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Regulating the stereomicrostructure, circularity and functionality of synthetic PHAs

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Biodegradable plastics, especially those that can biodegrade in uncontrolled enviroments, are of importance to help curb the global plastics crisis. Poly(3-hydroxyalkanoate)s (PHAs), which can be either microbially or chemically synthesized, are one of the rare classes of plastics that can biodegrade under both managed and unmanaged conditions. Besides this exceptional upside, PHAs can also be tuned to exhibit thermal, mechanical, and optical properties of commodity polymers including polyolefins, and they can be designed to be chemically recyclable towards a circular PHA economy or functionalized to acquire additional, diverse and/or improved properties. To enable such modularity in chemocatalytic PHAs, the development of stereoselective and controlled molecular catalysts, as well as the design of monomer structures and polymerization processes, is of primary importance. In this context, this Perspective article focuses on three recent advancements, including PHA stereomicrostructural engineering, melt-processability and chemical recyclability, and chemical functionalization.

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Introduction

Recently, especially within the past decade, research has focused heavily on searching for practical solutions to addressing the global plastics crisis.[1–4] Typical strategies aim to increase mechanical recycling rates, valorize waste plastics, design chemically recyclable polymers, or develop biodegradable plastics.[5–13] The development of biodegradable plastics represents an important part of this large effort to combat the plastics problem, especially concerning end-of-life issues and environmental protection. This becomes particularly important for application areas where plastics recovery, recycling, or reuse is highly challenging or nearly impractical.

Amongst many biodegradable plastics reported in the literature, the plastics belonging to the large family of poly(3-hydroxyalkanoate)s (PHAs)[14–19] are most unique, thanks to their distinct ability to biodegrade in both managed (industrial and home composting) and unmanaged (ocean, freshwater, and soil) environments,[20] as well as their largely tunable material properties.[21] The biological fermentation route to PHAs is recognized for its ability to take various inputs of biorenewable sources (biomass, fatty acids, plant oils, *etc.*) and produce stereoperfect (*R*)-PHAs that typically exhibit high molar mass, high melting points, and strong mechanical properties.[21–24] The simplest, most important member in the large PHA family is poly(3-hydroxybutyrate) (P3HB), with the methyl as the side-chain group or exocyclic substituent. A variety of PHA copolymers of P3HB incorporating other short, medium, or long side-chain length moieties can be biologically produced, depending on the growth conditions and feed substrates.[15,21,25,26]

As these materials are stereoperfect with pure (*R*) stereoconfigurations on the backbone stereogenic centers, they are highly crystalline, especially for short-chain PHAs such as P3HB and poly(3-hydroxyvalerate) (P3HV), imparting these PHAs with high ultimate tensile strength (σ_B) and melting temperature (T_m) values but also detrimentally making such PHAs extremely brittle, with negligible fracture strain properties or elongation at break (ε_B) of ~3%.[15] Currently, varying the stereochemistry of PHAs biologically presents a daunting challenge;[27] thus, the modulation of material properties of biological PHAs is confined to the copolymer composition, which is typically limited by the functional group tolerance of the bacteria or enzymes.

In contrast to the biological route to PHAs, the chemocatalytic route allows for modulation of the PHA stereochemistry through catalyst-controlled stereoselective polymerization processes, termed stereomicrostructural engineering.[14,28–30] Accessing these stereodiverse and functionalized PHAs requires the implementation of advanced molecular catalysts that can regulate the polymerization stereochemistry and tolerate monomer functionality. Herein, we highlight recent

