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Recent Advances in the Functionalization of Aliphatic Polyesters by Ring-Opening Polymerization

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Abstract

Two main strategies aiming at synthesizing aliphatic polyesters bearing pendant functional groups will be reported. The first one is based on the synthesis and the polymerization of lactones substituted by various functional groups. The direct grafting of functional groups onto aliphatic polyesters is the second strategy. Last but not least, the association of these two strategies is very promising in order to overcome their respective limitations.

Keywords : Ring-opening polymerization ; aliphatic polyester

1. Introduction

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

Aliphatic polyesters can be synthesized either by polycondensation or by ring-opening polymerization. At the one hand, the control imparted to polycondensation is limited. At the other hand, ring-opening polymerization (ROP) of lactones and lactides is a well-established process for the synthesis of aliphatic polyesters with predictable molecular weight, narrow molecular weight distributions, and well-defined end-groups. This review aims at reporting recent advances in the synthesis of functionalized aliphatic polyesters synthesized by ROP.

Two main strategies allowing synthesizing aliphatic polyesters bearing pendent functional groups might be distinguished[1] The first one is based on the synthesis and polymerization of lactones substituted by a functional group.[2] It is worth pointing out that the copolymerization of lactones with other functionalized monomers such as epoxides and carbonates is beyond the scope of this review.

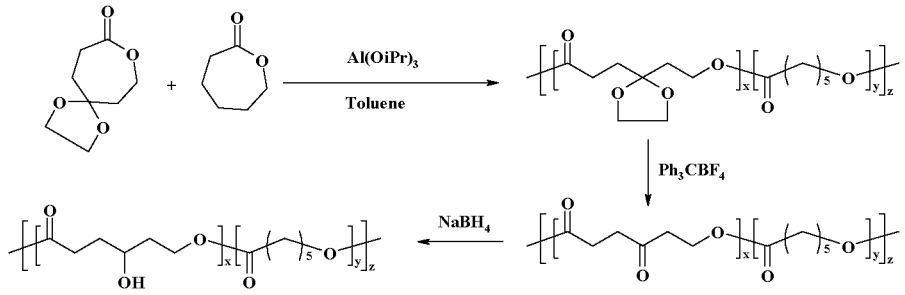
The direct grafting of functional groups onto aliphatic polyesters is the second strategy.

2. Ring-Opening Polymerization of Lactones Substituted by a Functional Group

In 1997, Tian et al. reported the synthesis of 1,4,8-trioxaspiro[4.6]-9-undecanone by the Baeyer-Villiger oxidation of 1,4-dioxaspiro[4.5]dedcan-8-one. This cyclic monomer was homopolymerized[3] and copolymerized[4] with oxepan-2-one (εCL for ε-caprolactone) as shown in Scheme 1.

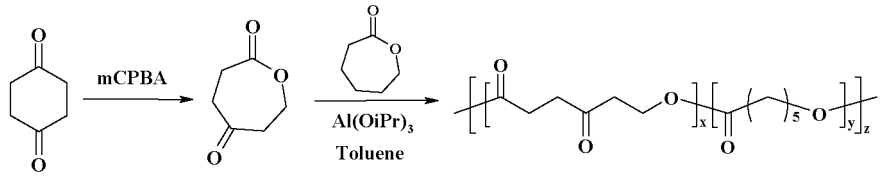
The functionalization of aliphatic polyesters by hydroxyl groups leads to increase in their hydrophilicity. Pendant hydroxyl groups are also very useful for further macromolecular engineering. For instance, ROP initiated by pendant hydroxyl groups is a route towards comb-shaped polyesters. Toward this end, the ketal groups of poly(εCL-*co*-oxepane-1,5-dione) were deprotected into ketones, which were finally reduced by sodium borohydride into pendant hydroxyl groups (Scheme 1).

Scheme 1. *Synthesis of PCL with pendent OH groups.*



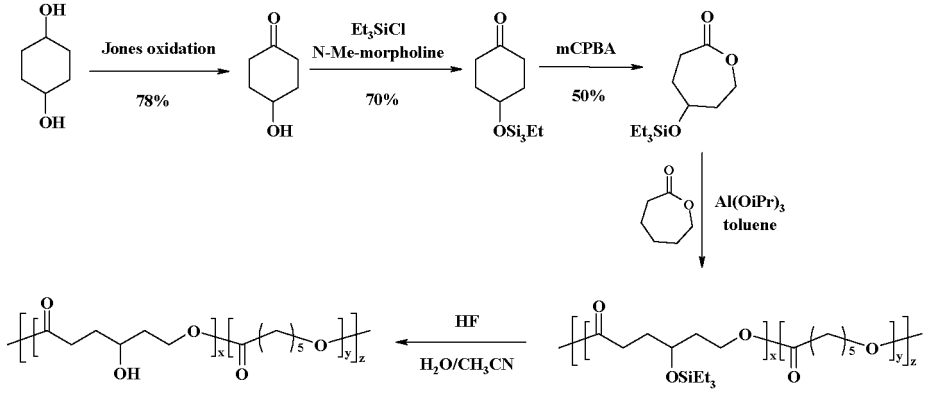
Later on, ketone-containing polyesters were synthesized by the more direct ROP of εCL and oxepane-1,5-dione, which was again synthesized by the Baeyer-Villiger oxidation of cyclohexane-1,4-dione (Scheme 2).[5] Nevertheless, aluminum isopropoxide was not an efficient initiator because the complexation with the ketone competes with the complexation with the ester, which is the first step of ROP. This problem was overcome by using tin(IV) alkoxides as initiators, which tolerates the presence of ketones, for reasons which yet remains unclear.

