Recent Advances in Metal-Mediated Stereoselective Ring-Opening Polymerization of Functional Cyclic Esters towards Well-defined Poly(hydroxy acid)s: From Stereoselectivity to Sequence-Control

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Minireview Article

Recent Advances in Metal-Mediated Stereoselective Ring-Opening Polymerization of Functional Cyclic Esters towards Well-defined Poly(hydroxy acid)s: From Stereoselectivity to Sequence-Control

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Keywords: Ring-opening Polymerization; Lactone; Diolide; *O*-Carboxyanhydride (OCA); Poly(hydroxy acid); Poly(hydroxyalkanoate) (PHA); Sequence-Controlled Polymer; Stereoselective Catalysis; Yttrium

Abstract

Poly(hydroxy acid)s are a family of biocompatible and (bio)degradable polyesters with various outcomes in different domains of application. To date, poly(hydroxy acid)s are best prepared by ring-opening polymerization (ROP) of the corresponding cyclic esters. Using racemic chiral monomers featuring side-chain groups enables to access, providing a stereoselective catalyst/initiator system is implemented, stereoregular functional polymers, thereby improving their physico-chemical properties and ultimately widening their range of uses. Here, we highlight a few important advances in metal-mediated stereoselective ROP of cyclic esters towards the synthesis of (functional) stereoregular poly(hydroxy acid)s that have recently been disclosed, emphasizing on (functional) β- and γ-lactones, diolide and *O*-carboxyanhydride (OCA) monomers and yttrium-based catalysis. Fine-tuning of the substituents flanked on the catalyst ligand enables reaching poly(hydroxy acid)s with syndiotactic and also isotactic microstructures. The stereocontrol mechanisms at work and their probable origin, relying on steric but also electronic factors imparted in particular by the ligand substituents, are discussed. Taking advantages of such stereoselective ROPs, original copoly(hydroxy acid)s with gradient or alternated patterns then become accessible from the use of mixtures of chemically different, oppositely configurated enantiopure monomers.

Introduction

Poly(hydroxy acid)s, including poly(α,β,γ-hydroxy acid)s, namely PAHAs, PBHAs – more commonly referred to as poly(hydroxyalkanoate)s (PHAs) –, PGHAs, respectively, are a class of polyesters that find a variety of packaging, agricultural, biomedical and pharmaceutical applications, thanks to their biocompatibility and (bio)degradability.[1] Most ubiquitous examples include the commercially available poly(lactide) (PLA), poly(glycolide) (PGA), and poly(lactide-*co*-glycolide) (PLGA) as PAHA representatives, and poly(3-hydroxybutyrate) (PHB) with a PBHA pattern (Chart 1). The former PAHAs are industrially produced from readily available inexpensive, renewable resources (e.g. corn, sugar cane, sugar beet) by ring-opening polymerization (ROP), while the latter PBHAs are prepared by fermentation from naturally occurring biomass-derived sugars (e.g. sucrose, glucose) using microorganisms that provide (only isotactic) PHAs. Poly(hydroxy acid)s feature different side-chain substituents along the backbone, thereby imparting chirality to each repeating units. The chemical (functional) nature of these side-groups and the successive enchainment of the chiral monomer units along the macromolecules – that is the regularity of the configurations of adjacent stereocenters along the polymer chain –, both dictate/modulate the physical, mechanical and biological properties of the resulting polymer materials by tailoring the composition and architecture of the polymers. Stereoregular polymers basically feature either isotactic (in which neighboring stereocenters have the same configurations) or syndiotactic (in which neighboring stereocenters adopt alternating configurations) structures. Such stereoregular polymers are most desirable since they are usually crystalline and thus show improved thermal and mechanical properties as compared to those of atactic (lack of regularity in the neighboring stereocenters) analogues. Side-chain functionality along poly(hydroxyl acid)s' backbone is further highly desirable since, besides providing a way to influence the physico-chemical properties, it offers a handle to chemically and/or biologically modify the scope of the polymer materials through post-polymerization side-chain modification. Sequence-controlled poly(hydroxy acid)s with various functionalities and microstructures thus directly widen the scope of the resulting materials.[2]

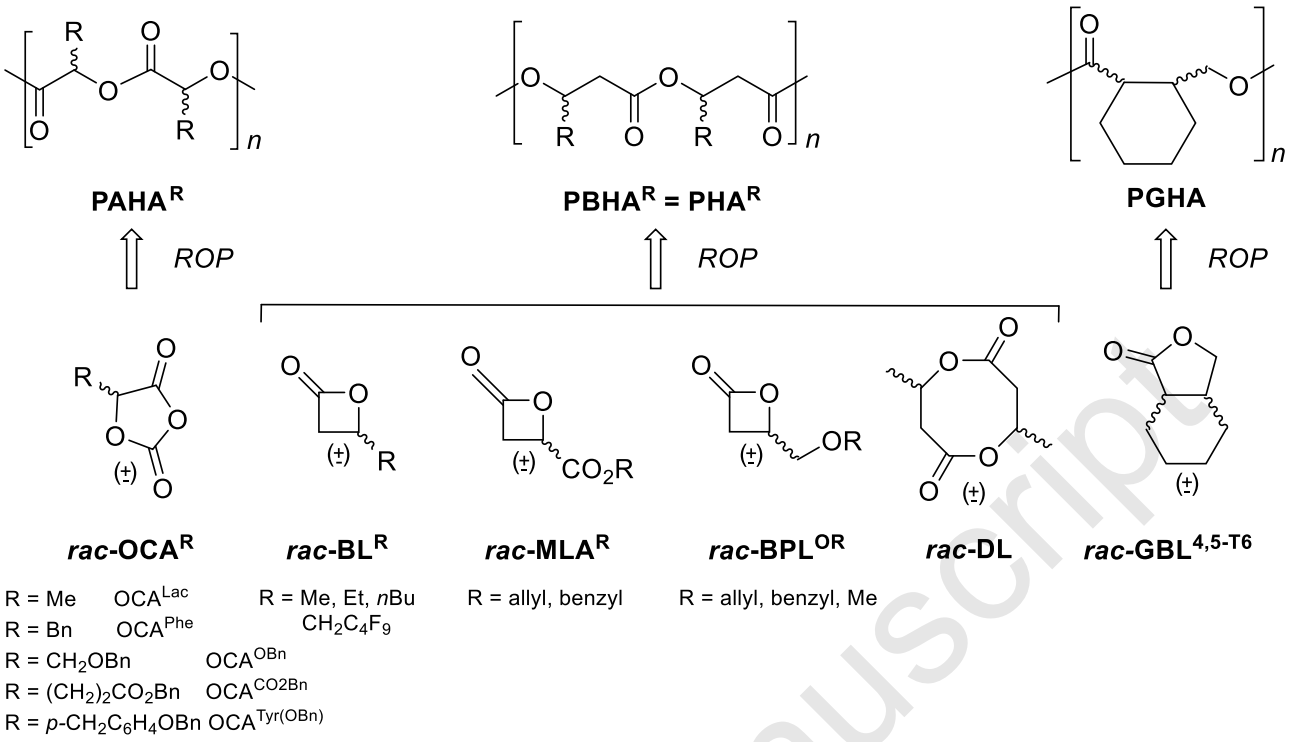


Chart 1. Poly(α,β,γ-hydroxy acid)s addressed in this review, namely PAHAs, PBHAs and PGHAs, and the corresponding cyclic ester monomers from which they can be synthesized by stereoselective metal-mediated ring-opening polymerization (ROP).

The homogeneous single-site metal-catalyzed living ROP of cyclic esters reaches high performances in terms of efficiency, i.e. activity, productivity, stereocontrol; it remains to date the best strategy toward the controlled synthesis of such well-defined stereoregular side-chain functionalized polyesters.[3] Polyesters with controlled macromolecular features including tuned molar mass values, narrow dispersities, limited undesirable side reactions (typically inter- and intra-molecular transesterifications), chain-end fidelity, monomer/repeating unit functionality, controlled polymer topology and microstructure (i.e. tacticity) are thus commonly synthesized. In that topical field, group 3 metal (rare earth) complexes have demonstrated unique performances: first, in their distinctive ability to successfully enable the ROP of a large variety of cyclic esters, including stable, low-strained, and hence usually reluctant to ring-open cyclic esters, and also in their capability to stereoselectively fine tune via the ligand catalyst the polymer's microstructure when starting from racemic mixtures of chiral monomers.[4] In this quest for polyesters exhibiting targeted stereoregularity and for highly efficient stereoselective catalyst systems, the pioneering work tackled the ROP of racemic lactide (*rac*-LA) for the synthesis of isotactic polylactide (PLA). Crystalline isotactic PLLA, commercially produced

from the ROP of enantiomerically pure (*S*,*S*)-LA, is arguably one of the most ubiquitous sustainable polymer alternative to common petrochemical-based plastics. Yet, in contrast to heterotactic PLA that is rather easily accessible, only a limited number of (always metal-based) catalyst/initiator systems enable the direct preparation of isotactic (sometimes stereocomplexed) PLA from the ROP of *rac*-LA.[5] Efforts on the design of ancillary ligands with fine-tuned substituents on their platform rewardingly provided a significant breakthrough in stereoselective ROP catalysis. This has been extended beyond LA to other chiral racemic cyclic ester monomers, among which in particular the family of β-lactones and *O*-carboxyanhydrides (OCAs). However, until very recent work, only syndiotactic or even atactic polymers derived from these latter monomers could be obtained.

