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Epimerization-suppressed organocatalytic synthesis of poly-L-lactide in supercritical carbon dioxide under plasticizing conditions

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ABSTRACT

Herein, an efficient (> 95% yield, > 99.0% ee) Brønsted acid-catalyzed synthetic method of poly-L-lactide (PLLA) in supercritical carbon dioxide ($scCO_2$) under plasticizing conditions is presented. High-performance liquid chromatography analysis of the PLLA hydrolysis products indicated that, as opposed to the case of organic solvents, the use of a nucleophilic catalyst in $scCO_2$ suppressed the epimerization. The highly stereochemically pure PLLA prepared by the developed method under metal-free conditions meets the criteria of medicinal/engineering applications.

Introduction

Polylactide (PLA), a biodegradable plastic that has attracted considerable attention as a carbon-neutral material,[1] contains numerous chiral centers in its polymer main chain and exhibits physical properties that are greatly influenced by its stereochemical purity.[2] Generally, mixing highly stereochemically pure poly-L-lactide (PLLA) and poly-D-lactide (PDLA) results in the formation of a stereocomplex with a higher melting point.[3] Although PLA is susceptible to enzymatic hydrolysis, common PLA-degrading enzymes can specifically degrade PLLA. Therefore, the incorporation of a D-isomer inhibits hydrolysis and decreases biodegradability.[4] Considering these advantages, methods for the synthesis of PLA with high stereochemical purity are much sought after.

Previously, metal catalyst-promoted ring-opening polymerization (ROP) of lactide has been reported as an efficient way to prepare PLA,[5] and the selective synthesis of L- or D-PLA from racemic lactide has been achieved by adjusting the chiral ligands of the abovementioned metal catalysts.[6] However, this approach raises certain safety concerns when thus-prepared PLA is used in medicinal and engineering applications, because the metal content of the product cannot be reliably reduced to zero.

Hedrick *et al.* developed a ring-opening PLA synthesis promoted by metal-free organocatalysts such as 4-(dimethylamino)pyridine (DMAP) in 2001,[7] and ever since, the organocatalytic approach has progressed considerably.[8] Hedrick *et al.* also reported that no epimerization was observed during the DMAP-catalyzed PLA synthesis at low temperature (35 °C). However, in the abovementioned study, the stereochemical purity of PLA was determined by ^{13}C NMR analysis, which lacks quantitative accuracy (Figure 1, eq. 1 and 2).[7]

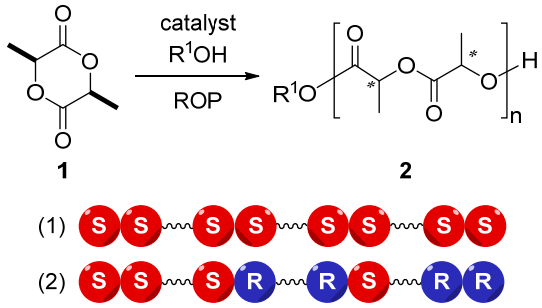
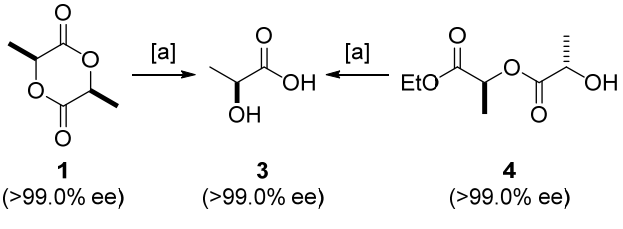
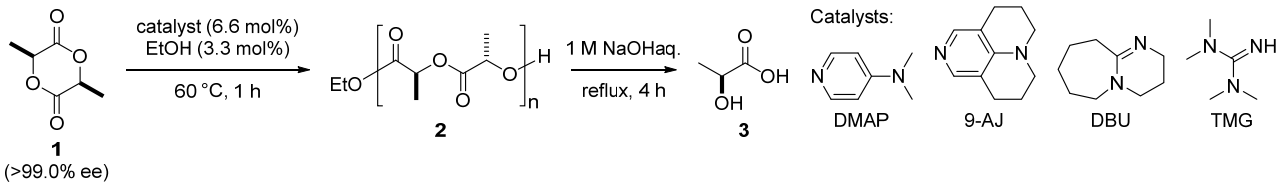


Fig. 1. Synthesis of highly stereochemically pure PLLA.



[a] 1 M NaOH, reflux, 4 h

Scheme 1. Hydrolysis of L-lactide (**1**) and dimer **4**.



Scheme 2. Organocatalyst-promoted synthesis of PLA in organic solvents and $scCO_2$.