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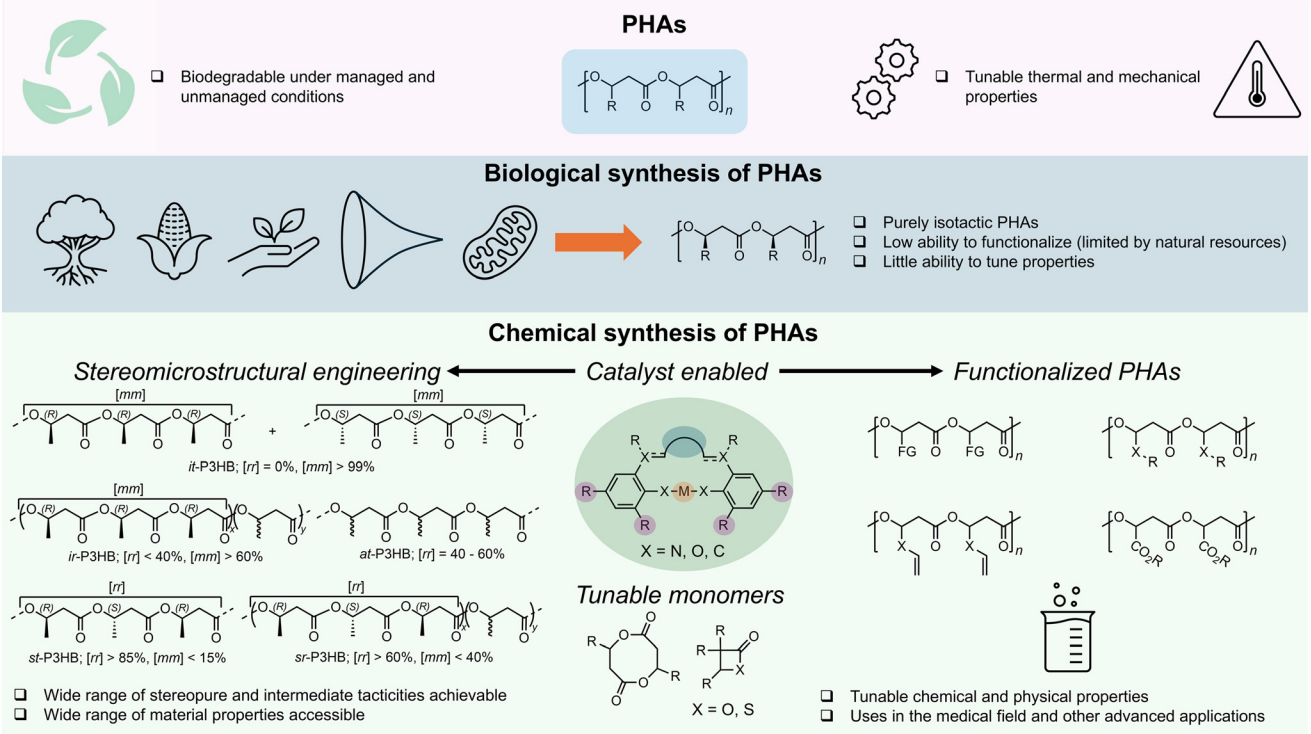

Fig. 1 Overview of PHAs, including biological and chemocatalytic routes, stereomicrostructural engineering, and functionalization of PHAs.

advances in the synthesis of stereodiverse and functionalized PHAs utilizing molecular catalysts, as well as thermally robust and chemically recyclable PHAs through monomer design (Fig. 1). We conclude this Perspective by laying out our vision for the future of PHAs, including critical issues that must be addressed to facilitate broader implementation of PHAs in the marketplace.

Stereomicrostructural engineering of PHAs

For decades, one of the major goals in the chemocatalytic routes to PHAs was to synthesize biomimetic stereoperfect (*sp*) isotactic (*it*)-P3HB (characterized as having a probability of *meso* diads, $P_m > 0.99$, and a percentage of *meso* triads, [*mm*] > 99%) as this P3HB exhibits an *it*-polypropylene (PP)-like melting temperature ($T_m \sim 175$ °C) and desirable tensile strength ($\sigma_B \sim 30$ MPa). As compared to the biological route to *it*-P3HB, which has slow kinetics and yields materials with high dispersity ($Đ > 2.0$) due to its nature of step-growth polymerization (SGP), the chemocatalytic route to P3HB *via* ring-opening polymerization (ROP) typically has fast kinetics, affords P3HB with low $Đ$ (as low as 1.01) due to its nature of chain-growth polymerization, and is more scalable and cost-effective. In 2018, Chen and Tang reported the first instance of biomimetic *sp*-*it*-P3HB through the ROP of the *racemic* eight-membered dimethyl diolide (*rac*-8DL^{Me}) with yttrium catalyst **1** (Fig. 2).[31] The catalyst system used in this work was also found to perform kinetic resolution on *rac*-8DL^{Me}. Recently, Coates and coworkers have also developed a bimetallic magnesium catalyst system, which performs kinetic resolution of *rac*-β-butyrolactone (*rac*-BBL) with stereoinversion of the polymerized monomer and results in *it*-P3HB with $P_m = 98\%$, the highest isotacticity achieved in the ROP of *rac*-BBL to date.[32] Notably, this catalyst system does not perform well in polymerizing (*S*)- or (*R*)-BBL as it was determined that the opposite enantiomer activates the chiral catalyst to perform the kinetic resolution.

