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Guanidinate Zn(II) Complexes as Efficient Catalysts for Lactide Homo- and Copolymerization under Industrially Relevant Conditions

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ABSTRACT: Poly(lactic acid) (PLA) is currently by far the most commercially relevant biodegradable polymer derived from bio-renewable sources. The industrial production of high molecular weight isotactic PLA is based on the ring-opening polymerization (ROP) of lactide (the dimeric lactone of lactic acid) promoted by Sn(II) 2-ethylhexanoate under solvent-free conditions at high temperatures (190−200 °C) in the presence of excess alcohol. Although a huge number of alternative catalysts have been reported in the literature, searching for better performance and lower toxicity, most studies were performed under conditions unsuitable for industrial processes, for example, at lower temperatures in solution. We report here the synthesis of two Zn(II) complexes supported by bulky monoanionic guanidinate ligands, which have been tested as catalysts for the ROP of L-lactide under both mild and industrially relevant conditions, that is, at 190 °C using technical grade L-lactide at a monomer/catalyst ratio up to 10^4 and excess alcohol. Interestingly, the Zn(II) catalysts also showed stability under the latter harsh conditions, showing activity comparable to that of the Sn catalyst and even lower monomer racemization. Moreover, they are able to copolymerize L-lactide with ε-caprolactone, affording either block or random copolymers depending on the reaction conditions.

KEYWORDS: poly(lactic acid), ring-opening polymerization, biopolymers, zinc catalysts, guanidinate ligands, poly(caprolactone), copolymers, high-temperature polymerization
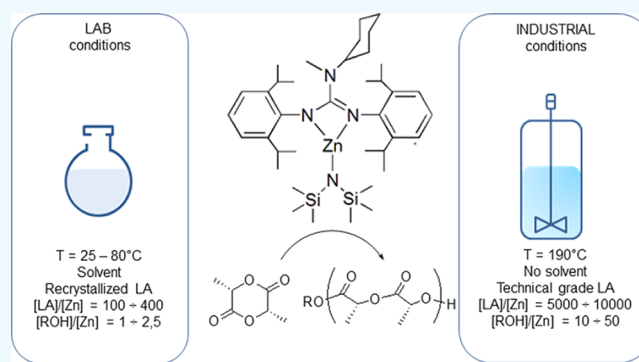
■ INTRODUCTION

The increasing environmental concerns about the end-of-life fate of non-degradable plastics used for packaging and non-durable applications, which already resulted in legislative restrictions to their use in many countries, stimulated both academic and industrial research efforts in developing new strategies to substitute traditional polymers by bio-based, bio-degradable alternatives.[1,2] Aliphatic polyesters, such as poly-(lactic acid) (PLA) and poly(ε-caprolactone) (PCL), are presently among the most interesting biodegradable alternatives to commodity polymers such as polyolefins, and they are already commercially available for uses in packaging, agricultural products, and for special applications in medicine.[3] In particular, PLA, with a world production exceeding 300 kt/year, which is increasing steadily, plays a prominent role since its monomer (lactide) is obtained by fermentation of glucose, derived from 100% annually renewable resources such as corn, sugarcane, or different biomass.[3] The industrial processes for the production of high molecular weight PLA are mainly based on the ring-opening polymerization (ROP) of L-lactide (L-LA)

in continuous reactors under solvent-free conditions at high temperatures (190−200 °C) using Sn(II) 2-ethylhexanoate [Sn(Oct)₂] as the catalyst and excess alcohol (which activates the tin complex and regulates the polymer molecular weight).[4] In fact, under the latter conditions, and at $[\text{L-LA}]_0/[\text{Sn}]_0$ molar ratio ≈10^4, Sn(Oct)₂ has a good performance in terms of activity and low racemization rate.[4] However, although the presence of residual Sn up to a limit of 20 ppm in commercial PLA has been approved by the US Food and Drug Administration, the cytotoxicity of these metal residues remains a matter of concern, especially for medical and food applications. For this reason, hundreds of different complexes based on non-toxic metals, including Mg, Ca, Zn, Fe, and Al,

have been reported in the literature in the last 20 years for the ROP of LA.[3,5−9] Although there are many examples of well performing catalysts[10−13] in terms of activity, controlled and, in some cases, stereoselective[14−16] polymerization, most of the reported catalysts have been tested under mild conditions, that is, in solution at temperatures ranging between 25 and 100 °C, which are very far from those of the industrial processes. Even in studies performed under solvent-free conditions, the typical temperatures tested range between 130 and 150 °C,[17−19] at which only the monomer is above the melting temperature, while the isotactic PLA (which is the only polymer produced in large scale) is not. The latter conditions would be impractical for industrial processes. Also, in most literature reports, the monomer is purified by recrystallization, while the industrial processes use a technical grade monomer.

Interestingly, Jones *et al.* reported Mg(II) and Zn(II) complexes bearing tridentate [N,N,O⁻] Schiff base ligands showing excellent performance under solvent-free conditions at 130 °C; some Zn complexes were also highly active at 180 °C using recrystallized L-LA and high monomer/catalyst ratios ([LA]/[Zn]/[ROH] = 10,000:1:100).[20]

More recently, Herres-Pawlis *et al.* reported some guanidine Zn[21] and Fe[22] complexes active in the ROP of lactide under conditions that were considered relevant for industrial processes. In particular, some complexes showed very high activities, "surpassing that of Sn(Oct)$_2$". They were tested at 150 °C using technical grade *rac*-lactide (which affords amorphous PLA). The activity of the Zn complex decreased rapidly by increasing the [monomer]$_0$/[catalyst]$_0$ ratio up to 5000:1.[21] The performance of the guanidine Fe complexes was compared with that of Sn(Oct)$_2$ at 150 °C using recrystallized L-LA and the [monomer]$_0$/[catalyst]$_0$ ratios ranging between 1000:1 and 5000:1.[21]

We report here the synthesis and characterization of two Zn(II) complexes bearing *anionic* guanidinate ligands[23] and their use as catalysts for the polymerization of L-LA, as well as its copolymerization with ε-caprolactone (ε-CL), *both* under mild conditions in solution at low [monomer]$_0$/[Zn]$_0$ ratios *and* under industrially relevant conditions, that is, at 190 °C without solvent using technical grade L-LA, excess alcohol, and high [monomer]$_0$/[Zn]$_0$ ratios (5000−10,000:1). The performance of the title catalysts was excellent in both cases, being comparable with that of Sn(Oct)$_2$ under the industrial conditions in terms of activity and even better in terms of low degree of racemization. Moreover, they efficiently promote the homo-polymerization of ε-CL and the random or block copolymerization of L-LA and ε-CL. As extensively reported in the literature, copolymerization of lactide and caprolactone has the potential to provide a variety of materials with tunable mechanical properties, shape memory behavior, degradation rate, and controlled drug release properties, which are of great interest for biomedical applications.[11,13,24−26] For this reason, the development of suitable catalysts able to control the comonomer incorporation in the caprolactone−lactide copolymers, affording structures ranging from random[25,26] to block,[11,13] is another important research target.

