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Isoselective Ring-Opening Polymerization of *rac*-Lactide from Chiral Takemoto's Organocatalysts: Elucidation of Stereocontrol

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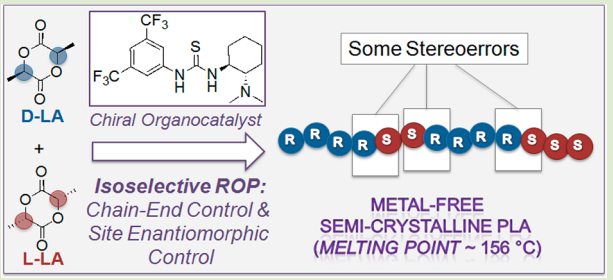
Supporting Information

ABSTRACT: Despite significant advances in organocatalysis, stereoselective polymerization reactions utilizing chiral organocatalysts have received very little attention, and much about the underlying mechanisms remains unknown. Here, we report that both commercially available (*R*,*R*)- and (*S*,*S*)-enantiomers of chiral thiourea-amine Takemoto's organocatalysts promote efficient control and high isoselectivity at room temperature of the ring-opening polymerization (ROP) of racemic lactide by kinetic resolution, yielding highly isotactic, semicrystalline and metal-free polylactide (PLA). Kinetic investigations and combined analyses of the resulting PLAs have allowed the stereocontrol mechanism, which eventually involves both enantiomorphic site control and chain-end control, to be determined. Moreover, epimerization of *rac*-LA to *meso*-LA is identified as being responsible for the introduction of some stereoerrors during the ROP process.



Tremendous developments have been made in the past two decades to employ organocatalysts in a variety of transformations. Mainly focused on asymmetric reactions, small organic catalysts operate under mild reaction conditions, without some of the shortcomings of biocatalysts, such as a complex structure/conformation/function relationship or lack of robustness.[1−6] Organocatalysts have also been introduced in macromolecular synthesis.[7−12] Their often lower toxicity in comparison to many metal-based catalysts is driving their development in, for instance, biomedical, personal beauty care, microelectronic device, and food packaging applications.[13−15] The possibility to transfer the chirality from an organocatalyst to the polymer backbone, i.e., stereoselective organocatalyzed polymerization, remains underexplored. This is perhaps surprising given the numerous chiral organic catalysts that are easily accessible. Control over stereoselectivity (stereocontrol) in some polymerization reactions is of paramount importance as the resulting tacticity of the polymer drastically affects the physical and mechanical properties of the final material.[16−22] Differences in tacticity lead to major differences in both the melting (T_m) and the glass transition (T_g) temperatures. An archetypal example of stereocontrolled polymer synthesis is the ring-opening polymerization (ROP) of lactide (LA).[23] Polylactide (PLA) is not only a biocompatible and biodegradable polymer but also manufactured from biorenewable sources such as corn starch or sugar cane. These features make PLA suitable for several applications, for instance, in the pharmaceutical and microelectronics fields or as a biodegradable plastic in packaging.[24−27] LA possesses two chiral centers. As such, it can exist in three distinct diastereoisomers, namely, DD-, LL- (commonly used as a racemic mixture, *rac*-LA), and DL- (*meso*-LA). With appropriate catalysts/initiators, stereospecific ROP enables a controlled insertion of monomers into the polymer backbone based on their stereochemistry.[28,29] While ROP of either enantiomer yields isotactic PLA, stereocontrolled ROP of *rac*- and *meso*-LA forms different microstructures (see Figure 1) with different properties. Poly(L-LA) (PLLA) exhibits a T_m around 160−180 °C, whereas atactic PLA is amorphous and brittle. The T_m value can be dramatically increased up to 230−240 °C when mixing equimolar amounts of PLLA and PDLA, owing to the formation of a stereocomplex.[16,19,21]

Stereocontrolled polymerization can be mediated by two distinct mechanisms, namely, chain end control (CEC) or enantiomorphic site control (ESC).[28,29] In the former case, control of the chirality is associated with the propagating chain end that in the transition state of the next monomer insertion defines the chirality of the next monomer unit to be inserted.

