Synthesis of Lactide/ ϵ -Caprolactone Quasi-Random Copolymer by Using Rationally Designed Mononuclear Aluminum Complexes with Modified β -Ketiminato Ligand

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ABSTRACT: A series of novel aluminum complexes containing bulky aryl- β -ketiminato ligands [ArN=CH-C₁₀H₇C₆H₅O]Al(CH₃)₂ (**3a**, Ar = C₆F₅; **3b**, Ar = C₆H₅; **3c**, Ar = 2,6^{-*i*}Pr₂C₆H₃) have been synthesized in high yields. These complexes were identified by ¹H and ¹³C NMR spectroscopy, elemental analysis, and X-ray structural analysis. All the aluminum complexes could efficiently catalyze the ROP of ε -caprolactone (ε -CL) and Lactide (LA) in a controlled manner. It was found that the steric effect of the ligand has less effect on the ROP of CL, while the polymerization rate of *L*-LA was suppressed significantly. More interestingly, this kind of catalysts can promote the random copolymerization of ε -CL and *L*-LA. The transesterification side reaction and the polymer composition could be adjusted by modulating the electronic and steric effects of the ligand. In

INTRODUCTION Aliphatic polyesters, as represented by polylactide (PLA) and polycaprolactone (PCL), have been regarded as a promising alternative to petroleum-based polymeric materials, because of their "green environmentallyfriendly" features.¹⁻¹⁰ More importantly, owing to remarkable biodegradable, nontoxic, biocompatible properties, they have also attracted considerable attentions in the pharmaceutical and biomedical field.9,11-14 Nonetheless, the drawbacks of physical properties of PLA and PCL limit their further application in certain field, such as drug delivery. PLA and PCL exhibit supplementary physical properties to some extent. For example, PLA exhibits good mechanical strength but poor elasticity, and it has a high degradation rate in vivo (about a few weeks) as well as low drug permeability.^{15,16} In sharp contrast, PCL exhibits not only high elasticity and thermal properties, but also remarkable drug permeability and slow degradation rate in vivo (\sim 1 year).¹⁷

paticular, compound **3c** could produce quasi-random copolymers without transesterification side reactions, as indicated by both the values of the reactivity ratios of the two monomers ($r_{LA} = 1.31$; $r_{CL} = 0.99$) and the similar average lengths of the caproyl and lactidyl sequences ($L_{CL} = 2.34$; $L_{LA} = 2.44$). Finally, a drug-random copolymer conjugates could be easily prepared by using **3c**, indicating a potential application of **3c** in pharmacutical and biomedical field. © 2017 Wiley Periodicals, Inc. J. Polym. Sci., Part A: Polym. Chem. **2017**, *00*, 000–000

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Thus, fine adjusting the composition and distribution of lactide and caprolactone repeat units along polymer chain will produce the copolymers with balanced drug permeability and biodegradable behavior, which can meet the requirement of various applications and is always the goal pursued in the pharmaceutical and medical fields. Thus, developing efficient catalyst for LA/ ϵ -CL copolymerization is highly demanded for this purpose.

So far, a great variety of organometallics have been used as the catalysts for polymerizations of LA and ε -CL, which range from traditional stannous^{18,19} catalysts to main group catalysts (Na,^{20–23}Mg,^{24–26} Al^{27–33}, and Ca^{34–36}) and transition metal (Zn^{35,37–43} and Ti⁴⁴) as well as rare earth catalysts.^{2,45–48} Nonetheless, seldom catalysts can strictly produce random copolymer poly(LA-*r*-CL), with the approximately equal in average length of lactidyl and caproyl

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1

Typically reported catalysts for random copolymer:



SCHEME 1 Typically reported complexes (A-D) and the catalyst (3a-c) used in present work for ε -CL/LA random copolymerization.

sequence $(L_{\text{LA}} = L_{\text{CL}} = 2)$.^{15,49,50} As an undoubted fact, the rates of homopolymerization of ε -CL and LA are sharply different. The ε -CL is consumed faster than LA in homopolymerization, whereas much slower than LA in the copolymerization.^{15,50,51} Their substantially distinct reactivity ratios usually result in block-like copolymers or gradient copolymers, whose degradation behavior and drug permeability are very different from those of random counterparts.⁴⁹⁻⁵² Although the transesterification side reaction can gradually convert the blocky or gradient copolymers into tendentially random ones in some case, it is hard to precisely control the distribution of LA or CL repeat units along the polymer chain.⁵³

As far as we concern, only very limited organometallic catalysts can successfully afford rigorously random *e*-CL/LA copolymers without transesterification. The elegant work of Nomura demonstrated a strictly random ϵ -CL/LA copolymer synthesized by a Salen-aluminum catalyst (A, Scheme 1). Introducing bulky ⁱPr₃Si groups in the ortho position of phenoxide groups significantly reduced the coordination ability of LA with Al center, which decreased the gap between the reactivity of ε-CL and LA in the copolymerization.⁵¹ Pellecchia developed a monomethyl aluminum complex with a pyrrolylpyridylamido ligand, which could promote the random copolymerization of LA and ϵ -CL ($r_{LA} = 1.17$; $r_{CL} = 1.36$) and finally yield real random copolymer with very similar average length of caproyl and lactidyl sequences ($L_{LA} = 2.5$; $L_{\rm CL} = 2.0$) (B, Scheme 1).¹⁵ Ma and Kan synthesized the mono- and dinuclear aluminum complexes bearing the racemic 6,6-dimethylbiphenyl bridged salen ligands, the complex was well-controlled, producing random copolymers with the average lengths of the caproyl and lactidyl sequences ($L_{LA} = 1.93$; $L_{CL} = 1.91$) in a feedstock of CL/LA = 1 and the values of the reactivity ratios of the two monomers $(r_{LA} = 1.17, r_{CL} = 0.80)$ (C, Scheme 1).⁵⁴ Besides, it was found that some chiral NNO-scorpionate zinc initiators also had good capabilities in ϵ -CL/LA random copolymerization (D, Scheme 1).⁵⁵

