

# Organocatalysis Applied to the Ring-Opening Polymerization of $\beta$ -Lactones: A Brief Overview

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**ABSTRACT:** Organocatalysis offers a number of prospects in the polymer community and presents advantages over metal based and bio-organic methods. The use of organic molecules for performing chemical reactions is not a new concept, and any research into organocatalytic reactions builds on a respected history. Compared to the organocatalysis of large lactones, which began in the early 2000s, the examples presented here will demonstrate that few metal-free initiating systems had been applied to  $\beta$ -lactones well before the beginning of the current millennium. These metal-free initiating systems present indisputable advantages over metal-based processes. In the following

paper, ring-opening polymerizations (ROPs) of various  $\beta$ -lactones for the preparation of poly(hydroxyalkanoate)s will be presented, as will the types of mechanisms involved, that is, zwitterionic and anionic, and cationic or supramolecular-based ROPs. The advantages and drawbacks of the different technics will be discussed in the domain, which, for us, is important in the overall production of bioplastics. © 2019 Wiley Periodicals, Inc. *J. Polym. Sci., Part A: Polym. Chem.* **2019**, *57*, 657–672

**KEYWORDS:**  $\beta$ -Lactones; biodegradable; organocatalysis; ring-opening polymerization; polyester

**INTRODUCTION** Lactones of the class of cyclic organic esters are usually formed by an intramolecular reaction between a carboxylic acid group and a hydroxyl (or halide) function and represent a very well-known class of heterocyclic monomers. Although the intramolecular esterification of hydroxycarboxylic acid takes place spontaneously when the formed ring is either a five- or a six-membered cycle, special synthetic methods are required for the preparation of larger or smaller lactones.<sup>1</sup> Among the small cyclic esters,  $\beta$ -lactones, that is, four-membered rings, also named 2-oxetanones, have attracted a lot of interest for the past 40 years, being recognized as key structures in various natural products, such as lipstatin, obafloquin, and salinosporamide A (Fig. 1).<sup>2</sup> Paradoxically, a few of those  $\beta$ -lactones, known as good to excellent alkylating agents, may present some carcinogenicity.<sup>3</sup> Among these,  $\beta$ -propiolactone (PL) appears to be one of the worst carcinogenic agents, demonstrating a dangerousness much higher than its methylated homologue, that is,  $\beta$ -butyrolactone (BL). Although both of these lactones will be presented in the following sections, it seems important to note that the ingenious utilization of the cyclic dimer of 3-hydroxybutyric acid renders the safer preparation of poly( $\beta$ -butyrolactone) possible.<sup>4,5</sup>

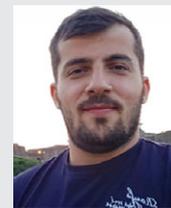
The intrinsic reactivity of  $\beta$ -lactones has also prompted researchers to investigate such cyclic esters as intermediates in the formation of an important class of molecules, such as  $\alpha$ -amino acids,<sup>6</sup> propionic acid,<sup>7</sup> or tetrahydrofuran derivatives.<sup>8</sup> More generally, the high strain of the  $\beta$ -lactone ring is reflected in important reactions, including decarboxylation, possible rearrangement in the presence of Lewis acid, nucleophilic-based ring opening, and reactions toward electrophiles in the presence of a base (Scheme 1).<sup>9</sup>

The interest in these molecules in the biomedical field has attracted extensive attention in recent years. Indeed, certain  $\beta$ -lactone derivatives will be marketed under the trademark “KymiaNova.”

The special attention given to  $\beta$ -lactones by the polymer community seems to have originated from the discovery of poly([R]-hydroxybutyrate) (P3HB) by Maurice Lemoigne in the 1920s. In 1925, Lemoigne described P3HB and isolated it from *Bacillus megaterium* in 1926.<sup>10,11</sup> Since then, P3HB has been discovered in various microorganisms<sup>12</sup> acting as a storage compound, as well as in bacterial membranes and tissues of plants and animals, where it presumably plays a role in ion channels.<sup>13–17</sup> P3HB, and poly(hydroxyalkanoate)s in general

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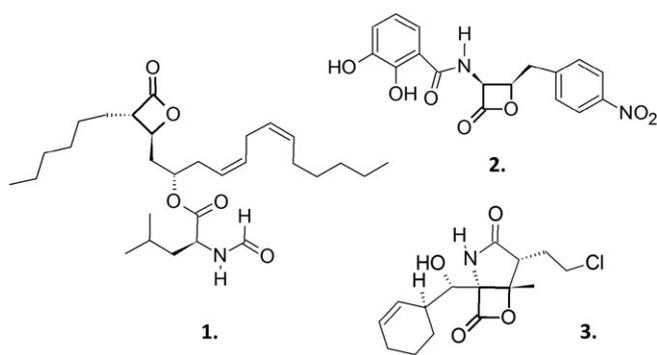
**Sandrine Cammas-Marion** received her Master II degree (1990) and PhD (1993) from the University Pierre et Marie Curie (France) in Macromolecular Sciences. She spent 2 years (1993–1995) in Japan as post-doctoral fellow (Prof. Kataoka & Okano). In 1995, she joined the CNRS as senior researcher. Her research focuses on the synthesis of biocompatible and degradable (co)polymers derived from the poly(malic acid), the formulation of multifunctional nanoparticles and the study of their *in vitro* effects.



**Olivier Coulembier** graduated from the University of Mons-Hainaut in 2005 and moved to Stanford University and the IBM Almaden Research Center to undertake periods of postdoctoral research under the supervision of Prof. Robert M. Waymouth and Dr. James L. Hedrick. Olivier is currently a Research Associate of the Belgian F.N.R.S. in the Laboratory of Polymeric and Composite Materials (LPCM) at the University of Mons. His research focuses on the (non)-organometallic ring-opening polymerization of cyclic monomers.



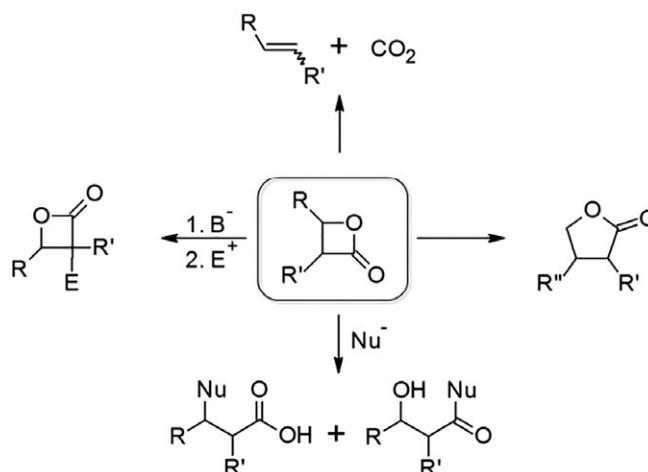
(PHA), represent a very important class of plastics. PHAs are formed naturally and are accumulated by various bacterial species,<sup>18,19</sup> such as *Pseudomonas oleovorans*, *Aureobasidium pullulans*, and *Physarum polycephalum*, and present thermo-mechanical properties similar to nondegradable polypropylene.<sup>20</sup> While PHAs initially found applications in packaging, they are now also used in numerous devices, drug delivery systems, and pro-drugs.<sup>21–23</sup> It is now reasonable to foresee even more success for this family of polymers knowing that the global PHA market is projected to grow to a bit <US\$94 million by 2021, with a compound annual growth rate of 4.88% (from 2016 to 2021).<sup>24</sup>



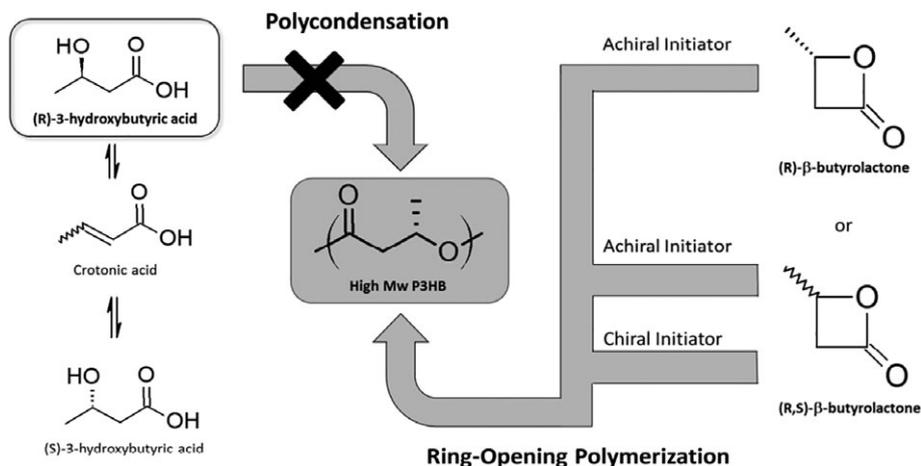
**FIGURE 1** Molecular structures of Lipstatin (1), Obafleurin (2), and Salinosporamide A (3).

Because of their tendency to be dehydrated and form crotonic acid, chiral hydroxyacids, such as (R)-3-hydroxybutyric acid, cannot be condensed to get high molar mass P3HBs, and only oligomers are obtained. On the contrary, chiral or achiral 4-methyl-2-oxetanone, named  $\beta$ -butyrolactone (BL), has been the subject of many ring-opening polymerization (ROP) studies (Fig. 2).<sup>25</sup>

Hall and Schneider investigated the polymerizability of various lactones in 1958.<sup>26</sup> They demonstrated that  $\beta$ -lactones



**SCHEME 1** Important reactions from (substituted)  $\beta$ -lactones.



**FIGURE 2** Efficient and inefficient routes to high-molecular-weight P3HB: interest in ROP process from  $\beta$ -butyrolactones.

present a negative  $\Delta G_{\text{polym}}$ , mainly due to the ring instability arising from strain, implying a thermodynamically feasible polymerization. Note here that, depending on the number and type of substituents, steric factors, and others, may preclude polymerization by a certain class of initiator. Metal-based ring-opening processes of (substituted)  $\beta$ -lactones have already been widely documented and represent the most important work realized so far. Less documented efforts have also been made in organocatalytic processes to avoid both metal traces trapped in the as-produced polymers, as these are troublesome for biomedical purposes,<sup>27</sup> and lipids and proteins, which may also be produced by microorganisms in bacteria cells when P3HBs are prepared.<sup>28</sup> As such, the current contribution aims to present the advances made on the ROP of (substituted)  $\beta$ -lactones driven by organic initiators or metal-free organocatalysts.