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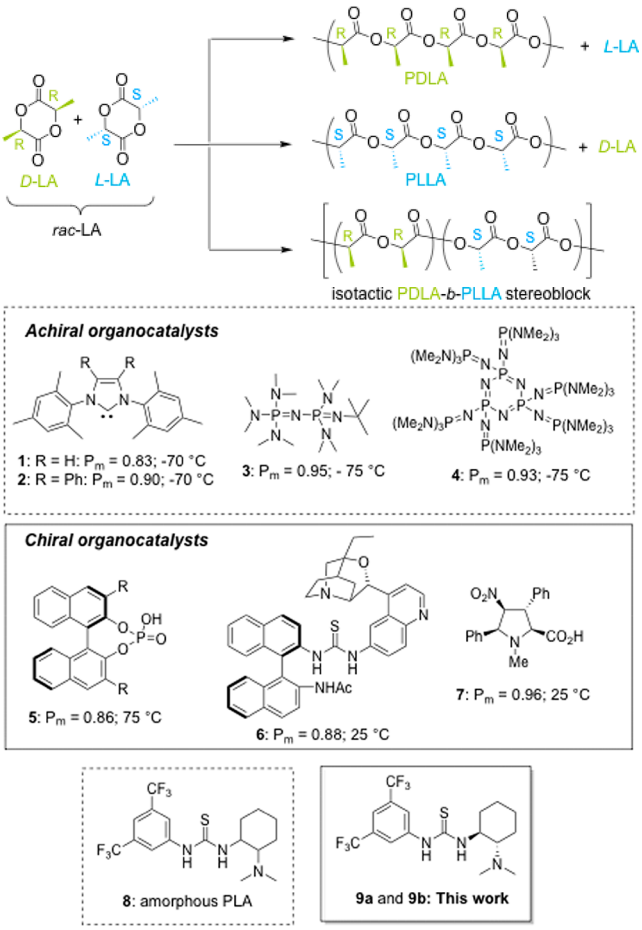

Figure 1. Stereoselective organocatalyzed ROP of *rac*-LA leading to metal-free and semicrystalline (except with **8**) PLA and organocatalysts employed for this purpose.

Such control is most commonly achieved using sterically hindered catalysts that reinforce a chiral environment. In contrast, in polymerizations mediated through an ESC mechanism, the chirality of the catalyst determines the chirality of the next monomer unit. In particular, the enantioasymmetric, i.e., by kinetic resolution, ROP of *rac*-LA involves the reaction of only one enantiomer to provide a chiral PLA, leaving the other enantiomer unchanged (Figure 1). Organometallic catalysts—typically based on aluminum or rare earths—that induce a "coordination−insertion" mechanism have been by far the most investigated for the stereocontrolled ROP of LA. Beyond these few examples, stereocontrol in the ROP of LA is more commonly achieved by chain-end control, even if the catalyst contains a chiral component (i.e., ligand).[23,30−37]

To date, only a handful of studies have focused on the stereocontrolled organocatalytic ROP of *rac*-LA using either achiral or chiral organic catalysts.[38−44] As with metal-based catalysis, stereoselective polymerization can be mediated by achiral species using steric hindrance. For example, when catalyzing the ROP of *rac*-LA by the *N*-heterocyclic carbene (NHC **1**, Figure 1) at −70 °C, Waymouth, Hedrick, and co-workers observed the formation of isotactic-enriched PLA, with a probability of forming meso dyads (P_m) of 0.83.[50] Isotactic enchainment could be enhanced for the ROP of *rac*-LA at −70 °C (P_m = 0.90) in the presence of the more sterically hindered NHC **2**.[45] Wade and co-workers employed the dimeric phosphazene organic base, P_2-*t*Bu, **3**, to obtain a P_m value of 0.95 for the ROP of *rac*-LA at −75 °C.[39] Very recently, Li and co-workers reported that cyclic trimeric phosphazene **4** enabled the synthesis of isotactic PLA with a P_m value up to 0.93 at −75 °C.[43] Chiral organocatalysts, including binaphthol-type phosphoric acids (**5**),[41] a *β*-isocupreidine/thiourea/chiral binaphthylamine (**6**),[28] and densely substituted proline-type amino acids (**7**)[42] were also investigated for the mediation of stereospecific ROP of *rac*-LA and provided a P_m value of 0.86, 0.88, and 0.96 at 75, 25, and 25 °C, respectively. Although excellent stereocontrol can be achieved from both chiral and achiral organocatalysts, ROP reactions are generally conducted at low temperatures (Figure 1), and/or a detailed investigation into the underlying stereocontrol mechanism is lacking, the understanding of which could aid future organocatalyst design to address the challenge of controlling polymer stereochemistry at more easily accessible and even elevated temperatures.

