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Lipases as Efficient Catalysts in the Synthesis of Monomers and Polymers with Biomedical Applications

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Abstract: Enzymatic polymerization shows to be an advantageous approach in polymer chemistry, particularly in the case of obtaining polymers required for biomedical applications, which are intented for human consumption. Enzymes apply procedures that are environmentally friendly involving waste minimization, hazard reduction, the efficient use of energy and the use of renewable sources. This paper reviews selected examples of the recent progress in lipase-catalyzed polymerization. The application of this hydrolase in the synthesis of polyesters, polycarbonates and polyamides following traditional mechanisms is covered. Moreover, lipase-catalyzed synthesis of novel vinyl copolymers and monomers is described.

Keywords: Lipase-catalyzed polymerization, monomers, biomedical applications.

1. INTRODUCTION

The enormous effect of polymers in Medicine is well known. The polymers that meet these functions belong to the family of biomaterials [1]. Polymers, metals and ceramics usually act together and in a complementary way in medical applications. For example, hip replacements and scaffolds for tissue engineering are carried out through the development and association of new alloys, ceramics and polymers, which can mimic the physical properties of tissues surrounding the implanted site [2]. The polymeric biomaterial can be derived either from nature or synthesized in the laboratory. In the case of hip replacements a biomimetic material was made of the biopolymer collagen and calcium phosphate which improves the mechanical properties of the collagen scaffold alone [3]. But the high cost of pure type I collagen restricts its applications. For this reason an analogue of collagen calcium phosphate material was developed and involves synthetic biodegradable polymers such as poly(α-hydroxyacids) and bioactive inorganic fillers that produce materials that may be useful for hard tissue replacement devices and as scaffolds for tissue engineering [4].

Throughout history, several materials have played an important role in the treatment of disease and the improvement of health care such as, for example, the use of gold in dentistry over two thousand years ago. With the advent of synthetic polymers at the end of the nineteenth century these materials also found biomedical application. For example, polymethylmethacrylate, PMMA, was used in dentistry from 1930's and cellulose acetate was used in dialysis tubing in the 1940's. Later, polyetherurethanes were used in artificial hearts and PMMA and stainless steel were used in total hip replacements [5,6]. During the last years, polymers have been widely used in various biomedical fields such as: contact lenses [7], kidney dialyzers [8], bone and cartilage repair [9], gene therapy [10], drug carriers, tissue engineering [11], etc.

These materials were initially adopted from other areas of science and technology without a substantial redesign for medical use. Although they helped a lot in new medical treatments, critical problems in biocompatibility, mechanical properties, degradation and numerous others areas remain. Today the challenge is to create new materials without these disadvantages. Therefore, the current scientific work in this field is characterized by a growing emphasis on identification of specific design parameters that are critical to performance, and taking into account of the need to integrate biomaterials design with new insights emerging from studies of cell-matrix interaction [12], cellular signaling processes [13] and developmental and systems biology [14]. The development of novel and efficient polymeric biomaterials requires interdisciplinary and collaborative efforts of researchers from diverse backgrounds, including materials scientists, biomedical engineers, chemists, biologists and clinicians.

Besides the need for new and appropriate polymers for biomedical applications, it is also necessary to consider the way in which these materials are obtained. This question becomes crucial because these polymers are intended for human consumption. Therefore a "green" approach in the synthesis of polymeric biomaterials is always welcome.

Nowadays, there is a global and increasing interest in the development of this kind of procedures involved in Green Chemistry concept [15]. Green Chemistry applies across the life cycle of a chemical product, including its design, manufacture and use. Accordingly, the procedures associated to Green Chemistry include waste minimization, hazard reduction, the efficient use of energy and the use of renewable sources. All these actions are designed to prevent pollution and reduce resource consumptions [16,17].

Biocatalysis is one of the most important tools for Green Chemistry and has emerged as an attractive alternative to conventional chemical catalysis [18].

Some advantageous features have contributed to the development of biocatalytic processes. The first is the high selectivity (chemo-, regio- and stereoselectivity) shown by enzymes, that allow the production of novel and enantiopure compounds that at the same time minimize the formation of by-products [19-21]. Another

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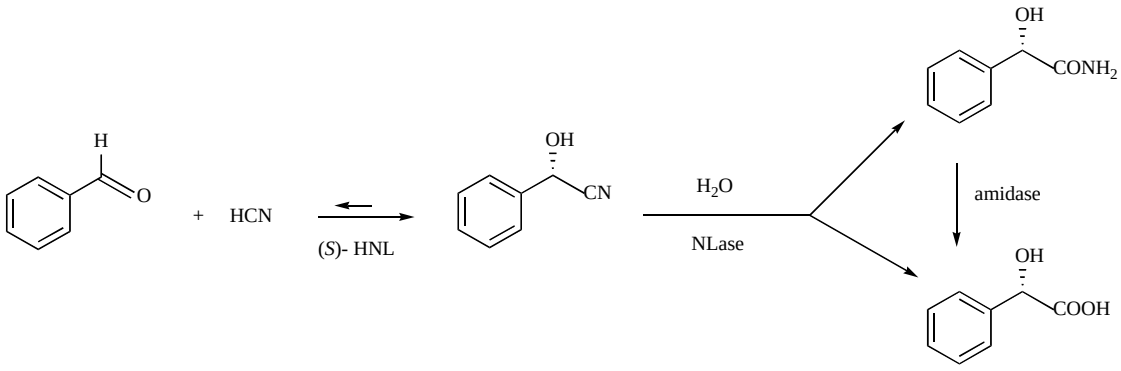


Scheme 1. One-pot conversion of benzaldehyde to (*S*)-mandelic acid with a triple decker CLEA.

advantage is the possibility of working in mild reaction conditions that are sufficient to run enzyme-catalysed reactions, reducing energy requirements. In addition, enzymes are non-toxic, can be reused and are biodegradable. These characteristics contribute to create environmentally friendly processes which are entirely consistent with the Green Chemistry concept. To bring this concept to concrete results it is necessary to integrate enzymatic transformations strategically into chemical reactions at the retrosynthetic level. This goal was achieved through the application of enzymes in the manufacture of pharmaceuticals [22,23]. Two relevant examples among hundreds are the obtention of the antidiabetic sitagliptin that uses a transaminase for the synthesis of a chiral amine [24] and the conversion of benzaldehyde to (*S*)-mandelic acid catalyzed by cross-linked enzyme aggregates (CLEAs) [25, 26]. This last reaction uses a combi-CLEA containing the *Morchella esculenta* hydroxynitrile lyase, in combination with a nitrilase and an amidase, to catalyze the formation of (*S*)-mandelic acid in 99% ee at 96% benzaldehyde conversion (Scheme **1**).

Enzymes are not limited to operate in their native aqueous media and some of them can efficiently act as catalysts of the biotransformation of a wide range of substrates in organic media. Among these classes of enzymes lipases are very important, being used in multiple applications such as the synthesis of pharmaceuticals [27], agrochemicals [28], vitamins [29], flavors [30], steroids [31], aminoacid derivatives [32], etc.

Taking into account the success achieved by the enzymes in small molecule organic synthesis, enzymatic catalysis has also been applied to polymer synthesis and functionalization. The aim of this review is to describe recent advances on the enzymatic synthesis of polymers, emphasizing the use of lipases as reaction catalysts and the potential biomedical applications of the materials. At the same time, some of our insights on lipase-catalyzed synthesis of monomers and polymers are shared.

2. ENZYME-CATALYZED POLYMERIZATION

Enzyme-catalyzed synthesis of polymers can be performed *in vivo* or *in vitro* [33]. *In vivo*, it takes place in living cells where enzymes catalyze the synthesis of all biopolymers, besides other biological substances, via metabolic or biosynthetic pathways. *In vitro*, enzymatic catalysis is achieved for the synthesis of polymers via two pathways:

a) Biosynthetic, for example in the synthesis of polyesters via fermentation using whole cells of microorganisms,
b) Non-biosynthetic, for example in the synthesis of a polymer catalyzed by an enzyme without involving the cell's metabolic system.

This last case (b) is called enzymatic polymerization, and it is defined as the chemical synthesis of polymers *in vitro*, via non-biosynthetic pathways, catalyzed by an isolated enzyme [34]. Depending on the reaction, *in vitro* operated enzymatic catalysis is close to or very similar to *in vivo* enzymatic catalysis. The advantageous characteristics shown by the enzymes such as: high turnover, reactions under mild conditions with respect to temperature, pressure, solvent, neutral pH, etc. and excellent reaction control of chemo-, regio- and stereoselectivities, can also realized *in vitro* depending on the catalyst [35]. Therefore, enzymatic polymerizations can prevent waste generation, limit the use of hazardous organic reagents, using water or ionic liquids as green solvents, design processes with higher energy efficiency and safer chemistry by conducting reactions at room temperature under ambient atmosphere. Moreover, an increase in atom efficiency by avoiding extensive protection and deprotection steps can be achieved.

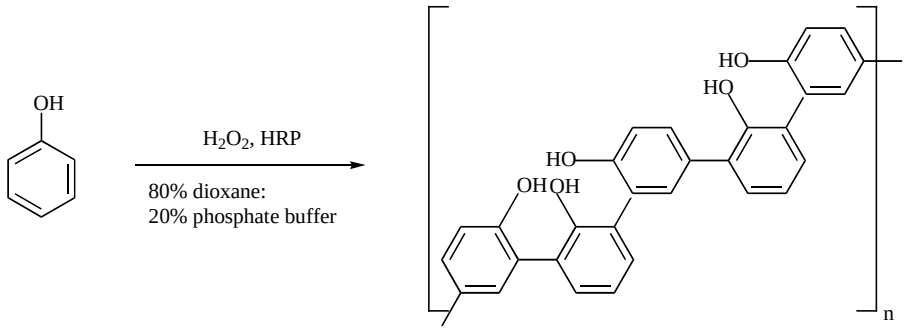
In polymer synthesis *in vitro*, the enzymatic polymerization seeks to reproduce the same characteristics that the enzymes show in vivo. When this happens, the following outcomes can be expected:

- new polymerization reactions
- polymers with new and controlled structures
- clean processes without by-products
- low energy processes
- good biodegradability of the polymeric products

These outcomes are often difficult to achieve when following conventional chemical procedures. Many useful polymers can be more easily synthesized by using the enzymes as the catalyst [36, 37].

Often the specificity of the enzyme by the substrate *in vitro*, it is not as strict as the enzyme-substrate relationship in the biosynthetic pathways [37]. This is important when attempting to generate polymers such as polyphenol and polyaniline where non-native substrates are being used. Some of these polymers synthetic procedures are carried out under harsh conditions including the use of concentrated strong acid solutions with pH = 1. The chemical synthesis of these polyaromatic polymers then generates a large volume of waste that must be treated and discarded. With the successful approach to polymer synthesis using peroxidases as biocatalyst, the amount of waste is reduced if not eliminated, since enzymatic synthesis is performed under mild conditions, with a pH around 5 (Scheme **2**) [38-41].

In the production of phenolic resins, enzymatic polymerization can be performed without using toxic formaldehyde, which is a necessary reagent for the production of conventional phenol-



Scheme 2. Horseradish peroxidase catalyzed synthesis of polyphenol.

Table 1. Enzyme-catalyzed Polymers

Enzyme Class	Enzyme	Polymers
hydrolases	glycosidases lipases proteases	polysaccharides polyesters polycarbonates polypeptides polyamides
oxidoreductases	peroxidades laccases	polyphenols polyanilines vinyl polymers
transferases	glycosyltransferases acyltransferases	polysaccharides cyclic oligosaccharides polyesters

formaldehyde resins like Resol or Novolac [42]. Another application of peroxidases is the treatment of wastewaters, where they catalyze the polymerization of toxic aromatic contaminants. The resulting polymers can be separated from the aqueous solution by filtration [43]. Taking into account the above mentioned advantages, enzymatic polymerization is of growing interest for synthetic chemists and even for large-scale industrial production [44-47].

Enzymes are categorized in six categories by the International Union of Biochemistry and Molecular Biology, based on the type of reaction they catalyze: oxidoreductases, transferases, hydrolases, ligases, isomerases and lyases [48]. Among these, hydrolases are most often used for enzymatic polymerization, because they are easily isolable due to their stability and widely available as commercial products. Oxidoreductases, transferases and ligases are also applied but to a lesser extent. *In vivo*, hydrolases, including glycosidades, lipases and proteases, are enzymes that catalyze a bond-cleavage reaction by hydrolysis. Under synthetic conditions they have been employed as catalysts for the reverse reaction: bond-forming reaction. Table **1** shows some examples of the wide array of polymers that can be synthesized through enzyme catalysis.

Typical examples of enzymatically produced macromolecules are the synthesis of polysaccharides [49,50], polyamides and polyesters [51-54] using hydrolases, and the synthesis of resins from phenols and anilines via peroxidase catalysis [38-44].

3. LIPASE-CATALYZED POLYMERIZATION

Lipases are serine hydrolases defined as triacylglycerol acylhydrolases (E.C. 3.1.1.3). In an aqueous environment, they catalyze the hydrolysis of the ester bond of tri-, di- and monoglycerides into fatty acids and glycerol. Nevertheless, they are also active on a broad range of substrates. In every case, the reaction is carried out at the interface of a biphasic system reaction, which results from the presence of an immiscible organic phase, containing the hydrophobic substrate, in water.

