6374 *Macromolecules* **2010**, *43*, 6374–6380
DOI: 10.1021/ma1008447

Macromolecules
ARTICLE

Organocatalytic Tunable Amino Acid Polymers Prepared by Controlled Radical Polymerization

Amanda C. Evans,[†] Annhelen Lu,[‡] Courtney Ondeck,[†] Deborah A. Longbottom,*[,†] and Rachel K. O'Reilly*[,‡]

[†]*Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge CB2 1EW, U.K., and* [‡]*Department of Chemistry, University of Warwick, Gibbet Hill Road, Coventry CV4 7AL, U.K.*

Received April 16, 2010; Revised Manuscript Received June 24, 2010

ABSTRACT: Two families of organocatalytically active polystyrene-based copolymers with tunable incorporations of 4-hydroxyproline have been synthesized using two different controlled radical polymerization technologies: nitroxide-mediated polymerization (NMP) and reversible addition−fragmentation chain transfer (RAFT) polymerization. Both of these methodologies allow ready access to a number of polymeric species with controllable molecular weights, narrow molecular weight distributions (ca. 1.2), and reliable functionality incorporations (between 3 and 26%). The organocatalytic activity and selectivity of the NMP-derived family of copolymers with variable incorporations of L-proline have been investigated using the aldol reaction, which provided high conversion to products (>95%) with very good diastereo- and enantioselectivities. We propose that these materials have potential as highly efficient recoverable organocatalyst supports whose solubility and loading can be readily tailored to the desired application.

Introduction

L-Proline and L-proline derivatives such as 4-hydroxy-L-proline (Figure 1) are well-established organocatalytic species, able to catalyze a number of chemical transformations in a highly efficient and enantioselective manner.[1] These transformations, which usually proceed in high yield and result in high diastereo- and enantioselectivities, include key organic reactions such as the aldol reaction, Michael addition, and Robinson annulation, among many others. For a more comprehensive overview of organocatalysis, see the following recent reviews in the area.[2−19] L-Proline is known to behave as a bifunctional substrate, and its nucleophilic secondary amine group in combination with the Brønsted acid activity of its carboxylic acid group renders it a particularly selective and efficient organocatalyst.

The controllable incorporation of L-proline-derived monomer units into highly defined polymeric species holds great interest for polymer and organic chemists alike. Such polymers could be readily used as diastereo- and enantioselective organocatalysts, with their degree of active monomer incorporation controllable, or tunable, via the copolymerization reaction. By altering both incorporations and polymeric backbones, these materials may be tuned to be environment or stimuli-responsive substances, allowing for solution-phase product evolution and facile recycling of the organocatalytically active polymer species.

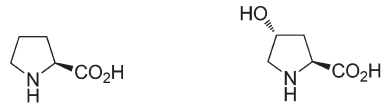
Until recently, controlled radical polymerization had not been used to incorporate proline-derived monomer units into copolymers in a manner that would leave these key organocatalytically active functional groups available to stabilize reaction transition states.[20,21] Endo and co-workers have reported the use of controlled radical polymerization techniques to facilitate the incorporation of both proline and hydroxyproline units into polyacrylamide backbones using the amino group as a functional tether;[22−25] however, this monomer incorporation strategy prevents the amino nitrogen from playing its necessary role in the formation of the catalytic enamine intermediate. In order to maintain L-proline's key active functional groups, the majority of reported organocatalytically active proline-based polymers have involved the attachment of a single L-proline derivative to a preformed polymer or bead, with polystyrene (PS)[26−29] and poly(ethylene glycol) (PEG)[30−32] dominating as supports for covalent attachment.[33,34] L-Proline derivatives have also been supported on dendrimers[35−37] and peptides[38,39] and incorporated into ionic liquids[40,41] in order to produce highly selective supported organocatalysts. Although a number of these approaches facilitate the incorporation of specific loadings, they do not generally allow for the addition of a second reactive center to the support.

Most recently, suspension copolymerization techniques have been used by Hansen and co-workers to synthesize methacrylate polymer beads incorporating L-proline derivatives and other organocatalytically active species. A high degree of selectivity and reactivity of this family of copolymers has then been demonstrated in a variety of reaction contexts.[42−45] This polymerization technique does result in functional monomer incorporation that is a direct reflection of equivalents of monomer added although it does not readily allow for the synthesis of more complex polymer architectures such as block copolymers. In addition, recent work by Gallardo described the synthesis of hydroxyproline-based methacrylic polybetaines and their catalytic activity in pure organic solvents.[46]

We are interested in developing the use of controlled radical polymerization techniques such as NMP[47−50] and RAFT[51−59] for the synthesis of further tunable organocatalytic polymers. Both NMP and RAFT are highly tolerant of functional groups and allow for the controlled polymerization of prefunctionalized monomers that yield well-defined polymers with unique properties and capabilities. In addition, the ability of CRP to allow for the chain extension and selective chain end functionalization of polymers is an important feature in the future applications of these materials. Copolymerization using both NMP and RAFT is well-precedented and facilitates access to a broad range of tunable polymeric architectures. In the case of RAFT-derived

*Corresponding authors. E-mail: dal28@cam.ac.uk (D.A.L.); r.k.o-reilly@warwick.ac.uk (R.K.O.).

 Published on Web 07/09/2010



L-Proline 4-Hydroxy-L-proline

Figure 1. Structures of L-proline and 4-hydroxy-L-proline.

copolymers, further structural diversity can be introduced at the polymer chain end via postpolymerization modification of the thiocarbonyl end groups.[60] The application of these controllable polymerization techniques should allow for the incorporation of organocatalytically active species, such as L-proline and its derivatives, into copolymeric species in a highly tolerable and tunable manner.

To this end, in 2009 our groups reported the application of RAFT polymerization chemistries for the synthesis of proline-functionalized polystyrenes in both mono- and bis-protected forms.[20] In this work 4-hydroxyproline provided a useful starting point for monomer construction, as the 4-hydroxy group afforded a means for attachment that would leave both amine and carboxylate functional groups available to potentially provide organocatalytic activity. However, racemization of the key stereocenter at *C*2 was observed during monomer synthesis, a phenomenon that did not impact that original work but did imply that an alternative strategy for monomer generation would be necessary in order to ensure that only enantiomerically pure monomeric units would be incorporated into polymer, an essential feature for the creation of organocatalytic materials.