Scheme 2. *Synthesis and polymerization of oxepane-1,5-dione.*

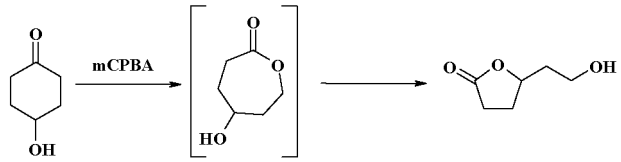


In order to prepare aliphatic polyesters with pendant hydroxyl groups, 5-triethylsilyloxyoxepan-2-one (γEt_3SiOεCL for 5-triethylsilyloxy-ε-caprolactone) was synthesized from cyclohexane-1,4-diol in three steps as shown in Scheme 3.[6, 7] The protection of the hydroxyl group prior to the Baeyer-Villiger is mandatory because hydroxyoxepan-2-one obtained by reaction of 4-hydroxycyclohexanone is not stable and rearrange into 5-(2-hydroxyethyl)dihydrofuran-2(3*H*)-one (Scheme 4).[8] γEt_3SiOεCL was copolymerized with εCL in order to obtain the corresponding statistical copolyesters.[6, 7] The deprotection of the hydroxyl group turned out to be difficult even under optimized conditions, especially for copolyesters with a γEt_3SiOεCL content higher than 50% due to the noxious transesterification reaction of an internal ester by the released hydroxyl group, which results in the formation of a five-membered lactone.[7] As a rule, the protecting group has to be stable enough to avoid deprotection prior to polymerization and has to be deprotected under mild conditions under which no degradation of the polyester takes place. These two conditions are contradictory and it is sometimes difficult to find a good compromise. To this respect, Hedrick et al. reported the synthesis and the polymerization 5-(benzyloxy)-oxepan-2-one. The benzyloxy group was deprotected by catalytic hydrogenolysis, which avoids the use of acidic conditions.[9] Last but not least, the intramolecular rearrangement can be avoided just by changing the structure of the lactone, which avoids the use of protection/deprotection reactions. Recently, several teams reported the synthesis of several stable lactones substituted by hydroxyl groups such as 5-(2-hydroxyethyl)oxepan-2-one,[10] 4-hydroxy-4-methyltetrahydro-2*H*-pyran-2-one,[11] 6-(hydroxymethyl)-1,4-dioxan-2-one,[12] and 5-(hydroxymethyl)-1,4-dioxan-2-one[13] (Scheme 5). It is worth recalling that these monomers are nothing but AB inimers, whose polymerization is a route to hyperbranched aliphatic polyesters.

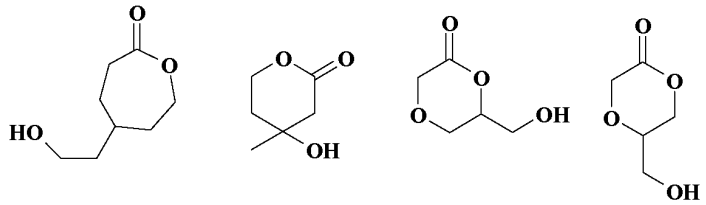
Scheme 3. *Synthesis and polymerization of γEt$_3$SiOεCL.*



Scheme 4. *Baeyer-Villiger oxidation of 4-hydroxycyclohexanone.*

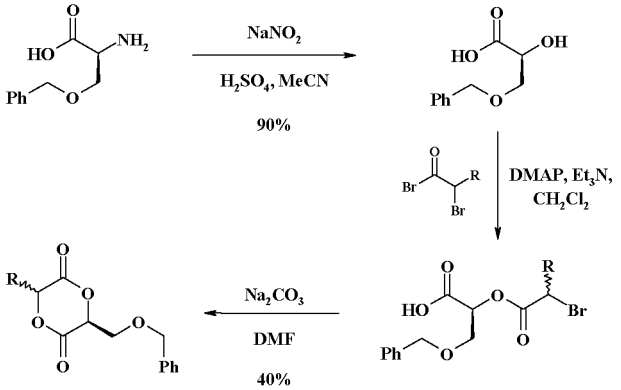


Scheme 5. *Stable lactones bearing hydroxyl groups.*



Very recently, Feijen et al. reported the synthesis of 3-(2-phenylethyl)-1,4-dioxane-2,5-dione and 3-methyl-6-(2-phenylethyl)-1,4-dioxane-2,5-dione, from serine (Scheme 6).[14] These monomers were homopolymerized and copolymerized with L-lactide[14] and εCL[15] A very similar procedure was implemented by Gerhardt et al. to synthesize 3-methyl-6-(2-phenylethyl)-1,4-dioxane-2,5-dione.[16]

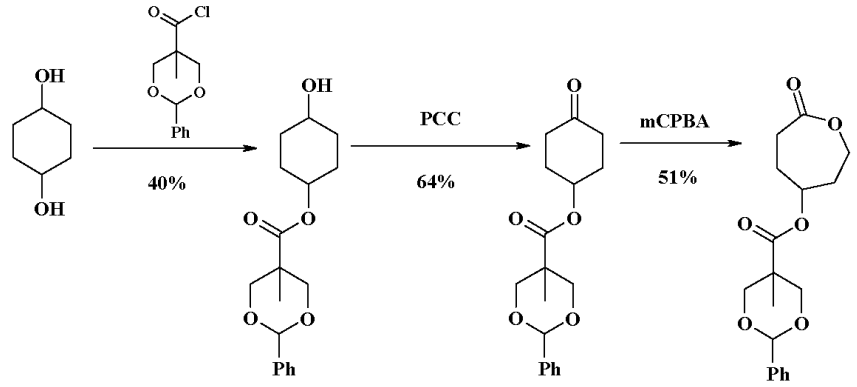
Scheme 6. *Synthesis and polymerization of 3-(2-phenylethyl)-1,4-dioxane-2,5-dione and 3-methyl-6-(2-phenylethyl)-1,4-dioxane-2,5-dione.*



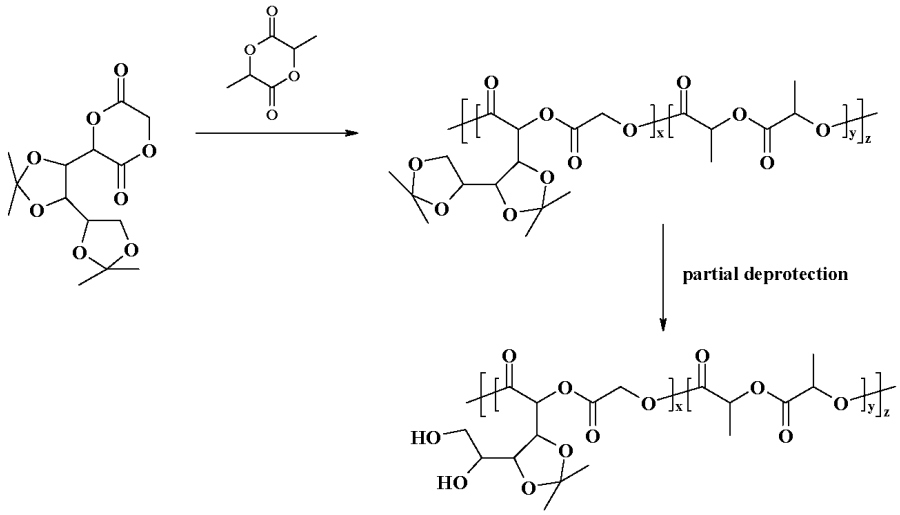
The synthesis of lactones substituted by protected diols such as 7-oxooxepan-4-yl 5-methyl-2-phenyl-1,3-dioxane-5-carboxylate[9] was also reported (Scheme 7).