Organocatalysts based on thioureas[44,46,47] and amines have been extensively investigated in ROP of LA,[48] owing to their high selectivity, minimizing the occurrence of chain transesterification and providing excellent control over molar mass and dispersity of the resulting PLA.[47] In particular, the monocomponent thiourea-based catalyst, **9a** or **9b**, known as Takemoto's catalyst,[49] incorporating both a thiourea and a tertiary amino group, operates by a bifunctional cooperative mechanism; i.e., the amino moiety activates the alcohol

Table 1. ROP of *rac*-LA in the Presence of the Chiral (*S,S*)-Takemoto's Organocatalyst[a]

run	$[LA]_0$:$[TUC]_0$:$[BnOH]_0$	T (°C)	t (h)	conv. (%)[c]	M_n (kg mol^{-1})[d]	$Đ_M$[d]	T_g (°C)	T_m[e] (°C)	P_m[f]
1	200:10:1	25	25	47	13.3	1.05	50	154	0.84
2	200:10:1	25	215	93	27.6	1.15	56	156	0.87
3	200:5:1	25	32	42	9.3	1.07	51	156	0.88
4	200:5:1	25	238	85	24.8	1.16	59	152	0.87
5	200:10:1	45	91	95	18.8	1.24	54	143	0.82
6	200:5:1	45	161	87	15.7	1.25	52	131	0.80
7[b]	200:10:1	85	90	54	10.0	1.83	58	141	0.85
8[b]	200:5:1	85	45	60	9.7	1.45	53	149	0.82

[a]Polymerizations were conducted in CH_2Cl_2 (1 M) unless otherwise stated. [b]Reactions performed in toluene (0.8 M); see Table S1 for ROP reactions utilizing the (*R,R*)-version. [c]Monomer conversion was determined by SEC in $CHCl_3$ and THF before polymer purification or by ^{1}H NMR spectroscopic analysis in $CDCl_3$. [d]Apparent number-average molar mass (M_n) and dispersity ($Đ_M$) values were determined by SEC in THF or $CHCl_3$ using polystyrene standards for calibration. [e]T_g and T_m values were determined by DSC from the 1st heating curve (SI). [f]Probability of finding mesodyads calculated from homonuclear decoupled ^{1}H and quantitative ^{13}C NMR spectra after deconvolution; calculations are based on ESC statistics.[52]

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initiator, whereas the thiourea group activates the monomer.[50] Most studies have employed the racemic version (**8**, Figure 1), except in one report by Hedrick, Waymouth, and co-workers in 2006,[44] where the (*R*,*R*)-TUC (**9a**) was applied and was observed to yield PLA with a P_m of 0.76,[51] roughly the same as for the racemic catalyst, although the mechanism by which the catalyst was able to stereoselect was not determined. Knowing the broad applicability of PLA with a controlled tacticity, and given the interest in preparing PLA free of any metallic residues, both chiral (*R*,*R*) and (*S*,*S*) and commercially available versions of the Takemoto catalyst, **9a** and **9b**, were here (re)investigated for the stereoselective ROP of *rac*-LA. This study reveals not only that unexpectedly this process yields semicrystalline PLA at room temperature as well as at higher temperatures but also that both mechanisms of stereocontrol, i.e., CEC and ESC mechanisms, operate during the ROP process.

