and 26.68 ppm. These $^{13}$C NMR spectroscopic results confirm that the results obtained by FTIR and $^{1}$H NMR spectroscopies result from a macromolecular thiol–ene reaction.

Additional indirect evidence for the macromolecular thiol–ene reaction was obtained via a simple control experiment in which TMPTA, HexAM, and DMPP were mixed in an NMR tube in THF at concentrations consistent with the 3-arm star syntheses (Fig. 8). As demonstrated previously, the C=C bonds in the presence of polymer are consumed very rapidly. However, in the *absence* of the thiol-terminated polymer the C=C bonds are clearly visible after only 5 min of 'reaction' indicating that their consumption is a direct result of reaction with thiol functional groups.

In addition to verifying that consumption of ene bonds occurs only in the presence of thiol-terminated polymer, this control experiment additionally confirms that DMPP does *not* catalyze the aza-Michael reaction, i.e. the addition of HexAM across the C=C bonds. Mechanistically, it is reasonable to propose that the DMPP catalyzed thiol–ene reaction proceeds via an ionic chain reaction in which addition of phosphine to an activated ene results in the formation of an intermediate, resonance stabilized carbon-centered enolate zwitterion. Such an intermediate has indeed been proposed for the phosphine-catalyzed addition of alcohols [45] and various carbon-centered nucleophiles [2] to a range of electron deficient enes [46] including acrylates. This strong ***base*** intermediate subsequently abstracts a proton from a thiol, yielding a thiolate that is a potent nucleophile capable of undergoing direct Michael addition to an activated ene forming an intermediate enolate which abstracts another proton from additional thiol, resulting in chain propagation, Scheme 2.

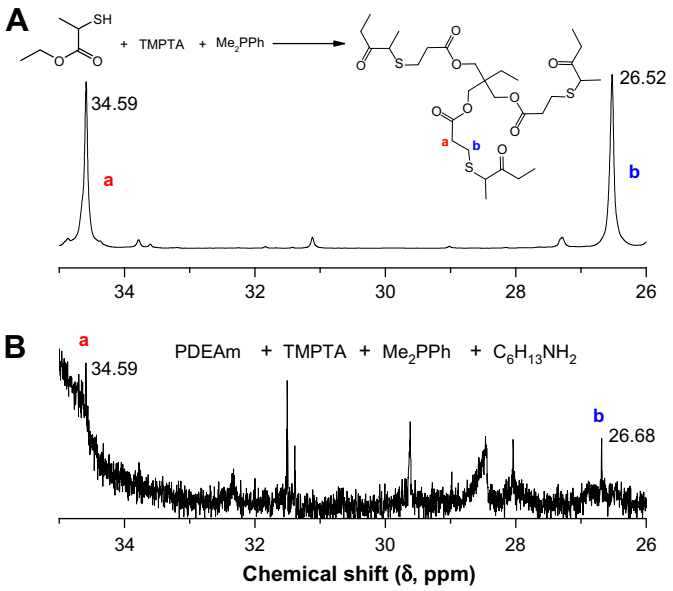



**Fig. 7.** (A) $^{13}$C NMR spectrum plotted between 35 and 26 ppm for the model reaction between ethyl-2-mercaptopropionate (1.8 μL, $1.4 \times 10^{-5}$ moles) and TMPTA (2.5 μL, $8.3 \times 10^{-6}$ moles) catalyzed by dimethylphenylphosphine (10.0 μL, 0.11 M), recorded after 5 min of reaction highlighting the resonances associated with successful thiol–ene reaction, and (B) the $^{13}$C NMR spectrum, plotted over the same range, for the polymeric version with PDEAm2 with added hexylamine (20.0 μL, 0.35 M) to cleave the dithioester end-groups.

