One-Pot Synthesis of α,ω-Chain End Functional, Stereoregular, Star-Shaped Poly(lactide)

Matthew J. Stanford and Andrew P. Dove*

Department of Chemistry, University of Warwick, Coventry, CV4 7AL, U.K.

Received August 31, 2008; Revised Manuscript Received November 18, 2008

ABSTRACT: The synthesis of stereoregular α,ω-chain end functional linear, telechelic, and star-shaped polymers and copolymers is reported using a one-pot chain end functionalization methodology. Aluminum methyl complexes are applied in combination with functional and multifunctional initiating species to synthesize stereoregular poly(lactide)s by the stereospecific ring-opening polymerization of *rac*-lactide. The quenching of the reactions with an excess of acid chloride functional molecules has enabled the in situ quantitative modification of the ω-chain ends of the polymers such that primary and secondary alkyl and aryl groups can be incorporated. This methodology has been extended to the synthesis of linear, telechelic, and star-shaped polymers with "click" functional handles for both copper-catalyzed Huisgen 1,3-dipolar cycloaddition and thiol−ene Michael additions and block copolymers through the application of a trithiocarbonate, suitable for mediating RAFT polymerization. This tolerant and mild method is used in the synthesis of star-shaped block copolymers with a biodegradable poly(lactide) core and results in poly(lactide)s that display increased resistance to degradation.

Introduction

Poly(lactide) (PLA) is an aliphatic poly(ester) that is biocompatible, biodegradable, and can be derived from renewable resources.[1,2] PLAs of well-defined molecular dimensions are commonly synthesized by the controlled ring-opening polymerization (ROP) of lactide.[3−10] In this manner, the molecular characteristics of the polymer chains such as end groups, molecular weight, and molecular weight distribution can be readily dictated. The combination of the "green" credentials of PLA with its facile degradability, readily available stereocontrol, and the high levels of control afforded by the ROP methodologies applied make it an appealing polymer for applications ranging from packaging to biomedicine and microelectronics.[1,2,4,11,12] Indeed, a great deal of research has focused on controlling both the polymer structure and functionality, including telechelic, star-shaped, and block copolymers, as well as the synthesis of stereoregular polymers from racemic feedstocks.

Functional poly(ester)-containing block copolymers are gaining interest as a consequence of their unique properties.[13−15] Both the comparatively nonaggressive degradability of PLA and the crystalinity arising from its stereoregular forms give it unique and useful characteristics that can be particularly attractive as part of a block copolymer. For example, the self-assembly of PLA-containing block copolymers in bulk or thin films provides nanostructured materials that can be transformed into nanoporous materials using "soft-etch" methodology that displays a decreased effect on other functional groups within the materials.[13,16−18] Stereoregular PLAs have been shown to vary in their physical properties with effects on crystalinity and T_m, which in turn affects the degradation rate of the polymer.[3,9,19] Furthermore, the interaction of complementary homochiral poly(L-lactide) and poly(D-lactide) leads to the formation of a stereocomplex, and their application as components in block copolymers can have significant effects on the properties of micellar structures thereby derived.[19−23] The development of facile chemistries that will enable the further exploitation of these interesting effects is projected to greatly enhance research in this area.

The controlled ROP of cyclic esters can be mediated by a range of species including metal-based complexes and salts,[3−5,9] small molecule organic catalysts,[6,7] and enzymes.[10] Undoubtedly, the most widely studied of these are metal-based catalysts with several being reported to exert high levels of control over the polymerization process. One major advantage of metal-based catalysts is the access to stereoregular PLAs at room temperature and above.[9] Of the range of metal complexes reported for the stereocontrolled ROP of lactide, aluminum complexes bearing various ancillary ligands have proven to be extremely versatile. The family of salen bearing aluminum complexes [where salen is *N*,*N*′-bis(salicylaldimine)-1,2-ethylenediamine] are particularly interesting with subtle changes in the ligand structure resulting in the ability to tune the tacticity of the polymers produced.[24−38] Stereocontrolled ROP has been achieved in this manner with both chiral and achiral ligands, and while the mechanism of stereocontrol for the latter complexes remains under debate,[25,26,28] they provide a useful tool for the synthesis of stereoregular PLAs.

The active aluminum alkoxide species are often derived in situ by the addition of an initiating alcohol to a methyl aluminum complex, thus potentially providing facile manipulation of the α-chain end group of the polymer by the judicious choice of initiating alcohol. While in simple linear polymers and block copolymers this approach provides sufficient versatility to prepare a wide range of materials, more complex copolymer structures such as telechelic, ABA/ABC, and star-shaped copolymers require additional functionalization at the ω-chain end of the polymer. Most commonly, quenching the polymerization with a protic source results in a hydroxyl ω-chain end from which further postpolymerization modification can be performed. Ideally, the manipulation of these chain ends would be performed in situ after completion of the polymerization. Dubois, Jérôme, and Tessyié reported that the isolation and reaction of the aluminum alkoxide species, generated from the triethylaluminum-catalyzed ROP of ε-caprolactone, with methacryloyl chloride in the presence of pyridine provided a simple methodology for the preparation of ω-chain end functional macromonomers.[39,40]

Herein we report the development of a one-pot synthetic technique allowing for the production of stereoregular poly(lactide)s with controlled functionality at both the α- and ω-chain ends. The availability of the chain ends for further functionalization is demonstrated through the use of "click"

* To whom correspondence should be addressed: Ph +44 (0)24 7652 4107; Fax +44 (0)24 7652 4112; e-mail a.p.dove@warwick.ac.uk.

10.1021/ma801977e CCC: $40.75
Published on Web 12/11/2008

chemistry. Finally, the syntheses of multiblock copolymers with a central PLA block and functional multiarm star polymers are demonstrated.

Experimental Section

Materials. *rac*-Lactide (Aldrich) was purified by recrystallization from dry dichloromethane and sublimation two times before use. Toluene for polymerizations was refluxed over sodium then distilled, degassed, and stored under a nitrogen atmosphere. All alcohol initiators were dried over suitable drying agents, distilled, and degassed. Acid chlorides were distilled from PCl_5 or $SOCl_2$ and stored over 4 Å molecular sieves. 4-(2-Hydroxyethyl)-10-oxa-4-azatricyclo[5.2.1.02,6]dec-8-ene-3,5-dione[41] and Al salen complexes (**1**, **2**, and **3**) were synthesized as previously reported in the literature.[29,38] All other chemicals and solvents were obtained from Aldrich and used as received.