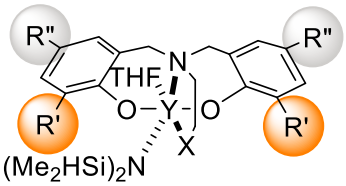
In this minireview, we highlight some recent achievements on the metal-mediated stereoselective ROP of cyclic esters towards the synthesis of (functional) poly(hydroxy acid)s, focusing on (functional) β- and γ-lactones, diolide, and OCAs. Quite strikingly, not only syndiotactic and isotactic polymers can now be efficiently produced from racemic mixtures of these monomers, but also original copoly(hydroxyalkanoate)s with gradient or alternated patterns prepared from mixtures of chemically different, oppositely configurated enantiopure monomers. It is shown that those stereoselective patterning methodologies rely on the combination of both the stereocontrol imparted by the catalytic system, and especially of the steric and electronic factors imparted by the ligand substituents, and of the chemical nature of the monomer unit(s).

From syndiotactic to isotactic PBHAs, PGHAs and PAHAs

Extensive studies by our group and others have evidenced that the *stereoselective* ROP of chiral racemic *β*-lactones is best achieved with group 3/rare-earth catalysts via coordination-insertion routes.[4, 6] Most typical and highly effective (pre)catalysts/initiators for this purpose are, arguably, yttrium complexes stabilized by dianionic, tetradentate diamino- or amino-alkoxy-bis(phenolate) ligands (Scheme 1). Such trivalent yttrium complexes bearing the tripodal {ON(X)O$^{R',R''}$}[6] or salan-type {ON^{R}N^{R}O$^{R',R''}$}[7,8] ligands show high activity in the ROP of a variety of cyclic esters, among which in particular the more reluctant *β*-lactones. These ROPs proceed readily under mild conditions, at room temperature, in a controlled fashion, delivering polymers with narrow dispersities ($Đ_M = M_w/M_n$ <1.3 typically) and predictable molar mass values; that is, molar masses dictated by the monomer-to-initiator ratio, the initiator being either the nucleophilic group of the yttrium complex itself (e.g. NH(SiMe$_2$)$_2$, O*i*Pr) or an exogenous

alcohol (most often isopropanol), added as a co-initiator or as a transfer agent when used in excess versus the yttrium precursor.[6b] Nonetheless, the most unique and valuable feature of these families of *achiral* Y{ON(X)O$^{R',R"}$} and Y{ON^{R}N^{R}O$^{R',R"}$} complexes is the ability to fine tune the stereocontrol of the polymerization by simply changing the nature of the substituents on the ligand: in the former series, onto the phenolate moieties – and most particularly the R' *ortho*-substituent,* the one which is obviously the closest to the active center – and, in the latter series, also onto the *N* atoms of the salan ligand framework. For *achiral* catalysts/initiators, microstructural NMR studies conducted on PHAs resulting from the ROP of different chiral racemic *β*-lactones, unsurprisingly showed that, just as for the even more investigated *rac*-LA, stereocontrol originates from a chain-end mechanism (CEM): that is, the chirality of each new incoming monomer is dictated by the chirality of the last monomer unit inserted into the growing polymer chain. In the vast majority of cases, CEM generates syndiotactic polymers, because the active species alternatively picks up monomers with opposite configuration to minimize steric tilting in the transition state. It was therefore not unexpected that the initial studies conducted on the benchmark cyclic esters, racemic *β*-butyrolactone (*rac*-BL^{Me})[9] and *rac*-LA, revealed that the Y{ON(X)O$^{R',R"}$} and Y{ON^{R}N^{R}O$^{t Bu2}$} complexes generate syndiotactic-rich poly(3-hydroxybutyrate) (PHB = PBHA^{Me}) and heterotactic-rich polylactide (PLA); and also that the syndiotacticity level, as determined by the probability of racemic linkage (P_r; P_r = 1 for a perfectly syndiotactic polymer, P_r = 0 for an isotactic one, and P_r = 0.5 for an atactic one), apparently increases with the steric bulkiness of the *ortho*-R' substituent on the {ON(X)O$^{R',R"}$} ligand framework. Whereas the latter trend is monotonous in the case of lactide (P_r = 0.55 (R' = Me), 0.81 (*t*Bu), 0.91 (CMe_2Ph), 0.95 (CMe_2*t*Bu), 0.95 (CPh_3)), the "most crowded" complexes hence being the best, it is not the case for the ROP of *rac*-BL^{Me} (P_r = 0.56 (R' = Me), 0.80 (*t*Bu), 0.83 ($CMe_2C_6H_4$(*p*-CF_3)), 0.91 (CMe_2Ph), 0.70 (CMe_2*t*Bu), 0.96 (CPh_3)). In this latter ROP, an electron-rich aryl group on the R' substituent is also beneficial and necessary for achieving high syndiotacticity. As discussed in details in a recent feature article,[10] this was accounted for by the occurrence of attractive C–H…*π*(aryl) interactions between the aryl groups from the R' *ortho*-substituent and the acidic C–H of the methylene of the last inserted monomer unit within the growing poly(alkoxybutyryl) chain; such so-called "second-sphere" or "non-covalent" interactions (NCIs)[11] are illustrated in Chart 2 (a).

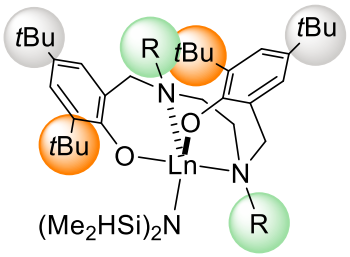
* For synthetic reasons, the *ortho*-R' and *para*-R" substituents in these (pro)ligands most usually prepared from the parent disubstituted salicaldehydes are often identical; nonetheless, (pro)ligands having different R' and R" substituents have been prepared and the corresponding yttrium complexes revealed a much less important role of the remote *para*-R" substituent, although slight differences in terms of activity, and to an even lesser extent, of stereoselectivity have been noted; see ref [6b].



Y{ON(X)O$^{R',R''}$}

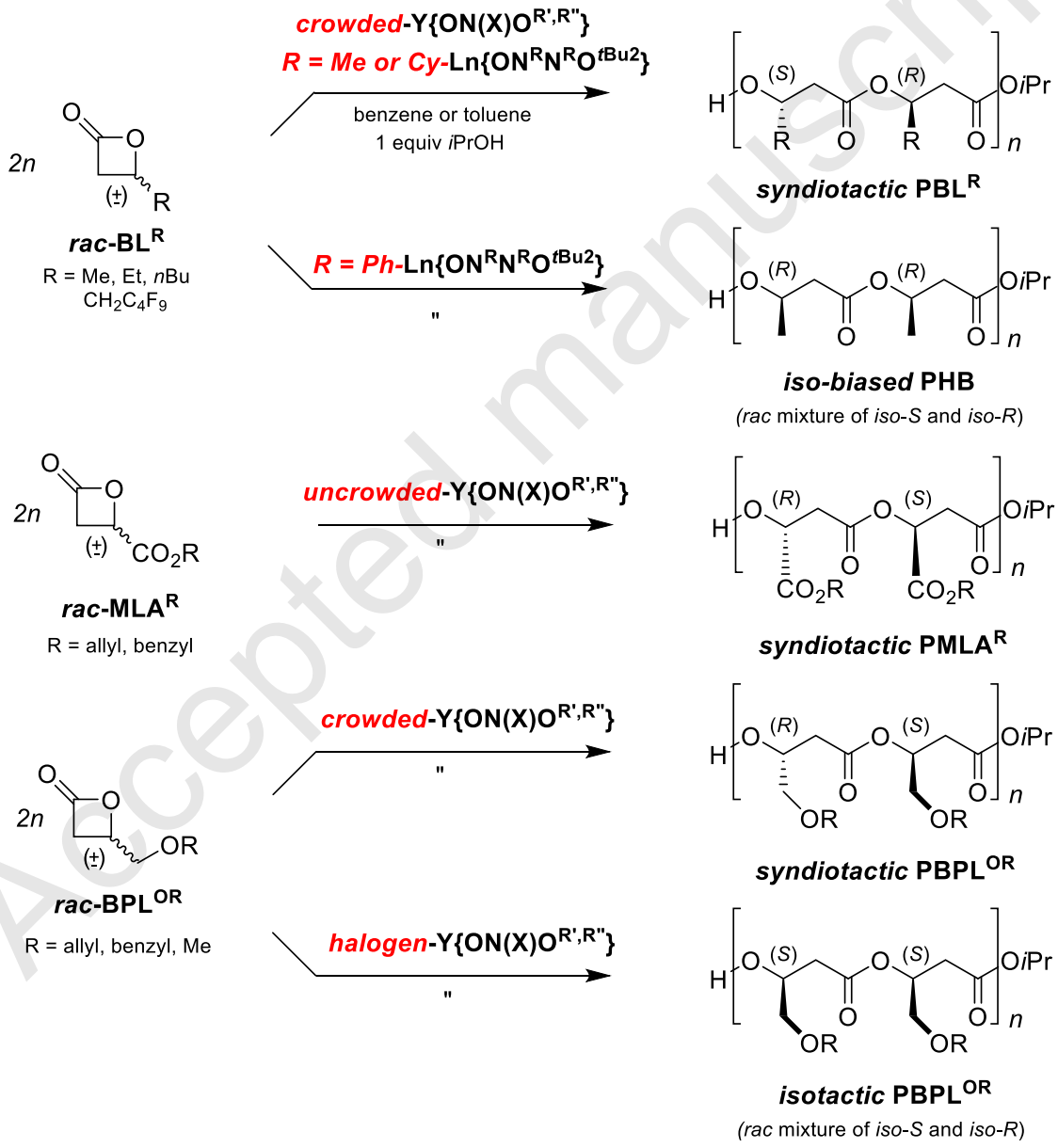
Carpentier and Guillaume: X = NMe_2, OMe

