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Strategies for the synthesis of block copolymers with biodegradable polyester segments

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The controlled synthesis of block copolymers offers great potential for the valorization of biodegradable polyesters, many of which can be bioderived. Combining polyester blocks with other oxygenated polymers through ring-opening polymerization (ROP) and copolymerization (ROCOP) reactions allows for the synthesis of new materials with tunable properties. In this review article, we describe recent advances in the synthesis of diblock and multiblock polyesters, as well as polyether and polycarbonate block copolymers bearing biodegradable polyester block segments. Due to the great diversity of oxygenated monomers available from petrochemical and biomass sources, a great number of polymerization strategies have been developed involving metal- and organo-catalysts with different degrees of control. This review aims to provide an overview of the strategies available for the synthesis of different block copolymers: from the more widespread sequential addition methods to the more rare systems displaying high degrees of kinetic control in a mixture of monomers or those with controlled switchable behavior.

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1. Introduction

Synthetic polymers are ubiquitous in modern life, with applications ranging from every-day packaging and textiles to more specialized use in biomedicine and electronics. Overwhelmingly, these materials are derived from non-renewable petrochemicals. Despite using less than 5% of total oil and natural gas production,[1] the global output of synthetic polymers is now well over 300 million tons a year and it is expected to keep growing in the foreseeable future.[2] This has raised serious concerns with regards to the very low recyclability of most polymers and their bio-accumulation in various ecosystems.[3] Thus, the development of synthetic polymer alternatives that include biobased and/or biodegradable building blocks is a pressing issue.

Biobased polymers are macromolecules derived directly from biomass or generated from monomers derived from it.[4] The large availability of functionalizable renewable resources

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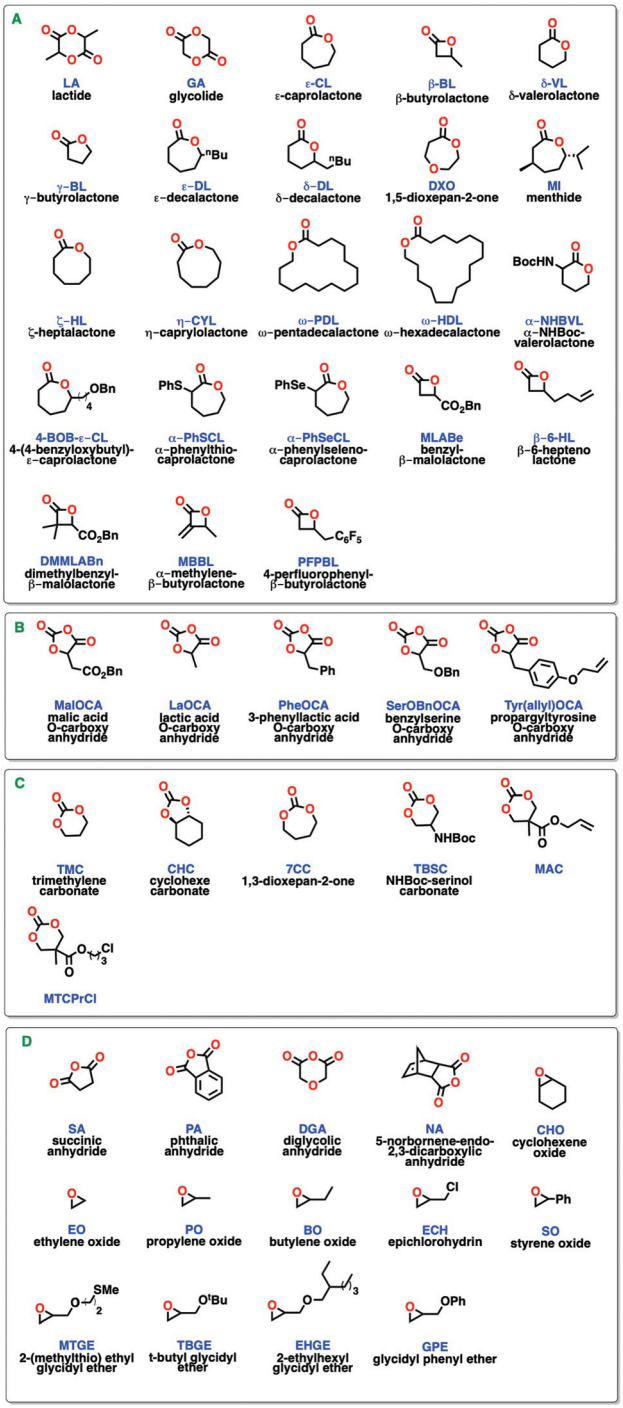
has spurred research in more sustainable polymeric materials, many of which are biodegradable polyesters.[5] The most common approaches for the utilization of biomass in synthetic polymers are: (i) isolation or chemical modification of natural polymers (*e.g.* poly(hydroxyalkanoates) from bacteria), (ii) modification of carbohydrates and triglycerides for the synthesis of new monomers (*e.g.* lactide, succinic acid) and (iii) direct extraction of monomers from natural oils (*e.g.* tulipalin A, limonene).[6] Another important research direction looks at the use of carbon dioxide (a renewable resource) in a copolymerization with epoxides.[7] Despite the great diversity of renewable feedstocks, currently, only 1% of all synthetic polymers produced yearly are biobased.[8] Some of the biggest barriers to their more widespread commercialization are the higher costs and current limited production scale.[9]

Biodegradable polymers are macromolecules that experience degradation (*i.e.* lowering of their molar mass) by a wide variety of biological activities.[10] While biodegradable polymers can be either derived from biomass or petrochemicals (*i.e.* not all biobased polymers are biodegradable and *vice versa*), nowadays a great proportion of the building blocks used for the synthesis of biodegradable polymers (Scheme 1) come from petrochemicals.[11] In order for greener polymers (*i.e.* bioderived and/or biodegradable) to become more prevalent, they are expected to exhibit properties comparable to those of traditional plastics as well as show new and complementary properties that open the door to new applications. Controlled synthesis of copolymers including biobased and/or biodegradable components has shown promising results, as the diversity of functionalities from renewable resources can be used to tune thermal and mechanical properties of the macromolecules and often allow for post-functionalization.[12] In particular, the use of block copolymers including polyester segments is attractive because of their tunable biodegradation, which has been applied in thermoplastic elastomers, polymeric polyols, phase compatibilizers, and polymer-drug conjugates.[13]

Most commonly, the synthesis of block copolymers including polyester units involves the coupling of a polyester with another block through post-functionalization, or the use of a pre-made block as a macroinitiator for the polymerization of a monomer. Such approaches comprise several steps and have been applied with success to some copolymers.[13b,14]

In this review, we summarize some of the most recent methods for the one-pot synthesis of block copolymers bearing biodegradable polyester segments, covering both metal- and organocatalyst systems active in the ring-opening polymerization (ROP) and ring-opening copolymerization (ROCOP) of biobased and non-biobased monomers (Scheme 1). The synthesis of stereoblock polyester sequences is not included, as the topic has been reviewed earlier.[15] Similarly, the combination of ROP and radical polymerization (RAFT or ATPR) for the synthesis of polyester–polyolefin copolymers has been recently reviewed and therefore is not included here.[14a,16] For applications of block copolymers, the reader can refer to recent review articles covering their applications in materials and biomedical science.[17]



Scheme 1 Some oxygenated monomers employed for the synthesis of polyester, polyether and polycarbonate blocks. (A) Cyclic esters/lactones, (B) *O*-carboxyanhydrides (OCAs), C = cyclic carbonates; D = anhydrides and epoxides.

2. Synthesis of polyester–polyester blocks

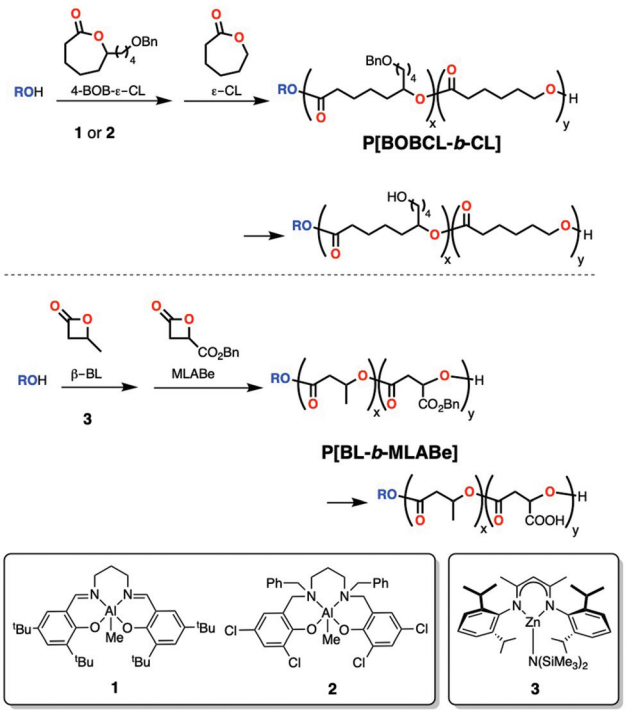
The synthesis of polyester-only block copolymers offers some illustrative examples of how the mechanical and thermal pro-

perties of materials can be engineered. For instance, poly (lactic acid) (PLA); one of the most successful biobased polyesters produced on an industrial scale, displays high tensile strength and high Young modulus that make it suitable for replacing polyolefins in some packaging applications.[18] However, its high intrinsic brittleness, low impact strength and thermal instability hinder its more widespread use.[19] Toughening of PLA and the synthesis of PLA thermoplastic elastomers has been achieved successfully by forming block copolymers with polycaprolactone (PCL)[20] and other biobased polyesters.[21] The synthesis of those block copolymers can be achieved through isocyanate or amine coupling of two preformed polyesters (forming a urethane or amide linkage).[22] In some cases, blocky architectures have been achieved using Novozym 435 (immobilized lipase B)[23] or through sequential polycondensation methods in the presence of a transesterification agent.[24] Due to a large variety of biobased diols and dicarboxylic acids available from biomass, polycondensation methods are an attractive route to a greater variety of block polyesters. However, they suffer from uncontrolled transesterification and frequently yield samples with large dispersities ($Đ > 2.0$).[25]

2.1. Synthesis of polyester–polyester block copolymers through the sequential feeding of monomers

2.1.1. Metal-catalyzed synthesis of polyester blocks through sequential addition of cyclic esters. The controlled ring-opening polymerization (ROP) of lactones is the preferred synthetic method to make polyester blocks. By far, the most common approach is the sequential addition of different cyclic esters in the presence of one or multiple suitable initiators. One of the main challenges to this methodology is inter- and intra-molecular transesterification reactions which can convert block-microstructures intro random copolymers with broad dispersities.[26] Using tin(II) octoate is not recommended for the synthesis of block architectures as it leads to significant transesterification and scrambling at high temperatures,[27] but it has been used successfully in block copolymerizations with lactide (LA) and ε-caprolactone (ε-CL) when the temperature was kept below 120 °C.[28] Other metal initiators have been applied to the controlled synthesis of block polyesters, yielding less dispersed copolymers. In particular, systems based on aluminum have been used the most often,[29] as well as rare-earth metals,[21b,30] indium,[31] zinc[32] and transition metals.[33]

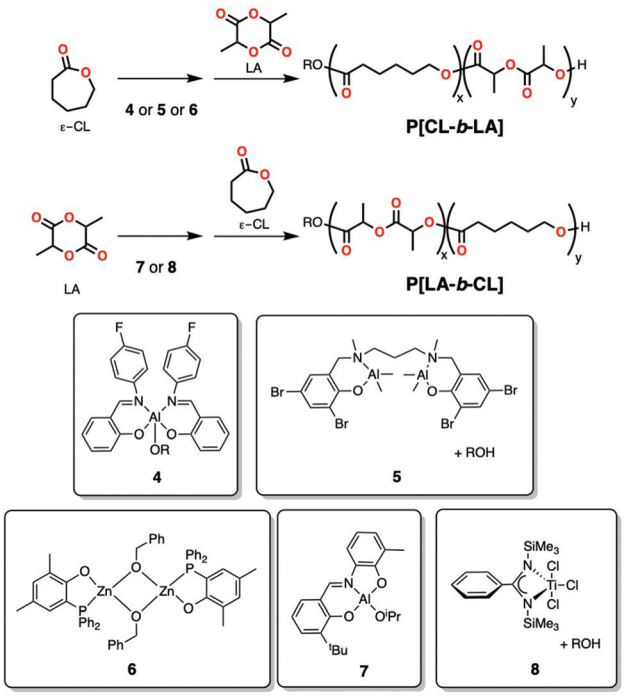
Most of the aluminum systems reported for ROP of cyclic esters are based on phenoxy-imine, salen- and salan-type alkyls or alkoxides that give access to different copolymer microstructures.[34] Shaver and co-workers reported that in the presence of alcohol both salen- and salan-type aluminium alkyl (**1** and **2**, Scheme 2) complexes were active at room temperature and up to 2500 equivalents of ε-CL in an immortal fashion to yield high molecular weight PCL with low dispersities ($Đ < 1.1$).[29b] Substituted ε-caprolactones proved difficult to polymerize; particularly in the 2- or 6-position, as no polymerization was achieved with (4*R*,7*S*)-4-methyl-7-(1-methylethyl) oxepan-2-one (menthide, MI), even at higher temperatures.



Scheme 2 Metal complexes for the block copolymerization of functionalized cyclic esters through sequential addition approach. Subsequent de-protection reactions form amphiphilic block copolymers.

