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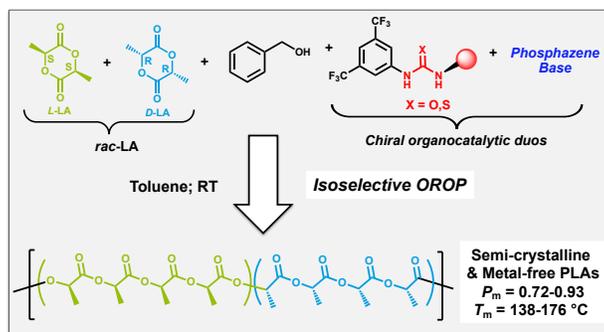
Structural Effect of Organic Catalytic Pairs Based on Chiral Amino(thio)ureas and Phosphazene Bases for the Isolelective Ring-Opening Polymerization of Racemic Lactide

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ABSTRACT: Polymer materials featuring stereocontrolled monomer units often exhibit drastically different properties than their stereorandom counterparts. Control over the polymer tacticity thus represents a powerful means to access functional polymers of modular thermomechanical properties. In the present work, a series of chiral amino(thio)ureas (**U1**, **TU1-TU5**) are used in duos with phosphazene organic bases for the stereoselective ring-opening polymerization (ROP) of racemic lactide (*rac*-LA). These chiral binary organocatalytic pairs allow for relatively fast, highly chemo- and isoselective ROP of *rac*-LA at room temperature in toluene, yielding semi-crystalline and metal-free stereoblock-like materials based on polylactide (PLA), with a melting temperature in the range 138-176 °C. The chiral dimethylaminourea, denoted as **U1**, shows faster ROP reactions relatively to its dimethylaminothiourea **TU1** analogue, when combined with any of the phosphazene bases, consistent with the formation of less stable intermediates from the urea relatively to the more acidic thiourea-containing counterpart. On the other hand, the tethered dialkylamino moiety of **TU1-TU3** is shown to have a non-innocent role both on the catalytic activity and the isoselectivity of the ROP process, whereby decreasing the basicity of this group leads to a decrease of the reaction rates. The active mechanism also proves to be dependent on the identity of the amino(thio)urea and the phosphazene base, and a mechanistic rationale for the experimental results is presented. Thus, the strongest organic base used in conjunction with **U1** and **TU1-TU5**, leading to high polymerization rate but lesser stereocontrol, induces an ionic-like mechanism. In contrast, organocatalytic pairs based on the least basic phosphazene favor a more associated mechanism involving hydrogen-bond interactions, providing slower ROP reactions, but producing highly isotactic PLAs.

INTRODUCTION.

The concept of asymmetric organic catalysis in molecular chemistry, *i.e.* use of non-metallic catalysts for creation of C-C or C-X bond with high stereoselectivity, has truly emerged in the early 2000's.¹⁻⁴ These developments, which were crowned in 2021 with the award of the Nobel Prize in Chemistry to McMillan and List,⁵ have led to organic catalysts constituting today the third pillar of catalysis, besides enzymes and metallic catalysts.¹⁻⁶ In contrast, adaptation of this concept in polymer synthesis, *i.e.* stereoselective polymerization employing chiral organic catalysts, is more recent and remains underexplored.⁷⁻¹⁶ In a more general way, organic catalysts, whether they are chiral or not, that can provide high stereoselectivity and high catalytic activity, in addition to operating under mild conditions, e.g. at room temperature or above, are rare.⁷⁻²² Yet, the use of small organic molecules for organic catalysis of polymerization is now part of the methodological toolbox in macromolecular synthesis.²³⁻²⁹ Depending on the structure of the organic catalyst, different mechanisms can operate, and this diversity of mechanistic pathways allows for improved polymerization rates, tuning of the selectivity and rational design of a variety of polymer architectures. Organic catalysis of polymerization can offer other advantages over metal-catalyzed reactions, such as a reduced toxicity and cost, easier catalyst synthesis and storage, tolerance to functional groups, and operation at elevated temperature and in a variety of solvents.²³⁻²⁹ Recent years have witnessed new achievements at the crossroads between organocatalysis and macromolecular science, for instance, through the use of organic catalysts for photopolymerization or for controlled radical polymerization, for chemical recycling and upcycling of synthetic polymers, or for designing covalent adaptative networks.³⁰

The quest for stereocontrol in polymerization is very much inspired by optically active naturally-occurring polymers, such as proteins, deoxyribonucleic acids or polysaccharides, which exhibit an incomparable level of structural control and possess unique functions.³¹⁻³³ A still thriving research area in polymer chemistry is thus the development of stereoselective polymerization methods that can be general to monomer structure. Related methods call for custom-designed catalysts that can provide high degree of stereoselectivity, while maintaining high catalytic activity and productivity.^{27,32} Semi-crystalline

materials of high tacticity (iso- or syndiotactic) can be obtained in this way, which exhibit enhanced physical and thermomechanical properties, when compared to counterparts showing no predominant tacticity (atactic). The stereoselective ring-opening polymerization (ROP) of cyclic esters, in particular of racemic lactide (*rac*-LA) leading to isotactic or syndiotactic polylactide (PLA), is emblematic of this area.^{27,34-37} PLA is one of the most widely used degradable and biocompatible polymers in the world.³⁸⁻³⁹ Another reason why PLA is attractive is because it can be derived from naturally-occurring resources (e.g. beet, sugarcane or corn).³⁸⁻⁴¹ Although annual global PLA production remains modest (about 300,000 tons in 2019) and has not yet reached that of petroleum-based commodity polymers, the physical properties of PLA make it a viable alternative for various applications, e.g. in the biomedical, packaging and microelectronics fields.^{27,32,34-43} With appropriate catalysts/initiators, ROP of LA enables to access a range of microstructures, not only from the three distinct stereoisomers, namely, D-LA, L-LA-, and DL (meso)-LA, but also from the racemic mixture of the D- and the L-LA (*rac*-LA). Thus, poly(L-LA) (PLLA) exhibits a melting temperature (T_m) around 160–180 °C, whereas atactic PLA is amorphous and brittle.^{35,36} Moreover, blending equimolar amounts of PLLA and PDLA increases the T_m value dramatically, up to 230–240 °C, due to the formation of a stereocomplex from the two polymeric enantiomers that can co-crystallize. Instead of blending the two homopolymers, PLA-based stereocomplexes or stereoblocks, *i.e.* made from the two LA monomer units of opposite configurations, may be obtained at lower cost by stereocontrolled ROP of *rac*-LA, leading to PLA-based materials of enhanced properties.^{35,36} Since the 1990s, and until recent years,⁴⁴⁻⁴⁹ the stereochemical control of the ROP of *rac*-LA has been intensively investigated using metal catalysts operating by coordination–insertion mechanism.^{35,36} As mentioned, however, specific design and/or storage of organometallic complexes can be demanding, in addition to their often-proven cytotoxicity. In that respect, organic catalysts have appeared as promising alternatives for the stereoselective ROP of *rac*-LA.⁷⁻²²

