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Synthetic Strategies for Biomedical Polyesters Specialties

Zinck Philippe

*Unité de Catalyse et Chimie du Solide, UCCS, Equipe Catalyse et Chimie Moléculaire,
UMR CNRS 8181, USTL-ENSCL, Université Lille – Nord de France,
France*

1. Introduction

Aliphatic polyesters are biocompatible and biodegradable polymers exhibiting good mechanical properties and hydrolyzability. They are among the best characterized and most studied biodegradable systems for temporary biomedical applications such as drug delivery systems, resorbable implants or tissue engineering scaffolds. Properties such as hydrophilicity and biodegradation can be tailored by the introduction of biologically relevant functional groups in the polymer. This chapter examines critically the various strategies implemented for this purpose.

Polyesters can be synthesized by polycondensation (step growth polymerization) or by ring opening polymerization (chain growth polymerization). A specific functionality can be introduced via these polymerizations using functionalized monomers or functionalized initiators. The presence of functional groups such as hydroxyls for instance can be detrimental for both polymerization methods, leading to deactivation and/or undesirable crosslinking reactions. Protection/deprotection chemistries are thus usually applied prior and after polymerization. These strategies will be presented and illustrated by relevant examples. Such multistep approaches provide interesting and sophisticated materials but require long production times and high production costs. For practical applications however, biomedical materials must also be cost-effective, introducing a balance between sophistication and ease of production. Recent advances enabling a one pot approach for each strategy are of particular interest (Zinck 2009) and are further presented and discussed in this frame.

The polyesters classically used for biomedical applications are poly(ϵ -caprolactone), poly(lactic acid), poly(glycolic acid) (Fig. 1) and their copolymers, and in a lesser extent, poly(3-hydroxybutyrate) and polyorthoesters. This chapter focuses essentially on the first three polyesters, with some extensions to other polyesters when the synthetic strategy or functionalization concept is judged relevant. These polyesters can be synthesized by the ring-opening polymerization of the corresponding cyclic ester (ϵ -caprolactone, lactide and glycolide, respectively, the two latter being dimers) and by polycondensation of the corresponding ω -hydroxyacid (6-hydroxyhexanoic, lactic and glycolic acids respectively). 6-hydroxyhexanoic acid is scarcely isolable, and the polycondensation route for the formation of poly(ϵ -caprolactone) is rarely used. Lactic acid has a stereocenter, and can be found as L-lactic acid, D-lactic acid or a racemic mixture of both forms. The lactide dimer exhibits thus

two diastereomeric forms. The most widely used forms of the polymer are poly(L-lactic acid) or poly(L-lactide) and poly(D,L-lactic acid) or poly(D,L-lactide).

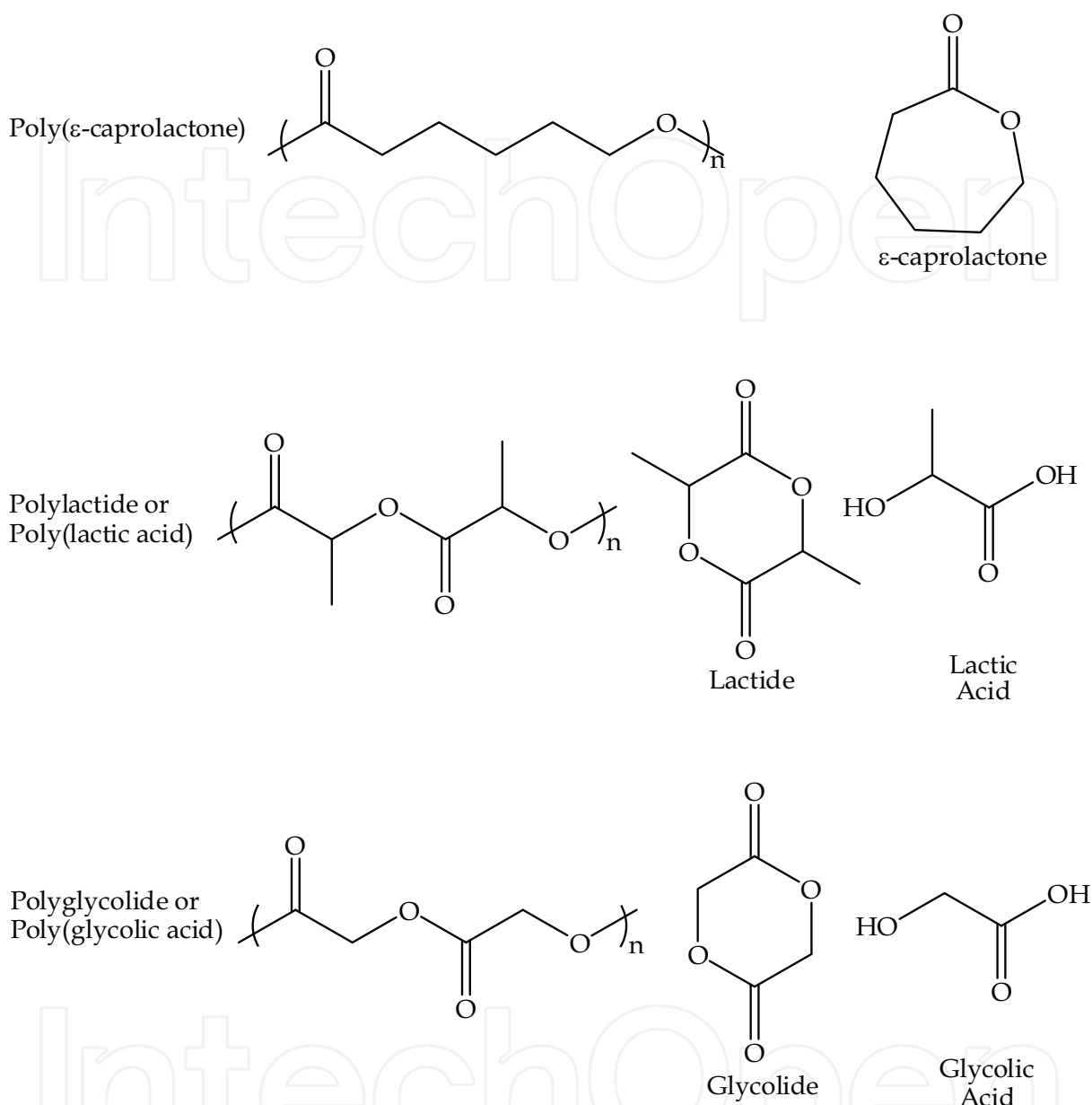


Fig. 1. Polyesters used for biomedical applications and their monomers

This chapter deals mainly with linear polymers and graft copolymers, with some extensions to star-shape polymers. Networks (*e.g.* hydrogels), dendrimers and hyperbranched macromolecules have not been considered. Post-polymerization modifications of the polymers have not been dealt with in a systematic manner, but appear when judged relevant for specific strategies. Metal mediated polymerizations can lead to the presence of residual metal traces in the material, which can be detrimental for the targeted applications. This can be circumvented by the use of organic molecules or enzymes as polymerization mediators. A particular emphasis on organocatalysis and enzymatic catalysis will be made in this frame. Recent approaches based on click chemistry will also be presented. This multistep strategy has gained much interest in the last years, due to its relative simplicity

and the tolerance of the groups formed. The chapter is divided into three sections covering the main strategies in the field of ring-opening polymerization, polycondensation and transesterification illustrated by several examples.

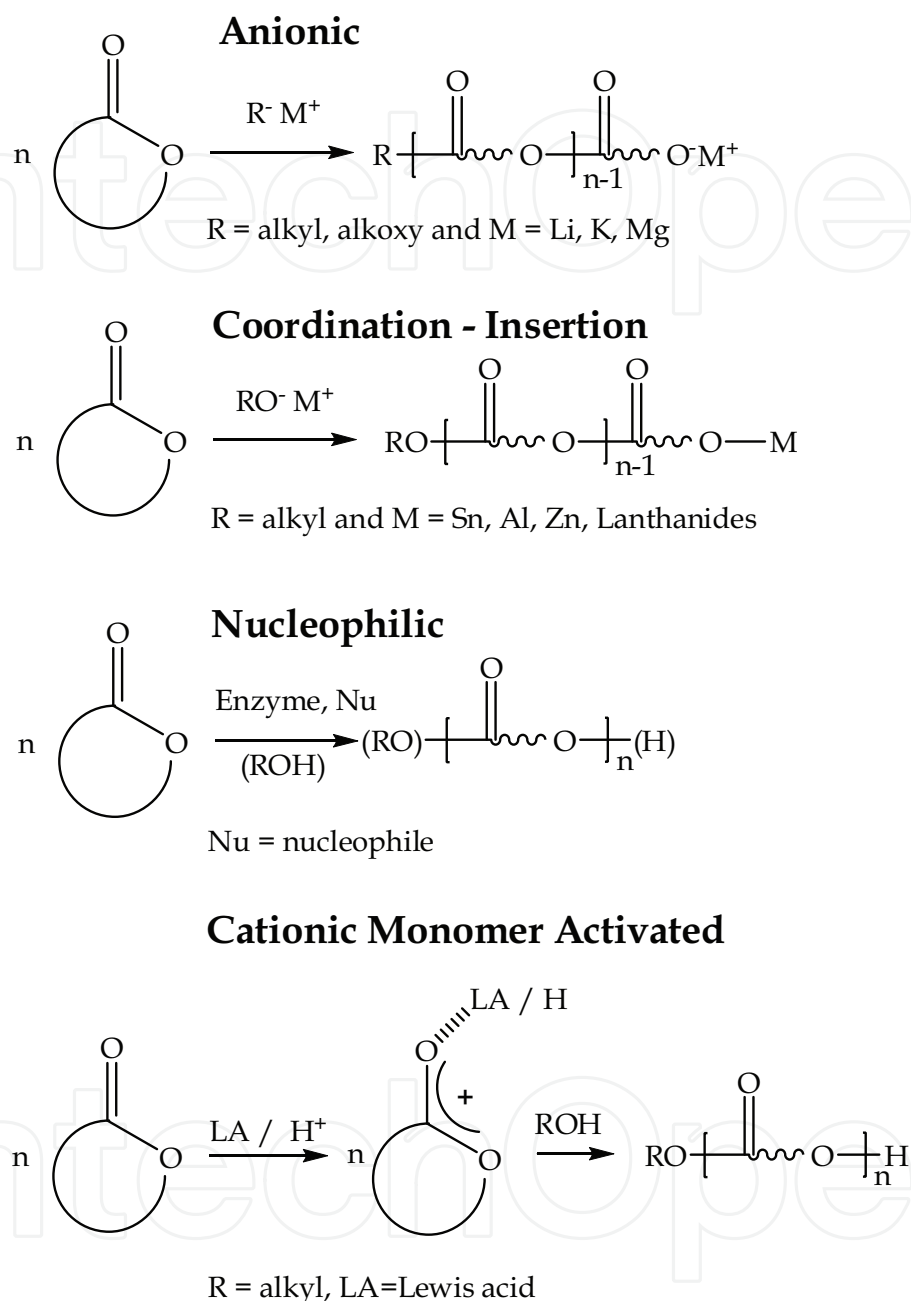


Fig. 2. Ring-opening polymerization mechanisms

2. Ring-opening polymerization

2.1 Basics and concepts

2.1.1 Ring-opening polymerization mechanisms

Ring-opening polymerization of cyclic esters can occur via different mechanisms, and readers interested in more details are invited to consult reviews on this subject (see for example Albertsson & Karma, 2003). The ring-opening polymerization pathways reported in

this chapter are anionic, coordination-insertion, nucleophilic and cationic, and are shown in Fig. 2. Organocatalytic ring-opening polymerization can be considered when using organic molecules as catalysts or initiators for the polymerization. It can be found here as nucleophilic polymerization or cationic monomer activated polymerization.