Our group has dedicated to developing novel aluminum catalysts for LA/E-CL copolymerization, and many kinds of them, ranging from mononuclear to binuclear catalysts, showed great success in synthesizing block and gradient copolyesters. For example, a mononuclear aluminum complexes containing N.O-bidentate β -ketiminato ligands (M. Scheme 1) could catalyze copolymerization of CL and LA in a controlled manner.⁵⁶ However, its less crowded space did not suppress the coordination of LA to Al center enough, only yielding gradient structure in the copolymerization of ɛ-CL/LA. Considering that increasing the steric hindrance of the catalyst is a straightforward strategy for reducing the reactivity of the LA in the random copolymerization, bulky aryl groups were introduced at the ortho position in the benzene ring (3a-c, Scheme 1). Thus, we documented the synthesis of aluminum complexes with modified β -ketiminato ligand and their applications in the random copolymerization of ϵ -CL and LA in present work. As expected, bulky group could retard the ROP of LA, while showed no significant effects on the CL copolymerization. Moreover, transesterification side reactions can be avoided at high conversion and/or high temperature, and quasi-random ϵ -CL/LA copolymer with similar average length of caproyl and lactidyl sequences can also be easily prepared.

EXPERIMENTAL

General Procedures and Materials

All manipulations of air and/or moisture-sensitive compounds were carried out under a dry and high purity nitrogen atmosphere using standard Schleck techniques or glovebox unless otherwise noted. All solvents were purified from an MBraun SPS system. The NMR data of ligands and complexes used were obtained using Bruker 400 MHz (400 MHz for ¹H, 75.5 MHz for ¹³C) spectrometer at 25 °C with CDCl₃ as a solvent. Elemental analyses were recorded on an elemental Vario EL spectrometer. Gel permeation chromatographic (GPC) measurements were carried out using a Waters instrument (515 HPLC pump) equipped with a Wyatt interferometric refractometer, eluted with CHCl₃ at 35 °C at 1 mL/min and narrow polystyrene standards as reference. Differential scanning calorimetry (DSC) measurements were carried out with a DSC1Star System (Mettler Toledo Instruments, Switzerland) under nitrogen atmosphere at a rate of 10 °C min⁻¹, and T_g values were collected after the second heating cycle. The geometries of the lactone-coordinated Al complexes were optimized in the gas phase without molecular symmetry constrains $M06-2X^{57}$ level of theory as implemented in the Gaussian software 09 program.⁵⁸ The all-electron basis set 6–311G(d,p) was applied to all atoms in the systems.

L-lactide was purified by crystallization from dry toluene. Benzyl alcohol was purified by distillation over sodium. ε -Caprolactone was dried with CaH₂ for 24 h at room temperature and then distilled under reduced pressure. Reagent grade Azidothymidine (AZT) which is widely used to prevent HIV was purchased from Aladdin. AlMe₃ in *n*-hexane was purchased from Acros and stored in a bottle in the dry box and was used as received.

Synthesis of β -Ketiminato Aluminum Complexes 3a-c $[C_6F_5N=CH-C_{10}H_7C_6H_5O]Al(CH_3)_2$ (3a)

Into a stirred solution of 2a (0.83 g, 2 mmol) in toluene (10 mL), AlMe₃ (1 M n-hexane solution, 2.05 mmol, 2.05 mL) was added dropwise over 10 min. After stirred for 8 h, the reaction mixture was concentrated in vacuo. The chilled-concentrated CH2Cl2 and n-hexane mixture solution was placed in the freezer (-20 °C) and afforded complex **3a**. Yield 0.86g (91%). ¹H NMR (400 MHz, CDCl₃): δ 7.47(d, J = 7.4 Hz, 1H, -N=C-H), 7.45-7.19 (m, 8H, Ar-H), 2.99 (t, J = 6.4 Hz, 2H, $-CH_2$ -), 2.61 (t, J = 6.8 Hz, 2H, Ar- CH_2 -), -1.15 (s, 6H, Al–CH₃). ¹⁹F NMR (377 MHz, CDCl₃): δ -149.40 (td, J = 13.7, 7.0 Hz, 2F, m-Ar-F), -157.81 (s, 2F, o-Ar-F) -161.63 (td, J = 22.5, 6.3 Hz, 1F, p-Ar-F). ¹³C NMR (100 MHz, CDCl₃): δ 178.74, 166.89, 144.35, 143.74, 142.81, 131.81, 130.76, 130.39, 128.23, 127.76, 127.10, 126.49, 107.70, 30.40, 26.39, -11.53. Anal. calcd. for C₂₅H₁₉AlF₅NO: C, 63.70; H, 4.07; N, 2.98. Found: C, 63.98; H, 4.12; N, 2.92.

