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Facile Synthesis of Biodegradable and Clickable Polymer

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Abstract

Biodegradable polymers have been used in environmental and biomedical engineering, but the lack of functional groups limits their applications. In the present work, we report a facile approach to synthesize a biodegradable and clickable polymer consisting of ε-caprolactone (CL) and allyl methacrylate (AMA) with phosphazene base as the catalyst via hybrid copolymerization, where AMA is selectively copolymerized leaving the allylic groups for click reaction. The facile and efficient approach can be used to functionalize biodegradable polymers and synthesize some new polymers under mild conditions.

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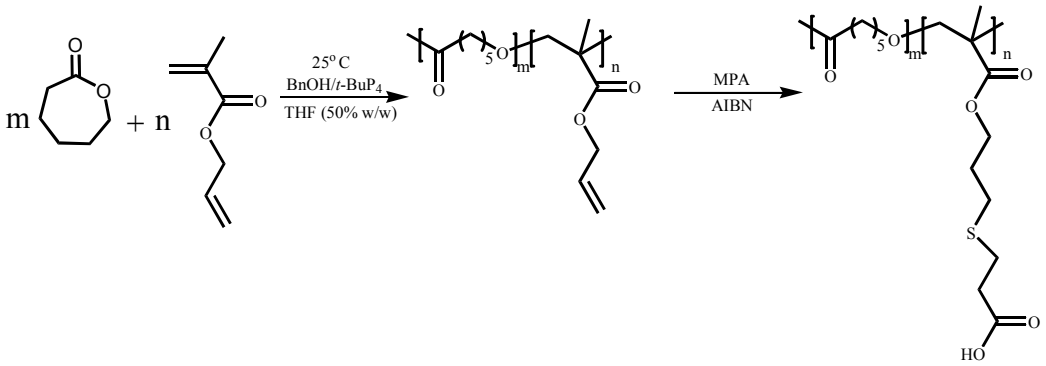
Introduction

Biodegradable polymers are increasingly important in environmental and biomedical engineering.[1-6] Yet, most of them are semi-crystalline and hydrophobic without functional groups, which limits their applications.[7-13] So far, some efforts towards functionalization of the polymers have been done. One approach is to use step-growth polymerization of multifunctionalized alcohol and acid, where the reactions are usually conducted at high temperatures, often giving rise to undesirable side reactions and unfavorable effects on their applications.[14,15] Another approach is to polymerize functionalized lactone or lactide monomers via ring-opening polymerization (ROP).[16-23] Because of the complicated procedure to synthesize functional monomers and the tedious protection/deprotection of functional groups in the polymerization, only a few of such polymers were successfully synthesized.[24-30] It is highly desired to design and develop functional biodegradable polymers with a facile procedure.

We have synthesized biodegradable polymers via hybrid copolymerization with (1-tert-butyl-4,4,4-tris(dimethylamino)-2,2-bis[tris(dimethylamino)phophoranylidena mino]-2Λ5,Λ5-catenadi(phosphazene) (*t*-BuP_4) as the catalyst.[31,32] On the other hand, as an efficient and simple approach, click chemistry has been used in design and synthesis of novel polymers.[33] Recently, we happened to find allyl methacrylate (AMA) can selectively copolymerize with ε-caprolactone (CL) via hybrid copolymerization with *t*-BuP_4 as the catalyst. Namely, AMA monomers are polymerized via methacrylic double bond leaving the allylic groups pendent to the copolymer (Scheme 1). Thus, the copolymers can be further functionalized through

via thio-ene click reaction. Due to the ester groups in the CL units, the copolymer is biodegradable. Here, we report the synthesis of the copolymer, and we attempt to provide a facile approach to functionalize biodegradable polymers.