Under synthetic conditions, low water activity, lipases also catalyze a large variety of synthetic reactions, particularly esterifications and transesterifications [55]. Lipases show also a promiscuous behavior, being able to catalyze transformations completely different from the reactions they originally evolved to perform such as Michael addition, Markovnikov addition and aldol condensation, that are only some few examples [56-59]. Due to this behavior, lipases have been used in multiple industrial activities: the resolution of chiral drugs (Flurbiprofen) [60], fat modification [61], biodiesel production [62] and for the synthesis of personal care product and cosmetics [63]. In addition, lipases are applied in various biotechnological fields such as cheese ripening [64], detergent [65], bioremediation [66], and in paper and pulp industry [67].

In the last decade, lipases appeared as excellent catalyst for polymerization reactions as a result of their broad substrate capacity, high activity and good stability in a wide range of reaction media. Lipases are efficient catalysts for the preparation of polyesters, polycarbonates and even polyamides, polyacrylamides and polyamidoamines. Moreover, a variety of different polymer structures such as block and graft copolymers have been prepared using chemoenzymatic approaches.

Regardless of the type of polymerization, condensation or addition, the immobilized lipase B of *Candida antarctica* (CAL B) is by far the most applied lipase in enzymatic polymerization. With the

name of Novozym 435, CAL B is physically absorbed onto the macroporous resin Lewatit VPOC 1600 (poly[methyl methacrylate-*co*-butyl methacrylate]) [68]. Besides being the most active lipase in this type of reactions, it is also simple to handle, stable and easily removed at the end of the polymerization. High costs of production of CAL B and other commercial enzymes restrict their use as biocatalysts. For this reason current research focuses on the study of different sources, supplements and substrates that let to obtain high value lipases using operational conditions that reduce the production costs at industrial scale. This can be achieved by using low cost lipases extracted from plants, such as *Carica papaya* lipase [69], culture media obtained from residues from the agro-industry, etc [70].

In the following sections, we will describe the application of lipases in the synthesis of various classes of polymers, particularly the synthesis of polyesters, polyamides and polyacrylates. A variety of enzymatic polyesters were successfully synthesized via ring opening polymerization of lactones [71-73], and concurrent ring opening and condensation copolymerization of lactones with diesters and diols [74-77], condensation polymerization of dicarboxylic acids with diols [78], transesterification reaction of diesters with diols [78,79] and polymerization of hydroxiacids [78]. Moreover, synthesis of aliphatic polycarbonates [80-81], poly(carbonate-co-esters) [82-84], and polyamides [85] have also been reported. Finally lipases can be involved in the synthesis of some vinyl polymers and monomers [33].

3.1. Lipase-Catalyzed Synthesis of Polyesters

The development of reproducible and efficient drug delivery systems requires a careful control of the properties and synthetic methods used to prepare the polymers to be used. Aliphatic polyesters such as poly-ε-caprolactones, polylactides, and polyglycolides can be prepared by two distinct mechanisms: (i) the ring opening polyaddition (chain polymerization), and (ii) polycondensation (step-growth polymerization).

A broad range of anionic, cationic or metallic catalysts have been reported in the synthesis of aliphatic polyesters. However, these catalysts are not appropriate in synthesis of polymers with biomedical applications due to their toxicity. Enzymes, such as lipases and esterases, being biodegradable can overcome this disadvantage and have been increasingly used as biocatalysts in the synthesis of polyesters.

3.1.1. Ring Opening Polymerization of Lactones

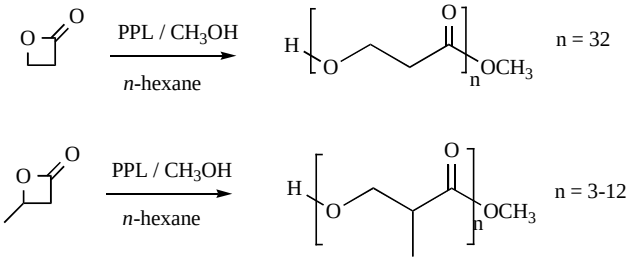
The synthesis of biodegradables and biocompatibles polymers derived from renewable sources, has been an attractive area of research in the last years. Many carbohydrate- and amino acid-based polymers have been reported in the literature [86-92]. The utility of the biocompatible polymers is also highlighted in biomedicine for degradable scaffolds and drug delivery applications [93-95]. Among the most studied aliphatic polymers are polyesters due to their applications, favorable biocompatibility and versatile synthetic accessibility.

The ring opening polymerization (ROP) mechanism allows quite good control of the polymer characteristics such as predictable molecular weight or narrow molecular weight distribution and is particularly well indicated for macromolecular engineering with the production of homo- and copolymers of various architectures [93,96]. Some advantages of ROP are that they do not need very high temperatures, the reaction times are short, there is no small molecule such as water or alcohol produced and it is possible to prepare high molecular weight polyesters in an easy way.

Enzymatic ring opening polymerization can increase the advantages showed by ROP because it provides an alternative route to the use of metal catalysts in the synthesis of aliphatic polyesters [53,71,97]. In particular, lipases catalyze the ROP of lactones, cyclic diesters and cyclic carbonates to prepare polyesters or polycarbonates. ROP of lactones has been the most studied enzymatic polymerization. It was discovered by Kobayashi group [98] and Knani group [99] independently in 1993. Different reaction parameters were investigated, such as enzyme source, concentration, temperature and solvent. The mechanism of polymerization is also well known [51,100,101].

Since then, lactones, lactides and cyclic carbonates of ring size between 4 and 17 have been polymerized using lipases from different sources [33,54,95,102-104]. The use of enzymes has an important advantage: the activity is not limited to small and medium ring size lactones but extends to macrocyclic esters [98,99]. It was shown that the larger the lactone ring size the lower its activity in chemical ROP, while the reverse trend was observed in enzymatic ring opening polymerization [105,106]. Polyhydroxyalkanoates (PHA) can be synthesized following this approach and are important in many industrial and biomedical applications because of their biocompatibility, biodegradability and attractive mechanical properties [107,108]. Temporary prostheses, controlled drug delivery devices, resorbable implants and tissue engineering scaffolds are some of the products made from these biodegradable polymers [109].

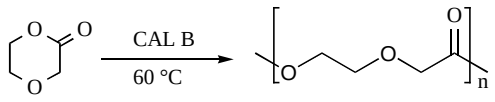
4-Membered lactones (β-propiolactone and substituted β-propiolactones) were polymerized by lipase-catalyzed ROP giving mixtures of linear polymers and cyclic oligomers with weight-average molecular weights of 2300 and 700, respectively (Scheme **3**) [110,114].



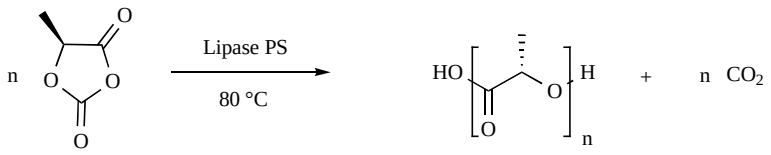
Scheme 3. Lipase-catalyzed ring opening polymerization of the 4-membered lactones.

Ring opening polymerization of the 5-membered lactone δ-butyrolactone has proved difficult, but it has been facilitated by copolymerization with other monomers [115].

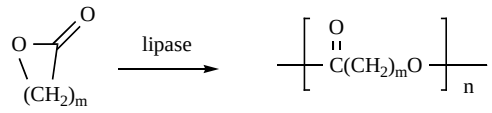
Ring opening polymerization of the 6-membered δ-valerolactone was systematically investigated by Kobayashi et al. [116,117]. It has also been possible to enzymatically polymerize other simple 6-membered lactones. Poly(1,4-dioxan-2-one) is an important biocompatible polymer with good flexibility and tensile strength, which has been widely used in biomedical applications. It has been synthesized using CAL B as catalyst and achieving M_w : 41000 [118,119].



Scheme 4. Lipase-catalyzed ring opening polymerization of the 1,4-dioxan-2-one.



Scheme 5. Lipase-catalyzed ring opening polymerization of the *O*-carboxylic anhydride derived from lactic acid.



m	Mn (g/mol)
4	19000
5	10000
6	23600
7	20700
8	16000
9	20000
10	12000
11	10600

Scheme 6. Lipase-catalyzed ring opening polymerization of the lactones with different ring size.

l-Lactide was difficult to be polymerized by lipase catalysis, however, d-lactide and a racemic mixture of d- and l-lactide have been polymerized by lipase catalysis [120,121]. Poly(l-lactide) of relatively high molecular weights (M_n up to 38400 g/mol) have also produced by *Pseudomonas* lipase-catalyzed ring opening polymerization of the *O*-carboxylic anhydride derived from lactic acid (Scheme **5**) [122].

ε-Caprolactone (ε-CL), a 7-membered lactone, is the most extensively studied to date. The ROP of ε-CL gives poly-6-hydroxyhexanoate (poly-ε-caprolactone), a semi crystalline polymer. The reaction was carried out under different reaction conditions and reaction mechanisms. Moreover, catalytic kinetics and molecular modeling have also been investigated [54,116,123-126]. Recently, it was studied the use of ionic liquids in enzymatic polymerization as an alternative solvent due to their high thermostability [127]. In order to enhance the large-scale commercial use of lipase mediated ROP, sonication has been recently evaluated. Ultrasonic irradiation of the reaction system greatly enhanced the rate of polymerization and the monomer conversion. Sonication improved the quality of the polymer produced, by enhancing its molecular weight, increasing its crystallinity and reducing its polydispersity [128].

In addition, due to the high reactivity of ε-CL, substituted ε-CLs have also been studied for lipase catalyzed ROP [117,199-131]. Enzymatic polymerization of 8-membered, 9-membered, 10-membered and 11-membered lactones has also been achieved using Novozym 435, but the lack of unique properties of these polymers, has attracted less attention [105,132].

Macrolides, larger ring-size lactones, were enzymatically polymerized, their lipase catalyzed ROP was more fast than ε-caprolactone giving M_n values greater than 10,000 g/mol (Scheme **6**) [105,132-137].

Ring opening copolymerization constitutes an alternative pathway to obtain polymers with specific desired features. For example, 15-pentadecanolide (PDL) was copolymerized by *Pseudomonas fluorescens* lipase and *Pseudomonas cepacia* lipase with other lactones such as δ-valerolactone, (δ-CL), ε-CL, 11-undecanolide (UDL) and 12-dodecanolide (DDL) [133a,138]. 15-Pentadecanolide (PDL) was also copolymerized con trimethylene carbonate [139] and 1,4-dioxan-2-one [72].

CAL B-catalyzed synthesis of copolyesters via copolymerization of three conventional monomers: a dialkyl diester (diethyl succinate), a diol (1,4-butanediol) and a lactone (PDL), has been recently reported. The syntheses were performed using a two-stage process: first step oligomerization under low vacuum followed by second step polymerization under high vacuum. The method relies on the use of vacuum to facilitate removal of ethanol by-product and to accelerate polymer chain growth, giving high molecular weight copolymers [73].

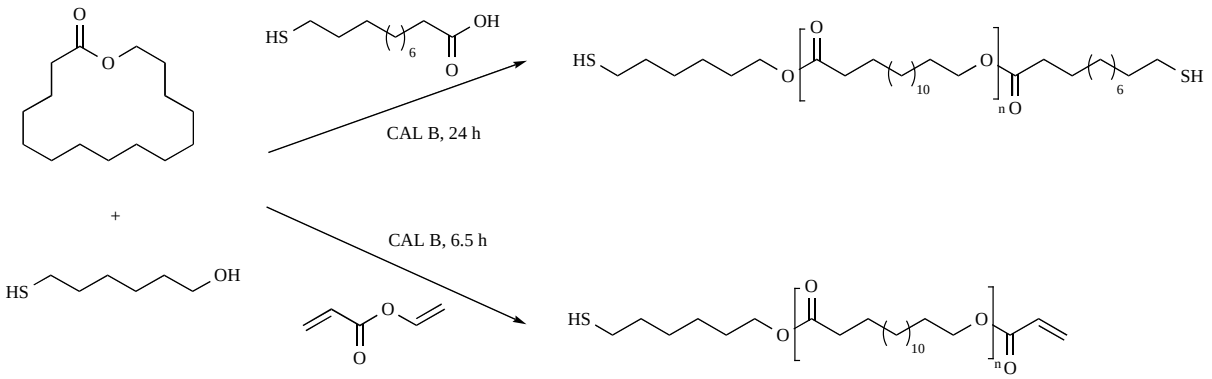
The study of end-group functionalization of polymers is of great interest because it allows preparing complex polymer with specific structures. A variety of functionalized polyesters were successfully synthesized by enzymatic ring opening polymerization using different types of functional initiators and terminators [140-142]. Thiol end groups are typically introduced in polyesters in a one-pot procedure using *Candida antarctica* lipase. For example, the synthesis of polypentadecalactone (PPDL) macromonomers containing thiols and acrylates by lipase chemistry makes it an interesting pathway to obtaining new materials [143,144].

A one-step, solvent-free enzymatic route to α,ω-functionalized polypentadecalactone (PPDL) macromonomers containing terminal thiols, acrylates, and methacrylates has been developed using *Candida antarctica* lipase B as an efficient catalyst. Difunctionalized polymers with a high fraction of thiol-thiol or thiol-acrylate end groups were obtained by mixing CAL B and PDL with equimolar amounts of functional initiator and terminator (Scheme **7**) [145].