RESULTS AND DISCUSSION

Synthesis and Characterization of Guanidinate Zn(II) Complexes. The guanidine proligands HL1 and HL2 were synthesized adapting a previously reported procedure.[27] Zn(II) complexes **1** and **2** were easily obtained by reaction of 1 equiv

of HL1 or HL2 with Zn[N(SiMe$_3$)$_2$]$_2$ in benzene at 80 °C for 24 h (yields 90% ÷ 95%, see Scheme 1).

Scheme 1. Synthesis of Zn(II) Complexes 1−2[a]

LH1: R$_1$ = CH$_3$; R$_2$ = Cy
LH2: R$_1$ = R$_2$ = CH$_2$CH$_3$

1: L1ZnN(SiMe$_3$)$_2$
2: L2ZnN(SiMe$_3$)$_2$
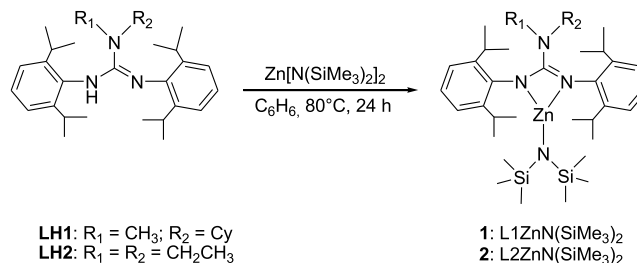
[a]Cy = cyclohexyl.

Heteroleptic monomeric structures for complexes **1** and **2** were assessed on the basis of full NMR analysis and of high-resolution mass spectra (see the Supporting Information, Figures S1−S6). Single crystals of complex **1** were obtained from hexane solutions cooled at −20 °C. The X-ray molecular structure is shown in Figure 1 (see Table S1 for selected bond distances and angles).
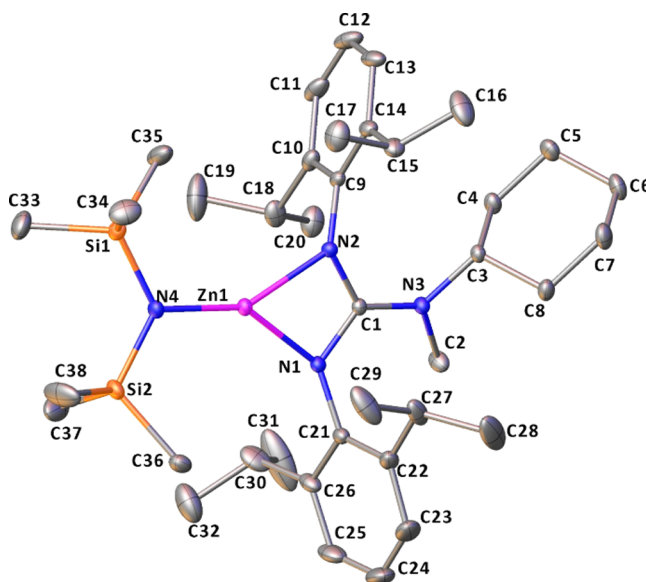

Figure 1. X-ray molecular structure of compound **1** (ORTEP). Hydrogen atoms were omitted for clarity. Ellipsoids were drawn at 10% probability level. The selected bond distances are Zn1−N4: 1.858(2) Å, Zn1−N2: 2.012(2) Å, Zn1−N1: 2.018(2) Å, Zn1−C1: 2.443(2) Å, N1−C1: 1.344(3) Å, N2−C1: 1.349(3) Å, and N3−C1: 1.358(3) Å. The selected bond angles are N2−Zn1−N1: 66.88(8)°, N4−Zn1−N2: 148.20(9)°, and N4−Zn1−N1: 144.86(9)°.

The zinc atom is three-coordinated, adopting an almost perfect trigonal planar geometry with an angular sum of 359.9(1)°. The Zn atom deviates by 0.039 Å from the triangle mean plane defined by N1, C1, and N2 atoms. The isopropyl-substituted aromatic moieties are almost perpendicular to the bidentate ligand plane. In detail, the dihedral angles between the triangle mean plane and the aromatic least-square planes are 83.67° (for C9···C14 mean plane) and 76.02° (for C21··· C26 mean plane), respectively.

The amido nitrogen atom N4 features the shortest distances with the Zn atom, 1.867(8) Å, while nitrogen atoms N1 and

N2 feature the longest distances, 2.018(2) and 2.012(2) Å, respectively.

These features agree with the known three-coordinated Zn compounds, as reported by us[13] and others.[28−30]

Ring-Opening Homo-polymerizations of Lactide and ε-CL under Mild Conditions. Complexes **1** and **2** were evaluated as catalysts for the ROP of L-LA under different conditions. Polymerization screenings were initially performed in solution at 25 °C (Scheme 2), and the obtained polymers were characterized by NMR and size exclusion chromatography (SEC) analyses. Some representative results are collected in Table 1.

Scheme 2. ROP of L-LA Initiated by Zn Complexes 1 and 2
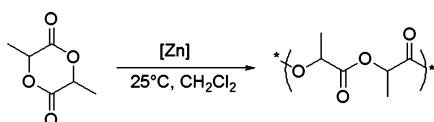
The reaction of Zn complex **1** with 200 equiv of L-LA in dichloromethane at 25 °C was sluggish, resulting in only 10% conversion in 1 h (run 1); however, in the presence of 1 equiv of isopropanol, **1** gave a 81% conversion in 15 min under the same conditions (run 2), suggesting that the bulky bis-(trimethylsilyl)amido ligand is a poor initiating group, as frequently observed. Complex **2** gave 72% monomer conversion in the presence of 1 equiv of alcohol under the same conditions (run 3), while use of tetrahydrofuran (THF) as a solvent resulted in a 95% conversion in 30 min (run 4). Increasing the alcohol/Zn complex **1** to 2.5 resulted in a higher conversion (98%) in the same time while maintaining a good agreement between the experimental and theoretical molecular weight (cf. runs 2 vs 5). A slightly lower reactivity was observed under the same conditions using THF as the solvent (see run 6). Finally, **1** converted almost quantitatively 400 equiv of L-LA in the presence of 2.5 equiv of alcohol in toluene at 80 °C. A polymerization run was also performed using rac-lactide under the same conditions of run 2, resulting in similar conversion and polymer molecular weight (cf. runs 2 vs 11). ^{1}H NMR analysis of the resulting polymer indicated that atactic PLA was produced, excluding any catalyst stereoselectivity (see Figure S11).