Thus, our new synthetic strategy for the preparation of L-proline-derived monomer units involves the use of an alternative coupling strategy which ensures the chirality of the proline is maintained upon tethering to the styrene scaffold. Herein we report the successful and tunable incorporation of a novel L-proline-derived styrenic monomer unit into polystyrene using two controlled radical polymerization techniques: nitroxide-mediated polymerization (NMP) and reversible addition−fragmentation chain transfer (RAFT) polymerization. We have employed a chain transfer agent (CTA) for our RAFT-mediated polymerizations that incorporates a pyrene moiety into the copolymer chain end. This widely employed fluorescent "reporter group" enables facile determination of end-group fidelity and tracking of the functional polymer in solution. These functional copolymers were then successfully deprotected, unveiling the amine and acid functionalities simultaneously, and their utility as highly selective organocatalytic materials is subsequently reported.

The ability to accurately "tune" the degree of L-proline incorporation into our copolymers provides us with a means to control and tune the solubility of our copolymers. One of the biggest drawbacks of using proline as an organocatalyst is its limited solubility in organic solvents, a property that a number of synthetic groups have addressed on a small-molecule scale.[61−65] We have attempted to address this issue of solubility by creating polymers with varying degrees of hydrophobicity and hydrophilicity, depending upon the degree of incorporation of the L-proline-derived monomer unit. This level of tuning provides us with a series of polymeric organocatalysts with varying solubilities that can be deployed, for example, under mild hydrophobic conditions and that have the potential to be recovered by posthydrophilic work-up. We propose that ultimately, by incorporating these supported catalysts into polymeric nanostructures, the materials can thus be tuned to provide small enzyme-like hydrophobic "pockets of reactivity" within an environmentally friendly aqueous environment.

Experimental Section

Unless otherwise stated, chemicals were used as received from Aldrich, Fluka, and Acros. Styrene was distilled over CaH_2 or filtered through a plug of silica prior to use and stored at −5 °C. AIBN (2,2′-azo-bis(isobutyronitrile)) was recrystallized twice from methanol and stored in the dark at 4 °C. Universal alkoxyamine initiator (*N*-*tert*-butyl-*O*-(1-(4-(chloromethyl)phenyl)ethyl)-*N*-(2-methyl-1-phenylpropyl)hydroxylamine), pyrene-functionalized RAFT initiator (**3**), and (2*S*,4*R*)-dibenzyl 4-hydroxypyrrolidine-1,2-dicarboxylate were prepared as reported in the literature.[20,50] Dialysis tubing was purchased from Medicell International Ltd. with a molecular weight cutoff of 7 kDa. ^{1}H NMR spectra were recorded at 400 or 500 MHz on a Bruker Avance DPX-400/DPX-500 spectrometer using $CDCl_3$ and d_6-DMSO. For spectra recorded in $CDCl_3$, residual protic solvent $CHCl_3$ ($\delta_H = 7.26$ ppm) was used as an internal reference. ^{13}C NMR spectra were recorded on the same spectrometers at 100 or 125 MHz, using the central resonance of $CDCl_3$ ($\delta_C = 77.0$ ppm) as the internal reference. For spectra recorded in d_6-DMSO, residual protic solvent DMSO ($\delta_H = 2.50$ ppm) was used as an internal reference. ^{13}C NMR spectra were recorded on the same spectrometers using the central resonance of d_6-DMSO ($\delta_C = 39.7$ ppm) as the internal reference. Size exclusion chromatography/gel permeation chromatography (SEC/GPC) measurements were performed using a Viscotek VE1122 solvent delivery system with a Viscotek VE3580 refractive index detection system using tetrahydrofuran as an eluent at a flow rate of 1 mL/min, unless otherwise stated. The molecular weights of polymers were calculated relative to 10 polystyrene standards (M_p 580−377 400 Da) with two PLgel 5 μm mixed C columns (300 mm × 7.5 mm).

Infrared spectroscopy was recorded on a Perkin-Elmer Spectrum 100 FT-IR spectrometer. UV−vis spectra were recorded on a Varian Cary 4000 UV−vis spectrophotometer in tetrahydrofuran unless otherwise stated. HPLC analysis was performed using supercritical fluid chromatography (SFC) on a Berger Minigram using a Chiralpak ADH column (0.46 × 25 cm). Specific rotation measurements were recorded in $CHCl_3$ on a Perkin-Elmer 241 polarimeter using a sodium source ($\lambda = 589$ nm). Mass spectroscopy data were obtained on a Bruker MicroTOF ESI. Microanalyses were performed using a CE-440 elemental analyzer. Hydrogenation was performed using a 100 mL Roth reactor at varying temperatures under varying atmospheres of hydrogen.

(2*S*,4*R*)-Dibenzyl 4-(4-vinylbenzoyloxy)pyrrolidine-1,2-dicarboxylate (1). A solution of 4-vinylbenzoic acid (1.0 g, 6.76 mmol, 1.20 equiv), EDCI·HCl (1.30 g, 6.76 mmol, 1.20 equiv), and DMAP (0.14 g, 1.1 mmol, 0.2 equiv) in DMF (10 mL) was added to a dry round-bottomed flask and stirred for 1 h until the solution changed from cloudy to transparent. Then a solution of (2*S*,4*R*)-dibenzyl 4-hydroxypyrrolidine-1,2-dicarboxylate (2.0 g, 5.6 mmol, 1.0 equiv) and DIEA (1.53 g, 11.8 mmol, 2.1 equiv) in DMF (8 mL) was added to the reaction. The reaction mixture was then stirred at room temperature for 7 days, at which point it was quenched with a saturated solution of cold ammonium chloride (10 mL), extracted with EtOAc (3 × 10 mL), and dried ($MgSO_4$), and the solvent was removed *in vacuo*. The crude product was purified by flash column chromatography (2:1, petroleum ether:EtOAc) to yield 1.96 g (71%) of **1** as a white crystalline solid. ^{1}H NMR (500 MHz, d_6-DMSO, 27 °C): δ 7.91 (2H, d, J = 8.5 Hz, H-6), 7.60 (2H, d, J = 8.5 Hz, H-7), 7.41−7.26 (10H, m, Ar), 6.81 (1H, dd, J = 17.5, 11.0 Hz, H-8), 6.01 (1H, d, J = 17.5, H-9b), 5.46 (1H, s, H-4), 5.43 (1H, d, J = 11.0 Hz, H-9a), 5.18 (1H, s, Bn)*, 5.11 (1H, s, Bn)*, 5.08 (1H, s, Bn)*, 5.02 (1H, s, Bn)*, 4.59 (1H, 2*t*, J = 7.5 Hz, H-2)*, 3.78 (2H, m, H-5a and H-5b)*, 2.63 (1H, m, H-3b)*, 2.37 (1H, m, H-3a)* (asterisk denotes rotamers). ^{13}C NMR (125 MHz, d_6-DMSO, 27 °C): δ 170.8, 164.5, 153.5, 141.4, 135.3, 131.2, 129.0, 128.9, 128.6, 127.6, 127.4, 127.3, 127.2, 127.1, 126.9, 126.2, 115.8, (71.4 and 72.1)*, 66.4, 66.0, (56.9 and 57.2)*, (51.3 and 51.7)*, (34.7 and 35.7)* (asterisk denotes rotamers). ^{1}H NMR (500 MHz, d_6-DMSO, 100 °C): δ 7.91 (2H, d, J = 8.0 Hz, H-6), 7.60 (2H, d, J = 8.0 Hz, H-7), 7.42−7.23 (10H, m, Ar), 6.83 (1H, dd, J = 17.0, 11.0 Hz, H-8), 5.94 (1H, d, J = 17.0, H-9b), 5.50 (1H, br s, H-4), 5.43 (1H, d, J = 11.0 Hz, H-9a), 5.15 (2H, s, Bn), 5.12 (2H, m, Bn), 4.61 (1H, t, J = 7.5 Hz, H-2), 3.82 (1H, dd, J = 10.0, 5.0 Hz, H-5a), 3.75