Our motivation was to achieve metal-free and semicrystalline PLAs at ambient temperature or above, rather than under more stringent conditions at very low temperature as previously reported.[39,43] Therefore, ROP experiments were carried out with both (*S*,*S*)- and (*R*,*R*)-TUCs in a temperature range of 25−85 °C. ROP reactions of *rac*-LA were performed in CH_2Cl_2 or in toluene using benzyl alcohol (BnOH) as initiator, in the presence of either the (*S*,*S*)- or the (*R*,*R*)-TUC (Tables 1 and S1, respectively). At room temperature, LA conversion reached 85% after 238 h for an initial $[LA]_0/[(R,R)\text{-TUC}]_0/[BnOH]_0$ ratio of 200/5/1, leading to a PLA with low dispersity and a number-average molar mass (M_n) that was consistent with that expected based on the monomer-to-initiator ratio (M_n = 24 800 g·mol^{-1}, $Đ_M$ = 1.16; Table 1, entry 4). Despite the process being slow, these conditions all enabled the formation of semicrystalline PLAs with an excellent control over molar masses, narrow dispersities ($Đ_M \leq 1.25$), and high chain-end fidelity. This was supported by combined analyses, including NMR spectroscopy (Figure S1), size exclusion chromatography, and MALDI-ToF mass spectrometry (Figure 2). In addition, apparent molar masses increased when increasing the initial monomer-to-initiator molar ratio. No evidence of transesterification was noted by MALDI-ToF MS analysis (no detection of a molar mass loss of 72 g mol^{-1}), highlighting the selectivity of both chiral Takemoto's catalysts for ring-opening reactions. The isotopic single distribution of peaks was consistent with the formation of an α-benzyloxy,ω-hydroxy PLA (cationized with sodium), with a peak-to-peak mass increment of 144 g·mol^{-1} corresponding to the molar mass of an LA monomer unit. Increasing the temperature from 25 to 45 °C did not alter the control of the ROP process, whereas side transesterifications were detected at 85 °C, especially when conversion was >90% (Table S1).

Intriguingly, DSC analysis of the (*S*,*S*)-TUC-derived PLA sample revealed a melting transition at T_m = 152 °C, thus contrasting what was expected from a polymer with an anticipated P_m = 0.76 based on previous reports of its use.[44] Interestingly, calculation of the P_m value using CEC statistics after analysis by both ^{1}H and quantitative ^{13}C NMR spectroscopy was consistent with these findings and evidenced the formation of a moderately isotactic PLA with the presence of a large *mmm* tetrad peak. Notably, Hedrick, Waymouth, and co-workers applied the CEC statistical model to which our results provided a comparable P_m; however, using an ESC statistical model,[52] a P_m = 0.87 was calculated, much more in line with the observation of crystallinity in the resultant PLA. These preliminary results prompted us to investigate more in-depth the mechanism of the ROP or *rac*-LA from chiral Takemoto's catalysts.

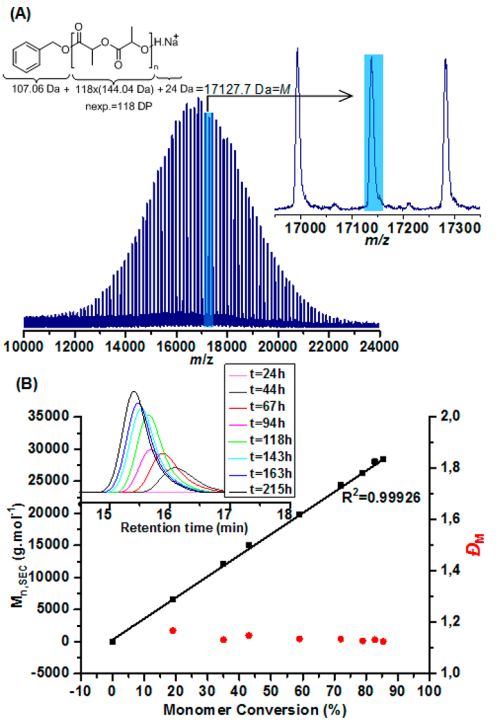

Figure 2. (a) MALDI-ToF mass spectrum of PLA obtained at 25 °C (Table 1, entry 2). (b) $M_{n,SEC}$ and dispersity ($Đ_M$) vs monomer conversion for PLA synthesized from (*S*,*S*)-TUC at RT. Inset: Size exclusion chromatograms of PLA during ROP (Table 1, entry 2).

