In Situ Versus Isolated Zinc Catalysts in the Selective Synthesis of Homo and Multi-block Polyesters

In Situ versus Isolated Zinc Catalysts in the Selective Synthesis of Homo and Multi-block Polyesters

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Dedicated to Prof. Robert E. Mulvey on the occasion of his 60th birthday.

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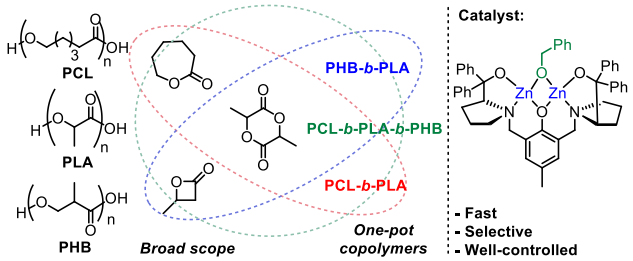

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Abstract

The *in situ* generation of metal-alkoxide complexes is a common initiation method in cyclic ester ring-opening polymerisation. Yet this method is often a "black box", where the species so generated are assumed to be the same as the isolated complex. We now demonstrate that an isolated Zn-benzoxide catalyst gives a remarkable reactivity enhancement in lactide ROP, with k_{obs} values 10 times higher than the *in situ* generated analogue. The dinuclear zinc catalyst, built using the Trost ProPhenol ligand, offers these excellent activities and good control over homopolymerisation of multiple cyclic esters (*rac*-lactide, ε-caprolactone and *rac*-β-butyrolactone). The stability of this isolated catalyst also controls chain exchange and back-biting, allowing for one-pot synthesis of multi-block polyesters without loss of activity, selectivity and control. To the best of our knowledge, this is the first catalyst reported for the selective preparation of block terpolymers of ε-CL, *rac*-LA and *rac*-β-BL.

Introduction

The ring-opening polymerisation (ROP) of cyclic esters is an efficient route to polyesters such as poly(lactic acid) (PLA), poly(ε-caprolactone) (PCL) and poly(3-hydroxybutyrate) (PHB). These and other aliphatic polyesters offer improved degradation rates compared to many conventional polymers and a wide range of applications including biomedical devices,[1] electronics and packaging.[2] Careful control over the polymer microstructure is key to tuning the material properties and requires the use of an appropriate catalyst; some of the most effective are homogeneous organometallic complexes. Many monometallic complexes, including (salen)Al,[3,4] [amino(trisphenolato)]Zr[5] and (phosphasalen)Y,[6] have accessed high catalyst activities, broad monomer scope and excellent control over the polymer stereochemistry.

Bimetallic catalysts have shown exciting promise in cyclic ester ROP, and bis-Zn complexes have been particularly successful (Fig. 1).[7–9] Zinc is an attractive metal for lactide (LA) ROP, as it is inexpensive, colourless, non-redox active and non-toxic; the lack of toxicity is strongly desirable for the use of PLA in biomedical applications.[10] To date, the most active bis-Zn catalyst reported for LA ROP is based on a macrocyclic bis(imino)diphenylamido ligand (Fig. 1, top right), where the activity is enhanced by close metal-metal proximity.[11] This mirrors studies in CO_2/epoxide ring-opening copolymerisation (ROCOP), which shares several mechanistic features with cyclic ester ROP (monomer coordination and nucleophilic attack), and where short intermetallic distances (3-8 Å) often give enhanced catalyst activities.[12–14] Notably, [(bis(imino)diphenylamido)ZnN($SiMe_3$)$_2$] remains highly effective at low catalyst loadings.[11] This opens up access to high M_n PLA and indicates that dinucleating ligands offer a method of maintaining metal-metal cooperativity at low catalyst loadings.[9,15] Studies have suggested that the catalyst solution-state structure (aggregation state and ligand conformation) can influence the

catalytic activity in ROP.[11,15–18] However, many organometallic precursors are still converted to the active metal-alkoxide catalyst *in situ* without investigation of the impact upon the structure and reactivity.

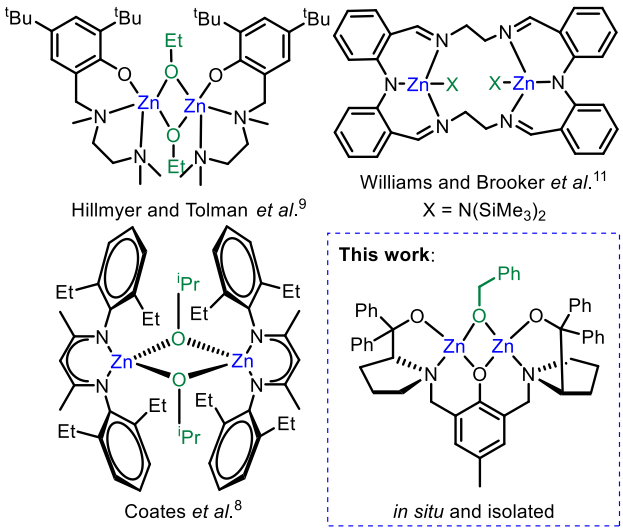


Figure 1. Highly active bis-Zn catalysts for LA ROP.

