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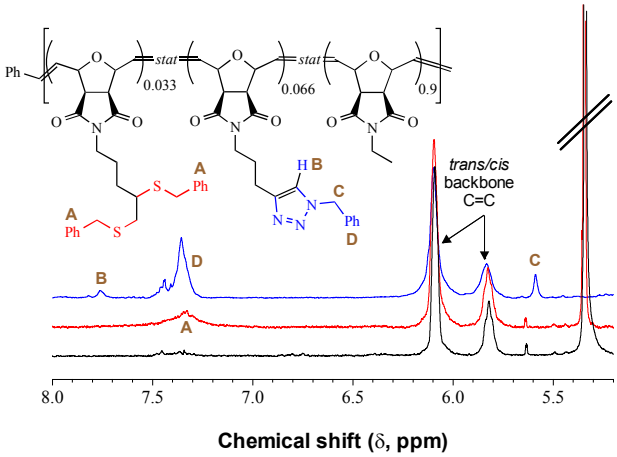

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# ROMP (Co)Polymers with Pendent Alkyne Side Groups: Post-polymerization Modification Employing Thiol-yne and CuAAC Coupling Chemistries

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The synthesis of a series of copolymers via ring-opening metathesis polymerization (ROMP) containing pendent trimethylsilyl-protected alkyne functional groups is described. Deprotection of the protected ynes yields copolymers with free alkyne functionality that can be utilized as a reactive handle for thiol-yne (TYC) and Cu-catalyzed alkyne-azide coupling (CuAAC) either independently or together.

## Introduction

The discovery and development of a suite of highly efficient modification chemistries has, in many ways, revolutionised polymer synthesis and post-polymerization transformations. These chemistries include the well-documented regiospecific, Cu-catalyzed reaction between an alkyne and an azide (the CuAAC reaction, commonly referred to as click chemistry), a suite of thiol-based reactions[1] such as the thiol-ene[2-12] (including both radical and thiol-Michael variants), thiol-yne,[13-17] thiol-isocyanate[18] and thiol-halo[19] reactions, certain heteroatom cycloaddition reactions,[20-22] oxime chemistry[23, 24] and the use of reactive polymeric scaffolds such as those containing highly activated esters[25-27] (pentafluorophenyl derivatives for example) or 2-vinyl-4,4-dimethylazlactone[28-33] species. All of these processes can allow for rapid synthesis of monomers, polymers and facilitate post-polymerization modification often, but not always, meeting the criteria to be accurately described as 'click' reactions. The CuAAC reaction is still the preeminent member of this family of chemistries and there is now an extensive volume of literature describing novel applications of this reaction. The thiol-based reactions have likewise attracted significant attention with the radical thiol-ene reaction being the most commonly employed.[2] The radical thiol-yne reaction can be considered as a sister-reaction to the radical thiol-ene reaction but also complementary to the CuAAC reaction. Hydrothiolation of an yne, under radical conditions, gives the 1,2-double addition adduct.[13, 34, 35] As with the thiol-ene, the thiol-yne reaction is broadly applicable and has been employed in monomer synthesis, polymer end-group modification,[36-38] side chain modification,[39, 40] dendrimer syntheses,[41-44] (hyper)branched molecule[14, 45-48] and (co)polymer synthesis[49-51] and network syntheses,[15, 16, 52-54] while non-radical versions have been used to prepare linear polymers.[55, 56]

Ring-opening metathesis polymerization (ROMP) is a transition metal-mediated polymerization process that is applicable to cyclic monomers of high-to-intermediate ring strain such as the (*exo*-7-oxa)norbornene family of substrates.[57-60] ROMP is a well-established polymerization technique that facilitates the preparation of (co)polymers with well defined molecular characteristics including pre-determined number average molecular weights ($\bar{M}_n$) and molar compositions, narrow molecular weight distributions, i.e. (co)polymers with low dispersities ($Đ_M = \bar{M}_w/\bar{M}_n \leq 1.30$) and advanced architectures such as block copolymers.[61-63] As a synthetic tool ROMP gives access to rather unique polymeric materials but importantly has a functional group tolerance that, nowadays, rivals the family of reversible deactivation radical polymerization processes.

Recently we have been exploring novel ways in which to combine ROMP with thiol-based coupling chemistries.[64-68] In particular we have focused on nucleophilic thiol-Michael and radical thiol-ene chemistries and have described the synthesis and (co)polymerization of a series of thioether based functional *exo*-7-oxanorbornenes,[64] the preparation of hyperbranched (co)polymers from difunctional *exo*-7-oxanorbornene substrates,[65] the synthesis and polymerization of dendron macromonomers[66] and the facile, quantitative hydrothiolation of a ROMP polymer backbone.[67]

Building on these studies we have recently been examining the feasibility of combining the radical thiol-yne reaction with ROMP-prepared (co)polymers. Herein we describe the synthesis of a series of yne-containing copolymers based on the *exo*-7-oxanorbornene family of monomers and demonstrate how by careful control of the monomer and copolymer structure it is possible to achieve quantitative thiol-yne modification of alkyne side groups even in the presence of internal backbone enes. Additionally, we highlight how the pendent yne groups are available for CuAAC reactions as well as facilitating the preparation of complex thioether derivatives via simultaneous/sequential thiol-yne reactions with different ynes as well as novel copolymers via sequential thiol-yne and CuAAC reactions.

## Experimental

All reagents were purchased from the Aldrich Chemical Company and used as received unless noted otherwise. (3a*R*,7a*S*)-2-Butyl-3a,4,7,7a-tetrahydro-1*H*-4,7-epoxyiso-indole-1,3(2*H*)-dione was prepared according to the previously reported procedure.[64]

### *Instrumentation*

Radical thiol-yne reactions were conducted in a 400W Rayonet RPR-200 photochemical reactor fitted with 16 x 2537Å light sources. A cylindrical reactor geometry was used (40 cm deep with a 16 cm radius), with each lamp arranged in a vertical orientation. The intensity of ultra-violet radiation at the centre of the chamber was approximately 1.65 x $10^{16}$ photons/sec/$cm^3$ and an equilibrium operating temperature of 44°C was typical. Mechanical stirring was provided via a compressed air powered magnetic stirrer and samples (loaded in UV-transparent RQV-7 and RQV-3 quartz test tubes) were suspended in the centre of the instrument.

High-resolution mass spectrometry of small molecules was performed on a Bruker Bio Apex II Fourier transform ion cyclotron resonance mass spectrometer (FT-ICR-MS). The system was fitted was 7 Tesla magnets and an Analytica source.

$^1$H and $^{13}$C NMR spectra of monomers and polymers were acquired on a Bruker DPX 300 MHz NMR spectrometer fitted with a 5 mm double resonance broad band BBFO z-gradient probe. $^1$H spectra were averaged from 32 scans while $^{13}$C were averaged over 256-1024 scans depending on sample concentration. Long relaxation delays of 10 sec. were required to achieve accurate integrations of the oxanorbornene derivatives. Deuterated solvents were purified by passage through a short column of anhydrous potassium carbonate to remove trace acidity and moisture. Spectra ad free induction decay (FID) Fourier transforms were processed using the Topspin software package and all data is reported as follows: chemical shift in ppm [multiplicity (s = singlet, d = doublet, dd = doublet of doublets, t = triplet, m = multiplet), coupling constants in Hertz, integration].

Infrared spectra were collected on a Thermo Nicolet 5700 FTIR spectrometer equipped with a single bounce diamond stage attenuated total reflectance (ATR) accessory. A resolution of 2 $cm^{-1}$ and a spectral window of 650 to 4000 wavenumbers was chosen and spectra were accumulated from 32 averaged scans.