Scheme 1. Synthesis of biodegradable and clickable polymer



Experimental Section

Materials

ε-Caprolactone (CL) from Aldrich was dried over calcium hydride (CaH_2) and distilled under reduced pressure prior to use. Benzyl alcohol (BnOH) from Aldrich was dried over sodium under a protrctive nitrogen protective atmosphere and distilled under vacuum after refluxing for hours. (tert-butyl-4,4,4-tris(dimethylamino)-2,2-bis[tris-(dimethylamino)phosphoranylidena-mino]-2Λ^5,4Λ^5-catenadi (phosphazene) (*t*-BuP_4) and 3-mercaptopropionic acid (MPA) from Aldrich were used as received. Allyl methacrylate (AMA) from Sinopharm was distilled over CaH_2 and stored under a nitrogen atmosphere at 0 °C. Tetrahydrofuran (THF) from Sinopharm was freshly distilled from sodium/benzophenone, and stored under an argon atmosphere. Other reagents from Sinopharm were used as received.

Characterization

Nuclear Magnetic Resonance. ^{1}H NMR and ^{13}C NMR were recorded on a Bruker ARX400 NMR spectrometer by using deuterated chloroform **(**$CDCl_3$**)** as solvent and tetramethylsilane (TMS) as internal standard.

Size Exclusion Chromatography (SEC). The molecular weight and polydispersity were obtained by SEC detection at 35 °C using a series of monodisperse polystyrenes as standards. The instrumentation consists of a Waters 1515 isocratic HPLC pump with 5 mm Waters styragel columns (guard, HR3, HR4, HR5, and HR6; the molecular weight ranges of the four HR columns are 500 to 30,000; 5,000 to 600,000; 50,000 to 4,000,000 and 200,000 to 10,000,000 g mol^{-}1, respectively); a Waters 717 PLUS auto-sampler; a Waters 2414 differential refractive index (dRI) detector with the wavelength 880 nm; and a Waters Breeze data manager. The eluent was HPLC grade THF delivered at 1.0 mL/min. For copolymer with carboxyls and its precursor, *N,N*-dimethylformamide (DMF) was used as the eluent.

Differential scanning calorimetry (DSC). DSC was conducted on a TA Instruments Q2000 under a nitrogen flow of 50 mL/min. Samples were quickly heated to 150 °C and hold for 10 min to remove thermal history, and then cooled to -80 °C at a rate of 10 °C/min. Finally, they were re-heated to 150 °C at the same rate.

Hybrid copolymerization of CL and AMA. A typical polymerization was performed as follows. CL (0.391 g, 3.1 mmol, 85 equiv), BnOH (3.90 μL, 0.04 mmol, 1.0 equiv), AMA (0.077 g, 0.6 mmol, 15 equiv), and THF (0.5 mL) were placed in a flamed and nitrogen purged round-bottom flask equipped with a magnetic stirrer.

t-BuP_4 (40 μL, 0.04 mmol, 1.0 equiv in hexane) was added through a rubber septum with a syringe to start the polymerization at 25 °C. The reaction was terminated with hydrochloric acid/methanol (1/20 v/v) after one hour. The product was dissolved in THF and precipitated into a large excess of methanol. After filtration the polymer was dried under vacuum. The copolymer is designated as CL_m-*co*-AMA_n, where *m* and *n* are the numbers of CL and AMA units, respectively. Homopolymerization of AMA or CL was carried out by using a similar procedure.

Thiol-ene click reaction. 0.1 g of CL-*co*-AMA containing 0.32 mmol ene groups, 16.5 mg of AIBN (0.2 equiv. to ene groups), and 10 equiv. of MPA were added into 2 mL of DMF, and stirred for 0.5 h. The mixture was then degassed via three freeze-pump-thaw cycles and subsequently flame-sealed. The ample was heated at 80 °C. The resulting functionalized copolymer was purified by precipitation in methanol, and dried under vacuum.

