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Stereoselective Ring-opening Polymerization of *rac*-Lactide by Bulky Chiral and Achiral *N*-heterocyclic Carbenes

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Abstract Despite the extraordinary success has been achieved in metal catalyst-promoted stereoselective ring-opening polymerization (ROP) of *rac*-lactide (*rac*-LA), well-controlled stereoselective *rac*-LA ROP by organic catalyst still remains a scientific challenge. Here we report our investigations into organocatalytic stereoselective ROP of *rac*-LA by utilizing novel bulky chiral and achiral *N*-heterocyclic carbenes (NHC), 1,3-bis-(1′-naphthylethyl)imidazolin-2-ylidene. The effect of polymerization conditions (*e.g.* solvent, temperature, alcohol initiator) on ROP behavior by these bulky NHCs has been fully studied, leading to the formation of isotactic-rich stereoblock polylactide (P_i = 0.81) under optimized conditions with high activity (Conv. = 98% in 30 min) and narrow molecular weight dispersity ($Đ$ = 1.05).

Keywords Polylactide; Ring-opening polymerization; Stereoselectivity; Organic catalyst; *N*-heterocyclic carbene

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INTRODUCTION

Polylactide (PLA), conventionally synthesized through the ring-opening polymerization (ROP) of lactide (LA), is a commercially implemented, notable biodegradable and biocompatible polymer derived from biorenewable resources, such as corn and other agricultural products, which has attracted considerable attention as a promising alternative to the petroleum-based commodity resins[1–10]. Due to two stereocentres of LA, it therefore contains three distinct diastereomers: DD-, LL-, DL-(*meso*)-lactide, and their mixture *rac*-LA (DD-/LL-LA = 50/50), leading to different stereochemistry of PLA and thus exhibiting different mechanical, physical, and degradation properties[2]. The synthesis of stereocomplex PLA directly from inexpensive feedstock *rac*-LA through stereoselective ROP has been an important synthetic target, as the resulting PLA shows higher melting temperature (T_m ~ 230 °C) than the corresponding isotactic poly(L-LA) (PLLA) and poly(D-LA) (PDLA) (T_m ~ 180 °C), which is highly desirable for application. Various achiral and chiral organometallic catalysts for stereoselective *rac*-LA ROPs have been reported, and two mechanisms are proposed for such stereoselectivity, including chain-end control in which the stereochemistry of the last inserted monomer defines the stereochemistry of the subsequent ring-opening step, and enantiomorphic site control where the chirality of the catalyst defines the stereochemistry of the monomer insertions[11–20]. Despite the extraordinary success has been accomplished in metal catalyst-promoted stereoselective *rac*-LA ROP, the applications of PLA in food packaging, biomedical, and microelectronic applications have motivated efforts to develop metal-free organic catalysts[21–24]. However, up to date, well-controlled stereoselective *rac*-LA ROPs by organic catalysts were very rare in previous literatures[25–29], which has only been achieved at very low temperature (~ –75 °C) by employing bulky phosphazene superbase (^{t}Bu-P$_2$, P_i = 0.95) or sterically encumbered *N*-heterocyclic carbenes (NHC, P_i = 0.90) as the catalysts that are postulated by a chain-end control with stereoerror mechanism (Scheme 1)[28, 29]. Herein, we report our investigations into organocatalytic stereoselective ROP of *rac*-LA utilizing novel bulky chiral and achiral NHCs (*R*,*R*-NHC-**1** and *rac*-NHC-**1**, Scheme 1) by introducing naphthyl groups on the nitrogen side to enhance the steric hindrance of the carbene center, which can catalyze the formation of isotactic-rich stereoblock PLA (P_i = 0.81) with high activity (Conv. = 98% in 30 min) and narrow molecular weight dispersity ($Đ$ = 1.05).

