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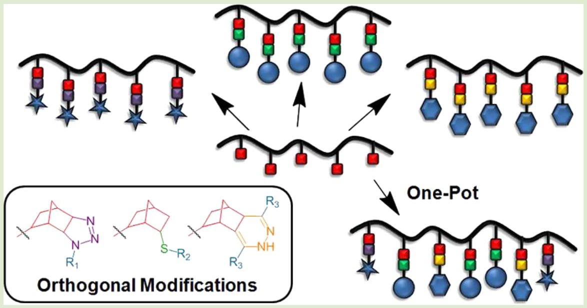
Orthogonal Modification of Norbornene-Functional Degradable Polymers

Rebecca J. Williams, Ian A. Barker, Rachel K. O'Reilly,* and Andrew P. Dove*

Department of Chemistry, University of Warwick, Gibbet Hill Road, Coventry, CV4 7AL, United Kingdom

S *Supporting Information*

ABSTRACT: Well-defined norbornene-functional poly(carbonate)s were prepared by ring-opening polymerization and utilized as multireactive polymeric scaffolds in a range of postpolymerization modifications. The norbornene-functional handles were shown to undergo facile reaction with azides via a 1,3-dipolar cycloaddition, tetrazines in the inverse electron demand Diels–Alder reaction and thiols via radical thiol-ene coupling. Furthermore, the above-mentioned chemistries were demonstrated in a sequential one-pot, three-step modification reaction illustrating the potential of these polymers as scaffolds to access multifunctionalized materials in an undemanding manner.



The design and synthesis of highly functional polymers is essential to fulfill the demands of advanced applications in materials science. Functional polymers can be prepared via two approaches: the synthesis and polymerization of specifically designed functional monomers or the postpolymerization modification of a polymer scaffold containing reactive groups. The latter of these approaches is particularly attractive as it allows the incorporation of functionalities that may be difficult to polymerize and can be used to prepare a library of functional polymers with relative ease, avoiding the need to optimize multiple monomer syntheses and polymerization conditions. A variety of highly efficient chemistries including "click" reactions have successfully been applied to prepare functional polymers via a postpolymerization route.[1−5] Recent work has seen the development of polymer scaffolds containing two or more reactive functionalities, allowing the preparation of multifunctional materials via orthogonal modifications and illustrating the utility of this approach.[6−10]

In recent years, the synthesis of degradable polymers has gained significant attention due to their increasing use in biomedical applications.[11] Aliphatic poly(carbonate)s represent a class of degradable polymer with great promise in this area due to their low toxicity and biocompatibility.[12] Poly(carbonate)s can be prepared by either polycondensation methods[13−15] or the ring-opening polymerization (ROP) of cyclic carbonate monomers,[16] with the latter approach offering excellent control over molecular weight, dispersity, and end-group fidelity. Introduction of functionality to the poly(carbonate) backbone allows precise control over the properties of the polymer and enables the attachment of relevant therapeutic and biological molecules. The development of a cyclic carbonate monomer scaffold based around 2,2′-bis(hydroxymethyl) propionic acid (bis-MPA) has enabled the preparation and subsequent polymerization of a range of functional carbonate monomers.[17,18] Methods to functionalize such polymers allow more facile access to a wider range of materials, including those with functional groups that are not compatible with ROP. Recent work by our group and others has demonstrated the postpolymerization modification of poly(carbonate)s bearing pendent allyl,[19−22] maleimide,[23] (meth)acrylic,[24] vinyl-sulfone,[25] alkyne,[26,27] and azide groups.[28,29]

