Simultaneous Dynamic Kinetic Resolution in Combination with Enzymatic Ring-Opening Polymerization

Jiaxiang Zhou, Wenxin Wang, Kristofer J. Thurecht, Silvia Villarroya, and Steven M. Howdle*

School of Chemistry, the University of Nottingham, University Park, Nottingham, NG7 2RD, Great Britain

Received June 27, 2006; Revised Manuscript Received August 11, 2006

ABSTRACT: We report the simultaneous dynamic kinetic resolution (DKR) of a secondary alcohol in combination with lipase-catalyzed ring-opening polymerization (ROP) of ϵ-caprolactone (ϵ-CL). (*R*,*S*)-1-Phenylethanol (PhE) was used as a model secondary alcohol and incorporated into poly(ϵ-caprolactone) (PCL) under DKR conditions. A total of 75% of the PhE was incorporated as (*R*)-PhE-PCL with over 99% enantio excess (*ee*) in 23 h. This methodology could provide a simple one-step approach to prepare enantiopure sustained release polymeric formulations of chiral species such as drugs or drug precursors bearing a secondary hydroxyl group.

Introduction

Nine of the top 10 drugs produced have active ingredients that are chiral.[1] Enantiomerically pure compounds are becoming more important, mainly due to the increasing need for such compounds in pharmaceutical and agricultural industry. As a result, asymmetric synthesis is playing an increasingly important role, and there has been spectacular development in this area.[2,3] Catalytic enantioselectivity can be achieved by either chemocatalysis or biocatalysis. Traditionally, this field has been dominated by metal catalysis, but recent work in biocatalysis has become an increasingly attractive alternative to conventional chemical methods. However, resolution of racemic mixtures is still the most common way to prepare enantiomerically pure compounds on an industrial scale.[4] To obtain a single enantiomer from such a mixture, one can resolve it either by conventional separation techniques or by using an existing difference in reactivity (kinetic resolution). Enzymes are usually very proficient tools to effect this second methodology. Lipase-catalyzed kinetic resolution (KR) of secondary alcohols is very efficient in terms of selectivity but suffers, as do all resolutions, from being limited to a maximum theoretical yield of 50%.[5,6] One of the most important strategies to increase the yield is the in-situ racemization of the slow-reacting enantiomer by transition metal catalysts. The combination of enzymatic resolution with in-situ racemization of the unreactive enantiomer leads to a dynamic kinetic resolution (DKR).[7−10] In this way, all of the racemic starting mixture can be used for transformation into one enantiomer. Various rhodium, iridium, and ruthenium complexes are known to catalyze rapid racemization of alcohols.[7−11,13] In particular, ruthenium complexes have proven to be compatible with lipase-catalysed kinetic resolution, and high yields and enantioselectivities have been obtained.[14−17]

In addition to kinetic resolution of alcohols, lipase is also capable of catalyzing the formation of polyesters via enzymatic ring-opening polymerization (eROP) of lactones and polycondensation reactions.[18−20] Various lactones have been polymerized to obtain biodegradable polyesters, and ROP has recently been combined with alternative polymerization methods to synthesize a range of block copolymers.[21−25] High enantioselectivity of lipases can be also seen in the production of chiral polymer. When a chiral lactone monomer such as 4-methyl-ϵ-caprolactone (4-MeCL) is used, the enzymatic polymerization of (*S*)-4-MeCL is much faster than (*R*)-4-MeCL, and hence chiral poly(4-MeCL) was synthesized with over 95% *ee*.[26,27] Chiral oligomers of 6-methyl-ϵ-caprolactone were also synthesized by iterative racemization and ring-opening cycles.[28] More recently, the lipase-catalyzed dynamic kinetic resolution polymerization from a racemic diol and a dicarboxylic acid derivative has been utilized for the synthesis of chiral polyesters.[29]

In this paper, we report the combination of lipase-catalyzed ring-opening polymerization (ROP) of ϵ-caprolactone (ϵ-CL) initiated from a chiral secondary alcohol 1-phenylethanol (PhE) which is simultaneously resolved via dynamic kinetic resolution in a one-pot approach. We demonstrate that a simple one-step approach (DKR-ROP) allows simultaneous incorporation and resolution of a secondary alcohol onto PCL. This system could potentially lead to a new route for enantiopure sustained release of drugs incorporating secondary alcohols during the degradation of PCL.