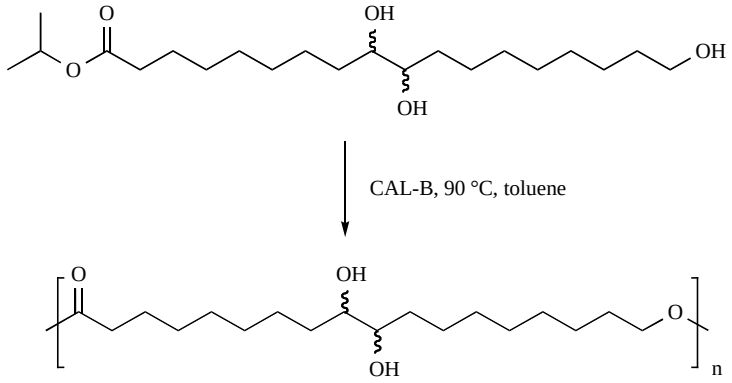
3.1.2. Polycondensation of Hydroxyacids

The step-growth polymerization is based on the condensation of hydroxyacids or mixtures of diacids or diesters and diols to form linear polyesters. As polycondensations are equilibrium reactions, removal of small molecules (water or alcohol) is required to shift the equilibrium to higher conversion. This can be achieved by azeotropic distillation of high boiling point solvents. However, the use of high boiling organic solvents is poorly compatible with formation of polymers with potential biomedical applications. Other major drawbacks of this mechanism are the high temperatures and long reaction times generally required that favor side reactions. Usually these polymerizations were carried out using acid or metals as catalysts but this is not desirable in the synthesis of materials for medical uses. Many hydrolases can be of the great utility as catalysts leading to desired polyesters under anhydrous conditions. The use of lipases as catalysts in condensation polymerization has been studied in great detail [79,100,146-154].

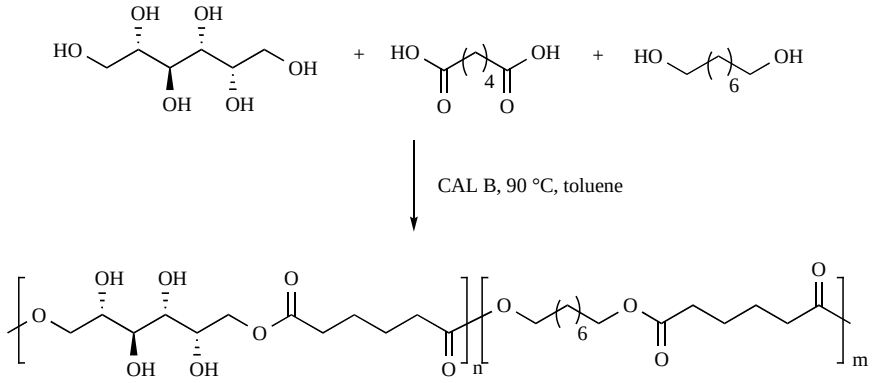
Esterification is the simplest condensation polymerization way. The lipase-catalyzed polymerization of 10-hydroxydecanoic acid is the first report about this mechanism [155]. The obtained polymer showed low molecular weight. With small hydroxyacids such as



Scheme 7. One-step, solvent-free pathway to α,ω-functionalized polypentadecalactone macromonomers with terminal thiols.



Scheme 8. Regioselective condensation of isopropyl aleuritate.



Scheme 9. Regioselective copolymerization of sorbitol, adipic acid and octanediol.

glycolic acid or lactic acid, small polymerization degree products were obtained [155,156]. Higher molecular weight products were enzymatically obtained using hydrophobic hydroxyacids. [51]. For example, a degree of polymerization of 100 was obtained in the CAL B-catalyzed polymerization of hydroxyacids with 10, 12 and 16 carbon atoms under vacuum and at high temperature [157].

Another advantage of the application of lipase catalysis in this type of polymerizations is its high regioselectivity [143,158]. Polyfunctional monomers can be directly polymerized without the use of protecting groups. For example, lipase B from *Candida antarctica* catalyzed regioselectively the polyesterification of glycerol and adipic acid leading to a polyhydroxylated low molecular weight polyester with very narrow polydispersity [16].

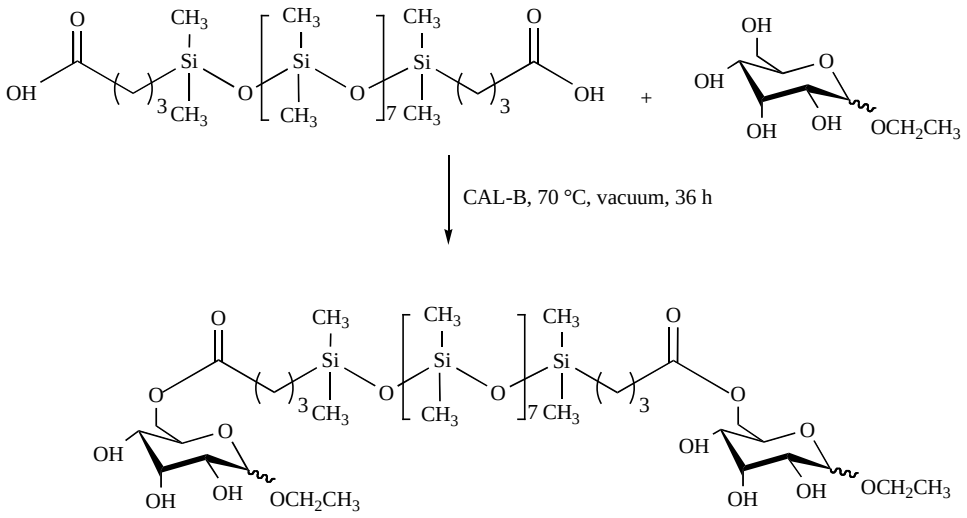
Regioselective was also observed in the CAL B-catalyzed condensation of isopropyl aleuritate, where the only primary alcohol was involved in the reaction (Scheme **8**) [136].

The Novozym 435-catalyzed copolymerization of sorbitol, adipic acid and octanediol afforded polymers with a regioselectivity of 95%. In this case the reaction also occurred predominantly at the primary alcohol groups (Scheme **9**) [160].

Moreover, enantioselectivity can also be achieved with Novozym 435: enantio-enriched polyesters were obtained from methyl 6-hydroxyheptaonoate, methyl 7-hydroxyoctaonoate, methyl 8-hydroxynonanoate and methyl 13-hydroxytetradecanoate [161].

3.1.3. Polycondensation of Diols and Diacid Derivatives

The *Aspergillus niger* lipase-catalyzed polymerization between a dicarboxylic acid and a diol producing oligomers has been firstly reported around 1984 [162]. In order to increase the degree of polymerization, the enzymatic condensation has been studied in different conditions such as ionic liquids [163,164], supercritical carbon dioxide [165] or in a solvent-free system [166,167].



Scheme 10. Lipase-catalyzed synthesis of sugar functionalized organosilicones**.**

An important aspect of condensation polymerization via transesterification is the activation of carboxylic acid group. This activation is normally carried out by esterification with alkyl, haloalkyl or vinyl groups [79,146,168]. The advantage of use of vinyl esters is that the process is irreversible and faster.

Recently, it was reported for the first time the use of lipase from *Candida sp.99-125* for polymerization of diethyl sebacate and 1,4-butanediol in the absence of organic solvents, obtaining high molecular weight poly(butylene sebacate) [169]. Poly(butylene sebacate) is a remarkable member of the polyester family and it can be used as a biodegradable thermoplastic and a biocompatible medical material [170].

The reactions were performed in two stages: first-stage reaction under atmospheric pressure followed by a second-stage reaction under vacuum process, which was crucial to produce high molecular weight polymers. By this method, the problem of phase separation normally occurring in the condensation of sebacic acid and 1,4-butanediol was avoided [169].

Poly(ε-caprolactone) (PCL), poly(dimethylsiloxane) (PDMS) and PET are some of the most commercially important polymers. PCL is a semi-crystalline homopolymer having a glass transition temperature of -60ºC and melting point in the range 59 to 64ºC, depending upon the crystalline nature and thermal history. Due to its slow biodegradation, PCL is ideally suited for long-term drug delivery [171]. PDMS has excepcional properties such as a very low glass transition temperature (-120ºC), low surface energy, high gas permeability, resistance to oxidation, biocompatibility, etc. These characteristics lead to materials for a wide range of potential applications [172,173].

Silicone polymers are of great interest because they are widely used in application as semiconductors, glasses, ceramics, plastics, elastomers, resins, mesoporous molecular sieves, optical fibers, coatings, insulators, moisture shields, photoluminescent polymers and cosmetics [174,175]. Furthermore, they have been applied in a wide range of medical devices, such as blood oxygenators, contact lenses, finger joints, catheters, blood pumps, breast implants, tubing, ophthalmologic implants, adhesives, tissue expanders and heart valves [175].

PDMS can be prepared either as a fluid, gel, elastomer, or resin depending on its structure and functionality [176]. The manufacture of these materials often requires high temperatures, high pressures or the use of caustic chemicals [177].

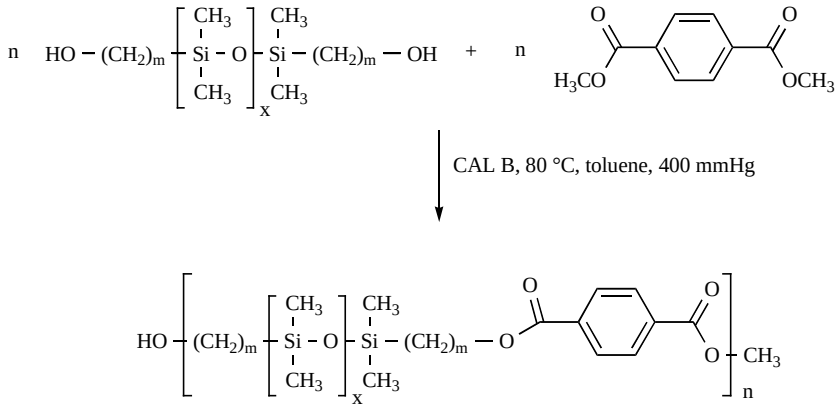
PET is a thermoplastic with excellent film forming and fiber properties [178]. Linear PDMS and PET are incompatible with respect to forming binary polymer blends. The coating or grafting of silicones onto PET fibers is an important technology for improving fiber processing and surface modification [179].

The conventional copolymerization methods to PDMS and PET copolymers shows several drawbacks associated to physical incompatibility issues and chemical issues regarding the catalysts and temperatures used [180].

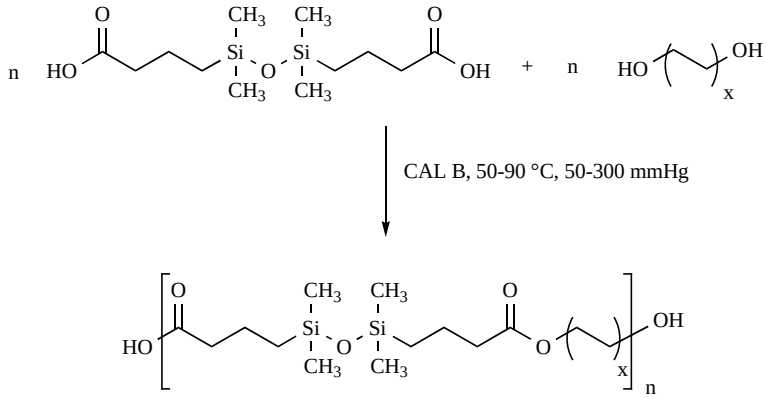
Linear silicone-modified aliphatic polyesters have been synthesized from polyols, diacids, diols, and hydroxyl-terminated PDMS via metal catalysis using titanium isopropoxide at high temperature [181]. Enzymatic catalysis is preferred to use of metals and several lipase-catalyzed polymerizations and copolymerizations of polydimethylsiloxanes have been carried out. For example, Novozyme 435 catalyzed the regioselective formation of ester bonds between organosilicon carboxylic diacids and a C1-*O*-alkylated sugar under mild reaction conditions: low temperature, neutral pH and solvent free. Specifically, the acid-functionalized organosilicones reacted with the primary hydroxyl group at the C6 position of α,β-ethyl glucoside during the regioselective esterification. The pure organosilicon-sugar conjugates were prepared in a one-step reaction without protection-deprotection steps and without activation of the acid groups (Scheme **10**) [182].

An enzymatic approach to building silicone aromatic polyesters (SAPEs) containing PDMS units into the respective polymeric chains under mild reaction conditions has been reported. Novozym 435 was used to enzymatically synthesize silicone aromatic polyesters (SAPEs) in toluene under mild reaction conditions. The SAPEs were synthesized using α,ω-(dihydroxyalkyl)-terminated poly(dimethylsiloxane). Each of the polymers was made by a transesterification reaction with dimethyl terephthalate (DMT) in toluene at 80-90 °C under vacuum (Scheme **11**) [183,184].

Several reports deal with the use of enzymes in synthesis of polysiloxanes [51,97]. Recently, it was reported the CAL B-catalyzed synthesis of silicone polyesters by the condensation polymerization of 1,3-bis(3-carboxypropyl)tetramethyldisiloxane with alkanediols (1,4-butanediol, 1,6-hexanediol and 1,8-octanediol) in the bulk under reduced pressure (Scheme **12**) [185].



Scheme 11. Lipase-catalyzed transesterification of α,ω-(dihydroxyalkyl) poly(dimethylsiloxane) with dimethyl terephthalate.



Scheme 12. CAL B-catalyzed polymerization of 1,3-bis(3-carboxypropyl)tetramethyldisiloxane with alkanediols.