Size exclusion chromatography (SEC) analysis of polymer samples was performed in *N,N*-dimethylacetamide [DMAc, 0.03% w/v LiBr, 0.05% 2,6-dibutyl-4-methylphenol (BHT)] at 50°C. Sample solutions were injected into a Shimadzu modular system comprising an SIL-10AD autoinjector, a Polymer Labs (PL) 5.0 μm bead-size guard column (50 x 7.5 $mm^2$) followed by four linear PL Styragel columns ($10^5$, $10^4$, $10^3$ and 500Å) and an RID-10A differential refractive index detector. A flow rate of 1.0 mL $min^{-1}$ was employed, and calibration was achieved with commercial narrow molecular weight distribution polystyrene standards with $\bar{M}_n$'s ranging from 500 to $10^6$ g $mol^{-1}$. For samples insoluble in DMAc, a similar system with THF as eluent operating at 40°C was employed.

### *Synthesis of (3aR,7aS)-2-ethyl-3a,4,7,7a-tetrahydro-1H-4,7-epoxyisoindole-1,3(2H)-dione (M4)*

*exo*-3,6-Epoxy-1,2,3,6-tetrahydrophthalic anhydride (1.66 g, 10.0 mmol) was suspended in MeOH/THF (1:1 v/v, 12.0 mL) and the mixture cooled to 0°C. A solution of ethylamine (0.66 mL, 10.0 mmol) in 2.0 mL of MeOH/THF (1:1 v/v) was added dropwise over 30 min. The solution was then stirred at 0°C for 30 min. and then for an additional 30 min. at room temperature. After the dropwise addition of hexamethyldisilazane (2.5 mL, 12.0 mmol), the reaction solution was heated to 65°C and refluxed for 72 h. After cooling to room temperature, the solvent was removed *in vacuo* and the resulting yellow residue was then dissolved in $CH_2Cl_2$. The organic phase was washed successively with sat. $NaHCO_3$, 2.0 M HCl and brine prior to being dried over $MgSO_4$. After filtering, the solvent was removed *in vacuo* giving an off-white solid that was recrystallized from $Et_2O$ to give the target compound as a white crystalline solid (1.5 g, 80% yield). $^1$H NMR (300 MHz, $CDCl_3$, ppm): δ = 1.19 (t, J = 7.2 Hz, 3H), 2.86 (s, 2H), 3.56 (q, J = 7.2 Hz, 2H), 5.30 (t, J = 1 Hz, 2H), 6.54 (t, J = 1 Hz, 2H). $^{13}$C NMR (75 MHz, $CDCl_3$, ppm): δ = 12.93, 33.91, 47.44, 80.89, 136.56, 176.10; HRMS: calcd. for $C_{10}H_{11}NO_3$ [M + $H^{+\bullet}$]: 194.208, found: 194.0812.

### *Synthesis of (3aR,7aS)-2-(prop-2-yn-1-yl)-3a,4,7,7a-tetrahydro-1H-4,7-epoxyisoindole-1,3(2H)-dione (2)*

*exo*-3,6-Epoxy-1,2,3,6-tetrahydrophthalic anhydride (16.6 g, 100 mmol) was suspended in MeOH/THF (1:1 v/v, 120 mL) and the mixture cooled to 0°C. A solution of propargylamine (6.4 mL, 100 mmol) in 20 mL of MeOH/THF (1:1 v/v) was then added dropwise over 30 min. The resulting solution was stirred at 0°C for 30 min. and then for an additional 30 min. at room temperature. After the dropwise addition of hexamethyldisilazane (25.0 mL, 120 mmol), the reaction solution was heated to 65°C and refluxed for 72 h. After cooling to room temperature, the solvent was removed *in vacuo*



and the resulting orange residue was then dissolved in $CH_2Cl_2$. The organic phase was washed successively with saturated $NaHCO_3$, 2.0 M HCl, brine and then was then dried over $MgSO_4$. After filtration the solvent was removed *in vacuo* yielding an off-white solid that was purified by recrystallization from acetone giving the target compound as a white solid. Yield: 89 %.

***Synthesis of (3a*R*,7a*S*)-2-(pent-4-yn-1-yl)-3a,4,7,7a-tetrahydro-1*H*-4,7-epoxyisoindole-1,3(2*H*)-dione (3)***

*exo*-3,6-Epoxy-1,2,3,6-tetrahydrophthalic anhydride (1.66 g, 10 mmol) was suspended in MeOH/THF (1:1 v/v, 12 mL) and the mixture cooled to 0°C. A solution of pentyn-1-amine (0.97 mL, 10 mmol) in 2.0 mL of MeOH/THF (1:1 v/v) was added dropwise over 30 min. The solution was stirred at 0°C for 30 min. and then for an additional 30 min. at room temperature. After the dropwise addition of hexamethyldisilazane (2.5 mL, 12.0 mmol) the reaction was heated to 65°C and then refluxed for 72 h. After cooling, the solvent was removed *in* vacuo and the orange residue dissolved in $CH_2Cl_2$. The organic phase was washed successively with sat. $NaHCO_3$, 2.0 M HCl, brine and then dried over $MgSO_4$. After filtration, the solvent was removed *in vacuo* to give an off-white solid that was purified by recrystallization from acetone to give **3** as a white solid (1.64 g, 71% yield). $^1$H NMR (300MHz, $CDCl_3$, ppm): δ = 1.82 (pentet, J = 7Hz, 2H), 1.97 (t, J = 2.5Hz, 1H), 2.19 (td, $J_1$ = 7Hz, $J_2$ = 2.5Hz, 2H), 2.84 (s, 2H), 3.59 (t, J = 7Hz, 2H), 5.27 (t, J = 1 Hz, 2H), 6.51 (t, J = 1 Hz, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$ , ppm): δ = 16.08, 26.36, 38.06, 47.41, 69.00, 80.94, 82.96, 136.54, 176.20; HRMS: calcd. for $C_{13}H_{13}NO_3$ [M + $Na^{+\bullet}$]: 254.0788, found: 254.0792.

***Synthesis of (3a*R*,7a*S*)-2-(3-(trimethylsilyl)prop-2-yn-1-yl)-3a,4,7,7a-tetrahydro-1*H*-4,7-epoxyisoindole-1,3(2*H*)-dione (M1)***

**2** was converted to the corresponding trimethylsilyl-protected alkyne derivative as follows:

**2** (18.08 g, 89 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (17.3 mL, 116 mmol) and AgCl (1.28 g, 9.0 mmol) were suspended in 180 mL of anhydrous distilled $CH_2Cl_2$ and the mixture heated to 40°C. Chlorotrimethylsilane (11.3 mL, 89 mmol) was then added dropwise over a period of 10 min. after which the resulting solution was left to stir for 24 h. at 40°C. The crude reaction mixture was washed successively with sat. $NaHCO_3$, 2.0 M HCl and brine before the organic layer was dried over anhydrous $MgSO_4$. Filtration and removal of the solvent *in vacuo* gave an off-white residue that was purified by flash chromatography ($SiO_2$, $CHCl_3$/EtOAc 1:1, $R_f$ = 0.55). The target compound, **5**, was obtained as a white crystalline solid (18.1 g, 74% yield). $^1$H NMR (300 MHz, $CDCl_3$, ppm): δ = 0.12 (s, 9H), 2.88 (s, 2H), 4.21 (s, 2H), 5.27 (t, J = 1 Hz, 2H), 6.50 (t, J = 1 Hz, 2H); $^{13}$C NMR (75 MHz, $(CD_3)_2SO$, ppm): δ = 0.20, 28.67, 47.73, 80.83, 87.28, 100.16, 136.99, 175.78; LRMS: calcd. for $C_{14}H_{17}NO_3Si$ [M + $H^+$]: 298.37, found: 298.3. IR (neat), $cm^{-1}$: υ = 2951, 2178, 1700, 1425, 1391, 1326, 1249, 1180, 1155, 1008, 959, 918, 839, 803, 760, 720.