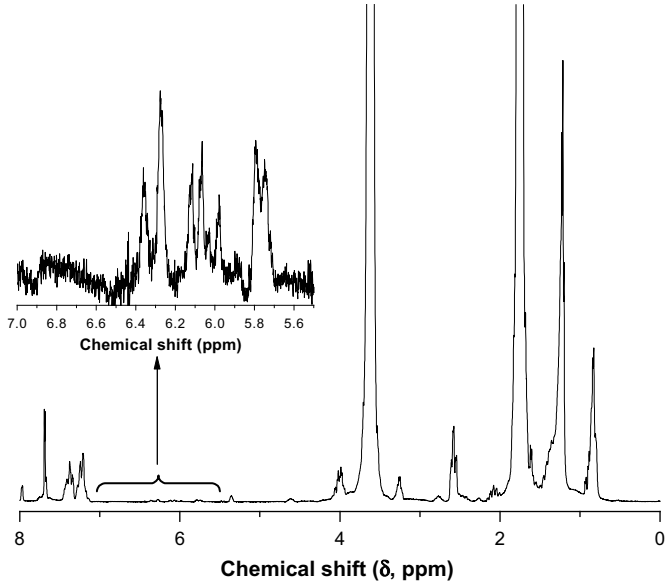



**Fig. 8.** $^1$H NMR spectrum, recorded in $CDCl_3$, of a mixture of TMPTA, hexylamine, and dimethylphenylphosphine with an expansion of the vinylic region shown inset demonstrating the retention of C=C bonds in the absence of thiol.

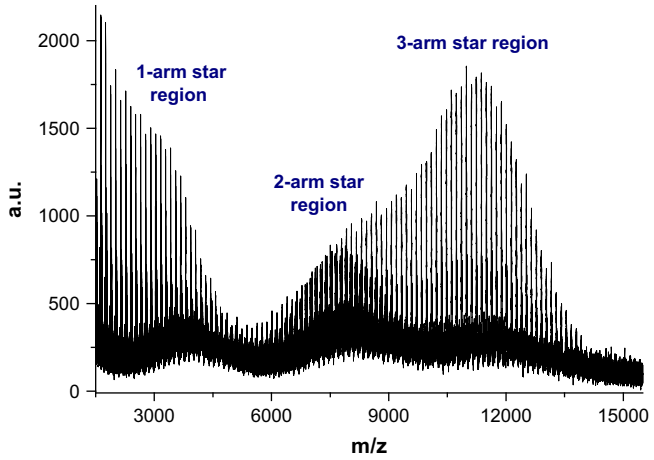
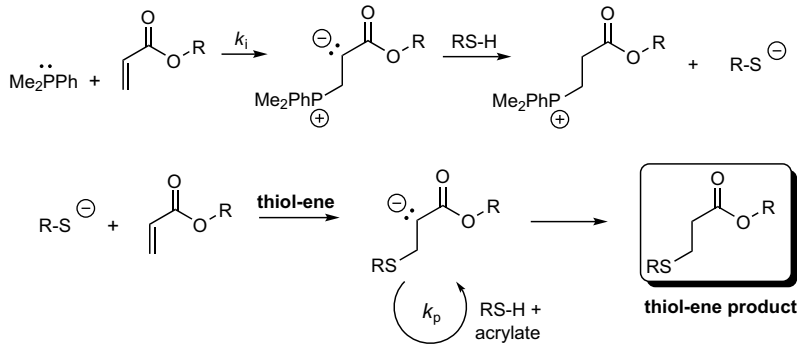



**Fig. 9.** MALDI-TOF MS trace of the PDEAm1 star product, plotted between $m/z = 1500$ and 15,500 highlighting the presence of the desired 3-arm star product along with the presence of 2- and 1-arm species.

Clearly, the intermediate carbon-centered enolate anion must be a sufficiently strong base to abstract a proton from a thiol molecule to induce the subsequent chain reaction. In the case of thiols, the intermediate enolate is sufficiently powerful to facilitate the deprotonation reaction ($pK_a$ of the thiol functional group is typically ~8–9). However, for DMPP to catalyze the addition of HexAM across the C=C bonds the intermediate base must be strong enough to deprotonate the primary amine, which has a $pK_a$ ~40. There is no question that the intermediate enolate is ***not*** sufficiently strong to deprotonate HexAM, i.e. the weaker acid/base pair is not formed.

