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Cinchona Alkaloids as Stereoselective Organocatalysts for the Partial Kinetic Resolution Polymerization of *rac*-Lactide

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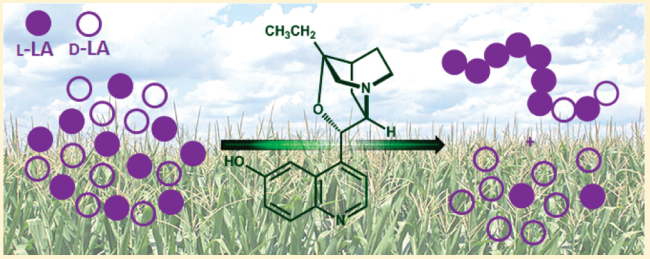
ABSTRACT: This work investigates, for the first time, cinchona alkaloids such as cinchonidine (CD) and β-isocupreidine (ICD) consisting of both a chiral nucleophilic amine catalyst site and an electrophilic hydroxy moiety, as bifunctional, stereoselective organocatalysts for the ring-opening polymerization (ROP) of L-lactide (L-LA) and *rac*-lactide (*rac*-LA). While the ROP of L-LA by CD is ineffective, the ROP of L-LA by ICD proceeds without noticeable epimerization, thus affording polylactide (PLA) with a quantitative isotacticity. The measured number-average molecular weight (M_n) is much higher than the expected M_n due to sluggish initiation by ICD, but when benzyl alcohol is added as an external protic initiator, the ROP is highly efficient and proceeds to high conversions without undesired transesterification reactions, thus producing PLA with a controlled M_n and a narrow molecular weight distribution of 1.12. More significantly, the ROP of *rac*-LA by ICD/alcohol affords crystalline isotactic-rich, stereogradient PLA that exhibits multiple melting-transition temperatures as a result of a partial kinetic resolution polymerization that preferentially polymerizes L-LA and kinetically resolves D-LA. Overall, this study uncovers the first kinetic resolution polymerization of *rac*-LA by an organocatalyst.



INTRODUCTION

The synthesis of polylactide (PLA) has been extensively investigated because PLA is one of the most commercially important biodegradable and biocompatible polymers, exhibiting a wide array of applications in packaging, microelectronics, and biomedical fields.[1] Furthermore, as petroleum resources continue to be depleted and efforts to reduce our current dependence on such resources are being made, there has been increased focus on polymers that can be synthesized from monomers derived from renewable resources.[2] In this context, PLA is an attractive polymer, as it can be readily produced from the ring-opening polymerization (ROP) of the bioderived monomer lactide.[1] LA monomers are available as enantiomerically pure LL-(L-LA), DD-(D-LA), or as a racemic mixture (*rac*-LA), and DL-(*meso*-LA) stereoisomers. Like other polymers having backbone stereocenters, the tacticity (stereomicrostructure) has a drastic effect on the polymer properties such as glass-transition temperature (T_g) and melting-transition temperature (T_m). For instance, heterotactic PLA exhibits a T_g of 49 °C and no noticeable T_m (thus an amorphous material)[3] while isotactic PLA shows a T_m of up to 180 °C and a T_g of about 50 °C.[1] It has been well documented that the ROP of the enantiopure LA monomer, in the absence of any epimerization, leads to PLA with quantitative isotacticity, and if isotactic L-PLA and D-PLA are mixed in a 1:1 ratio, a crystalline stereocomplex exhibiting a T_m of greater than 200 °C can be formed.[1] Stereoselective ROP of *rac*-LA has also been examined extensively;[1] in comparison, the stereoselective ROP of *meso*-LA has been studied to a much lesser extent.[4]

Metal-based catalysts or initiators have played a pivotal role in modern polymer synthesis, thanks to their high activity and remarkable ability to control precisely the structures of the resulting polymers such as molecular weight, molecular weight distribution, stereomicrostructure or tacticity, etc.; a recent example of such successes is the metal-mediated stereospecific, living coordination polymerization of functionalized vinyl monomers.[5] In the case of the ROP of LA, metal-based catalysts have also dominated the field, generally utilizing metal alkoxides for the coordination−insertion polymerization.[6] Benchmark contributions for the metal-mediated stereoselective polymerization of *rac*-LA include the stereoselective and kinetic resolution polymerization mediated by an optically active Schiff base aluminum complex, for the synthesis of stereogradient PLA[7] as well as the initially reported direct synthesis of the PLA stereocomplex, composed of a racemic mixture of isotactic L-PLA and D-PLA, by a racemic Schiff base aluminum complex.[8] However, the latter stereocomplex was shown by Ovitt and Coates to be actually isotactic stereoblock PLA.[9] Despite such major successes in the stereoselective ROP of LA by metal catalysts, inevitable contamination of the polymer product by trace metal residues can have non-negligible to even significant impacts on the overall quality of the final product, especially when it is applied to biomedical or microelectronic fields. Such considerations have provided a strong incentive for intensified research in utilizing metal-free organocatalysts in the ROP of cyclic esters, especially lactide and ε-caprolactone.[10]

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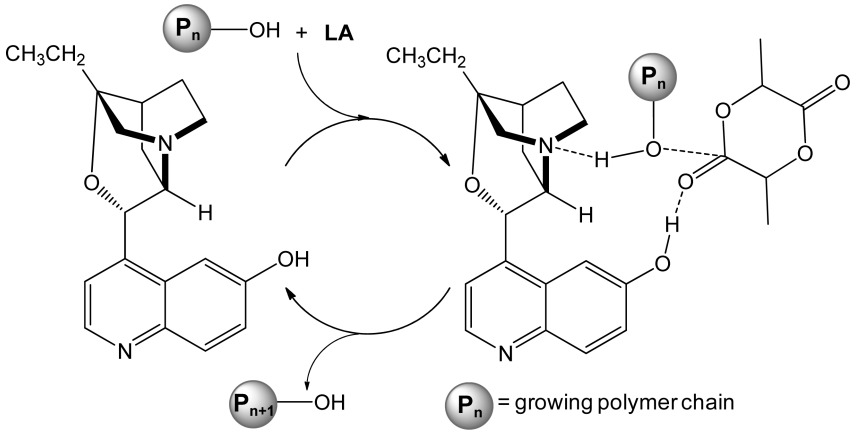
Scheme 1. Proposed Reaction Sequences in the ROP of LA Catalyzed by Bifunctional Oraganocatalyst ICD



