



Article

Organocatalytic Stereoselective Cyclic Polylactide Synthesis in Supercritical Carbon Dioxide under Plasticizing Conditions

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Abstract: Cyclic polylactide (cPLA) is a structural isomer of linear polylactide (PLA) although it possesses unique functionalities in comparison to its linear counterpart. Hitherto, the control of stereochemical purity in conventional cPLA synthesis has not been achieved. In this study, highly stereochemically pure cPLA was synthesized in the absence of a metal catalyst and organic solvent, which required high consumption of the residual monomer. The synthesis was conducted in supercritical carbon dioxide under CO₂ plasticizing polymerization conditions in the presence of an organocatalyst and thiourea additives. In comparison with the stereocomplexes synthesized through conventional methods, cPLA from L-lactide (cPLLA) and cPLA from D-lactide (cPDLA) were synthesized with higher stereochemical purity and improved thermal stability. Moreover, the method presented herein is environmentally friendly and thus, applicable on an industrial level.

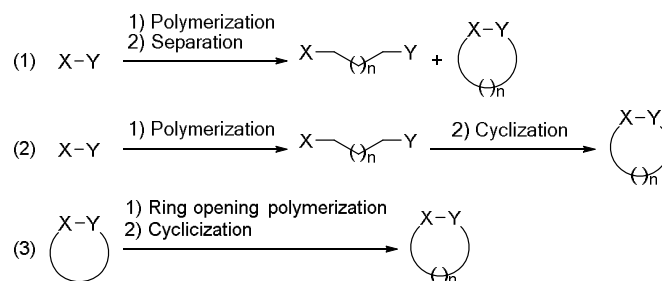
Keywords: organocatalyst; thiourea; cyclic polylactide; CO₂ plasticizing polymerization; stereocomplexes

1. Introduction

Linear polylactides (PLAs) have high biodegradability and biocompatibility, with their potential applications in the medical, pharmaceutical and materials fields having drawn a significant amount of attention [1–3]. Cyclic polylactide (cPLA), which is a structural isomer of PLA with a unique topology, also displays favorable properties [4–8]. For example, a study on the effect of cPLAs on tumor cells and tumor-bearing mice demonstrated that cPLAs effectively inhibit tumor cell growth [9]. Furthermore, in a recent study, cPLA was used as a stabilizer for palladium nanoparticles in the synthesis of a cPLA-clay hybrid material, which can be a recyclable catalyst, for use in the aminocarbonylation reaction of aryl halides with various amines [10]. Despite these attractive properties, cPLAs remain underexplored in comparison to linear PLAs both with respect to their synthesis and practical applications [10].

Until now, three strategies have been reported for the synthesis of cPLAs (Scheme 1): (1) polymerization and separation; (2) polymerization and cyclization; and (3) ring-opening polymerization (ROP) and cyclization. Strategy (1) has proved to be inefficient as even when fractionated by a reverse-phase octadecylsilyl (ODS) column chromatography, a mixture of linear

PLAs and *c*PLAs is obtained [11]. Strategy (2) requires several steps, although uniform *c*PLAs can be eventually separated using a gel filtration column [12–16]. Nevertheless, it is still inappropriate for large-scale syntheses. In contrast, strategy (3) allows for a simple and straightforward one-step synthesis of *c*PLAs. The latter of these strategies was reported in 2007 using an organocatalytic method [17–23], while researchers have used a metal complex catalytic method in 2011 [24–29].

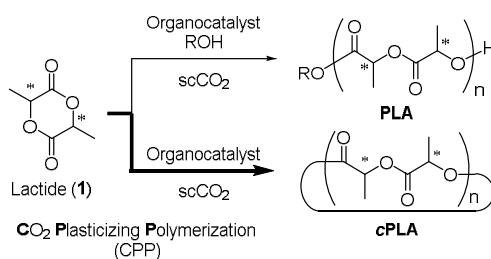


Scheme 1. Synthetic strategies of cyclic polylactide (*c*PLA).

According to these reports, *c*PLA was obtained with high conversion (85–97%), moderate polydispersity index (PDI = 1.22–3.60) and high number-average molecular weight ($M_n = 6400\text{--}69,000$). The metal complex catalysts displayed poor reactivity and required high temperatures (30–160 °C) and long reaction times (4–18.5 h). In contrast, the reaction efficiency of *N*-heterocyclic carbene (NHC) as an organocatalyst was extremely high and the polymerization reaction occurred within 30 s at 25 °C. However, there were several drawbacks in that the polymerization reactions were conducted in flammable or toxic organic solvents, such as THF or CH_2Cl_2 , and required drybox or Schlenk techniques under nitrogen, thereby limiting the potential for industrialization [19].