(1H, m, H-5b), 2.61 (1H, m, H-3b), 2.38 (1H, m, H-3a). ^{13}C NMR (125 MHz, d_6-DMSO, 100 °C): δ 170.8, 164.5, 153.5, 141.7, 135.4, 131.4, 129.2, 128.7, 128.4, 127.9, 127.8, 127.5, 127.3, 127.2, 126.8, 125.8, 116.8, 71.5, 66.4, 66.0, 57.5, 52.1, 35.4. Elem. Anal. Found C, 71.33; H, 5.61; N, 2.92 ($C_{29}H_{27}NO_6$); expected C, 71.74; H, 5.61; N, 2.88. ν_{max}(neat)/cm^{-1}: 1737 (C=O ester), 1702 (C=O carbamate), 1496 and 1453 (C=C aromatic). HR-ESI: $[M + H]^+$ 486.1918 (Calcd), 486.1922 (Found). $[\alpha]_D^{25} = -30$ ° ($c = 0.9$, $CHCl_3$).

General Procedure for the Polymerization of Styrene and Functional L-Proline Monomer. A general polymerization protocol adapted from literature precedent is reported. A solution of styrene (2.0 g, 0.019 mol), **1**, and CTA **3** or NMP initiator was added to a dry ampule containing a dry stirrer bar. The solution was degassed using 3−5 freeze−pump−thaw cycles, backfilled with nitrogen gas, sealed, and placed in a preheated oil bath at the required temperature (110 °C for RAFT polymerizations and 125 °C for NMP polymerizations). After a certain amount of time, an aliquot was removed for ^{1}H NMR analysis to determine percent conversion of monomer. The polymerization was quenched by the addition of a minimal amount of tetrahydrofuran (THF) and rapid cooling in liquid nitrogen. The THF/polymer solution was precipitated dropwise into rapidly stirred cold methanol (or petroleum ether), and the precipitated polymer was isolated from the solvent by filtration and dried in a vacuum oven at 40 °C overnight. Molecular weights and polydispersity indices were measured by GPC, and ^{1}H NMR spectroscopy was used for the determination of end-group functionality, percentage incorporation of monomer **1**, and molecular weight determination by integrating polymer backbone signals and characteristic monomer **1** signals relative to characteristic end-group signals.

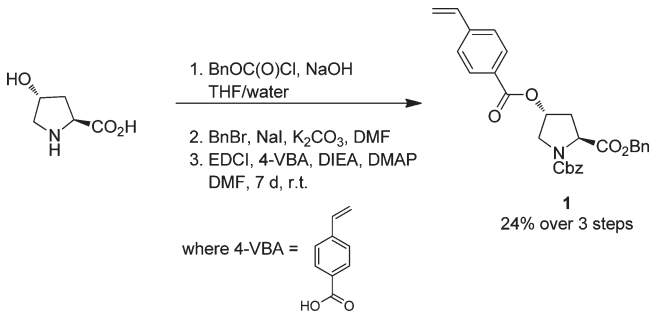
Representative Characterization Data for the Copolymerization of Styrene and Monomer 1 Using NMP, Polymers 2a−e. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.32−0.85 (3 H_s + 5H_p (polymer backbone of **1** (3H_p), and CH_2COC (2H_p)), 3.30−3.20 (1H_{eg}, m, PhC*H* of nitroxide end group), 3.90−3.73 (2H_p, br m, CH_2-NCbz), 4.60−4.50 (1H_p, d, C*H*CO$_2$Bn), 5.27−5.01 (4H_p, m, CH_2 on Cbz and Bn), 5.50 (1H_p, s, C*H*OCO), 7.50−6.40 (5H_s and 14H_p, m, aromatic peaks for styrene and **1**), where H_s = protons from polystyrene, H_p = protons from monomer **1** in polymer, and H_{eg} = protons from end group.

Representative Characterization Data for the Copolymerization of Styrene and Functional Monomer 1 Using RAFT, Polymers 4a−c. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.32−0.85 (3 H_s + 5H_p (polymer backbone of **1** (3H_p), and CH_2COC (2H_p)), 3.38−3.35 (2H_{eg}, br m, *CH*$_2$CO$_2$CH$_2$CH$_2$S), 3.53−3.51 (2H_{eg}, br m, CH$_2$CO$_2$CH$_2$*CH*$_2$S), 3.90−3.80 (2H_p, br m, CH_2NCbz), 4.24−4.23 (2H_{eg}, br m, CH$_2$ CH$_2$CO$_2$*CH*$_2$CH$_2$S), 4.60−4.50 (1H_p, d, C*H*CO$_2$Bn), 5.23−5.01 (4H_p, m, CH_2 on Cbz and Bn), 5.50 (1H_p, s, C*H*OCO), 7.50−6.40 (5 H_s, 4H_p, m, aromatic peaks for styrene and **1**), 8.15−7.84 (9H_{eg}, m, pyrene signals on polymer chain end).

General Protocol Used for All Percent Incorporations for the Deprotection of NMP-Derived Polymers Using Hydrogenation. Deprotection of NMP-derived polymers via hydrogenation was attempted using several conditions. A portion of the polymer (1.2×10^{-5} mmol, 1 equiv) was dissolved in 2 mL of solvent (EtOAc, toluene, etc.), and 100 mg of palladium on carbon (10 wt %) was then added. After 72 h, palladium was removed by filtration through Celite or a Pore 4 frit, solvent was removed *in vacuo,* and the resulting crude product was dried and analyzed for successful removal of Cbz and Bn groups. Specifically, the disappearance of ^{1}H NMR signals in the region δ 5.0−5.3 ppm (4H_p, m, CH_2 on Cbz and Bn) was focused upon. This region of the ^{1}H NMR spectrum was compared to the original polymer to determine the degree of deprotection.