General Considerations. All manipulations were performed under moisture- and oxygen-free conditions either in a nitrogen-filled glovebox or by standard Schlenk techniques. Gel-permeation chromatography (GPC) was used to determine the molecular weights and polydispersities of the synthesized polymers. The system comprised a Polymer Laboratories Midas autosampler and LC1120 HPLC pump equipped with a guard column (Polymer Laboratories PLGel 5 μM, 50 × 7.5 mm), two mixed D columns (Polymer Laboratories PLGel 5 μM, 300 × 7.5 mm), and a Polymer Laboratories ERC-7515A differential refractive index (DRI) detector. The mobile phase was chloroform/triethylamine (95/5) eluent at a flow rate of 1.0 mL min^{-1}, and samples were calibrated against linear poly(styrene) standards (540−2.9 × 10^4 g mol^{-1}) using Cirrus v3.0; elution time was standardized against that of toluene. ^1H and ^{13}C NMR spectra were recorded on a Bruker DPX-300, DPX-400, AC400, or DRX-500 spectrometer at 293 K unless stated otherwise. Chemical shifts are reported as δ in parts per million (ppm) and referenced to the chemical shift of the residual solvent resonances ($CDCl_3$ ^1H: δ = 7.26 ppm; ^{13}C δ = 77.16 ppm). Mass spectra were acquired by MALDI-ToF (matrix-assisted laser desorption and ionization time-of-flight) mass spectrometry using a Bruker Daltonics Ultraflex II MALDI-ToF mass spectrometer, equipped with a nitrogen laser delivering 2 ns laser pulses at 337 nm with positive ion ToF detection performed using an accelerating voltage of 25 kV. Solutions of trans-2-[3-(4-*tert*-butylphenyl)-2-methyl-2-propylidene]malonitrile (DCTB) as matrix (0.3 μL of a 10 g L^{-1} acetone solution), sodium trifluoroacetate as cationization agent (0.3 μL of a 10 g L^{-1} acetone solution), and analyte (0.3 μL of a 1 g L^{-1} DCM solution) were applied sequentially to the target followed by solvent evaporation to prepare a thin matrix/analyte film. The samples were measured in reflectron ion mode and calibrated by comparison to 2 × 10^3 and 5 × 10^3 g mol^{-1} poly(ethylene glycol) standards. Elemental analyses were performed by Warwick Analytical Services.

Preparation of Functional Poly(lactide)s. In a typical experiment, the chosen alcohol initiator (0.05 mmol) was added to an ampule containing a solution of aluminum catalyst (**1**) (0.05 mmol) and *rac*-lactide (0.144 g, 1 mmol) in toluene (1.25 mL) under an atmosphere of nitrogen. The sealed ampule was then heated to 70 °C for 4 h before being cooled in ice for 10 min. The ampule was then taken into a glovebox whereupon the chosen acid chloride was added (0.5 mmol) before resealing the ampule and heating at 70 °C for a further 120 h. The resulting polymer was precipitated in cold petroleum ether, collected by filtration, and dried in vacuo.

Procedure for Thiophenol−Maleimide Conjugation Reactions. Maleimide functionalized PLAs (0.003 mmol) were placed in a vial and sparged with N_2. Solvent (1 mL) was added with stirring to dissolve the PLA. NEt_3 (2.6 μL, 0.03 mmol) and thiophenol (1.05 equiv) were added to the solution. The solution was stirred for the allotted time before the functionalized polymer was recovered by precipitation into petroleum ether and dried under vacuum at 60 °C for 12 h.

Synthesis of Methoxypoly(ethylene glycol)-4-chloro-4-oxobutanoate (Me-PEG-COCl) (6). Prepared using a synthesis modified from the literature.[42] Poly(ethylene glycol) monomethyl ether (2.0 g, 3.6 mmol) was stirred under nitrogen with 10 equiv of succinyl chloride (4.4 mL, 36 mmol). The excess acid chloride was removed by repeated washing with hexanes/diethyl ether (4:1 v:v). ^1H NMR ($CDCl_3$, 400.0 MHz): 4.20 (t, 2H, CH_2OCO); 3.65 (m, 2H, CH_2CH$_2$OCO); 3.5−3.6 (s, 42H, CH_2OCH_2); 3.48 (t, 2H, CH_2OCH$_2$CH$_2$OCH$_3$); 3.31 (s, 3H, CH_3); 3.22 (s, 4H, OCOCH_2CH_2COCl); 3.16 (t, 2H, CH_2CH$_2$0CH$_3$); 2.64 (t, 2H, CH_2OCH$_3$).

Synthesis of Pentanedioyl Chloride Mono-[2-(3,5-dioxo-10-oxa-4-azatricyclo[5.2.1.02,6]dec-8-en-4-yl)ethyl] Ester (Maleimide-Functional Acid Chloride) (5). Glutaric anhydride (1.87 g, 16.4 mmol), DMAP (0.40 g, 3.3 mmol), and NEt_3 (9.4 mL, 82 mmol) were added to a solution of 4-(2-hydroxyethyl)-10-oxa-4-azatricyclo[5.2.1.$0^{2,6}$]dec-8-ene-3,5-dione (3.42 g, 16.4 mmol) in dichloromethane (50 mL). The reaction was stirred at 30 °C for 16 h. The solution was poured onto 1 M $HCl_{(aq)}$ (150 mL) and Et_2O (150 mL), the organic phase was collected, and the aqueous phase was extracted twice more with Et_2O (150 mL). The combined organic layers were dried over $MgSO_4$ and filtered, and the solvent was removed under vacuum to yield a white solid. Purification was carried out by washing with hot toluene (3.34 g, 10.3 mmol, 63%). ^1H NMR ($CDCl_3$, 400.0 MHz): 10.48 (br s, 1H, COO*H*); 6.52 (s, 2H, CH_{vinyl}); 5.27 (s, 2H, CH$_{vinyl}$C*H*(OR)CH); 4.24 (t, 2H, $^3J_{H-H}$ = 5.3 Hz, NCH$_2$CH_2O); 3.76 (t, 2H, $^3J_{H-H}$ = 5.3 Hz, NCH_2CH$_2$O); 2.87 (s, 2H, CH$_{vinyl}$CH(OR)C*H*); 2.42 (t, 2H, $^3J_{H-H}$ = 7.3 Hz, CH_2COOH); 2.36 (t, 2H, $^3J_{H-H}$ = 7.3 Hz, CH_2CH$_2$CH$_2$COOH); 1.92 (p, 2H, $^3J_{H-H}$ = 7.4 Hz, CH_2CH$_2$COOH). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75.5 MHz): 178.5 (*C*OOH); 176.1 (N*C*(O)CH); 172.5 (O*C*(O)CH$_2$); 136.4 (*C*H$_{vinyl}$); 80.8 (CH$_{vinyl}$*C*H(OR)CH); 60.6 (NCH$_2$*C*H$_2$O); 47.4 (CH$_{vinyl}$CH(OR)*C*H); 37.8 (N*C*H$_2$CH$_2$O); 32.8 (*C*H$_2$CH$_2$*C*H$_2$COOH); 19.4 (CH$_2$*C*H$_2$CH$_2$COOH). Anal. Calcd for $C_{15}H_{17}NO_7$: C 55.73; H 5.30; N 4.35. Found: C 55.53; H 5.31; N 4.34. The maleimide functional carboxylic acid was quantitatively converted to the acid chloride using oxalyl chloride (5 equiv) in a DCM solution under an atmosphere of nitrogen. The excess oxalyl chloride and DCM were removed under vacuum, yielding the expected product as a white solid. ^1H NMR ($CDCl_3$, 400.0 MHz): 6.52 (s, 2H, CH_{vinyl}); 5.26 (s, 2H, CH$_{vinyl}$C*H*(OR)CH); 4.25 (t, 2H, $^3J_{H-H}$ = 5.3 Hz, NCH$_2$CH_2O); 3.76 (t, 2H, $^3J_{H-H}$ = 5.3 Hz, NCH_2CH$_2$O); 2.99 (t, 2H, $^3J_{H-H}$ = 7.3 Hz, CH_2COCl); 2.87 (s, 2H, CH$_{vinyl}$CH(OR)C*H*); 2.36 (t, 2H, $^3J_{H-H}$ = 7.3 Hz, CH_2CH$_2$CH$_2$COCl); 1.98 (p, 2H, $^3J_{H-H}$ = 7.4 Hz, CH_2CH$_2$COCl). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75.5 MHz): 176.1 (N*C*(O)CH); 172.1 (O*C*(O)CH$_2$); 168.8 (*C*OCl) 136.6 (*C*H$_{vinyl}$); 81.0 (CH$_{vinyl}$-*C*H(OR)CH); 60.9 (NCH$_2$*C*H$_2$O); 47.5 (CH$_{vinyl}$CH(OR)*C*H); 37.8 (N*C*H$_2$CH$_2$O); 32.1 (*C*H$_2$CH$_2$*C*H$_2$COCl); 19.9 (CH$_2$*C*H$_2$CH$_2$COCl).