A kinetic study was performed by monitoring the polymerization of 300 equiv of L-LA promoted by complex **1** and 1 equiv of isopropanol (run 8), analyzing the ^{1}H NMR samples removed every 10 min, and plotting $\ln([\text{L-LA}]_0/[\text{L-LA}]_t)$ vs time (see Figure 2). A first-order dependence on the
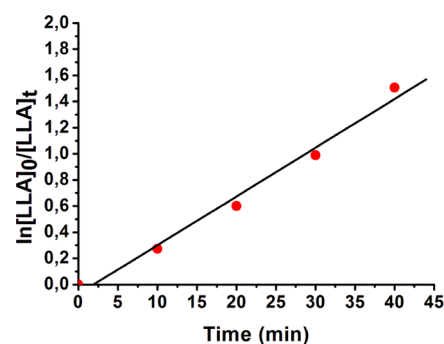

Figure 2. Pseudo-first-order kinetic plot for the ROP of L-LA promoted by **1**: $[\mathbf{1}]_0$ 5 mM; $[\text{L-LA}]/[\mathbf{1}]/[i\text{PrOH}] = 300/1/1$; $T = 25$ °C; and solvent=CH$_2$Cl$_2$. The kinetic data are the average of at least two experiments. $R = 0.998$. The pseudo-first-order rate is $(3.7 \pm 0.1) \times 10^{-2}$ min^{-1}.

concentration of lactide was found, with an apparent propagation rate constant of $(3.7 \pm 0.1) \times 10^{-4}$ min^{-1} at 298 K. The number-average molecular weight $[M_{\text{n(expt)}}]$ of the resulting PLA samples was found to increase linearly with time and with conversion (see Figure 3A,B).

An oligomeric PLA, prepared using L-LA/**1**/iPrOH in 20:1:1 mole ratio, was analyzed by ^{1}H NMR showing isopropyl ester $-\text{OCH(CH}_3)_2$ and hydroxyl $-\text{CH(CH}_3)\text{OH}$ end groups (see Figure S7). This finding suggests that the initiation occurs via the nucleophilic attack of the isopropoxide group to the coordinated monomer and that the termination occurs by hydrolysis of the growing chain. The same sample was also analyzed by MALDI ToF spectrometry, confirming that it consists only of linear oligomers H$-[\text{OCH(CH}_3)\text{C}(=\text{O})]_n-$OCH(CH$_3$)$_2$ (see Figure S8), while no cyclic oligomers were detectable. The above picture is confirmed by in situ ^{1}H NMR monitoring (CD$_2$Cl$_2$, 600 MHz, 25 °C) the reaction of complex **1**, isopropanol (1 equiv), and L-LA (2 equiv): the resonances attributed to the Zn$-$N(SiMe_3)$_2$ protons are replaced by those of the free amine HN(SiMe_3)$_2$, following

Table 1. ROP of L-LA, rac-LA, and ε-CL in Solution under Mild Conditions

run[a]	cat	[M]/[Zn]	[ROH]/[Zn]	solvent	T (°C)	time (min)	conv[b] (%)	TOF[c] (h^{-1})	M_{nSEC}[d] (kDa)	M_{nTHEO}[e] (kDa)	Đ[d]
1[f]	1	200	0	CH$_2$Cl$_2$	25	60	10	10	n.d.	n.d.	n.d.
2[f]	1	200	1	CH$_2$Cl$_2$	25	15	81	648	15.6	23.3	1.09
3[f]	2	200	1	CH$_2$Cl$_2$	25	15	72	576	19.2	20.7	1.05
4[f]	2	200	1	THF	25	30	95	380	27.6	27.4	1.20
5[f]	1	200	2.5	CH$_2$Cl$_2$	25	15	98	784	10.3	11.3	1.13
6[f]	1	200	2.5	THF	25	20	90	540	11.5	10.4	1.05
7[f]	1	400	2.5	toluene	80	30	99	792	16.0	16.3	1.28
8[f]	1	300	1	CH$_2$Cl$_2$	25	40	98	441	34.5	42.4	1.44
9[g]	1	200	1	CH$_2$Cl$_2$	25	30	84	336	19.2	19.2	1.10
10[g]	2	200	1	CH$_2$Cl$_2$	25	30	75	300	17.7	17.1	1.06
11[h]	1	200	1	CH$_2$Cl$_2$	25	15	76	608	16.8	21.9	1.06

[a]Reaction conditions: 10 μmol of Zn complex dissolved in 2 mL of solvent using recrystallized L-LA; ROH = iPrOH. [b]Conversion of monomer as determined by ^{1}H NMR spectral data. [c]TOF = (mol of monomer consumed/mol of Zn catalyst) × h^{-1}. [d]Measured by SEC vs polystyrene standards using the correction factor 0.58. [e]M_{nTHEO} (in g mol^{-1}) = MW$_{\text{monomer}}$ × ([M]$_0$/[Zn]$_0$) × conversion of monomer. [f]Monomer was L-LA. [g]Monomer was ε-CL. [h]Monomer was rac-LA.
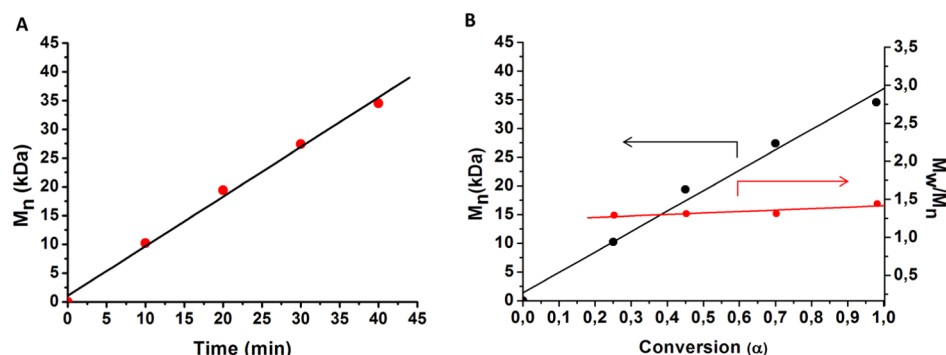
Figure 3. Plots of number-average molecular weights, M_n (kDa), *vs* time (min) (A) and *vs* monomer conversion determined by ^{1}H NMR (B) for a poly(L-lactic acid) (PLLA) produced by catalyst **1**.

the alcoholysis of the Zn−N amido bond (see Figure S10). Following the suggestion of a reviewer, we have also analyzed a polymer sample prepared in the absence of alcohol (sample of run 1 of Table 1): in this case, only cyclic low molecular weight PLAs were observed by MALDI ToF analysis, while macromolecules end-capped with amidinate or guanidinate end groups were not detected (see Figure S9).

