Reversible Addition Fragmentation Chain Transfer (RAFT) and Hetero-Diels−Alder Chemistry as a Convenient Conjugation Tool for Access to Complex Macromolecular Designs

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ABSTRACT: The combination of RAFT chemistry and the hetero-Diels−Alder (HDA) cycloaddition was successfully utilized in the synthesis of poly(styrene) (PS) star polymers with up to 4 arms. This variant of the "coupling onto" method of star polymer synthesis was investigated for two different RAFT end groups (diethoxyphosphoryldithioformate and pyridin-2-yldithioformate) and coupling agents bearing 2, 3, or 4 diene functional groups. When a diethoxyphosphoryldithioformate terminated polymer was reacted with the 2-, 3-, and 4-fold functionalized coupling agents, the yields of 2-arm star, 3-arm star, and 4-arm star polymers were 81%, 77%, and 65%, respectively, and when a pyridin-2-yldithioformate terminated polymer was reacted with the same coupling agents, the yields of 2-arm star, 3-arm star and 4-arm star polymers were 91%, 86% and 82% respectively. The HDA coupling reaction was monitored via UV/vis spectroscopy from the perspective of the RAFT end group as well as by ^{1}H NMR spectroscopy from the perspective of the diene functionality. The results of these investigations indicated that the phosphoryldiethoxydithioformate terminated polymer achieves 92% conversion within a 24 h time frame and the pyridin-2-yldithioformate terminated polymer achieves 96% conversion in 10 h. The 4-arm star polymers were also subjected to high-temperature environments, and GPC measurements indicated that complete cleavage of all 4 arms from the core was achieved in 24 h at 160 °C.

Introduction

The relationship between the form and function of polymeric materials is the fuel that drives the development of the set of tools with which organic chemists can construct macromolecules of predetermined architecture. Some of the more notable inclusions in this "toolbox" are the various forms of living/controlled free radical polymerization (CRP), which aim to combine the convenience of free radical chemistry with the control over molecular architecture that is offered by such techniques as living anionic polymerization.[1,2] More recently, the combination of these techniques with "click" chemistry has significantly diversified the contents of this "toolbox", which has allowed macromolecules with complex architecture to be synthesized with great ease.[3–6] An example of such structures is star polymers.

Star polymers have been the subject of intense investigation in the field of material science due to their compact structure, unusual solution properties, and unique rheological behavior.[7,8] Initially, living anionic polymerization has been the method of choice in the synthesis of such structures; however, very stringent reaction conditions and the limited range of monomers that may be used means that anionic polymerization is not as versatile nor as convenient as free radical techniques. More recently, the development of the CRP technologies has brought with it resurgence in interest in the synthesis of these architectures.[2,9,10]

Within the field of CRP, polymeric star architectures may be synthesized utilizing one of two general techniques: core-first[10–15] and arm-first.[16–19] The former technique involves the use of a multifunctional initiator whereby the arms of the star are grown from the core during the polymerization. With techniques such as reversible addition fragmentation chain transfer (RAFT), atom transfer radical polymerization (ATRP), and nitroxide mediated polymerization (NMP) having been successfully shown to produce well-defined stars by the core-first method, the RAFT process has been shown to be more cumbersome in attaining such structures.[17] The arm-first technique, as it is applied to CRP, initially involved the chain extension of linear polymers with a multivinyl cross-linker. Another approach to the arm-first technique involves the "grafting" or "coupling" of linear polymer segments onto a multifunctional core. This latter method is limited by the selectivity and efficiency of the reactions responsible for linking the linear segments to the core. It has only been recently that, with the advent of the Cu(I) catalyzed ligation of azides and alkynes,[20] there has been sharp increase in the reported syntheses of well-defined star polymers via the arm-first method[21–26] and in polymer chemistry in general.[27–29] This "click" reaction, as defined by Sharpless et al.,[30] bears the selectivity and efficiency necessary to make an arm-first strategy for star polymer synthesis viable.

In addition to the above-mentioned "click" reaction, the Diels−Alder cycloaddition between anthracene derivatives and maleimides has also been successfully used in the generation of a variety of well-defined polymeric architectures, including diblock copolymers,[31] triblock copolymers,[32] graft polymers,[33] and star polymers.[34] However, both of the strategies bear characteristics that may prove to be problematic in certain applications. For example, the requirement of using toxic copper catalysts in the classical "click" reaction would also have the requirement of a purification stage in the development of materials destined for biomedical application. With regard to the Diels−Alder "click" reaction, the high temperatures required make it unsuitable for use in forming polymeric conjugates from thermally unstable compounds. Another characteristic that both techniques share is that both the core and the polymer segments need to be prefunctionalized with the appropriate complementary moieties in addition to those responsible for performing the

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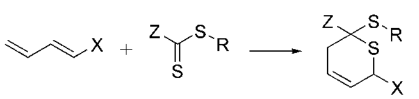
Scheme 1. Hetero-Diels−Alder Reaction of Electron-Deficient Dithioesters



controlled/living polymerization. For example, in the case of RAFT, the controlling agents must be equipped with azide/alkyne functionalities.[6,35,36]

Recently, Barner-Kowollik and Stenzel reported an alternative strategy for synthesizing polymer conjugates that is uniquely used with RAFT chemistry.[37] Here, controlling agents bearing electron-withdrawing Z-groups (benzyl (diethoxyphosphoryl)dithioformate and benzylpyridin-2-yldithioformate) were used in such a way that the thiocarbonyl functionality of the controlling agents was sequentially used for the CRP and as a reactive heterodienophile in a hetero-Diels−Alder (HDA) cycloaddition with an appropriate diene. It was shown that the tendency of electron-deficient dithioesters to undergo HDA cycloadditions (Scheme 1) can be successfully used for the formation of block copolymers from dissimilar monomer families. The HDA cycloadditions are facilitated by the use of a catalyst which enhances the electron-withdrawing nature of the RAFT Z-group. This can be achieved by using $\mathrm{ZnCl_2}$ as a Lewis acid in the case of the phosphoryl Z-group[38] and by trifluoroacetic acid (TFA) as a Brønsted acid in the case of the pyridinyl Z-group.[39] Although achieving the same effect, the catalysts were selected on the basis of the nature of their interaction with the RAFT Z-group: the $\mathrm{ZnCl_2}$ chelates with the oxygen on the phosphinyl group, whereas the $\mathrm{H^+}$ from the TFA protonates the nitrogen on the pyridinyl group. In order to verify the versatility of this method, we herein report the synthesis of star polymers by a combination of RAFT chemistry and the HDA cycloaddition. Poly(styrene) prepared by RAFT chemistry is coupled to a 2-arm, 3-arm, and 4-arm diene precursor to form star polymers with 2, 3, and 4 arms, respectively. The reaction used to generate these structures was then monitored via UV/vis spectroscopy and ^{1}H NMR spectroscopy from the perspective of the RAFT end group and the diene, respectively. Finally, in order to investigate the possibilities of induced cleavage of the 4-arm stars, the compounds were subjected to a high-temperature environment for 24 h, and subsequent GPC measurements were performed.