Organocatalysis is defined as being the acceleration of a chemical reaction with a substoichiometric amount of an organic compound, which does not contain any trace of metal atoms. The use of organic molecules for performing chemical reactions is not a new concept, and studies into organocatalytic reactions have a respected history, having achieved cyanohydrin synthesis<sup>29</sup> and the proline-catalyzed Robinson annulation.<sup>30</sup> Although most organo-based reactions concern the enantioselective preparation of small molecules, organocatalysis also offers a number of prospects in the polymer community, and proposes advantages over metal-based and bio-organic methods.<sup>31</sup> The term “organocatalysis” is often used incorrectly because most of time organic compounds are used in greater quantities than if used as a catalyst. While the term “activator” seems more appropriate, many authors consider that the terms “organo-catalyst” and “metal-free activator” are identical, and so they will be treated as such here, at least for the clarity of the text.

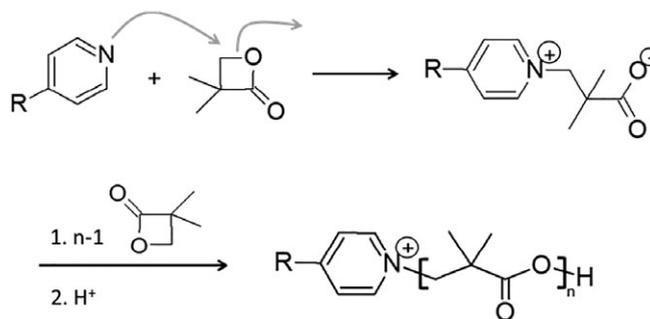
Interestingly, while the organocatalysis of large lactones seems to have begun in the early 2000s,<sup>32</sup> the examples presented in the following sections will demonstrate that few metal-free initiating systems had been applied to  $\beta$ -lactones well before the beginning of the current millennium. The rest

of the paper will be organized into two sections. These sections will present the different mechanisms that could be involved in  $\beta$ -lactone polymerization: (a) zwitterionic and anionic ROPs and (b) cationic or supramolecular-based ROPs.

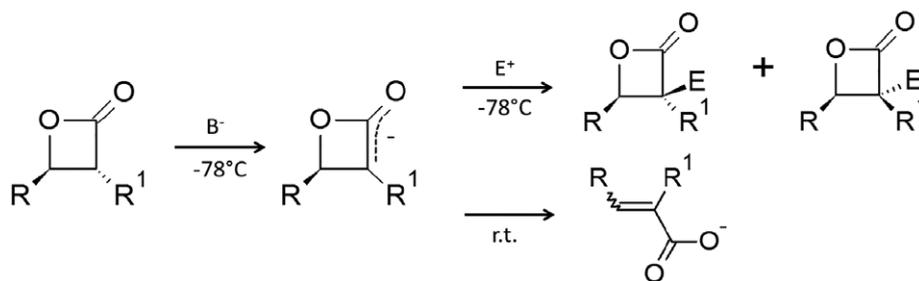
## ZWITTERIONIC AND ANIONIC METAL-FREE ROPS OF $\beta$ -LACTONES

### Pyridine-Based Initiation

$\beta$ -Lactones, such as  $\beta$ -propiolactone and  $\beta$ -pivalolactone, were polymerized by pyridine-based nucleophilic initiators more than 50 years ago.<sup>33–36</sup> All the accumulated data suggest zwitterionic ring-opening polymerization (ZROP). Such polymerization consists of a growing macromolecule bearing ionic chain carriers of opposite signs at either end, which then usually continues to grow from one of these.<sup>37</sup> In the past, the course of  $\beta$ -lactones ZROP was very intricate, involving chain- and step-growth kinetics as well as elimination reactions regarding the type of initiator and monomer used. In the presence of moderate bases,<sup>38</sup> such as 4-(*N,N*-dimethylamino)pyridine (DMAP), 4-methylpyridine or pristine pyridine, the ZROP of pivalolactone<sup>34</sup> proceeds by generating linear chains with one pyridinium ion and a carboxylate function as end groups, with the total absence of cyclic structures (Scheme 2). In the



**SCHEME 2** ZROP of pivalolactone by pyridine derivatives (R = H, pyridine; R = Me, 4-methylpyridine; R =  $-(\text{CH}_3)_2$ , DMAP).



**SCHEME 3**  $\beta$ -Elimination on an  $\alpha$ -substituted  $\beta$ -monoprotected 2-oxetanone.

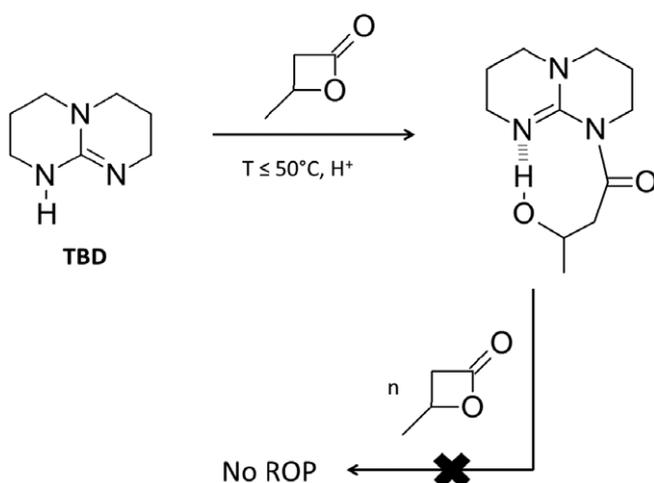
case of  $\beta$ -propiolactone and  $\beta$ -butyrolactone, the complete elimination of pyridinium ions and the formation of acrylate and crotonate end groups, respectively, were observed.<sup>34,39</sup>

The stereochemistry of  $\beta$ -elimination has been extensively studied and states that  $\beta$ -elimination, of any type, proceeds if the electron donating and accepting orbitals adopt a *syn* or *trans* arrangement.<sup>40,41</sup> In 1980, Mulzer and Kerkmann reported that  $\alpha$ -substituted  $\beta$ -monoprotected 2-oxetanones are incredibly stable due to an orthogonal orbital arrangement.<sup>42</sup> At low temperature ( $-78\text{ }^\circ\text{C}$ ), the ring-strained deprotected  $\beta$ -lactone can add electrophiles (in C-3), whereas an increase in temperature (to room temperature) allows acrylic acid derivatives to be quantitatively produced with an enthalpy of rearrangement of about  $-18\text{ kcal mol}^{-1}$  (Scheme 3).

Such a tendency to be the subject of a  $\beta$ -elimination is typical, and highly characteristic, of 2-oxetanones, and represents one of the main drawbacks during the ROP course of unprotected monomers.

#### Amidine/Guanidine-Based Initiating Systems

The ability of both amidine and guanidine to initiate the nucleophilic ZROP of  $\beta$ -lactones, such as BL, was initially



**SCHEME 4** Inability of BL to propagate due to the formation of a stable adduct between TBD and BL (in solution,  $T < 50\text{ }^\circ\text{C}$  and in the presence of a protic alcohol,  $\text{H}^+$ ).

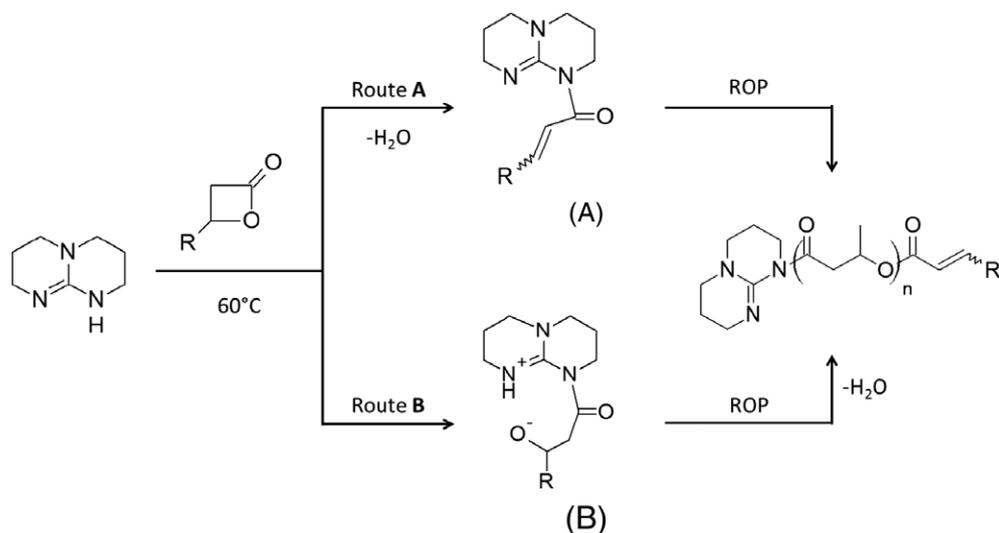
investigated by Hedrick et al.<sup>43</sup> The authors demonstrated that a 1:1 mixture of the monomer with 1,5,7-triazabicyclo [4.4.0]dec-5-ene (TBD) induces the formation of an acyl intermediate which is stabilized by the strong hydrogen bonding of the acidic proton of the ring-opened BL to the adjacent TBD nitrogen atom. Such a stable intermediate prevents all attempts to polymerize the monomer in solution with an alcohol initiator at low temperature ( $T < 50\text{ }^\circ\text{C}$ ) (Scheme 4). Theoretical calculations from Simon and Goodman effectively confirmed that the amide-like intermediate is indeed too stabilized, presenting an “insurmountable” energy barrier to propagation.<sup>44</sup>

Interestingly, Guillaume and coworkers discovered that performing the polymerization reaction in bulk at  $60\text{ }^\circ\text{C}$ , without using an exogenous protic initiator, allowed the production of polymers, highlighting the importance of both monomer concentration and temperature. Reactions were performed with the TBD guanidine and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) amidine allowing the homopolymerization of BL, and its copolymerization with benzyl- $\beta$ -malolactonate (MLABn).<sup>45–48</sup> Based on multinuclear NMR spectroscopies and MALDI-ToF spectrometry, the authors postulated a nucleophilic mechanism from two possible routes (Scheme 5) involving either the *in situ* generation of an *N*-acyl- $\alpha,\beta$ -unsaturated species (**A**) (Scheme 5, route A) or the generation of a zwitterionic intermediate (**B**) able to ring-open monomers (route B).