Experimental Section

Materials. Novozym-435 (10 wt % Lipase B from *Candida Antarctica* on a macroporous acrylic resin) was purchased from Novozymes. ϵ-Caprolactone (ϵ-CL, 99%) was purchased from Aldrich, dried over CaH_2 for 24 h under nitrogen, distilled under reduced pressure with three freeze−pump−thaw cycles, and stored under nitrogen until use. (*R*,*S*)-1-Phenylethanol (≥98%) and acetophenone (≥98%) were purchased from Fluka. Dichloro(*p*-cymene)-ruthenium(II) dimer ($[Ru(cymene)Cl_2]_2$) was purchased from Lancaster. *N*,*N*,*N*′,*N*′-Tetramethyl-1,3-propanediamine (TMPDA, 99+%) was purchased from Aldrich. Sodium hydrogen carbonate was purchased from Fisher Scientific.

General Procedure for the Kinetic Resolution−Enzymatic Ring-Opening Polymerization (KR-eROP). 0.40 g of Novozym-435 was weighed into a 50 mL flask, which was heated and maintained at 50 °C overnight while under vacuum. The vacuum was released by filling argon into the flask. Then 20 mL of toluene, 54 mmol of ϵ-CL, and 1 mmol of (*R*,*S*)-1-phenylethanol were added into the flask by syringes under an argon atmosphere. The reaction mixture was then heated and stirred at 70 °C. After certain time intervals, 1 mL of the reaction mixture was removed from the flask by syringe. The sample was then analyzed by chiral GC and NMR.

* Corresponding author: e-mail steve.howdle@nottingham.ac.uk; Tel +44 115 951 3486; Fax +44 115 951 3058.

10.1021/ma0614388 CCC: $33.50
Published on Web 09/20/2006

After the conversion of the ϵ-CL reached 90%, the reaction was stopped. The reaction mixture was diluted with 20 mL of toluene and filtered through a filter paper to remove the enzyme. The polymer product was precipitated into cold methanol, filtered, and dried under vacuum.

General Procedure for the Dynamic Kinetic Resolution in Combination with Enzymatic Ring-Opening Polymerization (DKR-eROP). 0.025 mmol of $[Ru(cymene)Cl_2]_2$ and 0.40 g of Novozym-435 were weighed into a 50 mL flask, which was heated and maintained at 50 °C overnight while under vacuum. The vacuum was released by filling argon into the flask. Then 20 mL of toluene, 54 mmol of ϵ-CL, 1 mmol of (*R*,*S*)-1-phenylethanol, 0.25 mmol of *N*,*N*,*N*′,*N*′-tetramethyl-1,3-propanediamine (TMPDA), and 0.5 mmol of acetophenone were added into the flask by syringes under an argon atmosphere. The reaction mixture was then heated and stirred at 70 °C. After certain time intervals, 1 mL of the reaction mixture was taken from the flask by syringe. The sample was then analyzed by chiral GC and NMR. After the conversion of the ϵ-CL reached 90%, the reaction was stopped. The reaction mixture was diluted with 20 mL of toluene and passed through an alumina column. The polymer product was precipitated into cold methanol, filtered, and dried under vacuum.

Hydrolysis of the PhE-PCL. 0.5 g of polymer, 0.5 g of Novozym-435, and 2 g of $NaHCO_3$ were weighed into a flask. 20 mL of toluene and 10 mL of water were then added. The $NaHCO_3$ was used to neutralize the carboxy group produced during hydrolysis of PCL. The flask was heated and stirred at 90 °C for 24 h. The toluene phase was then isolated and dried on a rotating evaporator. 1 mL of $CDCl_3$ was added to the residue to dissolve the 1-phenylethanol. The solution was subjected to NMR analysis, and the completion of hydrolysis was confirmed by the depletion of the signal at 5.90 ppm and the emergence of the signal at 4.90 (see Supporting Information). The solution was then analyzed by chiral GC to determine the enantiopurity of 1-phenylethanol produced by the hydrolysis.

