ACS Macro Letters

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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

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Cite This: *ACS Macro Lett.* 2022, 11, 1148−1155 Read Online

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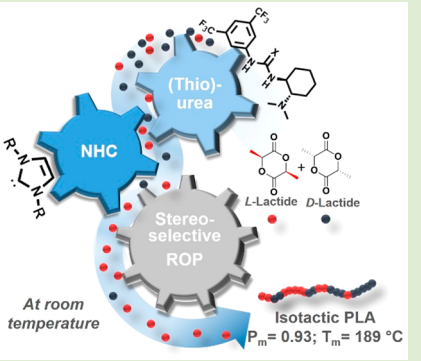
ABSTRACT: Stereochemical control during polymerization is a key strategy of polymer chemistry to achieve semicrystalline engineered plastics. The stereoselective ring-opening polymerization (ROP) of racemic lactide (*rac*-LA), which can lead to highly isotactic polylactide (PLA), is one of the emblematic 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 5−9 h) and a high stereoselectivity (probability of formation of meso dyads, P_m, 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, that is, a NHC bearing *tert*-butyl substituents (NHC_{tBu}), 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.[1,2] A powerful route in generating high polymer tacticity is by the so-called asymmetric polymerization,[3−6] a strategy that mainly relies on the use of metal catalysts to polymerize achiral, but prochiral, monomers, notably Ziegler−Natta/metallocene olefin polymerizations.[6,7] 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.[8] Ring-opening polymerization (ROP) of some optically active *N*-carboxyanhydrides or epoxides or of *L*-lactide is typical of such reactions.[9−14] In the asymmetric kinetic resolution polymerization (AKRP),[15] only one monomeric enantiomer of a racemic mixture is incorporated to provide the chiral polymer, leaving the other enantiomer unreacted strictly speaking.[15] Examples of such AKRPs include the ROP of racemic epoxides, episulfides, and lactide and mainly utilize chiral metallic catalysts,[8,16−22] for example, aluminic catalysts consisting of Schiff bases as ligands for asymmetric ROP of racemic lactide (*rac*-LA).[22−25]

Polylactide (PLA) is not only a biocompatible and biodegradable polymer, it is also manufactured from biorenewable sources such as corn starch, potato, or sugar cane.[26] PLA is particularly attractive for its intrinsic degradation, which can be triggered by different means according to the environment the PLA is exposed to.[27−29] These features make PLA suitable for several applications, for instance, in the pharmaceutical and microelectronics fields or as a biodegradable plastic in packaging.[30−33] PLA thus holds great promise to become a major commercialized biosourced 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.[34]

Good control over molecular parameters of PLA, and consequently of its properties, is provided by ROP of lactide. As LA possesses two chiral centers, 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.[8,21] While ROP of either enantiomer yields isotactic PLA, stereocontrolled ROP of *rac*- and *meso*-LA forms microstructures with different properties. Thus, poly(L-LA) (PLLA)

Received: August 1, 2022
Accepted: September 1, 2022

https://doi.org/10.1021/acsmacrolett.2c00457
ACS Macro Lett. 2022, 11, 1148−1155

exhibits a melting temperature (T_m) around 160−180 °C, whereas atactic PLA is amorphous and brittle. The T_m value can be dramatically increased, up to 230−240 °C, when mixing equimolar amounts of PLLA and PDLA, owing to the formation of a stereocomplex.[35,36]

As mentioned, stereocontrolled PLA synthesis can be achieved by asymmetric ROP of *rac*-LA from organometallic complexes in appropriate solvents.[8,21,37−41] Synthesis and 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.[42] Some organic catalysts, such as certain phosphazenes, have been found to be toxic.[43,44] 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,[45−47] adaptation of this concept in polymer synthesis, that is, 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.[48−53]

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.[54−56] 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 δ-valerolactone, ϵ-caprolactone,[57−59] *rac*-LA and *L*-LA,[60,61] and even the more challenging γ-butyrolactone.[62,63] 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.[64] Recently, we reported that the chiral aminothiourea Takemoto catalyst enabled to carry out the stereoselective ROP of *rac*-LA when associated with an organic phosphazene base.[65] Both a high catalytic activity (90% conversion within 3−8 h) 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.[44]