Chiral HPLC analysis of unreacted monomer revealed an enantiomeric excess (ee) of 32%, corresponding to a stereoselectivity factor ($s = k_D/k_L$) of 3.6 (Table S1, entry 4) at 42% monomer conversion in the presence of (*S*,*S*)-TUC, and s = 3.4 at 55% of monomer conversion using (*R*,*R*)-TUC (Table S1, entry 17). Unexpectedly, increasing the catalyst loading from 5 to 10 equiv led to a lower selectivity factor (s = 3.0; Table S1, entry 7); hence, a loading of 5 mol % relative to the initiator was maintained for the rest of the study.

As mentioned previously, (*S*,*S*)-TUC produced a semicrystalline PLA (T_m = 152 °C) with a strong isotactic predominance (*it*-PLA) and a P_m value of 0.87, as determined by ESC statistical analysis (Table 1, entry 4) in CH_2Cl_2 as solvent (Figure 3). The T_m value could be further increased to 167 °C by annealing the sample at 160 °C for 15 h. Two ROP reactions of *rac*-LA were carried out in bulk at 150 °C, using (*S*,*S*)-TUC, namely, using $[LA]_0/[(R,R)\text{-TUC}]_0/[BnOH]_0$ ratios equal to 200/5/1 and 200:10:1. However, the resultant PLAs did not show any melting point (T_m), indicating that (*S*,*S*)-TUC did not enable us to control the stereoselectivity of the ROP of *rac*-LA under bulk conditions at such a high temperature (Table S1, entries 14−15, and Figure S23).

In the case of (*R*,*R*)-TUC, a P_m value as high as 0.90 could be achieved in toluene (Table S1, entry 18) at room temperature, likely as a result of a solvent effect, toluene being less polar than DCM, increasing the probability for forming H-bondings. These P_m values, calculated by ESC statistical analysis, markedly contrasted with those reported

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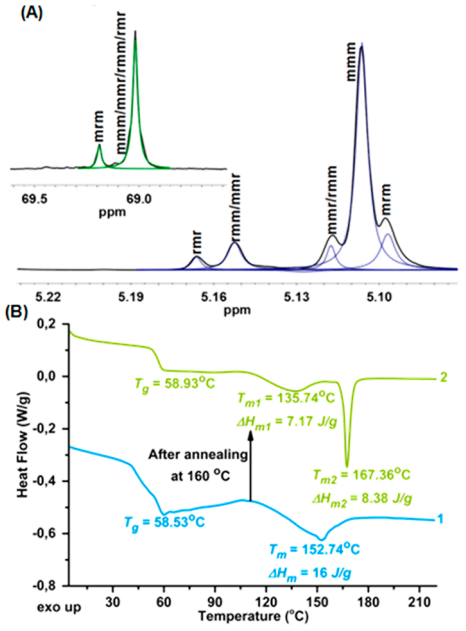

Figure 3. (a) Stacked homonuclear decoupled ^{1}H $\{^1$H$\}$ NMR spectrum (400 MHz, $CDCl_3$) of the methine region of PLA obtained from (*S,S*)-TUC at RT (Table 1, entry 2). Inset: quantitative ^{13}C NMR spectrum. (b) DSC thermogram (1st scan; 10 °C/min) of the initial (1) and annealed (2) PLA (Table 1, entry 4).

earlier where chiral thiourea-amines showed a modest stereoselectivity (P_m in the range 0.64−0.77).[44]

