

Bredereck's Reagent Revisited: Latent Anionic Ring-Opening Polymerization and Transesterification Reactions

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Abstract: The ring-opening polymerization of lactide with commercially available Bredereck-type reagents in the presence or absence of alcohol initiators was carried out affording polylactide with controlled molecular weight and narrow polydispersities. An anionic mechanism involving heterolytic cleavage to alkoxides is proposed, where these reagents function as latent anionic initiators for the ring-opening polymerization of lactide.

Keywords: anionic polymerization; Bredereck's reagent; carbene; organic catalysis; polylactide

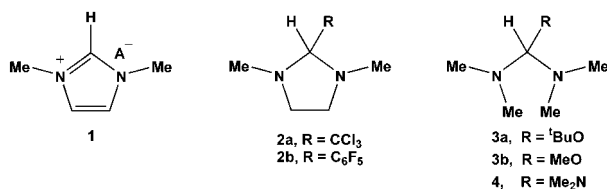
There has been a recent resurgence of interest in the development of organocatalytic reactions. Catalysis with simple organic molecules can provide an attractive alternative to organometallic catalysis, particularly in situations where residual metals or ligands compromise the purity or end-use of the product. Representative recent examples include MacMillan's elegant studies of highly enantioselective organocatalytic inter- and intramolecular Diels–Alders reactions, 1,3-dipolar cycloadditions, 1,4-conjugate Friedel–Crafts additions as well as the alkylation of indoles.^[1,2,3] Proline has proven to be an efficient organic catalyst for a variety of reactions such as the Mannich reaction to generate precursors to β -lactams,^[3] and several groups have reported effective non-enzymatic catalysts for the kinetic resolution of secondary alcohols using both “planar-chiral” phosphines^[4] and amine catalyst frameworks.^[2,5] Miller has devised several new functional peptides that catalyze the kinetic resolution of selected secondary alcohols^[6] as well as a variety of other transformations.^[7] Other noteworthy examples of organic catalysts include those of Fuji,^[8] Spivey,^[9] Oriyama,^[10] Vedejs,^[11] Breslow,^[12] Enders,^[13] and Rovis^[14] as well as extensive studies of biocatalysts.^[15]

We were recently challenged to develop effective organic polymerization reactions in an effort to develop

new materials for microelectronics, where residual metals must be avoided. During our initial survey of a variety of organic catalysts for the ring-opening polymerization (ROP) of cyclic esters we showed that nucleophilic catalysts such as tertiary amines,^[16] phosphines^[17] and stabilized singlet carbenes were effective polymerization catalysts for strained cyclic esters.^[18] Of these, the N-heterocyclic carbenes (NHCs) were by far the most active. Extensions of this work demonstrated that NHCs are also potent transesterification catalysts^[19] for a variety of esters and alcohols. Nevertheless, while NHCs are excellent transesterification catalysts, the convenience of these species as catalysts is compromised by their sensitivity to air and moisture, necessitating air-sensitive techniques. To this end, we have focused on strategies for generating the reactive N-heterocyclic carbenes *in situ*,^[20] including the deprotonation of imidazolium salts (**1**),^[21] or the thermolysis of adducts (**2**).^[22] Inspired by some of the original work of Arduengo, Wanzlick, Lappert and Bredereck,^[23,24,25] we reasoned that the commercially available compounds, *tert*-butoxybis(dimethylamino)methane (**3a**, also known as Bredereck's reagent), and tris(dimethylamino)methane (**4**),^[24,25] are reminiscent of other protected forms of N-heterocyclic carbenes^[20,22] and might be expected to show similar reactivity.

Alternatively, amination esters such as **3** and amide acetals such as **5** are known to thermally eliminate alkoxides and stabilized carbonium ions,^[24, 25, 31] and thus these reagents could also function as “latent” initiators^[27] for the anionic polymerization of cyclic esters.^[26] Here, we describe the use of Bredereck's reagent and related compounds as initiators for the ring-opening polymerization of cyclic esters and our initial studies on the mechanism of the polymerization.

The solution polymerization of L-lactide was investigated using a variety of alcohols as initiators in THF. Polymerizations were conducted in an inert atmosphere at 70 °C for 3 hours and quenched by the addition of a drop of water (Table 1). Alternatively, polymerization vials were placed directly into a vacuum oven at 70 °C



Scheme 1. Potential precursors to *N*-heterocyclic carbenes.