Silicon-containing block copolymers are particularly interesting because of the unique properties of polysiloxanes. Recently, poly(ε-caprolactone)-block-poly(dimethylsiloxane)-block-poly(ε-caprolactone) triblock copolymers (PCL-*b*-PDMS-*b*-PCL) were synthesized via the ring opening polymerization of ε-caprolactone in the presence of 3-hydroxypropyl terminated PDMS. The resulting triblock copolymers were incorporated into epoxy thermosets in order to prepare nanostructured thermosetting blends [186].

Several authors have reported the enzymatic copolymerization of PCL and PDMS with various other monomers/polymers such as poly(ethylene glycol), alkyl diacids/diols and sugars [187].

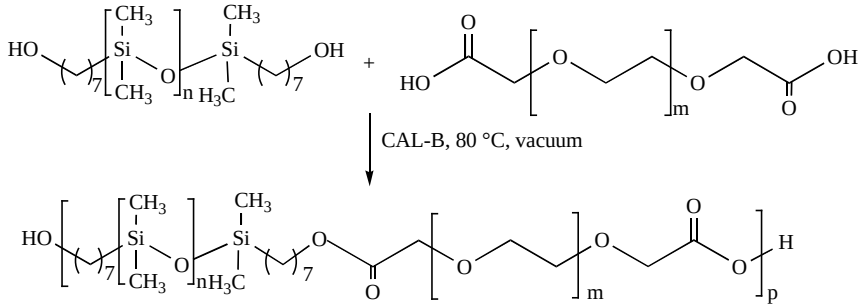
Immobilized lipase B from *Candida antarctica* was used to synthesize copolymers of poly(ε-caprolactone) (PCL) with α,ω-(dihydroxyalkyl) terminated poly(dimethylsiloxane) (PDMS). The reactions were carried out in toluene with a 1:2 w/v ratio of the monomers to solvent at 70ºC. The PCL-PDMS-PCL triblock copolymer composition was varied by changing the feed ratio of the reactants. The copolymers were semi-crystalline and the degree of crystallinity increased with the increase in the [CL]/[PDMS] feed ratio. The crystal structure in the copolymers was analogous to that of the PCL homopolymer. When the lipase was recovered and reused for the copolymerization, higher molecular weight copolymers were obtained upon a second use [188].

CAL B was also used to catalyze the condensation polymerization of two difuctional siloxane and poly(ethyleneglycol) (PEG) systems. PEG is a well known biomedical polymer with high biocompatibility and resistance to platelet and protein adsorption due to its mobility in aqueous environments [189].

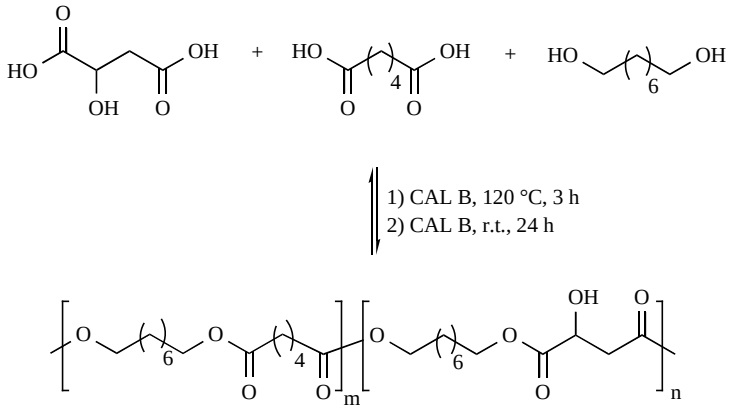
Poly(dimethylsiloxane)-poly(ethyleneglycol) (PDMS–PEG) copolymers are ideal candidates as biomaterials for wound dressing applications. PEG allows biomaterials to retain their excellent water swelling properties, whereas PDMS modifies its surface to inhibit protein adsorption [190]. However, amphiphilic PDMS–PEG copolymers were synthesized by using various metallic catalysts, which are unsuitable for biomedical applications. Recently, the enzymatic synthesis of PDMS–PEG copolymers under mild reaction conditions was carried out: 1,3-bis(3-carboxypropyl) tetramethyldisiloxane reacted with poly(ethylene glycol) (PEG) with different number-average molecular weight, and α,ω-(dihydroxy alkyl) terminated poly(dimethylsiloxane) reacted with α,ω-(diacid) terminated poly(ethyleneglycol). All the reactions were carried out without solvent at 80 °C and under reduced pressure. The thermal stability of the enzymatically synthesized copolymers was found to increase with increased dimethylsiloxane content in the copolymers (Scheme **13**) [191].

Poly(malic acid) and polyesters containing L-malic acid units are of the interest because of their remarkable advantages in temporary therapeutic applications. Many hydroxyl- or carboxyl functional pendant groups along the macromolecular chains of these polymers facilitate covalent prodrug attachment. By changing the ratios of monomers or varying the chemical structures of the pendant groups, the chemical properties of such copolymers can be adjusted for different applications [192-197].

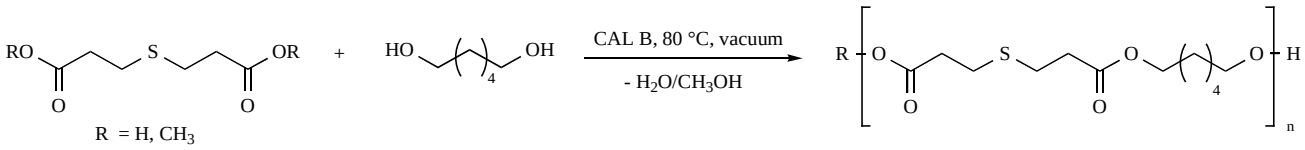
The CAL B catalyzed direct polycondensation of comonomers L-malic acid (L-MA), adipic acid (ADA) and 1,8-octanediol (OC) was reported. The selectivity of Novozym 435 led to the exclusive esterification of the malic acid carboxylic groups while leaving the



Scheme 13. Lipase-catalyzed polymerization of α,ω-(dihydroxy alkyl) terminated poly(dimethylsiloxane) reacted with α,ω-(diacid) terminated poly(ethyleneglycol).



Scheme 14. CAL B-catalyzed polycondensation of comonomers L-malic acid, adipic acid and 1,8-octanediol.



Scheme 15. CAL B-catalyzed transesterification of 3,3'-thiodipropionic dimethyl ester with α,ω–alkanediols.

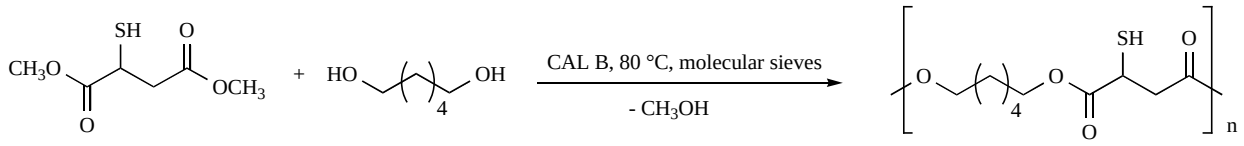
hydroxyl groups unreacted. Thus linear copolymers with each L-malic acid repeating unit along the main chain providing a hydroxyl group were prepared. The hydroxyl groups of the functional copolymers can be converted via simple chemical transformations into many other functional copolymers or directly used to conjugate bioactive molecules (Scheme **14**) [198].

Functional polyesters with antioxidative and/or antimicrobial properties are of great current interest as components of synthetic polymers for food packaging as well as cosmetical and technical applications. Such properties can be expected for sulfur-containing polycondensates such as polythioesters or polythioethers [199]. 3,3'-Thiodipropionic acid and other α,ω-thia-alkanedioic acids may also be used as starting materials for the enzyme catalyzed preparation of polyesters containing thioether or disulfide groups [200].

Sulfur-containing polythioesters can be prepared using microbial lipases as biocatalysts [201-203]. One important disadvantage of polythioesters is that they are persistent to microbial degradation [204,205], whereas the analogous polyoxoesters are degraded by microbial hydrolases [204,206,207]. It has been found that copolymeric polyesters may be more easily decomposed by microbial hydrolases than polythioesters [208,209]. Recently, it was developed an enzymatic process for the preparation of such functional polycondensates with antioxidative and antimicrobial properties by esterification and transesterification of 3,3'-thiodipropionic acid and its dimethyl ester, respectively, with α,ω–alkanediols. The Novozym 435-catalyzed reactions were carried out in mild conditions: moderate temperatures, solvent free, without drying agents and using slightly reduced pressure to remove reaction water or methanol. Under these conditions the preparation of such linear copolymeric polyoxoesters containing thioether functions does not require any material with deleterious effects on health and environment (Scheme **15**) [210].

Under similar conditions a copolymeric polyoxoesters containing branched-chain methylenethiol functions, i.e., poly(1,12-dodecanedioic acid-co-1-thioglycerol) and poly(diethyl 1,12-dodecanedioate-co-1-thioglycerol) was also obtained by Novozym 435-catalyzed polyesterification and polytransesterification of 1,12-dodecanedioic acid and diethyl 1,12-dodecanedioate, respectively, with 1-thioglycerol (3-mercaptopropane-1,2-diol) [211].

The polycondensation of hexane-1,6-diol and dimethyl 2-mercaptosuccinate using an enzyme as a catalyst was studied with the objective of synthesizing a polyester with free pendant mercapto groups. 1,6-Diol and dimethyl 2-mercaptosuccinate were readily polymerized by *Candida antarctica* lipase in bulk in the presence of molecular sieves 4 Å to produce the corresponding polyester with free pendant mercapto groups. The enzymatic polycondensation occurred selectively between the hydroxyl groups of hexane-1,6-diol and the carboxyl groups of dimethyl 2-mercaptosuccinate. The



Scheme 16. CAL B-catalyzed polymerization of 1,6-diol and dimethyl 2-mercaptosuccinate.

polymerizability of dimethyl mercaptosuccinate was independent of its stereochemistry, whereas the polycondensation of hexane-1,6-diol and dimethyl malate was strongly influenced by the stereochemistry of the latter. The polyester with pendant mercapto groups was rapidly cross-linked by air oxidation of the thiols to disulfides in DMSO (Scheme **16**) [212].

3.2. Lipase-Catalyzed Synthesis of Polycarbonates

3.2.1. Ring Opening Polymerization of Carbonates

Polycarbonates have attracted much attention due to their biodegradability, biocompatibility, and non toxicity. Moreover, the presence of hydrophilic functional groups enhances their biodegradability [213-218].

Lipase-catalyzed ROP is also an interesting alternative to prepare polycarbonates. Hydroxyacids are considered a highly convenient raw material because of their natural abundance and functional diversity.

In particular, L-tartaric acid has been extensively used in organic synthesis as a source of chirality, but its application in polymers has been somewhat limited to the synthesis of polyamides [217,218], polyesters [219], polyurethanes [220,221] and polycarbonates [222-224]. Degradable tartaric acid-based polymers have been prepared by condensation polymerization, which is limited by the removal of the condensate. Therefore ROP is a good alternative method to condensation starting from cyclic monomers.

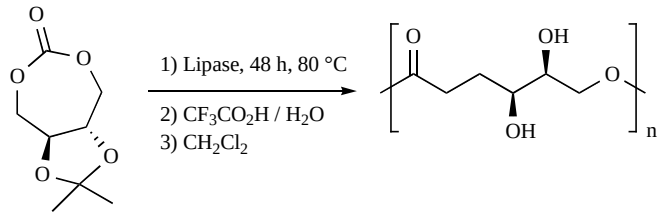
After the polymerization of the first cyclic carbonate, trimethylcarbonate (TMC), by ring opening polymerization by CAL B [225] and porcine pancreas lipase (PPL) [226], a variety of polycarbonates have been synthesized in order to search enhanced properties, such as hydrophilicity, permeability and mechanical properties [100,227-229].

Some synthesis of different polycarbonates via lipase-catalyzed ring opening polymerization of cyclic carbonate monomers have been reviewed recently [71].

Five- and six-membered cylic carbonate monomers have been polymerized via conventional chemistry or enzymatic ROP [34,54,105,106,134,230-232]. However, the polymerization of five-membered cyclic carbonates usually is associated with extensive decarboxylation [233].

Six-membered cyclic carbonates and its derivatives are the most studied and have been polymerized by anionic, cationic, and enzymatic catalysts [54,134,230-232]. Although aliphatic ROP of larger ring size carbonates have been reported in literature [234,235], there are only a few examples of polymerization of seven-membered cyclic carbonates.

Enzyme-catalyzed ROP presents the advantage to proceed without any decarboxylation. Seven-membered monomers are of great interest because of its higher polymerizability compared to smaller size ring carbonates. Recently, Bisht and coworkers have reported the first enzymatic ring opening polymerization of a seven-membered cyclic carbonate derived from tartaric acid [236]. The highest number-average molecular weight and optically active polycarbonate was obtained with the lipase Novozyme 435 (Scheme **17**).



Scheme 17. Enzymatic ring opening polymerization of a seven-membered cyclic carbonate derived from tartaric acid.

Unlike lactones, it was observed that large-sized cyclic carbonates show a low reactivity in ring opening polymerization [237]. Then, an alternative pathway to prepare polymers with the desired properties is copolymerization.

The presence of carbonate units in poly(carbonate-co-esters) has the advantage to generate neutral products of degradation, such as CO_2 and aliphatic diols. Cyclic carbonates have been polymerized with different cyclic monomers. For example, Novozym 435-catalyzed copolymerization of ω-pentadecalactone (PDL) and TMC was reported to yield highly crystalline poly(PDL-co-TMC) [139].

