

Ultra-Rapid Cerium(III)–NHC Catalysts for High Molar Mass Cyclic Polylactide

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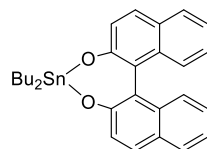
Polymerization, Catalysis, Cerium, Lanthanide, Polylactide, Cyclic, NHC

ABSTRACT: Cyclic polyesters could improve properties of degradable plastics, but routes to them that provide product with faster rates, higher molar mass and greater selectivity for cyclic vs. linear polymer are needed. Here, homogeneous Ce(III)–NHC catalysts show outstanding activities (TOF > 864,000 h⁻¹), excellent control and selectivity for cyclic PLA topology (>95%), yielding high molar mass PLA (60 < M_n < 250 kg mol⁻¹). They efficiently produce cyclic PLA from *rac*-lactide or L-lactide, and aliphatic cyclic polyesters from ε-caprolactone or β-butyrolactone. The enhanced performances are only achievable from combining cooperative Lewis acidic cerium(III) and hemilabile N-heterocyclic carbene functionalities.

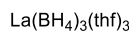
Polylactide (PLA) is a sustainable alternative to petrochemical-derived plastics.¹⁻² The linear polyester's properties depend upon its molar mass, architecture, stereochemistry and topology;³ currently these match some applications but there are recognized significant property limitations.³⁻⁵ The unusual, cyclic form of poly(lactide), cPLA displays faster crystallite nucleation, higher crystallinity, enhanced thermal stability and lower intrinsic viscosity than its linear congener.⁶⁻⁹ These are remarkable differences considering the two are topological isomers and differ in the placement of only one bond. Recent experimental studies of samples of cPLA with moderate molecular weight, and under optimized processing conditions agree with the predictions of these desirable polymer properties.⁸⁻⁹ However, the synthesis of pure cyclic polymers, and particularly those with higher molar mass, remains a challenge.

Cyclic PLA is most readily accessed *via* ring expansion polymerization, since intramolecular cyclization or chain end-coupling reactions are entropically limited and cannot produce the high molar masses needed.^{7,10-11} Current state-of-the-art catalysts exhibit either high selectivity, control or molar mass but not all three.⁷ Kricheldorf pioneered tin catalysts for macrocyclization which operate by accelerating intramolecular transesterification rates;¹²⁻¹⁴ Sn(IV) **A** (Chart 1) shows a turn-over-frequency (TOF) of 1300 h⁻¹ for L-lactide polymerization and yields 95% cyclic poly(L-lactide) (cPLLA) with M_n = 31 kg mol⁻¹ but with a dispersity >6