Interestingly, Vert et al. investigated the synthesis and polymerization of 3-(2,2,2',2'-tetramethyl-4,4'-bi-1,3-dioxol-5-yl)-1,4-dioxane-2,5-dione(DIPAGYL), which is nothing but a dilactone substituted by two acetonide groups, which can be partially deprotected into diols (Scheme 8).[17]

Scheme 7. *Synthesis of 7-oxooxepan-4-yl 5-methyl-2-phenyl-1,3-dioxane-5-carboxylate.*

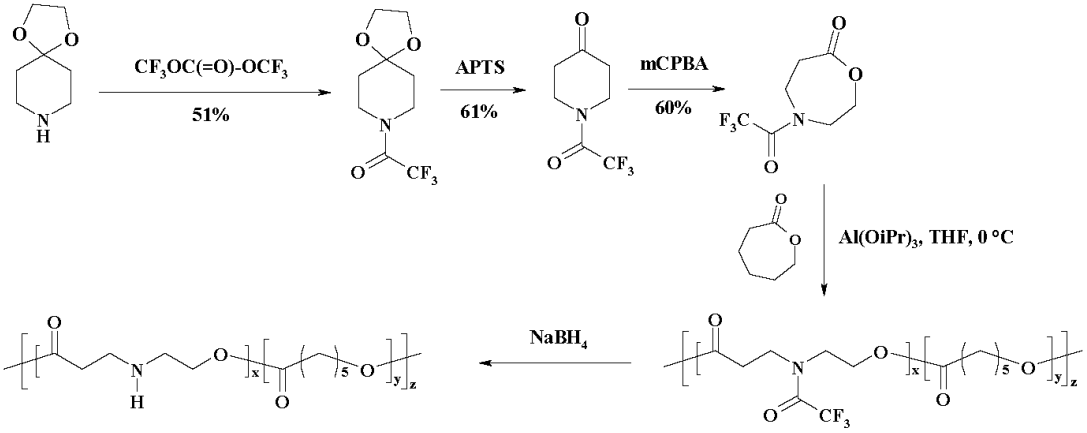


Scheme 8. *Copolymerization of DIPAGYL with lactide.*

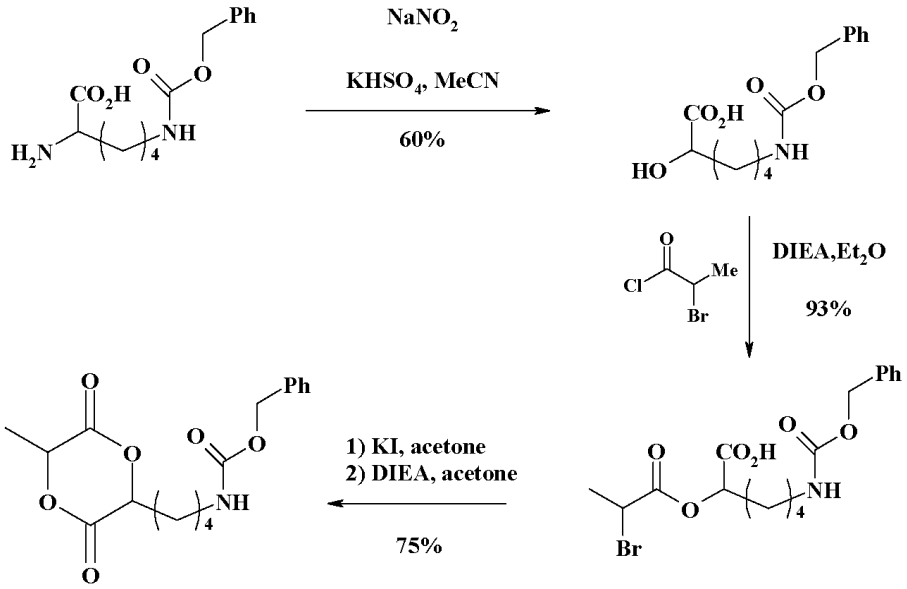


The synthesis and the polymerization of lactones substituted by amines are less common even tough they have a great potential for many applications. The synthesis of 4-(trifluoroacetyl)-1,4-oxazepan-7-one by a three-step process was reported by Hedrick et al. (Scheme 9). The deprotection of the amino group turned out to be complicated by the sensitivity of the aliphatic polyester. $NaBH_4$ was the most efficient reagent surveyed and mild conditions as well as short reaction times were required to minimize degradation.[9] More recently, Gerhardt et al. reported the synthesis of benzyl [(3,6-dioxo-1,4-dioxan-2-yl)methyl]carbamate from lysine (Scheme 10).[16]

Scheme 9. *Synthesis and polymerization of 4-(trifluoroacetyl)-1,4-oxazepan-7-one.*[9]

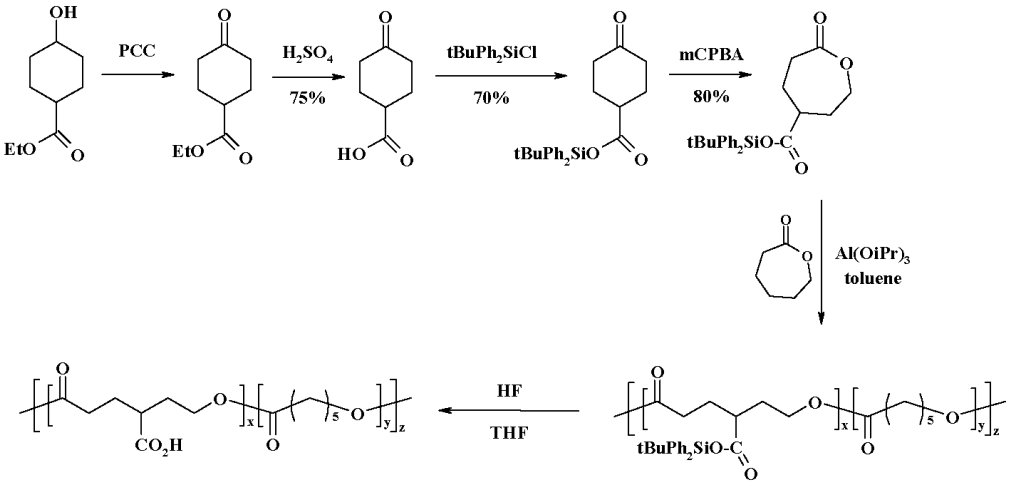


Scheme 10. *Synthesis and polymerization of benzyl [(3,6-dioxo-1,4-dioxan-2-yl)methyl]carbamate.*[16]



