Isoselective Ring-opening Polymerization of Racemic Lactide Catalyzed by N-heterocyclic Olefin/(Thio)urea Organocatalysts

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INTRODUCTION

As an important class of biocompatible and biodegradable polymers, isotactic polylactides (PLAs) have drawn considerable attention from academia and industry in recent years due to their excellent chemical and physical properties, such as crystallinity,[2] mechanical[3] and thermal resistance[4] etc. Typically, the stereoselective ring-opening polymerization (ROP) of low-cost racemic lactide (rac-LA) is a promising method for synthesizing isotactic PLAs.[4-6] The steric hindrance and electronic properties of catalysts employed in the stereoselective ROP of rac-LA have a crucial influence on polymerization stereoselectivities.[7-10] According to the literatures, most of the highly isoselective reports in ROP of rac-LA are catalyzed by metal-based catalysts, such as Al,[11-14] Zn,[15,16] Fe,[17] K,[18-20] Y,[21] In,[22] Lu,[23] Zr,[24] Mg,[25] etc. However, considering the increasing concerns in biomedical and microelectronic applications, organocatalytic ROP of rac-LA with high efficiency and stereoregularity is of significant advances as an alternative approach.

In last decade, only a few highly isoselective examples related to organocatalysts have been reported to obtain isotactic PLAs, including N-heterocyclic carbenes (NHCs),[26] phosphazene superbases (Bu-P$_2$ CTPB)[27,28] and densely substituted amino acids.[29] For instance, Waymouth and Hedrick[26] in 2006 reported a highly stereocontrolled ROP of rac-LA with $P_m$ (probability of forming a meso dyad) up to 0.90, using sterically demanding NHC under −70 °C (Fig. 1a).

Then, phosphazene superbases, ‘Bu-P$_2$’[27] and fancy CTPB[28] (Figs. 1b and 1c), were utilized and afforded high $P_m$ of 0.95 and 0.93, respectively. Recently, Mecerreyes and Cossío[29] demonstrated the densely substituted amino acids combined with DBU (Fig. 1d) can also promote isoselective polymerizations of rac-LA. The high stereoselectivity ($P_m$=0.90, 0.96) was attributed to the steric hindrance near the active species. Despite the development of organocatalysis in ROP of rac-LA, there is still much space for enrichment in terms of a new efficient and highly isoselective protocol.

In our recent research, a combination of N-heterocyclic olefins (NHOs) and thioureas/ureas (TUs/Us) was applied to the ROP of lactones, with notably high catalytic activities.[30,31] Lately, we found that this catalytic system could also achieve stereoselective polymerizations of rac-LA. In this context, NHO and TUs/Us with various structures were synthesized and applied into different catalytic systems of rac-LA ROP. Comparing catalytic activities and stereoselectivities of different combinations, the best catalytic system was selected. This work potentially will enrich organocatalysis toolboxes for the synthesis of isotactic PLAs materials.

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Received October 29, 2020; Accepted November 29, 2020; Published online January 5, 2021

Electronic Supplementary Information

Abstract The isoselective ring-opening polymerization of racemic lactide was achieved by combining N-heterocyclic olefin (NHO) with mono(thio)ureas or bis(thio)ureas as catalytic systems. The polymerization process shows high stereoselectivity, controllability and reactivity, delivering multi-block isotactic polylactides with high chain-end fidelity and narrow molecular weight distributions. The enhancement of catalytic performance was observed in the following order: bithiourea (DTU) < monothiourea (TU) < bisurea (DU) < urea (U). The highest $P_m$ (probability of forming a meso dyad) = 0.91 was observed at −70 °C when using NHO/U1 catalytic system and the high stereoselectivity was attributed to chain-end control mechanism.

