New Prospects for the Grafting of Functional Groups onto Aliphatic Polyesters. Ring-Opening Polymerization of α- or γ-Substituted ε-Caprolactone Followed by Chemical Derivatization of the Substituents

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Summary: Recent progress in the synthesis of aliphatic polyesters, substituted by pendent functional groups, has been reviewed. Two main strategies have to be distinguished. The first route consists of the ring-opening polymerization of ε-caprolactone substituted by various functional groups, protected if needed, in α- or γ-position. In a second strategy, the functional groups are grafted onto preformed polyesters chains in α-position of the carbonyl groups. α-chloro-ε-caprolactone is quite an interesting monomer because, after polymerization, the activated chloride can be easily derivatized by atom transfer radical addition and "click" chemistry, respectively. Similarly, γ-acrylic-ε-caprolactone is precursor of (co)polyesters well-suited to derivatization of the pendent double bonds by Michael addition.

Keywords: aliphatic polyesters; atom transfer radical addition; "click" chemistry Michael addition; ring-opening polymerization

Introduction

Biodegradable and biocompatible aliphatic polyesters are well-known biomaterials. Attachment of functional groups along the chain is highly desirable to tailor the macroscopic properties of these aliphatic polyesters, e.g. crystallinity, hydrophilicity, biodegradation rate, bioadhesion and mechanical properties. Moreover, pendent functional groups can be used to covalently attach molecules or probes of biological interest.

Ring-opening polymerization (ROP) of lactones and lactides is a well-established process for the synthesis of aliphatic polyesters with predictable molecular weight (M_n), a narrow molecular weight distribution, and well-defined end-groups. Among the wide range of catalysts/initiators able to promote the ROP of these cyclic esters,[1] tin and aluminum alkoxides are most commonly used. For the last few years, two main strategies have been proposed to synthesize aliphatic polyesters with pendent functional groups (Figure 1). The first one is based on the synthesis and polymerization of lactones substituted in α- or γ- position. [2] The grafting of functional groups in the α- position of the carbonyl of preformed polyester is the second strategy. [3–5]

After a short review of the functionalization of mainly poly(ε-caprolactone) (PCL), attention will be paid to derivatization of pendent double bonds by Michael addition and derivatization of activated chlorides by atom transfert radical addition and "click" chemistry, respectively.

Ring-Opening Ppolymerization of Lactones α- or γ-Substituted by Functional Groups

In 1997, Tian et al. reported on the synthesis of 1,4,8-trioxaspiro[4.6]-9-undecanone.

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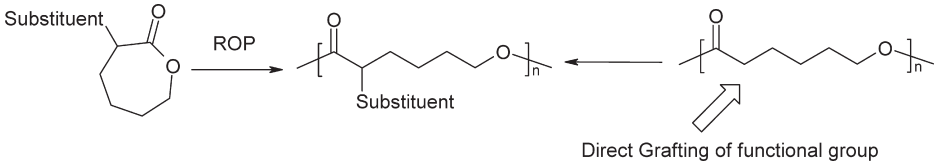

Figure 1.
Main strategies for the synthesis of aliphatic polyesters with pendent functional group.

This cyclic monomer was homopolymerized [6] and copolymerized [7] with ε-caprolactone as shown in Figure 2. The ketal groups were used as protected ketones, whose the reduction by sodium borohydride led to pendent hydroxyl groups.

Later on, a series of lactones substituted by bromides [8,9], acrylates [10] and terminal olefins [11,12] or containing ketones [13] were synthesized and homo- or copolymerized. Interestingly, Vert et al. investigated the synthesis and polymerization of 3-(1,2-3,4-tetraoxobutyl-diisopropylidene)dioxane-2,5-dione (DIPAGYL), a derivative of glycolide, substituted by acetonide, which can be partially deprotected into diol. [14] It must be noted that the synthesis of substituted lactones is most often a multistep process and that the final yield may be low. For a detailed description of the synthesis and polymerization of these monomers, the reader is referred to a review paper. [2]

This strategy was extended to the synthesis of functional poly(carbonate)s by ring-opening (co)polymerization of carbonates substituted by ketal [15], protected acid [16] and alcohol [17]. Copolymerization of lactones and lactide with 2,5-morpholinediones substituted by protected acids [18] and amines [19] was reported.