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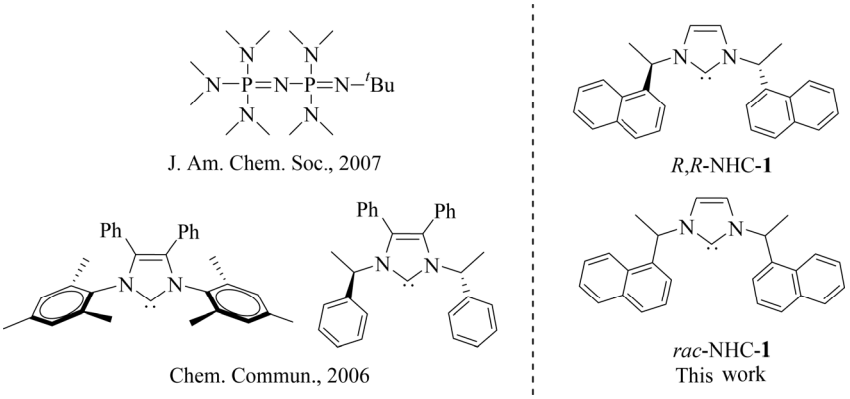

Scheme 1 Structures of organic catalysts for stereoselective ROP of *rac*-LA employed in previous literatures and in this study

EXPERIMENTAL

Materials, Reagents, and Methods

All synthesis and manipulations of air- and moisture-sensitive materials were carried out in flamed Schlenk-type glassware on a dual-manifold Schlenk line, or in an argon-filled glovebox. HPLC-grade organic solvents were first sparged extensively with nitrogen during filling 20 L solvent reservoirs and then dried by passage through activated alumina (for dichloromethane, DCM) followed by passage through Q-5 supported copper catalyst (for toluene, TOL) stainless steel columns. Tetrahydrofuran (THF) was degassed and dried over Na/K for 3 days, followed by distillation. *rac*-Lactide (*rac*-LA) was purchased from Aldrich Chemical Co. and purified by sublimation for twice. Benzyl alcohol (BnOH) was purchased from Alfa Aesar Chemical Co. and purified by distillation over CaH_2. 2,2-Diphenylethanol (Ph_2CHCH_2OH), diphenylmethanol (Ph_2CHOH) and 1-pyrenebutanol (PNOL) were purchased from Aldrich Chemical Co. and purified by dissolving in toluene over CaH_2, filtering after stirring for 3 days, and removing the solvent.

Synthesis of *R*,*R*-NHC-1 and *rac*-NHC-1

A round-bottomed flask was charged with (*S*)-1-naphthylethylamine (1.71 g, 10 mmol) in toluene (15 mL), and paraformaldehyde (0.30 g, 10 mmol) was added under intense stirring. After 30 min, the flask was then cooled to 0 °C, and another equivalent of (*S*)-1-naphthylethylamine (1.71 g, 10 mmol) and 3.3 mol/L aqueous HCl (3 mL, 10 mmol) were added dropwise. The solution was allowed to warm to the room temperature, and 40% aqueous glyoxal (1.45 mL, 10 mmol) was added. The resulting cloudy mixture was stirred for 12 h at 40 °C. After the mixture was cooled to room temperature, 100 mL of ether and 50 mL of saturated Na_2CO_3 solution were added, and the layers were separated. The aqueous layer was washed three times with 100 mL portions of ether, the volatiles were removed in vacuum, and the residue was extracted with 150 mL of CH_2Cl_2, dried over $MgSO_4$, and filtered. After removal of the solvent, the solid residue was broken down to a white hygroscopic powder by treatment with ether to afford *R*,*R*-**1a** with the yield of 60% ($[\alpha]^{29.8}_{589}$ = 85.1). ^{1}H-NMR (400 MHz, $CDCl_3$, δ, ppm): 12.12 (s, 1H, N—C<u>H</u>=N$^+$), 8.17 (d, *J* = 12 Hz, 2H, Ar-H), 7.89 (d, *J* = 8 Hz, 4H, Ar-H), 7.62 (t, *J* = 4 Hz, 2H, Ar-H), 7.45–7.56 (m, 6H, Ar-H), 6.89 (q, *J* = 8 Hz, 2H, C<u>H</u>CH$_3$), 6.70 (s, 2H, C<u>H</u>=C<u>H</u>), 2.23 (d, *J* = 8 Hz, 6H, CHC<u>H</u>$_3$).

