

# Reaching high stereoselectivity and activity in organocatalyzed ring-opening-polymerization of racemic lactide by the combined use of a chiral (thio)urea and a *N*-heterocyclic carbene.

Mohamed Samir ZAKY<sup>a</sup>, Anne-Laure WIROTIUS<sup>a</sup>, Olivier COULEMBIER<sup>b</sup>, Gilles GUICHARD<sup>c</sup> and Daniel TATON<sup>a\*</sup>

<sup>a</sup> Laboratoire de Chimie des Polymères Organiques (LCPO), UMR 5629, Université de Bordeaux, INP-ENSCBP, 16 av. Pey Berland, 33607 PESSAC cedex, France.

<sup>b</sup> Center of Innovation and Research in Materials and Polymers (CIRMAP), Laboratory of Polymeric and Composite Materials, University of Mons, Mons B-7000, Belgium.

<sup>c</sup> Univ. Bordeaux, CNRS, CBMN, UMR 5248, Institut Européen de Chimie et Biologie, 2 rue Robert Escarpit, F-33607 Pessac, France.

---

**ABSTRACT:** Stereochemical control during polymerization is a key strategy of polymer chemistry to achieve semi-crystalline engineered plastics. The stereoselective ring-opening polymerization (ROP) of racemic lactide (*rac*-LA), which can lead to highly isotactic polylactide (PLA), is one of the emblematic examples in this area. Surprisingly, stereoselective ROP of *rac*-LA employing chiral organocatalysts has been under-leveraged. Here we show that a commercially available chiral thiourea (TU1) – or its urea homologue (U1) - can be used in conjunction with an appropriately selected *N*-heterocyclic carbene (NHC) to trigger the stereoselective ROP of *rac*-LA at room temperature in toluene. Both a high organic catalysis activity (> 90% monomer conversion in 5-9h) and a high stereoselectivity (probability of formation of meso dyads, P<sub>m</sub>, in the range 0.82-0.93) can be achieved by thus pairing a NHC and a chiral amino(thio)urea. The less sterically hindered and the more basic NHC, *i.e.*, a NHC bearing *tert*-butyl substituents (NHC<sub>tBu</sub>), provides the highest stereoselectivity when employed in conjunction with the chiral TU1 or U1. This asymmetric organic catalysis strategy, as applied here in polymerization chemistry, further expands the field of possibilities to achieve bioplastics with adapted thermomechanical properties.

---

Controlling the stereochemistry of polymers is a potent method to enhance their thermomechanical properties.<sup>1,2</sup> A powerful route in generating high polymer tacticity is by the so-called asymmetric polymerization,<sup>3-6</sup> a strategy that mainly relies on the use of metal-catalysts to polymerize achiral -but prochiral- monomers, notably Ziegler-Natta/metalocene olefin polymerizations.<sup>6,7</sup> An alternative way to control the tacticity of synthetic polymers is to polymerize chiral and optically active monomers, provided no racemization takes place in the course of the polymerization. In the latter case, chiral polymers with optical activity can thus be achieved.<sup>8</sup> Ring-opening polymerization (ROP) of some optically active *N*-carboxyanhydrides or epoxides, or of *L*-lactide is typical of such reactions.<sup>9-14</sup> In the *asymmetric kinetic resolution polymerization (AKRP)*,<sup>15</sup> only one monomeric enantiomer of a racemic mixture is incorporated to provide the chiral polymer, leaving the other enantiomer unreacted strictly speaking.<sup>15</sup> Examples of such AKRPs include ROP of racemic epoxides, episulfides and lactide, and mainly utilize chiral metallic catalysts,<sup>8,16-22</sup> *e.g.* aluminic catalysts consisting of Schiff bases as ligands for asymmetric ROP of racemic lactide (*rac*-LA).<sup>22-25</sup>

Poly(lactide) (PLA) is not only a biocompatible and biodegradable polymer, it is also manufactured from bio-renewable sources such as corn starch, potato, or

sugarcane.<sup>26</sup> PLA is particularly attractive for its intrinsic degradation, which can be triggered by different means according to the environment PLA is exposed to.<sup>27-29</sup> These features make PLA suitable for several applications, for instance in the pharmaceutical and microelectronics fields, or as a biodegradable plastic in packaging.<sup>30-33</sup> PLA thus holds great promise to become a major commercialized bio-sourced and biodegradable polymer. However, PLA is brittle and exhibits poor elasticity, low thermal stability, low heat-distortion temperature, low rate of crystallization, and modest permeability to drugs, which still limits its further commercial developments.<sup>34</sup>

Good control over molecular parameters of PLA, and consequently of its properties, is provided by ROP of lactide. As LA possesses two chiral centres, 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 monomer units into PLA chains.<sup>8,21</sup> While ROP of either enantiomer yields isotactic PLA, stereo-controlled ROP of *rac*- and *meso*-LA forms microstructures with different properties. Thus, poly(*L*-LA) (PLLA) exhibits a melting temperature (T<sub>m</sub>) around 160-180 °C, whereas atactic PLA is amorphous and brittle. The T<sub>m</sub> value can be dramatically increased, up to 230-240 °C,

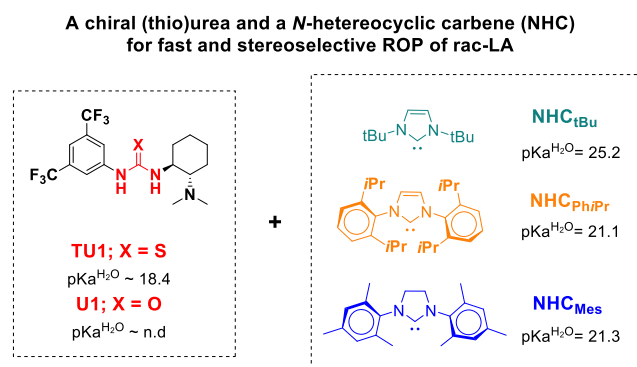
when mixing equimolar amounts of PLLA and PDLA, owing to the formation of a stereocomplex.<sup>35,36</sup>

As mentioned, stereocontrolled PLA synthesis can be achieved by asymmetric ROP of *rac*-LA from organometallic complexes in appropriate solvents.<sup>8,21,37–41</sup> Synthesis and/or storage of such complexes can be challenging, however, due to their sensitivity to humidity or oxygen, not to mention their often-proven cytotoxicity. In this context, organic catalysts have emerged as attractive alternatives for the stereoselective ROP of *rac*-LA.<sup>42</sup> Some organic catalysts, such as certain phosphazenes, have been found to be toxic.<sup>43,44</sup> Despite the emergence and development of asymmetric organic catalysis in molecular chemistry, which was crowned in 2021 with the award of the Nobel Prize in Chemistry to McMillan and List,<sup>45–47</sup> adaptation of this concept in polymer synthesis, *i.e.* stereoselective polymerization employing chiral organic catalysts, remains overlooked. Most of all, organic catalysts that would combine high stereoselectivity and catalytic activity, and operating at room temperature or above, are rare.<sup>48–53</sup>