The major drawback of this synthetic strategy is that any functional groups able to react with metal alkoxides (mainly aluminum and tin) involved in the polymerization must be protected prior to polymerization and deprotected after polymerization. [20–22] The choice of the protecting group is also an important issue because deprotection of too stable protecting groups can result in the polyester degradation. For instance, poly(ε-caprolactone) (PCL) containing more than 50 mol% of γ-triethylsilanolate (–$OSiEt_3$) could not be quantitatively converted into hydroxyl containing PCL without degradation.[23] Conversely, too labile protecting groups can be deprotected at least partly during the synthesis and purification of the monomer. Epoxides are not compatible with tin and aluminum alkoxides, such that they have to be incorporated by postpolymerization oxidation of pendent double bonds, for

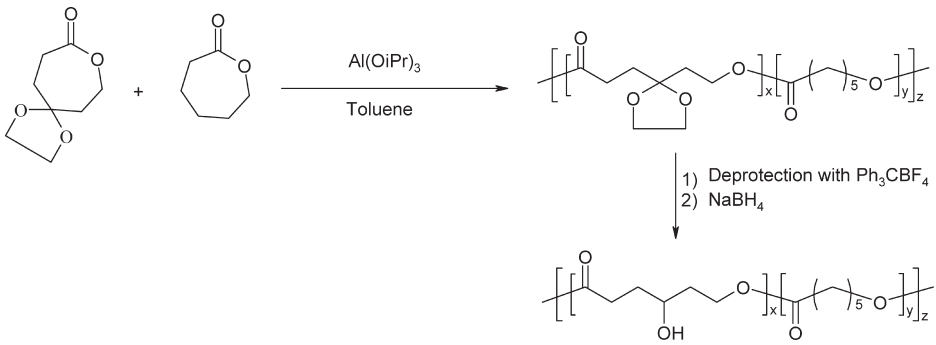

Figure 2.
Synthesis of PCL with pendent OH groups.

instance by m-chloroperbenzoic acid (mCPBA).[12,24]

The main advantage of using functional lactones is the possibility to have them purified prior to polymerization. Therefore, the final polymer is not contaminated by potentially toxic catalysts and/or chemicals as would be the case if the same functionalization reaction was carried out with preformed polymer chains.

A special type of functional lactones are macromonomers, thus lactones substituted by a polymer chain, for instance poly(ethylene oxide) (PEO). These macromonomers are precursors of graft copolymers, e.g, poly(ε-caprolactone-g-ethylene oxide) (PCL-g-PEO). Amphiphilic PCL-g-PEO [25] have been accordingly prepared, that form micelles in water and polylactide nanoparticles in water, as well. Similarly, Park et al. reported on the copolymerization of lactide with poly(ethylene oxide) (PEO) end-capped by an epoxide group.[26]

Direct Grafting of Functional Groups onto Aliphatic Polyesters

Grafting of functional groups onto preformed polymer chains, is a very appealing approach because a wide range of functional groups can be attached from a single precursor. A representative example was reported by Vert et al., [3–5] who metallated PCL by lithium diisopropylamide with formation of a poly(enolate), reactive towards electrophiles, such as carbon dioxide and benzaldehyde, thus precursors of acid and hydroxyl moieties, respectively (Figure 3). The implementation of this strategy is however limited by unavoidable chain degradation in competition with chain metallation.

Ring-Opening Polymerization of Suitably Substituted ε-Caprolactones Followed by Derivatization of the Substituent

In order to tackle the problems inherent to the routes shown in Figure 1, it appears that a combination of these two strategies into a two-step process might be a valuable alternative (Figure 4). Thus, ε-caprolactone substituted by properly selected functional group is first polymerized, followed by derivatization of the substituent into a variety of functional groups, polymeric or not, according to any reaction known in the state of the art. A wide range of aliphatic polyesters could accordingly be made available from a single precursor.

