Article published online: 2021-01-25

Controlled Ring-Opening Polymerization of *O*-Carboxyanhydrides to Synthesize Functionalized Poly(α-Hydroxy Acids)

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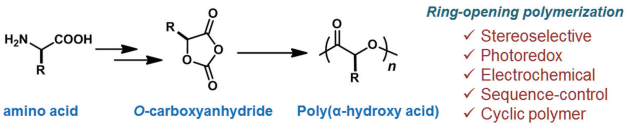

Received: 1.12.2020
Accepted after revision: 21.12.2020
DOI: 10.1055/s-0040-1722698; Art ID: om-20-0042rev

Abstract Poly(α-hydroxy acids), as a family of biodegradable polyesters, are valuable materials due to their broad applications in packaging, agriculture, and biomedical engineering. Herein we highlight and explore recent advances of catalysts in controlled ring-opening polymerization of *O*-carboxyanhydrides towards functionalized poly(α-hydroxy acids), especially metal catalyst-mediated controlled polymerization. Limitations of current polymerization strategies of *O*-carboxyanhydrides are discussed.

Key words polyesters, *O*-carboxyanhydrides, ring-opening polymerization, poly(α-hydroxy acids), stereoselective polymerization, electrochemical polymerization

Introduction

Plastic straw lodged in a turtle's throat? Fish trapped in six-pack rings, devoid of freedom and suffocating? Or seagulls found dead on beaches with plastic remnants in their guts? These horrifying images are increasingly prevalent in the media as a consequence of the ever-growing demand for plastic products.[1–3] Even though the idea of replacing petrochemical-based polymers with renewable and degradable alternatives was pitched in late 20th century,[4] efforts are still undergoing to improve on current methodologies, to search for sustainable options, and to ultimately generate variants with a simpler strategy, increased yield, and reduced waste.[5–7]

Among many degradable or recyclable polymers, poly(α-hydroxy acids) (PAHAs) have been long regarded as a type of industry-applicable, degradable, and biocompatible polymer to replace petrochemical-based polyolefins.[8–10] They have been widely used in biomedical engineering and food packaging. PAHAs can be synthesized through either polycondensation of hydroxy acid (e.g., lactic acid),[11] or the ring-opening polymerization (ROP) of lactide (LA) or lactones.[12] However, common aliphatic PAHAs, including poly(LA) (PLA), poly(glycolide), and poly(lactide-*co*-glycolide), have finite choices of side-chain functionalities, thereby preventing efficient fine-tuning of material properties.[10,13,14] Early work by Baker's group shows that PAHAs synthesized from functionalized cyclic diesters (or LAs) present a wide range of glass transition temperatures (T_g) from −46 °C to 100 °C.[15–18] However, the multistep synthesis of functionalized LAs is challenging; monomers are afforded in low yields while the polymerization reactivity significantly drops upon the introduction of pendant groups (Scheme 1, route i).[15,19,20] These disadvantages limit the use of functionalized LAs as a viable raw material to prepare PAHAs.[20,21]

Alternative strategies have been developed to access monomers that can be easily synthesized and polymerized. Noticeably, a five-membered heterocycle 1,3-dioxolan-4-one that bears both ester and acetal groups has been recently developed by the groups of Miller[22] and Shaver (Scheme 1, route ii).[23,24] Either through copolymerization with LAs for acetal retention[22] or ROPs via the deliberation of formaldehyde, this monomer provides an inexpensive strategy to prepare PAHAs. However, the ROP strategy for 1,3-dioxolan-4-one requires further development as the obtained polymers have relatively low molecular weights (MWs; < 20 kDa) due to side reactions; and the ROP procedures demand constant removing of formaldehyde from the reaction solution.[23,24]

Another group of promising five-membered cyclic monomers, *O*-carboxyanhydrides (OCAs), have gained significant attention over the last decade (Scheme 1, route iii).[10,25] Pioneered by Bourissou's group,[26] OCAs can bear various functional groups (Scheme 1),[27,28] a promising trait that offers the manipulation of physicochemical, thermal, and mechanical characteristics to the end product. Even

Biosketches

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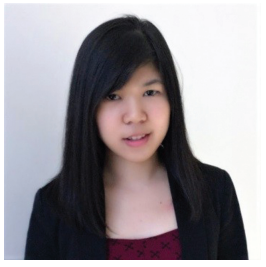
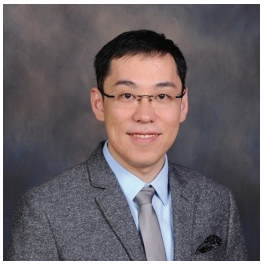


Ai Lin Chin graduated *magna cum laude in cursu honorum* from Tennessee Technological University in 2015 with a B.S. in Chemical Engineering and a minor in Mathematics. She received her Master of Engineering in 2019 and is currently a PhD student under the guidance of Dr. Rong Tong at the Virginia Polytechnic Institute and State University. Her research interest focuses on the development of drug delivery systems with applications in cancer therapy.