"***crowded***": R', R" = *t*Bu, CMe_2Ph, CMe_2tBu, CPh_3
"***uncrowded***": R', R" = Me, F, Cl, (Br)
"***halogen***": R', R" = F, Cl, Br...

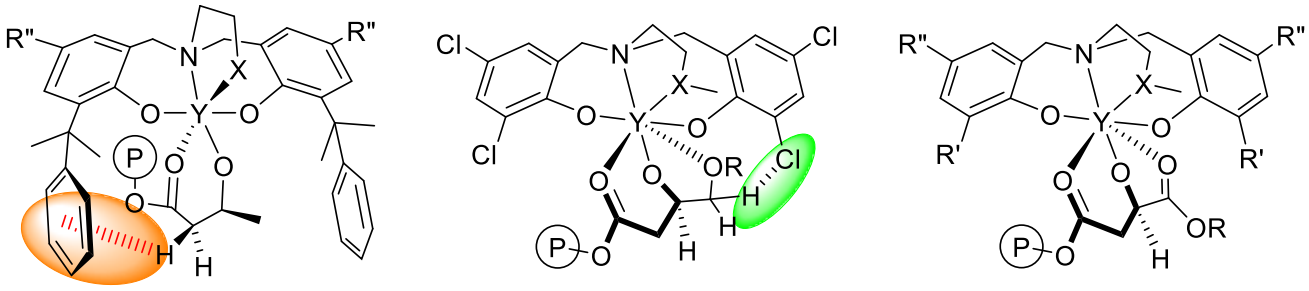


Ln{ON^{R}N^{R}O^{tBu2}}

Coates and Thomas: R = Me; Ln = Y
Cui et al.: R = Ph, Cy or *t*Bu; Ln = Y, Yb



Scheme 1. Access to syndiotactic or isotactic poly(*β*-hydroxyalkanoate)s (PBHAs) from the ROP of racemic *β*-lactones with achiral yttrium complexes.[6-10]



π(aryl)···H–C(butyryl) (a) **π(aryl)···H–C(butyryl)** (b) **Y-malolactonate** (c)

Chart 2. Illustration of putative "non-covalent interactions" (NCIs) at work in stereoselective ROP of *rac*-BL^{Me} (a), *rac*-BPL^{OR} (b), and of the multi-coordinated species in ROP of *rac*-MLA^{R} (c) with yttrium{ON(X)O$^{R',R"}$} catalysts.[6b,10]

In 2009, Coates and Thomas reported that the ROP of *rac*-BL^{Me} and related *β*-lactones bearing alkyl side-groups higher than Me, using the yttrium-salan complex Y{ON^{Me}N^{Me}O^{tBu2}} also generates highly syndiotactic PBHAs (P_r = 0.90–0.94).[7] In 2018, Cui and collaborators revisited this chemistry by tuning the substituents on the N atoms of the salan ligand framework, and further using ytterbium(III) in addition to yttrium(III) complexes for the ROP of *rac*-BL^{Me}.[8] Independently of the nature of the metal center – which essentially affects the activity, the larger yttrium metal being always the most active –, the tacticity of PHB is drastically impacted by the substituents on the bridging N atoms: cyclohexyl substituents lead to syndiotactic-enriched PHB (P_r up to 0.78) while phenyl groups induce the formation of isotactic-enriched PHB (probability of meso linkage, $P_m = 1 - P_r$, up to 0.77), and *tert*-butyl groups give atactic PHB (P_m ca. 0.5). The nature of the stereocontrol mechanism operative with these systems, CEM or enantiomorphic-site control mechanism (ESM),[12] was not established. Although the tacticity values remain below 0.80, these latter results constitute a remarkable example that solely tuning the substituents from cyclohexyl (or methyl as per Coates and Thomas[7]) to phenyl groups on the bridging N atoms of Y-salan complexes, can induce a switch of the polymerization selectivity from syndiotactic to isotactic. An open question that remains is whether this switch, and in particular the formation of isotactic-rich PHB, is driven by sterics or rather by the aryl nature of the *N*-phenyl substituents, which would be reminiscent of the above-mentioned C–H…π(aryl) NCIs.

Our group did confirm that syndio-stereocontrol in the ROP of 4-alkoxymethylene-*β*-propiolactones (BPL^{OR}s) with Y{ON(X)O$^{R',R"}$} catalysts/initiators increases with the

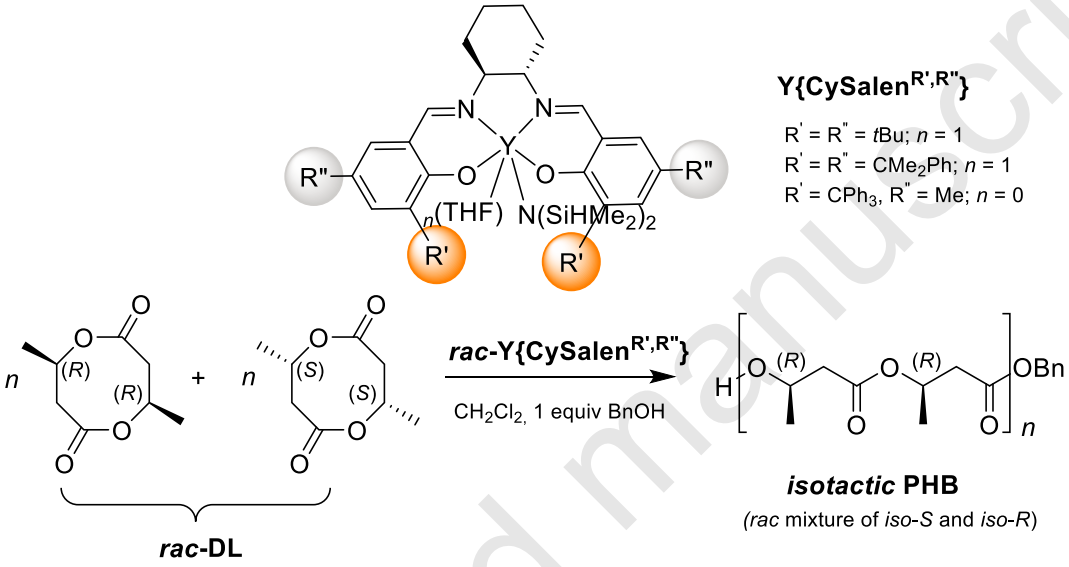
bulkiness of simple R' alkyl *ortho*-substituents on the ligand (Scheme 1). Yet, further studies conducted on this class of functional *β*-lactones with catalysts bearing on the ligand "electronically-active" substituents such as halogens,[10] or on another class of racemic functional *β*-lactones, namely *β*-malolactonates (MLA^{R}s),[13] led to completely different trends in terms of stereocontrol and showed that the "bulky ligand = syndiotactic PHA" model is far too simplistic and suffers from many exceptions.

