Ring-Opening Polymerization of Cyclic Esters and Carbonates with (Thio)urea/Cyclopropenimine Organocatalytic Systems

Romain Morodo[1], David M. Dumas[1], Jia Zhang[1], Kai H. Lui[1], Paul J. Hurst[1], Riccardo Bosio[2], Luis M. Campos[3], Nathaniel H. Park[2], Robert M. Waymouth[1,*] and James L. Hedrick[2,*]

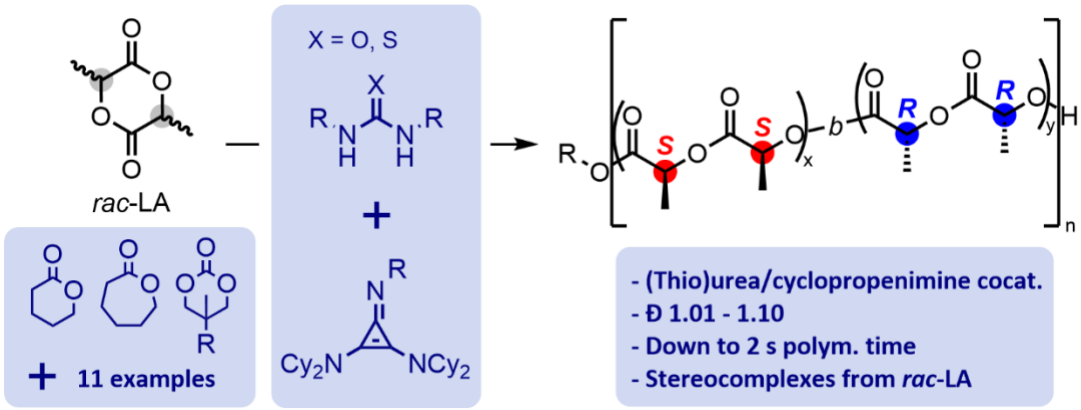
[1]*Department of Chemistry, Stanford University, Stanford, California 94305-5080, United States.*

Email: waymouth@stanford.edu

[2]*IBM Almaden Research Center, San Jose, California 95120, United States.*

Email: hedrick@us.ibm.com

[3]*Department of Chemistry, Columbia University, New York, NY, 10027, United States.*



For Table of Contents use only.

Abstract

Organocatalyzed ring-opening polymerization is a powerful tool for the synthesis of a variety of functional readily degradable polyesters and polycarbonates. We report the use of (thio)ureas in combination with cyclopropenimine bases as unique catalyst for the polymerization of cyclic esters and carbonates with a large span of reactivities. Methodologies of exceptionally effective and selective cocatalyst combinations were devised to produce polyesters and polycarbonates with narrow dispersity (Đ = 1.01 – 1.10). Correlations of the pK_a of the various ureas and cyclopropenimine bases revealed the critical importance of matching the pK_a of the two cocatalysts to achieve the most efficient polymerization conditions. It was found that promoting strong H-bonding interactions with a noncompetitive organic solvent, such as CH_2Cl_2, enabled greatly accelerated polymerization rates. The stereoselective polymerization of *rac*-lactide afforded stereoblock poly(lactides) that crystallize as stereocomplexes, as confirmed by wide-angle x-ray scattering.

Organocatalytic ring-opening polymerization (OROP) of various monomers such as cyclic esters, carbonates and derivatives is a versatile synthetic strategy for functional, biocompatible and biodegradable materials.[1–8] Over the last two decades the advancement of OROP has facilitated the discovery of new materials for a wide range of applications.[9–16]

From the developed catalysts, H-bond donors such as (thio)ureas exhibit broad functional group tolerance and high selectivity by minimizing competitive transesterification reactions affording narrow dispersity.[17,18] The most effective organocatalytic systems usually include a base paired with a (thio)urea that facilitates either an anionic (pK_a base-H^+ > pK_a (thio)urea) or a cooperative (pK_a base-H^+ < pK_a (thio)urea) mechanism. For a given base it was shown that the maximal activity is reached when the pK_a of the base and (thio)urea are closely matched.[19] While ureas typically exhibit a higher activity compared to their thiourea equivalents, they are more prone to self-association compared to thioureas potentially leading to solubility issues or reduced substrate-catalyst interactions.[20,21]

Previously, bases such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU),[19,22] *N*-heterocyclic carbenes (NHCs)[23,24] or phosphazene derivatives[25–28] have been used with success to provide highly active and/or (stereo)selective OROPs when used in combination with (thio)ureas. To expand the range of bases used with urea cocatalysts, we targeted cyclopropenimines (CPI)[29] as a class of accessible, soluble, stable, tunable and inexpensive bases as cocatalysts with (thio)ureas. Protonation of the CPI imino nitrogen generates a resonance-stabilized cyclopropenium ion. Some of these strong Brønsted bases were shown to have a comparable basicity to guanidines and phosphazenes.[29,30] Structural diversification of CPIs can be conveniently accessed by changing the pendant groups attached to the imino nitrogen atom or the cyclopropene ring, providing a diverse range of CPI platforms. In the context of OROP, a CPI has been previously shown to be a competent catalyst for the polymerization of *L*-lactide.[31] The absence of any initiator revealed a competitive initiation mechanism through an enolate formation from lactide producing poly(lactides) (PLAs) with broad dispersity (Đ = 1.3 – 1.6). Herein we show that (thio)urea/CPI

organocatalysts lead to the fast, selective and convenient OROP of a variety of cyclic esters and carbonates. The critical importance of a pK_a match between the (thio)urea cocatalyst and the CPI base for optimal polymerization kinetics and narrowly dispersed polymers was demonstrated. Moreover, higher rates are observed in CH_2Cl_2 than in THF, which can be attributed to enhanced H-bonding interactions in solvents of lower donor number.[32] The stereoselective OROP of *rac*-lactide with urea/CPI combinations affords stereoblock PLLA-*b*-PDLA polymers (Pm up to 0.88) that crystallize as stereocomplexes with melting temperatures up to 173 °C. The (thio)urea/CPI systems proved to be highly versatile due to their convenient access and tunability while offering a remarkable (stereo)selectivity and activity with a proper (thio)urea/CPI pairing and solvent selection to polymerize a broad variety of lactones and cyclic carbonates.