In the glovebox, a 20 mL glass vial was charged with *R*,*R*-**1a** (1.03 g, 2.5 mmol) and 20 mL of THF. To the suspension, ^{t}BuOK (0.84 g, 7.5 mmol) was added under intense stirring. After addition, the reaction mixture kept stirring for another 30 min, and the suspension gradually turned to red. The solvent was then removed under reduced pressure, affording red viscous oil which was extracted with toluene to remove unreacted ^{t}BuOK and KCl. Upon removal of the toluene under reduced pressure, *R*,*R*-NHC-**1** was obtained as red viscous oil with the yield of 80%. ^{1}H-NMR (400 MHz, C_6D_6, δ, ppm): 8.61 (d, *J* = 8 Hz, 2H, Ar-H), 7.66 (d, *J* = 8 Hz, 2H, Ar-H), 7.61 (d, *J* = 8 Hz, 2H, Ar-H), 7.39 (t, *J* = 8 Hz, 4H, Ar-H), 7.26 (q, *J* = 8 Hz, 4H, Ar-H), 6.40 (q, *J* = 4 Hz, 2H, C<u>H</u>CH$_3$), 6.25 (s, 2H, C<u>H</u>=C<u>H</u>), 1.96 (d, *J* = 8 Hz, 6H, CHC<u>H</u>$_3$).

1,3-Bis-(1′-naphthylethyl)imidazolium chloride and 1,3-bis-(1′-naphthylethyl)imidazolin-2-ylidene (*rac*-NHC-**1**) were prepared by the same procedure with the similar yield and NMR spectra.

In a dry 200 mL Schlenk flask, benzil (1 g, 4.8 mmol) and 1-(naphthalen-1-yl)ethan-1-amine (6.5 g, 38 mmol) were dissolved in 140 mL of toluene. $TiCl_4$ (0.68 mL) was then added and the solution was stirred at 100 °C for 12 h. After the mixture was cooled to room temperature, H_2O was added to quench the reaction, and the toluene layer was then separated, dried over $MgSO_4$ and filtered. The solvent was removed under vacuum to yield yellow oil. The crude product was then purified by column chromatography (hexane/CH_2Cl_2) and recrystallization in ethanol to afford **2a** (1.84 g, 74% yield). ^{1}H-NMR (400 MHz, $CDCl_3$, δ, ppm): 8.20–6.82 (m, 41H), 5.51–5.48 (m, 1H), 4.97 (dd, *J* = 6.4 Hz, 1H), 4.69 (dd, *J* = 6.4 Hz, 1H), 3.7 (dd, *J* = 7.04 Hz, 1H), 1.89 (d, *J* = 6.4 Hz, 1H), 1.65 (d, *J* = 6.3 Hz, 3H), 1.26 (d, *J* = 5.9 Hz, 6H), 0.69 (d, *J* = 6.4 Hz, 3H). MALDI-TOF mass spectrum calculated for $C_{38}H_{33}N_2^+$: 517.70; Found 517.26.

To a suspension of AgOTf (0.1750 g, 0.68 mmol) in 4.6 mL of CH_2Cl_2 was added chloromethyl pivalate (0.1030 g, 0.68 mmol) and the resulting suspension was stirred for 45 min which was then transferred *via* syringe to a vial containing a solution of **2a** (0.24 g, 0.47 mmol) in CH_2Cl_2, and the resulting solution was stirred in a sealed tube in the dark at 40 °C for 20 h. After the mixture was cooled to room

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temperature, the reaction was quenched with methanol and the solvent evaporated in vacuum. The characteristic signals of **2b** were not observed in ^{1}H-NMR analysis of crude product, indicating that the failure of the cyclization was due to too sterically bulky structure.