Work towards the goal of stereoperfection has also been carried out through the polymerization of *rac*-BBL using **8**[33] and **9**[34] as well as towards *sp* syndiotactic (*st*) P3HB using **7** (characterized as having a probability of *racemic* diads, $P_r > 0.99$, and percentage of *racemic* triads, [*rr*] > 99%).[35] These works, along with the pioneering report of Carpentier and co-workers, which showed that *st*-P3HB with $P_r = 0.94$ can be produced by the ROP of *rac*-BBL with yttrium catalysts incorporating the tetradentate alkoxy-amino-bis(phenolate) ligand (**11**, **12**),[36,37] have advanced our understanding of catalyst structure–polymer stereomicrostructure relationships, more specifically how molecular catalysts use their symmetry as well as steric and electronic effects to control stereomicrostructures of P3HB materials. Even though these contributions are notable, they still do not solve the problem of *sp*-P3HB's brittleness as both *it*- and *st*-P3HB are highly crystalline and extremely brittle. Further catalyst development has been necessary to solve this brittleness issue and enhance the mechanical toughness.

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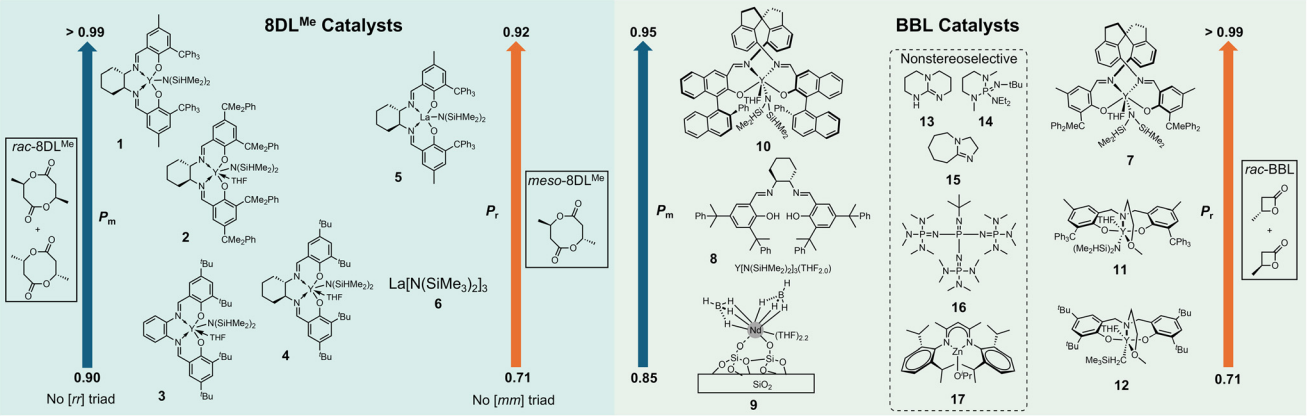

Fig. 2 Structures of representative molecular catalysts for ROP engineering of PHA stereomicrostructures.

An abundance of work has also been focused on creating new molecular catalysts, both metallic and organic types, for the ROP of BBL.[14] Typically, these catalysts impart some stereocontrol but lead to materials with long or very short segments of stereoperfect regions, which either impart a high degree of crystallinity, making the material brittle, or lead to mostly amorphous softer materials. Recently, Reiger and coworkers developed an *in situ* generated yttrium catalyst system (**8**), which yields iso-rich *ir*-P3HB. Although its isotacticity and T_m are only moderately high (P_m up to 0.89, T_m up to 154 °C), it exhibits good mechanical properties with σ_B = 21.1 MPa and ε_B = 392% (P_m = 0.84).[33] Robinson and coworkers developed a dual catalysis approach to generate stereoblock *it-b*-atactic (*at*) P3HB through irreversible chain transfer ROP of *rac*-BBL with sequential addition of yttrium and zinc complexes.[38] Chen and coworkers previously reported the synthesis of *it-b-st* P3HB from the diastereoselective polymerization of a mixture of *rac*-8DL^{Me} and *meso*-8DL^{Me}.[39]