Results and Discussion

AMA contains a reactive methacrylic double bond and a less reactive allylic group.[34,35] In principle, the selective polymerization of the double bonds in methacrylic groups can yield a polymer with pendent double bonds. It is reported that the allylic groups are involved in the free radical polymerization even at the early stage, but they are free from anionic polymerization at a temperature below -45 °C. Fortunately, the anionic polymerization catalyzed by phosphazene base (e.g. *t*-BuP_4) can be conducted at room temperature.[36] Thus, we first studied the homopolymerization of AMA catalyzed by *t*-BuP_4 at 25 °C in THF by using benzyl

alcohol (BnOH) as the initiator. The molar ratio of [AMA]/[*t*-BuP$_4$]/[BnOH] is 100/1/1. The reaction system turns yellow as soon as the catalyst is introduced, and finally a polymer soluble in THF with number-average molecular weight ($M_{n.SEC}$) of 2.69×10^4 g/mol is obtained.

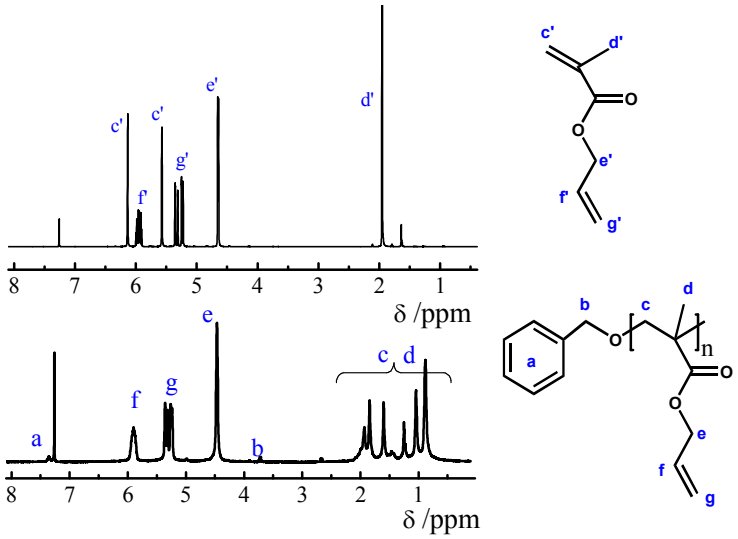


Figure 1. ^{1}H NMR spectra of AMA and PAMA in $CDCl_3$.

Figure 1 shows the ^{1}H NMR spectra of AMA and PAMA in $CDCl_3$. The proton signals at chemical shift 5.54 and 6.11 ppm corresponding to the methacrylic double bond of the AMA monomer disappear completely and new multiplets assigned to -C*H*(CH_3)CH_2- and -CH(CH_3)C*H*$_2$- emerge at 0.73-2.08 ppm in PAMA ^{1}H NMR spectrum. Allylic proton signals for C*H*$_2$=CH- and CH_2=C*H*- change from 5.04-5.14 ppm and 5.73-5.82 ppm to 5.17-5.40 ppm and 5.87-6.01 ppm, respectively. This is the direct evidence that the polymerization happens regarding methacrylic double bonds instead of allylic groups. Moreover, the integral of olefinic protons signal is almost 1.5 times larger than that of -OC*H*$_2$ protons signals, consistent with the theoretical

value calculated from the structural formula of the polymer. The facts further indicate that the allylic group of the monomer is not involved in the polymerization. In other words, *t*-BuP$_4$ can selectively catalyze the polymerization regarding methacrylic double bonds at room temperature with allylic double groups free from the polymerization.

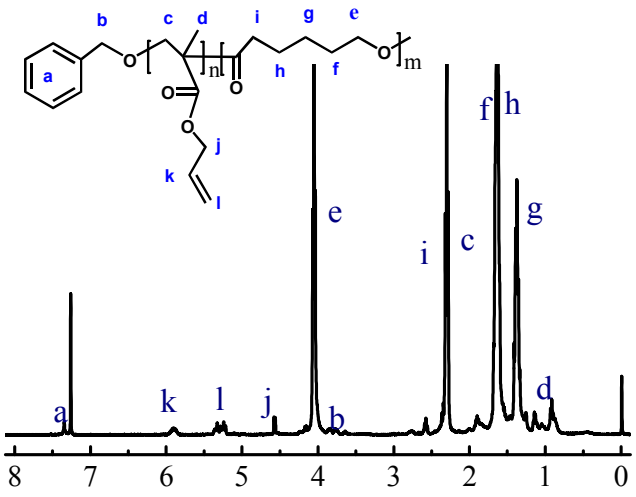


Figure 2. ^{1}H NMR spectrum of CL_{77}-*co*-AMA_{17} in $CDCl_3$.