Substitution at the 4-position of the ring allowed for a relatively faster and more controlled polymerization at high temperatures, thus 10 equivalents of 4-(4-benzyloxybutyl)-ε-caprolactone (4-BOB-ε-CL) were polymerized at 70 °C in 2 hours. Cooling down the reaction mixture to room temperature followed by addition of 90 equivalents of ε-CL formed a diblock copolymer with monomodal distribution and low dispersity (M_n = 15 600 Da; $Đ$ = 1.15), ruling out transesterification.[29b] Block copolymers of 4-BOB-ε-CL contain benzyloxy groups that can be deprotected to give free hydroxy groups and can also be used as initiators for the synthesis of brush copolymers. Using the same catalysts, this group also reported the successful copolymerization of L-LA and different alkyl substituted β-butyrolactones at 85 °C to make triblock copolymers with good control (M_n = 33 700 Da; $Đ$ = 1.16).[35] β-butyrolactones are challenging monomers to polymerize due to poor ring-opening selectivity (where *O*-acyl or *O*-alkyl bond cleavage are possible) and the formation of crotonization side-products.[36]

Zaitsev, Kostjuk and co-workers reported bulky iminophenolate aluminum alkoxides that were relatively controlled in the polymerization of ε-CL or *rac*-LA at high temperatures (but showed higher dispersities under monomer starved conditions).[37] The fluorinated initiator (**4**, Scheme 3) allowed for a more controlled synthesis of block copolymer, first polymerizing ε-CL and then *rac*-LA under neat conditions at 130 °C with moderate molecular weight and dispersity (M_n = 13 200 Da; $Đ$ = 1.27). Dinuclear salan aluminium system in the presence of an alcohol (**5**, Scheme 3) has also been reported to give

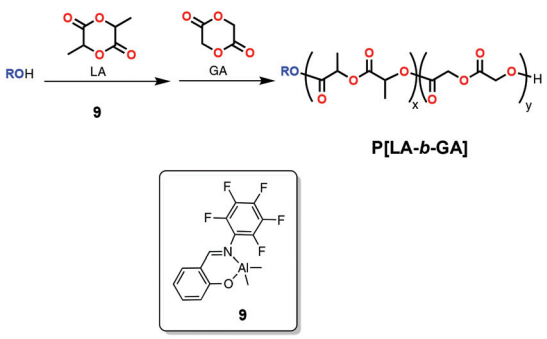


Scheme 3 Metal complexes for the block copolymerization of lactide and ε-caprolactone through sequential addition.

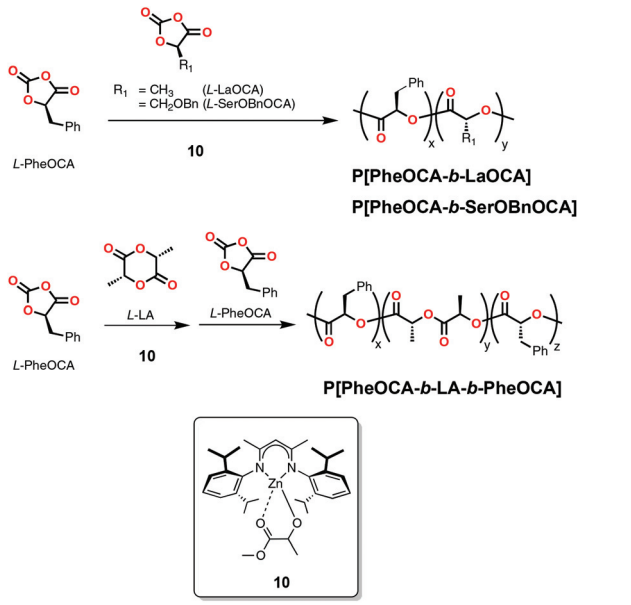
defined block copolymers of ε-CL and L-LA by sequential addition, but only by the initial polymerization of ε-CL followed by lactide.[34e] Matsubara and co-workers reported an aluminum isopropoxide complex (**7**, Scheme 3) bearing half-salen-type ligands that could polymerize first *rac*-LA and then ε-CL in a sequential manner to form block copolymers (M_n = 11 500 Da; $Đ$ = 1.24) at 70 °C in pyridine (to suppress dimerization of Al complexes).[29c]

Pappalardo and co-workers employed a salicylaldiminate aluminum alkyl complex (**9**, Scheme 4) in the presence of alcohol for the block copolymerization of LA and glycolide (GA) through sequential addition method.[38] Under the reaction conditions studied (xylenes, 130 °C), analysis by $^{13}C\{^1H\}$ NMR spectroscopy showed only homosequence triads, supporting the formation of a block copolymer through a living mechanism (with good agreement between experiment and theoretical molecular weight). Interestingly, switching to the simultaneous addition of monomers formed either blocky-structures or totally random copolymers depending on the reaction conditions used (solution or bulk polymerization). Previously, the same group reported a very similar aluminum alkyl complex active in the block copolymerization of *rac*- or L-LA with ε-CL through a sequential addition method in toluene at 70 °C.[34f]

Zinc and indium initiators have been reported for the sequential block copolymerization of L- or D-LA with other cyclic esters. In particular, phosphinophenolate zinc alkoxide complexes reported by Dagorne, Avilés and co-workers were well-behaved initiators for the synthesis of PCL-*b*-PLLA, but not when lactide was polymerized first, as it's been observed for most aluminum systems (**6**, Scheme 3).[39] The molecular weights obtained with this system were higher than the theoretical values suggesting low initiation efficiency (M_n = 22 830 Da; $Đ$ = 1.05). Guillaume and co-workers reported a zinc β-diketiminate amide complex (**3**, Scheme 2) that, in the presence of alcohol, was capable of copolymerizing challenging *rac*-β-butyrolactone (β-BL) with benzyl-β-malolactone (MLABe) in a sequential manner (only when BBL was polymerized first).[40] Later, Chen, Tong and co-workers employed a lactate version of this catalyst (**10**, Scheme 5) for the ROP of different enantiopure *O*-carboxyanhydrides (OCAs) in a sequential manner to form diblock copolymers with controlled molecular weight and isotactic microstructure (no epimerization).[41] One of these monomers, L-3-penyllactic acid-*O*-carboxyanhydride (L-PheOCA) was polymerized in a sequential manner with L-LA to form triblock copolymers with excellent control over the



Scheme 4 Salicylaldiminato aluminum alkyl complex for the block-copolymerization of lactide and glycolide through sequential addition.



Scheme 5 Zinc β-diketiminate complex active in the block-copolymerization of enantipure OCAs and lactide without epimerization.

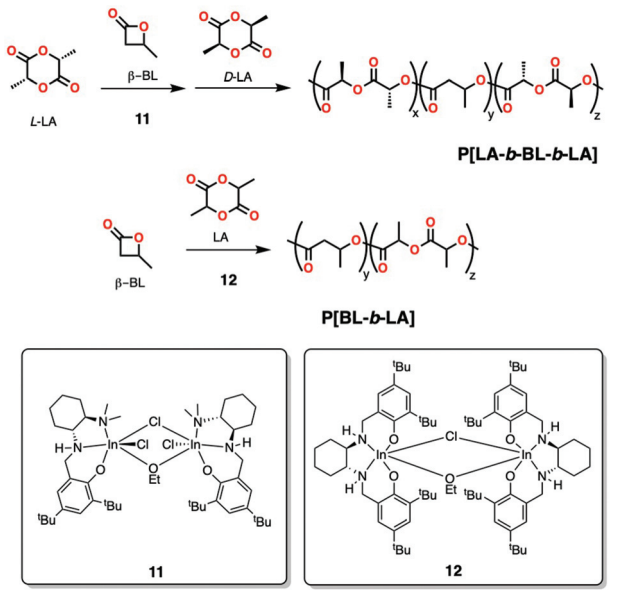
molecular weight (M_n = 32 300 Da; $Đ$ = 1.05). Due to their easy synthesis from natural amino acids, OCAs have become attractive monomers for the synthesis of polyesters with functionalizable side groups and therefore tunable physicochemical properties.[42]

Mehrkhodavandi and co-workers reported the application of a very active dinuclear indium catalyst (**11**, Scheme 6) in the synthesis of triblock copolymers of L- and D-LA with *rac*-β-BL.[31b] The high molecular weight copolymers (M_n = 138 000 Da; $Đ$ = 1.22) were made through three consecutive additions and behaved as thermoplastic elastomers with improved mechanical properties over block copolymers of lactide isomers.[31b] Later, the same group reported another indium catalyst (**12**, Scheme 6) supported by a salan ligand that could polymerize LA in an immortal fashion to make linear and star block-copolymers when exposed to air and moisture. With this system, diblock copolymers of LA and β-BL were synthesized at room temperature with good control (M_n = 48 600 Da; $Đ$ = 1.01).[31c]

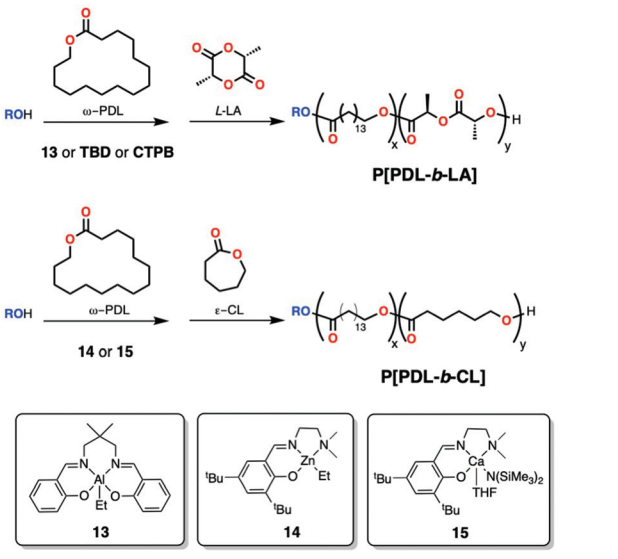
Using Hillmyer and Tolman's simple system[43] for the syndio-selective polymerization of *rac*-LA (indium trichloride, triethylamine and an alcohol), Martin-Vaca, Bourissou and co-workers reported the copolymerization of ε-CL and ε-decanolactone (ε-DL) (Scheme 1) to diblock copolymers with good control (M_n up to 22 000 Da; $Đ$ = 1.24) and showed no evidence of transesterification regardless of the order of monomer addition.[44]

Transition metal complexes have been used with success in the sequential block-copolymerization of lactide and other cyclic esters. Interestingly, a titanium(IV) amidinate complex (**8**, Scheme 3) in the presence of an alcohol was reported to synthesize both PCL-*b*-PLA and PLA-*b*-PCL through sequential addition of ε-CL and L-LA (M_n = 12 200 Da; $Đ$ = 1.41). Block microstructure was confirmed by the predominance of CL–CL and LA–LA sequences in $^{13}C\{^1H\}$ NMR analysis.[33a] Also using group 4 metals, Jones and co-workers reported bimetallic zirconium and hafnium trisphenolate alkoxide complexes for the sequential polymerization of *rac*-β-BL and *rac*-LA to make both PHB-*b*-PLA (M_n = 38 900 Da; $Đ$ = 1.33) and PLA-*b*-PHB (M_n = 41 700 Da; $Đ$ = 1.09).[45]

Over the past decade, the ROP of macrolactones has attracted a lot of interest as a result of their long aliphatic backbone that resembles low density poly ethylene (LDPE),[46] with the added advantage of a higher biodegradability imparted by the ester group. Despite their limited degradation under physiological conditions, they can be biocompatible[47] and their copolymerization with smaller monomers can tune their physical properties for different applications.[26d,48] In 2015, Duchateau and co-workers reported a salen aluminum alkyl complex (**13**, Scheme 7) capable of copolymerizing in a sequential manner ω-pentadecalactone (ω-PDL) and L-LA in *p*-xylene at 100 °C to high molecular weight block copolymer with moderate dispersity (M_n = 144 000 Da; $Đ$ = 1.50).[49] DSC analysis confirmed block microstructure, with two clear melting transitions. Interestingly, block copolymers could only be made if ω-PDL was polymerized first, but not through reverse order of addition, demonstrating the lack of reactivity of a secondary alkoxide group towards macrolactone ROP. Previously, it was found that polymerization of ω-PDL with ε-CL with the same catalyst formed only random copolymers due to uncontrolled transesterification, while tridentate iminophenolate complexes of calcium and zinc (**14** and **15**, Scheme 7) were capable of forming such block copolymers in toluene at 100 °C (M_n not reported).[50] In contrast, the analogous tridentate iminophenolate aluminum complex (bearing the same ligand framework) only produced random copoly-



Scheme 6 Indium alkoxide complexes active in the block-copolymerization of lactide and butyrolactone through sequential addition.