***Synthesis of (3a*R*,7a*S*)-2-(5-(trimethylsilyl)pent-4-yn-1-yl)-3a,4,7,7a-tetrahydro-1*H*-4,7-epoxyisoindole-1,3(2*H*)-dione (M2)***

**3** was converted to the corresponding trimethylsilyl-protected alkyne derivative as follows:

**3** (1.64 g, 7.1 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (1.38 mL, 9.2 mmol) and AgCl (0.1 g, 0.7 mmol) were suspended in 15.0 mL of anhydrous distilled $CH_2Cl_2$ and the mixture heated to 40°C. Chlorotrimethylsilane (0.90 mL, 7.1 mmol) was added dropwise and the resulting solution left to stir for 24 h. at 40°C. The crude reaction mixture was washed successively with sat. $NaHCO_3$, 2.0 M HCl and brine before the organic layer was dried over anhydrous $MgSO_4$. Removal of the solvent *in vacuo* furnished an off-white solid that was purified by flash chromatography ($SiO_2$, $CHCl_3$/EtOAc 1:1, $R_f$ = 0.65). The target compound, **6**, was obtained as a white crystalline solid (1.90 g, 88% yield). $^1$H NMR (300 MHz, $CDCl_3$, ppm): δ = 0.10 (s, 9H), 1.30 (t, J = 6.5 Hz, 1H), 1.84 (pentet, J = 7.5 Hz, 2H), 2.26 (t, J = 7.5 Hz, 2H), 2.86 (s, 2H), 3.60 (t, J = 7.5 Hz, 2H), 5.30 (t, J = 1 Hz, 2H), 6.55 (t, J = 1 Hz, 2H).

***Synthesis of benzylazide***

$NaN_3$ (1.0 g, 15.3 mmol) was added to a glass vial equipped with a magnetic stir bar. To this was added a 1:1 mixture of acetone and water (25 mL). Benzyl bromide (0.525 g, 3.1 mmol, 0.2 eq) was added drop wise and the mixture stirred at room temperature for 24 h. The crude product was extracted with $CH_2Cl_2$ (2 x 25 mL) and the combined organic layers were dried over $MgSO_4$. After filtration, the solvent was removed *in vacuo* yielding the crude product that was purified by flash chromatography ($SiO_2$, petroleum spirits/ethyl acetate 3:2 $R_f$ = 0.47). Benzylazide was obtained as a light yellow oil (0.36 g, 90% yield). $^1$H NMR (300 MHz, $CDCl_3$, ppm): δ = 4.39 (s, 2H), 7.42 (m, 5H); $^{13}$C NMR (75 MHz, $CDCl_3$, ppm): δ = 52.0, 127.1, 138.7.

***Ring opening metathesis homopolymerization***

Below is given a typical procedure for the homopolymerization of (3a*R*,7a*S*)-2-(3-(trimethylsilyl)prop-2-yn-1-yl)-3a,4,7,7a-tetrahydro-1*H*-4,7-epoxyisoindole-1,3(2*H*)-dione (**M1**). An identical procedure was adopted for all other relevant homopolymerizations.

To a glass vial (25.0 mL capacity) equipped with a magnetic stir bar was added **M1** (0.5 g, 1.82 mmol). Grubbs' first generation initiator ($RuCl_2(PCy_3)_2CHPh$, 0.05 mmol for a target molecular weight of 10,000) was added to a second vial. Both vials were capped with a rubber septum and their head-space thoroughly sparged with $N_2$. $CH_2Cl_2$ (1.0 mL, $N_2$ sparged) was then added to each vial via cannula. The initiator solution was then transferred directly into the stirred monomer solution via cannula and the polymerization allowed to proceed for 60 min. The polymerization was quenched with ethyl vinyl ether (1.0 mL) and left to stir for 30 min. before the polymer was isolated by precipitation into a large excess of hexane. Following

Buchner filtration and washing with hexane the polymer was dried *in vacuo*.

***Statistical ROMP copolymerization***

Below is given the procedure for the statistical ROMP copolymerization of (3a*R*,7a*S*)-2-(5-(trimethylsilyl)pent-4-yn-1-yl)-3a,4,7,7a-tetrahydro-1*H*-4,7-epoxyisoindole-1,3(2*H*)-dione (**M2**) with (3a*R*,7a*S*)-2-ethyl-3a,4,7,7a-tetrahydro-1*H*-4,7-epoxyisoindole-1,3(2*H*)-dione (**M4**). This general procedure was adopted for other statistical copolymer syntheses.

**M4** (0.45 g, 2.33 mmol, 90 mol%) and **M2** (0.079 g, 0.26 mmol, 10 mol%) were added to a glass vial (25.0 mL capacity) equipped with a magnetic stir bar. Grubbs' first generation initiator ($RuCl_2(PCy_3)_2CHPh$) (0.053 mmol for a target molecular weight of 10,000) was added to a second glass vial. Both vials were capped with a rubber septum and their head-space sparged with $N_2$. $CH_2Cl_2$ (1.0 mL, $N_2$ sparged) was then added to each vial via cannula. The initiator solution was then transferred directly into the stirred monomer solution via cannula and the polymerization allowed to proceed for 60 min. The polymerization was quenched with ethyl vinyl ether (1.0 mL) and left to stir for 30 min. before the polymer was isolated by precipitation into a large excess of hexane. Following Buchner filtration and washing with hexane the polymer was dried *in vacuo*.

***Removal of trimethylsilyl protecting group***

The removal of the trimethylsilyl protecting group from the 80:20 **M3**:**M1** statistical copolymer is described below. This deprotection strategy was applied to all other trimethylsilyl-protected alkynes.

The **M3**:**M1** copolymer (1.0 g, 0.86 mmol with respect to the protected alkyne group) was added to a glass vial equipped with a magnetic stir bar. The vial was capped with a rubber septum and then purged with $N_2$. Anhydrous degassed THF (2.0 mL) and glacial acetic acid (1.5 eq., 1.29 mmol) diluted in THF (2.0 mL) were added to the reaction vial via cannula. The reaction vial was cooled to 0°C and 1.0 M tetra-*n*-butylammonium fluoride in THF (1.29 mL, 1.29 mmol) was added dropwise over a period of 5 min. The solution was stirred at 0°C for 30 min., warmed to room temperature and then stirred for a further 30 min. The deprotected copolymer was isolated by precipitation into excess water, collected by Buchner filtration, washed and freeze dried.

***Cu(I)-catalyzed alkyne azide coupling***

The CuAAC coupling of benzyl azide is described below. The approach was also adapted for azido-2-deoxy-2-glucose.

Deprotected copolymer (0.20 g, 0.184 mmol with respect to free alkyne functionality) and CuI (7.0 mg, 0.037 mmol) were added to a glass vial equipped with a magnetic stir bar. The vial was sealed with a rubber septum and purged benzylazide (29.4 mg, 0.221 mmol, 1.2 eq.) diluted in purged THF (4.0 mL) was transferred into the polymer-CuI mixture via cannula. The solution was then heated to 65°C for 2h. The modified copolymer was isolated by precipitation into excess hexane, recovered by Buchner filtration, washed with hexane and dried *in vacuo*.