In general, the available methodologies fail to control the stereochemistry of PLAs, which is one of the most important parameters in material development as it has a significant effect on the properties [30,31]. In fact, in most examples of *c*PLA syntheses, racemic lactides are employed and thus, control of the stereochemical purity is insufficiently achieved. To the best of our knowledge, the stereocomplexes of *c*PLA were reported in 2011 by Waymouth et al. [19]. However, the fraction of isotactic (*iii*) tetrads of *c*PLA prepared from L-lactide was 0.81–0.83, suggesting that epimerization occurred during the polymerization step. Recently, Kricheldorf et al. reported a racemization-free polymerization, in which a cyclic tin catalyst was employed under bulk polymerization conditions, but a high temperature (160 °C) was required [29].

Based on our previous findings on the synthesis of stereochemically pure linear PLA [32], in this study, we have developed a method for the synthesis of highly pure *c*PLA in the absence of metals, organic solvents or residual monomers. Instead, the approach employs an organocatalyst in supercritical carbon dioxide (scCO_2) under CO_2 plasticizing polymerization (CPP) conditions at low temperatures. The results were promising as both L- and D-*c*PLA were synthesized in high stereochemical purity from L- and D-lactide **1**, respectively (Scheme 2), which are hereafter denoted as *c*PLLA and *c*PDLA, respectively. An improvement in the thermal properties of the stereocomplexes was also observed.



Scheme 2. ROP of lactide, which creates PLA and *c*PLA.

2. Materials and Methods

2.1. Materials

In this study, 1-(3,5-Bis(trifluoromethyl)phenyl)-3-cyclohexyl thiourea was synthesized according to literature procedures [33]. All other chemicals and solvents were commercially available and used as received. L-Lactide was provided by Ricoh Co., Ltd. (Tokyo, Japan), while CO₂ was obtained from Air Liquide Kogyogas Ltd. (Tokyo, Japan).

2.2. Synthesis

Polymerization reactions were conducted in a scCO₂ reaction system using the TVS-N2-type portable reactor (20 MPa, 260 °C) manufactured by Taiatsu Techno Corporation (Tokyo, Japan) with the JASCO PU-1586 scCO₂ pump (JASCO Corporation, Tokyo, Japan). L-Lactide (1, 864 mg, 6.0 mmol, 1.0 eq) and the organocatalyst (4-(dimethylamino)pyridine (DMAP), 0.40 mmol, 6.6 mol %) were added to a 12-mL pressure-resistant reactor, before the mixture was heated to 60 °C using a water bath. The vessel was charged with scCO₂ (60 °C, 10 MPa) and the solution was stirred for 5 min. The reaction mixture was allowed to stand for 5 h, before the pressure was reduced from supercritical to atmospheric, yielding cPLA as a white solid. For the thiourea-mediated cPLLA synthesis, 1-(3,5-bis(trifluoromethyl)phenyl)-3-cyclohexyl thiourea (1 mol %) was added to the mixture of lactide and DMAP. This mixture was subjected to the polymerization reaction for 2.5 h as described above.

cPLLA and cPDLA samples with different number-average molecular weights were isolated by preparative gel permeation chromatography (GPC) using a recycling high performance liquid chromatography (HPLC) system (YMC LC-Forte/R, YMC CO., Ltd., Kyoto, Japan) with a YMC-GPC T30000 (21.2 mm × 600 mm) and YMC-GPC T4000 (21.2 mm × 600 mm) columns in series (CHCl₃ as the eluent, flow rate of 6.0 mL/min). For preparation of the stereocomplex of cPLA [19], cPLLA (50 mg) and cPDLA (50 mg) were dissolved separately in 5 mL of CH₂Cl₂. These solutions were mixed together in a 20-mL flask and stirred for 5 min at room temperature. The solvent was evaporated slowly (200 torr) at room temperature, before the residue was dried under a vacuum to remove the residual solvent. The resulting material was used for DSC measurements.