2.1.2 Statistical, sequential block copolymerizations and end functionalization

The simplest strategies used for modifying the properties of a polymer are statistical and sequential block copolymerizations (Fig. 3). Copolymerization involves the use of more than one monomer. When two monomers are polymerized simultaneously, the polymerization is called statistical. In a sequential block copolymerization, one of the monomers is polymerized in a first step, and the second monomer is polymerized after completion of the first step. The polymerization has to be living in this case, *i.e.* the active species has to be stable at the end of the first step. Numerous catalytic systems developed in the recent years for the ring-opening polymerization of cyclic esters enables statistical and sequential block copolymerization of lactide, glycolide and ϵ -caprolactone. Copolymers between poly(lactic acid) and poly(glycolic acid) can also be synthesized by polycondensation techniques, and enables to confer more hydrophilicity to the resulting copolymer and a higher degradation rate in comparison with pure poly(lactic acid). Of interest is also the combination of polyesters with poly(ethylene glycol), a water-soluble polymer also called poly(ethylene oxide), which confers also hydrophilicity to the resulting materials (the structure of poly(ethylene glycol) can be seen in Fig. 19). Such a combination can be done by numerous ways that will be presented in this chapter. The anionic sequential block copolymerization of ethylene glycol and D,L-lactide for example results in the formation of such block copolymers (Yasugi et al., 1999).

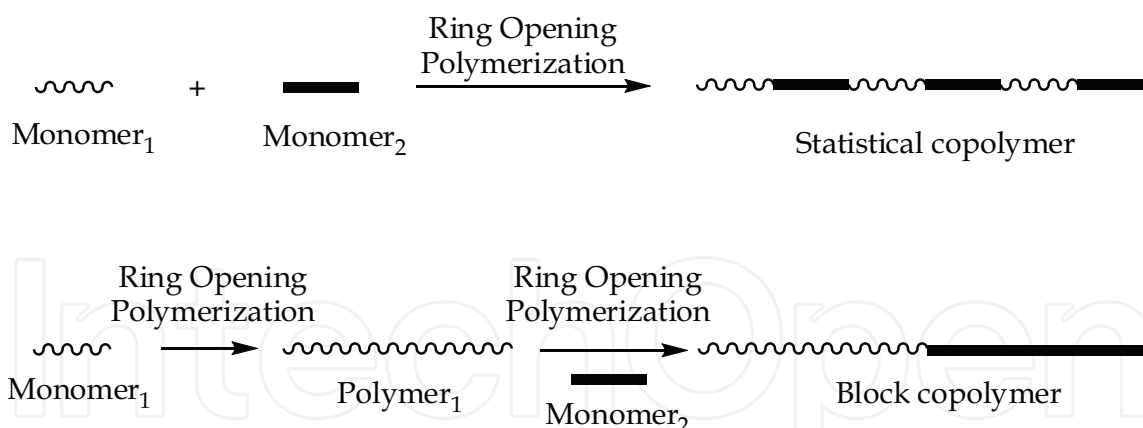


Fig. 3. Statistical and sequential block copolymerizations

The living character of certain polymerizations enables also a sequential end functionalization of the polymer. Instead of a second monomer, a functional group is introduced at the end of the first step, leading to a sequential end-functionalization of the polymer. This differs from one-pot end functionalization, where the functionalized compound is introduced at the beginning of the polymerization, as discussed in section 2.2. Coupling reactions can also be performed. For example, telechelic carboxylic chlorides end-capped poly(ethylene glycol) can react with the hydroxyl end group of poly(ϵ -caprolactone) to yield triblock copolymers (Morikawa et al., 2008).

2.1.3 Graft copolymerizations

Graft copolymers represent another kind of architecture that can be obtained. The synthesis of graft copolymers can be realized by three different ways (Fig. 4). In the grafting from method, the grafts are polymerized starting from the polymeric backbone, which can be considered as a macroinitiator. The graft can also be introduced on the monomer, whose polymerization leads to the graft copolymer. This is known as the grafting through process. In the grafting onto approach, a polymer end-capped with a reactive group is grafted onto the macromolecular backbone via reaction with another reactive group.

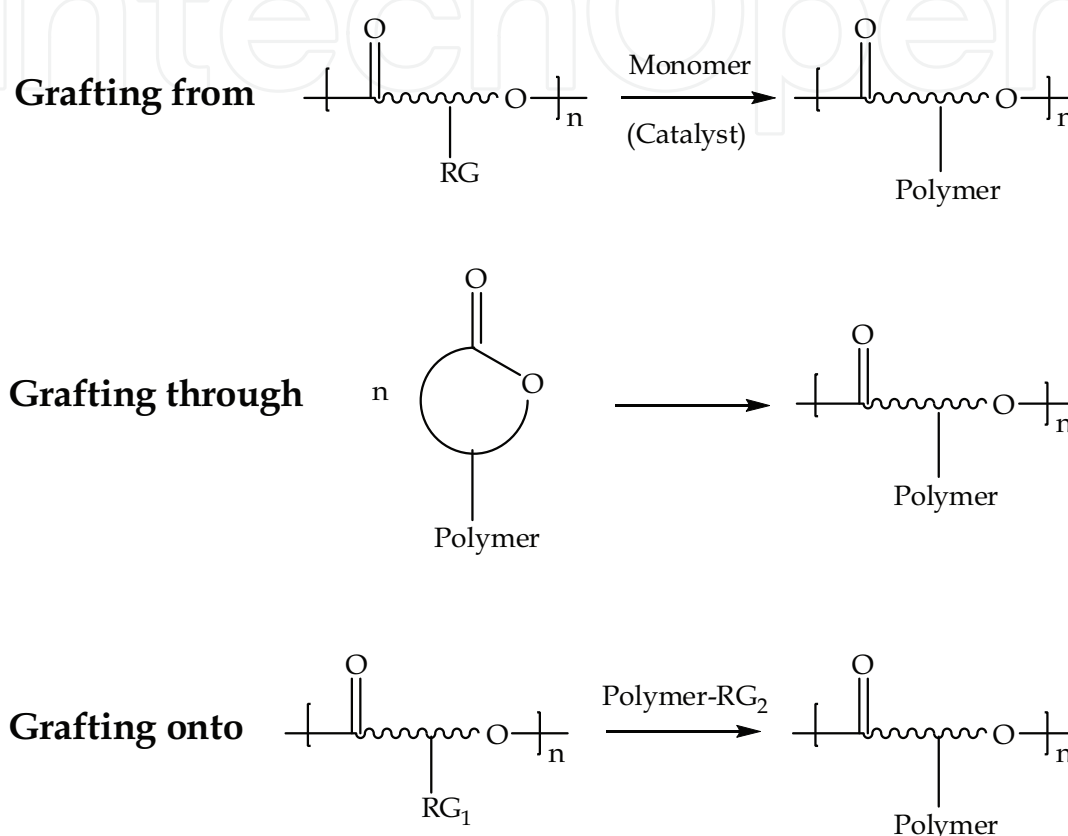
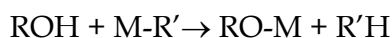


Fig. 4. Graft copolymerization strategies. RG represents a reactive group

2.2 One-pot end functionalization and grafting from methods (Fig. 5)

Ring opening polymerization can occur via anionic, coordination-insertion, nucleophilic or cationic mechanism. Alcohols and/or alkoxy groups can initiate the growth of one macromolecular chain for these polymerizations (see Fig. 2). The general functionalization strategy consists in the use of relevant hydroxyl bearing compounds:

- i. to modify the initiator of anionic and coordination/insertion ring-opening polymerization



- ii. as a co-initiator, as presented in Fig. 2 for nucleophilic and cationic mechanisms.

The presence of high amount of hydroxyl groups is thus detrimental, and protection/deprotection chemistries are usually applied in the presence of highly hydrophilic compounds such as carbohydrate derivatives. This will be presented for anionic and coordination/insertion ring opening polymerization in section 2.2.1 and 2.2.2 respectively.

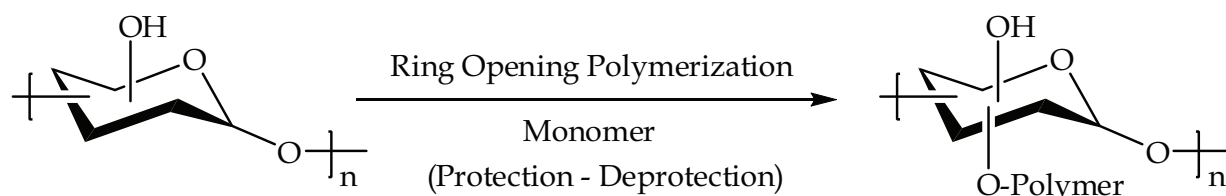


Fig. 5. End functionalization and grafting from methods, using carbohydrates as polymerization initiators

The use of regioselective catalysts such as enzymes or certain organic molecules can lead to regioselective end-functionalization and/or grafting from approaches without protection/deprotection steps. This will be presented in sections 2.2.3 and 2.2.4, respectively. Section 2.2 focuses essentially on carbohydrates derivatives for the end-functionalization of polyester, regarding the scope of the article. Note that the overall strategy can also be applied to the synthesis of block copolymers, using hydroxyl end-capped polymers such as poly(ethylene glycol) for instance as ROH initiator (via organocatalytic (Nyce et al., 2003) and coordination/insertion (Choi et al., 2006) ring opening polymerization).

2.2.1 Anionic ring-opening polymerization

The strategy consists here to use the carbohydrate compound as the counter-ion of the metal catalyst (Fig. 6, Ouchi et al., 2001). Protected D-glucose bearing an hydroxyl in the C1 position is allowed to react with the ^tBuOK anionic initiator to form the corresponding glucosate. This latter compound is used to polymerize L-lactide in tetrahydrofuran at room temperature. Subsequently, the removal of O-protecting benzyl groups in the terminal carbohydrate can be carried out by hydrogenolysis with Pd/C to obtain D-glucose-end-capped poly(L-lactide). Number-average molecular weights of 5700 g/mol were reported with polydispersity index of 1.35. Due to the living character of anionic polymerization, this strategy can also be used to synthesize monosaccharide end-capped poly(D,L-lactide)-*block*-polyethylene glycol copolymers (Yasugi et al., 1999).