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.[66−68] 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 cofactor with enzymes such as carboxylases and transketolases.[68] 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 aminothiourea 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 the presence of benzyl alcohol

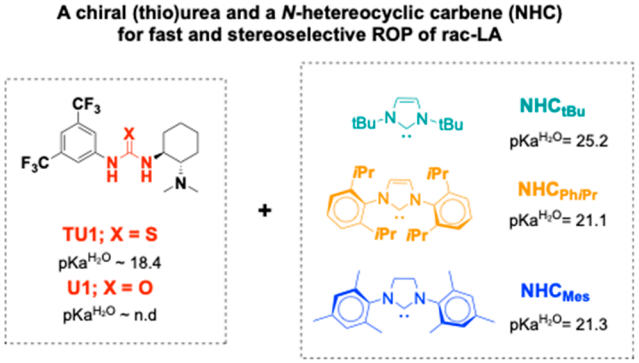


Figure 1. Binary organocatalytic systems based on a (thio)urea and a NHC here studied for the stereoselective ROP of *rac*-LA.

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, that is, NHC_{tBu} (pK_a^{H2O} = 25.2) provides both the most active and the highest stereocontrol.[69,70]

When used alone, that is, in the absence of any base, both (*R*,*R*) and (*S*,*S*) enantiomers of chiral aminothiourea Takemoto's organocatalysts (TU1) allowed conducting the ROP of *rac*-LA with a rather high isoselectivity, yielding isotactic-enriched PLA.[71] Kinetic studies showed that both chain end control (CEC) and enantiomorphic site control (ESC) mechanisms occurred concomitantly.[71] 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-di-t-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_{PhiPr}, pK_a^{H2O} = 21.1) were then combined with either the chiral aminothiourea (TU1) or the aminourea (U1, Figure 1).[69,70,72,73] 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 (SI, Scheme S1). ROP reactions were first carried out in absence of the amino(thio)urea, that is, in the presence of the three different NHCs used alone, under the following conditions: $[rac\text{-LA}]_0/[\text{BnOH}]_0/[\text{NHC}]_0$ = 200/1/1. In all cases, high monomer conversion could be reached (89−95% in 3−4 h), achieving PLAs of dispersity ($Đ$) lower than 1.34 (Table 1, runs 1−3). A slight shoulder in the high molar mass region was noted (SI, Figures S1−S3), which can be attributed to some adverse transesterification reactions of the PLA backbone.[66] Analysis by ^{1}H NMR of these samples unambiguously showed the presence of protons due to both benzyloxy and CHOH end groups, (SI, Figure S4). All these NHC-derived PLA compounds did not show any crystallinity (SI, Figures S5−S7), denoting no occurrence of stereocontrol during the ROP of *rac*-LA at RT. Analysis by homodecoupled ^{1}H NMR spectroscopy of these PLAs confirmed their atactic character, with a probability of formation of meso dyads (P_m) ranging from 0.67 to 0.69 (SI, Figures S8−S10). In sharp contrast, the binary organocatalysts consisting of any of the

https://doi.org/10.1021/acsmacrolett.2c00457
ACS Macro Lett. 2022, 11, 1148−1155

Table 1. ROP of *rac*-LA Using the (Thio)Urea/NHC Binary Organocatalytic System[a]