Keywords N-heterocyclic olefin; (Thio)urea; Organocatalyst; Ring-opening polymerization; Isoselective polymerization; Polylactide

Citation: Wang, Z. Y.; Xu, G. Q.; Zhou, L.; Lv, C. D.; Yang, R. L.; Dong, B. Z.; Wang, Q. G. Isoselective ring-opening polymerization of racemic lactide catalyzed by N-heterocyclic olefin/thio)urea organocatalysts. Chinese J. Polym. Sci. 2021, 39, 709–715.
EXPERIMENTAL

General Considerations

All reactions were carried out under a dry argon (Ar) atmosphere, using standard Schlenk techniques. The polymerizations were performed in an Ar-filled glovebox (O₂ and water levels below 0.1 ppm) unless stated otherwise. All reagents were used without further purification, unless otherwise stated. Benzyl alcohol (BnOH, AR), NH₃·H₂O (25.0%–28.0%), tetrahydrofuran (THF, AR), ethyl acetate (99.7%), methanol (99.0–99.5%), ethyl ether (99.7%), methanol (99.7%), and toluene (AR) were purchased from Sinopharm Chemical Reagent. Iodomethane (MeI, AR) was dried by distillation over sodium with benzophenone as the drying agent. 3,5-dicyano-2-(trifluoromethyl)aniline were purchased from Meryer. THF (99.5%) and acetaldehyde (99.7%) were received from Energy Chemical. Potassium bis(trimethylsilyl)amide (KHMDS, 1 mol/L in THF, 99.5%) and acetaldehyde (99.7%) were received from Energy Chemical. Potassium bis(trimethylsilyl)amide (KHMDS, 1 mol/L in THF) was purchased from Aladdin. 3,5-bis(trifluoromethyl)phenyl isothiocyanate and 3,5-bis(trifluoromethyl)-phenyl isocyanate were purchased from Alfa Aesar. 15.25-cyclohexa-1,2-diamine was purchased from Aladdin. 15.25-1,2-diphenyl-1,2-diaminothiooxazaine and 3,5-bis(trifluoromethyl)laniline were purchased from Meryer. THF was dried by distillation over sodium with benzophenone as the indicator under a nitrogen atmosphere and then stored in a glovebox for no longer than 4 weeks. CH₃Cl₂ and toluene were dried over CaH₂ and toluene were vacuum distilled. Racemic lactide (rac-LA, 99%), 3,5-bis(trifluoromethyl)aniline were purchased from Meryer. THF (99.5%) and acetaldehyde (99.7%) were received from Energy Chemical. Potassium bis(trimethylsilyl)amide (KHMDS, 1 mol/L in THF) was purchased from Aladdin. 3,5-bis(trifluoromethyl)phenyl isothiocyanate and 3,5-bis(trifluoromethyl)-phenyl isocyanate were purchased from Alfa Aesar. 15.25-cyclohexa-1,2-diamine was purchased from Aladdin. 15.25-1,2-diphenyl-1,2-diaminothiooxazaine and 3,5-bis(trifluoromethyl)laniline were purchased from Meryer. THF was dried by distillation over sodium with benzophenone as the indicator under a nitrogen atmosphere and then stored in a glovebox for no longer than 4 weeks. CH₃Cl₂ and toluene were dried over CaH₂ and vacuum distilled. rac-LA was recrystallized from anhydrous toluene. N-heterocyclic olefin (NHO)[30–33] and thioureas/ureas (TUs/Us)[34] were prepared according to the literature methods.

Methods

All nuclear magnetic resonance spectra (¹H-NMR and ¹³C-NMR) were collected at 25 °C on the 400 MHz (for ¹H) and 100 MHz (for ¹³C) Bruker AV400M NMR instrument. Chemical shifts are quoted on the δ scale in ppm referencing to residual solvent and trimethylsilane (TMS) at 0 ppm as internal reference. For homonuclear decoupled ¹H-NMR spectroscopic analysis, relaxation time was measured and fixed to 2.04 s. Samples were obtained in CDCl₃ solutions with the decoupling pulse based on the methyl region (δ=1.5 ppm). Gel permeation chromatography (GPC) was used to determine the molecular weight analysis and molecular weight distributions of the obtained polymers, which were performed on an Agilent Viscotek VE2001 GPC, Viscotek Corporation, USA. A chromatographic assembly comprised a PLgel MIXED-B 10 μm, 7.5 mm × 300 mm, guard column, and equipped with an Agilent 1100 series refractive-index detector. THF (Thermo Fisher Scientific, HPLC grade) was used as eluent and the polymer samples (the samples concentration: 1 mg/mL) were run at a flow rate of 1.0 mL/min. The calibration curves for GPC analysis were calibrated with the polystyrene (PS) standards. For all the prepared polymers, the Mₙ values were calculated via the universal calibration principle or Mark-Houwink parameters.