In 2016, Waymouth *et al.* have established that the combined use of a (thio)urea with an appropriate base can generate corresponding (thio)imidate ion pairs, acting as particularly efficient dual catalytic systems of polymerization reactions.<sup>54–56</sup> The potential of such a combination involving a (thio)urea organic catalyst has been further leveraged by different research groups, notably to polymerize various cyclic esters, including  $\delta$ -valerolactone,  $\epsilon$ -caprolactone<sup>57–59</sup> *rac*-LA and *L*-LA,<sup>60,61</sup> and even the more challenging  $\gamma$ -butyrolactone.<sup>62,63</sup> In view of inducing some stereocontrol, Liu *et al.* employed a nonchiral binary urea/alkoxide catalyst for the stereoselective ROP of *rac*-LA. A PLA with a  $P_m$  value of 0.93 was thus achieved, but at  $-60$  °C.<sup>64</sup> Recently, we reported that the chiral aminothiurea Takemoto catalyst enabled to carry out the stereoselective ROP of *rac*-LA when associated with an organic phosphazene base.<sup>65</sup> Both a high catalytic activity (90% conversion within 3–8h) and a very high stereoselectivity ( $P_m = 0.96$ ,  $T_m = 187$  °C) could be achieved at room temperature. Despite excellent (stereo)control and high catalytic activity, the cytotoxicity of residual phosphazene derivatives remains an issue.<sup>44</sup>

Here we envisioned to pair a chiral amino(thio)urea catalyst with a *N*-heterocyclic carbene (NHC), as a new asymmetric organic catalysis strategy to achieve both high polymerization activity and stereoselectivity. NHCs have been extensively investigated as organocatalysts for polymer synthesis.<sup>66–68</sup> This is due to their near unlimited structural diversity, which allows manipulating their steric and electronic properties. In biological systems, benzoin condensation reactions are catalyzed by thiamine as a co-factor with enzymes such as carboxylases and transketolases.<sup>68</sup> These reactions proceed through an NHC-type intermediate formed by deprotonating the thiazolium ring, demonstrating that NHCs can be generated at biological pH. Here we wish to report a chiral binary organocatalysis system consisting of either the chiral aminothiurea Takemoto catalyst or its urea homologue, used in conjunction with a NHC (**Figure 1**). This unique

combination enables to achieve high organocatalytic activity and stereoselectivity, in addition of a highly efficient control over the molecular weights and the dispersity of the resulting PLAs. The ROP of *rac*-LA operates in presence of benzyl alcohol as initiator *via* a cooperative activation mechanism, whereby the extent of interaction between the NHC and the chiral (thio)urea dramatically influences the catalytic activity and the stereoselectivity. Namely, use of the NHC showing the highest  $pK_a$  value, *i.e.*  $NHC_{tBu}$  ( $pK_a^{H2O} = 25.2$ ) provides both the most active and the highest stereocontrol.<sup>69,70</sup>



**Figure 1.** Binary organocatalytic systems based on a (thio)urea and a NHC here studied for the stereoselective ROP of *rac*-LA.

When used alone, *i.e.* in absence of any base, both (*R,R*) and (*S,S*) enantiomers of chiral aminothiurea Takemoto's organocatalysts (**TU1**) allowed conducting the ROP of *rac*-LA with a rather high isoselectivity, yielding isotactic enriched PLA.<sup>71</sup> Kinetic studies showed that both chain end control (CEC) and enantiomeric site control (ESC) mechanisms occurred concomitantly.<sup>71</sup> However, ROP reactions proved particularly sluggish. The other control experiment involving the aminourea homologue, **U1**, could reduce the polymerization time by almost 24 h compared to the thiourea **TU1**, without significant reduction in stereoselectivity (**Table 1, run 4**). Nevertheless, catalytic activity remained very poor. Three distinct NHCs, which were characterized by different  $pK_a$  values, namely, 1,3-dit-butylimidazol-2-ylidene ( $NHC_{tBu}$ ,  $pK_a^{H2O} = 25.2$ ), 1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene ( $NHC_{Mes}$ ,  $pK_a^{H2O} = 21.3$ ) and 1,3-bis(2,6-diisopropylphenyl)imidazolidin-2-ylidene ( $NHC_{Ph<sub>3</sub>Pr}$ ,  $pK_a^{H2O} = 21.1$ ) were then combined with either the chiral aminothiurea (**TU1**) or the aminourea (**U1**, **Figure 1**).<sup>69,70,72,73</sup> The ROP of *rac*-LA was typically conducted at room temperature (RT) in toluene, by introducing the NHC, the amino(thio)urea in this order, followed by benzyl alcohol (BnOH) serving as initiator and *rac*-LA (**ESI, Scheme S1**). ROP reactions were first carried out in absence of the amino(thio)urea, *i.e.*, in presence of the three different NHCs used alone, under the following conditions:  $[rac-LA]_0/[BnOH]_0/[NHC]_0 = 200/1/1$ . In all cases, high monomer conversion could be reached (89–95 % in 3–4 h), achieving PLAs of dispersity ( $\bar{D}$ ) lower than 1.34 (**Table 1, runs 1–3**). A slight shoulder in the high molar mass region was noted (**ESI, Figures S1–S3**), which can be attributed to

some adverse transesterification reactions of the PLA backbone.<sup>66</sup> Analysis by <sup>1</sup>H NMR of these samples unambiguously showed the presence of protons due to both benzyloxy and CHOH end groups, (ESI, **Figure S4**). All these NHC-derived PLA compounds did not show any crystallinity (ESI, **Figures S5-S7**), denoting no occurrence of stereocontrol during the ROP of *rac*-LA at RT. Analysis by homodecoupled <sup>1</sup>H NMR spectroscopy of these PLAs confirmed their atactic character, with a probability of

formation of meso dyads (P<sub>m</sub>) ranging from 0.67 to 0.69 (ESI, **Figures S8-S10**). In sharp contrast, the binary organocatalysts consisting of any of the three NHCs combined with either **U1** or **TU1** yielded highly semi-crystalline PLA's, in all cases.

**Table 1. ROP of *rac*-LA using the (thio)urea/NHC binary organocatalytic system.<sup>a</sup>**

Run	Catalyst (C)	[M] <sub>0</sub> /[C] <sub>0</sub> /[I] <sub>0</sub>	Time (min)	Conv (%) <sup>b</sup>	$\overline{Mn}_{calcd}$ (kg/mol) <sup>c</sup>	$\overline{Mn}_{exp}$ (kg/mol) <sup>d</sup>	$\overline{D}$ <sup>c</sup>	P <sub>m</sub> <sup>e</sup>	T <sub>m</sub> (°C) <sup>f</sup>	T <sub>g</sub> (°C) <sup>f</sup>
1	NHC <sub>PhIPr</sub>	200:1:1	180	92	26	29	1.20	0.67	-	50
2	NHC <sub>Mes</sub>	200:1:1	240	95	27	30	1.31	0.69	-	52
3	NHC <sub>tBu</sub>	200:1:1	240	89	25	33	1.34	0.69	-	53
4	U1	200:5:1	214(h)	93	27	25	1.09	0.85	138	57
5	NHC <sub>tBu</sub> /TU1	200:(1/1): 1	360	94	27	24	1.08	0.89	184	56
6	NHC <sub>tBu</sub> /U1	200:(1/1): 1	300	≥99	28	27	1.11	0.86	164	50
7	NHC <sub>PhIPr</sub> /TU1	200:(1/1): 1	480	86	24	22	1.07	0.88	156	51
8	NHC <sub>PhIPr</sub> /U1	200:(1/1): 1	360	89	25	24	1.09	0.84	147	57
9	NHC <sub>Mes</sub> /TU1	200:(1/1): 1	530	89	25	24	1.05	0.87	160	51
10	NHC <sub>Mes</sub> /U1	200:(1/1): 1	360	91	26	23	1.07	0.82	132	49
11	NHC <sub>tBu</sub> /TU1	200:(1/3): 1	360	90	28	29	1.06	0.93	189	58
12	NHC <sub>tBu</sub> /U1	200:(1/3): 1	300	97	27	24	1.05	0.88	168	63
13 <sup>g</sup>	NHC <sub>tBu</sub> /TU1	200:(1/3): 1	300	94	27	25	1.09	0.86	160	60
14 <sup>h</sup>	NHC <sub>tBu</sub> /TU1	200:(1/3): 1	300	≥99	28	30	1.08	0.81	149	50
15 <sup>i</sup>	NHC <sub>tBu</sub> /TU1	200:(1/3): 1	60	88	25	29	1.21	0.78	-	51
16 <sup>j</sup>	NHC <sub>tBu</sub> /TU1	200:(1/3): 1	60	85	24	27	1.19	0.72	-	48