For this strategy to be successful, the following criteria should be satisfied: (1) as direct synthesis as possible of the substituted monomer to be first polymerized (one or two steps), (2) this monomer should comply with controlled (co)-polymeriza-

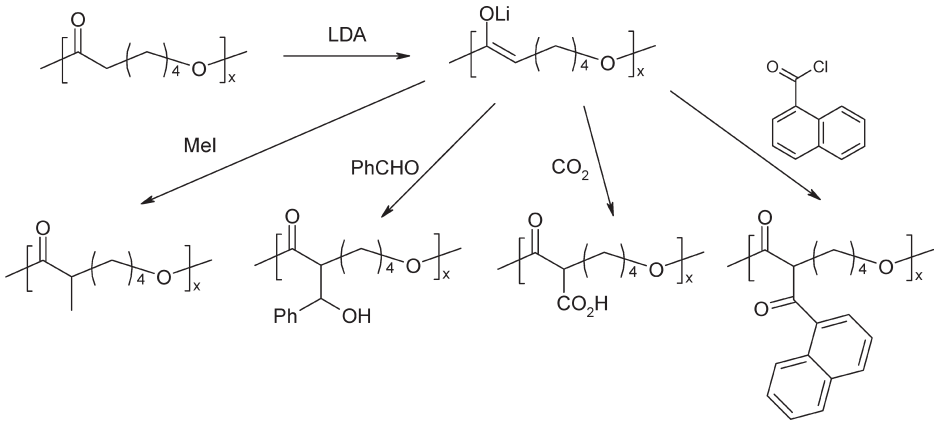

Figure 3.
Chemical derivatization of PCL by an anionic route.

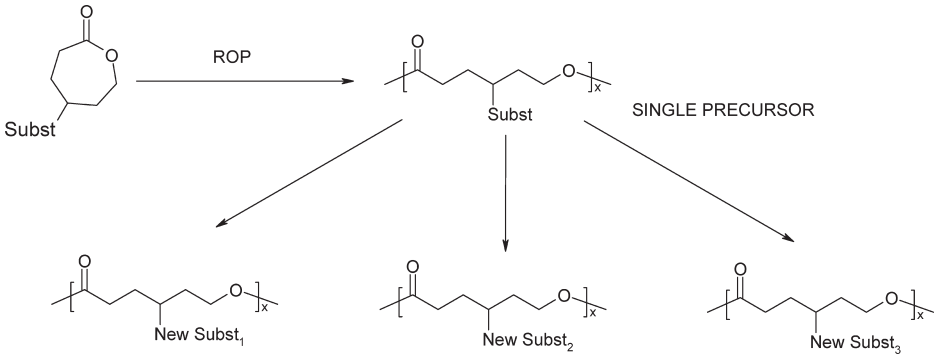

Figure 4.
ROP of substituted ε-caprolactone into a unique precursor followed by its chemical derivatization into various functional aliphatic polyesters.

tion, (3) the envisioned derivatization reactions should be carried out under mild conditions in order to (i) avoid chain degradation, (ii) avoid protection/deprotection of the functions to be incorporated, (iii) favor quantitative reaction even at high content of functional groups.

An example of this strategy was reported by Emrick et al. who copolymerized ε-caprolactone with an unsaturated derivative, followed by conversion of the pendent double bonds into diols and esterification of these hydroxyl groups with PEO end-capped by a carboxylic acid (Figure 5).[27]

Mayes et al. reported on the grafting of aminooxy-terminated poly(ethylene oxide) (PEO) onto the ketone groups of poly (ε-caprolactone-co-oxepane-1,2-dione) [28], that was synthesized according a procedure reported by some of us [13] (Figure 6). Nevertheless, copolymers with a high content of ketone are insoluble in organic solvents, which restricts the content of any functional group to low values.

The Michael Addition

Recently, thiols were added onto pendent acrylate groups of PCL. Indeed, γ-acrylic-ε-CL was synthesized according to a three-step procedure [29] and copolymerized with εCL into poly (γ-acrylic-εCL-co-εCL) copolymers (Figure 7). Thiol end-capped PEO was then added onto the pendent acrylic groups of PCL (content of acrylic units = 18 mol%) in the presence of pyridine (THF, room temperature, 300h