Metal-based catalysts can selectively form block copolymers that self-assemble into materials with superior properties and applications including thermoplastic elastomers, adhesives and lithography.[19] Block copolymers of ε-CL/LA have applications as drug delivery agents and nerve guides,[20,21] combining the drug permeability, elasticity and thermal properties of PCL with the mechanical properties and degradation rate of PLA ($t_{1/2}$ *in vivo* = a few weeks; PCL, $t_{1/2}$ *in vivo* = 1 year).[22–25] Copolymerisation of LA and β-BL can give materials with improved mechanical properties, higher degradation rates and lower melting points than naturally-occurring PHB, yet examples of selective catalysts for PLA-PHB block copolymers remain rare.[26–31] However, sequential addition of D-LA, *rac*-β-BL and L-LA was previously used by Mehrkhodavandi *et al.* to generate triblock poly(lactic acid-*block*-*rac*-β-butyrolactone-*block*-lactic acid) copolymers using dinuclear indium catalysts.[32] Catalysts based on Al, La, Sm, Sn, Ti and Zr have been reported

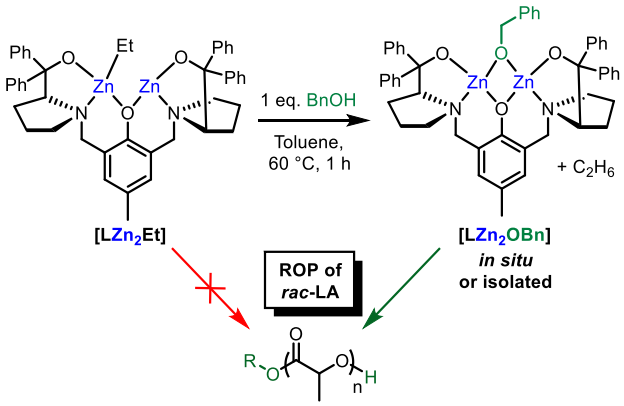
for selective ε-CL/LA copolymerisation, albeit with relatively long reaction times.[33–38] Zinc catalysts remain underexplored despite the excellent activities and selectivities demonstrated for cyclic ester homopolymerisation. The efficient, controlled one-pot synthesis of di- and tri-block copolymers *via* ROP opens up a broad range of degradable materials with tuneable properties, yet remains a synthetic challenge, which is partly due to transesterification reactions that can randomise the polymer structure. Here, we explore a bimetallic zinc-benzoxide complex, based on a commercially available dinucleating ligand scaffold, for the selective preparation of homopolymers and block copolymers.

Results and Discussion

Complex **LZn$_2$Et** (Scheme 1) is an interesting catalyst precursor for cyclic ester ROP as the close metal-metal proximity facilitated efficient CO_2/epoxide ROCOP.[39] While **LZn$_2$Et** has catalysed enantioselective organic transformations,[40,41] it is typically generated and used *in situ* without full characterisation. To probe the solution state structure, we prepared **LZn$_2$Et** through **LH$_3$** deprotonation with Et_2Zn (2 equiv.) and characterised the product by NMR spectroscopy, mass spectrometry and elemental analysis (refer to ESI). ^{1}H NMR spectroscopic analysis highlights the asymmetry of **LZn$_2$Et**, suggesting two inequivalent zinc sites where one zinc bears a highly nucleophilic/Brønsted basic ethyl group and the other forms a Zn-THF Lewis acid/base adduct (Fig S1).[39,42–44] These two features are key in ROP based on the coordination-insertion mechanism.[4,45]

Whilst **LZn$_2$Et** was inactive towards *rac*-lactide (*rac*-LA) ROP under the conditions tested (Table 1), addition of benzyl alcohol initiator (BnOH, 1 equiv.) gave excellent conversions of 87% after 10 minutes (60 °C in toluene solvent). Reaction between **LZn$_2$Et** and 1 eq. BnOH in toluene-

d_8 was monitored by ^{1}H NMR spectroscopy, which indicated the rapid loss of ethyl resonances at 1.94 and 1.13 ppm and the formation of ethane gas (0.81 ppm, Fig. S3 and S10). The polymerisation was relatively well-controlled, displaying first-order kinetics in monomer and a linear relationship between M_n and monomer conversion, as well as narrow to moderate dispersities ($Đ$ = 1.07 – 1.22). However, there was some discrepancy between the observed and calculated M_n values. In addition to the expected α-benzoxy, ω-hydroxy end-capped polymer chains, MALDI-ToF analysis showed a second series featuring ligand end-groups in the late stages of the polymerisation.

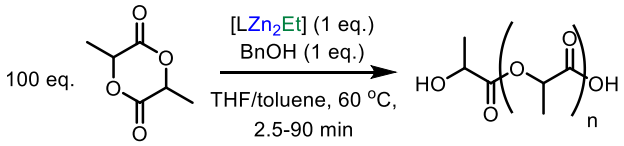


Scheme 1. Synthesis and reactivity of **LZn$_2$Et** and **LZn$_2$OBn** towards *rac*-LA ROP.