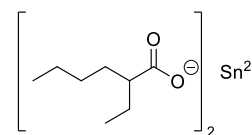
([Sn]:[LA] 1:2000, 170 °C).¹³⁻¹⁴



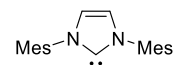
A (2018)¹⁴



C (2015)¹⁶



B (2020)¹⁵



D (2007)¹⁷

Chart 1: Known catalysts for cyclic PLA production.¹⁴⁻¹⁷

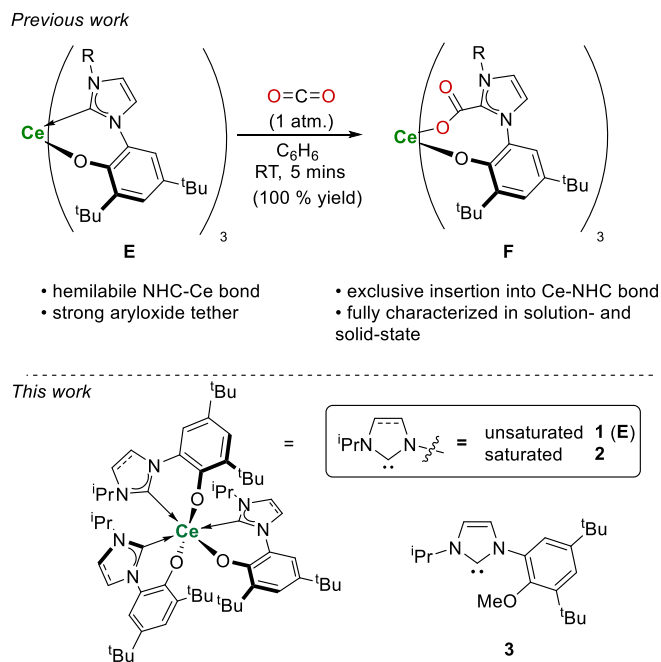
Moreover, these tin catalysts recently produced cPLLA with an unexpectedly high T_m of 190–196 °C (PLLA T_m is usually 174–184 °C), although it must be noted that highly specific annealing and crystallization conditions were required.^{13, 18} Indeed, when used without added alcohol cocatalyst, and under very specific conditions the industry-standard Sn(II)-2-ethylhexanoate catalyst (**B**, Chart 1), has very recently been shown able to produce significant quantities of cPLLA with moderate activity. The reaction must be carried out in the melt and with [Sn]:[LA] > 1:400 (a [Sn]:[LA] 6000:1 melt reaction at 160 °C yields 95–99% cPLLA, M_n = 115 kg

mol⁻¹, $\bar{D} = 2.2$, TOF of 3000 h⁻¹).¹⁵ A few other metal catalysts also produce cPLA by lactide ring-expansion or intramolecular transesterification mechanisms and, relevant here, the only known lanthanide catalyst (**C**, Chart 1) showed a moderate TOF of 2310 h⁻¹ in the melt phase and produced cPLLA with low molar mass of 18 kg mol⁻¹ ([C]:[LA] 1:1000, 130 °C).^{16, 19-20}

Waymouth and co-workers pioneered some of the most active organocatalysts for cPLA, introducing the zwitterionic ring-opening polymerization (zROP) mechanism. These catalysts are typically neutral nucleophiles, such as N-heterocyclic carbenes (NHCs), and during polymerization generate zwitterionic propagating intermediates featuring electrostatically attracted chain ends.^{6-8, 17} Sophisticated mechanistic studies revealed that the formation of cPLA occurs through intramolecular transesterification facilitated by the close proximity of the chain ends. The NHC-catalyzed zROP, exhibits more complex kinetic behavior than production of linear polyesters and the interplay between the concentrations of free carbene and zwitterionic propagating intermediate strongly influences activity. The overall M_n of the cyclic polymer is largely dependent upon the inherent ratio of the rates of propagation and cyclization for a specific catalyst/monomer system, and less dependent on the initial monomer loading. This means that the overall molar mass accessed by these catalysts tends to be lower and is typically <31 kg mol⁻¹.²¹ Activity values can be excellent, for example one of the best NHC catalysts (**C**, Chart 1), yields cPLA with an impressive TOF of 8760 h⁻¹ and with $M_n = 18$ kg mol⁻¹, $\bar{D} = 1.17$ ([D]:[LA] 1:200, 25 °C).¹⁷ These versatile catalysts can also make cyclic polyesters from ϵ -caprolactone (CL),²²⁻²³ β -butyrolactone (β -BL)²⁴ and other lactones.²⁵⁻³⁵

Previously, some of us have reported Sc(III) and Y(III) complexes featuring labile NHC-alkoxide ligands for CO₂ activation and lactide ROP.³⁶⁻³⁷ The heterobidentate ligands make strong Ln-O bonds and support the NHC hemilability that is critical to the binding, activation and catalytic conversions of oxygenated substrates. The Ce(III) complex **E** selectively activates CO₂ to give the Ce-tris-imidazolium carboxylate complex (**F**, Scheme 1).³⁸ The CO₂ is inserted exclusively between the Ce-NHC bonds, and in some cases

can be catalytically functionalized. Importantly, the Ce-O_{Ar} bonds remain intact in both solution and the solid-state. We hypothesized that by analogy with all the above, lactide insertion into the hemilabile Ce-NHC bonds should yield viable polymerization catalysts, and without co-initiator the catalysts could yield cyclic products, by operating in a similar manner to the NHC-catalyzed zROPs reported by Waymouth, but with an additional tethered Lewis acid, to yield cyclic products.