<sup>a</sup> Polymerizations were performed in dry toluene at 25 °C with [*rac*-LA]<sub>0</sub> = 0.08 M. <sup>b</sup> Monomer conversion determined by <sup>1</sup>H NMR in CDCl<sub>3</sub> using integrals of the characteristic signals. <sup>c</sup>  $M_{n,calc} = M_{LA}(144.13 \text{ g}\cdot\text{mol}^{-1}) * ([LA]_0/[I]_0) * \text{conversion} + M_{BnOH}(108.14 \text{ g}\cdot\text{mol}^{-1})$ . <sup>d</sup> Determined by SEC in THF relative to PS standards using a correcting factor of 0.58.<sup>74</sup> <sup>e</sup> Determined by homonuclear decoupled <sup>1</sup>H NMR. <sup>f</sup> Determined by DSC. <sup>g</sup> Polymerization performed in toluene at 45 °C. <sup>h</sup> Polymerization performed in toluene at 80 °C. <sup>i</sup> Polymerization performed in bulk at 125 °C. <sup>j</sup> Polymerization performed in bulk at 160 °C.

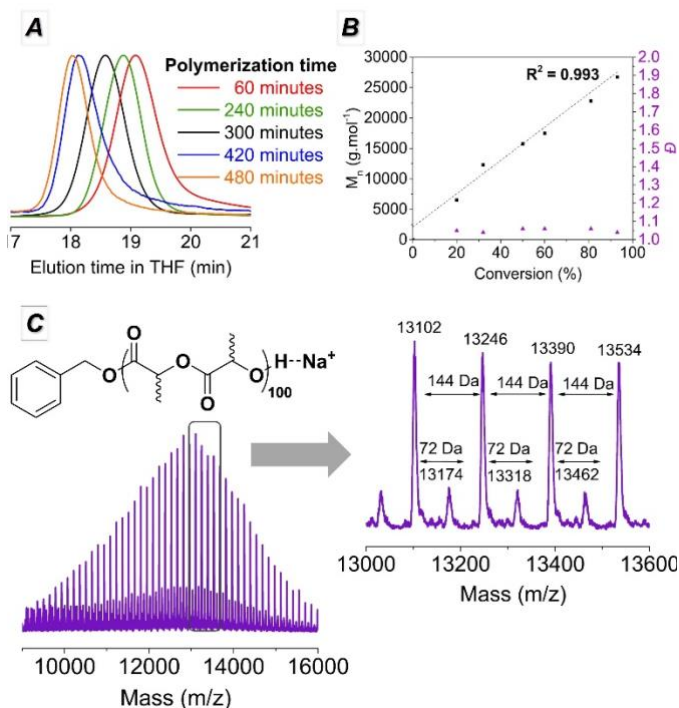
The ROP of *rac*-LA was carried out in toluene at RT under the following conditions: [*rac*-LA]<sub>0</sub>/[BnOH]<sub>0</sub>/[NHC]<sub>0</sub>/[amino(thio)urea]<sub>0</sub> = 200/1/1/1. A better control over the dispersity, relatively to the urea- or thiourea-free experiments, could be achieved ( $\overline{D} < 1.20$  in general), indicating that side reactions could be minimized when employing **U1** or **TU1**. The controlled character of the NHC/amino(thio)urea-catalyzed ROP of *rac*-LA was also attested by i) the linear increase of the molar masses (M<sub>n</sub>)

with the monomer conversion (**Figure 2.A and 2.B**), and ii) observation of a main distribution of peaks by MALDI-ToF mass spectrometry, with a peak-to-peak mass increment of 144 g·mol<sup>-1</sup> due to the molar mass of one LA monomer unit (**Figure 2.C**). Though, the minimal population of peaks showing a loss of molar mass of 72 g·mol<sup>-1</sup> is due to the occurrence of some transesterification reactions. The main structure could be ascribed to the formation of α-benzyloxy,ω-hydroxy PLA's, confirming the high selectivity

of the chiral binary organocatalytic based on the NHC and the amino(thio)urea.

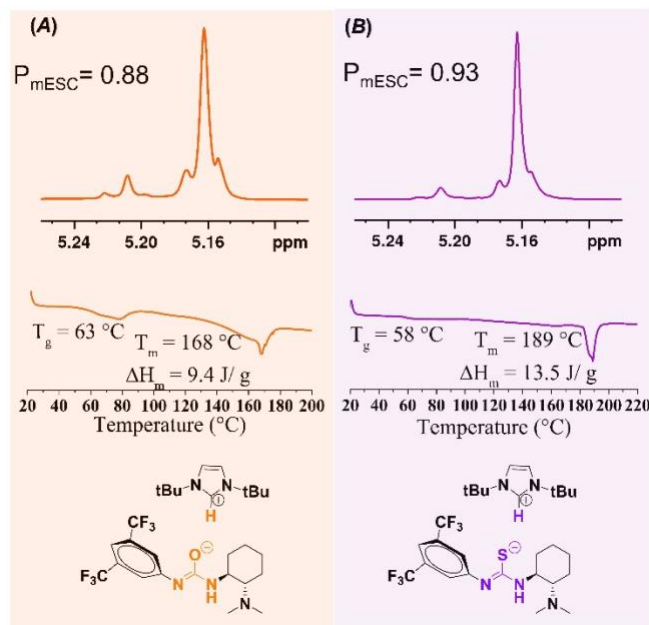
As expected, **U1** led to faster ROP reactions relatively to its aminothiurea **TU1** counterpart, irrespective of the NHC employed (*e.g.*, **run 5** vs. **run 6**, or **run 7** vs. **run 8**, **Table 1**). This result is indeed consistent with the lower tendency towards deprotonation of the less acidic urea, establishing weaker H-bond interactions and forming less stable, hence more reactive adducts in association with a given base (here the NHC), relatively to the more acidic thiourea-containing counterpart.<sup>75-77</sup> An increase of the amino(thio)urea to the NHC ratio, *i.e.* using  $[\textit{rac-LA}]_0/[\text{BnOH}]_0/[\text{NHC}]_0/[\text{amino(thio)urea}]_0 = 200/1/1/3$  did not have any significant influence on the polymerization kinetics, as monomer conversion remained approximately the same (**Table 1**, **run 11-12**).