2.2.2 Coordination – insertion

The strategy is close to that reported for anionic polymerization, *i.e* the carbohydrate compound serves as counter-ion of the catalyst metal. The main difference resides in the possibility of rapid and reversible chain transfer for coordination – insertion ring opening polymerization. The reaction can operate in the presence of excess alcohol *vs.* catalyst metal, leading to the growth of several macromolecular chains per metal atom (Fig. 7).

One may distinguish here end functionalization and grafting from strategy. The polymerization starts from a single compound such as monosaccharide for the former, while the grafting from method starts from a polymer such as a polysaccharide for the latter. Poly(ϵ -caprolactone) (Hamaide et al., 2001) and poly(L-lactide) (Bernard et al., 2003) were polymerized starting from protected monosaccharides, yielding monosaccharides end-capped polymers and eventually nanoparticles (Hamaide et al., 2001). The number-average molecular weight and polydispersity indexes were up to 4000 g/mol *vs.* polystyrene standards and 1.2 for poly(L-lactide) (Bernard et al., 2003) and up to 10 000 g/mol and 1.1 for poly(ϵ -caprolactone) (Hamaide et al., 2001). Linear protected carbohydrates end-capped poly(D,L-lactide) (Tang et al., 2008 – Fig. 8) and macrocyclic polycaprolactone were also synthesized by this way (Kricheldorf & Stricker, 2000 – Fig. 9) as well as poly(ethylene

glycol)-*block*-poly(ϵ -caprolactone) copolymers (Choi et al., 2006). The polymerization is initiated by a hydroxyl end-capped poly(ethylene glycol) in this latter case.

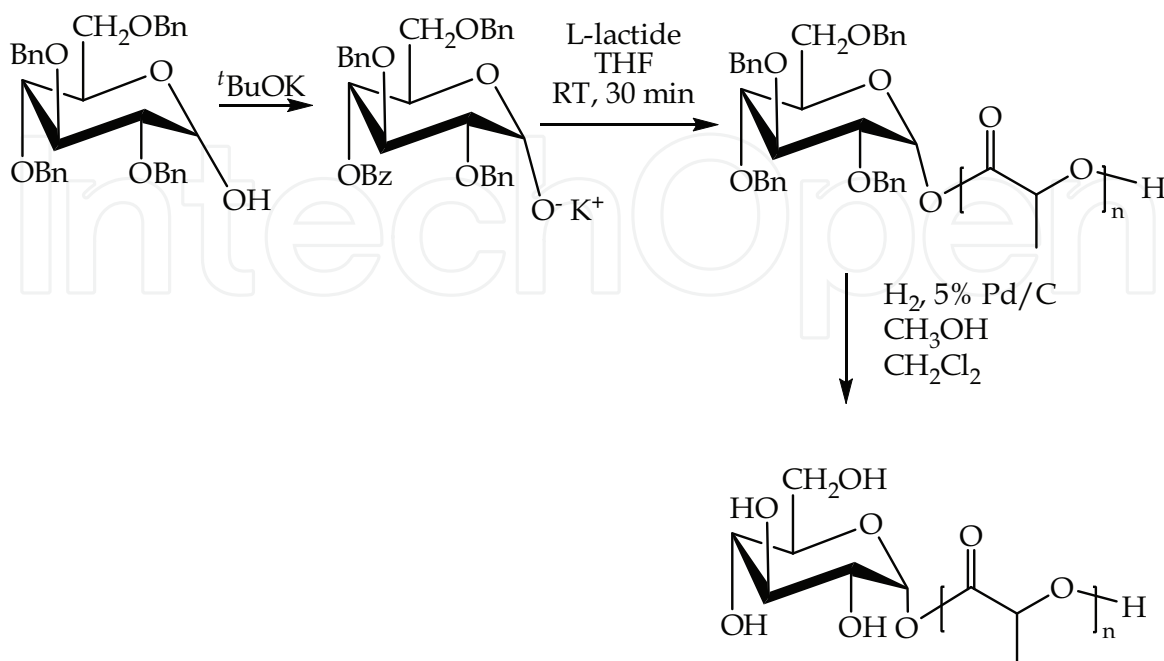


Fig. 6. Poly(L-lactide) end functionalization via anionic ring-opening polymerization (Ouchi et al., 2001) - Bn = benzyl

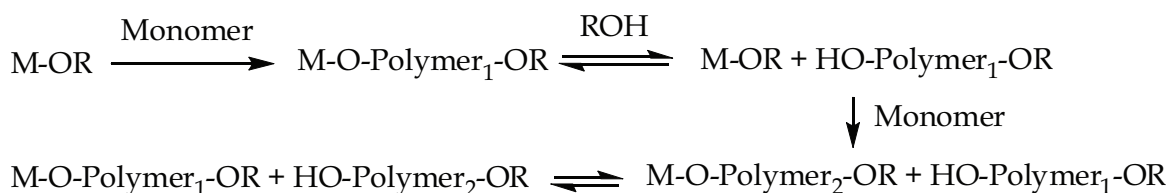


Fig. 7. Transfer reactions in coordination/insertion ring-opening polymerization conducted in the presence of excess alcohol *vs.* catalyst

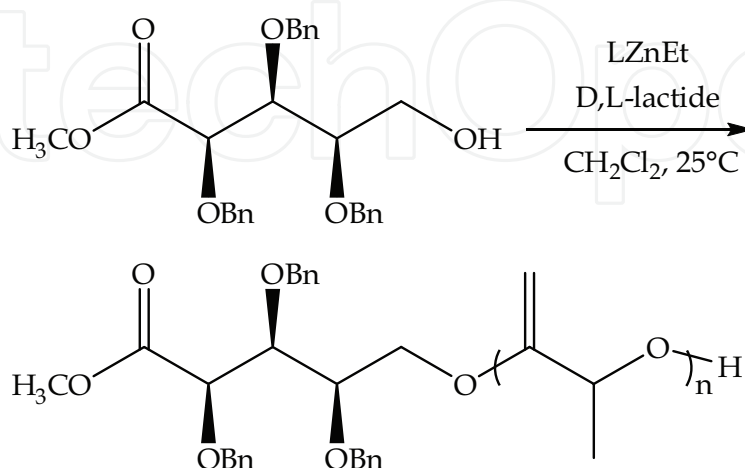


Fig. 8. Poly(D,L-lactide) end functionalization via coordination/insertion ring-opening polymerization using linear derivatives (Tang et al., 2008)

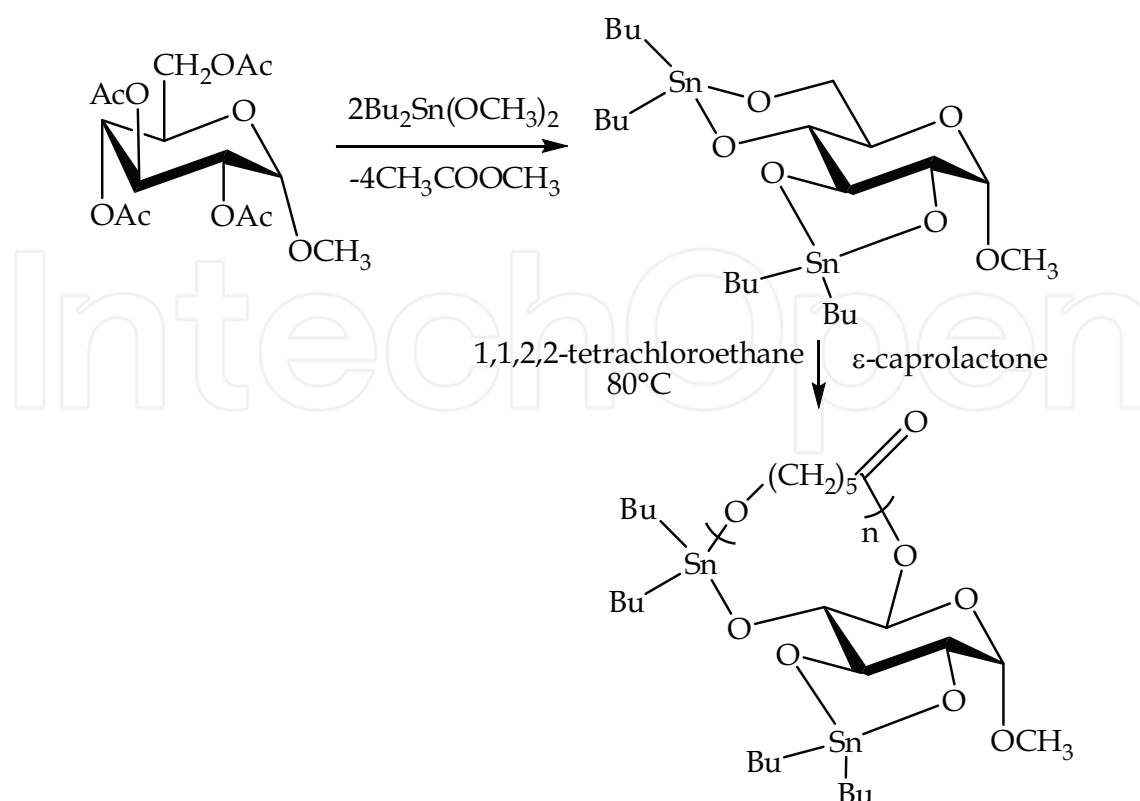


Fig. 9. Macrocyclic poly(ϵ -caprolactone) (Kricheldorf & Stricker, 2000) - Ac = CH_3CO -

Coordination/insertion ring-opening polymerization was also used for grafting from approaches. Dextran was used as an initiator for the grafting from approach, leading to poly(ϵ -caprolactone)-*graft*-dextran (Ydens et al., 2000) and poly(D,L-lactide)-*graft*-dextran copolymers (Nouvel et al., 2004). The polysaccharide was protected in a first step, and could be easily deprotected after the polymerization (Fig.10). Aluminum, tin and zinc alkyls or alkoxy are the most widely used catalysts for the strategies presented in this section.

2.2.3 Enzymatic ring opening polymerization

Poly(ϵ -caprolactone) was functionalized by this way using *Candida antartica* lipase B (Novozym 425, Córdova et al., 1998) and porcine pancreatic lipase (Bisht et al., 1998). The reactions were conducted at 60-70°C in bulk, using alkyl galacto- and glucopyranoside as carbohydrate initiators. The reactions conducted without protection - deprotection steps were found to be highly regioselective, the oligo(ϵ -caprolactone) chains formed being attached by an ester link to the primary hydroxyl moiety of the carbohydrate initiator (Fig. 11). Weight-average molecular weights around 4000 g/mol were reported with polydispersity indexes around 1.3 using *Candida antartica* lipase B (Córdova et al., 1998), while weight-average molecular weights of 2200 g/mol (*vs.* polystyrene standards) were reported for porcine pancreatic lipase (Bisht et al., 1998). The resulting carbohydrate end-capped oligo(ϵ -caprolactone) can be further used for the synthesis of multi-arm poly(lactide-*co*-(ϵ -caprolactone)) via coordination/insertion ring opening polymerization (Deng et al., 1999). The oligo(ϵ -caprolactone) hydroxyl end group is first protected by lipase catalyzed acetylation, and the remaining carbohydrate free hydroxyl groups can further initiate the polymerization of L-lactide mediated by tin octanoate (Fig. 11).