To expand the scope of postpolymerization functionalization strategies we sought to design a poly(carbonate) scaffold containing a reactive functionality that could undergo multiple orthogonal modification reactions by simply varying reaction stimuli, such as temperature or UV irradiation. The norbornenyl group is an attractive reactive handle for such a purpose. As a consequence of their highly strained ring structure, norbornenes exhibit extremely high reactivity during thermal and UV-initiated thiol-ene radical additions,[30−32] are excellent dienophiles in the inverse electron demand Diels–Alder reaction with tetrazines,[33−37] undergo reaction in 1,3-dipolar cycloadditions[38−42] and are the archetypal monomers for ring-opening metathesis polymerizations.[43,44] Hence, in this study, we report the synthesis and ROP of a novel norbornene functional cyclic carbonate monomer for the preparation of multireactive polymer scaffolds and their postpolymerization functionalization via the heat promoted 1,3-dipolar cycloaddition reaction with azides, the inverse electron demand Diels–Alder reaction with tetrazines and the radical addition of thiols promoted by UV irradiation, demonstrating the functionalization chemistries both individually and in a sequential one-pot reaction.

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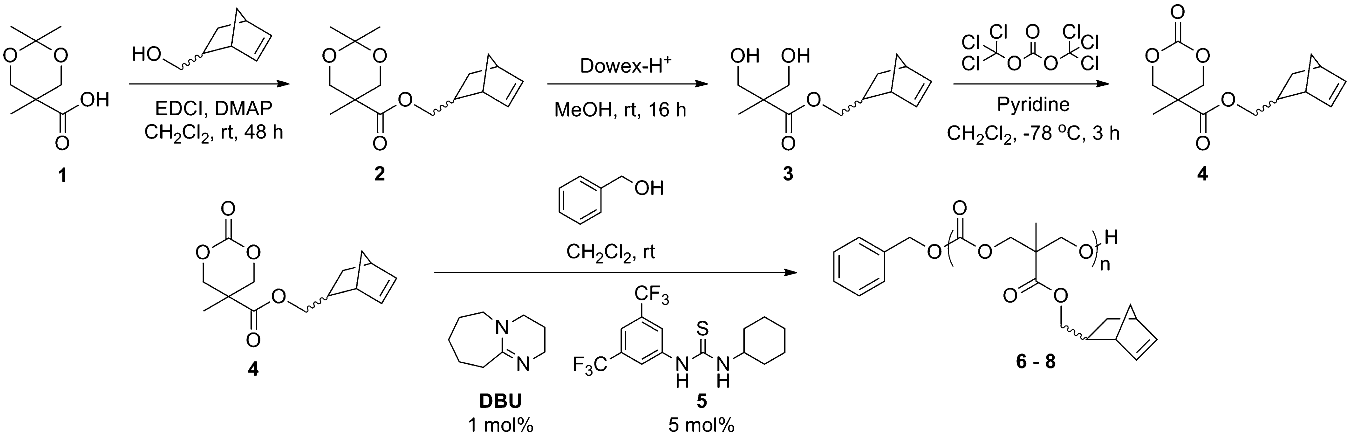
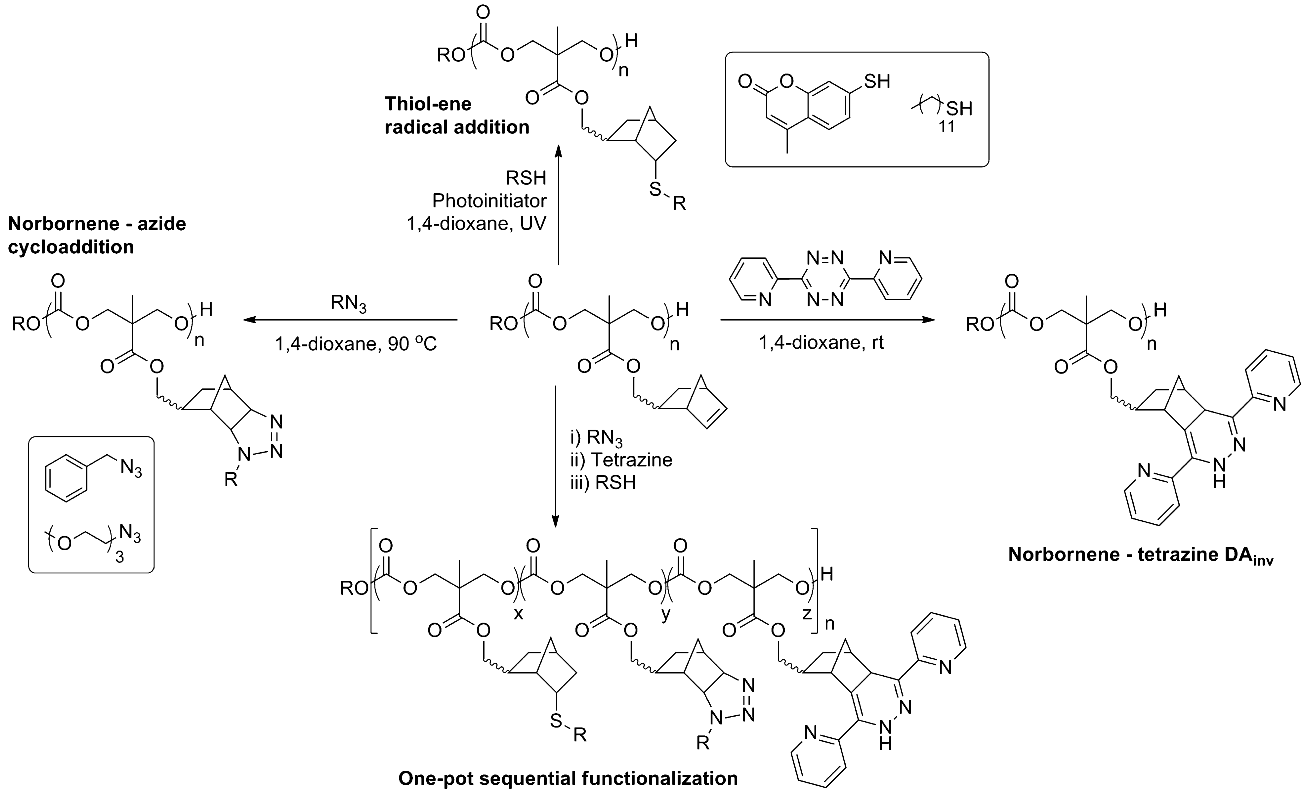
Scheme 1. Synthesis and Ring-Opening Polymerization of Norbornene-Functional Cyclic Carbonate Monomer, 4