To assess the effectiveness of the CPI/(thio)urea catalyst systems, we first investigated the polymerization of both racemic (*rac*-LA) and *L*-lactide (*L*-LA) with 3 different ureas **U-(1-3)**, the *N*-cyclohexyl **CPI-1** and *N*-butyl **CPI-2** in THF at 25 °C (Figure 1). The polymerization of *rac*-LA in THF with **U-1**/**CPI-1** proceeded to 96% conversion within 45 s and yielded PLA with a narrow dispersity (Đ = 1.03) and a degree of polymerization (DP) of 103 (*vs*. DP_{th} of 96, Table 1, entry 1). **U-2**/**CPI-1** displayed similar behavior with a conversion of 91% after 30 s and a dispersity of Đ = 1.02 (entry 2). With the less acidic **U-3** and **CPI-1** in THF, the activity was significantly lower (82% conv. after 3.5 h) and yielded PLA with a broader dispersity (Đ = 1.31, entry 3). Correlation of the activities with the pK_a's (DMSO, determined by UV-Vis spectrophotometric titration, see Figure 1 and Supporting Information) of the ureas and protonated CPI's revealed the critical importance of a close matching[19] of the pK_a of the urea employed and that of the CPI conjugate acid. For example, the **U-1**/**CPI-1** combination matches well (pK_a (**U-1**) = 13.8 and pK_a (**CPI-1-H**$^+$) = 14.7) and exhibits an associated high catalytic activity and a narrow dispersity (entry 1). MALDI-TOF analysis of the PLA obtained with **U-1**/**CPI-1** demonstrated a single population of polymeric chains (δ m/z = 144) with minimal transesterification reactions even at a high monomer conversion (Figure 2(a) and

Supporting Information). Likewise, **U-2** (pK_a = 15.8) presents a close pK_a match with **CPI-1-H$^+$** and the **U-2**/**CPI-1** combination also led to a high catalytic activity coupled with a narrow dispersity (entry 2). Conversely, the use of **U-3** (pK_a = 22.6) in combination with **CPI-1** presents a pK_a mismatch with a significantly slower reaction rate and a broader dispersity (Đ = 1.31, entry 3 and Figure 2(b)). Moreover, for OROP of *rac*-LA in THF with the mismatched pair **U-3**/**CPI-1** or with **CPI-1** in the absence of the urea, the molar masses determined by SEC were lower than that predicted (Table 1, entries 3, 4, 5 and 12), indicative of competitive initiation, likely by enolization of lactide.[31]

Polymerization rates were observed to be faster in dichloromethane (CH_2Cl_2) than in THF as *rac*-LA polymerized to 93% conversion within 2 s with **U-1**/**CPI-1** (entry 6) and 98% with **U-2**/**CPI-1** (entry 7) while maintaining low dispersity. The slower **U-3**/**CPI-1** combination was also significantly faster in CH_2Cl_2 than in THF and afforded PLA with a narrow dispersity (Đ = 1.06, Table 1, entry 8). MALDI-TOF analysis of this sample revealed ions separated by δ m/z = 72 (Figure 2(c)), indicating that while the ROP with **U-3**/**CPI-1** in CH_2Cl_2 is more highly controlled than in THF (Table 1 entry 8 vs 3), the high sensitivity of the MALDI analysis indicates that some minor amount of transesterification occurs with **U-3**/**CPI-1** in CH_2Cl_2. The less active thiourea (**TU**) in combination with **CPI-1** required 10 min of reaction time in CH_2Cl_2 to achieve a conversion of 93%, followed first order kinetics in monomer concentration (see Supporting Information) and yielded polymers of low dispersity (Đ = 1.02, entry 9). The higher polymerization rates observed in CH_2Cl_2 are consistent with enhanced H-bonding interactions in this solvent relative to THF.[32,33] H-bonding effects have been proposed to be a critical driver and component of (thio)urea-catalyzed OROP as a part of a cooperative mechanism where the base activates the alcoholic initiator/chain-end while the (thio)urea cocatalyst activates the monomer,[19,34,35] thus, improving H-bonding effects through solvent selection can influence catalyst activity and selectivity.

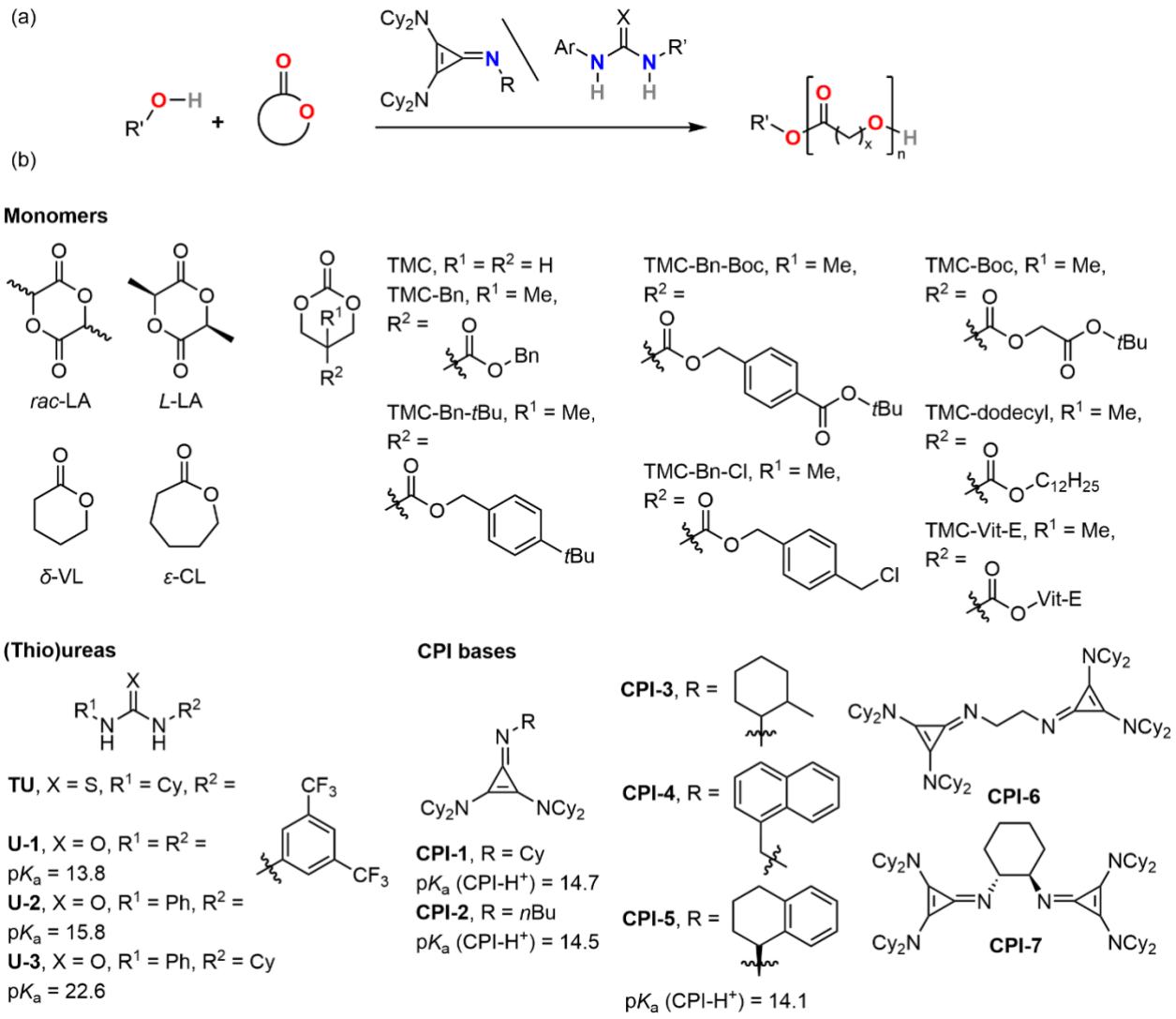


Figure 1. (a) Ring-opening polymerization of lactones and cyclic carbonates using (thio)urea/CPI organocatalysts. (b) Scope of monomers and cocatalysts used for this study (pK_a values were determined in DMSO).