In this context, we have recently developed a new approach to isoselective ROP of *rac*-LA utilizing chiral organocatalytic pairs.¹⁵⁻¹⁶ These works have been inspired by the methodology established by the

Waymouth group, where a (thio)urea combined with an appropriate (organic or metallic) base generates very effective (thio)imidate ion pairs.⁵⁰⁻⁵² Such dual catalytic systems indeed provide both high catalytic activity and high selectivity in ROP reactions. This methodology involving interaction of the (thio)urea with the base has been leveraged by many other research teams, as reviewed recently.^{29,53-54} In our case, we have developed chiral versions of organocatalytic pairs, associating a chiral dimethylaminothiourea and a phosphazene or a *N*-heterocyclic carbene (NHC) as organic base.¹⁵⁻¹⁶ We have found that this mode of stereocontrol strongly depends on the extent of interaction between the base and the chiral (thio)urea, which eventually enable modulation of both the polymerization rate and the stereoselectivity. Herein we wish to discuss the effect of a structural variation of new chiral organocatalytic duos on both the stereocontrol and catalytic activity of the ROP of *rac*-LA. Several chiral amino(thio)ureas used in conjunction with different phosphazene bases were thus evaluated to achieve distinct goals of our research efforts (Figure 1). Namely, we aimed at i) accessing semi-crystalline and metal-free PLAs at room temperature, ii) polymerizing *rac*-LA in a stereocontrolled manner while maintaining appreciable reaction rates, and iii) providing a detailed investigation into the underlying stereocontrol mechanism, as a function of the identity of the organocatalytic pair.

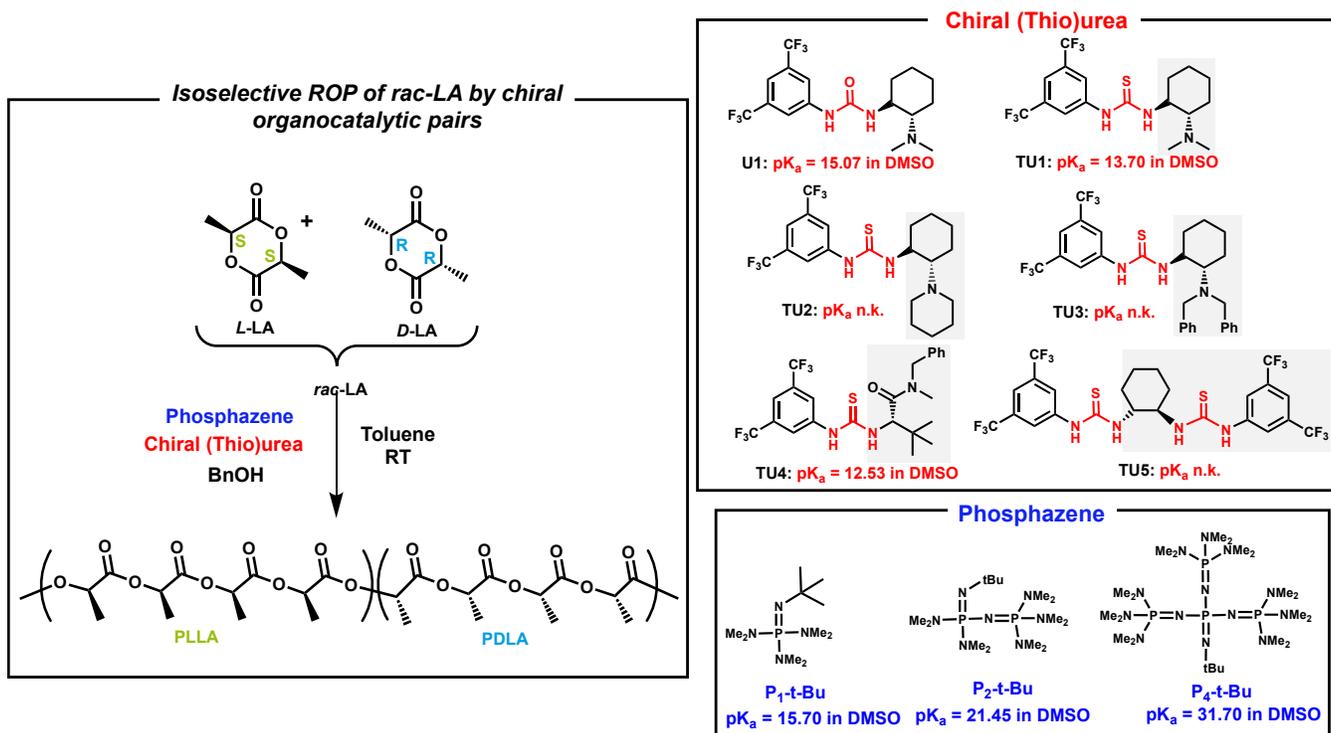


Figure 1. Isoselective ROP of *rac*-LA from organic catalytic pairs associating a chiral amino(thio)urea (U1 or TU1-TU5) and a phosphazene base (P₁-t-Bu, P₂-t-Bu or P₄-t-Bu); n.k.= not known.

RESULTS AND DISCUSSION.

ROP reactions of *rac*-LA were carried out in toluene at room temperature (RT) using benzyl alcohol (BnOH) as initiator, in presence of various organocatalytic pairs. These consist in the combination of an organic Brønsted phosphazene base of varied basicity (P₁-t-Bu or P₂-t-Bu or P₄-t-Bu) and a chiral amino(thio)urea (U1 or TU1-TU5), as depicted in Figure 1. The phosphazene base and the (thio)urea were first introduced in the reaction vessel in this order, followed by BnOH and *rac*-LA. The reaction conditions, including the molar ratios between the different partners, and the results of these ROP experiments are summarized in Table 1 (see also ESI). We previously reported that, when used in absence of any base, chiral versions of TU1 allowed achieving predominantly isotactic PLAs, owing to the occurrence of both chain end control (CEC) and enantiomorphic site control (ESC) mechanisms.¹¹ However, the catalytic activities observed under such base-free conditions were found to be very low, with these reactions requiring several days to reach completion at RT. In contrast, most of organocatalytic pairs involving P₂-t-Bu or P₄-t-Bu allowed polymerizing *rac*-LA within a time scale of a few hours (e.g.

Table 1, **entry 1 vs. entry 5**, **entry 2 vs. entries 6-12**, **entry 3 vs. entries 13,15,21** and **entry 4 vs. entries 14,16,23**), highlighting the beneficial effect of combining **TU1-TU5** (or **U1**) with the more basic phosphazenes. These conditions also allowed synthesizing semi-crystalline PLAs, in almost all cases, presumably owing to a high level of stereocontrol during ROP of *rac*-LA, as discussed further.