Synthesis of NHO (Scheme 1)

Synthesis of 1

Acetaldehyde (3.8 mL, 68.4 mmol, 1.5 equiv.) was added to a solution of ammonium hydroxide (25%–28%, 30 mL), and 2,3-butanedione (4.0 mL, 45.6 mmol, 1.0 equiv.) was added dropwise to the reaction mixture. The mixed solution was stirred overnight at room temperature. The reaction system was quenched by 40 mL of 2 mol/L hydrochloric acid aqueous solution, and diluted with ether (50 mL × 3). Then, K₂CO₃ was added to the water phase until no more bubbles. The water phase was extracted with CH₂Cl₂ and then the organic phase was dried over Na₂SO₄ and filtered. The filtrate was dried with a rotary evaporator and dried in vacuum to constant weight to obtain a yellow solid (1.61 g, 32% yield). ¹H-NMR (CDCl₃, δ ppm): 7.32 (s, 1 H, NH), 2.30 (s, 3 H, C—CH₃), 2.10 (s, 6 H, C—CH₃).

Scheme 1 Synthetic route to NHO.

Synthesis of 2

Compound 1 (1.38 g, 12.5 mmol, 1.0 equiv.) and K₂CO₃ (3.80 g, 27.5 mmol, 2.2 equiv.) were added to 15 mL of dry CH₂CN. After 1.5 h stirring at 70 °C, the reaction system was cooled to room temperature. CH₃Cl₂ (2.0 mL, 31.3 mmol, 2.5 equiv.) was added dropwise to the reaction mixture, and the mixture was refluxed for two days. Upon cooling to room temperature, the solvent was evaporated and the solid residue was dissolved in CH₂Cl₂. The suspension was filtered through celite, washed with THF (30 mL × 3), and the filtrate was concentrated to afford a white solid (3.18 g, 96% yield). ¹H-NMR (CDCl₃, δ ppm): 3.75 (s, 6 H, N—CH₃), 2.84 (s, 3 H, C—CH₃), 2.26 (s, 6 H, C—CH₃).

Synthesis of NHO

NHO was prepared by deprotonation of the corresponding precursor salt 2 (0.53 g, 2.0 mmol) using KHMDS (1 mol/L in THF, 2.0 mL) in 5 mL of dry THF. The mixture was stirred at room temperature for 6 h. The resulting suspension was filtered under an argon atmosphere, and the filtrate was dried under high vacuum to afford a pale yellow solid (0.26 g, 93% yield). Then the NHO was stored in a glove box at −25 °C. ¹H-NMR (δ ppm): 2.67 (s, 2 H, C—CH₃), 2.53 (s, 6 H, N—CH₃), 1.42 (s, 6 H, C—CH₃).

Synthesis of TU(U) (Scheme 2)

Typical synthesis procedures are as follows. The depicted thioureas (TUs) and ureas (Us) were prepared by mixing the appropriate amine and isocyanate (isothiocyanate) in MeOH.
solvent. The solution was stirred in the room temperature. Then solvent was washed with vacuum and the products were purified by washing with hexanes three times. After vacuum filtration, the filter residue was vacuum drying at 50 °C for 24 h. For full characterization of TU1, U1, DTU1, DTU2, DU1 and DU2 see the cited literature.

\[
R_1-NH_2 + S/O=C=N-R_2 \xrightarrow{\text{MeOH}} R_1-N=O/S-R_2
\]

Scheme 2  Synthetic route to TU(U).

Typical Procedure for Polymerization of rac-LA by NHO/TU1(U1)

Typical polymerization procedures are as follows. In an Ar-filled glovebox, the catalysts of NHO (0.01 mmol, 1.0 equiv.), TU1/U1 (0.02 mmol, 2.0 equiv) and initiator of BnOH (0.02 mmol, 2.0 equiv.) were dissolved in 0.5 mL of THF in a Schlenk tube. The mixture solution was stirred at determined temperature for 30 min. Then rac-LA (1.0 mmol, 100 equiv) was dissolved in 0.5 mL of THF, and added to the mixture solution immediately. The reaction mixtures were stirred at determined temperature. After the polymerization was completed, benzoic acid was added. The product was isolated by precipitation in cool methanol followed by drying thoroughly under vacuum.