General Polymerization Procedures

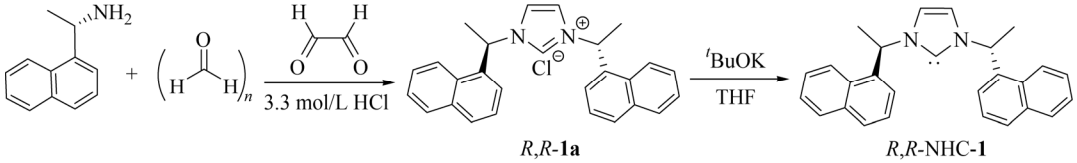
Polymerizations were performed either in 20 mL glass reactors inside the inert glovebox for room temperature (RT) runs or 25 mL flame-dried Schlenk flasks interfaced to the dual-manifold Schlenk line for runs using an external temperature bath. The reactor was charged with a predetermined amount of monomers, solvent, and/or initiator. For the runs at room temperature, the polymerization was initiated by rapid addition of a predetermined amount of catalyst in the solvent *via* a gastight syringe. For the runs using an external temperature bath, the reactor was sealed, taken out of glovebox, and then immersed in the external temperature bath under the predetermined temperature. After equilibration at the desired polymerization temperature, the polymerization was initiated by rapid addition of a predetermined amount of catalyst in the solvent *via* a gastight syringe. After a desired period of time, the polymerization was quenched by addition of 1 mL of benzoic acid/$CHCl_3$ (10 mg/mL), and a 0.2 mL of aliquot was taken from the reaction mixture and prepared for ^{1}H-NMR analysis to obtain monomer conversion data. The quenched mixture was then precipitated into 100 mL of cold methanol, filtered, washed with methanol to remove the unreacted monomer, and dried in a vacuum oven at RT to a constant weight.

Polymer Characterizations

Polymer microstructures were determined by ^{1}H-NMR and ^{13}C-NMR spectra recorded on a Varian Inova 400 MHz spectrometer. Chemical shifts for ^{1}H- and ^{13}C-NMR spectra were referenced to internal solvent resonances and were reported as parts per million relative to $SiMe_4$. Polymer number-average molecular weights (M_n) and dispersity ($Đ = M_w/M_n$) values were measured by gel permeation chromatography (GPC) analyses carried out at 25 °C and a flow rate of 1.0 mL/min, with THF as the eluent on a Waters University 1515 GPC instrument equipped with a Waters 2414 refractive-index detector and three Waters Styragel columns connected in series. The instrument was calibrated with 10 PMMA standards, and chromatograms were processed with Waters Empower™ 3 software. Melting-transition temperatures (T_m) and glass-transition temperatures (T_g) were measured by differential scanning calorimetry (DSC) on a Discovery DSC 2500, TA Instrument. The first heating rate was 10 K/min, while the cooling rate was 3 K/min and the second heating rate was 10 K/min.

RESULTS AND DISCUSSION

Scheme 2 outlines the synthetic route to *R*,*R*-NHC-**1** using modified literature procedures[30, 31]. The chiral imidazolium salt (*R*,*R*-**1a**) was synthesized with moderate yield of 60% *via* facile one-step ring closure started from inexpensive materials including chiral amine, glyoxal, and paraformaldehyde, which proceeded without any racemization ($[\alpha]^{29.8}_{589}$ = 85.1). The subsequent deprotonation of the chiral imidazolium salt to free carbene *R*,*R*-NHC-**1** was carried out by utilizing excess ^{t}BuOK as the base in THF instead of NaH/liquid ammonia in previous literature. Note that the deprotonation reaction was accomplished quantitatively in 30 min without any detectable side reactions through monitoring the reaction by ^{1}H-NMR spectra. After the reaction, THF was removed under vacuum and the resulted crude product was extracted by toluene to remove KCl and unreacted ^{t}BuOK, affording *R*,*R*-NHC-**1** as red viscous oil with the isolated yield of 80%. The comparison of ^{1}H-NMR spectra between *R*,*R*-**1a** and *R*,*R*-NHC-**1** is provided in Fig. 1. The disappearance of the characteristic signal at 12.1 ppm attributed to the acidic methine proton of the imidazolium moiety demonstrated the successful deprotonation and conversion into *R*,*R*-NHC-**1**. 1,3-Bis-(1′-naphthylethyl) imidazolium chloride and corresponding *rac*-NHC-**1** were prepared by the same procedure using achiral amine as the starting material. To further enhance the steric hindrance of NHC catalyst, we also tried to synthesize the 1,3-bis-(1′-naphthylethyl)-4,5-diphenyl-imidazolium salt (**2b**) by introducing phenyl rings on the carbene backbone (Scheme 3). However, due to sterically demanding structure, one-step cyclization method used in the synthesis of **1a** was failed for **2b**. Instead, two steps including the formation of bis-[1-(naphthalen-1-yl)ethyl]-1,2-diphenylethane-1,2-diimine (**2a**) and subsequent cyclization in the presence of chloromethyl pivalate and AgOTf were employed for synthesis of **2b**[29]. Because of the steric repulsion between naphthyl and phenyl rings, the structure of **2a** exists axial chirality, leading to complex ^{1}H-NMR spectrum in which the peaks can be assigned to different sets of isomers. Moreover, the MALDI-TOF mass spectrum showed a major molecular ion peak of 517.26 identical to the calculated value of 517.70, further confirming the successful synthesis of **2a**. However, when the obtained **2a** was treated with chloromethyl pivalate and AgOTf, the characteristic signal corresponding to acidic methine proton of the imidazolium moiety of **2b** cannot been observed in ^{1}H-NMR spectrum, indicating the failure of cyclization presumably caused by too sterically bulky structure. The synthesis of naphthyl-substituted imidazolium salt with smaller group on the backbone, such as two methyl groups or