Analysis by homodecoupled <sup>1</sup>H NMR spectroscopy of these RT **U1**(or **TU1**)/NHC-derived PLAs revealed the formation of highly isotactic-enriched polymers,  $P_m$  values being found in the range 0.82 – 0.93 (**Table 1**, **run 5-12**). The best stereocontrol was achieved using 3 equivalents of



**Figure 3.** (A) SEC traces of PLA crude sample at different conversions (**Table 1**, **run 5**), (B) Plots of  $M_n$  (square, black) and  $M_w/M_n$  (triangle, purple) for PLA synthesis (**Table 1**, **run 5**) and (C) Experimental MALDI ToF MS of PLA using  $\text{NHC}_{\text{tBu}}/\text{TU1}$ .

**TU1** combined with 1 equivalent of  $\text{NHC}_{\text{tBu}}$ , giving a semi-crystalline PLA with a  $T_m$  value as high as 189°C and a  $P_m$  value of 0.93 (**Table 1**, **run 11**; **Figure 3.B**), which compares well with values that can be obtained from some metal-based catalysts.<sup>8,21</sup> In a general manner, the **TU1**/NHC-based organocatalysts provided higher stereoselectivity than catalytic systems employing the urea **U1** homologue. In other words, combining **TU1**/NHC yielded slightly slower ROP kinetics, but an improved



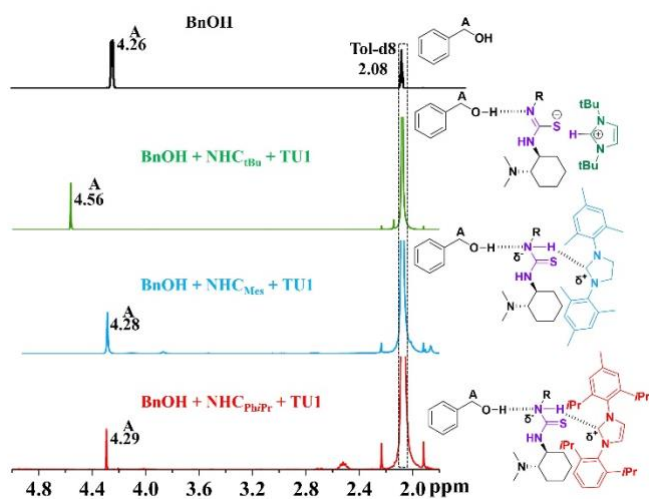
**Figure 2.** (A) Homodecoupled <sup>1</sup>H NMR spectrum of the methine region (at the top) and DSC thermogram (at the bottom; 1<sup>st</sup> scan; 10 °C min<sup>-1</sup>) of the PLA produced by  $\text{NHC}_{\text{tBu}}/\text{U1}$  (1/3) (**Table 1**, **run 12**; orange curves) and (B) homodecoupled <sup>1</sup>H NMR spectrum of the methine region (at the top) and DSC thermogram (at the bottom, 1<sup>st</sup> scan; 10 °C min<sup>-1</sup>) of the PLA produced by  $\text{NHC}_{\text{tBu}}/\text{TU1}$  (1/3) (**Table 1**, **run 11**; purple curves).

stereocontrol, in comparison to its **U1**/NHC counterpart (**Figure 3**). For instance, when using 3 equivalents of **U1** paired with 1 equivalent of  $\text{NHC}_{\text{tBu}}$ , a  $P_m$  value of 0.88 and a  $T_m$  of 168 °C were achieved (**Table 1**, **run 12**; **Figure 3.A**). This can be related to the extent of interaction/deprotonation existing between the (thio)urea motif and the carbene, as discussed further.

Remarkably, ROP experiments carried out at 40 and 80 °C maintained some stereoselectivity, PLA showing a  $P_m$  value of 0.86 and 0.81 and a  $T_m$  value of 160 and 149 °C, respectively (**Table 1**, **run 13-14**; ESI, **Figure S11-S12**). These results are very promising as stereocontrol of the ROP of *rac*-LA by an organocatalysis pathway most often requires low temperatures, sometimes cryogenic conditions.<sup>78-80</sup>

Attempts to polymerize *rac*-LA at higher temperatures, namely, at 125 and 160 °C, under solvent-free conditions ( $[\textit{rac-LA}]_0/[\text{BnOH}]_0/[\text{NHC}]_0/[\text{amino(thio)urea}]_0 = 200/1/1/3$ ), gave predominantly isotactic-enriched PLA's, with a  $P_m$  value of 0.74 and 0.70, respectively, yet precluding the crystallization of PLA chains (**Table 1**, **run 15-16**; ESI, **Figure S13-S14**).

Further kinetic experiments involving **NHC**/**TU1** (or **U1**) allowed the propagation rate constant ( $k_{\text{obs}}$ ) to be determined, as a means to estimate any preference of the organic catalyst for a given monomer (*D*-LA vs. *L*-LA). Monitoring the ROP of *rac*-LA revealed a first-order kinetic including two distinct slopes ( $k_{\text{obs}}^{-1} = 0.0059$ ,  $k_{\text{obs}}^{-1} = 0.0023$ ; ESI, **Figure S15**), with a decrease in rate observed after 200



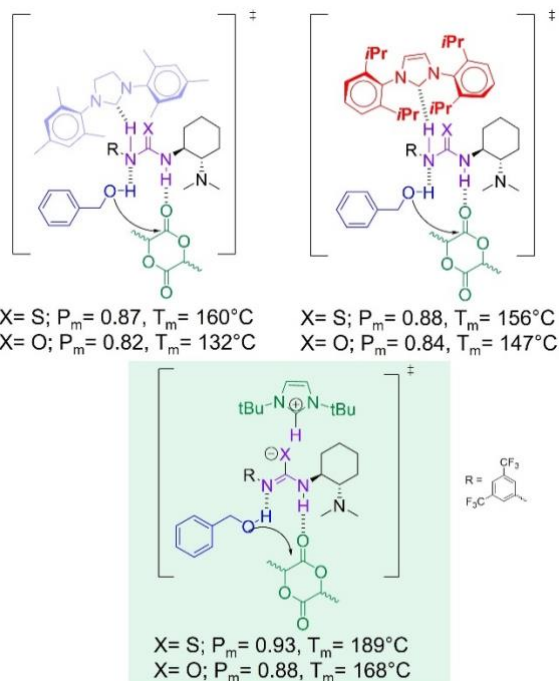
**Figure 4.** Stacked  $^1\text{H}$ -NMR experiments from equimolar amounts of BnOH/ $\text{NHC}_{\text{tBu}}$ /TU1, BnOH/ $\text{NHC}_{\text{Mes}}$ /TU1 and BnOH/ $\text{NHC}_{\text{PhiPr}}$ /TU1 in dry toluene- $d_8$  at room temperature.  $\text{R} = 3,5$ -bis(trifluoromethyl)benzyl and  $\text{R}' = \text{C}_8\text{H}_{16}\text{N}$ .

minutes. This deceleration is ascribed to the preferential consumption of a given enantiomeric monomer by the chiral amino(thio)urea, indicating that the chirality of the catalyst defines the stereochemistry of the subsequent monomer insertion during chain propagation. In other words, these results suggest the occurrence of a predominant enantiomorphic site control mechanism (ESC) during the ROP of *rac*-LA catalyzed by the combined use of the chiral aminothiourea and the NHC base.