Methods. a. Chiral GC Analysis. Chiral gas chromatography (GC) was carried out using a Shimadzu GC 2010 with a Supelco betadex 110 column (30 m × 0.25 mm i.d., 0.25 μm film) and an FID. Samples were injected using a Shimadzu AOC-20i autosampler. Injection and detection temperatures were set at 180 and 300 °C, respectively. Oven temperature was initially set to 120 °C (8 min) and then ramped at 30 °C/min to 180 °C and held for 2 min. Helium was used as carrier gas. Acetophenone, (*R*)-1-phenylethanol, and (*S*)-1-phenylethanol are eluted from the column at around 4.5, 6.1, and 6.4 min, respectively (Figure S1).

b. Polymer Characterization. Molecular weight and molecular weight distribution of polymers were obtained by gel permeation chromatography (PL-120, Polymer Labs) with an RI detector. The columns (30 cm PLgel Mixed-C, 2 in series) were eluted by THF and calibrated with polystyrene standards. All calibration and analysis were performed at 40 °C and a flow rate of 1 mL/min. NMR spectra were recorded in $CDCl_3$ using a Bruker DPX 300 MHz spectrometer. All spectra were referenced to $CHCl_3$ at 7.26 ppm.

c. Calculation. The conversion of (*R*)- and (*S*)-1-phenylethanol was calculated directly from the decrease of the area of each peak on the GC trace. During KR-ROP, the yield of 1-phenylethanol was calculated from the decrease of the sum of the peak area of (*R*)- and (*S*)-1-phenylethanol. Since acetophenone can be a byproduct during the racemization, the yield of 1-phenylethanol during DKR-ROP was calculated by the decrease of the sum of the area of the three peaks (acetophenone and (*R*)- and (*S*)-1-phenylethanol). The enantio excess (*ee*) was calculated as follows: $ee = (R - S)/(R + S)$, where R and S represent the area of the GC peaks of the (*R*)- and (*S*)-1-phenylethanol, respectively. Conversion of ϵ-CL was obtained from the NMR spectrum of an aliquot of the reaction mixture (Figure S-3, $(b + c)/(b + c + c') \times 100\%$). The DP of PCL was calculated by the ratio of the signal intensity at 3.64, 4.08, and 5.90 ppm (Figure S3, $(b + c)/2a$).

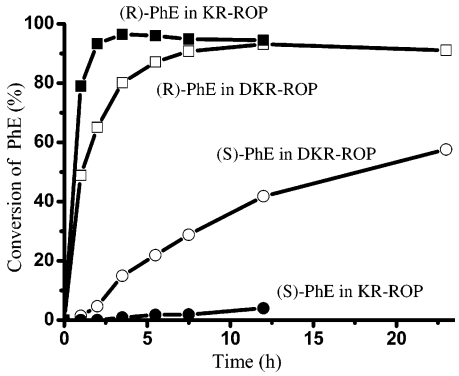

Figure 1. Conversion of (*R*,*S*)-PhE during KR-ROP and DKR-ROP. (Only negligible conversion of (*S*)-PhE was observed in KR-ROP, while a significant conversion of (*S*)-PhE to (*R*)-PhE was observed in DKR-ROP.) Data were obtained by chiral GC.

Results and Discussion

The KR-ROP of ϵ-CL was initially performed to assess the selectivity and kinetics of Novozym-435. The reaction was carried out in 20 mL of toluene with 54 mmol of ϵ-CL, 1 mmol of (*R*,*S*)-PhE, and 0.40 g of Novozym-435 at 70 °C. Phenylethanol was used as a chiral initiator for the enzymatic catalyzed ROP of CL in a 1:54 molar ratio to the monomer. The conversion of each enantiomer was plotted against the reaction time (Figure 1) and followed with chiral GC. As expected for an enzyme-catalyzed reaction, over 90% of the (*R*)-PhE was consumed by initiating polymerization of PCL in the first 2 h of reaction. Under these conditions there was negligible conversion of the (*S*)-PhE, even after 12 h. This suggests that only a little (*S*)-PhE starts reacting after most of the *R*-enantiomer is consumed. In this respect, the resolution of a secondary alcohol with caprolactone as an acylating agent in the presence of Novozym-435 fulfils the basic requirement for KR, i.e., that reaction rate of one enantiomer is much larger than that of the other.[8] The experiment confirms very clearly the enantioselectivity of the lipase, where only the *R*-enantiomer was incorporated as initiator into the PCL homopolymer and the *S*-enantiomer remained unreacted in the mixture. Moreover, this control reaction showed that no racemization occurred in the absence of the transition metal system.