The polymerisation was significantly faster in toluene solvent compared to THF. While 21% conversion was obtained after 1 hour in THF, 79% conversion took just 7 minutes in toluene (Table 1). DOSY analysis suggested that this enhanced activity was not caused by differences in the catalyst aggregation state, as **LZn$_2$Et** was monomeric in both d_8-THF and d_8-toluene (Fig S6-S7). However, DOSY analysis suggests that in neat THF the solvent was in coordinative equilibrium with **LZn$_2$Et**, whereas THF was non-coordinated in d_8-toluene. These observations suggest that excess THF may block LA coordination and reduce the rate of ring-opening.[46] Supporting this hypothesis, addition of 2 and 100 equivalents of THF per dinuclear catalyst significantly decreased the conversion after 10 min, from 87% (neat toluene), to 80% (2 equiv. THF), down to 58% (100

equiv. THF). Toluene solvent presents a challenge for LA solubility, which was addressed by "pre-stirring" LA in toluene at 60 °C prior to the addition of **LZn$_2$Et** and BnOH (refer to ESI for details). Unfortunately, **LZn$_2$OBn** did not exhibit stereocontrol for *rac*-LA ROP, resulting in atactic PLA (P_s = 0.48-0.50, Table 1). Polymerisation of L-LA led to isotactic PLA, albeit at approximately half the rate observed for *rac*-LA and with a significant induction period of approximately 7.5 min, which was not detected for *rac*-LA (Figure S12). This difference in initiation implies that the chiral ligand of **LZn$_2$OBn** (*S*,*S*) is structurally arranged with a preference for D-LA coordination and insertion to initiate the polymerisation.[8,47,48] While the difference in propagation rates could imply that **LZn$_2$OBn** prefers polymerisation of D-LA, the production of an atactic polymer combined with a lack of transesterification (determined by MALDI-ToF analysis) suggests that other factors are also important such as solubility differences between *rac*-LA and L-LA. The induction period observed for L-LA may arise from structural rearrangement of the ligand to facilitate coordination, which may influence the catalyst geometry and thus activity.

Table 1. ROP of *rac*-LA catalysed by *in situ* generated **LZn$_2$OBn**:



Entry	Time (min)	Conv[a] (%)	$M_{n,obs}$[b] (Da)	$M_{n,calc}$[c] (Da)	$Đ$[b]	P_s[d]
1[e]	60	21	-	-	-	-
2[e]	90	50	-	-	-	-
3[f]	10	0	-	-	-	-
4	2.5	35	2000	5100	1.18	0.48
5	5	56	4500	8100	1.22	0.48
6	7	79	7100	11400	1.08	-

7	10	87	8100	12500	1.07	0.50
8	11	89	8400	12800	1.09	-
9[g]	10	58	3400	8400	1.11	0.52
10[h]	10	80	5200	11500	1.07	-

[LA] = 1 M in toluene. *rac*-LA and complex **LZn$_2$Et** pre-stirred separately for 3 min in toluene at 60 °C before mixing and initiation with BnOH. [a] Conversion calculated using ^{1}H NMR spectroscopy. [b] $M_{n,obs}$ and $Đ$ determined by gel permeation chromatography using polystyrene standards in THF. Values corrected by Mark Houwink factor (0.58).[49] [c] $M_{n,calc}$ of polymers calculated from the monomer conversion $M_{n,calc} = M_0$ x ([M]/[I]) x conversion assuming 1 chain per catalyst centre. [d] Determined by homodecoupled ^{1}H NMR spectroscopy. [e] [*rac*-LA] = 1 M in THF. *Rac*-LA and **LZn$_2$Et** weighed out into the same vial and not pre-stirred separately for 3 min before initiation with BnOH. [f] No BnOH used. [g] 100 eq. of THF added with respect to **LZn$_2$Et**. [h] 2 eq. of THF added with respect to **LZn$_2$Et**.

To address the low M_n values obtained using *in situ* generated **LZn$_2$OBn**, this complex was isolated, characterised and tested in *rac*-LA ROP. Unlike the **LZn$_2$Et** precursor, ^{1}H NMR spectroscopic analysis suggests **LZn$_2$OBn** is symmetrical, attributed to OBn bridging two metal centres (Figure S3).[50–56] Intriguingly, the isolated complex was an order of magnitude more active than the *in situ* analogue (isolated **LZn$_2$OBn**, k_{obs} = 3.5 x 10^{-2} s^{-1}; *in situ* **LZn$_2$OBn**, k_{obs} = 3.6 x 10^{-3} s^{-1}) under identical reaction conditions (toluene solvent, 60 °C). Isolated **LZn$_2$OBn** also displayed good catalytic activities at lower catalyst loadings of 0.2 mol% and 0.1 mol%, producing PLA with M_n values above 50, 000 g mol^{-1} (Entry 10, Table 2). The isolated catalyst is amongst the most active zinc complexes reported for LA ROP (refer to Table S3 for details),[8,9,11] and displays good control over the M_n and dispersity (Table 2). The observed activity differences may originate from slower initiation with *in situ* generated **LZn$_2$OBn**, possibly from incomplete reaction between **LZn$_2$E**t and BnOH in the presence of LA. Notably, unreacted BnOH could act as a chain-transfer agent, resulting in narrower $Đ$ values than observed with isolated **LZn$_2$OBn**. However, careful inspection of the M_n data suggests that this is not the full explanation. With isolated **LZn$_2$OBn**, the observed M_n values are slightly higher than the calculated values, at both room temperature and 60 °C, suggesting that not all of the catalyst is active (Tables S2 and 2). In