Scheme 2 Synthetic route to 1,3-bis-[(*R*,*R*)-1′-naphthylethyl]imidazolium chloride (*R*,*R*-**1a**) and also the free carbene 1,3-bis-[(*R*,*R*)-1′-naphthylethyl]imidazolin-2-ylidene (*R*,*R*-NHC-**1**)

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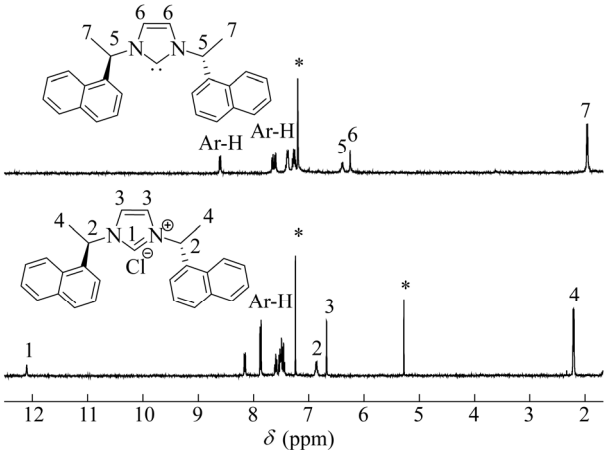
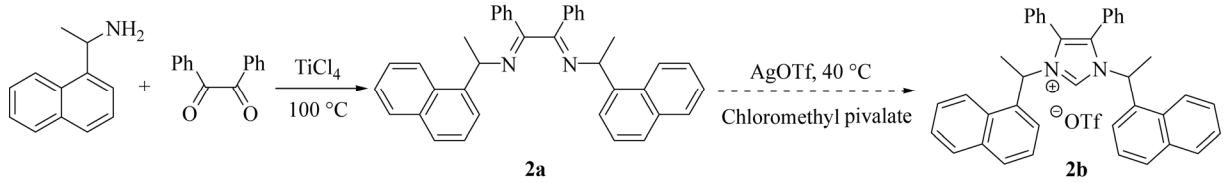


Fig. 1 Comparison of ^{1}H-NMR spectra: (top) *R*,*R*-NHC-**1** (C_6D_6), (bottom) *R*,*R*-**1a** ($CDCl_3$)

one methyl group and one phenyl group, is in the current progress.

The obtained *R*,*R*-NHC-**1** and *rac*-NHC-**1** were employed for *rac*-LA ROP, and the results are summarized in Table 1. When ROP was carried out in DCM at room temperature (RT), *R*,*R*-NHC-**1** exhibited high activity with conversion of 95.1% achieved in 30 min, affording PLA with moderate isotacticity (P_i = 0.64, Table 1, run 1). Using 1-pyrenebutanol (PNOL) as the initiator, similar activity and stereoselectivity can be observed (Table 1, run 1 versus run 3). Decreasing the polymerization temperature from RT to –78 °C with or without PNOL all led to the significant enhancement of isotacticity (P_i = 0.75, Table 1, runs 2 and 4). More importantly, compared with ROP in the absence of PNOL, ROP in the presence of PNOL became much more controlled when it was carried out at –78 °C, providing PLA with extremely narrow molecular weight dispersity ($Đ$ = 1.03, Table 1, run 4). This result is different from the previous literature in which the dispersity was narrow even at room temperature[29]. Although *R*,*R*-NHC-**1** and *rac*-NHC-**1** in present work have much bulkier naphthyl groups on the nitrogen side compared with phenyl rings in previously reported NHC catalyst[29], the naphthyl groups are allowed to rotate to avoid the crowded carbene center at room temperature. In sharp contrast, the rotation of phenyl rings on the nitrogen side in previously reported NHC catalyst is restricted[29] due to the repulsion between phenyl ring on the nitrogen side and two phenyl rings on the carbene backbone. As a result, the carbene center of NHC catalyst in present work is actually less sterically hindered at room temperature. Therefore, the nucleophilic attack of NHC-activated alcohol initiator/chain end to the carbonyl group of lactide monomer has no obvious difference from that to carbonyl group of polymer in our catalytic system, leading to undesired transesterification at room temperature, thus resulting in broad dispersity of polymer. When the temperature decreases to –78 °C, the rotation of the naphthyl groups is presumably restricted and the carbene center of NHC catalyst becomes steric hindrance, which brings about the selective nucleophilic attack of NHC-activated alcohol initiator/chain end to the carbonyl group of lactide monomer, leading to controlled ROP with narrow dispersity of polymer and also