Table 1. Polymerization of lactide with **3** and **4**.^[a]

Catalyst	Conditions	DP	M_w/M_n	Yield/%
	THF, 70 °C, 3h	70	1.09	76
	THF, 70 °C, vacuum, 10 min	50	1.12	60
	THF, 70 °C, 3h	70	1.11	91
	THF, 70 °C, vacuum, 10 min	95	1.11	96

^[a] Catalyst/initiator ratio = 1.5, $[M]_0/[I]_0 = 100$.

where near quantitative monomer conversion (~94–99%) was realized within 15–20 min. concurrent with evaporation of the solvent. The latter polymerization conditions were primarily used to screen different conditions. The catalyst/initiator ratio investigated ranged from 0.5 to 2.0 for each catalyst; under these conditions, optimal results were obtained at a catalyst/initiator ratio of 1.5.

The polymer molecular weights of the ring-opened cyclic esters closely tracked the monomer to initiator ratio (M/I) and yield consistently narrow polydispersities (Figure 1). The GPC traces of polylactide initiated from 1-pyrenebutanol and catalyzed by either **3** or **4** using both the refractive index and UV detectors (410 and 350 nm) show the distribution of pyrene throughout the sample (Figure 2) and corroborate ¹H NMR studies indicating the presence of one initiator per polymer chain. These results reveal that these commercially available reagents are effective catalysts for controlled polymerizations to polylactides, an important class of biodegradable, biocompatible, and bio-renewable materials.^[28]

To illustrate the generality of this method, we also briefly investigated the activity of **3a** and **4** for other transesterification reactions. The condensation of dimethyl terephthalate with excess ethylene glycol in THF at 70 °C (3 h) in the presence of **3a** or **4** (3.5–5.0 mol %) cleanly generated bis(2-hydroxyethyl) tere-

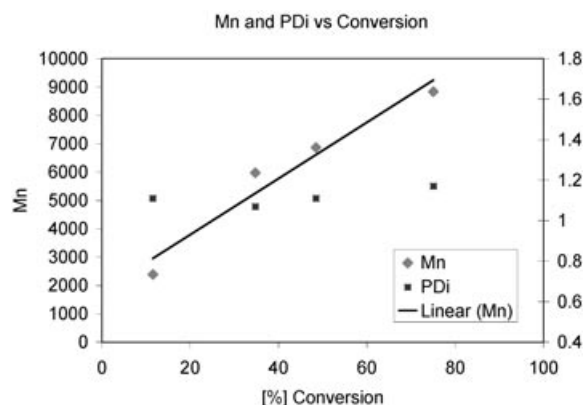


Figure 1. Plot of M_n and PDI versus conversion.

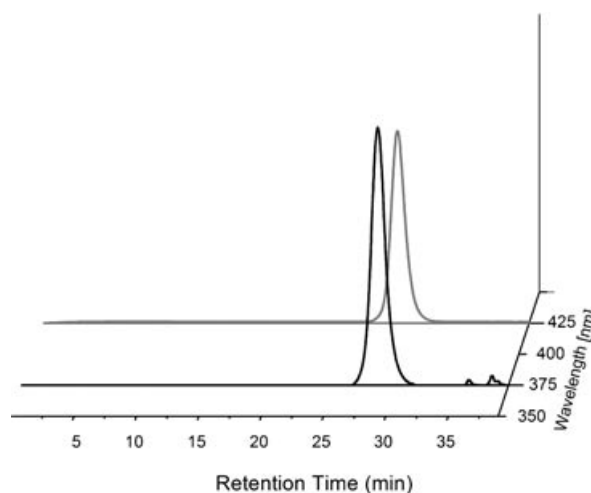
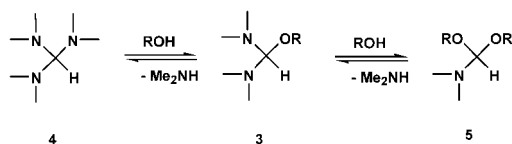


Figure 2. GPC trace of polylactide initiated from 1-pyrenebutanol.

phthalate, an important intermediate in the formation of poly(ethylene terephthalate), in 70 and 72% isolated yields, respectively.

The chemistry of orthoamides, aminal esters, and amide acetals has been investigated in detail^[24,25] as reagents in organic chemistry, but we are unaware of examples where these species have been used for polymerization reactions. Commercial samples of Bredereck's reagent **3a** are typically mixtures of **3a**, **4** and bis(*tert*-butoxy)dimethylaminomethane, due to the well-known equilibration of these species in the presence of proton sources (Scheme 2).^[24,25] Thus, polymerizations catalyzed by **3a** or **4** in the presence of alcohol initiators likely lead to an equilibrium mixture of **3a**, **4**, and **5a** ($R = t\text{-Bu}$).