Complexes **1** and **2** were also evaluated as catalysts for the ROP of ε-CL (Scheme 3).

Scheme 3. ROP of ε-CL Initiated by Zn Complexes 1 and 2
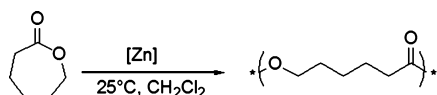
Both complexes initiated the polymerization of ε-CL at room temperature in CH_2Cl_2 at $[\varepsilon\text{-CL}]_0/[Zn]_0/[ROH]_0 =$ 200:1:1, giving 84 and 75% conversions in 30 min, respectively (Table 1, runs 9 and 10). The reactivity of Zn complexes toward ε-CL was lower than that toward lactide under the same polymerization conditions (*cf.* run 2 *vs* run 9 and run 3 *vs* run 10 in Table 1), while the opposite situation is more common, with a few exceptions.[31]

The obtained polymers were characterized by ^{1}H NMR (see Figure S12) and SEC analyses. Polymers showed a monomodal and narrow molecular weight distribution with experimental (corrected) number-average molecular weights in perfect agreement with the calculated values.

ROP of L-LA under Industrially Relevant Conditions. As mentioned in the Introduction section, while most literature studies concerning catalysts for the ROP of LA are focused on optimization of the performance under mild conditions (room temperature, recrystallized monomer at low monomer/catalyst ratios, using solvents such as dichloromethane, THF, or toluene), the industrial processes work under much harsher conditions, in the melt at $T = 190-200\ °C$, using an unpurified technical grade monomer at very high monomer:catalyst molar ratios (5000−10,000) and excess alcohol with respect to $Sn(Oct)_2$ to regulate the molecular weight by terminating the chain growth and initiating a new chain. Under the latter conditions, the polymerization is defined "immortal". Thus, we have tested complex **1** under more severe conditions relevant for industrial applications, that is, at 190 °C without solvent, using a technical grade monomer at increasing monomer/catalyst and alcohol/catalyst ratios (see Table 2). Under the latter conditions, Zn catalyst **1** plus 2 equiv of benzyl alcohol converted almost quantitatively 200 equiv of LA in 5 min (run 12). Notably, at $[LA]_0/[Zn]_0 = 5000$, the monomer conversion in 1 h was 77% using 10 equiv of alcohol (run 13) and 94% using 50 equiv of alcohol (run 14). For comparison, $Sn(Oct)_2$ gave 94% conversion in 1 h using $[LA]_0/[Zn]_0 = 5000$ and 10 equiv of alcohol (run 18). Thus, the activity and stability of Zn catalyst **1** is comparable to that of $Sn(Oct)_2$ even under the severe conditions used in industrial processes, as also confirmed by comparative kinetic experiments, resulting in pseudo-first-order rate constants $k_{(Sn)} = 2.1 \pm 0.1 \times 10^{-2}\ s^{-1}$ and $k_{(Zn)} = 1.6 \pm 0.1 \times 10^{-2}\ s^{-1}$, respectively (see the Experimental Section and Figure S16).

MALDI-ToF MS analysis of a low molecular weight PLA sample produced at 190 °C by using Zn catalyst **1** and benzyl alcohol showed the presence of linear macromolecules having −OH and $-OCH_2Ph$ end groups. A minor distribution of oligomeric cyclic macromolecules was also observed, as usually

Table 2. ROP of L-LA in the Melt at High Temperature[a]

run	BnOH (equiv)	L-LA (equiv)	time (min)	conversion %[b]	$M_{n(expt)}$[c] (kDa)	$M_{n(theo)}$[d] (kDa)	Đ[c]
12	2	200	5	98	16.5	14.1	1.7
13	10	5000	60	77	55.0	55.5	1.5
14	50	5000	60	94	20.7	12.0	1.6
15	25	10,000	95	87	52.0	50.1	1.4
16	50	10,000	120	94	43.2	27.1	1.4
17[e]	50	10,000	120	97	n.d.[f]	n.d.	n.d.
18[e]	10	5000	60	94	88.4	67.7	2.0
19[e]	100	10,000	120	94	14.0	13.5	1.7

[a]Reaction conditions: catalyst **1** = 10 μmol, no solvent, and $T = 190\ °C$. [b]Determined from ^{1}H NMR. [c]Determined by SEC in THF *vs* polystyrene standards. [d]$M_{n(theo)}$ calculated according to $144.13 \times ([LA]_0)/([BnOH]_0) \times$ monomer conversion. [e]Catalyst = $Sn(Oct)_2 = 10$ μmol. [f]n.d. = not determined.

found for polymerizations at high temperatures, due to intramolecular transesterification reactions, while polymer fractions end-capped by either amido or guanidinate fragments were not detected (see Figure S14). As suggested by a reviewer, a similar polymerization run was performed in the absence of alcohol: in this case, ^{1}H NMR analysis showed the presence of some macromolecules end-capped with $-$N-$(SiMe_3)_2$ end groups, but again, no guanidinate end groups were detected (see Figure S15).