Scheme 2. Individual and One-Pot Functionalizations of Norbornene-Functional Poly(carbonate) Scaffolds



The norbornene-functional cyclic carbonate monomer, **4**, was prepared in three steps from the acetonide-protected analogue of 2,2′-bis(hydroxymethyl) propionic acid, **1**, that in turn was prepared according to the literature.[45] Coupling of **1** with 5-norbornene-2-methanol, followed by hydrolysis of the acetyl groups of **2**, yielded the norbornene-functional diol, **3**, which was subsequently ring-closed using triphosgene to afford the monomer **4** in 49% overall yield (Scheme 1). The analysis of **4** by ^{1}H NMR, ^{13}C NMR, elemental analysis, and mass spectrometry was consistent with the expected product.

Ring-opening polymerizations of **4** were conducted in $CDCl_3$ or CH_2Cl_2 at room temperature, where $[\mathbf{4}]_0 = 0.5$ M. Monomer conversion was followed by ^{1}H NMR spectroscopy by comparing the reduction of the CH_2 signals at $\delta = 4.70$ and 4.20 ppm with the appearance of a broad signal at $\delta = 4.29$ ppm that corresponds to the poly(carbonate) backbone. Polymerizations were quenched with acidic Amberlyst A15 H^{+} resin to remove the basic cocatalyst before purification by column chromatography to remove residual monomer and catalyst. Application of 1 mol % 1,8-diazabicycloundec-7-ene (DBU) and 5 mol % 1-(3,5-bis(trifluoromethyl)phenyl)-3-cyclohexylthiourea (**5**) as cocatalysts,[17,46] with benzyl alcohol as the polymerization initiator and an initial monomer to initiator ratio ($[M]_0/[I]_0$) of 20, resulted in 90% monomer conversion after 7 h. Analysis of the resulting polymer by size exclusion chromatography (SEC) after purification revealed a monomodal trace with a dispersity value, $Đ_M$, of 1.14. ^{1}H NMR spectroscopy confirmed a degree of polymerization (DP) of 19 by integration of the aromatic protons of the polymer end-group at $\delta = 7.36$ ppm against the norbornene alkene signals at $\delta = 6.15-5.91$ ppm (Figure S3). The end-group fidelity of the polymer was further confirmed by matrix-assisted laser