As previously noted, the CPI bases are competent catalysts in the absence of (thio)ureas, but are less active and yield polymers with higher dispersity than those carried out in combination with urea cocatalysts. Polymerization using **CPI-2** in the absence of any (thio)urea cocatalyst proceeded to 85% conversion after 3 h in THF and to 95% after 5 min in CH_2Cl_2, but yielded polymers with slightly broader dispersity (entries 5 and 10, respectively). The poor solubility of the catalytic systems in toluene precluded systematic investigations in this solvent. Polymerization of enantiopure *L*-LA proceeded similarly to *rac*-LA

but with slightly accelerated polymerization rates (entries 11 and 12 vs. 1 and 3, respectively). High molecular weight polymers (500 equiv. of *L*-LA, 98% conv., 65 kDa) were also obtained using a similar procedure (see Supporting Information).

The (thio)urea/CPI catalytic systems are also effective for a range of lactone and carbonate monomers with different reactivities (Table 1). The polymerization of δ-valerolactone (δ-VL) using **U-1**/**CPI-1** (entry 13) afforded polyvalerolactone within 45 min, while the less reactive ε-caprolactone (ε-CL) required 19 h to reach a high conversion in THF (entry 14). The reaction time for ε-CL could be reduced to 7 h by switching the solvent to CH_2Cl_2 (entry 18). On the other hand, attempted polymerizations of ε-CL with the pK_a-mismatched **U-3**/**CPI-1** combination or with **CPI-1** in absence of a urea cocatalyst led to no observable monomer conversion even after more than 18 h (entries 16 and 17, respectively).

Various functional carbonate monomers[36–39] were investigated to further expand the scope of materials/applications of the (thio)urea/CPI pairs as organocatalytic systems. Model carbonate TMC was polymerized within 5 min to a high conversion of 98% and a narrow dispersity (Đ = 1.04) using **U-1**/**CPI-1** in THF (entry 19). The **U-1**/**CPI-1** pair polymerized TMC-Bn to 96% conversion in 30 s (entry 21), while the **TU**/**CPI-1** system took significantly longer (entry 20). Structurally related TMC-Bn-*t*Bu, TMC-Bn-Boc and TMC-Bn-Cl displayed similar reactivities affording high conversion values (>90%) and narrow dispersity (Đ = 1.05 – 1.08) within 30 s of reaction time (entries 22 – 24). On the other hand, TMC-Boc required 5 min of reaction time to afford 88% of conversion and additionally led to a broader dispersity (Đ = 1.29) compared to the other cyclic carbonates (entry 25). Dodecyl- and vitamin-E- functionalized TMC-dodecyl and TMC-Vit-E both displayed high reactivities (86 – 95% conv.) with narrow dispersity materials after 30 s of reaction time (entries 26 and 27) further extending scope of polymerizable carbonates with (thio)urea/CPI pairs.

Table 1. Polymerization of various cyclic esters and carbonates in presence of a (thio)urea/cyclopropenimine organocatalytic system.[a]

Entry	Monomer	Urea/ TU	Base	Solvent	Time	Conv. (%)[b]	DP[b]	$Mn_{calc.}$ (kDa)	$Mn_{exp.}$ (kDa)[c]	Đ[c]
1	*rac*-LA	**U-1**	**CPI-1**	THF	45 s	96	103	14	13.7	1.03
2		**U-2**	**CPI-1**	THF	30 s	91	98	13.2	17.4	1.02
3		**U-3**	**CPI-1**	THF	3.5 h	82	93	11.9	5.8	1.31
4		**U-3**	**CPI-2**	THF	2 h	90	96	13.1	7.8	1.15
5		none	**CPI-2**	THF	3 h	85	84	12.4	5.3	1.28
6		**U-1**	**CPI-1**	CH_2Cl_2	2 s	93	83	13.5	13.9	1.05
7		**U-2**	**CPI-1**	CH_2Cl_2	2 s	98	100	14.2	15.7	1.04
8		**U-3**	**CPI-1**	CH_2Cl_2	120 s	96	112	14	12.5	1.06
9		**TU**	**CPI-1**	CH_2Cl_2	600 s	93	108	13.5	22.4	1.02
10		none	**CPI-2**	CH_2Cl_2	300 s	95	109	13.8	8.5	1.17
11	*L*-LA	**U-1**	**CPI-1**	THF	10 s	94	98	13.7	18	1.04
12		**U-3**	**CPI-1**	THF	2 h	86	90	12.5	5.5	1.36
13	*δ*-VL	**U-1**	**CPI-1**	THF	45 min	83	87	8.4	9.6	1.04
14	*ε*-CL	**U-1**	**CPI-1**	THF	19 h	97	105	11.2	10.7	1.10
15		**U-2**	**CPI-1**	THF	16 h	87	96	10	14.4	1.04
16		**U-3**	**CPI-1**	THF	22.5 h	0				
17		none	**CPI-1**	THF	18.5 h	0				
18		**U-1**	**CPI-1**	CH_2Cl_2	7 h	92	107	10.6	17.5	1.07
19[d]	TMC	**U-1**	**CPI-1**	THF	300 s	98	47	5.1	8.9	1.04
20[e]	TMC-Bn	**TU**	**CPI-1**	THF	40 min	95	46	12	10.6	1.08
21[e,f]	TMC-Bn	**U-1**	**CPI-1**	THF	30 s	96	43	12.2	12.5	1.06
22[d,f]	TMC-Bn-*t*Bu	**U-1**	**CPI-1**	THF	30 s	91	39	14.1	13.6	1.05
23[d,f]	TMC-Bn-Boc	**U-1**	**CPI-1**	THF	30 s	92	43	16.3	12.7	1.07
24[d,f]	TMC-Bn-Cl	**U-1**	**CPI-1**	THF	30 s	94	34	13.5	11.4	1.08
25[e,f]	TMC-Boc	**U-1**	**CPI-1**	THF	300 s	88	38	12.2	9.7	1.29
26[e,f]	TMC-dodecyl	**U-1**	**CPI-1**	THF	30 s	95	52	15.7	20.3	1.06
27[e]	TMC-Vit-E	**U-1**	**CPI-1**	THF	30 s	86	44	24.8	10.7	1.09

[a]General conditions (unless otherwise stated): Initiator = 4-methylbenzyl alcohol, [monomer]/[(thio)urea]/[CPI]/[initiator] = 100:2:1:1, 25 °C, $conc._{Monomer}$ = 1 M, N_2 atmosphere. [b]Determined by ^1H NMR. [c]Determined by SEC calibrated with polystyrene standards, Mn correcting factors for PLA = 0.58, for PVL = 0.57 and for PCL = 0.56,[40] entries 19-27: no correcting factor applied. [d][monomer]/[(thio)urea]/[CPI]/[initiator] = 50:2.5:1:1. [e][monomer]/[(thio)urea]/[CPI]/[initiator] = 50:2:1:1. [f]Initiator = 4-methylbenzyl 3-hydroxy-2-(hydroxymethyl)-2-methylpropanoate.