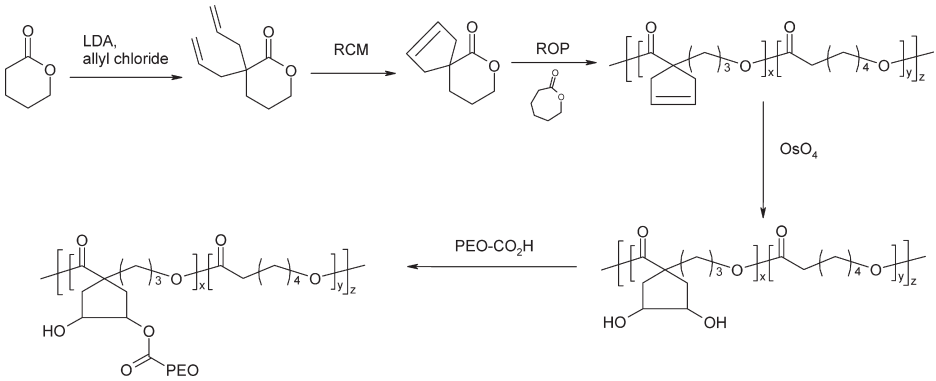

Figure 5.
Grafting of PEO onto PCL according to Emrick et al. [27]

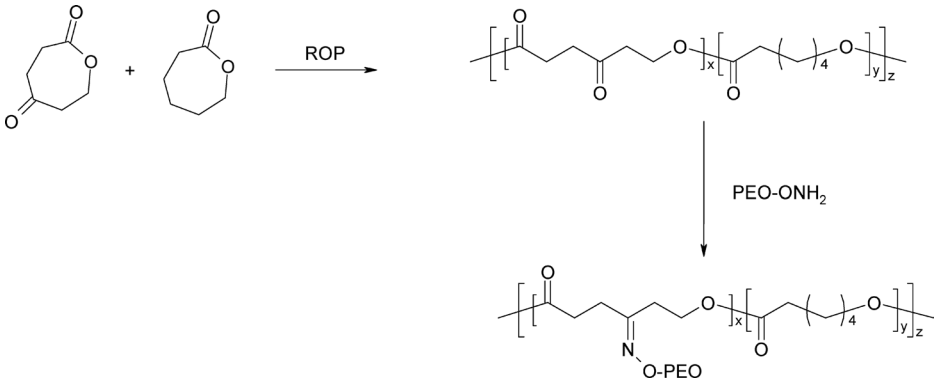

Figure 6.
Grafting of PEO onto PCL according to Mayes et al. [28]

[pyridine]/[thiol]/[acrylate] = 15/10/1).[30] The poly(CL-g-EO) graft copolymer was formed as result of 65% conversion of the acrylic units. These experimental conditions were extended to the addition of mercaptoacetic acid, the acrylic conversion being 71% after 75h. Remarkably, no cumbersome protection/deprotection reaction was needed for attaching acid groups onto PCL. No degradation was either observed. Nevertheless, the Michael reaction is not quantitative; with the risk of cross-linking through the residual acrylic groups. Last but not least, the control of the homopolymerization of γ-acrylic-ε-CL is limited by a backbiting reaction producing γ-acryloxyethyl-γ-butyrolactone, [31]. The main advantage of the Michael addition is