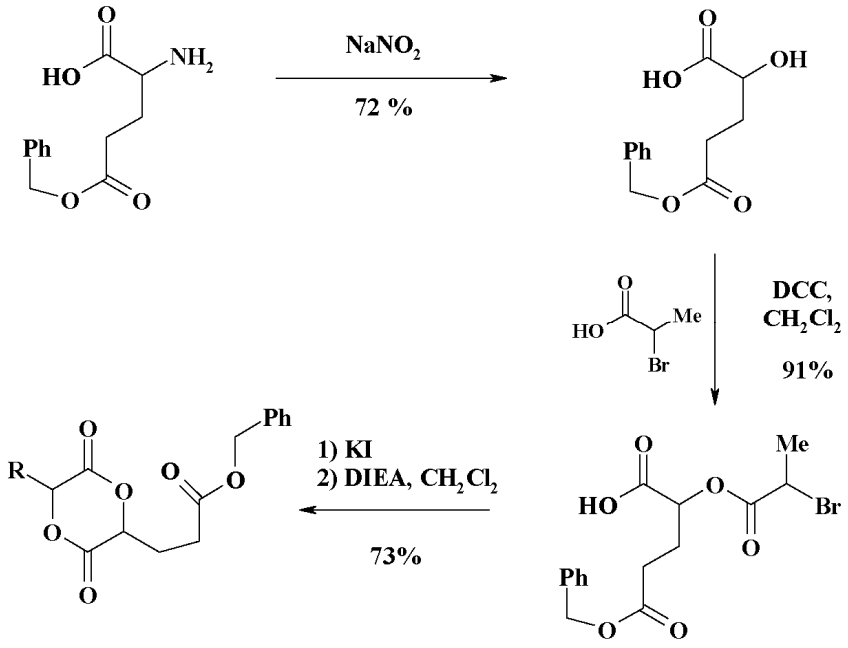
The functionalization of aliphatic polyesters by carboxylic acids is another approach allowing increasing their hydrophilicity. Carboxylic acids being not tolerated by aluminum and tin alkoxides, which are the initiators for ROP, it was again necessary to use protection/deprotection reactions. At the one hand, Lecomte et al. reported on the silyl-protected 7-oxooxepane-4-carboxylic acid (Scheme 11).[18] At the other hand, Hedrick et al. proposed to protect the carboxylic as benzyl or t-butyl esters as an alternative.[9] The deprotection after polymerization was easily carried out under non degrading conditions. Nevertheless, the purification of the monomer turned out to be a key issue due to undesired deprotection of the carboxylic acid. Due to the presence of acidic impurities, the homopolymerization was not easy to carry out. This problem was tackled by using t-butyldiphenylsilyloxy protecting groups more stable than the more usual t-butyldimethylsilyloxy protecting groups. The polymerization was controlled when initiated by aluminum isopropoxide. It is worth noting that the polymerization of phenyl 4-oxooxetane-2-carboxylate (or benzyl β-malolactonate) yields poly(benzyl β-malolactonate), which can finally be deprotected into poly(β-malic acid) by catalytic hydrogenation, as recently reviewed elsewhere.[19]

Scheme 11. *Synthesis and polymerization of the silyl-protected 7-oxooxepane-4-carboxylic acid.*



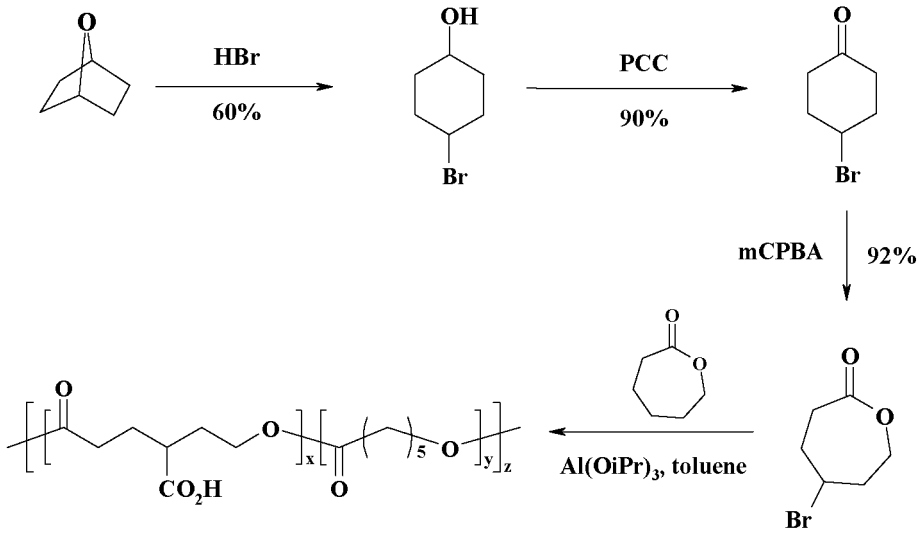
Very recently, Gerhardt et al. reported on the synthesis of benzyl 3-(5-methyl-3,6-dioxo-1,4-dioxan-2-yl)propanoate from glutamic acid (Scheme 12).[16]

Scheme 12. *Synthesis and polymerization of benzyl 3-(5-methyl-3,6-dioxo-1,4-dioxan-2-yl)propanoate.*



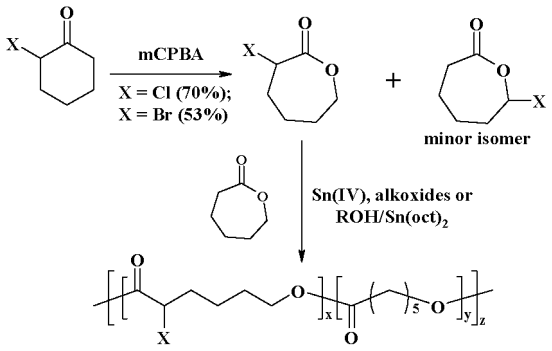
Much attention has been paid on the synthesis of halogen-containing aliphatic polyesters because the halogen function can be used for further chemical transformations such as elimination and quaternization reactions.[20] Detrembleur et al. reported the synthesis of 5-bromooxepan-2-one (γBrεCL for γ-bromo-ε-caprolactone) synthesized by a three-step strategy shown in Scheme 13.[21] The homopolymerization of γBrεCL and its copolymerization with εCL was under control when aluminum isopropoxide is used as an initiator.