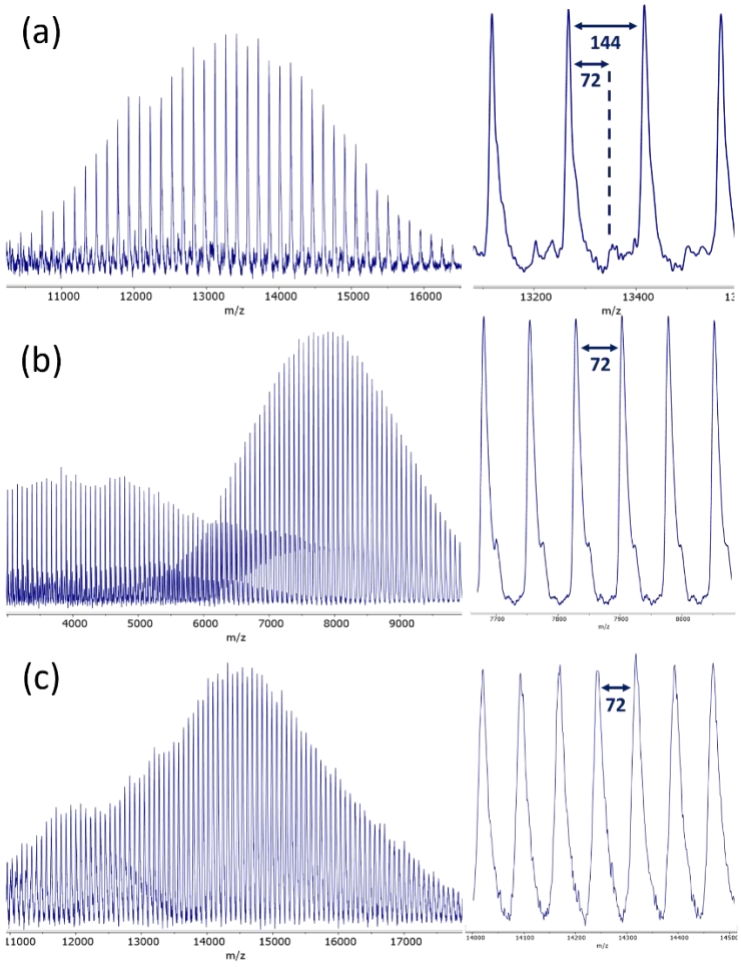


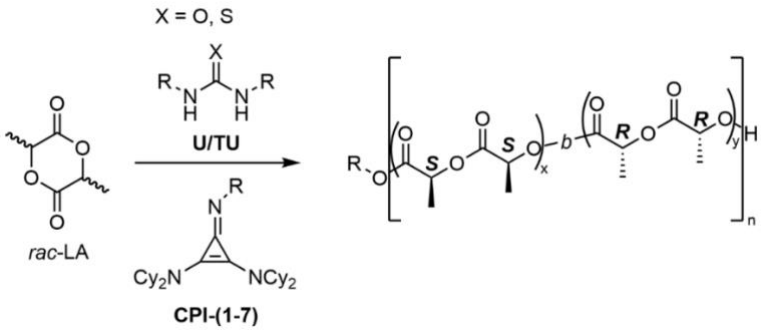
Figure 2. MALDI-TOF spectra of PLA samples obtained using: (a) a **U-1**/**1** catalytic system in THF (see also Table 1, entry 1), (b) a **U-3**/**CPI-1** catalytic system in THF (see also Table 1, entry 3) and (c) a **U-3**/**1** catalytic system in CH_2Cl_2 (see also Table 1, entry 8).

The application of (thio)urea/CPI organocatalytic systems for the stereoregular synthesis of PLA from *rac*-LA was investigated. The stereoselective polymerization of lactide has been reported for a variety of achiral and chiral catalysts.[25–27,41–43] For achiral catalysts, stereoselective polymerization of *rac*-LA occurs by a chain-end control mechanism,[43] where the stereochemistry of the last-enchained unit exhibits a preference for enchaining monomers of similar configuration.[44] We[45] and others[46] had previously shown that sterically-demanding achiral *N*-heterocyclic carbenes can exhibit high stereoselectivity for the polymerization of *rac*-LA. As the steric demands of the CPI can easily be modified by changing the pendant groups of the *N*-imine or the cyclopropene ring, we sought to assess the potential of (thio)urea/CPI catalyst

systems for stereoselective polymerization. Here, we surveyed a series of CPI bases (**1**–**7**) in combination with **U-1** for the room temperature polymerization of *rac*-LA (Table 2). Each of the catalyst systems exhibited modest stereoselectivity, yielding PLAs with isotacticities ranging from Pm = 0.74 - 0.79, as determined by homonuclear decoupled ^{1}H NMR measurements.[42,45] While higher stereoselectivities have been observed with other (thio)urea/base pairs,[23,25,27] the high activities for these urea/CPI catalysts (Table 1 and 2) illustrate the range of reactivities and stereoselectivities that can be obtained by appropriate cocatalyst combinations.

The nature of the substituents on the CPI base did not appear to have a significant effect on the stereospecificity (entries 2-8). While the rates were higher in CH_2Cl_2 relative to THF, there was little effect on the stereoselectivity for **U-1**/**CPI-1** (Table 2, entry 2 vs. 9), but a slight decrease for **U-2**/**CPI-1** (entry 12 vs. 13). The **U-2**/**CPI-1** catalyst pair yielded a slightly higher stereoselectivity than that of the **U-1**/**CPI-1** catalyst (entries 2 vs. 12). At lower temperatures, the OROP stereoselectivity increased. Polymerization of *rac*-LA with the **U-2**/**CPI-1** catalyst at – 36 °C in THF was complete in 2 h and afforded isotactic PLA with an average Pm of 0.88 (entry 17). This PLA sample yielded a melting point of 173 °C, which is higher than the isotactic PLA obtained from the polymerization of enantiomerically pure *L*-LA with **U-1**/**CPI-1** (T_m = 168 °C, Table 2, entry 1). The high melting points are suggestive of crystalline stereocomplexes[47] of PDLA and PLLA sequences,[41,48–51] which would result from a stereoblock PDLA-*b*-PLLA microstructure by a chain-end control mechanism.[25–27,42,43] To confirm this, the sample of PLA with a Pm of 0.88 (Table 2, entry 17) was analyzed by wide-angle x-ray scattering (WAXS). The scattering pattern observed (see Supporting Information, Figure S38) is consistent with crystallization of this sample as the stereocomplex.[52–55] These data indicate that the stereoselective polymerization of *rac*-LA by **U-2**/**CPI-1** catalyst at – 36 °C in THF yields a stereoblock PLLA-*b*-PDLA.

