An atom-efficient conjugation approach to well-defined block copolymers using RAFT chemistry and hetero Diels–Alder cycloaddition†

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The tendency of electron-deficient dithioesters to undergo hetero Diels–Alder cycloadditions is successfully used to generate polymer conjugates between a RAFT-polymerized poly(styrene) and a diene-terminated poly(ε-caprolactone).

The generation of well-defined complex macromolecular architectures plays an important role in contemporary polymer science. The development of controlled/living polymerization methods[1] as well as efficient modification reactions for polymers has highly contributed to this development. In the case of the latter, the use of the copper(I) catalyzed azide–alkyne 1,3-cycloaddition as an efficient coupling reaction has seen a great increase in the past three years.[2] The copper(I) catalyzed variant of the Huisgen 1,3-cycloaddition[3] was presented in 2002[4] and was used in the context of polymer chemistry by Hawker, Sharpless and co-workers in 2004 for the first time.[5] However, other cycloaddition reactions have been reported to be suitable to fulfil the 'click'-criteria[6] and have been successfully used for polymer couplings.[7] In the majority of the reported examples, however, different functionalities are required for the controlled/living polymerization and for the post-polymerization coupling reaction. Therefore either both functionalities are combined in one (initiator) molecule (*e.g.* alkyne and azide functionalized reversible addition–fragmentation chain transfer (RAFT) agents)[8] or pre-polymerized macromolecules are equipped with an appropriate function (*e.g.* bromo substitution of polymers prepared by atom transfer radical polymerization (ATRP)).[9]

The present contribution describes two examples for the combination of a RAFT-polymerized poly(styrene) (PS) with a diene-terminated poly(ε-caprolactone) (PCL) in a hetero Diels–Alder (HDA) cycloaddition yielding well-defined PS–PCL block copolymers. In this atom-efficient approach, the dithioester function was sequentially used for the controlled RAFT polymerization and as the reactive heterodienophile for a polymer–polymer coupling. The PS chains with appropriate dithioester end-groups could be obtained using benzyl (diethoxyphosphoryl)dithioformate (**1a**) and benzyl

pyridin-2-yldithioformate (**1b**) in a RAFT polymerization process.[10] It is known that electron-deficient dithioesters similar in structure to compounds **1a,b** are excellent heterodienophiles in [4 + 2] cycloadditions.[11] However, the present contribution establishes for the first time that these structures as end-groups in polymeric systems behave in a similar manner and can be used for the formation of polymer conjugates.

The RAFT agents **1a,b** were prepared as described in the literature.[10] The RAFT polymerization of styrene was carried out in the presence of **1a,b** and 2,2′-azobis(isobutyronitrile) (AIBN) at 60 °C (Scheme 1). The polymerization was stopped at low monomer conversion to ensure a high RAFT end-group concentration. PS **3a,b** were obtained with a number average molecular weight (M_n) of 2820 g mol^{-1} and 2230 g mol^{-1},
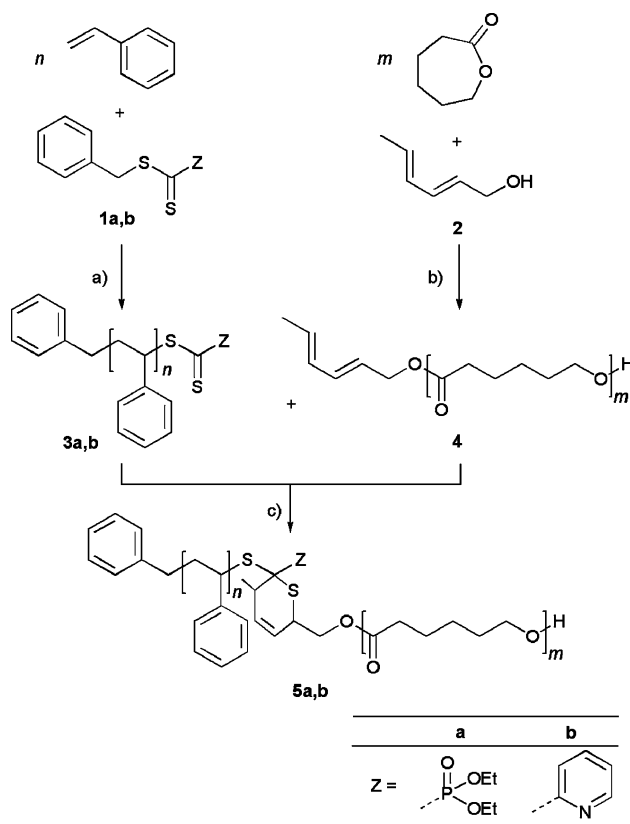
Scheme 1 Preparation of PS **3a,b** and PCL **4** followed by their coupling *via* a HDA cycloaddition. (a) RAFT polymerization, AIBN, 60 °C; (b) ROP, lipase, 70 °C; (c) ZnCl$_2$ (1 eq.), 50 °C, 24 h for **3a** and TFA (1.1 eq.), 50 °C, 2 h for **3b**.