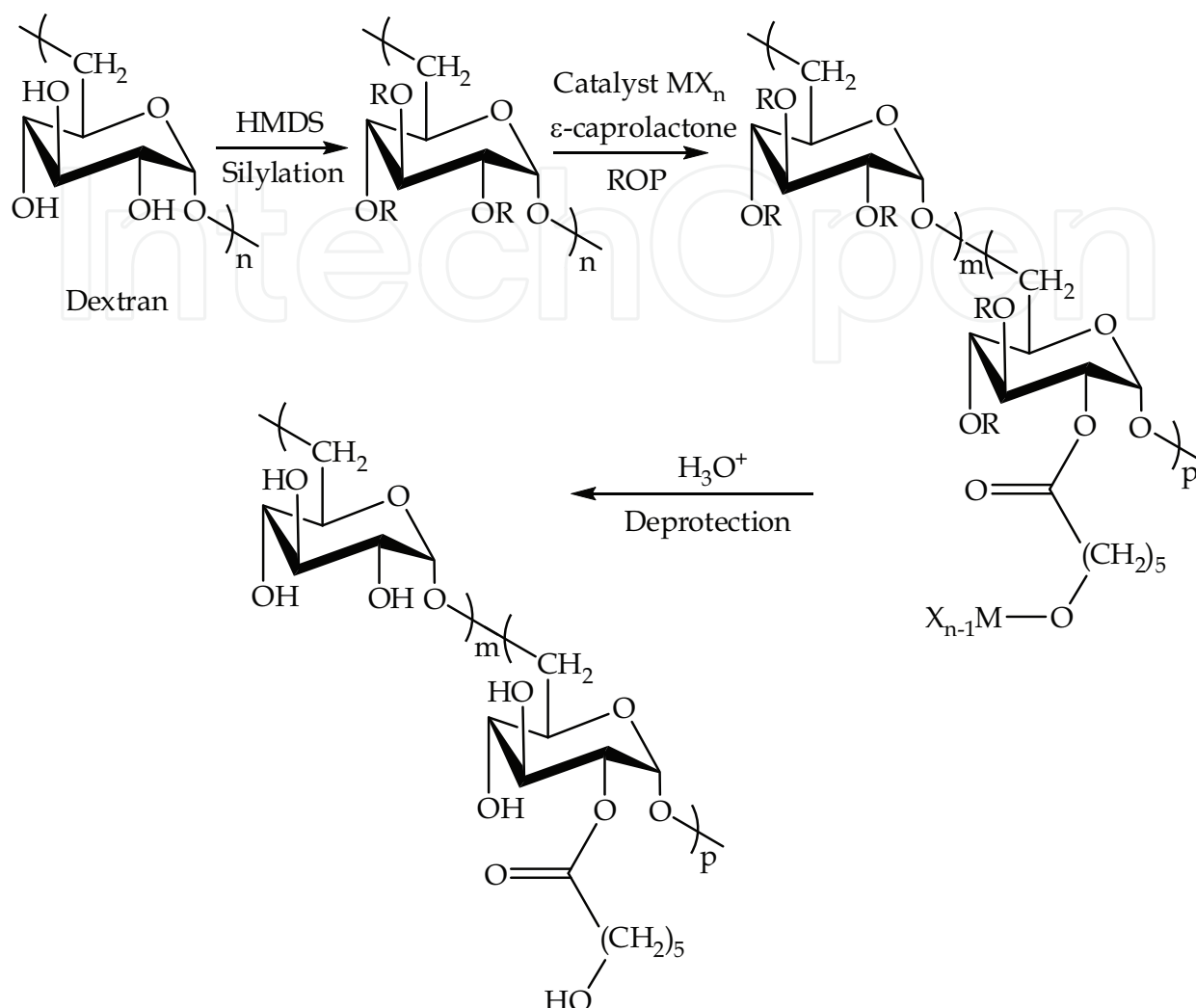


Fig. 10. Synthesis of poly(ϵ -caprolactone)-graft-dextran via coordination/insertion ring-opening polymerization (Ydens et al. 2000) - HMDS = 1,1,1,3,3,3-Hexamethyldisilazane, R = $-\text{Si}(\text{CH}_3)_3$ or H.

2.2.4 Organocatalysis

Personn et al. (2004) reported the use of lactic acid as a catalyst for the ring-opening polymerization of ϵ -caprolactone initiated by unprotected mono, di and tri-saccharides. The reaction was conducted at 120°C in bulk. The main products were regioselectively acylated on the primary hydroxyl groups of the carbohydrate end groups. Weight-average molecular weights of 2000 g/mol (*vs.* polystyrene standards) were reported with polydispersity indexes of 1.5. This one-step approach conducted without protection - deprotection steps lead to both carbohydrate (major product) and lactic acid end-capped poly(ϵ -caprolactone), as lactic acid also initiates the polymerization of ϵ -caprolactone under the experimental condition reported. (Fig. 12)

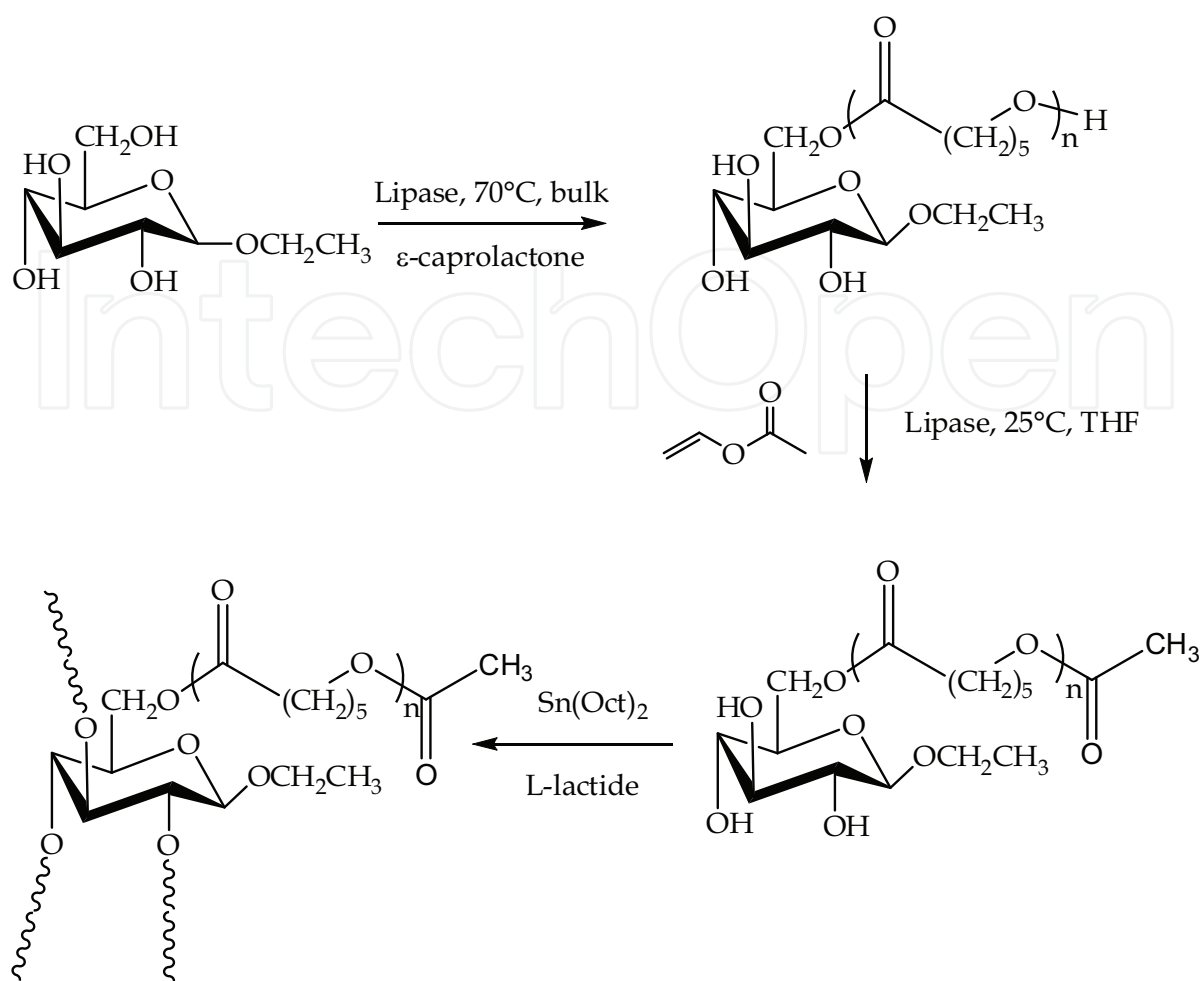


Fig. 11. Regioselective one-step poly(ϵ -caprolactone) end functionalization via enzymatic ring-opening polymerization (Bisht et al., 1998) and subsequent multiarm formation via coordination/insertion ring-opening polymerization of L-lactide (Deng et al., 1999) - Ethylglucopyranoside consists of a mixture of α - and β -anomers

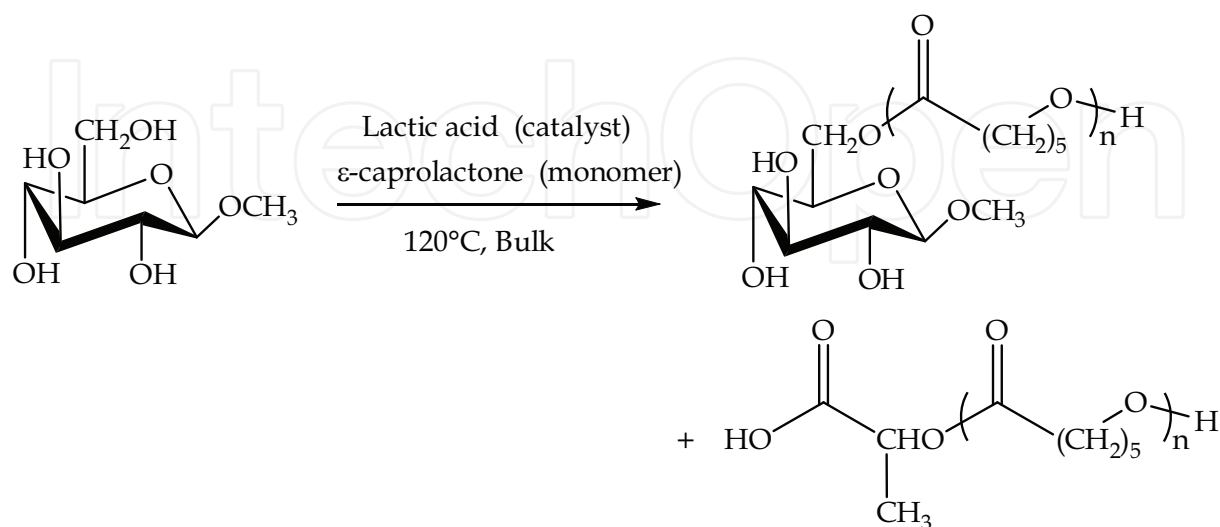


Fig. 12. One-pot poly(ϵ -caprolactone) end functionalization via organocatalytic ring-opening polymerization (Persson et al., 2004)