Considering all the above data, including the achievement of relatively high monomer conversions,  $T_m$  values up to but not exceeding 189 °C indicating the absence of stereocomplexes, seem to imply that the incorporation of the two LA enantiomers takes place sequentially, *i.e.*, introducing one enantiomer preferentially first, then the other, but with some defects in the resulting block in each case. Stereocontrol taking place during the TU1 (or U1)/NHC-mediated ROP of *rac*-LA would thus generate marginally flawed stereoblocks incorporating some stereoregions, thus precluding the formation of PLA materials of very high melting point (see **Scheme S2** in ESI).

Mixtures containing equimolar amounts of the pair of organic catalysts -TU1 (or U1), each of the three NHCs- and BnOH were further analyzed by  $^1\text{H}$  NMR spectroscopy in toluene- $d_8$  at RT, in order to probe the interactions involved between the reaction partners. As a matter of fact, the deprotonation state of U1 and TU1 was found to strongly depend on the NHC employed, as summarized in **Figure 4** (see also ESI, **Figure S16**) showing typical  $^1\text{H}$  NMR spectra of these reaction mixtures. Thus,  $\text{NHC}_{\text{tBu}}$  as the most basic carbene in this series ( $\text{p}K_{\text{a}}^{\text{H}_2\text{O}} = 25.2$ ) enabled to fully deprotonate both the aminothiourea TU1 and the aminourea U1, resulting in the formation of the imidazolium (thio)imidate ion pair. Introduction of BnOH generated the corresponding imidazolium benzyloxide ion pair ( $\text{BnO-Im}^+$ , green line, **Figure 4** and **S16**). This is evidenced by a reduced deshielding effect of the methylene

protons (**A**, **Figure 4**) in the BnOH/TU1/ $\text{NHC}_{\text{tBu}}$  (1/1/1) mixture ( $\delta = 4.56$  ppm), relatively to the free BnOH ( $\delta = 4.26$  ppm). A weaker deshielding effect of methylene protons of BnOH, was observed in the case of the BnOH/aminothiourea/ $\text{NHC}_{\text{Mes}}$  (1/1/1) mixture, relatively to free BnOH ( $\delta = 4.28$  vs. 4.26 ppm, **Figure 4**).



**Figure 5.** Different mechanisms involved in the stereoselective ROP of *rac*-LA depending on the nature of the NHC.

All the above results, including the screening of different catalyst combinations and the model experiments monitored by  $^1\text{H}$  NMR, allowed us to infer the role of the different constituents, and to propose a differentiated mechanism, depending on the nature of the NHC. As highlighted in **Figure 5**, the less basic  $\text{NHC}_{\text{PhiPr}}$  and  $\text{NHC}_{\text{Mes}}$  are thought to induce a more associated reaction mechanism, involving hydrogen-bond interactions (**Figure 4** and **S16**). Yet, and in contrast to our previous findings that a weaker phosphazene base favored higher stereocontrol, while a stronger phosphazene base provided faster polymerization but lesser stereocontrol,<sup>65</sup> here the less basic NHCs do not provide the higher stereoselectivity during the ROP of *rac*-LA. This marked difference between NHCs and phosphazene bases may be due to steric hindrance provided by these  $\text{NHC}_{\text{PhiPr}}$  and  $\text{NHC}_{\text{Mes}}$ , precluding an optimal stereoselective ROP of *rac*-LA, likely owing to a lack of accessibility of the monomer to the (thio)urea motif. Better stereocontrol was eventually achieved from the more basic, and at the same time the less sterically hindered NHC, namely,  $\text{NHC}_{\text{tBu}}$ . When used in conjunction with U1 or TU1,  $\text{NHC}_{\text{tBu}}$  generated a fully deprotonated chiral amino(thio)urea, in the form of imidazolium imidate or thioimidate ion pair, which proved to be both particularly active and highly stereoselective. Work is in progress to elucidate the exact role played by the dimethylamino group in these polymerizations. As it can

indeed behave as a H-acceptor motif, we cannot exclude the possibility that this group may interact with the initiator, and thus contribute to the catalytic activity of the thiourea-NHC pair. Various (thio)ureas of different substitution pattern are currently investigated in our group to clarify this point.

In summary, we propose a novel strategy for the asymmetric organocatalyzed ring-opening polymerization of racemic lactide by judiciously pairing a NHC with a commercial chiral aminourea or aminothiourea. This new catalytic system shows a synergistic and highly efficient effect for semi-crystalline and metal-free PLA synthesis at room temperature, providing a high catalytic activity (90% conversion in 5-9 h) and very high stereoselectivity ( $P_m$  of 0.82-0.93 and  $T_m$  of 132-189 °C), by presumably forming stereoblock-type PLA materials. Combinations involving **U1** (or **TU1**) and the more basic and less sterically hindered carbene, NHC<sub>tBu</sub>, provided the higher stereocontrol *via* a selective ionic-like mechanism from a chiral imidazolium imidate or thioimidate. It is conceivable that other catalytic pairs involving a chiral organocatalyst associated with a base could induce a highly isoselective process *via* optimal kinetic resolution. These results open new opportunities for asymmetric organic catalysis of polymerization in general, and offer new options for the production of well-defined PLA-based stereocomplexes or stereoblocks with improved thermomechanical properties.

## ASSOCIATED CONTENT

The Supporting Information is available free of charge *via* the Internet at <http://pubs.acs.org>."

## AUTHOR INFORMATION

### Corresponding Author

\*E-mail: [taton@enscbp.fr](mailto:taton@enscbp.fr)

## ACKNOWLEDGMENT

The authors are grateful to CNRS, the French Ministry of Education and Research and to the Agence Nationale de la Recherche (ANR) HCO\_for\_LLAC (grant #18-CE07-0018-02).