To confer polyolefin-like properties to P3HB without employing the copolymerization strategy,[40] which does not conform to the mono-material design principle,[41] the diolide monomer platform needs to be implemented. In 2023, Chen and coworkers showed that installation of controlled stereodefects into P3HB through the ROP of *meso*-8DL^{Me} with a commercially available lanthanum catalyst (**6**) leads to syndio-rich *sr*-P3HB (P_r = 0.77, no [*mm*] triads due to the structure of *meso*-8DL^{Me}), which exhibits a high fracture strain (ε_B > 400%), high tensile strength (σ_B = 34 MPa), excellent toughness (U_T = 96 MJ m^{-3}), high optical clarity, and a large processing window (difference between T_m and degradation temperature, T_d, of 141 °C).[28] Furthering this work, high-molar-mass *ir*- and *sr*-P3HB synthesized using the diolide platform and complex **2** or **3** resulted in ultra-tough and ductile (ε_B > 800%) materials with excellent optical clarity.[42] Blending these chemocatalytic P3HB materials with biological *sp*-P3HB gave new P3HB materials with synergistic thermal and mechanical properties. However, when the *ir*-P3HB obtained from the ROP of *rac*-BBL was blended with bio-P3HB, enhanced properties were not observed, emphasizing the necessity of synthesizing P3HB from *rac*-8DL^{Me} for enhancing toughness of bio-P3HB as well as T_m and modulus of *ir*- and *sr*-P3HB.[42]

This stereomicrostructural engineering work has been mainly focused on P3HB, but other PHAs have also been synthesized with diverse stereomicrostructures. For example, P3HV has been synthesized from both 8DL^{Et} and β-valerolactone (BVL) with *sr*, *ir*, and intermediate *st* and *it* stereomicrostructures.[40,43] Increasing the length of the alkyl chain provides access to a wider range of thermal and mechanical properties, such as decreased glass transition temperature (T_g) below −30 °C, enabling packaging applications in cold environments. Again, these stereomicrostructures were imparted by the catalyst used, which has also been shown for PHAs with longer alkyl substituents, aryl substituents, more elaborate substituents, and (alternating) copolymers.[14,40,44,45] In an effort to expand the scope of PHAs, stereoselective polymerization of *racemic* β-thiobutyrolactone (*rac*-TBL) generated sulfurated PHA poly(3-thiobutyrolactone) (P3TB).[46] Increasing the ionic radius (S > O) by utilizing a thiolactone monomer enabled access to topologically diverse, stereocontrolled cyclic *st*- and *it*-P3TB using various catalysts (**6**, **12**, *etc.*).[46,47]

Tuning the properties of PHAs by regulating their stereomicrostructure is a developed field that is still fast growing. There is still a wealth of knowledge to be gained in this space by further tuning the catalyst and monomer structures and their close covalent- and/or non-covalent interactions during the ROP process. Furthermore, there are application spaces that need to be explored for these stereodiverse PHAs.

Thermally robust and chemically recyclable PHAs

One of the major pitfalls of semi-crystalline *it*-PHAs is their propensity to degrade ($T_{d5\%}$ ~ 250 °C) near their T_m or in melt (*i.e.*, lack of melt-processability) due to the facile *cis*-elimination enabled by the presence of reactive α-hydrogens. Four

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notable advances have been made to enhance the thermal stability and enable chemical recyclability of PHAs.

The first was by Liu and coworkers where they designed a four-membered lactone fused with a five-membered ring at the α- and β-carbons of the lactone, effectively eliminating one of the α hydrogens, which enabled chemical recycling through a multi-step process, although the T_d values were still similar to a typical PHA (213 °C for the *trans*-PHA and 268 °C for the *cis*-PHA; Fig. 3A).[48]

Second, through the ROP of α-methylated BBL, Coates and coworkers synthesized an α-methylated PHA that could be chemically recycled through a proposed multi-step process, with noticeably enhanced T_d values relative to a typical PHA (269 to 289 °C; Fig. 3B).[49] The α-methylated PHA is also found to be intrinsically crystalline, much like the tacticity-independent crystallinity observed in the α,α-dimethylated PHA.[50]