The present contribution provides a simple and synthetically nondemanding pathway to well-defined macromolecular star-shaped architectures which provides a convenient exemplification for this new synthetic technique.

Experimental Section

Materials and Characterization. Benzyl (diethoxyphosphoryl)dithioformate (**1a**)[40] and benzylpyridin-2-yldithioformate (**1b**)[41] were synthesized according to the literature. Styrene (≥99%, Aldrich) was passed through a column of basic alumina (Ajax Finechem) and stored at −19 °C. 2,2′-Azobis(isobutyronitrile) (AIBN, DuPont) was recrystallized twice from methanol before use and stored at 4 °C. *trans,trans*-2,4-Hexadien-1-ol (97%, Aldrich), 1,4-bis(bromomethyl)benzene (97%, Aldrich), 1,3,5-tris(bromomethyl)benzene (97%, Aldrich), 1,2,4,5-tetrakis(bromomethyl)benzene (95%, Aldrich), THF (≥99.9%, anhydrous, water <30 ppm, Sigma-Aldrich), and trifluoroacetic acid (99%, Sigma-Aldrich) were used as received. Zinc chloride (97.1%, Sigma) was stored over phosphorus pentoxide (≥97%, Fluka). GPC measurements were performed on a Shimadzu modular system, comprising an autoinjector and a Polymer Laboratories 5.0 μm bead size guard column (50 × 7.5 mm), followed by three linear PL columns (10^5, 10^4, and 10^3 Å) and a differential refractive index detector using THF as the eluent at 40 °C with a flow rate of 1 mL $\mathrm{min^{-1}}$. The GPC system was calibrated using linear poly(styrene) standards ranging from 540 to 2×10^6 g $\mathrm{mol^{-1}}$. Peak splitting of the GPC traces was performed using the deconvolution method (Gaussian area) with the Peak Fit program. The structures of the synthesized compounds were proven by ^{1}H and ^{13}C NMR spectroscopy using a Bruker DPX 300 spectrometer at 300 MHz for hydrogen nuclei and 75 MHz for carbon nuclei. All samples were dissolved in $\mathrm{CDCl_3}$. The δ-scale was calibrated to the according solvent signal at 7.258 ppm (^{1}H) and 76.98 ppm (^{13}C). The kinetic analysis by ^{1}H NMR spectroscopy was performed on a Bruker DMX 500 spectrometer at 500 MHz with $\mathrm{CDCl_3}$ as solvent at 50 °C. UV/vis spectroscopy was performed using a Cary 300 Bio UV/vis spectrophotometer (Varian) featuring a thermostated sample cell holder (50 °C). Absorption was measured in chloroform solution from 350 to 850 nm with a resolution of 1 nm in a 10 mm UV cuvette.

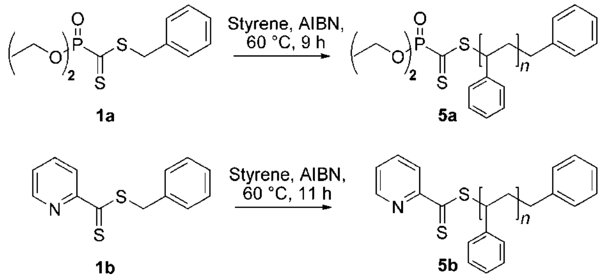
General Procedure for the Synthesis of (*trans,trans*-Hexa-2,4-dienyloxy)methylbenzenes (2−4). The according bromomethylbenzene derivative (3 mmol) and sodium hydride (60% suspension in oil, 1.1 equiv of bromine groups) were placed in a Schlenk flask. Under a nitrogen atmosphere, THF (dry, 30 mL) was added at room temperature. At 0 °C a solution of *trans,trans*-2,4-hexadien-1-ol (1.1 equiv of bromine groups) in 5 mL of THF was added dropwise. After complete addition, the mixture was allowed to warm to room temperature and was stirred for a further 8 h. 30 mL of aqueous ammonium chloride solution (1 M) was then added in order to destroy residual sodium hydride, which was followed by a 3-fold extraction with 30 mL of diethyl ether. After removal of the solvent under vacuum, the product was isolated via column chromatography (silica/*n*-hexane/ethyl acetate).