Synthesis of 4-(Chlorocarbonyl)benzyldodecyl Carbonotrithioate (7). Prepared using a synthesis modified from the literature.[43] K_3PO_4 (2.10 g, 10 mmol) was added to a stirred solution of dodecanethiol (2.00 g, 10 mmol) in 40 mL of acetone at ambient temperature. The solution was allowed to stir for 1 h before CS_2 (2.26 g, 30 mmol) was added. The now yellow solution was warmed to 40 °C and stirred for a further 1 h. 4-(Bromomethyl)benzoic acid (2.12 g, 10 mmol) was added, and the reaction stirred at 40 °C for 16 h. The resultant solid was collected and partitioned between toluene (150 mL) and water (150 mL); the toluene was collected and washed a further three times with water (150 mL) before the resulting yellow solid was washed twice with acetone (50 mL) and dried in a vacuum desiccator over P_2O_5 for 72 h (3.1 g, 76% yield). ^1H NMR in $(CD_3)_2SO$ at 70 °C: δ 7.85 (d, 2H, $^3J_{H-H}$ = 7.3 Hz, Ar*H*); 7.38 (d, 2H, $^3J_{H-H}$ = 7.3 Hz, Ar*H*); 4.71 (s, 2H, ArCH_2S); 3.39 (t, 2H, $^3J_{H-H}$ = 7.2 Hz, SCH_2CH$_2$); 1.67 (quintet, 2H, $^3J_{H-H}$ = 7.2 Hz, SCH$_2$CH_2); 1.22−1.42 (m, 18H, C_9H_{18}); 0.88 (t, 3H, $^3J_{H-H}$ = 7.2 Hz, CH_3). $^{13}C\{^1H\}$ NMR $(CD_3)_2SO$: 224.1 (*C*S$_3$); 167.9 (*C*OOH); 138.8 (Ar); 131.8 (Ar); 129.8 (Ar); 129.1 (Ar); 68.1 (ArCH$_2$); 37.1 (SCH$_2$); 36.7, 31.7, 29.4, 29.3, 29.2, 29.1, 28.8, 28.6, 28.0, 22.4 ($C_{10}H_{22}$); 14.2 (*C*H$_3$). Conversion to the acid chloride was carried out quantitatively in an excess of thionyl chloride under an atmosphere of nitrogen. ^1H NMR ($CDCl_3$, 400.0 MHz): δ 8.06 (d, 2H, $^3J_{H-H}$ = 7.3 Hz, ArH); 7.48 (d, 2H, $^3J_{H-H}$ = 7.3 Hz, ArH); 4.68 (s, 2H, ArCH_2S); 3.36 (dd, 2H, SCH_2CH$_2$);

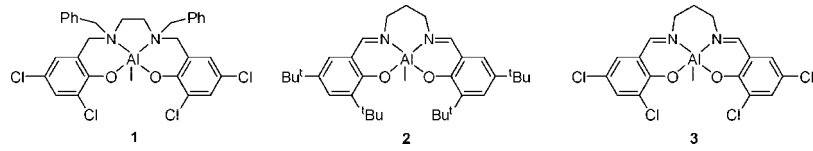


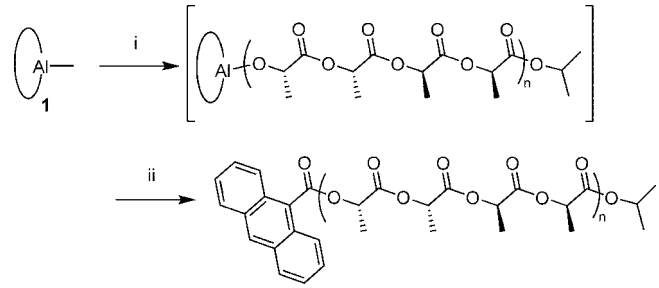
Figure 1. Aluminum complexes applied as catalysts in the stereoregular ROP of lactide.[29,38]

1.69 (quintet, 2H, $^3J_{H-H} = 7.1$ Hz, SCH_2CH_2); 1.22−1.40 (m, 18H, C_9H_{18}); 0.88 (t, 3H, $^3J_{H-H} = 7.1$ Hz, CH_3). $^{13}C\{^1H\}$ NMR $(CD_3)_2SO$: 222.0 (CS_3); 167.2 (COCl); 143.5 (Ar); 142.9 (Ar); 131.1 (Ar); 129.1 (Ar); 118.5 (ArCH$_2$); 41.9 (SCH$_2$); 40.1, 39.5, 36.8, 31.3, 29.0, 29.0, 28.9, 28.8, 22.1 ($C_{11}H_{22}$); 13.9 (CH_3).

Preparation of PLA−PS Block Copolymers. RAFT CTA-functionalized PLA (14) (0.01 mmol) was dissolved in 200 μL of toluene and 60 μL of styrene. The solution was freeze−pump−thawed four times before being heated to 120 °C for 16 h. The resulting block copolymer was precipitated in cold petroleum ether, collected by filtration, and dried in vacuo.

Degradation of the PLA-Containing Polymers. PLA was dissolved in a solution of toluene:methanol 80:20 before addition of TBD. The solution was stirred in a sealed ampule at the desired temperature for the allotted time period. The resulting polymer was precipitated in cold, acidified methanol, collected by filtration, and dried in vacuo.

Scheme 1. In Situ Functionalization of the ω-Chain End of Heterotactic PLA[a]



[a] (i) IPA, 2*n* equiv *rac*-lactide, toluene, 70 °C, 4 h; (ii) in situ addition of anthranoyl chloride, 70 °C, 120 h.