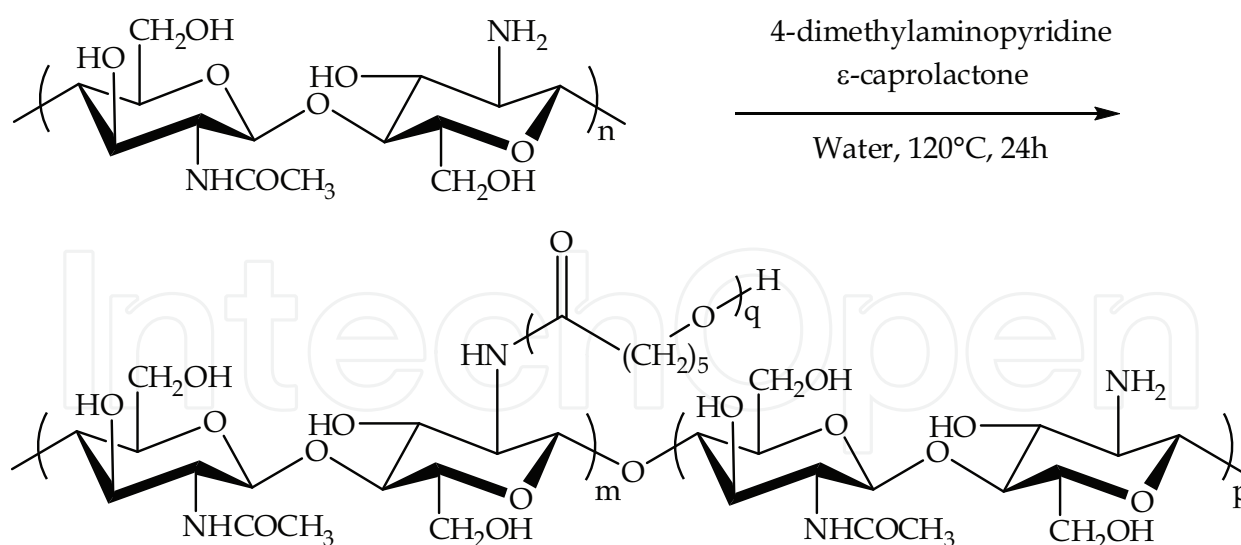


Fig. 13. Synthesis of poly(ϵ -caprolactone)-*graft*-chitosan via organocatalytic ring-opening polymerization (Feng et al. 2004)

The grafting from approach was also applied using organocatalysis. Feng et al. (2004) reported the synthesis of poly(ϵ -caprolactone)-*graft*-chitosan using 4-dimethylaminopyridine as a catalyst and water as a swelling agent starting from unprotected chitosan. The amino group of chitosan initiated the graft polymerization of ϵ -caprolactone through the chitosan backbone, while the hydroxyl group (HO-CH₂) of chitosan did not react (Fig. 13). Unprotected cyclodextrins were also used as initiators for the ring opening polymerization of lactones in the absence of catalysts. The yield remains modest for the polymerization of ϵ -caprolactone initiated by β -cyclodextrin in bulk at 100°C, but the reaction was shown to be regioselective, yielding a polymer attached to the C2-hydroxyl group of a single glucopyranose unit of the cyclodextrin (Takashima et al., 2004).

2.3 Use of functionalized compounds as (co-)monomers

The polymerization of functionalized cyclic esters represented in Fig. 14 is often rendered difficult by the chemical nature of the functional group. The latter must not interfere with the ring-opening polymerization, or has to be protected. Deprotection of sensitive functional groups and/or derivatization are thus applied, in addition to the synthesis of the functionalized monomer. This section presents some of the strategies developed in this field.

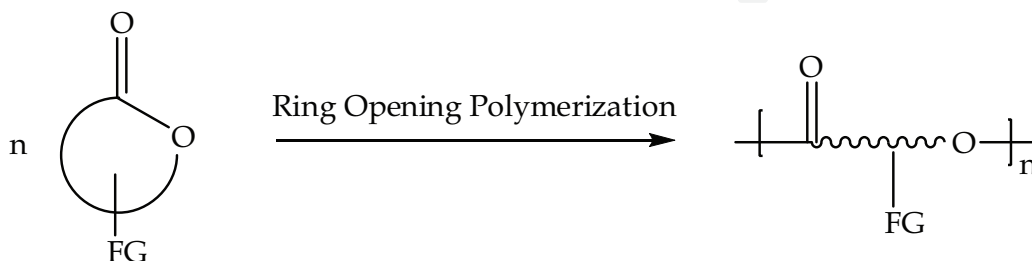


Fig. 14. Use of functionalized compounds as monomer or comonomer for the ring-opening polymerization of cyclic esters - FG represents a functional group

2.3.1 Protection strategies

A typical example of the synthesis of a cyclic ester bearing a protected hydroxyl group is presented in Fig. 15 (Trollsas et al., 2000). The ϵ -caprolactone derivative is generated by the Bayer-Villiger oxidation of the corresponding cyclohexanone, and is polymerized using tin octanoate, followed by the deprotection of the hydroxyl group. The authors reported also

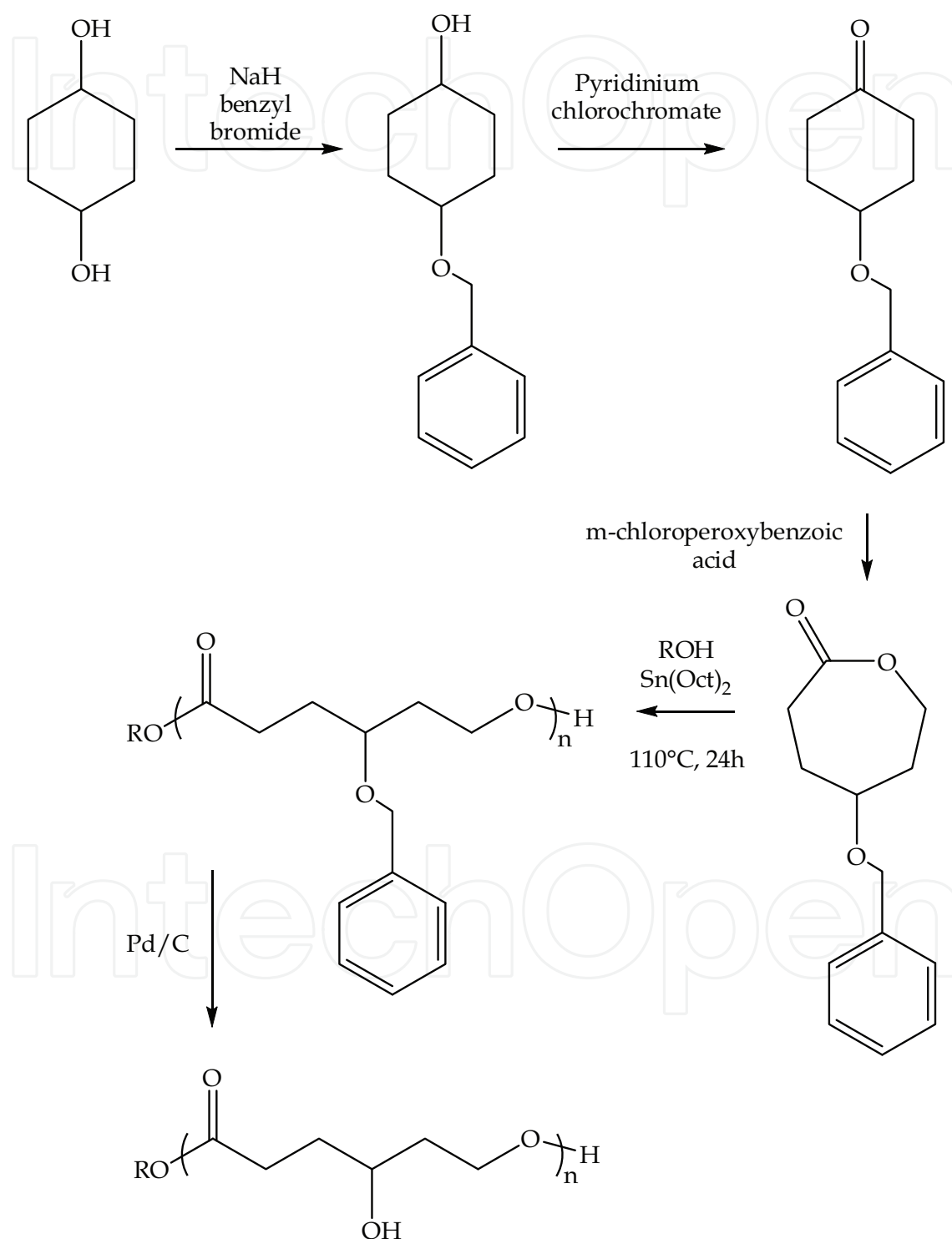


Fig. 15. Synthesis and polymerization of cyclic esters bearing a protected hydroxyl group (Trollsas et al., 2000)

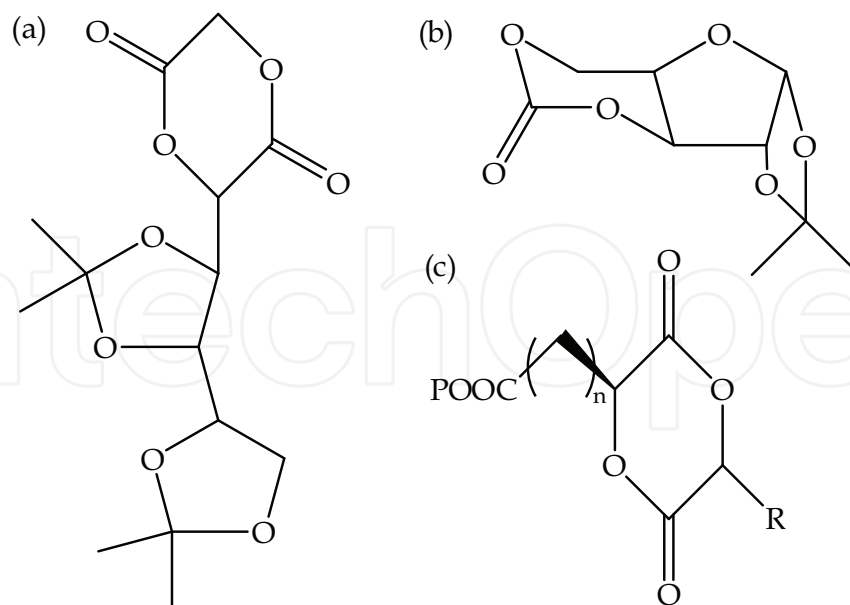


Fig. 16. Examples of carbohydrate derived monomers : 3-(1,2,3,4-tetraoxobutylidene)-isopropylidene)dioxane-2,5-dione ((a), Benabdillah et al., 1999), 1,2-o-isopropylidene-[D]-xylofuranose-3,5-cyclic carbonate ((b), Chen & Gross, 1999) and 1,4-dioxane-2,5-diones featuring pendant carboxyl groups (P = protecting group, $x=1$, $R=CH_2COOP$; $x=1$, $R=H$; $x=2$, $R=CH_3$, Thillaye du Boulay et al., 2008)

the synthesis of bishydroxyl, amino, and carboxyl functionalized poly(ϵ -caprolactone) using similar strategies. New carbohydrate derived cyclic esters or carbonate monomers where the functional groups are protected have also been synthesized (Fig. 16). They can be further polymerized or co-polymerized with classical polyester precursors.