General Protocol Used for All Percent Incorporations for the Deprotection of NMP-Derived Polymers Using Hydrobromic/Acetic Acid. A sample of NMP polymer (0.017 mmol, 1 equiv) was taken up in 45% HBr in acetic acid (5 mL) and allowed to stir at room temperature for 2 days. This solution was then directly precipitated into cold isopropanol and isolated by filtration. The resulting pink precipitate was dried and analyzed for successful removal of Cbz and Bn groups (disappearance of ^{1}H NMR signals in the region δ 5.0−5.3 ppm (4H_p, m, CH_2 on Cbz and Bn)) (see Figure S5).

Scheme 1. Synthesis of Monomer 1



General Protocol for the Organocatalytic Application of NMP-Derived Polymers to the Aldol Reaction. A sample of polymer (26% incorporation, 10 mol %, 25 mg) was dissolved in DMSO (0.75 mL); deionized water (0.25 mL) followed by 4 equiv of cyclohexanone (103 μL, 1.0 mmol, 4.0 equiv) was then added, and the solution was allowed to stir for 30 min. 4-Nitrobenzaldehyde (38 mg, 0.25 mmol, 1.0 equiv) was subsequently added, and the reaction mixture was allowed to stir for 24 h at room temperature. The reaction was quenched with aqueous lithium bromide (10 mL, 4 wt %) and partitioned into ethyl acetate (10 mL). The aqueous layer was extracted into ethyl acetate (2×10 mL), and the organic layers were combined and dried over $MgSO_4$. Analysis of the aqueous layer by NMR and IR analyses confirmed the presence of the polymer. The solvent was removed *in vacuo*, and the crude residue was analyzed by ^{1}H NMR for diastereomer ratios (syn:anti ratios calculated by comparison of the integration of the signals at 5.4 ppm (syn) with 4.9 ppm (anti)). The crude residue was then either directly analyzed by supercritical fluid chromatography (SFC) or purified by column chromatography (2/1 to 1/1, 40−60 petroleum ether/ethyl acetate).

(*S*)-2-((*R*)-Hydroxy(4-nitrophenyl)methyl)cyclohexan-1-one, 6. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23 (2H, d, $J = 8.7$ Hz), 7.53 (2H, d, $J = 8.7$ Hz), 4.92 (1H, dd, $J = 8.4$, 3.2 Hz), 4.10 (1H, d, $J = 3.2$ Hz), 2.35 (3H, m), 2.05 (1H, m), 1.53 (5H, m). ^{13}C NMR (150 MHz, $CDCl_3$): δ 214.8, 148.4, 147.6, 127.9, 123.6, 74.0, 57.2, 42.7, 30.8, 27.7, 24.7. HR-ESI: $[M + Na]^+$ 272.0901 (Calcd), 272.0908 (Found). $[\alpha]_D^{25} = +8.0°$ ($c = 1.3$, $CHCl_3$). HPLC: Daicel Chiralpak AD-H, SFC (20% 1/1, isopropanol/ethanol in CO_2), 2 mL/min recorded at 210 nm, 100 bar t_R(minor) = 10.50 min and t_R(major) = 14.42 min. Based on repeated injections the errors in ee were estimated at ca. 4−5%. Based on the analysis of multiple integrations, the errors in syn/anti ratio were estimated at ca. 3%.

Results and Discussion

Bis-Protected Monomer Synthesis, 1. In order to successfully incorporate a hydroxyproline-derived functionality into a polystyrene-based copolymer, the catalytically active acid and amino functional groups on the proline-derived monomer were protected prior to controlled radical copolymerization. It was desirable to employ a universal deprotection strategy in order to reveal both of these functional groups simultaneously once monomer incorporation into a polystyrene backbone had been achieved: thus, benzyl carbamate and benzyl ester were selected for this purpose.

Monomer **1** was readily synthesized in three steps and 24% overall yield from commercially available 4-hydroxyproline

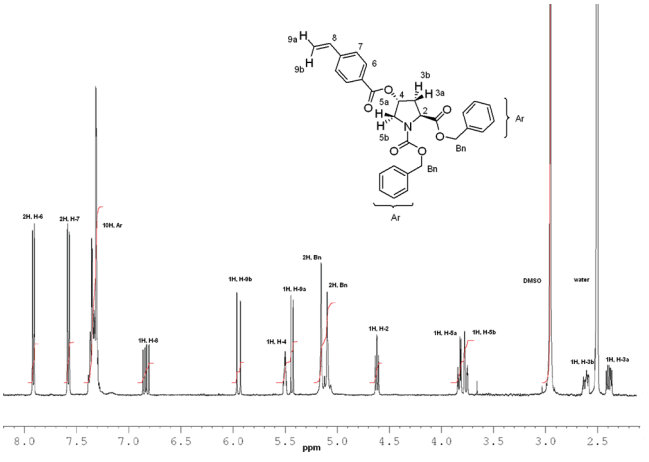
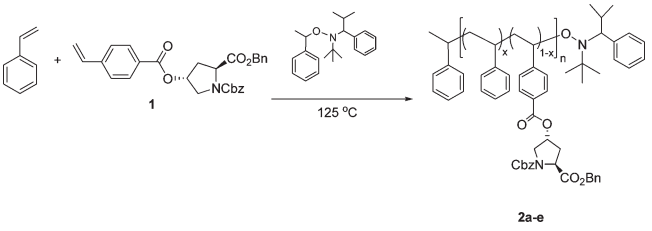


Figure 2. ^{1}H NMR spectrum of monomer **1** in d_6-DMSO (100 °C, 500 MHz).

Scheme 2. NMP of Cbz/Benzyl Proline Monomer 1 and Styrene



(Scheme 1). Carbamate protection of the secondary amine was followed by benzylation of the carboxylic acid; the resulting bis-protected secondary alcohol was then coupled to 4-vinylbenzoic acid using standard esterification conditions, affording desired monomer product **1**. High-temperature NMR at 100 °C resolved all rotameric effects observed in room temperature spectra and confirmed that the revised monomer synthesis maintains optical purity, resulting in a single diastereoisomer of product **1** (Figure 2).

NMP-Mediated Copolymerization of Bis-Protected Monomer 1 with Styrene. Incorporation of bis-protected monomer **1** into a polystyrene copolymer was achieved using two different controlled radical polymerization strategies. Initially, we focused on using NMP-mediated copolymerization techniques for the incorporation of monomer **1** into a polystyrene backbone, employing the well-established universal alkoxyamine initiator reported by Hawker and co-workers (Scheme 2).[49] Conditions for such an NMP-mediated polymerization of monomer **1** with styrene were unprecedented at that time, but it was pleasing to find that when standard conditions for the polymerization of styrene were employed, well-defined polymers with a range of tailorable incorporations of **1** were afforded (Table 1).

