Journal of Macromolecular Science, Part A
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597274

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To cite this Article Liu, Xu , Li, Keran , Feng, Xinliang and Cao, Ya(2009) 'Preparation of Propargyl-terminated Polylactide by the Bulk Ring-opening Polymerization', Journal of Macromolecular Science, Part A, 46: 10, 937 — 942
To link to this Article: DOI: 10.1080/10601320903158230
URL: http://dx.doi.org/10.1080/10601320903158230

Journal of Macromolecular Science®, Part A: Pure and Applied Chemistry (2009) **46**, 937–942

ISSN: 1060-1325 print / 1520-5738 online
DOI: 10.1080/10601320903158230

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Preparation of Propargyl-terminated Polylactide by the Bulk Ring-opening Polymerization

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Received March 2009, Accepted April 2009

Propargyl-terminated polylactide was prepared by bulk ring-opening polymerization of *L*-lactide (LLA) at 105°C in the presence of 3-methyl-1-pentyn-3-ol as the initiator and $Sn(Oct)_2$ as the catalyst. A significant decline of the alkynes chain-end functionality was observed by ^1H NMR even at the early stage of the polymerization. The most probable reason is the intermolecular oxidative coupling of the propargyl end groups. Propargyl-terminated polylactide having higher chain-end functionality (f = 86%) and low polydispersity (PDI = 1.22) was prepared with the addition of *N,N,N′,N″,N″*-pentamethyldiethylenetriamine, whose huge steric hindrance provides the protective effect of propargyl groups.

Keywords: Polylactide, bulk ring-opening polymerization, propargyl end groups, protection reaction

1 Introduction

Due to their unique biodegradability and biocompatibility, aliphatic polyesters such as polylactide (PLA), poly(ε-caprolactone) (PCL) and polyglycolide (PGA) have been increasingly used in biomedical fields in recent years (1–5). However, the applications of these polyesters are limited for their strong hydrophobicity and no functional groups in the polymer backbones. The introduction of functional groups or hydrophilic segments to these aliphatic polyesters has gained great attention (6).

To date, numerous successful modification examples have been reported, including the chain-end functionalized aliphatic polyesters with thiol- (7), amino- (8), hydroxyl, carboxy-, allyl (9), phosphoryl choline (10), saccharide groups (11), and poly(ethylene oxide) blocks (12) through post modification of polyesters or ring-opening polymerization (ROP) initiated by the reagents having functional groups.

Recently, as its high selectivity, mild reaction conditions, quantitative yields, and almost no byproducts, the click chemistry (13–15), that is Cu(I)-catalyzed Huisgen 1,3-dipolar cycloaddition of azides and terminated alkynes, has been widely used for synthesis of end- or pendent functionalized polymers (16–18), new monomers and macromonomers (19, 20), block copolymers, star, or cyclic polymers (21–23), and dendrimers (24). Among these reactions, the synthesis of propargyl-functionalized polymers has gained much more attention. For example, propargyl-terminated aliphatic polyesters are important intermediates for the synthesizing block polymers or introducing a set of functionalities to the end group under mild conditions.

The simple method to prepare propargyl-functionalized polyesters is to use post-polymerization modifications (25). However, post-polymerization is often cumbersome and easily causes degradation of polyesters during the reactions. Some groups synthesized propargyl-terminated aliphatic polyesters through ROP initiated by alkynols. Nevertheless, many functional groups, such as hydroxyl, carboxyl, epoxides and alkynyl are not tolerated with the metal alkoxides involved in ROP. Thus, a protection/deprotection reaction is usually needed. For avoiding these protection reactions, some groups used solution polymerization at 25°C to synthesize propargyl-terminated poly(ε-caprolactone) (26, 27). However, PLA were often prepared by bulk ring-opening polymerizations at high temperature. Because the propargyl groups are very active, the synthesis of propargyl-terminated PLA by bulk polymerization still proves to be challenging.