$[C_6H_5N=CH-C_{10}H_7C_6H_5O]Al(CH_3)_2$ (3b)

Synthesis for **3b** was performed according to the procedure as that of **3a**, except ligand **2b** (0.65 g, 2 mmol) was used. Complex **3b** was obtained 0.68g (89% yield) as yellow microcrystals. ¹H NMR (400 MHz, CDCl₃): δ 7.71 (s, 1H, N=C-H), 7.43-7.14 (m, 13H, Ar-H), 2.95 (t, *J* = 6.8 Hz, 2H, -CH₂--), 2.61 (t, *J* = 7.2 Hz, 2H, Ar-CH₂--), -1.09 (s, 6H, Al-CH₃). ¹³C NMR (100 MHz, CDCl₃) δ : 173.83, 164.08, 147.77, 143.42, 143.3 142.84, 131.07, 130.61, 130.55, 129.50, 128.30, 127.64, 126.78, 126.2, 126.08, 121.80, 106.53, 30.52 (s), 26.46, -9.69. Anal. calcd. for C₂₅H₂₄AlNO: C, 78.71; H, 6.34; N, 3.67. Found: C, 79.15; H, 6.39; N, 3.62.

$[2,6^{-i}Pr_2C_6H_3N=CH-C_{10}H_7C_6H_5O]Al(CH_3)_2$ (3c)

Synthesis for **3c** was performed according to the procedure as that of **3a**, except **2c** (0.818 g, 2 mmol) was used. Yield 0.81 g (86%). ¹H NMR (400 MHz, CDCl₃): δ 7.37 (s, 1H, N=C-H), 7.35 -7.14 (m, 11H, Ar-H), 3.10 (s, *J* = 6.8 Hz, 2H, ^{*i*}Pr-CH), 2.94 (t, *J* = 6.8 Hz, 2H, -CH₂--), 2.54 (t, *J* = 7.2 Hz, 2H, Ar-CH₂--), 1.20 (d, *J* = 6.8 Hz, 6H, ^{*i*}Pr-CH₃), 1.07 (d, *J* = 6.8 Hz, 6H, ^{*i*}Pr-CH₃), -1.17 (s, 6H, Al-CH₃). ¹³C NMR (100 MHz, CDCl₃): δ 173.18, 167.86, 143.47, 143.26, 143.22, 142.9, 142.6, 130.62, 130.41, 128.33, 127.64, 127.15, 126.75, 126.22, 123.85, 105.45, 30.65, 27.93, 26.25, 25.81, 22.83, -10.56. Anal. calcd. for C₃₁H₃₆AlNO: C, 79.97; H, 7.79; N, 3.01. Found: C, 80.38; H, 7.92; N, 2.94.

Homopolymerization of $\epsilon\text{-}CL$ and LA

The typical polymerization procedure is as follows (Table 2 Run 1). All glassware used for polymerizations was ovendried. In a glovebox, a 10 mL Schlenk tube was charged 3 mL toluene solution of aluminum complex (25 μ mol), BnOH (25 μ mol). The mixture solution was stirred for 10 min, and 2 mL toluene solution of ϵ -CL (5.0 mmol) was added to the mixture solution. The reaction mixture was then placed into an oil bath pre-heated at 70 $^\circ \text{C}.$ After the desired time, the polymerization reaction stopped by adding formic acid (0.5 mL), and aliquot of the reaction mixture was sampled with a pipet for determining the monomer conversion by ¹H NMR spectroscopy. The resultant reaction mixture was poured into methanol and the white polymer was separated by filtration. The raw polymer was purified by dissolving in CH₂Cl₂ and precipitating from methanol three times. Homopolymerization of LA was performed according to the procedure as that of CL, except LA was used.

General Procedure of Random Copolymerization

The similar procedure is followed for the synthesis of all the copolymers (Table 3 Run 3). In a glovebox, a 10 mL Schlenk tube was filled with 1 mL toluene solution of aluminum complex (25 μ mol), BnOH (25 μ mol). The mixture solution was stirred for 10 min, then 1.5 mL toluene solution of ϵ -CL (2.5 mmol) and LA (2.5 mmol) was added simultaneously to the mixture solution. The reaction mixture was placed into an oil bath stirred at 100 °C. After the desired time, the polymerization reaction stopped by adding formic acid (1.0 mL), and an aliquot of the reaction mixture was sampled with a pipet for determining the monomer conversion by ¹H NMR spectroscopy. The resultant reaction mixture was poured into methanol. The obtained raw copolymer was purified by dissolving in CH₂Cl₂ and precipitated from rapidly stirring methanol, and the pure copolymer was collected by filtration and then dried in vacuo at 40 °C overnight. The drug-polymer conjugate was synthesized according to the procedure aforementioned by using AZT as an initiator.

RESULTS AND DISCUSSION

Synthesis of Aluminum Complexes and Structural Studies

The ligands were synthesized according to our previously reported procedure (Scheme S1 in supporting information).^{56,59}





SCHEME 2 The synthetic route for complexes 3a-c.