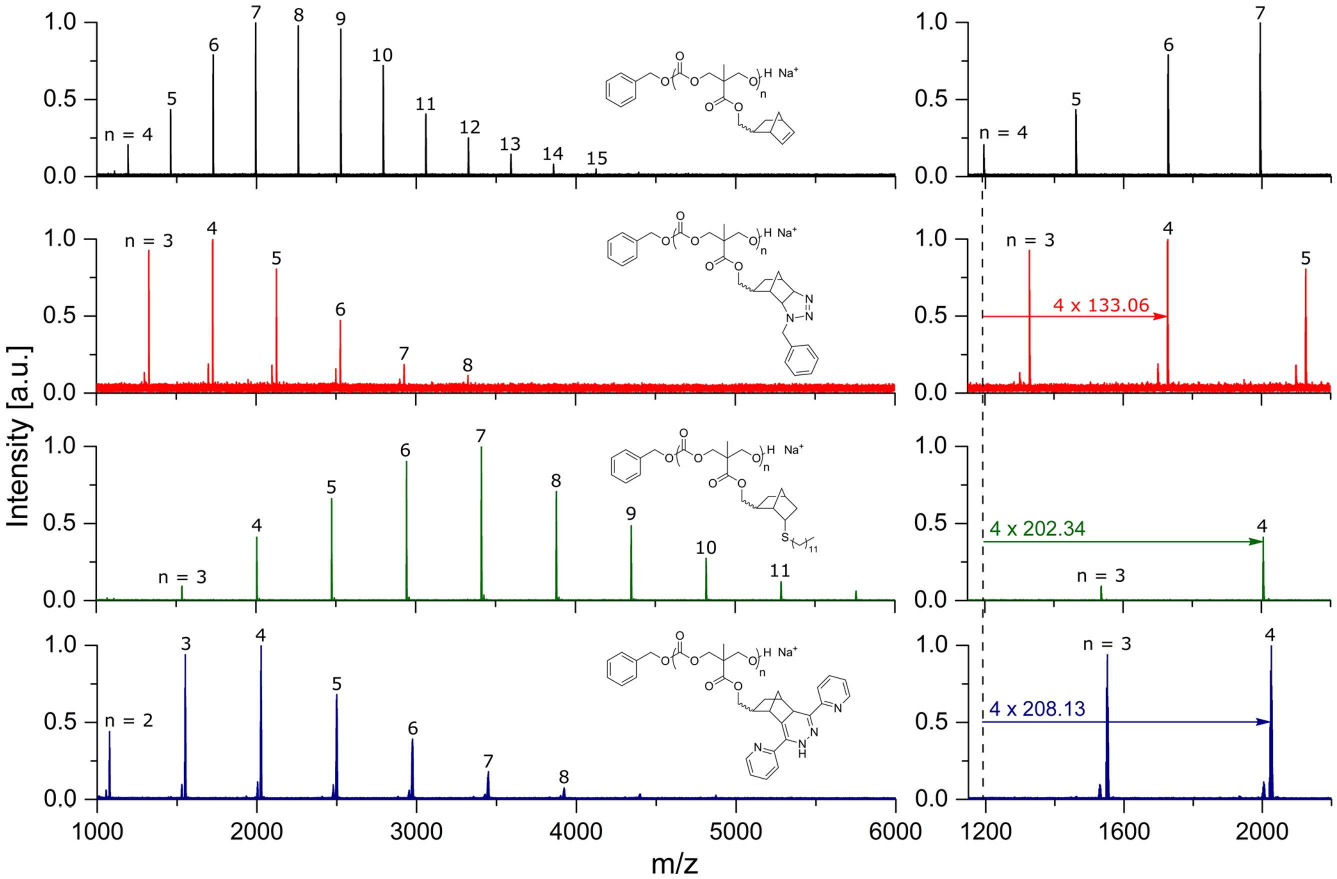


Figure 1. MALDI-ToF MS analysis (reflectron mode) of norbornene-functional poly(carbonate) (**6**, DP = 12) prior to postpolymerization modification, after postpolymerization modification with benzyl azide (**6a**), 3,6-di-2-pyridyl-1,2,4,5-tetrazine (**6c**), and 1-dodecanethiol (**6d**).