As a third approach, Chen and coworkers created truly chemically recyclable PHAs from the ROP of α,α-dimethylated BBL, which leveraged the Thorpe–Ingold effect to enable not only depolymerization of the PHA back to the lactone monomer, but also melt-processability with much enhanced T_d up to 335 °C and T_m up to 243 °C (Fig. 3C).[51] Simple, achiral phosphazene superbase ^{t}Bu-P$_4$ (**16**) was used as a catalyst for the ROP of this trimethylated lactone. Polymerization of various stereoisomers of the lactone resulted in semicrystalline *at*-, *ir*-, and *it*-PHAs, demonstrating tacticity-independent crystallinity.[50] Lastly, Chen and coworkers extended the α,α-dimethylation strategy to propiolactone, producing α,α-disubstituted propionate PHAs that are not only thermally robust (T_d up to 373 °C and T_m up to 266 °C) but also chemically recyclable *via* two (SGP and ROP) closed-loops (Fig. 3D).[52] The α,α-dimethylated PHAs described here solve the critical issues associated with the chemical recycling and thermal resistance of PHAs. These advances should promote the PHA circularity and expand PHA applications to textile fibers and other high-end specialty applications.

Functionalized PHAs

As described above, stereoselective ROP towards aliphatic PHAs has resulted in the production of biocompatible, stereodiverse, high-performance plastics with viable commercial utility, but they are still limited in terms of the breadth of their applications. In particular, the high hydrophobicity of P3HB limits its biomedical applications, making functionalization with hydrophilic groups through post-polymerization modifications or monomer design to introduce hydrophilic pendant groups, the most common approaches to broaden their usage in aqueous environments.

Introducing allylic groups onto PHAs that serve as functional handles for further chemical transformations is an effective strategy for producing functional PHAs, which are not directly accessible through bio- or chemo-synthetic routes on account of many catalysts' functional group intolerances. Allylic PHAs have long been accessible through biological fermentation,[53,54] but this work heavily relies upon the synthesis of poly(3-hydroxy-octanoate-*co*-3-hydroxy-10-undecenoate) (PHOU) with high dispersity values ($Đ$ ~2.0–3.0) and uncontrolled vinyl incorporation. This was resolved through random copolymerization of *rac*-BBL with *rac*-BL^{allyl} using yttrium complex **18a**, leading to the corresponding monodisperse *st*-PHA copolymer (P_r = 0.80–0.84) and up to 80% *rac*-BL^{allyl} incorporation (Fig. 4).[55] Although the homopolymer from *rac*-BL^{allyl} is amorphous, exhibiting a T_g ~ −44 °C, the PHA copolymers are semicrystalline with T_m values of 104–109 °C. The vinyl groups in the copolymers can be readily converted to hydroxy and epoxy groups with quantitative yields. The resulting hydroxy- and epoxy-functionalized PHAs

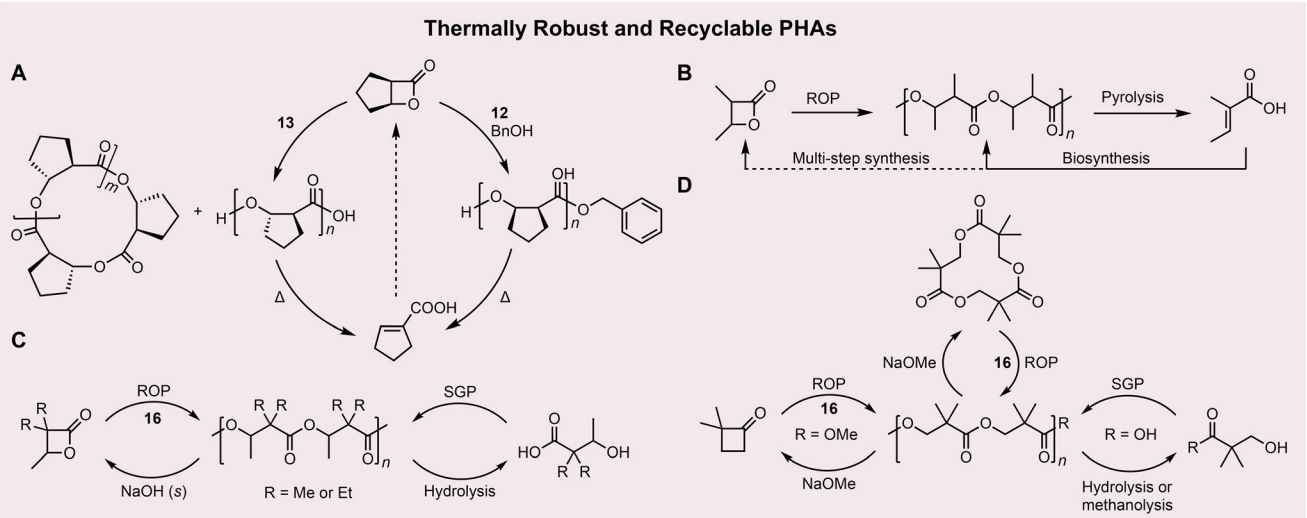

Fig. 3 Highlighted examples of thermally robust and chemically recyclable PHAs.