As a consequence of kinetic resolution, the major disadvantage of this method is that only a maximum of 50% of the total amount of phenylethanol is used to initiate the polymerization. This can be overcome by dynamic kinetic resolution (DKR). A DKR-ROP reaction was carried out in 20 mL of toluene with 54 mmol of ϵ-CL, 1 mmol of (*R*,*S*)-PhE, 200 mg of Novozym-435, 0.025 mmol of $[Ru(cymene)Cl_2]_2$, 0.25 mmol of *N*,*N*,*N*′,*N*′-tetramethyl-1,3-propanediamine (TMPDA), and 0.5 mmol of acetophenone at 70 °C. The selected racemization system has been reported recently as an easy to handle and stable catalytic system, which when combined with a lipase-catalyzed resolution provides efficient dynamic kinetic resolution of secondary alcohols.[30] DKR-ROP demonstrated significant consumption of (*R*)-PhE while (*S*)-PhE was simultaneously converted to (*R*)-PhE and incorporated into the PCL (Figure 1). This clearly demonstrates that the transition metal system was effectively racemizing (*S*)-PhE to (*R*)-PhE and subsequently initiating the formation of PCL by lipase-catalyzed ROP. Thus, more alcohol was effectively available as initiator for polymerization.

This strategy represents an exceptional case of DKR: only the (*R*)-1-phenylethanol is enantioselectively acylated by caprolactone at short times, and the resulting end-group primary alcohol reacts with a caprolactone monomer unit to yield PCL

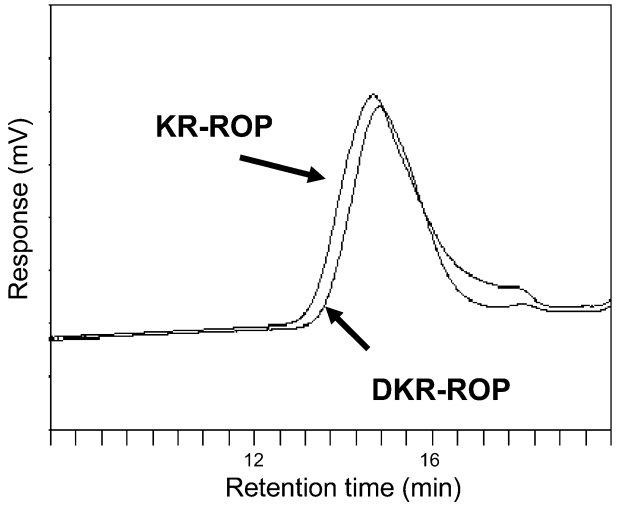

Figure 2. GPC traces for the PCL homopolymer obtained via KR-ROP and DKR-ROP. KR-ROP yielded a slightly higher molecular weight product than that obtained by DKR-ROP.

homopolymer. Additionally, the (*S*)-1-phenylethanol is racemized in situ by the ruthenium system and converted to (*R*)-1-phenylethanol, which then takes part in the initiation of caprolactone.

Acetophenone was added to the system to accelerate the racemization. The rate-accelerating effect of the ketone can be explained by the faster addition of the ruthenium hydride to the ketone brought about by the higher concentration.[7] The model racemization system that we have selected is considerably slower than other systems, since after 24 h a significant amount of (*S*)-phenylethanol still remains in the mixture (Figure 1). However, this work clearly shows that our approach is feasible. In addition, by optimizing the initiator structure and/or racemization system, we anticipate the improvements in the rate of conversion for the slower monomer will be realized. The fact that *S*-enantiomer is converted to *R*-enantiomer slowly and progressively during the time is considered to be an advantage since the amount of initiator fed to the system is controlled. This will prevent initiator saturation of the system and will lead to the generation of higher molecular weight PCL homopolymer.

The PhE-PCL products were also analyzed by GPC which showed that KR-ROP yields higher molecular weight (M_n = 16 000 Da, PDI = 2.15) polymer than that obtained in DKR-ROP (M_n = 14 200 Da, PDI = 1.94) (relative to polystyrene standards) (Figure 2). This is due to the higher concentration of initiator that is available in the DKR case.