Scheme 1: Catalyst design and reactivity principles demonstrated by CO₂ insertion across the Ce-C_{carbene} and new catalysts for ROP.³⁸

Building on this hypothesis, we have now studied three potential catalysts for the ring-opening polymerization of lactide. All polymerizations were conducted at room temperature, in THF ([LA] = 0.5 M) (Table 1). The catalysts are: Ce(III) complex **1**;³⁸ new complex **2** which features saturated NHC ligand groups; and NHC organocatalyst **3**, the aryloxy-protected NHC ancillary ligand (Scheme 1, Table 1, SI 1.o).

Table 1: Ring opening polymerization of *rac*-LA to form cyclic PLA using catalysts 1-3 and A-D.

Entry	Cat	[LA]/[Cat]	Time [s]	Conv. ^b [%]	$M_n^{c,d}$ (GPC) [kg mol ⁻¹]	$M_n^{b,e}$ (theo) [kg mol ⁻¹]	\bar{D}^c	TOF [h ⁻¹]
1 ^a	1	300	15	100	61	43	1.67	72000
2 ^a	1	1200	30	81	114	138	1.65	115200
3 ^a	1	5000	30	31	119	223	1.68	186000
4 ^a	1	5000	60	90	250	648	1.53	270000
5 ^a	2	1200	5	96	135	166	1.85	829440
6 ^a	2	5000	15	72	253	519	1.59	864000
7 ^a	3	300	15	90	22	39	1.89	64800
8 ^a	3	5000	120	trace	ND	ND	ND	ND
9 ^{f,14}	A	2000	1.5 h	ND	31	288	6.2	1300
10 ^{g,15}	B	6000	2.0 h	ND	115	432	2.2	3000
11 ^{h,16}	C	1000	20 min	77	18	37	1.62	2310
12 ^{i,17}	D	200	60	73	18	21	1.17	8760

^aConditions: [LA] = 0.5 M, THF, 25 °C. ^bBy integration of methine resonances of lactide (5.02 ppm) and cPLA (5.15 ppm) in the ¹H NMR spectra of crude reaction products (Figs. S11-12). ^cBy GPC, using THF as the eluent, and calibrated using narrow MW polystyrene standards (Figs.S13-18). ^dTheoretical M_n are calculated from the monomer conversion data and assume one initiation per catalyst. ^eLiterature catalyst: tested neat at 180 °C. ^fLiterature catalyst: tested neat at 160 °C. ^gLiterature catalyst: tested neat at 130 °C. ^hLiterature catalyst: tested at [LA] = 0.6 M, THF, 25 °C.

Catalysts **1** and **2** show outstanding activity in cPLA synthesis, exceeding performances of other metal or organocatalysts by several orders of magnitude. Catalyst **1** shows very high activity, polymerizing 300 equiv. of lactide in just 15 seconds to give atactic PLA (Table 1, #1, Fig. S11). It shows excellent performance at low catalyst loadings, fully converting 5000 equiv. of lactide within 1 minute; operating with a TOF of 270,000 h⁻¹ (Table 1, #2-4). The PLA produced here has a high molar mass ($M_n > 100$ kg mol⁻¹) and the molar mass increases as catalyst loading is reduced, reaching an exceptionally high value of 250 kg mol⁻¹ (Table 1, #1-4). Complex **2**, featuring the electron-donating, saturated NHC ligands,³⁹ shows outstanding activity, reaching complete conversion of 1200 equiv. of lactide in just 5 seconds and fully converting 5000 equiv. in 15 seconds (Table 1, #5-6). The TOF of 864,000 h⁻¹ is three times higher than **1** under equivalent conditions and makes it the most active catalyst yet reported for the synthesis of cPLA. It also produces PLA of high molar mass reaching values of 253 kg mol⁻¹. The enhanced activity for **2**, compared to **1**, is rationalized by the increased Lewis basicity of the NHC moieties coupled with the increased steric bulk. Both factors enhance the lability of the key metal-ligand bonds, as confirmed by comparison of the solid-state structures which show significantly longer Ce-NHC bonds in complex **2** than in **1** (average Ce-C distances determined by single crystal X-ray diffraction studies: **1** = 2.742(6) Å; ³⁸ **2** = 2.777(3) Å Table S3).