Scheme 13. *Synthesis and polymerization of benzyl 3-(5-methyl-3,6-dioxo-1,4-dioxan-2-yl) propanoate.*

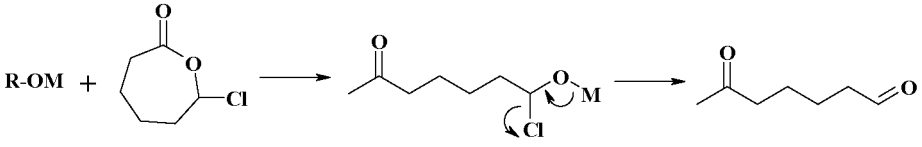


Later on, a more direct strategy was implemented by Lenoir et al. who reported the synthesis of 3-chlorooxepan-2-one (αClεCL for α-chloro-ε-caprolactone) in only one step by the Baeyer-Villiger oxidation of 2-chlorocyclohexanone (Scheme 14).[22] It is worth noting that the Baeyer-Villiger reaction is not 100% selective as witnessed by the formation of 7-chlorooxepan-2-one as a minor isomer. It is mandatory to carefully remove 7-chlorooxepan-2-one prior to polymerization because this isomer inhibits the polymerization by a mechanism shown in Scheme 15. A slight drawback of αClεCL compared to γBrεCL is its lower thermal stability at room temperature and αClεCL needs to be stored at -20°C. The polymerization of this monomer was not under control when initiated by aluminum alkoxides for reasons which remain unclear. Nevertheless, this polymerization of αClεCL can be successfully initiated by tin(IV) alkoxides[22] and by alcohols in the presence of tin octoate.[23] More recently, the same approach was used by Wang et al. to synthesize 3-bromoooxepan-2-one but the thermal stability of this monomer was not mentioned.[24]

Scheme 14. *Synthesis and polymerization of αClεCL and αBrεCL.*



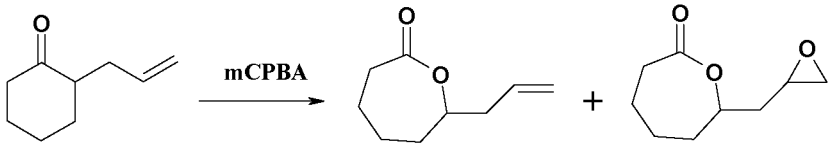
Scheme 15. *Inhibition mechanism of ROP in the presence of 7-chlorooxepan-2-one.*



The synthesis of unsaturated aliphatic polyesters is highly desirable because they can be crosslinked and also the double bond can be converted into other functionalities, for instance by dihydroxilation and epoxidation reactions.[20, 25]

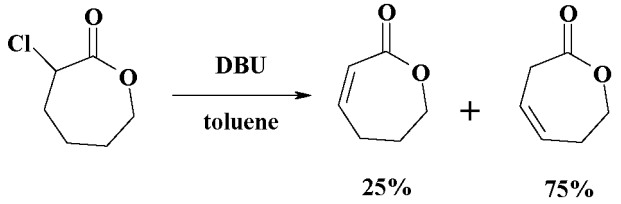
Mecerreyes et al. proposed the synthesize of 7-(prop-2-en-1-yl)oxepan-2-one by the Baeyer-Villiger oxidation of 2-(prop-2-en-1-yl)cyclohexanone but this reaction was not very efficient because epoxidation of the double bond could not be avoided, which limits the yield (Scheme 16).[26]

Scheme 16. *Synthesis of 7-(prop-2-en-1-yl)oxepan-2-one.*



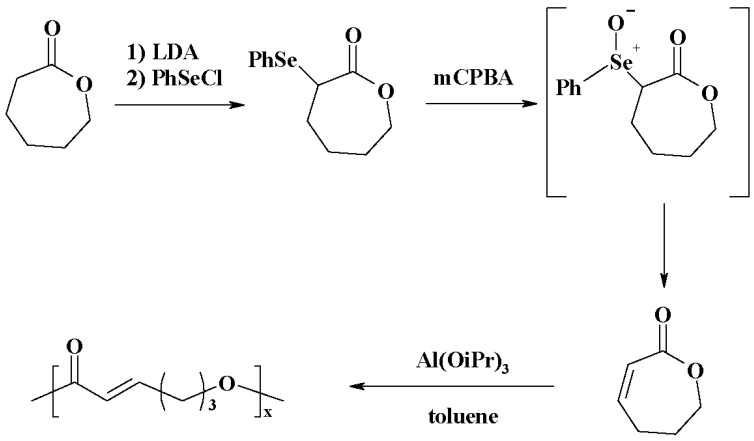
Lactones functionalized with an endocyclic double bond were obtained by the elimination reaction of αClεCL.[27] Nevertheless, this reaction was again not selective because a mixture of 6,7-dihydrooxepin-2(5*H*)-one and of 6,7-dihydrooxepin-2(3*H*)-one was obtained (Scheme 17). The two isomers were separated by chromatography. Interestingly, 6,7-dihydrooxepin-2(3*H*)-is an unusual monomer, which can be polymerized by two distinct mechanism. At the one hand, the ROP can be initiated by aluminum alkoxides.[27] At the other hand, the polymerization can also be carried out by a ring-opening metathesis mechanism. Indeed, 6,7-dihydrooxepin-2(3*H*) was successfully mediated by the Schrock's catalyst, even though the control of the polymerization was poor.[28]

Scheme 17. *Synthesis of 7-(prop-2-en-1-yl)oxepan-2-one.*



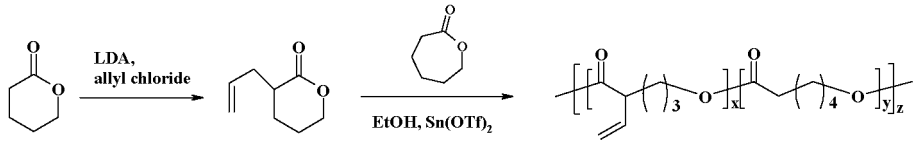
After these first reports, more selective syntheses were reported. Lou et al. reported the selective synthesis of 6,7-dihydrooxepin-2(5*H*)-one by a strategy based on the elimination of a selenoxide shown in Scheme 18.[29]