Typical Procedure for Polymerization of rac-LA by NHO/DTUs/Us(DUs)

Typical polymerization procedures are as follows. In an Ar-filled glovebox, the catalysts of NHO (0.01 mmol, 1.0 equiv.), DTUs/Us (0.01 mmol, 1.0 equiv.) and initiator of BnOH (0.02 mmol, 2.0 equiv.) were dissolved in 0.5 mL of THF in a Schlenk tube. The mixture solution was stirred at a determined temperature for 30 min. Then rac-LA (1.0 mmol, 100 equiv) was dissolved in 0.5 mL of THF, and added to the mixture solution immediately. The reaction mixtures were stirred at determined temperature. After the polymerization was completed, benzoic acid was added. The product was isolated by precipitation in cool methanol followed by drying thoroughly under vacuum.

### RESULTS AND DISCUSSION

As depicted in Fig. 2, NHO and TUs/Us with different structures were synthesized from commercially available reagents. The polymerization performance of NHO/TUs(Us) catalytic systems was investigated in THF, and the results are compiled in Table 1. Microstructures of resultant PLAs were determined by the analysis of the methine region through homonuclear decoupled \(^1\)H-NMR spectroscopy, and the corresponding \(P_n\) values were calculated by using Bernoullian statistics approach.\(^{[35,36]}\)

First, a combination of mono-thiourea TU1 and NHO was tested for ROP of rac-LA at room temperature (Table 1, run 1). In the presence of BnOH as initiator, the polymerization proceeded smoothly with 96% conversion in 5 min, delivering the corresponding PLAs with a controlled number-average molecular weight (\(M_n\)) of 5.9 kg/mol and narrow molecular weight distribution (MWD) of 1.19. Moreover, a high iso-

### Table 1  Stereoselective ring-opening polymerization of rac-LA by NHO/TU1(U1).

| Run | TU/U | Temp. (°C) | Time | Conv. | \(M_n\) (kg/mol) | \(D\) | \(M_{n,calc}\) (kg/mol) | \(P_n\) |
|-----|------|-----------|------|-------|-----------------|-----|-----------------|-------|
| 1   | TU1  | r.t.      | 5 min| 96%   | 5.90            | 1.19| 6.92            | 0.81  |
| 2   | U1   | r.t.      | 30 s | 96%   | 5.37            | 1.15| 6.92            | 0.76  |
| 3   | DTU1 | r.t.      | 40 min| 96%  | 6.64            | 1.15| 6.92            | 0.70  |
| 4   | DTU2 | r.t.      | 15 min| 95%  | 4.30            | 1.18| 6.85            | 0.81  |
| 5   | DU1  | r.t.      | 5 min| 97%   | 7.65            | 1.20| 6.99            | 0.75  |
| 6   | DU2  | r.t.      | 5 min| 97%   | 5.20            | 1.13| 6.99            | 0.72  |
| 7   | TU1  | -40       | 20 min| 98%  | 6.48            | 1.23| 7.06            | 0.83  |
| 8   | U1   | -40       | 1 min| 96%   | 5.76            | 1.18| 6.92            | 0.86  |
| 9   | DU1  | -40       | 22 h | 86%   | 4.46            | 1.18| 6.20            | 0.85  |
| 10  | DU2  | -40       | 1.5 h| 92%   | 4.81            | 1.13| 6.63            | 0.85  |
| 11  | DU1  | -40       | 30 min| 97%  | 8.06            | 1.30| 6.99            | 0.80  |
| 12  | DU2  | -40       | 5 min| 95%   | 6.34            | 1.19| 6.85            | 0.86  |
| 13  | DU2  | -78       | 24 h | 62%   | 3.00            | 1.12| 4.46            | 0.83  |
| 14  | TU1  | -70       | 10 min| 95%  | 7.92            | 1.16| 6.85            | 0.88  |
| 15  | DU2  | -70       | 1 min| 97%   | 5.94            | 1.16| 6.99            | 0.91  |