1,4-Bis((*trans,trans*-Hexa-2,4-dienyloxy)methyl)benzene (2). Yield: 1.0 g (83%). $R_{\mathrm{f}} = 0.66$ (*n*-hexane/ethyl acetate = 5:1). ^{1}H NMR (300 MHz, $\mathrm{CDCl_3}$, 25 °C): $\delta = 7.31$ (s, 4H, arom.), 6.21 (dd, $^{3}J_{\mathrm{HH}} = 15$ Hz, $^{3}J_{\mathrm{HH}} = 10$ Hz, 2H, $-\mathrm{OCH_2CHC}\mathbf{H}\mathrm{(CH)_2CH_3}$), 6.06 (ddq, $^{3}J_{\mathrm{HH}} = 15$ Hz, $^{3}J_{\mathrm{HH}} = 10$ Hz, $^{4}J_{\mathrm{HH}} = 1$ Hz, 2H, $-\mathrm{OCH_2(CH)_2C}\mathbf{H}\mathrm{CHCH_3}$), 5.70 (dq, $^{3}J_{\mathrm{HH}} = 14$ Hz, $^{3}J_{\mathrm{HH}} = 7$ Hz, 2H, $-\mathrm{OCH_2(CH)_3C}\mathbf{H}\mathrm{CH_3}$), 5.66 (dt, $^{3}J_{\mathrm{HH}} = 15$ Hz, $^{3}J_{\mathrm{HH}} = 6$ Hz, 2H, $-\mathrm{OCH_2C}\mathbf{H}\mathrm{(CH)_3CH_3}$), 4.49 (s, 4H, $\mathrm{PhC}\mathbf{H}_2\mathrm{O}-$), 4.02 (d, $^{3}J_{\mathrm{HH}} = 6$ Hz, 4H, $-\mathrm{OC}\mathbf{H}_2\mathrm{CH}-$) 1.75 (dd, $^{3}J_{\mathrm{HH}} = 7$ Hz, $^{4}J_{\mathrm{HH}} = 1$ Hz, 6H, $-\mathrm{C}\mathbf{H}_3$) ppm. ^{13}C NMR (75 MHz, $\mathrm{CDCl_3}$, 25 °C): $\delta = 138$ ($\mathbf{C}_{\mathrm{arom}}-\mathrm{CH_2}-$), 133 ($-\mathrm{OCH_2CH}\mathbf{C}\mathrm{H(CH)_2CH_3}$), 131 ($-\mathrm{OCH_2(CH)_2}$-$\mathbf{C}\mathrm{HCHCH_3}$), 130 ($-\mathrm{OCH_2(CH)_3}\mathbf{C}\mathrm{HCH_3}$), 128 ($\mathbf{C}_{\mathrm{arom}}-\mathrm{H}$), 127 ($-\mathrm{OCH_2}\mathbf{C}\mathrm{H(CH)_3CH_3}$), 71.7 ($-\mathrm{O}\mathbf{C}\mathrm{H_2CH}-$), 70.7 ($\mathrm{Ph}\mathbf{C}\mathrm{H_2O}-$), 18.1 ppm ($-\mathbf{C}\mathrm{H_3}$).

1,3,5-Tris((*trans,trans*-Hexa-2,4-dienyloxy)methyl)benzene (3). Yield: 0.71 g (79%). $R_{\mathrm{f}} = 0.55$ (*n*-hexane/ethyl acetate = 5:1). ^{1}H NMR (300 MHz, $\mathrm{CDCl_3}$, 25 °C): $\delta = 7.24$ (s, 3H, arom.), 6.22 (ddt, $^{3}J_{\mathrm{HH}} = 15$ Hz, $^{3}J_{\mathrm{HH}} = 11$ Hz, $^{4}J_{\mathrm{HH}} = 1$ Hz, 3H, $-\mathrm{OCH_2CHC}\mathbf{H}\mathrm{(CH)_2CH_3}$), 6.07 (ddq, $^{3}J_{\mathrm{HH}} = 15$ Hz, $^{3}J_{\mathrm{HH}} = 10$ Hz, $^{4}J_{\mathrm{HH}} = 1$ Hz, 3H, $-\mathrm{OCH_2(CH)_2C}\mathbf{H}\mathrm{CHCH_3}$), 5.71 (dq, $^{3}J_{\mathrm{HH}} = 14$ Hz, $^{3}J_{\mathrm{HH}} = 7$ Hz, 3H, $-\mathrm{OCH_2(CH)_3C}\mathbf{H}\mathrm{CH_3}$), 5.66 (dt, $^{3}J_{\mathrm{HH}} = 15$ Hz, $^{3}J_{\mathrm{HH}} = 6$ Hz, 3H, $-\mathrm{OCH_2C}\mathbf{H}\mathrm{(CH)_3CH_3}$), 4.49 (s, 6H, $\mathrm{PhC}\mathbf{H}_2\mathrm{O}-$), 4.03 (d, $^{3}J_{\mathrm{HH}} = 6$ Hz, 6H, $-\mathrm{OC}\mathbf{H}_2\mathrm{CH}-$) 1.75 ppm (dd, $^{3}J_{\mathrm{HH}} = 7$ Hz, $^{4}J_{\mathrm{HH}} = 1$ Hz, 9H, $-\mathrm{C}\mathbf{H}_3$). ^{13}C NMR (75 MHz, $\mathrm{CDCl_3}$, 25 °C): $\delta = 139$ ($\mathbf{C}_{\mathrm{arom}}-\mathrm{CH_2}-$), 133 ($-\mathrm{OCH_2CH}\mathbf{C}\mathrm{H}$-$\mathrm{(CH)_2CH_3}$), 131 ($-\mathrm{OCH_2(CH)_2}\mathbf{C}\mathrm{HCHCH_3}$), 130 ($-\mathrm{OCH_2(CH)_3}$-$\mathbf{C}\mathrm{HCH_3}$), 127 ($\mathbf{C}_{\mathrm{arom}}-\mathrm{H}$), 126 ($-\mathrm{OCH_2}\mathbf{C}\mathrm{H(CH)_3CH_3}$), 71.7 ($-\mathrm{O}\mathbf{C}\mathrm{H_2CH}-$), 70.5 ($\mathrm{Ph}\mathbf{C}\mathrm{H_2O}-$), 18.1 ppm ($-\mathbf{C}\mathrm{H_3}$).