## REFERENCES

- Worch, J. C.; Prydderch, H.; Jimaja, S.; Bexis, P.; Becker, M. L.; Dove, A. P. Stereochemical Enhancement of Polymer Properties. *Nat. Rev. Chem.* **2019**, *3*, 514–535.
- Tutoni, G.; Becker, M. L. Underexplored Stereocomplex Polymeric Scaffolds with Improved Thermal and Mechanical Properties. *Macromolecules* **2020**, *53*, 10303–10314.
- Pino, P.; Galimberti, M.; Prada, P.; Consiglio, G. Enantioselective Hydro-Oligomerization (Protio- or Deuterio-) of  $\alpha$ -Olefins. *Die Makromol. Chemie* **1990**, *191*, 1677–1688.
- Coates, G. W.; Waymouth, R. M. Enantioselective Cyclopolymerization: Optically Active Poly(Methylene-1,3-Cyclopentane). *J. Am. Chem. Soc.* **1991**, *113*, 6270–6271.
- Coates, G. W.; Waymouth, R. M. Chiral Polymers via Cyclopolymerization. *J. Mol. Catal.* **1992**, *76*, 189–194.
- Coates, G. W.; Waymouth, R. M. Enantioselective Cyclopolymerization of 1,5-Hexadiene Catalyzed by Chiral Zirconocenes: A Novel Strategy for the Synthesis of Optically Active Polymers with Chirality in the Main Chain. *J. Am. Chem. Soc.* **1993**, *91*, 91–98.
- Brintzinger, H. H.; Fischer, D.; Mülhaupt, R.; Rieger, B.; Waymouth, R. M. Stereospecific Olefin Polymerization with Chiral Metallocene Catalysts. *Angew. Chemie Int. Ed. English* **1995**, *34*, 1143–1170.
- Tschan, M. J.-L. J. L.; Gauvin, R. M.; Thomas, C. M. Controlling Polymer Stereochemistry in Ring-Opening Polymerization: A Decade of Advances Shaping the Future of Biodegradable Polyesters. *Chem. Soc. Rev.* **2021**, *50*, 13587–13608.
- Shakaroun, R. M.; Jéhan, P.; Alaaeddine, A.; Carpentier, J. F.; Guillaume, S. M. Organocatalyzed Ring-Opening Polymerization (ROP) of Functional  $\beta$ -Lactones: New Insights into the ROP Mechanism and Poly(Hydroxyalkanoate)s (PHAs) Macromolecular Structure. *Polym. Chem.* **2020**, *11*, 2640–2652.
- Li, H.; Ollivier, J.; Guillaume, S. M.; Carpentier, J.-F. Tacticity Control of Cyclic Poly(3-Thiobutyrate) Prepared by Ring-Opening Polymerization of Racemic  $\beta$ -Thiobutyrolactone. *Angew. Chemie* **2022**, e202202386.
- Jérôme, C.; Lecomte, P. Recent Advances in the Synthesis of Aliphatic Polyesters by Ring-Opening Polymerization. *Adv. Drug Deliv. Rev.* **2008**, *60*, 1056–1076.
- Rasines Mazo, A.; Allison-Logan, S.; Karimi, F.; Chan, N. J. A.; Qiu, W.; Duan, W.; O'Brien-Simpson, N. M.; Qiao, G. G. Ring Opening Polymerization of  $\alpha$ -Amino Acids: Advances in Synthesis, Architecture and Applications of Polypeptides and Their Hybrids. *Chem. Soc. Rev.* **2020**, *49*, 4737–4834.
- Herzberger, J.; Niederer, K.; Pohlit, H.; Seiwert, J.; Worm, M.; Wurm, F. R.; Frey, H. Polymerization of Ethylene Oxide, Propylene Oxide, and Other Alkylene Oxides: Synthesis, Novel Polymer Architectures, and Bioconjugation. *Chem. Rev.* **2016**, *116*, 2170–2243.
- Mezzasalma, L.; Dove, A. P.; Coulembier, O. Organocatalytic Ring-Opening Polymerization of L-Lactide in Bulk: A Long Standing Challenge. *Eur. Polym. J.* **2017**, *95*, 628–634.
- Xu, G.; Mahmood, Q.; Lv, C.; Yang, R.; Zhou, L.; Wang, Q. Asymmetric Kinetic Resolution Polymerization. *Coord. Chem. Rev.* **2020**, *414*, 213296.
- Walsh, D. J.; Hyatt, M. G.; Miller, S. A.; Guironnet, D. Recent Trends in Catalytic Polymerizations. *ACS Catal.* **2019**, *9*, 11153–11188.
- Williams, C. K. Synthesis of Functionalized Biodegradable Polyesters. *Chem. Soc. Rev.* **2007**, *36*, 1573–1580.
- Clayman, N. E.; Morris, L. S.; Lapointe, A. M.; Keresztes, I.; Waymouth, R. M.; Coates, G. W. Dual Catalysis for the Copolymerisation of Epoxides and Lactones. *Chem. Commun.* **2019**, *55*, 6914–6917.
- Beament, J.; Mahon, M. F.; Buchard, A.; Jones, M. D. Aluminum Complexes of Monopyrrolidine Ligands for the Controlled Ring-Opening Polymerization of Lactide. *Organometallics* **2018**, *37*, 1719–1724.
- Spassky, N.; Wisniewski, M.; Pluta, C.; Le, A. Highly Stereoelective Polymerization of Rac- ( D , L ) -Lactide with a Chiral Schiff ' s Base / Aluminium Alkoxide Initiator. *Macromol. Chem. Phys.* **1996**, *2637*, 2627–2637.
- Stanford, M. J.; Dove, A. P. Stereocontrolled Ring-Opening Polymerisation of Lactide. *Chem. Soc. Rev.* **2010**, *39*, 486–494.
- Ovitt, T. M.; Coates, G. W. Stereochemistry of Lactide Polymerization with Chiral Catalysts: New Opportunities for Stereocontrol Using Polymer Exchange Mechanisms. *J. Am. Chem. Soc.* **2002**, *124*, 1316–1326.
- Spassky, N.; Wisniewski, M.; Pluta, C.; Borgne, A. Le. Highly Stereoelective Polymerization of Rac-(D,L)-Lactide with a Chiral Schiff's Base/Aluminium Alkoxide Initiator. *Macromol. Chem. Phys.* **1996**, *197*, 2627–2637.
- Pilone, A.; Press, K.; Goldberg, I.; Kol, M.; Mazzeo, M.; Lamberti, M. Gradient Isotactic Multiblock Poly(lactides) from Aluminum Complexes of Chiral Salalen Ligands. *J. Am. Chem.* **2014**, *136*, 2940–2943.
- Hador, R.; Botta, A.; Venditto, V.; Lipstman, S.; Goldberg, I.; Kol, M. The Dual-Stereocontrol Mechanism: Heteroselective Polymerization of Rac-Lactide and Syndioselective