2.3.2 Non-sensitive functional groups and derivatization

The synthesis of ϵ -caprolactone bearing allyl or cyclopentene pendent groups that are not sensitive to ring opening polymerization was reported (Mecerreyes et al., 2000 and Parish & Emrick 2004). The resulting monomer can be copolymerized with ϵ -caprolactone and lactide, and derivatization can be further performed, such as bromination, epoxidation, and hydrosilylation of the allyl group. The obtention of graft copolymers with poly(ethylene glycol) is also possible by conversion of the cyclopentene groups to 1,2-diols, and coupling of the hydroxyl groups to poly(ethylene glycol)-carboxylic acid derivatives. This latter approach, known as grafting onto, is presented in the next section using click chemistry.

2.3.3 Grafting onto methods and click chemistry

Grafting onto methods knows a recent regain of interest due to the development of click chemistry. Click chemistry considers reactions that can be carried out under mild conditions, in the presence of various functional groups, leading to high yields and to the generation of few or none harmless by-products. Among the reactions used in click chemistry, the most popular is the copper(I)-catalyzed alkyne-azide cycloaddition represented in Fig. 17. The application of this reaction for *in vitro* and *in vivo* studies suggests that the resulting 1,2,3-triazole group is biocompatible.

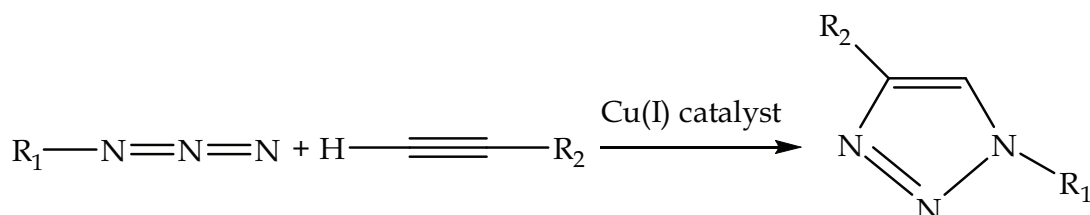


Fig. 17. Copper(I)-catalyzed alkyne-azide cycloaddition

The use of click chemistry for the functionalization of polyesters has also been reported for block copolymerization and for the synthesis of star-shaped polymers (Lecomte et al. 2008), but the most interesting strategies remain the grafting onto and grafting through approaches. The latter will be briefly described in the next paragraph. For the grafting onto strategy, cyclic esters bearing an azide or alkyne functional group are synthesized in the first step, followed by ring-opening polymerization and the grafting of an azide or alkyne end-capped polymer onto the functionalized polyester backbone.

Parrish et al. (2005) pioneered this approach synthesizing a α -propargyl- δ -valerolactone that was further copolymerized with ϵ -caprolactone (Fig. 18). The resulting alkyne grafted aliphatic polyester served as backbone for clicking oligopeptide moieties and poly(ethylene glycol) onto the backbone. The synthesis of other monomers of interest such as α -azide- ϵ -caprolactone (Riva et al., 2005) and 3,6-dipropargyl-1,4-dioxane-2,5-dione (Jiang et al., 2008) and subsequent polymerization and grafting have also been reported in the literature, leading notably to poly(ethylene glycol)-*graft*-poly(ϵ -caprolactone) and -polylactides, respectively. Note that the reactive groups used for the grafting onto method can also be introduced by post-polymerization modification of a chloro-functionalized polyester backbone (Riva et al., 2005).

2.3.4 Grafting through methods

In this approach, a cyclic ester bearing a pendant macromolecular chain is synthesized and polymerized. Poly(ethylene glycol) chains end-capped by an ϵ -caprolactone unit have been synthesized by living anionic ring-opening polymerization of ethylene oxide initiated by the potassium alkoxide of 1,4-dioxaspiro[4,5]decan-8-ol, followed by derivatization of the acetal into a ketone and the Baeyer-Villiger oxidation of the ketone into a lactone (Rieger et al., 2004). The polymerization of this monomer lead to poly(ethylene glycol)-*graft*-poly(ϵ -caprolactone). This is represented in Fig. 19. Click chemistry can also be used for the synthesis of poly(ethylene glycol) macromonomers based on ϵ -caprolactone and lactide (Riva et al., 2005 and Jiang et al., 2008, respectively).

3. Polycondensation (Fig. 20)

The synthesis of polyesters can take place by polycondensation of diols with diacids (AA - BB) or by the polycondensation of hydroxyacids (AB), leading to the formation of water as by-product. The reaction often takes place under vacuum to remove the water formed. High molecular weights are generally difficult to achieve. The section begins with the description of melt/solid polycondensation, a strategy developed to obtain high molecular weight poly(lactid acid) and poly(glycolic acid). The introduction of functional groups into polyesters by polycondensation is rendered difficult by the sensitivity of the functional groups, often secondary alcohols, to the polymerization. The brief description of protection

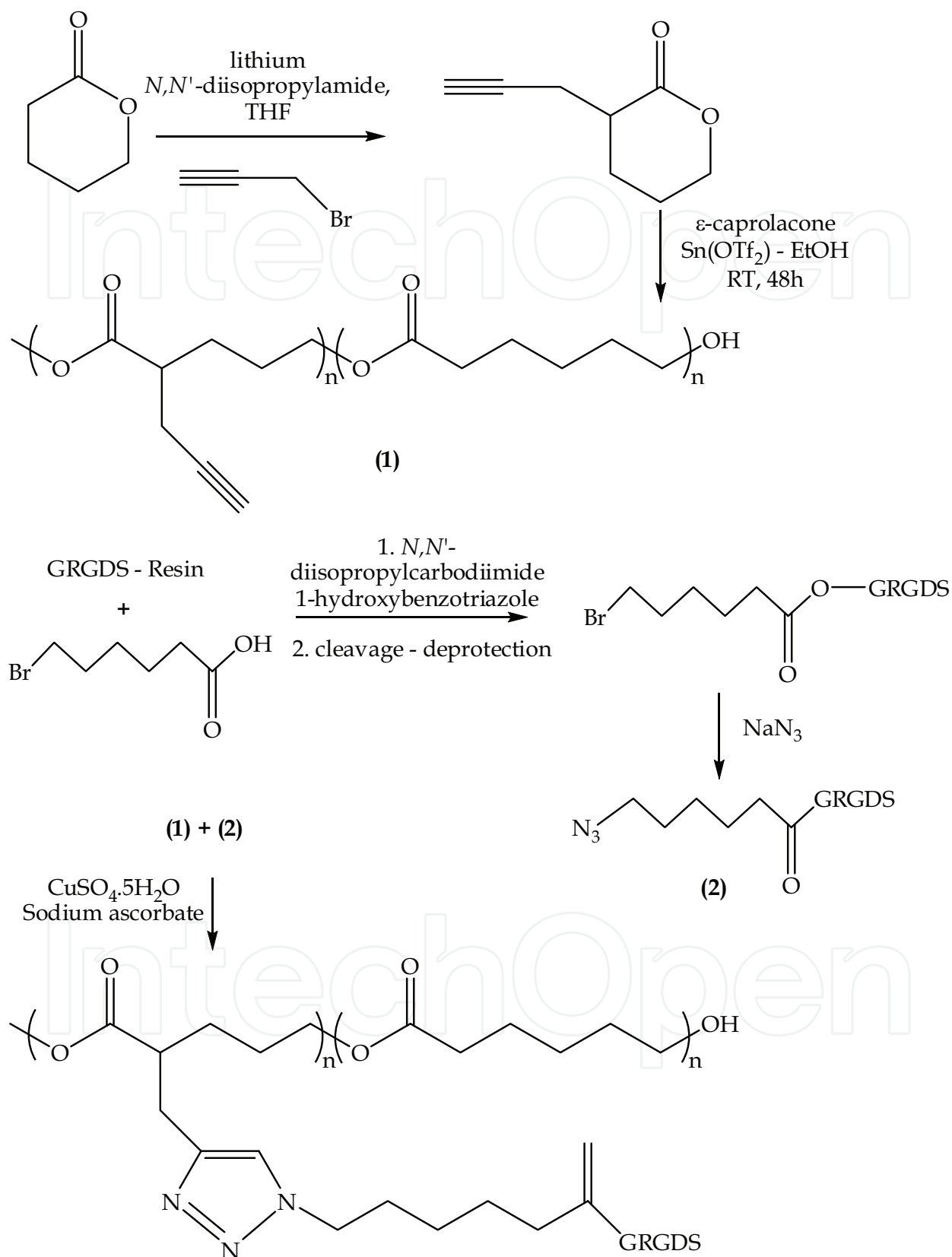


Fig. 18. Synthesis of oligopeptide-*graft*-aliphatic polyester via click chemistry and grafting onto approach (Parrish et al., 2005) - GRDS is an oligopeptide sequence.