With the aim of subsequently preparing block copolymers of PLA by click chemistry, here we synthesized propargyl-terminated PLA by ring-opening polymerization with 3-methyl-1-pentyn-3-ol as the initiator and stannous octoate as the catalyst. During the bulk polymerization, a great deal of active terminal alkynes of propargyl-end PLA is lost. As we know, active alkynes groups are extremely important for click chemistry (15). In this

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paper, we reported a successful preparation of propargyl-terminated PLA in the presence of *N,N,N′,N″,N″*-pentamethyldiethylenetriamine (PMDETA). We found that active hydrogen of alkynes groups in the ring-opening polymerization of PLA could be protected by PMDETA added. The obvious advantage is that PMDETA is also used as the ligand in the click reactions. The residual PMDETA in the propargyl-terminated PLA has no effect on the subsequent click reaction. This provides a facile way to prepare propargyl-terminated PLA with high propargyl-end functionality and without complicated protection/deprotection reactions.

2 Experimental

2.1 Materials

Toluene was distilled from metallic sodium and benzophenone. *L*-lactide (Tianyuan biological chemistry Co. Ltd., 99.8%) was purified by recrystallization from toluene and dried under vacuum at room temperature. *N,N,N′,N″,N″*-pentamethyldiethylenetriamine (PMDETA, Aldrich, 99%) and Stannous octoate ($Sn(Oct)_2$, Sigma, 95%) were used as received. 3-methyl-1-pentyn-3-ol (Aldrich, 98%) was distilled before use. Unless otherwise specified, all the chemicals were used as received.

2.2 Synthesis of Propargyl-Terminated PLA by Bulk Polymerization

The typical procedure of bulk ring-opening polymerization of PLA is described here (Table 1, sample 1-a): 14.4 mmol LA were added into 25 mL flamed-dried flask with a stir bar via a syringe. Purged with dry nitrogen for 10 min and then evaporated under vacuum at 80°C for 1 h to remove water completely. Backfilled with nitrogen and cooled to room temperature. 3-methyl-1-pentyn-3-ol solution (0.48 mmol, 0.5 mL of a 0.96 M solution in toluene), and $Sn(Oct)_2$ solution (0.048 mmol, 0.5 mL of a 0.096 M solution in toluene) were added to the flask under a nitrogen environment. The flask was then placed in a thermostated oil bath at 105°C for 40 min. After the polymerization, the mixture was quickly cooled to room temperature, precipitated into an excess amount of diethyl ether, filtered off, and vacuum dried at room temperature for 24 h.

^{1}H-NMR ($CDCl_3$)δ (TMS, ppm): 5.14-5.23(−C*H*(CH_3)OCO−), 4.33-4.38 (HOC*H*(CH_3)CO−), 2.56(−C≡C*H*), 1.48-1.59(−CH(C*H*$_3$)OCO−), 0.99-1.05(−CH_2C*H*$_3$)

2.3 Synthesis of Propargyl-Terminated PLA with PMEDTA

The synthetic procedure was quite similar to that of the preparation of propargyl-terminated PLA, except that PMDETA was mixed in a $Sn(Oct)_2$ solution and then added to the flask.

2.4 Characterization

^{1}H NMR experiments were carried out on a Bruker 400 MHz NMR instrument using $CDCl_3$ as the solvent and tetramethylsilane as the internal reference. The molar masses and their distribution for the polymer samples were determined by GPC on a Waters system equipped with a set of three Ultrastyragel columns (HT2, HT3, and HT4; 30 cm × 7.8 mm; 10 μm particles; exclusion limits: 100–10000, 500–30000, and 5000–600000 g/mol, respectively), Waters 515 HPLC pump, Waters 717plus Autosampler and an online Waters 2414 refractive index detector maintained at 35°C. THF was used as the mobile phase (1 mL/min), and polystyrene samples as the standards in the calibration of the molar masses.