Examination of the ^{1}H NMR spectra of the copolymers (**2a**−**e**) synthesized using NMP afforded ready identification of the signals resulting from monomer **1** (specifically the two benzylic singlets at 5.0−5.3 ppm) for quantification and confirmation of successful incorporation of monomer **1** into the styrene backbone. Comparison of the integration of the peaks assigned to the copolymer with those assigned to the NMP end group (3.2−3.3 ppm, m, PhC*H* (nitroxide)) allows for molecular weight determination, assuming complete end-group fidelity. The polydispersities of all of the NMP-derived polymers were low (1.1−1.2), and molecular weights determined by GPC analysis relative to polystyrene standards were found to be in most cases quite close to those determined by NMR analysis.

Table 1. Summary of the Bulk NMP-Mediated Copolymerization of Styrene with 1 at 125 °C

sample	relative equivalents[a]	% incorporation of **1**[b]	M_n(NMR),[c] kDa	M_n(GPC),[d] kDa	M_w/M_n[d]
2a	97:3:1	3	11.9	11.3	1.10
2b	95:5:1	5	12.6	11.0	1.11
2c	92.5:7.5:1	7	15.6	13.4	1.10
2d	90:10:1	10	16.0	14.5	1.19
2e	80:20:1	26	18.4	16.1	1.13

[a] Ratio of [styrene]:[**1**]:[alkoxyamine]. [b] Calculated by ^{1}H NMR spectroscopy in $CDCl_3$. [c] Calculated by ^{1}H NMR spectroscopy in $CDCl_3$. [d] Samples were measured by GPC (THF) using polystyrene standards.

Kinetic studies using the alkoxyamine initiator for the copolymerization of styrene and monomer **1** (95:5:1, [styrene]:[**1**]:[alkoxyamine]) were performed in order to further evaluate the polymerization. It was possible to determine the conversion for both monomers during the polymerization by ^{1}H NMR spectroscopy, and this was used to generate plots of $\ln([M]_0/[M])$ against time for both **1** and styrene in the same copolymerization reaction. These plots confirmed pseudo-first-order behavior of the copolymerization and indicated a constant radical concentration during the polymerization. These kinetic plots (Figure S1) also make explicit the increased polymerization rate of **1** relative to styrene, with **1** polymerizing faster than styrene (k_p(styrene) = 0.0056 min^{-1} and k_p(**1**) = 0.0152 min^{-1}). This indicates that the resultant polymers are composed of a blocky-type structure. Evidence for controlled radical polymerization was also demonstrated by the linear dependence of molecular weight (M_n) on overall percentage conversion of both monomers by the close correlation of experimental with theoretical molecular weight values and by the decreasing polydispersity indices with increasing conversion (Figure S2).

RAFT-Mediated Copolymerization of Bis-Protected Monomer 1 with Styrene. In order to widen the scope of the controlled radical polymerization methods for the incorporation of bis-protected monomer **1** into a polystyrene copolymer, we proceeded to utilize RAFT-mediated in addition to NMP-mediated polymerization techniques. An advantage of exploring the RAFT polymerization method is the ready incorporation of functional units at the polymer chain end: therefore, we sought to incorporate a fluorescent handle into our polymer structure using a pyrene−trithiocarbonate charge-transfer agent (CTA, **3**) which we have previously reported.[20] This CTA can be employed for polymer fluorescent labeling and was used in a number of RAFT-mediated copolymerizations of styrene and **1** to yield a range of copolymers (**4a**−**c**) with various incorporations of **1** (Scheme 3).

As the polymerization of similar styrene-functionalized monomers had not been reported in the literature, a range of reagent ratios were first investigated using standard RAFT conditions for unfunctionalized styrenic derivatives. Using these conditions, we thus optimized the copolymerization and were able to obtain L-proline-functionalized copolymers with controlled molecular weights and polydispersities (Table 2). Monomer conversion was determined, as for the NMP-derived copolymers, by examination of ^{1}H NMR data, comparing polymer backbone integrals with those for characteristic benzylic proton signals resulting from monomer **1** (two benzylic multipets at 5.0−5.2 ppm). Integral comparison between signals assigned to copolymer with the characteristic end-group signals from the pyrene functionality (7.8−8.2 ppm) afforded theoretical molecular weight estimates (M_n(NMR)) of the resultant polymer, reliant upon the assumption of complete end-group fidelity.

Scheme 3. RAFT-Mediated Copolymerization of Styrene and 1 Using a Pyrene−CTA, 3

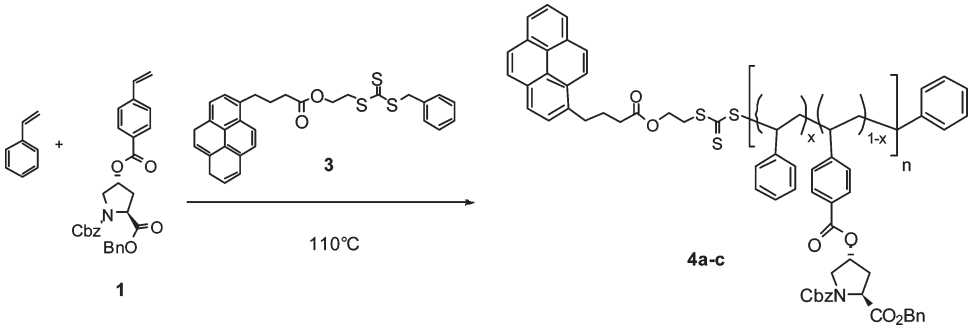
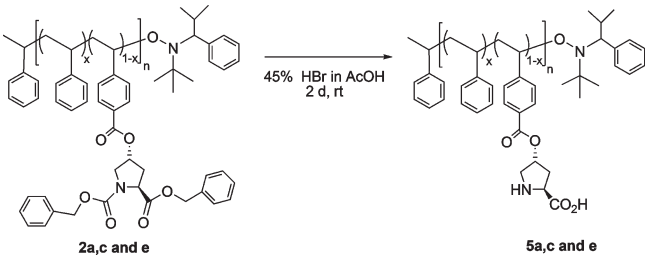


Table 2. RAFT-Mediated Bulk Copolymerization Conditions for Styrene and 1

sample	relative equivalents[a]	% incorporation of **1**[b]	M_n(NMR),[c] kDa	M_n(GPC),[d] kDa	M_w/M_n[d]
4a	95:5:1	5	10.2	9.2	1.15
4b	92.5:7.5:1	7	9.7	8.3	1.16
4c	90:10:1	9	12.5	11.7	1.19

[a] Ratio of [styrene]:[**1**]:[**3**]. [b] Calculated by ^{1}H NMR spectroscopy in $CDCl_3$. [c] Calculated by ^{1}H NMR spectroscopy in $CDCl_3$. [d] Samples were measured by GPC (THF) analysis using polystyrene standards.