We first compared the behavior of the chiral dimethylaminothiourea **TU1** – known as the Takemoto catalyst – with its urea counterpart **U1**, under strictly identical conditions (**runs 5-12**). Combinations involving **TU1** with **P1-t-Bu** or **P2-t-Bu** for the ROP of *rac*-LA were discussed in our previous paper,¹⁵ but not those involving **TU1** and **P4-t-Bu** (see **Figure S1**), neither catalytic pairs based on **U1** (see **Figures S2-S4**). A body of evidence allowed attesting that excellent control of ROP reactions was achieved using **phosphazene/U1** in duos, including i) the presence of protons due to both benzyloxy and CHOH end groups, (**Figure 2A**) as observed by ¹H NMR spectroscopy, ii) a linear increase of the obtained molar masses (M_n) with the conversion of *rac*-LA, iii) inspection of the MALDI-ToF mass spectrum showing a main distribution of peaks, with an expected peak-to-peak mass increment of 144 g·mol⁻¹ corresponding to the molar mass of one LA monomer unit (**Figure 2B**). The main structure was attributed to the formation of α -benzyloxy, ω -hydroxy PLAs. These data allowed us to confirm the high selectivity of the chiral organocatalytic pairs based on phosphazene and **U1**. On the other hand, **U1** led to faster ROP reactions relatively to **TU1**, when combined with both phosphazenes **P2-t-Bu** and **P4-t-Bu** (*e.g.* **entry 5 vs. entry 6**; see also **Figure 3**). This is consistent with ureas being less acidic than thiourea analogues. When associated with a phosphazene base, **U1** thus generates less stable and more reactive pairs, compared to the more acidic **TU1** combined with the same phosphazene. Pairing **P1-t-Bu** with **U1**, however, led to a very sluggish ROP reaction (**entry 12**), presumably due to a mismatch between the acidity of the urea motif of **U1** and the too weak basicity of **P1-t-Bu**. Finally, increasing the **U1** to the phosphazene molar ratio, *i.e.* using $[rac\text{-LA}]_0/[BnOH]_0/[P1\text{-t-Bu}]_0/[U1]_0 = 200/1/1/3$ did not significantly affect the apparent polymerization rate (**entries 6 to 8** and **9 to 11**).

Table 1. ROP of *rac*-LA using chiral catalytic pairs based on (thio)urea (**T**)U and phosphazene (**P**) base.^{a,b}

Entry	Catalytic system	[M] ₀ /[P] ₀ /[(T)U] ₀ /[I] ₀	Time ^c (h)	Conv. ^d (%)	$\overline{Mn}_{\text{calcd}}^e$ (kg/mol)	$\overline{Mn}_{\text{exp}}^f$ (kg/mol)	\overline{D}^f	P_m^g	T_m^h (°C)	T_g^h (°C)
1	TU1 ⁱ	200/0/1/1	238	85	24	22	1.06	0.87	152	45
2	U1 ^j	200/0/1/1	214	93	27	25	1.09	0.85	138	57
3	TU2	200/0/1/1	260	90	29	23	1.07	0.86	150	58
4	TU3	200/0/1/1	260	82	23	20	1.04	0.83	127	56
5	P₄/TU1	200/1/1/1	1	>99	28	25	1.20	0.85	145	52
6	P₄/U1	200/1/1/1	0.25	≥ 99	28	26	1.16	0.81	127	53
7	P₄/U1	200/1/2/1	0.25	≥ 99	28	25	1.20	0.81	139	50
8	P₄/U1	200/1/3/1	0.25	≥ 99	28	26	1.18	0.84	154	49
9	P₂/U1	200/1/1/1	0.75	97	27	25	1.05	0.85	151	52
10	P₂/U1	200/1/2/1	0.75	98	28	26	1.05	0.85	161	57
11	P₂/U1	200/1/3/1	0.75	98	28	25	1.04	0.88	168	66
12	P₁/U1	200/1/1/1	96	37	10	7	1.04	-	-	-
13	P₄/TU2	200/1/1/1	1	> 99	28	26	1.20	0.78	-	53
14	P₄/TU3	200/1/1/1	4	94	27	24	1.17	0.72	-	51
15	P₂/TU2	200/1/1/1	9	94	27	23	1.08	0.87	155	51
16	P₂/TU3	200/1/1/1	24	90	26	21	1.11	0.79	138	46
17	P₁/TU2	200/1/1/1	120	93	27	25	1.04	0.91	175	57
18	P₁/TU3	200/1/1/1	120	40	11	7	1.04	-	-	-
19	P₄/TU1	200/1/2/1	1	> 99	28	27	1.17	0.85	160	53
20	P₄/TU1	200/1/3/1	1	> 99	28	26	1.17	0.86	160	50
21	P₄/TU2	200/1/5/1	5	94	27	26	1.08	0.81	145	47
22	P₂/TU2	200/1/5/1	18	83	24	21	1.03	0.89	167	59
23	P₄/TU3	200/1/5/1	9	91	26	23	1.05	0.78	-	53
24	P₂/TU3	200/1/5/1	48	89	25	24	1.04	0.83	148	55
25	P₄/TU4	200/1/1/1	24	≥ 99	28	26	1.04	0.81	146	47
26	P₄/TU5	200/1/1/1	2	≥ 99	28	25	1.08	0.78	-	40
27	P₂/TU4	200/1/1/1	48	≥ 99	28	27	1.07	0.89	168	53
28	P₂/TU5	200/1/1/1	4	≥ 99	28	26	1.04	0.84	146	49
29	P₁/TU4	200/1/1/1	120	78	22	19	1.04	0.90	172	51
30	P₁/TU5	200/1/1/1	96	≥ 99	28	25	1.06	0.81	148	46
31	P₂/TU4	200/1/3/1	72	89	25	23	1.04	0.93	176	51
32	P₂/TU5	200/1/3/1	9	92	26	23	1.04	0.87	158	56
33	P₂/TU4	200/1/2/1	48	93	27	25	1.06	0.89	165	50
34	P₂/TU5	200/1/2/1	4	> 99	28	24	1.04	0.83	142	49

^aPolymerizations were performed in dry toluene at 25 °C with $[rac\text{-LA}]_0 = 0.08$ M, in presence of BnOH as initiator (I); (T)U and P stand for (thio)urea and phosphazene, respectively. ^bResults of ROP reactions utilizing **TU1** in presence of **P₂** or **P₁** can be found in ref. 15. ^cReaction time in hour (h). ^dMonomer conversion determined by ¹H NMR in CDCl₃ using integrals of the characteristic signals. ^e $\overline{Mn}_{\text{calcd.}} = M_{\text{LA}}(144.13 \text{ g}\cdot\text{mol}^{-1}) * ([\text{LA}]_0/[\text{I}]_0) * \text{conversion} + M_{\text{BnOH}}(108.14 \text{ g}\cdot\text{mol}^{-1})$. ^fDetermined by SEC in THF relative to PS standards using a correcting factor of 0.58.⁵⁵ ^gDetermined by homonuclear decoupled ¹H NMR. ^hMelting point (T_m) and glass transition temperature (T_g) determined by DSC. ⁱSee ref. 11. ^jSee ref. 16.