Scheme 18. *Synthesis of 6,7-dihydrooxepin-2(5H)-one.*

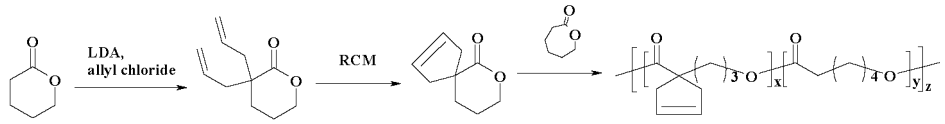


Emrick et al. reported on the synthesis of 3-(prop-2-en-1-yl)tetrahydro-2*H*-pyran-2-one by reaction of tetrahydro-2*H*-pyran-2-one (δVL for δ-valerolactone) and LDA into the corresponding enolate followed by reaction with 3-bromoprop-1-ene (Scheme 19). It is worth nothing that the yield of this reaction depends the size of the lactone, as shown by the lowest yield obtained for the allylation of εCL even under optimized conditions. 3-(prop-2-en-1-yl)tetrahydro-2*H*-pyran-2-one was homopolymerized and copolymerized with εCL by ethanol the presence of $Sn(OTf)_2$.[30] In another work, Emrick et al. reported on the synthesis of 7-oxaspiro[4.5]dec-2-en-6-one by a strategy based on ring closing metathesis as shown in Scheme 20.[31]

Scheme 19. *Synthesis and polymerization of 3-(prop-2-en-1-yl)tetrahydro-2H-pyran-2-one.*

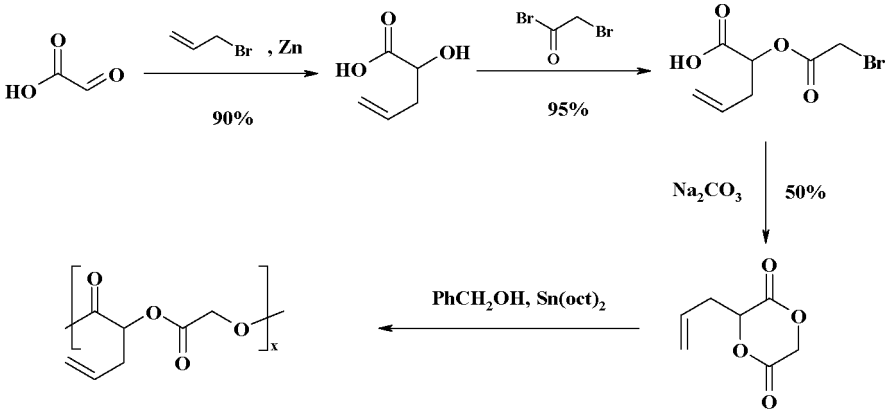


Scheme 20. *Synthesis of 7-oxaspiro[4.5]dec-2-en-6-one.*



Interestingly, the synthesis and the polymerization of 3-(prop-2-en-1-yl)-1,4-dioxane-2,5-dione, which is nothing but an allyl-substituted glycolide, was reported by Hennink et al. (Scheme 21).[25]

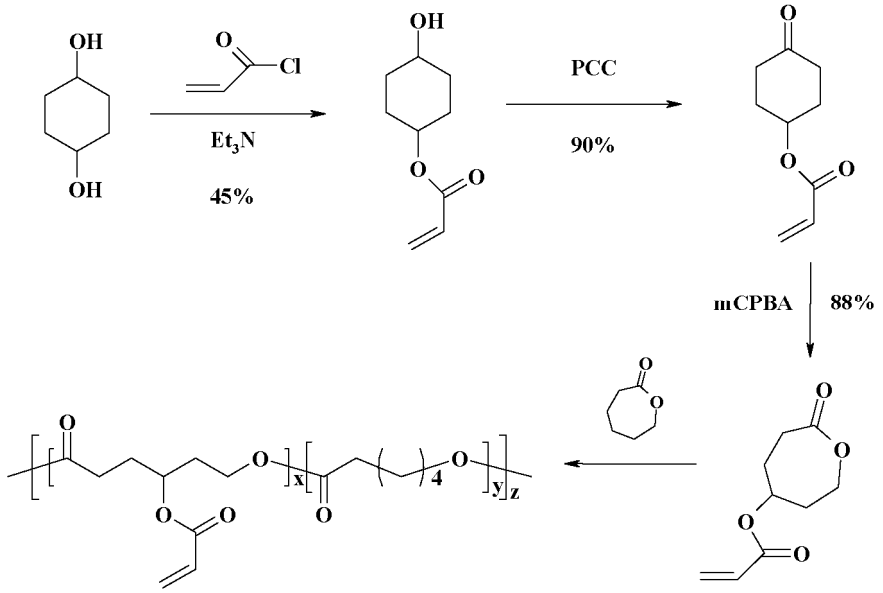
Scheme 21. *Synthesis and polymerization of 3-(prop-2-en-1-yl)-1,4-dioxane-2,5-dione.*



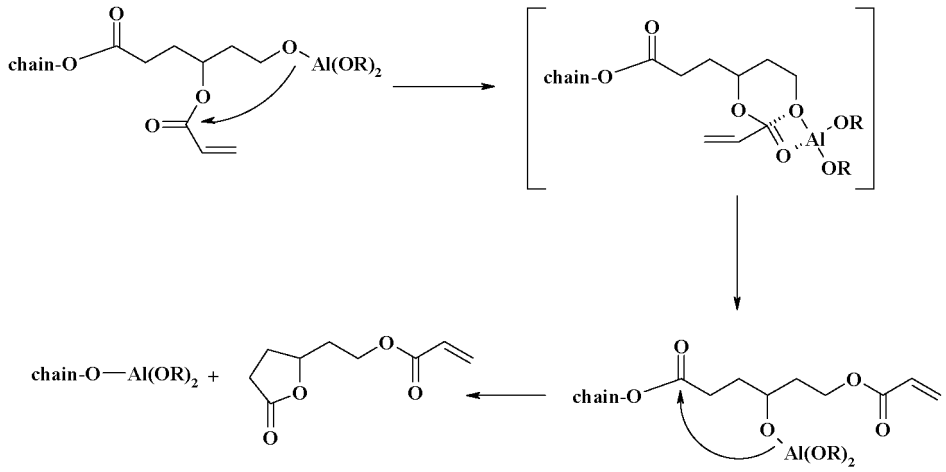
7-oxooxepan-4-yl prop-2-enoate is the first reported example of a difunctional monomer polymerizable by two different controlled processes: ROP and atom transfer radical polymerization (ATRP).[32] This monomer was synthesized by a three-step strategy shown in Scheme 22 and was homo- and copolymerized with εCL by ring-opening by using aluminum isopropoxide as an initiator. Later on, a two-step backbiting reaction was observed during this polymerization, which results in the formation of 2-(5-oxotetrahydrofuran-2-yl)ethyl prop-2-enoate by the mechanism shown in Scheme 23.[33] Nevertheless, the extent of this side reaction is less important as long as the temperature is low and the reaction is stopped rapidly after complete monomer conversion. The driving force of this side reaction is the very favorable formation of a five-membered ring. In order to overcome this issue, the acrylic functionality was introduced in another position. Toward this end, Li et al. synthesized 1-(2-oxooxepan-3-yl)ethyl prop-2-enoate by a three-step process shown in Scheme 24.[34] It is worth noting that all these lactones substituted by acrylic groups are not stable owing to noxious radical reactions. These lactones

have to be stored in the presence of a radical scavenger at -20°C.