Seminal work by Hedrick and co-workers revealed the first organocatalyzed living ROP of L-LA catalyzed by strongly basic amines.[11] Hedrick et al. also showed that *N*-heterocyclic carbenes (NHCs) are excellent organocatalysts for the efficient and rapid ROP of L-LA[12] and later utilized sterically encumbered NHCs for the stereoselective ROP of both *rac*- and, to some extent, *meso*-LA.[13] Although the stereoselectivity (measured by P_m, the probability of forming a *meso* dyad) of sterically encumbered NHCs for the ROP of *rac*-LA at 25 °C is only modest (P_m = 0.59), lowering the polymerization temperature to −70 °C significantly increased the P_m value to 0.90. On the other hand, a hindered chiral analogue behaved similarly, pointing to a chain-end control mechanism for both achiral and chiral NHCs.[13] Further studies by Hedrick, Waymouth, and co-workers have extended the scope of the ROP of LA using other types of organocatalysts, including thiourea-amines,[14] triazabicyclodecene,[15] guanidines,[16] and phosphazene bases.[17] The phosphazene-catalyzed ROP of *rac*-LA affords modestly isotactic PLA (P_m = 0.72) at 20 °C but highly isotactic PLA (P_m = 0.95) at −75 °C.[17] Such polymerization manifolds typically consist of a basic functionality that can activate an appropriate initiator, generally an alcohol, via H-bonding, thus turning the initiator or the growing chain end into a stronger nucleophile for the ring-opening events. In some cases, by possessing also an electrophile that can activate the monomer via H-bonding with the carbonyl oxygen of the monomer, these organocatalysts become bifunctional, thus making the monomer more susceptible to nucleophilic attack.[14−16,18] Recently, Bibal and co-workers reported the crystal structure of L-LA activated, via H-bonding, with an amido-indole organocatalyst, providing support for the monomer activation mechanism proposed for the ROP of LA.[19] In efforts to achieve stereoselective and possible kinetic resolution polymerization of *rac*-LA, Hedrick and co-workers employed thiourea cocatalysts coupled with chiral tertiary amines for the ROP of *rac*-LA to give isotactic-rich PLA at room temperature with P_m ranging from 0.64 to 0.77. However, the resulting PLA showed no T_m (an amorphous material), and even when the polymerization was allowed to proceed to a 90% monomer conversion, the unreacted monomer was still not enantioenriched[20] (thus no kinetic resolution). More recently, Hedrick et al. utilized a chiral bifunctional guanidine for the ROP of *rac*-LA, but it also showed modest stereoselectivity (P_m = 0.56), even when the polymerization was conducted at 0 °C (P_m = 0.62).[16a] Overall, there have been tremendous advancements in the organocatalyzed ROP of LA, but the kinetic resolution polymerization of *rac*-LA by an organocatalyst for the synthesis of stereoblock or stereogradient PLA *still remained a challenge*.

Cinchona alkaloids are one of the earliest known classes of organocatalysts and have been well-established as highly enantioselective catalysts in numerous organic transformations.[21] However, to the best of our knowledge, cinchona alkaloids have not been utilized as ROP catalysts. Possessing both an electrophilic alcohol (e.g., cinchonidine, CD) or phenol (e.g., *β*-isocupreidine,[22] ICD) and a nucleophilic tertiary amine—both H-bonding donor and acceptor moieties—we reasoned that cinchona alkaloids exhibit the essential characteristics to serve as *bifunctional organocatalysts* for the ROP of LA (Scheme 1). Furthermore, as cinchona alkaloids are optically active, they provide an excellent opportunity to investigate their ability to perform the stereoselective and kinetic resolution polymerization of *rac*-LA. Accordingly, described herein are the successful ROP of L-LA catalyzed by ICD alone or in combination with externally added initiators (Scheme 2) to afford quantitatively isotactic L-PLA as well as the kinetic resolution polymerization of *rac*-LA to produce crystalline isotactic-rich stereogradient PLA that exhibits multiple T_m's. We have also investigated potential effects of externally added protic initiators on the polymerization characteristics and properties of the resulting polymer.

EXPERIMENTAL SECTION

Materials, Reagents, and Methods. All reactions were carried out in flamed Schlenk-type glassware on a dual-manifold Schlenk line, a high-vacuum line, or in an argon or nitrogen-filled glovebox. HPLC-grade organic solvents were sparged extensively with nitrogen during filling of the solvent reservoir and then dried by passage through activated alumina (THF and CH_2Cl_2) followed by passage through Q-5-supported copper catalyst (for toluene) stainless steel columns. NMR spectra were recorded on a Varian Inova 300, 400, or 500 MHz spectrometer. Chemical shifts were referenced to internal solvent resonances and are reported as parts per million relative to tetramethylsilane.