Professor Rong Tong received his B.S. degree in Macromolecular Science from Fudan University in 2005. He received his PhD degree in Materials Science and Engineering from the University of Illinois at Urbana-Champaign in 2010, advised by Dr. Jianjun Cheng. He was a postdoctoral associate at both Massachusetts Institute of Technology (Langer lab) and Harvard Medical School (Kohane Lab) during 2010 to 1015. He is currently an Assistant Professor in the Department of Chemical Engineering at Virginia Polytechnic Institute and State University. His research interests include polymer chemistry, nanomedicine, biomaterials, and targeted cancer therapy. He is the recipient of Thieme Chemistry Journals Award (2020), Class of Influential Researcher of *Industrial & Engineering Chemistry Research* (2017), Emerging Investigator of *Biomaterials Science* (2017), and American Chemical Society AkzoNobel Award in polymer chemistry (2010).

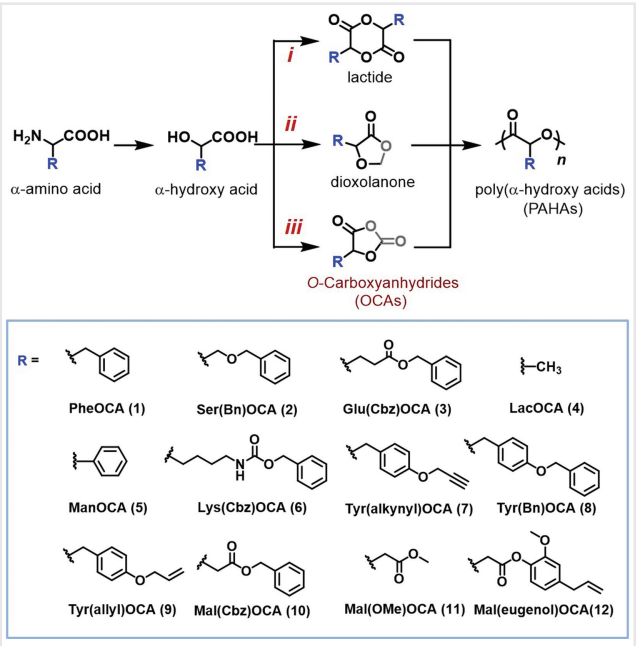
though OCAs are simply the *O*-analogs of *N*-carboxyanhydrides, early research shows them to be more stable with less chance of polymerization even under extreme conditions such as 90 °C in nitrobenzene.[29] Additionally, the ROP of OCAs offers a facile route to PAHAs with various pendant groups under mild conditions, a stark contrast to methods of polycondensation that entail high temperatures and aggressive reaction conditions.[30,31] The liberation of CO_2 that helps relieve ring strain enables OCA to become more reactive compared to LA.[26] Notably, the initial synthesis of OCAs involves using toxic phosgene or diphosgene.[25,32] A safe alternative, bis(trichloromethyl) carbonate,[33] has been recently developed for OCA synthesis.[34,35] Often, activated charcoal and acid scavengers are incorporated to decompose excess phosgene and remove hydrochloric acid that is produced as a byproduct.[36,37]

The easy access to OCA monomers promotes the development of numerous polymerization strategies to prepare functionalized PAHAs. In this review, we discuss the recent development of organocatalysts and metal catalysts for controlled ROP of OCAs. Important advances in stereoselective ROP methods that provide stereoregular and sequence-controlled PAHAs are highlighted. Some challenges in catalyst development and the preparation of functionalized materials will be featured.

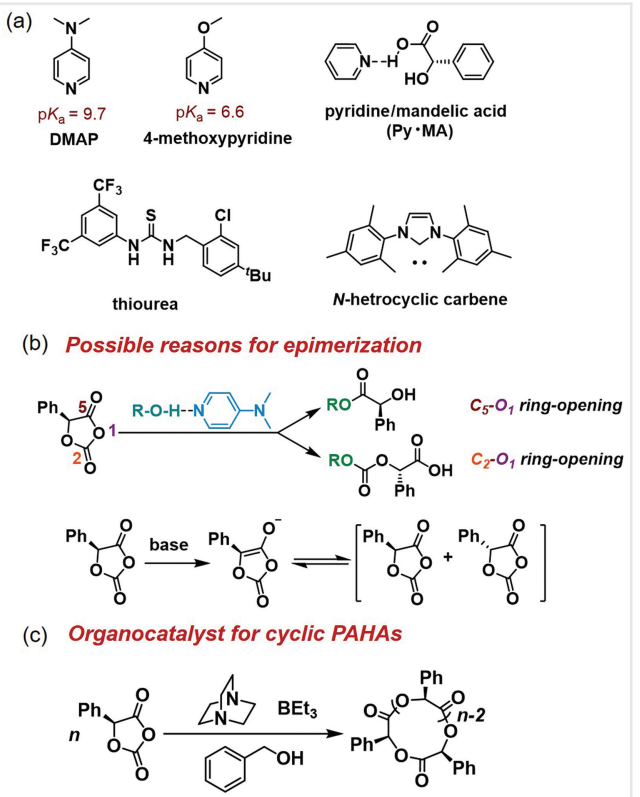
Organocatalysts for *O*-Carboxyanhydride Polymerization

In 1983, the polymerization of L-**4** was first attempted by Kricheldorf's group with less than satisfactory results.[36] Decades later, Bourissou's group pioneered efforts towards the ROP of L-**4** and its functionalized derivatives using 4-dimethylaminopyridine (DMAP) in the presence of protic initiators (Scheme 2a).[26] The polymerization of L-**4** only takes 5 minutes to complete in the presence of DMAP and *neo*-pentanol at room temperature, while the same catalysts with L-LA requires at least 4 days under heating. This DMAP/alcohol initiator pairing in catalyzing the ROP of L-**4** is also able to tolerate primary and secondary alcohols, showing that steric hindrance and electronic substituents of the alcohol do not markedly affect the initiation of the polymerization.[26]

Inspired by the increased reactivity of L-**4**, endeavors were undertaken to synthesize and polymerize functionalized OCAs using a similar pyridine-based/alcohol catalytic system.