In further experiments, both D- and L-LA were polymerized using each chiral TUC in order to provide evidence for the stereoselective mechanism. The corresponding first-order kinetic plots (Figure 4) evidenced that (*S,S*)-TUC preferentially polymerized D-LA, whereas incorporation of L-LA was consistently favored using (*R,R*)-TUC. These kinetic studies enabled us to recalculate the selectivity factor: $s = k_D/k_L = 5$ and $s = k_L/k_D = 4.6$ for (*S,S*)-TUC and (*R,R*)-TUC, respectively. The latter values proved slightly higher than those determined above by chiral HPLC. Kinetic study of *rac*-LA ROP revealed first-order kinetic plots with two distinct slopes (k_1 = 0.014, k_2 = 0.009). A decrease in rate after roughly 65 h was observed with both the (*S,S*)- and the (*R,R*)-TUCs. Given the differing preference of each of the two chiral TUCs for the two monomers (D-LA and L-LA), this deceleration could be correlated to the preferential consumption of a given enantiomer by a given TUC, i.e., to the selectivity factor. These results suggest that an ESC mechanism may be dominant. To further test this, ROP was conducted at elevated temperature. Interestingly, a P_m value as high as 0.82 could be obtained at 85 °C (Table 1, entry 8; see also Table S1, entry 22), further corroborating this stereoselective mechanism and potentially explaining the discrepancy in results between our study and that of Hedrick, Waymouth, and co-workers.[44] Notably, however, DSC analysis of the PLA prepared at 85 °C was consistent with an amorphous polymer with crystallinity only appearing after annealing at 150 °C for 13 h (Figure S3, T_m = 149 °C). Thus, formation of long stereoblocks or even of a stereocomplex showing a high T_m value (>180 °C) can be here ruled out.

Calculations of P_m values as a function of one or the other mechanism, i.e., CEC or ESC (Tables S2 and S3), lead to differing results, and clearly, the mechanism of catalyst operation is critical in studies such as this. Assuming *it*-PLA would form by a CEC mechanism exclusively, relative tetrad intensities would be expected as follows:[53] [*mrm*] = [*rmm*] ≠ [*rmr*]. In this case, stereoblocks could be generated when a growing PLA chain incidentally incorporated the LA enantiomer of opposite configuration to that of the last inserted enantiomer. This would create a stereoerror from which "normal" growth would form a new stereoblock of opposite configuration to the previous one (Figure 5).

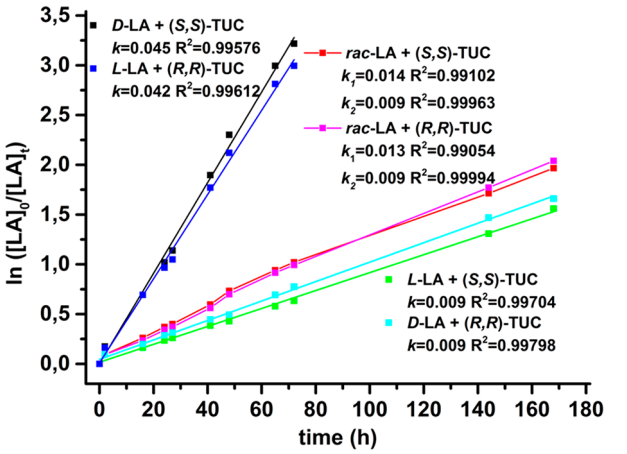

Figure 4. Kinetic plots of the ROP of *rac*-LA, D-LA, and L-LA catalyzed by (*S,S*)-TUC and (*R,R*)-TUC in CH_2Cl_2 at RT in the presence of BnOH as a initiator: $[LA]_0$:[TUC]:[BnOH] = 200:5:1.