2.3. Characterization

The conversion by polymerization was determined through ¹H NMR analysis. ¹H NMR (300 MHz) spectra were recorded using the JEOL JNM-AL spectrometer (JEOL, Tokyo, Japan) at ambient temperature. The spectra were recorded using CDCl₃ as a solvent and tetramethylsilane (TMS) as an internal standard ($\delta = 0$ ppm). The number- and weight-average molecular weights (M_n, M_w) and polydispersity index (PDI = M_w/M_n) of the products were determined by gel permeation chromatography (GPC) analysis using the SHIMADZU LC-5A pump (SHIMADZU, Kyoto, Japan) and JAI R1-3H RI detector (Japan Analytical Industry Co., Ltd., Tokyo, Japan) with GPC column GPC K-806L (Shodex, Tokyo, Japan, 8.0 mm × 300 mm, flow rate 0.8 mL/min), using polystyrene as a standard and CHCl₃ as an eluent. LAssoft CDS-Lite software (LAssoft, Ltd., Chiba, Japan) was used for the molecular weight calculations.

The topology of the polymer product being cyclic rather than linear was confirmed by ¹H NMR and matrix assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF-MS) (Supplementary Materials, Figures S1 and S2). The mass spectra were recorded using ultrafleXtreme mass spectrometry (MALDI-TOF-MS, Bruker Japan, Yokohama, Japan). For MALDI-TOF-MS measurements, the cPLA was dissolved in CHCl₃. *Trans*-2-[3-(4-*tert*-butylphenyl)-2-methyl-2-propenylidene]malononitrile (DCTB) was used as the matrix and silver trifluoroacetate was added as a cation source.

In order to hydrolyze the polymer materials, an aqueous solution of NaOH (1 M, 10 mL) was added to the polymer. After 4 h under reflux conditions, the mixture was cooled down to the ambient temperature and an aqueous solution of HCl (2 M, 5.5 mL) was added. The resulting lactic acid

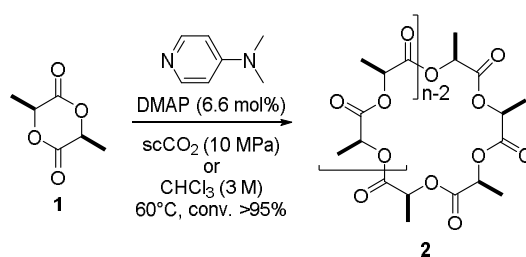
was analyzed by chiral HPLC. The HPLC analysis was conducted under the following conditions: SUMICHIRAL OA5000 column (Sumika Chemical Analysis Service, Ltd., 4.6 mm × 150 mm, flow rate 1.0 mL/min) with 2 mM CuSO₄ aq/2-propanol = 95:5; UV detection at 254 nm (L-lactide: retention time = 8.5 min; D-lactide: retention time = 10.3 min) (Supplementary Materials, Figure S3).

Differential scanning calorimetry (DSC) analysis was performed using SHIMADZU DSC-60 (SHIMADZU, Kyoto, Japan). For DSC measurements, a 5-mg sample was heated from 25 to 250 °C at 10 °C/min rate under an argon flow (50 mL/min). The data collection interval was 1.0 s.

3. Results and Discussion

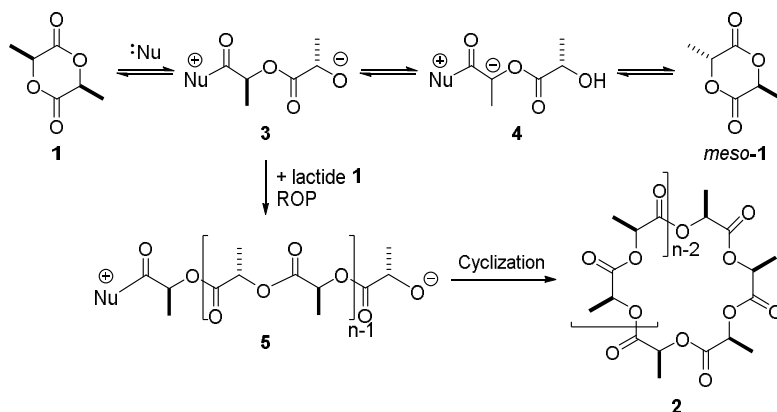
The synthesis of *c*PLA via an organocatalytic ROP was examined according to previous findings on the synthesis of stereochemically pure linear PLA (Table 1) [32]. Notably, ¹H NMR analysis of the polymerization reaction mixture showed that the remaining unreacted monomers were less than 5% in any of the polymerization reactions. The monomer conversion rate and weight of the recovered polymer were both higher than 95%. In the conventional solution polymerization method, the reaction was slow and resulted in the formation of amorphous *c*PLLA with low stereochemical purity, which was determined by HPLC analysis after hydrolysis of *c*PLLA to lactic acid (Table 1, entry 1). In contrast, the reaction proceeded smoothly in *sc*CO₂ and crystalline *c*PLLA was obtained in a high enantiomeric excess (ee) of 90.5% (Table 1, entry 2). The success of the polymerization reaction under *sc*CO₂ conditions was attributed to the high concentration conditions similar to those in bulk polymerization and uniform conditions similar to those in solution polymerization. We refer to this process as a CO₂ plasticizing polymerization (CPP) method [32]. Under CPP conditions, epimerization was suppressed since the reactive zwitterionic intermediate (**3**) was less likely to be solvated by *sc*CO₂ (dielectric constant (ε_r) = 1.15 at 10 MPa, 60 °C) as this has a lower ε_r than pentane (ε_r = 1.84) and hexane (ε_r = 1.89) [34,35]. Thus, this allows for the ROP to be preferred over the epimerization, which would form the *meso*-lactide **1** (Scheme 3). It was assumed that the stereochemical purity of *c*PLLA could be improved by increasing the polymerization consumption rate of the monomer. Thus, the additives that selectively activated the carbonyl group of L-lactide were investigated (Figure 1). In particular, 1-(3,5-bis(trifluoromethyl)phenyl)-3-cyclohexylthiourea accelerated the ROP reaction and improved the stereochemical purity, giving an ee of 93.5% (Table 1, entry 3). Given the success of the reaction using L-lactide, the same reaction conditions were applied to the ROP of D-lactide, with *c*PDLA being obtained in high stereoselectivity (entries 4 and 5). The PDI of the *c*PLA formed herein was 1.20–1.60, which was comparable to that obtained via the previously reported NHC catalytic method (1.3–1.4) [19].