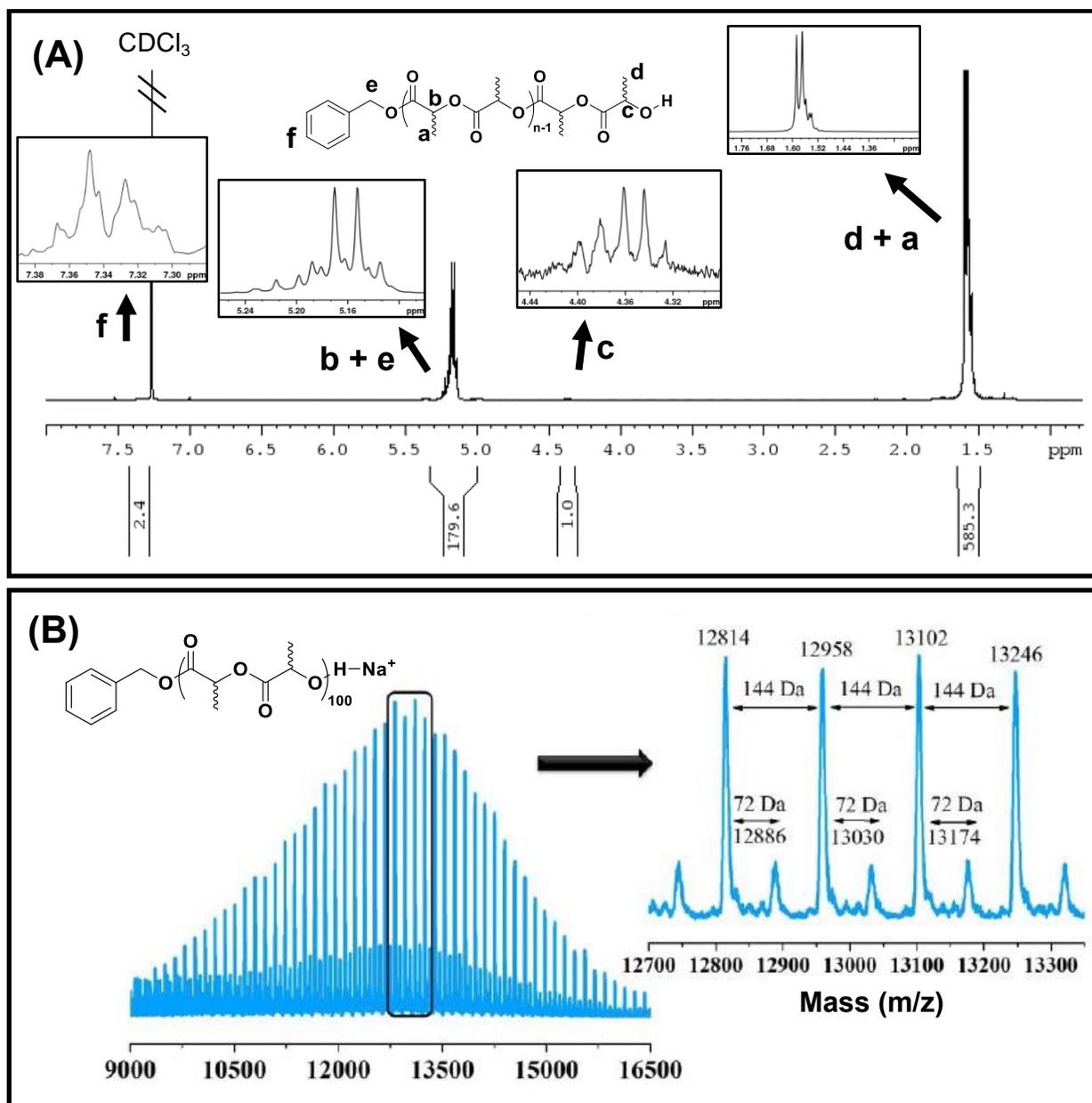


Figure 2. (A) ^1H NMR spectrum (400 MHz, CDCl_3); (B) experimental MALDI ToF mass spectrum of PLA synthesized from **U1/P₂-t-Bu** (entry 9, Table 1).

In terms of stereocontrol, these ROP reactions led to highly isotactic-enriched PLAs characterized by a probability of forming meso dyads (P_m) in the range 0.72 – 0.93 (Table 1). This was evidenced by analyzing PLA samples by homodecoupled ^1H NMR spectroscopy. However, organocatalytic pairs based on **U1** and phosphazenes **P₂-t-Bu** and **P₄-t-Bu** proved less stereoselective than analogous pairs based on **TU1**. In other words, combining **TU1/P₂-t-Bu** and **TU1/P₄-t-Bu** were found slower, but provided higher stereocontrol, compared to **U1/P₂-t-Bu** and **U1/P₄-t-Bu** (Figure 3; see also Figures S2-S3). As reported

in our previous work,¹⁵ a very high isoselectivity ($P_m = 0.96$ and $T_m = 187$ °C), could be reached using 4 eq. of **TU1** combined with 1 eq. of **P1-t-Bu**. These differentiated reactivities and stereoselectivities between **U1** and **TU1** in association with phosphazene bases can be explained by a different extent of interaction between the (thio)urea motif and the base. These interactions can be probed by ¹H NMR spectroscopy from reaction mixtures involving stoichiometric amounts of **TU1** (or **U1**) and each the phosphazene, and then with BnOH.¹⁵ The deprotonation state of the (thio)urea motif of **U1** and **TU1** was thus found to strongly depend on the phosphazene base (ESI, **Figure S4**). The strongest base, **P4-t-Bu**, was found to deprotonate **U1** similarly to **TU1**, *i.e.* forming loose phosphazanium imidate ion pair, which upon further introduction of BnOH, resulted in the formation of a phosphazanium benzyloxide ion pair (**Figure 3** and **S4**). This could be evidenced by a pronounced deshielding effect of the methylene protons of BnOH (**A**, **Figure S4**) in the BnOH/**U1**/**P4-t-Bu** equimolar mixture, relatively to the free BnOH. Upon using the less basic **P2-t-Bu** phosphazene with **U1**, this deshielding effect proved weaker. In the latter case, a more associated interaction by hydrogen-bonding rather than full deprotonation of the urea can be postulated. This result contrasts with our previous findings using **TU1**/**P2-t-Bu**, which was found to provide an ionic-like mechanism through the formation of an ion pair, while an associated mechanism was suggested when using **TU1** with the less basic **P1-t-Bu** phosphazene.¹⁵ As highlighted in **Figure 3**, the organocatalytic pair consisting of **P2-t-Bu**/**U1** is thus thought to provide similar hydrogen bonding and associated mode than **TU1**/**P1-t-Bu**.