L-Lactide (L-LA), *rac*-lactide (*rac*-LA), butylated hydroxytoluene (BHT, 2,6-di-*tert*-butyl-4-methylphenol), *p*-toluenethiol (TSH), and benzyl alcohol (BnOH) were purchased from Sigma-Aldrich. The lactide monomers were purified by sublimation. BHT was recrystallized from hexanes prior to use. Cinchonidine (CD), *β*-isocupreidine (ICD),

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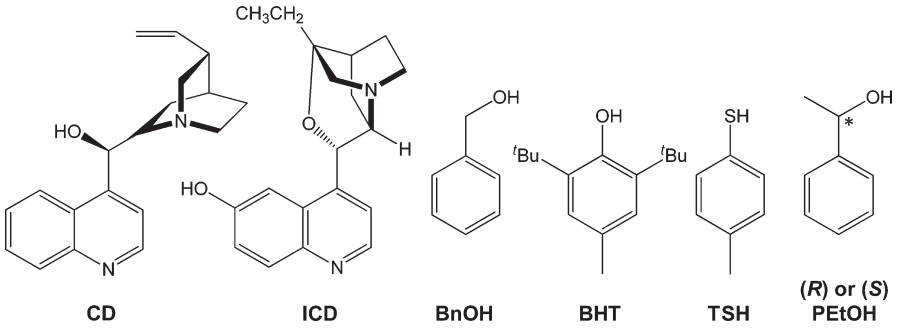
Scheme 2. Structures of Organocatalysts and Protic Initiators Employed in This Study



(*R*)-1-phenylethanol [(*R*)-PEtOH], and (*S*)-1-phenylethanol [(*S*)-PEtOH] were purchased from TCI America and used as received.

General Polymerization Procedures. Polymerizations were performed in 30 mL glass reactors inside the glovebox for ambient temperature (~25 °C) runs or in 25 mL Schlenk flasks interfaced to a dual-manifold Schlenk line with an external temperature bath for runs at other temperatures. In a typical polymerization reaction, ICD (29.9 mg, 96.3 μmol) and an external initiator (as specified in the polymerization tables) were dissolved in 5.0 mL of dichloromethane. Immediately thereafter, lactide (1.39 g, 9.64 mmol) was added as a solid to the vigorously stirred solution. Polymerizations were quenched at the time specified in the tables with 5 mL of methanol, and the polymer was precipitated into 50 mL of methanol and collected by filtration before being washed extensively with methanol to remove any catalyst residue or unreacted monomer. For the neat polymerization of LA under melt conditions, a glass tube was charged with monomer, cinchona alkaloid, initiator, and stir bar and sealed in a glovebox, before being placed in a 140 °C preheated oil bath. After a predetermined time interval, the reaction mixture was allowed to cool to room temperature, dissolved in a minimum amount of CH_2Cl_2, and precipitated into hexanes. Polymers were then dried at ambient temperature overnight in a vacuum oven. At specified times 0.2 mL aliquots were withdrawn from the solution and quenched into septum sealed vials containing 0.7 mL of undried "wet" $CHCl_3$. Percent conversion was then calculated by comparing the integration of the methine protons of the unreacted monomer to the methine protons of the polymer.

Polymer Characterizations. The low-molecular-weight PLA sample was analyzed by matrix-assisted laser desorption/ionization time-of-flight mass spectroscopy (MALDI-TOF MS); the experiment was performed on an Ultraflex MALDI-TOF mass spectrometer (Bruker Daltonics) operated in positive ion, reflector mode using a Nd:YAG laser at 355 nm and 25 kV accelerating voltage. A thin layer of a 1% NaI solution was first deposited on the target plate, followed by 1 μL of both sample and matrix (dithranol, 10 mg/mL in 50% ACN, 0.1% TFA). External calibration was done using a peptide calibration mixture (4−6 peptides) on a spot adjacent to the sample. The raw data were processed in the FlexAnalysis software (version 2.4, Bruker Daltonics). Gel permeation chromatography (GPC) analyses of the polymers were carried out at 40 °C and a flow rate of 1.0 mL/min, with $CHCl_3$ as the eluent, on a Waters University 1500 GPC instrument coupled with a Waters RI detector equipped with four 5 μm PL gel columns (Polymer Laboratories). Chromatograms were processed with Waters Empower software (version 2002); number-average molecular weight (M_n) and molecular weight distribution (MWD = M_w/M_n) of polymers were given relative to PMMA standards. Glass transition temperatures (T_g) and melting temperatures (T_m) of the polymers were measured by differential scanning calorimetry (DSC) on a DSC 2920 (TA Instruments). Polymer samples were first heated to 200 at 20 °C/min, equilibrated at this temperature for 3 min, then cooled to 0 at 10 °C/min, held at this temperature for 3 min, and reheated to 200 at 10 °C/min. All thermal data were obtained from the *second* scan. Tacticity of polymers was determined from the methine region of the homo-decoupled ^{1}H NMR spectrum. P_m, the probability of forming a new isotactic dyad, was calculated utilizing methods established in the literature.[23]

Kinetic Resolution of *rac*-LA. The kinetic resolution of *rac*-LA was carried out using the polymerization procedure as already described above. At predetermined time intervals 0.2 mL aliquots were withdrawn from the polymerization reaction using a syringe and quickly quenched into 1 mL septum cap sealed vials containing 0.6 mL of undried "wet" $CDCl_3$ mixed with 250 ppm of BHT. The quenched aliquots were analyzed by ^{1}H NMR for monomer conversion. The solvent was removed via roto-vap, and the unreacted monomer was extracted with a 1:1 hexanes:^{i}PrOH solution, filtered through a 0.2 μm syringe filter, and the % *ee* of the monomer was measured using an Agilent 1100 Series HPLC with a flow rate of 1.0 mL/min, utilizing a Chiracel IA column at 25 °C (70:30 hexanes:^{i}PrOH; 1.0 mL/min; L-LA: 5.1 min; D-LA: 5.5 min). The selectivity factor, *s*, was determined from the equation $s = \{\ln[(1 - c)(1 - ee)]\}/\{\ln[(1 - c)(1 + ee)]\}$, where *c* is the monomer conversion and *ee* is the enantiomeric excess of the unreacted monomer.[24]

RESULTS AND DISCUSSION

ROP of L-LA by Cinchona Alkaloids. As depicted in Scheme 1, we hypothesized that cinchona alkaloids that possess both H-bonding donor and acceptor moieties could potentially serve as bifunctional organocatalysts for the ROP of LA. Being one of the most widely used alkaloids, CD was first examined for the ROP of L-LA to probe if epimerization occurred during the course of polymerization, but we found it to be inactive in DCM at ambient temperature up to 24 h. Reasoning that CD may be too sterically bulky to be an effective initiator, we added a commonly employed initiator, BnOH, but also found no polymerization even after 5 days. All further experiments, including the use of more acidic protic initiators BHT and TSH, increasing the amount of an external initiator (BHT, up to 10 equiv relative to CD), and performing the polymerization by either CD/BnOH or CD/BHT under neat, monomer melt conditions (140 °C), did not bring about noticeable polymerization in all cases.