One of the essential requirements of a potential industrial catalyst is the low degree of L-LA racemization under the harsh process conditions. Interestingly, the homonuclear-decoupled ^{1}H NMR spectrum (see Figure 4A) of a sample of PLA
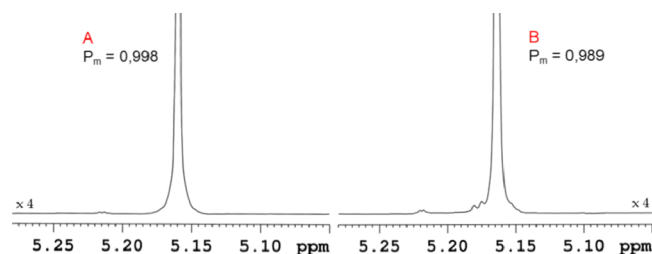

Figure 4. Expansion of the methine region of a homonuclear-decoupled ^{1}H NMR [CDCl$_3$, 400 MHz, spectra of PLA samples polymerized by **1** (A, sample of run 16) and by Sn(Oct)$_2$ (B, sample of run 17)].

obtained using zinc catalyst **1** (run 16 of Table 2) showed that stereo errors are practically absent (P_m = 0.998). For comparison, a sample of PLA obtained with Sn(Oct)$_2$ under similar conditions (run 17 of Table 2) has a P_m = 0.989 (Figure 4B). Differential scanning calorimetry (DSC) analysis of the two samples also showed similar features: T_m = 168.8 °C and ΔH_m = 55.7 J/g for the sample prepared by Zn (run 16), T_m = 170.4 °C, and ΔH_m = 54.2 J/g for the sample prepared by Sn (run 17) (see Figures S17 and S18). The molecular weights and molecular weight distributions show some deviations from the theoretical ones, especially for polymerizations performed at very high monomer/catalyst ratio and excess alcohol: this typically also occurs for the Sn catalyst under the industrial conditions.

Ring-Opening Copolymerization of Lactide and ε-CL. With Zn complexes/alcohol system successfully affording the homo-polymerization of both lactide and ε-CL, we investigated their block copolymerization. We found that the order of monomer addition was critical, as ε-CL could not be polymerized after LA, as frequently observed:[12,15,32] in fact, a two-step polymerization starting with L-LA and followed by the addition of ε-CL after full consumption of the first monomer did not result in the formation of any copolymer. On the other hand, reversing the order of addition of the monomers led to formation of a PCL-*b*-PLLA block copolymer. In fact, a di-block copolymer was obtained by allowing to react 10 μmol of Zn complex **1**, 1 equiv of isopropanol, and 200 equiv of ε-CL at 25 °C in CH$_2$Cl$_2$ for 30 min and then adding 200 equiv of L-LA, continuing the polymerization for further 30 min (see the Experimental Section). The formation of a di-block copolymer was confirmed by the increase of the molecular weight after the addition of the second monomer and by the monomodal SEC curve (see Figure 5). Accordingly, the ^{1}H and ^{13}C NMR spectra revealed the exclusive presence of CL$-$CL and LA$-$LA

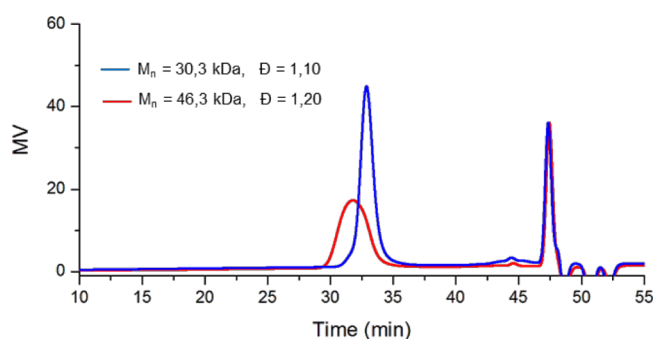homo-sequences, while hetero-sequences were not detected (see Figures S19 and S20).

Figure 5. SEC traces overlay for PCL (first block, blue curve) and PLLA-*b*-PCL (red curve).

Random ε-CL/L-LA copolymerization was also investigated: reactions under the mild conditions used for the homo-polymerization, for example, in CH$_2$Cl$_2$ at 25 °C, did not afford any random copolymer. Thus, the copolymerization of L-LA and ε-CL was explored in toluene at 100 °C using complex **1** as the catalyst and variable feeds of L-LA and ε-CL. The main results are reported in Table 3.

^{1}H NMR analysis of the copolymers in CDCl$_3$ (see Figures S22 and S23) indicated a good agreement between the monomer incorporation into the macromolecules and the feed ratio. L-LA was always completely consumed, while some ε-CL (1 ÷ 8%) remained unreacted. The fractions of CL/LA hetero-dyads were determined from the ^{1}H NMR spectra as described in the literature.[26] All the obtained copolymers have highly random microstructures (hetero-dyads $\geq$ 48%).

The chain microstructure of the copolymers with different compositions was determined by ^{13}C NMR spectroscopy.[33] The carbonyl region of the NMR spectrum of a random ε-CL/L-LA copolymer is shown in Figure 6.[34] The average length of the blocks (L_{CL} and L_{LA}) was calculated as previously reported in the literature.[34] It is noteworthy that the signal at 171 ppm, due to the triad having a half-lactide unit between two CL units, is indicative of the occurrence of transesterification reactions, involving the cleavage of lactidyl groups, which lead to the formation of CLC or CLLLC chain sequences (L = half lactidyl group and C = caproyl group). This finding confirms that copolymerization of LA and CL occurs only by transesterification processes activated at high temperature in agreement with the absence of copolymer formation at ambient temperature.

Thermal analysis of the copolymers by DSC between $-$100 and $+$200 °C (see Figure 7) did not show any melting peak, but only glass transitions with T_g values intermediate between those of the pure homopolymers (T_g = 58.8 °C for PLLA and T_g = $-$60.2 °C for PCL) in good agreement with the theoretical ones calculated by the Fox equation.

Finally, Zn complex **1** was also tested in the copolymerization of L-LA and ε-CL in bulk at 190 °C. The Zn catalyst also showed high stability and activity under these harsh conditions, affording copolymers with compositions coherent with the monomer feed ratio and random sequences (see runs 25 and 26, Table 3).

Table 3. Ring-Opening Copolymerization of L-LA and ε-CL

run	F_{CL}/F_{LA}[a]%	time (min)	T (°C)	C_{CL}/C_{LA}[b] (%/%)	F_{CL}[c] (%)	hetero-dyads[c]%	L_{CL}/L_{LA}[d]
20[e]	0/100	30	100	0/100			
21[e]	30/70	60	100	93/100	35	81	1.19/1.68
22[e]	50/50	60	100	99/100	53	60	1.41/1.11
23[e]	70/30	60	100	97/100	70	48	2.04/0.92
24[e]	100/0	30	100	100/0	100		
25[f]	30/70	120	190	85/100	30	62	1.50/2.25
26[f]	50/50	120	190	83/100	47	73	1.41/1.55