The conversion of ϵ-CL and the degree of polymerization (DP) of PhE-PCL can be calculated from ^{1}H NMR spectra. Greater than 90% ϵ-CL conversion was achieved in both KR-ROP and DKR-ROP. However, a lower DP of PhE-PCL (ca. 80) was found in DKR-ROP compared to KR-ROP (ca. 100) at the same monomer conversion (Figure 3). This lower DP of PhE-PCL in DKR-ROP can be clearly related to the higher concentration of initiating alcohol that is present in the DKR case. Thus, more initiator gives rise to a larger number of shorter polymer chains. This is also evident in the GPC trace (Figure 2) whereby the trace for polymer formed by DKR-ROP has a much broader tail (to low molecular weight) and hence a higher PDI.

Water can also act as a competing initiator to form PCL homopolymer. Despite exhaustive measures to remove all the water from the system, it is still possible to find a small quantity of PCL homopolymer initiated by adventitious water present in the system. This leads to the PCL with a carboxylic acid end

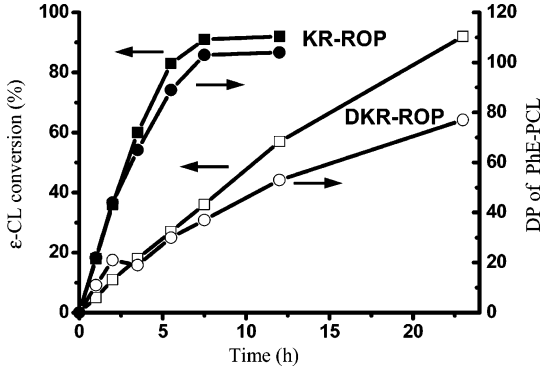

Figure 3. Conversion of ϵ-CL and DP of PhE-PCL during KR-ROP and DKR-ROP [■, ϵ-CL conversion in KR-ROP; □, ϵ-CL conversion in DKR-ROP; ●, DP of PhE-PCL in KR-ROP; ○, DP of PhE-PCL in DKR-ROP]. (Lower DP of PhE-PCL was obtained in DKR-ROP than in KR-ROP at the same monomer conversion.)

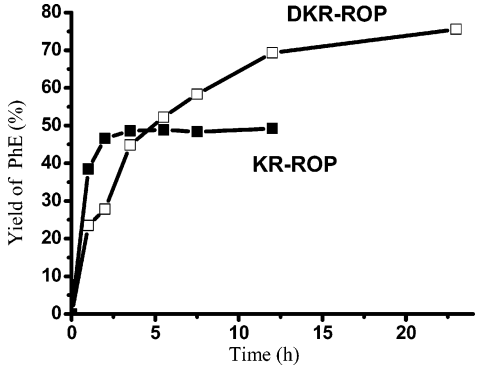

Figure 4. Yield of PhE during KR-ROP and DKR-ROP. Yields increased from a maximum of 50% in the KR-ROP to greater than a 75% yield in DKR-ROP. Here we have calculated the yield of PhE as the percentage of PhE incorporated in the polymer relative to the initial amount of (*R*,*S*)-PhE.

group rather than phenylethanol end group. To quantify the composition of this product, the end group of the polymer product was analyzed using oxalyl chloride treatment as described in the literature.[31] The amount of PCL homopolymer with chain-end carboxylic acid groups was determined by ^{1}H NMR upon the addition of oxalyl chloride to give the percentage of water-initiated PCL homopolymer (see Supporting Information for a detailed explanation and ^{1}H NMR spectra). The results of end-group analysis confirm that water-initiated PCL was typically less than 15% for both cases KR-ROP and DKR-ROP. This value is typical for water initiation of PCL in a toluene system and is also very similar to the analogous reactions using a bifunctional initiator in supercritical carbon dioxide.[32]

The rate of polymerization for DKR-ROP was significantly slower than that observed for the KR-ROP (Figure 4). This suggests that the ruthenium catalyst has a retardation effect over the enzymatic polymerization, leading to a slower conversion of ϵ-CL. Others have observed such transition metal retardation upon lipase-catalyzed reactions.[26,33] These authors reported that both Ni and Cu inhibit or retard the catalytic activity of Novozym-435. It seems likely, then, that Ru may have a similar effect on the activity of the enzyme, and this is reflected in the different reaction rates that we observed (Figure 4).

We have demonstrated that yields may be raised from a maximum of 50% in the KR-ROP to greater than a 75% yield using DKR-ROP. Optimization of this process is currently underway in order to obtain better yields.