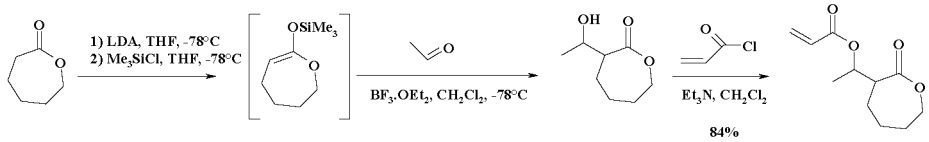
Scheme 22. *Synthesis and polymerization of 7-oxooxepan-4-yl prop-2-enoate.*[32]



Scheme 23. *Two-step backbiting reaction in the polymerization of 7-oxooxepan-4-yl prop-2-enoate initiated by aluminum isopropoxide.*[33]



Scheme 24. *Synthesis of 1-(2-oxooxepan-3-yl)ethyl prop-2-enoate.*[34]

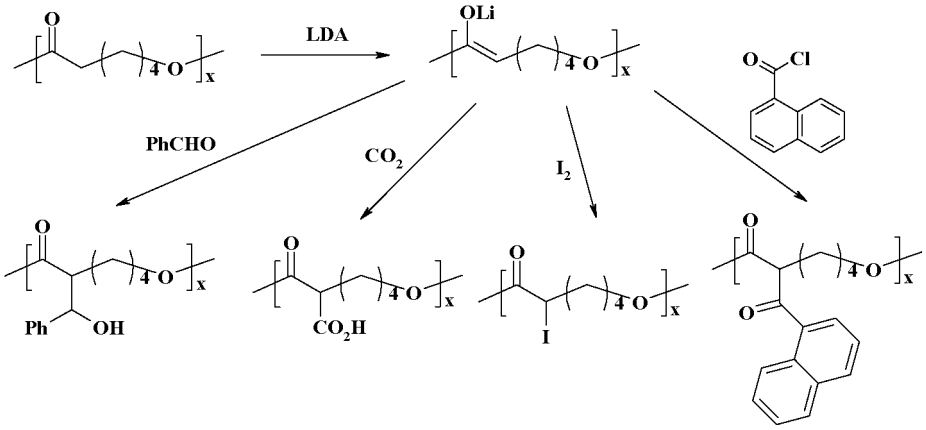


3. Direct grafting of Functional Groups onto Aliphatic Polyesters

The synthesis of lactones substituted by functional groups requires too often a multi-step synthesis at the expense

of the final yield, which can be quite low. In order to tackle these drawbacks, the grafting of functional groups onto preformed polyester chains is a very appealing approach because a wide range of functional groups can be attached from a single precursor and the synthesis of substituted monomers is no more required, which is a huge advantage. Besides, the functionalization of aliphatic polyesters by alcohols and carboxylic acids is very efficient without using protection and deprotection reactions because functionalization takes place after polymerization. A representative example was reported by Vert et al.,[35, 36-38] who metallated PCL by LDA with formation of a poly(enolate), which was then reacted with several electrophiles for further functionalization. (Scheme 25). The implementation of this strategy is however limited by unavoidable chain degradation in competition with chain metallation. It is difficult to reach functionalization efficiencies higher than 30%, which can be a limitation for several applications.

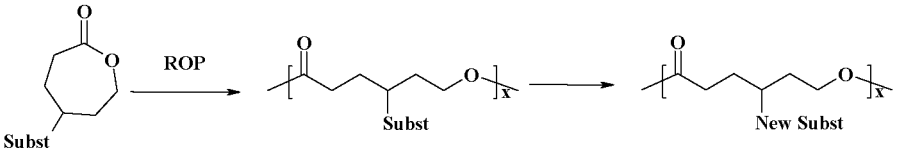
Scheme 25. *Chemical derivatization of PCL by an anionic route.*



4. Ring-Opening Polymerization of Suitably Substituted eCLs Followed by Derivatization of the Substituent

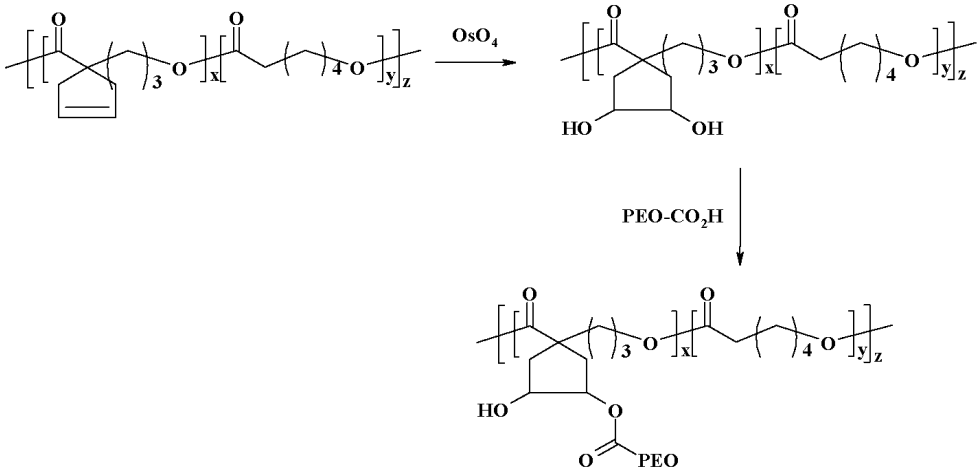
In order to tackle the problems inherent to the routes discussed earlier, it appears that a combination of these two strategies into a two-step process might be a valuable alternative (Scheme 26).[1] Thus, εCL substituted by a suitable functional group is first polymerized, followed by the derivatization of the substituent into various functional groups. A wide range of aliphatic polyesters could accordingly be made available from a single precursor.

Scheme 26. *ROP of substituted ωCL followed by its chemical derivatization into various functional aliphatic polyesters.*



For this strategy to be successful, the following criteria should be satisfied: (1) The synthesis of the substituted monomer should be as direct as possible and the yield should be high (2) this monomer should comply with controlled (co)polymerization, (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) favour quantitative reaction even at high content of functional groups.