3 Results and Discussion

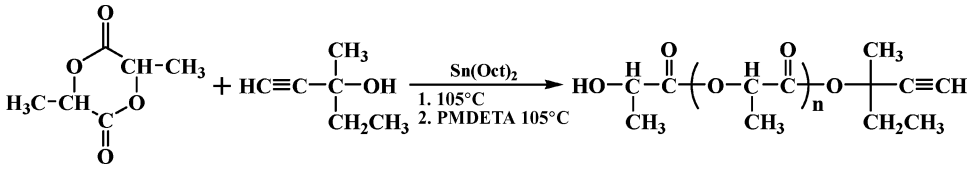
3.1 Preparation of Propargyl-Terminated PLA by Bulk Polymerization

Under rigorously anhydrous conditions, the bulk polymerization of *L*-lactide was conducted at 105°C with

Table 1. Reaction conditions, yield, molecular weight, PDI and chain-end functionality for the polylactide prepared by ring-opening polymerization without PMDETA added[a]

Sample	*[M]/[I]*[b]	*Time*	M_n^c *(NMR)*	M_n^d *(GPC)*	M_w/M_n^e	*Yield*[f] *(%)*	*Chain-end functionality*[g] *(%)*
1-a	30	40 min	6,700	13,200	1.45	49.0	30
1-b	30	1 h	4,900	14,500	1.38	53.0	43
1-c	30	3 h	7,300	12,800	1.26	74.4	41
1-d	30	4 h	7,800	19,200	1.31	70.3	45
1-e	30	24 h	6,000	12,900	1.82	75.2	47
1-f	15	4 h	2,900	9,900	2.64	61.1	46
1-g	60	4 h	8,200	16,600	1.22	74.8	44

[a]The polymerization was carried out at 105°C with 3-methyl-1-pentyn-3-ol as an initiator; [Initiator]:[$Sn(Oct)_2$] = 10:1 (molar ratio); [b]Molar ratio of monomer to initiator; [c]Calculated from ^{1}H-NMR spectroscopy; [d]Determined by GPC; [e]Estimated by GPC calibrated by PS standard; [f]Determined gravimetrically; [g]Chain-end functionality calculated by Equation 1.



Sch. 1. Ring-opening Strategy for Synthesizing Propargyl-terminated Polylactide.

stannous octoate as a catalyst and 3-methyl-1-pentyn-3-ol as an initiator (Scheme 1). Figure 1 shows ^{1}H-NMR spectrum of typical progargyl-terminated PLA prepared. The number average molecular weight (M_n) of poly(*L*-lactide) was determined by average integral signal ratios of methine protons of PLA (H**c**, 5.14–5.23 ppm) to the terminal methine protons (H**e**, 4.33–4.38 ppm). The signal at 2.57 ppm ascribed to the alkyne proton indicated that 3-methyl-1-pentyn-3-ol participated in the initiating polymerization of LA and the alkynes unit remained in PLA chain. The percentage of alkynes remained (Functionality (%)) can be estimated by an integral ratio of peak a (H_a) to peak b (H_b) (Fig.1 inset):

$$\text{Functionality}(\%) = \frac{H_a}{H_b/3} \times 100\% \qquad (1)$$

Reaction conditions and properties for the PLA prepared by common ring-opening polymerization are summarized in Table 1. Whether the polymerization conditions (reaction time, molar ratio of monomer to initiator, et al.) change or not, the percentage of chain-end functionality (f_n) of PLA prepared by bulk polymerizations is almost about 40%. A significant loss of the active hydrogen of terminal alkyne in the ring-opening polymerizations was observed even at the early stage of reactions.