As previously demonstrated [36], MALDI-TOF MS serves as a convenient method for verifying 3-arm star formation. Fig. 9 shows the experimentally determined MALDI-TOF MS spectrum of the product obtained from the reaction of PDEAm1 ($M_n = 3800$ via end-group analysis) with TMPTA, DMPP and HexAM employing CHCA as the MALDI-TOF MS matrix. The observed mass spectrum clearly confirms the presence of the 3-arm star products with a major distribution centered at ~11,000 a.m.u. However, in addition to the 3-arm star products there are clearly distributions that are due to the presence of both 2- and 1-arm species. There are at least two possible sources for these products. Firstly, it should be reiterated that commercially available TMPTA has a listed purity of 83–100% with the major contaminants being trimethylolpropane ***di***acrylate and trimethylolpropane ***mono***acrylate. Given that TMPTA was used as received these impurities will clearly result in the formation of the 1- and 2-arm star products.

A second source of 1- and 2-arm fragments is a direct result of the MALDI-TOF MS experiment, i.e. the MALDI-TOF MS-induced fragmentation of high-arm stars to lower-arm stars [47]. This is not uncommon and fragmentation of analyte under MALDI-TOF MS experimental conditions is well documented and is known to be dependent on variables including the nature of the matrix and the laser pulse energy. Evidence for such fragmentation can be extracted from the MALDI-TOF MS trace in Fig. 9. For example, Fig. 10A shows an expansion in the 3-arm star region highlighting a peak with $m/z = 11{,}500$. From this peak we can estimate the average molecular mass of each arm since we know the exact molecular weight of the core fragment and the likely cationic species. Since no specific cationizing species was added we assume that the ionized species is either $[3\text{-arm star} + H]^+$, $[3\text{-arm star} + Na]^+$, or $[3\text{-arm star} + K]^+$. Based on our previous observations, PDEAm is known to readily form adducts with $Na^+$, and so the peak with $m/z = 11{,}500$ is likely due to $[3\text{-arm star} + Na]^+$. Therefore, the molecular weight of the 3-arm star is $11{,}500 - 23 = 11{,}477$ g/mol. Given that the core fragment has a molecular mass of 296 g/mol then the average molecular mass of each arm can be calculated to be 3727 g/mol. For the purpose of analysis and the identification of 1- and 2-arm fragments derived from fragmentation in the instrument we are assuming that the fragmentation can occur at the points indicated in Fig. 10A (blue, red, and green lines). These may not be the only fragmentation points but are the only positions we will consider here. In the case of the 3-arm star, fragmentation could occur at one, two or all three




**Scheme 2.** Proposed anionic (enolate) chain mechanism for the phosphine-catalyzed addition of a thiol to an activated acrylic double bond.