To determine the enantiopurity of the PhE incorporated in the polymer chain, the PhE-PCL was enzymatically hydrolyzed

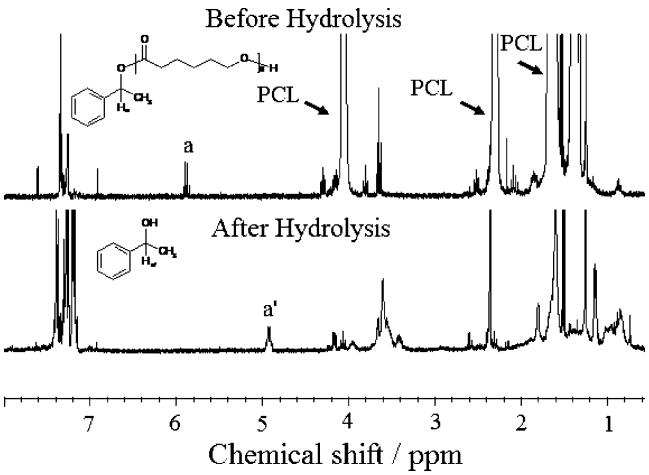

Figure 5. ^{1}H NMR spectra of PhE-PCL obtained in DKR-ROP before and after hydrolysis. The removal of the PCL from the product after hydrolysis is confirmed by NMR analysis.

according to the literature.[34] The polymer was hydrolyzed in the presence of Novozym-435 and $NaHCO_3$ in toluene/water (2:1) at 90 °C for 24 h. $NaHCO_3$ was used to neutralize the carboxy group during the hydrolysis of PCL. The hydrolysis was followed by ^{1}H NMR, and the completion was confirmed by the depletion of the signal at 5.90 ppm (H_a) and the emergence of the new signal at 4.90 ppm (Figure 5) belonging to the methine proton ($H_{a'}$). All product was successfully hydrolyzed under these conditions, and the crude was evaporated and subjected to analysis. No trace of PhE-PCL remained in the mixture after the degradation reaction. The released PhE was analyzed by chiral GC in order to calculate the enantiomeric excess. We have already demonstrated that the enzyme shows negligible activity toward (*S*)-PhE enantiomer; thus, enzymatic hydrolysis was active only upon the (*R*)-PhE-PCL, and complete hydrolysis yields free (*R*)-PhE. In both KR-ROP and DKR-ROP, the polymer products were (*R*)-PhE-PCL with *ee* greater than 99%.

Conclusion

In conclusion, we have demonstrated simultaneous dynamic kinetic resolution combined with enzymatic ring-opening polymerization. This methodology could provide a very simple one-step approach to prepare enantiopure covalently tethered sustained release formulations of chiral species bearing a secondary hydroxyl group.

Acknowledgment. The authors thank Dr. P. Stephenson, C. Yan, Helen R. Hobbs, P. Clark, P. Gooden, K. Benaissi, B. Kondor, A. Chapman, and Prof. M. Poliakoff for their kind help and advice on GC analysis. We thank the Marie Curie Research Training Network (BIOMADE, Contract MRTN-CT-2004-505147) for financial support (J.Z. and S.V.) and the Dutch Polymer Institute (Project 488, K.J.T.). S.M.H. is a Royal Society Wolfson Research Merit Award Holder.