Intriguingly, attempts to apply the same process (from TBD) to the  $\alpha,\alpha$ -protected version of MLABn, named (R,S)-benzyl-carbonyl-3,3-dimethyl-2-oxetanone (dMMLABn), failed. A reinvestigation of the mechanism,<sup>49</sup> using  $^1\text{H}/\text{DOSY}$  NMR and MALDI/ESI-MS techniques, demonstrated that unprotected  $\beta$ -lactones, such as BL, are actually majorly obtained from an anionic process involving the *in situ* generation of crotonate species and minorly by the nucleophilic route postulated by Guillaume (Scheme 6).

#### Tertiary Amine used and Ammonium Initiating Systems

The ability of tertiary amines, such as triethylamine (TEA), to react with carbonyl groups by a nucleophilic attack was first discussed more than 40 years ago.<sup>50</sup> Kricheldorf et al.<sup>35,36</sup> used the nucleophilic behavior of tertiary alkylamines to carry out the ZROP of the  $\alpha$ -substituted pivalolactone (PVL). Polymerizations were carried out on three aliphatic tertiary amines (namely TEA, diazabicyclooctane [DABCO], and



**SCHEME 5** Proposed mechanisms for the unprotected  $\beta$ -lactones ROP from TBD and DBU in bulk at 60 °C (Illustration with TBD only for clarity. If  $R = -CH_3$ , BL monomer;  $R = -CO_2C_7H_7$ , MLABn monomer).

2-ethyloxazoline [2-EOX]) in NMP at 20 °C and 100 °C for 48 and 24 h, respectively. Quantitative polymerizations from DABCO were obtained whatever the temperature used.

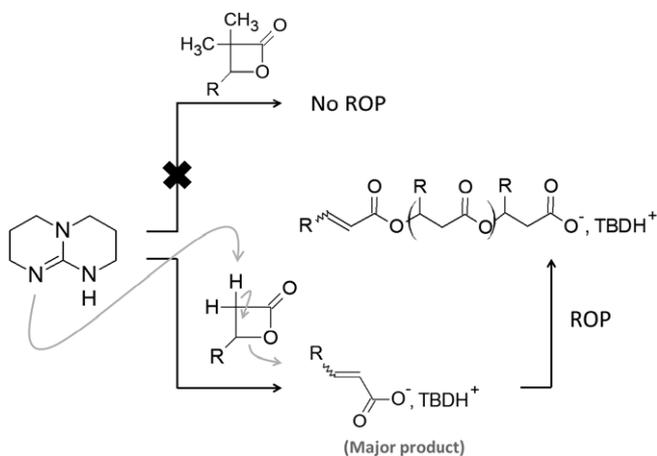
Note here that no molecular characterizations, that is, molar masses and dispersities, were provided by the authors. MALDI-ToF mass spectrometry of the as-obtained DABCO-initiated PVL exclusively displayed mass peaks of linear chains obtained from a chain growth process from both nitrogens. As far as TEA and 2-EOX were concerned, a 100 °C temperature was required to reach 98% and 50% conversions, respectively. In both cases, the ZROP of PVL was the prevailing process, but this was hampered by side reactions, such as initiation by water when TEA was used, and the formation of cyclic oligolactones from the 2-EOX initiation. The authors concluded that the cyclization process came from an end-to-end reaction between the nucleophilic carboxylate end group

and the electrophilic methylene group of the oxazolidine moieties (Scheme 7).

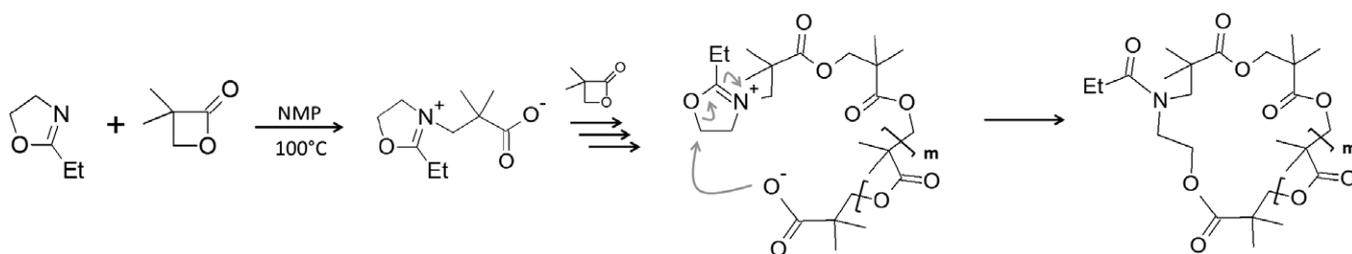
In contrast to unsubstituted  $\beta$ -lactones or  $\alpha$ -substituted  $\beta$ -lactones<sup>51</sup>,  $\beta$ -substituted  $\beta$ -lactones could not polymerize with weak nucleophile initiators<sup>52</sup> and an activation of the latter was generally required.<sup>53–55</sup> In the late 1970s, Vert and Lenz discovered that MLABn could, however, be polymerized by TEA. Such an ROP facility was attributed to the electron withdrawing nature of the benzyl ester  $\beta$ -substituent, which enhances the rate of nucleophilic attack and overcomes any steric effect.<sup>56</sup> From a sufficiently purified MLABn, that is, purified by column chromatography and distilled twice, the bulk polymerization carried out at 40 °C allowed the production of 50,000 g mol<sup>-1</sup> PMLABn ( $\bar{M}_n = 1.4$ ) in 30 days. The slow polymerization was not controlled and appeared dependent on both the temperature and the solvent. The authors demonstrated that reducing the polymerization temperature from 60 °C to 40 °C reduced the rate of transfer more than the rate of propagation, resulting in higher molar masses.<sup>57,58</sup> Such an effect was not observed when the polymerizations were carried out in solutions (THF, DCM, or benzene), which, in all cases, presented an ever-poorer control. As demonstrated by <sup>1</sup>H-NMR analysis, the initiation of the reaction occurs with the generation of a zwitterionic species, whereas transfer reactions are mainly caused by the abstraction of a hydrogen atom in the  $\alpha$  position of the carbonyl group, leading to fumarate derivatives (Scheme 8).

Neither vinyl nor vinylidene-type protons were observed, ruling out any possible transfer reaction to the hydrogen located in  $\alpha$  to the substituent ester. The same conclusions were also drawn from the ROP of optically pure MLABn.<sup>59</sup>

In the search for initiating systems leading to a certain biomimicry, carboxylic acid salts with bulky ammonium counterions have been employed. Arnold and Lenz used tetraethylammonium

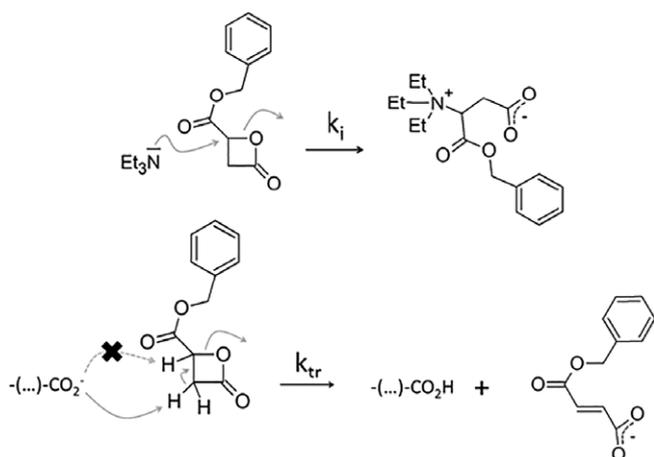


**SCHEME 6** Comparison of ROP reactions from TBD between  $\alpha, \alpha'$ -protected  $\beta$ -lactones and unprotected ones.