***Sequential thiol-yne/CuAAC modification of the deprotected M4-M2 copolymer***

100 mg of the deprotected **M4**-**M2** copolymer (0.052 mmol with respect to free yne) was weighed into a quartz vial equipped with a magnetic stir bar to which was then added $CH_2Cl_2$ (2.0 mL). A stock solution of 2,2-dimethoxy-2-phenylacetophenone (DMPA) (6.68 mg, 0.026 mmol, 50 mol%,) in 2.5 mL of $CH_2Cl_2$was prepared and a 25 µL (0.5 mol%) aliquot was added to the quartz vial. A second stock solution of benzyl mercaptan (40 µL, 0.343 mmol, 660 mol%) in 2.5 mL of $CH_2Cl_2$was also prepared and a 250 µL (66 mol%) aliquot was added. The vial was capped with a rubber septum, thoroughly sparged with $N_2$ and loaded into a Rayonet RPR-200 photoreactor where it was irradiated with UV light (253.7nm, $1.65x10^{16}$ photons/sec/$cm^3$) under stirring for 30 min. The product was precipitated in $Et_2O$, centrifuged and dried *in vacuo* to yield the 33% modified substrate. 50 mg of the partially modified substrate (0.0174 mmol with respect to the alkyne) and ca. 0.1 mg of CuI (0.0005 mmol, 3 mol%) were weighed into a glass vial equipped with a magnetic stirrer bar. THF (1.0 mL) was transferred into the vial before capping with a rubber septum and thoroughly sparging with $N_2$. A stock solution of benzyl azide (34.8 mg, 0.262 mmol, 1500 mol%) in 10 mL of purged THF was prepared and a 1.0 mL aliquot (0.0262 mmol, 150 mol%) was cannulared into the reaction vial. The vial was heated at 65°C for 4 h, at which point the polymer was precipitated into excess $Et_2O$, centrifuged and dried *in vacuo* to yield the fully modified product.

***Optimized UV thiol-yne reaction***

Deprotected copolymer (0.1 g, 0.05 mmol with respect to alkyne) was added to a quartz vial equipped with a magnetic stir bar. This was dissolved in benzene (2.0 mL) and the vial capped with a rubber septum. A stock solution of DMPA (6.4 mg, 0.025 mmol, 50 mol%) in 2.5 mL of benzene was prepared and a 25 µL (0.5 mol%) aliquot injected into the vial. Benzyl mercaptan (12.9 µL, 0.11 mmol, 2.2 eq.) was also injected by syringe and the vial inserted into a Rayonet RPR-200 photochemical reactor. The sample was irradiated for 10 min. at 235.7 nm. The product was isolated by precipitation into an excess of hexane, recovered by Buchner filtration, washed with hexane and then dried *in vacuo*.

## Results and Discussion

We have recently been investigating novel approaches for combining ROMP with thiol-ene chemistry.[64-68] Extending these studies we decided to examine approaches for incorporating alkyne functional groups into ROMP-prepared (co)polymers that could be exploited in radical thiol-yne and CuAAC reactions.

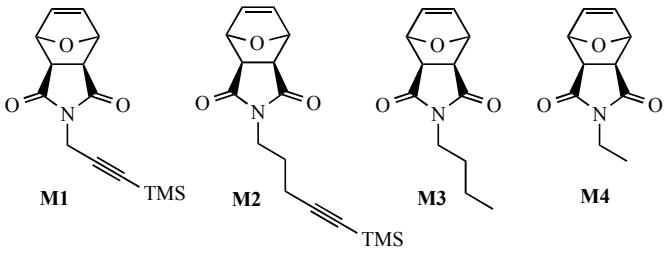



Figure 1. Chemical structures of (3a*R*,7a*S*)-2-(3-(trimethylsilyl)prop-2-yn-1-yl)-3a,4,7,7a-tetrahydro-1*H*-4,7-epoxyisoindole-1,3(2*H*)-dione (**M1**), (3a*R*,7a*S*)-2-(5-(trimethylsilyl)pent-4-yn-1-yl)-3a,4,7,7a-tetrahydro-1*H*-4,7-epoxyisoindole-1,3(2*H*)-dione (**M2**), (3a*R*,7a*S*)-2-butyl-3a,4,7,7a-tetrahydro-1*H*-4,7-epoxyisoindole-1,3(2*H*)-dione (**M3**) and (3a*R*,7a*S*)-2-ethyl-3a,4,7,7a-tetrahydro-1H-4,7-epoxyisoindole-1,3(2H)-dione (**M4**).

Initially, we prepared **2** ((3a*R*,7a*S*)-2-(prop-2-yn-1-yl)-3a,4,7,7a-tetrahydro-1*H*-4,7-epoxyisoindole-1,3(2*H*)-dione) and then converted it to the TMS-protected species **M1**, Figure 1. The TMS species was prepared since repeated attempts to induce homopolymerization of the free alkyne monomer with Grubbs' first generation catalyst (G1), $RuCl_2(PCy_3)_2CHPh$, were unsuccessful. This is in contrast to a report from Binder and Kluger who prepared **2**, although it was synthesized via a different route to the one reported herein,[69] and reported its direct ROMP with G1. However, polymerization was not controlled with resulting $Đ_M$'s = 1.5-1.8. The poor polymerization control was attributed to poisoning of the G1 initiator by the free yne group.

As far as we are aware this is the first example of a TMS-alkyne *exo*-7-oxanorbornene monomer although TMS-protected alkyne norbornene monomers are known.[70] Previously, we briefly noted its use in the preparation of a single example of a sugar-based AB diblock copolymer[64] although at the time did not evaluate its basic polymerization features. Given this, we initially evaluated the basic homopolymerization characteristics of **M1** employing the G1 ROMP initiator. Figure 2 shows the kinetic and evolution of molecular weight plots for the homopolymerization of **M1** for a target $\overline{M}_n$ of 10,000 at quantitative monomer conversion.

The homopolymerization of **M1** proceeds to near quantitative conversion and exhibits an essentially linear pseudo first order kinetic plot (Figure 2A) from which an apparent $k_p$ of 0.169 $s^{-1}$ can be calculated. This value is consistent with other *exo*-7-oxanorbornene monomers polymerized with G1 under similar conditions.[64, 71-73] The evolution of molecular weight, as determined by end group analysis via $^1$H NMR spectroscopy, is also essentially linear although does indicate slightly higher than expected values at low conversions. In all instances the $Đ_M$ values are low and remain ≤ 1.15. Closer inspection of the kinetic data indicates a negative deviation signifying gradual deactivation of the active species in the latter stages of polymerization. However, the first indication of downward curvature does not occur until ca. 90% monomer conversion. So, while the TMS group is effective in shielding the G1 initiator from competing, deactivating-type, reactions under monomer starved conditions associated with the alkyne functional group it appears these undesirable reactions cannot be completely suppressed. These results indicate that while **M1** can be effectively (co)polymerized it should be polymerized second in block copolymer syntheses or, if polymerized first, the second monomer should be added before 90% conversion of **M1** giving a slightly tapered species.