run	catalyst (C)	$[M]_0/[C]_0/[I]_0$	time (min)	conv[b] (%)	$\overline{M}_{n,calcd}$[c] (kg/mol)	$\overline{M}_{n,exp}$[d] (kg/mol)	$Đ$[c]	P_m[e]	T_m[f] (°C)	T_g[f] (°C)
1	NHC_{PhiPr}	200:1:1	180	92	26	29	1.20	0.67		50
2	NHC_{Mes}	200:1:1	240	95	27	30	1.31	0.69		52
3	NHC_{tBu}	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_{tBu}/TU1	200:(1/1):1	360	94	27	24	1.08	0.89	184	56
6	NHC_{tBu}/U1	200:(1/1):1	300	≥99	28	27	1.11	0.86	164	50
7	NHC_{PhiPr}/TU1	200:(1/1):1	480	86	24	22	1.07	0.88	156	51
8	NHC_{PhiPr}/U1	200:(1/1):1	360	89	25	24	1.09	0.84	147	57
9	NHC_{Mes}/TU1	200:(1/1):1	530	89	25	24	1.05	0.87	160	51
10	NHC_{Mes}/U1	200:(1/1):1	360	91	26	23	1.07	0.82	132	49
11	NHC_{tBu}/TU1	200:(1/3):1	360	90	28	29	1.06	0.93	189	58
12	NHC_{tBu}/U1	200:(1/3)1:	300	97	27	24	1.05	0.88	168	63
13[g]	NHC_{tBu}/TU1	200:(1/3):1	300	94	27	25	1.09	0.86	160	60
14[h]	NHC_{tBu}/TU1	200:(1/3):1	300	≥99	28	30	1.08	0.81	149	50
15[i]	NHC_{tBu}/TU1	200:(1/3):1	60	88	25	29	1.21	0.78		51
16[j]	NHC_{tBu}/TU1	200:(1/3):1	60	85	24	27	1.19	0.72		48

[a]Polymerizations were performed in dry toluene at 25 °C with $[rac\text{-LA}]_0$ = 0.08 M. [b]Monomer conversion determined by ^{1}H NMR in $CDCl_3$ using integrals of the characteristic signals. [c]$M_{n,calc}$ = MLA(144.13 g·mol^{-1})·($[LA]_0/[I]_0$)·conversion + MBnOH (108.14 g·mol^{-1}). [d]Determined by SEC in THF relative to PS standards using a correcting factor of 0.58.[74] [e]Determined by homonuclear decoupled ^{1}H NMR. [f]Determined by DSC. [g]Polymerization performed in toluene at 45 °C. [h]Polymerization performed in toluene at 80 °C. [i]Polymerization performed in bulk at 125 °C. [j]Polymerization performed in bulk at 160 °C.

three NHCs combined with either U1 or TU1 yielded highly semicrystalline PLA's, in all cases.

The ROP of *rac*-LA was carried out in toluene at RT under the following conditions: $[rac\text{-LA}]_0/[BnOH]_0/[NHC]_0/[amino(thio)urea]_0$ = 200/1/1/1. A better control over the dispersity, relative to the urea- or thiourea-free experiments, could be achieved ($Đ$ < 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_n) with the monomer conversion (Figure 2A,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^{-1} due to the molar mass of one LA monomer unit (Figure 2C). Though the minimal population of peaks showing a loss of molar mass of 72 g·mol^{-1} 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 relative to its aminothiourea 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 toward 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), relative to the more acidic thiourea-containing counterpart.[75−77] An increase in the amino(thio)urea to the NHC ratio, that is, using $[rac\text{-LA}]_0/[BnOH]_0/[NHC]_0/[amino(thio)urea]_0$ = 200/1/1/3 did not have any significant influence on the polymerization kinetics, as monomer conversion remained approximately the same (Table 1, runs 11 and 12).

Analysis by homodecoupled ^{1}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