To assess which of these intermediates is the likely catalyst precursor, we independently prepared the *N,N*-dimethylformamide dimethyl acetal **5b** ($R = \text{Me}$)^[25] and methoxybis(dimethylamino)-methane **3b** ($R = \text{Me}$)^[29] and investigated their activity for the polymerization of lactide. These experiments were carried out *in the absence of an alcohol initiator* as we anticipated that these



Scheme 2. The Bredereck equilibria.

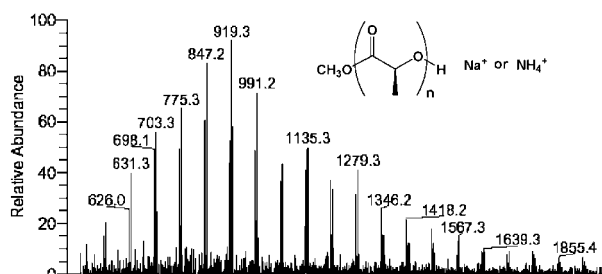


Figure 3. +ESI mass spectrum of oligolactide.

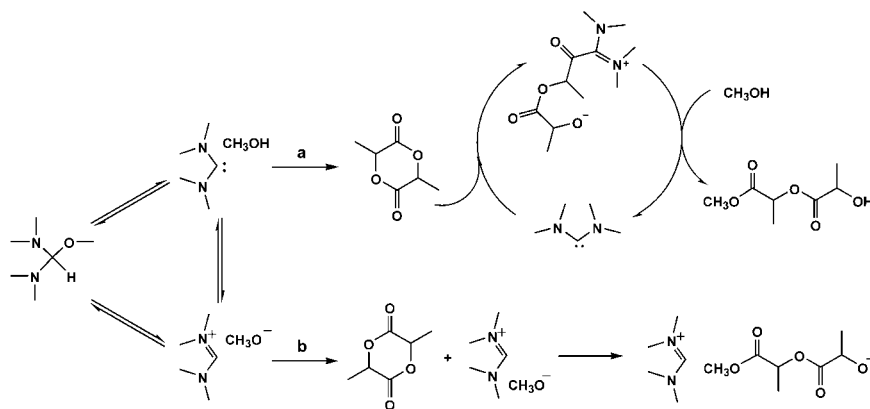
species might be able to function both as catalysts and initiators for ring-opening reactions. At 70 °C in THF, neither orthoamide **4** nor the amide acetal **5b** showed any activity for the ring-opening of lactide in the absence of an alcohol initiator; **5b** was also inactive in the presence of alcohol initiators, indicating that this compound is likely a dormant species. In contrast, the aminal ester **3b** initiated the polymerization of lactide in the absence of an added alcohol initiator within 15 min at 70 °C to give a 68% yield of isolated polylactide (DP = 75) with a polydispersity of 1.18. Analysis of oligomers produced from **3b** at an initial monomer/initiator ratio $[M]_0/[I]_0 = 10$ by ^1H NMR shows a characteristic methyl peak at 3.67 ppm in CDCl_3 , which was assigned to the methyl ester end group. The +ESI mass spectrum also shows methoxy-terminated oligomers charged with either sodium or ammonium cations (Figure 3). The observation of odd-numbered oligomers reveals that under these conditions (15 min, 70 °C) transesterification reactions have occurred. These results reveal that the aminal ester

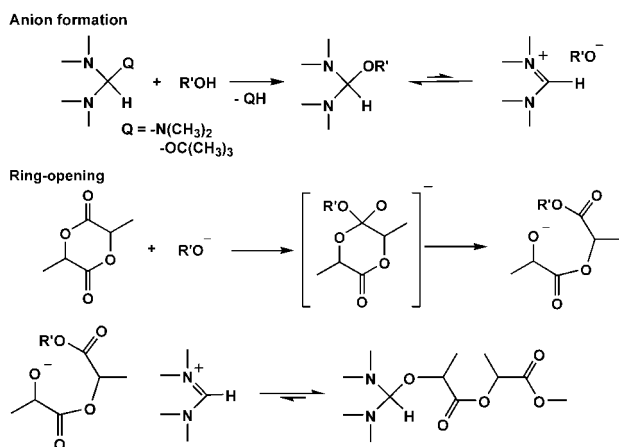
3b, the methoxy analogue of the Bredereck reagent, functions as a single-component initiator for the controlled polymerization of lactide, whereas the orthoamide **4** and amino acetal **5b** are inactive.