The selectivity of these catalysts to produce cPLA is very

high. For example, the MALDI-ToF spectrum of a deliberately low molar mass PLA sample, produced using **1** (**1**:LA = 1:50) shows only signals attributed to cyclic polymer, and cyclic polymer ring-opened by the matrix dithranol (Fig. 1A, Table 1, #1, Fig. S27).

Transesterification occurs as the peaks corresponding to cyclic PLA are separated by 72 a.m.u, i.e., half of a lactide unit. Further evidence supporting cyclic PLA formation comes from the lack of observable chain end groups by ¹H NMR spectroscopy, for cPLA obtained by treatment of **1** with 50 or 300 equivalents of LA (Table 1 #1, Table S1 #1, Fig. S11, S24-25). For comparison, a sample of linear PLA prepared using **1** in the presence of three equiv. of isopropanol, shows the expected integrals for the isopropoxy ester end groups (Table S1, Fig. S25). Since MALDI-ToF and NMR end group analysis are only effective for polymers in the lower M_w regime, GPC and intrinsic viscosity measurements were used for the analysis of the high molar mass cPLA samples ($M_n > 100$ kg mol⁻¹). Both techniques fully substantiate cyclic PLA formation (see Table S1 #3 for a comparison with high M_w linear PLA). GPC analysis reveals that the cyclic PLA sample shows lower intrinsic viscosity (IV) than an analogous linear PLA sample (Fig. 1B); this difference arises from the smaller hydrodynamic radius of cPLA compared to linear chains. The ratio $[\eta]_{\text{cyclic}}/[\eta]_{\text{linear}}$ is 0.68 which is in excellent agreement with calculated and experimental values obtained for other cyclic PLA samples.⁴⁰ A note regarding presentation of molecular weight values is warranted; in this work uncorrected M_n , deter-

Table 2: Ring opening polymerization of selected lactones using catalysts 1 and 2

Entry	Cat	[M]	[LA]/[Cat]	Time	Conv. ^c [%]	M_n^c (GPC) [kg mol ⁻¹]	M_n^b (theo) [kg mol ⁻¹]	\bar{D}^c	TOF [h ⁻¹]
1 ^a	1	L-LA	300	15 s	92	81	39	2.01	66240
2 ^a	1	L-LA	5000	60 s	62	401	447	1.17	186000
3 ^a	2	L-LA	5000	30 s	76	373	548	1.20	456000
4 ^a	1	ϵ -CL	300	3 min	74	39	32	1.31	4440
5 ^a	1	β -BL	100	17 h	26	1.9	1.5	2.51	1.5
6 ^b	1	β -BL	100	20 min	73	6.4	6.3	1.38	219

^aConditions: [Monomer] = 0.5 M, THF, 25 °C. ^bConditions: [β -BL] = 2.0 M, PhMe, 25 °C. ^cFrom integration of normalized methine resonances of L-LA (5.02 ppm), PLLA (5.15 ppm), ϵ -CL (4.69 ppm), PCL (4.54 ppm), β -BL (4.72 ppm) and P(β -BL) (5.60 ppm) in the ¹H NMR spectra of crude reaction products (SI 5.0). ^dBy GPC, CHCl₃ eluent for PLLA, THF eluent for PCL and P(β -BL), calibrated using narrow MW polystyrene standards without correction (Figs. S35-40). ^eTheoretical M_n calculated from monomer conversion data, assuming one initiation per catalyst.

mined by gel permeation chromatography (GPC) are presented as the use of correction factors determined for linear PLA is not appropriate (Table 1).