Table 1. Nucleophilic and basic organocatalyst-promoted syntheses of PLA in organic solvents and $scCO_2$.[a]

Entry	Catalyst	Solvent	Conversion (%)[b]	Mn[c]	PDI[d]	ee of **3** (%)[e]
1[f]	DMAP	CH_2Cl_2	79	3800	1.18	98.0
2[g]	DMAP	$CHCl_3$	> 95	3900	1.23	88.0
3	DMAP	$scCO_2$	> 95	4100	1.10	96.5
4	9-AJ	$CHCl_3$	> 95	4100	1.24	89.5
5	9-AJ	$scCO_2$	> 95	4900	1.27	94.0
6	DBU	$CHCl_3$	> 95	4100	1.90	59.0
7	DBU	$scCO_2$	> 95	5900	2.88	81.0
8	TMG	$CHCl_3$	> 95	4100	1.90	89.5
9	TMG	$scCO_2$	> 95	4800	1.63	89.5
10[h]	Sn cat.[j]	toluene	> 95	4200	1.36	> 99.0
11[i]	Sn cat.[j]	Neat	89	3100	1.79	88.0

[a] Procedure: A 12 mL pressure-resistant vessel was charged with L-lactide (1, 864 mg, 6.0 mmol, 1.0 equiv), catalyst (0.40 mmol, 6.6 mol%), and ethanol (11.6 μL, 0.2 mmol, 3.3 mol%), and the mixture was warmed to 60 °C using a water bath. $scCO_2$ (60 °C, 10 MPa) was introduced into the vessel and the mixture was stirred for 5 min. After 1 h without stirring, the pressure was reduced to ambient values, and the produced PLA (white solid) was removed.

[b] Determined by ^{1}H NMR.

[c] Determined by gel permeation chromatography (GPC) using polystyrene as a standard.

[d] Polydispersity index (PDI, Mw/Mn).

[e] Determined by HPLC after hydrolysis of PLA to lactic acid.

[f] Polymerization was carried out at 35 °C for 30 h.

[g] Polymerization was carried out for 20 h (for 5 h, 65% conv., Mn = 2900, PDI = 1.19, ee = 93.5%).

[h] Polymerization was carried out for 5 h under reflux condition.

[i] Polymerization was carried out at 200 °C.

[j] Tin(II) 2-ethylhexanoate.

Recently, we reported the organocatalytic synthesis of metal-, organic solvent-, and residual monomer-free PLA in supercritical carbon dioxide ($scCO_2$) under CO_2 plasticizing polymerization (CPP) conditions using low temperature (60 °C) and a short reaction time (1 h).[9] In the present work, this CPP method was applied to the synthesis of PLA with high stereochemical purity and a quantitative method was established to determine the extent of epimerization (Figure 1).

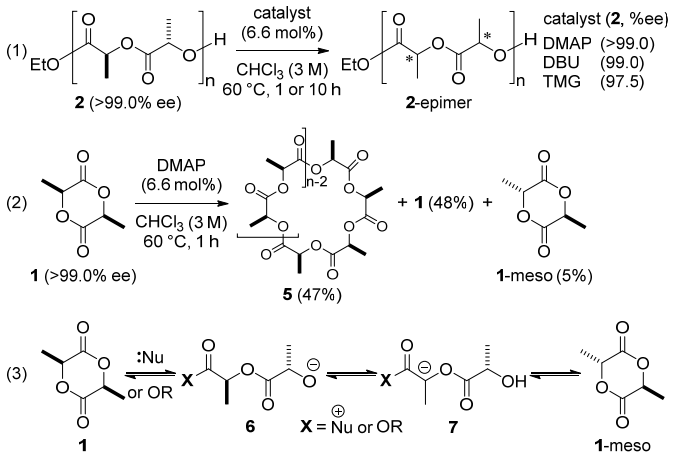
Results and discussion

Usually, the stereochemical purity of PLA is determined based on its stereoregularity using ^{13}C and ^{1}H NMR spectroscopy.[10] However, the inherently poor quantitativeness of NMR analysis complicates the accurate determination of the degree of epimerization. To mitigate this problem, chiral HPLC was used in this study to determine the enantiopurity of lactic acid (**3**) produced by the hydrolysis of PLA, since the abovementioned hydrolysis is known to proceed without epimerization when performed using NaOH solution at room temperature[11] or under hydrothermal conditions.[12]

Based on these reports, highly enantiopure (> 99.0% ee) lactide **1** and dimer **4** were hydrolyzed in 1 M aqueous NaOH at reflux. No epimerization was observed under these conditions (Scheme 1), thereby demonstrating that **1** and **4** could not be deprotonated at the α-position even by a strong base such as NaOH. The utilization of this simple hydrolysis technique allowed the evaluation of the degree of epimerization of both the polymer and unreacted monomer.