In fact, in the ROP of *rac*-MLA^{R}s, highly syndiotactic polymers (PMLA^{R}s) are produced with "uncrowded" Y{ON(X)O$^{R',R"}$} catalysts/initiators bearing small R' *ortho*-substituents such as methyl or chloro (P_r > 0.95) (Scheme 1); bulkier substituents afford polymers with lower levels of syndiotacticity (P_r = 0.86 (*t*Bu), 0.81 (CMe_2Ph), 0.68 (CPh_3)).[10,13] Even more surprisingly, in the ROP of *rac*-BPL^{OR}s, Y{ON(X)O$^{R',R"}$} catalysts/initiators bearing halogens as R' substituents (F, Cl, Br) afford highly isotactic PBPL^{OR}s (P_m = 0.90–>0.95; Scheme 1)![10,14] This latter case of isoselectivity also calls for NCIs[11], where the halogen *ortho*-substituent on the ligand apparently induces attractive interactions with methylene hydrogens of the last inserted monomer within the growing polymer chain; this was supported by DFT computations (Chart 2, b). For the ROP of *rac*-MLA^{R}s, while DFT computations fail to provide informative data so far, we suspect that, in contrast to other *β*-lactones, the alkoxycarbonyl side-group of the last inserted monomer unit in the growing PMLA^{R} chains coordinates onto the metal center (through the O atom), thereby generating active species with a higher coordination number (Chart 2, c); this may therefore require less bulky (Me, Cl) R' *ortho*-substituents on the ligand for an optimal chain-end stereocontrol. Further studies with new families of *β*-lactones are ongoing in our laboratory to further explore these hypotheses and to shed light on the exact origins of these different, yet subtle stereocontrol modes. Anyway, the above results underpin the very high potential of yttrium complexes bearing such {ON(X)O$^{R',R"}$} ligand platforms and their synthetic usefulness for preparing, nearly at will, PHAs with various levels of tacticity (*vide infra*).

The nearly perfect isoselective (P_m > 0.95) ROP of *rac*-BPL^{OR} with the halogen(chloro)-substituted yttrium catalyst is quite a unique example; indeed, no other racemic *β*-lactones – even *rac*-BL^{Me}, the simplest and by far the most studied one since the 1960s – could be polymerized in a highly isoselective manner so far with a molecular catalyst.[15] In 2018, Chen and Tang reported an exciting result, that is the synthesis of perfectly isotactic (P_m = 0.99) PHB via the yttrium-catalyzed ROP of a cyclic dimer of 3-hydroxybutyrate, namely the eight-membered racemic cyclic diolide (*rac*-DL) (Scheme 2).[16] DL can be readily derived from bio-

sourced dimethyl succinate, either as the *rac* or *meso* diastereomer; it is a class of monomers that was unexplored in ROP till Chen's report. Considering the significantly increased sterics present in DL relative to *β*-BL^{Me}, the authors anticipated a probable higher degree of stereochemical control in the ROP of DL, thereby potentially generating highly stereoregular PHB materials. In fact, ROP of *rac*-DL proceeds effectively with rare earth-based catalysts via a coordination/insertion route. The simple achiral catalyst system, obtained from the combination of La(N(SiMe$_3$)$_2$)$_3$ with BnOH as a co-initiator (generating *in situ* the corresponding La-benzyloxide active species), proves effective but returns PHB with only a slight isotactic bias (P_m = 0.70–0.74). The Y{ON(O)O$^{R',R''}$} systems (R', R'' = *t*Bu or CMe$_2$Ph) are less active, especially the more bulky cumyl-substituted one, and also afford an isotactic bias (P_m = 0.76). It is noteworthy that, although modest, these yet noticeable P_m values obtained with achiral catalysts/initiators, indicate a distinctive propensity of the DL monomer to induce the formation of synthetic isotactic PHB. Highly isoselective ROP of *rac*-DL (P_m = 0.88–0.99) is achieved using yttrium catalysts associated to chiral salen ligands; the most effective one bears a very bulky *ortho*-trityl substituent (Y{CySalen$^{R',R''}$} with R' = CPh$_3$, R'' = Me, Scheme 2), yet maintaining a significant polymerization activity (TurnOver Frequency > 20 mol(DL) mol(Y)$^{-1}$ min^{-1}) at room temperature. Used as a racemic mixture, complex Y{CySalen$^{R',R''}$} produces essentially stereo-perfect, pure isotactic PHB ([*mm*], isotactic triad made up of two adjacent meso diads > 99%), with high molar mass (up to 154 kg mol^{-1}), narrow dispersity ($Đ_M$ = 1.01–1.07), high crystallinity and, as a result, a high melting temperature (T_m) up to 171 °C. When the yttrium-salen complex is used in enantiopure form, a perfect kinetic resolution polymerization of *rac*-DL is achieved, with the selective conversion of one particular enantiomer of the monomer (i.e. (*R*,*R*)-Y{CySalen$^{R',R''}$} consumes exclusively (*S*,*S*)-DL, and *vice-versa*), even after extended reaction times, indicative of exclusive catalyst-site selectivity for the ROP. Based on this observation, the authors concluded that an ESM is operative for the stereoselective ROP process; in line with the abovementioned ability of achiral catalysts to generate PHB with a significant isotactic bias from the ROP of *rac*-DL, one can assume also that a synergistic combination between CEM and ESM controls most likely takes place in this reaction.[12b] When using a racemic catalyst for the polymerization, the resulting polymer is predominately a mixture of (*R*)-PHB and (*S*)-PHB; formation of trace amounts of the stereoblock polymer [(*R*)-PHB]-*b*-[(*S*)-PHB] may result from prolonged exposure to the catalyst which slowly promotes transesterification (as evidenced by the broadening of $Đ_M$ values up to 1.20). Yet, the latter side reaction can be inhibited by limiting the reaction time and/or by reducing the catalyst amount in the feed (monomer loadings up to 1,600 mol(DL)

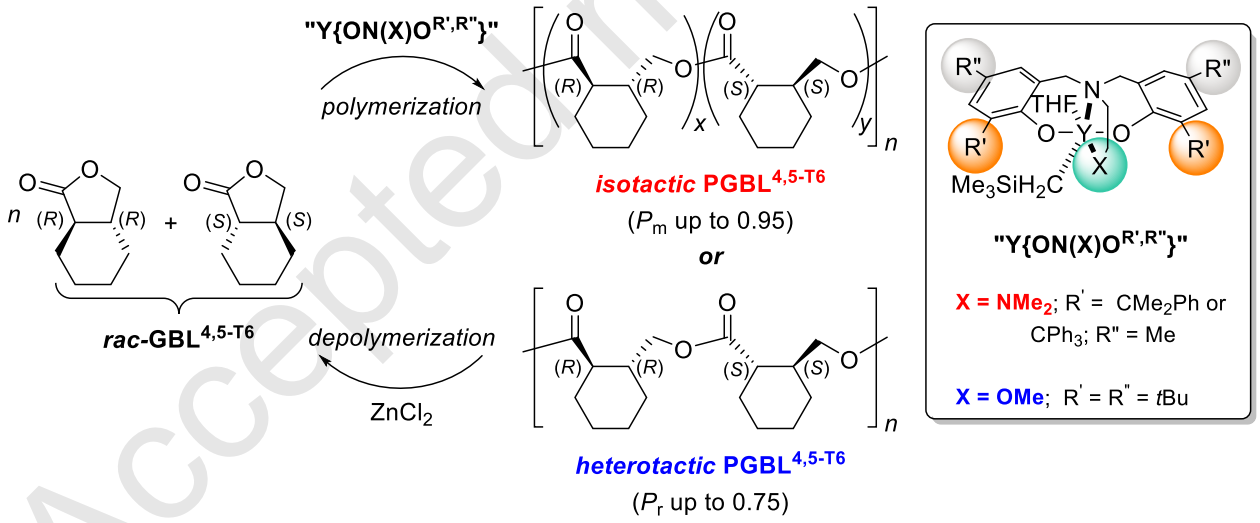
mol(Y)$^{-1}$). Remarkably, the high stereoselectivity of the *rac*-Y{CySalen$^{R',R''}$} catalyst observed towards *rac*-DL does not apply to the ROP of *rac*-BL^{Me}: the latter polymerization was not only sluggish but also non-stereoselective, producing atactic PHB. This clearly evidences the singularity of the diolide monomer and the plethora of opportunities for discovering new polymer materials that the ROP of *rac*-DL, of its *meso* diastereomer, or as well as of related cyclic dimers or trimers of other *β*-hydroxyacids, opens up. Overall, these recent results exemplify a paradigm shift in the stereoselective ROP of cyclic esters and the chemical synthesis of PBHAs.