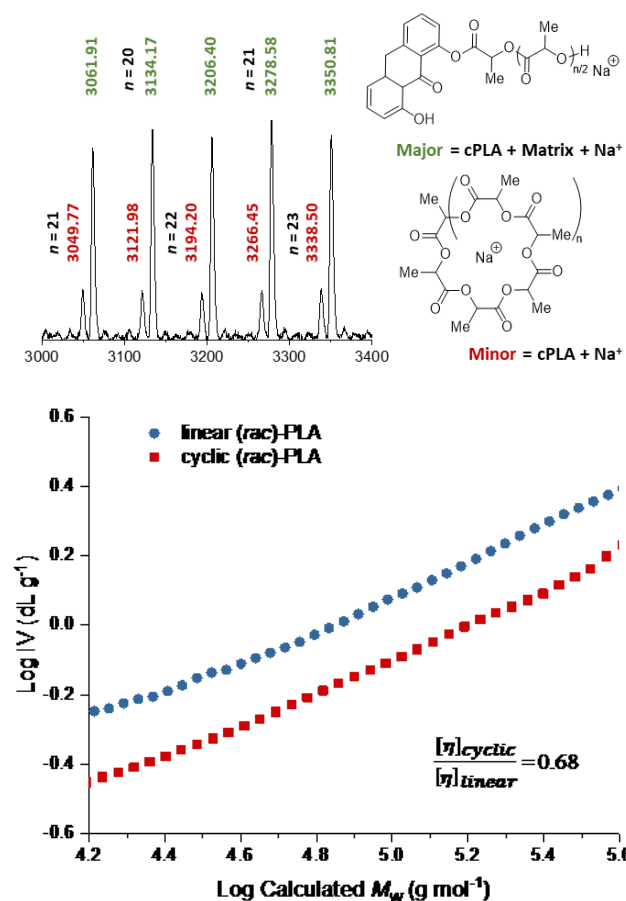


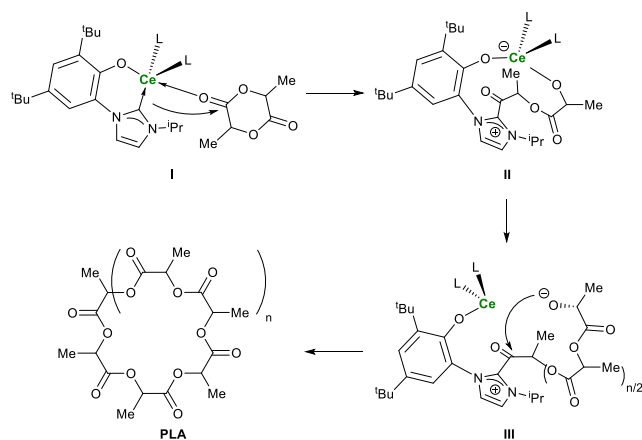
Figure 1A (top): Characterization data for cyclic PLA formed using 1 or 2. Top: Magnified MALDI-ToF spectrum of cyclic PLA prepared as per Table S1, #1, full spectrum, Figure S27. **Figure 1B** (bottom): Log(Intrinsic Viscosity) vs. Log(M_w) for cyclic and linear PLA. cPLA as per Table 1, #4 (1:5000 = 1:LA; [LA] = 0.5 M; THF); linear PLA as per Table S1, #3 (1:1:5000 = 1:PrOH:LA; [LA] = 0.5 M; THF).