To confirm reproducibility, an organocatalytic ROP of **1** was conducted according to a previously reported epimerization-avoiding procedure[7] and found that this reaction was not complete even after 30 h. HPLC analysis of the hydrolysis products indicated that the occurrence of epimerization decreased the enantiopurity of the product to 98.0% ee (Scheme 2, Table 1, entry 1). To increase the product yield, the reaction was carried out at 60 °C in $CHCl_3$. However, after 20 h under these conditions, the product enantiopurity decreased to 88.0% ee (entry 2). In contrast, under CPP conditions (60 °C, 10 MPa) in $scCO_2$, the polymerization reaction was complete within 1 h and the obtained product exhibited an increased enantiopurity of 96.5% ee (entry 3). Similar to DMAP, nucleophilic and basic organocatalysts (9-azajulolidine (9-AJ), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), and 1,1,3,3-tetramethylguanidine (TMG)) suppressed the epimerization under CPP conditions (entries 4–9). Furthermore, using a conventional catalyst, tin(II) 2-ethylhexanoate,[5] did not lead to epimerization in toluene after 5 h polymerization (entry 10), although it did progress to a significant extent under the high-temperature conditions employed in commercial bulk polymerization (entry 11).

Epimerization in nucleophilic or basic organocatalyst-promoted PLLA synthesis is presumed to be caused by

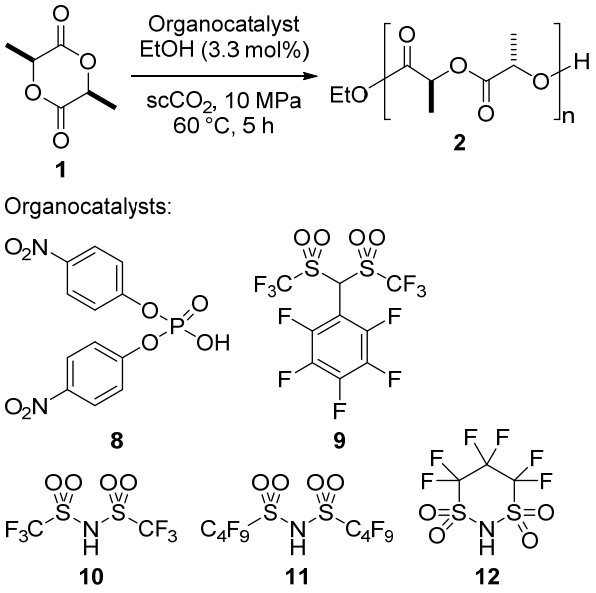


Scheme 3. Proposed epimerization mechanisms.

deprotonation at the methine carbon. To shed further light on the mechanism of this epimerization, DMAP, DBU, or TMG was added to a solution of PLA in chloroform, and the resulting mixture was stirred at 60 °C for 10 h (DMAP) or 1 h (DBU and TMG). Notably, there was no substantive decrease in enantiopurity, which implied that the epimerization was extremely slow (Scheme 3-1). Therefore, in order to confirm the epimerization of lactide **1**, it was polymerized in the absence of an initiator, and the recovered unreacted monomer was shown to contain *meso*-lactide **1** (Scheme 3-2). The nucleophilic addition of the catalyst to L-lactide afforded intermediate **6**, which has a considerably acidic α-methine proton. Therefore, the corresponding carbon could be deprotonated by the zwitterion, with the subsequent re-protonation affording L-lactide and epimerized *meso*-lactide (Scheme 3-3). In fact, the higher extent of epimerization observed for DBU compared to that for DMAP was ascribed to the higher nucleophilicity of the former.[13] However, although 9-AJ is also more nucleophilic than DMAP,[13] the presence of substituents at the 3- and 5-positions of the pyridine ring in the former case presumably led to steric hindrance, which inhibited the deprotonation and intramolecular cyclization processes. Although the reason for why epimerization was suppressed in $scCO_2$ as compared to $CHCl_3$ is unclear, this phenomenon could be ascribed to the formation of polymerization-promoting highly reactive anionic intermediates. These intermediates were not stabilized by $scCO_2$ in view of its low dielectric constant (ε_r = 1.37 at 10 MPa, 40 °C),[14] which is similar to those of pentane (ε_r = 1.84) and hexane (ε_r = 1.89), and therefore, the occurrence of deprotonation-induced epimerization was suppressed.

Epimerization promoted by deprotonation is unavoidable when nucleophilic or basic organocatalysts are used. However, the $Sn(Oct)_2$-catalyzed polymerization of L-lactide via Lewis acid activation reportedly proceeded without epimerization at low temperature (Table 1, entry 10).