Since BnOH, when combined with suitable nucleophiles such as NHC, has been proven an effective initiator for the ROP of LA, we tempted to attribute the lack of the ROP activity to the inability of the tertiary amine of CD to effectively activate the alcohol initiator and/or to CD not being a bifunctional catalyst, despite the fact that the OH group at C9 does not form a five-membered ring via possible intramolecular H-bonding with the tertiary amine N atom,[25] because its alcohol moiety is not acidic

Table 1. Selected Results for the Polymerization of L-LA by ICD[a]

run no.	external initiator	time (h)	conv[b] (%)	M_n(calc) (kDa)	M_n(exp)[c] (kDa)	MWD[c] (M_w/M_n)
1	none	44.0	39.8	6.05	34.6	1.28
2	none	126	57.9	8.66	45.8	1.31
3	BnOH	31.5	86.3	12.5	14.4	1.12
4	BHT	20.5	14.9	2.37	21.9	1.37
5	BHT	47.7	31.2	4.72	34.0	1.38
6	BHT	94.5	42.4	6.33	43.2	1.43
7	TSH	23.0	63.9	9.33	17.6	1.29
8	TSH	29.5	73.5	10.7	19.7	1.27
9	TSH	44.0	90.7	13.2	23.7	1.25
10	TSH	52.0	91.9	13.4	24.4	1.25

[a] Conditions: 5 mL of dichloromethane (DCM) at ambient temperature (~25 °C); [L-LA] = 1.93 M; [ICD] = [initiator] = 19.3 mM. [b] Measured by NMR. [c] Measured by GPC.

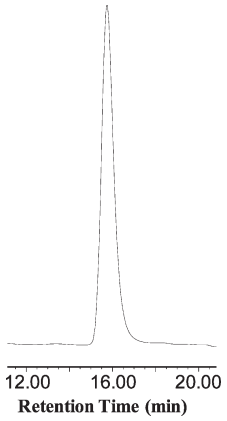


Figure 1. GPC trace of L-PLA produced by ICD/BnOH; M_n = 14.4 kDa, M_w/M_n = 1.12 (run 3, Table 1).

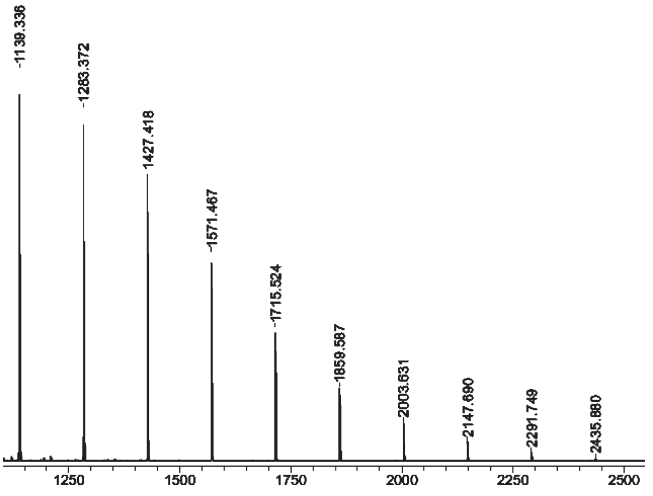


Figure 2. A section of the MALDI-TOF mass spectrum (plotted as intensity [a.u.] vs m/z) of the low-molecular-weight L-PLA produced by ICD/BnOH.

enough to effectively activate the monomer (cf. Scheme 1). On the basis of this reasoning, we next turned our attention to ICD because (a) the ICD amine is a stronger base and nucleophile than the CD amine due to the reduced steric hindrance on the ICD nitrogen and increased ring strain of the tricyclic framework;[26] (b) possessing a more acidic phenol moiety, ICD could serve as a true bifunctional organocatalyst in the ROP of LA; and (c) the configuration at C9 is *S* in ICD, compared to the *R* configuration for C9 in CD. Indeed, using ICD alone (1 mol %), the polymerization of L-LA in DCM at ambient temperature proceeded to 39.8% and 57.9% monomer conversions after 44 and 126 h, respectively (runs 1 and 2, Table 1). The isolated polymers had MWDs of 1.28 and 1.31, but the measured M_n's of 34.6 and 45.8 kDa are much higher than the expected M_n's of 6.05 and 8.66 kDa based on the monomer feed ratios and the monomer conversions, presumably due to inefficient initiation by ICD.