Scheme 4. Deprotection of Copolymers 2a, 2c, and 2e



Polymer Deprotection Strategies. In order to create an organocatalytically active polymer-supported catalyst, it was necessary to deprotect both the amine and the acid groups of polymer-incorporated monomer **1** via the planned simultaneous deprotection strategy. Initially hydrogenation was employed to remove both carbamate (Cbz) and the benzyl (Bn) protecting groups on both NMP and RAFT-derived copolymers. However, it was disappointing to find that thorough trials using a range of solvents, pressures, temperatures, bases, and even sonification conditions provided only surprisingly poor results for both sets of polymers **2a**−**e** and **4a**−**c** (maximum ca. 25% deprotection), and therefore an alternative method for protecting group removal was required. The NMP-derived copolymers were selected for this purpose, and results detailing this study and subsequent catalytic trials are detailed below.

Deprotection of NMP-Derived Copolymers 2a−**e.** Following the failure of hydrogenation conditions to remove the two protecting groups, it was pleasing to find that simultaneous removal of both the carbamate and the benzyl protecting groups could be achieved upon exposure of the NMP copolymer to a 45% solution of hydrogen bromide in acetic acid over a 48 h period at ambient temperature (Scheme 4). These conditions yielded complete deprotection of both Cbz and Bn groups in high yield (80−92%) as confirmed by disappearance of benzylic signals at 5.0−5.3 ppm in the ^{1}H NMR spectrum (Figure S2). Using these conditions, we were able to fully deprotect copolymers possessing 3, 7, and 26% incorporation of monomer **1** (from samples **2a**, **2c**, and **2e**, respectively). In addition, the resulting copolymers **5a** and **5c** were further analyzed by GPC analysis (with THF as an eluent) and showed only a slight increase in polydispersity from the starting polymer, which may be due to the interaction of the functional groups with the columns used for GPC analysis (M_w/M_n's ca. 1.20) (Table S1). We were unable to examine the higher loading polymer **5e** using GPC techniques, probably due to strong interactions of the free L-proline units with the GPC columns used for analysis.

Organocatalytic Properties of NMP-Derived Copolymers. In order to evaluate the organocatalytic properties of our copolymers, the well-precedented aldol reaction was chosen for initial trials. These were conducted using the copolymer **5e**, which has the highest loading of functionality (26% incorporation by ^{1}H NMR analysis). This incorporation of functional polymer corresponds to a loading of ca. 1 mmol/g, which compares well with typical literature loadings for supported L-proline catalysis. We began our studies with a solvent screen to optimize both diastereo- and enantioselectivity for a commonly examined aldol reaction between cyclohexanone and nitrobenzaldehyde (Scheme 5, Table 3).[44] Normally, L-proline reactions are performed in polar solvents to promote solubility of the organocatalyst, and frequently polar aprotic solvents such as DMSO or DMF have proven to be the optimal media in which to conduct these reactions. In this case, given the high proline content unfortunately

Scheme 5. Screening for Solvent Conditions for Aldol Condensation Catalyzed by 4e

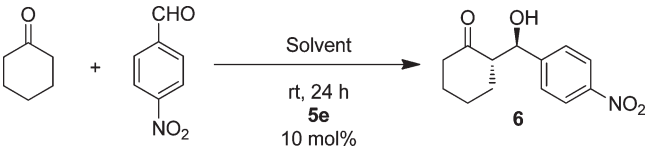


Table 3. Results for Solvent Screening Conditions

entry	solvent	% conversion[a]	syn/anti[b]	% ee[c]
1	THF		no reaction	
2	CH_2Cl_2		no reaction	
3	CH_3CN		no reaction	
4	H_2O	8	18/82	84
5	DMF	52	15/85	82
6	DMSO	31	11/89	91
7	DMF/water (1/1)	95	3/97	94
8	DMF/water (3/1)	95	3/97	94
9	DMF/water (1/3)	98	5/95	94
10	DMSO/water (3/1)	99	3/97	97
11	DMSO/water (1/3)	96	5/95	97

[a] Evaluated by ^{1}H NMR spectroscopy. [b] Evaluated by ^{1}H NMR spectroscopy. [c] Evaluated by SFC analysis.

Scheme 6. Screening for Catalyst Loading Conditions

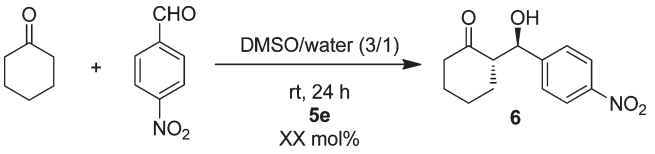


Table 4. Results for Catalyst Loading Screen

entry	loading (mol %)	% conversion[a]	syn/anti[b]	% ee[c]
1	10	99	3/97	97
2	5	62	3/97	95
3	1	22	3/97	92
4	5[d]	98	3/97	98
5	1[e]	96	3/97	98

[a] Evaluated by ^{1}H NMR spectroscopy. [b] Evaluated by ^{1}H NMR spectroscopy. [c] Evaluated by SFC analysis. [d] Reaction allowed to run for 48 h. [e] Reaction allowed to run for 72 h.

the polymer solubility was an issue in THF, CH_2Cl_2, and MeCN (Table 3, entries 1−3), leading to no reaction in each of these cases. Although 8% conversion was observed in water (Table 3, entry 4), the hydrophobic nature of the polystyrene backbone prevented complete dissolution of the copolymer and hence hindered organocatalytic activity. A switch to DMF or DMSO afforded complete copolymer dissolution, but over a 24 h time period only moderate to low conversions were observed, albeit with fairly good diastereo- and enantioselectivities (Table 3, entries 5 and 6). Given the gradient structure of the copolymers, and the subsequent hydrophobic/hydrophilic balance inherent within them, it was postulated that subtle conformational effects which hinder organocatalytic activity might exist in different solvent systems. Therefore, it was thought that a means toward optimizing solvent might be achieved by combining aqueous with organic in order to allow complete dissolution and organocatalyst exposure to substrate. Gratifyingly, when solvent mixtures of either DMF or DMSO with water were used, excellent conversions, diastereo- and enantioselectivities were observed (Table 3, entries 7−11), and the optimal system proved to be a 3:1 mixture of DMSO:water (Table 3, entry 10), providing the desired aldol product **6** in 99% conversion, 3/97 dr (syn/anti) and 97% ee (compared to the reaction under identical conditions with L-proline which afforded only 11% conversion, 14/86 dr (syn/anti) and 90% ee). It is interesting to note that further studies using this solvent system have already demonstrated that the reaction is at 40% conversion in 3 h, and more detailed kinetic analysis is currently underway.