As shown in Table 1, the average number molecular weight of PLA measured by ^{1}H-NMR is much smaller than that measured by GPC. M_n (^{1}H-NMR) is nearly a half of M_n (GPC). Figure 2 shows GPC traces of PLA (sample 1-a, 1-b and 1-d) with broad peaks. With the prolonged reaction time, molecular weight of PLA increases and the polydispersity indices (M_w/M_n) of the polymers are mostly higher than 1.3 in most cases. Note that all traces of PLA present clear shoulders at the high molecular weight regions. We found the molecular weight corresponded to the shoulder is nearly twice larger than the peak molecular weight, indicating the coupling of two molecules. Therefore, the intermolecular oxidative coupling of the propargyl-end groups into diyne may cause the twice larger molecular weight determined by GPC and the low percentage of alkyne groups remained.

3.2 Bulk Ring-opening Polymerization of Lactides with PMDETA

N,N,N′,N″,N″-pentamethyldiethylenetriamine (PMDETA) is one important ligand in the click reactions. Interestingly, it could play a protection role on the alkyne end groups in the bulk ring-opening polymerization of lactides. Results of polymerizations with PMDETA under different reaction conditions are summarized in Table 2. The chain-end functionality of alkynes was also determined by ^{1}H-NMR signals at 2.57 ppm (a) and 0.99–1.05 ppm (b) ascribed to the active hydrogen and the methyl protons of alkyne

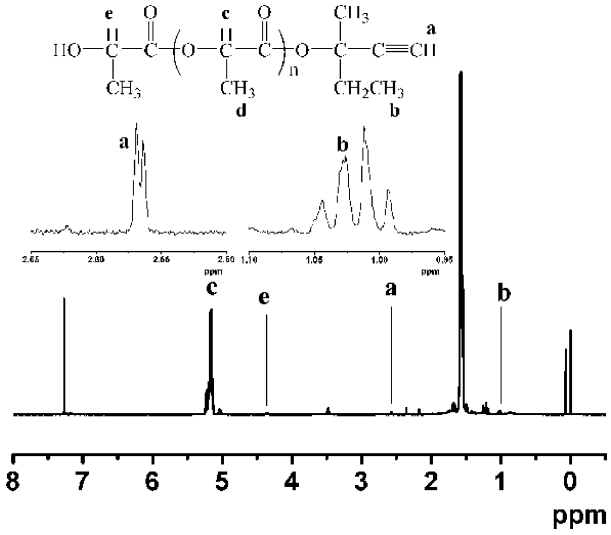


Fig. 1. ^{1}H-NMR spectrum of propargyl-terminated PLA (sample 1-b) in $CDCl_3$.

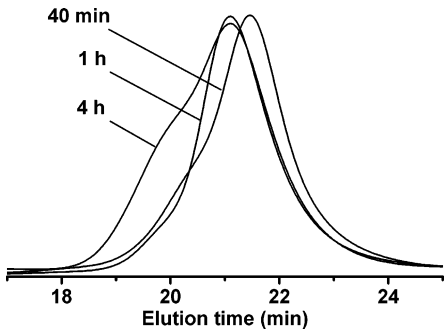


Fig. 2. GPC traces of PLA (samples **1-a**(40 min), **1-b**(1 h) and **1-d** (4 h)).

Table 2. Reaction conditions and properties of PLA prepared by bulk ring-opening Polymerization with PMDETA[a]

Sample	*[M]/[I]/[PMDETA]/[Sn(Oct)$_2$]*	*Time (h)*	*Mn[b] (NNR)*	*Mn[c] (GPC)*	*Yield[d] (%)*	*Chain-end functionality (%)[e]*
2-a	300:10:0.5:1	4	8,000		85	66
2-b	300:10:1:1	4	9,100	15,400	72	69
2-c	300:10:2:1	4	8,400		56	58
2-d	300:10:10:1	4	8,200		46	18
3-a	300:10:1:1	4	9,100	15,400	72	69
3-b	300:15:1:1	4	7,700	11,400	66	68
3-c	300:17.5:1:1	4	7,600		79	70
3-d	300:20:1:1	4	6,100	10,700	70	**86**
3-e	300:22.5:1:1	4	6,600		48	31
3-f	300:25:1:1	4	4,100		49	35
3-g	300:30:1:1	4	2,600		48	38