To address the inefficient initiation issue, we utilized external initiators to examine their effects on the polymerization characteristics. Among the three protic initiators investigated (BnOH, BHT, and TSH), BnOH proved to be most effective. Thus, the ICD/BnOH system achieved a 86.3% monomer conversion at 25 °C in 31.5 h, yielding a polymer with a narrow MWD of 1.12 and a controlled M_n of 14.4 kDa (run 3, Table 1, Figure 1). Accordingly, this polymerization had a high initiator efficiency initiator efficiency, $I^* = M_n(\text{calcd})/M_n(\text{exptl})$, where $M_n(\text{calcd}) = \text{MW(LA)} \times [\text{LA}]_0/[\text{initiator}]_0 \times \text{conversion \%} +$ MW of chain-end groups, over 85%. The rate of monomer consumption can be drastically enhanced by performing the reaction under the neat, monomer melt condition (140 °C), achieving 51.7% monomer conversion in 4 h. However, the PLA isolated under this condition was not quantitatively isotactic, and there was a large fraction of low-molecular-weight oligomers. The sterically bulky BHT was a poor initiator, reaching only 42.4% monomer conversion at 25 °C after 94.5 h; the resulting PLA had a much higher M_n (43.2 kDa) and a broader MWD (1.43) than the PLA produced by ICD/BnOH (run 6 vs 3). It is apparent that the results achieved by ICD/BHT are similar to those achieved by ICD alone, which is not surprising since both ICD and BHT possess the same phenolic initiating moiety. The most acidic initiator TSH performed somewhat between BnOH and BHT in all regards, reaching 91.9% monomer conversion at 25 °C in 52 h and yielding a polymer with a M_n of 24.4 kDa and a MWD of 1.25 (run 10). Noteworthy is that, in accord with the H-bonding mechanism proposed in Scheme 1, NMR experiments showed clear H-bonding formed between ICD and BnOH in CD_2Cl_2 and that no polymerization activity was observed when THF was utilized as the solvent; the latter observation is consistent with that observed by Hedrick and co-workers with their thiourea-based bifunctional organocatalyst system.[14]

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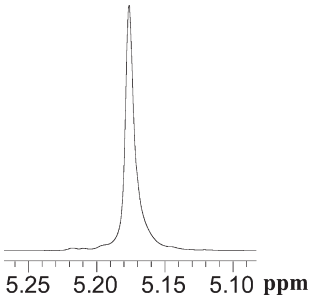

Figure 3. Methine region of homonuclear decoupled ^{1}H NMR spectrum (500 MHz, $CDCl_3$, 50 °C) of L-PLA (run 3, Table 1).

Overall, the polymerization by the ICD/BnOH system is well controlled, as evidenced by the good agreement between the experimental and theoretical M_n and a narrow MWD of 1.12 observed for the PLA it produced. To determine if this polymerization involves transesterification or not and also examine end-group fidelity, we analyzed a low-molecular-weight L-PLA produced by ICD/BnOH using MALDI-TOF mass spectrometry (Figure 2). A plot of the m/z values vs the number of LA repeat units (n) yielded a straight line with a slope of 144 and an intercept of 131. The slope corresponds to the mass of LA, whereas the intercept is a sum of the masses of Na^+ (from the added NaI) and the chain-end group which corresponds to a formula of C_7H_8O (i.e., the BnOH initiator). Notably, no peaks separated by m/z = 72 were observed, indicating the absence of transesterification. Polymerizations by ICD alone, ICD/BHT, and ICD/TSH yielded polymers with much higher M_n than expected and also broader MWDs (1.2−1.4). However, the MWD for each system stayed within a narrow range at different monomer conversions, even with the prolonged reaction times and high monomer conversions: 1.28−1.31 for runs 1−2 by ICD alone, 1.37−1.43 for runs 4−6 by ICD/BHT, and 1.25−1.29 for runs 7−10 by ICD/TSH. These results suggest that the relative broader MWD observed for the PLA produced by the systems other than ICD/BnOH is likely resulted from slow initiation, not transesterification side reactions. Furthermore, in all cases, the polymerization proceeds in absence of epimerization, and the polymers produced have quantitative isotacticity, as evidenced by NMR (Figure 3) and thermal data (Figure 4). For example, the polymer produced by ICD/BnOH (run 3, Table 1) shows quantitative isotacticity by the homonuclear decoupled ^{1}H NMR (Figure 3) and a single T_m of 162 °C by DSC (Figure 4). This T_m value is comparable with the reported values for the L-PLA produced by thiourea-amine (T_m = 160 °C)[20] and phosphazene base (T_m = 163 °C, M_n = 25.8 kDa)[17a] organocatalysts that are known not to cause epimerization. As controls, none of the initiators employed herein were able to initiate the ROP of L-LA alone.

Stereoselective Polymerization of *rac*-LA by ICD. Having demonstrated the ability of ICD to catalyze the ROP of L-LA without noticeable epimerization and transesterification side reactions (vide supra), we next investigated characteristics of the ROP of *rac*-LA catalyzed by ICD. In the ROP of *rac*-LA, five idealized scenarios can occur (although more realistically, the polymerization will not strictly follow one), and each scenario produces different stereo forms of PLA (Scheme 3). First, there can be no stereoselectivity, yielding atactic, amorphous PLA. Second, if monomer enchainment taking place at the active center occurs alternatingly between two enantiomers of

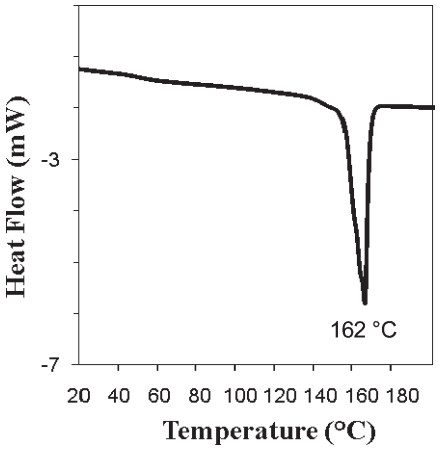

Figure 4. DSC trace (at heating and cooling rate of 10 °C/min, second scan) for L-PLA (run 3, Table 1).

