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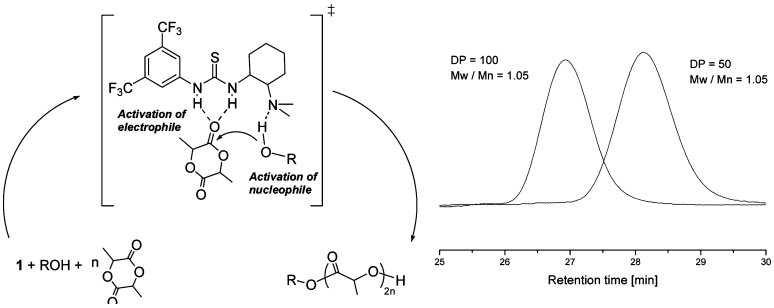

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Thiourea-Based Bifunctional Organocatalysis: Supramolecular Recognition for Living Polymerization

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The development of biodegradable polymers as resorbable biomaterials and, more recently, as commodity thermoplastics from renewable resources has received significant attention. Synthetic routes to these polyesters generally employ transition metal compounds to effect the ring-opening polymerization (ROP) of a cyclic ester monomer.[1] There has been a recent resurgence of interest in organocatalytic methods as an alternative to organometallic reagents.[2] These methods are proving particularly useful in situations where residual metals may compromise the purity of the product, an important consideration for microelectronic and biomedical applications. During our initial survey of a variety of organic catalysts for the ROP of cyclic esters, we showed that nucleophilic catalysts, such as tertiary amines, phosphines, and, in particular, stabilized singlet carbenes, were effective polymerization catalysts for strained cyclic esters.[3]

Catalysis employing hydrogen bonding for substrate activation has been shown to be an effective and versatile strategy in a wide variety of transformations, analogous to many enzymatic pathways.[4] Jacobsen[5] has exploited a variety of urea and thiourea-based catalysts for Strecker, Mannich, Pictet−Spengler, and hydrophosphonylation reactions. These catalysts were proposed to activate a variety of carbonyl and sulfoxide substrates for stereoselective C−C bond forming reactions.[5−7] Takemoto[8] demonstrated that chiral bifunctional organic catalysts containing thiourea and tertiary amino groups effectively activated nitro compounds for enantioselective aza-Henry and Michael reactions. Similarly, Berkessel[9] demonstrated the dynamic kinetic resolution of azalactones using urea-based chiral bifunctional catalysts. This catalyst motif is versatile in design as the hydrogen bonding group, and its strength can be tailored, as well as steric congestion, stereochemistry, etc. In our initial experiments, we used the bifunctional catalyst **1** developed by Takemoto (Scheme 1).[8] We anticipated that the thiourea and amine functional groups of these bifunctional catalysts could activate both the monomer and alcohol to catalyze the ROP of cyclic esters.

The catalytic behavior of **1** in the polymerization of lactide was studied in CH_2Cl_2 (1 M) at 25 °C using pyrenebutanol as the initiator in the presence of 5 mol % of **1**. At a monomer-to-initiator ratio of 100 ([M]/[I] = 100), lactide was converted to polylactide with 97% conversion after 48 h. The polylactide generated exhibited a number average molecular weight M_n = 23 000 g/mol (degree of polymerization DP = 100) with a very narrow polydispersity (M_w/M_n = 1.05; Table 1). The polymerization exhibited characteristics of a living polymerization as evidenced by the linear correlation between M_n (measured by ^{1}H NMR) and monomer conversion, the close correlation between the theoretical and experimental molecular weights, and polydispersities below 1.07 throughout the reaction (Figure 1).

Scheme 1. Thiourea−Amine Catalysts

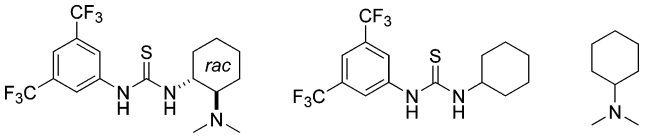

Table 1. Properties of Poly(lactide)s

[M]/[I]	time[a] (h)	conv %[b]	DP[b,c]	M_n GPC[d]	PDI[d]
20	24	97	21	5200	1.08
50	32	98	53	12300	1.05
100	48	97	103	23000	1.05
200	105	98	215	42000	1.05
500	144	95	*e*	*e*	*e*

[a] With 5 mol % of **1**; [LA] = 1 M in CH_2Cl_2. [b] Determined by ^{1}H NMR. [c] Degree of polymerization. [d] Determined by gel permeation chromatography. [e] Not soluble in THF.

Variation of the [M]/[I] ratio led to narrowly dispersed poly(lactide)s with molecular weights matching those predicted for DP's from 20 to 200 (Table 1). The polydispersities are extremely low and remained invariant at high monomer conversions (95−100%). For example, when poly(*rac*-lactide) (M_n = 21 300, M_w/M_n = 1.06, measured by GPC) was left to react with the catalyst for a further 4 days after complete monomer conversion, analysis of the polylactide revealed a M_n = 20 900 g/mol and PDI = 1.07; these results strongly imply that even after extended reaction periods minimal transesterification is observed. This was confirmed by ^{13}C NMR spectroscopy (Figure S1). Moreover, analysis of isotactic poly(L-lactide) by ^{13}C NMR spectroscopy and differential scanning calorimetry (T_m = 170 °C) clearly shows that racemization does not occur (Figures S1 and S4).