Table 1. Organocatalytic *c*PLA synthesis in supercritical carbon dioxide (*sc*CO₂).



Entry	Solvent	Time (h)	M _n ^(a)	PDI ^(b)	ee (%) ^(c)
1	CHCl ₃	120	12,700	3.11	39.0
2	<i>sc</i> CO ₂	5	5500	1.40	90.5
3 ^(d)	<i>sc</i> CO ₂	2.5	11,000	1.60	93.5
4 ^(e)	<i>sc</i> CO ₂	5	6000	1.31	91.0
5 ^(d,e)	<i>sc</i> CO ₂	2.5	6800	1.20	97.0

^(a) Determined by GPC analysis using a polystyrene standard. ^(b) Polydispersity index. ^(c) Determined by HPLC analysis after hydrolysis of the polymer to lactic acid. ^(d) 1-(3,5-Bis(trifluoromethyl)phenyl)-3-cyclohexyl thiourea (1 mol%) was added. ^(e) D-Lactide (*ent*-1) was used.



Scheme 3. Competitive reaction between polymerization (and hence, cyclization) and epimerization.

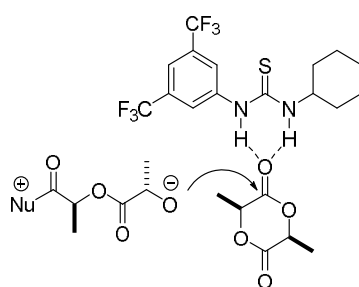


Figure 1. Activation of L-lactide monomer by a thiourea additive.

In the *c*PLA synthesis, since a cyclic structure was formed via an intramolecular cyclization, the PDI could not be improved unless the linear intermediate of the same molecular weight is selectively cyclized.

Similar to PLA, *c*PLA has been known to form a stereocomplex of *c*PLA (*sc-c*PLA) [19,36,37]. In this work, *c*PDLA was synthesized according to the same procedure as that of *c*PLLA, while differential scanning calorimetry (DSC) was applied to create *sc-c*PLA (Figure 2). Interestingly, although the molecular weight was lower than the one reported in the literature (Table 2, entries 1 and 2 vs. 3), the measured melting point was higher than the previously reported value [19], which indicates stronger intermolecular forces. The melting point of *sc-c*PLA with the highest stereochemical purity was 212 °C. As the stereochemical purity decreased, the melting point decreased to 207 °C (Table 2, entries 1 vs. 2). Therefore, we can conclude that the higher stereochemical purity of the D- and L-forms led to stronger intermolecular interactions between the two forms in the stereocomplex and hence, a higher melting point (Figure 3). In addition, similar to the case of the stereocomplex of *c*PLA, the melting point of *c*PLA itself also depended on the stereochemical purity.

Table 2. DSC measurements of the stereocomplex of *c*PLA.