[a]Monomer molar % composition in the feed. [b]% conversion of each monomer determined by ^{1}H NMR analysis of the final reaction mixture. [c]CL mol % content in the copolymer. [d]Average sequence length of the caproyl and lactidyl units as determined by ^{13}C NMR analysis. [e]Runs performed in 2 mL of toluene at 100 °C using Zn complex **1** = 10 μmol; total amount of CL + LA = 5 mmol; benzyl alcohol as a cocatalyst; and $[BnOH]_0/[Zn]_0$ = 1. [f]Runs performed in bulk at 190 °C using the same amounts of Zn, monomers, and alcohol as in [e].
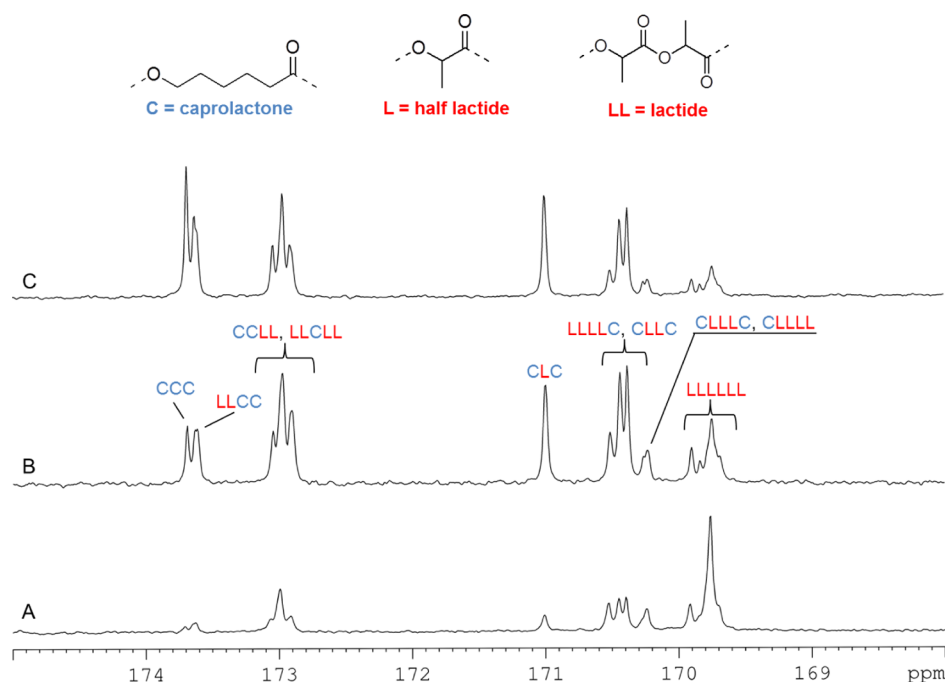

Figure 6. Carbonyl region of the ^{13}C NMR spectra (CDCl$_3$, 25 °C, 125 MHz) of the copolymer sample of run 22, Table 3.
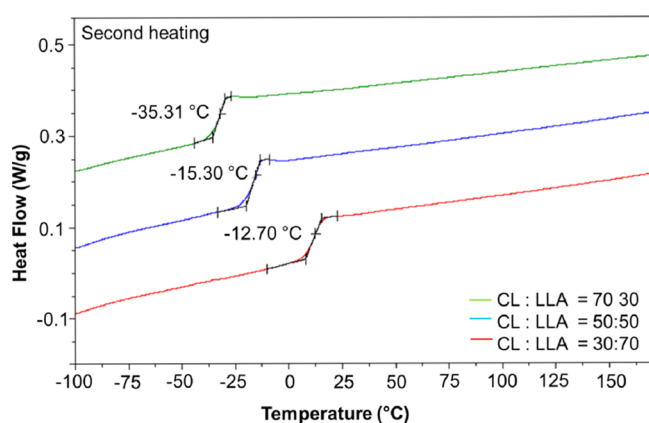

Figure 7. DSC thermograms of the copolymer samples of runs 21 (green), 22 (blue), and 23 (red), Table 3.

■ CONCLUSIONS

We have prepared two three-coordinate heteroleptic guanidinate Zn(II) complexes and used them as initiators for the ring-opening homo-polymerization and copolymerization of L-LA and ε-CL. Under mild conditions (e.g., in methylene chloride solution at 25 °C), the complexes promoted the homo-polymerization of the two monomers with high activity in a well-controlled reaction. More importantly, the catalyst stability and performance in the ROP of L-LA also remained excellent under conditions very similar to those used in industrial processes, that is, at T = 190 °C, using unpurified technical grade L-LA at very high monomer/catalyst molar ratios (5000−10,000) and excess alcohol. Under the latter conditions, the Zn catalyst **1** showed activity comparable with that of the industrial catalyst Sn(Oct)$_2$, while its performance in terms of isotacticity of the PLLA produced (owing to low monomer racemization) was even better.

Moreover, **1** promoted efficient copolymerization of L-LA and ε-CL: at room temperature in solution, a PCL-b-PLLA di-block copolymer was obtained, while in the melt at high temperature, random CL/LA copolymers could be produced owing to extensive transesterification reactions.

In conclusion, the title catalysts could be a realistic alternative for industrial processes aimed at elimination of Sn residues in PLA-based materials for medical and food packaging applications.

■ EXPERIMENTAL SECTION

Materials. All manipulations of moisture and air-sensitive chemicals were performed under an inert atmosphere as described previously.[13] All solvents, as well as the added alcohols, were dried as described previously.[13] Deuterated solvents were purchased from Aldrich and stored in the glovebox over 3 Å molecular sieves before use. Monomers (Sigma-Aldrich) were purified prior to use: lactide was purified by crystallization from dry toluene and then stored over P_2O_5; ε-CL was dried with CaH_2 for 24 h at room temperature, distilled under reduced pressure, and stored over 3 Å molecular sieves. Technical grade L-LA used for polymerizations at high temperature was purchased from Corbion (PURASORB®L: water content < 0.02%, total residual solvent < 0.1%) and used without purification.

All other chemicals were commercially available and used as received unless otherwise stated.