Table 2. Stereoregularity studies of the organocatalyzed ring-opening polymerization of *rac*-LA with (thio)urea/CPI catalytic systems.[a]



Entry	Urea/TU (equiv.)	Base	T (°C)	Solvent	Time (s)	Conv. (%)[b]	DP[b]	Đ[c]	P_m[d]	T_m (°C)[e]
1[f]	**U-1 (2)**	**CPI-1**	25	THF	10	94	98	1.04	1	168
2		**CPI-1**	25	THF	45	96	103	1.03	0.77	
3		**CPI-2**	25	THF	30	94	106	1.02	0.74	
4		**CPI-3**	25	THF	30	94	111	1.04	0.74	
5		**CPI-4**	25	THF	30	86	103	1.01	0.77	
6		**CPI-5**	25	THF	30	91	107	1.02	0.76	
7[g]		**CPI-6**	25	THF	30	67	80	1.02	0.79	
8[g]		**CPI-7**	25	THF	30	91	93	1.03	0.77	
9		**CPI-1**	25	CH_2Cl_2	2	93	83	1.05	0.78	
10	**U-1 (3)**	**CPI-1**	25	THF	45	96	107	1.03	0.80	
11	**U-1 (5)**	**CPI-1**	25	THF	45	94	88	1.03	0.80	
12	**U-2 (2)**	**CPI-1**	25	THF	30	91	98	1.02	0.82	
13		**CPI-1**	25	CH_2Cl_2	2	98	100	1.04	0.74	
14	**U-2 (3)**	**CPI-1**	0	THF	60	97	114	1.05	0.84	
15		**CPI-1**	-15	THF	60	97	101	1.04	0.85	169
16[h]		**CPI-1**	25	THF	1 h	94	220	1.02	0.79	
17[h]		**CPI-1**	-36	THF	2 h	>99	232	1.05	0.88	173
18	**TU (2)**	**CPI-1**	25	CH_2Cl_2	600	93	108	1.02	0.80	
19	none	**CPI-2**	25	THF	3 h	85	84	1.28	0.71	
20	none	**CPI-2**	25	CH_2Cl_2	300	95	109	1.17	0.71	

[a]General conditions (unless otherwise stated): monomer = *rac*-LA, initiator = 4-methylbenzyl alcohol, [monomer]/[CPI]/[initiator] = 100:1:1, room temperature, $conc._{Monomer}$ = 1 M, N_2 atmosphere. [b]Determined by ^{1}H NMR. [c]Determined by SEC. [d]Probability of finding mesodyads along the polymeric chain calculated by homonuclear decoupled ^{1}H NMR after deconvolution; calculations based on Bernouilli statistics (chain-end control mechanism). [e]Determined by DSC. [f]Monomer = *L*-lactide. [g]0.5 equiv. of difunctional CPI used. [h][monomer]/[CPI]/[initiator] = 200:1:1.

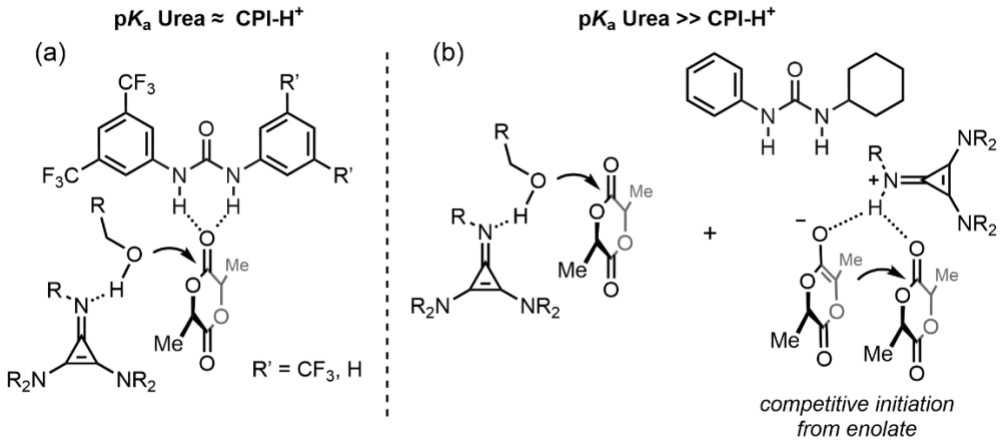


Figure 3. Proposed mechanisms for monomer activation using urea/CPI cocatalysts with (a) closely matched urea and CPI pK_a's and (b) a less acidic urea (pK_a urea >> CPI-H$^+$).

Organic catalysts derived from ureas and CPI bases exhibit high activity, selectivity and versatility for the ring-opening polymerization of a range of lactones and cyclic carbonates. The highest activities are observed for urea/CPI combinations where the pK_a's of the urea are similar[19,20] to that of the conjugate acid CPI-H$^+$. Higher activities are observed in CH_2Cl_2 than in THF, indicating that H-bonding interactions are enhanced in solvents of lower donor number.[32] These results are consistent with different modes of monomer and alcohol activation depending on the solvent and relative acidity of the cocatalyst pairs (Figure 3). For ureas that are not readily deprotonated by the CPI base in a given solvent, activation of the alcohol by the base facilitates attack on the lactone activated by H-bonding to the urea (Figure 3 (a)).[2,3,19,56] For the least acidic urea **U-3**, the lower molecular weights observed in THF and similar activities observed with and without **U-3** in THF (Table 1, entries 3 vs. 5) are consistent with a minimal role for the urea in THF and competitive initiation by lactide enolization (Figure 3 (b)).[31]

The stereoselective polymerization of *rac*-LA with urea/CPI cocatalysts yields polylactides with isotacticities ranging from Pm = 0.74 - 0.88. The nature of the substituents on the CPI base (chiral or

achiral) or the solvent did not have a significant effect on the stereoselectivity which is most readily attributed to a chain-end control mechanism. Higher stereoselectivities were observed at lower temperatures; with **U-2**/**CPI-1** catalyst at – 36 °C in THF yields a stereoblock PLLA-*b*-PDLA, which crystallizes as a high-melting (T_m = 173 °C) stereocomplex.

Experimental Section

Polymerization of *rac*-LA in THF using U-1/CPI-1 catalytic system (Table 1, entry 1)

In an N_2-filled glovebox, stock solutions of the initiator (4-methylbenzyl alcohol, 0.1 M), CPI base (**CPI-1**, 0.1 M), urea (**U-1**, 0.2 M) and monomer (*rac*-LA, 2 M) were prepared in THF. Then, 1 mL of the monomer solution (2 mmol, 100 equiv.) was added to a Teflon-capped vial containing a stir bar. In a separate vial, 0.2 mL of the initiator solution (0.02 mmol, 1 equiv.), 0.2 mL of the base solution (0.02 mmol, 1 equiv.), 0.2 mL of the urea solution (0.04 mmol, 2 equiv.) and 0.4 mL of THF were mixed, homogenized, and added to the Teflon-capped vial containing the monomer solution under stirring to initiate the polymerization. After 45 s, the reaction was quenched by a large excess of benzoic acid in THF and the Teflon-capped vial was removed from the glovebox for analysis of an aliquot (^{1}H NMR, conv. 96%). The solvent was evaporated under reduced pressure and the resulting polymer was washed 3 times with portions of MeOH. Finally, the material was dried under reduced pressure prior to analysis (^{1}H NMR: DP = 103, Pm = 0.77; SEC: Đ = 1.03, Mn = 13.7 kDa).

pK_a determination of CPI-1 base by spectrophotometric titration

In a N_2-filled glovebox, 3 mL of a stock solution of 48 mM 9-(phenylthio)-9*H*-fluorene (**PhS-FH**) indicator (pK_a = 15.4) was added to a dry quartz cuvette. Three aliquots of 48 mM **CPI-1** were then added to the cuvette; the final volumes of **CPI-1** after each addition were 60 µL, 80 µL, and 100 µL. After each addition of **CPI-1**, the absorbance at λ_{max} = 453 nm increased. The absorbance value was used to directly calculate the concentration of the deprotonated indicator and, subsequently, of neutral **CPI-1**, and protonated **CPI-**

1 (see also Supporting Information). The molar extinction coefficient used for these calculations (ε = 1902 $L \cdot mol^{-1} \cdot cm^{-1}$) was obtained from a Beer-Lambert plot created from an earlier pK_a determination experiment. The titrations provided three values for K_{eq}, which led to an average calculated pK_a of 14.7 ± 0.1 for the conjugate acid of **CPI-1**.