contrast, the M_n values from the *in situ* catalyst are lower than expected. Perhaps the aggregation state of the catalyst is also important? To answer this question, **LZn$_2$OBn** was investigated using DOSY analysis. While **LZn$_2$Et** is monomeric in d_8-toluene, **LZn$_2$OBn** is a dimer (refer to ESI for details). These results suggest *in situ* generation of metal-alkoxy catalysts can influence the aggregation state and therefore the catalyst activity. It is plausible that Lewis basic *rac*-LA could reduce the aggregation state of the isolated **LZn$_2$OBn** dimer to a monomer. As the rapid reaction between **LZn$_2$OBn** and *rac*-LA prevented DOSY investigations into monomer coordination and aggregation state, γ-valerolactone (γ-VL) was used as this cyclic ester is challenging to polymerise.[57] Instead of decreasing the aggregation state of **LZn$_2$OBn**, γ-VL increased the aggregation state, suggesting that cyclic esters can bridge between metal centres and modify the aggregation state (refer to ESI for details). Whilst *in situ* alcoholysis of an organometallic precursor is a popular method of initiating ROP, there are surprisingly few accounts of the difference between *in situ* generation *vs*. isolation of the catalyst. Ejfler *et al*. reported that isolated dimers, **[L'ZnOR]$_2$** (L' = aminonaptholate), were less active and controlled than the *in situ* generated analogues.[18] This was attributed to the formation of different catalyst structures when alcoholysis of **[L'ZnEt]$_2$** was performed in the presence of LA, with complex dynamic equilibria influenced by the order of addition and the nature of the alcohol (methanol/BnOH/1-phenylethanol) and ligand. These studies highlight the importance of understanding of the catalyst solution-state chemistry to access improved activities and polymerisation control.

The MALDI data reveals an α-benzoxy, ω-hydroxy end-capped series at low LA conversion, however, some ligand end groups are also observed at high conversions. Ligand end groups were also reported by Chakraborty *et al.* with a Trost ligand zirconium complex, **(LH)$_2$Zr**, in the absence of an alcohol initiator.[58] These observations suggest that with **LZn$_2$OBn**, the ligand

becomes non-innocent in the late stages of the reaction, where transesterification becomes competitive with propagation. It seems likely that transesterification occurs *via* cleavage of the Zn-O(ligand) bond, which undergoes nucleophilic attack upon an ester carbonyl of the growing polymer chain (Scheme S1). As the polymer chain grows, the steric strain of forming cyclic products decreases, which may favour transesterification. The analogous ethyl complex, **LZn$_2$Et**, is inactive towards LA ROP in the absence of BnOH, suggesting that Zn-O(ligand) groups cannot initiate ROP. DOSY analysis of the quenched PLA oligomer revealed that the ligand and PLA chains have identical diffusion coefficients (Fig. S20). This suggests that transesterification reactions promoted by Zn-O(ligand) groups can occur even with oligomeric chains at high conversions. However, it cannot be unequivocally ruled out that the identical diffusion coefficients arise from similarity between the catalyst (870 g mol^{-1}) and oligomeric PLA (monomer = 144 g mol^{-1}). Nozaki *et al*. reported that dimeric Zn-Et complex [Et$_2$Zn$_2$((*S*)-diphenyl(pyrroridin-2-yl)methanol)] can initiate CO$_2$/epoxide ROCOP through CO$_2$ insertion into the Zn-O(ligand) bond.[59] In contrast, the addition of ethanol generated a Zn-OEt complex that efficiently initiated CO$_2$/epoxide ROCOP, leading to enhanced control and narrow dispersities. The improved initiation efficiency was attributed to a lack of chelate stabilisation for the Zn-OEt initiating group. A similar effect may occur with **LZn$_2$Et**/**LZn$_2$OBn**, where increased stabilisation due to chelation prevents the Zn-O(ligand) groups from initiating ROP, in spite of the apparent similarity in pK_a between the benzoxide initiator and the substituted benzoxide groups of the Trost ligand.

Table 2. ROP of *rac*-LA with isolated **LZn$_2$OBn**:

Entry	Time (min)	Conv[a] (%)	$M_{n,obs}$[b] (Da)	$M_{n,calc}$[c] (Da)	$Đ$[b]	% active cat.
1[d,e]	0.08	38	8600	5500	1.23	64
2[d,f]	0.33	66	12000	9500	1.42	80
3	0.67	74	13100	10700	1.42	82
4[d,g]	1.25	92	16400	13300	1.36	81
5	2	99	19900	14300	1.35	72
6[h]	4	91	29300	26200	1.20	45
7[i]	20	71	49100	51200	1.09	21
8[i,j]	5	82	46700	59100	1.08	25
9[k]	20	24	26000	34600	1.06	13
10[j,k]	10	43	52300	62000	1.12	12

100:1 [LA]:[**LZn$_2$OBn**], [LA] = 1 M in toluene, 60 ºC. LA and **LZn$_2$OBn** pre-stirred separately for 3 min in toluene at 60 ºC before mixing. [a] Conversion calculated using ^{1}H NMR spectroscopy. [b] $M_{n,obs}$ and $Đ$ determined by gel permeation chromatography using polystyrene standards in THF. Values corrected by Mark-Houwink factor (0.58).[49] [c] $M_{n,calc}$ of polymers calculated from the monomer conversion $M_{n,calc} = M_0$ x ([M]/[I]) x conversion assuming 1 chain per catalyst centre. [d] Determined by homodecoupled ^{1}H NMR spectroscopy. [e] $P_s = 0.48$ [f] $P_s = 0.52$ [g] $P_s = 0.50$ [h] 200:1 [LA]:[**LZn$_2$OBn**]. [i] 500:1 [LA]:[**LZn$_2$OBn**]. [j] 120 ºC. [k] 1000:1 [LA]:[**LZn$_2$OBn**].