Scheme 1 Overview of the synthesis of poly(α-hydroxy acids) (PAHAs) from α-amino acids and α-hydroxy acids via different monomer routes. Various *O*-carboxyanhydrides (OCAs) bearing pendant functional groups have been reported for the synthesis of functionalized PAHAs.



Scheme 2 The use of organocatalysts for the ring-opening polymerization (ROP) of OCAs. (a) Representative organocatalysts have been used for the ROP of OCAs. (b) The proposed mechanisms of epimerization during the ROP using organocatalysts. (c) The synthesis of cyclic PAHAs via the use of triethylboron, 1,4-diazabicyclo-[2.2.2]octane, and benzyl alcohol.

For example, L-**3** synthesized from γ-benzyl-L-glutamic acid was polymerized up to 18 kDa,[32] while L-**6** originating from carbobenzyloxy-protected L-lysine achieved a MW of 45 kDa with MW distribution (*Đ*) of 1.06.[38] Cheng and coworkers dominated the advancement of therapeutics delivery-driven polymerizations of functionalized OCAs as seen in work presenting ROPs of serine-derived **2**, tyrosine-derived **7**, and disulfide-containing camptothecin-poly(**7**) conjugate, all of which achieved impressively low *Đ* values with potential biological and pharmaceutical applications.[14,39,40]

In contrast to the noticeable drop in reactivity of LA when pendant functionalities are introduced,[19,20,41,42] OCA demonstrates relatively stable reactivity in the presence of aliphatic and aryl functional groups. Therefore, it is not surprising that copolymers of OCAs can be easily synthesized. Block and random copolymers of L-**3** and L-**4** are synthesized with regulated MWs catalyzed by DMAP.[32,43]

However, in 2011, the occurrence of epimerization in the ROP of L-**10** was uncovered by Pounder et al. via NMR studies.[44] The epimerized polymerization is proposed as a result of deprotonation of the acidic methine proton in **10**. Similar epimerization also occurred to the ROP of L-**2**, and L-**5**, all containing acidic α-protons.[45] Lowering the basicity of the organocatalyst is efficient in suppressing the epimerization reaction without negatively affecting the reactivity of the catalyst (Scheme 2b). A fine balance was struck with 4-methoxypyridine as it demonstrated well-controlled polymerization with only a minor degree of racemization of L-**10** (Scheme 2a).[44] Copolymerization with L-**4** was also achieved using the substituted L-**12** with bulky eugenol side chain in the presence of 4-methoxypyridine.[46] However, when pyridine-based catalysts were examined for the ROP of L-**5**, trends in catalytic activities do not correlate with the basicity of the pyridines. Interestingly, the adduct of mandelic acid and pyridine (Py·MA; Scheme 2a), which can be recrystallized, allows for the preparation of isotactic poly(L-**5**) with MWs up to 48 kDa.[47] Density functional theory calculation suggests that the basic activation of the OH moiety in MA is energetically favored via hydrogen bonding for the ring opening of L-**5**, compared to pathways involving direct nucleophilic attack by the pyridine moiety.[47]

The involvement of hydrogen bond and base activation inspired the use of a bifunctional thiourea–pyridine catalyst for stereoregular polymerization of OCAs. Tao, Wang, and co-workers screened out an active thiourea–pyridine catalyst that leads to controlled ROP of L-**5** with minimal epimerization ($P_m > 0.90$; P_m, the maximum probability of *meso* dyad formation; Scheme 2a). Such a bifunctional catalyst features a synergistic effect between the donating

ability of the thiourea moiety and the weaker basic characteristic of the substituted pyridine ring, which help control stereoregular ROPs of other OCAs — L-**1**, L-**2**, L-**4**, L-**6**, and L-**10** — with P_m values over 0.99.[35] However, the resulted polymers have $Đ$ values over 1.2 and the obtained MWs are often below 20 kDa.

Other than pyridine-based catalysts, ROP of OCA can also be performed with *N*-heterocyclic carbenes (NHCs, Scheme 2a) and enzymes. Finding success in the ROP of lactones, NHCs, including imidazolium carbenes and triazolium carbenes, were effectively applied to the living ROP of L-**4** with feeding ratios (FRs) up to 200/1.[48] A panel of substituted NHC catalysts was investigated and less-sterically hindered NHCs were observed to have higher catalytic activity but less thermal stability, weaker control of polymerization, and more likely to dimerize. Star-shaped diblock copolymer of L-**4** and L-**5** were also synthesized using NHC. However, high-MW polymers cannot be achieved when using NHCs.