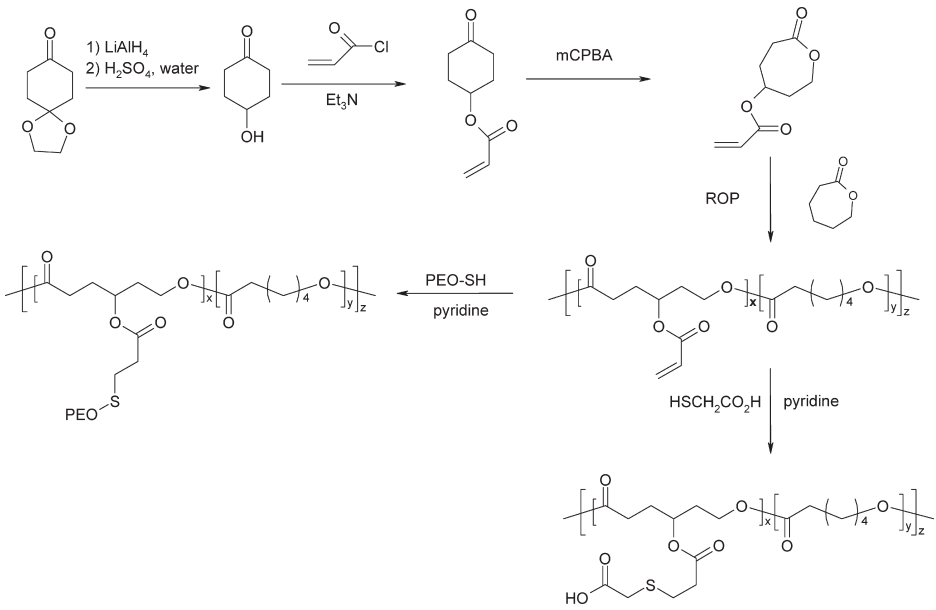

Figure 7.
Derivatization of pendent acrylic unsaturation of PCL by Michael addition.

that no organometallic catalyst, that might be detrimental to biomedical applications, is needed.

In a similar approach, thiols were grafted onto pendent epoxides, prepared by oxidation of unsaturated aliphatic polyesters by mCPBA.[12]

Atom Transfer Radical Addition

Atom transfer radical addition (ATRA) is mediated by organometallic catalysts, which are known for tolerance towards aliphatic polyesters.[32] This reaction is well-suited to chloride activated by a carbonyl group. On that basis, a three-step strategy detailed in Figure 8 was devised that fits the general scheme shown in Figure 4. [34,35] First, α-chlorocyclohexanone was converted into the parent lactone (αClεCL) by oxidation with m-CPBA. Then, αClεCL was copolymerized with εCL in a well-controlled manner, the initiator being a tin(IV) alkoxide.[33] Finally, 3-buten-1-ol was quantitatively grafted onto PCL by CuBr/Me_6TREN meditated ATRA in DMF at 65 °C for 4 h.[34] Again, no protection was needed and no chain degradation was observed by SEC. [34] Moreover, ATRA of α-methoxy, ω-acrylate-PEO (M_n (PEO = 750) onto poly(αClεCL-co-εCL) (M_n =17500 ; 48 αClεCL units) yielded a graft copolymer, with 9 PEO grafts.[35] However, 18 chlorinated units per chain were lost by reduction during ATRA. The situation was worst when vinyl acetic acid was substituted for 3-buten-1-ol. Indeed, no ATRA took place, and all the chlorinated units were reduced. The activity of the catalyst was decreased by using HMTETA as a ligand instead of Me_6TREN. Then, no parasitic reduction of the chlorides occurred and ATRA was observed with a moderate yield of 32% after 24 h. Finally, ATRA was quantitative at higher temperature (85 °C instead of 65 °C), although chains were degraded simultaneously.

As a rule, ATRA does not meet the third criteria of the general strategy shown in Figure 4. Moreover, the stoichiometric amount of the copper catalyst with respect to activated chlorides, which is needed in ATRA, contaminates the final polyester, which may be unacceptable depending on the end-use of the polymer.

Click Reactions

Nowadays, much attention is paid to copper catalyzed 1,3-Huisgens cycloadditions between azides and alkynes, thus to reactions which are known for quantitative yield, under very mild conditions, from cheap and easily available reagents.[36] Potential of this reaction into the macromolecular engineering of aliphatic polyesters was investigated.

Emrick et al. reported on the cycloaddition of an azido-end-capped PEO onto PCL bearing pendent alkynes.[37] The ''click'' reaction was conducted in water in the

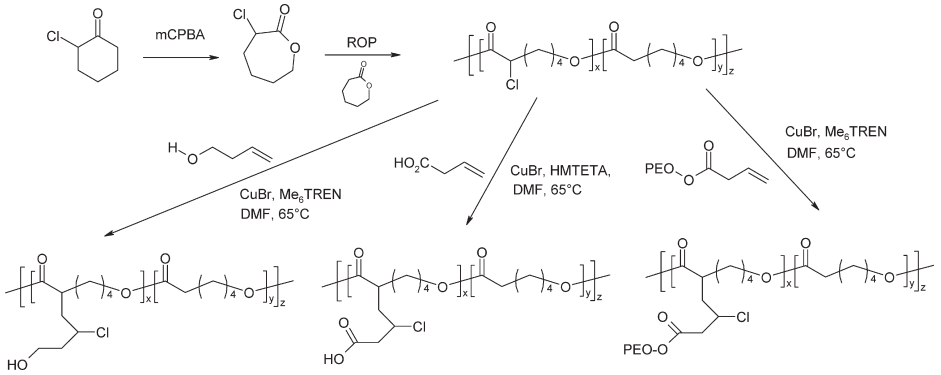

Figure 8.
Derivatization of the α-chloride pendent groups of PCL by atom transfer radical addition.