To compare the performances of 1 and 2 to a structurally related NHC organocatalyst, polymerizations were also conducted using the N-aryloxy-substituted NHC 3 (note the OH group must be protected to prevent undesirable chain transfer reactions) (Table 1, #7-8). At high catalyst loading (1:300), but otherwise identical conditions to 1 or 2, catalyst 3 shows nearly equivalent activity to 1 (TOF 3 = 64, 800 vs. TOF 1 = 72, 000 h⁻¹). However, upon reducing its loading the beneficial bifunctionality of catalysts 1 and 2 becomes evident. Catalyst 3 yields only trace PLA when exposed to 5000 equiv. of lactide, whereas catalysts 1 or 2 achieve fast and complete polymerization within seconds. Although the precise mechanism for these polymerizations is beyond the scope of this first report, at high catalyst loading 1 or 2 may polymerize lactide using only one of the three available NHC ligands, resulting in similar rates to the metal-free catalyst. As the catalyst loading is reduced, it seems likely that all three NHC ligands participate in polymerization as the ratio of theoretical to experimental M_n increases. It is likely that the Ce(III) ion also plays an important role particularly given the significantly faster rates compared to D under equivalent conditions.

Comparing our catalysts to the literature, Table 1, #9-12, shows that 2 tolerates significantly lower loadings than Sn(IV) A, and >600 times higher activity (TOF = 860,000 h⁻¹ vs. 1300 for A). It also produces PLA with ~8 times higher M_n and shows improved polymerization control with narrower dispersity (\bar{D} = 1.5-1.7), c.f. A (\bar{D} = 6).¹⁴ Compared to Sn(II) catalyst B, catalyst 2 shows >250× higher TOF at >100 °C lower reaction temperature. Additionally, 2 also displays >350× higher rates than lanthanide borohydride C and produces PLA with 8× higher M_n . Indeed, it was noted that C could not achieve M_n > 25 kg mol⁻¹ due to transesterification rate limitations.²⁰ Finally, 2 is 100× more active than the free NHC D, and delivers this enhanced activity at 25× lower catalyst loading.¹⁷ It also produces PLA of >10× high molar mass.

In the production of cPLA, catalysts 1 and 2 also compare favorably with some of the best catalysts reported for linear

PLA production. For example, **2** shows 10× higher rate than an Y(III)-phosphasalen catalyst ([Y]:[LA] 1:1000, 25 °C, TOF = 77,600 h⁻¹)⁴¹ and 30× higher rate than a Ca(II)-phenoxide catalyst ([Ca]:[LA] 1:500, 60 °C, TOF = 28,200 h⁻¹).⁴² Catalysts **1** or **2** can also produce linear PLA if *iso*-propanol is added as co-catalyst, affording PLA with molar masses between 50–150 kg mol⁻¹, but with lower rates and less control than the corresponding cyclic polymer syntheses. The exact identity of the active catalyst in the presence of alcohol is currently unknown, but it is most likely that a cerium ‘ate’ isopropoxide complex is formed. Here, chain growth occurs from the activated alcohol by a standard coordination-insertion mechanism, while the higher charge at the metal strengthens the Ce-C_{carbene} bond, rendering the NHC component of the catalyst inactive.⁴³ A model in which chain transfer and termination by any excess alcohol and by the aryloxy groups on the ligand affords molecular weight values in reasonable agreement with theoretical values (Table S1, Figs S20–23).



Scheme 2: Proposed pathway for cyclic PLA formation using Ce-NHC catalysts **1** and **2**.

It is proposed that the formation of cyclic polymer proceeds by lactide coordination at Ce(III) (I) which reduces the barrier to nucleophilic attack and ring-opening by the labile NHC moiety (Scheme 2). Mechanistic studies conducted by Waymouth, suggest that initiation is rate limiting in NHC catalyzed zROP of lactide.²¹ One reason for the significantly better performances of **1** and **2** vs organocatalysts **3** and **D** could be that the presence of Lewis acidic Ce(III) accelerates coordination and initiation. The active propagating intermediate is proposed as a zwitterionic intermediate II where the anionic chain-end is stabilized by coordination to the Ce(III). Propagation occurs by a series of lactide coordination, anionic chain-end nucleophilic attack and ring-opening steps (III). Propagation may occur from one or more of the NHC sites, perhaps rationalizing the high activity at very low catalyst loading. Waymouth’s model also shows a rate of propagation that is significantly faster than the rate of cyclisation, yielding high molecular weight PLA.²¹ Our recent reports on the bifunctional manner in which **1** inserts carbon dioxide or other heteroallenes into the Ce-C_{NHC} bond(s) in **1** provides a model for lactide insertion.³⁸ The precise number of insertions is likely to be