1,2,4,5-Tetrakis((*trans,trans*-Hexa-2,4-dienyloxy)methyl)benzene (4). Yield: 0.82 g (53%). $R_{\mathrm{f}} = 0.50$ (*n*-hexane/ethyl acetate = 5:1). ^{1}H NMR (300 MHz, $\mathrm{CDCl_3}$, 25 °C): $\delta = 7.24$ (s, 2H, arom), 6.22 (ddt, $^{3}J_{\mathrm{HH}} = 15$ Hz, $^{3}J_{\mathrm{HH}} = 11$ Hz, $^{4}J_{\mathrm{HH}} = 1$ Hz, 4H, $-\mathrm{OCH_2CHC}\mathbf{H}\mathrm{(CH)_2CH_3}$), 6.07 (ddq, $^{3}J_{\mathrm{HH}} = 15$ Hz, $^{3}J_{\mathrm{HH}} = 10$ Hz, $^{4}J_{\mathrm{HH}} = 1$ Hz, 4H, $-\mathrm{OCH_2(CH)_2C}\mathbf{H}\mathrm{CHCH_3}$), 5.71 (dq, $^{3}J_{\mathrm{HH}} = 14$ Hz, $^{3}J_{\mathrm{HH}} = 7$ Hz, 4H, $-\mathrm{OCH_2(CH)_3C}\mathbf{H}\mathrm{CH_3}$), 5.66 (dt, $^{3}J_{\mathrm{HH}} = 15$ Hz, $^{3}J_{\mathrm{HH}} = 6$ Hz, 4H, $-\mathrm{OCH_2C}\mathbf{H}\mathrm{(CH)_3CH_3}$), 4.49 (s, 8H, $\mathrm{PhC}\mathbf{H}_2\mathrm{O}-$), 4.03 (d, $^{3}J_{\mathrm{HH}} = 6$ Hz, 8H, $-\mathrm{OC}\mathbf{H}_2\mathrm{CH}-$) 1.75 ppm (dd, $^{3}J_{\mathrm{HH}} = 7$ Hz, $^{4}J_{\mathrm{HH}} = 1$ Hz, 9H, $-\mathrm{C}\mathbf{H}_3$). ^{13}C NMR (75 MHz, $\mathrm{CDCl_3}$, 25 °C): $\delta = 136$ ($\mathbf{C}_{\mathrm{arom}}-\mathrm{CH_2}-$), 133 ($-\mathrm{OCH_2CH}\mathbf{C}\mathrm{H}$-$\mathrm{(CH)_2CH_3}$), 131 ($-\mathrm{OCH_2(CH)_2}\mathbf{C}\mathrm{HCHCH_3}$), 130 ($-\mathrm{OCH_2(CH)_3}$-$\mathbf{C}\mathrm{HCH_3}$), 129 ($\mathbf{C}_{\mathrm{arom}}-\mathrm{H}$), 127 ($-\mathrm{OCH_2}\mathbf{C}\mathrm{H(CH)_3CH_3}$), 70.5 ($-\mathrm{O}\mathbf{C}\mathrm{H_2CH}-$), 69.2 ($\mathrm{Ph}\mathbf{C}\mathrm{H_2O}-$), 18.0 ppm ($-\mathbf{C}\mathrm{H_3}$).

Scheme 2. Polymerization of Styrene with Benzyl (Diethoxyphosphoryl)dithioformate (1a) and Benzyl Pyridin-2-yldithioformate (1b)



Synthesis of PS (5a,b). A solution of styrene (80 mL, 0.70 mol), RAFT agent **1a,b** (1.62×10^{-3} mol), and AIBN (0.043 g, 0.27×10^{-3} mol) was prepared and placed in a 250 mL round-bottom flask. The flask was subsequently purged with nitrogen for 30 min to remove any residual oxygen. The polymerization reaction was performed at 60 °C. After a specified reaction time (9 h for **1a** and 11 h for **1b**), the reaction was suspended by the addition of hydroquinone and the subsequent quenching of the reaction flask in an ice/water mixture. The polymers **5a,b** were isolated by a 2-fold precipitation in cold methanol.

Synthesis of Star Polymers by HDA Cycloaddition of PS 5a with Multifunctional Coupling Agents 2, 3, and 4 (6a, 7a, 8a). A solution of PS **5a** (47 mg, 13×10^{-6} mol), multifunctional coupling agent **2**, **3**, **4** (1.0 equiv of diene), and 1 equiv of $ZnCl_2$ (1.8 mg, 13×10^{-6} mol) in 200 μL of chloroform was kept at 50 °C for 24 h. The solvent was removed under vacuum, and the residue directly analyzed by GPC in THF.

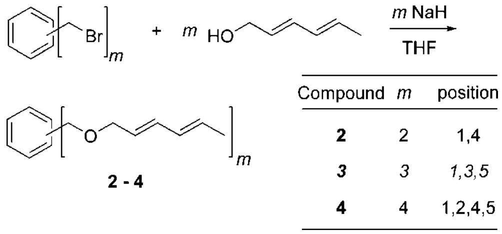
Monitoring of the Reaction between PS 5a and 2 by UV/vis Spectroscopy. PS **5a** (216 mg, 60×10^{-6} mol) and 1.0 equiv of $ZnCl_2$ (8.2 mg, 60×10^{-6} mol) was dissolved in 700 μL of chloroform. The resulting solution was added to a solution of **2** (2 mg, 60×10^{-6} mol) in 500 μL chloroform in a UV cuvette immediately prior to placing in the preheated (50 °C) cuvette holder of the UV/vis spectrophotometer. The reaction was allowed to proceed at this temperature for 25 h.

Synthesis of Star Polymers by HDA Cycloaddition of PS 5b with Multifunctional Coupling Agents 2, 3, and 4 (6b, 7b, 8b). A solution of PS **5b** (47 mg, 13×10^{-6} mol), multifunctional coupling agent **2**, **3**, **4** (1.0 equiv of diene), and 1.2 equiv of TFA (1.2 μL, 15.6×10^{-6} mol) in 200 μL of chloroform was kept at 50 °C for 24 h. The solvent was removed under vacuum and the residue directly analyzed by GPC (THF).

Monitoring of the Reaction between PS 5b and 2 via ^{1}H NMR Spectroscopy. A solution of PS **5b** (88 mg, 25×10^{-6} mol) and **2** (7.5 mg, 25×10^{-6} mol) in 900 μL of $CDCl_3$ was prepared in a NMR tube. A solution of TFA (23 μL, 30×10^{-6} mol) in 100 μL of $CDCl_3$ was added immediately prior to placing the tube in the NMR spectrometer. Spectra of the reaction mixture were taken every 10 min over a period of 24 h at 50 °C.