The extraordinary selectivity of this catalyst system for polymerization relative to transesterification is unusual. To test this, the reaction between methyl benzoate and either ethanol or 2-propanol in the presence of **1** (5 mol %, 1 M CH_2Cl_2) gave no evidence for transesterification (48 h) and resulted in the quantitative recovery of methyl benzoate. These data suggest that the low polydispersities and exceptional control observed are a consequence of selective transesterification of lactide relative to the open chain esters. Presumably, the ring strain of lactide provides both a driving force for the polymerization and a kinetic preference for polymerization relative to transesterification using catalyst **1**.

To further corroborate the living nature of the polymerization, a chain extension experiment was carried out. Polymerization of lactide using pyrene butanol as the initiator and 5 mol % of **1** with 100 equiv of lactide [M]/[I] = 100 yielded polylactide with a DP of 103 (^{1}H NMR) and a PDI of 1.05 after 48 h. An additional 100

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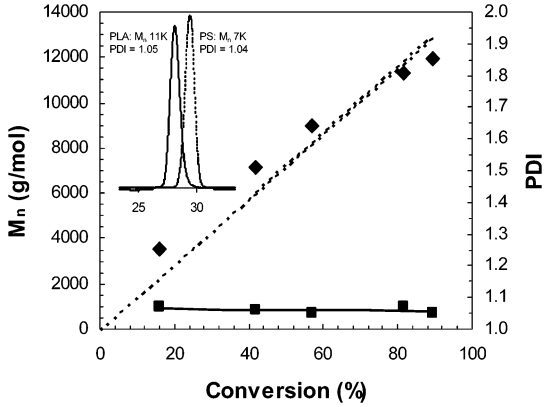


Figure 1. M_n (diamonds) and PDI (squares) versus % monomer conversion for polymerization of lactide with **1**. Theoretical M_n (dashed line). A typical GPC trace is shown together with a polystyrene standard to facilitate comparison.

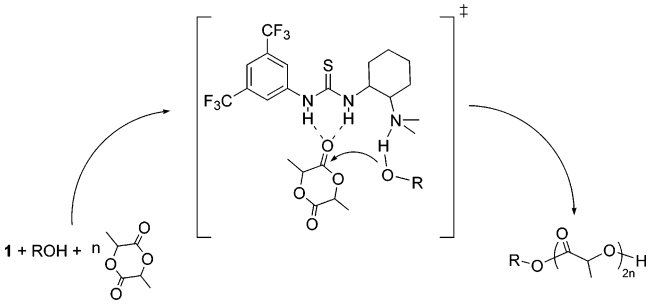
equiv of lactide was then added. After 48 h, the polylactide exhibited a DP of 215 (^{1}H NMR), and the polydispersity remained unchanged (1.05). This catalyst system is also effective for the synthesis of block copolymers; a hydroxyl-end-capped poly(*N*,*N*-dimethylacrylamide) macroinitiator (M_n = 4100 g/mol, PDI = 1.07) was used to initiate the polymerization of lactide using catalyst **1** or **2** in CH_2Cl_2 to generate poly(*N*,*N*-dimethylacrylamide)-*b*-poly(lactide) block copolymer. The resulting polymer had M_n = 16 900 g/mol, PDI = 1.07 after 72 h.

The initiation efficiency was investigated by analysis of the end-groups of a DP 20 polymer initiated from 4-pyrene-1-butanol by ^{1}H NMR spectroscopy. For this sample, the only end-groups observed were the α-ester from the initiating alcohol and the *β*-hydroxyl chain-ends, which is indicative of one initiator per polymer chain (Figure S2). In addition, analysis of the gel permeation chromatography (GPC) traces of the polymer using both refractive index and UV detectors (410 and 350 nm, respectively) clearly shows distribution of pyrene throughout the sample (Figure S3). This corroborates the ^{1}H NMR analysis and establishes the fidelity of initiation from the alcohol initiator. Moreover, a single turnover reaction using catalyst **1** (5% loading), lactide, and excess benzyl alcohol (1 M CH_2Cl_2) yielded the expected benzyl dilactate.

We postulate that catalysis proceeds by bifunctional activation of the carbonyl of a lactide monomer via hydrogen bonding to the thiourea group and of the initiating/propagating alcohol by the Bronsted basic (tertiary amino) group of the catalyst, similar to the mechanism proposed by Berkessel.[9] Nucleophilic ring-opening of the lactide leads to propagation, whereby the ring-opened lactide forms the propagating alcohol for the subsequent addition of monomer (Scheme 2).

The bifunctional nature of the catalysis was probed by attempts to polymerize lactide in the presence of (i) a thiourea, **2**; (ii) *N*,*N*-dimethylcyclohexylamine, **3**; and (iii) both **2** and **3**. Polymer was only obtained when **2** and **3** were present at the same time (M_n = 12 500, PDI = 1.1), indicating that the bifunctional nature of the catalyst is critical, but that both activating units are not required in a single catalyst. The implication that hydrogen bonding is critical for catalysis was studied by performing polymerizations in different solvents. Polymerization was observed in non-hydrogen bonding solvents, such as chloroform, methylene chloride, and toluene. In contrast, no polymerization was observed in tetrahydrofuran and

Scheme 2. Polymerization of Lactide by **1**



dimethylformamide (Table S1). As these solvents are likely to bind avidly to the thiourea, these results imply that the ability of the catalyst to activate the monomer through hydrogen bonding is essential for polymerization of lactide, consistent with the mechanism proposed in Scheme 2.

In summary, the bifunctional catalyst **1** exhibits exceptional selectivity in the ring-opening polymerization of lactide for the synthesis of well-defined poly(lactide)s of narrow polydispersity. While these catalysts exhibit lower activities than some of the more active transition metal[1] or organic catalysts,[3] the high selectivity for polymerization relative to transesterification provides exciting opportunities for the synthesis of well-defined polylactide architectures with end-group fidelity.

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Supporting Information Available: Figures S1−S4, Table S1, and the experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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