Results and Discussion

The application of a range of initiating alcohols has been demonstrated to result in the synthesis of PLAs displaying selective α-chain end functionality derived from the initiator, which upon quenching with a protic source results in a ω-hydroxyl chain end. Postpolymerization modification can be readily performed to furnish a range of functionality. In line with the report by Dubois, Jérôme, and Tessyié in which an isolated Al-capped poly(ε-caprolactone) was reacted with methacryloyl chloride in the presence of pyridine,[39,40] we began to examine if a one-pot methodology to perform this transformation by in situ quenching of the polymerization reaction could be achieved. Furthermore, we postulated that the application of the sterically hindered catalysts **1**−**3** (Figure 1) would provide access to heterotactic, atactic, and isotactic stereoblock PLAs, respectively, without the requirement to isolate the metal containing species or addition of extraneous base.

The stereocontrolled ROP of *rac*-lactide initiated by isopropanol (IPA) was carried out using **1** as previously described at 70 °C in toluene solution.[29,38] For a targeted DP = 20, after 4 h the reaction mixture was crash cooled by plunging the reaction ampule into an ice bath. Subsequent addition of 10 equiv of anthranoyl chloride and stirring the resultant solution at 70 °C enabled the isolation of a heterotactic PLA with isopropyl and anthracene end groups after precipitation in cold petroleum ether to remove excess anthranoyl chloride (Scheme 1).

^{1}H NMR analysis of the resultant polymer (Figure 2a) unambiguously shows the presence of the anthracene functionality in a concentration comparable to that of the α-chain end isopropyl functionality. Furthermore, GPC analysis of the polymer using both DRI and UV detection demonstrates the UV-active anthracene group is distributed throughout the polymer (DRI: M_n = 3470 g mol^{-1}, PDI = 1.08; UV: M_n = 3330 g mol^{-1}, PDI = 1.11). MALDI ToF MS analysis (Figure 2b) exclusively reveals peaks that correspond to the predicted molecular weights. Importantly, comparison to a polymerization quenched with methanol demonstrates that quenching the polymerization in this manner has no adverse effect on the polymer chain, with low polydispersity being maintained (MeOH quench: PDI = 1.11; anthranoyl chloride quench: PDI = 1.08). Additionally, the peaks in the MALDI-ToF spectrum are exclusively separated by 144 Da, indicating that very little transesterification occurs even after the increased reaction times at high temperature.

The versatility of this reaction was investigated by applying (Salen)aluminum catalysts which demonstrate a preference for the synthesis of other stereoregular PLAs (with their resultant different steric and electronic demands), different PLA chain lengths, and a range of functional acid chlorides. All of the catalysts applied in this study were successfully applied in this one-pot process, thus enabling the synthesis of a range of highly stereoregular PLAs to be realized. As illustrated in Table 1, the method also proceeds effectively using a range of acid chlorides including primary and secondary alkyl, aryl, and pyridyl. Notably, attempts to quench the polymerization with pivaloyl chloride did not result in functionalization of the ω-chain end of the polymer, most likely reflecting the increased steric demands of the tertiary α-carbon in combination with the bulky ancillary ligand of the ROP catalyst. In all cases, analysis of the polymers by NMR, GPC, and MALDI-ToF MS (see Supporting Information) revealed that the narrow dispersity of the polymers was maintained and complete end-group conversion was observed with molecular weights measured matching closely to those calculated.

Application of the simple methodology that has been introduced here enables the facile synthesis of α- and ω-chain end functional, stereoregular PLAs that would be particularly useful in the synthesis of telechelic and star-shaped polymers. Generation of the catalytic alkoxide species in situ enables initiation from multifunctional alcohols. In this manner, initiation from 1,3-propanediol, 1,1,1-tris(hydroxymethyl)ethane, and dipentaerythritol in the presence of **1** at 70 °C resulted in the synthesis of telechelic, 3-arm, and 6-arm star-shaped polymers, respectively. In the latter case, the aluminum alkoxide complex was prepared in situ before addition of *rac*-lactide to overcome the poor solubility of the dipentaerythritol in toluene. Quenching these reactions by addition of benzoyl chloride resulted in the appropriate ω-chain end multifunctional heterotactic PLAs ([LA]/[OH] = 10: I = 1,3-propanediol, M_n = 3590 g mol^{-1}, PDI = 1.12; I = 1,1,1-tris(hydroxymethyl)ethane, M_n = 7100 g mol^{-1}, PDI = 1.05; I = dipentaerythritol, M_n = 9130 g mol^{-1}, PDI = 1.16).

Further practical application of these techniques requires the incorporation of functionality at the chain ends. Obviously, the

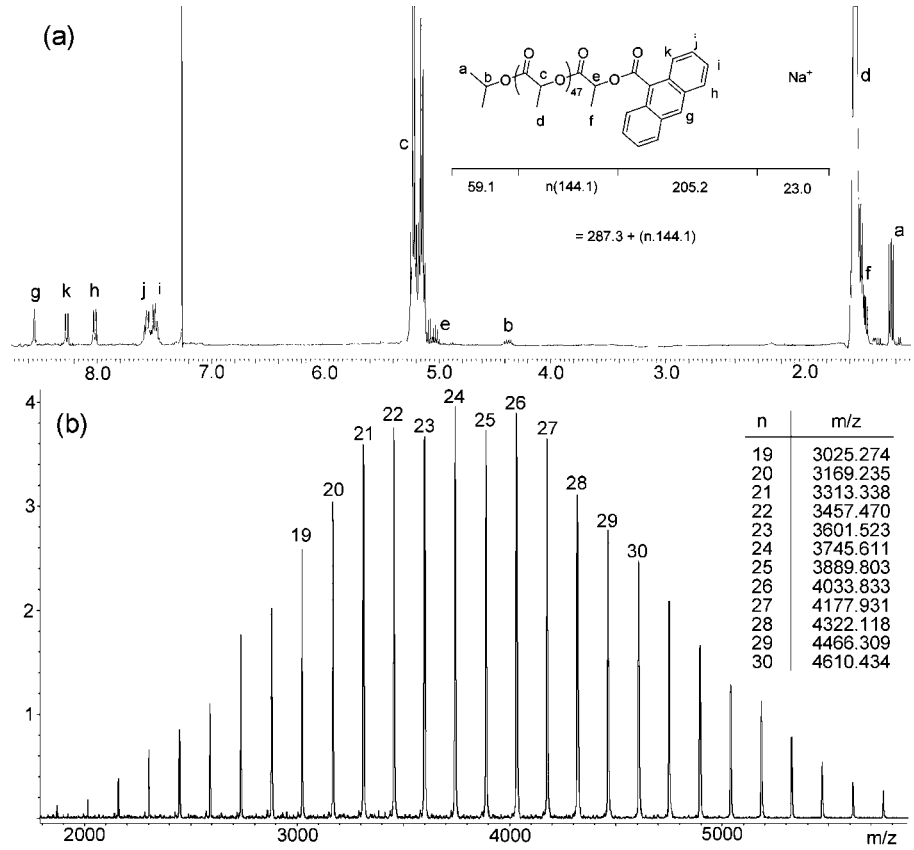


Figure 2. (a) ^{1}H NMR spectrum (heterotactic stereochemistry not shown) and (b) MALDI ToF MS of anthracene functionalized PLA.