**SCHEME 7** Preparation of PPVL macrocycles as obtained by the ZROP of PVL from 2-EOX.

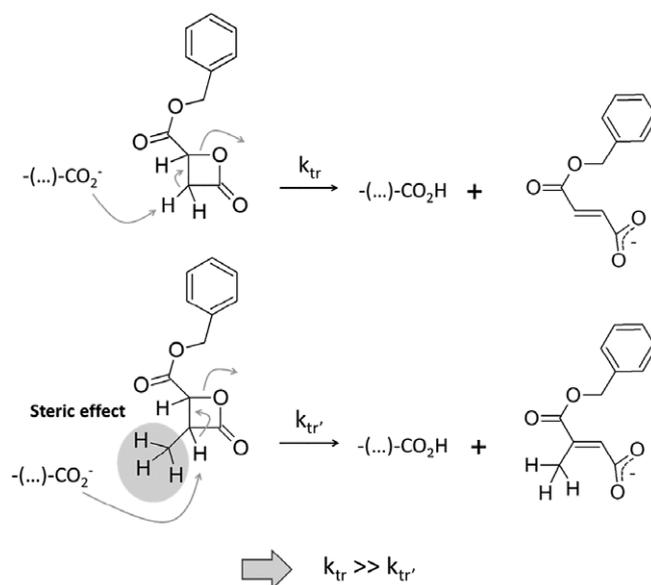
benzoate (TEAB) as an initiator to perform the bulk ROP of optically active alkyl malolactonates at 60 °C.<sup>60</sup> Whatever the alkyl group present on the lactone (Me, Et, <sup>i</sup>Pr, or Be), almost all quantitative conversions were obtained in 5–7 days. In the peculiar case of optically pure MLABn, molecular masses (as determined by SEC analysis) were limited to 73,000 g mol<sup>-1</sup> with a dispersity index of 2.2. Identical kinetics were also observed by Guérin et al. who prepared optically active poly(4-alkyloxycarbonyl-2-oxetanone)s in 3 days from TEAB under identical experimental conditions ( $M_p \sim 60,000$  g mol<sup>-1</sup>).<sup>61</sup> Later on, it was demonstrated that extensive purifications of not only the monomer, MLABn, but also of all the intermediate molecules in the synthesis of MLABn, allowed PMLABn to be obtained with molar masses as high as 170,000 g mol<sup>-1</sup> and close to theoretical molar masses calculated from the monomer to initiator ratio. Such results were obtained by anionic ROP of highly purified MLABn in bulk at 40 °C in the presence of benzoate tetraethylammonium as an initiator.<sup>62</sup> As compared to poly(malolactonate)s obtained from a TEA-initiating system, the rate of polymerizations recorded from a TEAB initiator are much higher, allowing a roughly four to six times faster reaction. At the time of the study, no information was provided on possible transfer reactions to the monomer. Such poisoning reactions were, however, clearly stated later by the same research team. Performing homopolymerization and copolymerization reactions in bulk at 37 °C from TEAB, the authors observed, using <sup>1</sup>H-NMR analysis, the presence of terminal



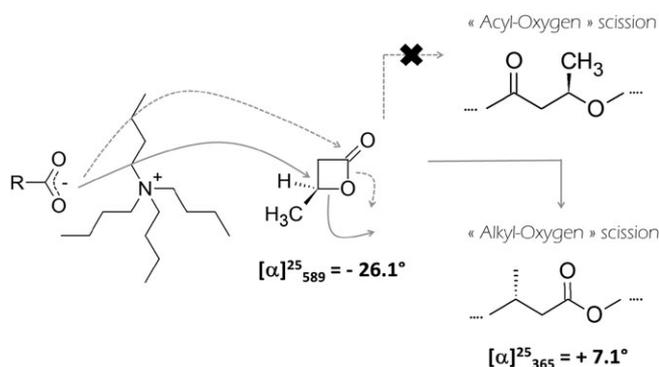
**SCHEME 8** Initiation ( $k_i$ ) and transfer ( $k_{tr}$ ) processes observed during the ROP of MLABn from TEA (Cation counterion omitted in the propagation step for more clarity).

fumaric vinyl protons affecting the anionic ROP of various  $\alpha$ -unsubstituted  $\beta$ -lactones.<sup>63</sup> Very interestingly, protecting such lactones in  $\alpha$  position prevents proton elimination by steric hindrance as the ROP of racemic ((3S,4R)-(3R,4S))-3-methyl-4-benzyloxycarbonyl-2-oxetanone allowed poly(malolactonate) structures of 780,000 g mol<sup>-1</sup> (Scheme 9) to be prepared in 3 days.<sup>64</sup>

As the electrostatic interactions between the voluminous ammonium cation and the carboxylate group are weaker than on tight ion pairs,<sup>65</sup> the reactive ammonium-based carboxylate salts were thought to be good candidates to promote the ROP of the recalcitrant BL monomer. To the best of our knowledge, Kurcok et al. were the first to report such an investigation.<sup>55</sup> The authors demonstrated that salts of carboxylic acids, such as tetrabutylammonium acetate (TBAAC) and tetrabutylammonium hydroxybutanoic acid (TBAHB), are more active than alkali-based carboxylic salt, such as sodium acetate (NaAc). Polymerizations realized in bulk at 25 °C allowed a PBL sample characterized by a molar mass of 172,000 g mol<sup>-1</sup> and a dispersity of 1.2 to be prepared in 500 h. Here, note that an efficient purification method is imperative to obtaining a



**SCHEME 9** Transfer ability comparison of (R,S)-benzyl- $\beta$ -malolactonate (up) and (R,S)-3-methyl-(R,S)-4-benzyl- $\beta$ -malolactonate (down) (Cation counterion omitted for clarity).



**SCHEME 10** Alkyl-oxygen bond cleavage involved in ROP of BL from TBA salts.

high-purity monomer with reproducible properties, offering the possibility to produce high molar mass PBL.<sup>66</sup> Optical rotation measurements concluded that the mode of ring opening from both ammonium salts primarily involved the cleavage of the bond between the  $\beta$ -carbon and the oxygen of the optically pure (S)-BL ( $[\alpha]_{589}^{25} = -26.1^\circ$ ),<sup>67</sup> that is, by an “alkyl-oxygen” cleavage with configuration inversion (Scheme 10). As evidenced by <sup>1</sup>H-NMR and ESI-MS spectroscopy, chain-transfer reactions to the monomer were also observed by the presence of crotonate species.

In 2008, Kurcok et al. demonstrated that the reaction rates of anionic ROPs of BL from various carboxylate salts are strongly dependent on both the solvent polarity and the size of the counterion.<sup>68</sup> Studies were undertaken comparing various metal-based carboxylates, activated by crown-ether (or not), to tetrabutylammonium acetate (TBAA) in benzene, THF and DMSO. These studies demonstrated that performing ROPs at 25 °C, and for a  $[BL]_0 \sim 8 \text{ mol L}^{-1}$ , the polymerization rates increase with a decrease in anion-cation interactions in the following order:  $K^+/Kryptofix^{\text{®}} 222 \approx TBAA > K^+/18C6 > Na^+/18C6 > Na^+/15C5 > K^+$ . When TBAA is used as an initiator, the apparent rate constants are higher in low-polar THF ( $\epsilon = 7.6$ ;  $k_p^{\text{app}} = 503 \times 10^{-5} \text{ L mol}^{-1} \text{ s}^{-1}$ ) compared to highly polar DMSO ( $\epsilon = 46.7$ ;  $k_p^{\text{app}} = 186 \times 10^{-5} \text{ L mol}^{-1} \text{ s}^{-1}$ ). The authors explain the phenomenon as the competition of the two following effects: the decrease in carboxylate activity caused by its solvation and the anion activation caused by its counterion solvation.

### Phosphazene-Based Initiating Systems

Due to their high basicity, non-nucleophilic nature, and good solubility in various organic solvents, Brønsted phosphazene superbases have been employed in the polymerizations of various cyclic esters.<sup>45,69–73</sup> While such bases are mainly used to turn exogenous protic moieties into nucleophilic

initiators through the deprotonation or activation of weak nucleophiles,<sup>74,75</sup> Guillaume et al. demonstrated that the 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP) phosphazene, used alone, can act as a nucleophilic initiator when performing the bulk ROP of BL and MLABn at 60 °C.<sup>45</sup> Due to their shielding of positive charges shifting the ionic equilibrium toward the free ionic species (Scheme 11), phosphazene-based carboxylic salts were also used as potent initiators for the anionic ROP of BL.<sup>66</sup>

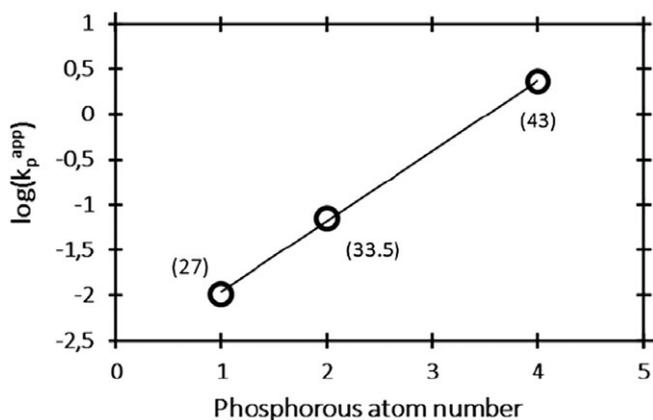
Three phosphazene bases of different basicities and sizes, namely *tert*-butylimino-tris(dimethylamino)phosphorane ( $P_1$ -*t*-Bu), 1-*tert*-butyl-2,2,4,4,4-pentakis(dimethylamino)-2 $\lambda^5,4\lambda^5$ -catenadi(phosphazene) ( $P_2$ -*t*-Bu) and 1-*tert*-butyl-4,4,4-tris(dimethylamino)-2,2-bis[tris(dimethylamino) phosphoranylidenamino]-2 $\lambda^5,4\lambda^5$ -catenadi(phosphazene) ( $P_4$ -*t*-Bu), were used. Carboxylate salts were prepared with 1-pyrene acetic acid ( $[\text{phosphazene}]_0/[\text{pyrene}]_0 = 1$ ) and the polymerizations were performed in THF at 21 °C for an initial monomer concentration of 2 mol L<sup>-1</sup>. As for the ammonium-based carboxylate salts, the authors demonstrated that the anionic ROP of BL from phosphazene-based carboxylic acids presents an increased activity when the interaction between the carboxylate anion and its protonated phosphazene counterion is weakened by an improved separation of the positively and negatively charged species. The stronger  $P_4$ -*t*-Bu base ( $pK_a^{\text{MeCN}} = 43$ ) was believed to improve the stabilization of the positively charged proton abstracted from the 1-pyrene acetic acid, leading to the initiating system becoming enriched with more active loose pairs. The ratio of the recorded apparent polymerization rate constants ( $k_p^{\text{app}}$ ) was equal to 1, 6.8, and 219 for  $P_1$ -*t*-Bu,  $P_2$ -*t*-Bu, and  $P_4$ -*t*-Bu, respectively. Interestingly, an empirical linear dependence between the number of phosphorous atoms (and then the basicity) of the phosphazene base and the logarithm of the apparent polymerization rate constants was observed by the authors (Fig. 3).