Characterization Methods. NMR spectra were recorded using either a Bruker Advance 300, or 400, or a Bruker 600 MHz Ascend 3 HD spectrometer as detailed in a previous paper.[13]

Molecular weights (M_n and M_w) and polydispersities ($Đ$) were measured by SEC at 30 °C on a Waters 1525 binary system equipped with a Waters 2414 RI detector as detailed in a previous paper.[13]

High-resolution and MALDI-TOF mass spectra were obtained on a Bruker solariX XR FT-ICR mass spectrometer as previously described.[13]

DSC analysis was performed on a TA Q2000 (TA Instruments) as previously described.[26]

X-ray Crystallography. A suitable crystal (0.45 × 0.32 × 0.29 mm) was inserted in a 0.3 mm Lindemann under inert atmosphere in a dry box and measured at 296 K with a Bruker D8 QUEST diffractometer equipped with a PHOTON 100 detector using Cu Kα radiation (λ = 1.54178 Å). Indexing was performed using APEX3.[35] Data integration and reduction were performed using SAINT.[35] Absorption correction was performed by a multi-scan method in SADABS.[35]

The structure was solved by direct methods using SIR2014[36] and refined by means of full matrix least squares based on F^2 using the program SHELXL.[37]

Non-hydrogen atoms were refined anisotropically, and hydrogen atoms were positioned geometrically and included in structure factor calculations, but not refined. Crystal structures were drawn using OLEX2.[38]

Crystal data and refinement details: formula $ZnC_{38}H_{66}N_4Si_2$, FW 700.49, system: monoclinic, space group $P2_1/n$, a = 12.0060(17) Å, b = 21.222(4) Å, c = 17.521(3) Å, β = 107.299(10)°, V = 4262.3(13) Å³, Z = 4, D_x = 1.092 g cm⁻³, μ = 1.537 mm⁻¹, F_{000} = 1520, R_1 (6346 $I > 2\sigma I$) = 0.0533, wR_2 (all data) = 0.1689, no. of reflections = 7922, no. of param. = 421, GooF = 1.114, ρ_{min} = −1.047 e Å⁻³, and ρ_{max} = 0.635 e Å⁻³

Synthesis and Characterization. The ligand precursors (E)-1-cyclohexyl-2,3-bis(2,6-diisopropylphenyl)-1-methylguanidine (LH1) and (E)-2,3-bis(2,6-diisopropylphenyl)-1,1-diethylguanidine (LH2) were synthesized by adapting reported procedures.[27,39]

Synthesis of (E)-1-Cyclohexyl-2,3-bis(2,6-diisopropylphenyl)-1-methylguanidine (Mixture of Isomers) (LH1). N-Methylcyclohexylamine (3.3 mL, 25.30 mmol) was dissolved in 100 mL of THF and cooled to −20 °C before 15.9 mL of n-butyl lithium (25.44 mmol, 1.6 M in n-hexane) was added. The solution was allowed to warm up to room temperature and stirred for 1 h. After adding 8.21 g of bis(2,6-diisopropylphenyl)carbodiimide (22.64 mmol), the solution was heated under reflux for 1 h. After cooling to room temperature, the solvent was drawn off and 100 mL of diethyl ether together with 40 mL of water was added. The organic phase was separated, and the aqueous layer was extracted with diethyl ether (3 × 30 mL). The combined ether phase was dried with sodium sulfate. After filtration, the ether was removed under reduced pressure to remain a white solid, which was recrystallized from boiling ethanol to yield colorless crystals (9.69 g, 90%).

¹H NMR (399.8 MHz, CDCl₃, 296 K): δ 1.22 (s, 3H, NCH₃), 0.93−1.62 (m, 10H, CH₂), 1.22 (d, 6H, CH(CH₃)₂), 1.28 (d, 6H,

CH(CH₃)₂), 1.42 (d, 6H, CH(CH₃)₂), 1.50 (d, 6H, CH(CH₃)₂), 2.84 (tt, 1H, NCH), 3.17 (sept, 4H, CH(CH₃)₂), 4.95 (s, 1H, NH), 6.95−7.26 (m, 6H, ArH). ¹³C{¹H} NMR (105.4 MHz, CDCl₃, 296 K): δ 20.3, 20.8, 20.9, 21.2, 22.0, 22.7 (CH(CH₃)₂), 24.3, 24.4, 24.7 (CH₂), 26.9, 27.0, 27.2, 27.8, 28.0, 28.1 (CH(CH₃)₂), 29.0, 29.1, 29.5 (CH₂), 56.2, 57.8 (HCN), 120.9, 121.5, 122.1, 122.6, 123.6, 125.2, 127.4, 131.5, 133.1, 138.4, 143.3, 143.8, 144.3, 146.6, 146.9 (ArC), 150.1, 157.9 (CN₃).

Synthesis of (E)-2,3-Bis(2,6-diisopropylphenyl)-1,1-diethylguanidine (Mixture of Isomers) (LH2). Diethylamine (2.6 mL, 25.10 mmol) was dissolved in 100 mL of THF and cooled to −20 °C before 15.9 mL of n-butyl lithium (25.44 mmol, 1.6 M in n-hexane) was added. The solution was allowed to warm up to room temperature and stirred for 1 h. After adding 8.20 g of bis(2,6-diisopropylphenyl)carbodiimide (22.61 mmol), the solution was heated under reflux for 1 h. After cooling to room temperature, the solvent was drawn off and 100 mL of diethyl ether together with 40 mL of water was added. The organic phase was separated, and the aqueous layer was extracted with diethyl ether (3 × 30 mL). The combined ether phase was dried with sodium sulfate. After filtration, the ether was removed under reduced pressure to obtain a white solid, which was recrystallized from boiling ethanol to yield colorless crystals (8.87 g, 90%).

¹H NMR (399.8 MHz, CDCl₃, 296 K): δ 0.40 (t, 6H, CH₂CH₃), 0.93 (t, 6H, CH₂CH₃), 1.15 (d, 6H, CH(CH₃)₂), 1.22 (d, 6H, CH(CH₃)₂), 1.28 (d, 6H, CH(CH₃)₂), 1.37 (d, 6H, CH(CH₃)₂), 1.39 (d, 6H, CH(CH₃)₂), 2.98 (q, 4H, CH₂CH₃), 3.19 (sept, 4H, CH(CH₃)₂), 4.95 (s, 1H, NH), 6.95−7.26 (m, 6H, ArH). ¹³C{¹H} NMR (105.4 MHz, CDCl₃, 296 K): δ 12.3 (CH₂CH₃), 21.9, 22.0, 22.9 (CH(CH₃)₂), 24.1, 25.3 (CH₂), 28.2, 28.5, 29.0 (CH(CH₃)₂), 41.5, 42.4 (HCN), 122.1, 122.8, 123.7, 124.2, 126.6, 128.9, 132.0, 134.6, 136.0, 139.7, 142.8, 144.8, 145.3, 145.6, 148.0 (ArC), 150.1, 160.4 (CN₃).