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† Electronic supplementary information (ESI) available: Detailed experimental section, NMR and ESI-MS data. See DOI: 10.1039/b718180a

Table 1 Polymer characterization

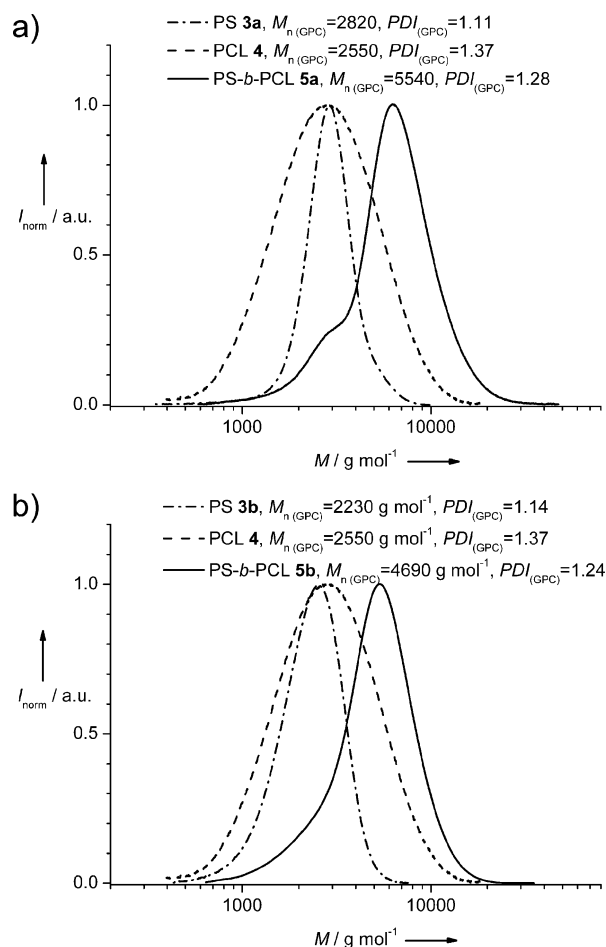| Polymer	$M_{n,\text{theo}}{}^a$/g mol^{-1}	$M_{n,\text{exp}}{}^b$/g mol^{-1}	$PDI_{\text{exp}}{}^b$
PS **3a**	—	2820	1.11
PS **3b**	—	2230	1.14
PCL **4**	—	2550^c	1.37^c
PS-b-PCL **5a**	5370	5540	1.28
PS-b-PCL **5b**	4780	4690	1.24

^{a} Calculated by the sum of the individual building blocks. ^{b} Measured by GPC in THF (calibration with PS standards). ^{c} Values for PCL are corrected by applying the Mark–Houwink relationship ($K = 13.95 \times 10^{-5}$ dL g^{-1}, $\alpha = 0.786$).

Fig. 1 Overlay of molar mass distributions (GPC) for (a) PS **3a**, PCL **4** and PS-b-PCL **5a** and (b) PS **3b**, PCL **4** and PS-b-PCL **5b**.

respectively and low polydispersity indices (PDI) of 1.11 and 1.14, respectively (Table 1), confirming the controlled character of the polymerization.