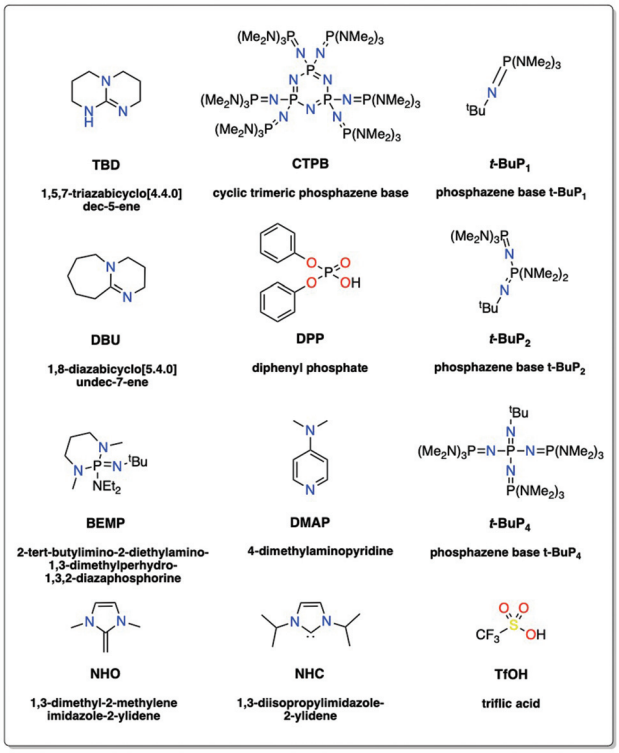
Scheme 7 Aluminum, zinc and calcium complexes for the block-copolymerization of ω-pentadecalactone and lactones through sequential addition.

mers by sequential addition due to extensive transesterification.[51]

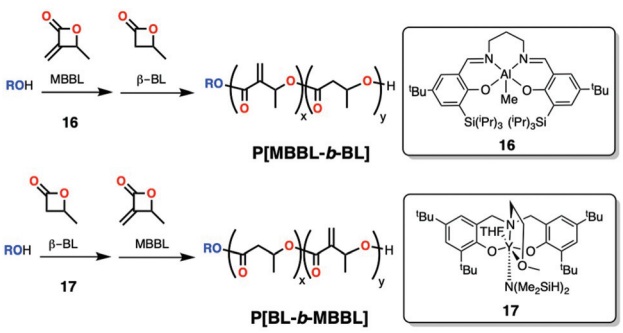
Later, Lu and coworkers reported the copolymerization of the racemic functionalized lactone α-methylene-β-butyrolactone (*rac*-MBBL) with *rac*-β-BL using two different catalysts (**16** and **17**, Scheme 8).[52] Due to the specific stereoinduction exerted by each catalyst (the aluminum complex formed *syndio*-rich PMBBL block and the yttrium complex formed syndio-rich PHB/PBL block), different diblock semi-crystalline copolymers with distinct thermal properties were formed.

2.1.2. Organo-catalyzed synthesis of polyester blocks through sequential addition of cyclic esters. Given the continuous development of highly efficient organocatalysts for the ROP of cyclic esters, various metal-free systems have also been developed for the synthesis of different polyester blocks (Scheme 9). These systems are not only interesting from the viewpoint of green chemistry, but can also be applied for the synthesis of specialized biomedical and electronic devices where trace metal is undesirable.[53] ROP using organocatalysts can proceed through: (i) electrophilic activation of the monomer (*e.g.* using organic acids), (ii) nucleophilic activation of the monomer (*e.g.* using pyridines, phosphines, carbenes), (iii) chain-end nucleophilic attack (*e.g.* using bases) or through a combination of these methods.[54]

Some of the most common bases, 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU), 1,5,7-triazabicyclo[4.4.0] dec-5-ene (TBD) and 2-tert-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP) (Scheme 9) have been reported by Guillaume and coworkers to synthesize block copolymers of *rac*-β-BL and benzyl-β-malolactone (MLABe) with relatively high molecular weight (M_n = 73 500 Da; $Đ$ = 1.44), regardless of the order of monomer addition.[40] In comparison, zinc β-diketiminate amide complex (**3**) and alcohol system reported by the same group could only form blocks under these conditions only if β-BL was polymerized first (Scheme 2). As there was no chain-transfer agent (*i.e.* alcohol) in these polymerizations using organocatalysts, the organic bases were covalently attached to the polymer chain end. The use of TBD afforded polymers with slightly reduced dispersities compared to DBU and BEMP, but high monomer concentration conditions were



Scheme 9 Some common organocatalysts active in the ROP of cyclic esters.



Scheme 8 Aluminum and yttrium complexes for the block-copolymerization of butyrolactones through sequential addition.

needed in order to inhibit transesterification, which has been reported with TBD.[55] Block copolymers including benzyl-β-malolactone (MLABe) units (Scheme 1) have shown promising drug-delivery activity through the hydrolysis of its benzyl groups, affording amphiphilic block PMLA-*b*-PHB that can assemble into nanoparticles.[56]

Using bases in the presence of an alcohol can afford a higher degree of control to the block copolymerization through the formation of alkoxides with tunable basicity. In 2014, Hadjichristidis and coworkers reported that phosphazene base *t*-BuP_2 (Scheme 9) in the presence of various aliphatic and aromatic alcohols polymerized ε-CL with excellent control of the molecular weight and subsequently copolymerized L-LA to form PCL-*b*-PLLA with excellent control of the molecular weight and low dispersities (M_n = 14 900 Da; $Đ$ = 1.15).[57] Using TBD in the presence of benzyl alcohol, He and coworkers achieved the polymerization of α-substituted δ-valerolactones (bearing thioether-amino and thioether-alkyl chains of different lengths) in a sequential manner to form block copolymers (Scheme 10) with good control (M_n = 5458 Da; $Đ$ = 1.18).[58] This block copolymer showed applicability in gene delivery, with higher efficiency compared to its random counterpart and excellent biocompatibility compared to common non-viral carriers. Later, Li and coworkers used a new cyclic phosphazene base CTPB (Scheme 9) in the presence of benzyl alcohol for the sequential ROP of γ-butyrolactone (γ-BL) and L-LA (Scheme 10) to form block copolymers with

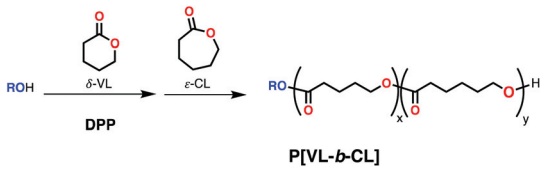
relatively good control (M_n up to 20 500 Da; $Đ$ = 1.62). This was the first report of a block copolymer of γ-BL,[59] whose unfavorable ROP thermodynamics require low polymerization temperatures, giving products with relatively high dispersities.[60]

Using organic acids in the presence of an alcohol can also lead to controlled polymerizations through an activated monomer mechanism. In 2014 Martín-Vaca, Bourissou and coworkers applied this strategy for the polymerization of *rac*-β-BL using triflic acid and *n*-pentanol or 1,4-butanediol followed by the polymerization of ε-CL to give diblock or triblock copolymers with medium molecular weight (M_n = 6670 Da; $Đ$ = 1.21 for diblock).[61] Other organic acids such as diphenyl phosphate (DPP) have been the synthesis of block copolymers, in particular for δ-valerolactone (δ-VL) and ε-CL regardless of the monomer addition order (Scheme 11).[62] Years later, Guo and coworkers employed commercially available dibutyl phosphate and 3-phenyl-1-propanol under industrial-relevant conditions (neat, 180 °C) to form block copolymers PCL-*b*-PVL with medium molecular weight and remarkably low dispersities (M_n up to 5340 Da; $Đ$ = 1.11).[63]

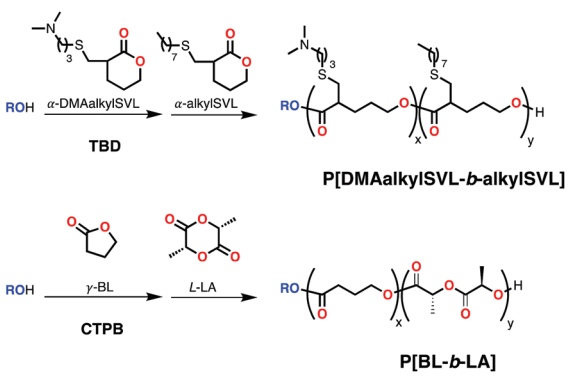
Some organocatalyst systems have also been applied to the block copolymerization of macrolactones to give high molecular weight products. In 2015, Dubois, Todd and coworkers reported that TBD in the presence of an alcohol was capable of polymerizing ω-PDL and L-LA in a sequential manner (Scheme 7): first in bulk at 100 °C, then at 25 °C in $CHCl_3$ to prevent transesterification in the lactide polymerization step (M_n = 107 910 Da; $Đ$ = 1.11). The block nature of the copolymer was corroborated by ^1H, $^{13}C\{^1H\}$ and DOSY NMR spectroscopy.[64] More recently, Liu, Li and coworkers adopted a similar strategy for the synthesis of PPDL-*b*-PLA (M_n = 37 800 Da; $Đ$ = 1.73) using cyclic trimeric phosphazene base (CTPB) in toluene at 80 °C without evidence of scrambling by transesterification.[65]

Recently Hadjichristidis and coworkers reported a dual organocatalyst approach for the synthesis of block copolymers using ω-PDL or ω-hexadecalactone (ω-HDL) and smaller lactones δ-VL or ε-CL.[66] The system involved the use of strong phosphazene base *t*-BuP_4 (Scheme 9) with alcohol for the polymerization of the macrolactone in toluene at 80 °C, followed by neutralization using an equimolar amount of protic acid diphenyl phosphate (DPP) and the addition of weaker phosphazene base *t*-BuP_2 with the smaller lactone to avoid transesterification (Scheme 12). This catalyst-switch strategy produced block copolymers PPDL-*b*-PCL, PPDL-*b*-PVL, PHDL-*b*-PCL and PHDL-*b*-PVL (M_n up to 83 300 Da; $Đ$ = 1.92).

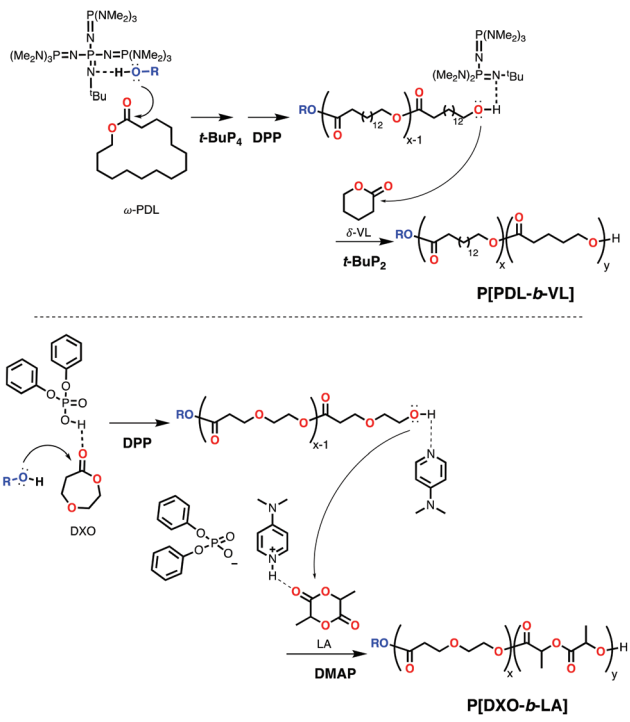
Another example of a dual organocatalyst approach was reported by Kakuchi and coworkers (Scheme 12).[67] By switching from diphenyl phosphate (DPP) activation in the presence of an alcohol to 4-(dimethylamino)pyridine (DMAP) activation, they achieved the synthesis of PVL-*b*-PLLA (M_n = 11 600 Da; $Đ$ = 1.16) and PCL-*b*-PLLA (M_n = 12 600 Da; $Đ$ = 1.12) in a sequential, one-pot procedure. Also, 1,5-dioxepan-2-one (DXO) was polymerized with this system to form PDXO-*b*-PLLA (M_n = 12 100 Da; $Đ$ = 1.08). PDXO is a highly amorphous polymer and more prone to hydrolysis compared to PCL or PLA.[68] A similar strategy was used by Li, Guo and coworkers, who reported the synthesis of block copolymers PVL-*b*-PLLA (M_n = 12 200 Da; $Đ$ = 1.09) and PCL-*b*-PLLA (M_n = 13 800 Da;



Scheme 11 Block copolymerization of δ-VL and ε-CL using organic acid diphenyl phosphate (DPP) and alcohol through sequential addition.



Scheme 10 Block copolymerization of cyclic esters using organobases and alcohol through sequential addition.



Scheme 12 Catalyst-switch strategy for the block-copolymerization of cyclic esters through sequential addition of monomers.

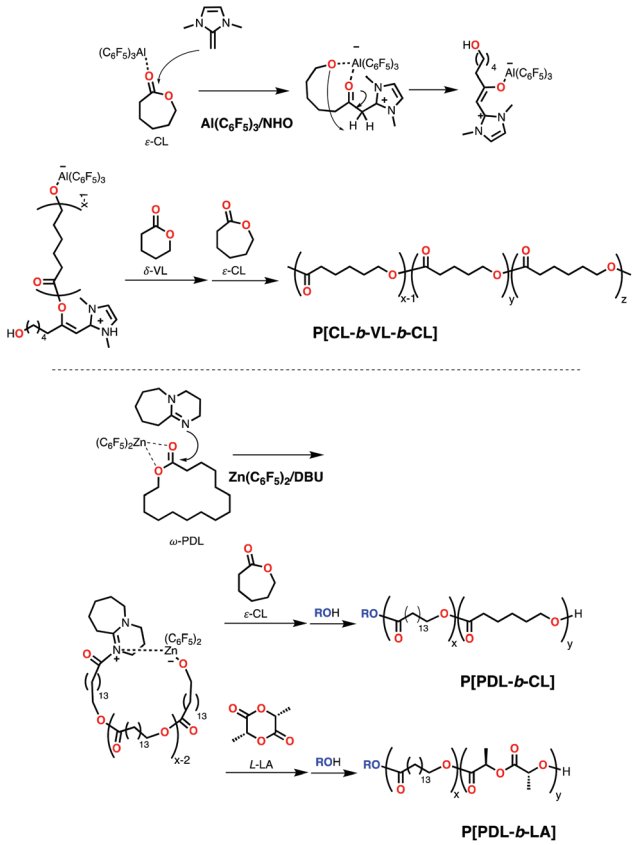
$Đ$ = 1.06).[69] Using a reverse switch, Lin, Li and coworkers could polymerize first *rac*-LA (employing benzyl alcohol and DBU) followed by a 2-substituted δ-VL (using an excess of DPP) to yield amphiphilic block copolymers.[70]

Exploiting synergistic effects between different types of organocatalysts (an electrophile and a nucleophile) has opened the door to some of the most active and controlled systems capable of sequential copolymerization of different cyclic esters at room temperature. For example, Dove and coworkers applied a thiourea/amine system with an alcohol for the rapid block copolymerization of substituted glycolide and L-LA (M_n up to 24 160 Da; $Đ$ = 1.07).[71] Similarly, Li, Liu and coworkers reported a thiourea/CTPB system with different alcohols to give in a matter of minutes PVL-*b*-PCL (M_n = 12 700 Da; $Đ$ = 1.16).[72]

2.1.3. Mixed organo- and metal-catalyzed synthesis of polyester blocks through sequential addition of cyclic esters. Despite their structural simplicity and high activity, virtually all organocatalysts can suffer from inactivity or lack of control when presented with different monomer combinations.[55,73] While the catalyst-switch strategy (*vide supra*) can be used to overcome this issue, it is limited in scope and restricted to specific catalysts pairs. Efforts to develop a universal catalytic system for the block copolymerization of a wide range of cyclic esters have recently focused on exploiting synergistic effects between Lewis bases (organobases) and Lewis acids (metal complexes/salts). This is usually done with careful optimization of the Lewis acid and base combination employed (in order to avoid irreversible binding of the pair and to maximize catalytic activity).