Associated Content

Experimental supporting data, pK_a determination methods and characterization data (NMR spectra, SEC chromatograms, DSC thermograms and WAXS data) are provided in the Supporting Information.

Authors Information

Corresponding authors

Robert M. Waymouth - Department of Chemistry, Stanford University, Stanford, California 94305-5080, United States; Email: waymouth@stanford.edu

James L. Hedrick - IBM Almaden Research Center, San Jose, California 95120, United States; Email: hedrick@us.ibm.com

Authors

Romain Morodo - Department of Chemistry, Stanford University, Stanford, California 94305-5080, United States.

David M. Dumas - Department of Chemistry, Stanford University, Stanford, California 94305-5080, United States.

Jia Zhang - Department of Chemistry, Stanford University, Stanford, California 94305-5080, United States.

Kai H. Liu - Department of Chemistry, Stanford University, Stanford, California 94305-5080, United States.

Paul J. Hurst - Department of Chemistry, Stanford University, Stanford, California 94305-5080, United States.

Riccardo Bosio - IBM Almaden Research Center, San Jose, California 95120, United States.

Luis M. Campos - Department of Chemistry, Columbia University, New York, NY, 10027, United States.

Nathaniel H. Park - IBM Almaden Research Center, San Jose, California 95120, United States.

Authors Contributions

R.M. and D.M.D. performed the polymerization experiments and analyzed the results. J.L.H. synthetized the cyclopropenimine bases. J.Z. and K.H.L. performed the pK_a determinations. R.M. and J.Z. designed the experiments. R.B. performed the synthesis and polymerization of the carbonates and the SEC and DSC analyses. R.M. and J.Z. performed the MALDI-TOF analyses. R.M. wrote the Manuscript and Supporting Information with input from all authors. R.M.W. and J.L.H. directed and supervised the project. All authors reviewed the Manuscript prior to submission.

Notes

The authors declare no competing interests.

Acknowledgements

This material is based on work supported by the National Science Foundation under Grant No. GOALI NSF CHE-2002933. R.M. was supported by a Post-doctoral Research Fellowship from the Belgian American Educational Foundation (B.A.E.F.). Pedro Arrechea is gratefully acknowledged by the authors for his help regarding the MALDI-TOF analyses.

References

(1) Kamber, N. E.; Jeong, W.; Waymouth, R. M.; Pratt, R. C.; Lohmeijer, B. G. G.; Hedrick, J. L. Organocatalytic Ring-Opening Polymerization. *Chem. Rev.* **2007**, *107* (12), 5813–5840. https://doi.org/10.1021/cr068415b.

(2) Kiesewetter, M. K.; Shin, E. J.; Hedrick, J. L.; Waymouth, R. M. Organocatalysis: Opportunities and Challenges for Polymer Synthesis. *Macromolecules* **2010**, *43* (5), 2093–2107. https://doi.org/10.1021/ma9025948.

(3) 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* (11), 1047–1053. https://doi.org/10.1038/nchem.2574.

(4) Hu, S.; Zhao, J.; Zhang, G.; Schlaad, H. Macromolecular Architectures through Organocatalysis. *Prog. Polym. Sci.* **2017**, *74*, 34–77. https://doi.org/10.1016/j.progpolymsci.2017.07.002.

(5) Zhang, X.; Fevre, M.; Jones, G. O.; Waymouth, R. M. Catalysis as an Enabling Science for Sustainable Polymers. *Chem. Rev.* **2018**, *118* (2), 839–885. https://doi.org/10.1021/acs.chemrev.7b00329.

(6) Zhang, Q.; Song, M.; Xu, Y.; Wang, W.; Wang, Z.; Zhang, L. Bio-Based Polyesters: Recent Progress and Future Prospects. *Prog. Polym. Sci.* **2021**, *120*, 101430. https://doi.org/10.1016/j.progpolymsci.2021.101430.

(7) Yuan, P.; Sun, Y.; Xu, X.; Luo, Y.; Hong, M. Towards High-Performance Sustainable Polymers via Isomerization-Driven Irreversible Ring-Opening Polymerization of Five-Membered Thionolactones. *Nat. Chem.* **2022**, *14* (3), 294–303. https://doi.org/10.1038/s41557-021-00817-9.

(8) Jadrich, C. N.; Pane, V. E.; Lin, B.; Jones, G. O.; Hedrick, J. L.; Park, N. H.; Waymouth, R. M. A Cation-Dependent Dual Activation Motif for Anionic Ring-Opening Polymerization of Cyclic Esters. *J. Am. Chem. Soc.* **2022**, *144* (19), 8439–8443. https://doi.org/10.1021/jacs.2c01436.

(9) Goffin, A.-L.; Habibi, Y.; Raquez, J.-M.; Dubois, P. Polyester-Grafted Cellulose Nanowhiskers: A New Approach for Tuning the Microstructure of Immiscible Polyester Blends. *ACS Appl. Mater. Interfaces* **2012**, *4* (7), 3364–3371. https://doi.org/10.1021/am3008196.

(10) Tsao, Y.-Y. T.; Wooley, K. L. Synthetic, Functional Thymidine-Derived Polydeoxyribonucleotide Analogues from a Six-Membered Cyclic Phosphoester. *J. Am. Chem. Soc.* **2017**, *139* (15), 5467–5473. https://doi.org/10.1021/jacs.7b01116.

(11) McKinlay, C. J.; Vargas, J. R.; Blake, T. R.; Hardy, J. W.; Kanada, M.; Contag, C. H.; Wender, P. A.; Waymouth, R. M. Charge-Altering Releasable Transporters (CARTs) for the Delivery and Release of mRNA in Living Animals. *Proc. Natl. Acad. Sci.* **2017**, *114* (4). https://doi.org/10.1073/pnas.1614193114.

(12) Benner, N. L.; McClellan, R. L.; Turlington, C. R.; Haabeth, O. A. W.; Waymouth, R. M.; Wender, P. A. Oligo(Serine Ester) Charge-Altering Releasable Transporters: Organocatalytic Ring-Opening

Polymerization and Their Use for *in Vitro* and *in Vivo* mRNA Delivery. *J. Am. Chem. Soc.* **2019**, *141* (21), 8416–8421. https://doi.org/10.1021/jacs.9b03154.

(13) Patel, B. B.; Walsh, D. J.; Kim, D. H.; Kwok, J.; Lee, B.; Guironnet, D.; Diao, Y. Tunable Structural Color of Bottlebrush Block Copolymers through Direct-Write 3D Printing from Solution. *Sci. Adv.* **2020**, *6* (24), eaaz7202. https://doi.org/10.1126/sciadv.aaz7202.