Scheme 3 Synthetic route to bis-[1-(naphthalen-1-yl)ethyl]-1,2-diphenylethane-1,2-diimine (**2a**) and 1,3-bis-(1′-naphthylethyl)-4,5-diphenyl-imidazolium triflate (**2b**)

Table 1 Results of *rac*-LA ROPs by *R*,*R*-NHC-**1** and *rac*-NHC-**1** [a]

Run	Initiator	Solvent	Temperature (°C)	Time (min)	Conv. [b] (%)	M_n [c] (kg/mol)	$Đ$ [c]	P_i [d]
1	–	DCM	25	30	95.1	26.2	1.38	0.64
2	–	DCM	–78	30	88.3	69.4	2.26	0.75
3	PNOL	DCM	25	30	97.9	23.7	1.66	0.66
4	PNOL	DCM	–78	30	86.6	23.4	1.03	0.75
5	BnOH	DCM	–78	30	98.0	17.8	1.05	0.81
6	Ph_2CHOH	DCM	–78	30	99.0	36.3	1.61	0.68
7	Ph_2CHCH_2OH	DCM	–78	30	98.0	44.8	1.95	0.70
8 [e]	PNOL	DCM	–78	30	95.0	25.7	1.03	0.75
9	–	THF	–78	11	72.8	40.6	1.97	0.65
10	PNOL	THF	–78	30	83.5	18.7	1.69	0.68
11	–	TOL	–78	30	99.0	48.2	1.95	0.77
12	PNOL	TOL	–78	30	99.0	10.4	1.05	0.79
13	–	THF	25	10	85.0	n.d.	n.d.	0.68
14 [f]	–	THF	25	10	99.0	n.d.	n.d.	0.65

[a] Conditions: *rac*-LA = 0.2196 g (1.52 mmol), *rac*-LA/*R*,*R*-NHC-**1**/Initiator = 100/1/1, $[rac\text{-LA}]_0$ = 0.9 mol/L for the runs in DCM and THF, $[rac\text{-LA}]_0$ = 0.1 mol/L for the runs in TOL; [b] Determined by ^{1}H-NMR spectra; [c] Number-average molecular weight (M_n) and dispersity ($Đ = M_w/M_n$) were determined by GPC at 25 °C in THF relative to PMMA standard; [d] Determined by the analysis of all of the tetrad signals in the methine region of de-convoluted homonuclear-decoupled ^{1}H-NMR spectra[32]; [e] ROP was promoted by *rac*-NHC-**1** under the same conditions; [f] ROP of L-LA by *R*,*R*-NHC-**1**