Based on the activities and control observed with LA, **LZn$_2$OBn** was also tested for ε-CL ROP. Isolated **LZn$_2$OBn** displayed excellent catalytic activity (k_{obs} = 5.3 x 10^{-3} s^{-1}, Fig. 2, left), and is one of the few bis-Zn catalysts reported for ε-CL ROP. Other bis-Zn systems include an anilido-aldimine zinc-alkyl complex reported by Mu *et al*., which converts 98 % of ε-CL in 1 min at 70°C ([ε-CL]:[cat]:[I] = 100:1:2; [ε-CL] = 3 M in toluene),[60] and a dinuclear amido zinc-alkyl complex employed by Chakraborty and Chen to form 62 % yield of PCL after 2 h at room temperature ([ε-CL]:[cat]:[I] = 200:1:0; [ε-CL] = 1 M in toluene).[61] With both *in situ* generated and isolated

LZn$_2$OBn, the initiation of ε-CL ROP was faster than that observed for *rac*-LA, which was attributed to the improved solubility of ε-CL in toluene and the high ring strain of ε-CL. Rapid alcoholysis, initiation and early propagation followed by a slower first-order propagation has been reported for other ROP systems.[48,62] The similar activities of the *in situ* generated and isolated catalysts could arise from the improved solubility and stronger Lewis basicity of ε-CL compared to LA, as suggested by the FT-IR carbonyl shifts [υ(C=O) = 1770 cm^{-1} for LA; υ(C=O) = 1732 cm^{-1} for ε-CL].[63] Therefore, ε-CL may reduce the aggregation state of isolated **LZn$_2$OBn** catalyst to a monomer, i.e. the same species as when **LZn$_2$OBn** is formed *in situ*. The slower propagation rate for ε-CL may also give the catalyst more time to rearrange in solution upon monomer addition. Complex **LZn$_2$OBn** also demonstrated good polymerisation control, with narrow to moderate dispersities and good agreement between the observed and calculated M_n (Fig. 2, right).

MALDI-ToF analysis shows only α-benzoxy, ω-hydroxy end-capped PCL. The absence of ligand end groups supports the hypothesis that the Zn-O(ligand) bonds do not initiate ROP; instead, the ligand becomes involved in transesterification in the late stages of the reaction. With ε-CL as the monomer, there is a greater separation between the Zn-O(ligand) unit and the first carbonyl group on the growing polymer chain, disfavouring nucleophilic attack (Scheme S1).

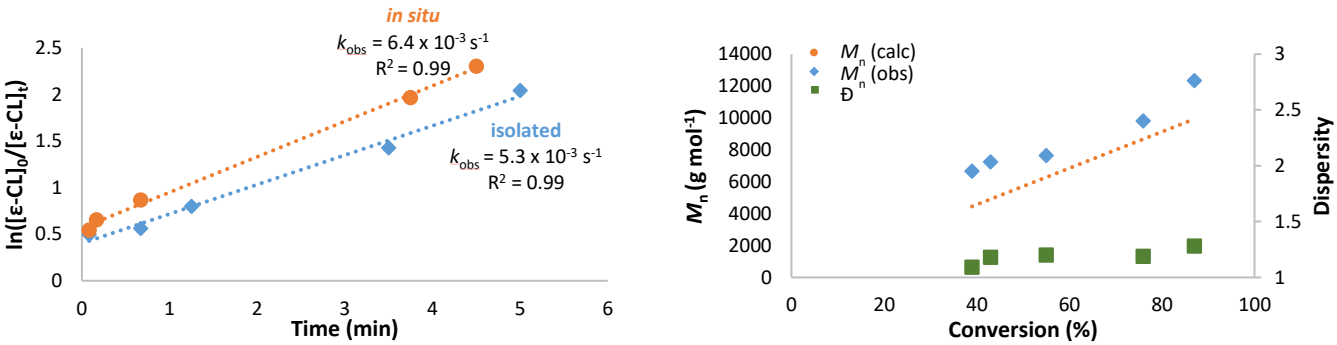


Figure 2. LHS: Plots of ln([ε-CL]$_0$/[ε-CL]$_t$) *vs*. time (min) for the ROP of ε-CL with *in situ* generated and isolated **LZn$_2$OBn** (100 eq. of ε-CL in toluene, [ε-CL] = 1 M, 60 °C). RHS:

Comparison between experimental and calculated M_n values and dispersity values at increasing conversions of ε-CL in presence of isolated **LZn$_2$OBn**.