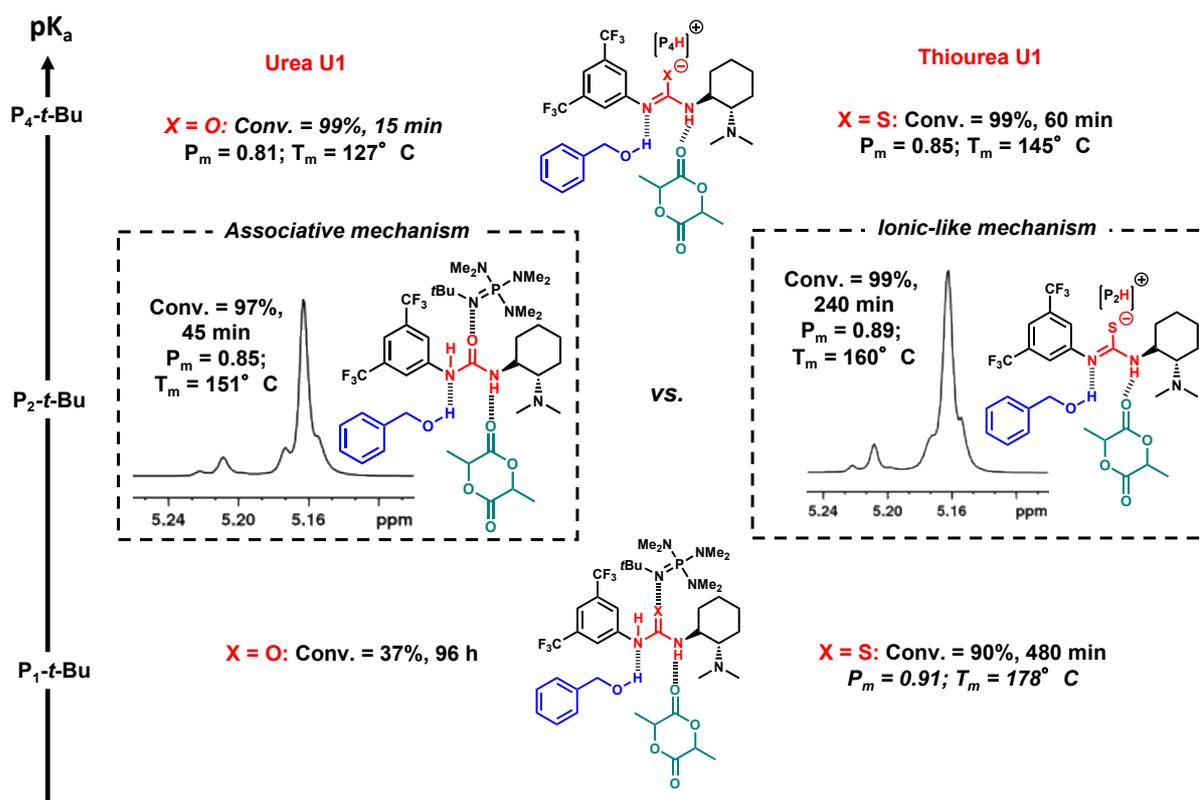


Figure 3. Overview of the comparative reactivity and stereochemical control between urea **U1** and thiourea **TU1**, and underlying activation (associative vs. ionic) mechanisms, during the ROP of *rac*-LA initiated by BnOH, as a function of the phosphazene base; in the dashed frames, results of homodecoupled ^1H NMR spectra of the methine region are shown and correspond to the use of the **P₂-t-Bu** phosphazene base.

We then sought to elucidate the role that the dimethylamino group of **U1** and **TU1** could play during ROP reactions of *rac*-LA. It is indeed notorious that this group can behave as a H-acceptor motif, so that the possibility that it can contribute to the catalytic activity cannot be ruled out. We thus decided to evaluate chiral pairs based other commercially available amino-thioureas of different substitution pattern (**TU1** to **TU5**, **Figure 1**) in presence of the same phosphazenes, for the ROP of *rac*-LA (**Table 1**, **entries 13** to **34**; see also **Figures 4**). ROP reactions were first studied in toluene using **TU2-TU3** in absence of any phosphazene (**entries 3-4**, **Figure S5**). To our knowledge, these chiral aminothioureases have not been reported before for a use in ROP. They are expected to operate following a similar bifunctional cooperative mechanism to that of **TU1** used alone,¹⁵ whereby the tertiary amino group activates the initiator,

while the thiourea moiety interacts with the carbonyl group of the lactide. It can be assumed that the pK_a value of **TU1** to **TU3** is quite close. The potential differences we want to highlight here relate to the decrease of basicity of their dialkylamino function. In general, the rates obtained with **TU2-TU3** proved very low, requiring more than a week to reach 80-90% monomer conversion. The replacement of a dimethyl cyclohexyl amine group (**TU1**) into a cyclohexyl piperidine group (**TU2**), and then by a diphenyl cyclohexyl amine group (**TU3**) in the structure of the catalyst led to a significant rate reduction (**entries 1, 3-4**). This could be ascribed to a reduced basicity of the dialkylamino group. Despite such slow kinetics, **TU1-TU3** led to isotactic enriched and semi-crystalline PLAs, as evidenced by homonuclear decoupled 1H NMR spectra and thermograms obtained by DSC (**Figure S5**). Thus, **TU2** and **TU3** produced a PLA with a P_m value of 0.86 and 0.83, and a T_m value of 150 °C and 127 °C, respectively (**entries 3-4**).

In order to improve the catalytic performance and gain in stereoselectivity, **TU2** and **TU3** were associated to **P1-t-Bu**, **P2-t-Bu** and **P4-t-Bu**. The polymerizations were carried out under the same conditions as with **TU1**, *i.e.* at room temperature in toluene, using initial ratios $[rac-LA]_0/[BnOH]_0/[phosphazene]_0/[TU]_0 = 200/1/1/1$. These new organocatalytic pairs allowed significantly improving the reactivity of the ROP reactions of *rac*-LA (**entries 13-34**; see also **Figures S6 to S17**), while maintaining good control over the molecular weight and dispersity (D) of the resulting PLAs (**Figure 4**). For instance, the **P2-t-Bu/TU2** pair catalyzed the ROP of *rac*-LA with 94% conversion in 9 h, producing a PLA with $D = 1.08$ (**entry 15**). Polymerization using **TU3** combined with **P2-t-Bu** was found to be much slower, with a 90% conversion in 24 h and a D value of 1.11 for the obtained PLA (**entry 16**). Using the weaker phosphazene base, **P1-t-Bu** with **TU2**, a low-dispersity PLA ($D = 1.04$) was achieved for a 93% conversion after 120 h (**entry 17**), while combining **P1-t-Bu** with **TU3** led a conversion of only 40% after 120 hours (**entry 18**). Finally, the **P4-t-Bu/TU2** pair achieved 99.6% conversion of *rac*-LA in only

1 h, resulting in a PLA of dispersity of 1.22, while a 93% conversion in 4 h was obtained from the **P₂-t-Bu/TU3** (entries **13** and **14**, respectively). In other words, for a given phosphazene base, thioureas featuring a more basic tertiary amine group enabled higher polymerization rates (**TU1** > **TU2** > **TU3**), highlighting the non-innocent role of the dialkylamino group on the catalytic activity. The evolution of the number average molecular weights (M_n), as determined by SEC (values obtained after applying a Mark-Houwink correction factor of 0.58),⁵⁵ as a function of monomer conversion for the ROP of *rac*-LA catalyzed by the **P₂-t-Bu/TU2** and **P₂-t-Bu/TU3** pair, respectively, is presented in **Figure 4A-B**. The linear growth of M_n values with monomer conversion indicated the absence of transfer reactions and a good control of the ROP process. This was supported by analysis by MALDI-ToF mass spectrometry for both pairs, showing a main distribution of peaks again corresponding to the expected α -benzyloxy, ω -hydroxy PLA-type structure (**Figures S6-S7**).