Table 1. Preparation of ω-Chain End Functionalized Poly(lactide)s[a]

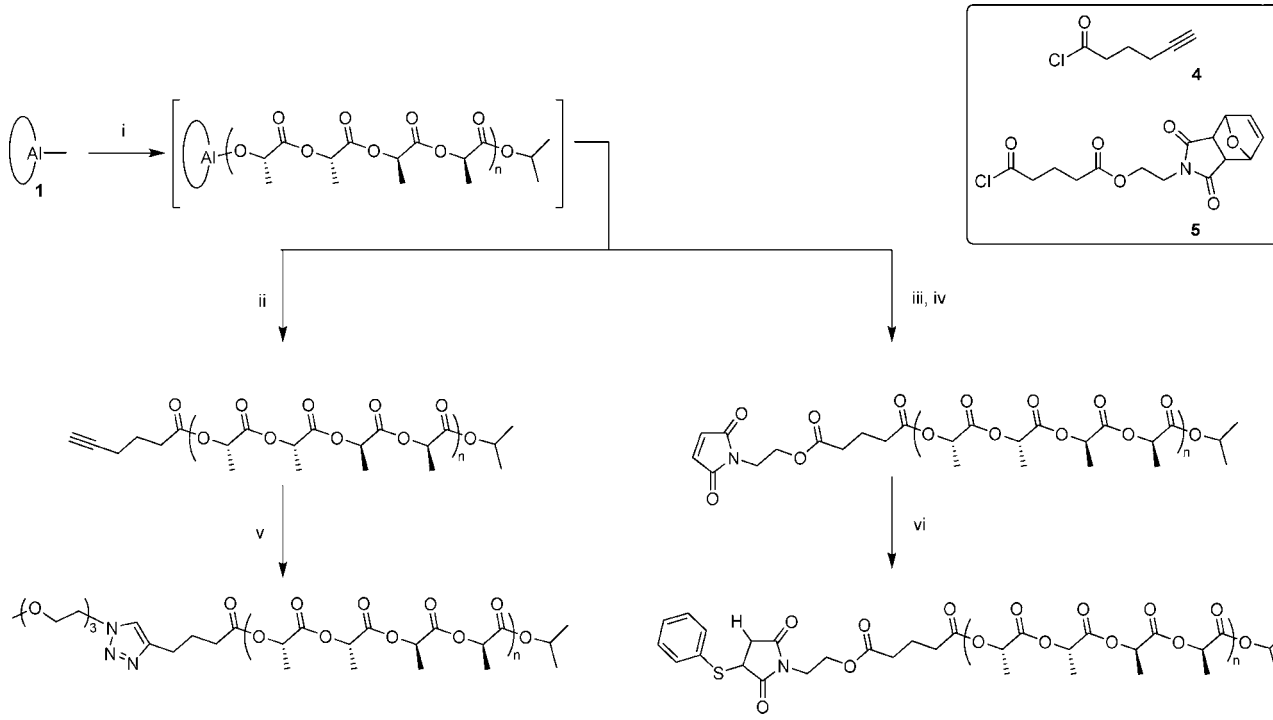
entry	target DP[b]	quenching agent[c]	catalyst	M_n(GPC), g mol^{-1} [d]	PDI[d]	mass (calc)[e]	mass (MALDI)[e]
1	20	methanol	**1**	3970	1.11	2965.1	2965.4
2	20	acetyl chloride[f]	**1**	3810	1.09	3223.5	3224.0
3	20	hexanoyl chloride	**1**	3760	1.07	3063.2	3063.8
4	20	benzoyl chloride	**1**	3890	1.09	3069.2	3069.4
5	20	isonicotinoyl chloride	**1**	4040	1.07	3070.2	3070.7
6	20	anthranoyl chloride	**1**	3470	1.08	3169.3	3169.2
7	20	isobutyroyl chloride	**1**	3890	1.08	3035.2	3035.4
8	20	pivaloyl chloride	**1**			3047.9	2965.3
9	10	hexynoyl chloride	**1**	2530	1.07	1618.2	1617.9
10	10	maleimide acid chloride (**5**)	**1**	3730	1.12	1829.4	1761.3[g]
11	10	Me-PEG-COCl	**1**	3110	1.06		—[h]
12	20	benzoyl chloride	**2**	3870	1.10	3069.2	3069.4
13	20	benzoyl chloride	**3**	3730	1.22	3069.2	3069.6
14	10	benzoyl chloride	**1**	1760	1.13	1628.2	1628.9
15	50	benzoyl chloride	**1**	9000	1.06		
16	100	benzoyl chloride	**1**	17 440	1.06		

[a] Polymerization reactions carried out using catalysts as previously described in the literature using isopropanol initiator. [b] Targeted degree of polymerization. [c] Reactions were stirred at 70 °C for 120 h in each case. [d] Determined by GPC analysis. [e] Calculated and determined by MALDI-ToF MS for a single DP20 polymer chain. [f] Pyrene butanol applied as initiating alcohol. [g] The furan-protected maleimide deprotects during analysis resulting in a calculated DP20 mass = 1761.5. [h] MALDI ToF of the block copolymer not suitable for characterization.

application of acid chloride species in the presence of aluminum alkoxides limits the range of applicable functional groups. The recent heightened interest in the application of "click" chemistry for polymer modification provides orthogonal modification strategies that are tolerant to a wide range of other functional groups.[44,45] To this end we synthesized and applied alkyne and azide functional acid chlorides, thus furnishing the multifunctional polymers with groups that would undergo the copper-catalyzed Huisgen 1,3-dipolar cycloaddition reaction.

The synthesis of alkyne chain end functional PLA was successfully realized by quenching with hexynoyl chloride, converted from the corresponding carboxylic acid by treatment with $SOCl_2$. Attempts to perform the Huigsen 1,3-dipolar cycloaddition at the chain ends of simple linear heterotactic PLAs have been hampered, possibly by the presence of the polyester backbone. While previous reports have demonstrated several mild methodologies for the "click" functionalization of side-chain functional poly(ester)s by this methodology,[46−49] functionalization of PLA chain ends has not been reported. In our studies we were unable to realize conversions above ~40% using the conditions employed (Scheme 2). Attempts to drive the reaction to completion by the application of more forcing conditions reported elsewhere resulted in degradation of the polymer chain. Our attention turned to examine other conditions for "click" reactions, previously reported to be tolerant of polyesters.[49] In a previous communication, we have demonstrated that the reaction of thiol-containing molecules and maleimide-functional PLAs proceeds in a 1:1 ratio, under mild

Scheme 2. Synthesis and Subsequent "Click" Reactions of ω-Chain End Functionalized PLA[a]



[a] (i) IPA, *rac*-lactide, toluene, 70 °C, 4 h; (ii) **4**, toluene, 70 °C, 120 h; (iii) **5**, toluene, 70 °C, 120 h; (iv) 100 °C, vacuum; (v) azido triethylene glycol, CuI, TEA, THF, 7 days, RT (40% conversion achieved); (vi) PhSH, NEt_3, DCM, 16 h, RT.