(14) Song, Y.; Elsabahy, M.; Collins, C. A.; Khan, S.; Li, R.; Hreha, T. N.; Shen, Y.; Lin, Y.-N.; Letteri, R. A.; Su, L.; Dong, M.; Zhang, F.; Hunstad, D. A.; Wooley, K. L. Morphologic Design of Silver-Bearing Sugar-Based Polymer Nanoparticles for Uroepithelial Cell Binding and Antimicrobial Delivery. *Nano Lett.* **2021**, *21* (12), 4990–4998. https://doi.org/10.1021/acs.nanolett.1c00776.

(15) Haabeth, O. A. W.; Lohmeyer, J. J. K.; Sallets, A.; Blake, T. R.; Sagiv-Barfi, I.; Czerwinski, D. K.; McCarthy, B.; Powell, A. E.; Wender, P. A.; Waymouth, R. M.; Levy, R. An mRNA SARS-CoV-2 Vaccine Employing Charge-Altering Releasable Transporters with a TLR-9 Agonist Induces Neutralizing Antibodies and T Cell Memory. *ACS Cent. Sci.* **2021**, *7* (7), 1191–1204. https://doi.org/10.1021/acscentsci.1c00361.

(16) Zhang, J.; Lui, K. H.; Jadrich, C. N.; Jia, Y.; Arrechea, P. L.; Hedrick, J. L.; Waymouth, R. M. Contrasting Roles of Counterions in Anionic Ring-Opening Polymerization Mediated by Heterocycle Organocatalysts. *ACS Catal.* **2023**, *13* (24), 16097–16104. https://doi.org/10.1021/acscatal.3c04772.

(17) Lin, B.; Waymouth, R. M. Urea Anions: Simple, Fast, and Selective Catalysts for Ring-Opening Polymerizations. *J. Am. Chem. Soc.* **2017**, *139* (4), 1645–1652. https://doi.org/10.1021/jacs.6b11864.

(18) Jain, I.; Malik, P. Advances in Urea and Thiourea Catalyzed Ring Opening Polymerization: A Brief Overview. *Eur. Polym. J.* **2020**, *133*, 109791. https://doi.org/10.1016/j.eurpolymj.2020.109791.

(19) Lin, B.; Waymouth, R. M. Organic Ring-Opening Polymerization Catalysts: Reactivity Control by Balancing Acidity. *Macromolecules* **2018**, *51* (8), 2932–2938. https://doi.org/10.1021/acs.macromol.8b00540.

(20) Schreiner, P. R. Metal-Free Organocatalysis through Explicit Hydrogen Bonding Interactions. *Chem. Soc. Rev.* **2003**, *32* (5), 289. https://doi.org/10.1039/b107298f.

(21) Howlader, P.; Das, P.; Zangrando, E.; Mukherjee, P. S. Urea-Functionalized Self-Assembled Molecular Prism for Heterogeneous Catalysis in Water. *J. Am. Chem. Soc.* **2016**, *138* (5), 1668–1676. https://doi.org/10.1021/jacs.5b12237.

(22) Lombardo, V. M.; Dhulst, E. A.; Leitsch, E. K.; Wilmot, N.; Heath, W. H.; Gies, A. P.; Miller, M. D.; Torkelson, J. M.; Scheidt, K. A. Cooperative Catalysis of Cyclic Carbonate Ring Opening: Application Towards Non-Isocyanate Polyurethane Materials: Cooperative Catalysis of Cyclic Carbonate Ring Opening. *Eur. J. Org. Chem.* **2015**, *2015* (13), 2791–2795. https://doi.org/10.1002/ejoc.201500313.

(23) Zaky, M. S.; Wirotius, A.-L.; Coulembier, O.; Guichard, G.; Taton, D. 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. *ACS Macro Lett.* **2022**, *11* (9), 1148–1155. https://doi.org/10.1021/acsmacrolett.2c00457.

(24) Nederberg, F.; Lohmeijer, B. G. G.; Leibfarth, F.; Pratt, R. C.; Choi, J.; Dove, A. P.; Waymouth, R. M.; Hedrick, J. L. Organocatalytic Ring Opening Polymerization of Trimethylene Carbonate. *Biomacromolecules* **2007**, *8* (1), 153–160. https://doi.org/10.1021/bm060795n.

(25) 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* (31), 3777–3780. https://doi.org/10.1039/D0CC08022E.

(26) Liu, Y.; Zhang, J.; Kou, X.; Liu, S.; Li, Z. Highly Active Organocatalysts for Stereoselective Ring-Opening Polymerization of Racemic Lactide at Room Temperature. *ACS Macro Lett.* **2022**, *11* (10), 1183–1189. https://doi.org/10.1021/acsmacrolett.2c00425.

(27) Zaky, M. S.; Guichard, G.; Taton, D. Structural Effect of Organic Catalytic Pairs Based on Chiral Amino(Thio)Ureas and Phosphazene Bases for the Isoselective Ring-Opening Polymerization of