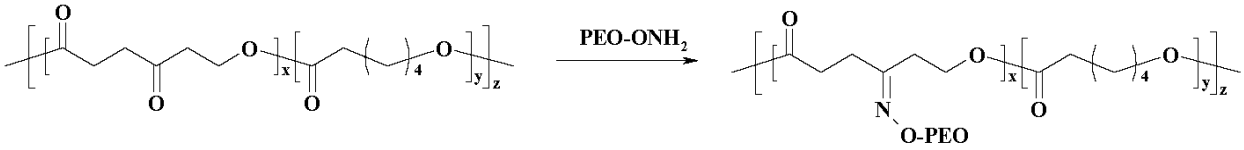
Scheme 27. *Grafting of PEO onto PCL according to Emrick et al.*[27]



An example of this strategy was reported by Emrick et al. who implemented an esterification reaction of carboxylic acid-terminated PEO and a copolyester attached by pendant hydroxyl groups (Scheme 27).[31] This process could be easily extended to other functionalizations just by changing the structure of the carboxylic acid. The main limitation of this approach relies on tedious synthesis of aliphatic polyesters bearing pendant alcohols, as pointed out in "Polyelectrolyte Stars and Cylindrical Brushes Made by ATRP: New Building Blocks in Nanotechnology".

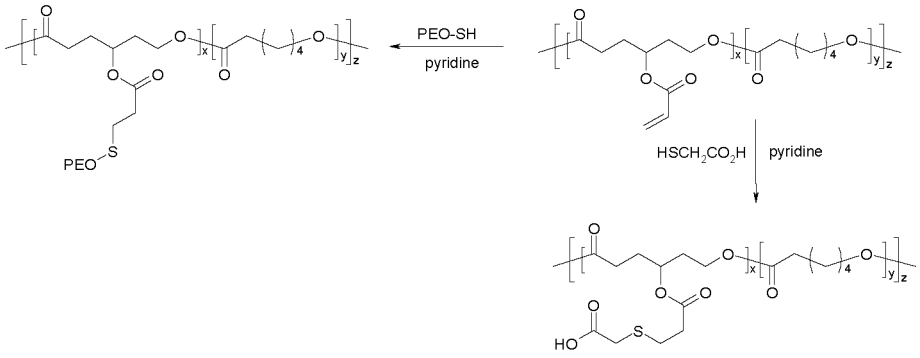
Mayes et al. reported the grafting of aminooxy-terminated PEO onto the ketone groups of poly(εCL-*co*-oxepane-1,2-dione) (Scheme 28).[39] The synthesis of the starting polyester is direct as shown in Scheme 2. Nowadays, these functionalizations have been extended to hydrazines[40] and to other aminooxy small molecules[41, 42] It is also worth noting that the coupling of amines by reductive animation was investigated by Wooley et al. but the efficiency turned out to be not sufficient[43] One important issue is the low solubility of copolyesters with a high content of oxepane-1,2-dione in many organic solvents, which might limit the extent of functionalization.

Scheme 28. *Grafting of PEO onto PCL according to Mayes et al.*



Recently, thiols were added onto pendant acrylate groups of PCL.[44] For example, thiol end-capped PEO was added onto the pendant acrylic groups of PCL (content of acrylic units = 18 mol%) in the presence of pyridine (THF, room temperature, 300 h [pyridine]/[thiol]/[acrylate] = 15/10/1). 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 75 h. Interestingly, no degradation was observed and no cumbersome protection/deprotection reaction was needed. Nevertheless, the Michael reaction is not quantitative and there is a risk of cross-linking through the residual acrylic groups.

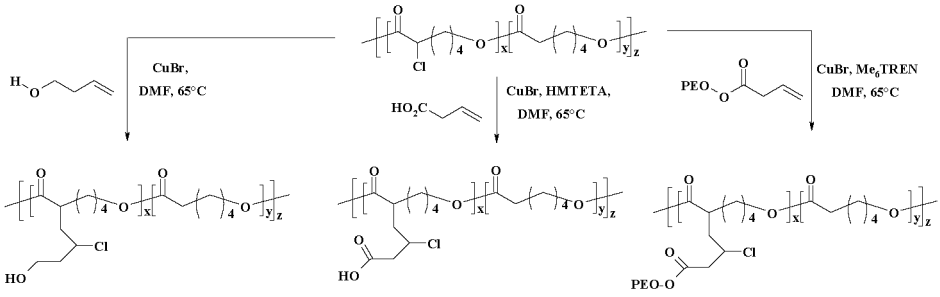
Scheme 29. *Derivatization of pendent acrylic unsaturations of PCL by Michael addition.*



In a similar approach, thiols were grafted onto PCL attached with pendant epoxides.[20, 27] Nevertheless, the synthesis of aliphatic polyesters bearing pendant epoxides is quite complicated because a two-step approach is needed; the synthesis of unsaturated aliphatic polyesters being the first step and the epoxidation of double bonds being the second step.

The synthesis of α-chlorinated PCL is straightforward (Scheme 14) and chlorides activated by a carbonyl group are well suited to react by atom transfer radical addition (ATRA). Several alkenes substituted by various functional groups were grafted onto PCL by ATRA mediated by CuBr/Me_6TREN (Scheme 30).[45] No protection was needed and no chain degradation was observed by SEC. Moreover, ATRA of α-methoxy, ω-acrylate-PEO (M_n (PEO = 750) onto poly (αClεCL-co-εCL) (M_n = 17,500 ; 48 αClεCL units) yielded a graft copolymer, with nine PEO grafts.[46] However, 18 chlorinated units per chain were lost by reduction during ATRA. The situation got worse when but-3-enoic acid was used because only reduction was observed. Interestingly, no parasitic reduction of the chlorides occurred by using HMTETA instead of Me_6TREN as a ligand but the activity of the catalyst was decreased. ATRA took place with a moderate yield of 32% after 24 h. Increase of the temperature (85°C instead of 65°C) allows reaching completeness but chains were then degraded simultaneously. 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.

Scheme 30. *Derivatization of the α-chloride pendant groups of PCL by ATRA.*



5. Conclusions

Nowadays, the synthesis of aliphatic polyesters bearing pendant functional groups remains challenging. The synthesis and the ROP of a wide range of functional lactones have been reported. Nevertheless, a multi-step synthesis of the monomer is often required and the global yield might be low. The direct functionalization of aliphatic polyesters is a very direct approach. Nevertheless, many reactions used until now are not quantitative or are performed under conditions which are not mild enough to prevent degradation from occurring. It is thus highly desirable to implement more efficient reactions and copper mediated azide-alkyne cycloaddition, which is nothing but the most widely used "click" reaction, is very promising.

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