Scheme 2. Access to isotactic poly(*β*-hydroxybutyrate) (PHB) from the ROP of racemic diolide (DL) with chiral yttrium-salen complexes.[16]

The aforesaid versatility of the yttrium complexes bearing {ON(X)O$^{R',R''}$} ligand platforms was further recently documented by Chen's group. In their search for new, high-performance polymer materials that can be chemically depolymerized back to the monomer in a quantitative yield and purity, so as to establish a virtuous circular life-cycle, they studied the ROP of the five-membered γ-butyrolactone (GBL) and of related fused six-five bicyclic lactones, namely 3,4-*trans*-cyclohexyl and 4,5-*trans*-cyclohexyl fused γ-butyrolactone (GBL$^{3,4\text{-T6}}$ and GBL$^{4,5\text{-T6}}$, respectively).[17] These rather stable monomers can be best polymerized under mild conditions with La(N(SiMe$_3$)$_2$)$_3$/ROH or Y{ON(X)O$^{R',R''}$}(CH$_2$SiMe$_3$)/ROH catalyst/initiator combinations. Most strikingly, with the latter systems, Chen and coworkers demonstrated that upon tuning the X capping moiety of the tripodal {ON(X)O$^{R',R''}$} ligand, the stereoselectivity of the ROP of *racemic* GBL$^{4,5\text{-T6}}$ can be switched from syndiotactic (X = OMe)

to isotactic (X = NMe_2) (Scheme 3).[18] In fact, only the highly sterically crowded trityl-substituted complex Y{ON(NMe_2)$O^{CPh3,Me}$} features a significant isoselectivity at room temperature (P_m = 0.77), all the other ones bearing a (slightly) less bulky $CMePh_2$, cumyl (CMe_2Ph) or *tert*-butyl *ortho*-substituent, no matter the X side-arm group, return slightly iso-biased or atactic materials (P_m = 0.50–0.65). However, upon lowering the temperature down to –65 °C, the Y{ON(X)$O^{R',R"}$} catalysts remain active (albeit with poor conversions for the bulkiest trityl-substituted one), and afford the corresponding poly(GBL$^{4,5\text{-T6}}$)s (PGBL$^{4,5\text{-T6}}$s) with more pronounced stereoselectivities, with P_m up to 0.95 for the trityl-substituted one with X = NMe_2 and P_m down to 0.25 for the *t*Bu-substituted one with X = OMe. Correspondingly, the sterically more hindered Y{ON(NMe_2)$O^{CMePh2/CPh3,Me}$} complexes afford crystalline isotactic PGBL$^{4,5\text{-T6}}$ with a T_m up to 171 °C. Microstructure statistical analysis by ^{13}C NMR of the carbonyl and methylene regions of the spectra, indicate that both heteroselectivity and isoselectivity originate from a CEM, although the reversal of stereoselectivity upon changing the X capping group could not be rationalized thus far. This nevertheless further demonstrates the high versatility and immense potential of this class of tunable catalysts/initiators.

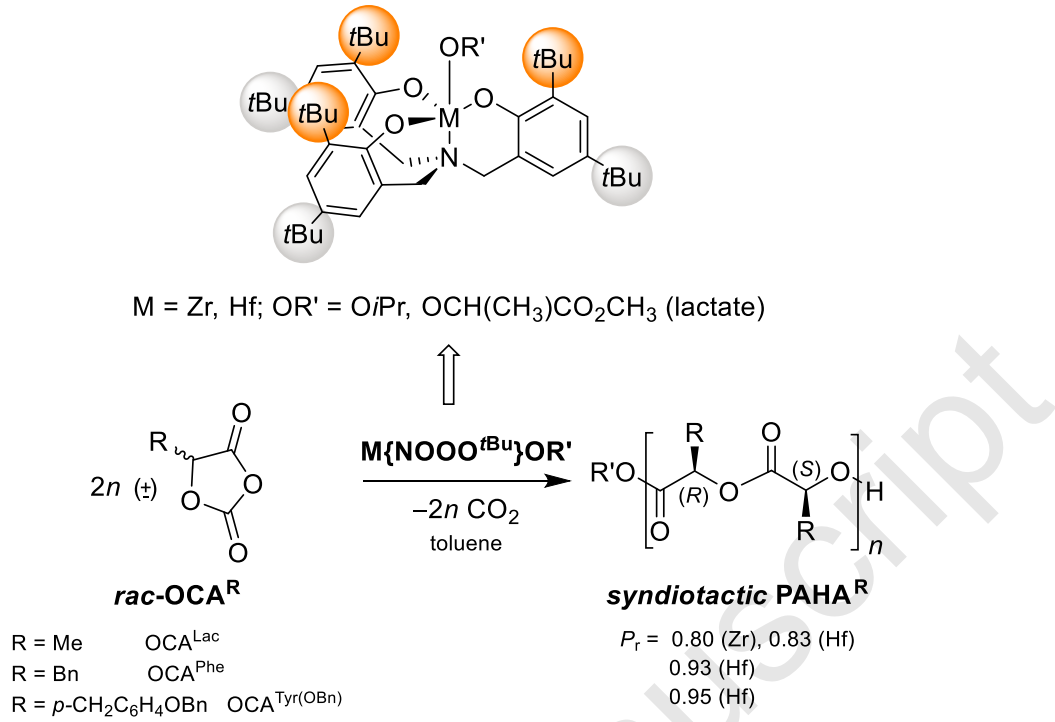


Scheme 3. Access to isotactic or heterotactic PGBL$^{4,5\text{-T6}}$ with full recyclability from the ROP of racemic *trans*-cyclohexyl-ring-fused γ-butyrolactone (*rac*-GBL$^{4,5\text{-T6}}$) with achiral yttrium complexes.[18]

Besides poly(*β*-hydroxyalkanoate)s (PBHAs, i.e. PHAs), poly(*α*-hydroxyalkanoate)s (PAHAs) are another kind of topical materials that feature biocompatibility and biodegradability. Ubiquitous PAHAs include PLA, PGA, and PLGA, which have important

commercial applications, notably as biomedical devices and packaging materials.[19] Yet, apart from these "blockbusters", the applications of PAHAs are somewhat restricted because of the short diversity of side-chain functionalities for modulating their physico-chemical properties. To this aim, attention has been paid in the past decades to synthesizing PAHAs via the ROP of OCA^Rs to enrich the diversity of PAHAs and eventually enhance their properties and widen their applications. OCAs are activated monomers derived from *α*-hydroxy acids or amino acids, many of which are available in nature, and therefore possess rich side-chain functionalities. As pioneered and successfully demonstrated by different groups for the synthesis of PLA from *L*-OCA^{Lac}, controlled ROP of OCA^Rs to produce $PAHA^R$s (with concomitant release of CO_2), can be efficiently mediated by organocatalysts and also, but to a lesser extent, by metal-based catalysts.[20] However, regardless of the type of catalyst employed, stereoselective polymerization of OCA^Rs was unknown until very recently.

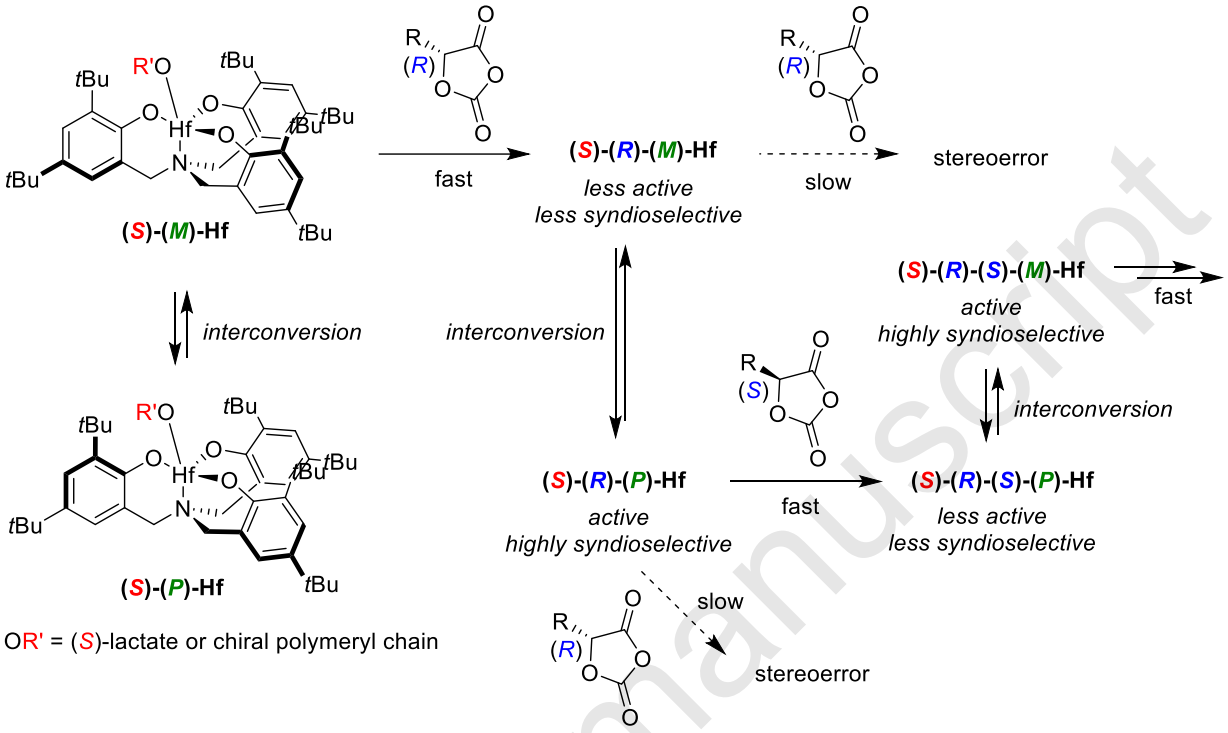
A breakthrough in that field was reported by the group of Wu in 2017.[21] Using the zirconium/hafnium-aminotris(phenolato) alkoxide catalysts/initiators previously reported by the group of Davidson for the hetero-stereoselective ROP of *rac*-LA,[22] they achieved for the first time the syndioselective ROP of different racemic OCA^Rs with P_r values in the range 0.80–0.95 (Scheme 4). The reactions could proceed at room temperature. Yet, the reaction rate and also the control of molar mass values prove to be significantly impacted by the nature of the initiating alkoxy group on the metal complex: for the benchmark ROP of 100 equiv. of *rac*-OCA^{Lac}, while Zr- and Hf-isopropoxide complexes require 1.5 h and 24 h, respectively, for complete monomer conversion and return PLA with broad dispersities ($Đ_M$ = 1.57–1.63), both Zr- and Hf-lactate complexes require only 20 min and the polymers display narrower dispersity ($Đ_M$ = 1.12–1.23). These results hint at a much better initiation efficiency of the lactate complexes compared to their isopropoxide analogues, which may originates from the different coordination environments around the metal centers. NMR and MALDI-ToF MS studies confirm a coordination-insertion mechanism, with $PAHA^{Lac}$ macromolecules end-capped by the isopropoxy or lactate initiating group, respectively. The Hf complexes induce a slightly better syndiotacticity than the Zr analogues. If the P_r values remain modest for PLA (0.80–0.84), they reach up to 0.93–0.95 for $PAHA^R$s derived from the bulkier *rac*-OCA^{Phe} and *rac*-$OCA^{Tyr(OBn)}$ monomers; as expected, this is at the expense of reactivity as the ROP of the latter monomers requires 14 h and 50 h for 81% and 90% conversion of only 50 equiv. of OCA, respectively.