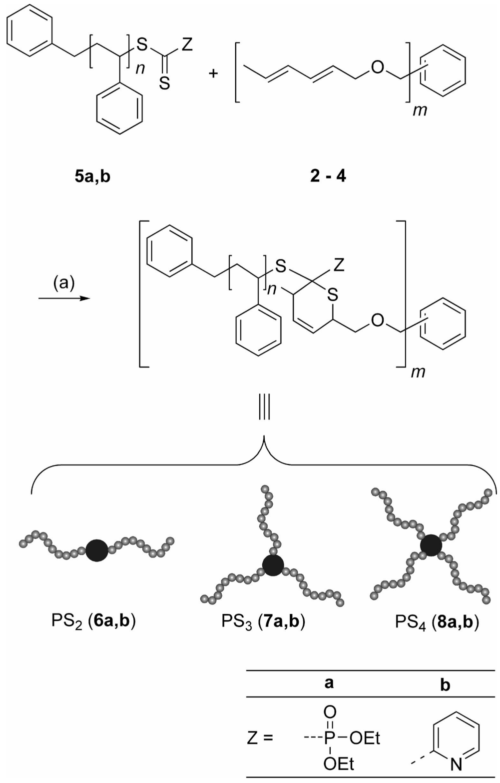
High-Temperature Treatment of PS_4 (8a,b). PS_4 **8a,b** was dissolved in toluene (2 mL) in a pressure tube and kept at 160 °C for 24 h. The solvent was removed under vacuum and the residue analyzed by GPC in THF.

Scheme 3. Synthetic Pathway to Multi-Diene Coupling Agents 2−4



Compound	m	position
2	2	1,4
3	*3*	*1,3,5*
4	4	1,2,4,5

Scheme 4. Star Polymers via the Hetero-Diels−Alder Cycloaddition[a]



[a] Conditions: (a) 1.0 equiv of $ZnCl_2$ for **5a** or 1.2 equiv of TFA for **5b**, chloroform, 50 °C, 24 h.

Results and Discussion

The linear PS precursors, from which the subsequent star polymers were prepared, were synthesized by the RAFT polymerization of styrene using controlling agents **1a,b** (Scheme 2) and AIBN as the initiator. The reaction was stopped at low monomer conversion to ensure a high RAFT end-group concentration. Linear PS **5a,b** were obtained with a number-average molecular weight (M_n) of 3600 and 3500 g mol^{-1}, respectively, and low polydispersity indices (PDI) of 1.10 and 1.15, respectively, as determined by GPC analysis in THF. It is known that dithioesters similar in structure to **1a,b** show a high Diels−Alder reactivity.[38,39] Their ability to be used as controlling agents in the RAFT polymerization of styrene has been shown to be not as effective as most of the more common RAFT agents.[40,41] However, for the molecular weight range utilized in the present study, compounds **1a,b** adequately control the polymerization of styrene in addition to being effective heterodienophiles; thus, they fulfill both purposes.

The multifunctional coupling agents **2−4** were obtained by etherification of the corresponding bromomethylbenzenes with *trans,trans*-2,4-hexadien-1-ol (Scheme 3). The commercially available *trans,trans*-2,4-hexadien-1-ol has been proven to be a very useful diene as its ester in the HDA approach to polymer conjugates.[37] In the present contribution, the above diene is transformed into its ether in the simple synthesis of **2−4** which could be obtained in good yields.

Synthesis and Characterization of Star Polymers using PS 5a. The coupling reactions of PS **5a** with coupling agents **2−4** were performed in chloroform solution at 50 °C in the presence of $ZnCl_2$ (1.0 equiv), as illustrated in Scheme 4. After a reaction time of 24 h, the initially pink solutions (the color of the PS by virtue of its RAFT end group) had turned colorless.

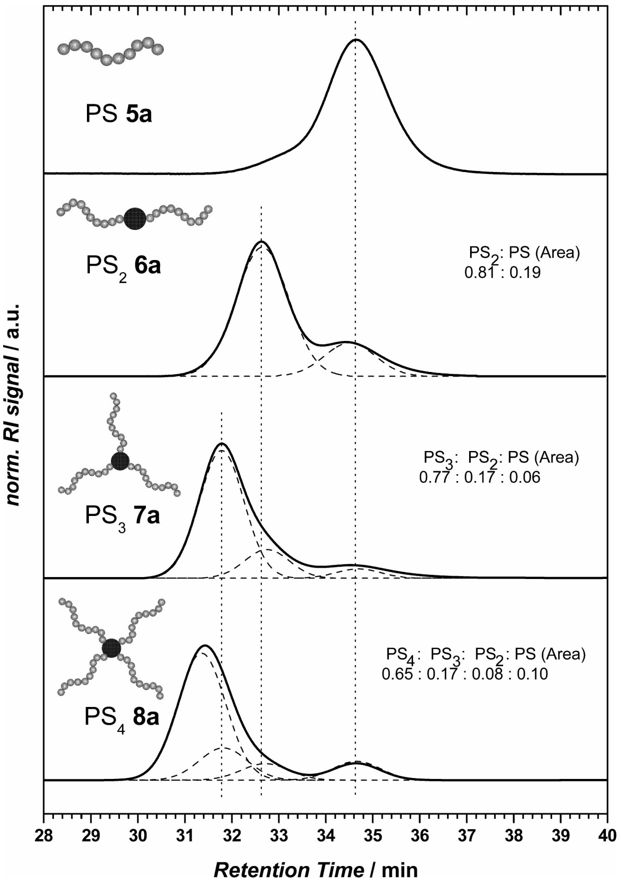


Figure 1. Comparative GPC traces of PS **5a** with coupling products PS_2 **6a**, PS_3 **7a**, and PS_4 **8a**. The dashed lines represent the results of deconvolution via peak splitting.

Table 1. Characterization of PS 5a,b and Its Coupling Products

	$M_n{}^a{}_{(\text{theoretical})}$/ g mol^{-1}	$M_n{}^b{}_{(\text{GPC})}$/ g mol^{-1}	$M_n{}^c{}_{(\text{decon})}$/ qag mol^{-1}	$\text{PDI}^b{}_{(\text{GPC})}$	$\text{PDI}^c{}_{(\text{decon})}$
PS **5a**		3600		1.10	
PS_2 **6a**	7 500	6000	7 600	1.13	1.03
PS_3 **7a**	11 200	7700	11 100	1.16	1.06
PS_4 **8a**	14 900	9000	12 300	1.28	1.03
PS **5b**		3500		1.15	
PS_2 **6b**	7 300	5600	7 300	1.16	1.05
PS_3 **7b**	10 900	7900	10 900	1.16	1.04
PS_4 **8b**	14 500	8810	12 900	1.24	1.03

[a] Calculated by the sum of the individual building blocks. [b] Determined by GPC in THF with RI detector (calibration with linear PS standards). [c] Values determined from deconvoluted GPC data after peak splitting using Gaussian function.