The aluminum complexes with bulky β -ketiminato ligands were effectively prepared with good yield via the alkane elimination reaction between AlMe₃ (1.05 equiv.) and the corresponding neutral ligand (Scheme 2). The complexes without aryl shelter M1 and M2 were also prepared to investigate the effects of the steric hindrance on the behavior of polymerization catalysis. The successful formation of Al complexes can be clearly identified by ¹H and ¹³C NMR spectra (Figs. S1-S7 in supporting information). Resonance peaks assigned to -OH proton around 11.5 ppm disappeared and sharp single peaks assigned to Al— CH_3 protons ranging from -1.09 to -1.17 ppm were clearly traced. Meanwhile, the peaks of $R_2N=CH$ proton shifted to upfield, indicating the formation of the desired complexes. Furthermore, single crystals of complexes **3a-c** suitable for X-ray crystallographic analysis was grown from CH₂Cl₂ and *n*-hexane solution. The data collection and refinement data of the analysis are listed in Table S1 (see supporting information), and the selected bond lengths and angles are summarized in Table 1.

In the solid state, each of the Al centers was coordinated by two alkyl groups, as well as oxygen and nitrogen atoms from the ligand, forming a distorted tetrahedral geometry (Fig. 1 and Figs. S8 and S9 in supporting information). It is obvious that the introduced aryl group serves as a shelter that protects the aluminum center. The dihedral angle C(6)-C(7)-C(8)-C(9) between the benzene ring and tetralone plane of **3c** (74.47°) is much larger than those of **3b** (64.11°) and **3a** (58.85°) (Table 1). The six-membered Al-N-C-C-C ring in 3b is nearly planar, while it is distorted in 3a and 3c. The dihedral angel between O-Al-N plane and N-C(3)-C(4)-C(5)-O plane for 3a and 3c is 3.32° and 33.09°, respectively. Moreover, dihedral angle C(25)-C(20)-N-C(3) between N-C(3)-C(4)-C(5)-O plane and C(20)-C(21)-C(22)-C(23)-C(24)-C(25) plane increased in the order **3b** $(61.86^{\circ}) < 3a (66.71^{\circ}) < 3c$ (81.67°). All these results clear indicated that 3c exhibits more crowded coordination environment than **3a** and **3b**.

Homopolymerization of *L*-LA and ε-CL

The polymerization was conducted in the absence of an alcohol initiator. No monomer conversion was observed,

TABLE 1	Selected	Bond	Distances	(Å)	and	Angles	(°) f	or	Com-
plexes 3a	a−c								

Bond Distances (Å) and Angles(°)	3a	3b	3c
AI—O	1.8097(9)	1.7991(9)	1.8046(8)
AI—N	1.9567(11)	1.9465(11)	1.9452(9)
AI-C1	1.9486(14)	1.9555(15)	1.9512(12)
AI–C2	1.9514(15)	1.9597(15)	1.9595(13)
N—C3	1.3329(16)	1.3184(16)	1.3150(13)
N-C20	1.4210(15)	1.4362(16)	1.4471(12)
O—C5	1.2956(14)	1.3045(15)	1.3046(12)
C3—C4	1.3942(17)	1.4127(18)	1.4131(14)
C4—C5	1.4052(17)	1.3865(18)	1.3949(13)
O—AI—N	93.40(4)	93.45(5)	92.74(4)
C1—AI—C2	112.24(6)	117.90(7)	118.88(6)
AI—N—C3	122.20(8)	122.00(9)	118.40(7)
O—AI—C1	109.42(5)	110.64(6)	111.89(5)
O—AI—C2	112.99(5)	110.89(6)	109.92(5)
N—AI—C1	112.24(6)	110.59(6)	110.88(5)
N—AI—C2	103.81(6)	110.71(6)	109.44(5)
C5—O—AI	131.51(8)	129.50(8)	123.77(6)
C20-N-AI	119.89(8)	120.58(8)	124.04(6)
O—C5—C4	122.58(11)	123.21(11)	122.91(9)
C3—C4—C5	122.62(11)	121.96(11)	121.06(9)
N—C—C—C—O planar/ N-substituent	66.71	61.86	81.67
Phenyl planar/ tetralone planar	58.85	64.11	74.47
O—AI—N planar/ N—C—C—C—O planar	3.32	14.69	33.09

indicating that the complexes **3a-c** were not the real active species in the polymerization. The homopolymerization of ε -CL and *L*-LA by complexes **3a-c** in the presence of 1 equiv.



FIGURE 1 Molecular structure of complex **3c** with thermal ellipsoids at the 30% probability level. Hydrogen atoms are omitted for clarity.