Table 2. Click Functionalization of the PLA ω-Chain End

		before thiophenol conjugation		after thiophenol conjugation	
entry	initiating alcohol	M_n[c]	PDI[c]	M_n[c]	PDI[c]
1	propan-2-ol[a]	3730	1.12	3870	1.10
2	propanediol[b]	4080	1.08	4140	1.08
3	1,1,1-tris(hydroxymethyl)ethane[b]	7740	1.05	7340	1.15
4	dipentaerthritol[b]	10 250	1.12	9440	1.09

[a] [LA]/[OH] = 20. [b] [LA]/[OH] = 10. Conjugations carried out under an atmosphere of nitrogen, using 1.05 equiv of thiophenol, 2 equiv of TEA as catalyst in DCM. [c] Obtained from GPC.

conditions to completion within a few hours.[50] Furthermore, no degradation of the PLA backbone was observed. Here, a furan-protected maleimide functional acid chloride, **5**, was used to quench linear, telechelic, and star-shaped polymers. Following deprotection at 100 °C for 16 h under vacuum, the maleimide functional PLAs (Table 2, entries 1−4) can be easily obtained. In this case reaction with thiophenol was applied to demonstrate the applicability of this methodology for the quantitative chain end conversion of the stereoregular polymers synthesized. In all cases, complete conversion is demonstrated via the disappearance of the maleimide vinyl resonance at $\delta = 6.8$ ppm (Figure 3) and the appearance of aromatic peaks of the thiophenol functionality ($\delta = 7.2-7.4$ ppm). MALDI-ToF analysis also corroborates quantitative conversion with the shift of the entire distribution by 110 Da in each case (see Supporting Information).

Extension of this methodology also enables the ready synthesis of block copolymers with a central, stereoregular, PLA block by quenching the ROP with either an acid chloride functional polymer or initiator for further polymerization. A poly(ethylene glycol) (PEG) mono methyl ether, with an average M_w of 550 (Aldrich), was converted to the acid chloride (**6**) by treatment with succinyl chloride. Quenching the polymerization with this macromolecular acid chloride resulted in a PLA−PEG block copolymer ([M]/[I] = 10; MeOH quench: $M_n = 1640$ g mol^{-1}, PDI = 1.18; after Me-PEG-COCl quench: $M_n = 3100$ g mol^{-1}, PDI = 1.06). The combination of ROP with controlled

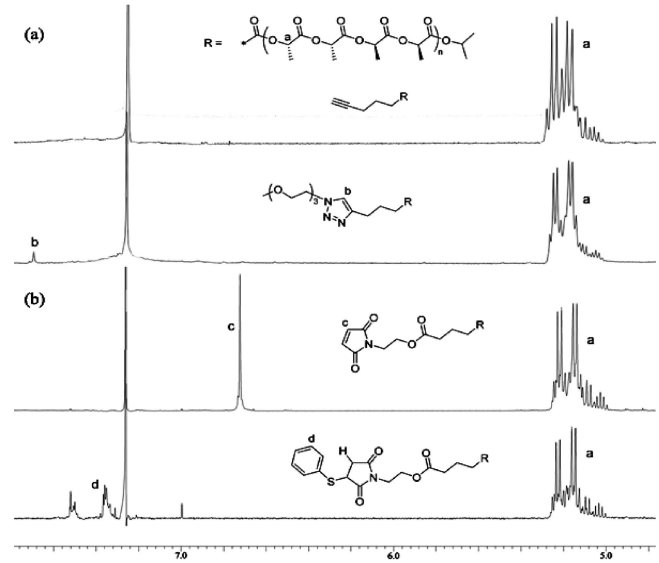
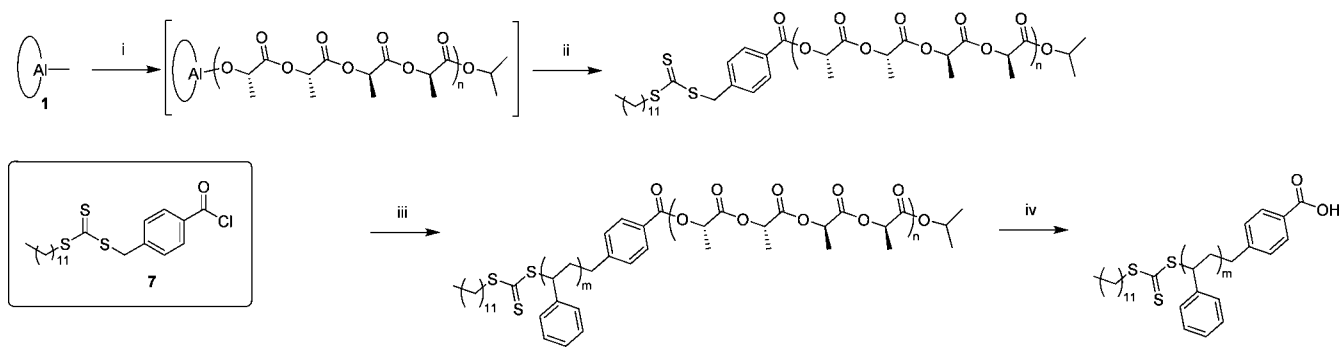


Figure 3. ^{1}H NMR analysis demonstrating "click" conjugation with (a) azido triethylene glycol (integrals: resonance $a = 20$; $b = 0.4$) and (b) thiophenol (integrals: resonance $a = 20$; $c = 2.4$; $d = 6.0$).

radical polymerization strategies such as reversible addition−fragmentation chain transfer (RAFT) enables access to a wide range of highly functional, partially degradable block copoly-

Scheme 3. Synthesis and Subsequent Degradation of PLA-*b*-PS[a]



[a] (i) IPA, *rac*-lactide, toluene, 70 °C, 2 h; (ii) **7**, toluene, 70 °C, 120 h; (iii) styrene, toluene, 16 h, 120 °C; (iv) TBD, MeOH, toluene, 72 h, 110 °C.