Entry	<i>c</i> PLA	M _n	PDI	Ee (%)	T _m (°C)	T _m (<i>sc-c</i> PLA) (°C)
1	<i>c</i> PDLA	6800	1.20	97.0	152	212
	<i>c</i> PLLA	11,000	1.60	93.5	149	
2	<i>c</i> PDLA	6000	1.31	91.0	143	207
	<i>c</i> PLLA	5500	1.40	90.5	145	
3 ^(a)	<i>c</i> PDLA	26,000	1.40	(0.81) ^(b)	132	179
	<i>c</i> PLLA	30,000	1.30	(0.83) ^(b)	135	

^(a) Data reported in reference 19. ^(b) Fraction of isotactic tetrads.

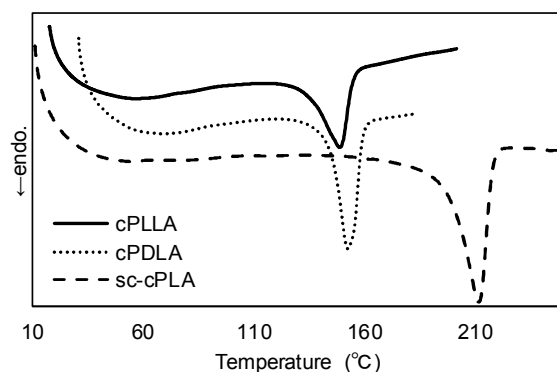


Figure 2. DSC measurements of the stereocomplex of cPLA (Table 2, entry 1).

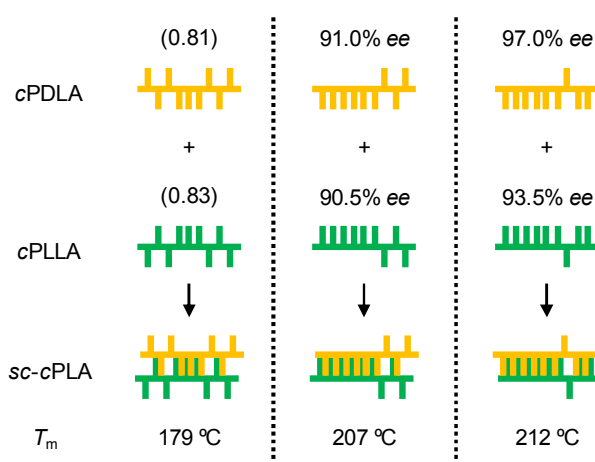


Figure 3. Effect of stereochemical purity on the intermolecular interactions in the stereocomplex formation.

Subsequently, the effect of the ring size on the thermal stability was investigated (Table 3 and Figure 4). Three stereocomplex samples with different number-average molecular weights were prepared using cPLLA and cPDLA, which are shown in Table 2, entry 2. These were obtained and purified by a preparative GPC. Sample 1, which had very different molecular weights of cPLLA and cPDLA, had a melting point of 190 °C (Table 3, entry 1). In Sample 2, a more moderate difference in the molecular weight distribution led to an increase in the melting point to 200 °C (Table 3, entry 2). Finally, the smallest difference in the molecular weights in sample 3 gave the highest melting point (Table 3, entry 3). These results suggested that the degree of formation of the stereocomplex depended not only on the stereochemical purity, but also on the ring size (and similarities thereof) because the overlapping portion between cPLLA and cPDLA was limited due to a different radius of the curvature.

Table 3. Stereocomplex of PLA with different ring sizes.

Entry	cPLA	Mn	PDI	T_m (sc-cPLA)
1	cPDLA	7900	1.18	190
	cPLLA	2600	1.20	
2	cPDLA	5100	1.23	200
	cPLLA	7400	1.23	
3	cPDLA	6000	1.31	207
	cPLLA	5500	1.40	