Recently, *Candida antarctica* lipase B-catalyzed synthesis of poly (ω-pentadecalactone-co-butylene-co-carbonate) (PPBC) via ring opening was reported [82]. The copolymerizations of diethyl carbonate (DEC), 1,4-butanediol (BD) and PDL were performed in two steps: first-step oligomerization under low vacuum followed by second-step polymerization under high vacuum (Scheme **18**).

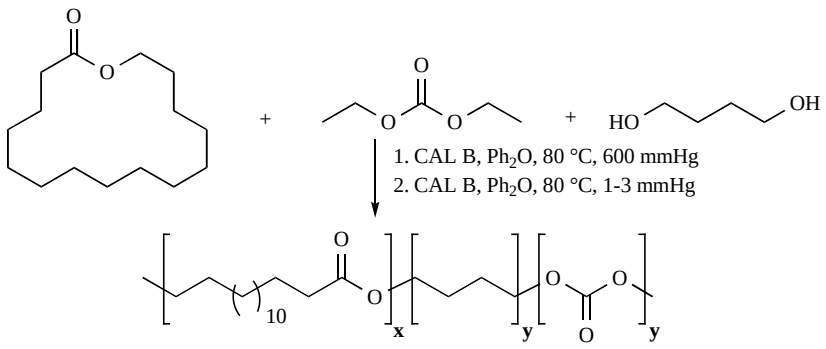
3.2.2. Polycondensation of Diols and Dialkylcarbonates

Aliphatic polycarbonate polyols have a wide range of potential applications and can be designed to be biodegrade when placed in the appropriate environment [238-240].

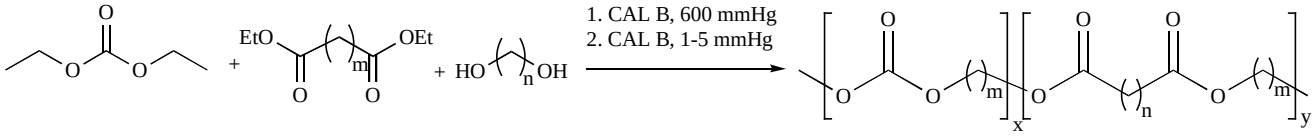
The additional free hydroxyl functional groups in polycarbonate polyols provide sites for attachment of dyes, flame retardants, bioactive molecules, or cross-linking of materials. In addition, polycarbonate polyols are already in use as intermediates in the manufacture of polyurethanes for high-performance coating applications [241,242].

Aliphatic polycarbonates are produced chemically through polycondensation of aliphatic diols with dialkyl carbonates, cyclic glycol carbonates, or diphenyl carbonates. But these synthetic methods show some disadvantages such as the presence of metal residue in the final polymer, severe reaction conditions and undesirable side reactions.

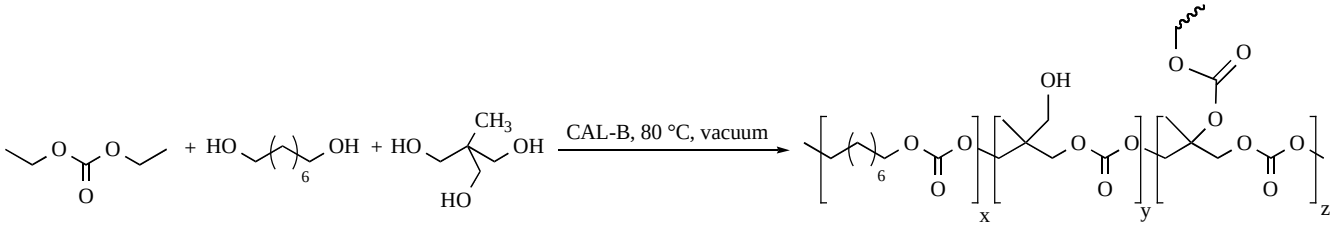
A desirable, environmentally benign method for preparing aliphatic polycarbonates is via enzyme-catalyzed polycondensation routes using dialkyl carbonate and diol as substrates. For example, polycarbonate synthesis using CAL B as catalyst from diethyl carbonate and different long chain diols (C3-C8) monomers was reported [243,244].



Scheme 18. CAL B-catalyzed synthesis of poly (ω-pentadecalactone-co-butylene-co-carbonate).



Scheme 19. CAL B-catalyzed polycondensations from diethyl carbonate, diesters and diols.



Scheme 20. CAL B-catalyzed terpolymerization of diethyl carbonate, 1,8-octanediol, and tris(hydroxymethyl)-ethane.

Most recently, high molecular weight poly(hexamethylene carbonate) (PHC) was synthesized via condensation of diethyl carbonate with 1,6-hexanediol catalyzed by immobilized *Candida antarctica* Lipase B. Polymerizations were performed by a first stage oligomerization at low vacuum (600 mmHg pressure) followed by a second stage polymerization under high vacuum (1-5 mmHg pressure). Enzymatic polycarbonate synthesis was performed in diphenyl ether and solvent free [245].

High molecular weight and low polydispersity poly(butylene carbonate-*co*-butylene succinate) and poly-(hexamethylene carbonate-*co*-hexamethylene adipate) were obtained via CAL B-catalyzed polycondensations from diethyl carbonate and the corresponding diesters and diols. By adjusting reactant stoichiometry, poly(carbonate-*co*-ester) macromers containing predominantly hydroxyl end groups were synthesized. Furthermore, aliphatic poly(carbonate-*co*-esters) has been also synthesized through transesterification of aliphatic polycarbonates with polyesters using CAL B catalysis. The transesterification method allowed formation of both random and block copolymers (Scheme **19**) [83].

Very recently, it was reported the first study describing an enzyme catalyzed pathway to polycarbonate polyols. With CAL B as catalyst, terpolymerizations of diethyl carbonate, 1,8-octanediol, and tris(hydroxymethyl)-ethane were performed at 80 °C using a pressure-varied two-stage process to minimize evaporative loss of diethyl carbonate. Varying the reaction conditions, both linear low molecular weight polycarbonate polyol prepolymer and high molecular weight branched polycarbonate polyols were prepared. The described two-stage synthesis allowed control of the polymer molecular weight, degree of branching, and free hydroxyl content (Scheme **20**) [246].

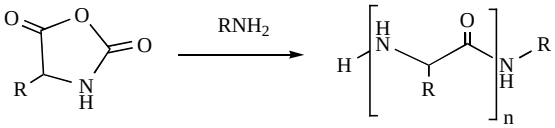
3.3. Lipase-Catalyzed Synthesis of Polyamides

As a general rule, polyamides are polymers containing recurring amide groups -CONH-. Among polyamides a distinction has to be made and they can be classified into two groups. The first one corresponds to polyamides that include all synthetic polymer that contain amide bonds, for example the commercially successful nylon 6,6. The second group is formed by the polypeptides which are made from α-aminoacids. β-Peptoids, obtained from β-aminoacids, can also be considered as part of this second group.

Polyamides such as nylons are produced in industry by amidation of dicarboxylic acid with diamines, self- amidation of amino acids or ring opening polymerization of lactams. Their synthesis consumes a lot of energy as polymerizations are usually carried out at temperatures higher than 200°C. Under these conditions the processes are complicated since thermal degradation reactions lead to cyclization, changes in the balance of reactive end groups, branching and eventual gelation [247]. These chemical changes have a harmful effect on the final product quality in terms of processability, physical properties, and the presence of undesirable degradation products in the polymer.

Polypeptides are a class of polyamides with a wide variety of functions in living nature. They are part of the structure of living bodies (i.e. hairs, nails, tendons and muscles), regulate biological reactions (hormones, enzymes) and are used in construction (spider silk, mussel attachment fibers). The variety in structure and function combined with the biodegradability has made polypeptides

interesting compounds for application in cosmetics [248], medicine [249] and fabrics [250]. The ring opening polymerization of α-aminoacid-*N*-carboxyanhydrides (NCA's) is the preferred method for the *in vitro* polymerization of α-amino acids. Although this method provides great control over chain length and composition a major drawback in the production of NCA's is the use of toxic phosgene compounds (Scheme **21**) [251].



Scheme 21. Ring opening polymerization of α-aminoacid-*N*-carboxyanhydrides.

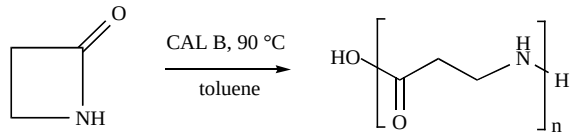
The drastic conditions required in the synthesis of polyamides can be avoided by using enzymes as catalysts. By reducing energy consumption, waste production and the use of toxic chemicals, enzymes can offer a green alternative for conventional processes to produce polyamides involving high temperatures (>200 °C) and thus preventing the undesired thermal degradation and toxic chemicals like phosgene in peptide synthesis.

In analogy with the synthesis of polyesters, two main approaches were involved in the lipase-catalyzed synthesis of polyamides: ring opening polymerization of lactam rings and condensation of diesters with diamines.

3.3.1. Ring Opening Polymerization of Lactams

Although CAL B proved to be successfully used for the synthesis of polyesters from cyclic starting materials as it was above mentioned in this work, little has been reported on the preparation of polyamides catalyzed by this enzyme [252].

Schwab et al. have described the first approach for a synthesis of unbranched poly(β -alanine), nylon 3, by enzymatic ring opening polymerization starting from unsubstituted β -lactam (2-azetidinone, β -propiolactam) (Scheme **22**). A low molecular weight product was obtained with an average degree of polymerization limited to DP: 8 by its solubility in the reaction medium [253].



Scheme 22. Enzymatic synthesis of poly(β-alanine).

The enzymatic hydrolysis of β−lactams is a convenient method to obtain enantiomeric pure β−amino acids but the number of lipases available for this reaction is limited due to the irreversible binding of β-lactams to the serine in the active site of some lipases and proteases [254]. For this reason β−lactams are used in antibiotics such as peniciline. *Candida antarctica* lipase B is not inhibited by lactams and it is capable of performing the enantioselective ring opening of β-lactams without deactivation as shown by Fülop and coworkers [255].

Regarding to application of CAL B in lactam polymerization, from a collection of lactam rings with 4, 6, 9 and 13 members only the 4-member ring, β-propiolactam, was a good substrate. The polymerization was performed in toluene at 55°C for 96 h and it was necessary to dry CAL B before use. It proceeded with poor yield and with a maximum chain length of only 18 units and an average length of 8. Only β-propiolactam was a suitable monomer in CAL B catalysis and the other possible monomers such as β-alanine and β-alanine ethyl ester did not give satisfactory results.

With the purpose of understanding the mechanism of CAL B-catalyzed ring opening polymerization of lactams, that appeared to be different from that proposed for lactones, the molecular basis of the ring opening reaction of β-lactam ring and the elongation of the monomer toward a poly(β-alanine) was studied by computational simulation. Molecular modeling techniques using docking tools, molecular dynamics, and QM/MM procedures were employed. As a result, it was proposed a catalytic cycle for the oligomerization of β -lactam that rationalizes the activation of the monomer, the chain elongation by additional β -lactam molecules, and the termination of the polymer chain [256].

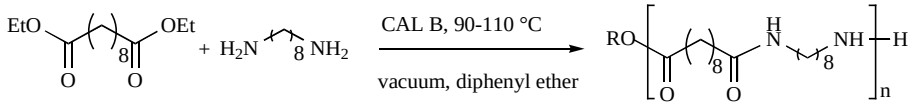
3.3.2. Polycondensation of Diamines and Diacid Derivatives

The production of polyamides by condensation involves the reaction between amines and esters, through a nucleophilic acyl substitution in the ester by the amino group of the amine. Lipases can be used to catalyze aminolysis and ammonolysis reactions for the preparation of different amides and for the chiral resolution of esters, amines, and aminoalcohols in organic solvents [257]. The lipase-catalyzed aminolysis of a variety of esters through *Rhizomucor miehei* lipase and the immobilized *Candida antarctica* lipase B catalysis [258-262] was reported. Other lipases and esterases can be employed in these reactions but are less versatile in substrate tolerance and stability towards organic solvents [20,263].

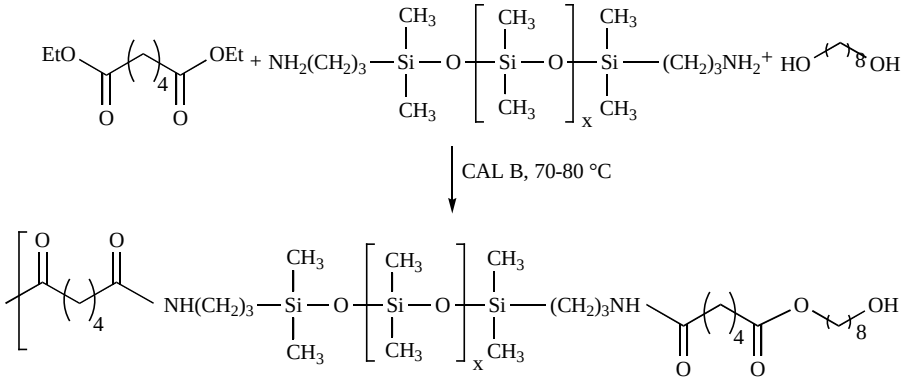
However, to the best of our knowledge the obtention of polyamides from polycondensation reactions between diesters with alkyl diamines using a lipase as a catalyst has not been well studied. This could be attributed to two reasons: a) due to their high melting point (Tm), intermediates of the reaction can solidify before growing to long chains and b) the polyamides can only be dissolved in strongly acidic solvents such as concentrated H_2SO_4, trifluoroacetic acid, etc. [264]. Literature reports about the influence of temperature on the conversion and molecular weight of lipase-catalyzed ROP to obtain polyesters, show that the activity of the lipase depends on the substrate as well as on the reaction conditions. Therefore, at high temperature and low pH, enzymes cannot display their catalytic activity.