Catalyst loadings of 10, 5, and 1 mol % were then evaluated for organocatalytic activity by varying the amount of added polymer **5e**, and it was found that in order to achieve efficient (24 h) conversion, a 10 mol % loading of catalyst was optimal (Scheme 6, Table 4). However, allowing extended reaction times was found to result in negligible differences in conversion as well as diastereo- and enantioselectivities when comparing the 10 mol % loading with both the 5 mol % and even 1 mol % loading. Thus, lower loadings of polymer organocatalyst can be used as long as extended reaction times are also allowed.

Finally, different monomer **1** incorporations for the NMP-derived copolymers (**5a, 5c**, and **5e**) were evaluated for organocatalytic activity using a 10 mol % catalyst loading (Scheme 7, Table 5). It was observed that the copolymers all demonstrated excellent organocatalytic activity regardless of the percentage incorporation of monomer **1**, resulting in high conversions and diastereo- and enantioselectivities for the three copolymers

Scheme 7. Screening for Optimal Proline Loading Conditions

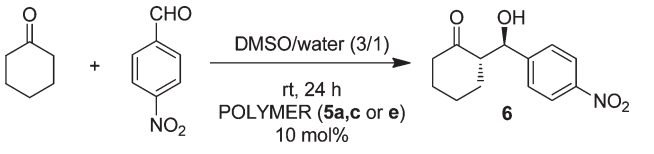


Table 5. Results for Optimal Loading Conditions Screen

entry	polymer incorporation (%)	% conversion[a]	syn/anti[b]	% ee[c]
1	26 (**5e**)	99	3/97	97
2	7 (**5c**)	97	5/95	97
3	3 (**5a**)	95	5/95	98

[a] Evaluated by ^{1}H NMR spectroscopy. [b] Evaluated by ^{1}H NMR spectroscopy. [c] Evaluated by chiral SFC analysis.

evaluated. Of interest is that the lower incorporations of **1** in copolymers **5a** and **5c** actually afforded increased organic solvent solubility (in solvents such as chloroform and tetrahydrofuran), a highly sought-after property for L-proline-derived organocatalysts, and a key result indicating the solvent tunability of this family of copolymers for optimized organocatalysis.

Conclusions

We here report the successful incorporation of hydroxyproline-derived monomer units into a polystyrene backbone using two different controlled radical polymerization techniques, NMP and RAFT. These copolymers all demonstrate a high degree of polymerization control, with low polydispersities and tunable degrees of active monomer incorporation. The family of NMP-derived copolymers has been deprotected and utilized in an organocatalytic intermolecular aldol reaction, resulting in very high conversions and excellent diastereo- and enantioselectivities. Given the novelty and remaining scope of this work, a great deal remains to be explored in future investigations. The organocatalytic activity of the RAFT-derived copolymers remains to be evaluated, and a thorough investigation of the material properties of both families of copolymers as well as their correlation with monomer incorporation tuning must also be carried out. We propose that the application of controlled radical polymerization techniques toward the creation of unique tunable organocatalytic materials can be used to incorporate other active organocatalytic monomers, and there remain a variety of other reaction contexts in which both families of copolymers reported here could be used as organocatalysts.

Acknowledgment. The EPSRC, Leverhulme Trust, and Royal Society are thanked for financial support as are the University of Cambridge and University of Warwick. D.A.L. thanks Homerton College and the Department of Chemistry for support, A.C.E. thanks Murray Edwards College, and C.O. thanks the Churchill Foundation for supporting this work. Professor Steven V. Ley and Dr. Richard Turner are thanked for SFC access and support. Alan Dickerson and Dr. Patricia Irele are thanked for obtaining elemental analysis data. The GPC equipment used in this research was obtained through Birmingham Science City: Innovative Uses for Advanced Materials in the Modern World (West Midlands Centre for Advanced Materials Project 2), with support from Advantage West Midlands (AWM) and part funded by the European Regional Development Fund (ERDF).