The ring-opening polymerization (ROP) of ε-caprolactone was performed under enzymatic conditions at 70 °C in the presence of a lipase resin and trans,trans-2,4-hexadien-1-ol (**2**) as the initiator (Scheme 1). The ^{1}H-NMR spectrum of the obtained 2,4-hexadienoyl terminated PCL **4** showed the presence of both the polymer backbone and the vinylic protons. A comparison of the intensities of the vinylic protons with the terminal hydroxymethylene protons revealed the quantitative functionalization of the polyester.[12] According to GPC measurements, **4** was found to have an $M_n = 2550$ g mol^{-1} and PDI = 1.37 (Table 1).

The coupling reaction between **3a** and **4** via HDA cycloaddition was performed at 50 °C in chloroform solution and in the presence of zinc chloride (Scheme 1). A complete conversion was found after a reaction time of 24 h. Fig. 1a shows the molar mass distribution of the obtained PS-b-PCL copolymer **5a**. In comparison to the starting materials **3a** and **4**, the reaction product **5a** shows an increase in molar mass ($M_n = 5540$ g mol^{-1}) which is consistent with the calculated value and a distribution width between those of **3a** and **4** (PDI = 1.28). A shoulder at about 2800 g mol^{-1} can be observed and is attributed to remaining PS **3a**. Such occurrences of residual polymer precursor have previously been encountered and could be easily removed by further purification steps.[13] Under similar conditions, using trifluoroacetic acid (TFA) as the catalyst, quantitative conversion of PS **3b** with PCL **4** was achieved in just two hours (Scheme 1). The corresponding molar mass distributions are presented in Fig. 1b, which shows an increase in molar mass ($M_n = 4690$ g mol^{-1}) and a distribution width between those of **3b** and **4** (PDI = 1.24). Due to the number of possible stereo/regioisomers of the 3,6-dihydro-2H-thiopyran ring in **5a,b**, the obtained NMR data are complex. However, in the ^{1}H- and ^{13}C-NMR spectra of the obtained PS-b-PCL **5a,b** it is possible to observe the disappearance of two (β- and ε-positions) of the four vinylic protons and of the vinylic carbons, respectively.[12] In **5a,b**, polymer segments are linked through the formation of a 3,6-dihydro-2H-thiopyran ring, the stability of which has been briefly investigated.[14] It was found that no decomposition occurs under thermal treatment. However, this will be further investigated in a forthcoming study.