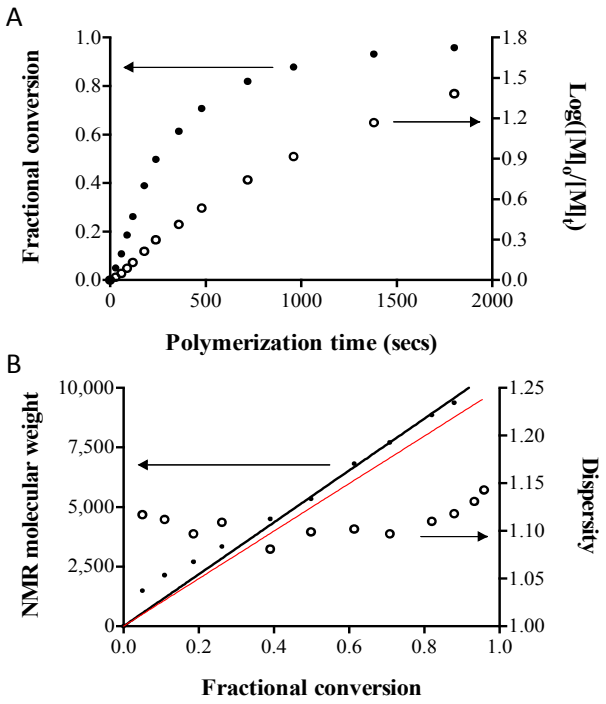



Figure 2. (A) Fractional conversion and pseudo first order kinetic plot and (B) evolution of molecular weight, as determined by NMR spectroscopy, and dispersity, as determined by SEC, for the homopolymerization of **M1** with $RuCl_2(PCy_3)_2CHPh$ in $CH_2Cl_2$ at ambient temperature.

Having demonstrated that **M1** can be homopolymerised in a near ideal fashion under standard ROMP conditions we next prepared a statistical copolymer of **M1** with **M3** with a target molar composition of 80:20 **M3**:**M1** and theoretical $\overline{M}_n$ of 10,000 at quantitative conversion. $^1$H NMR analysis revealed a composition essentially identical to the target ratio and an absolute $\overline{M}_n$ of 10,400. SEC analysis revealed a symmetric, unimodal molecular weight distribution with a measured $Đ_M$ of 1.11, Figure 3A and C.

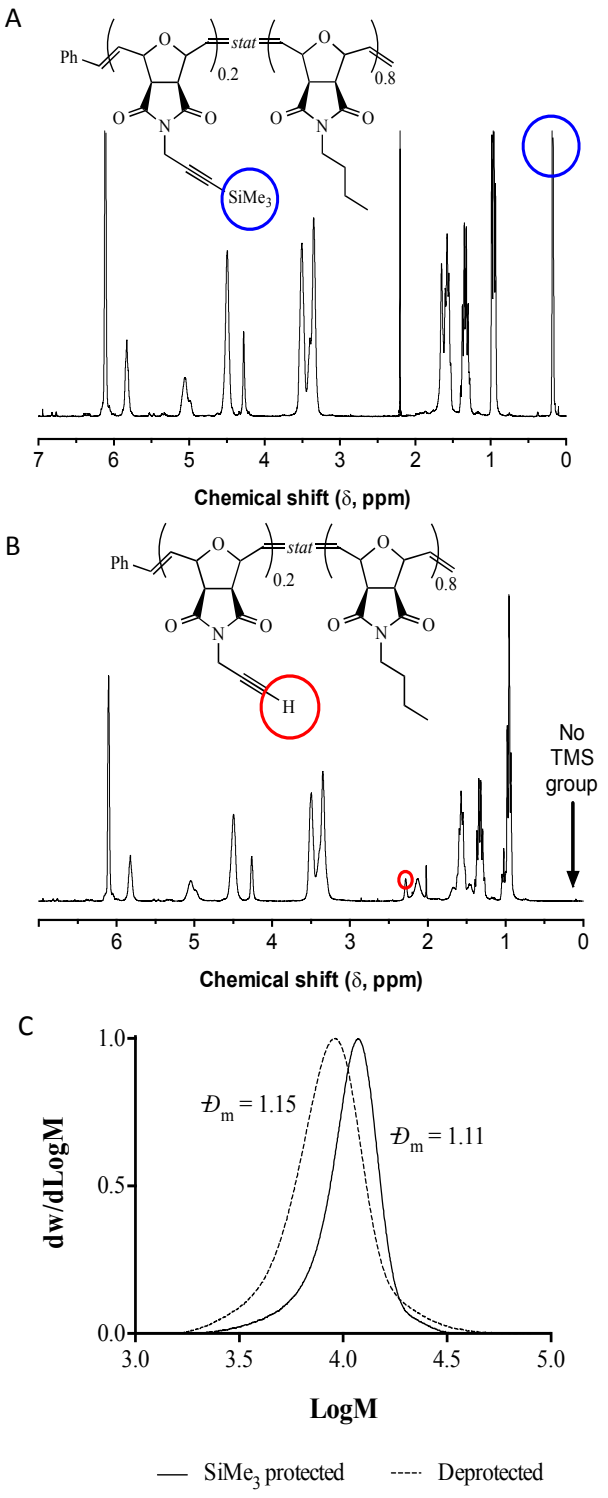
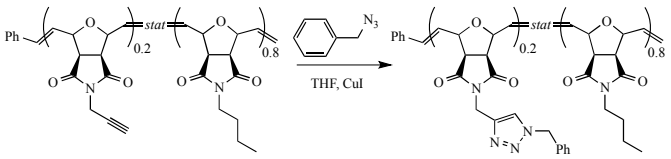



Figure 3. (A) $^1$H NMR spectrum, recorded in $CDCl_3$, of the precursor statistical **M1**:**M3** copolymer highlighting the presence of the trimethylsilyl protecting groups, (B) $^1$H NMR spectrum, recorded in $CDCl_3$, of the same statistical **M1**:**M3** copolymer after treatment with $Bu_4NF$ to removing the protecting groups, and (C) the molecular weight distributions for the statistical copolymer before and after removal of the trimethylsilyl protecting groups.

With the well-defined nature of the **M3**:**M1** copolymer confirmed, the copolymer was reacted with $Bu_4NF$ to remove the trimethylsilyl protecting groups and liberate free alkyne functional groups. Figure 3B shows the $^1$H NMR spectrum of the deprotected copolymer. The complete disappearance of the trimethylsilyl signal coupled with the appearance of the –CH resonance at ca. δ = 2.3 ppm, associated with the free alkyne, confirm quantitative deprotection. SEC analysis of the deprotected copolymer indicated the expected decrease in molecular weight after removal of the TMS group coupled with a slight increase in $Đ_M$ to 1.15, Figure 3C.

The primary motivation for preparing this copolymer was to evaluate the ability to perform highly efficient coupling reactions on the liberated free yne groups. When considering radical thiol-yne reactions on a ROMP (co)polymer containing free alkyne groups there are two important considerations. As noted above, we have previously reported the ability to quantitatively modify the *ene* groups in a ROMP polymer *backbone* via radical-mediated thiol-ene chemistry. Therefore, one important consideration is whether it is possible to *selectively* modify yne side groups while leaving the backbone internal enes intact under radical-mediated conditions. Secondly, it is well known that radical-based thiol reactions on enes or ynes in side groups can result in non-quantitative conversion and or the occurrence of undesirable side reactions especially at higher concentrations of the reactive pendent groups. In particular, cyclization and crosslinking reactions can be problematic.[9, 74, 75] The initial 80:20 **M3**:**M1** statistical copolymer was targeted specifically to address this second issue while selectivity was addressed in terms of reaction conditions based on the anticipated difference in reactivity of internal backbone enes versus pendent terminal yne functional groups.