Racemic Lactide. *Macromolecules* **2023**, *56* (10), 3607–3616. https://doi.org/10.1021/acs.macromol.3c00462.
(28) Hua, G.; Franzén, J.; Odelius, K. Phosphazene-Catalyzed Regioselective Ring-Opening Polymerization of *Rac*-1-Methyl Trimethylene Carbonate: Colder and Less Is Better. *Macromolecules* **2019**, *52* (7), 2681–2690. https://doi.org/10.1021/acs.macromol.8b02591.
(29) Bandar, J. S.; Lambert, T. H. Enantioselective Brønsted Base Catalysis with Chiral Cyclopropenimines. *J. Am. Chem. Soc.* **2012**, *134* (12), 5552–5555. https://doi.org/10.1021/ja3015764.
(30) Nacsa, E. D.; Lambert, T. H. Higher-Order Cyclopropenimine Superbases: Direct Neutral Brønsted Base Catalyzed Michael Reactions with α-Aryl Esters. *J. Am. Chem. Soc.* **2015**, *137* (32), 10246–10253. https://doi.org/10.1021/jacs.5b05033.
(31) Stukenbroeker, T. S.; Bandar, J. S.; Zhang, X.; Lambert, T. H.; Waymouth, R. M. Cyclopropenimine Superbases: Competitive Initiation Processes in Lactide Polymerization. *ACS Macro Lett.* **2015**, *4* (8), 853–856. https://doi.org/10.1021/acsmacrolett.5b00421.
(32) Gutmann, V. Solvent Effects on the Reactivities of Organometallic Compounds. *Coord. Chem. Rev.* **1976**, *18* (2), 225–255. https://doi.org/10.1016/S0010-8545(00)82045-7.
(33) Cook, J. L.; Hunter, C. A.; Low, C. M. R.; Perez-Velasco, A.; Vinter, J. G. Solvent Effects on Hydrogen Bonding. *Angew. Chem. Int. Ed.* **2007**, *46* (20), 3706–3709. https://doi.org/10.1002/anie.200604966.
(34) Dove, A. P.; Pratt, R. C.; Lohmeijer, B. G. G.; Waymouth, R. M.; Hedrick, J. L. Thiourea-Based Bifunctional Organocatalysis: Supramolecular Recognition for Living Polymerization. *J. Am. Chem. Soc.* **2005**, *127* (40), 13798–13799. https://doi.org/10.1021/ja0543346.
(35) Chuma, A.; Horn, H. W.; Swope, W. C.; Pratt, R. C.; Zhang, L.; Lohmeijer, B. G. G.; Wade, C. G.; Waymouth, R. M.; Hedrick, J. L.; Rice, J. E. The Reaction Mechanism for the Organocatalytic Ring-Opening Polymerization of L-Lactide Using a Guanidine-Based Catalyst: Hydrogen-Bonded or Covalently Bound? *J. Am. Chem. Soc.* **2008**, *130* (21), 6749–6754. https://doi.org/10.1021/ja0764411.
(36) Suriano, F.; Coulembier, O.; Hedrick, J. L.; Dubois, P. Functionalized Cyclic Carbonates: From Synthesis and Metal-Free Catalyzed Ring-Opening Polymerization to Applications. *Polym Chem* **2011**, *2* (3), 528–533. https://doi.org/10.1039/C0PY00211A.
(37) Tempelaar, S.; Barker, I. A.; Truong, V. X.; Hall, D. J.; Mespouille, L.; Dubois, P.; Dove, A. P. Organocatalytic Synthesis and Post-Polymerization Functionalization of Propargyl-Functional Poly(Carbonate)s. *Polym Chem* **2013**, *4* (1), 174–183. https://doi.org/10.1039/C2PY20718D.
(38) Dai, Y.; Zhang, X. Recent Development of Functional Aliphatic Polycarbonates for the Construction of Amphiphilic Polymers. *Polym. Chem.* **2017**, *8* (48), 7429–7437. https://doi.org/10.1039/C7PY01815K.
(39) Jehanno, C.; Demarteau, J.; Mantione, D.; Arno, M. C.; Ruipérez, F.; Hedrick, J. L.; Dove, A. P.; Sardon, H. Synthesis of Functionalized Cyclic Carbonates through Commodity Polymer Upcycling. *ACS Macro Lett.* **2020**, *9* (4), 443–447. https://doi.org/10.1021/acsmacrolett.0c00164.
(40) Save, M.; Schappacher, M.; Soum, A. Controlled Ring-Opening Polymerization of Lactones and Lactides Initiated by Lanthanum Isopropoxide, 1. General Aspects and Kinetics. *Macromol. Chem. Phys.* **2002**, *203* (5–6), 889–899. https://doi.org/10.1002/1521-3935(20020401)203:5/6<889::AID-MACP889>3.0.CO;2-O.
(41) Kakuta, M.; Hirata, M.; Kimura, Y. Stereoblock Polylactides as High-Performance Bio-Based Polymers. *Polym. Rev.* **2009**, *49* (2), 107–140. https://doi.org/10.1080/15583720902834825.
(42) Stanford, M. J.; Dove, A. P. Stereocontrolled Ring-Opening Polymerisation of Lactide. *Chem Soc Rev* **2010**, *39* (2), 486–494. https://doi.org/10.1039/B815104K.
(43) Tschan, M. 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* (24), 13587–13608. https://doi.org/10.1039/D1CS00356A.

(44) Brintzinger, H. H.; Fischer, D.; Mülhaupt, R.; Rieger, B.; Waymouth, R. M. Stereospecific Olefin Polymerization with Chiral Metallocene Catalysts. *Angew. Chem. Int. Ed. Engl.* **1995**, *34* (11), 1143–1170. https://doi.org/10.1002/anie.199511431.
(45) Dove, A. P.; Li, H.; Pratt, R. C.; Lohmeijer, B. G. G.; Culkin, D. A.; Waymouth, R. M.; Hedrick, J. L. Stereoselective Polymerization of Rac- and Meso-Lactide Catalyzed by Sterically Encumbered N-Heterocyclic Carbenes. *Chem. Commun.* **2006**, No. 27, 2881. https://doi.org/10.1039/b601393g.
(46) Jensen, T. R.; Breyfogle, L. E.; Hillmyer, M. A.; Tolman, W. B. Stereoelective Polymerization of d,l-Lactide Using N-Heterocyclic Carbene Based Compounds. *Chem. Commun.* **2004**, No. 21, 2504. https://doi.org/10.1039/b405362a.
(47) Ikada, Y.; Jamshidi, K.; Tsuji, H.; Hyon, S. H. Stereocomplex Formation between Enantiomeric Poly(Lactides). *Macromolecules* **1987**, *20* (4), 904–906. https://doi.org/10.1021/ma00170a034.
(48) Tsuji, H.; Ikada, Y. Stereocomplex Formation between Enantiomeric Poly(Lactic Acid)s. 6. Binary Blends from Copolymers. *Macromolecules* **1992**, *25* (21), 5719–5723. https://doi.org/10.1021/ma00047a024.
(49) Tsuji, H.; Yamamoto, S.; Okumura, A.; Sugiura, Y. Heterostereocomplexation between Biodegradable and Optically Active Polyesters as a Versatile Preparation Method for Biodegradable Materials. *Biomacromolecules* **2010**, *11* (1), 252–258. https://doi.org/10.1021/bm901113v.
(50) Bandelli, D.; Alex, J.; Weber, C.; Schubert, U. S. Polyester Stereocomplexes Beyond PLA: Could Synthetic Opportunities Revolutionize Established Material Blending? *Macromol. Rapid Commun.* **2020**, *41* (1), 1900560. https://doi.org/10.1002/marc.201900560.
(51) Wang, X.; Prud'homme, R. E. Differences Between Stereocomplex Spherulites Obtained in Equimolar and Non-Equimolar Poly(L-lactide)/Poly(D-lactide) Blends. *Macromol. Chem. Phys.* **2011**, *212* (7), 691–698. https://doi.org/10.1002/macp.201000704.
(52) Shin, E. J.; Jones, A. E.; Waymouth, R. M. Stereocomplexation in Cyclic and Linear Polylactide Blends. *Macromolecules* **2012**, *45* (1), 595–598. https://doi.org/10.1021/ma202184j.
(53) Samuel, C.; Cayuela, J.; Barakat, I.; Müller, A. J.; Raquez, J.-M.; Dubois, P. Stereocomplexation of Polylactide Enhanced by Poly(Methyl Methacrylate): Improved Processability and Thermomechanical Properties of Stereocomplexable Polylactide-Based Materials. *ACS Appl. Mater. Interfaces* **2013**, *5* (22), 11797–11807. https://doi.org/10.1021/am403443m.
(54) Kurokawa, N.; Hotta, A. Thermomechanical Properties of Highly Transparent Self-Reinforced Polylactide Composites with Electrospun Stereocomplex Polylactide Nanofibers. *Polymer* **2018**, *153*, 214–222. https://doi.org/10.1016/j.polymer.2018.08.018.
(55) Cui, J.; Yang, S.-G.; Zhang, Q.; Liu, F.; Ungar, G. Poisoning by Purity: What Stops Stereocomplex Crystallization in Polylactide Racemate? *Macromolecules* **2023**, *56* (3), 989–998. https://doi.org/10.1021/acs.macromol.2c02067.
(56) Pothupitiya, J. U.; Hewawasam, R. S.; Kiesewetter, M. K. Urea and Thiourea H-Bond Donating Catalysts for Ring-Opening Polymerization: Mechanistic Insights via (Non)Linear Free Energy Relationships. *Macromolecules* **2018**, *51* (8), 3203–3211. https://doi.org/10.1021/acs.macromol.8b00321.