TABLE 2 Homopolymerization of ε-CL and *L*-LA by Complexes **3a–c**^a

Run	Complex	Mono	[Mono]:[OH]:[AI]	Time (min)	Conv. ^b (%)	TOF^{c} (h ⁻¹)	$M_{\rm n,theo}{}^{\rm d}$ (×10 ⁴)	$M_{\rm n}^{\rm e}$ (×10 ⁴)	$M_{ m w}/M_{ m m}$
1	3a	ε-CL	200:1:1	60	96.3	192	2.20	3.16	1.26
2	3b	ε-CL	200:1:1	60	97.2	194	2.22	2.56	1.27
3	3c	ε-CL	200:1:1	5	26.3	631	0.60	0.87	1.18
4	3c	ε-CL	200:1:1	10	37.2	446	0.85	1.24	1.17
5	3c	ε-CL	200:1:1	20	64.0	384	1.50	1.82	1.20
6	3c	ε-CL	200:1:1	30	72.5	290	1.65	2.04	1.24
7	3c	ε-CL	200:1:1	40	84.3	252	1.91	2.47	1.28
8	3c	ε-CL	200:1:1	50	90.7	217	2.06	2.57	1.25
9	3c	ε-CL	200:1:1	60	95.4	190	2.18	2.87	1.28
10	M1	ε-CL	200:1:1	60	93.2	186	2.10	2.65	1.25
11	M2	ε-CL	200:1:1	60	>99	200	2.28	2.41	1.29
12	3a	<i>L</i> -LA	100:1:1	210	69.4	19.8	1.01	1.11	1.23
13	3b	<i>L</i> -LA	100:1:1	210	62.3	17.8	0.91	0.98	1.20
14	3c	<i>L</i> -LA	100:1:1	120	30.6	12.3	0.45	0.47	1.23
15	3c	<i>L</i> -LA	100:1:1	180	42.3	14.1	0.62	0.69	1.25
16	3c	<i>L</i> -LA	100:1:1	210	54.6	15.6	0.79	0.84	1.27
17	3c	<i>L</i> -LA	100:1:1	240	63.2	15.8	0.91	0.95	1.27
18	3c	<i>L</i> -LA	100:1:1	270	69.5	15.4	1.01	1.03	1.28
19	3c ^f	<i>rac</i> -LA	100:1:1	210	52.1	14.9	0.75	0.87	1.29
20	M1	<i>L</i> -LA	100:1:1	210	90.4	25.8	1.30	1.66	1.25
21	M2	<i>L</i> -LA	100:1:1	210	76.1	21.7	1.10	1.47	1.22

^a 25 μ mol of Al complex, [CL] = 1 mol L⁻¹and [LA] = 2 mol L⁻¹ in toluene, [OH] = BnOH, 70 °C for CL and 80 °C for LA.

^b Monomer conversion was determined by ¹H NMR analysis.

^c Non-optimized turnover frequency calculated over the whole reaction time.

^d Calculated $M_{n,\text{theo}} = [\epsilon\text{-CL}]_o/[\text{OH}] \times \text{conv.} (\epsilon\text{-CL}) \times M_{CL} + M_{\text{BnOH}}$, Calculated $M_{n,\text{theo}} = [\text{LA}]_o/[\text{OH}] \times \text{conv.}(\text{LA}) \times M_{\text{LA}} + M_{\text{BnOH}}$.

of benzyl alcohol was further investigated, and the typical results were summarized in Table 2. The complexes of 3a-c displayed very similar catalytic activity for the ROP of ε -CL, the monomer could be consumed almost completely within 60 min (Table 2). A linear relationship was observed between the monomer conversions and the number-average

^e Experimental M_n values were determined by GPC analysis and calibrated against polystyrene standard and corrected by the equation: $M_n = 0.56 \times M_{n(GPC)}$ for PCL and $M_n = 0.58 \times M_{n(GPC)}$ for PLA.

^f P_m of PLA can be derived from the methine region of ¹³C NMR spectrum, $P_m = 0.45$, $[mmm] = P_m(1 + P_m)/2 = 0.33$.

molecular weight (M_n) of the polymers (Fig. 2 and Figs. S10 and S11 in supporting information). The rate of the ROP was first-order dependent on the monomer concentration by catalyst **3c** (Fig. 3 and Figs. S12 and S13 in supporting information). The apparent rate constant of ROP of ε -CL was found to be 0.049 min⁻¹ for **3a**, 0.051 min⁻¹ for **3b**, and 0.046



FIGURE 2 M_n and M_w/M_n versus monomer conversion in the ROP of ε -CL initiated by **3c**/BnOH system.



FIGURE 3 The kinetcis of ROP of CL catalyzed by 3c/BnOH system.



TABLE 3 (Copoly	merization	of e-CL	and L-LA	with	Different	Catal	/sts ²
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					Conv.° (%	%)						
Run	Cat	<i>T</i> (°C)	L _{LA} ^b	L _{CL} ^b	LA	CL	F_{LA}^{d} (%)	$M_{\rm n,raw}^{\rm e}$ (10 ⁴)	$M_{\rm n}^{\rm f}$ (10 ⁴)	$M_{\rm n,th}^{~~g}$ (10 ⁴)	PDI	
1	M1	80	3.92	1.75	98.0	96.2	53.3	3.23	1.84	2.44	2.07	
2	M2	100	2.94	1.91	99.1	95.3	48.9	3.61	2.05	2.53	1.60	
3	3a	80	2.85	2.55	94.3	92.6	51.7	4.83	2.75	2.42	1.53	
4	3a	100	3.78	2.99	100	98.0	50.7	5.43	3.09	2.56	1.56	
5	3b	80	2.62	1.65	88.3	70.1	60.2	3.94	2.25	2.13	1.40	
6	3b	100	2.68	1.90	94.3	91.9	54.8	4.65	2.63	2.41	1.47	
7	3c	80	2.75	1.97	85.5	73.5	53.7	4.71	2.68	2.07	1.39	
8	3c	100	2.44	2.34	97.1	97.9	50.1	4.81	2.74	2.52	1.42	
9	3c	120	1.93	1.88	99.9	99.9	50.5	5.04	2.89	2.58	1.40	
10	3c ^h	100	2.20	2.39	41.6	38.7	54.1	2.07	1.18	1.04	1.31	

 a Reaction conditions: 25 μmol of catalyst in 2.5 mL of toluene, [ϵ -CL]/ [L-LA]/[Al]/BnOH = 100:100:1:1, and copolymerization at 80 °C for 8 h or 100 °C for 10 h.