Additionally, Brønsted acid-catalyzed ROP featuring a monomer activation mechanism similar to that of Lewis acid catalysis, has recently been reported. For example, the following Brønsted acids have been successfully used for PLLA synthesis in CH_2Cl_2 (although they still require long reaction times): triflic acid (3.3 mol%, 24 h, >95% conversion, Mn = 1800, PDI = 1.38),[15] triflimide (10 mol%, 192 h, 91% conversion, Mn = 4070, PDI = 1.15),[16] and diphenyl phosphate (DPP)/DMAP (DPP 6 mol%, DMAP 18 mol%, 28 h, 93% conversion, Mn = 6830, PDI = 1.24).[17] Therefore, the use of acidic organocatalysts is expected to suppress epimerization. Indeed, the use of phosphoric acid catalyst **8** afforded non-epimerized PLLA, albeit in low yield (Scheme 4, Table 2, entry 1).[18] Since fluorinated compounds generally have a good affinity with $scCO_2$, the catalytic ability of fluorinated catalysts would be higher in $scCO_2$ because of a high solubility and low dielectric constant than that in conventional organic solvent. Therefore, we selected the fluorinated Brønsted acids **9**-**12** as a catalyst. C–H-acidic catalyst **9** exhibited low reactivity (entry 2),[19] which was greatly improved in the case of N–H-acidic catalysts. Notably, the polymerization reaction was complete within 5 h in $scCO_2$, whereas a reaction



Scheme 4. Brønsted acid–promoted syntheses of PLLA in organic solvents and $scCO_2$.

Table 2. Brønsted acid-catalyzed PLLA synthesis in $scCO_2$.[a]

Entry	Catalyst (mol%)	Conversion (%)[b]	Mn[c]	PDI[d]	ee (%)[e]
1	**8** (6.6)	14	1100	1.27	> 99.0
2	**9** (2.0)	29	< 1000	2.46	98.5
3	**10** (2.0)	> 95	3000	1.33	> 99.0
4	**11** (6.6)	> 95	2800	1.36	> 99.0
5	**12** (2.0)	> 95	5200	1.34	> 99.0

[a] Procedure: A 12 mL pressure-resistant vessel was charged with L-lactide (1, 864 mg, 6.0 mmol, 1.0 equiv), catalyst (0.12 mmol, 2.0 mol% or 0.40 mmol, 6.6 mol%), and ethanol (11.6 μL, 0.2 mmol, 3.3 mol%), and the mixture was warmed to 60 °C using a water bath. $scCO_2$ (60 °C, 10 MPa) was introduced into the vessel, and the mixture was stirred for 5 min. After 5 h without stirring, the pressure was reduced to ambient values and the produced PLLA (white solid) was removed.

[b] Determined by ^{1}H NMR.

[c] Determined by GPC with polystyrene standard.

[d] Polydispersity index (Mw/Mn).

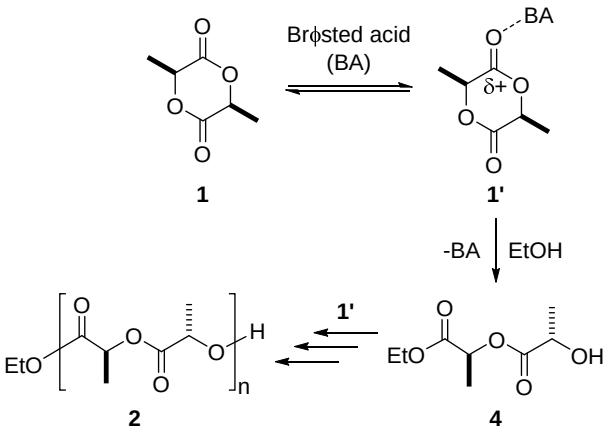
[e] Determined by HPLC after hydrolysis of PLA to lactic acid.

time of 192 h was required in CH_2Cl_2.[16] Also, cyclic sulfonimide **12** as well as linear sulfonimides **10** and **11** effectively catalyzed ROP and furnished PLLA without any reduction in stereochemical purity (entries 3–5). Although there is the difference of the Mn depending on the catalysts, the reason is still unclear.

In view of the above results, electrophilic Brønsted acids were concluded to activate the carbonyl group of the L-lactide monomer, affording activated monomer **1'** that is more electrophilic than **1** and can undergo nucleophilic ring-opening by the initiator or propagating chain-end alcohol, which results in ROP and regeneration of the catalyst (Scheme 5). Although the acidic catalyst–promoted ROP of L-lactide was slow in CH_2Cl_2 (vide supra), high reactivity was observed in $scCO_2$ because activated **1'** was less susceptible to solvation in the latter low-dielectric-constant solvent.

Conclusion

In summary, compared to conventional polymerization in organic solvents, Brønsted acid catalyst-promoted synthesis of PLLA in $scCO_2$ under CO_2 plasticizing polymerization conditions featured the advantage of reduced epimerization degree, thereby affording PLLA and PDLA of high stereochemical purity, which could be potentially used as materials for medical and engineering applications.



Scheme 5. Proposed mechanism of Brønsted acid-catalyzed ROP in $scCO_2$.

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The authors declare no competing financial interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.XX.

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