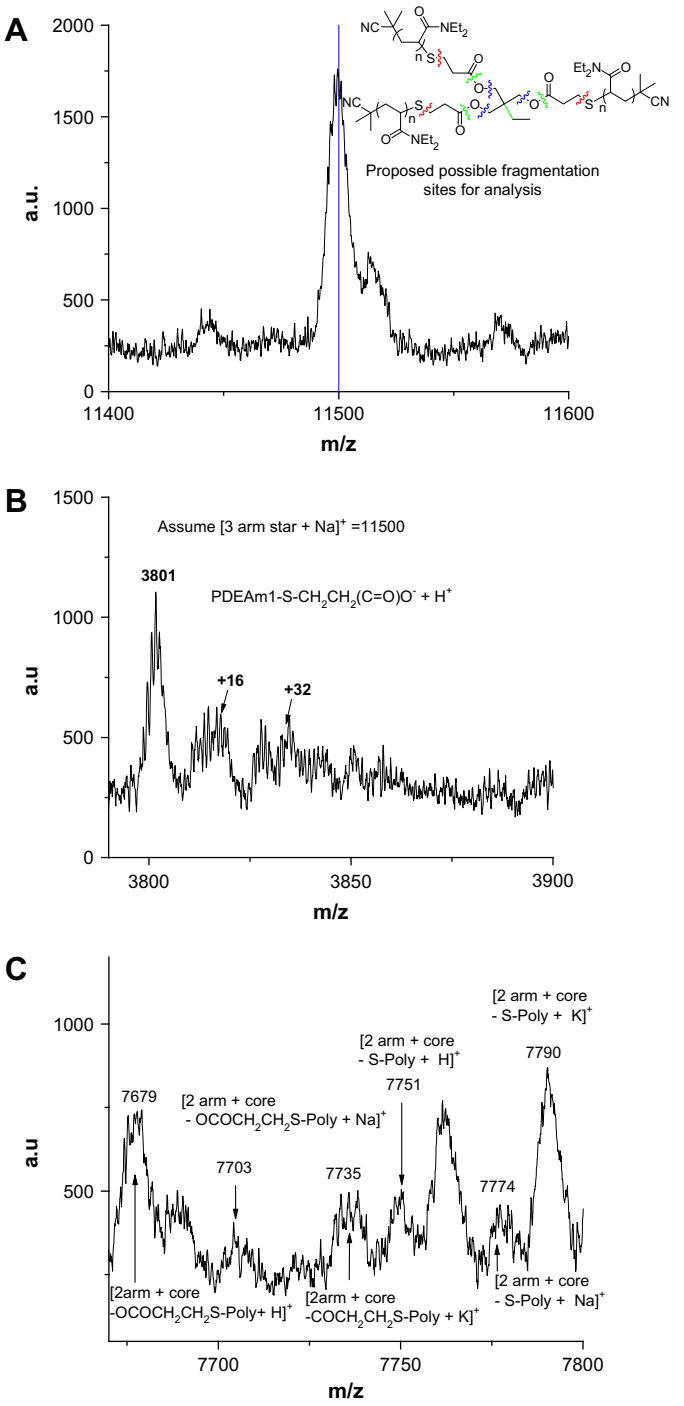



**Fig. 10.** (A) MALDI-TOF MS trace plotted between $m/z = 11{,}400$ and 11,600 highlighting the presence of a 3-arm star based on PDEAm1 with an $m/z = 11{,}500$ (assumed to be [3-arm PDEAm + Na]$^+$). Shown inset is the generic structure of a DEAm-based 3-arm star with possible fragmentation sites noted, (B) the same MALDI-TOF MS trace plotted between $m/z = 3790$ and 3900 (part of the 1-arm star region) showing the presence of a species with $m/z = 3801$ which corresponds to a star arm formed by MALDI-induced fragmentation (structure shown inset), along with the presence of peaks at $m/z = 3801 + 16$ and $3801 + 32$ that may species associated with oxidized sulfur atoms, and (C) the same MALDI-TOF MS trace plotted between $m/z = 7670$ and 7800 (part of the 2-arm region) showing the presence of a series of peaks assigned to various 2-arm species formed via fragmentation reactions of the 3-arm star.

distinct positions yielding 1- and 2-arm products. Cleavage of the C–O bonds (blue lines) yields a polymer chain that is terminated with a carboxylate group; in this case the cleaved product will be PDEAm1–S–$CH_2$–$CH_2$–$CO_2^-$ + $H^+$. Based on the calculated average molecular mass of an arm, as noted above, plus the $CH_2$–$CH_2$–$CO_2^-$ + $H^+$ portion gives a species with a molecular weight of 3800 g/mol. Fig. 10B shows an expansion of Fig. 9 in the region $m/z = 3790$–3900. The major peak in this region has an $m/z$ value of 3801 which agrees almost exactly with the predicted value. In addition, peaks are observed at +16 and +32 $m/z$ that *may* be due to the sulfoxide and sulfone respectively formed from the oxidation of the thioether functionality in the polymer chains.

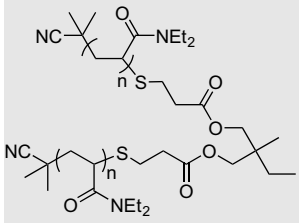
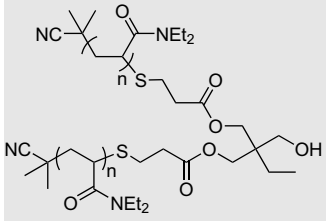
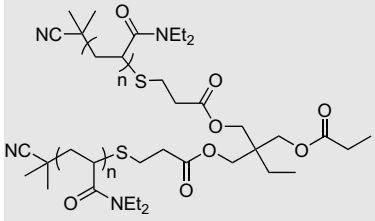
Analysis of the $m/z = 7670$–7800 region, Fig. 10C, indicates the presence of products that can be assigned to 2-arm stars with molecular masses consistent with species formed by fragmentation of the corresponding 3-arm stars at all three of the indicated points shown in Fig. 10A. Table 2 shows the chemical structures of the major 2-arm star fragments in this region as well as the measured and theoretical molecular weights associated with $H^+$, $Na^+$, and $K^+$ each species.