Scheme 4. Access to syndiotactic poly(*α*-hydroxyalkanoate)s (PAHA^{R}s) from the ROP of racemic *O*-carboxyanhydrides (OCA^{R}s) with Zr- and Hf{NOOO^{tBu2}} complexes.[21]

^{13}C NMR analysis of the resulting polymer is consistent with a first-order chain-end stereocontrol. However, using the ROP of *rac*-OCA^{Lac} as model reaction, the syndioselectivity decreases with temperature (P_r = 0.83 at 25 °C, 0.75 at −40 °C, 0.72 at −60 °C). This is inconsistent with a "regular" CEM in which only chirality of the growing polymer chain-end controls the configuration of the next incoming monomer. To account for this unusual behavior, the authors referred to a stereocontrol mechanism so-called "enhanced chain-end control", as initially suggested by Davidson and co-workers for the heteroselective ROP of *rac*-LA using the same complexes, in which both the growing chain-end and the chiral center of metal are important (Scheme 5).[22] This mechanism involves the interconversion of the two diastereomer forms in which the complex exists ((*S*)-(*M*)-Hf and (*S*)-(*P*)-Hf)), due, on one hand, to the chirality of the lactate initiating group and later of the growing polymer chain, and, on the other hand, to the axial chirality imparted at the metal center by the C_3-symmetric ligand.[21] One of the two diastereomers is supposed to be more syndioselective and also more active than the other one. Because interconversion between the two diastereomers is slower at lower temperatures, the less active and less syndioselective species accumulates and eventually generates more stereo-defects. Although the actual occurrence of such "enhanced" CEM was

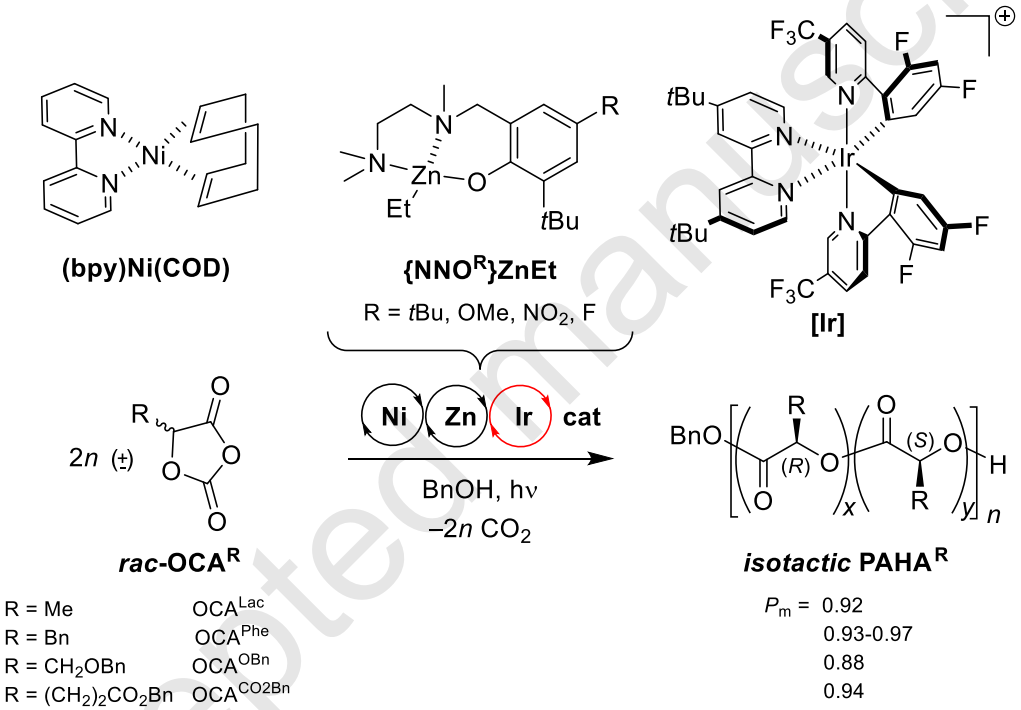
not unambiguously evidenced, these results provide another example of a likely synergistic combination between CEM and ESM, as mentioned above.



Scheme 5. Illustration of the "enhanced chain-end control" mechanism possibly operative in the syndioselective ROP of racemic *O*-carboxyanhydrides (OCA^{R}s) with the Hf{NOOO^{tBu2}} complex.[21]

In 2018, Xie and Tong disclosed another powerful strategy to stereoselectively ring-open polymerize racemic OCA^{R}s.[23] Using a catalytic system made of photoredox [Ni]/[Ir] catalysts coupled with a Zn complex supported by an achiral diaminophenolate ligand – a catalytic system previously elaborated for the non-epimerizing ROP of enantiopure OCAs –, they synthesized stereoblock PAHAs that are highly isotactic (P_m = 0.88–0.97), show high molar mass (M_n > 70,000 g mol^{-1}) and very low dispersities ($Đ_M$ < 1.06) (Scheme 6).[24] The {NNO^{R}}ZnEt complex is converted upon addition of an alcohol (BnOH) into a Zn-alkoxide species, that is the ROP active species which operates via coordination-insertion. The {NNO^{R}}Zn(OR) species logically affects the control over the molar mass values, the best results being obtained with R electron-donating groups (*t*Bu, OMe); it does also influence the stereoselectivity of the reaction and the bulky *t*Bu leads to the overall highest performance (P_m = 0.93–0.97); in fact, replacing {NNO^{tBu}}ZnEt by Zn(N(SiMe$_3$)$_2$)$_2$ in the ROP of *rac*-OCA^{Phe}

returned, instead of high isotacticity, a polymer with a modest isotactic bias (P_m = 0.66-rather atactic vs. 0.97, respectively). Interestingly, the Ni complex accelerates the reaction and also the stereoselectivity (P_m = 0.85 in the absence of (bpy)Ni(COD) vs. 0.97), presumably because of increased reaction rates. Based on detailed kinetic studies, spectroscopic analyses, and quantum chemical simulations which suggest that the stereoselective step of the polymerization arises from steric interactions between the chiral OCA monomer and salicylidene moiety of the Zn catalyst, and the fact that all catalyst components are achiral, the authors proposed a chain-end stereocontrol mechanism. This constitutes another rare example of CEM operative for the synthesis of isotactic/stereoblock polymers.