[a]The polymerization was carried out at 105°C with 3-methyl-1-pentyn-3-ol (3M) as initiator; [LA]:[Sn(Oct)$_2$] = 300:1 (molar ratio); [b]Calculated from ^{1}H-NMR spectroscopy; [c]Determined by GPC; [d]Determined gravimetrically; [e]Chain-end functionality calculated by Equation 1.

group, respectively. In some cases, the chain-end functionality of alkynes increases more than 70% with the addition of PMDETA. For example, chain-end functionality of sample 3-d is about 86%. This indicates that PMDETA could protect the active hydrogen of alkynes group in the polymerization.

The effect of the amount of PMDETA added on chain-end functionality is shown in Figure 3. Chain-end functionality of alkyne elevates from 40% to nearly 70% with the addition of PMDETA (0.5 or 1 molar ratio of PMDETA to Sn(Oct)$_2$). However, a greater addition of PMDETA causes a rapid decrease of the chain-end functionality. When the molar ratio of [PMDETA]/[Sn(Oct)$_2$] is about 10, the functionality is down to 18%. It is probably attributed to the two opposite effects of PMDETA in the polymerization. On the one hand, PMDETA may protect the active hydrogen of alkynes group in the polymerization for its huge steric hindrance. On the other hand, the active hydrogen

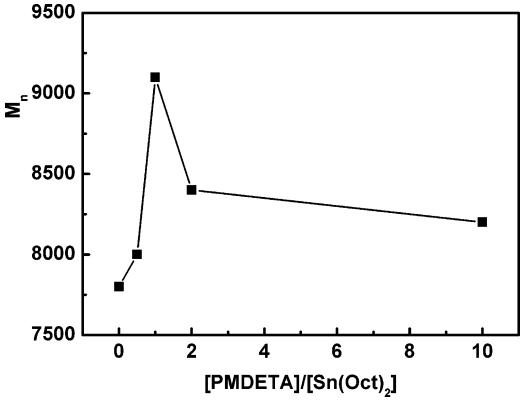


Fig. 4. Plot of M_n vs. molar ratio of [PMDETA]/[Sn(Oct)$_2$] for bulk polymerization of *L*-lactide at 105°C with PMDETA added.

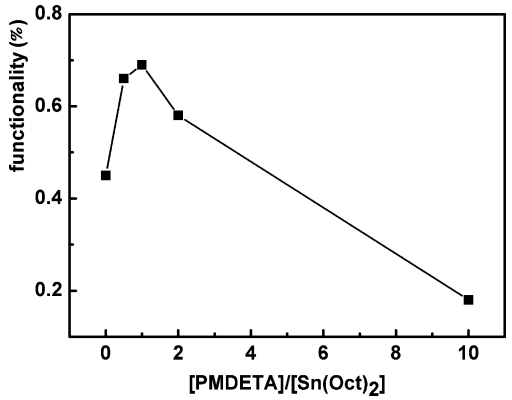


Fig. 3. Plots of chain-end functionality vs. molar ratio of [PMDETA]/[Sn(Oct)$_2$] for the bulk polymerization of *L*-lactide at 105°C with PMDETA added.

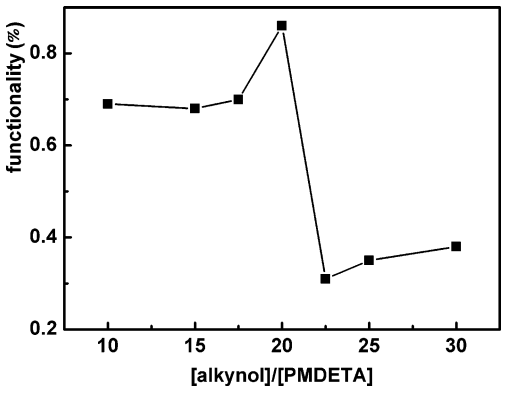


Fig. 5. Chain-end functionality vs. molar ratio of [alkynol]/[PMDETA] for the bulk polymerization of *L*-lactide at 105°C with [PMDETA]/[Sn(Oct)$_2$]=1.