PBL chains of 14,500 g mol<sup>-1</sup> molar mass (conv.  $\sim 87\%$ ) were prepared for 1 h from a 1-pyrene acetic acid/ $P_4$ -*t*-Bu salt. Attempts to push the conversion up resulted in the appearance of transfer reactions, as attested to by the increase in the dispersity, going from 1.16 (87% conv.) to 1.31 (99% conv.), and the decrease in the apparent molar mass ( $M_{n\text{SEC}} = 12,600 \text{ g mol}^{-1}$ ).

A perfectly controlled and “living” ROP process, using these phosphazene-based carboxylic acid salts, was reported by polymerizing the  $\alpha,\alpha$ -protected version of the  $\beta$ -lactones, eliminating any possible proton elimination reaction.<sup>71</sup>  $P_1$ -*t*-Bu,  $P_2$ -*t*-Bu, and  $P_4$ -*t*-Bu phosphazene bases were investigated for the polymerization of [R,S]-4-benzylcarbonyl-3,3-dimethyl-2-oxetanone (dMMLABn) in the presence of carboxylic acid



**SCHEME 11** Ionic species equilibria adapted from Ref. 66.



**FIGURE 3** Dependence of the apparent polymerization rate constant on the number of phosphorous atoms in the used phosphazene base (Numbers in brackets correspond to the  $\text{p}K_a^{\text{MeCN}}$  of each phosphazene base). Figure adapted from data reported in the Ref. 66.

initiators in THF at 21 °C.<sup>71</sup> As attested to by SEC and MALDI-MS analyses, these polymerizations proceed by an “O-alkyl” scission of the monomer and are characterized by an excellent control in terms of the polyester molar mass and the end-group fidelity. The authors report the same kinetic behavior as that observed during the BL ROP with an extremely active  $\text{RCOO}^-$ ,  $\text{P}_4$ -*t*-Bu. $\text{H}^+$  initiator. More than simply being efficient, the use of  $\text{P}_4$ -*t*-Bu allowed a PdMMLABn characterized by a number-average molar mass higher than  $1.5 \times 10^6 \text{ g mol}^{-1}$  to be synthesized. With a molar mass of almost 2 million  $\text{g mol}^{-1}$ , this polymer is the highest ever obtained in the ROP of  $\beta$ -lactones.

### N-Heterocyclic Carbene-Based Initiating Systems

The demonstration by Breslow showed that stabilized singlet carbenes derived from thiamine cofactors are nucleophilic catalysts,<sup>76</sup> and the pioneering works of Wanzlick and coworkers<sup>77–81</sup> on the deprotonation of thiazolium and imidazolium salts, are considered to be the first steps in the use of N-heterocyclic carbenes (NHCs) as nucleophilic catalysts.<sup>82</sup> The first reported example of NHC catalyzing  $\beta$ -lactone polymerization was used for the ROP of BL in the presence of the 1,3-bis-(2,4,6-trimethylphenyl)imidazole-2-ylidene (IMes) NHC from pyrene-butanol in THF at 25 °C.<sup>83</sup> By using a  $[\text{IMes}]_0/[\text{ROH}]_0$  ratio of 1.5, the obtained PBL molar mass was closely tracked the monomer-to-initiator ratio, whereas the final dispersity was as narrow as 1.15. At that time, encompassing such a result with that of various other (di)lactone polymerizations, Hedrick proposed two possible mechanisms based either on an anionic/basic “chain-end” mechanism, where the carbene activates the initiating/propagating alcohol by H-bonding, or on a monomer-activated “nucleophilic” mechanism, involving a zwitterionic intermediate, but no information was given on the type of ring cleavage, that is, “O-acyl” or “O-alkyl” scission.

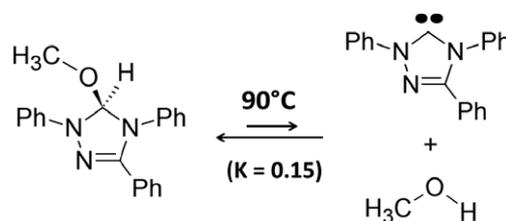
Investigations of the ring breaking mechanism were conducted between 2006 and 2007 by Hedrick and coworkers by

studying the  $\beta$ -lactone ROP from the 1,3,4-triphenyl-4,5-dihydro-1*H*-1,2,4-triazol-5-ylidene carbene, named triazole.<sup>84–86</sup> In contrast to alkoxyimidazolyl-2-ylidenes that readily dissociate at room temperature, Enders demonstrated that the elimination of methanol from the methoxytriazole adduct occurs at high temperature (Scheme 12).<sup>87,88</sup> Later on, <sup>1</sup>H-NMR investigations allowed an equilibrium constant of 0.15 at 90 °C to be determined, suggesting that all attempts of ROP reactions should be done at high temperature to ensure the formation of active triazole NHC in the medium.<sup>85</sup>

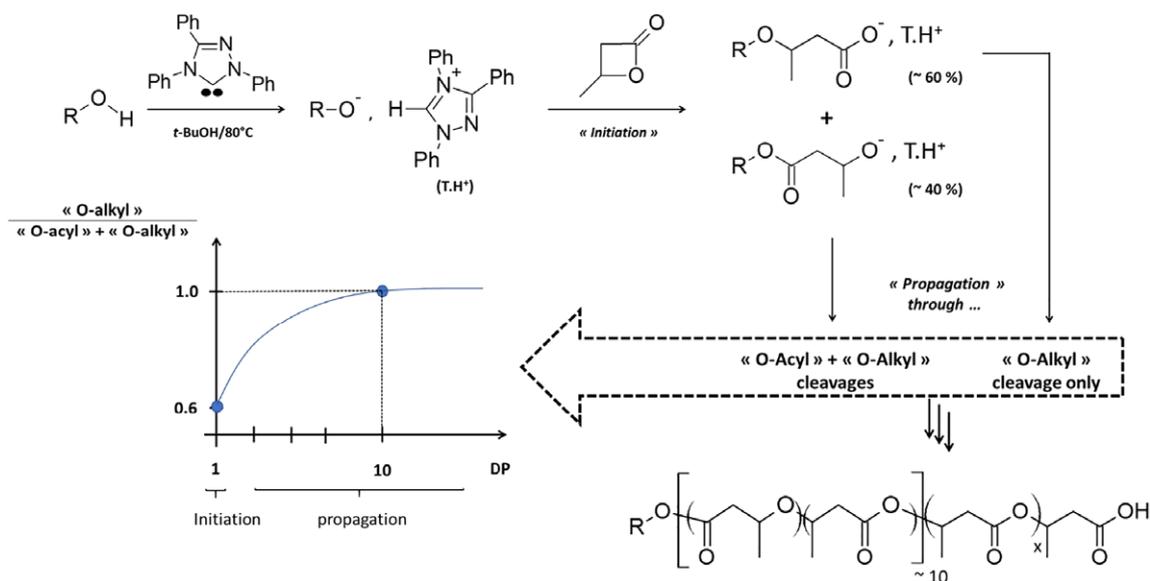
For this reason, the polymerization of BL from an equimolar mixture of triazole and MeOH was first carried out at 80 °C in toluene. <sup>1</sup>H-NMR analyses revealed an uncontrolled process in which PBL chains are end-capped by either an  $\alpha$ -methoxy group or a crotonate moiety, suggesting both “O-acyl” and “O-alkyl” pathways. Reasoning that the basicity of the triazole carbene might lead to undesired elimination reactions, generating crotonate initiators, *tert*-butyl alcohol was used as a cosolvent to favor adduct formation, minimizing the concentration of free triazole. *Tert*-Butyl alcohol cannot initiate the BL ROP but could react reversibly with the triazole to form the corresponding adduct.<sup>89</sup>

Under these conditions, the use of the triazole carbene with *t*-BuOH as a cosolvent, intended to enhance propagation over detrimental deprotonation side reactions and to minimize crotonate formation, was successful for the polymerization of BL for molecular weight targets below 200 (in a toluene/*t*-BuOH mixture).