For each of the theoretical $m/z$ values calculated (based on the assumption that we are dealing with fragmentation of the [3-arm star + Na]$^+$ species with an $m/z = 11{,}500$) then it is possible to identify a major peak in this range that is within several units of the theoretical value. It should be noted that the observed peak centered around $m/z = 7735$ could also be due to 2-arm species formed by the addition of the thiol-terminated homopolymer to trimethylolpropane ***di***acrylate as well as to 2-arm star formed by the fragmentation of a 3-arm star at one of the points indicated in green.

Supporting the MALDI-TOF MS data, the SEC traces in Fig. 11 qualitatively indicate the successful formation of the star polymers. The trace at higher retention volume (solid line) is for the PDEAm1 homopolymer while the second chromatogram (dotted line) represents the resulting star polymer. Several points are worth highlighting. While the chromatogram for the precursor homopolymer is symmetrical and narrow ($M_w/M_n = 1.15$) the trace for the 3-arm star polymer is distinctly non-symmetric, somewhat broad ($M_w/M_n = 1.35$) and has an $M_p$ (peak maximum molecular weight) that is not 3× that of the homopolymer. Each of these points is readily explained. The non-symmetric nature of the chromatogram, i.e. tailing to higher retention volume, is due to both the excess of PDEAm homopolymer initially added and the presence of some '2-arm' star products. This is *not* a result of incomplete reaction, with the acrylate groups in the TMPTA since we demonstrated above (Fig. 6) that there are no detectable double bonds after reaction, but most likely due to the presence of the *diacrylate* impurity in TMPTA. Indeed, as noted above the TMPTA is not pure with the diacrylate and monoacrylates being the major impurities. The disagreement between the $M_p$ values for the DEAm homopolymer and the 3-arm star product is also expected based on the known hydrodynamic properties of linear versus star polymers. Specifically, star polymers have higher densities than their linear counterparts and thus smaller hydrodynamic volumes for identical molecular masses, a feature that is borne out in the SEC results.

Having verified successful 3-arm star formation using a combination of FTIR spectroscopy, $^1H/^{13}C$ NMR spectroscopy, MALDI-TOF MS, and SEC in the presence of HexAM and DMPP a control experiment was performed to eliminate the possibility of consumption of the C=C bonds in TMPTA via a radical process. An NMR experiment was set-up with PBA under exactly the same conditions as noted previously (see Fig. 6) except that 2 wt% TEMPO was also added. If the consumption of C=C bonds occurred via a radical pathway then the presence of TEMPO would, presumably, completely inhibit consumption by serving as a radical trap, or at least have a very significant effect on the reaction rate and yields. Fig. 12 shows the $^1H$ NMR spectrum of the reaction recorded after 5 min with the vinylic region shown inset. There is little/no evidence of any vinylic hydrogens confirming that the C=C bonds are *not* consumed via a radical pathway.

**Table 2**
Proposed structures of possible two-arm stars formed via fragmentation reactions along with the theoretical and measured *m*/*z* values for the $H^+$, $Na^+$, and $K^+$ adducts.

| 2-Arm species | $H^+$, *m*/*z* theory | $H^+$, *m*/*z* observed | $Na^+$, *m*/*z* theory | $Na^+$, *m*/*z* observed | $K^+$, *m*/*z* theory | $K^+$, *m*/*z* observed |
|---|---|---|---|---|---|---|
|  | 7681 | 7679 | 7703 | 7703 | – | – |
|  | – | – | – | – | 7739 | 7735 |
|  | 7754 | 7751 | 7776 | 7774 | 7795 | 7794 |