Catalyst **LZn$_2$OBn** also displayed good activities for *rac*-β-BL ROP. Optimising the reaction conditions showed that the highest catalytic activities were observed under neat conditions, which also gave improved stereocontrol and molecular weight control compared to reactions performed in toluene (Figure 3, Table S4). It is difficult to draw comparisons between the theoretical and experimental (SEC) M_n values for PHB, as no reliable correction factor has been reported and SEC analysis of higher molecular weight PHB is known to be problematic.[64] Similarly to ε-CL ROP, the initiation was faster than propagation, particularly in toluene, which was attributed to the rapid dissolution of *rac*-β-BL. A maximum conversion of 60% was reached, which is attributed to the polymerisation/depolymerisation equilibrium under the conditions tested. Within *rac*-β-BL ROP, there are a limited number of catalysts that combine speed with M_n and tacticity control.[65] In nature, PHB produced by bacteria is isotactic with all stereocentres in the *R* configuration, resulting in high crystallinity and low thermostability and making this polymer industrially irrelevant.[66,67] Generation of syndiotactic-enriched PHB therefore opens up an exciting possibility of preparing materials with novel properties. Syndiotactic control has been achieved using complexes of La (P_s = 0.86), Sc (P_s = 0.60),[64] Sn (P_s = 0.70),[68,69] and Y (P_s = 0.94, 0.87).[64,70] To the best of our knowledge, **LZn$_2$OBn** is the first zinc-based catalyst to generate PHB with syndiotactic control, with P_s values in the range 0.65-0.70.[71–75]

Similar to PLA, MALDI-ToF analysis of PHB revealed α-benzoxy, ω-hydroxy end-capped chains, with a second series possibly featuring ligand end groups at high conversions. This might suggest that transesterification with the ligand occurs in the late stages of *rac*-β-BL ROP, as

propagation slows down. Importantly, the Zn-O(ligand) unit is closer to the adjacent PHB carbonyl group compared to PCL (refer to ESI for details), which presumably facilitates ligand reactivity. Elimination reactions to form crotonate or carboxy PHB end groups can be catalysed by [(BDI)Zn(O^{i}Pr)],[72] Al(O^{i}Pr)$_3$[76] and tin-based catalysts.[77–79] While MALDI-ToF analysis showed no evidence of crotonate or carboxy end groups, trace resonances of the crotonate groups were observed by ^{1}H NMR spectroscopy (5.81 and 7.00 ppm), suggesting that **LZn$_2$OBn** may promote elimination reactions (refer to ESI for further details). These findings agree with the M_n values determined by ^{1}H NMR spectroscopy (Table S4), which were approximately half the calculated M_n values.

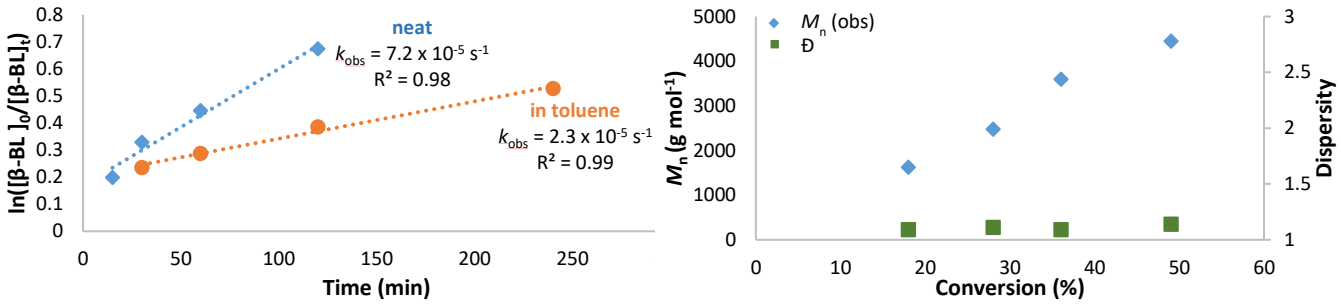


Figure 3. LHS: Plots of ln([β-BL]$_0$/[β-BL]$_t$) *vs*. time (min) for *rac*-β-BL ROP with isolated **LZn$_2$OBn** (when in toluene: 100 eq. of *rac*-β-BL in toluene, [β-BL] = 2.45 M). RHS: Plot of experimental M_n (SEC) and dispersity values *vs*. *rac*-β-BL conversion (%) (isolated **LZn$_2$OBn**, neat conditions, 60 °C).

As **LZn$_2$OBn** successfully initiated *rac*-LA, ε-CL and *rac*-β-BL ROP, the preparation of diblock copolymers was investigated. Firstly, **LZn$_2$OBn** was used in the rapid, selective and well-controlled synthesis of poly(ε-caprolactone-*block*-lactic acid) through a one-pot method with sequential monomer introduction. The order of addition was essential to selectively synthesise a