- Polymerization of Meso-Lactide by Chiral Aluminum Salan Catalysts. *Angew. Chemie - Int. Ed.* **2019**, *58*, 14679–14685.
- (26) Lim, L. T.; Auras, R.; Rubino, M. Processing Technologies for Poly(Lactic Acid). *Prog. Polym. Sci.* **2008**, *33*, 820–852.
- (27) Saeidlou, S.; Huneault, M. A.; Li, H.; Park, C. B. Poly(Lactic Acid) Crystallization. *Prog. Polym. Sci.* **2012**, *37*, 1657–1677.
- (28) Qi, X.; Ren, Y.; Wang, X. New Advances in the Biodegradation of Poly(Lactic) Acid. *Int. Biodeterior. Biodegradation* **2017**, *117*, 215–223.
- (29) Madhavan Nampoothiri, K.; Nair, N. R.; John, R. P. An Overview of the Recent Developments in Polylactide (PLA) Research. *Bioresour. Technol.* **2010**, *101*, 8493–8501.
- (30) Belletti, G.; Buoso, S.; Ricci, L.; Guillem-Ortiz, A.; Aragón-Gutiérrez, A.; Bortolini, O.; Bertoldo, M. Preparations of Poly(Lactic Acid) Dispersions in Water for Coating Applications. *Polymers* **2021**, *13*, 1–19.
- (31) Im, S. H.; Im, D. H.; Park, S. J.; Chung, J. J.; Jung, Y.; Kim, S. H. Stereocomplex Polylactide for Drug Delivery and Biomedical Applications: A Review. *Mol.* **2021**, *26*, 2846.
- (32) Kadina, Y. A.; Razuvaeva, E. V.; Streltsov, D. R.; Sedush, N. G.; Shtykova, E. V.; Kulebyakina, A. I.; Puchkov, A. A.; Volkov, D. S.; Nazarov, A. A.; Chvalun, S. N. Poly(Ethylene Glycol)-b-Poly(D,L-Lactide) Nanoparticles as Potential Carriers for Anticancer Drug Oxaliplatin. *Mol.* **2021**, *26*, 602.
- (33) Wulf, K.; Goblet, M.; Raggi, S.; Teske, M.; Eickner, T.; Lenarz, T.; Grabow, N.; Paasche, G. PLLA Coating of Active Implants for Dual Drug Release. *Mol.* **2022**, *27*, 1417.
- (34) Masutani, K.; Kimura, Y. *PLA Synthesis and Polymerization*; **2014**.
- (35) Tsuji, H. Poly(Lactide) Stereocomplexes: Formation, Structure, Properties, Degradation, and Applications. *Macromol. Biosci.* **2005**, *5*, 569–597.
- (36) Tsuji, H.; Iguchi, K.; Arakawa, Y. Stereocomplex- and Homo-Crystallization Behavior, Structure, Morphology, and Thermal Properties of Crystalline and Amorphous Stereo Diblock Copolymers, Enantiomeric Poly(L-Lactide)-b-Poly(DL-Lactide) and Poly(D-Lactide)-b-Poly(DL-Lactide). *Polymer* **2021**, *213*, 123226.
- (37) Bian, S.; Abbina, S.; Lu, Z.; Kolodka, E.; Du, G. Ring-Opening Polymerization of Rac-Lactide with Aluminum Chiral Anilido-Oxazolinone Complexes. *Organometallics* **2014**, *33*, 2489–2495.
- (38) Marin, P.; Tschan, M. J. L.; Isnard, F.; Robert, C.; Haquette, P.; Trivelli, X.; Chamoreau, L. M.; Guérineau, V.; del Rosal, I.; Maron, L.; Venditto, V.; Thomas, C. M. Polymerization of Rac-Lactide Using Achiral Iron Complexes: Access to Thermally Stable Stereocomplexes. *Angew. Chemie - Int. Ed.* **2019**, *58*, 12585–12589.
- (39) Yuntawattana, N.; McGuire, T. M.; Durr, C. B.; Buchard, A.; Williams, C. K. Indium Phosphasalen Catalysts Showing High Isolelectivity and Activity in Racemic Lactide and Lactone Ring Opening Polymerizations. *Catal. Sci. Technol.* **2020**, *10*, 7226–7239.
- (40) Qu, Z.; Duan, R.; Pang, X.; Gao, B.; Li, X.; Tang, Z.; Wang, X.; Chen, X. Living and Stereoselective Polymerization of Rac-Lactide by Bimetallic Aluminum Schiff-Base Complexes. *J. Polym. Sci. Part A Polym. Chem.* **2014**, *52*, 1344–1352.
- (41) Sun, Z.; Duan, R.; Zhang, H.; Pang, X.; Wang, X.; Chen, X. Highly Stereoselective Polymerization of Racemic Lactide by Bimetallic Schiff Base Complexes. *J. Renew. Mater.* **2015**, *3*, 82–90.
- (42) Ottou, W. N.; Sardon, H.; Mecerreyes, D.; Vignolle, J.; Taton, D. Update and Challenges in Organo-Mediated Polymerization Reactions. *Prog. Polym. Sci.* **2016**, *56*, 64–115.
- (43) Khalil, A.; Saba, S.; Ribault, C.; Vlach, M.; Loyer, P.; Coulembier, O.; Cammas-marion, S. Synthesis of Poly ( Dimethylmalic Acid ) Homo- and Copolymers to Produce Biodegradable Nanoparticles for Drug Delivery: Cell Uptake and Biocompatibility Evaluation in Human Heparg Hepatoma Cells. *Polymers* **2020**, *12*, 1–22.
- (44) Xia, Y.; Shen, J.; Alamri, H.; Hadjichristidis, N.; Zhao, J.; Wang, Y.; Zhang, G. Revealing the Cytotoxicity of Residues of Phosphazene Catalysts Used for the Synthesis of Poly(Ethylene Oxide). *Biomacromolecules* **2017**, *18*, 3233–3237.
- (45) MacMillan, D. W. C. The Advent and Development of Organocatalysis. *Nature* **2008**, *455*, 304–308.
- (46) Seayad, I.; List, B. Asymmetric Organocatalysis. *Org. Biomol. Chem.* **2005**, *3*, 719–724.
- (47) Press release: The Nobel Prize in Chemistry **2021** <https://www.nobelprize.org/prizes/chemistry/2021/press-release/> (accessed Apr 10, 2022).
- (48) Lim, J. Y. C.; Yuntawattana, N.; Beer, P. D.; Williams, C. K. Isolelective Lactide Ring Opening Polymerisation Using [2]Rotaxane Catalysts. *Angew. Chemie Int. Ed.* **2019**, *58*, 6007–6011.
- (49) Jiang, X.; Zhao, N.; Li, Z. Stereoselective Ring-Opening Polymerization of Rac-Lactide Catalyzed by Squaramide Derived Organocatalysts at Room Temperature. *Chinese J. Chem.* **2021**, *39*, 2403–2409.
- (50) Liu, S.; Li, H.; Zhao, N.; Li, Z. Stereoselective Ring-Opening Polymerization of Rac-Lactide Using Organocatalytic Cyclic Trimeric Phosphazene Base. *ACS Macro Lett.* **2018**, *7*, 624–628.
- (51) Miyake, G. M.; Chen, E. Y. X. Cinchona Alkaloids as Stereoselective Organocatalysts for the Partial Kinetic Resolution Polymerization of Rac-Lactide. *Macromolecules* **2011**, *44*, 4116–4124.
- (52) Sanchez-Sanchez, A.; Rivilla, I.; Agirre, M.; Basterretxea, A.; Etxeberria, A.; Veloso, A.; Sardon, H.; Mecerreyes, D.; Cossío, F. P. Enantioselective Ring-Opening Polymerization of Rac-Lactide Dictated by Densely Substituted Amino Acids. *J. Am. Chem. Soc.* **2017**, *139*, 4805–4814.
- (53) Moins, S.; Hoyas, S.; Lemaure, V.; Orhan, B.; Chiaie, K. D.; Lazzaroni, R.; Taton, D.; Dove, A. P.; Coulembier, O. Stereoselective Rop of Rac-and Meso-Lactides Using Achiral Tbd as Catalyst. *Catalysts* **2020**, *10*, 1–8.
- (54) Lin, B.; Waymouth, R. M. Urea Anions: Simple, Fast, and Selective Catalysts for Ring-Opening Polymerizations. *J. Am. Chem. Soc.* **2017**, *139*, 1645–1652.
- (55) Lin, B.; Waymouth, R. M. Organic Ring-Opening Polymerization Catalysts: Reactivity Control by Balancing Acidity. *Macromolecules* **2018**, *51*, 2932–2938.
- (56) Zhang, X.; Jones, G. O.; Hedrick, J. L.; Waymouth, R. M. Fast and Selective Ring-Opening Polymerizations by Alkoxides and Thioureas. *Nat. Chem.* **2016**, *8*, 1047–1053.
- (57) Zhou, L.; Xu, G.; Mahmood, Q.; Lv, C.; Wang, X.; Sun, X.; Guo, K.; Wang, Q. N-Heterocyclic Olefins and Thioureas as an Efficient Cooperative Catalyst System for Ring-Opening Polymerization of  $\delta$ -Valerolactone. *Polym. Chem.* **2019**, *10*, 1832–1838.
- (58) Coderre, D. N.; Fastnacht, K. V.; Wright, T. J.; Dharmaratne, N. U.; Kiesewetter, M. K. H-Bonding Organocatalysts for Ring-Opening Polymerization at Elevated Temperatures. *Macromolecules* **2018**, *51*, 10121–10126.
- (59) Jiang, Z.-L.; Zhao, J.-P.; Zhang, G.-Z. Readily Prepared and Tunable Ionic Organocatalysts for Ring-Opening Polymerization of Lactones. *Chinese J. Polym. Sci.* **2019**, *37*, 1205–1214.
- (60) Jiang, Z.; Zhao, J.; Zhang, G. Ionic Organocatalyst with a Urea Anion and Tetra-n-Butyl Ammonium Cation for Rapid, Selective, and Versatile Ring-Opening Polymerization of Lactide. *ACS Macro Lett.* **2019**, *8*, 759–765.
- (61) Xia, Y.; Chen, Y.; Song, Q.; Hu, S.; Zhao, J.; Zhang, G. Base-to-Base Organocatalytic Approach for One-Pot Construction of Poly(Ethylene Oxide)-Based Macromolecular Structures. *Macromolecules* **2016**, *49*, 6817–6825.
- (62) Shen, Y.; Zhao, Z.; Li, Y.; Liu, S.; Liu, F.; Li, Z.; Lim, J. Y. C.; Yuntawattana, N.; Beer, P. D.; Williams, C. K. A Facile Method to Prepare High Molecular Weight Bio-Renewable Poly( $\gamma$ -Butyrolactone) Using a Strong Base/Urea Binary Synergistic Catalytic System. *Polym. Chem.* **2019**, *10*, 1231–1237.