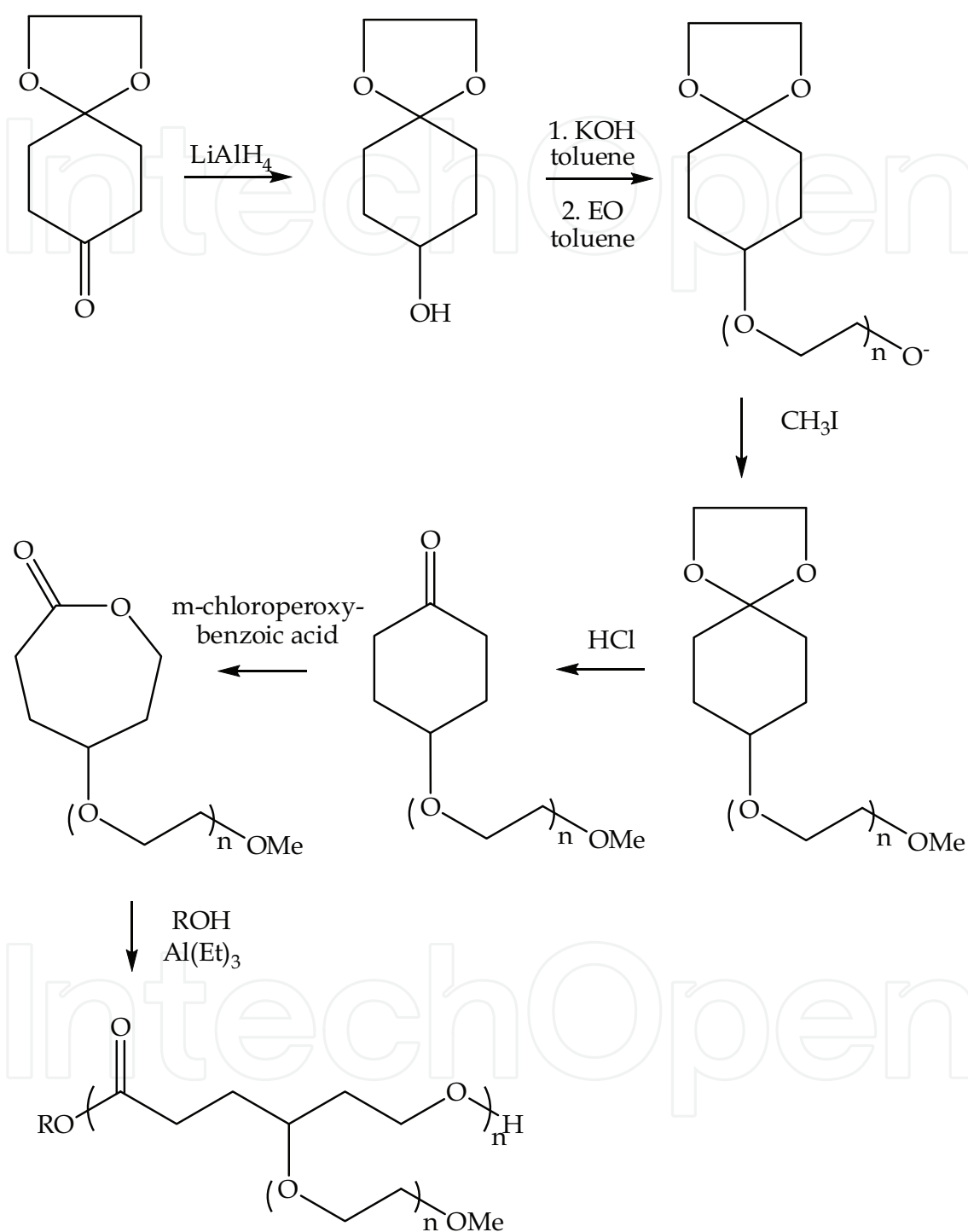


Fig. 19. Synthesis of poly(ethylene glycol)-*graft*-poly(ϵ -caprolactone) copolymers via the grafting through method (Rieger et al., 2004). EO = ethylene oxide.

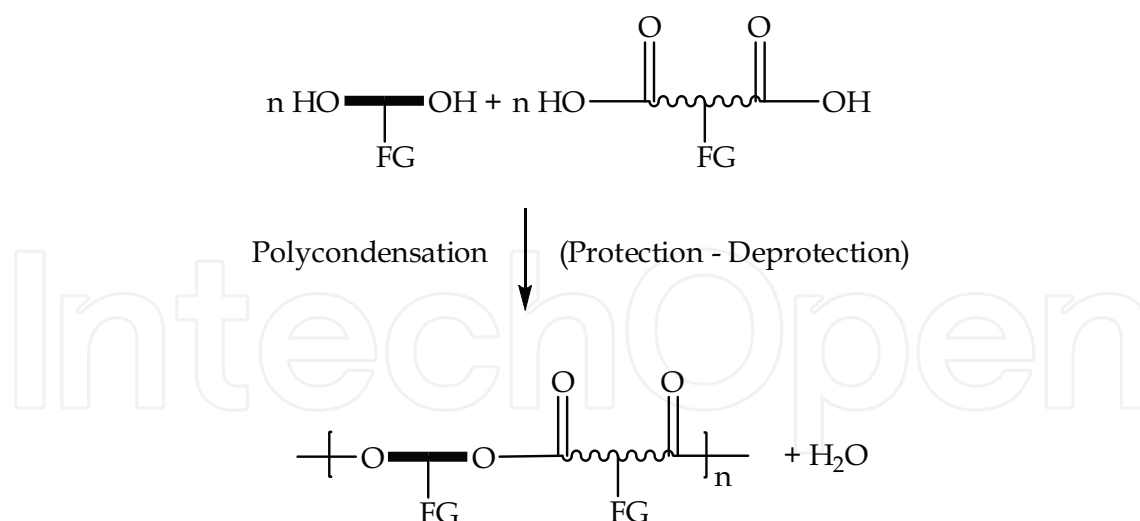


Fig. 20. Polycondensation. FG represents a functional group.

strategies used for this purpose is followed by recent advances in one-step strategies enabling the functionalization of polyesters by polycondensation without the need to protect the functional group, *i.e.* enzymatic and Lewis acid catalysis. Note that these one-pot strategies lead to polyesters bearing multiple functional groups along the polymeric backbone.

3.1 Melt and solid polycondensation

The acid form of ϵ -caprolactone, 6-hydroxyhexanoic acid, is scarcely isolable, and thus, poly(ϵ -caprolactone) is rarely synthesized by polycondensation techniques. Lactic and glycolic acids are in turn naturally occurring products, and their polymers and copolymers can also be made via polycondensation. A major drawback is the removal of the water formed during the polymerization, leading often to modest number-average molecular weight. This drawback can be overcome via melt and solid polycondensation techniques.

Melt polycondensation is conducted under reduced pressure at high temperature, starting from oligomers of the targeted polymer. One may distinguish melt polycondensation from solid polycondensation; in the former case, the polymerization is conducted at a temperature above the melting temperature of the polymer. For example, the melt polycondensation of oligo(L-lactic acid) was conducted using SnCl_2 combined to protonic acids such as *p*-toluenesulfonic acid monohydrate or *m*-phosphoric acid (Moon et al., 2000). Weight average molecular weights up to 100 000 g/mol were obtained. The crystallization of the so-obtained poly(L-lactic acid) and subsequent solid polycondensation at temperature below the melting temperature lead to weight average molecular weights up to 500 000 g/mol using similar catalytic systems (Moon et al., 2001). Melt/solid polycondensation can also be applied to oligo(glycolic acid) (Takahashi et al., 2000).

3.2 Protected monomers

The introduction of functional groups such as secondary hydroxyls is rendered difficult by the possible reaction of these groups with the acid functionality, leading to cross-linking and gelation. The strategy consists thus usually in the protection of secondary alcohols on a functional compound, or to the synthesis of monomers where the secondary hydroxyl functions are protected. There are numerous works dealing with the synthesis of new

monomers with protected functional groups, often starting from carbohydrate derivatives. For example, protected gluconic acid in the form of 2,4,3,5-di-O-methylene-D-gluconic acid can be polymerized with benzoyl chloride (Mehltretter & Mellies 1955). The same strategy can also be applied to AA-BB polycondensation (Metzke et al., 2003, among others).

3.3 One step introduction of functional groups into polyesters

The synthesis of linear polyesters via one step polycondensation of monomers bearing secondary pendant hydroxyl groups relies on the selectivity of specific catalysts toward primary alcohols. Using such catalysts, the acid functionality reacts with primary alcohols, but not with lateral secondary alcohols, avoiding cross-linking and gelation. This can be done by enzymatic and Lewis acid catalysis.

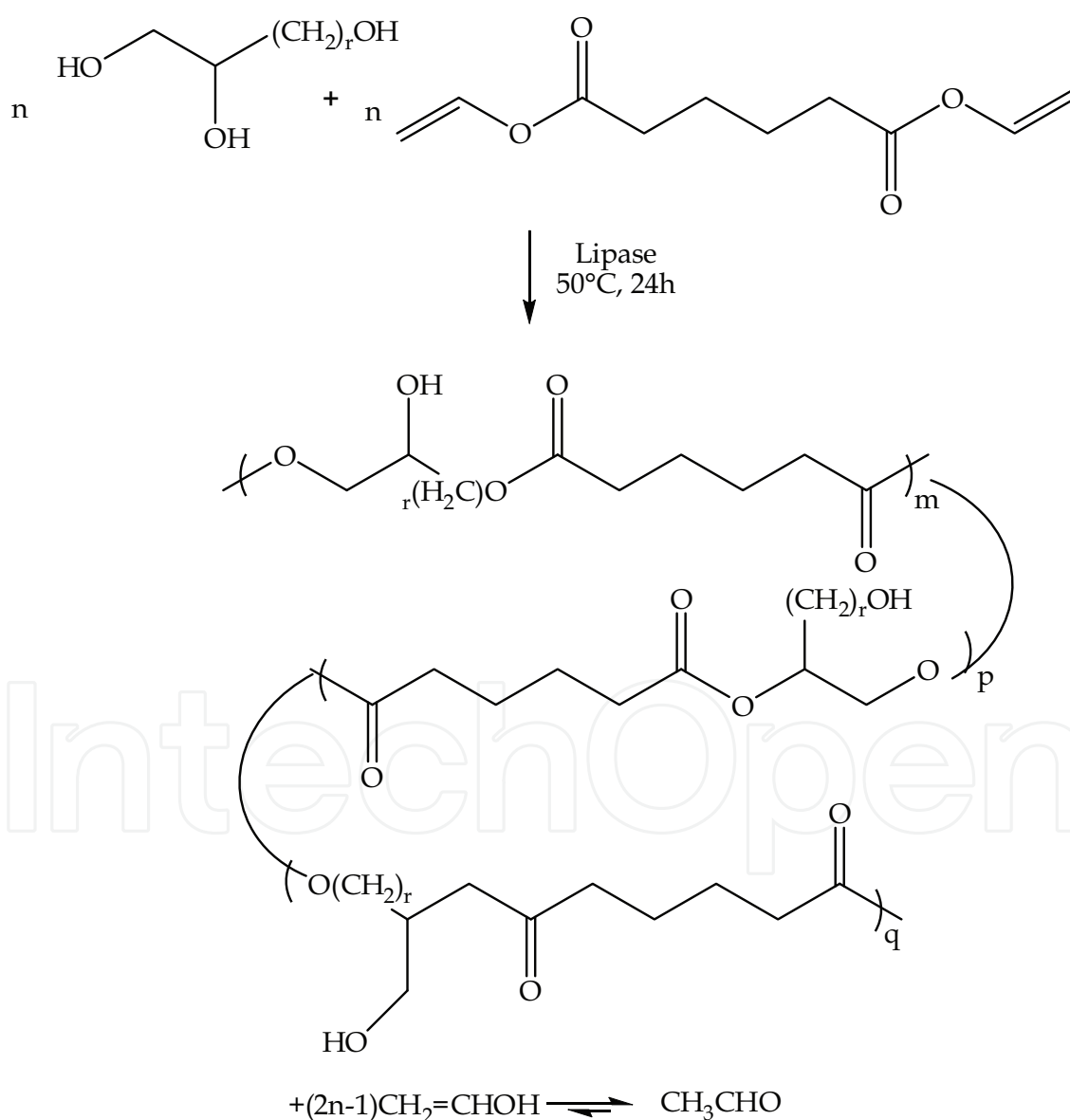


Fig. 21. Lipase catalyzed regioselective polycondensation between triols and divinyl adipate. $R=1$, glycerol, $R=2$, 1,2,4-butanetriol, and $R=4$, 1,2,6 trihydroxyhexane (Kline et al., 1998)

3.3.1 Enzymatic catalysis

Enzymatic catalyzed polycondensation enables a one-step synthesis of hydroxyl pendant polyesters using renewable resources as the polyol monomer. Using Novozyme-435 lipase and *Candida antarctica* lipase B, glycerol, 1,2,4-butanetriol and 1,2,6 trihydroxyhexane can be copolymerized with divinyl esters to yield low to high molecular weight linear hydroxypolyesters (Kline et al. 1998, Uyama et al. 2001 - Fig. 21). The reaction is regioselective, as the pendant hydroxyl groups in the polymer are mainly secondary. Glycerol can also be copolymerized with adipic acid and 1,8-octanetriol using Novozyme-435, yielding a few intermolecular crosslinks in addition to hydroxyl pendant groups (Kumar et al. 2003). Carbohydrate polyols such as sorbitol (Fig. 22) and alditols were also successfully copolymerized with 1,8-octanediol and adipic acid using the aforementioned enzyme as catalyst (Kumar et al., 2003, Hu et al., 2006).