monomer, then heterotactic PLA is produced.[27] Third, isotactic PLA with stereomultiblock microstructures can be produced through exchanging of growing polymer chains between two enantiomeric catalyst centers.[9] Fourth, if the initial ring-opening is nonstereoselective, but the subsequent ROP is stereoselective via chain end control, then there will exist an equal number of initially opened L-LA or D-LA propagating species that will subsequently polymerize L-LA and D-LA stereoselectively, giving rise to a racemic mixture of isotactic L-PLA and D-PLA. Fifth, if an enantiomeric chiral catalyst is stereospecific, there exists a possibility for the kinetic resolution polymerization of *rac*-LA; in a perfect kinetic resolution polymerization, at 50% monomer conversion, the polymer would be composed of entirely one enantiomer, while the other enantiomer would be left resolved. If the polymerization was allowed to continue, then a diblock copolymer could be synthesized, composed of blocks of each enantiomeric monomer; this diblock polymer could form the crystalline stereocomplex with a single, enhanced T_m. However, as the concentration of one enantiomer is decreased, the relative reactivity ratios for polymerization of each enantiomer will become similar, and the final product will most likely be isotactic-*block*-heterotactic or isotactic-*block*-isotactic-rich stereogradient polymer exhibiting two or possibly more T_m's.[7]

To investigate what type of PLA could be formed and by which scenario in the ROP of *rac*-LA catalyzed by ICD, we employed identical conditions to those used in the polymerization of L-LA ([LA]/[ICD] = 100, 5 mL of DCM, 25 °C). One observation immediately stood out in the ROP of *rac*-LA: this polymerization is slower than that of L-LA, indicating that the polymerization of D-LA by ICD is unfavored, as compared to the polymerization of its enantiomer. Specifically, in the absence of any additional initiator, the polymerization of *rac*-LA by ICD alone reached only 26.4% conversion after 73 h (run 11, Table 2). Nonetheless, this polymerization yielded isotactic-rich PLA, as indicated by a P_m value of 0.69. The slower ROP of *rac*-LA, relative to L-LA, became more apparent when BnOH was used as the initiator; the polymerization of *rac*-LA needed 61.5 h to reach a 90.4% monomer conversion (run 13, Table 2), compared to about half the time (31.5 h) needed to achieve the similar conversion (run 3, Table 1). On the other hand, the M_n's of the polymers produced by both polymerizations are similar and the MWDs are identical, 1.12. The initiator efficiency is similarly high; for

Scheme 3. Idealized Five Possible Scenarios in the ROP of *rac*-LA

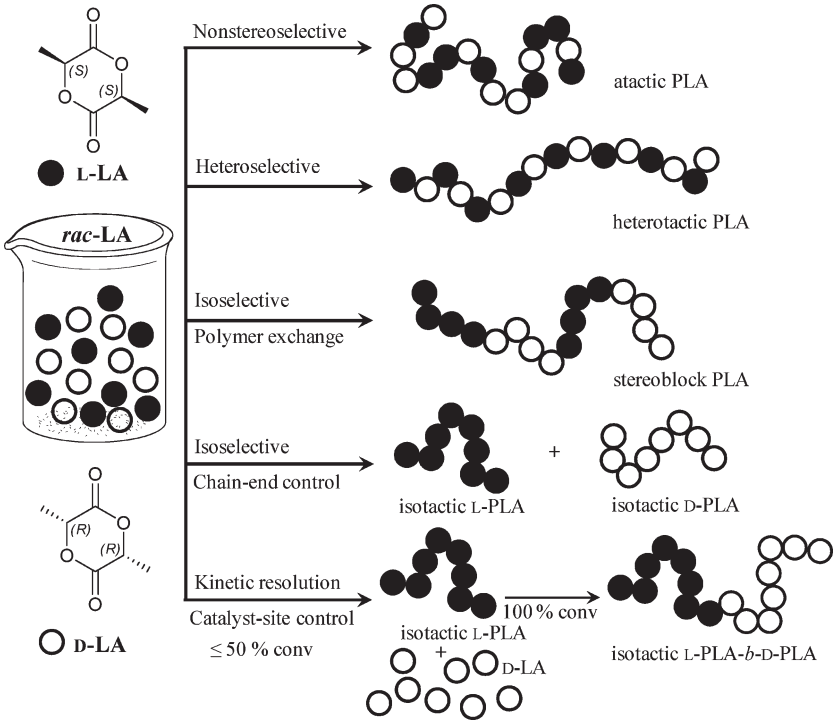

Table 2. Selected Results for the Stereoselective Polymerization of *rac*-LA by ICD[a]

run no.	added initiator (equiv)	time (h)	conv[b] (%)	M_n[c] (kDa)	MWD[c] (M_w/M_n)	P_m[b]
11	none	73.0	26.4	23.3	1.25	0.69
12	BnOH (1)	16.4	48.4	7.39	1.13	n.d.
13	BnOH (1)	61.5	90.4	11.5	1.12	0.68
14	BnOH (5)	14.0	86.8	3.68	1.11	0.73
15	BnOH (10)	14.0	91.2	2.78	1.11	0.75
16[d]	BnOH (10)	76.0	84.7	2.41	1.13	0.71
17	BHT (1)	73.0	34.8	21.1	1.23	0.65
18	TSH (1)	73.0	68.7	16.1	1.17	0.64
19	TSH (5)	61.5	76.2	7.08	1.32	0.67
20	TSH (10)	61.5	88.3	5.07	1.20	0.66
21	(*S*)-PEtOH (1)	31.5	66.6	10.6	1.14	0.65
22	(*S*)-PEtOH (5)	19.5	88.3	6.97	1.16	0.71
23	(*R*)-PEtOH (1)	31.5	62.0	11.1	1.13	0.68
24	(*R*)-PEtOH (5)	19.5	89.7	4.13	1.17	0.73

[a] Conditions: 5 mL of DCM; 25 °C; [*rac*-LA] = 1.93 M; [ICD] = 19.3 mM. n.d. = not determined. [b] Measured by NMR. [c] Measured by GPC. [d] Ran at 0 °C in 10 mL of DCM.

example, the calculated I^* is 96% for run 12. Importantly, at a high monomer conversion of 90.4%, the polymerization remains equally stereoselective, with $P_m = 0.68$.