Following the pioneering contributions of Amgoune,[74] Bourissou,[74] Dove,[73a] Naumann[75] and coworkers, where inactive DMAP or a N-heterocyclic olefin (NHO) were rendered active in the polymerization of LA, ε-CL or ω-PDL with high activity and control in the presence of magnesium or zinc compounds, Zhang and his group reported the synthesis of block polyesters of ε-CL and δ-VL in a living fashion to high molecular weight copolymers (Scheme 13) and excellent control (M_n = 72 100 Da; $Đ$ = 1.15 for triblock) using $Al(C_6F_5)_3$ and NHO (Scheme 9) as a Lewis pair.[76] The mechanism of polymerization involved an initiation step by the nucleophilic attack of the NHO base to a monomer unit activated by the Lewis acid. This forms a propagating imidazolium-enolate group (Scheme 13) that is controlled in further ROP and remains as chain-end group in the block copolymers.[76]

Recently, Li and coworkers reported the block copolymerization of ω-PDL/ε-CL (M_n = 79 900 Da; $Đ$ = 1.90) and ω-PDL/LA (M_n = 87 900 Da; $Đ$ = 1.80) through sequential addition using $Zn(C_6F_5)_2$ and DBU (Scheme 9) in the presence of an alcohol (Scheme 13).[77] The mechanism proceeds similarly to the previous system with initial dual activation of the monomer by the Lewis acid and base to form a propagating alkoxide species active in sequential copolymerization (Scheme 13), but in this case the close interaction of the ion pair allows for the control synthesis of cyclic copolymers in the absence of alcohol. When an alcohol is added, linear diblock structures could be obtained (Scheme 13). However, randomization of the block structure was detected in the case of PPDL-*b*-PCL after prolonged reaction times under the conditions studied (xylene, 110 °C). Neither PPDL-*b*-PLA nor cyclic PPDL-*b*-PCL (prepared without alcohol addition) showed evidence of scrambling by transesterification under these conditions.[77]



Scheme 13 Mechanism of ROP of cyclic esters using different Lewis pairs for the synthesis of block copolymers through sequential addition.

2.2. Synthesis of polyester–polyester block copolymers through simultaneous feeding of monomers

Simultaneous synthesis of block copolymers that follow the same ROP mechanism can be challenging and requires that the different monomers have very different reactivities with a particular catalyst, implying that one gets consumed much faster than the other (kinetic control), but even in that case transesterification in the system can turn blocky structures into random copolymers. For example, polymerization of unsaturated macrolactones such as globalide (macrolactone) and 1,5-dioxepan-2-one (DXO) formed random copolymers in the presence of Novozym 435 as a catalyst (Candida Antarctica Lipase B immobilized). This scrambling occurred despite the different reactivity ratios of those two monomers.[78]

Waymouth and coworkers addressed this issue in 2011, reporting Zwitterionic ROP as a strategy for gradient (block-like) copolymers in the simultaneous copolymerization of ε-CL and δ-VL with nucleophilic N-heterocyclic carbenes.[79] Both

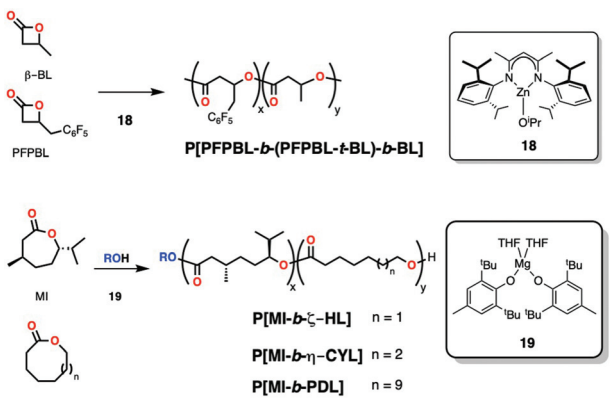
linear and cyclic products (obtained in the presence and absence of alcohol respectively) contained a larger fraction of homo-dyads than hetero-dyads by $^{13}C\{^1H\}$ NMR spectroscopy compared to the control experiment with tin(II) octoate, corroborating the blocky-structure of the copolymers.

2.2.1. Metal-catalyzed synthesis of polyester blocks through the simultaneous addition of cyclic esters. More commonly, kinetic control has been reported for some metal complexes, capable of discriminating between monomers of different steric hindrance and ring-strain. Coates and coworkers reported a zinc β-diketiminate isopropoxide complex (**18**, Scheme 14) that was active in the polymerization of 4-membered lactones 3-substituted with fluorinated sidechains in toluene at 50 °C.[80] An equimolar mixture of the fluorinated lactones and *rac*-β-BL in the presence of this catalyst gave tapered block copolymers, as the fluorinated lactones reacted much faster than their non-fluorinated analogues.

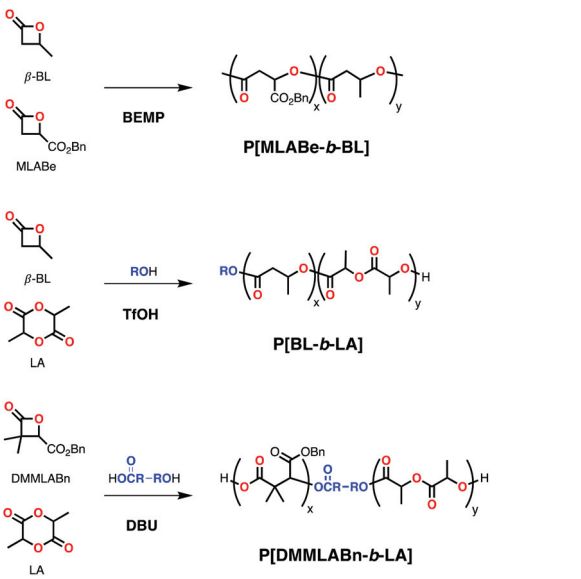
Recently, Dove and coworkers reported a simple magnesium phenoxide complex (**19**, Scheme 14) for the block-copolymerization of 3,6-disubstituted lactone menthide (MI) and larger lactones with minimal ring-strain like ζ-heptalactone (ζ-HL, 8-membered ring) or η-caprylolactone (η-CYL, 9-membered ring) in toluene at 80 °C (Scheme 14). In a mixture of monomers, the magnesium complex polymerized the more reactive MI followed by the less strained lactone to give block-like macromolecules (M_n up to 18 400 Da; $Đ$ = 1.50), as evidenced by the presence of major homocoupling carbonyl diads in $^{13}C\{^1H\}$ NMR spectroscopy (with only a minor presence of heterocoupling diads). Previously, the same group had reported a similar degree of kinetic control in the polymerization of MI and ω-PDL (Scheme 14) as evidenced by conversion profiles and $^{13}C\{^1H\}$ NMR spectroscopy (M_n = 13 800 Da; $Đ$ = 2.41).[26c] Their rationale behind the kinetic control exhibited by this catalyst was that the initial formation of PMI block is "locked" against transesterification side reactions (due to the presence of methyl and isopropyl groups in each monomer unit) and once MI has been depleted, the second block starts forming and can only undergo transesterification mostly within itself. In contrast, reaction of MI with a more reactive lactone (such as ε-CL) forms completely random copolymers as the more reactive small monomer will react first and any incorporation of MI added at the chain end will rapidly be pushed to the middle of the chain by fast transesterification. Random copolymers in this case were evidenced by equal integration of homocoupling and heterocoupling diads in NMR spectroscopy.[81]

2.2.2. Organo-catalyzed synthesis of polyester blocks through the simultaneous addition of cyclic esters. Among the different organocatalysts (TBD, DBU and BEMP, Scheme 9) explored by Guillaume and coworkers[40] for the block copolymerization of *rac*-β-BL and MLABe (Scheme 2), only BEMP was capable of forming block copolymers (Scheme 15) from the simultaneous addition of monomers (M_n = 15 000 Da; $Đ$ = 1.65), polymerizing first more sterically hindered MLABe and then *rac*-β-BL (despite homopolymerizations having very similar rates). In comparison, TBD and DBU only polymerized MLABe in the simultaneous addition, indicating inhibition in the polymerization of *rac*-β-BL, although no detailed mechanistic studies were presented.[40]

In 2013, Basko and coworkers reported another organocatalytic system capable of block-copolymerization with simultaneous feeding of monomers: triflic acid (TfOH, Scheme 9) in the presence of alcohol copolymerized *rac*-β-BL and L-LA in CH_2Cl_2 at room temperature through an activated monomer mechanism. The conversion profile showed that *rac*-β-BL was polymerized quickly with this system (in less than an hour) and L-LA was consumed following an induction period after full conversion of *rac*-β-BL (Scheme 15). Formation of a block copolymer (M_n = 3420 Da; $Đ$ = 1.20) was corroborated by $^{13}C\{^1H\}$ NMR spectroscopy and thermo gravimetric analysis (TGA).[82]



Scheme 14 Zinc and magnesium complexes active in the synthesis of block and block-like copolymers through the simultaneous addition of monomers.



Scheme 15 Synthesis of block copolymers by different organocatalysts with simultaneous feeding of monomers.

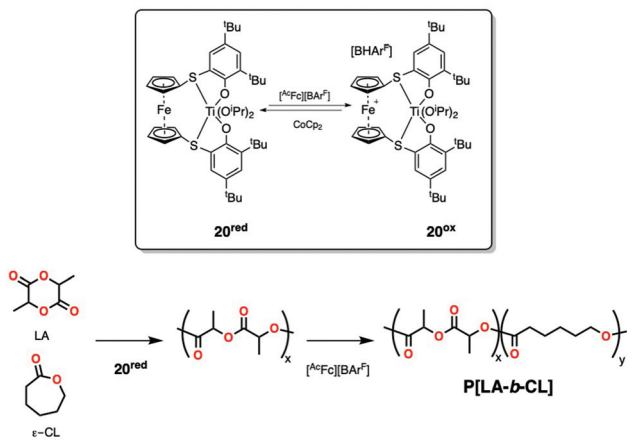
Exploiting the previously reported *O*-alkyl cleavage ROP of β-lactones catalyzed by carboxylate salts,[83] Coulembier and coworkers employed a bifunctional hydroxyl-carboxylic acid initiator in the presence of DBU to achieve dual activation of β-lactone 2,2-dimethylbenzyl-β-malolactone (DMMLABn) and lactide in the simultaneous addition of monomers (Scheme 15).[84] The dual polymerization occurs first by an acid-base reaction between the carboxylic group in the initiator and DBU, forming a carboxylate group that polymerizes DMMLABn (with a carboxylate-propagating species). The carboxylate propagating species also works as an activator of the alcohol chain-end to polymerize LA (with an alcohol-propagating species). The resulting block copolymers (M_n = 12 450 Da; $Đ$ = 1.46), however suffered from transesterification and large dispersities when long reaction times were applied.