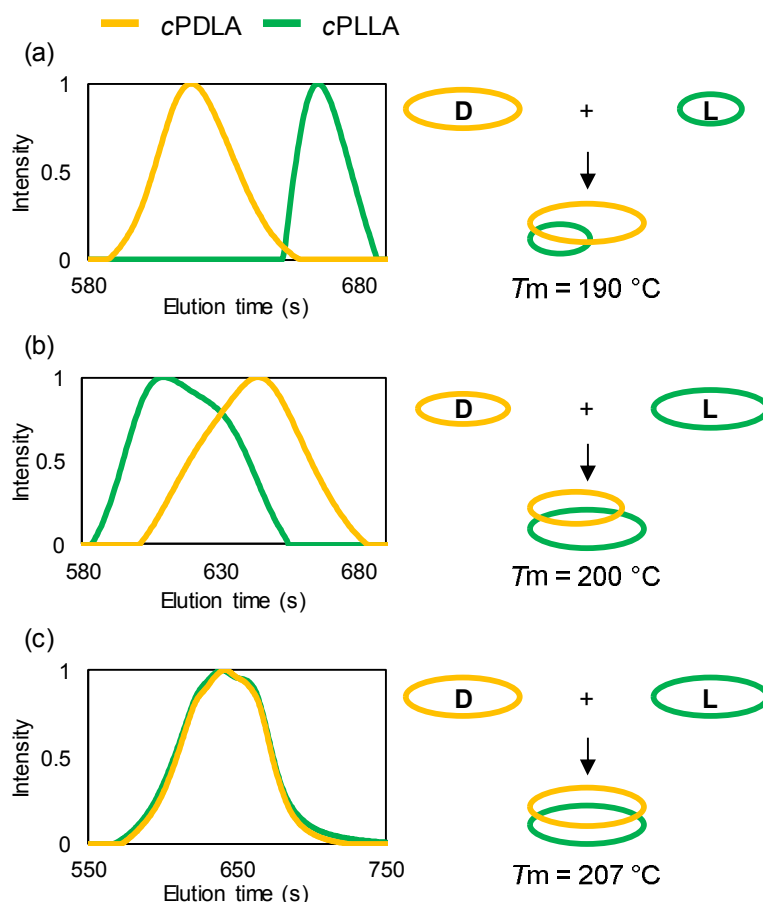


Figure 4. GPC traces of cPLA with different ring sizes and images of sc-cPLA.

4. Conclusions

In this study, highly stereochemically pure cPLA was synthesized in the absence of a metal catalyst or organic solvent, which required high consumption of the residual monomer. The synthesis was conducted in scCO₂ under CO₂ plasticizing polymerization conditions in the presence of an organocatalyst and thiourea additives. In this approach, the epimerization of the obtained cPLA was suppressed and the stereochemical purity was higher than those obtained from conventional methods, although the control of stereochemical purity in conventional cPLA synthesis has not yet been achieved. In comparison to stereocomplexes synthesized through the conventional methods, cPLA from L-lactide (cPLLA) and cPLA from D-lactide (cPDLA) stereocomplexes were synthesized with higher stereochemical purity and improved thermal stability. Based on these results, we concluded that the method presented herein could meet the increasing demands of medical and material applications in terms of safety and high functionality in the large-scale industrial manufacturing of cPLA and in academic research.

Supplementary Materials: The experimental and ¹H NMR spectroscopic and analytic data are available online at <http://www.mdpi.com/2073-4360/10/7/713/s1>.

Author Contributions: All authors contributed equally. N.M. conceived and designed the experiments; S.Y. and Y.N. performed the experiments and analyzed the data; K.S. and T.N. contributed reagents/materials/analysis tools; M. wrote the paper.

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Conflicts of Interest: The authors declare no conflict of interest.