Afterwards, we studied the copolymerization of AMA with CL with benzyl alcohol as the initiator in THF at 25 °C. Like in the case of homo-polymerization of AMA, the reaction system turns yellow as soon as *t*-BuP$_4$ is introduced. Meanwhile, the viscosity increases, indicating the formation of polymer. In comparison with the ^{1}H NMR spectra of PCL and PAMA hompolymers (see Figure 1 and Figure S1 in supporting information), we know all the signals attributed to the protons of CL and AMA units are available in the ^{1}H NMR spectrum in Figure 2. Thus, *t*-BuP$_4$

successfully catalyze the hybrid copolymerization of AMA and CL. The signals at 5.54 and 6.11 ppm due to the methacrylic double bond of the AMA monomer disappear completely, indicating that the methacrylic double bonds are selectively polymerized via hybrid copolymerization. The molar fraction of -OCH_2 proton signals is twice of allylic groups in AMA units, indicating that allylic double bonds are not involved in the polymerization. From the ^{1}H NMR spectrum, we know that the molar ratio of AMA (F_{AMA}) in the copolymer is approximately equal to the feed ratio (f_{AMA}). Thus, the copolymer composition can be modulated by varying the monomer feed.

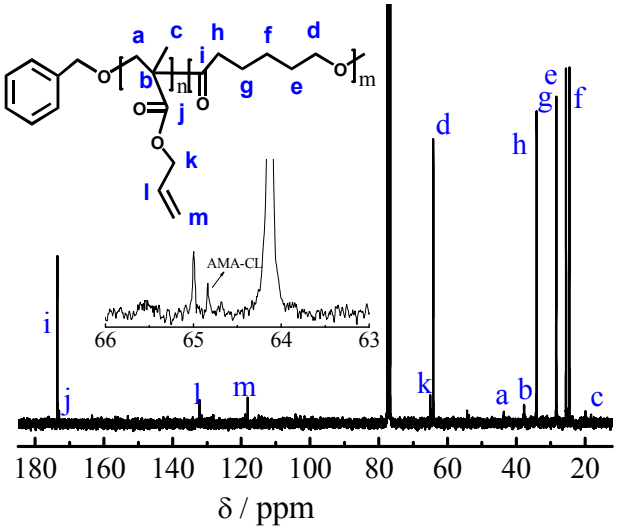


Figure 3. ^{13}C NMR spectra of CL_{77}-*co*-AMA_{17} in $CDCl_3$.

Figure 3 shows the ^{13}C NMR spectra of a CL-*co*-AMA copolymer. The assignments were made by comparison with the ^{13}C NMR spectra of the corresponding homopolymers (See Figure S2 and Figure S3 in supporting information). The peaks at 173.7-173.8 ppm, 64.1-64.3 ppm, 33.7-33.8 ppm,

28.6-28.8 ppm, 25.4-25.6 ppm and 24.0-24.2 ppm are assigned to the carbons in CL units. The peaks at 173.1-173.2 ppm, 132.4-132.5 ppm, 118.1-118.3ppm, 64.9-65.0 ppm, 43.4-43.5 ppm, 37.3-37.4 ppm and 19.5-19.8 ppm are to the carbons in AMA units. Particularly, the carbonyl peak at 64.7-64.8 ppm is due to the secondary carbons (-*C*H_2CH(CH_3) of AMA unit adjacent to a CL unit, indicating that the product is copolymer instead of a mixture of copolymer and PCL homopolymer.