Table 3. GPC Data for Synthesis and Degradation of Multiarm Stars

		RAFT quenched PLA		PLA-*b*-PS[a]		PS after degradation[b]	
entry	initiating alcohol	M_n	PDI	M_n	PDI	M_n	PDI
1	none			7 600	1.28	7380	1.32
2	propan-2-ol	2490	1.08	8 950	1.26	8050	1.34
3	propandiol	6190	1.09	17 190	1.33	7890	1.35
4	1,1,1-tris(hydroxymethyl)ethane	8790	1.11	23 490	1.22	7450	1.39
5	dipentaerthritol	9490	1.04	24 030	1.18	7420	1.42

[a] Styrene, toluene, 16 h, 120 °C (80 equiv of monomer to macro-CTA; all experiments terminated at ca. 50% monomer conversion). [b] TBD (5 equiv), MeOH:toluene (1:5), 72 h, 110 °C [polymer] = 5 mg/mL.

mers.[51] The RAFT chain transfer agent (**7**), 4-(chlorocarbonyl)benzyldodecyl carbonotrithioate (Scheme 3), was synthesized by reaction of thionyl chloride with the corresponding carboxylic acid, in turn synthesized in a recently reported one-pot procedure.[43] Chain end functionalization of linear, telechelic, and star-shaped polymers was successfully achieved using the one-pot quenching methodology reported, with the presence of the RAFT chain transfer agent being demonstrated by both ^{1}H NMR and MALDI-ToF MS analysis of the resultant polymers. The polymerization of styrene from the PLA macro-CTAs was undertaken in toluene solution (30 vol % styrene) at 120 °C. In all cases, ^{1}H NMR and GPC analysis of the resultant copolymers confirmed the chain extension of the PLAs in line with the expected conversion of the styrene, producing linear, telechelic, and star-shaped block copolymers (Figure 3).

In order to confirm that PS was successfully grown from the PLA telechelic and star-shaped polymers, degradation by transesterification of the PLA was performed using MeOH in the presence of 1,5,7-triazabicyclo[4.4.0]dec-5-ene, TBD, at 110 °C. The GPC data for the degraded polymers were representative of the polystyrene produced from a non-macroinitiator; in each case only linear poly(styrene) chains of roughly the same molecular weight remained (Scheme 2 and Table 3). Notably, under milder conditions degradation of the PLA from the block copolymers was ineffective. Further investigations of this effect were undertaken by monitoring the degradation of linear and 6-arm star PLAs with −OH, −Ph (from benzoyl chloride quench), and −poly(styrene) end groups using in situ ^{1}H NMR spectroscopy (Table S1). In order to clearly observe the resonances attributable to the PLA, reduced molar concentrations of TBD were applied such that 1 mol equiv (to polymer) of TBD was applied in a 20:80 d_4-MeOD:d_8-toluene solution (10 mg/mL). After 24 h at 100 °C the resonances attributed to the methine resonances in the −OH end-capped polymers (δ = 5.10−5.25 ppm) had largely been reduced to baseline noise, and subsequent analysis by GPC revealed no polymer chains were present. However, under the same conditions, the −Ph and −poly(styrene) end-capped PLAs displayed no significant degradation (only a slight broadening of in the PDI for the −Ph end-capped PLA). Under more forcing conditions (48 h at 110 °C) the −Ph end-capped PLAs displayed significant degradation such that only very low oligomers remained in the case of both linear and star polymers M_n = ca. 1000 g mol^{-1} (initial M_ns: linear 3890 g mol^{-1}, 6-arm star = 9130 g mol^{-1}). Again, however, the PLA-*b*-PS block copolymers displayed no significant degradation; only a slight broadening in PDI was observable by GPC. Under the higher TBD loadings required to degrade the PLA component in these block copolymers (5 mol equiv of TBD (to copolymer), 110 °C in 20:80 MeOH:toluene, 5 mg/mL) it was notable that the molecular architecture also affected the degradation behavior of the polymers such that the star-shaped polymers resisted degradation for a significantly longer time period in comparison to the linear chains. We postulate that these effects are a combination of the inhibition of autocatalyzed degradation by the polymer chain end[52] and a consequence of the inaccessibility of the modified polymer cores arising from poor solubility and greater protection offered by the larger polymeric groups.

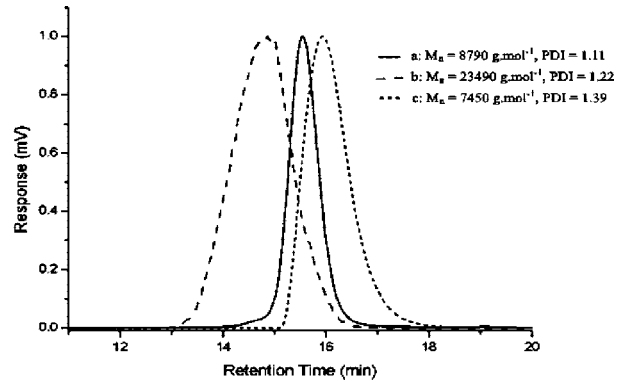


Figure 4. GPC traces for (a) 3-arm heterotactic PLA star-shaped polymer, (b) 3-arm (heterotactic PLA)-*b*-PS star-shaped polymer, and (c) PS after degradation of poly(ester).

Conclusion

In conclusion, we have demonstrated a one-pot synthetic route for the synthesis of a range of α- and ω-chain end functionalized poly(lactide)s that is tolerant to functionality such that handles for "click" chemistry and molecules suitable for the mediation of mechanistically distinct polymerizations can be incorporated. We have further extended this methodology to allow for the synthesis of functionalized telechelic and star-shaped polymers as well as showing the synthesis of block copolymers via two different approaches. The modification of the chain ends of the PLAs renders the polymers significantly more resistant to degradation.

Acknowledgment. The Research Councils UK (RCUK) are acknowledged for funding a fellowship to A.P.D. We gratefully acknowledge the support provided by EPSRC (EP/C007999/1) for the purchase of the Bruker Ultraflex MALDI-ToF MS instrument in addition to the provision of funding, including a studentship for M.J.S., to support this work (EP/D079136/1).