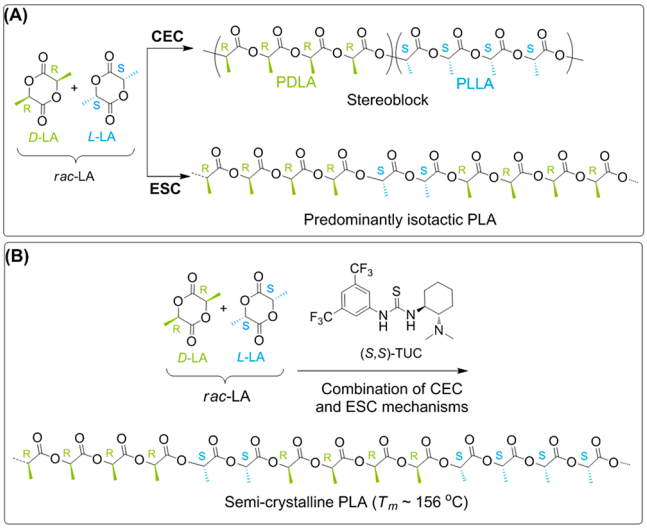

Figure 5. (a) Chain-end control (CEC) vs site enantiomorphic control (ESC) mechanism during the ROP of *rac*-LA. (b) Proposed mechanism using the chiral Takemoto's catalyst, here with a (*S,S*) configuration. Pale blue frames point out the stereoerrors.

Conversely, the ESC mechanism should generate single insertion stereoerrors of the type −*RRRRSSRRR*−/−*SSSSRRSSSS*− (see Figure 5). In the latter case, the tetrad ratio should be [*rmr*] = [*mmr*] = [*rmm*] = 2/[*mrm*].[52] The *rmr* signal is a clear indicator of mechanism. Analysis of the NMR spectra of the PLAs produced here (Figure 3a) revealed the tetrad ratios to be [*rmr*] = 0.030 [*mmr*] = 0.055 [*rmm*] = 0.096 and [*mrm*] = 0.13, which were consistent with neither the ESC

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nor the CEC mechanism, thus strongly suggesting that both mechanisms concomitantly occurred (Figure 5b).

Attempts to polymerize *meso*-LA at RT in the presence of the (*S*,*S*)-TUC led to an amorphous PLA (Table S1, entry 16, Figure S24). In the event of an exclusive ESC mechanism, a syndiotactic PLA should be obtained, while a heterotactic PLA is expected following the CEC mechanism. This result can again be explained by the concomitant occurrence of the two mechanisms.

Epimerization of *rac*-LA to form *meso*-LA is a side event, which can bias the stereocontrol, creating additional stereoerrors. As a result of epimerization, the probability for forming −*RSR*− sequences increases, thus decreasing the P_m value. Monitoring of the ROP of *rac*-LA in a conversion range of 74−87% allowed us to calculate the [*meso*-LA]/[unreacted *rac*-LA] ratio, which was found equal to 13, 17, and 26% at 25, 45, and 85 °C, respectively. Corresponding extent of epimerization, as determined through the [*meso*-LA]/[PLA] ratios, was as follows: 1, 1.2, and 1.9%, respectively (Figure S4). Thus, although these data show that epimerization did occur, the content in resulting *meso*-LA ratio remained very low during the whole ROP process and was considered as negligible. The higher epimerization at higher temperature, i.e., 2% at 85 °C, might explain the reduced crystallinity and hence T_m observed by DSC under these conditions.

In summary, the ROP of *rac*-LA using either chiral version of Takemoto's thiourea-amine catalyst (TUC) enables the formation of semicrystalline PLA free of any metallic residues, at room temperature, as a result of a highly isoselective ROP process. This study sheds light on the origin of the stereocontrol, evidencing the concomitant occurrence of both CEC and ESC mechanisms. Despite some epimerization, transforming *rac*- to *meso*-LA, isoselectivity remains high without the need to work at very low temperature, in the presence of the (*R*,*R*)- and the (*S*,*S*)-TUC. The former organocatalyst preferentially incorporates L-LA, whereas the (*S*,*S*)-catalyst preferentially polymerized D-LA. The selectivity for one or the other LA enantiomer can thus be switched by changing the configuration of the Takemoto's catalyst. Work is in progress to design organocatalysts that could combine both a high stereoselectivity and catalytic activity at room temperature and above.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsmacrolett.8b00852.

Materials, instrumentation, polymerization procedure, related NMR spectra, and DSC thermograms (PDF)

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Notes

The authors declare no competing financial interest.

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