Table 1. Characteristic data of CL-*co*-AMA copolymers

Sample	$Conv_{.CL}$	$Conv_{.AMA}$	f_{AMA} [a]	F_{AMA} [b]	$M_{n.th}$ [c] (10^4 g/mol)	$M_{n.NMR}$ [d] (10^4 g/mol)	$M_{n.SEC}$ [e] (10^4 g/mol)	PDI
PCL	90.3		0	0	1.04	0.99	2.47	1.25
PAMA		93.2	1.00	1.00	1.19	1.17	2.69	1.29
CL_{89}-*co*-AMA_{10}	97.7	99.3	0.08	0.10	1.14	1.15	2.38	2.14
CL_{77}-*co*-AMA_{17}	95.5	96.5	0.15	0.18	1.12	1.10	2.13	2.18
CL_{62}-*co*-AMA_{30}	92.6	92.1	0.30	0.33	1.09	1.05	2.24	1.91

[a] Molar fraction of AMA in the comonomer feed;
[b] Molar fraction of AMA units in the copolymer measured by ^{1}H NMR;
[c] Theoretical molecular weight;
[d] Number-average molecular weight measured by ^{1}H NMR;
[e] Calibration with polystyrene standards.

Figure 4 shows the SEC curves for CL-*co*-AMA copolymers. Clearly, the copolymer has a broad and multimodal distribution. As reported before, this is because several active centers coexist in the hybrid copolymerization.[31] The number-average molecular weight measured by SEC ($M_{n.SEC}$) and ^{1}H NMR ($M_{n.NMR}$) in Figure 2 together with the theoretical value ($M_{n.th}$) are summarized in Table 1. Clearly, $M_{n.NMR}$ is close to $M_{n.th}$, but they are smaller than $M_{n.SEC}$. This is understandable because the SEC measurements with monodisperse polystyrenes as the standard only give relative molecular weight.

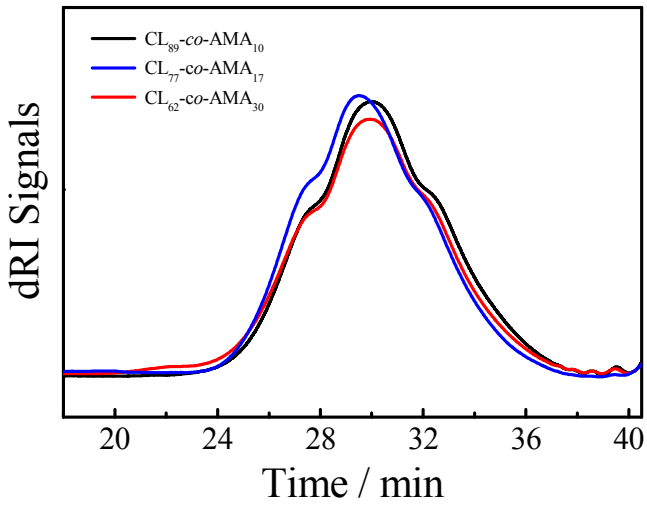


Figure 4. SEC curves for CL-*co*-AMA copolymers.

We also examined the copolymers with different AMA fractions by DSC (Figure 5). PCL is a crystalline polymer with a glass transition temperature (T_g) at -60.0 ºC and a melting temperature (T_m) at 57.4 ºC, whereas PAMA is an amorphous polymer with a T_g at 86.3 ºC. Each copolymer has only one T_g, further indicating that the product is a copolymer instead of a mixture of copolymer and homopolymers. The copolymerization profoundly influences the crystallization. Either CL_{89}-*co*-AMA_{10} or CL_{77}-*co*-AMA_{17} exhibits a double melting peak, indicating they are crystalline polymers. Clearly, the long PCL segments in the copolymer are responsible for the crystallization. The double melting peak is attributed to the secondary crystallization.[37] For CL_{89}-*co*-AMA_{10}, the melting peak locates at 36.0 ºC and 43.4 ºC. For CL_{77}-*co*-AMA_{17}, it is at 25.6 ºC and 36.9 ºC. Accordingly, the melting peak shifts to lower temperature as AMA content increases. For CL_{62}-*co*-AMA_{30}, the melting peak is no longer observed because the PCL segments are too short to fold and crystallize