desorption ionization time-of-flight mass spectrometry (MALDI-ToF MS) analysis that revealed a single sodium-charged distribution with regular spacings equal to the monomer repeat unit (m/z = 266) and a benzyl alcohol end-group. Further investigation of the living characteristics of the polymerization of **4** revealed linear correlations between number-average molecular weight (M_n) and monomer conversion and M_n versus $[M]_0/[I]_0$, as well as the observation of low dispersity values ($Đ_M \leq 1.2$) throughout all polymerizations (Figure S4). The high levels of control observed during the polymerization of **4** highlights the orthogonality of norbornene functionality with respect to the organocatalyzed ROP of cyclic carbonates.

Following the successful preparation of well-defined norbornene functionalized poly(carbonate) scaffolds, a range of postpolymerization modifications were investigated, namely, the 1,3-dipolar cycloaddition of norbornenes and azides, the inverse electron demand Diels–Alder (DA_{inv}) reaction between norbornenes and tetrazines, and the radical addition of thiols to norbornenes (Scheme 2). The polymer modifications were initially studied separately using both a DP = 100 (**7**) scaffold, as well as a lower molecular weight scaffold of DP = 12 (**6**) to assist with the ready characterization of the modified polymers by MALDI-ToF MS (Figures 1 and S5). 1,4-Dioxane was chosen as the solvent for the polymer modifications as it is an excellent solvent for poly(carbonate)s and was found to be compatible with all three reactions.

As a consequence of the limited number of reports of norbornene-azide 1,3-dipolar cycloadditions in the literature,[42,47,48] a model reaction between an excess of benzyl azide and 5-norbornene-2-methanol was performed. Analysis by ^{1}H NMR spectroscopy revealed a 63% conversion after 14 h when undertaken at 90 °C. Hence, for polymer functionalizations a large excess of benzyl azide (10 equiv) was used to drive the reaction to completion and also shorten reaction times. Degradation of the poly(carbonate) backbone was observed for prolonged heating at 90 °C in the presence of benzyl azide, as evidenced by the appearance of a low molecular weight tail during SEC analysis (Figure S6). Monitoring the polymer functionalization by ^{1}H NMR spectroscopy revealed that after 14 h >99% of the norbornene units had been consumed, as evidenced by the reduction of the corresponding norbornene resonances at δ = 6.15–5.91 ppm (Figure S7). The modified polymers were precipitated into cold methanol to remove excess benzyl azide before being further analyzed. SEC analysis of the precipitated polymers showed an increase in molecular weight, while the dispersities of the polymers remained low (Table 1 and Figure S14). Analysis of the DP = 12 polymer by MALDI-ToF MS revealed a new sodium-charged distribution consistent with addition of benzyl azide to the pendent norbornene groups, as observed by an increase of repeat unit from m/z = 266 to 399. A second distribution of much lower intensity was also observed, which corresponds to the loss of molecular nitrogen from one pendent group per polymer chain (Figure 1). We postulate that this loss of nitrogen occurs upon ionization by the laser.

The norbornene-azide cycloaddition was further demonstrated using triethyleneglycol monomethyl ether (TEG) azide.