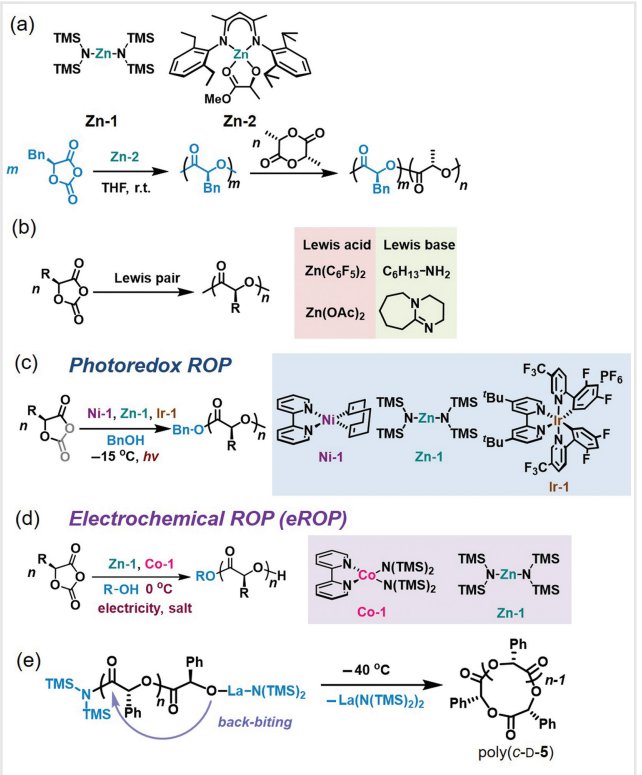
Additionally, lipase-loaded beads and Novozym 435 were reported by Bourissou's group to realize the ROP of **4**, with moderate MWs and low $Đ$ values at 80 °C.[49] Even though the availability of biocatalysts is still lacking when compared to synthetic organocatalysts, the nontoxic nature of these biocatalysts elevates their values in the production of medical commodities.

Besides the efforts of preparing linear PAHAs, recently, the synthesis of cyclic PAHAs has been explored via the use of organocatalysts. The polymer with cyclic topology shows unique properties—such as intrinsic viscosity, degradation, crystallinity, T_m (melting temperature), and T_g—that are significantly different from its linear counterparts.[50,51] Organocatalysts such as NHCs or strong bases, including 1,8-diazabicyclo[5.4.0]undec-7-ene, have shown to mediate the zwitterionic ROP to synthesize cyclic PLA in the absence of alcohol as the protic source.[51] Similarly, cyclic polymerization of OCAs can be achieved by the use of triethylboron, 1,4-diazabicyclo-[2.2.2]octane (DABCO), and benzyl alcohol (BnOH), reported by Yang's group (Scheme 2c).[52] The proposed zwitterionic mechanism of such cyclic ROP suggests that DABCO forms an active zwitterionic species with BnOH and triethylboron, which is followed by ring opening of OCA, and the polymerization is terminated by nucleophilic attack of the terminal alkoxide on carbonyl to yield cyclic polymers. Notably, the cyclic poly(L-**1**) exhibits slight epimerization with a P_m value of 0.83 and $Đ < 1.2$, and improved thermal stability compared to its linear analog.

Metal Catalysts for *O*-Carboxyanhydride Polymerization

As the progress in developing an organocatalytic system for effective ROP of OCAs was slowly approaching a bottleneck, a pivotal move was made in the early 2010s to deviate towards the incorporation of organometallic catalysts in the polymerization process for elevated catalytic reactivity and improved control. Metal catalysts for the ROP of heterocycle monomers have shown remarkable control on the polymerization MWs, kinetics, and stereoselectivity.[13,21,53,54] Several organometallic catalysts that promote ROP of lactones or copolymerization of epoxides and CO_2 were tested for ROP of OCAs in early studies, including Sn^{II} Co^{III}, Nd^{III}, Cr^{III}, Al^{III}, Y, and La complexes.[55–58] However, the ROP of OCAs using these metal complexes cannot be achieved in a controlled manner, in which the MW of the obtained polymer is predictably linear to the monomer-to-catalyst FRs with a narrow $Đ$.

The first success was demonstrated by Cheng and Tong's work of using Zn complexes with β-diiminate ligands ((BDI)Zn complexes) to achieve well-controlled ROP of various OCAs (L-**1**, L-**2**, L-**4**, L-**5**, L-**7**; Scheme 3a).[45,59] No epimerization for poly(L-**2**) and poly(L-**5**) was observed in the homonuclear decoupled ^{1}H NMR spectra, in contrast to



Scheme 3 The use of metal catalysts for the ROP of OCAs. (a) Zn complexes that can mediate the ROP of lactones have been used for the ROP of OCAs, and the block copolymerization of OCAs and LAs via sequential additions of monomers. (b) The Lewis pair, a metal complex as a Lewis acid and a Lewis base, has been used for the ROP of OCAs. (c) Scheme of controlled photoredox ROP of OCAs mediated by Ni/Zn/Ir complexes. (d) Scheme of controlled electrochemical ROP (eROP) of OCAs mediated by Co/Zn complexes. (e) Scheme of the synthesis of cyclic poly(**5**) via the use of a La complex.