a combination of relative monomer and catalyst concentrations. Chain termination and formation of cyclic chains occurs through intramolecular transesterification steps (III) facilitated by Ce(III) coordination of the terminal anionic chain end. The much higher molar mass values obtained using these bifunctional catalysts compared to simple NHCs imply that chain propagation events are easier/faster than transesterification and ring-closing steps that would release a smaller macrocyclic product. Another possibility is that the Ce-aryloxy bond could ring open the coordinated lactide monomer in line with traditional metal-aryloxy/alkoxide coordination insertion polymerizations. This mechanistic pathway would likely lead to the production of linear PLA with incorporation of the ligand framework into the product, which is never observed under the reaction conditions without co-initiator. Furthermore, based on our previous studies, reactions of these anionic tethered carbenes occur exclusively across the Ln-C bond, and the anionic tether’s function is to prevent ligand dissociation.

To explore the broader utility of these catalysts, the conversion of other cyclic esters into cyclic polyesters was studied (Table 2). Catalyst **1** polymerizes L-LA with a slightly reduced rate to that for *rac*-LA (Table 2 #2), yielding cyclic PLLA with $M_n > 400$ kg mol⁻¹. The slightly diminished rate compared to *rac*-LA can be attributed to the extremely viscous reaction medium at 0.5 M in THF. The polymerization occurred without detectable epimerization of the stereocenters (Fig. S30). The ability to polymerize without racemization is useful since zROP using organocatalysts can suffer from epimerization. The $c[\eta]_{\text{cyclic}}/[\eta]_{\text{linear}} = 0.70$, giving confidence in the high selectivity for cyclic topology (Fig. S27).⁴⁰ As mentioned earlier, tin catalyst **A** (chart 1) was recently reported to produce cPLLA with an unexpectedly high T_m of 190–196 °C (PLLA T_m is usually 174–184 °C), although specific annealing and crystallization conditions were required.^{13, 18} Initial studies using the cyclic and linear PLLA samples prepared using **1**, show equivalent T_m values of 172 °C, determined by DSC. Future investigations will focus on comparing crystallization rates and percentage crystallinity for the samples, as well as understanding better the potential for specific annealing conditions (Fig. S43–44).

The polymerization of ϵ -caprolactone (ϵ -CL) using catalyst **1** (Table 2, #4) showed an activity of 4500 h⁻¹. The activity is significantly lower than for lactide which is consistent with previous observations that NHC catalyzed zROP of ϵ -CL is also a lot slower and is more sensitive to carbene steric and electronic properties.⁴⁴ **1** was tested with 100 equiv. of β -BL but resulted in only 26% conversion after 17 h (Table 2, #5), again consistent with reports for NHC catalysts.²⁴ In contrast, the same polymerization using **1** and an equivalent of *i*PrOH gave linear poly(β -BL) with a TOF of 200 h⁻¹ (Table 2, #6).

In summary, new rare-earth catalysts deliver high molar mass cyclic PLA with outstanding rates at low loadings.

The extremely high activities are only achieved by the combination of the Lewis acid Ce(III) and the Lewis basic NHC group. The catalyst featuring a saturated NHC is the most active and both catalysts are able to produce other cyclic polyesters from lactones. Future investigations into the catalysis and the properties of these high molar mass cyclic polyesters are warranted.

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SUPPORTING INFORMATION

Electronic Supplementary Information (ESI) available: detailed experimental procedures for catalyst synthesis and polymerizations, catalyst and polymer characterization data, and crystallographic details (PDF). See DOI: 10.1039/xxxxxxx.

Crystallographic information file for 2, CCDC: 1986496(CIF).

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