Figure 1 shows the GPC trace of the linear PS **5a** in comparison to those of the coupling products PS_2 **6a**, PS_3 **7a**, and PS_4 **8a**. The shift of the distributions to lower retention times with increasing arm number is clearly observed. The M_n values of the coupling products (Table 1) increase with arm number; however, they depart further and further away from the theoretical values. This is attributed to two factors. First, because of the relatively compact structure of star polymers, increases in observed molecular weight become less and less pronounced with increasing arm number. Second, the determination of M_n values takes into consideration remaining precursor material, which tends to skew the observed M_n to lower values and leads to an increase in PDI values.

The reduction in hydrodynamic volume that arises when linear polymers are arranged in star formations leads to underestimated values for the M_n as determined from GPC measurements. As such, the synthesis of star polymers with 2, 3, and 4 arms was performed in order to directly show the evolution of the molecular weight distributions of star polymers with increasing number of arms. Furthermore, because of the successive increase in the number of arms from the linear PS **5a** to PS_4 **8a**, it is possible to deconvolute the GPC data via peak splitting. The peak splitting technique allows the observed mass distribution of the various coupling products to be broken down into its constituent distributions. For example, the observed mass distribution of the 4-arm star PS_4 **8a,b** represents the sum of the mass distributions of the desired 4-arm star as well as any 3-arm and 2-arm star material that is formed in the reaction and any remaining precursor. Since the star polymers are built up successively in terms of arm number, it is possible to define the position (i.e., the retention time) of the expected side products, and using a Gaussian approximation to the individual distributions of these products, a fit to the experimental data may be achieved. The data acquired from this fitting procedure enables the estimation of the M_n and PDI values for the desired product by manual calculation and may also be used to determine the fraction of styrene units that are present in the desired product.

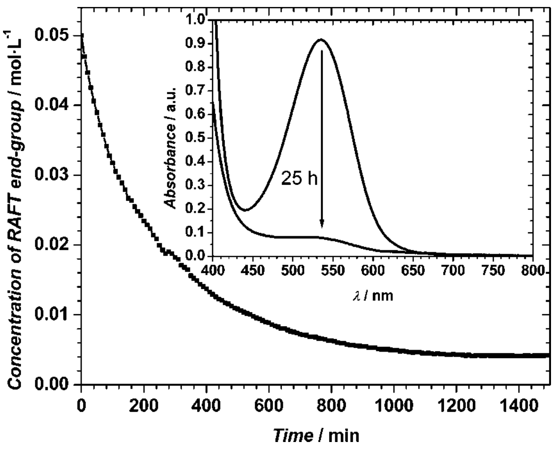


Figure 2. Monitoring the concentration of the RAFT end group of PS **5a** as a function of time in its reaction with coupling agent **2**. The UV/vis spectra prior to and after reaction are presented in the inset.

The result of peak splitting of the GPC trace of PS_2 **6a** indicates that the area ratio of diblock PS and linear PS **5a** precursor is 0.81:0.19 (Figure 1). Further analysis of the deconvoluted data indicates that the corrected value of M_n of PS_2 **6a** is in close agreement with the theoretical value (Table 1). The decrease in PDI suggested by the deconvoluted data is consistent with polymer−polymer couplings. Similar analyses were performed on the GPC traces of PS_3 **7a** and PS_4 **8a**. In the case of the former, the area ratio of 3-arm star, PS_2, and PS precursor is 0.77:0.17:0.06, indicating that 94% of the styrene units are incorporated into a coupling product. In the case of the latter, the area ratio of 4-arm star, 3-arm star, PS_2, and PS precursor is 0.65:0.17:0.08:0.10, indicating that 90% of the styrene units are incorporated in a coupling product. The analyses of the deconvoluted data of PS_3 **7a** and PS_4 **8a** both yield the expected decrease in PDI (Table 1). The corrected value of M_n for PS_3 **7a** shows a more distinctive increase in molecular weight, while that of PS **8a** is markedly lower than the theoretical value and is attributed to the compact structure of the star polymer in relation to its linear analogue.

The coupling reaction between PS **5a** and coupling agent **2** was also followed by UV/vis spectroscopy. The use of this analytical technique was deemed to be ideal to follow the conversion of the chromophoric RAFT end group ($\lambda_{\max} = 535$ nm) to the colorless 3,6-dihydro-2*H*-thiopyran ring that is formed during the reaction (Scheme 4). The inset of Figure 2

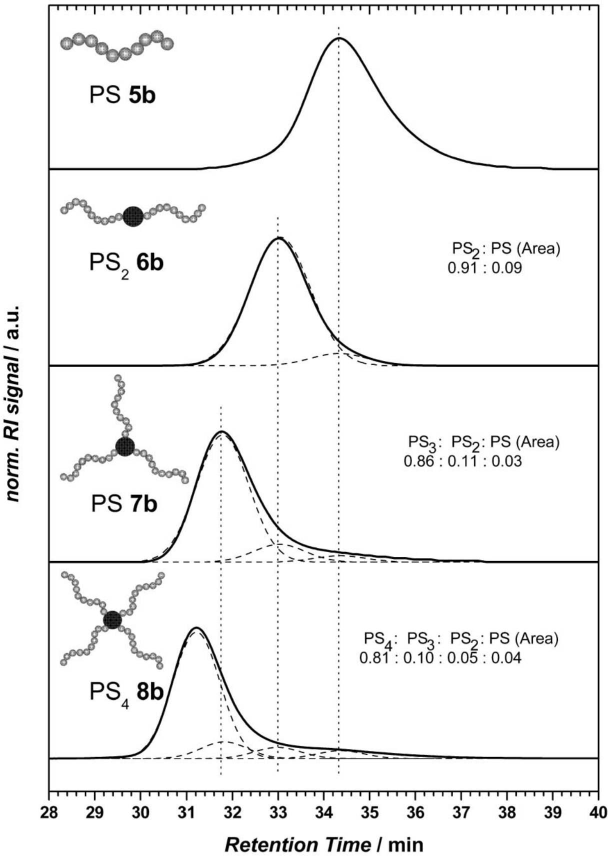


Figure 3. Comparative GPC traces of PS **5b** with coupling products PS$_2$ **6b**, PS$_3$ **7b**, and PS$_4$ **8b**. The dashed lines represent the results of deconvolution via peak splitting.