similar ROP performed using organocatalysts such as DMAP. Notably, monomeric **Zn-2** complex, rather than the dimeric (BDI)ZnO^{i}Pr complex, could efficiently initiate and promote chain propagation. **Zn-2** could also achieve one-pot block copolymerization of LAs and OCAs, regardless of the addition sequence (Scheme 3a). Additionally, macro-initiators such as mPEG$_{5k}$ (methoxy poly(ethylene glycol) with a MW of 5k) could also initiate the ROP of **7**, mediated by (BDI)Zn complex, to give an amphiphilic block copolymer that was then followed by Cu^{I}-catalyzed click chemistry to afford redox-responsive core cross-linked micelles for drug delivery application.[60]

As many metal complexes for ROPs of lactones are Lewis acids (e.g., Zn, Mg, and Al complexes), one emerging strategy is to pair these Lewis acids with Lewis bases to form Lewis pairs that initiate ROP via zwitterionic mode.[61–67] Such a method has been applied to the ROP of lactones, and LA to prepare cyclic polyesters.[68–70] Recently, Yang's group[71] demonstrated that a Lewis-pair catalytic system, a primary amine (1-hexyl-NH$_2$) as a Lewis base and Zn(C_6F_5)$_2$ as a Lewis acid (Scheme 3b), could mediate the controlled ROP of OCAs. Note that such a Lewis pair has been applied for ROPs of LA and ε-caprolactone.[69] The proposed mechanism involves a Lewis pair-catalyzed initiation and coordination–insertion chain growth process via a quick transformation of Zn(C_6F_5)$_2$ to Zn-alkoxide. However, the application of this Lewis-pair catalytic system is limited to the polymerization of L-**1** with FRs < 200 at 50 °C. In continuance to previous findings, Yang and coworkers identified another simple Lewis pair consisting of 1,8-diazabicycloundec-7-ene (DBU) and Zn(OAc)$_2$ to promote the ROP of L-**1** at room temperature (Scheme 3b).[72] Notably, during the screening of Lewis pairs, Lewis acids such as Mg, Al, Sn^{IV}, and Fe^{III} salts were found to be inefficient in such Lewis-pair-mediated ROP of OCAs. However, this catalytic system requires alcohol as an initiator and could not yield polymers with MWs over 20 kDa, along with the detection of epimerization (P_m = 0.88 for poly(L-**1**)).

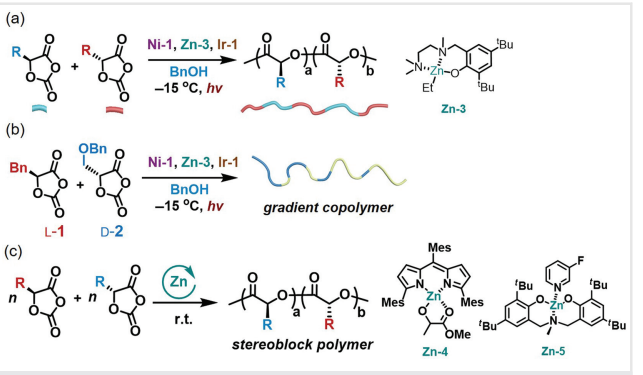
Although various Zn complexes have been developed for the ROP of OCAs, the polymerization using metal complexes often results in products with low MWs (less than 30 kDa).[45,73] The inefficient chain propagation in metal-catalyzed ROP of OCAs has been identified as the main problem in preventing the synthesis of high-MW PAHAs.[73] Indeed, mechanistic studies using (BDI)Zn to copolymerize epoxide and CO_2 indicate the equilibrium between Zn-alkoxide and Zn-carbonate.[74,75] Notably, the development of viable synthetic methods to prepare high-MW PAHAs is critical since the mechanical properties, thermal properties, and crystallization behavior of the polymer is believed to be directly correlated to its MW, as supported by research in PLA.[76,77]

Aware of substantial studies on metal catalyst-mediated *N*-carboxyanhydride polymerization,[78,79] and the emerging use of photoredox catalysts with metal catalysts for decarboxylation,[80,81] in 2017, our group developed a **Ni-1**/**Zn-1**/**Ir-1** photoredox catalytic system to mediate controlled photoredox ROP of L-**1**, allowing for the production of PAHAs with MWs up to 140 kDa and narrow *Đ* values (<1.1; Scheme 3c).[73] This catalytic system could be successfully applied to other OCAs (**2**, **3**, and **4**) as well. Notably, all components of this catalytic system were necessary for the controlled polymerization results: Ni/Ir photocatalysts are responsible for decarboxylation to synthesize high-MW polymers; while Zn-alkoxide at the chain end is crucial for chain propagation. Interestingly, the oxidative addition of the Ni^0 complex to the OCA occurs at the O_1–C_5 position regioselectively, which is followed by photoexicted-**Ir-1**-mediated decarboxylation, and transmetalation with Zn-alkoxide for efficient chain propagation.[73] It should be pointed out that a low-temperature reaction condition is necessary to avoid Ni-mediated decarbonylation side reaction that stops the chain propagation.