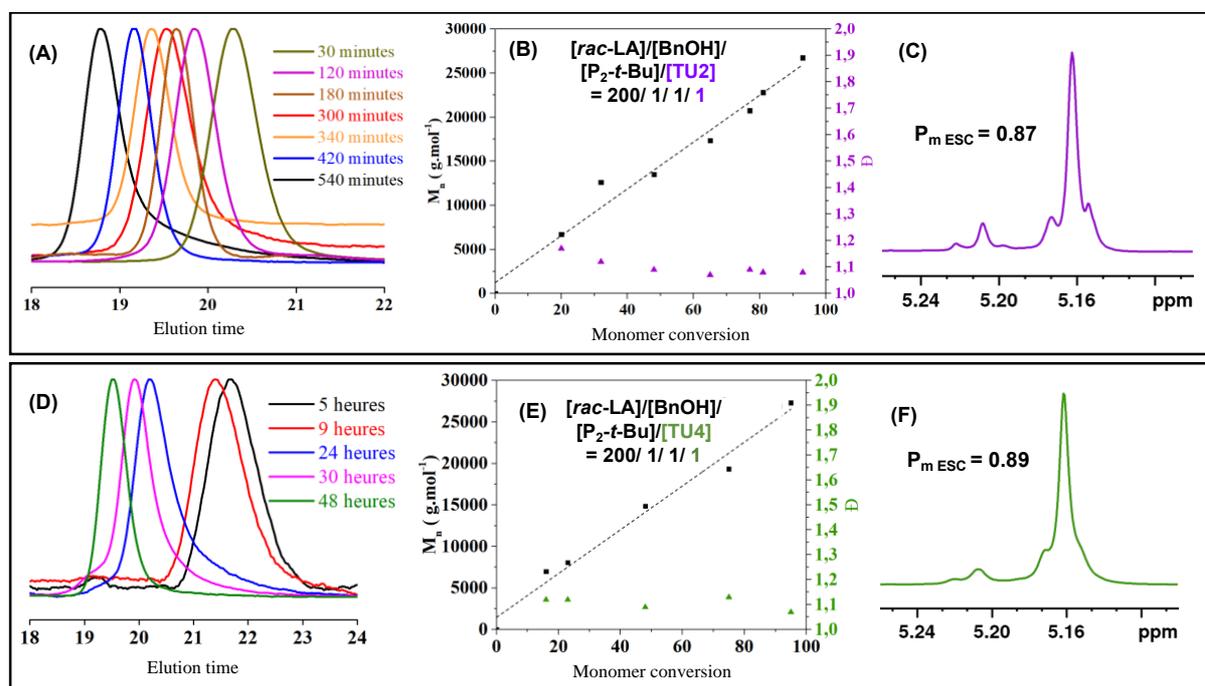


Figure 4. Experimental data of PLA synthesis using **P₂-t-Bu** combined with **TU2** (entry **15**) or with **TU4** (entry **27**), respectively: **(A)** and **(D)** SEC traces of PLA samples at different monomer conversions; **(B)** and **(E)** plots of M_n and M_w/M_n values as a function of monomer conversion; **(C)** and **(F)** homodecoupled ¹H NMR spectrum of the methine region.

The stereoselectivity of the ROP process mediated by organocatalytic pairs based on **TU2** and **TU3** was again evaluated through the determination of P_m values by decoupled homonuclear ^1H NMR and ^{13}C NMR spectroscopy. These data evidenced the formation of isotactic PLAs, with P_m values in the range 0.78-0.91 (Table 1; **Figures S8-S11**). The strongest **P4-t-Bu** base combined with either **TU2** or **TU3** provided moderately isotactic PLAs, with P_m values of 0.78 and 0.72, respectively (**entries 13** and **14**; **Figures S8-S9**). PLA synthesized from the **P2-t-Bu/TU2** pair showed a higher degree of stereoselectivity than PLA produced from **P2-t-Bu/TU3** ($P_m = 0.87$ and 0.79 , respectively; **entries 15-16**; **Figures S8-S9**), suggesting that the more sterically hindered **TU3** does not provide optimal stereocontrol. Remarkably, the less hindered and weaker phosphazene base **P1-t-Bu** combined with **TU2** achieved a P_m value as high as 0.91 (**entry 17**; **Figure S8**). As observed previously with the Takemoto catalyst **TU1** paired with **P1-t-Bu**, high stereocontrol is promoted, likely *via* an associative mechanism involving hydrogen interactions (see **Figure 6**).¹⁵ Note, however, that only 40% of monomer conversion was achieved after several days in the case of the **P1-t-Bu/TU3** catalytic pair, not enabling to precipitate that PLA and analyze its tacticity. Using 5 equivalents of aminothiourea over phosphazene bases slightly improved the stereoselectivity, though at the expense of the reactivity as ROP reactions turned out to be slower (see for instance **entry 13 vs. 21**, **entry 15 vs. 22** or **entry 16 vs. 24**). Thermal properties of PLAs produced from these **phosphazene/TU** catalytic pairs, as investigated by DSC, correlated quite well with the extent of stereocontrol and related P_m values observed (**Figures S12-S14**). These DSC analyses indeed revealed the formation of semi-crystalline PLAs with a melting temperature (T_m) in the range 145-168 °C, depending on the combination between the phosphazene and the aminothiourea (**Table 1**).

As in the previous experiments utilizing **U1** and **TU1**, the interactions involved between **TU2-TU3**, the phosphazene base and BnOH were scrutinized by ^1H NMR spectroscopy in

toluene-d₈, from equimolar amounts of each component, one example being shown in **Figure 5** (see also **Figure S15**). Based on our findings from the **P1-t-Bu/TU1**,¹⁵ one could assume that the weak **P1-t-Bu** base would promote stereocontrol *via* an associative mechanism involving hydrogen interactions. Stronger bases such as **P4-t-Bu** or **P2-t-Bu** would instead lead to faster kinetics, but slightly less stereocontrol. Thus, addition of BnOH to the reaction adduct from **P4-t-Bu/TU2** led to the corresponding phosphazanium alkoxide ion pair (**Figure 5**). This was confirmed by a deshielding effect of methylene A protons in the BnOH/**TU2/P4-t-Bu** (1/1/1) mixture. This effect was less manifest in the case of the BnOH/**TU3/P4-t-Bu** mixture, compared to **TU2** ($\delta = 4.68$ vs. 4.79 ppm, **Figure S15**), which was attributed to the more basic amino group in **TU2** rel. to **TU3**. Similar observations were made using the weaker phosphazene base **P2-t-Bu**. These results are in agreement with the lower reactivity observed with **TU3** rel. to **TU2**, highlighting that the tertiary dialkylamino group plays an important role. Finally, this deshielding effect was very mitigated using the weaker phosphazene base, **P1-t-Bu**, in the case of BnOH/**TU1** or **TU2/P1-t-Bu** mixtures (1/ 1/ 1), compared to free BnOH ($\delta = 4.38$ and 4.32 vs. 4.26 ppm for free BnOH; red lines, **Figure 5**).