However, since the CuAAC reaction is still the benchmark 'click' reaction we initially evaluated the reaction of the 80:20 **M3**:**M1** copolymer with benzylazide to confirm the general availability of the pendent yne groups for chemical modification, Scheme 1.




Scheme 1. Modification of the free alkyne groups in the M3:M1 statistical copolymer with benzylazide, catalysed by CuI in THF

Figure 4A shows the $^1$H NMR spectrum for the product obtained from the above reaction. The complete disappearance of the alkyne signal at δ = ~2.25 ppm coupled with the stoichiometric increases of aromatic and triazole signals (δ = 7.35 and 7.90 respectively) indicate successful and quantitative reaction. This was reinforced by 2 dimensional HSQC and HMBC NMR spectroscopic measurements. Both the short (1 bond) and long (2-3 bond) carbon-proton interactions were

entirely consistent with the expected structure. As an example, the HMBC spectrum, with diagnostic long-range triazole C-H coupling is shown in Figure 4B.

It is also important that the post-modification process not disrupt the well-defined structure of the parent copolymer. SEC analysis of the free alkyne copolymer before and after reaction with benzylazide indicated little-to-no change in the shape or dispersity associated with the molecular weight distribution.

Having demonstrated that the free pendent yne groups in the **M3**:**M1** copolymer are available for reaction we next examined the possibility of performing radical thiol-yne modification of the side groups. As noted, while we have previously demonstrated that backbone 'enes' can be hydrothiolated under radical conditions we anticipated a sufficient difference in reactivity between these enes and the pendent ynes to allow for selective modification. As terminal species, the yne groups are significantly more accessible and reactive compared to the internal backbone enes[76] and given that internal enes are also susceptible to a *cis*/*trans* isomerization process in the presence of thiyl radicals,[77-79] further lower their reactivity, it was hoped these features would mitigate the relative lower abundance of the pendent yne groups allowing for selective hydrothiolation. Additionally, we reported previously that while quantitative hydrothiolation of the internal backbone enes could be accomplished with a wide range of thiols, quantitative reaction required extended reaction times of ca. 60 h.[67] Initial thiol-yne reactions with the **M3**:**M1** copolymer were performed with benzyl mercaptan in benzene in the presence of 0.5 mol% photoinitiator (DMPA) with a slight excess of thiol and employing an irradiation time of 30 min. at 235.7 nm.

Figure 5A shows the $^1$H NMR spectrum of the product obtained after a 30 min. irradiation time. Under these conditions we do observe selective hydrothiolation of the pendent yne groups vs. the backbone enes. The presence of the aromatic groups associated with benzyl mercaptan are clearly visible at ca. $\delta$ = 7.4 ppm (highlighted in blue) but we also observe residual yne groups (highlighted in red). The integrals of either of these signals with the backbone enes (highlighted in green) indicate a degree of modification of ca. 25 %. A ratio of the backbone enes with the pendent allylic species at $\delta$ = 4.50 and 5.05 ppm confirm the backbone enes remain unchanged. This result clearly suggests that selective hydrothiolation is possible although is non-quantitative under these specific conditions. We next extended the reaction time to 5 h – still well below the time required to effect quantitative hydrothiolation of the backbone C=C bonds. Figure 5B shows the $^1$H NMR spectrum of the product. While the absence of any detectable yne suggests effective double hydrothiolation we also observe a significant decrease in the intensity of the backbone enes and a larger then expected signal associated with the aromatic groups due to competing backbone hydrothiolation. Even after further optimisation of the reaction conditions we were unable to achieve the desired selectivity between the backbone enes and pendent yne groups in the **M3**:**M1** copolymer with best results indicating ca. 50% modification of the yne groups prior to the occurrence of undesirable backbone reactions.

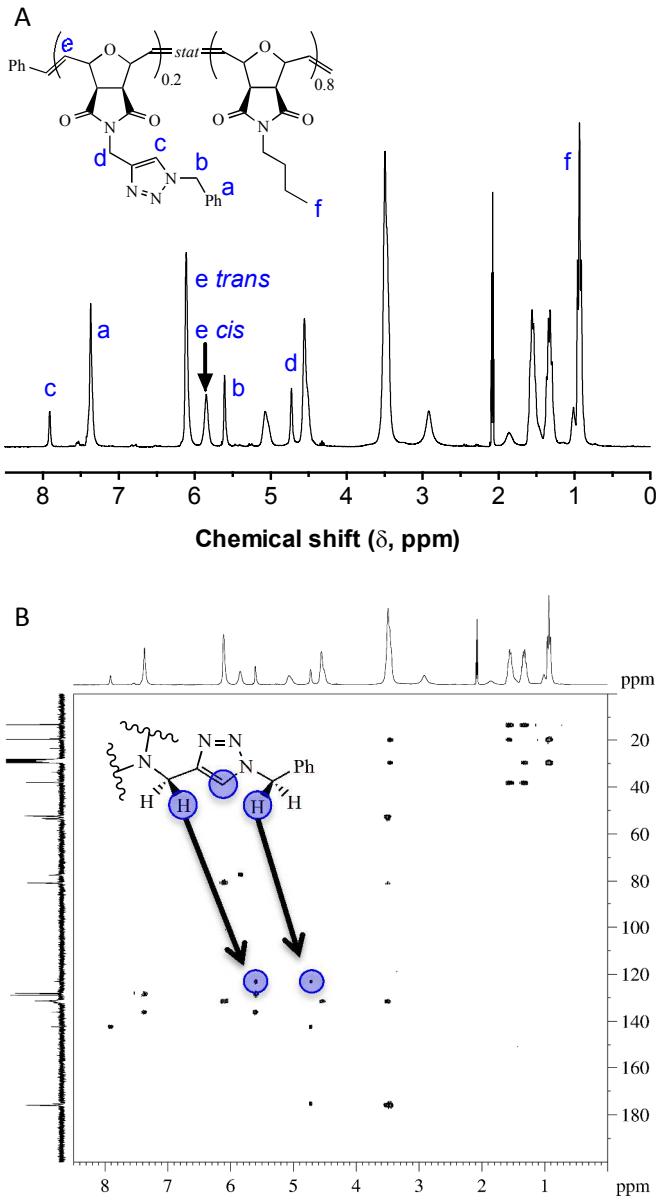



Figure 4. (A) $^1$H NMR spectrum, recorded in $d_6$-acetone, of the benzyltriazole adduct obtained from the reaction of the **M3**:**M1** copolymer with benzylazide under Cu catalysis, and (B) the HMBC spectrum of the same triazole adduct highlighting the long C-H interactions due to successful triazole formation.