shows the absorbance of the RAFT end group of PS **5a** (λ = 400−800 nm). The monitoring of this absorbance over a period of 25 h yielded the concentration−time relationship presented in the main section of Figure 2, which indicates that the conversion of the thiocarbonyl group in **5a** reached a constant value of 92% after 24 h. This finding is consistent, within the limitations of both methods, with the results obtained from peak splitting of the GPC traces, taking into consideration that the GPC traces are influenced by unfunctionalized PS whereas the UV/vis spectra are not.

Synthesis and Characterization of Star Polymers Using PS 5b. Concurrent with the previous set of investigations, PS **5b** was also reacted with coupling agents **2**−**4** to yield star polymers PS$_2$ **6b**, PS$_3$ **7b**, and PS$_4$ **8b**, the GPC traces of which are presented in Figure 3. It is clear to observe the shift in the molecular weight distributions to lower retention times with increasing arm number. The elution peak of PS$_2$ **6b** is a combination of diblock PS and linear PS precursor. The result of peak splitting indicates that the area ratio of these species (PS$_2$ and linear PS precursor) is 0.91:0.09. Likewise, the elution peak of PS$_3$ **7b** is comprised of 3-arm star polymer, PS$_2$ polymer, and linear polymer precursor, the area ratios of which is 0.86:0.11:0.03. Furthermore, the elution peak of PS$_4$ **8b** is comprised of 4-arm star polymer and other star material of lower functionality. The area ratio of these four species (4-arm star, 3-arm star, PS$_2$, and linear PS precursor) is 0.81:0.10:0.05:0.04. In all cases, more that 90% of the styrene units are incorporated in a coupling product (91% for PS$_2$ **6b**, 97% for PS$_3$ **7b**, and 96% for PS$_4$ **8b**).

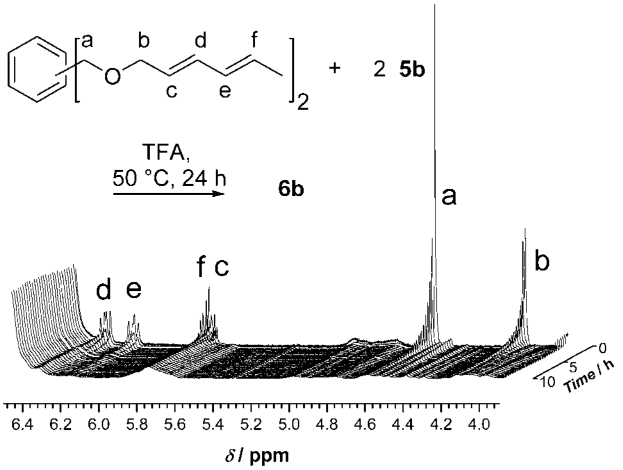


Figure 4. Overlay of ^{1}H NMR spectra (6.5−3.9 ppm region) of the reaction mixture of PS **5b** and coupling agent **2**.

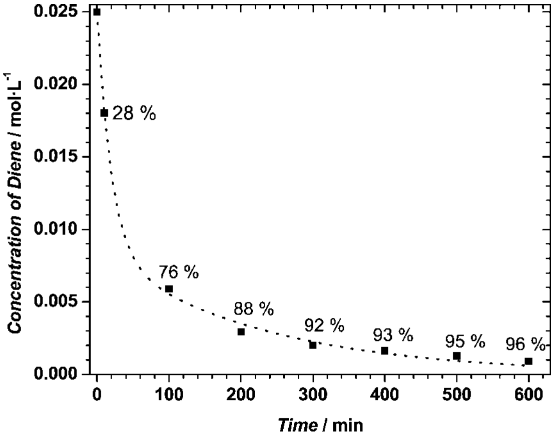


Figure 5. Concentration of diene with respect to time in the reaction of PS **5b** with coupling agent **2**.

Table 1 summarizes the mass distribution data for the star polymers synthesized from PS **5b**. While the M_n values determined from GPC measurements increase with growing arm number, the M_n values determined from the deconvoluted data more distinctly show this increase. The PDI values of the deconvoluted data, which are distinctly lower than that of the precursor, are also consistent with the formation of star polymers.

The reaction of PS **5b** with coupling agent **2** was also performed in an NMR tube in CDCl$_3$ solvent in order to monitor the progress of the reaction by ^{1}H NMR spectroscopy. This technique was selected in preference to UV/vis spectroscopy for two main reasons, the first of which is the fact that the presence of TFA catalyst in the reaction mixture imparts color to the final coupling product. The second reason for using ^{1}H NMR spectroscopy is that the reaction may be monitored with respect to the coupling agent, rather than the RAFT end group, which was the case with UV/vis spectroscopy.