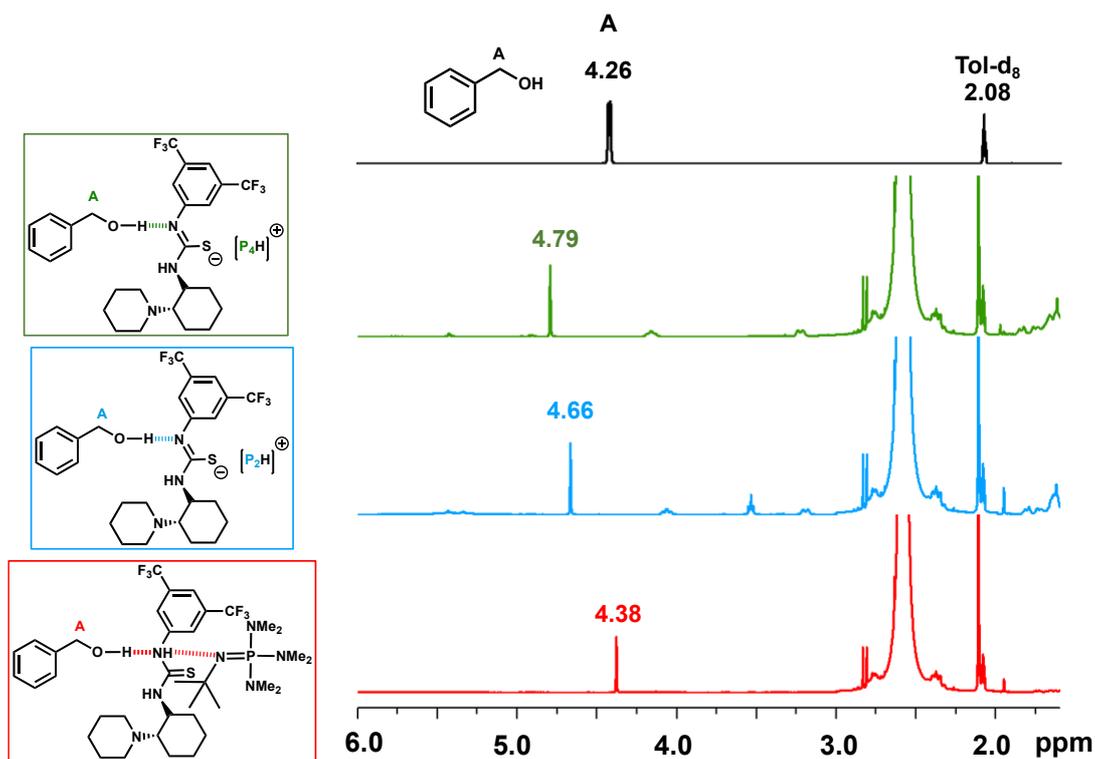


Figure 5. Stacked ^1H NMR spectra from equimolar amounts of BnOH/ **P₄-t-Bu**/TU2 (green), BnOH/ **P₂-t-Bu**/TU2 (blue), and BnOH/**P₁-t-Bu** /TU2 (red) in dry toluene- d_8 at room temperature.

A last series of ROP experiments was carried out using chiral thioureas free of dialkylamino group, namely, **TU4** and **TU5** (Figure 1; see also Figure 6 and Figures S16-S22). Whereas **TU4** is a mono-thiourea featuring an additional amide group, **TU5** is a bis-thiourea, which was expected to drastically increase the polymerization rate, as reported by Kiesewetter *et al.* with non-chiral bis- and tris-(thio)ureas.⁵⁶⁻⁵⁷ Both thioureas **TU4** and **TU5** were again combined with the phosphazene bases to polymerize *rac*-LA (entries 25-34, Table 1). As anticipated, the bis-thiourea **TU5** associated with **P₄-t-Bu** caused a clear acceleration of the reaction, compared to the monothiourea-based pair **TU4/P₄-t-Bu**, without any loss of control being noted (entry 25). The ROP reaction employing **TU5/P₄-t-Bu** went to completion in only 2 h, compared to 24 h for the **TU4/P₄-t-Bu** pair. As observed with the other thioureas, weaker bases led to slower reaction rates, the **TU5/P₂-t-Bu** pair achieving complete conversion within 4 h (entry 28; Figure S16), while **TU4/P₂-t-Bu** required 48 h (entry 27) to reach completion of the ROP process, although preserving control of the ROP of *rac*-LA (see Figure

4C-D). The weakest base in this series, **P₁-t-Bu**, when combined with **TU4** and **TU5**, gave very low conversion rates. Thus, the ROP reaction catalyzed by the **TU5/P₁-t-Bu** pair reached full conversion after 96 h (**entry 30**), while the polymerization reached only 78% conversion even after 120 h using the **TU4/P₁-t-Bu** pair (**entry 29**). Overall, we observed that, upon decreasing the basicity of the dialkylamino group (from **TU1** to **TU3**), until this donor effect is totally removed by introducing an amide group (**TU4**), led to a decrease in catalytic activity.

Examination of both the tacticity and related thermal properties of PLAs synthesized from **TU4** and **TU5** by NMR spectroscopy and DSC, respectively, showed some differences depending on the phosphazene base employed (**Figures S17-S22**). Combining **TU4** and **TU5** with **P₄-t-Bu** thus produced moderately isotactic PLAs, with P_m values of 0.81 and 0.78, respectively (**entries 25-26; Figures S17, S19**). On the other hand, the PLA obtained from the **P₂-t-Bu/TU4** showed a slightly higher degree of stereoselectivity than the **P₂-t-Bu/TU5**-derived sample ($P_m = 0.89$ and 0.84 , respectively; **entries 25-26**). This might be explained by the presence of the chiral cyclohexyl-type central group onto the thiourea motif within the structure of **TU5**, which might decrease the hydrogen bond donor character. This hypothesis was indeed put forward by Nagasawa *et al.* in the case of Morita-Baylis-Hillman reactions catalyzed by chiral thioureas.⁵⁸ By finally pairing the **TU5/P₁-t-Bu**, an isotactic-enriched PLA was obtained with a P_m value of 0.81, while the same base associated with **TU4**, gave a P_m value of 0.90, but after a conversion of only 78%, (**entries 30** and **29**, respectively; **Figures S17, S19**).

Additional kinetic investigations involving organocatalytic pairs based on **P₂-t-Bu** and **TU1-5** (or **U1**) all revealed a first-order kinetic with two distinct slopes (ESI, **Figure S23**) due to a deceleration phenomenon. This could be consistent with a preferential consumption of one particular monomer (*D*-LA or *L*-LA) by the chiral amino(thio)urea, suggesting a prevalent contribution of the enantiomorphic site control mechanism (ESC) during the ROP of *rac*-LA

mediated by these chiral catalytic pairs.¹⁵⁻¹⁶ However, the difference in slopes between the two linear variations is quite small, which may indicate that both ESC and chain end control (CEC) mechanisms operate concomitantly. On the basis of kinetic studies, we had highlighted the occurrence of both mechanisms in our previous work using thiourea **TU1** alone.¹¹ We can assume that the same is true in the present study.