References

1. Thakur, V.K.; Thakur, M.K. *Handbook of Polymers for Pharmaceutical Technologies: Biodegradable Polymers*; Scrivener Publishing LLC: New York, NY, USA, 2015; Volume 3, pp. 1–583. [[CrossRef](#)]
2. Rieger, B.; Kunkel, A.; Coates, G.W.; Reichardt, R.; Dinjus, E.; Zevaco, T.A. *Synthetic Biodegradable Polymers*; Springer: Berlin/Heidelberg, Germany, 2012; Volume 245, pp. 1–364.
3. Lendlein, A.; Sisson, A. *Handbook of Biodegradable Polymers: Isolation, Synthesis, Characterization and Applications*; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2011; pp. 1–405.
4. Nomura, K.; Ohara, H. Synthesis and function of cyclic poly(lactic acid) and oligo(lactic acid). *Mini-Rev. Org. Chem.* **2017**, *14*, 35–43. [[CrossRef](#)]
5. Tezuka, Y. *Topological Polymer Chemistry: Progress of Cyclic Polymers in Syntheses, Properties and Functions*; World Scientific Publishing Co., Pte., Ltd.: Singapore, 2013; pp. 1–352.
6. Yamamoto, T.; Tezuka, Y. Cyclic and multicyclic topological polymers. In *Complex Macromolecular Architectures: Synthesis, Characterization, and Self-Assembly*; Hadjichristidis, N., Hirao, A., Tezuka, Y., DuPrez, F., Eds.; John Wiley & Sons (Asia) Pte. Ltd.: Singapore, 2011; pp. 3–19.
7. Endo, K. Synthesis and properties of cyclic polymers. In *New Frontiers in Polymer Synthesis*; Kobayashi, S., Ed.; Springer: Berlin/Heidelberg, Germany, 2008; Volume 217, pp. 121–183.
8. Roovers, J. Organic cyclic polymers. In *Cyclic Polymers*, 2nd ed.; Semlyen, J.A., Ed.; Kluwer Academic Publishers: Dordrecht, The Netherlands, 2000; pp. 347–384.
9. Takada, S.; Nagato, Y.; Yamamura, M. Effect of cyclic polylactates on tumor cells and tumor bearing mice. *Biochem. Mol. Biol. Int.* **1997**, *43*, 9–17. [[CrossRef](#)] [[PubMed](#)]
10. Prasad, A.V.; Biying, A.O.; Ling, W.Y.; Stubbs, L.P.; Zhu, Y. Synthesis and new application of green and recyclable cyclic poly(L-lactide)-clay hybrid. *J. Polym. Sci. Part A Polym. Chem.* **2013**, *51*, 4167–4174. [[CrossRef](#)]
11. Kato, H.; Naganushi, Y. Preparation of L-Lactic Acid Condensation Products for Cancer Treatment. JPH06336427A, 6 December 1994.
12. Osaka, I.; Watanabe, M.; Takama, M.; Murakami, M.; Arakawa, R. Characterization of linear and cyclic polylactic acids and their solvolysis products by electrospray ionization mass spectrometry. *J. Mass Spectrom.* **2006**, *41*, 1369–1377. [[CrossRef](#)] [[PubMed](#)]
13. Osaka, I.; Yoshimoto, A.; Watanabe, M.; Takama, M.; Murakami, M.; Kawasaki, H.; Arakawa, R. Quantitative determination of cyclic polylactic acid oligomers in serum by direct injection liquid chromatography tandem mass spectrometry. *J. Chromatogr. B* **2008**, *870*, 247–250. [[CrossRef](#)] [[PubMed](#)]
14. Sugai, N.; Yamamoto, T.; Tezuka, Y. Synthesis of orientationally isomeric cyclic stereoblock polylactides with head-to-head and head-to-tail linkages of the enantiomeric segments. *ACS Macro Lett.* **2012**, *1*, 902–906. [[CrossRef](#)]
15. Josse, T.; De Winter, J.; Dubois, P.; Coulembier, O.; Gerbaux, P.; Memboeuf, A. A tandem mass spectrometry-based method to assess the architectural purity of synthetic polymers: A case of a cyclic polylactide obtained by click chemistry. *Polym. Chem.* **2015**, *6*, 64–69. [[CrossRef](#)]
16. Stanford, M.J.; Pflughaupt, R.L.; Dove, A.P. Synthesis of stereoregular cyclic poly(lactide)s via “thiol-ene” click chemistry. *Macromolecules* **2010**, *43*, 6538–6541. [[CrossRef](#)]
17. Culkun, D.A.; Jeong, W.H.; Csihony, S.; Gomez, E.D.; Balsara, N.R.; Hedrick, J.L.; Waymouth, R.M. Zwitterionic polymerization of lactide to cyclic poly(lactide) by using *N*-heterocyclic carbene organocatalysts. *Angew. Chem. Int. Ed.* **2007**, *46*, 2627–2630. [[CrossRef](#)] [[PubMed](#)]
18. Jeong, W.; Shin, E.J.; Culkun, D.A.; Hedrick, J.L.; Waymouth, R.M. Zwitterionic polymerization: A kinetic strategy for the controlled synthesis of cyclic polylactide. *J. Am. Chem. Soc.* **2009**, *131*, 4884–4891. [[CrossRef](#)] [[PubMed](#)]
19. Shin, E.J.; Jones, A.E.; Waymouth, R.M. Stereocomplexation in cyclic and linear polylactide blends. *Macromolecules* **2012**, *45*, 595–598. [[CrossRef](#)]