## 4. Summary/Conclusions

Described herein is a detailed examination of a convergent synthetic approach to 3-arm star polymers via a macromolecular thiol–ene click reaction. Well-defined precursor homopolymers of *N*,*N*-diethylacrylamide (DEAm), and *n*-butyl acrylate (BA) were prepared via RAFT using 1-cyano-1-methylethyl dithiobenzoate as the RAFT agent and AIBN as the source of primary radicals. Key to this approach is the specific use of RAFT-synthesized (co)polymers since such materials serve as convenient masked terminal thiol bearing materials capable of undergoing post-polymerization reactions. When the hexylamine-mediated cleavage of the dithioester end-groups is conducted in the presence of dimethylphenylphosphine (DMPP) and trimethylolpropane triacrylate, sequential cleavage/

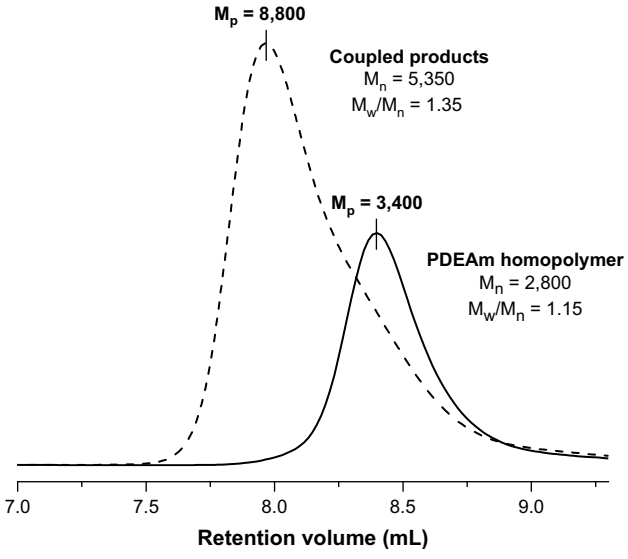



**Fig. 11.** SEC traces (RI signal) of the PDEAm1 homopolymer and the corresponding 3-arm star polymer with the $M_n$, $M_p$, and $M_w/M_n$ values listed.

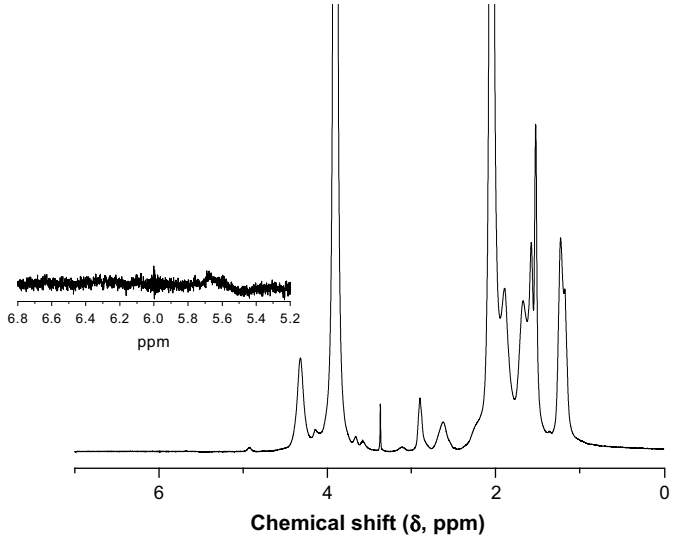



**Fig. 12.** $^1H$ NMR spectrum, recorded in $CDCl_3$, after 5 min of reaction between PBA, TMPTA, dimethylphenylphosphine, hexylamine, and TEMPO demonstrating the complete disappearance of C=C bonds (the vinylic region is expanded in the inset), verifying that the reaction does not proceed via a radical process.

thiol–ene reactions occur to yield the target 3-arm star polymers as verified by a combination of $^{1}H/^{13}C$ NMR spectroscopy, FTIR spectroscopy, size exclusion chromatography, and MALDI-TOF MS. DMPP is demonstrated to serve two important roles. Firstly, it acts as an extremely potent *nucleophilic* catalyst for the macromolecular thiol–ene reaction, which is proposed to propagate by a very reactive ionic carbon-centered enolate chain process that is not inhibited by any water that may be present. Secondly, it serves to prevent/inhibit disulfide formation between thiol-terminated polymers that can be a problem when the end-group reduction is performed only in the presence of amine. Control experiments confirmed that the ene bonds are only consumed in the presence of thiol and that the reaction does not proceed via a radical pathway.

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