To further confirm the efficiency of the HDA cycloaddition, a model reaction of PCL **4** with RAFT agents **1a,b** (Scheme 2) was carried out. The resulting PCL **6** with a modified end-group could be easily isolated by precipitation and was studied according to its end-group composition. For reasons as mentioned above, the observation of the reaction progress via NMR spectroscopy is complex. However, the characteristic change in the pattern of vinylic protons is clearly visible (as a typical example see Fig. 2a) and consistent with the supposed formation of **6,7**.
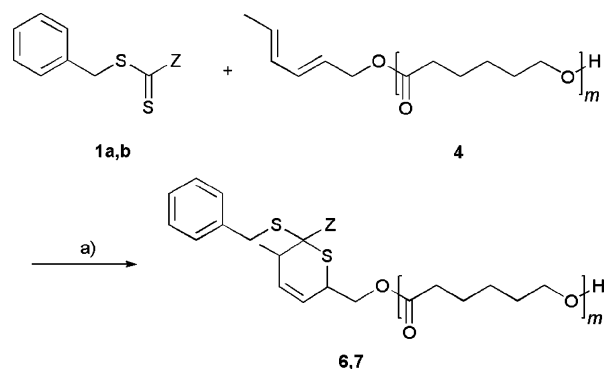
Scheme 2 Conversion of PCL **4** with RAFT agents **1a,b**. (a) ZnCl$_2$ (1 eq.), 50 °C, 24 h for **1a** and TFA (1.1 eq.), 50 °C, 2 h for **1b**.
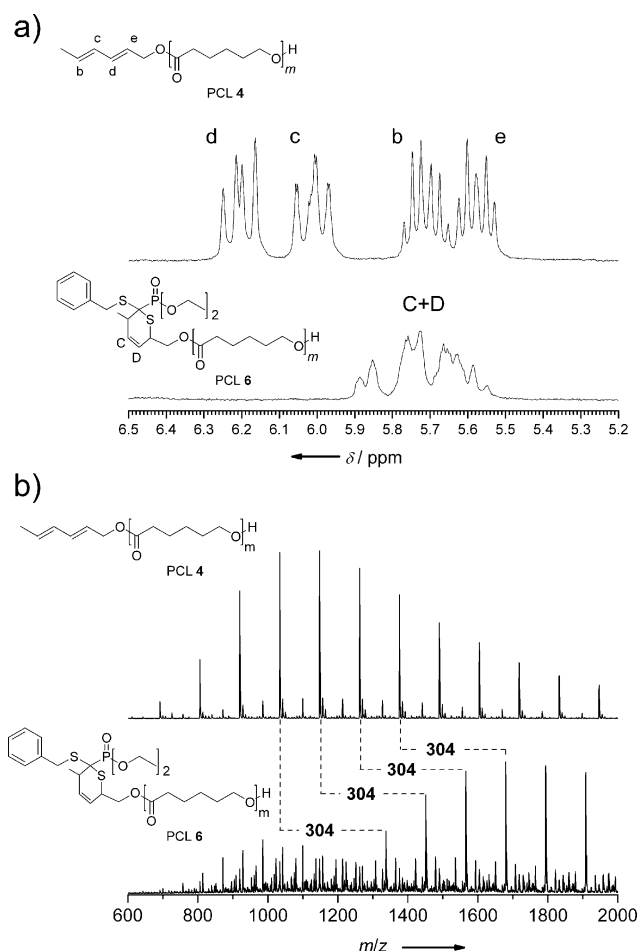
Fig. 2 PCL prior to (**4**) and after (**6**) reaction with **1a**; (a) 6.5–5.2 ppm region of the ^{1}H-NMR spectra and (b) ESI-MS spectra.[12,15]

HDA cycloadditions can be successfully used to generate polymer conjugates. In two examples, PS **3a,b**, obtained after controlled polymerization with RAFT agents **1a,b**, were used to form PS-*b*-PCL copolymers **5a,b** after reaction with a 2,4-hexadienoyl terminated PCL **4**. This atom-efficient method features a high selectivity, quantitative conversion, the absence of dry/inert procedures and can be performed under moderate conditions with a non-toxic catalyst in the case of **1a** or with Brønsted acids in the case of **1b**. It contributes therefore to the expansion of the field of efficient polymer conjugation. Further investigations will focus on the generation of more complex macromolecular architectures and on the development of further highly HDA efficient RAFT agents.

Considering that the number of possible isomers may differ in their spectroscopic properties but not in their mass, electrospray ionization mass spectrometry (ESI-MS) measurements were performed. Fig. 2b shows the ESI-MS spectra of **4** prior to and after reaction with **1a**. In the spectrum of **4** one series of signals dominates, which can be assigned to the different chain lengths of the functionalized polyester **4**.[15] In the spectrum of a sample of the modified PCL **6** the complete series of PCL signals is shifted by 304 to higher *m/z* values (M_{exact}(**1a**) = 304.04 g mol^{-1}). Even though a number of signals of lower intensity can be found, they can be partially assigned to different molecular ions of **6** (*e.g.* double charged species with a maximum in intensity around $m/z = 10^3$).[15] Even though signals which correspond to **4** appear in the spectrum (14% of the main peak), a careful MS-MS investigation suggests that their occurrence can be explained by the retro-HDA of **6** under ESI-MS conditions and not by an incomplete conversion of **4**. Similar results were found for a model reaction between **1b** and **4**.[14]

It can be confirmed from the above described results that the tendency of electron-deficient dithioesters to undergo

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15 A detailed peak assignment of the ESI-MS spectra of **4**, **6** and **7** is included in the ESI†.