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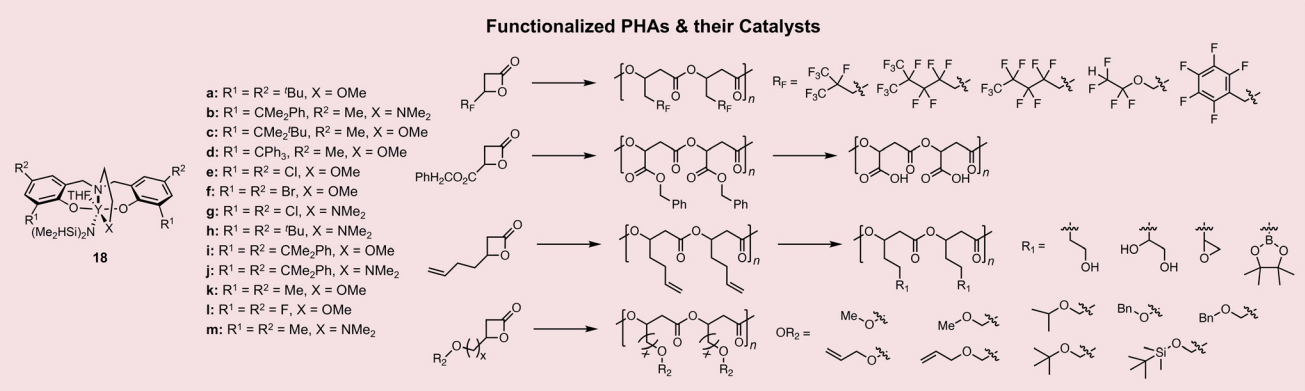

Fig. 4 Structures of representative molecular catalysts for functionalized PHAs and PHA post-functionalization.

showed no change in their stereomicrostructure, but only minor variations in their thermal properties as a result of the chemical modifications, evidencing that the backbone of the polymer remained unaffected by the change in functionality.

These types of structural changes are emblematic of the functional utility of an allylic pendant group, and they have since been exploited as an anchoring site for biologically active molecules in drug delivery.[56] For example, the dihydroxylated PHA showed increased controlled release kinetics for encapsulated L-leuprolide acetate, which was attributed to the formation of hydrogen bond networks.[57] Later it was observed that β-diiminate (BDI) zinc alkoxide catalyst **17** can stereoselectively polymerize *rac*-BL^{allyl}, resulting in an *ir*-PHA (P_m = 0.61).[58] In seeking to expand the therapeutic applications of PHAs, the allyl-functionalized, *ir*- and *sr*-PHAs were next subjected to quantitative hydroboration, which did not alter the backbone length or stereochemistry, but did increase the T_g of the resulting PHAs from ∼−40 °C to −4 °C.[58] Boronate substituents are attractive therapeutic targets due to their potential uses in cancer therapy as well as interaction with sugars, which could enable their use for insulin delivery. Most recently an olefin-functionalized PHA copolymer was utilized for accessing reprocessable, recyclable, and biodegradable elastomeric vitrimers through installation of dynamic boronic ester bonds by the thiol–ene "click" chemistry.[59]