\(^a\) Unless otherwise specified, reaction conditions are [NHO]:[TU/U]:[BnOH] = [rac-LA] = 1:2:100, [NHO]:[DTU/DU] = [BnOH] = [rac-LA] = 1:2:100 in THF. \(^b\) Determined by \(^1\)H-NMR in CDCl\(_3\) using integrals of the characteristic signals. \(^c\) Number-average molar mass (\(M_n\)) and dispersity values were determined by GPC in THF at 23 °C using polystyrene standards for calibration, and corrected using the factor 0.58 for PLA. \(^d\) Calculated from the molecular weight of rac-LA × [LA]/[BnOH] × conversion + \(M_{n,calc}\). \(^e\) Determined by homonuclear decoupled \(^1\)H-NMR spectroscopy.

[https://doi.org/10.1007/s10118-021-2535-x](https://doi.org/10.1007/s10118-021-2535-x)
selectivity of $P_m=0.81$ was obtained. This result indicated that NHO/TU1 catalytic system displays high performance in polymerization reactivity, controllability and selectivity. Remarkably, with NHO and mono-urea U1, a high conversion of 96% was achieved in just 30 s, albeit with a slight reduction of selectivity ($P_m=0.76$, Table 1, run 2). Generally, urea catalyst with similar $p_K$ value (TU1=13.2, U1=13.8) exhibited higher catalytic activity than thiourea, which is consistent with other reported literatures. Inspired by the preliminary polymerization results, four bis(thio)ureas DTUs/DUs featuring rigid linkers were synthesized and investigated (Table 1, runs 3–6). For DTU1, the monomer conversion reached 96% after 40 min, affording the PLAs with $P_m$ of 0.70 and narrow MWD of 1.15 (Table 1, run 3). Comparing with TU1, the polymerization rate and selectivity of DTU1 decreased obviously, which suggests that “an activated-TU mechanism” was absent in this polymerization process. Moreover, same selectivity ($P_m=0.81$) while low activity (5 min versus 15 min) was observed in the case of DTU2 (run 4). The activity decline of DTU1 and DTU2 might be due to the increase of steric hindrance. However, replacing DTU1, DTU2 with DU1, DU2, the ROPs gave 97% monomer conversions in 5 min, affording the corresponding PLAs with moderate $P_m$ of 0.75 and 0.72, respectively (Table 1, runs 5 and 6).

To increase polymer tacticities, the effects of temperature on the polymerization were investigated. As expected, when the reaction temperature dropped to −40 °C, the selectivity of all catalysts was improved visibly (Table 1, runs 7–12). Using NHO/TU1 as catalyst, a slight improvement of isoselectivity (0.83 versus 0.81) was observed (Table 1, run 7). Surprisingly, when utilizing NHO/U1 as catalyst, a significant enhancement of isoselectivity (0.86 versus 0.76) was found without obvious activity reduction (30 s versus 1 min, Table 1, run 8). In sharp contrast, the catalytic activities of DTU1/2 were dramatically decreased at −40 °C, despite with high selectivity (Table 1, runs 9 and 10, $P_m=0.85$). For example, in NHO/DTU1 catalytic system, 22 h was required to obtain 86% monomer conversion (Table 1, run 9). Moreover, the catalytic activity of DU1 and DU2 is between U1 and DTUs (Table 1, runs 11 and 12). A high $P_m$ of 0.86 was also achieved when using DU2 with NHO as catalyst (Table 1, run 12).