 $^{\rm b}$ Average sequence length of caproyl unit and lactidyl unit was determined by $^{\rm 13}{\rm C}$ NMR.

^c Monomer conversion was determined by ¹H NMR.

^d LA content in the copolymer determined by ¹H NMR.

 \min^{-1} for **3c**, further suggesting the similar activity of **3a-c** in the ROP of CL. The predicable molecular weights (MWs) and narrow molecular weight distributions (MWDs) suggested that the ROP of ε -CL catalyzed by **3a-c** proceeded in a controlled manner.

It was noted that introducing bulky substituent has negligible effects on ε -CL polymerization, as evidenced by the very similar catalytic activities of complexes with bulky group as the corresponding counterparts without aryl group shelter (Run 1 vs. 10; Run 9 vs. 11, Table 2). This observation kept good consistent with the results documented by Nomura who also found that the bulky groups showed less effect on the ROP of smaller CL.⁴⁸

By sharp contrast, introducing bulky group significantly retarded the polymerization of LA (Runs 12-21, Table 2). For example, high monomer conversion up to 90.4% could be achieved in 3.5 h by complex M1. However, only 69.4% of LA was consumed within 3.5 h under the same conditions by 3a. Similar phenomenon was also observed in the ROP of LA by using M2 and 3c. This observation is significant for the goal of synthesizing random LA/CL copolymer whose properties will be different from the gradient and block copolymer. Meanwhile, the catalytic activities of complexes **3a-c** decreased in the order 3a > 3b > 3c, exhibiting strong dependences on the substituent groups of the imino moiety. Complex 3a with electron-withdrawing group $-C_6F_5$ exhibited relatively higher catalytic activity (TOF: 19.8 h^{-1}), owing to its stronger Lewis acidity of Al center. While complex 3c containing bulky 2,6-¹Pr₂C₆H₃ group showed lowest activity among these complexes (TOF: 15.6 h^{-1}). It is noted that the ROP of lactone proceeds via coordination-insertion mechanism and involves many transition states and key species. 29,60 The first step is the coordination of lactide to the

^e Determined by GPC in CHCl₃ using polystyrene as a standard.

 $^{\rm f}$ $M_{\rm n}$ = $M_{\rm n,GPC(raw)}$ imes CL (mole percent in copolymer) imes 0.56 + $M_{\rm n,GPC(raw)}$

imes LA (mole percent in copolymer) imes 0.58.

 $^{\rm g}$ $M_{\rm n,th}$ = ([&-CL]/[BnOH]) \times conv. (CL) \times $M_{\rm CL}$ + ([LA]/[BnOH]) \times conv. (LA) \times $M_{\rm LA}$ + $M_{\rm BnOH}$.

^h Copolymerization at 100 °C for 4 h.

Al enter via the carbonyl oxygen of the lactone through the van der Walls complex. To understand the effects of the aryl group on the coordination of CL and LA with Al complex, density functional theory (DFT) calculations were conducted. However, it was suggested that the introduction of aryl group had negligible effects on the coordination of CL and LA with Al complexes (Fig. S15 in supporting information). Thus, we envisioned that the aryl group may have more profound influence on the intermediates and transition state in the nucleophilic attack and ring-opening steps.⁶¹ The corresponding DFT calculations are in progress.

The ROP of L-LA catalyzed by **3a-c** proceeded in a controlled manner as well, as evidenced by the predictable molecular weight and narrow molecular distributions. The resulting macromolecular chain is capped with the hydroxyl group at one end and the BnO- group at the other end (Fig. S14 in supporting information). In addition, no monomer conversion was observed in a controlled experiment without BnOH initiator (Run 8, Table S4). These results suggested that the ROP of LA may proceed via a coordination insertion mechanism. rac-LA polymerization was further conducted to evaluate the stereo-control of complex 3c (Run 19, Table 2). There is no obvious difference between the homopolymerization of rac-lactide and L-Lactide, suggesting that the enantiomers L-LA and D-LA have similar polymerization kinetics. The $P_{\rm m}$ of PLA obtained by **3c** was determined by ¹³C NMR spectrum (Table 2). It was found that $P_{\rm m} = 0.45$ and the $[mmm] = P_m(1 + P_m)/2 = 0.33^{.37}$ Therefore, **3c** exhibits no stereo-selectivity in the ROP of rac-LA.