More acidic external initiators such as BHT (run 17, Table 2) and TSH (run 18, Table 2) experienced the same reduction of the polymerization rate when comparing *rac*-LA with L-LA. The stereoselectivity achieved with either initiator was identical ($P_m \sim 0.65$) within a typical experimental error of ~2%. Analysis of the resulting polymer M_n data clearly shows that, as in the ROP of L-LA, BnOH is the most efficient initiator of the three for the ROP of *rac*-LA. Considering the low polymerization rate for the ROP of *rac*-LA, we next increased equivalents of initiator for the polymerization. Thus, adding 5 equiv of BnOH, under otherwise identical conditions, resulted in a drastic increase in the rate of monomer consumption, achieving 86.8% monomer conversion in 14 h (run 14), over the polymerization with just 1 equiv of BnOH (run 13); this rate enhancement was accompanied by a slight increase in stereoselectivity to $P_m = 0.73$ (run 14 vs P_m of 0.68 for run 13). Accordingly, the increased initiator concentration led to a decrease in M_n (3.68 kDa in run 14 vs 11.5 kDa in run 13), but no change in MWD (1.11). A further increase of the added BnOH to 10 equiv continued to enhanced the rate of

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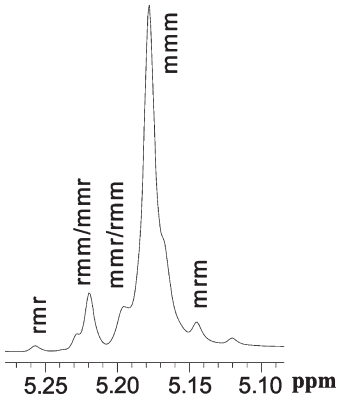

Figure 5. Methine region of homonuclear decoupled ^{1}H NMR spectrum (500 MHz, $CDCl_3$, 50 °C) of isotactic-rich PLA (P_m = 0.75, run 15, Table 2).

polymerization and decrease the polymer M_n, albeit less significantly (run 15, Table 2), but this had negligible to no effects on the polymer MWD and the stereoselectivity (P_m = 0.75, Figure 5). Lowering the polymerization temperature to 0 °C required the polymerization be performed in 10 mL of DCM (due to the poor solubility of *rac*-LA at this temperature) and drastically reduced the rate of polymerization, achieving 84.7% monomer conversion in 76 h (run 16, Table 2). These trends also held when TSH was used as the initiator; thus, the rate of monomer consumption increased as the equivalent of TSH added was increased from 1 to 5 to 10, which also led to a decrease in M_n from 16.1 to 7.08 to 5.07 kDa, respectively, with slight variations in MWD, from 1.17 to 1.32, and minimal changes in P_m, 0.67−0.64 (runs 18−20, Table 2).

As BnOH proved to be the superior initiator, we were curious if there were any effects of using its chiral derivatives on the initiation of the polymerization and stereoregularity of the resulting polymer. To this end, we utilized enantiomeric (*S*)- or (*R*)-1-phenylethanol (PEtOH) as the initiator. Using 1 or 5 equiv of (*S*)-PEtOH (runs 21 and 22) or (*R*)-PEtOH (23 and 24) as initiator and ICD as catalyst, P_m of the resulting polymers experienced minimal to no change, compared to the polymers produced using the BnOH initiator. Additionally, the polymerizations of *rac*-LA by ICD/(*S*)-PEtOH and ICD/(*R*)-PEtOH gave initiator efficiencies from 80 to 90%, which are noticeably lower than that observed for the polymerization by ICD/BnOH (I^* = 96%, vide supra), suggesting that these two chiral initiators are somewhat less efficient than their less bulky, achiral analogue BnOH. The same trend held when 5 equiv of (*S*)- or (*R*)-PEtOH was used. Noteworthy are the observed narrow and nearly constant MWDs (1.13−1.17, runs 21−24) for all the polymers produced by chiral PEtOH initiators, similar to the polymers produced by BnOH (1.11−1.13, runs 12−16).

Kinetic Resolution Polymerization of *rac*-LA by ICD. The above results showed that ICD can catalyze the stereoselective ROP of *rac*-LA to afford isotactic-rich PLA. However, whether this polymerization is operated by a chain-end control mechanism (where catalyst chirality plays a minimal role in the polymerization and no resolution of the monomer occurs) or the kinetic resolution polymerization of *rac*-LA is performed by a site-control mechanism (where chiral catalyst preferentially polymerizes one enantiomer to afford both the enantiomerically enriched polymer and unreacted monomer) was a key question

Table 3. Select Results for the Kinetic Resolution Polymerization of *rac*-LA by ICD[a]

run no.	added initiator (equiv)	time (h)	conv[b] (%)	*ee*[c] (%)	*s* (k_S/k_R)
25	none	73.0	26.4	7.5	1.6
26	BnOH (1)	16.4	48.4	45.1	4.4
27	BnOH (5)	14.0	86.8	71.8	2.2
28[d]	BnOH (5)	45.2	61.6	11.0	1.3
29	BnOH (10)	14.0	91.2	71.1	1.9
30[e]	BnOH (10)	15.3	61.2	58.9	3.8
31	BHT (1)	73.0	34.8	8.6	1.5
32	TSH (1)	24.0	45.5	23.8	2.2
33	TSH (5)	16.4	51.9	49.8	4.3
34	TSH (10)	16.4	62.3	50.5	2.9
35	(*S*)-PEtOH (1)	31.5	66.6	47.6	2.5
36	(*S*)-PEtOH (5)	6.50	59.1	50.6	3.3
37	(*R*)-PEOH (1)	31.5	62.0	36.9	2.2
38	(*R*)-PEOH (5)	6.50	58.0	42.9	2.8