Supporting Information Available: Additional MALDI-ToF spectra for a range of functional polymers. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Drumright, R. E.; Gruber, P. R.; Henton, D. E. *Adv. Mater.* **2000**, *12*, 1841–1846.
(2) Auras, R.; Harte, B.; Selke, S. *Macromol. Biosci.* **2004**, *4*, 835–864.
(3) Jerome, C.; Lecomte, P. *Adv. Drug Delivery Rev.* **2008**, *60*, 1056–1076.
(4) Albertsson, A. C.; Varma, I. K. *Biomacromolecules* **2003**, *4*, 1466–1486.
(5) Dechy-Cabaret, O.; Martin-Vaca, B.; Bourissou, D. *Chem. Rev.* **2004**, *104*, 6147–6176.
(6) Kamber, N. E.; Jeong, W.; Waymouth, R. M.; Pratt, R. C.; Lohmeijer, B. G. G.; Hedrick, J. L. *Chem. Rev.* **2007**, *107*, 5813–5840.
(7) Bourissou, D.; Moebs-Sanchez, S.; Martin-Vaca, B. *C. R. Chim.* **2007**, *10*, 775–794.
(8) Wu, J. C.; Yu, T. L.; Chen, C. T.; Lin, C. C. *Coord. Chem. Rev.* **2006**, *250*, 602–626.
(9) Nakano, K.; Kosaka, N.; Hiyama, T.; Nozaki, K. *J. Chem. Soc., Dalton Trans.* **2003**, 4039–4050.
(10) Varma, I. K.; Albertsson, A. C.; Rajkhowa, R.; Srivastava, R. K. *Prog. Polym. Sci.* **2005**, *30*, 949–981.
(11) Albertsson, A. C.; Varma, I. K. *Adv. Polym. Sci.* **2002**, *157*, 1–40.
(12) Uhrich, K. E.; Cannizzaro, S. M.; Langer, R. S.; Shakesheff, K. M. *Chem. Rev.* **1999**, *99*, 3181–3198.
(13) Hillmyer, M. A. *Adv. Polym. Sci.* **2005**, *190*, 137–181.
(14) Duncan, R. *Nat. Rev. Drug Discovery* **2003**, *2*, 347–360.
(15) Martina, M.; Hutmacher, D. W. *Polym. Int.* **2007**, *56*, 145–157.
(16) Chen, L.; Phillip, W. A.; Cussler, E. L.; Hillmyer, M. A. *J. Am. Chem. Soc.* **2007**, *129*, 13786–13787.
(17) Zalusky, A. S.; Olayo-Valles, R.; Wolf, J. H.; Hillmyer, M. A. *J. Am. Chem. Soc.* **2002**, *124*, 12761–12773.
(18) Cavicchi, K. A.; Russell, T. P. *Macromolecules* **2007**, *40*, 1181–1186.
(19) Tsuji, H. *Macromol. Biosci.* **2005**, *5*, 569–597.
(20) Bishara, A.; Kricheldorf, H. R.; Domb, A. J. *Macromol. Symp.* **2005**, *225*, 17–30.
(21) Kang, N.; Perron, M. E.; Prud'homme, R. E.; Zhang, Y. B.; Gaucher, G.; Leroux, J. C. *Nano Lett.* **2005**, *5*, 315–319.
(22) Kim, S. H.; Nederberg, F.; Zhang, L.; Wade, C. G.; Waymouth, R. M.; Hedrick, J. L. *Nano Lett.* **2008**, *8*, 294–301.
(23) Hu, J. L.; Han, Y. D.; Zhuang, X. L.; Chen, X. S.; Li, Y. S.; Jing, X. B. *Nanotechnology* **2007**, *18*, 18.
(24) Zhong, Z. Y.; Dijkstra, P. J.; Feijen, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 4510–4513.
(25) Chisholm, M. H.; Patmore, N. J.; Zhou, Z. P. *Chem. Commun.* **2005**, 127–129.
(26) Nomura, N.; Ishii, R.; Yamamoto, Y.; Kondo, T. *Chem.—Eur. J.* **2007**, *13*, 4433–4451.
(27) Pang, X.; Du, H. Z.; Chen, X. S.; Wang, X. H.; Jing, X. B. *Chem.—Eur. J.* **2008**, *14*, 3126–3136.
(28) Chisholm, M. H.; Gallucci, J. C.; Quisenberry, K. T.; Zhou, Z. P. *Inorg. Chem.* **2008**, *47*, 2613–2624.
(29) Hormnirun, P.; Marshall, E. L.; Gibson, V. C.; White, A. J. P.; Williams, D. J. *J. Am. Chem. Soc.* **2004**, *126*, 2688–2689.
(30) Majerska, K.; Duda, A. *J. Am. Chem. Soc.* **2004**, *126*, 1026–1027.
(31) Nomura, N.; Ishii, R.; Akakura, M.; Aoi, K. *J. Am. Chem. Soc.* **2002**, *124*, 5938–5939.
(32) Ovitt, T. M.; Coates, G. W. *J. Am. Chem. Soc.* **1999**, *121*, 4072–4073.
(33) Ovitt, T. M.; Coates, G. W. *J. Am. Chem. Soc.* **2002**, *124*, 1316–1326.
(34) Radano, C. P.; Baker, G. L.; Smith, M. R. *J. Am. Chem. Soc.* **2000**, *122*, 1552–1553.
(35) Zhong, Z. Y.; Dijkstra, P. J.; Feijen, J. *J. Am. Chem. Soc.* **2003**, *125*, 11291–11298.
(36) Spassky, N.; Wisniewski, M.; Pluta, C.; LeBorgne, A. *Macromol. Chem. Phys.* **1996**, *197*, 2627–2637.
(37) Du, H. Z.; Pang, X.; Yu, H. Y.; Zhuang, X. L.; Chen, X. S.; Cui, D. M.; Wang, X. H.; Jing, X. B. *Macromolecules* **2007**, *40*, 1904–1913.
(38) Hormnirun, P.; Marshall, E. L.; Gibson, V. C.; Pugh, R. I.; White, A. J. P. *Proc. Natl. Acad. Sci. U.S.A.* **2006**, *103*, 15343–15348.
(39) Dubois, P.; Jerome, R.; Teyssie, P. *Makromol. Chem., Macromol. Symp.* **1991**, *42−3*, 103–116.
(40) Dubois, P.; Jerome, R.; Teyssie, P. *Macromolecules* **1991**, *24*, 977–981.
(41) Mantovani, G.; Lecolley, F.; Tao, L.; Haddleton, D. M.; Clerx, J.; Cornelissen, J.; Velonia, K. *J. Am. Chem. Soc.* **2005**, *127*, 2966–2973.
(42) Crisci, L.; Della Volpe, C.; Maglio, G.; Nese, G.; Palumbo, R.; Rachiero, G. P.; Vignola, M. C. *Macromol. Biosci.* **2003**, *3*, 749–757.
(43) Skey, J.; O'Reilly, R. K. *Chem. Commun.* **2008**, 4183–4185.
(44) Hawker, C. J.; Fokin, V. V.; Finn, M. G.; Sharpless, K. B. *Aust. J. Chem.* **2007**, *60*, 381–383.
(45) Lutz, J. F. *Angew. Chem., Int. Ed.* **2007**, *46*, 1018–1025.
(46) Jiang, X.; Vogel, E. B.; Smith, M. R.; Baker, G. L. *Macromolecules* **2008**, *41*, 1937–1944.
(47) Li, H. Y.; Riva, R.; Jerome, R.; Lecomte, P. *Macromolecules* **2007**, *40*, 824–831.
(48) Parrish, B.; Breitenkamp, R. B.; Emrick, T. *J. Am. Chem. Soc.* **2005**, *127*, 7404–7410.
(49) Riva, R.; Schmeits, S.; Jerome, C.; Jerome, R.; Lecomte, P. *Macromolecules* **2007**, *40*, 796–803.
(50) Pounder, R. J.; Stanford, M. J.; Brooks, P.; Richards, S. P.; Dove, A. P. *Chem. Commun.* **2008**, 5158–5160.
(51) Perrier, S.; Takolpuckdee, P. *J. Polym. Sci., Part A: Polym. Chem.* **2005**, *43*, 5347–5393.
(52) Kurokawa, K.; Yamashita, K.; Doi, Y.; Abe, H. *Biomacromolecules* **2008**, *9*, 1071–1078.

MA801977E