Copolymerization of *L*-LA and ε-CL

To confirm the optimal catalyst for synthesizing random copolymers, copolymerizations of ϵ -CL and *L*-LA with



FIGURE 4 ¹H NMR spectrum of PLA-co-PCL synthesized using **3c** (Run 3, Table 3, CDCl₃, 25 °C). [Color figure can be viewed at wileyonlinelibrary.com]

complexes **3a-c** were investigated under the conditions of a ε-CL/L-LA/Al/BnOH ratio of 100/100/1/1 at different temperature. Besides, complexes M1 and M2 were also used as the references to catalyze CL/LA copolymerization, to investigate the effects of introduced benzene ring on the copolymerization behavior and microstructures of the copolymer. The resultant polymers were characterized by ¹H and ¹³C NMR spectroscopy, GPC (Table 3). The CL/LA molar ratio in the copolymer was determined through the integrated values of the methylene signal of CL segment around 4.0 ppm and the methine signal of LA around 5.2 ppm (Fig. 4). The average length of the lactidyl (L_{LA}) and caproyl (L_{CL}) sequences can be calculated from the integrals of the triads sequences signals according to previously reported methods.^{62,63} The average length of L-LA (L_{LA}) sequence in the copolymer produced by **M1** is 3.92, whereas the average length of CL (L_{CL}) sequence is 1.75 (Run 1 in Table 3), indicating that the consumption of L-LA was faster than CL and the copolymer had gradient microstructure ($L_{CL} = L_{LA} = 2$ for an ideal random copolymer). The conversion of LA and CL in the copolymerization was traced by ¹H NMR (Fig. S16 in supporting information), further confirming that L-LA was converted more rapidly in the copolymerization.

By contrast, complex 3a showed great tendency to produce a quasi-random copolymer ($L_{LA} = 2.85$ and $L_{CL} = 2.55$). These results clearly indicated that increasing the steric hindrance of catalyst could significantly narrow the gap in polymerization rate of LA and CL, which was beneficial for preparing random copolymer (Run 3, Table 3). However, a sharp resonance peak at 171.1 ppm assigned to a single lactic ester unit between two CL units (CLC) was detected in the resultant copolymer obtained by M1 and 3a, indicating the presence of transesterification side reaction (Fig. 5). The presence of transesterification may induce a broader molecular weight distribution (Runs 1 and 3, Table 3). Compared with complex M1, 3a could produce copolymer with less CLC content, suggesting that the bulky steric hindrance could also suppress the transesterification side reaction. Further substituting the electron-withdrawing group $-C_6F_5$ (3a)



with benzene group (**3b**) in the imine moiety, the transesterification could be eliminated at 80 °C while maintaining the random microstructure of the copolymer ($L_{LA} = 2.62$ and $L_{CL} = 1.65$) (Run 5, Table 3).

Considering that the transesterification side reaction could be favored at higher temperature, LA/CL copolymerizations catalyzed by 3b were further conducted at 100 °C. As shown in Figure 5, the resonance peak assigned to CLC segment could be clearly observed, suggesting the presence of transesterification at high temperature by using **3b**. Excitingly, the transesterification side reaction could be eliminated completely by using catalyst 3c with bulkier substituent group 2,6-^{*i*}Pr₂C₆H₃ even when the copolymerization was conducted at higher temperature (100 °C and 120 °C) (Runs 8 and 9, Table 3). By contrast, transesterification side reaction could be observed in the copolymerization catalyzed by M2, as evidenced by the appearance of the CLC resonance peak at 171.1 ppm. This observation further supported that the aryl group in 3c could eliminate the transesterification reaction. The resultant copolymer obtained by 3c shows a quasi-random structure, as evidenced by the very similar average length of the lactidyl (L_{LA}) and caproyl (L_{CL}) sequences (Table 3). To further confirm complex 3c could produce random copolymer, the reactivity ratios r_{LA} and r_{CL} were further determined by conducting CL/LA copolymerization with low monomer conversion (Table S4 and Fig. S17 in supporting information). The values of monomer reactivity ratios were found to be $r_{CL} = 0.99$ and $r_{LA} = 1.31$, which indicated that the two monomers were almost synchronously incorporated into the polymer chain during the copolymerization, and quasi-random polymer would be obtained. Taking all



FIGURE 5 ¹³C NMR spectra of the copolymers obtained at different temperatures (CDCl₃, 25 °C). [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 4 Copolymerization of ε-CL and L-LA with Different Molar Ratio by Using 3c^a

				Conv	.° (%)							
Run	[LA]:[CL] (mol:mol)	$L_{\rm LA}^{\rm b}$	L _{CL} ^b	LA	CI	$F_{\rm LA}{}^{\rm d}$ (%)	$M_{\rm n}^{\rm e}$ (10 ⁴)	$M_{\rm n,th}^{\rm f}$ (10 ⁴)	PDI	$T_{g,th}^{g}$ (°C)	$T_{g,DSC}^{h}$ (°C)	T _{m,DSC} ^h (°C)
1	40:160	1.61	4.08	100	98	19.1	2.90	2.56	1.42	-41.1	-40.4	39.5
2	80:120	2.45	2.46	100	94	45.9	2.47	2.40	1.49	-12.2	-9.9	-
3	100:100	2.75	1.97	85.5	73.5	53.7	2.68	2.07	1.39	-3.1	-1.46	-
4	120:80	4.27	1.90	91.4	78.7	69.5	2.59	2.21	1.38	16.1	14.5	-
5	160:40	7.22	1.40	89.1	78.1	84.1	2.41	2.18	1.41	35.0	34.9	145.0

 a Reaction conditions: 25 μmol of Al complex in 2.5 mL of toluene, 80 $^\circ C$ for 8 h, ([LA]+[CL]):[AI]:[OH] = 200:1:1.

^b Average sequence length of the caproyl unit and the lactidyl unit was determined by ¹³C NMR analysis.

^c Monomer conversion was determined by ¹H NMR analysis.

^d LA mole ratio in the copolymer determined by ¹H NMR.