Figure 4 shows an overlay of ^{1}H NMR spectra of the reaction mixture of PS **5b** and coupling agent **2** at 20 min intervals. Now, since a nonsymmetric diene is utilized, there are two possible regioisomers of the 3,6-dihydro-2*H*-thiopyran ring in the coupling products, which itself contains three chiral centers. Consequently, the large number of possible stereo/regioisomers of the coupling products renders monitoring of the HDA coupling reaction via the NMR spectroscopy complex. However, progress of the reaction is indicated by the disappearance of the vinylic protons (d and e in Figure 4) and the disappearance of aliphatic protons (a and b in Figure 4). The series of NMR spectra obtained were then used to generate Figure 5, which

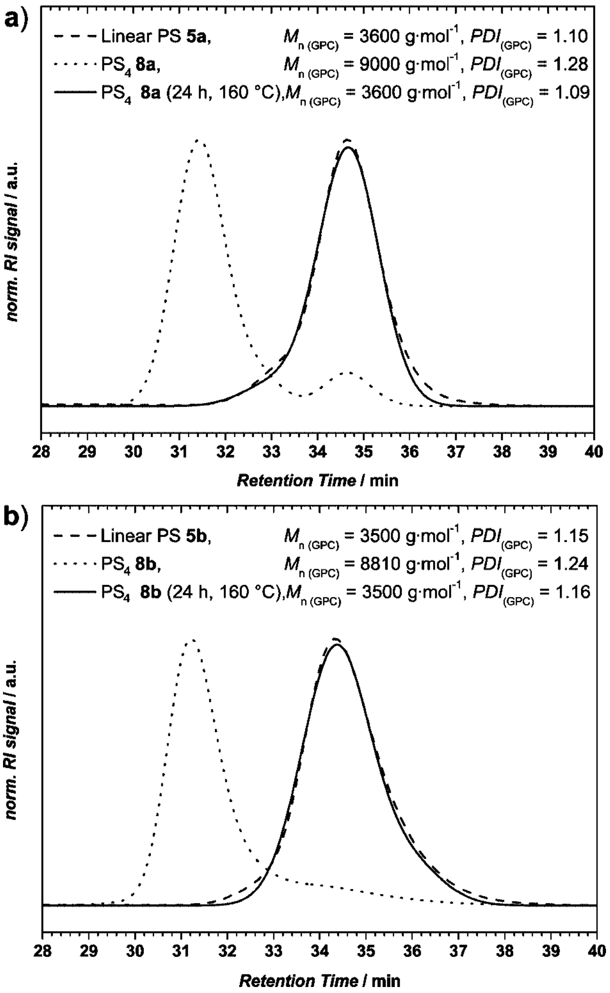
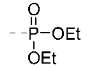
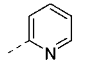


Figure 6. GPC traces of (a) PS **5a**, PS$_4$ **8a**, and its degradation product and (b) PS **5b**, PS$_4$ **8b**, and its degradation product.

Table 2. Performance of PS with Different RAFT End Groups

	 $-\!-\mathrm{P}(=\mathrm{O})(\mathrm{OEt})\mathrm{OEt}$	
Catalyst	$ZnCl_2$	TFA
Conversion (Time)	92 % (24 h)	96 % (10 h)
Initial color of reaction mixture	Pink	Red
Final color of reaction mixture	Colorless	Pale Yellow
Cleavage Conditions	160 °C/ 24 h	160 °C/ 24 h

shows the concentration of the diene function in the coupling agent **2** as a function of time. The data suggest that a 96% conversion of the diene is achieved in just 10 h (91% as approximated from GPC peak splitting) which is consistent with previous observations[37] that the pyridinyldithioester is, under the applied conditions, a more efficient heterodienophile than the phosphoryldithioester. The consistency between the NMR results and the GPC approximation is also observed and confirms that the pyridinyldithioester end group is a more effective heterodienophile by virtue of the higher conversions obtained.

Thermal Cleavage of Star PS$_4$ 8a,b. It has been well established that thioacetals and thioketals undergo fragmentation under such conditions as oxidative[42] and thermal.[43] Furthermore, the 3,6-dihydro-2*H*-thiopyran ring has been shown to fragment under radical conditions[39] and may also undergo a retro-Diels−Alder reaction.[38] Therefore, the investigation of the conditions under which the cleavage of these structures may be induced can be used in the design of macromolecular architectures with predetermined or targeted fragmentation patterns. It has been shown that the 3,6-dihydro-2*H*-thiopyran ring as a linking agent in polymer conjugates is stable for at least 24 h at 60 °C.[37] In the present investigation, the star polymers PS$_4$ **8a,b** were dissolved in an excess of toluene and subjected to thermal environments ranging from 80 to 160 °C. Interestingly, it was observed that the successive increase in the thermal treatment of the polymers brought about a successively increasing degree of fragmentation, with quantitative cleavage achieved after 24 h at 160 °C.

Figure 6a compares the GPC traces of PS$_4$ **8a** and its product to that of the original linear precursor PS **5a.** The M_n and PDI of the degradation product (3600 g mol^{-1} and 1.09, respectively) is in excellent agreement with the corresponding values of the precursor PS **5a** (3600 g mol^{-1} and 1.10, respectively), thus indicating the thermal treatment of the 4-arm star polymer was successful in the cleaving of all arms to recover linear PS.

Similarly, the complete induced fragmentation of PS$_4$ **8b** to its linear PS constituents was achieved at 160 °C, as is shown in Figure 6b. The product was found to have a $M_n = 3500$ g mol^{-1} and a PDI of 1.08, which is consistent with the precursor PS **5b**. The exploration of more variant conditions such as pH and oxidative environments on the degradation trends of the above-mentioned systems will be conducted in a forthcoming study as will the design of novel targeted-degradation materials.

In summary, an overall comparison of the performance of both RAFT end groups is presented in Table 2. While both RAFT agents **1a,b** are simple to synthesize, **1a** requires three synthetic stages, which can be performed successively in a one-pot synthesis, and a single purification stage, making it relatively simple to prepare in comparison to the vast majority of other RAFT agents. It has been shown that the pyridinyldithioester end group has superior reactivity toward the HDA cycloaddition; however, the phosphoryldithoester end group undergoes the same reaction with a benign catalyst, and our findings suggest that the reaction, although slow, can take place without the use of a catalyst.

Conclusions

The synthesis of star polymers with up to 4 arms by a combination of RAFT chemistry and the HDA cycloaddition has proven to be successful by the above-described results. In two examples, PS **5a,b** prepared by controlled polymerization with RAFT agents **1a,b** were used to form star polymers with up to 4 arms after reaction with multidiene containing coupling agents **2**−**4**. The present work verifies the ability of the HDA cycloaddition/RAFT chemistry combination to be useful in the convenient synthesis of macromolecules of predetermined complex architecture. It therefore successfully represents a viable technique that attempts to widen the synthetic tool box that is available to the organic chemist to advance the field of materials research.

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