2.2.3. Redox-switchable systems for the synthesis of polyester blocks through the simultaneous addition of cyclic esters. Some of the most exquisite systems offer control in ROP of cyclic esters through external stimuli such as redox-,[85] allosteric-,[86] or thermal-switches.[73a,87]

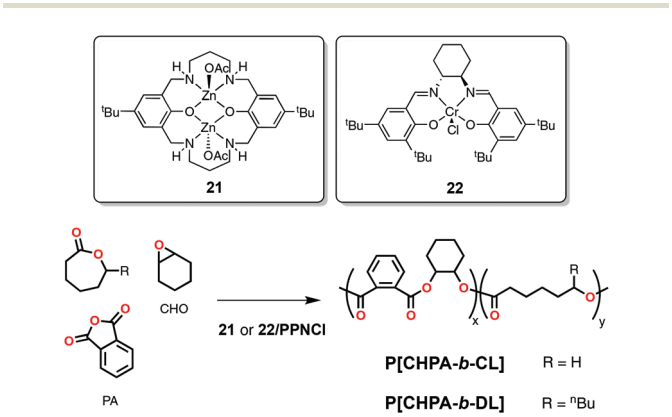
Diaconescu and coworkers exploited ligand conformational changes through redox switching for the block copolymerization of very similar monomers L-LA and ε-CL.[88] The authors tested different zirconium and titanium alkoxide complexes supported by redox-active ferrocene-based ligands. Block copolymerization in a mixture of monomers was achieved by chemical redox switching using a titanium complex (**20^{red}**, Scheme 16) that on its reduced form was active in LA polymerization and on its oxidized form (**20^{ox}**, Scheme 16) was much more active for ε-CL polymerization, yielding PLA-*b*-PCL (M_n = 3230 Da; $Đ$ = 1.12). Narrow dispersity indicated a controlled polymerization, but only low conversions of monomer were achieved (as an increase in reaction times led to a decrease in substrate selectivity). Formation of multiblock copolymers through several switches was not reported.[88a]

2.2.4. ROP/ROCOP systems for the synthesis of polyester blocks through simultaneous addition of monomers. Another common strategy for the synthesis of polyester block copolymers is tandem catalysis involving two different mechanisms. Methods to switch polymerization cycles *in situ* are attractive because of their convenience and also the increased diversity of blocks accessible.[11b] In 2015, Williams and coworkers reported one of the first catalysts active in both ROP of cyclic esters and ring-opening copolymerization (ROCOP) of epoxides and anhydrides leading to the controlled formation of triblock and multiblock polyesters. The dinuclear zinc aryl complex employed was reacted with a diol *in situ*, showing high activity in the copolymerization of phthalic anhydride (PA) and cyclohexene oxide (CHO) with high selectivity (>99% polyester linkages), and good control of the molecular weight. When mixing the two monomers with ε-decalactone (ε-DL) at 100 °C and using excess of epoxide as the solvent, the zinc catalyst catalyzed the ROCOP first with high selectivity (as no change in ε-DL concentration was detected during this period) and once the PA was consumed, the catalyst proceeded to polymerize the lactone. Formation of block copolymers by this methodology was attested by $^{13}C\{^1H\}$ and ^1H DOSY NMR spectroscopy (M_n = 15 900 Da; $Đ$ = 1.21). The ability of this catalyst to switch between two different polymerization cycles was rationalized by the very different rates of insertion of PA and ε-DL into the zinc alkoxide bond.[89]

Using a variation of this catalyst, a dinuclear zinc acetate complex (**21**, Scheme 17) Williams and coworkers reported the formation of block copolymers from mixtures of PA, CHO and ε-CL (M_n = 22 500 Da; $Đ$ = 1.46). DFT studies performed on this system revealed that selectivity results from lower activation barriers (lower for anhydride insertion) and more stable linkages during polymerization (more thermodynamically stable ester linkages from ROCOP).[90] The same group also reported that commercially available chromium(III) salen complex (**22**, Scheme 17) was competent in both ROP of ε-DL and ROCOP of different anhydrides with CHO in the presence of an equimolar amount of bis(triphenylphosphoranylidene) imminium



Scheme 16 Redox-switchable system active in the one-pot block copolymerization of lactide and ε-caprolactone with simultaneous feeding of monomers.



Scheme 17 Catalysts active in the tandem ROCOP of anhydrides/epoxides and ROP of lactones for the synthesis of polyester block copolymers.

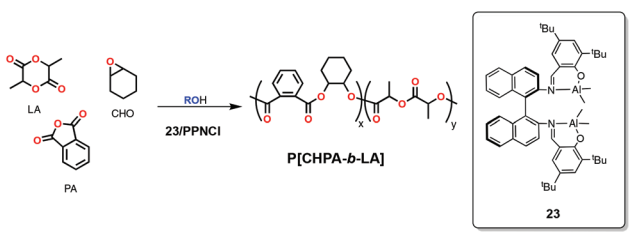
chloride (PPNCl) as a cocatalyst. Polymerizations were carried out under immortal conditions at 100 °C in toluene-d_8 using 1,2-cyclohexanediol as a chain-transfer agent to yield low molecular weight triblock copolymers with good control (M_n = 4430 Da; $Đ$ = 1.20). In a similar way to the bimetallic zinc complex **21**, the chromium salen complex **22** showed high selectivity to alternating polyesters through ROCOP in a mixture of different monomers with high activity and no significant ROP activity. Once the anhydride was consumed catalyst switched to ROP of ε-DL. The large scope of anhydrides tested allowed for post-functionalization through the thiol-ene reaction.[91]

More recently, Mazzeo and coworkers employed a bimetallic aluminum alkyl complex bearing salen-type ligands with dinaphthalene Schiff bases (**23**, Scheme 18) in the same reaction using PA, CHO and L-LA in toluene at 110 °C and in the presence of isopropyl alcohol and PPNCl as a cocatalyst. Formation of an alkoxide species *in situ* was active in ROCOP, but with a lower selectivity (81% polyester linkages) compared to William's systems (*vide supra*).[90] Following ROP of lactide formed a block copolymer with high molecular weight (M_n = 61 000 Da; $Đ$ = 1.44).[92]

In contrast to metal-base systems, organocatalysts do not typically combine ROCOP and ROP in a controlled fashion for the synthesis of block copolymers from a mixture of monomers. One of rare example was reported independently by Zhao,[93] Wang, Li and their coworkers[94] and involved the use of a non-nucleophilic phosphazene base (*t*-BuP_1) with alcohol at 60 or 100 °C for the polymerization of PA with different epoxides and *rac*-LA.[93] As it was observed with the metal-based systems (*vide supra*), ROCOP of PA and epoxides took place first with high selectivity, followed by ROP of LA in a tandem mechanism giving diblocks, triblocks or pentablocks with very good control (M_n up to 31 300 Da; $Đ$ = 1.09).

3. Synthesis of polyether–polyester blocks

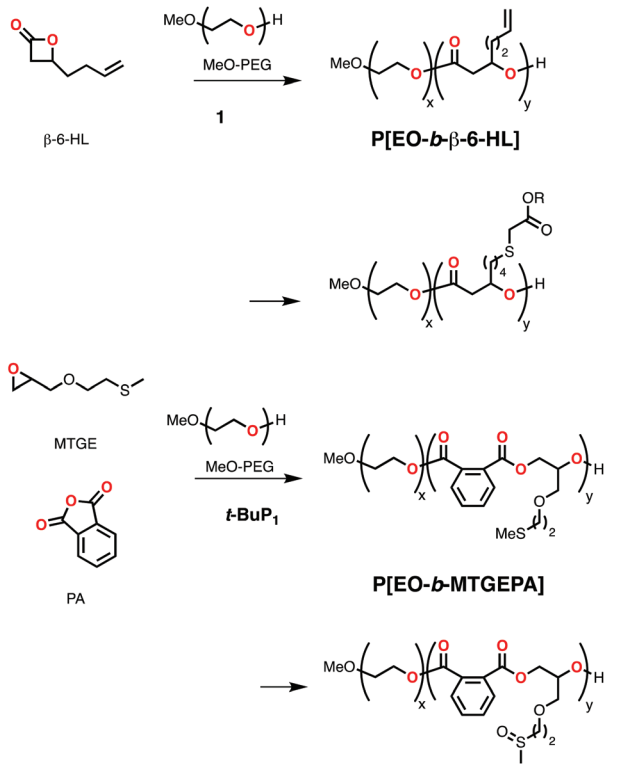
Polyester–polyether block copolymers can be synthesized by ROP of cyclic ethers and lactones. Although multiple metal-based initiators and organocatalysts have been reported to give a controlled polymerization of these molecules, very often a catalytic system optimal for the polymerization of one monomer is inactive or leads to uncontrolled polymerization of the other. Consequently, many of the synthetic procedures reported for the synthesis of polyester–polyether blocks require multiple steps involving different catalytic systems and the purification of intermediates. Some approaches include controlled polycondensation reactions between two preformed polymers[95] and their linkage through post-functionalization (*e.g.* click reactions).[96]



Scheme 18 Aluminum complex active in the tandem ROCOP of anhydrides/epoxides and ROP of lactide for the synthesis of polyester block copolymers.

By far the most common synthetic strategy involves using commercially available polyethers such as polyethylene glycol/oxide (PEG/PEO), polytetramethylene oxide (PTMO), polypropylene oxide (PPO) or poloxamers as macroinitiators in the ROP of the cyclic ester in the presence of a suitable catalyst. In this fashion, block copolymers of LA,[97] ε-CL,[98] δ-VL,[83b,99] β-BL,[100] ω-PDL,[101] *O*-carboxyanhydrides (OCAs)[102] and other functionalized monomers[103] have been accessed. In particular, ROP of OCAs has attracted significant interest due to their straightforward synthesis from naturally abundant precursors and easy access to functionalized monomers.[104] Other functionalized monomers based on ε-CL and LA have also been employed in their copolymerization with PEG macroinitiators to make diblock and triblock copolymers.[105]

The most widely used initiator for these polymerizations is tin(II) octoate, which works well with most common 6- or 7-membered rings in the presence of a hydroxy-capped polyethers, yielding polyester–polyether block copolymers with good control over molecular weight (dispersities as low as 1.1, given that a monodispersed macroinitiator is used). In order to copolymerize PEG and 4-membered lactones, Gillies and coworkers employed a salen aluminum alkyl complex **1** (Scheme 2) to polymerize challenging β-6-heptenolactone (β-6-HEL, Scheme 1) with excellent control in the presence of MeO-PEG (M_n = 2000 Da) forming amphiphilic diblocks (M_n = 12 910 Da; $Đ$ = 1.03) that could be subsequently functionalized through the thiol-ene reaction for application in drug delivery (Scheme 19).[106] Another notable exception is the polymerization of OCAs. Using organocatalysts such as DMAP or 4-methoxypyridine, Dove and coworkers have reported the polymerization of OCAs derived from malic acid (L- or D-MalOCA) in the presence of MeO-PEG (M_n = 7500 Da) to give amphiphilic diblock copolymers (M_n = 9400 Da; $Đ$ = 1.04) that form stable stereocomplexed micelles in solution.[102b] Polymerization of macrolactone ω-PDL or bioderived δ-decalactone (δ-DL) has also been achieved using organocatalyst TBD in the presence of diamino- or dihydroxy-capped PEG macroinitiator to give amphiphilic triblock copolymers.[101,107] Other organocatalytic systems such as DBU,[99] sparteine/thioureas[108] and phosphazene base *t*-BuP_2[57] have also been employed for the polymerization of cyclic esters in the presence of polyether macroinitiators. ROCOP of anhydrides and epoxides has also been performed in the presence of a polyether macroinitiator to make block copolymers. Recently, Xiao, Chen and coworkers employed phosphazene base *t*-BuP_1 in the presence of MeO-PEG (M_n = 5000 Da) for the polymerization of 2-(methylthio)ethylglycidyl ether (MTG, Scheme 1) and PA to make an amphiphilic block copolymer



Scheme 19 Synthesis of amphiphilic polyether–polyester block copolymers using PEG as a preformed block. Subsequent reactions lead to post-modification of the hydrophobic block in the copolymer.

(M_n = 12 500 Da; $Đ$ = 1.03) with redox-responsive properties for application in drug delivery (Scheme 19).[109]

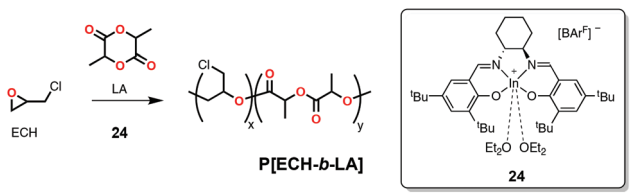
3.1. Synthesis of polyether–polyester blocks through the sequential feeding of monomers

The synthesis of amphiphilic polyester–polyether block copolymers has attracted a considerable attention as a route to novel drug and gene delivery vehicles with pH- or light-responsive properties.[110] While PEG has been the polyether of choice in these copolymers due to its wide availability, low toxicity, solubility in water and favorable pharmacological properties,[111] its use as a preformed block offers limited possibilities of functionalization. It is reasonable to expect a greater chemical diversity from more versatile synthetic methods. Combining the ROP of epoxides with other ring-opening polymerization and copolymerization reactions is an attractive strategy to access new polyester–polyether block copolymers with tunable properties.

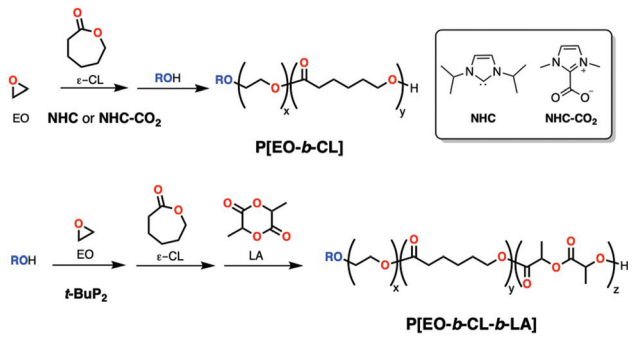
3.1.1. Metal-catalyzed synthesis of polyether–polyester blocks through the sequential polymerization of epoxides and cyclic esters. Using a bimetallic salen aluminum complex active in both ROP of CHO and cyclic esters, Mazzeo and coworkers synthesized PCHO-*b*-PCL (M_n = 11 100 Da; $Đ$ = 1.97) and PCHO-*b*-PLA (M_n = 11 000 Da; $Đ$ = 1.57) through the sequential feeding of CHO and ε-CL/L-LA. Interestingly, simultaneous feeding of the monomers afforded only the polyester even after prolonged reaction times.[112] Employing more Lewis acidic titanium and zirconium isopropoxide complexes bearing 8-hydroxyquinoline ligands, Chand and coworkers reported formation of blocky structures with simultaneous feeding of *t*-butyl glycidyl ether (*t*BGE) (Scheme 1) and L-LA by a faster polymerization of the cyclic ester.[113] No simultaneous feeding was attempted in this case.