Scheme 6. Access to isotactic stereoblock poly(*α*-hydroxyalkanoate)s (PAHAs) from the ROP of racemic *O*-carboxyanhydrides (OCA^{R}s) with the {NNO^{tBu}}ZnEt/BnOH/[Ni]/[Ir] system.[24]

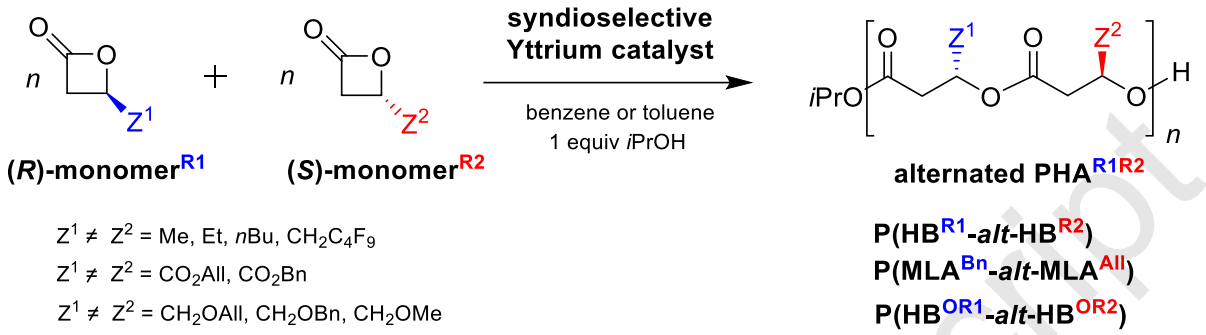
From syndiotactic homopoly(hydroxyalkanoate)s to alternated copoly(hydroxyalkanoate)s

Alternating copolymers are of great interest, as demonstrated by the ubiquitous position of some natural polymers such as DNA and peptides/proteins in key processes of life.[2] It is rather easy to prepare alternating copolymers when using two very different comonomers such as epoxides and CO_2 or CO, epoxides and anhydrides, or alkenes and CO, because the mechanism can

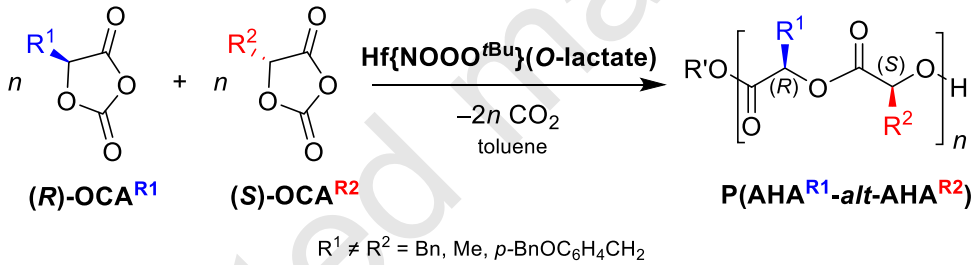
simply not enchain two monomer units of the same type, or because it is a highly disfavored process. On the other hand, it is much more challenging to prepare alternating copolymers using two comonomers from a same chemical class, because they obviously follow the same insertion mechanism, with only minute details differentiating them.

The idea to use the stereoselective ability of a ROP catalyst to prepare alternating copolymers of slightly chemically different monomers was introduced in 2009 by Coates and Thomas.[7] They succeeded in the highly alternating ROP of chemically different chiral *β*-alkyllactones of opposite absolute configuration using a syndioselective catalyst. In this process, the catalyst Y{ON^{R}N^{R}O^{tBu2}} operates by only differentiating the monomers according to their absolute/relative configuration, so as to ultimately enchain units of opposite configuration regardless of the chemical nature of the side-chain. Because a 50:50 mixture of two different monomers with opposite configuration is used, this may eventually end up in the formation of a perfectly alternated copolymer. Even though the chemical differentiation of the two monomers selected in this initial work is minimal – e.g. the length of a side-alkyl chain in a *β*-lactone, or a functional group in a remote position from the chiral center and cyclic ester – , the degree of alternation of the resulting copolymer, as evidenced and quantified by NMR and mass spectrometry analyses, reflects essentially the syndioselective ability of the catalyst/initiator implemented. This seminal concept was first used by Thomas and Coates in the copolymerization of mixtures of non-functional *β*-lactones BL^{R}s (Scheme 7).[7] The alternation degrees reach up to 90–92%. Our group then extended this process to functional *β*-lactones, namely alkyl *β*-malolactonates (MLA^{R}s) varying by the nature of the side alkoxycarbonyl chain (Scheme 7).[13] The appropriate choice of the side functionalities can allow inducing a much more contrasted chemical differentiation by simple post-polymerization treatment. Hence, for instance, starting from a 50:50 mixture of (*R*)-benzyl and (*S*)-allyl *β*-malolactonate, copolymerization with a syndioselective Y{ONNO^{Cl2}}/HO*i*Pr catalyst system and subsequent hydrogenolysis/hydrogenation gives rise to a unique, highly alternated (> 95%) copolymer successively enchaining hydrophilic *β*-malic acid and lipophilic propyl *β*-malolactonate units.[13] Similarly, the copolymerization of 50:50 mixtures of oppositely configurated 4-alkoxymethylene-*β*-propiolactones (BPL^{OR}s) with Y{ON(X)O^{Cumyl2}}/HO*i*Pr proceeds in a highly alternating fashion (up to 94%).[25] The concept was also successfully exploited by the group of Wu for the precise alternating sequence-controlled copolymerization of equimolar mixtures of oppositely configurated OCAs (D-OCA^{Phe} and L-OCA$^{Tyr(OBn)}$; D-OCA^{Lac} and L-OCA^{Phe}) with the syndioselective Hf{NOOO^{tBu2}}lactate complex (Scheme

8).[21] The alternation degrees are ca. 95% for mixtures of the two sterically crowded and well-discriminated OCA^{Phe} and OCA$^{Tyr(OBn)}$; however, the alternation drops to ca. 80% when the less discriminating OCA^{Lac} is a component of the comonomers' mixture.



Scheme 7. Access to highly alternated copoly(*β*-hydroxyalkanoate)s (PHAs) from the ROP of 50:50 mixtures of oppositely configurated *β*-lactones of a given chemical class with syndioselective Y{ON^{R}N^{R}O^{tBu2}}, Y{ONOO^{Cl2}}, or Y{ONOO^{Cum2}} complexes.[7,10,13,25]



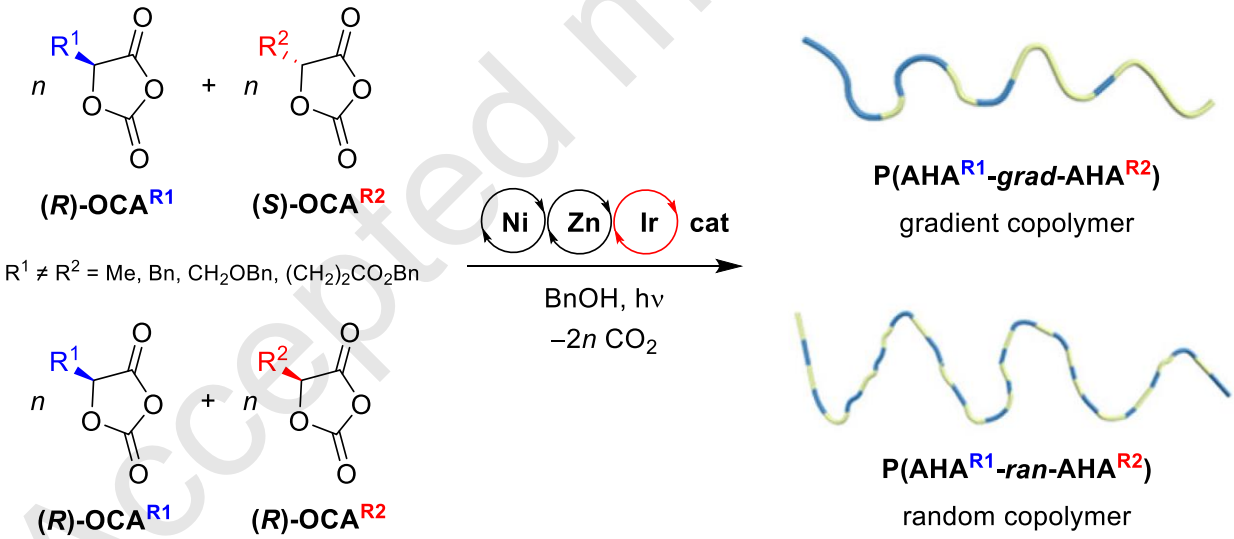
Scheme 8. Access to highly alternated poly(*α*-hydroxyalkanoate)s (PAHA^{R1R2}s) from the ROP of 50:50 mixtures of oppositely configurated *O*-carboxyanhydrides (OCA^{R1,R2}s) with a syndioselective Hf{NOOO^{tBu2}} complex.[21]

From isotactic homopoly(hydroxyalkanoate)s to gradient copoly(*α*-hydroxyalkanoate)s

Using their isoselective {NNO^{tBu}}ZnEt/BnOH/[Ni]/[Ir] system for the ROP of *rac*-OCA^{R}s, Xie and Tong investigated the ROP of mixtures of enantiomerically pure but different OCA^{R}s (Scheme 9).[24] Comonomers with opposite chirality are required for accessing copolymers with a distinctive, namely gradient, microstructure. Indeed, as expected from the use of an isoselective catalyst and of chemically different but closely similar monomers, copolymerization of two OCA^{R}s that have the same chirality result in random copolymers (characterized by broad, unresolved ^{1}H and ^{13}C NMR resonances). On the other hand, the

authors evidenced that gradient copolymers (characterized by distinct and well-resolved ^{1}H and ^{13}C NMR resonances) are recovered from the ROP of equimolar mixtures of (*R*)- OCA^{Phe} with (*S*)-OCA^{OBn}, (*S*)-OCA^{CO2Bn} or (*S*)-OCA^{Lac}, of (*R*)-OCA^{OBn} with (*S*)-OCA^{CO2Bn}; reversing the chirality of each of the monomers in these latter mixtures does not affect either the polymerization results or the polymer microstructure. However, copolymerization of (*R*)-OCA^{CO2Bn} with (*S*)-OCA^{Lac} affords a random copolymer, because the two monomers have essentially the same reactivity.