Supporting Information Available: Detailed experimental part for the treatment of oxalyl chloride; calculation of conversion and DP of the PCL homopolymer; chiral GC traces for the enantiomers. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Rouhi, A. M. *Chem. Eng. News* **2004**, *82*, 47.
(2) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; John Wiley & Sons: New York, 1994.
(3) Koskinen, A. *Asymmetric Synthesis of Natural Products*; John Wiley & Sons: New York, 1993.
(4) Breuer, M.; Ditrich, K.; Habicher, T.; Hauer, B.; Kesseler, M.; Sturmer, R.; Zelinski, T. *Angew. Chem., Int. Ed.* **2004**, *43*, 788−824.
(5) Ghanem, A.; Aboul-Enein, H. Y. *Tetrahedron: Asymmetry* **2004**, *15*, 3331−3351.
(6) Ghanem, A.; Aboul-Enein, H. Y.*Chirality* **2005**, *17*, 1−15.
(7) Huerta, F. F.; Minidis, A. B. E.; Backvall, J. E. *Chem. Soc. Rev.* **2001**, *30*, 321−331.
(8) Pamies, O.; Backvall, J. E. *Chem. Rev.* **2003**, *103*, 3247−3261.
(9) Pamies, O.; Backvall, J. E. *Curr. Opin. Biotechnol.* **2003**, *14*, 407−413.
(10) Pamies, O.; Backvall, J. E. *Trends Biotechnol.* **2004**, *22*, 130−135.
(11) Dinh, P. M.; Howarth, J. A.; Hudnott, A. R.; Williams, J. M. J.; Harris, W. *Tetrahedron Lett.* **1996**, *37*, 7623−7626.
(12) Koh, J. H.; Jeong, H. M.; Park, J. *Tetrahedron Lett.* **1998**, *39*, 5545−5548.
(13) Pamies, O.; Backvall, J. E. *Chem.—Eur. J.* **2001**, *7*, 5052−5058.
(14) Persson, B. A.; Larsson, A. L. E.; Le Ray, M.; Backvall, J. E. *J. Am. Chem. Soc.* **1999**, *121*, 1645−1650.
(15) Kim, M. J.; Ahn, Y.; Park, J. *Curr. Opin. Biotechnol.* **2002**, *13*, 578−587.
(16) Karvembu, R.; Prabhakaran, R.; Natarajan, K. *Coord. Chem. Rev.* **2005**, *249*, 911−918.
(17) Martin-Matute, B.; Edin, M.; Bogar, K.; Kaynak, F. B.; Backvall, J. E. *J. Am. Chem. Soc.* **2005**, *127*, 8817−8825.
(18) Gross, R. A.; Kumar, A.; Kalra, B. *Chem. Rev.* **2001**, *101*, 2097−2124.
(19) Kobayashi, S.; Uyama, H.; Kimura, S. *Chem. Rev.* **2001**, *101*, 3793−3818.
(20) Varma, I. K.; Albertsson, A. C.; Rajkhowa, R.; Srivastava, R. K. *Prog. Polym. Sci.* **2005**, *30*, 949−981.
(21) Uyama, H.; Kobayashi, S. *Chem. Lett.* **1993**, *7*, 1149−1150.
(22) Kumar, A.; Gross, R. A. *Biomacromolecules* **2000**, *1*, 133−138.
(23) Loeker, F. C.; Duxbury, C. J.; Kumar, R.; Gao, W.; Gross, R. A.; Howdle, S. M. *Macromolecules* **2004**, *37*, 2450−2453.
(24) Duxbury, C. J.; Wang, W. X.; de Geus, M.; Heise, A.; Howdle, S. M. *J. Am. Chem. Soc.* **2005**, *127*, 2384−2385.
(25) Villarroya, S.; Zhou, J. X.; Duxbury, C. J.; Heise, A.; Howdle, S. M. *Macromolecules* **2006**, *39*, 633−640.
(26) Peeters, J.; Palmans, A. R. A.; Veld, M.; Scheijen, F.; Heise, A.; Meijer, E. W. *Biomacromolecules* **2004**, *5*, 1862−1868.
(27) Al-Azemi, T. F.; Kondaveti, L.; Bisht, K. S. *Macromolecules* **2002**, *35*, 3380−3386.
(28) van As, B. A. C.; van Buijtenen, J.; Heise, A.; Broxterman, Q. B.; Verzijl, G. K. M.; Palmans, A. R. A.; Meijer, E. W. *J. Am. Chem. Soc.* **2005**, *127*, 9964−9965.
(29) Hilker, I.; Rabani, G.; Verzijl, G. K. M.; Palmans, A. R. A.; Heise, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 2130−2132.
(30) Riermeier, T. H.; Gross, P.; Monsees, A.; Hoff, M.; Trauthwein, H. *Tetrahedron Lett.* **2005**, *46*, 3403−3406.
(31) Mahapatro, A.; Kalra, B.; Kumar, A.; Gross, R. A. *Biomacromolecules* **2003**, *4*, 544.
(32) Zhou, J.; Villarroya, S.; Wang, W.; Wyatt, M.; Duxbury, K. J.; Thurecht, K. J.; Howdle, S. M. *Macromolecules* **2006**, *39*, 5352.
(33) Meyer, U.; Palmans, A. R. A.; Loontjes, T.; Heise, A. *Macromolecules* **2002**, *35*, 2873−2875.
(34) Kobayashi, S.; Uyama, H.; Takamoto, T. *Biomacromolecules* **2000**, *1*, 3−5.

MA0614388