More recently, Mehrkhodavandi and coworkers reported a cationic indium complex (**24**, Scheme 20) capable of polymerizing epoxides such as epichlorohydrin (ECH, Scheme 1) in a cationic mechanism and subsequently could polymerize *rac*-LA in a coordination-insertion mechanism to form block copolymers (Scheme 20).[114] The rationale in this case was that cationic polymerization of the epoxides led to the formation of a polyether block with a cationic chain-end (active in epoxide polymerization) and an alkoxide chain-end bound to a neutral indium species (active in lactide polymerization). Some of the block copolymers prepared in this fashion exhibited increased ductility and stiffness compared to *rac*-lactide homopolymer of similar molecular weight.[114] A disadvantage of this strategy was the lower-than-expected molecular weights based on the monomer to initiator ratios attributed to back biting and transesterification reactions.

3.1.2. Organo-catalyzed synthesis of polyether–polyester blocks through the sequential polymerization of epoxides and cyclic esters. In contrast to metal-based systems, different organocatalyst-based systems have been employed individually or in combination for the sequential ROP of epoxides and lactones to block copolymers. A very common problem of reported systems that are active in both the ROP of epoxides and lactones is transesterification, as epoxides require stronger bases for their polymerization.[111] A notable exception is N-heterocyclic carbenes; first reported by Hedrick, Waymouth and coworkers to be highly efficient in the living polymerization of cyclic esters,[115] and later employed by Gnanou, Tatou and coworkers in the zwitterionic polymerization of ethylene oxide (EO). Using the N-heterocyclic carbene (NHC) 1,3-diisopropylimidazol-2-ylidene (Scheme 9), linear polyethers were synthesized with the addition of a protic terminating agent (*i.e.* water or benzyl alcohol) and block copolymers were formed *in situ* (M_n = 10 400 Da; $Đ$ = 1.08) with the subsequent addition of ε-CL (Scheme 21).[116] Later, Limbach and coworkers adapted this strategy using more stable NHC-CO_2 precursors that could generate free NHCs *in situ* when heated to 120 °C



Scheme 20 Cationic indium complex active in the block copolymerization of epichlorohydrin and lactide through the sequential addition of monomers.



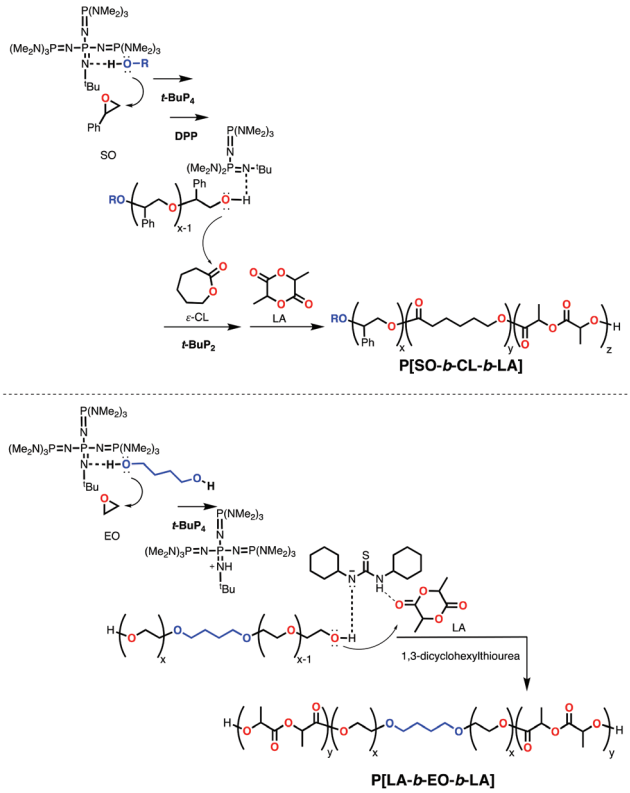
Scheme 21 Catalysts active in the sequential polymerization of ethylene oxide and cyclic esters.

reaching good catalytic activities in the formation of block copolymers in a sequential fashion (Scheme 21).[117]

Another initiator that shows controlled reactivity towards epoxides and cyclic esters is phosphazene *t*-BuP_2 (Scheme 9). Hadjichristidis and coworkers reported its rather slow activity in the polymerization of EO (days) through activation of 3-phenyl-1-propanol or water in a pseudo-anionic mechanism. Subsequent addition of ε-CL formed block copolymers in a living fashion that allowed further addition of L-LA for multiblock synthesis (M_n = 4600 Da; $Đ$ = 1.03), but only in that order as ε-CL couldn't be polymerized after L-LA (Scheme 21). In this case, the choice of phosphazene base is crucial as the use of the more basic *t*-BuP_4 brings about extensive transesterification in the polyesters blocks and less basic *t*-BuP_1 is not active in epoxide ROP.[118]

To improve upon their phosphazene polymerization system, Hadjichristidis and coworkers reported a catalyst-switch strategy using strong base *t*-BuP_4 (Scheme 9) in the presence of an alcohol for the fast polymerization of epoxides, followed by an addition of protic diphenyl phosphate (DPP) in excess to quench the phosphazene base. After a couple of minutes, δ-VL or ε-CL were added to the reaction mixture and were polymerized by the remaining DPP in an activated monomer mechanism, forming block copolymers with excellent control. This was not only faster than the previously reported, but also showed living epoxide ROP and allowed the use of bulkier butylene oxide (BO) together with EO for the synthesis of triblock PBO-*b*-PEO-*b*-PCL (M_n = 15 100 Da; $Đ$ = 1.09).[119] This methodology was later expanded to the block copolymerization of bulky epoxides BO or 2-ethylhexyl glycidyl ether (EHGE) (Scheme 1) with bulky, bioderived 5-substituted δ-valerolactones.[120] As DPP is not a suitable initiator for LA polymerization, the strategy was modified by addition of a stoichiometric amount of DPP (to phosphazene base) after polymerization with *t*-BuP_4. Subsequent addition of *t*-BuP_2 and cyclic esters allowed the formation of triblock copolymers (Scheme 22) PSO-*b*-PCL-*b*-PLA (M_n = 13 700 Da; $Đ$ = 1.16) by the sequential polymerization of styrene oxide (SO), ε-CL and L-LA.[121]

Similar catalyst-switch strategies have been reported with other organocatalysts. In 2016, Zhao and coworkers employed



Scheme 22 Catalyst-switch strategy for the block-copolymerization of epoxides and cyclic esters through the sequential addition of monomers.

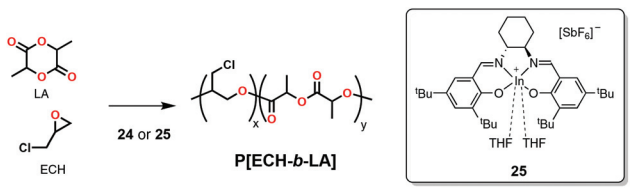
a base-to-base switch approach involving initial polymerization of EO by *t*-BuP_4 in the presence of 1,4-butanediol followed by addition of stoichiometric 1,3-dicyclohexylthiourea (to phosphazene base). Deactivation of strong phosphazene-alkoxide complex led to the formation of a weaker thioureate anion and an alcohol in an equilibrium that could polymerize either L-LA or ε-CL. This base attenuation strategy allowed for the formation of triblock copolymers (Scheme 19) at room temperature with excellent control PLA-*b*-PEO-*b*-PLA (M_n = 9900 Da; $Đ$ = 1.01) and PCL-*b*-PEO-*b*-PCL (M_n = 21 100 Da; $Đ$ = 1.11).[122] The mechanism at play might be a dual activation of the monomer and the chain-end as previously described by Waymouth and coworkers in their very active and selective thiourea/alkoxide systems.[123] Using activator 1,3-diphenylthiourea with higher acidity significantly affected the polymerization of ε-CL (but not of L-LA), giving very low conversions even at 40 °C. The even more acidic activator 1,3-bis[3,5-bis(trifluoromethyl)phenyl]thiourea (pK_a 8.5, DMSO[124]) was not active in any cyclic ester polymerizations, evidencing that the basicity of the ureate plays a key role in the modulation of alkoxide strength. Guo and coworkers adopted a similar switching strategy polymerizing first glycidyl phenyl ether (GPE) through an anionic mechanism with tetrabutylammonium fluoride (TBAF) at 50 °C. Cooling down the reaction mixture to room temperature and adding a mixture of 1-(3,5-bis(trifluoromethyl)phenyl)-3-phenylthiourea and LA

formed block copolymers with good control and no transesterification over extended periods of time (M_n = 7600 Da; $Đ$ = 1.19). Not surprisingly, these optimal conditions favorable for LA could not form block copolymers with ε-CL.[124]

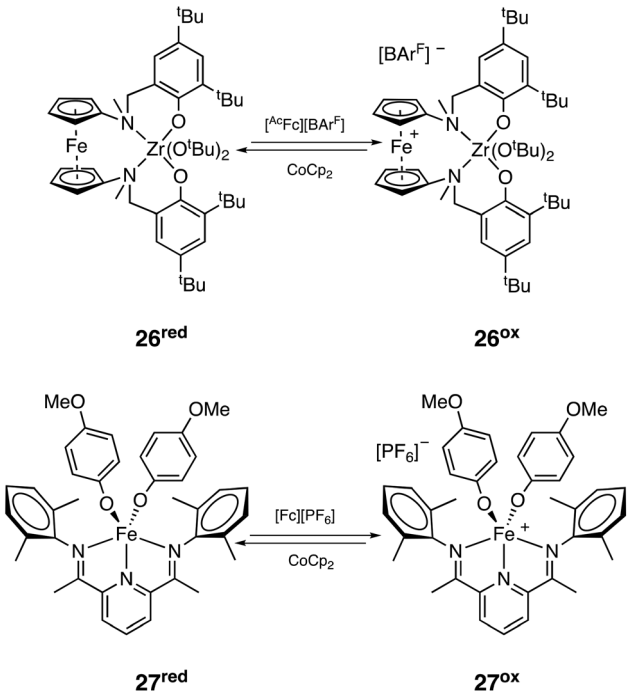
3.2. Synthesis of polyether–polyester blocks through simultaneous feeding of monomers

Cationic complex **24** (Scheme 20) as well as complex **25** (Scheme 23)[125] were reported by Mehrkhodavandi and coworkers to form block copolymers from epoxide and cyclic ester mixtures through the coupling of cationic and coordination-insertion mechanisms (Scheme 23). The complexes could polymerize a mixture of epichlorohydrin (ECH) and *rac*-LA in 1 hour at 130 °C forming block copolymers with monomodal molecular weight distributions, but with a significantly lower-than-expected molecular weight (based on monomer to initiator ratios), even more when compared to the sequential addition method (*vide supra*).[125] When comparing the two complexes, the authors found that complex **24** with the bigger and less-coordinating tetrakis(3,5-bis(trifluoromethyl)phenyl) borate (BAr^F) as counterion yielded more controlled copolymerization (M_n = 64 447 Da; $Đ$ = 1.35) than **25** (M_n = 10 130 Da; $Đ$ = 2.67).

3.2.1. Redox-switchable systems for the synthesis of polyether–polyester blocks through the simultaneous addition of epoxides and cyclic esters. Some of the most impressive systems capable of selective polymerization of epoxides and LA in a mixture of monomers base their activity on redox switches. Further expanding their work on redox catalysis, Diaconescu and coworkers applied a zirconium alkoxide complex supported by a ferrocene-based ligand in the block copolymerization of CHO and L-LA (Scheme 24).[126] In contrast to previously studied ferrocene-based titanium complexes applied in the block copolymerization of L-LA and ε-CL, this system exhibited a highly orthogonal activity for the epoxide and cyclic ester couple. Starting from the oxidized version of the catalyst (**26^{ox}**, Scheme 24), CHO was polymerized with only trace conversion of LA. Addition of a reductant ($CoCp_2$) activated LA polymerization forming PCHO-*b*-PLA (M_n = 12 300 Da; $Đ$ = 1.44). Reverse switch starting from the reduced version of the catalyst (**26^{red}**, Scheme 24) was not as controlled due to side reactions of the added oxidant acetyl ferrocenium tetrakis (3,5-bis(trifluoromethyl)phenyl)borate ([^{Ac}Fc][BAr^F]) with CHO, but block copolymers with good control could still be formed



Scheme 23 Cationic indium complex active in the block copolymerization of epichlorohydrin and lactide through the simultaneous addition of monomers.