Supporting Information Available: Figures showing the kinetics of the NMP and RAFT polymerization of styrene and **1**, ^{1}H NMR spectra before and after deprotection, characterization data for the polymers **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Berkessel, A.; Groger, H. *Asymmetric Organocatalysis - From Biomimetic Concepts to Applications in Asymmetric Synthesis*; Wiley-VCH: Weinheim, 2005.
(2) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138.
(3) Hayashi, Y.; Sumiya, T.; Takahashi, J.; Gotoh, H.; Urushima, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 958.
(4) Jarvo, E. R.; Miller, S. J. *Tetrahedron* **2002**, *58*, 2481.
(5) List, B. *Synlett* **2001**, 1675.
(6) List, B. *Tetrahedron* **2002**, *58*, 5573.
(7) Marigo, M.; Jorgensen, K. A. *Chem. Commun.* **2006**, 2001.
(8) Notz, W.; Tanaka, F.; Barbas, C. F., III *Acc. Chem. Res.* **2004**, *37*, 580.
(9) List, B. *Chem. Commun.* **2006**, 819.
(10) Guillena, G.; Ramon, D. J. *Tetrahedron: Asymmetry* **2006**, *17*, 1465.
(11) Guillena, G.; Nejera, C.; Ramon, D. J. *Tetrahedron: Asymmetry* **2007**, *18*, 2249.
(12) Pellissier, H. *Tetrahedron* **2007**, *63*, 9267.
(13) de Figueiredo, R. M.; Christmann, M. *Eur. J. Org. Chem.* **2007**, 2575.
(14) Enders, D.; Grondal, C.; Huttl, M. R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570.
(15) Gaunt, M. J.; Johansson, C. C. C.; McNally, A.; Vo, N. T. *Drug Discovery Today* **2007**, *12*, 8.
(16) Melchiorre, P.; Marigo, M.; Carlone, A.; Bartoli, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 6138.
(17) Dondoni, A.; Massi, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 4638.
(18) Bertelsen, S.; Jorgensen, K. A. *Chem. Soc. Rev.* **2009**, *38*, 2178.
(19) Paradowska, J.; Stodulski, M.; Mlynarski, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 4288.
(20) Evans, A. C.; Skey, J.; Wright, M.; Qu, W. J.; Ondeck, C.; Longbottom, D. A.; O'Reilly, R. K. *J. Polym. Sci., Part A: Polym. Chem.* **2009**, *47*, 6814.
(21) O'Reilly, R. K. *Polym. Int.* **2010**, *59*, 568.
(22) Mori, H.; Matsuyama, M.; Endo, T. *Macromol. Chem. Phys.* **2009**, *210*, 217.
(23) Mori, H.; Kato, I.; Endo, T. *Macromolecules* **2009**, *42*, 4985.
(24) Mori, H.; Iwaya, H.; Nagai, A.; Endo, T. *Chem. Commun.* **2005**, 4872.
(25) Mori, H.; Iwaya, H.; Endo, T. *Macromol. Chem. Phys.* **2007**, *208*, 1908.
(26) Font, D.; Sayalero, S.; Bastero, A.; Jimeno, C.; Pericas, M. A. *Org. Lett.* **2008**, *10*, 337.
(27) Gruttadauria, M.; Salvo, A. M. P.; Giacalone, F.; Agrigento, P.; Noto, R. *Eur. J. Org. Chem.* **2009**, 5437.
(28) Alza, E.; Rodriguez-Escrich, C.; Sayalero, S.; Bastero, A.; Pericas, M. A. *Chem. Eur. J.* **2009**, *15*, 10167.
(29) Alza, E.; Pericas, M. A. *Adv. Synth. Catal.* **2009**, *351*, 3051.
(30) Benaglia, M.; Puglisi, A.; Cozzi, F. *Chem. Rev.* **2003**, *103*, 3401.
(31) Chai, L. T.; Wang, Q. R.; Tao, F. G. *J. Mol. Catal. A: Chem.* **2007**, *276*, 137.
(32) Revell, J. D.; Gantenbein, D.; Krattiger, P.; Wennemers, H. *Biopolymers* **2006**, *84*, 105.
(33) Gruttadauria, M.; Giacalone, F.; Noto, R. *Adv. Synth. Catal.* **2009**, *351*, 33.
(34) Andreae, M. R. M.; Davis, A. P. *Tetrahedron: Asymmetry* **2005**, *16*, 2487.
(35) Bellis, E.; Kokotos, G. *J. Mol. Catal. A: Chem.* **2005**, *241*, 166.
(36) Bellis, E.; Kokotos, G. *Tetrahedron* **2005**, *61*, 8669.
(37) Kehat, T.; Portnoy, M. *Chem. Commun.* **2007**, 2823.
(38) Akagawa, K.; Sakamoto, S.; Kudo, K. *Tetrahedron Lett.* **2005**, *46*, 8185.
(39) Becker, M. L.; Liu, J. Q.; Wooley, K. L. *Chem. Commun.* **2003**, 180.
(40) Aprile, C.; Giacalone, F.; Gruttadauria, M.; Marculescu, A. M.; Noto, R.; Revell, J. D.; Wennemers, H. *Green Chem.* **2007**, *9*, 1328.
(41) Miao, W. S.; Chan, T. H. *Adv. Synth. Catal.* **2006**, *348*, 1711.
(42) Kristensen, T. E.; Vestli, K.; Jakobsen, M. G.; Hansen, F. K.; Hansen, T. *J. Org. Chem.* **2010**, *75*, 1620.
(43) Kristensen, T. E.; Vestli, K.; Hansen, F. K.; Hansen, T. *Eur. J. Org. Chem.* **2009**, 5185.
(44) Kristensen, T. E.; Vestli, K.; Fredriksen, K. A.; Hansen, F. K.; Hansen, T. *Org. Lett.* **2009**, *11*, 2968.
(45) Kristensen, T. E.; Hansen, F. K.; Hansen, T. *Eur. J. Org. Chem.* **2009**, 387.
(46) Doyaguez, E. G.; Parra, F.; Corrales, G.; Fernandez-Mayoralas, A.; Gallardo, A. *Polymer* **2009**, *50*, 4438.
(47) Listigovers, N. A.; Georges, M. K.; Odell, P. G.; Keoshkerian, B. *Macromolecules* **1996**, *29*, 8992.
(48) Georges, M. K.; Veregin, R. P. N.; Kazmaier, P. M.; Hamer, G. K. *Macromolecules* **1993**, *26*, 2987.
(49) Hawker, C. J.; Bosman, A. W.; Harth, E. *Chem. Rev.* **2001**, *101*, 3661.
(50) Benoit, D.; Chaplinski, V.; Braslau, R.; Hawker, C. J. *J. Am. Chem. Soc.* **1999**, *121*, 3904.
(51) Chiefari, J.; Chong, Y. K.; Ercole, F.; Krstina, J.; Jeffery, J.; Le, T. P. T.; Mayadunne, R. T. A.; Meijs, G. F.; Moad, C. L.; Moad, G.; Rizzardo, E.; Thang, S. H. *Macromolecules* **1998**, *31*, 5559.
(52) Moad, G.; Rizzardo, E.; Thang, S. H. *Acc. Chem. Res.* **2008**, *41*, 1133.
(53) Moad, G.; Rizzardo, E.; Thang, S. H. *Aust. J. Chem.* **2006**, *59*, 669.
(54) Moad, G.; Rizzardo, E.; Thang, S. H. *Aust. J. Chem.* **2005**, *58*, 379.
(55) Lowe, A. B.; McCormick, C. L. *Prog. Polym. Sci.* **2007**, *32*, 283.
(56) Perrier, S.; Takolpuckdee, P. *J. Polym. Sci., Part A: Polym. Chem.* **2005**, *43*, 5347.
(57) Barner-Kowollik, C.; Perrier, S. *J. Polym. Sci., Part A: Polym. Chem.* **2008**, *46*, 5715.
(58) Barner-Kowollik, C.; Buback, M.; Charleux, B.; Coote, M. L.; Drache, M.; Fukuda, T.; Goto, A.; Klumperman, B.; Lowe, A. B.; McLeary, J. B.; Moad, G.; Monteiro, M. J.; Sanderson, R. D.; Tonge, M. P.; Vana, P. *J. Polym. Sci., Part A: Polym. Chem.* **2006**, *44*, 5809.
(59) Goto, A.; Fukuda, T. *Prog. Polym. Sci.* **2004**, *29*, 329.
(60) Willcock, H.; O'Reilly, R. K. *Polym. Chem.* **2010**, *1*, 149.
(61) Cobb, A. J. A.; Shaw, D. M.; Longbottom, D. A.; Gold, J. B.; Ley, S. V. *Org. Biomol. Chem.* **2005**, *3*, 84.
(62) Cobb, A. J. A.; Longbottom, D. A.; Shaw, D. M.; Ley, S. V. *Chem. Commun.* **2004**, 1808.
(63) Yamamoto, Y.; Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126*, 5962.
(64) Hartikka, A.; Arvidsson, P. I. *Tetrahedron: Asymmetry* **2004**, *15*, 1831.
(65) Berkessel, A.; Koch, B.; Lex, J. *Adv. Synth. Catal.* **2004**, *346*, 1141.