Among the few reported examples, Cheng and Gu published the solvent free polycondensation of diethylene triamine with dialkylesters. They showed that different lipases catalyze the polymerization at temperatures from 50 to 90 °C resulting in polyamides with Mw of 3,000−15,000. In their experiments a high temperature and a nitrogen flow assisted the removal of the leaving group (methanol) in favor of the uncatalyzed reaction [265].

Polyamides such as nylon-8,10, nylon-8,13, nylon-6,13 and nylon-12,13 with M_n about 5000 were synthesized in two or three steps using CAL B lipase as a biocatalyst and the corresponding diesters and diamines Scheme **23** [266].



Scheme 23. CAL B-catalyzed polycondensation reaction between DES and DAO.



Scheme 24. CAL B-catalyzed polymerization of diethyl adipate, 1,8-octanediol, and α,ω-(diaminopropyl) poly(dimethylsiloxane).

To demonstrate the mechanism and to predict the reaction rate of lipase-catalyzed polycondensation reactions between 1,8-diaminooctane (DAO) and diethyl sebacate (DES), kinetic studies were performed. Moreover, single setp polycondensation between DES and DAO were carried out in the range of 60 to 150°C to study CAL B activity at different temperatures. This work also reported an enzymatic method to produce a new series of poly(amide-co-ester)s.

In the field of copolymers, silicone polyesteramides have been prepared by various methods in the last years. Silicone-based polymers can be used in numerous applications due to their versatile and unique properties. Among polysiloxanes, PDMS is one of the most widely investigated materials that is also recognized for its biocompatibility [267]. Haupt *et al.* described the synthesis of water-soluble PDMS with pendant sugar moieties for potential biomedical applications [268]. These polymers have both a hydrophobic backbone, providing chemical and biological stability, and natural hydrophilic saccharide side-chain residues (glycopolymers) that enable tailoring of amphiphilic character and bioactivity [269].

Generally, siloxane-based copolymers and polyamides are synthesized by chemical methods, under harsh conditions, that promote uncontrolled redistribution and side reactions [270]. High polymerization temperatures and acid/base catalysts cause decomposition of useful functional groups. The use of coupling reagents, such as dicyclohexylcarbodiimide, due to work under mild reaction conditions, can preserve sensitive moieties. However, they are inefficient since they require one molecule of coupling agent per bond forming step and are not regioselective.

Gross and coworkers reported for the first time the enzymatic synthesis of polymers consisting of organosilicone esters or amides prepared by enzyme catalysis [271]. In one example, a reaction between dimethyl adipate and a diamine disiloxane, performed in bulk at 70 ℃ for 12 h and catalyzed by CAL B, afforded an organosilicone polyamide with M_n = 2100.

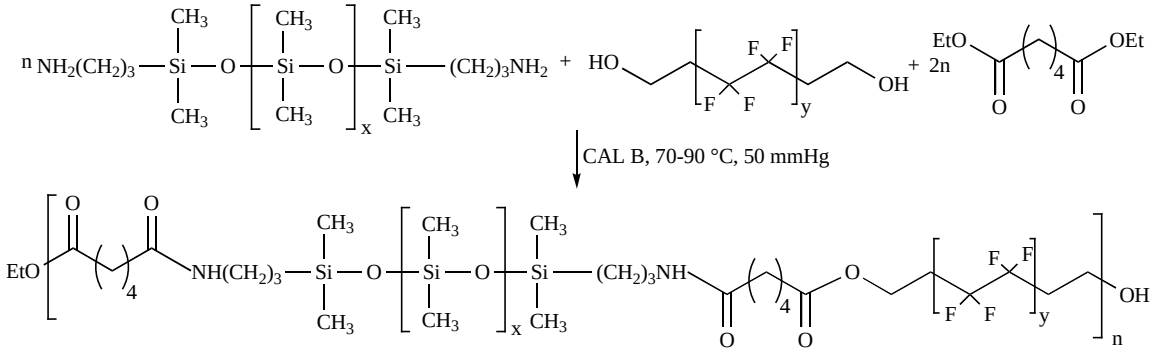
Later, Sharma and co-workers have reported the lipase-catalyzed synthesis of aliphatic polyesteramides with poly-(dimethylsiloxane) blocks in the bulk at 70 °C under reduced pressure (10-20 mmHg). In this system immobilized *Candida antarctica* lipase on macroporous acrylic resin beads was used as the enzyme under mild reaction conditions to perform the polycondensation reaction using various feed mole ratios of diethyl adipate, 1,8-octanediol, and α,ω-(diaminopropyl) poly(dimethylsiloxane). M_n values ranged from 6 to 11 kDa (Scheme **24**) [180].

This approach was extended to the synthesis of silicone fluorinated aliphatic polyesteramides (SFAP) [272]. In this work fluorosilicones have fluorocarbons alternating with the siloxane segments in the main chain. The fluorosilicones are synthesized by conventional chemistry techniques based on the condensation of silanes and chlorosilanes, under harsh conditions and employing platinum based materials or strong mineral acids or bases as catalysts. Furthermore, for biomedical and pharmaceutical applications, the use of multiple steps for residual catalyst removal may be required. Following the enzymatic approach the SFAPs were synthesized by incorporating both the fluorinated aliphatic segments and the dimethylsiloxane segments into the same linear chain backbone. Immobilized lipase B from *Candida antarctica* was used to catalyze the reactions to prepare fluorosilicones containing both amide and ester linkages. Simultaneous reactions of an amidation between α,ω -aminopropyl terminated poly(dimethylsiloxane) (APDMS) and diethyl adipate (DEA) and a transesterification between diethyl adipate and different fluorinated alkanediols (FADs), respectively were conducted. The condensation reactions were carried out in the bulk, in the temperature range 70-90 °C and under reduced pressure (50 mmHg), obtaining the highest molar mass fluorosilicones around of 27 kDa with the 3,3,4,4,5,5,6,6-octa-fluoro 1,8-octanediol monomer (Scheme **25**).

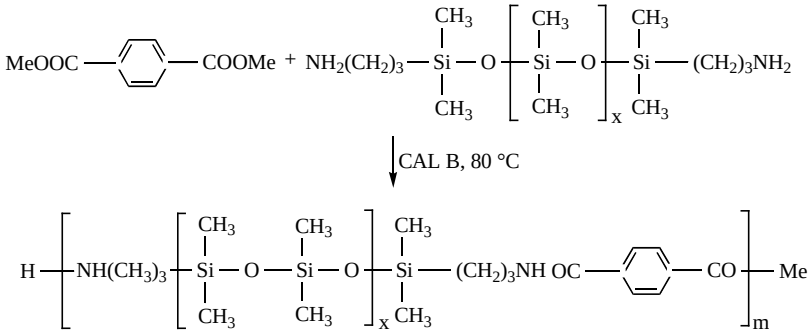
Candida antarctica lipase B was used to enzymatically synthesize silicone aromatic polyesters (SAPEs) and silicone aromatic polyamides (SAPAs) in toluene under mild reaction conditions (Scheme **26**) [183].

SAPAs were synthesized using α,ω-(diaminopropyl)-terminated poly(dimethylsiloxane) (APTPDMS, having two different molar masses, Mn, 1000 and 4700 g mol^{-1}, respectively). Each of the polymers was made by a transesterification reaction with dimethyl terephthalate (DMT) in toluene at a temperature in the range of 80-90 °C under vacuum. Toluene was employed as the solvent in order to solubilize the DMT in the reaction mixture. The methanol by-product was recovered from the reaction mixture along with the toluene by applying vacuum, and thus the transesterification reaction was driven forward.

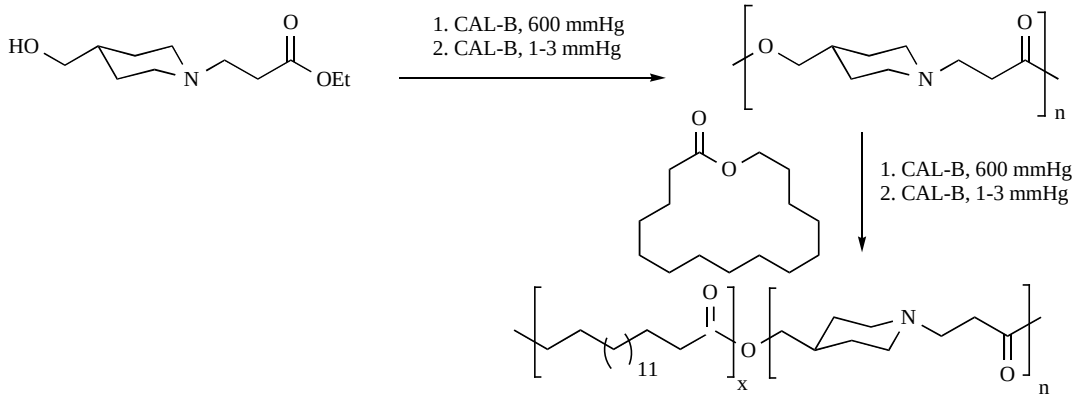
Cationic, amino-bearing polymers are important materials that can serve as non-viral vectors for gene delivery to treat various genetic disorders, including cancers [273]. These polymers are capable of condensing plasmid DNA via electrostatic interactions to form nanometer-sized polyelectrolyte complexes (polyplexes) or solid nanoparticles, protecting DNA against extracellular nuclease degradation, and facilitating transportation of DNA into cell compartments through cellular barriers [274]. Among cationic polymers



Scheme 25. Lipase-catalyzed synthesis of silicone fluorinated aliphatic polyesteramides.



Scheme 26. Lipase-catalyzed polyamidation of α,ω-(diaminopropyl)-terminated poly(dimethylsiloxane) with dimethyl terephthalate.



Scheme 27. Lipase-catalyzed EHMPP polymerization and EHMPP-PDL copolymerization.

which have been proposed and evaluated for gene transfection applications, poly(β-aminoesters) (PBAEs) and polyamidoamines (PAAs) have been synthesized by enzymatic procedures. Polyesters containing tertiary amino substituents are specially promising due to their biodegradability, low cytotoxicity and excellent transfection efficiency [275]. PBAEs can be prepared via conjugate addition between diacrylate and amine comonomers or by using expensive and unstable acid chloride such as the synthesis of poly(*N*-methyldiethyleneamine sebacate) with sebacoyl chloride and *N*-methyldiethanolamine.

Recently, a lipase-catalyzed synthesis of a novel poly(β-aminoester) derived from an ω-hydroxy-β-amino ester monomer (ethyl 3-(4-(hydroxymethyl)piperidin-1-yl)propanoate (EHMPP)), and poly(lactone-co-β-amino ester) copolymers was reported [276]. EHMPP was prepared under mild conditions via Michael addition of 4-piperidinylmethanol with ethyl acrylate. Later, through a lipase-catalyzed condensation polymerization, EHMPP afforded poly [3-(4-(methylene)piperidin-1-yl)propanoate] (poly(MPP) or PMPP) with Mw: 13200. Ring opening and condensation copolymerization of EHMPP with ω-pentadecalactone (PDL) yielded novel poly(PDL-co-MPP) copolymers. Depending on PDL:EHMPP feed ratio the copolymers showed M_w from 15900 to 27200 Da. PMPP and poly(PDL-co-MPP) are a new type of biodegradable poly(β-aminoesters) that are potentially useful biomaterials for specific biomedical applications such as gene delivery (Scheme **27**).

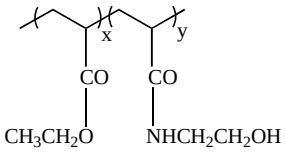
3.3.3. Polyaddition

In the last years, the promiscuous behavior of lipases has been studied by several research groups [56-59]. Lipase-catalyzed reactions involving ethyl acrylate and alkanolamines were studied in

detail. It has been observed that the products and reaction mechanisms depended on various parameters, such as lipase nature, concentration of reactants, etc. So, lipase-catalyzed reaction between ethyl acrylate and ethanolamine afforded β-aminoesters [258] and hydroxyalkylacrylamides [267,268], useful as monomers as described in Section 4 of this review, and also acrylic materials and polyamidoamines.

Binary and ternary polymers of hydroxyalkylacrylamides, ethyl acrylate and acrylic acid, known as hydrophobically modified polyacrylamides, have attracted increased interest over the past decades due to their biomedical applications [277]. This family of polymers is generally obtained by micellar radical polymerization and reversible addition-fragmentation chain transfer (RAFT) polymerization [278,279]. The polydispersity of the products synthesized by these methods is between 3.1 and 5.8 depending on time of reaction.

With the aim to decrease the polidispersity of this type of materials, several acrylic copolymers containing, at random, sequences of poly(ethyl acrylate) and poly(*N*-(2-hydroxyethyl)acrylamide) were synthesized through an enzymatic way using *Candida antarctica* lipase B [280]. The hydrophobically modified polyacrylamides were obtained from ethyl acrylate as the only monomer starting material in a chain polymerization process (Scheme **28**).



Scheme 28. Hydrophobically modified polyacrylamides.

In the presence of ethanolamine, the enzyme not only catalyzed the chain polymerization of ethyl acrylate but also the aminolysis of the pendant ester groups. Scheme **29** shows a possible enzymatic way in the formation of the copolymers.

The products showed low molecular weight and high monodispersity. The behavior of the lipase constitutes a new example of enzymatic catalytic promiscuity. Other enzymes, such as horseradish peroxidase, have been used to catalyze addition polymerizations of commodity vinyl monomers [281-283], but at this moment, this is the only report of lipase-mediated vinyl monomer polymerization.