- (63) Zhang, C. J.; Hu, L. F.; Wu, H. L.; Cao, X. H.; Zhang, X. H. Dual Organocatalysts for Highly Active and Selective Synthesis of Linear Poly( $\gamma$ -Butyrolactone)s with High Molecular Weights. *Macromolecules* **2018**, *51*, 8705–8711.
- (64) Kan, Z.; Luo, W.; Shi, T.; Wei, C.; Han, B.; Zheng, D.; Liu, S.; Kan, Z.; Liu, S.; Han, B.; Shi, T.; Wei, C. Facile Preparation of Stereoblock PLA from Ring-Opening Polymerization of Rac-Lactide by a Synergetic Binary Catalytic System Containing Ureas and Alkoxides. *Front. Chem.* **2018**, *6*, 1–9.
- (65) Zaky, M. S.; Wirotius, A.-L.; Coulembier, O.; Guichard, G.; Taton, D. A Chiral Thiourea and a Phosphazene for Fast and Stereoselective Organocatalytic Ring-Opening-Polymerization of Racemic Lactide. *Chem. Commun.* **2021**, *57*, 3777–3780.
- (66) Kamber, N. E.; Jeong, W.; Gonzalez, S.; Hedrick, J. L.; Waymouth, R. M. N-Heterocyclic Carbenes for the Organocatalytic Ring-Opening Polymerization of  $\epsilon$ -Caprolactone. *Macromolecules* **2009**, *42*, 1634–1639.
- (67) Naumann, S.; Dove, A. P. N-Heterocyclic Carbenes as Organocatalysts for Polymerizations: Trends and Frontiers. *Polym. Chem.* **2015**, *6*, 3185–3200.
- (68) Marion, N.; Díez-González, S.; Nolan, S. P. N-Heterocyclic Carbenes as Organocatalysts. *Angew. Chemie Int. Ed.* **2007**, *46*, 2988–3000.
- (69) Magill, A. M.; Cavell, K. J.; Yates, B. F. Basicity of Nucleophilic Carbenes in Aqueous and Nonaqueous Solvents - Theoretical Predictions. *J. Am. Chem. Soc.* **2004**, *126*, 8717–8724.
- (70) Higgins, E. M.; Higgins, E. M.; Armstrong, J.; Massey, R. S.; Alder, R. W.; O'Donoghue, A. M. C. PK as of the Conjugate Acids of N-Heterocyclic Carbenes in Water. *Chem. Commun.* **2011**, *47*, 1559–1561.
- (71) Orhan, B.; Tschan, M. J.-L.; Wirotius, A.-L.; Dove, A. P.; Coulembier, O.; Taton, D. Isoselective Ring-Opening Polymerization of Rac-Lactide from Chiral Takemoto's Organocatalysts: Elucidation of Stereocontrol. *ACS Macro Lett.* **2018**, *7*, 1413–1419.
- (72) Rossini, E.; Bochevarov, A. D.; Knapp, E. W. Empirical Conversion of PKa Values between Different Solvents and Interpretation of the Parameters: Application to Water, Acetonitrile, Dimethyl Sulfoxide, and Methanol. *ACS Omega* **2018**, *3*, 1653–1662.
- (73) Jakab, G.; Tancon, C.; Zhang, Z.; Lippert, K. M.; Schreiner, P. R. (Thio)Urea Organocatalyst Equilibrium Acidities in DMSO. *Org. Lett.* **2012**, *14*, 1724–1727.
- (74) Kowalski, A.; Duda, A.; Penczek, S. Polymerization of l,l-Lactide Initiated by Aluminum Isopropoxide Trimer or Tetramer. *Macromolecules* **1998**, *31*, 2114–2122.
- (75) Gómez, D. E.; Fabbrizzi, L.; Licchelli, M.; Monzani, E. Urea vs. Thiourea in Anion Recognition. *Org. Biomol. Chem.* **2005**, *3*, 1495–1500.
- (76) Takemoto, Y. Recognition and Activation by Ureas and Thioureas: Stereoselective Reactions Using Ureas and Thioureas as Hydrogen-Bonding Donors. *Org. Biomol. Chem.* **2005**, *3*, 4299–4306.
- (77) Zhang, Z.; Schreiner, P. R. (Thio)Urea Organocatalysis—What Can Be Learnt from Anion Recognition? *Chem. Soc. Rev.* **2009**, *38*, 1187–1198.
- (78) Liu, S.; Li, H.; Zhao, N.; Li, Z. Stereoselective Ring-Opening Polymerization of Rac-Lactide Using Organocatalytic Cyclic Trimeric Phosphazene Base. *ACS Macro Lett.* **2018**, *7*, 624–628.
- (79) Zhang, L.; Nederberg, F.; Messman, J. M.; Pratt, R. C.; Hedrick, J. L.; Wade, C. G. Organocatalytic Stereoselective Ring-Opening Polymerization of Lactide with Dimeric Phosphazene Bases. *J. Am. Chem. Soc.* **2007**, *129*, 12610–12611.
- (80) Li, H.; Ai, B. R.; Hong, M. Stereoselective Ring-Opening Polymerization of Rac-Lactide by Bulky Chiral and Achiral N-Heterocyclic Carbenes. *Chinese J. Polym. Sci. (English Ed.)* **2018**, *36*, 231–236.