with the incorporation of so many AMA units. On the other hand, each copolymer exhibits only one glass transition temperature (T_g) between those of PCL (-60.0 ºC) and PAMA (86.3 ºC) homopolymers. For CL_{89}-*co*-AMA_{10}, CL_{77}-*co*-AMA_{17} and CL_{62}-*co*-AMA_{30}, T_gs are -55.6 ºC, -55.3 ºC and -54.3 ºC, respectively. Clearly, the T_g of the copolymer increases with AMA content. The facts further indicate that AMA segments are randomly distributed along the polymer chain.

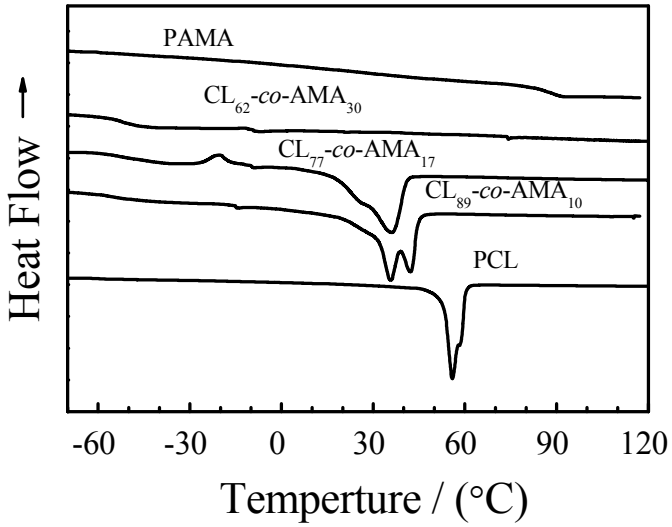


Figure 5. DSC curves of CL-*co*-AMA copolymers, where the heating rate is 10 °C/min.

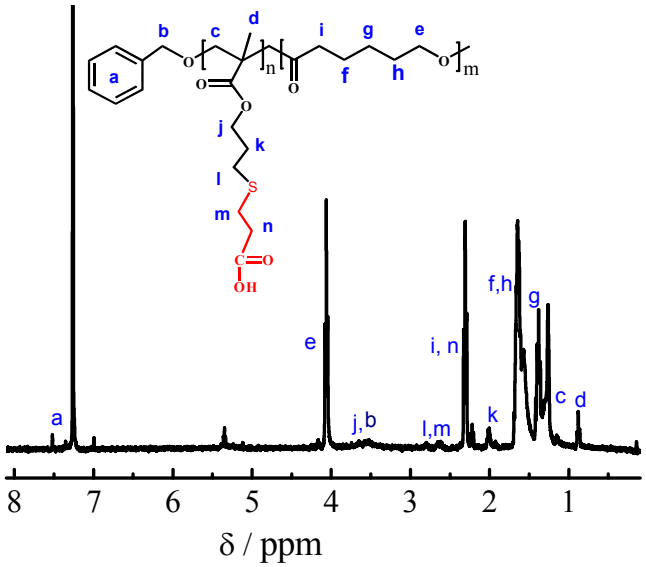


Figure 6. ^{1}H NMR spectrum of CL_{77}-*co*-AMA_{17} after the thiol-ene coupling.

Thiol-ene click reaction is a robust and versatile method for post-polymerization modification of polymers.[33,38-41] Here, the thiol-ene coupling reaction of the ene polymers with MPA is conducted by using AIBN as the radical initiator. With the carboxyls, the copolymer become more hydrophilic and biodegradable, so that they can be adaptable to the application about drug delivery. Other functional groups can be also attached via thiol-ene reaction. The copolymer with carboxyls has a good solubility in DMF indicating that no cross-linking reaction happens. After the thiol-ene reaction, the molecular weight of the copolymer detected by SEC changes 3.46×10^4 g/mol from 2.79×10^4 g/mol and the polydispersity varies from 2.04 to 1.98. Figure 6 shows the ^{1}H NMR spectrum of the modified copolymer. The proton signals at chemical shift 5.16-5.46 and 5.82-5.61 ppm corresponding to the allylic double bonds completely disappear while new signals at 1.96-1.97 and 2.57-2.89 ppm assigned to MPA groups come out, clearly indicating the successful coupling. Note that the pendant allylic double bonds in the copolymer can react with not only MPA

but also any other compounds with –SH or R−CH=CH_2 groups, so that the polymers can be chemically modified via click reaction, Baeyer-Villiger oxidation or cross-linking reactions.[38-42]