20. Prasad, A.V.; Stubbs, L.P.; Zhun, M.; Zhu, Y.H. Zwitterionic ring opening polymerization of lactide by metal free catalysts: Production of cyclic polymers. *J. Appl. Polym. Sci.* **2012**, *123*, 1568–1575. [[CrossRef](#)]
21. Kricheldorf, H.R.; Lomadze, N.; Schwarz, G. Cyclic polylactides by imidazole-catalyzed polymerization of L-lactide. *Macromolecules* **2008**, *41*, 7812–7816. [[CrossRef](#)]
22. Brown, H.A.; De Crisci, A.G.; Hedrick, J.L.; Waymouth, R.M. Amidine-mediated zwitterionic polymerization of lactide. *ACS Macro Lett.* **2012**, *1*, 1113–1115. [[CrossRef](#)]
23. Zhang, X.Y.; Waymouth, R.M. Zwitterionic ring opening polymerization with isothiureas. *ACS Macro Lett.* **2014**, *3*, 1024–1028. [[CrossRef](#)]
24. Yao, L.; Wang, L.; Pan, X.; Tang, N.; Wu, J. Synthesis, characterization and catalytic activity of salen-(sodium)₂ and (salen)₂-lanthanum-sodium complexes. *Inorg. Chim. Acta* **2011**, *373*, 219–225. [[CrossRef](#)]
25. Weil, J.; Mathers, R.T.; Getzler, Y.D.Y.L. Lactide cyclopolymerization by an alumatrane-inspired catalyst. *Macromolecules* **2012**, *45*, 1118–1121. [[CrossRef](#)]
26. Piedra-Aroni, E.; Ladavière, C.; Amgoune, A.; Bourissou, D. Ring-opening polymerization with Zn(C₆F₅)₂-based lewis pairs: Original and efficient approach to cyclic polyesters. *J. Am. Chem. Soc.* **2013**, *135*, 13306–13309. [[CrossRef](#)] [[PubMed](#)]
27. Piromjitpong, P.; Ratanapanee, P.; Thumrongpatanaraks, W.; Kongsaree, P.; Phomphrai, K. Synthesis of cyclic polylactide catalysed by bis(salicylaldiminato)tin(II) complexes. *Dalton Trans.* **2012**, *41*, 12704–12710. [[CrossRef](#)] [[PubMed](#)]
28. Wongmahasirikun, P.; Prom-On, P.; Sangtrirutnugul, P.; Kongsaree, P.; Phomphrai, K. Synthesis of cyclic polyesters: Effects of alkoxy side chains in salicylaldiminato tin(II) complexes. *Dalton Trans.* **2015**, *44*, 12357–12364. [[CrossRef](#)] [[PubMed](#)]
29. Kricheldorf, H.R.; Weidner, S.M.; Scheliga, F. Cyclic poly(L-lactide)s via ring-expansion polymerizations catalysed by 2,2-dibutyl-2-stanna-1,3-dithiolane. *Polym. Chem.* **2017**, *8*, 1589–1596. [[CrossRef](#)]
30. Farah, S.; Anderson, D.G.; Langer, R. Physical and mechanical properties of PLA, and their functions in widespread applications—A comprehensive review. *Adv. Drug Deliv. Rev.* **2016**, *107*, 367–392. [[CrossRef](#)] [[PubMed](#)]
31. Martin, O.; Avérous, L. Poly(lactic acid): Plasticization and properties of biodegradable multiphase systems. *Polymer* **2001**, *42*, 6209–6219. [[CrossRef](#)]
32. Mase, N.; Nakaya, N. Organocatalytic synthesis of highly pure linear- and cyclic-polylactide in supercritical carbon dioxide. In Proceedings of the Symposium on Molecular Chirality Asia 2016, Osaka, Japan, 22 April 2016; No. PB-33.
33. Pratt, R.C.; Lohmeijer, B.G.G.; Long, D.A.; Lundberg, P.N.P.; Dove, A.P.; Li, H.; Wade, C.G.; Waymouth, R.M.; Hedrick, J.L. Exploration, optimization, and application of supramolecular thiourea-amine catalysts for the synthesis of lactide (co)polymers. *Macromolecules* **2006**, *39*, 7863–7871. [[CrossRef](#)]
34. Wesch, A.; Dahmen, N.; Ebert, K.H. Measuring the static dielectric constants of pure carbon dioxide and carbon dioxide mixed with ethanol and toluene at elevated pressures. *Ber. Bunsengesellsch. Phys. Chem.* **1996**, *100*, 1368–1371. [[CrossRef](#)]
35. Moriyoshi, T.; Kita, T.; Uosaki, Y. Static relative permittivity of carbon dioxide and nitrous oxide up to 30 MPa. *Ber. Bunsengesellsch. Phys. Chem.* **1993**, *97*, 589–596. [[CrossRef](#)]
36. Tsuji, H. Poly(lactide) stereocomplexes: Formation, structure, properties, degradation, and applications. *Macromol. Biosci.* **2005**, *5*, 569–597. [[CrossRef](#)] [[PubMed](#)]
37. Ikada, Y.; Jamshidi, K.; Tsuji, H.; Hyon, S.H. Stereocomplex formation between enantiomeric poly(lactides). *Macromolecules* **1987**, *20*, 904–906. [[CrossRef](#)]