 $^{\rm e}$ $\textit{M}_{\rm n}$ = $\textit{M}_{\rm n,GPC(raw)}$ \times CL (mole percent in copolymer) \times 0.56 + $\textit{M}_{\rm n,GPC(raw)}$

imes LA (mole percent in copolymer) imes 0.58.

these into account, complex **3c** was a promising catalyst for synthesizing random ϵ -CL/LA copolymers without transesterification. For a 1:1 ratio of the CL/LA in the feed, the $L_{\rm CL}$ and $L_{\rm LA}$ values were \sim 2 not only at full conversion but also at low monomer conversion (41.6% for LA and 38.7% for CL, Run 10 in Table 3).

Because of its superior catalytic performance to **3a** and **3b**, the copolymerizations of CL and LA with different feed ratio were further conducted by complex **3c** and the typical results are summarized in Table 4. The copolymer compositions kept good consistent with CL/LA molar ratio in the feed. Obviously, both the $L_{\rm CL}$ and $L_{\rm LA}$ increased as the relative monomer amount in the feed increased (Fig. 6). The glass transition temperature ($T_{\rm g}$) of the resultant copolymers was further analyzed by the DSC. The copolymers with molar ratio [CL]:[LA] = 40:160 and [LA]:[CL] = 160:40 are semicrystalline, with $T_{\rm m}$ of 39.5 °C and 145 °C, respectively. In all



174.0 173.5 173.0 172.5 172.0 171.5 171.0 170.5 170.0 169.5 169.0

FIGURE 6 Carbonyl range of ¹³C NMR spectra of copolymers of Runs 1–5 in Table 4. [Color figure can be viewed at wileyon-linelibrary.com]

 $^{\rm f}$ $M_{\rm n,th}$ = ([&-CL]/[BnOH]) \times conv. (CL) \times $M_{\rm CL}$ + ([LA]/[BnOH]) \times conv. (LA) \times $M_{\rm LA}$ + $M_{\rm BnOH}$.

 g Theoretical values calculated by Fox equation, by using for the T_g of the homopolymers the following literature values: PCL: -60 °C; PLLA: 57 °C.

^h Determined by DSC.

cases, the copolymer samples showed only one $T_{\rm g}$ between -60 °C of PCL and 45 °C of PLA, and the $T_{\rm g}$ increased with the increasing of the LA content in the copolymer chain (Fig. S18 in supporting information). The experimental values of the $T_{\rm g}$ were in good agreement with the theoretical values calculated by the Fox equation, further indicating that the copolymers exhibited random structures (Fig. 7).

Finally, the possibility of preparing drug–polymer conjugates by means of direct random copolymerization of CL and LA initiated by a hydroxyl function of the drug was explored. Such drug–polymer conjugate is a promising drug delivery, because the permeability and release of the drug could be controlled by modulating the relative CL/LA content in the polymer chain. A conjugate of Azidothymidine (AZT, 3'-Azido-3'-deoxythymidine) and a random CL/LA copolymer was prepared form ROP of CL and LA promoted by the combination of the drug and complex **3c** in present work. AZT was the first reverse transcriptase inhibitor licensed for clinical use by food and drug administration (FDA) and it remains an important component in highly active



FIGURE 7 Experimental and theoretical T_g of CL/LA copolymers as a function of the mole fraction of ϵ -CL unit.

antiretroviral therapy medicine. AZT is an amphiphilic compound and tends to partition between the lipid bilayers and the aqueous milieu of liposomes, thus resulting in a low drug entrapment and significant drug leakage from the vesicles over time. Modifying the molecular structure may improve the stability and extend the half-life of the human body.^{64,65} The successful formation of the drug-polymer conjugates could be confirmed by ¹H NMR (Fig. S19 in supporting information). The resulting conjugates were capped with the hydroxyl group at one end and the AZT group at the other end. This result indicated that the presence of drug did not interfere with the CL/LA random copolymerization, enabling the preparation of drug-polymer conjugates with tuned properties.

CONCLUSIONS

developed a series novel Al We of complexes $[ArN = CH - C_{10}H_7C_6H_5O]Al(CH_3)_2$ (3a, $Ar = C_6 F_5;$ 3b, Ar = C_6H_5 ; **3c**, Ar = 2,6^{-*i*}Pr₂C₆H₃) that could catalyze the random copolymerization of ε -CL and L-LA by rationally designing a modified β -ketiminato ligand with bulky steric hindrance. Introducing an aryl group at the ortho position in the benzene ring significantly reduced the gap between the reactivity of LA and CL in the polymerization, allowing to synthesize random CL and LA copolymer. The transesterifcation side reaction and the polymer composition could be adjusted by modulating the electronic and steric effects of the ligand. Especially, compound 3c could produce quasirandom copolymer with similar average lengths of the caproyl and lactidyl sequences ($L_{CL} = 2.34$; $L_{LA} = 2.44$). The random copolymerization could be further confirmed by the values of the reactivity of the two monomers ($r_{LA} = 1.31$; $r_{\rm CL} = 0.99$). Futhermore, the thermal charaterization of the copolymers also indicated amorphous materials whose T_{g} were modifiable in the range of -60 and 80 °C by adjusting the relative content of L-LA and CL. A drug-random copolymer conjugates could be easily prepared by using 3c, which made these catalysts possess potential applications in biomedical field.

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