Scheme 24 Redox-switchable system active in the copolymerization of cyclohexene oxide and lactide in a mixture of monomers.

through sequential addition PLA-*b*-PCHO-*b*-PLA (M_n = 16 900 Da; $Đ$ = 1.25).[126] Byers and coworkers also reported a redox switching system based on a bis(imino)pyridine iron complex that could cycle between neutral iron(II) (**27^{red}**, Scheme 24) and cationic iron(III) (**27^{ox}**, Scheme 24) with orthogonal activity towards *rac*-LA and CHO. Interestingly, diblock copolymers (M_n up to 12 500 Da; $Đ$ = 1.40) could be formed with the system switching from both the oxidized and reduced forms, but always with some formation of PCHO homopolymer (which could be removed by selective precipitation). Block copolymers synthesized by the sequential addition of monomers had similar properties to those synthesized by simultaneous feeding, further confirming the selectivity of the system in a mixture of monomers.[127] Some years later, the same group reported an adaptation of their iron system to make it work under electrochemical switches, obviating the need of adding sacrificial redox agents (M_n up to 40 300 Da; $Đ$ = 1.80).[128]

3.2.2. ROP/ROCOP systems for the synthesis of polyether–polyester blocks through the simultaneous addition of epoxides and anhydrides. As the selective formation of block copolymers from monomer mixtures by ROP of epoxides and cyclic esters is not straightforward, much research has focused on the ROCOP of anhydrides and epoxides, driven by the excellent results in the combination of ROCOP and ROP for the synthesis of polyester–polyester blocks with a high control (*vide supra*). Nozaki and coworkers[129] pioneered this strategy reporting different manganese(III) and iron(IV) corrole complexes with electron withdrawing substituents that in the pres-

ence of cocatalyst bis(triphenylphosphoranylidene)-iminium pentafluorobenzoate ($PPNOBzF_5$) were active in the ROCOP of glutaric anhydride (GA) and PO to give perfectly alternating polyesters. When the epoxide was added in excess compared to the anhydride, the formation of a polyether block took place right after anhydride consumption, yielding diblock copolymers (M_n = 23 700 Da; $Đ$ = 1.50).[129] More recently, Williams and coworkers exploited a similar strategy for the well-controlled synthesis of multiblock polyester–polyether macromolecules.[130] Employing a commercial salen chromium(III) chloride catalyst (**22**, Scheme 17) in the presence of PPNCl and alcohol as a chain-transfer agent, different substituted epoxides could be copolymerized with different anhydrides to give highly alternating polyesters (>95% polyester linkages). Once the anhydride was totally consumed the system could switch to a ROP mechanism in the presence of excess epoxide to make polyester–polyether block copolymers. Although the same system was reported earlier for the synthesis of polyester–polyester blocks in mixtures of anhydrides, CHO and ε-DL with no evidence of polyether formation (*vide supra*),[91] here the use of monosubstituted epoxides (instead of CHO) provided a lower barrier for epoxide homopolymerization. Using 1,2-cyclohexanediol as a chain-transfer agent, the system could be switched several times between ROCOP and ROP by further additions of anhydride and epoxide. This very convenient chemical switch strategy allowed isolation of multiblock copolymers of up to 15 blocks (M_n = 17 800 Da; $Đ$ = 1.38), with the notable advantage of producing functionalized polymer structures with controlled molecular weights.[130]

Another promising strategy employs Lewis acid/base pairs for the synthesis of these block copolymers. Building up on their previous work,[131] Wang, Li and coworkers applied the synergistic effect between phosphazene *t*-BuP_2 and BEt_3 for the ROCOP of PA and butylene oxide (BO) in the presence of a diol to give a linear polyester. Starting the polymerization with 2 equivalents of BEt_3 per phosphazene equivalent and an excess of BO makes possible the switch to BO ROP after all anhydride has been consumed, forming the desired triblock copolymers with good control (M_n up to 113 100 Da; $Đ$ = 1.14). As the *t*-BuP_2 phosphazene alone is weak to induce BO polymerization and also leads to significant transesterification in the polyester synthesis, the authors hypothesized that the addition of the Lewis acid serves two purposes: one being the tuning of alkoxide nucleophilicity and the other being epoxide activation for polymerization (through an activated monomer mechanism). This methodology was applied to different epoxides and anhydrides, maintaining excellent control.[132] Also, Zhao and coworkers reported a similar system based on *t*-BuP_1 and BEt_3 for the block copolymerization in mixtures of PA and PO or EO. Due to the lower basicity of *t*-BuP_1, polymerization trials required only 0.3–0.5 equivalents of BEt_3 to form controlled blocks (M_n up to 117 300 Da; $Đ$ = 1.12). An excess of Lewis acid slowed down ROCOP and led to a premature epoxide polymerization before full anhydride consumption precluding clean block formation.[133] This observation proved to be critical to later expand the scope of these systems (*vide infra*).

To further demonstrate the high versatility of the Lewis acid/base approach for switchable block copolymerizations in mixtures of monomers, Zhao, Ling and coworkers showed recently its applicability to the ROP of epoxides and cyclic esters. Using *t*-BuP_2 phosphazene and BEt_3 in different proportions, the catalytic system could switch from ROP of epoxides (excess of BEt_3) to the ROP of δ-VL or ε-CL (excess of *t*-BuP_2) in a clean manner and with no transesterification, by just adding Lewis acid or Lewis base. This elegant system could also form uncommon block copolymers of reversed sequence such as PCL-*b*-PEO and PEO-*b*-PCL-*b*-PEO, which are difficult to obtain with more traditional synthetic methods that employ preformed PEG/PEO. With multiple switches, a pentadecablocks could be formed with excellent control (M_n = 40 000 Da; $Đ$ = 1.07).[134]

4. Synthesis of polycarbonate–polyester blocks

Aliphatic polycarbonates are an attractive class of materials with tunable glass transition temperatures,[135] high toughness[136] and biodegradability.[137] They can be synthesized from the ROP of 5-, 6- or 7-membered ring cyclic carbonates, many of which can be readily accessed from glycerol, a byproduct of biodiesel synthesis.[138] Block copolymers containing polyester and polycarbonate segments are fully biodegradable materials that show improved toughness (in comparison to the polyester homopolymer) as well as improved stability and ductility.[139]

4.1. Synthesis of polycarbonate–polyester blocks through polymerization of cyclic carbonates and cyclic esters

4.1.1. Metal-catalyzed synthesis of polycarbonate–polyester blocks through polymerization of cyclic carbonates and cyclic esters. 6-Membered ring trimethylene carbonate (TMC, Scheme 1) has been block-copolymerized with L-LA to yield copolymers with improved elongation at break (compared to PLA). Using benzyl alcohol or 1,3-propanediol as chain-transfer agents and their previously reported zinc β-diketiminate amide complex (**3**, Scheme 2), Guillaume, Carpentier and coworkers reported the sequential polymerization of TMC first (at 60 °C) and then L-LA (at 100 °C) to yield diblock (M_n = 85 000 Da; $Đ$ = 1.56) and triblock (M_n = 77 150 Da; $Đ$ = 1.50) copolymers.[140] In the same study, it was shown that organocatalysts DMAP and BEMP (Scheme 9), as well as $Al(OTf)_3$ were also active for this block copolymerization in the presence of an alcohol, but with lower reactivities compared to **3**. Interestingly, the simultaneous addition of monomers still produced in some cases blocky-microstructures with different reactivity profiles for the different monomers (despite showing similar rates in the sequential addition): the zinc β-diketiminate complex **3** polymerized first and preferentially L-LA, while $Al(OTf)_3$ first polymerized preferentially TMC.[140] Polymerization with the simultaneous addition using organocatalyst TBD gave random copolymers.[141] Later, the same group applied a similar sequential addition strategy (first

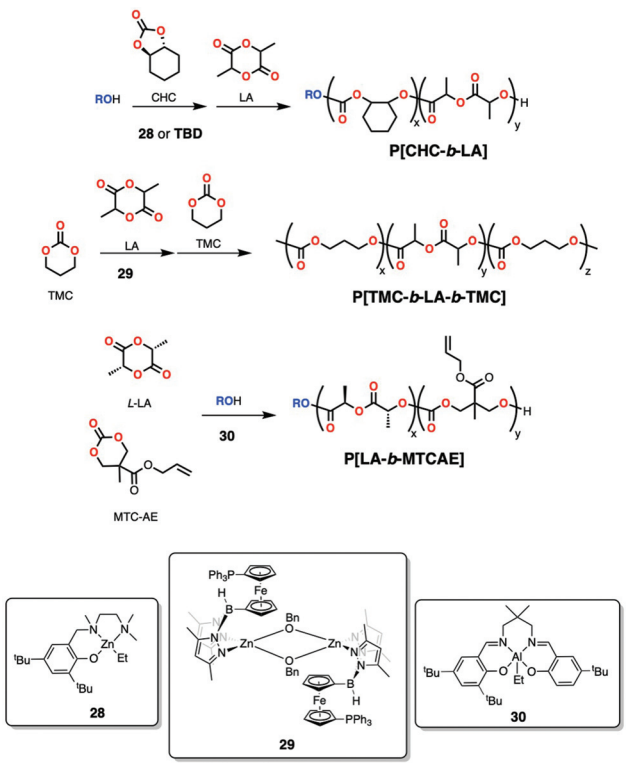
cyclic carbonate ROP at 60 °C followed by lactone ROP at 100 °C) to accomplish the block copolymerization of *rac*- or *R*,*R*-*trans*-cyclohexene carbonate (CHC, Scheme 9) with L-LA (M_n up to 28 000 Da; $Đ$ = 1.7) using a diaminophenolate zinc alkyl complex in the presence of an alcohol (**28**, Scheme 25).[142] Similar results could be obtained with organobase TBD or with yttrium amide $Y[N(SiMe_3)_2]_3$, but with lower activities. Very importantly, no decarboxylation (a side-reaction that leads to the formation of ether linkages) was observed in any of the products. Copolymerization carried out in the reverse order (first LA, then CHC) afforded random copolymers *via* extensive transesterification, just as simultaneous feeding of monomers also yielded random copolymers.[142]

As the order of addition of monomers is often an issue for these systems, formation of polyester–polycarbonate multiblock copolymers is not easily attainable. Recently, Diaconescu and coworkers reported the first system that allows multiple additions of L-LA and TMC to yield multiblock copolymers. The bimetallic zinc complex supported by heteroscorpionate ligands with pendant ferrocene groups (**29**, Scheme 25) could polymerize both monomers in a living fashion and support multiple addition of monomers to make tri, tetra and pentablock copolymers (M_n up to 58 900 Da; $Đ$ = 1.49) with monomodal molecular weight distributions and a characteristic diffusion coefficient by DOSY NMR spectroscopy.[143]

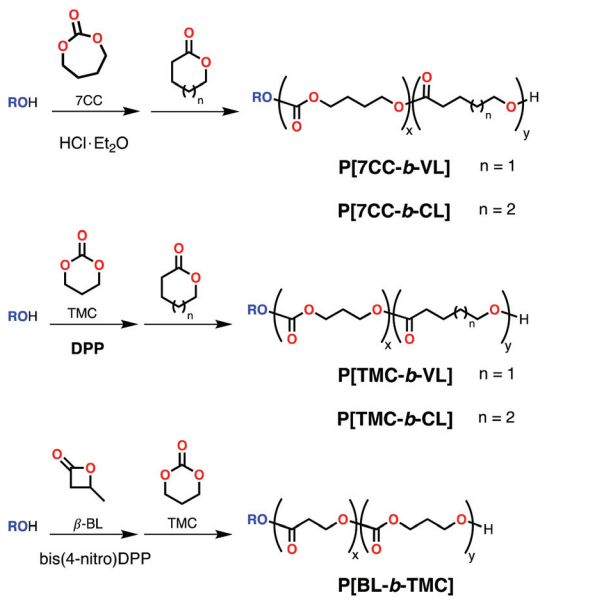
Exploiting significantly different rates of ROP of L-LA and functional cyclic carbonate (MTC-AE) (Scheme 9) with a highly isoselective aluminum complex (**30**, Scheme 25), Cui, Liu and coworkers reported the synthesis of blocky-copolymers with the *simultaneous* addition of monomers.[144] In comparison, highly heteroselective complex **2** (Scheme 2) only produced random copolymers under the same conditions.

4.1.2. Organo-catalyzed synthesis of polycarbonate–polyester blocks through polymerization of cyclic carbonates and cyclic esters. Larger 7-membered cyclic carbonate 1,3-dioxepan-2-one (7-CC, Scheme 9) has been block copolymerized in a controlled fashion with ε-CL and δ-VL through sequential addition using a strong Brønsted acid (HCl etherate) in the presence of an alcohol or water (Scheme 26). The polymerization followed an activated-monomer mechanism and behaved in a living fashion, yielding block copolymers with low dispersities (close to 1.1).[145] Also following an activated-monomer mechanism, Kakuchi and coworkers have reported the sequential synthesis of diblocks PTMC-*b*-PVL (M_n = 9760 Da; $Đ$ = 1.14), PTMC-*b*-PCL (M_n = 10 500 Da; $Đ$ = 1.12) and PBL-PTMC (M_n = 7170 Da; $Đ$ = 1.21) with good control using alcohols and DPP (Scheme 9) or significantly more acidic bis(4-nitro)DPP bearing electron withdrawing groups (Scheme 26).[146] Block copolymers of TMC with LA could also be obtained in a similar fashion (using DPP/alcohol), but only with co-addition of DMAP during the LA polymerization step (as DPP/alcohol system alone does not polymerize LA).

An important advantage of cyclic carbonates over cyclic esters is their greater diversity of functional side-groups available by chemical synthesis, requiring either 1,2- or 1,3-diols or an olefin, which can often come from bioderived sources.[147] Such side-groups can impart hydrophilicity to polycarbonates or allow for incorporation of cargo molecules. In 2011, Song and coworkers reported the ROP of an azido-functionalized cyclic carbonate with L-LA using organobase DBU and an



Scheme 25 Sequential polymerization of cyclic carbonates and lactide.