Subjecting a polymer to stoichiometric amounts of chemical reagents to perform post-polymerization modifications could induce cleavage along the backbone and/or other undesired side reactions. Hence, modifications under mild conditions are preferred for their reliability in achieving the desired transformations. A promising example of such a strategy is the mild hydrogenolysis of poly(benzyl β-malolactonate) (PMLA^{Bn}) to produce hydrophilic poly(malic acid) (PMLA), which can be biometabolized,[60] making it attractive for biomedical applications.[16,61–63] It was also shown to be possible to polymerize benzyl β-malolactone (MLA^{Bn}) using organobases **13–15**, leading to the corresponding amorphous PHA with T_g ∼ −46 °C.[64] This strategy was extended to facilitate the synthesis of random and diblock copolymers from *rac*-BBL[65] or cyclic carbonates,[66,67] both of which were utilized to produce defined nanoparticles with low-to-no cytotoxicity with cell types that would make them useful for liver-targeted drug delivery applications.[66,68–70] Specifically, PMLA-*b*-P3HB copolymer nano-objects showed no cytotoxicity in HepaRG and SK-MEL-28 cells at low concentrations (<88 μg mL^{-1}) and mild toxicity at high concentrations (88–320 μg mL^{-1}).[66] Similar cell viability was also evidenced using poly(trimethylene carbonate) (PTMC)-*b*-PMLA[68] and polyethylene glycol (PEG)-*b*-PMLA^{Bn} copolymers.[70] Specific cell-type cytotoxicity is not the only limiting factor in drug delivery, and potential immune responses must be screened in further studies. This open question was addressed for PMLA-*b*-P3HB and PMLA-*b*-PTMC, in which favorable uptake by HepaRG cells and reduced macrophage uptake was observed for PMLA-*b*-P3HB due to the favorable balance of hydrophilic and hydrophobic blocks.[69] A series of tetradentate alkoxy-amino-bis(phenolate)-ligated yttrium complexes (**11**, **18b–e**) were next screened for their activity towards MLA^{Bn}, resulting in the production of a range of semicrystalline *st*-PMLA^{Bn} PHAs. The greatest syndioselectivity was achieved using **18d** with Cl *ortho* and *para* substituents on the ligand backbone, resulting in a PHA with P_r up to >0.95 and T_m up to 117 °C. This syndioselective polymerization strategy was extended to produce semicrystalline *st*-PMLA^{all} (P_r > 0.95, T_m up to 112 °C; **18c**) and *st*-PMLA^{Me} (P_r up to 0.92, T_m up to 212 °C; **18d**),[71] demonstrating the functional group tolerance of this series of complexes and their potential utility in producing other functional PHAs (Fig. 4).[61]

The most direct way to produce hydrophilic PHAs is through polymerization of hydrophilic monomers, which posed a challenge due to functional group intolerance with known catalysts. Lactone monomers of 3-hydroxy-propiolactone (BPL^{CH_2OR}) can be stereoselectively polymerized using **18a**, **18d**, **18f–j**, and **18l** with an informative trend in stereoselectivity depending on the pendant group of the monomer (Fig. 4). It was found that a given catalyst's *ortho*-substituent on the ligand backbone dictates the stereoselective polymerization of *rac*-BPL^{CH_2OR} monomers (R = methyl, allyl, benzyl).[72–74] Bulky *ortho* groups such as cumyl (–Me$_2$Ph, **18h**,

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18i) resulted in *sr*- to *st*-PHAs with P_r = 0.81–0.90 across all monomers, while chlorine groups (**18d**, **18f**) yielded *ir*- to *it*-PHAs with P_m = 0.90–0.93. Some of these PHAs are semicrystalline; for example, *sr*-P3HB^{CH_2OAllyl} (P_r = 0.81) showed a T_m of 85 °C, and *sr*-P3HB^{CH_2OMe} (P_r = 0.81) displayed a T_m of 116 °C. These improved thermal properties may imply their potential utility in packaging applications and warrant further characterization of their tensile properties, if increased molar masses above their entanglement molecular weights can be reached.

Follow-up studies that expanded the range of stereoregular P3HB^{CH_2OR} materials through the use of different pendant groups concluded that the methylene hydrogens on the pendant exocyclic substituent have non-covalent interactions with the ligands of catalysts **18f**, **18g**, **18i** and **18l**, which dictate whether tactic functionalized P3HB materials are formed or not (Fig. 4).[75–77] This finding was further confirmed in a subsequent report, where a BPL with the pendant group $-CH_2OCF_2CHF_2$ was polymerized with **18b**, **18f**, and **18g** to produce *st*-PHA (P_r up to 0.87) and *at*-PHA using **18l**, demonstrating stereoselectivity trends based on the *ortho* and *para* substituent identities in the ligand backbone alongside non-covalent interactions with the monomer exocyclic group.[78] The continued mechanistic evaluation of the catalyst stereoselectivity represents an important part of ongoing research in this field, aiding in the prediction of material properties of the resulting polymers for specifically targeted applications.