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relatively higher stereoselectivity. Fixing the polymerization temperature at –78 °C, the alcohol initiators having different steric bulk and acidity including PNOL, BnOH, Ph_2CHOH, and Ph_2CHCH_2OH were screened. It is noteworthy that using BnOH not only can further enhance P_i to 0.81, but also can maintain the controlled polymerization with narrow dispersity ($Đ$ = 1.05, Table 1, run 5). The comparison of homonuclear decoupled ^{1}H-NMR spectra of PLAs obtained at different polymerization temperatures is depicted in Fig. 2. In sharp contrast, switching to Ph_2CHOH and Ph_2CHCH_2OH led to uncontrolled polymerization, affording PLA with relatively low P_i and broad dispersity (Table 1, runs 6 and 7). Moreover, ROP by *rac*-NHC-**1** was also examined, which exhibited identical monomer conversion, stereoselectivity, and molecular weight to that of *R*,*R*-NHC-**1** (Table 1, run 8), indicating that the stereoselectivity of ROP is derived from chain-end control rather than enantiomorphic site control. The effect of solvents on the ROP behavior by catalyst *R*,*R*-NHC-**1** at –78 °C was investigated. ROP carried out in the relatively non-polar toluene showed similar polymerization results to ROP in DCM (Table 1, runs 9 and 10), while using THF as the solvent led to polymer with relatively low P_i and broad dispersity (Table 1, runs 11 and 12). The thermal analysis *via* differential scanning calorimetry (DSC) shows that the obtained isotactic-rich PLA (P_i = 0.75) has a T_m at around 150 °C and a T_g at 50 °C (Fig. 3), indicating the formation of semi-crystalline PLA and stereoblock microstructure.

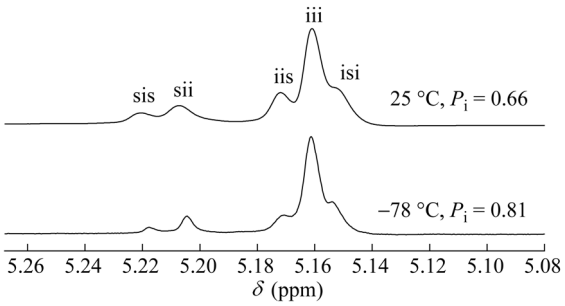

Fig. 2 Methine region of homonuclear decoupled ^{1}H-NMR spectra of poly(*rac*-LA)s obtained at different polymerization temperatures (Table 1, runs 3 and 5)

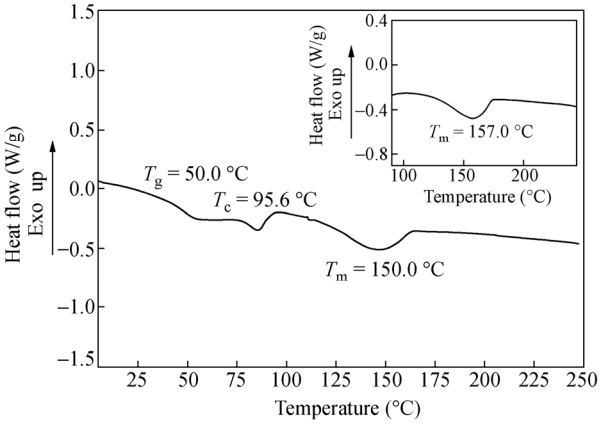

Fig. 3 DSC curves of poly(*rac*-LA)s obtained at low polymerization temperature with P_i of 0.75 (Table 1, run 4) and 0.81 (Table 1, run 5, inset), respectively

CONCLUSIONS

In summary, this contribution reports our investigations into stereoselective ROP of *rac*-LA by NHC organic catalysts. Through facile one-step ring closure reaction started from inexpensive materials and the subsequent deprotonation, novel bulky chiral and achiral NHCs with naphthyl groups substituted on the nitrogen side were successfully synthesized in a good yield. The study of effect of polymerization conditions on ROP behavior indicated that low polymerization temperature (–78 °C) and suitable solvent (toluene and DCM) are in favor of enhancing the stereoselectivity of *rac*-LA ROP. The comparison of ROPs by chiral and achiral NHCs reveals that the stereoselectivity is derived from chain-end control mechanism. Under optimized conditions, isotactic-rich stereoblock PLA (P_i = 0.81) with high activity (Conv. = 98% in 30 min) and narrow molecular weight dispersity ($Đ$ = 1.05) has been achieved. The steric hindrance of the carbene center of NHC nitrogen is presumably the major factor for stereocontrol ROP of *rac*-LA, besides the influence of polymerization conditions (solvent, alcohol initiator, *etc.*). To achieve it, two important aspects, including the enhancement of steric hindrance of substituent on nitrogen and the restriction of its steric position by the substituent on the backbone, should be met. To verify our speculation, the syntheses of naphthyl-substituted NHCs with two phenyl rings, two methyl groups or one phenyl ring and one methyl group on the backbone, as well as their ROP behavior towards *rac*-LA are in the current progress.

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