An end-group analysis of the PBL chains revealed the presence of a carboxylic acid end group, suggesting that carboxylates are eventually propagating species of the ROP.<sup>86</sup> The nature of the active centers formed at various stages of the polymerization were studied in both <sup>1</sup>H- and <sup>31</sup>P-NMR spectroscopies. Both alkoxide and carboxylate groups were found at the early stages of the reaction, whereas the relative number of carboxylate end groups increased during polymerization to finally represent the only propagating center for DPs higher than 10 (Scheme 13). As alkoxide initiating species, produced by deprotonation of the initiating alcohol, are rapidly converted into carboxylate active centers, the authors used a carboxytriazole adduct to initiate the BL ROP. In *t*-BuOH, at 80 °C, the BL ROP from a 1-pyrene-acetic acid/triazole initiating system allowed PBL chains of 32,000  $\text{g mol}^{-1}$  ( $\mathcal{D} = 1.15$ ) to be produced in 19 h ( $[\text{BL}]_0 = 5 \text{ mol L}^{-1}$ ). This



**SCHEME 12** Equilibrium between the methoxytriazole and both pristine methanol and triazole carbene at 90 °C.



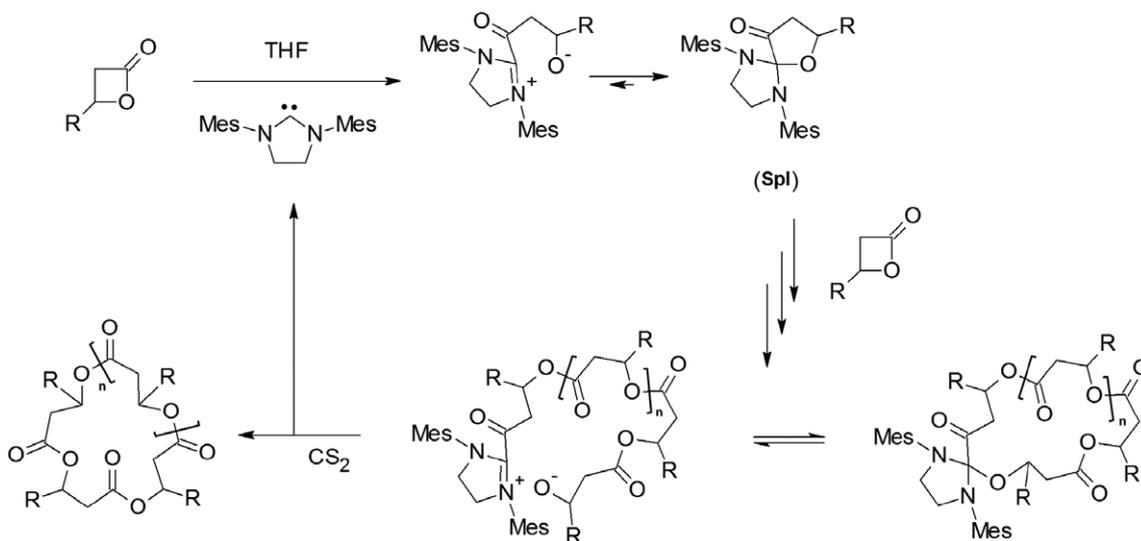
**SCHEME 13** “O-Alkyl” and “O-acyl” cleavage competition during the BL ROP for an equimolar ROH/triazole mixture at 80 °C in *t*-BuOH. [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

was achieved with an apparent rate constant similar to that recorded with 1-pyrene-methanol. In 2011, the ability of triazole to lead a BL ROP from carboxylic acid moieties was also applied to the preparation of grafted structures.<sup>90</sup> The authors interestingly demonstrated that a carboxytriazole adduct presents a much lower enthalpy of thermal dissociation than that recorded for the covalent methanol adduct (67 vs. 215 J/g).

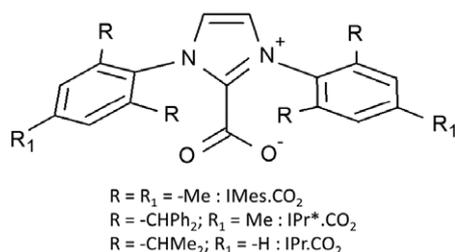
In the absence of a protic initiator, the ZROP of  $\beta$ -lactones, such as PL and BL, with saturated IMes (SIMes) carbene led to polymers of a cyclic nature.<sup>91</sup> The authors discovered that reacting the SIMes with one equivalent of BL generates a

zwitterion, which collapses to an isolable spiro imidazolidine compound (**Spl**) (Scheme 14).

DFT calculations indicated that this compound was generated due to the release of the ring strain from the four-membered lactone to the benefit of a five-membered ring. The polymerizations presented characteristics of a “living” process, with a linear semilog plot evolution and molecular weights tracking the initial  $[M]_0/[SIMes]_0$  molar ratios. The authors proposed a mechanism involving a reversible collapse of the zwitterionic species to macrocyclic spirocycles all along the propagation. Such a ring-expansion reaction was also found to be feasible from IMes NHC while polymerizing the self-activated



**SCHEME 14** ZROP of  $\beta$ -lactones using SIMes carbene.



**SCHEME 15** NHC carboxylate (NHC.CO<sub>2</sub>) adducts used by Thomas et al.

dMMLABn.<sup>49</sup> The reaction was performed in THF at 21 °C for a [dMMLABn]<sub>0</sub> of 1.45 mol L<sup>-1</sup> and a [dMMLABn]<sub>0</sub>/[IMes]<sub>0</sub> initial ratio of 116. After 28 min (conv. ~ 0.6), MALDI-MS analysis confirmed the cyclic nature of the as-prepared PdMMLABn, presenting a low dispersity ( $\mathcal{D}$  = 1.34) and an experimental absolute molar mass (13,600 g mol<sup>-1</sup>) in good agreement with the theoretical one ( $M_{n,th}$  = 16,200 g mol<sup>-1</sup>).

Inspired by the works of Taton and coworkers on imidazol(in)ium hydrogen carbonates and imidazol(in)ium carboxylates (NHC.CO<sub>2</sub>) adducts,<sup>92,93</sup> Thomas et al. reported the use of various NHC.CO<sub>2</sub> as potent initiating systems for the ROP of BL (Scheme 15).<sup>94</sup> To that end, three adducts, namely IPr.CO<sub>2</sub> (IPr = 1,3-bis(2,6-diisopropylphenyl)imidazole-2-ylidene), IMes.CO<sub>2</sub> (IMes = 1,3-bis(2,4,6-trimethylphenyl)imidazole-2-ylidene), and IPr\*.CO<sub>2</sub> (IPr\* = imidazole-2-ylidene), were prepared and tested under different conditions.

When polymerizations were carried out in bulk at 60 °C ([BL]<sub>0</sub>/[NHC.CO<sub>2</sub>]<sub>0</sub> = 100), both IMes.CO<sub>2</sub> and IPr.CO<sub>2</sub> presented similar activities (10 min, conv. ~ 80%), which were much higher than that observed for the bulkier IPr\*.CO<sub>2</sub> (50 min, conv. ~ 60%).

In the specific case of IMes.CO<sub>2</sub>, a good control was observed in bulk, because the experimental molar masses tracked the theoretical ones for DPs ranging from 150 to 2000. As compared to the polymerizations performed with ammonium-based carboxylate salts, the kinetics appeared faster in polar DMSO and acetonitrile than in less polar THF and toluene when the ROPs were conducted in solution from IMes.CO<sub>2</sub> at 60 °C. Mechanistic studies, mainly based on MALDI-MS/MS analyses, and DFT calculations, suggested that the ROPs of BL from IMes.CO<sub>2</sub> and IPr.CO<sub>2</sub> adducts were initiated from the salt and proceeded by

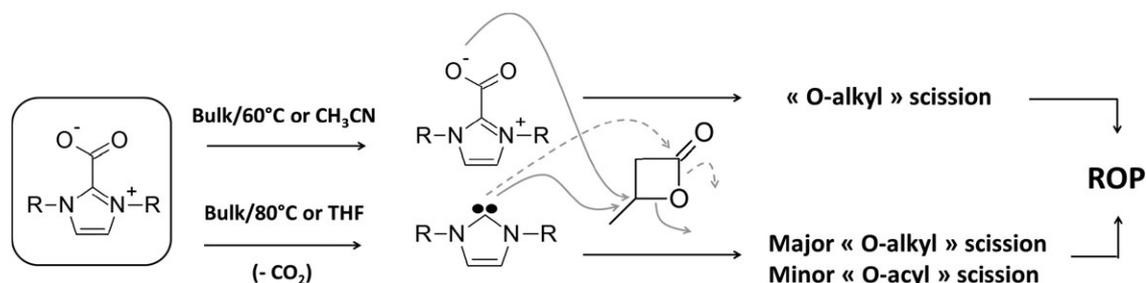
an “O-alkyl” bond cleavage when the polymerizations were carried out in acetonitrile or in bulk at 60 °C. In comparison, a less polar THF or a higher temperature (80 °C) favored the decarboxylation of both adducts and an initiation from the free corresponding carbene (Scheme 16).

### CATIONIC AND SUPRAMOLECULAR ACTIVATED METAL-FREE ROPS OF $\beta$ -LACTONES

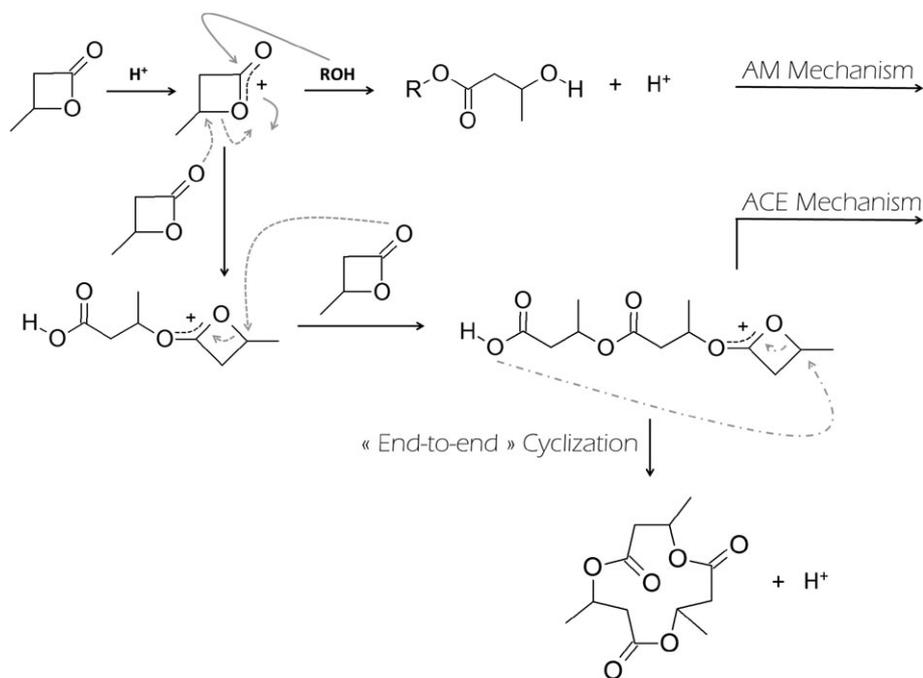
To the best of our knowledge, the first statement on a cationic metal-free ROP of 2-oxetanones dates from 1948.<sup>95</sup> Shaver et al. reported that the use of concentrated sulfuric acid for the polymerization of PL in bulk at 60–80 °C allowed oligo(PL) of low molar masses (~860 g mol<sup>-1</sup>) to be produced. Pohl et al. speculated that the use of a stronger acid in a relatively nonpolar environment could contribute to a greater degree of reaction control.<sup>96</sup> By polymerizing BL in toluene at 35 °C using trifluoromethanesulfonic acid as a catalyst (triflic acid [TFA]) and methanol as an initiator, PBL chains of 4600 g mol<sup>-1</sup> ( $\mathcal{D}$  = 1.12) were obtained in 10 h. While an “O-acyl” bond cleavage process was postulated, the mechanism of that polymerization was not elucidated in detail.