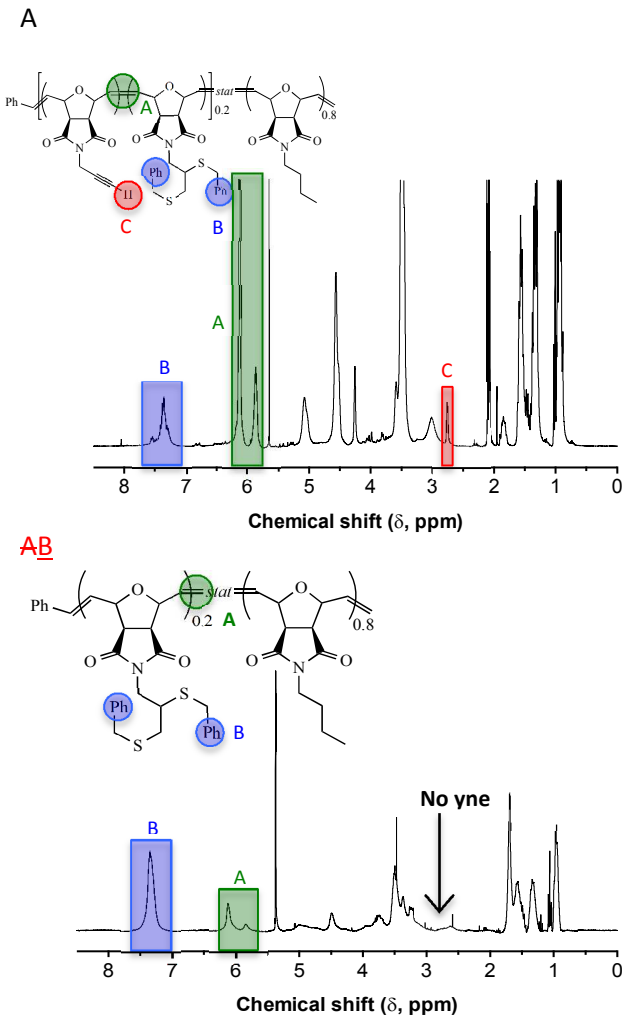



Figure 5. (A) $^1$H NMR spectrum, recorded in $d_6$-acetone, of the product obtained after the treatment of the **M3**:**M1** copolymer with benzyl mercaptan for 30 min and (B) $^1$H NMR spectrum, recorded in $CD_2Cl_2$, of the product obtained after the treatment of the same **M3**:**M1** copolymer with benzyl mercaptan for 5 h.

It was hypothesized that steric hindrance may be a contributing factor to the observed non-selective hydrothiolation reactions and to address this two additional monomers, **M2** and **M4** Figure 1, were prepared. **M2** was prepared giving a monomer with a longer alkyl spacer between the TMS-protected alkyne and the imide group while **M4** was synthesized to give a monomer that would impart reduced steric congestion about the pendent yne group when incorporated in a copolymer with **M4**. A parent **M4**:**M2** copolymer (target $\bar{M}_n$ = 10,000; target composition: 90:10) was prepared (absolute $\bar{M}_n$ as judged by $^1$H NMR end-group analysis = 10,500) and the TMS protecting group subsequently removed in the same fashion as the **M3**:**M1** copolymer ($\bar{M}_{n,NMR}$ = 10,150; $\bar{M}_{n,SEC}$ = 20,100; $Đ_M$ = 1.20).

With the free-yne **M4-M2** statistical copolymer in hand we next examined the radical thiol-yne reaction of the pendent yne groups with benzyl mercaptan. Since previous experiments with the **M3**:**M1** statistical copolymer suggested an optimum reaction time of ca. 2.5 h (although this was not wholly selective in its product distribution it did give the best ratio of desired thiol-yne vs. thiol-ene hydrothiolation products) we initially examined the same conditions for the **M4-M2** copolymer. Interestingly, the 2.5 h. reaction time yielded a product not dissimilar to that obtained for the **M3**:**M1** copolymer after 5 h., *i.e.* complete consumption of the pendent yne groups but also significant reaction of the internal backbone enes. Since the **M4**:**M2** copolymer appeared to undergo hydrothiolation much more rapidly than the **M3**:**M1** (even though it contained fewer yne groups) we examined the reaction at significantly shorter reaction times, starting with 2, 5, 10 and 20 min. Figure 6 shows a waterfall plot of $^1$H NMR spectra recorded for the products obtained from the reaction of the **M4**:**M2** copolymer with benzyl mercaptan over this time span with peaks normalized to the backbone ene signals.

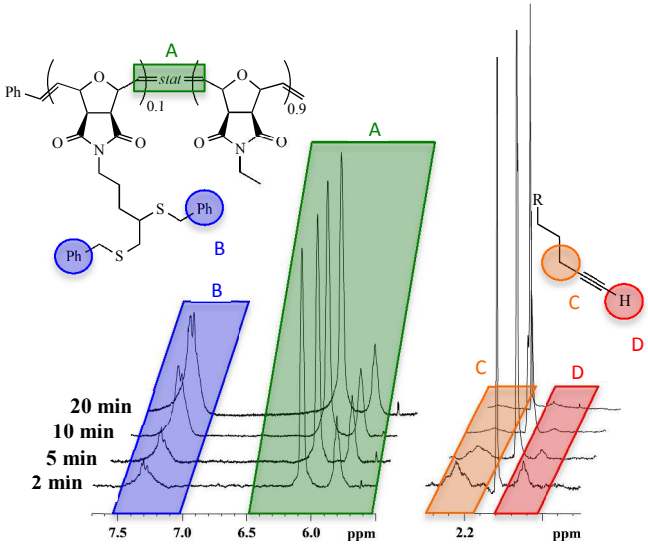
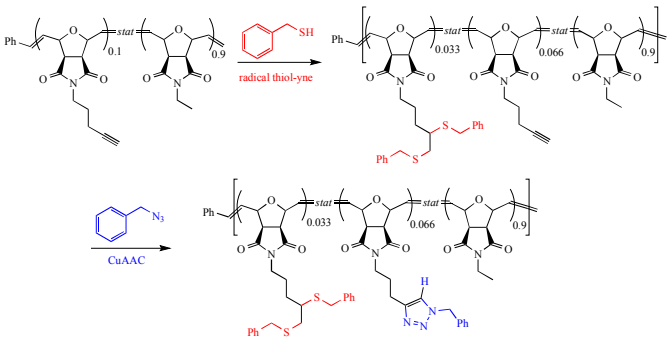



Figure 6. A series of stacked $^1$H NMR spectra, recorded in $CD_2Cl_2$, for the products obtained from the reaction of poly(**M4**-*stat*-**M2**) with benzyl mercaptan highlighting the selective hydrothiolation of the pendent yne functional groups versus the internal backbone C=C bonds.

Interestingly, the data in Figure 6 indicates a significantly enhanced reactivity of the pendent yne groups in the **M4**:**M2** copolymer versus the **M3**:**M1** species suggesting that steric hindrance was, at least in part, responsible for the observed hydrothiolation results associated with the **M3**:**M1** copolymer. A comparison of the integrals associated with the yne and aromatic resonances indicates a rapid reaction with 43, 57 and 91 % consumption of the yne groups after 2, 5 and 10 min respectively (with no apparent competing backbone hydrothiolation). After 20 min reaction the yne groups are completely consumed while the aromatic integral was slightly larger than expected implying the possible onset of competing backbone addition. However, these results clearly show that with the **M4** and **M2** building blocks selective side group

functionalization is achievable while leaving the backbone ene groups largely, if not completely, intact.

To demonstrate the complimentary nature of the thiol-yne and CuAAC reactions we next examined the possibility of performing consecutive thiol-yne/CuAAC reactions[80] on the **M4**-**M2** copolymer, Scheme 2, an alternative, for example, to sequential CuAAC reactions on yne-containing (co)polymers such as those reported by Cooper and Emrick.[81]




Scheme 2. Sequential radical thiol-yne and Cu-mediated alkyne-azide coupling reactions in the post-polymerisation modification of the **M4**-**M2** statistical copolymer with benzyl mercaptan and benzyl azide respectively.