Motivated by the Ni/Zn/Ir photoredox catalytic system, our group proceeded to investigate a new electrochemical Co/Zn catalytic system.[82] We note that the current large-scale production of PLA relies on constant high temperature; however, the light is a less energy-efficient stimulus because photonic flux decreases exponentially with the depth of the reaction medium, as dictated by the Beer–Lambert law. On the other hand, electrochemical reactions are among the most energy-efficient chemical reactions that enable the addition or removal of electrons to drive chemical reactions. The success of Ni/Zn/Ir systems suggests that the decarboxylation step can be accelerated via the photoexcited electron transfer, which encourages us to look for catalysts that can replace Ni/Ir photocatalysts for electrochemical reactions. We first found that the **Co-1** complex can replace **Ni-1**/**Ir-1** photocatalysts to achieve ROP of OCA at 0 °C to facilitate highly controlled ROP of OCAs. We then screened various electrochemical polymerization conditions (eROP) to identify the optimal galvanostatic conditions (constant current at 4 mA) that enable the synthesis of isotactic high-MW PAHAs with >140 kDa and narrow MW distribution within 2–3 hours (*Đ* < 1.1; Scheme 3d). During the eROP process, the **Co-1**/OCA intermediate forms by means of anodic oxidation, before undergoing cathodic reduction for decarboxylation, followed by transmetalation with the Zn catalyst to produce Zn-alkoxide terminus for productive chain propagation. Notably, no epimerization occurs even for poly(L-**5**). The copolymerization can also be achieved by sequential addition of OCA monomers. These promising results suggest that our eROP method could potentially have applications owing to energy efficiency and scalability using recyclable electrodes.

Another intriguing use of metal catalysts is to synthesize cyclic polymers. Chen's group reported that La(N(TMS)$_2$)$_3$ can mediate the ROP of γ-butyrolactone to produce cyclic polyesters.[50] Recently, Xu and coworkers found that the use of La(N(TMS)$_2$)$_3$ at –40 °C also allows for the synthesis of cyclic

poly(D-**5**) with a P_m value up to 0.93 and a MW ~ 29 kDa (Scheme 3e).[83] Notably, both cyclic and linear poly(D-**5**) can be found when using La(N(TMS)$_2$)$_3$ at 25 °C, and the mechanistic studies suggest that the intramolecular chain termination predominates at low temperature to yield a cyclic polymer. Xu and coworkers also found that the topologies of polymers significantly impact the thermal properties: the stereocomplex from cyclic poly(**5**) exhibits two endothermic peaks (T_m) at 131 and 172 °C, while the linear stereocomplex of linear poly(**5**) only have one T_m at 163 °C. It remains unknown whether such a method can be extended to other OCA monomers.



Scheme 4 Isoselective ROP of OCAs mediated by Zn complexes. (a) Scheme of photoredox isoselective ROP of OCAs to synthesize stereoblock copolymers, mediated by Zn/Ni/Ir catalysts. (b) The same catalytic system allows for the one-pot synthesis of gradient copolymers. (c) Other Zn complexes also mediate isoselective ROP of OCAs to generate stereoblock copolymers.

Stereoselective and Stereosequence-Controlled Polymerization of *O*-Carboxyanhydrides

It is well known that the physical and chemical properties of polyesters are closely related to their tacticity, such as isotactic and syndiotactic microstructures.[84,85] For example, syndiotactic polystyrene is a highly crystalline material with a T_m of 270 °C, whereas atactic polystyrene is viscous.[86] Additionally, compared to homopolymers, sequence-controlled copolymers would provide an increased possibility for achieving polyester diversity with more favorable properties.[87–90] For instance, the copolymer of allyl and benzyl β-malolactonates catalyzed by Y complex showed higher T_m as the alternating level increases.[91] Therefore, the search for a new catalytic system for enriched control of the microstructure of copolymers is crucial. Despite efforts devoted to the synthesis of stereoregular polyesters by stereoselective ROP of racemic LA and lactones,[92–101] relatively few well-defined metal catalysts are available for stereoselective polymerization of racemic OCA monomers.

The reactivity of Zn complexes for the ROP of OCAs[45] encouraged researchers to exploit the stereoselective ROP to prepare functionalized PAHAs with various microstructures (e.g., stereoblock, syndiotactic, and stereocomplex microstructures). In 2018, our group reported the synthesis of stereoblock polyesters with a high P_m value of 0.97 by expanding our previously presented Ni/Zn/Ir photoredox catalytic system.[102] A less bulky tridentate Schiff base ligand was screened to form **Zn-3** complex (Scheme 4a) that mediates stereocontrolled polymerization of racemic OCAs. It is also important to highlight that this catalytic system could afford highly stereoblock (*sb*) poly(*sb*-**1**) with high MWs (~78 kDa). The mechanistic study suggests a chain-end-control mechanism; a stereoerror occurs during the chain propagation and the other enantiomer is incorporated and enchained. Notably, the stereoblock poly(*sb*-**1**) showed a T_m of 172 °C, whereas the T_m of the atactic poly(*rac*-**1**) (*rac*, racemic) was not observed, indicating the influence that polymer microstructures have on the thermal properties.