Polyamidoamines (PAMAMs) are a family of polymers with interesting properties that can be exploited in biomedical applications [284]. These polymers are generally non toxic and contain hydrolyzable bonds in their main backbone that allow degradation in aqueous media within days or weeks depending on their structure. Due to their versatile chemical structure and functionality, as well as to their variable aggregation behaviour in solution, such as the formation of micelles or vesicles, PAMAMs are applicable as carriers for the delivery of various products with biological activity [285]. Moreover, PAMAMs have a tremendous water solubilizing power, therefore, even complexes with extremely insoluble drugs are highly water soluble [286].

Regarding to the synthesis of linear polyamidoamines (PAAs), which can be considered as linear analogs of the important family of PAMAM dendrimers, a large library of them has been designed and prepared for various biological applications [287]. However, the full potentials of these polymers cannot be fully exploited, since they are usually synthesized via polyaddition reactions. Due to the statistical step-growth mechanism, products with a polydispersity ~ 2 are obtained and the amido- and amino groups are, in part, irregularly arranged along the macromolecular chain [288].

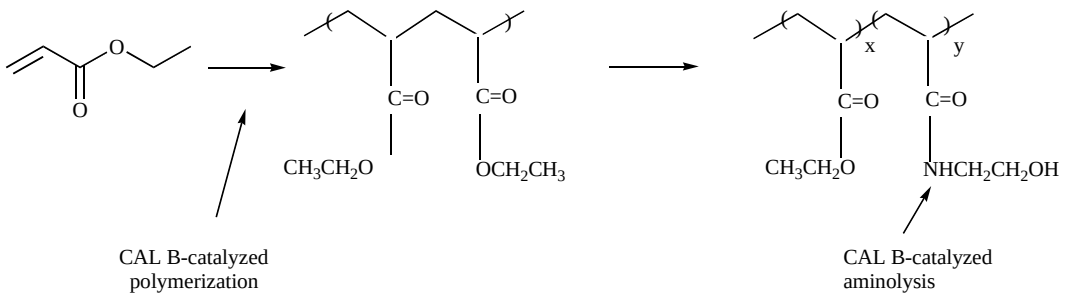
A straightforward strategy for the direct synthesis of well-defined PAAs by using enzymes as biocatalysts in a clean and easy procedure was reported [289]. By polymerization of ethyl acrylate with *N*-methyl-1,3-diaminopropane, catalyzed by immobilized *Candida antarctica* lipase B, a low molecular weight polyamidoamine with a high monodispersity was obtained. Moreover, it is interesting to remark its well-defined arrangement along the macromolecular chain with a novel repetitive unit containing only one amide function (Scheme **30**).

The enzymatic catalysis is highly regioselective. A two-step mechanism was proposed: in the first CAL B catalyzes the synthesis of the acrylamide monomer by aminolysis of ethyl acrylate by the primary amino group of *N*-methyl-1,3-diaminopropane. Then, in a second step the acrylamide is polymerized through a lipase-catalyzed aza-Michael addition (Scheme **31**).

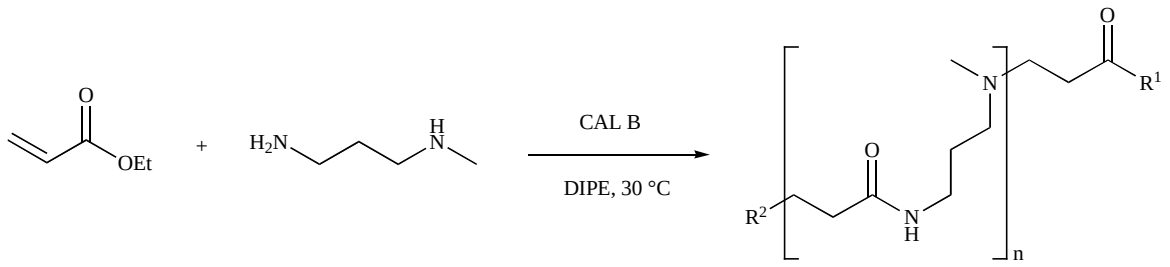
4. LIPASE-CATALYZED SYNTHESIS OF MONOMERS

Generally the monomers used in biocatalytic polymerization are not different from those used in polymerizations carried out by traditional methods such as diacids, diols, diesters, diamines, vinyl monomers, etc. For this reason, literature about lipase-catalyzed synthesis of monomers is limited. Lipases have been applied as useful catalysts in the synthesis of special monomers containing sensitive groups towards acid medium and harsh conditions and particularly in the selective synthesis of chiral monomers and natural products derivatives. In this section some examples of lipase application to the synthesis of this kind of monomers will be described.

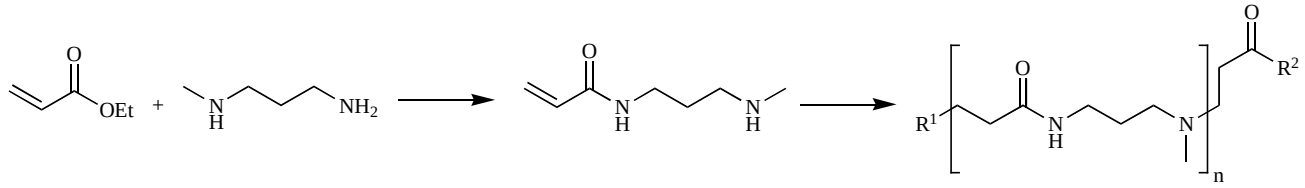
Beginning with chiral diacids as monomers for polycondensation, it is interesting to mention the lipase-catalyzed synthesis of optically active 2,4-dihydroxyglutaric acid. The application of this acid has been limited so far by the lack of efficient methods for the



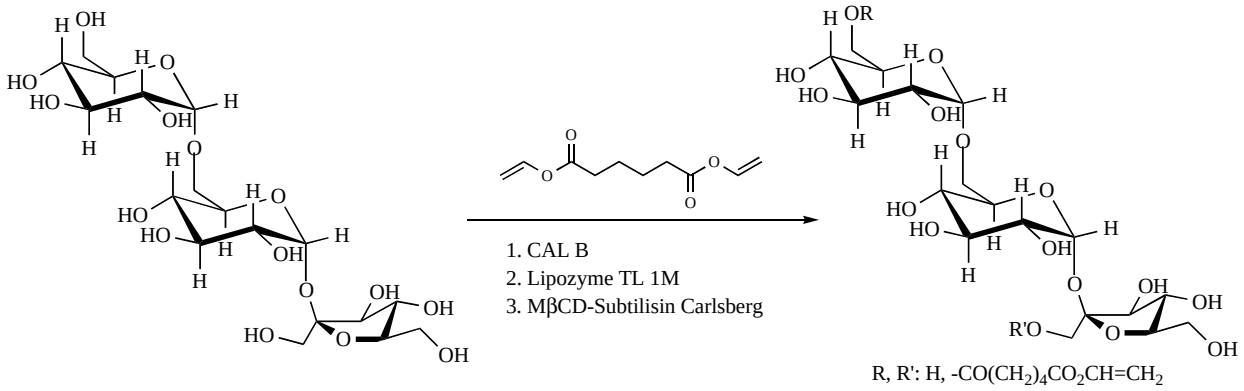
Scheme 29. Possible enzymatic ways in the formation of the copolymers.



Scheme 30. CAL B-catalyzed polymerization of ethyl acrylate and *N*-methyl-1,3-diaminopropane.



Scheme 31. Possible enzymatic route for obtaining polyamidoamines.



Scheme 32. Enzymatic transesterification of raffinose with divinyl adipate.

preparation of the two enantiomeric forms. The enzymatic method uses a lipase-catalyzed kinetic resolution of diol anti and a desymetrisation of diol meso [290].

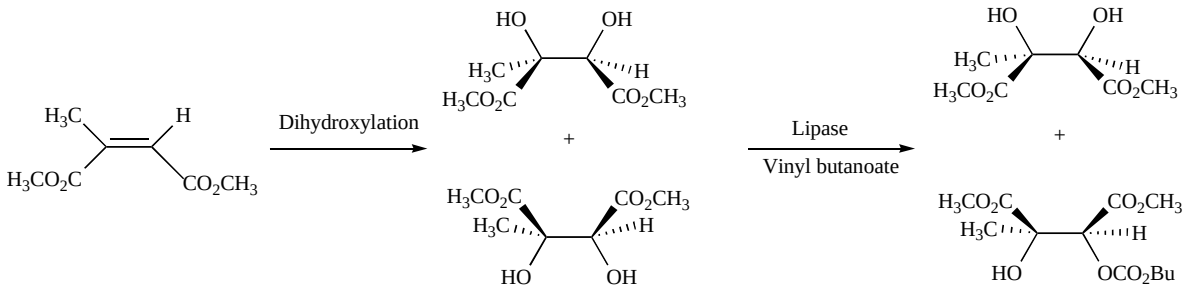
As another example involving glutaric acid derivatives, the lipase-catalyzed synthesis of diesters of 2-oxo-glutaric acid was reported [291]. The treatment of 2-oxoglutaric acid with several primary alcohols in the presence of CAL B afforded the corresponding 2-oxoglutarate dialkyl esters in almost quantitative yields. The preparation of these compounds had been previously reported according to the known chemical procedures by refluxing the acid with the corresponding alcohol in toluene with p-toluenesulfonic acid as a catalyst. Due to α-ketoacids, such as 2-oxoglutaric acid, undergo decarboxylation fairly readily, yields were poor. The enzymatic procedure improved remarkably this result. Higher chain diesters of 2-oxoglutaric acid were also prepared through a lipase-catalyzed procedure using *Carica papaya* lipase which is a very economic auto-immobilized biocatalyst derived from agrowastes, available on a large scale [292].

Synthetic polymers containing sugar branches have attracted considerable interest due to their role as biomimetic analogues, their potential for commercial applications and their biodegradability [293]. Commercially available lipases were screened for their ability to acylate regioselectively sucrose and trehalose with divinyladipic acid ester. Lipase B from *Candida antarctica* catalyzed the synthesis of sucrose 6, 6'-O-divinyladipate and trehalose 6, 6'-O-divinyladipate in acetone. These diesters were then employed as monomers in polycondensation reactions with various diols, aliphatic and aromatic, catalyzed by CAL B in organic solvents to yield linear polyesters with Mw's up to 22,000 Da [294].

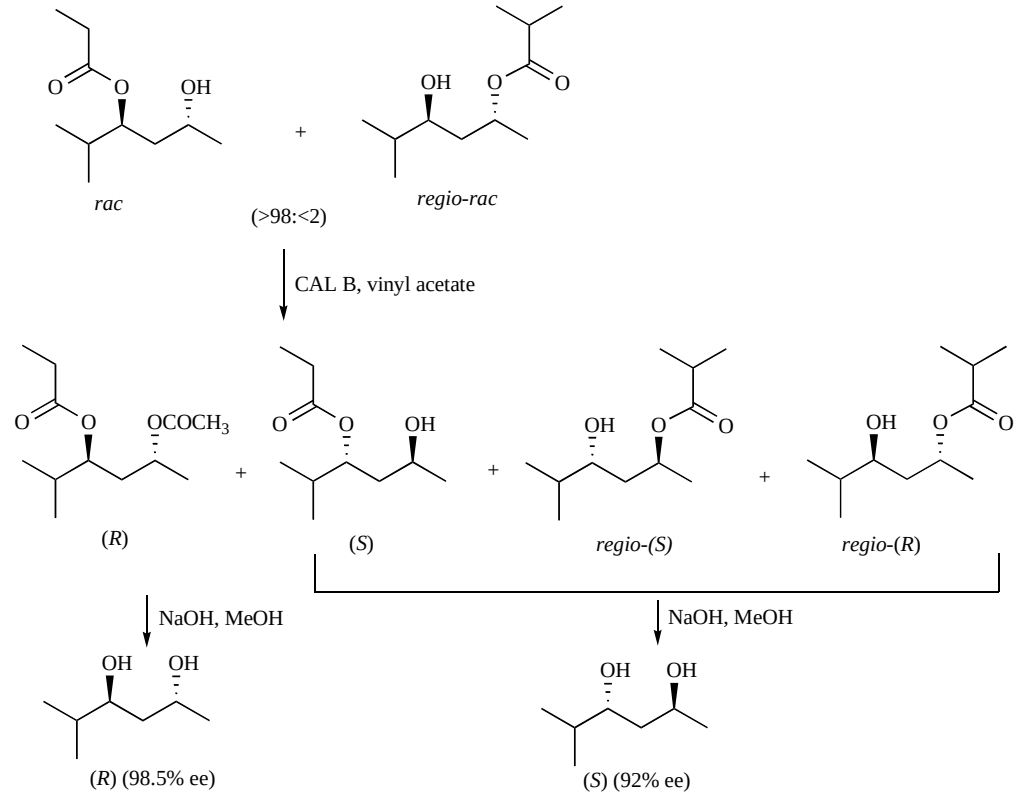
In the case of trisaccharides, the enzymatic transesterification of raffinose and melezitose with divinyl adipate using two lipases (CAL B and Lipozyme TL IM) and the protease subtilisin Carlsberg was described (Scheme **32**).

Polymerizable vinyladipoyl sugar esters prepared with lipase catalysis have been used as substrates for a second acylation step catalyzed by the protease. Diesters were obtained with high selectivity although the isolated yields were slightly lower than those obtained for the corresponding monoester derivatives. This two-step enzymatic approach allows regioselective control in the incorporation of the sugar inside the polymer structure [295].