3.3.2 Lewis acid catalysis

Lewis acid catalyzed polyesterification is another type of chemistry enabling a one step synthesis of linear polyesters bearing pendant hydroxyl groups. Using trifluoromethane sulfonate salts (known as triflate - $M(\text{OSO}_2\text{CF}_3)_n$), sorbitol and glycerol were successfully copolymerized with diacids (Takasu et al. 2007). Lewis acid catalysis is rather versatile as diacids bearing pendant hydroxyl groups such as tartaric and malic acids could also be copolymerized selectively with diols in bulk and under reduced pressure. The resulting polyesters had low to average molecular weights. The procedures are represented in Fig. 23.

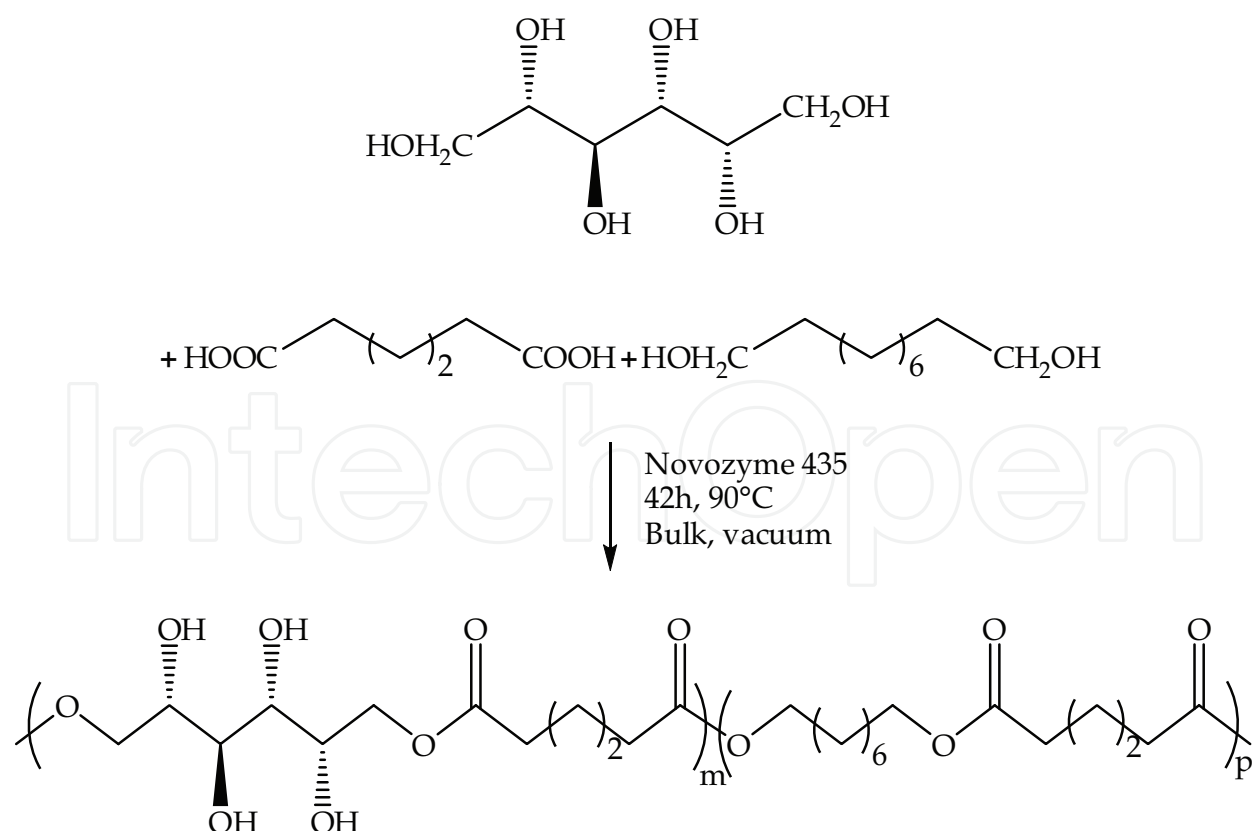


Fig. 22. Novozyme-435-catalyzed regioselective polymerization of sorbitol with adipic acid and 1,8-octanetriol (Kumar et al., 2003)

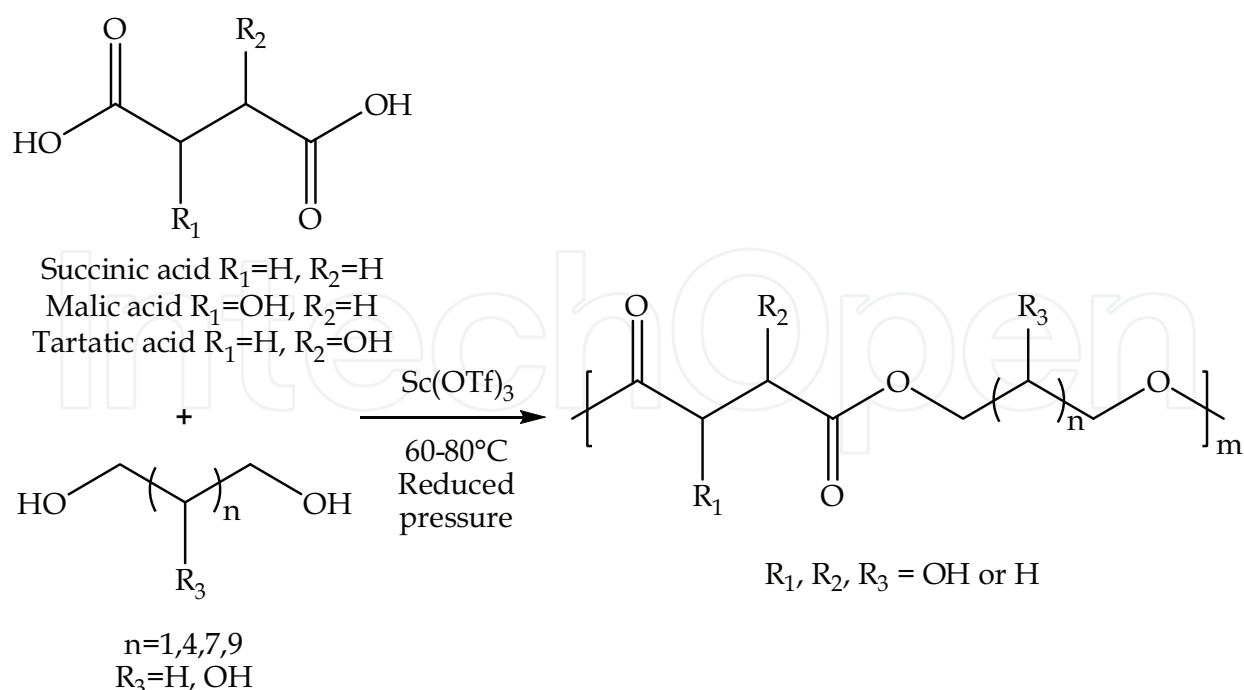


Fig. 23. Scandium triflate catalyzed regioselective polycondensation of dicarboxylic acids and diols having pendant hydroxyl groups (Takasu et al., 2007)

4. Transesterification

The principle of transesterification is presented in Fig. 24. The reaction can start from an ester and an alcohol, or from two ester groups. Transesterification commonly occurs in the molten state, producing first block copolymers and finally statistical copolymers.

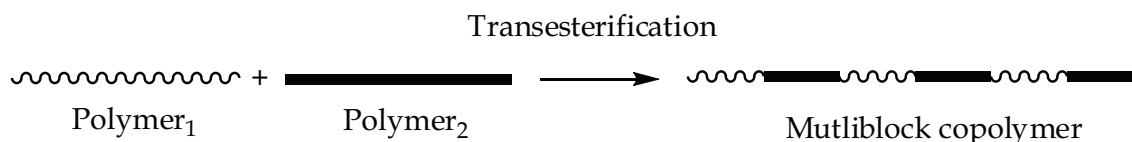


Fig. 24. Transesterification

Transesterification of poly(D,L-lactide) and polyethylene glycol was reported in acetone, without catalysts, leading to copolymers with number-average molecular weights up to 6000 g/mol (Piskin et al., 1995). The polymer precursors exhibit number average molecular weights between 2000 and 4000 g/mol. Additional purification steps are necessary in order to remove the remaining homopolymer. The resulting copolymer was shown to form micelles, poly(D,L-lactide) being the hydrophobic segment and polyethylene glycol the hydrophilic segment, and were further used as drug carriers. The composition of the copolymer can be simply changed by varying the ratio of polymer precursors. The molecular weight of the resulting copolymer can be significantly increased starting from precursors of higher molecular weight. Using succinic acid as chain extender for polyethylene glycol, poly(L-lactide) and poly(D,L-lactide) of high molecular weight and titanium isopropoxide as transesterification catalyst, molecular weight up to 40 000 g/mol *vs.* polystyrene standards could be achieved (Mai et al. 2009).

5. Conclusion

The synthetic strategies for the functionalization of polyesters are numerous, and result in a great diversity of polyesters specialties for potential biomedical applications. Various architectures can be synthesized, including statistical and block copolymers, as well as graft and star-shape copolymers. Ring-opening polymerization leads generally to higher molecular weights than polycondensation, and has been more studied. Enzymatic and organocatalyzed ring-opening polymerization are particularly interesting, as they enable one-pot regioselective end-functionalizations of polyesters by carbohydrate derivatives notably, without protection/deprotection steps. Regioselective polymerization can also be conducted by polycondensation, considering enzymatic and Lewis acid catalysis. This leads to a higher number of functionalities along the polymeric backbone, which can only be achieved by protection / deprotection strategies or derivatization considering ring-opening polymerization. Transesterification leads on the other side to interesting microstructures, and can be conducted without catalysts in certain conditions.

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