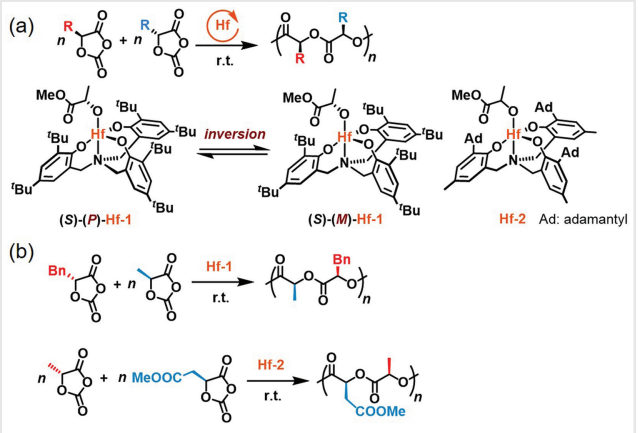
Our group also successfully synthesized a series of gradient polymers by using a one-pot **Zn-3**/**Ni-1**/**Ir-1** catalytic system (Scheme 4b).[102] Both NMR spectra and kinetic studies of the performed one-pot copolymerization of L-**1** and D-**2** proved that this catalytic system afforded highly isotactic poly(L-**1**-*grad*-D-**2**) due to their different polymerization rates. On the contrary, although the polymerization rates of L-**1** and L-**2** were significantly different, this catalytic system affords random copolymer poly(L-**1**-*co*-L-**2**). These gradient copolymers provided MWs of 23–43 kDa and narrow $Đ$ values of 1.01–1.04. Based on the kinetics plots, the order of polymerization rates of OCA monomers is deduced to be $k(\mathbf{1}) > k(\mathbf{4}) \approx k(\mathbf{3}) > k(\mathbf{2})$. Therefore, the prerequisites for gradient copolymerization of two different monomers using such catalytic systems are to have monomers with opposite chirality and significantly different polymerization rates.

Similar isoselectivity results of Zn complexes were recently reported by Wu's group: a Zn complex (**Zn-4**) with a dipyrrin ligand could mediate isoselective ROP of *rac*-**1**, *rac*-**4**, and *rac*-**8** via a chain-end-control mechanism, with P_m values of 0.95–0.97 at −70 °C (Scheme 4c), whereas the P_m value mediated by the (BDI)Zn complex was only about 0.72 for *rac*-**4**.[103] However, it is noted that significant epimerization was observed during the ROP process for L-**5**, which was not observed when using (BDI)Zn complexes[45] or even **Zn-1** without ligands.[83]

Wu and coworkers also reported that an aminobisphenolate Zn complex (**Zn-5**), paired with 3-fluoropyridine, a weak Lewis base, along with *rac*-(methyl mandelate) as an initiator, could mediate isoselective ROP of *rac*-**5** with a high P_m of 0.92 at −50 °C (Scheme 4c).[104] Severe epimerization occurred in the absence of 3-fluoropyridine,

and polymerization almost ceased to happen without the Zn complex, suggesting the necessity of a Lewis pair to eliminate epimerization. Notably, poly(*sb*-**5**) ($P_m = 0.92$) showed a higher T_g value of 93 °C when compared to the atactic poly(*rac*-**5**) ($P_m = 0.60$, $T_g = 83$ °C).

A breakthrough for syndioselective ROP of OCAs occurred when Wu's group reported Zr or Hf-alkoxides with aminotris (phenolate) ligands to efficiently control syndioselective ROP of *rac*-**4** in 2017 (Scheme 5a).[34] The Hf-alkoxide complex (**Hf-1**) affords syndiotactic polyesters at room temperature with high P_r values of 0.80–0.95 (P_r, the maximum probability of racemic dyad formation). The decrease of polymerization temperature from 25 °C to −60 °C, however, results in reduced P_r values from 0.83 to 0.72. The chain-end diastereoisomers could likely be converted to each other at room temperature, whereas the decreased temperature slows such a conversion rate, which agrees well with the proposed mechanism of ROP of LA (Scheme 5a).[105,106] However, such a syndioselective catalytic system is still unable to synthesize stereoselective polymers with high MWs (only ~10 kDa).

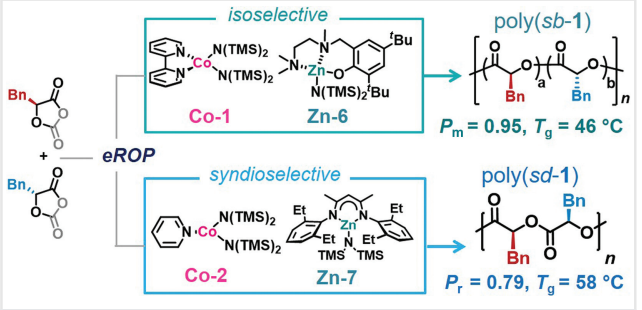


Scheme 5 Syndioselective ROP of OCAs mediated by Hf complexes. (a) The development of two Hf complexes for syndioselective ROP of OCAs. The inversion of Hf diastereoisomers is proposed to present syndioselectivity during the enchainment. (b) Alternating copolymerization of two OCA monomers with opposite chirality, mediated by different Hf complexes.