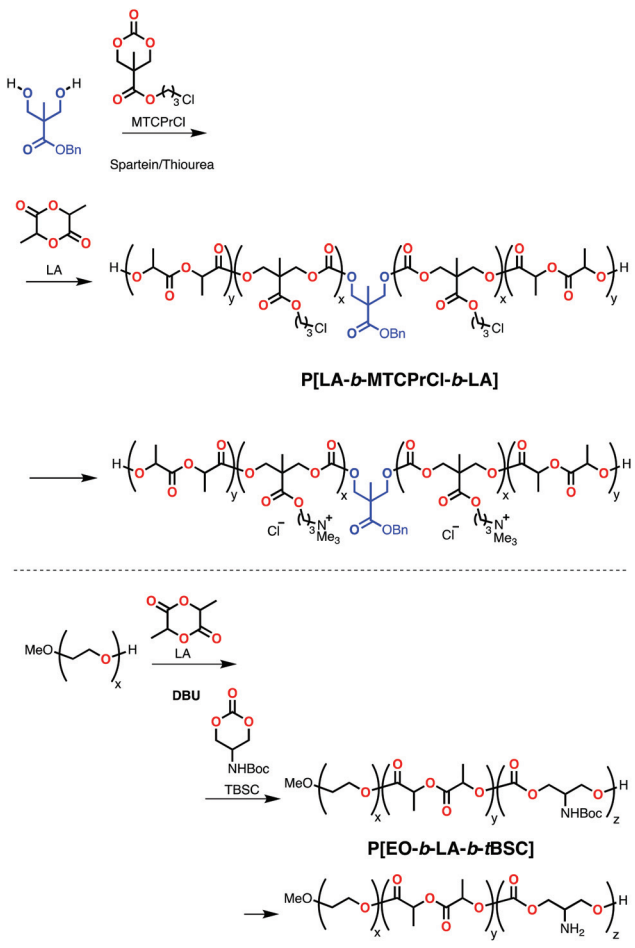


Scheme 26 Sequential polymerization of cyclic carbonates and cyclic esters using organic and inorganic acids as initiators in the presence of alcohols.

alcohol to make block and random copolymers that could later be reacted with different alkynes to install different functional groups in the polymer backbone.[148]

Following their reports on the synthesis of 5-functionalized 5-methyltrimethylene carbonates (MTCs),[149] Hedrick and coworkers reported the synthesis of a triblock copolymer with a polycarbonate core bearing pending halide groups that could be post-functionalized to quaternary ammonium groups with antimicrobial activity. Block copolymer synthesis was achieved through the sequential polymerization of the MTC first, followed by addition of D-LA using a diol and a spartein/thiourea couple (Scheme 27).[150] Alexander, Taresco and coworkers employed a trimethylene carbonate derived from serinol (*t*BSC) to form triblock amphiphilic copolymers PEG-*b*-PLA-*b*-*t*BSC using DBU and methyl PEG as a macroinitiator. The block copolymer could be deprotected and post-functionalized to bear a drug molecule by reaction of the free amine groups in the carbonate backbone (Scheme 27).[151]

Using TBD (Scheme 9) and an alcohol for the polymerization of ε-CL and a functionalized cyclic carbonate, Albertsson and coworkers reported a sequential polymerization involving switches in temperature.[152] In this system, TBD/alcohol first polymerized ε-CL at 30 °C (only to low conversions to avoid transesterification) and then the reaction mixture was cooled to −40 °C, followed by addition of the cyclic carbonate. Under these conditions the cyclic carbonate was polymerized to full conversion in a matter of minutes and CL ROP was suppressed. Subsequent cycles of heating and cooling/addition of cyclic carbonate afforded multiblock copolymers.



Scheme 27 Block copolymerization of functionalized cyclic carbonates and lactide through sequential addition.

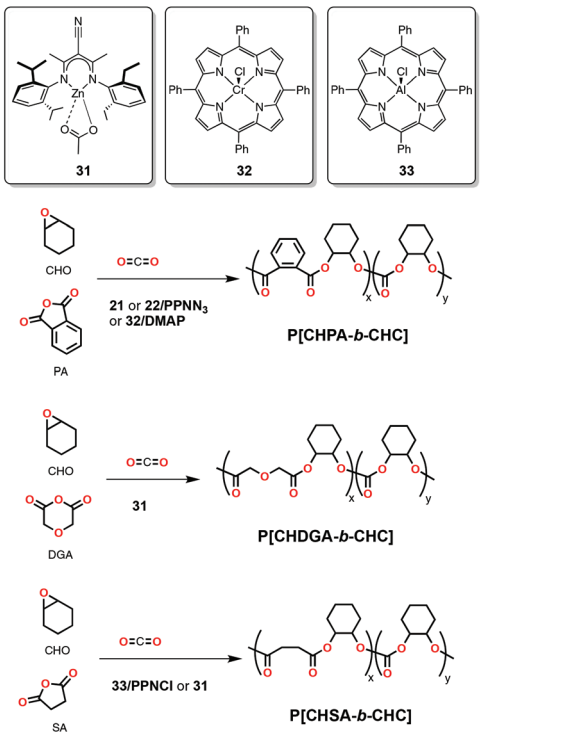
4.2. ROP/ROCOP Systems for the synthesis of polycarbonate–polyester blocks involving carbon dioxide incorporation

Using waste CO_2 as a reagent for the synthesis of polycarbonates is a powerful strategy with potential economic and environmental benefits.[153] Alternating ROCOP of petrochemically- or bio-derived epoxides with CO_2 offers a route to more sustainable homopolymers and copolymers through combination with other ROCOP and ROP mechanisms with exquisite control.[154]

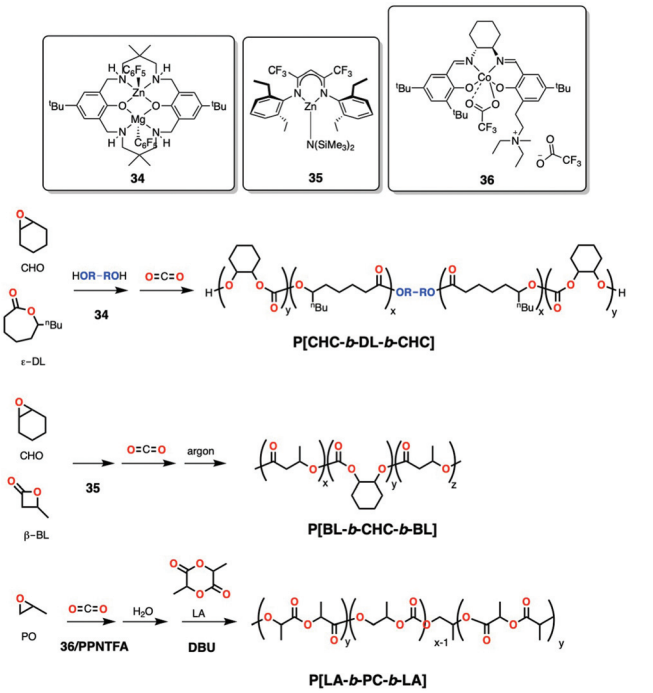
By far, the most common approach for the synthesis of polycarbonate–polyester blocks that incorporate CO_2 in their backbone combines ROCOP of epoxides and CO_2 with ROCOP of epoxides and anhydrides. In 2008, Coates and coworkers re-applied their previously reported zinc β-diketiminate acetate complex[155] (**31**, Scheme 28) to the synthesis of block copolymers in a mixture of monomers. Using such complex, mixtures of diglycolic anhydride (DGA) or succinic anhydride (SA) with cyclohexene oxide (CHO) could be polymerized in the presence of CO_2 to form block copolymers of perfectly-alternating polyesters and polycarbonate (Scheme 28) by means of kinetic resolution/control, *i.e.* anhydride/epoxide coupling having a much faster rate and therefore preceding CO_2/epoxide coupling.[156]

Independently, the Darensbourg[157] and Duchateau[158] research groups re-applied previously reported chromium(III) salen complex (**22**, Scheme 17) and phorphirine complex (**32**, Scheme 28) in the presence of different cocatalysts to the synthesis of block copolymers in mixtures of phthalic anhydride (PA) or other anhydrides with CHO/CO_2 (Scheme 28) following a similar kinetic control profile. Later, analogous cobalt(III) salen complex and aluminum phorphirine complex (**33**, Scheme 28) would also be developed for similar block copolymerizations.[159]

Similarly, Williams and coworkers have applied their dizinc acetate catalyst (**21**, Scheme 17) to the polymerization of mixtures of PA/CHO and CO_2 without the need for a cocatalyst.[90] Using DFT and spectroscopic analysis to study the high degree of kinetic selectivity, the authors showed that the acetate catalyst initially reacts with an epoxide monomer to form an intermediate alkoxide species which is common to both ROCOP mechanisms. This alkoxide not only has a lower kinetic barrier for PA insertion, but also forms a thermodynamically more stable ester linkage that propagates to form the polyester block, which explains the more favored ROCOP of anhydride/epoxide. Once the PA has depleted, the alkoxide intermediate (with a preformed polyester block) can incorporate CO_2 forming a polycarbonate block. Later, other dinuclear zinc- and magnesium-systems (homo- and heteronuclear)



Scheme 28 Metal catalysts (with and without cocatalysts) active in the tandem ROCOP of epoxides and anhydrides and ROCOP of epoxides and carbon dioxide.



Scheme 29 Metal catalysts (with and without cocatalysts) used alone or in conjunction with organobases active in the coupling of ROP of cyclic esters with ROCOP of epoxides and carbon dioxide.

would be developed by the same group for similar block copolymerizations.[160]

A different approach for the synthesis of polycarbonate–polyester blocks involves combining ROP of cyclic esters with ROCOP of epoxides and CO_2. This strategy is not only attractive because of the expanded monomer scope, but also because of the peculiarity of many of these systems for being directly switched on/off by the presence of CO_2. For example, the dizinc acetate catalyst (**21**, Scheme 17) reported by Williams group has been reported to form block copolymers in a mixture of CHO and ε-CL through the formation of an intermediate alkoxide species (produced by insertion of one CHO into the Zn–OAc bond) that is active in both ROCOP and ROP cycles.[90,161] In the presence of CO_2 gas (approx. 1 bar), ROCOP takes precedence and shuts down completely ROP: this is due to the rapid insertion of CO_2 into the metal alkoxide bond to form a Zn–carbonate bond active in ROCOP and inactive in ROP. In the absence of CO_2, ROP takes over. Likely, this is due to the slower insertion of ε-CL into the metal–alkoxide bond to form a polycarbonate–polyester block. As has been shown previously, this bimetallic system shows unprecedented chemoselectivity in a mixture of epoxides, lactones, anhydrides and CO_2 that allows the synthesis of polyester–polyester blocks and different polycarbonate–polyester blocks. This is attributed in part to the very different rates of insertion into the intermediate Zn–alkoxide bond, following the order PA (fastest) > CO_2 > ε-CL (slowest).[90] Other variations of this catalyst have been proposed with similar kinetic and switch effects.[139c,162] For instance, in order to make block copolymers including bioderived ε-decanolactone (ε-DL, Scheme 1), an analogous zinc-magnesium heteronuclear complex was developed (**34**, Scheme 29). Using a two-step methodology in the presence of a bifunctional initiator (1,2-cyclohexanediol), triblock copolymers with high toughness and elongation at break were obtained.[139c]

Also following a multi-step approach, Rieger and coworkers employed a zinc β-diketiminate amidate complex (**35**, Scheme 29) for the synthesis of polyester–polycarbonate diblock and triblock copolymers from mixtures of β-BL and CHO.[163] Interestingly, the ROP of the cyclic ester could also be switched off in this system by addition of CO_2, but only at high pressures (40 bar). Low CO_2 pressures (3 bar) in a mixture of monomers yielded totally random copolymers product of simultaneous ROP and ROCOP mechanisms.

In order to incorporate PLA blocks into polycarbonates, Darensbourg and coworkers reported a tandem catalytic approach involving a salen cobalt(III) complex (**36**, Scheme 29) with PPNTFA (PPN trifluoroacetate) as cocatalyst and organobase DBU.[164] Initial polymerization of propylene oxide (PO) and CO_2 using **36** and cocatalyst system yielded the initial polycarbonate block. Subsequent addition of water formed hydroxy end-groups, which could subsequently react with added LA/DBU to form triblock copolymers (Scheme 29). Other multicomponent systems have been reported for tandem ROCOP/ROP.[165]

5. Conclusions

With the constant development of new functionalized monomers and more selective catalytic systems, the controlled synthesis of block copolymers including biodegradable and/or bioderived components has experienced impressive advances in the last 20 years. The development of new synthetic methodologies has opened the door to new materials with tunable properties. While the most common synthetic approach is the sequential addition of monomers polymerizable by ROP or ROCOP methods, systems that can switch between different catalytic cycles by internal or external stimuli in a mixture of monomers offer the greatest advantage by yielding well-defined polymer sequences that can be tailored according to the reactivities of the different monomers (*e.g.* TMC > ε-CL > LA) or a specific application.

In general, metal-catalysts tend to display higher activities and can exert different degrees of stereocontrol in polymerizations, but they typically require a lengthy synthesis and therefore are not always readily available. In contrast, relatively simple organocatalysts can show high activities, while being more readily accessible and ideal for applications where trace metals are undesirable. Combination of metal catalysis (or other Lewis acids for the matter) with organocatalysis has shown promising results in the synthesis of uncommon block copolymers with high activities and offers great potential in the future development of more versatile tools applicable to a greater arrange of monomers.

Similarly, combination of ROP and ROCOP mechanisms in one catalytic system (typically a metal complex) has opened the door to new block compositions with exquisite control. Future combination with other mechanisms of polymerization will certainly expand the applications of new block copolymer architectures.

Reducing number of synthetic and purification steps as well as energy consumption in accordance with green chemistry principles will simplify synthetic protocols, making novel block copolymers architectures more accessible for different applications. In particular, the biomedical field that relies heavily on poly(ethylene) glycol (PEG) can benefit greatly from more versatile synthetic protocols and the study of new amphiphilic block copolymer architectures.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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