These original results reveal that the isoselective character of a catalyst system can also be fruitfully exploited, namely for the production of controlled gradient microstructures from the ROP of mixtures of chemically different enantiopure monomers of a given class. Opposite configurations and also significantly differentiated reactivity are necessary for successful control of the gradient microstructure. Related investigations conducted in our group on the ROP of mixtures of oppositely configurated BPL^{OR} monomers with the aforementioned isoselective halogen(chloro)-substituted yttrium catalyst Y{ON(X)O^{Cl2}} lead to similar observations, and will be reported in due course.[26]



Scheme 9. Access to gradient poly(*α*-hydroxyalkanoate)s (PAHA^{R1R2}s) from the ROP of mixtures of various pairs of enantiomers of *O*-carboxyanhydrides (OCA^{R1,R2}s) with the {NNO^{tBu}}ZnEt/BnOH/Ni/Ir system (see Scheme 6).[24]

Summary and Outlook

Precision synthetic poly(hydroxy acid)s, including stereoregular homopolymers and alternated copolymers, have been successfully designed from group 3 metal-catalyzed ROP of mixtures of chiral cyclic monomers (Table 1). Dianionic, tetradentate diamino- or amino-alkoxy-bis(phenolate) {ON(X)O$^{R',R"}$} and {ON^{R}N^{R}O$^{R',R"}$} yttrium complexes have demonstrated unique ability in the iso- and syndio-selective polymerization of (functional) β-lactones (*rac*-BL^{R}s, *rac*-MLA^{R}s, *rac*-BPL^{OR}s, *rac*-DL), γ-butyrolactones (*rac*-GBL^{R}s), and *O*-carboxyanhydrides (*rac*-OCA^{R}s), providing the corresponding PHA^{R}s, PGBL^{R}s, and PAHA^{R}s, respectively. The combination of the metal's ligand framework featuring appropriate R' substituents in *ortho*-position of the phenolates, with the functional cyclic ester monomer, is the key to a successful and specific stereocontrol. CEM is most often at play in these highly selective ROPs but the nature of the operative NCIs appears to be quite different: they may be either repulsive and driven by sterics, with bulky substituents favoring most often syndiotactic/alternated enchainments, as commonly thought, although more results evidence that isotactic polymerizations can also be achieved by this process; perhaps more interestingly, several recent results shed light on NCIs that are attractive in nature, involving aryl groups or halogens on the ligand and acidic hydrogens of the growing polymer chain. Unprecedented isotactic PHAs (PHB, PBPL^{OR}s), PGHAs (PGBL^{R}s), and PAHAs (POCA^{R}s), and syndiotactic PHAs (PBL^{R}s, PBPL^{OR}s, PMLA^{R}s) and PAHAs (POCA^{R}s) have been thus prepared. Out of the many challenges that still exist in this ROP chemistry, which is clearly not as mature as some may think, a major one will be to understand and rationalize these NCIs, so as to be able to implement them for preparing "at will" syndio or isoselective systems. Obviously, this will require gathering more data, by extending the number of monomer-catalyst combinations that feature such marked "NCI effects" (which may well rely on serendipity at this stage), but also by extensive mechanistic studies, in particular preparation and structural studies of key intermediates evidencing NCI between monomer coordinated on (model) active sites.

Table 1. Overview of highly stereoregular poly(hydroxy acid)s prepared from metal-catalyzed ROP of racemic monomers.

	Monomer	Catalyst	Polymer	Ref.
Syndiotactic	*rac*-BL^{R} (R = Me, Et, *n*Bu, $CH_2C_4F_9$)	*crowded*-Y{ON(X)$O^{R',R''}$}	PHB (P_r > 0.90)	6
		(Y){$ON^{Me}N^{Me}O^{tBu2}$}	PBL^{R} (P_r = 0.90–0.94)	8
	rac-MLA^{R} (R = allyl, Bn)	*uncrowded*-Y{ON(X)$O^{R',R''}$}	$PMLA^{R}$ (P_r > 0.95)	13
	rac-BPL^{OR} (R = Me, allyl, Bn)	*crowded*-Y{ON(X)$O^{R',R''}$}	$PBPL^{OR}$ (P_r = 0.79–0.90)	10
	rac-$GBL^{4,5\text{-}T6}$	Y{ON(OMe)$O^{R',R''}$}	*het*-$PGBL^{4,5\text{-}T6}$ (P_r up to 0.75)	17,18
	rac-OCA^{R} R = Me, Bn, *p*-$CH_2C_6H_4OBn$)	(Zr/Hf){$NOOO^{tBu}$}OR'	$PAHA^{R}$ (P_r = 0.80 (Zr), 0.83–0.95 (Hf))	21
Isotactic	*rac*-BL^{R} (R = Me, Et, *n*Bu, $CH_2C_4F_9$)	(Y/Yb){$ON^{Ph}N^{Ph}O^{tBu}$}	PHB (P_m = 0.77)	9
	rac-BPL^{OR} (R = Me, allyl, Bn)	*halogen*-Y{ON(X)$O^{R',R''}$}	$PBPL^{OR}$ (P_m = 0.90–0.95^{+})	10,14
	rac-DL	*rac*-Y{$CySalen^{R',R''}$}	PHB (P_m = 0.99)	16
	rac-$GBL^{4,5\text{-}T6}$	Y{ON(NMe_2)$O^{R',R''}$}	$PGBL^{4,5\text{-}T6}$ (P_m up to 0.95)	17,18
	rac-OCA^{R} (R = Me, Bn, CH_2OBn, $(CH_2)_2CO_2Bn$)	{NNO^{tBu}}ZnEt (+(bpy)Ni(COD)/[Ir])	$PAHA^{R}$ (P_m = 0.88–0.97)	24

Further exploiting the stereoselective ROP inherent to these catalysts/initiators, unprecedented heterotactic-enriched $PGBL^{R}$s and highly alternated PHA^{R1R2}s and $PAHA^{R1R2}$s copolymers have been profitably obtained from the ROP of equimolar mixtures of oppositely configurated γ-, *β*-lactones and OCAs of a given/same chemical class of comonomers, using the syndioselective Y{ON(OMe)O^{tBu2}}, and Y{$ON^{R}N^{R}O^{tBu2}$}, Y{$ONOO^{Cl2}$}, or Y{$ONNO^{Cum2}$}, and Hf{$NOOO^{tBu2}$} complexes, respectively. The multicomponent {NNO^{tBu}}ZnEt/BnOH/Ni/Ir system uniquely affords either gradient or random $PAHA^{R1,R2}$ copolymers. The stereoselective patterning ROP methodology from racemic monomers, reviewed herein on poly(hydroxy acid)s, is highly efficient and, in principle, extendable to a

range of diversely functionalized original polyesters. In this objective, an important challenge will be to design catalyst systems that exert a very strong stereoselective control (in particular syndioselective) but also minimal kinetic differentiation, so that they can be applied onto mixtures of (oppositely configurated) monomers with more significant chemical differentiation. So far, admittedly, this methodology proved to be operative only on mixtures of monomers of a given class of *β*-lactones with minimal, peripheral modifications (i.e., the ester moiety of *β*-malolactonates, the ether moiety of 4-alkoxymethylene-*β*-propiolactones, the substituent of *O*-carboxyanhydrides); one obvious reason, which may remain an essential limitation of the methodology, is the different kinetic ROP regime (rates) between those classes of monomers. Yet, one can confidently expect that some optimized catalyst systems should be able to operate, upon strict stereocontrol, the alternated copolymerization of mixtures of (oppositely configurated) monomers taken from these different classes of monomers. This is a key to access directly (i.e., without post-polymerization modification) original alternated copolymers.

These latest achievements in the ROP synthesis of stereoregular (co)polymers of functionalized poly(hydroxy acid)s, featuring a precise control of monomer(s) sequences combined with the regular distribution of functional and reactive side-chain groups along their backbone, enable to access highly precise polyesters previously synthetically difficult to obtain, and pave the way to the next generation of functional polyesters with original properties and applications.[2] The precise control of monomers sequences and the exact placement of functional side-chain groups along poly(hydroxyl acid)s' backbone, are currently main challenges for the next-generation of synthetic polymers.[2] Definitely, despite its maturity, stereoselective ROP has still much to be discovered and to offer!

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