Further lowering the reaction temperature to −78 °C, for DTU2, only 62% conversion was gained at 24 h and the $P_m$ was not improved (Table 1, run 13). However, TU1 displayed delightful catalytic properties at low temperature of −78 °C, with high polymerization selectivity ($P_m=0.89$) and activity ($n$=96% in 1 h) achieved (Table 1, run 14, Fig. 4a). Once again, urea catalysts, such as DU2 and U1, exhibited much better catalytic performance at low temperatures than thiourea TU1 and DTUs (Table 1, runs 15 and 16). With DU2, a high $P_m$ of 0.88 was achieved in 10 min (Table 1, run 15). For U1, the highest $P_m$ of 0.91 was achieved in just 1 min (Table 1, run 16, Fig. 4b). Combining all above results, it can be concluded that the enhancement of catalytic performance was observed in the following order: DTU1>TU1>DU1>U1. Comparing the $p_K$ values of (thio)ureas (TU1=13.2, U1=13.8), the higher stereoselectivity using NHO/U1 might introduce a stronger interaction between the monomer and the propagating chain end with more basic urea anions, which provides bulkier steric as well. Besides, as shown in Fig. 3, a clear chain end structure was present in the polymer chain. All prepared PLAs showed sharp and unimodal GPC peaks (Fig. 4c, Figs. S4–S6 in the electronic supplementary information, ESI). As illustrated in Fig. 5, the molecular weight of PLA linearly increased with feeding ratio and monomer conversion. All these experimental data highlighted the controlled nature of the NHO/TUs(Us) catalytic system.

In order to deeply understand the stereocontrol mechanism, unreacted lactide at low conversions was separated from the reaction system and tested by chiral HPLC (high performance liquid chromatography) measurement (Fig. 4d). No obvious enantiomeric excess ($ee$) was found, which means that polymerization rates of D-LA and L-LA are roughly same, and thus the high stereoselectivity was attributed to homochiral chain-end control mechanism.

Besides, the MALDI-TOF of PLAs showed the main series of peaks at $m/z = 108 + 23 + 144 \times n$, corresponding to the primary sequences of BrOH + Na + n × LA, which indicated a linear PLAs and end-capped with benzoxly group (Fig. S9 in ESI). The $^1$H-NMR spectrum of NHO/TU1 revealed that the more acidic NH proton signal of TU1 disappeared due to the deprotonation by NHO, which confirmed the formation of thiourea anion and an imidazolium counterion (Fig. S10 in ESI). A possible catalytic process was proposed as shown in Scheme 3. Firstly, deprotonation of TU/U by NHO forms the active (thio)urea anions, which are the real catalytic species. Similar to TBD (1,5,7-triazabicyclo[4.4.0]dec-5-ene [42,43].
mechanism, (thio)urea anions activate lactide and benzyl alcohol simultaneously through double hydrogen bonding. The new incoming monomer was differentiated by the chain-terminal stereochemistry, which prefer the same geometry. When stereo-errors happened, the lactide with opposite chirality began to propagate into the polymer chain, and a multiblock isotactic PLAs was gained eventually.

Fig. 4 Homonuclear decoupled $^1$H-NMR spectra of (a) PLA from Table 1, run 14 and (b) PLA from Table 1, run 16; (c) GPC curves of PLAs produced (Table 1, runs 14 and 16); (d) Chiral HPLC curves of lactide from Table 1, run 15 at 41% conversion (top) and standard rac-LA sample (bottom).

Scheme 3 Proposed mechanism for stereoselective ROP of rac-LA using NHO/TU(U) catalytic system.
CONCLUSIONS

In summary, an isoselective and controlled ROP of rac-LA was achieved by using NHO/TUs(Us) organocatalysts. The catalytic performance was observed in the following order: DTU<7TU<8DU<8U. The highest $P_m=0.91$ was obtained when using NHO/U1 catalytic system at $-70^\circ$C. These NHO/TUs(Us) catalytic systems enable to obtain multiblock isostatic PLAs with narrow molecular weight distributions and well-defined end groups. The chiral HPLC measurement demonstrated that the high stereoselectivity was attributed to chain-end control mechanism. This work provides a convenient synthetic route to isostatic polymers and further investigations of stereoselective polymerization of more monomer types are still in progress in our laboratory.

Electronic Supplementary Information

Electronic supplementary information (ESI) is available free of charge in the online version of this article at https://doi.org/10.1007/s10118-021-2535-x.

ACKNOWLEDGMENTS

This work was financially supported by the National Key R&D Plan (No. 2017YFC1104800), the National Natural Science Foundation of China (Nos. 21901249 and 21950410529), Taishan Scholars Program of Shandong Province (No. tsqn201812112), and “135” Projects Fund of CAS-QIBEBT Director Innovation Foundation and DICP & QIBEBT United Foundation (No. UN201701).

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