As a result of the high syndioselectivity of **Hf-1** for *rac*-**1** ($P_r = 0.93$), *rac*-**4** ($P_r = 0.84$), and *rac*-**8** ($P_r = 0.95$), Wu's group also attempted the control of copolymer microstructure using OCA monomers with different configurations (Scheme 5b).[34] The resulting poly(D-**1**-*alt*-L-**8**) shows a high alternation value of 0.95. This particular catalytic system affords alternated poly(L-**1**-*alt*-D-**4**) as well. Furthermore, the configuration of initiators (L- or D-methyl lactate) in **Hf-1** has no effects on the alternating probability.

Wu and coworkers further reported another Hf alkoxide complex with bulky adamantyl groups (**Hf-2**; Scheme 5a) that exhibited excellent syndioselectivity for *rac*-**4** with a P_r of 0.91, but a poor syndioselectivity for *rac*-**11** with a P_r of 0.46.[107] The polymerization rate for *rac*-**11** was slow, as the bulky adamantyl group likely impeded the monomer incorporation. Intriguingly, when the copolymerization of D-**4** and L-**11** was carried out at room temperature, alternating poly(D-**4**-*alt*-L-**11**) was successfully synthesized with an alternation level of 86% (Scheme 5b). It was proposed that the significantly reduced rate of ROP of L-**4** than that of *rac*-**4** and the low rate of ROP of **11** could be vital for the high alternating efficiency in this system. On the other hand, when D-**4** was replaced with L-**4**, the polymerization exhibits slower reaction rates with poorly controlled alternating sequences, confirming that the chain end prefers the incorporation of monomers with opposite chirality. However, in all cases, such alternating polymers have low MWs (<10 kDa).

Recently, our group disclosed a new electrochemical pathway to achieve the stereoselective ROP of *rac*-OCAs (Scheme 6).[82] When a current was applied, the **Co-1**/**Zn-6** catalytic system offered stereoblock poly(*sb*-**1**) with a MW of 67.6 kDa and a high P_m value of 0.95. On the contrary, the **Co-2**/**Zn-7** catalytic system produced syndiotactic poly(*sd*-**1**) (*sd*, syndiotactic) with a MW of 46.2 kDa and a P_r value of 0.79. However, a similar phenomenon was not observed in the stereoselective ROP of *rac*-**4**, since both the **Co-1**/**Zn-6** and **Co-2**/**Zn-7** catalytic systems afforded stereoblock polymers. Aside from the ligand of the metal complex, this indicated that the side-chain functionalities of OCA monomers also influenced stereoselectivity during the electrochemical polymerization process.



Scheme 6 Co/Zn complex-mediated stereoselective eROP of racemic **1**. The selection of different catalysts could enable the synthesis of poly(**1**) with different microstructures and glass transition temperatures (T_g).

Conclusions and Outlook

This review describes the recent achievements for a wide range of catalysts that can moderate the ROP of OCAs, as well as homopolymers and copolymers with diverse architectures and functionalities. Considering the countless catalysts for the ROP of LA, relatively few catalysts (especially organometallic catalysts) have been identified to mediate a highly controlled

ROP of OCAs despite recent prominent progress. The synthesis of high MW polyesters via ROP of OCA still faces formidable challenges due to inactive chain propagation at high monomer-to-catalyst FRs.[21,27,73] And more simplified catalytic systems and mild methods without using external stimuli are worth exploring. Topology-controlled ROP of OCA, e.g., the preparation of cyclic PAHAs, could offer an enhanced scope and an access to diverse materials even based on the same monomers. Additional efforts should be also directed to close the urgent gap in creating highly stereoselective and sequence-controllable ROP that allows for immediate access to functionalized PAHAs, as similar remarkable controls have been achieved in the ROP of lactones and other heterocyclic monomers.[108–112] One of the foreseeable challenges is the scale-up of monomer synthesis. Unlike monomers of LA and many anhydrides that have seen success under large-scale industrial production,[113] most of OCA monomers are subjected to repetitive recrystallization for potential industrial scale-up.[28] Additionally, residual catalysts including organic and organometallics in polymers would restrict prospective applications due to toxicity and the possibility of promoting polymer degradation during processing.[114] Currently, liquid extraction using ether or methanol is the conventional method to remove residual catalysts below the ppb concentration level,[73,82,115] but this method may not be environmentally sustainable due to the use of organic solvents. Therefore, green and solvent-free methods remain to be explored for the purification of PAHAs, such as CO_2-laden water.[116]

Advances in synthetic methods are expected to lead to functionalized polymers with attractive properties and applications. In regard to materials, systematic studies on the physical and thermal properties of the functionalized PAHA copolymers (gradient copolymers or alternating copolymers) are still lacking, especially investigations into physicomechanical behavior and other functional performances of these valuable polyesters. This can be attributed to difficulties in using current methods to produce high-MW PAHAs as aforementioned. Many PAHAs with MWs less than 5 kDa cannot be used for practical applications.[18] A very recent study has demonstrated that the high-MW poly(**1**) (150 kDa) had 4-fold higher tensile strength than its low-MW counterpart (41 kDa),[117] which highlights the importance of the preparation of high-MW PAHAs. Lastly, the study for degradability and recyclability of these newly synthesized PAHAs is still underway and further effort is essential for their eventual translation into consumer-friendly applications, such as biomedical applications.

Funding Information

This work was supported by start-up funding from Virginia Tech, American Chemical Society Petroleum Research Fund (57926-DNI-7), and the National Science Foundation (CHE-1807911).

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