block copolymer; the PCL block had to be prepared first, followed by the addition of LA. This observation correlates with the reactivity ratios of LA and ε-CL, as well as previous studies with other catalysts.[33–38] Similar sequential monomer addition strategies have also been employed to prepare di- to octa-stereoblocks of D-LA and L-LA.[80,81] The block copolymer was characterised using GPC analysis, with an increase in M_n from 8100 g mol^{-1} to 32900 g mol^{-1} upon *rac*-LA addition (using uncorrected M_n values due to two different monomers, Fig. S41). DSC analysis gave single T_m (54.7 °C) and T_g (-61.3 °C) values, which match literature reports for PCL suggesting that no randomisation occurs (Fig. S42).[82,83] The absence of T_m and T_g values for the PLA block was attributed to the amorphous nature and the overlap of the T_m and T_g values of PCL and PLA, respectively. DOSY analysis revealed a single diffusion coefficient for both the PCL and PLA blocks, suggesting that the two blocks are connected (Fig. S38). Providing further support for the formation of a block copolymer, ^{1}H NMR resonances were present for PCL and PLA blocks, with only trace resonances observed for the CL-LA linking units at 2.3 and 4.1 ppm (Fig. S39). The ^{13}C NMR spectrum showed only resonances corresponding to the PCL and PLA blocks (Fig. S40).[84] In contrast, initial preparation of the PLA block followed by addition of ε-CL generated a random/gradient copolymer (Figure S43). The random/gradient copolymer structure was assigned from the ^{1}H NMR spectra based on the ratio between the block PLA/PCL resonances and the linkages between these blocks. The relative integrals of the CL-LA *vs*. CL-CL linkages were 1.00 *vs*. 0.63 irrespective of whether *rac*-LA was added first or simultaneously with ε-CL, suggesting a relatively weak gradient copolymer structure (refer to ESI for further details). This randomisation is attributed to the rate of transesterification becoming competitive with the rate of propagation; the rate of *rac*-LA ROP (k_{obs} = 3.5 x 10^{-2} g mol^{-1}) was approximately seven times faster than ε-CL ROP (k_{obs} = 5.3 x 10^{-3} s^{-1}) under identical reaction conditions (*vide supra*). When

starting with ε-CL followed by *rac*-LA, the faster propagation of *rac*-LA prevents transesterification, effectively supressing this side reaction to enable the selective synthesis of block copolymers. There are some reports that living PLA* chains do not initiate ε-CL polymerisation, however this challenge has previously been overcome using aminodiol supported Ti-alkoxides, dimethyl(salicylaldiminato)Al complexes and an *in situ* generated (diphenolate)Al-alkoxide complex to selectively generate di- and triblock copolymers.[37,85,86] To the best of our knowledge, **LZn$_2$OBn** is the fastest and most controlled catalyst reported for the selective production of poly(ε-caprolactone-*block*-lactic acid).[33–38] The polymerisation reached completion in just 7 minutes (PCL block, 50 equivalents ε-CL, 93% conversion in 5 minutes; PLA block, 50 equivalents *rac*-LA, 95% conversion in 2 minutes) with narrow *Đ* (1.1). In contrast, other catalysts often require prolonged reaction times (1-96 h, albeit under a range of different reaction conditions) and typically generate poly(ε-caprolactone-*block*-lactic acid) with broader dispersities (1.2-1.8).[33–38]

To selectively prepare poly(β-butyrolactone-*block*-lactic acid) in one-pot, a similar strategy was exploited, beginning with *rac*-β-BL ROP followed by *rac*-LA ROP. The resultant polymer was identified as poly(*rac*-β-butyrolactone-*block*-lactic acid) on the basis of DOSY studies, GPC analysis and ^{1}H NMR spectroscopic analysis (Fig. S50 – S52). Reversing the order of monomer addition also generated poly(*rac*-β-butyrolactone-*block*-lactic acid) with good control, demonstrating that *rac*-β-BL ROP can be initiated by a living PLA* chain. Unfortunately, the selective one-pot synthesis of block poly(ε-caprolactone-*block*-*rac*-β-butyrolactone) was unsuccessful, independent of whether the PCL or PHB block was prepared first. Both GPC analysis and DOSY studies suggested that PCL and PHB homopolymers were produced (Fig. S44

– S47), which was attributed to the slower propagation of ε–CL and *rac*-β-BL enabling side reactions such as transesterification and polymerisation/depolymerisation equilibria.

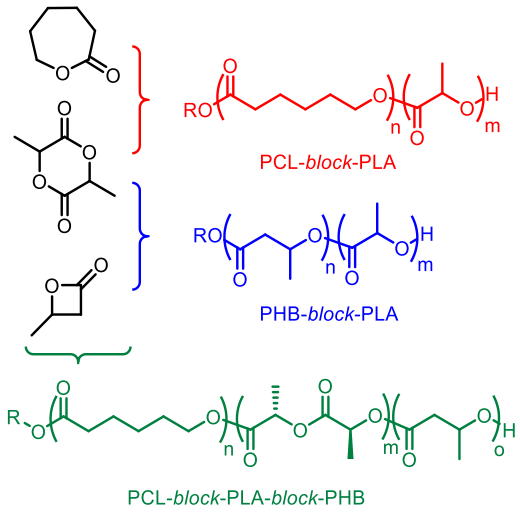


Figure 4. Copolymerisation of *rac*-LA, ε–CL and *rac*-β-BL to produce di- and ter-block copolymers using isolated **LZn$_2$OBn** (toluene, 60 °C).