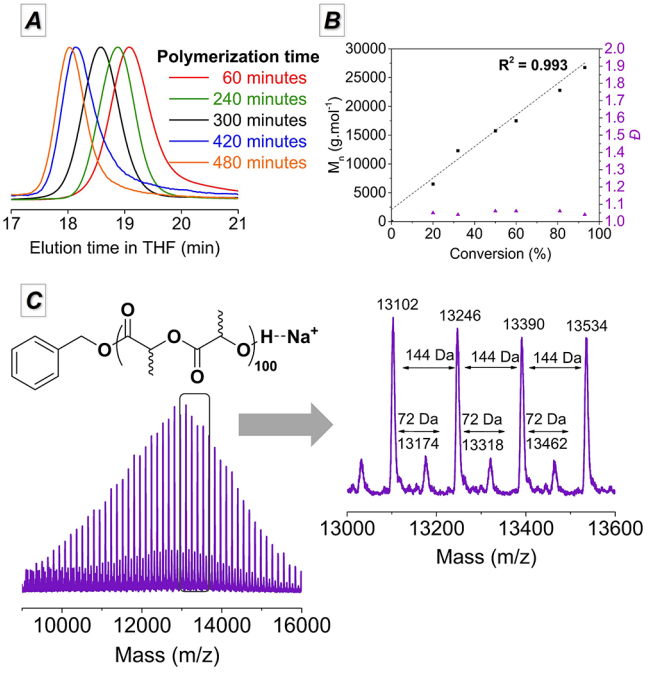


Figure 2. (A) SEC traces of PLA crude sample at different conversions (Table 1, run 5), (B) Plots of M_n (square, black) and M_w/M_n (triangle, purple) for PLA synthesis (Table 1, run 5), and (C) experimental MALDI ToF MS of PLA using NHC_{tBu}/TU1.

the range 0.82−0.93 (Table 1, runs 5−12). The best stereocontrol was achieved using 3 equiv of TU1 combined with 1 equiv of NHC_{tBu}, giving a semicrystalline PLA with a T_m value as high as 189 °C and a P_m value of 0.93 (Table 1, run 11; Figure 3B), which compares well with values that can be obtained from some metal-based catalysts.[8,21] 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 stereocontrol, in

https://doi.org/10.1021/acsmacrolett.2c00457
ACS Macro Lett. 2022, 11, 1148−1155

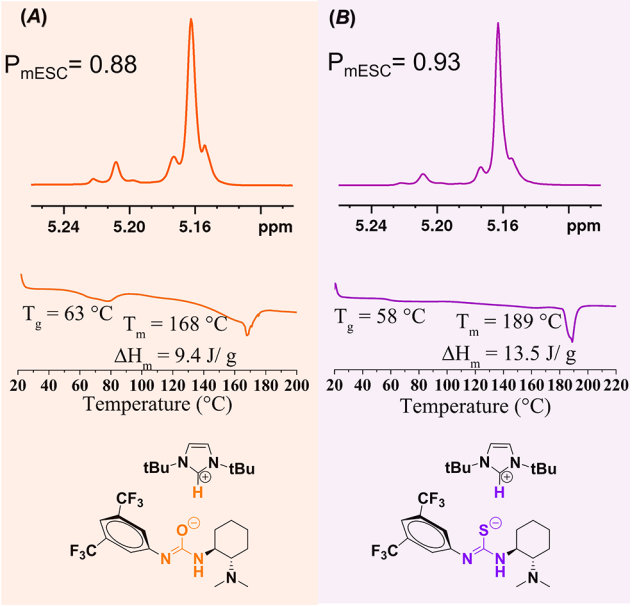


Figure 3. (A) Homodecoupled ^{1}H NMR spectrum of the methine region (at the top) and DSC thermogram (at the bottom; 1st scan; 10 °C min^{-1}) of the PLA produced by NHC$_{tBu}$/U1 (1/3; Table 1, run 12; orange curves) and (B) homodecoupled ^{1}H NMR spectrum of the methine region (at the top) and DSC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

comparison to its U1/NHC counterpart (Figure 3). For instance, when using 3 equiv of U1 paired with 1 equiv of NHC$_{tBu}$, a P_m value of 0.88 and a T_m of 168 °C were achieved (Table 1, run 12; Figure 3A). 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, runs 13 and 14; SI, Figures S11 and 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.[78−80]

Attempts to polymerize *rac*-LA at higher temperatures, namely, at 125 and 160 °C, under solvent-free conditions ([*rac*-LA]$_0$/[BnOH]$_0$/[NHC]$_0$/[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, runs 15 and 16; SI, Figures S13 and S14).

Further kinetic experiments involving NHC/TU1 (or U1) allowed the propagation rate constant (k_{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 ($k_{obs}{}^{-1}$ = 0.0059, $k_{obs}{}^{-1}$ = 0.0023; SI, Figure S15), with a decrease in rate observed after 200 min. 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, that is, 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 stereoerrors, thus precluding the formation of PLA materials of very high melting point (see Scheme S2 in the SI).