presence of $CuSO_4$ and sodium ascorbate as catalyst. At least in our hands, PCL was partly degraded under these conditions.

Some of us converted the chloride units of poly(αClεCL-co-εCL) into azides, followed by ''click'' reaction with functional alkynes (Figure 9).[38] In order to restrict the PCL degradation as much as possible, the ''click'' reaction was carried out at a lower temperature (35 °C instead of 80 °C) and in an organic solvent (THF) rather than in water, compared to the conditions previously used by Emrick et al. Cycloaddition of both propargyl benzoate mediated by CuI and triethylamine (NEt_3) and 3-dimethylaminoethyl-1-propyne mediated by CuI turned out to be quantitative at 35 °C in THF and no significant degradation was observed by SEC [38] (Figure 9). It is worth noting that CuI was used in catalytic amount (0.1 equivalent with respect to the azide groups), which is a significant improvement compared to ATRA, which requires a stoichiometric amount of copper catalyst. An additional advantage of this ''click'' reaction is tolerance towards many organic functions. Indeed, polycationic polyesters were prepared by using N,N,N-triethylammonium propargyl bromide as the alkyne reagent. PCL-g-PEO were also synthesized by reaction of an alkyne end-group of PEO (ω-alkyne-PEO) with poly(αN$_3$εCL-co-εCL). The grafting efficiency was approximately 30% in line with the yield reported for ATRA. Importantly, no degradation was detected by SEC analysis.

''Click'' reaction is also superior to other derivatization reactions in that high content of pendent functional groups can be considered. Indeed, the aforementioned cycloaddition was complete in THF when poly(αN$_3$εCL) ($M_n = 46000$; $M_w/M_n = 1.6$) was reacted with propargyl benzoate.

Remarkably, the very mild experimental conditions used in ''click'' reactions allow them to be extended to the functionalization of polylactide known for higher sensitivity to chain degradation than PCL. The success of this strategy was exemplified by the reaction of ω-alkyne-PEO with poly(αN$_3$εCL-co-LA), provided that the OH end-groups of the copolylactide chains were previously esterified with acetyl chloride (Figure 10).

The activated chlorides of poly(αClεCL-co-εCL) can thus be derivatized by either

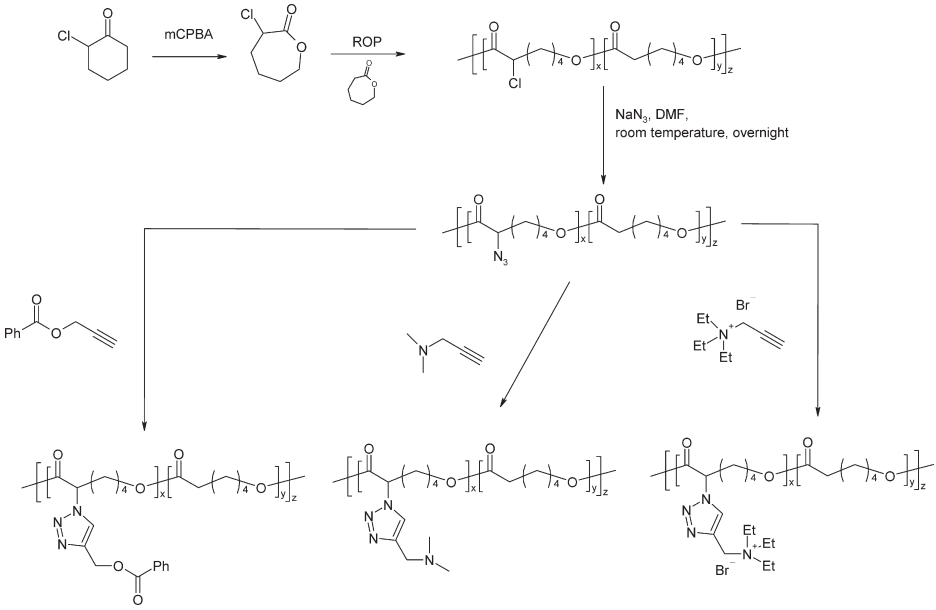

Figure 9.
Derivatization of pendent azide groups of PCL by ''click'' reactions.