Table 1. Postpolymerization Modifications of Norbornene-Functional Poly(carbonate)s[a]

polymer	functional group	M_n[b] (kDa)	$Đ_M$[b]
6		2.8	1.21
7		24.5	1.11
8		9.5	1.12
6a	benzyl azide	4.9	1.10
7a	benzyl azide	25.6	1.16
6b	TEG azide	4.4	1.14
6c	dipyridyltetrazine[c]	3.5	1.23
7c	dipyridyltetrazine[c]	25.7	1.08
6d	dodecanethiol	6.0	1.13
7d	dodecanethiol	39.6	1.18
6e	coumarin thiol[d]	4.7	1.30

[a] Reactions performed in 1,4-dioxane, where [norbornene] = 0.04 M. [b] Determined by SEC analysis using THF as eluent against poly(styrene) standards. [c] 3,6-Di-2-pyridyl-1,2,4,5-tetrazine. [d] 7-Mercapto-4-methylcoumarin.

The successful functionalization was confirmed by ^{1}H NMR spectroscopic analysis, evidenced by the reduction of the norbornene double bond signals and the appearance of three signals at δ = 3.65, 3.56, and 3.39 ppm that correspond to the TEG group (Figure S8). The molecular weight distribution of the polymer remained narrow after functionalization, with an increase in molecular weight observed by SEC analysis (Table 1 and Figure S14). The modified polymer was found to exhibit a lower critical solution temperature (LCST) of 17 °C in aqueous solution, demonstrating how postpolymerization functionalization can provide access to thermoresponsive hydrophilic poly(carbonate)s (Figure S9).

The reaction between tetrazines and norbornenes has recently been shown to be quantitative for the side-chain and end-group functionalization of polymers.[35,49] Hence, for our studies, an equimolar amount of 3,6-di-2-pyridyl-1,2,4,5-tetrazine to pendent norbornene functionality was used and reaction mixtures were stirred for 10 h at room temperature in dioxane. The characteristic color change from pink to pale yellow indicated completion of the reaction, as further confirmed by ^{1}H NMR spectroscopy, that revealed a complete loss of the norbornene alkene signals at δ = 6.15−5.91 ppm and appearance of new signals between δ = 9.31 and 7.18 ppm (Figure S10). SEC analysis of both the DP = 12 and DP = 100 modified polymers revealed little change in molecular weight distribution (Table 1 and Figure S14). MALDI-ToF MS analysis of the DP = 12 polymer revealed an increase in repeat unit from m/z = 266 to 474, which corresponds to the addition of a dipyridyltetrazine on each repeat unit. In addition to the major sodium-charged distribution, a minor proton-charged distribution was also observed (Figure 1).

Finally, the radical addition of 1-dodecanethiol to the norbornene-functional scaffolds was investigated. An excess of thiol was used to limit coupling of the norbornene groups[20] and 2-benzyl-2-(dimethylamino)-4′-morpholinobutyrophenone (0.015 equiv) was used as the radical photoinitiator. After 1.5 h of UV irradiation, the polymers were precipitated into cold methanol. Analysis of the precipitated polymers by ^{1}H NMR spectroscopy showed the disappearance of the norbornene alkene signals and the appearance of signals corresponding to the addition of dodecanethiol, notably the triplet at δ = 0.88 ppm and quartet at δ = 2.50 ppm arising from the dodecyl chain-end and CH_2 group adjacent to the thioether (Figure S11). MALDI-ToF MS analysis of the DP = 12 modified polymer revealed a single sodium-charged distribution with the expected increase in repeat unit (m/z = 266 to 468; Figure 1). SEC analysis of the thiol-ene modified polymer showed an increase in molecular weight, while again retaining low dispersity values (Table 1 and Figure S14). The radical addition of pro-fluoroscent 7-mercapto-4-methylcoumarin was also investigated. After 1.5 h of UV irradiation, ^{1}H NMR spectroscopic analysis revealed the complete loss of norbornene double bond signals and the appearance of resonances that correspond to the ring structure of the coumarin moiety between δ = 7.69 and 6.11 ppm and the methyl group at δ = 2.31 ppm (Figure S12). The UV-vis spectrum of the polymer after modification showed an absorbance maximum at 335 nm, consistent with successful addition of the pro-fluorescent thiol to the polymer chain (Figure S13).