The development of a more diverse range of functionalized PHAs has also been sought to expand their thermal and mechanical properties. Biosynthetic approaches have produced many functionalized PHAs, enlarging their breadth to include PHAs bearing pendant groups such as chlorines,[79,80] fluorines,[81–83] bromines,[84] aromatics,[85,86] esters,[87] thioesters,[88] epoxys,[89] phenoxys,[90–93] and others.[94–96] These routes have relied on copolymerization strategies by which bacteria incorporate unusual functional groups from a given feedstock alongside more traditional feedstocks, creating random PHA copolymers typically with a low amount of functionality.

Fluorinated PHAs were first targeted biosynthetically for their increased hydrophobicity and thermal transitions, but failed to make an impact due to low incorporation of fluorinated feedstocks.[82,83] Coates and coworkers sought to produce highly fluorinated PHA homopolymers *via* a two-step process: carbonylation of fluorinated epoxides to four-membered β-lactone monomers, followed by the ROP using **17** to afford fluorinated PHAs.[97] These fluorinated PHAs showed increased T_g over their non-fluorinated counterparts and anticipated higher hydrophobicity.

Aromatic PHAs represent another synthetic target towards high-T_g PHAs imparted by the rigid aromatic groups. The stereoselective ROP of the *rac*- and *meso*-dibenzyl eight-membered diolide (8DL^{Bn}) using **2** enabled access to *it*- and *st*-poly (3-hydroxy-4-phenylbutyrate) (P3H4PhB) as well a series of random and diblock copolymers with other diolide-derived PHAs.[44] Stereoperfect *it*-P3H4PhB (P_m > 99%) and *st*-P3H4PhB (P_r = 92%) each exhibited a significantly increased T_g up to 43 °C. *Rac*-8DL^{Bn} was copolymerized with *meso*-8DL^{Bu} to provide a soft, elastomeric *st*-P3HHp polymer, which exhibited a high $T_{d5\%}$ of 281 °C, high fracture strain ($\varepsilon_B \sim$ 191%) and good tensile strength ($\sigma_B \sim$ 22.7 MPa).

Continued innovation in the realm of unusual PHAs derived chemosynthetically with designer monomers can unlock access to a diverse range of novel PHAs with unprecedented material properties.

Future of synthetic PHAs

With the dawn of stereomicrostructural engineering and functionalization of PHAs as well as PHA monomer design, we foresee the future of PHAs as incredibly bright. The amount of versatility that can be imbued in PHAs through these three approaches is vast and will continue to enable PHAs to be used in interdisciplinary applications. We predict the implementation of these PHAs in (multi-layered) packaging applications, textiles, adhesives, agriculture, biomedical fields, and high-end applications, especially in areas where biodegradability and/or biocompatibility are of primary importance.

Even with the great success achieved in the last decades, there are still several challenges that need to be overcome for the widespread implementation of PHAs. First, the synthesis of (lactone or diolide) monomers and (metal-based) catalysts needs to be further advanced to be more cost-effective and environmentally benign. Developing full chemical circularity of PHAs to recover their monomers in high selectivity and purity, and combined biocatalytic and chemocatalytic processes, present perhaps the most effective solutions to tackle this challenge. Second, the lack of closed-loop recycling for most of the current PHAs must be overcome to render their chemical circularity towards a circular PHA economy. Regenerating the highly strained lactone or the diolide monomers, essential for the ROP with fast kinetics and full monomer conversion, may be chemically unfeasible for some monomer structures adopting this ideally direct, short circular pathway, but leveraging an additional catalytic step could still close the entire circular loop. Third, to facilitate the industrial adoption of the chemocatalytic PHAs, large-scale product development must be comprehensively investigated *via* industrial processing and fabrication conditions. The PHA community across academia and industry needs to work together collaboratively on solving these issues, and we are optimistic about them being resolved in the near future so as to promote the applications of sustainable and affordable PHAs.

Author contributions

E. C. Q. and C. R. P.: writing – original draft preparation, writing – review & editing, and investigation; S. M. G. and E. Y.-X. C.: supervision, project administration, funding acquisition, and writing – review & editing.

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Data availability

No primary research results, software or code have been included and no new data were generated or analyzed as part of this review.

Conflicts of interest

There are no conflicts to declare.

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