Synthesis of Complex L1ZnN(SiMe₃)₂. A solution of the proligand L1H (207.3 mg, 0.38 mmol) in benzene (3.0 mL) was added into a solution of Zn[N(SiMe₃)₂]₂ (154.5 mg, 0.40 mmol) in benzene (2.0 mL). The resulting mixture was stirred at 80 °C for 24 h. The solvent was removed *in vacuo*, and the solid residue was washed using dry hexane to obtain a white powder (yield: 278 mg, 95%). ¹H NMR (C₆D₆, 600 MHz, 298 K): δ 7.10 (m, 6H, Ar), 3.66 (sept, J = 6.6 Hz, 4H, CH(CH₃)₂), 3.41 (m, Cy), 2.12 (s, 3H), 1.39 (d, J = 4.4 Hz, 12H, CH(CH₃)₂), 1.33 (d, J = 6.6 Hz, 12H, CH(CH₃)₂), 1.23 (m, Cy), 1.19 (m, Cy), 0.82 (m, Cy), 0.58 (m, Cy), 0.16 (s, 18H, NSi(CH₃)₃). ¹³C NMR (150 MHz, C₆D₆, 298 K): δ 167.15, 143.22, 142.89, 124.75, 123.81, 57.96, 31.15, 30.22, 28.48, 25.85, 25.48, 25.13, 23.08, 5.55.

Synthesis of Complex L2ZnN(SiMe₃)₂. The reaction was performed as mentioned above, allowing to react proligand L2H (215.8 mg, 0.42 mmol) and Zn[N(SiMe₃)₂]₂ (174 mg, 0.45 mmol) in 5 mL of benzene and obtaining a white powder (yield: 282 mg, 92%). ¹H NMR (600 MHz, C₆D₆, 298 K): δ 7.10 (m, 6H, Ar), 3.66 (sept, J = 6.6 Hz, 4H, CH(CH₃)₂), 2.81 (q, J = 7.2 Hz, 4H, CH₂CH₃), 1.37 (d, J = 6.6 Hz, 12H, CH(CH₃)₂), 1.29 (d, J = 6.6 Hz, 12H, CH(CH₃)₂), 0.30 (t, J = 7.2 Hz, 6H, CH₂CH₃), 0.15 (s, 18H, NSi(CH₃)₃). ¹³C NMR (150 MHz, C₆D₆, 298 K): δ 168.51, 143.42, 142.43, 124.88, 123.95, 41.76, 28.25, 25.19, 23.25, 11.71, 5.52. HRMS (ESI+) m/z: found, 658.39 [L₂ZnN(SiMe₃)₂⁺].

Homopolymerizations of Lactide and ε-CL under Mild Conditions. Polymerization runs were performed in a magnetically stirred glass flask, charged sequentially with a solution of the monomer in the solvent, a solution of the guanidinate zinc complex, and, where specified, a solution of alcohol (see Tables 1 and 2). At the end of each reaction, a small fraction of the polymerization mixture was taken and quenched in wet CDCl₃ for ¹H NMR quantification of the monomer conversion; the remaining reaction mixture was quenched with a few drops of wet CH₂Cl₂ dissolved in CH₂Cl₂ and precipitated in methanol. The obtained polymer was collected by filtration and dried under vacuum at 60 °C for 16 h.

Homopolymerizations of Lactide under Industrially Relevant Conditions. In a typical polymerization run, a magnetically stirred reactor vessel was charged with non-purified technical grade L-

LA, guanidinate zinc complex, and benzyl alcohol. The reaction mixture was stirred for the prescribed time at 190 °C. Then, the polymerization was terminated by exposing it to air at room temperature. The crude product was dissolved in CH_2Cl_2 and precipitated in methanol. The workup was carried out as described above.

Kinetic Experiments. Five 10 mL vials were loaded with 2 μmol of initiator, 2 μmol of benzyl alcohol, and 2 mmol of technical grade L-LA and were immediately stirred at 190 °C. After specified time intervals, each reaction mixture was quenched in air at 0 °C and an aliquot of the crude material was sampled to determine the monomer conversion via ^{1}H NMR spectroscopy. All the experiments were made at least in duplicate.

Diblock (PCL-b-PLA) Copolymer Synthesis. The reactor vessel was charged with 1.5 mL of CH_2Cl_2 solution of Zn complex **1** (10 μmol, 5.1 mg), 1 equiv of isopropanol (10 μmol, 0.5 mL of a CH_2Cl_2 solution 0.02 M), and 200 equiv of ε-CL (2 mmol, 0.228 g) and stirred at 25 °C. After 30 min, an aliquot of the PCL material was sampled, and 200 equiv of LLA (2 mmol, 0.288 g) was added continuing the polymerization for further 30 min. The reaction was terminated by quenching with a few drops of wet CH_2Cl_2. The mixture was completely dissolved in CH_2Cl_2 and precipitated in methanol. The obtained copolymer was collected by filtration and further dried in a vacuum oven at 60 °C for 16 h. The full conversion of both monomers was determined via ^{1}H NMR spectroscopy (99% for ε-CL and 97% for LLA). The experimental number-average molecular weights and molecular weight distributions were determined via SEC chromatography [PCL: M_{nSEC} (correct) = 30.3 kDa, M_{nTHEO} = 21.9 kDa, Đ = 1.1; (PCL-b-PLLA) diblock: M_{nSEC} (correct) = 46.3 kDa, M_{nTHEO} = 56.8 kDa, and Đ = 1.2].

Copolymerizations of Lactide and ε-CL in Solution. The reactor vessel was charged sequentially with lactide, ε-CL, zinc complex, benzyl alcohol, and 2 mL of toluene. The mixture was thermostated at 100 °C and stirred for 1 h. Then, the polymerization solution was quenched with a few drops of CH_2Cl_2, an aliquot of the mixture was sampled to monomer conversion determination via ^{1}H NMR analysis, and the mixture was completely dissolved in CH_2Cl_2 and precipitated in hexane. The workup of the crude product was carried out as described above.

Copolymerizations of Lactide and ε-CL in the Melt. The reactor vessel was charged sequentially with lactide, ε-CL, zinc complex, and benzyl alcohol. The mixture was thermostated at 190 °C and stirred for 2 h. Then, the polymerization was terminated by exposing it to air at room temperature. The crude product was dissolved in CH_2Cl_2 and precipitated in hexane. The workup was carried out as described above.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsapm.1c00552.

^{1}H NMR, ^{13}C NMR, and ^{1}H spectra of complexes and polymers; MALDI-ToF mass spectrum; and DSC thermogram (PDF)

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Notes

The authors declare no competing financial interest.
CCDC-2063965 (compound **1**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.

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