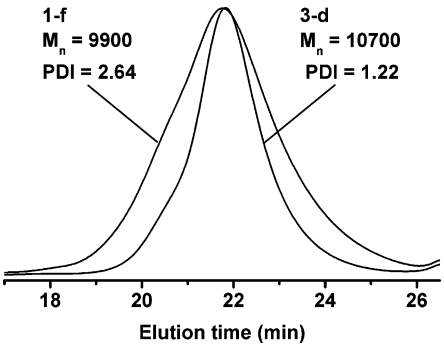


Fig. 6. GPC traces of PLA (samples 1-f and 3-d).

atoms of alkyne groups in the polymerization are unstable at the high alkalinity caused by higher concentration of PMDETA.

Figure 4 shows M_n determined by ^{1}H-NMR vs. the molar ratio of [PMDETA]/[$Sn(Oct)_2$]. M_n of PLA prepared with PMDETA added is higher than that of PLA without PMDETA, demonstrating that the addition of PMDETA does not decrease the molecular weight of propargyl-terminated PLA in the bulk polymerization.

Figure 5 shows the influence of the amount of 3-methyl-1-pentyn-3-ol on the chain-end functionality ([PMDETA]/[$Sn(Oct)_2$]=1). When the ratio of [alkynol]/[PMDETA] is below 20, the functionality shows a steady increase with the increasing ratio of [alkynol]/[PMDETA]. It achieves a maximum for 86% at [alkynol]/[PMDETA] = 20. However, when [alkynol]/[PMDETA] is above 20, the functionality drops sharply. This reflects that a low amount of PMDETA added could not protect all molecules initiated by the alkynol.

GPC traces of propargyl-terminated PLA prepared with PMDETA (sample 3-d) and without PMDETA (sample **1-f**) are shown in Figure 6. In the case of **1-f**, the propargyl-terminated PLA exhibits a very broad trace with high polydispersity index of 2.64. Whereas for **3-d**, unimodal GPC trace is recorded with low polydispersity index of 1.22, and the shoulder attributed to the coupling of two molecules almost disappears. This result proves again PMDETA can protect the propargyl-end groups and prevents the coupling of two molecules.

4 Conclusions

Propargyl-terminated polylactide was synthesized through bulk ring-opening polymerization with 3-methyl-1-pentyn-3-ol as an initiator and $Sn(Oct)_2$ as a catalyst at 105°C. The analysis of chain-end functionality of polylactide by ^{1}H-NMR revealed that the active hydrogen of terminal alkynes disappeared during the polymerization. The most probable reason is the intermolecular oxidative coupling of the propargyl end groups into diyne. We found the addition of PMDETA can prevent coupling of two molecules and protect the propargyl-end groups. One of the best reaction conditions for synthesizing polylactide with high chain-end functionality was [alkynol]:[PMDETA]:[$Sn(Oct)_2$] = 20:1:1.

Acknowledgement

The authors are grateful to National Natural Science Foundation of China (50773043) and the Project-sponsored by SRF for ROCS, SEM. for financial support of this work.