The principal mechanism of the cationic ROP of lactone monomers is called the “active chain-end” (ACE) mechanism. In ACE, propagation proceeds with the nucleophilic attack of an oxygen atom in the monomer on a  $\beta$ -carbon atom in the tertiary oxonium ion located at the growing chain end. When the propagation proceeds with an attack of the oxygen atom of the terminal hydroxyl group on the carbonyl carbon atom in the protonated monomer molecule, a competing mechanism, named the “activated monomer” (AM) mechanism, could occur.<sup>97</sup> In 2013, Kubisa et al. performed the homopolymerization of BL in CH<sub>2</sub>Cl<sub>2</sub> at room temperature with isopropanol as the initiator and triflic acid as the catalyst.<sup>98</sup> The authors elegantly demonstrated that for [BL]/[ROH] ratios <30, PBL chains were obtained with a good control in terms of the molar masses and the end-groups’ nature (initiation from isopropanol only) through an AM mechanism.

For higher [BL]/[ROH] ratios, macromolecules were formed not only from the attack of the activated BL by HO-group (AM process) but also by the reaction of the protonated monomer with another monomer molecule (ACE process).



**SCHEME 16** NHC carboxylates initiating the BL ROP under various conditions.



**SCHEME 17** AM and ACE mechanisms (including cyclic structure formation) hypothetically involved during the cationic ROP of BL. Note that cationic intermediates are represented free of their proton for clarity.

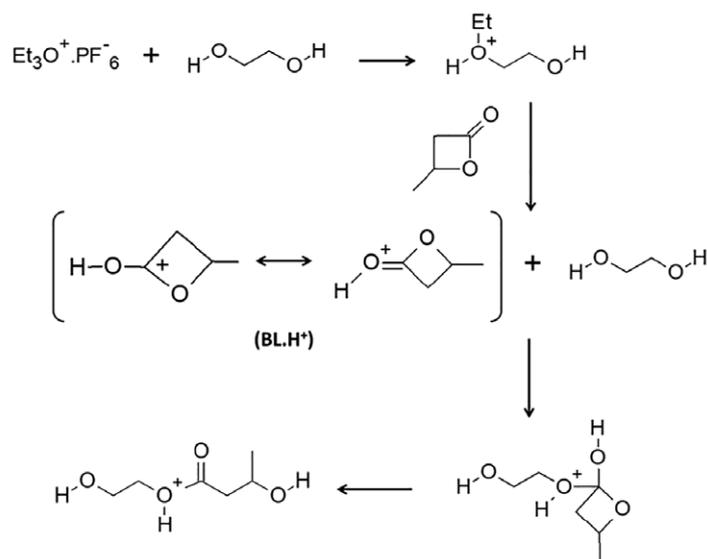
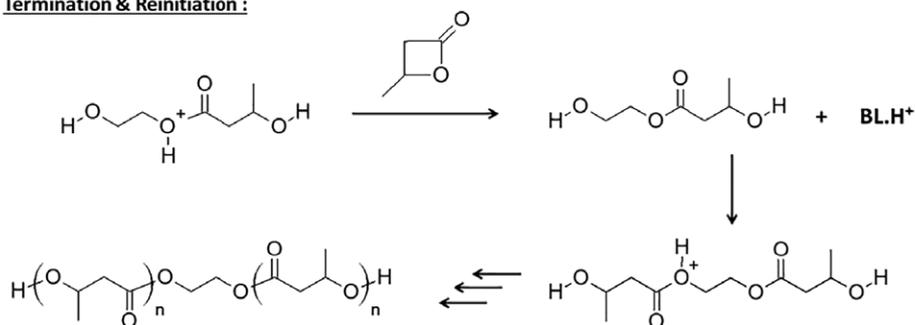
This eventually leads to the formation of cyclic PBL by end-to-end closure as attested to by MALDI-MS analysis (Scheme 17).

At the same time, Bourissou and Martin-Vaca realized a detailed study of BL ROP with both methane and trifluoromethane sulfonic acid catalysts, named MSA and TFA, respectively.<sup>99</sup> As compared to Kubisa, the polymerizations were realized in  $C_6D_6$  at 30 °C, using *n*-pentanol as the initiator. It appeared that TFA was a much more efficient catalyst than MSA in terms of kinetics and control of the reaction. While the ROP of BL from MSA ( $DP = 80$ ;  $[ROH]_0/[MSA]_0 = 1/3$ ) necessitated 26 h to get a high monomer conversion from a  $[BL]_0$  of 8 mol  $L^{-1}$ , TFA proved significantly more active, only requiring 9 h at a  $[BL]_0$  of 4 mol  $L^{-1}$ . Both polymerizations proceeded by “O-acyl” bond cleavage, however, as attested to by MALDI-MS analysis, several populations, in addition to that of *n*-pentyl ester end-capped PBL, were observed in the MSA-catalyzed process. <sup>1</sup>H-NMR analysis revealed that <0.2% of the PBL end groups were of crotonate nature when TFA was used as a catalyst, while the experimental molar masses increased linearly with the BL-to-*n*-pentanol initiating molar ratio. The selectivity of the ROP of BL in favor of “O-acyl” bond breaking, and the absence of a crotonization reaction, independently observed by Kubisa and Bourissou and Martin-Vaca, showed TFA to be quite a unique candidate for promoting the copolymerization of BL with larger lactones—including lactide and  $\epsilon$ -caprolactone—known to only propagate from hydroxyl chain ends.

In 1991, Okamoto reported the possibility of performing the cationic ROP of  $\beta$ -lactones, such as BL, from a mixture of alkylating agent and an exogenous alcohol.<sup>100</sup> In his study,

Okamoto used ethylene glycol as the initiator and triethyloxonium hexafluorophosphate (TEOP) as the catalyst. During the initiation of the process, each TEOP alkylated the most nucleophilic alcohol reactant and subsequently transferred its proton to the BL monomer. The protonated monomer was then attacked by the pristine ethylene glycol to open the end-capped charged oxetanone. The transfer and reinitiation steps then occurred successively to ensure the overall propagation process (Scheme 18). By performing the reaction in bulk, and for an initial BL-to-ethylene glycol molar ratio of 20, 96 h were necessary to reach a conversion of 84% (in a three-step procedure reaction) by a “O-acyl” bond cleavage, as attested to by both IR and NMR spectroscopies. Although no information was provided by the author regarding the molar mass, the PBL sample was characterized by a narrow dispersity value of 1.19 but was also slightly contaminated by crotonate end-groups.

Inspired by the discovery that diphenyl phosphate (DPP) acts as a “dual activator” during the polymerization of various lactones and cyclic carbonates,<sup>101–103</sup> in 2014, Kakuchi et al. investigated the efficiency of such activation in the BL ROP.<sup>104</sup> A comparison was carried out using both DPP ( $pK_a = 3.72$ ) and the more acidic bis-(4-nitrophenyl) phosphate (BNPP,  $pK_a = 1.77$ ). The polymerizations were performed in toluene from 3-phenyl-1-propanol and for a monomer-to-initiator ratio of 50. The authors demonstrated that BNPP is much more efficient than DPP, allowing controlled PBL chains at 60 °C with an initial alcohol-to-BNPP ratio of 2. As attested to by <sup>1</sup>H-NMR and MALDI-MS analyses, the conversions had to be limited to 80–85% to prevent poisoning reactions, such as crotonization. Under such conditions, the experimental molar

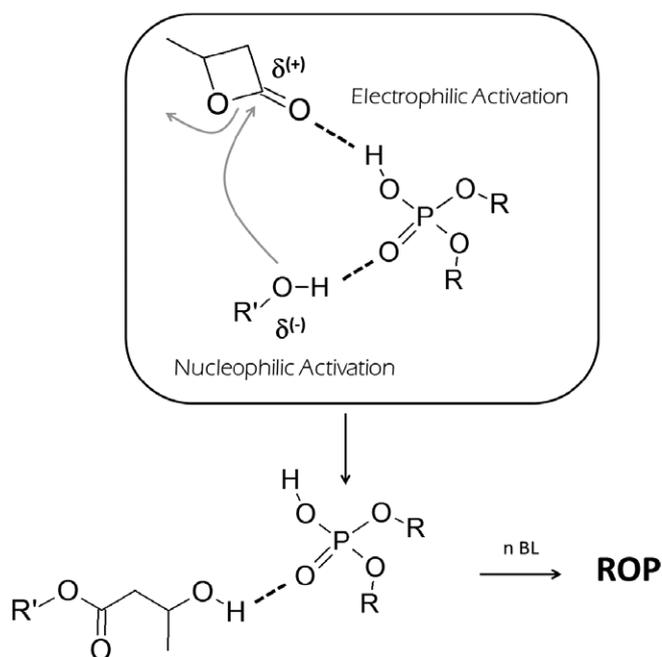
**Initiation :****Termination & Reinitiation :****SCHEME 18** Three-step mechanism involved in the ROP of BL from a TEOP/ethylene glycol initiating system.