Following the success of the individual postpolymerization functionalization reactions, a sequential one-pot triple functionalization strategy was investigated. Functional reagents were chosen that would be easily distinguishable by ^{1}H NMR spectroscopy, namely, TEG azide, dipyridyltetrazine, and 1-dodecanethiol. As the least efficient reaction, the norbornene-azide cycloaddition was undertaken first. A norbornene-funtional poly(carbonate) scaffold, **8** (DP = 35), was heated at 90 °C for 1 h in the presence of 10 equiv of TEG azide, after which approximately 30% of norbornene groups had reacted. Control experiments showed that an excess of unreacted azide would have no deleterious effects on the subsequent functionalizations. The reaction was then cooled to room temperature before the addition of 0.5 equiv of dipyridyltetrazine per remaining norbornene group and stirred at room temperature until the solution lost its pink color, which indicates the complete consumption of tetrazine units. Finally, 1-dodecanethiol and the photoinitiator were added to the reaction mixture, which was subsequently irradiated with UV light for 2 h. SEC analysis of the crude reaction mixture after each step revealed the molecular weight distribution of the polymer remained narrow and monomodal (Figure 2). The one-pot orthogonally functionalized polymer was purified by precipitation into hexane. The ^{1}H NMR spectrum of the

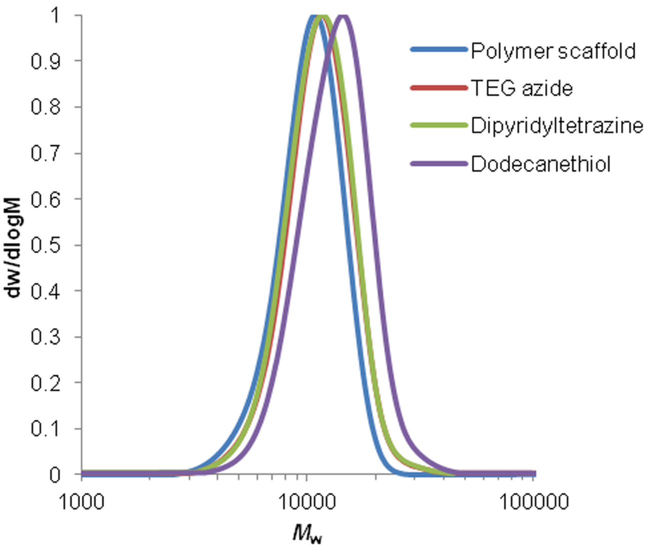


Figure 2. SEC chromatograms of a one-pot three-step modification of norbornene-functional poly(carbonate), **8**.

precipitated polymer showed signals corresponding to all three functional groups, specifically the aromatic signals between δ = 9.32 and 7.21 ppm from reaction with dipyridyltetrazine, the three signals at δ = 3.62, 3.53, and 3.36 ppm corresponding to the TEG functionality and the significant increase in integral of the peak at δ = 1.24 ppm and the appearance of a triplet at δ = 0.86 ppm corresponding to the incorporation of 1-dodecanethiol (Figure S15). ^{1}H NMR spectroscopic analysis also revealed a small proportion of unmodified norbornene groups (ca. 10%), which was thought to be a consequence of the increased steric crowding of the poly(carbonate) backbone that prevented complete functionalization from occurring.

A new approach for the synthesis of multifunctionalized polymers has been shown where a single polymeric scaffold containing a reactive handle, in this case norbornene functionality, can undergo multiple postpolymerization modifications both individually and sequentially in an orthogonal one-pot process. This approach creates a new platform for the preparation of complex multifunctional materials where an extensive library of functionalized polymers can be prepared by simply varying the combinations and relative proportions of functional reactants in an undemanding one-pot, multistep process. For example, the physical properties of a polymer may be changed by the introduction of hydrophilic and responsive functionalities while also tagging polymers with fluorescent or biologically relevant molecules.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and NMR and SEC data. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: a.p.dove@warwick.ac.uk; r.k.o-reilly@warwick.ac.uk.

Notes

The authors declare no competing financial interest.

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