As **LZn$_2$OBn** selectively prepared diblock poly(ε-caprolactone-*block*-lactic acid) and poly(*rac*-β-butyrolactone-*block*-lactic acid), the preparation of poly(ε-caprolactone-*block*-lactic acid-*block*-*rac*-β-butyrolactone) terpolymers was investigated (Table 3). The order of addition was again key to achieving good selectivity and suppressing transesterification. In line with observations from the diblock copolymer synthesis, sequential addition of ε-CL, *rac*-LA then *rac*-β-BL gave the optimum selectivity. The block structure of the terpolymer was identified through GPC and DSC analysis, DOSY studies and ^{1}H NMR spectroscopic analysis (Fig. S53 – S56). Notably, switching the order to ε-CL followed by *rac*-β-BL then *rac*-LA gave a bimodal distribution in the GPC analysis, suggesting that a mixture of homo- and co-polymers was formed. A difference from the diblock studies was that addition of *rac*-β-BL as the final monomer gave improved control over

the selectivity. Under the optimised conditions, the maximum conversion of *rac*-β-BL obtained was around 60%, whereas high monomer conversions of 96% were observed for both ε-CL and *rac*-LA. These findings suggest that unreacted *rac*-β-BL interfered with the polymerisation of ε-CL and *rac*-LA, presumably through competition with the other monomer(s) for coordination to **LZn$_2$OBn**, ring-opening and insertion into the growing polymer chain. To the best of our knowledge, **LZn$_2$OBn** is the first catalyst that can selectively prepare block terpolymers based on ε-CL, *rac*-LA and *rac*-β-BL, demonstrating high catalyst activities as well as excellent control over the block structure.

Table 3: Copolymerisation of ε-CL, *rac*-LA and *rac*-β-BL *via* sequential monomer addition with isolated **LZn$_2$OBn**:

Entry	**1st M**	**2nd M**	**3rd M**	**M:M:M ratio**	**% conv. 1st M^a**	**% conv. 2nd M^a**	**% conv. 3rd M^a**	**$M_{n,obs}$^{b} (Da)**	**$Đ$^{b}**
1	ε-CL	-		33:0:0	96	-	-	9300	1.20
2^c	ε-CL	*rac*-LA		33:33:0	91	96	-	19100	1.12
3^d	ε-CL	*rac*-LA	β-BL	33:33:33	88	99	28	25900	1.13

M = monomer. *rac*-LA, ε-CL and **LZn$_2$OBn** were pre-stirred separately for 3 min in toluene at 60 ^{o}C before mixing and initiation of polymerization. [a] Conversion calculated using ^{1}H NMR spectroscopy. [b] $M_{n,obs}$ and $Đ$ determined by gel permeation chromatography using polystyrene standards in THF. [c] [ε-CL] = 0.52 M, [*rac*-LA] = 0.33 M in toluene. [d] [ε-CL] = 0.52 M, [*rac*-LA] = 0.33 M, [β-BL] = 0.33 M in toluene. β-BL was injected *via* a micropipette.

Conclusions

The *in situ* conversion of a metal-alkyl precursor to a metal-alkoxide species is a widely used method of initiating ROP, yet it can lead to different solution-state chemistries and influence the catalytic activity. Notably, isolated **LZn$_2$OBn** outperforms the *in situ* generated analogue by an

order of magnitude in *rac*-LA ROP. **LZn$_2$OBn** also displays excellent catalyst activities for a range of cyclic esters, including *rac*-LA, ε-CL and *rac*-β-BL; this exceptional activity and versatility has been exploited to achieve the selective one-pot synthesis of poly(ε-caprolactone-*block*-lactic acid) and poly(*rac*-β-butyrolactone-*block*-lactic acid). To the best of our knowledge, **LZn$_2$OBn** is the fastest catalyst reported for poly(ε-caprolactone-*block*-lactic acid), and the first catalyst to selectively prepare poly(ε-caprolactone-*block*-lactic acid-*block*-β-butyrolactone) in a one-pot synthesis, leading to a range of block polyesters. Dinuclear zinc complexes are amongst the front runners in cyclic ester ROP, and some of the best performing systems are dimeric with two sites that may operate independently. In contrast, **LZn$_2$OBn** contains just one initiating group. The high activities observed herein may therefore arise from cooperativity between the two metals, where one Lewis acidic Zn centre coordinates a cyclic ester, and the second Zn bears the alkoxide group (OBn or the polymer chain) to perform nucleophilic attack upon the coordinated monomer. The development of bi-metallic, mono-initiator catalysts offers a promising route to exploit metal-metal cooperativity and achieve both high activities and careful control over the polymer structure.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: xxxxxxx.

Experimental details, NMR, EA, MS characterisation data, polymer MALDI-TOF, GPC and DSC characterisation, kinetic and DOSY NMR studies, supplementary experiments.

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Notes

The authors declare no competing financial interest.

Acknowledgements

We would like to thank the CRITICAT Centre for Doctoral Training and Engineering and Physical Sciences Research Council (Ph.D. studentship to W. G.; Grant EP\L016419\1, funding to M. P. S.; Grants EP\S025200\1 and EP\P026095\2), Royal Society (J. A. G., Grant RSG\R1\180101), British Ramsay Memorial Trust (J. A. G.) and L'Oréal-UNESCO For Women in Science (J. A. G.) for funding. Dr Yuechao Xu is thanked for running DSC polymer analysis.

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