masses tracked the theoretical ones for targeted DPs ranging from 20 to 120. By performing the polymerization at 8 mol L<sup>-1</sup>, 9.5 h allowed PBLs characterized by a  $M_{n,NMR}$  of 10,650 g mol<sup>-1</sup> and a dispersity value of 1.39 to be produced. The mechanistic investigation suggested that BNPP presents a dual activation ability due to two substrate recognition sites, such as Brønsted acidic and basic sites, leading *in-fine* to PBL chains obtained by “O-acyl” cleavage of the BL monomer (Scheme 19). The authors took advantage of the high initiation selectivity to start polymerizations from a wide variety of alcohols and to synthesize block copolymers with  $\epsilon$ -caprolactone and trimethylene carbonate monomers. Very interestingly, because the hydroxyl proton of the phosphoric acid acts as Brønsted acid, activating the BL monomer, while the phosphoryl oxygen acts as a Brønsted base, activating the initiating/propagating alcohol, the weak acidic character of the BNPP is sufficient to promote the ROP process (as compared to pure cationic activator, such as TFAA, characterized by a  $pK_a$  of -14).

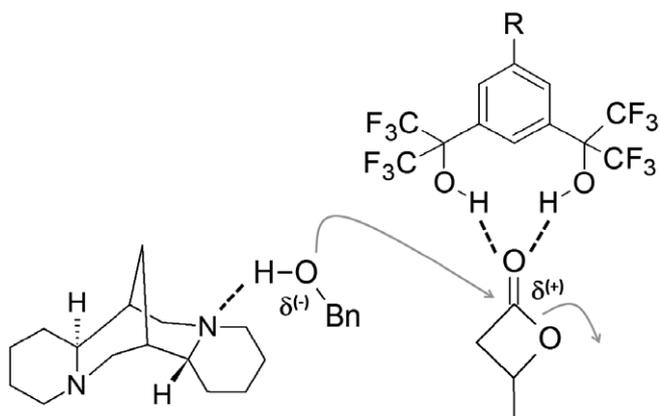
Such a concept of “dual interaction” through a “supramolecular interacting system” has also been applied by Harada et al. by promoting the BL ROP from cyclodextrins (CDs).<sup>105,106</sup> The authors demonstrated that  $\alpha$ - and  $\beta$ -CDs both initiate and

catalyze the BL ROP in bulk at 100 °C by forming an inclusion complex with the monomer. IR analysis indicates that the appropriate combination of CDs ( $\alpha$  or  $\beta$ , not  $\gamma$ ) forms a hydrogen bond between the carbonyl oxygen of the BL and the hydroxyl group of the CD to activate the monomer in the CD cavity. After 96 h, and for a  $[BL]_0$ -to- $[CD]_0$  of 15, both  $\alpha$ - and  $\beta$ -CDs allowed CD-tethered PBL chains of about 5000 g mol<sup>-1</sup> and dispersity values higher than 2.3 to be produced.

Another efficient “multiple reversible noncovalent activating” system was elaborated by Hedrick et al. using a bimolecular system composed of (-)-sparteine (SP) and fluorinated tertiary alcohols (FtAs).<sup>107</sup> In such a concept, the bulky electron-withdrawing fluorinated groups of FtA serve to increase the acidity of the initiating/propagating alcohol, whereas steric factors reduce the nucleophilicity of the FtA and prevent their participation in the initiation or chain-transfer reactions. While the hydrogen-bonding capability of FtA was proved by NMR and DFT calculations, the authors demonstrated that the BL monomer could be polymerized in C<sub>6</sub>D<sub>6</sub> from benzyl alcohol as the initiator, 3,5-bis-(1,1,1,3,3,3-hexafluoro-2-hydroxypropyl)phenyl methacrylate (HFA) as the catalyst, and SP as the co-catalyst ( $[BL]_0/[ROH]_0 = 425$ ,  $[HFA]_0/[SP]_0 = 5$ ), leading to PBL chains of 11,000 g mol<sup>-1</sup> in an extensive 357-h reaction time (Scheme 20).



**SCHEME 19** BL ROP dual activation process from a BNPP catalyst ( $R = -C_6H_4NO_2$ ;  $R'$  = initiating or propagating radical).



**SCHEME 20** Bimolecular activating process implied in the BL ROP as promoted from benzyl alcohol using an HFA/SP catalytic complex ( $R = \text{methacryloyl}$ ).

## CONCLUSIONS

The eventual ambition of the research has always been concentrated on the enhancement of selectivity, polymerization rates, and the choice of functional groups for polymerization reactions. Organic catalysts have proven to be of broad utility for the generation of PHAs of various architectures. The indisputable advantages of organic catalysts over metal- and enzymatic-structures, in both microelectronic and biomedical applications, maximize the chances of these structures being industrially used, knowing that the global PHA market is projected to grow to a bit <\$94 million by 2021.

The contribution of organocatalysts has led to a wide range of synthetic procedures for the polymerization of  $\beta$ -lactones. Many organocatalysts have proven to be successful through different mechanisms and pathways, all the while exhibiting rates that could exceed those of organometallic compounds. Coming from the chemical structure of the lactones, polymerization in the presence of an organocatalyst goes through two possible pathways: the “O-alkyl” and “O-acyl” pathways. The polymerization reaction can proceed through any of these cleavages, solely or through both routes concurrently, with different percentages, depending on the nature of the organocatalytic system used.<sup>38,43,45,55,56,94,99,104,107</sup> In this highlight, we have attempted to clearly identify which organocatalysts could either activate  $\beta$ -lactone monomers, or the propagating chain-ends, to perfectly design large nanostructures, and how they do this.

Although researchers have continued to study metal-based catalysts for the polymerization of  $\beta$ -lactones,<sup>108,109</sup> the different facets of other research have allowed new metal-free catalytic systems to be developed. Compared to metal-based catalysts, these organocatalysts allow for new polymer topologies to be prepared. In this contribution, we have presented the different organocatalysts that have been studied by researchers with overviews of the mechanisms, monomer activation, and initiation of the polymerization reactions. Among those inducing a zwitterionic polymerization route, *N*-heterocyclic carbenes provide a new strategy for precision polymer synthesis.<sup>35,38,43,57,60</sup> Their ability to act as initiator, or to reversibly activate exogenous protic initiators, allows various molecular architectures, that is, linear, cyclic and jellyfish, to be produced.<sup>83–86,91</sup> The non-nucleophilic phosphazene-based catalytic systems also have a respected role in the well-defined macromolecular design<sup>45,66,76</sup> because they allow polymers of molar masses up to 2 million  $\text{g mol}^{-1}$  to be created in an unprecedented manner.<sup>76</sup>

In addition, cationic ROP of  $\beta$ -lactones have been thoroughly investigated through different organocatalyzed polymerization reactions. The activation of  $\beta$ -lactone monomer units in the presence of an alcohol in acidic conditions extends the options for new organocatalytic systems. Other catalysts, such as fluorinated sulfonic acids or phosphates, that interestingly allow the double activation of  $\beta$ -lactones, are further examples of organocatalysts that have been discovered thanks to the drive to enhance the existing organocatalysis polymerization conditions.<sup>99,105–107</sup>

Over the last few years, the numerous organocatalysts that have been discovered and employed in the polymerization reaction of  $\beta$ -lactones have encouraged scientists to intensify their research activity to enhance and study other potential families of organocatalysts. The successful research has permitted scientists to go to the next level by industrializing the synthesis of  $\beta$ -lactones, such as  $\alpha,\alpha,\beta$ -trisubstituted lactones, which can facilitate research in polymer science regarding polymerization catalysis, as well as their corresponding polymers that can be applied in the fields of nanoscience and nanomedicine.

As for organocatalysis applied to the ROP of larger lactones,<sup>31</sup> challenges remain, particularly in terms of stereoselectivity. Asymmetric acyl transfer reactions can be envisaged. Such a process uses a chiral organocatalyst which participates in the nucleophilic attack on an acyl donor to lead to a reactive chiral acyl salt. Nucleophilic attack on this salt then provides the acylated product.<sup>110</sup> The unquestioned strength of phosphazene bases in inducing the preparation of highly active carboxylic acid salts could also inspire emulation in the enantioselective polymerization of  $\beta$ -lactones. Quite recently, Simon and Paton reported on the addition of nitroalkanes and phosphonates to benzaldehyde catalyzed by a chiral phosphazene catalyst developed by Ooi and co-workers.<sup>111</sup> Mechanistically, the mode of action of this class of phosphazene resembles the role established for guanidines involving a single molecule to interact both with the nucleophile and the electrophile.<sup>31</sup> From the calculations, and their interpretations in terms of steric interactions, it seems interesting to foresee such catalysts as promising candidates for inducing a certain stereoselectivity. Very interestingly, the wide choice of organic bases and acids, in terms of size and activity, gives us the possibility to envision the preparation of a plethora of organic salts. To date, some of these salts have already been used as catalysts in ROP processes of middle lactones,<sup>112–114</sup> sometimes mimicking the catalytic triad of enzymes.<sup>115</sup> As none of these processes have been applied to (un)functionalized  $\beta$ -lactones, this leaves the doors wide open to a very productive future.

#### ACKNOWLEDGMENTS

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