[a] Conditions: 5 mL of DCM unless indicated otherwise; [*rac*-LA] = 1.93 M; [ICD] = 19.3 mM. [b] Measured by NMR. [c] *ee* of unreacted monomer, measured by chiral HPLC. [d] Ran in 5 mL of toluene. [e] Ran at 0 °C in 10 mL of DCM.

that needs to be addressed. Accordingly, after obtaining monomer conversion data through analysis of the reaction aliquots by ^{1}H NMR, we removed all volatiles and extracted the unreacted monomer with a 1:1 hexanes:^{i}PrOH solution. Subsequent filtration successfully separated the polymer from the unreacted monomer that was then analyzed by chiral HPLC to determine the selectivity factor, *s*, of the polymerization at a given monomer conversion.

In all polymerizations L-LA was shown to be preferentially polymerized by ICD, thus kinetically resolving D-LA to various extents. For a polymerization without additional initiator, the unreacted monomer had a 7.5% *ee* at a 26.4% monomer conversion, giving a minimal *s* value of 1.6 (run 25, Table 3). Addition of 1 equiv of BnOH significantly increased resolution of D-LA to 45.1% *ee* at 48.4% conversion and the *s* value to 4.4 (run 26). Increasing the amount of BnOH to 5 or 10 equiv (relative to ICD) speeded up the polymerization and achieved 86.8% or 91.2% monomer conversion in 14 h, at which stage the *ee* of the resolved D-LA was 71.8% (run 27) or 71.1% (run 29). Lowering the polymerization temperature to 0 °C achieved 58.9% *ee* of the resolved D-LA at 61.2% monomer conversion, still giving a very modest *s* factor of 3.8. Examining possible solvent effects, we performed the polymerization in THF, which completely shut down the polymerization, and in toluene, which significantly slowed down the polymerization and also reduced the degree of kinetic resolution (run 28 vs 27).

As anticipated, the kinetic resolution polymerization by ICD/BHT gave similar results to those by ICD alone (run 31 vs 25). The more acidic TSH led to selectivity factors ranging from 2.2 to 4.3, depending on how many equivalents of TSH were employed (runs 32−34), which are similar to those values achieved by BnOH. Chiral initiators (*S*)- and (*R*)-PEtOH also yielded similar selectivity factors (runs 35−38). It is apparent that the selectivity factors achieved herein are only modest, but in general, these results show that the more efficient initiators lead to higher *s* values (i.e., BnOH vs BHT or ICD as initiator). A more important finding here is that the stereoselectivity in the

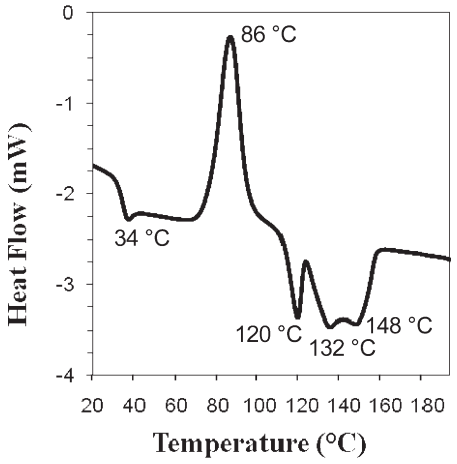

Figure 6. DSC trace (second scan after heating to 200 °C in the first heating cycle) of stereogradient PLA via ROP of *rac*-LA by ICD (run 29, Table 3).

polymerization of *rac*-LA catalyzed by ICD is due to its ability to affect the kinetic resolution polymerization, thereby leading to polymers and monomers enantioenriched or stereogradient polymers at high monomer conversions. This conclusion was further confirmed by the thermal properties of the resulting polymer. The polymer produced by ICD/10 equiv BnOH (91.2% conversion, run 29, Table 3) exhibited three T_m's at 148, 132, and 120 °C (Figure 6). These melting transitions presumably correspond to PLA segments with different levels of isotactic enrichment, produced at early, mid, and late stages of the polymerization as the L-LA monomer concentration decreases gradually. Furthermore, a T_g of 34 °C was observed, which relates to the isotactic-rich polymer segments. There also showed a crystallization temperature of 86 °C on this second scan trace after heating the sample to 200 °C in the first heating cycle under the current DSC conditions (see Experimental Section).

CONCLUSIONS

In summary, this contribution represents the first report on the ROP of LA using cinchona alkaloids as organocatalysts and also the first successful kinetic resolution polymerization of *rac*-LA by an organocatalyst. As CD does not possess the needed characteristics to effectively activate the monomer or initiator, it is inactive for the ROP of LA. In contrast, the bifunctional ICD, bearing the more acidic phenol and the more basic tertiary amine moieties, catalyzes the ROP of L-LA independently or with added initiators such as benzyl alcohol. In particular, the polymerization by the ICD/BnOH system is highly efficient and proceeds to high conversions without noticeable epimerization or transesterification side reactions, thereby producing PLA with a controlled M_n and narrow MWD (1.12). More significantly, ICD also catalyzes the stereoselective polymerization of *rac*-LA, through the kinetic resolution polymerization, affording either both the polymer and the monomer partially enantioenriched with L-LA and D-LA, respectively, or crystalline stereogradient PLA if the polymerization is allowed to proceed to high conversions. The use of chiral alcohol initiators in lieu of achiral ones has showed no significant effects on the kinetic resolution and, in general, more efficient initiators lead to higher selectivity factor values. Overall, the selectivity factors achieved in the current kinetic resolution polymerization are only modest, and a search for more advanced cinchona alkaloids organocatalysts is needed to enhance the stereoselectivity of the kinetic resolution polymerization. Our efforts currently underway are specifically directed toward achieving that goal.

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