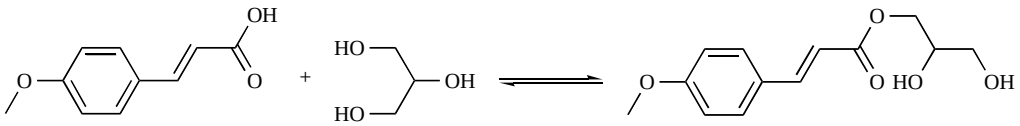
In the field of diols, lipases have contributed to synthesize several chiral monomers. By combination of a stereospecific dihydroxylation of alkenes and a lipase-catalyzed enantioselective resolution, it was possible to obtain enantiopure vicinal diols and enantiopure hydroxybutanoates [296]. Osmium catalyzed dihydroxylation of selected alkenes gave racemic dihydroxy compounds with one tertiary and one secondary stereocenter. Subsequent transesterifications utilizing the secondary alcohol function, catalyzed by CAL B, gave satisfactory *E*-values. In this way, alkenes were converted into enantiopure vicinal diols and enantiopure hydroxyl butanoates (Scheme **33**).



Scheme 33. Lipase-catalyzed enantioselective resolution of vicinal diols.



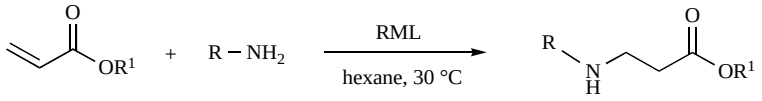
Scheme 34. Lipase-catalyzed kinetic resolution of 1,3-anti-diol monoesters.



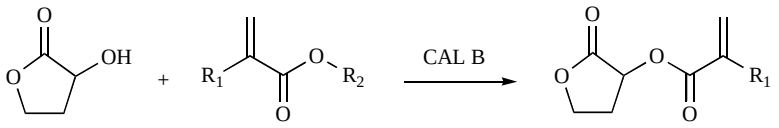
Scheme 35. Lipase-catalyzed esterification of 4-methoxycinnamic acid with glycerol.

A practical method for the synthesis of highly enantiomerically enriched and unsymmetrically substituted 1,3-*anti*-diols has been developed based upon an enzymatic kinetic resolution of 1,3-*anti*-diol monoesters. The substrates were easily available in one step and complete diastereocontrol through the zirconium-catalyzed aldol-Tishchenko reaction of diacetone alcohol and aldehydes. *Candida antarctica* lipase B effectively catalyzed the acetylation of the *R*-carbinol enantiomer with vinyl acetate and furnished the 1,3-*anti*-diol diesters in yields close to 50% and 98 to 99% *ee* from which the free 1,3-*anti*-diols were obtained through alkaline hydrolysis in identical *ee*. The unreactive (*S*)-1,3-*anti*-diol enantiomers were obtained in slightly lower enantiomeric excess due to a slow acyl migration in the substrates (Scheme **34**) [297].

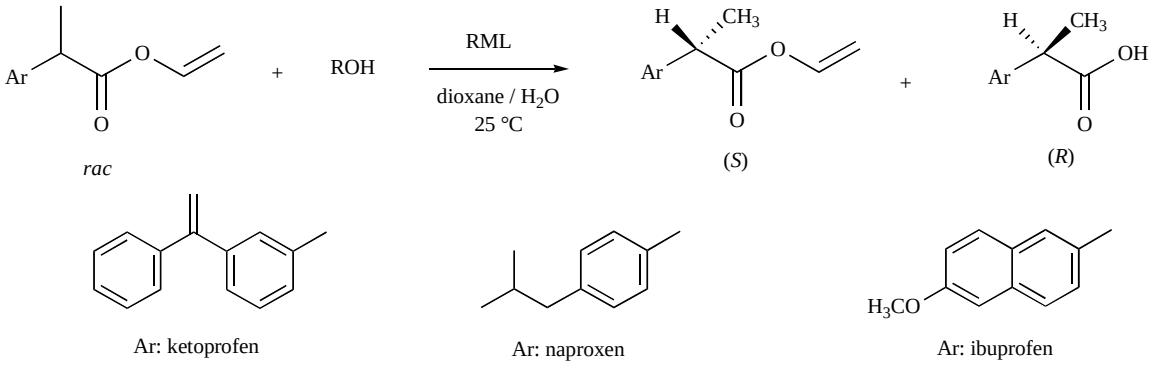
Regarding glycerol derivatives as monomers, recently the enzymatic esterification of 4-methoxy cinnamic acid with glycerol was reported. The reaction was performed in organic solvents using immobilized lipase from *Candida antarctica* B. The results of the enzymatic esterification were compared with reported chemical esterification in toluene using p-toluensulfonic acid as catalyst, and the lipase-catalyzed method was found to be superior in terms of conversion yields and priority to the formation of monoester (Scheme **35**) [298].



Scheme 36. Lipase-catalyzed synthesis of β-amino esters.



Scheme 37. Lipase-catalyzed synthesis of γ-butyrolactone methacrylate.



Scheme 38. Lipase-catalyzed resolution of 2-arylpropionic acids.

β-Amino esters comprises an important group of compounds, useful as synthetic precursors for β-peptoid and monomers in the synthesis of poly(β-aminoester)s, linear cationic polymers used as efficient gene delivery vectors [299]. The good performance of *Rhizomucor miehei* lipase (RML) as catalyst in the synthesis de *N*-substituted β-aminoesters was reported [262]. The lipase showed a high selectivity in the catalysis of the aza-Michael addition of mono- and bifunctional amines (hydroxyalkyl- and diamines) to alkyl acrylates, achieving the formation of the Michael monoaduct as the only product in high yield and purity. In the case of diamines as nucleophiles, the lipase catalyzed the addition of only one of the two amino groups showing high substrate specificity (Scheme **36**).

Finally, lipases have catalyzed the synthesis of a number of vinyl monomers used as starting materials in the synthesis of various acrylate and methacrylate polymers, widely used in biomedical applications. Acrylation reactions using an enzyme offer several advantages. First, an enzymatic reaction allows much lower temperature than chemical reaction. Second, polymerization inhibitor is not required for unwanted polymerization through reactive acrylic double bonds. Moreover, an enzymatic reaction enables more specific catalysis, meaning that acrylic functionality can be introduced more easily.

Hydroxy functional acrylates and methacrylates are interesting precursors for hydrophilic and water-soluble polymers which are promising functional polymers for biotechnological applications [300], including biomedical and pharmaceutical products such as contact lenses, dental materials, optical lenses, encapsulated cells, carriers for controlled drug delivery as well as hydrogels [301].

Acrylate monoesters have been synthesized on a preparative scale by the regioselective enzymatic transesterification of a range of diols dissolved in ethyl acrylate using a commercial lipase from *Chromobacterium viscosum* [302].

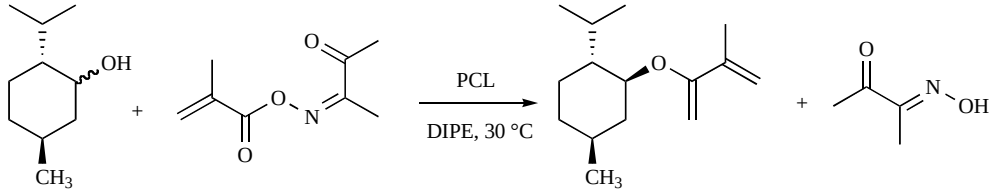
Extending the study to methacrylic esters, *Candida antarctica* lipase B catalyzed the transacylation of methyl acrylate and methyl methacrylate with diols and triols. Methyl methacrylate was the less efficient acyl donor due to the higher sterical hindrance in the enzymatic transacylation. Under the reaction conditions high yields of the mono-acylated products were obtained indicating that CAL B catalyzed regioselectively the acylation of the primary hydroxyl groups. In comparison with the chemical catalyzed route no selectivity was observed for unsubstituted diols. For substituted diols more mono-acylated product was formed in the lipase-catalyzed reaction than in the chemical catalyzed one [303].

The effect of acyl donors on the acrylation of labile compounds such as 2-hydroxy-γ-butyrolactone by lipase B from *Candida antarctica* was investigated [304]. Among acyl donors, vinyl methacrylate was selected to synthesize γ-butyrolactone methacrylate (GBLMA). Enzyamtically synthesized GBLMA can be applicable as a monomer for synthesis of photoresist resin (Scheme **37**).

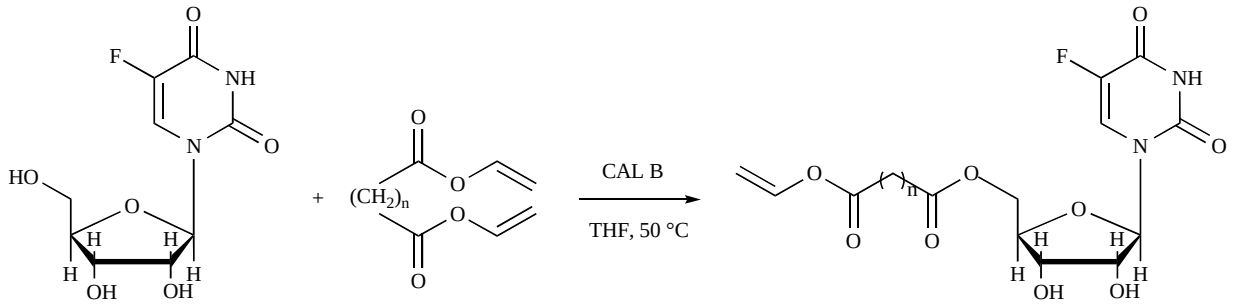
Previous pharmacological studies of profens (ketoprofen, naproxen and ibuprofen) have indicated the gastrointestinal side effects due to the acidic moiety of the profen. Therefore, extensive modifications have been made to prepare the ester prodrug of profens, which can temporarily mask their acidic moiety (Scheme **38**) [305].

An irreversible enzymatic resolution of 2-arylpropionic acids, using a *Rhizomucor miehei* lipase and their vinyl esters as activated substrates by hydrolysis as well as transesterification, was investigated [306]. The obtained enantiopure vinyl esters are useful polymerizable profen prodrugs that can be used for the preparation of optically active macromolecular drugs. These polymers can effectively control the rate of the drug release and administered at low doses, increase the therapeutic benefit.

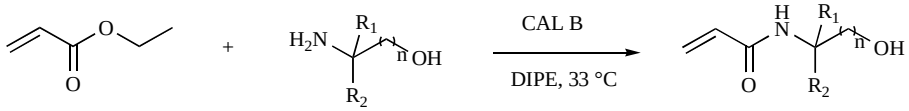
Optically active methacrylate ester of (–)-menthol was synthesised by enantioselective transesterification of (±)-menthol using *Pseudomonas cepacia* lipase (PCL) as a biocatalyst. Methyl methacrylate, vinyl methacrylate and 2,3-butanedione mono-oxime methacrylate were used as acylating agents. Oxime methacrylate gave better conversion as compared to the other acyl donors. (−)-Menthyl methacrylate was obtained with 96% yield and 98% enantiomeric excess [307]. The newly synthesized terpenyl monomer



Scheme 39. Lipase-catalyzed enantioselective transesterification of racemic menthol.



Scheme 40. Lipase-catalyzed synthesis of 5-fluorouridine divinyl esters.



Scheme 41. Lipase-catalyzed synthesis of substituted acrylamides.

could then be polymerized for its potential use as a sustained release perfume (Scheme **39**).

In the field of nucleosides, the selective synthesis of monosaccharide derivatives and polymeric prodrugs of 5-fluorouridine (5-FUR) have been developed [308]. A series of vinyl 5-FUR esters were prepared with high acylation regioselectivity at 5-OH, by transesterification of 5-FUR and divinyl dicarboxylates catalyzed by CAL B (Scheme **40**).

Moreover, a series of polymeric prodrugs of 5-FUR with the different linker lengths were prepared by the chemo-polymerization of vinyl 5-FUR esters in DMF initiated by azobisisobutyronitrile.

Substituted acrylamides have also been prepared through lipase catalyzed acylations. An efficient procedure for the CAL B-catalyzed preparation of *N*-hydroxyalkylacrylamides from ethyl acrylate and several linear and branched alkanolamines has been reported [260, 261]. The most interesting products are *N*-(2-hydroxxyethyl)-acrylamide (HEA), the monomer used in the synthesis of polymeric matrices with application in capillary electrophoresis and *N*-(2-amino-2-methyl-1-propyl)-acrylamide, precursor of 2-acrylamido-2-methylpropane sulfonic acid (AMPS) used in many areas such as water treatment, oil field and hydrogels for medical applications (Scheme **41**).

5. CONCLUSION

Lipase-catalyzed polymerizations have developed into a positive and flexible approach in the synthesis of materials with biomedical applications. The increased knowledge of the scope as well as the few drawbacks of this procedure made possible the synthesis of a large variety of homo- and copolymers. Special characteristics of the lipases, such as their high selectivity, the possibility of working in mild reaction conditions that reduces energy requirements, to be non-toxic, recyclable and biodegradable, contribute to create environmentally friendly processes. For this reason lipases are applied to develop new materials through processes difficult to achieve by the traditional chemical way. As examples, the synthesis of multifunctional polymers, materials with high monodispersity and well-defined arrangement along the macromolecular chain with novel repetitive units, have been reported in the last years and are described in this work. Is highly desirable that a combined multidisciplinary effort in the field of biocatalysis, polymer chemistry and bioengineering lead us to a significant advance in the production of materials that are more and more like to those found in nature.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflict of interest.

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