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}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 states of U1 and TU1 were found to strongly depend on the NHC employed, as summarized in Figure 4

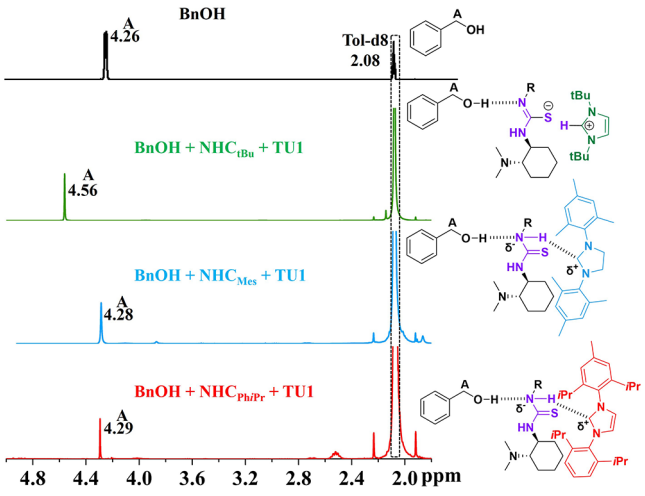


Figure 4. Stacked ^{1}H NMR experiments from equimolar amounts of BnOH/NHC$_{tBu}$/TU1, BnOH/NHC$_{Mes}$/TU1, and BnOH/NHC$_{PhiPr}$/TU1 in dry toluene-d_8 at room temperature. R = 3,5-bis-(trifluoromethyl)benzyl and R′ = $C_8H_{16}N$.

(see also SI, Figure S16) showing typical ^{1}H NMR spectra of these reaction mixtures. Thus, NHC$_{tBu}$ as the most basic carbene in this series ($pK_a{}^{H2O}$ = 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 (BnO$^-$Im$^+$, green line, Figures 4 and S16). This is evidenced by a reduced deshielding effect of the methylene protons (Figure 4A) in the BnOH/TU1/NHC$_{tBu}$ (1/1/1) mixture (δ = 4.56 ppm), relatively to the free BnOH (δ = 4.26 ppm). A weaker deshielding effect of methylene protons of BnOH, was observed in the case of the BnOH/aminothiourea/NHC$_{Mes}$ (1/1/1) mixture, relatively to free BnOH (δ = 4.28 vs 4.26 ppm, Figure 4).

All the above results, including the screening of different catalyst combinations and the model experiments monitored by ^{1}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

https://doi.org/10.1021/acsmacrolett.2c00457
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5, the less basic NHC_{PhiPr} and NHC_{Mes} are thought to induce a more associated reaction mechanism, involving hydrogen-bond

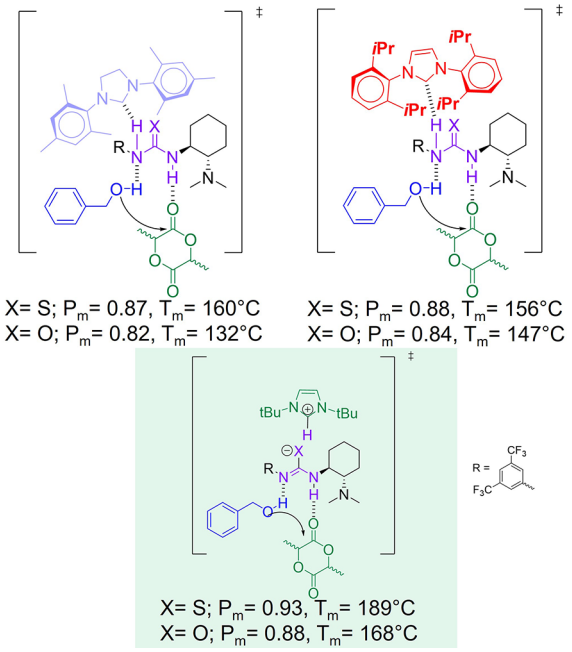

Figure 5. Different mechanisms involved in the stereoselective ROP of *rac*-LA depending on the nature of the NHC.

interactions (Figures 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,[65] 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 NHC_{PhiPr} and NHC_{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, NHC_{tBu}. When used in conjunction with U1 or TU1, NHC_{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 semicrystalline 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_{tBu}, 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

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsmacrolett.2c00457.

Experimental details and supporting figures and scheme (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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).

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