Conclusions

In conclusion, we have synthesized a clickable and biodegradable polymer via hybrid copolymerization. The polymer can be further chemically modified by click coupling reaction. This approach is facile and simple to perform under mild conditions. It should find applications in development of functional biomaterials used in environmental and biomedical engineering.

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References:

(1) M. Tang, M. Purcell, J. A. M. Steele, K. Y. Lee, S. McCullen, K. M. Shakesheff, A. Bismarck, M. M. Stevens, S. M. Howdle and C. K. Williams, *Macromolecules*, 2013, **46**, 8136.

(2) R. Sua, H. Yang, Y. Leua, M. Huab and R. Lee, *React. Funct. Polym.,* 2012, **72**, 36.

(3) O. Jazkewitsch, A. Mondrzyk, R. Staffel and H. Ritter, *Macromolecules,* 2011, **44** 1365.

(4) H. Seyednejad, A. H. Ghassemi, C. F. van Nostrum, T. Vermonden and W. E. Hennink, *J. Control. Release,* 2011, **152**, 168.

(5) M. K. Kiesewetter, E. J. Shin, J. L. Hedrick and R. M. Waymouth, *Macromolecules,* 2010, **43**, 2093.

(6) A. Arbaoui and C. Redshaw, *Polym. Chem.,* 2010, **1**, 801.

(7) M. Labet and W. Thielemans, *Chem. Soc. Rev.,* 2009, **38**, 3484.

(8) P. Lecomte, R. Riva, C. Jérôme and R. Jérôme, *Macromol. Rapid Commun.,* 2008, **29**, 982.

(9) X. W. Jiang, E. B. Vogel, M. R. Smith III and G. L. Baker, *J. Polym. Sci. Part A: Polym. Chem.,* 2007, **45**, 5227.

(10) L. S. Nair, and C. T. Laurencin, *Prog. Polym. Sci.,* 2007, **32**, 762.

(11) S. J. Hollister, *Nat. Mater.,* 2005, **4**, 518.

(12) A. -C. Albertsson and I. K. Varma, *Biomacromolecules,* 2003, **4**, 1466.

(13) C. Jérôme and P. Lecomte, *Adv. Drug Deliv. Rev.,* 2008, **60**, 1056.

(14) A. Rodriguez-Galan, L. Franco and J. Puiggali, *Polymers,* 2011, **3**, 65.

(15) W. H. Carothers and J. A. Arvin, *J. Am. Chem. Soc.,* 1929, **51**, 2560.

(16) F. Coumes, V. Darcos, D. Domurado, S. Li and J. Coudane, *Polym. Chem.,* 2013, **4**, 3705.

(17) J. A. Castillo, D. E. Borchmann, A. Y. Cheng, Y. F. Wang, C. Hu, A. J. Garcia and M. Weck, *Macromolecules,* 2012, **45**, 62.

(18) N. E. Kamber, W. Jeong, R. M. Waymouth, R. C. Pratt, B. G. G. Lohmeijer and J. L. Hedrick, *Chem. Rev.,* 2007, **107**, 5813.

(19) S. Penczek, M. Cypryk, A. Duda, P. Kubisa and S. Słomkowski, *Prog. Polym. Sci.,* 2007, **32**, 247.

(20) J. Wu, T.-L. Yu, C.-T. Chen and C.-C. Lin, *Coord. Chem. Rev.,* 2006, **250**, 602.