As one reviewer noted, some PLA samples having similar P_m values show different T_m values (e.g. **Table 1, entries 6, 7, 21 and 30**). This may be related to the aforementioned discussion regarding the co-existence of both ESC and CEC mechanisms. As their relative contribution during the ROP reaction can vary from one catalytic pair to the other, the differences in stereoerrors generated can impact the crystallinity properties from sample to sample, without changing the P_m values so much. It seems however risky here to correlate directly the values of P_m and T_m .

All these results tend to demonstrate that PLAs synthesized at room temperature from the phosphazene/chiral (thio)urea catalytic pairs are constituted of stereoblocks resulting from the incorporation of the two distinct LA enantiomers in a sequential manner. The presence of some microstructural defects, *i.e.* stereoerrors, in the building blocks would explain why we did not observe a melting point above 190°C, these defects limiting the co-crystallization of the blocks.

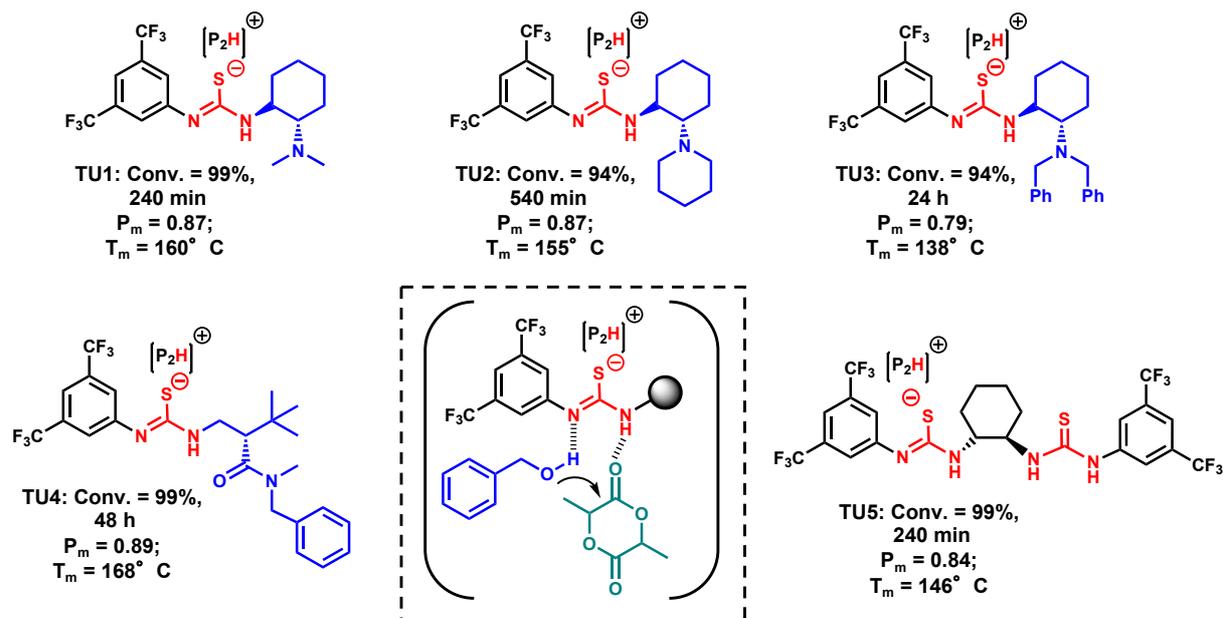


Figure 6. Substituent effect of the thiourea motif on the reactivity and isoselectivity during the ROP of *rac*-LA initiated by BnOH, in presence of organocatalytic pairs based on the chiral dialkylamino thioureas **TU1-TU5** and the **P₂-t-Bu** phosphazene base.

CONCLUSION

We expand the toolbox for polymerizing racemic lactide isoselectively, by appropriately associating a phosphazene organic base with a chiral aminourea or aminothiourea in catalytic duos. Such organocatalytic pairs operate synergistically in toluene at room temperature and provide appreciable catalytic activity (> 90% conversion in 5-9 h) and high stereoselectivity (P_m of 0.72-0.93) depending on the constitution of the pair. Semi-crystalline and metal-free PLA materials constituted of marginally flawed stereoblocks of opposite configuration, *i.e.* incorporating some stereoerrors, can thus be achieved with a melting point in the range 138-176 °C. Screening experiments involving different organic catalyst combinations, as well as model reactions as monitored by ^1H NMR, also allowed us to elucidate the underlying reaction mechanism depending on the identity of the organocatalytic pair involved, as summarized in **Figure 6**. Thus, the most basic **P₄-t-Bu** base provides higher polymerization rate, but lesser stereocontrol and operates by an ionic-like mechanism involving ion pair, when used in

conjunction with urea **U1** and thioureas **TU1-TU5**. In contrast, organocatalytic pairs based on the less basic phosphazene, **P1-t-Bu**, induce a more associated mechanism involving hydrogen-bond interactions. This can favor the production of highly isotactic PLAs only if **P1-t-Bu** is appropriately paired with a (thio)urea showing an acidity matching the basicity of **P1-t-Bu** (e.g. **U1** or **TU1-TU2**, rather than **TU3**). However, the high degree of stereocontrol takes place at the expense of reactivity, which is moderate with this particular base, leading to substantially lower reaction rates. In the end, a good compromise to provide both high reactivity and high selectivity can be achieved by using organocatalytic pairs based on **P2-t-Bu** and some chiral amino(thio)ureas, namely, **U1**, **TU1**, **TU2** and **TU5**. Whereas the **TU1/P2-t-Bu** pair operates by an ionic-like mechanism involving an ion pair during ROP of *rac*-LA, an associated-like mechanism is thought to take place using **P2-t-Bu/U1**. On the other hand, through the use of **TU1** to **TU4** combined with phosphazene bases, the dialkylamino moiety was shown to have a non-innocent role on the catalytic activity. Decreasing the basicity of this group indeed leads to a decrease of the reaction rates.

Overall, these results open new options for stereoselective polymerization employing chiral organocatalytic pairs for the production of well-defined PLA-based stereocomplexes or stereoblocks. Among the options to further improve the stereoselectivity of the ROP process, one can think that a decrease in temperature would be favorable. However, and conversely, a perspective to this work and an ultimate goal sought would be to conduct these ROP reactions at high temperature under bulk (solvent-free) conditions, as L-lactide is industrially polymerized, e.g. using tin-based catalysts. This work also offers new opportunities for the stereocontrolled polymerization of other cyclic monomers (e.g. epoxides) or of polar vinyl monomers, such as alkyl methacrylates. Work in this direction is in progress in our team.

ASSOCIATED CONTENT

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

Experimental procedures, characterization of polymers.

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