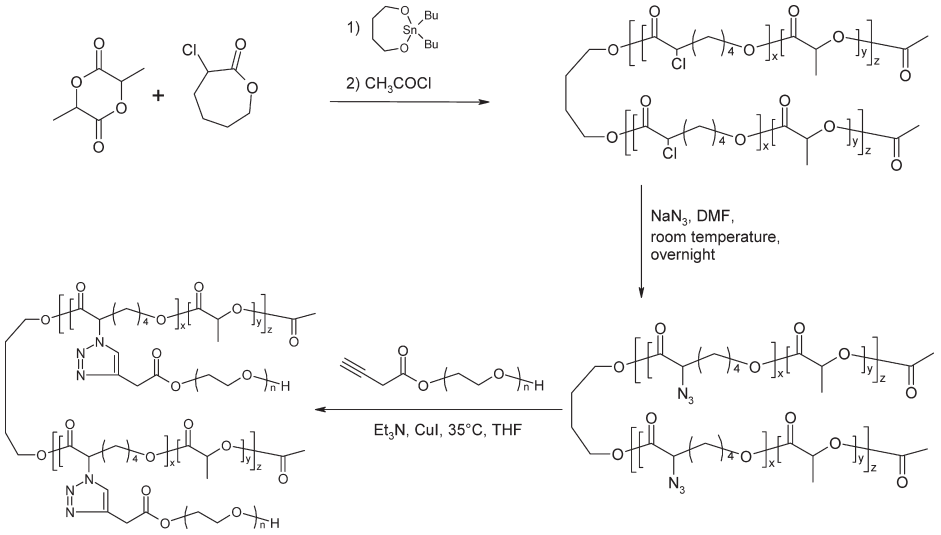

Figure 10.
Synthesis of P(LA-g-EO) by combining ROP and "click" chemistry.

ATRA or 1,3-Huisgen cycloadditions. Eventough the "click reaction" requires an extra step compared to ATRA (comparison of figures 8 and 9), it is more effective. This superiority is reinforced by the fact that the additional step, i.e., substitution of chlorides by azides, and the cycloaddition can be carried out in one-pot, thus without isolating the intermediate azide containing copolymer. In a representative example, poly(α-ClεCL-co-εCL) ($M_n = 22000$; $M_w/M_n = 1.5$) was reacted with 5 equivalents of sodium azide in DMF at room temperature overnight. 5 equivalents of propargyl benzoate were then added to the reaction mixture, and the "click" reaction was quantitative at 35 °C for 3 h. A slight increase in the polydispersity index was observed ($M_w/M_n = 1.7$).

Conclusion

For the last few years, many aliphatic polyesters were prepared by ring-opening (co)polymerization of lactones substituted by various functional groups, protected if needed. The direct grafting of duly functionalized derivatives under non degrading conditions remained, until recently, a very difficult task. Nevertheless, a strategy that combines of ring-opening (co)polymerization of α-chloro-ε-caprolactone with "click" reaction is very promising. This strategy requires 4 steps: (i) synthesis of αClεCL by the Baeyer-Villiger oxidation of the parent α-chlorocyclohexanone, (ii) polymerization of αClεCL, (iii) substitution of chloride by sodium azide, and (iv) 1,3-Huisgens cycloaddition. Moreover, the two last steps can be performed in one-pot. The success of the grafting of PEO onto copolymers of lactide and αClεCL paves the way to the grafting of functional groups onto aliphatic polyesters, more sensitive to degradation than PCL. Synthesis of these new copolymers and their potential applications will be reported in forthcoming publications. It must be noted that azide substituted ε-caprolactone can be synthesized followed by "click" reaction" with the purpose to increase the range of functional ε-caprolactones. This approach is under current investigation.

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