(21) J. M. W. Chan, H. Sardon, A. C. Engler, J. M. García and J. L. Hedrick, *ACS Macro Lett.,* 2013, **2,** 860.

(22) O. Coulembier, P. Degée, J. L. Hedrick and P. Dubois, *Prog. Polym. Sci.,* 2006, **31**, 723.

(23) D. Mecerreyes, R. D. Miller, J. L. Hedrick, C. Detrembleur and R. Jérôme, *J. Polym. Sci.; Part A: Polym. Chem.,* 2000, **38**, 870.

(24) H. Kim, J. V. Olsson, J. L. Hedrick and R. M. Waymouth, *ACS Macro Lett.,* 2012, **1**, 845.

(25) Y. Sarazin, B. Liu, T. Roisnel, L. Maron and J.-F. Carpentier, *J. Am. Chem. Soc.,* 2011, **133**, 9069.

(26) S. E. Habnouni, V. Darcos and J. Coudane, *Macromol. Rapid Commun.,* 2009, **30**,

165.

(27) S. Tempelaar, L. Mespouille, P. Dubois and A. P. Dove, *Macromolecules,* 2011, **44**, 2084.

(28) M. Tang, Y. Dong, M. M. Stevens and C. K. Williams, *Macromolecules,* 2010, **43**, 7556.

(29) D. P. Sanders, K. Fukushima, D. J. Coady, A. Nelson, M. Fujiwara, M. Yasumoto and J. L. Hedrick, *J. Am. Chem. So.,* 2010, **132**, 14724.

(30) I. Taniguchi, A. M. Mayes, E. W. L. Chan and L. G. Griffith, *Macromolecules,* 2005, **38**, 216.

(31) H. J. Yang, J. B.Xu, S. Pispas and G. Z. Zhang, *Macromolecules,* 2012, **45**, 3312.

(32) H. J. Yang, J. B. Xu and G. Z. Zhang, *Sci. China Chem.,* 2013, **56**, 1101.

(33) T. P. Lodge, *Macromolecules,* 2009, **42**, 3827.

(34) H. Zhang and E. Ruckenstein, *J. Polym. Sci., Part A: Polym. Chem.,* 1997, **35**, 2901.

(35) T. Kitayama, E. Masuda, M. Yamagachi and K. Hatada, *Polym. J.,* 1992, **24**, 817.

(36) T. Pietzonka and D. Seebach, *Angew. Chem. Int. Ed.,* 1993, **32**, 716.

(37) W. Liu and C. M. Dong, *Macromolecules,* 2010, **43**, 8447.

(38) I. Tijunelyte, J. Babinot, M. Guerrouache, G. Valincius, B. Carbonnier. *Polymer*, 2012, **53**, 29.

(39) A. B. Lowe, *Polym. Chem.*, 2010, **1**, 17.

(40) H. C. Kolb, M. G. Finn and K. B. Sharpless, *Angew. Chem., Int. Ed.,* 2001, **40**, 2004.

(41) C. E. Hoyle and C. N. Bowman, *Angew. Chem. Int. Ed.,* 2010, **49**, 1540.

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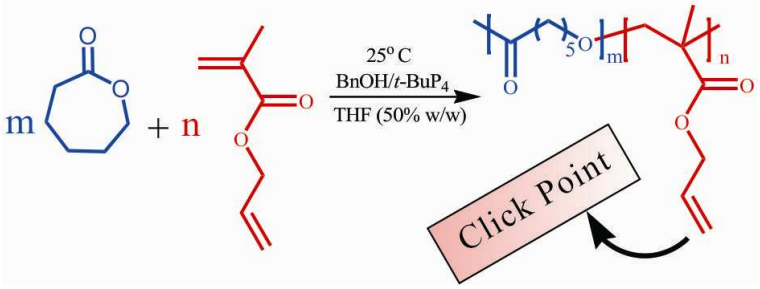

We report a facile approach to synthesize a biodegradable and clickable polymer consisting of ε-caprolactone (CL) and allyl methacrylate (AMA) with phosphazene base as the catalyst via hybrid copolymerization.