References

1. Uhrich, K.E., Cannizzaro, S.M., Langer, R.S. and Shakesheff, K.M. (1999) *Chem. Rev.*, 99, 3181–3198.
2. Jeong, B., Bae, Y.H., Lee, D.S. and Kim, S.W. (1997) *Nature*, 388, 860–862.
3. Kowalski, A., Duda, A. and Pencaek, S. (2000) *Macromolecules*, 33, 689–695.
4. Carnahan, M.A., Middleton, C., Kim, J., Kim, T. and Grinstaff, M.W. (2002) *J. Am. Chem. Soc.*, 124, 5291–5293.
5. Gonzalez, R. and Ramshaw, B. (2003) *J. Am. Surg.*, 69, 471–476.
6. Lecomte, P., Riva, R., Schmeits, S., Rieger, J., Butsele, K.V., Jérôme, C. and Jérôme, R. (2006) *Macromol. Symp.*, 240, 157.
7. Carrot, G., Hilborn, J.G., Trollsas, M. and Hedrick, J.L. (1999) *Macromolecules*, 32, 5264.
8. Lu, F.Z., Xiong, X.Y., Li, Z.C., Du, F.S., Zhang, B.Y. and Li, F.M. (2002) *Bioconjugate Chem.*, 13, 1159.
9. Córdova, A., Iversen, T. and Hult, K. (1999) *Polymer*, 40, 6709–6721.
10. Nederberg, F., Bowden, T. and Hilborn, J. (2004) *Macromolecules*, 37, 954.
11. Yasugi, K., Nakamura, T., Nagasaki, Y., Kato, M. and Kataoka, K. (1999) *Macromolecules*, 32, 8024.
12. Allen, C., Yu, Y.S. and Maysinger, D. (1998) *Bioconjugate Chem.*, 9, 564–572.
13. Kolb, H.C., Finn, M.G. and Sharpless, K.B. (2001) *Angew. Chem.*, 113, 2056–2075.
14. Kolb, H.C., Finn, M.G. and Sharpless, K.B. (2001) *Angew. Chem. Int. Ed.*, 40, 2004–2021.
15. Rostovtsev, V.V., Green, L.G., Fokin, V.V. and Sharpless, K.B. (2002) *Angew. Chem. Int. Ed.*, 41, 2596–2599.
16. Lutz, J.-F., Börner, H.G. and Weichenhan, T. (2006) *Macromolecules*, 39, 6376.
17. Gao, H.F., Louche, G., Sumerlin, B.S., Jahed, N., Golas, P. and Matyjaszewski, K. (2005) *Macromolecules*, 38, 8979.
18. Malkoch, M., Thibault, R.J., Drockenmuller, E., Messerschmidt, M., Voit, B., Russell, T.P. and Hawker, C.J. (2005) *J. Am. Chem. Soc.*, 127, 14942,
19. Vogt, A.P. and Sumerlin, B.S. (2006) *Macromolecules*, 39, 5286.
20. Thibault, R.J., Takizawa, K., Lowenheilm, P., Helms, B., Mynar, J.L., Fréchet, J.M.J. and Hawker, C.J. (2006) *J. Am. Chem. Soc.*, 128, 12084.
21. Agut, W., Taton, D. and Lecommandoux, S. (2007) *Macromolecules*, 40, 5653–5661.
22. Altintas, O., Hizal, G. and Tunca, U. (2006) *J. Polym. Sci., Part A: Polym. Chem.*, 44, 5669.
23. Laurent, B.A. and Grayson, S.M. (2006) *J. Am. Chem. Soc.*, 128, 4238.

24. Malkoch, M., Schleicher, K., Frockemuller, E., Hawker, C.J., Russell, T.P., Wu, P. and Fokin, V.V. (2005) *Macromolecules*, 38, 3663.
25. Mespouille, L. and Vachaudez, M. (2008) *Reactive & Functional Polymers*, 68, 990–1003.
26. Xu, N., Lu, F.Z., Du, F.S. and Li, Z.C. (2007) *Macromol. Chem. Phys*., 208, 730–738.
27. He, X.H., Liang, L.Y., Xie, M.R., Zhang, Y.Q., Lin, S.L. and Yan, D.Y., (2007) *Macromol. Chem. Phys*., 208, 1797–1802.