In the first step, the **M4**-**M2** copolymer was reacted with benzyl mercaptan under radical conditions to effect a thiol-yne reaction. Stoichiometry and reaction time was controlled to limit conversion of the yne groups. Figure 7 shows a waterfall plot of three $^1$H NMR spectra plotted between δ = 8.0 and 5.2 ppm and highlights the change in the aromatic region of the parent **M4**-**M2** copolymer (black spectra) after sequential thiol-yne (red spectra) and Cu-mediated benzyl azide coupling (blue spectra). In the parent homopolymer we do observe a very small signal at ca. δ = 7.4 ppm that is associated with the Ph end group derived from G1 during its synthesis. After reaction with benzyl mercaptan under radical mediated conditions we observe an increase in the aromatic region associated with successful thiol-yne addition (signal labelled A). A comparison of the integral of this signal with that associated with the residual yne (not shown, or the $CH_2$ group in the pendent side chain α to the free yne, also not shown) indicates that ca. 33% of the free yne groups have been modified (this corresponds to just over 3% of all pendent groups in the copolymer).

The thiol-yne reaction was followed by a Cu-mediated coupling of the residual yne groups with benzylazide. Three key features, highlighted, in the $^1$H NMR in Figure 7 confirm successful triazole formation. We see a further increase in the aromatic signals at δ = ca. 7.35 (labelled D) associated with the introduction of additional Ph groups from benzyl azide although the integral value of this resonance is slightly higher than expected. Additionally, we observe two new signals, labelled B and C, at δ = ca. 7.75 and 5.6 ppm respectively. These are specifically associated with the triazole and are entirely consistent with the signals labelled C and B in Figure 4A. After the CuAAC reaction there is no evidence of remaining yne groups. We also note, that in all instances we observed no detectable change in the signals associated with the backbone-ene functional groups further highlighting the selectivity of this approach. Importantly, the SEC traces of the parent and modified copolymers are essentially unchanged after sequential modification. Chromatograms remain symmetric and unimodal although a slight increase in the dispersity is observed after the first thiol-yne modification step.

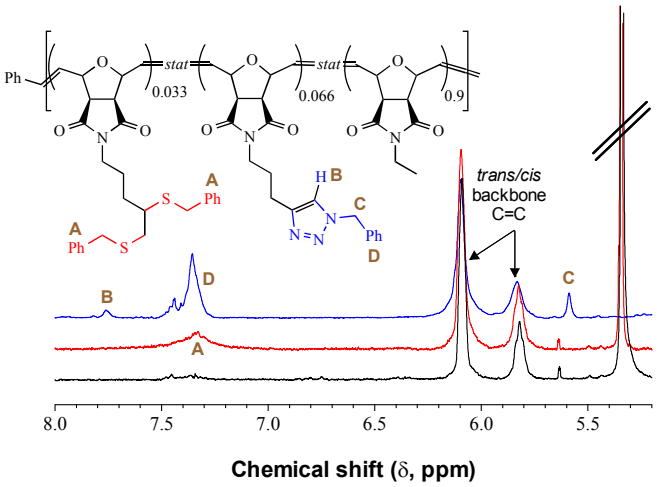



Figure 7. A waterfall plot of $^1$H NMR spectra, recorded in $CD_2Cl_2$ (black and red) and $d_6$-acetone (blue), plotted between δ = 8.0 and 5.2 ppm (normalized to the backbone *trans/cis* ene resonances between δ = ca. 5.75 and 6.15 ppm) highlighting the change in the aromatic region after sequential radical thiol-yne reactions with benzyl mercaptan and Cu-mediated triazole formation with benzyl azide.

The ability to conduct simultaneous or sequential thiol-yne reactions with 2, or more, thiols is also a plausible approach to multifunctionalization of such yne-containing copolymers. We briefly examined the sequential reaction of 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranose followed by benzyl mercaptan. $^1$H NMR analysis however proved problematic and clean, well-resolved spectra could not be obtained. However, SEC analysis qualitatively indicated successful modification, Figure 8.

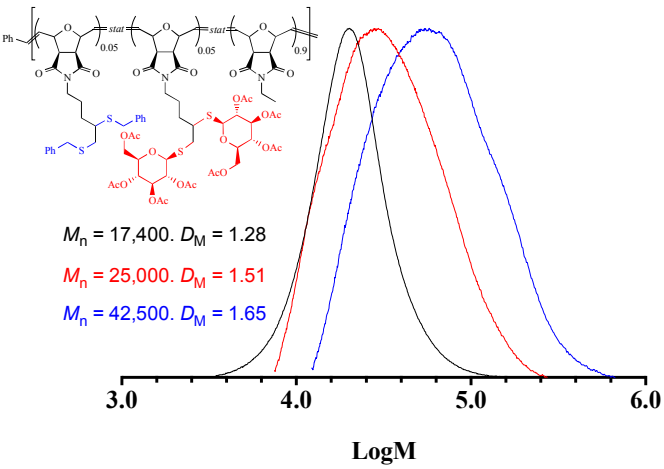


Figure 8. SEC traces for the parent **M4**-**M2** copolymer (black), the product after ca. 50% reaction of the pendent yne groups with 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranose (blue), and the product after reaction of the remaining yne groups with benzyl mercaptan under radical mediated conditions (red).

The black molecular weight distribution represents the parent **M4**-**M2** copolymer while the red distribution represents the product obtained after reaction of ca. 50 mol% of the free yne groups with the protected sugar thiol 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranose. Finally, the blue distribution is the product obtained after reaction of the remaining yne groups with benzyl mercaptan. While the distributions remain unimodal and near symmetric, in both instances we observe a noticeable increase in the dispersity that might be due to undesirable side reactions such as crosslinking although we do not have direct evidence for this as this point. While we believe this data demonstrates such thiol-yne/thiol-yne reactions are possible it is clearly not optimised and we are currently examining this process in more detail.

## Conclusions

The preparation of novel *exo*-7-oxanorbornene monomers, including examples containing trimethylsilyl (TMS)-protected alkyne groups is reported. We have demonstrated that the TMS-based monomers can be readily homo- and co-polymerized in a controlled manner employing the Grubbs' first generation initiator $RuCl_2(PCy_3)_2CHPh$. Removal of the TMS groups yields (co)polymers with free yne functional pendent groups that are amenable to reaction with azides and thiols. In a copolymer containing 20 mol% (3a*R*,7a*S*)-2-(prop-2-yn-1-yl)-3a,4,7,7a-tetrahydro-1*H*-4,7-epoxyisoindole-1,3(2*H*)-dione with 80 mol% (3a*R*,7a*S*)-2-butyl-3a,4,7,7a-tetrahydro-1*H*-4,7-epoxyiso- indole-1,3(2*H*)-dione (**M3**-**M1** copolymer) the free ynes readily underwent the CuAAC reaction with benzylazide giving the triazole derivative quantitatively as judged by NMR spectroscopy. In contrast, while amenable to radical thiol-yne modification with benzyl mercaptan the targeted selectivity between the backbone enes and pendent ynes could not be fully realized. Switching the basic parent system to a copolymer with significantly reduced steric hindrance around the free pendent yne groups and also containing a lower molar fraction of yne (**M4**-**M2** copolymer) resulted in a system in which the pendent yne groups *could* be selectively functionalized in the presence of the backbone ene groups. Additionally, we demonstrated the ability to perform sequential radical thiol-yne and CuAAC modifications on the same copolymer highlighting the complimentary nature of these two highly efficient processes. Finally, we noted preliminary observations regarding sequential thiol-yne reactions as a means of preparing novel functional materials. Qualitatively the approach seems viable although we have not identified optimized conditions at this point.

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