As the Bredereck reagent **3a** and **4** are known to react with enolizable ketones and esters,^[24,25] we carried out labeling experiments to test for the enolization of lactide. Ring-opening of lactide with 10 equivs. of CH_3OD in the presence of **4** at 25 °C in $\text{THF-}d_8$ cleanly afforded methyl lactate, a trace amount of methyl dilactate, aminal ester **3b**, amide acetal **5b**, and dimethylamine after 10 min. Analysis of this reaction by ^1H NMR showed no evidence for deuterium incorporation at the α -position of methyl lactate indicating that under these conditions, ring-opening of lactide is faster than enolization.

The polymerization of lactide in the presence of either **3** or **4** and alcohol could proceed by either a nucleophilic or anionic mechanism. If **3b** is indeed a precursor to a stabilized carbene, then the ring-opening of lactide could proceed *via* a nucleophilic pathway as outlined in Scheme 3, path a. Alternatively, aminal esters are known to cleave heterolytically to generate alkoxides and the formamidine salts,^[31] and thus could function as latent anionic initiators^[27] for ring-opening polymerization (Scheme 3, path b).

In an effort to assess whether **4** might provide a source of carbene, we investigated the thermolysis of **4** in the presence and absence of diethylamine. Thermolysis of **4** at 130 °C under vacuum led to quantitative recovery of **4** with no evidence for the generation of the carbene or the stable tetrakis(*N,N*-dimethylamino)ethylene, a known reaction product of dialkylamino carbenes.^[30] Likewise, thermolysis of **4** in the presence of diethylamine in benzene- d_6 at 80 °C gave no evidence for amine exchange. However, deuterium incorporation was observed into **3b** and **5b** upon reaction of **4** with lactide and CH_3OD . The incorporation of deuterium into **3b** and **5b** is most readily explained by the reversible elimination of methanol from **3b** to generate a small amount

Scheme 3. Possible pathways for ring-opening polymerization by **3b**.



Scheme 4. Proposed mechanism for ROP by **3** and **4**.

of the bis(dimethylamino)carbene^[31] which exchanges with CH₃OD (Scheme 3). Brown has investigated the reversible formation of formamidinium ion and carbene intermediates from **5b** in methanol solution^[31] and found that both processes compete but that the formation of methoxide salt is much faster than the formation of the corresponding carbene.

Neither mechanism is ruled out by these experiments; nevertheless, we currently favor a latent anionic mechanism for the polymerization of lactide by **3a** and **4** (Scheme 4).^[32] The reaction of **3a** or **4** with a primary alcohol initiator yields the aminate ester **3b**, which we propose is in equilibrium with the formamidinium salt of the alkoxide.^[24,25,31] Ring-opening of the lactide by the alkoxide provides a propagating anion. This anion can continue to ring-open lactide through an anionic mechanism. As the formamidinium counterion is also an electrophile, it is possible that the propagating anion is reversibly captured by the counterion, leading to reversible deactivation of the propagating anion. While we have no definitive evidence for the reversible capture of the propagating anion, it seems likely in view of the well-known chemistry of formamidinium species^[24,25,31] and may be partially responsible for the exceptional control that we observe for the ring-opening polymerizations observed in the presence of **3** and **4**.

In summary, the ring-opening polymerization of lactide with commercially available Bredereck-type reagents in the presence of or absence of alcohol initiators is an efficient method for the synthesis of polylactides of controlled molecular weight and narrow polydispersities. Although these compounds were initially envisioned as precursors to stabilized carbenes, alternative mechanisms involving heterolytic cleavage to alkoxides are likely competitive, suggesting that these reagents can function as latent anionic initiators for ring-opening polymerization reactions.

Experimental Section

General Remarks

Commercial reagents and solvents were purchased from Aldrich and used without further purification. Deuterated NMR solvents were purchased from Cambridge Isotope Laboratories, Inc. ¹H and ¹³C nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance 400 or Varian 300 spectrometer. ¹H and ¹³C NMR chemical shifts were referenced to the residual solvent peak. Gel permeation chromatography was performed in tetrahydrofuran (THF) on a Waters chromatograph equipped with four 5-μm Waters columns (300 mm × 7.7 mm) connected in series with increasing pore size (10, 100, 1000, 10⁵, 10⁶ Å). A Waters 410 differential refractometer and 996 photodiode array detector were employed. Modulated differential scanning calorimetry (MDSC) measurements were recorded on a TA Instruments DSC 2920 with a ramp rate of 10 degrees per minute under a nitrogen atmosphere. Thermal gravimetric analysis (TGA) measurements were recorded on a TA Instruments Hi-Res 2950 with a ramp rate of 10 degrees per minute under a nitrogen purge.

General Procedure for the ROP of Lactide

A vial equipped with a stir bar was charged with L-lactide (400 mg, 2.8 mmol) and dissolved in 1 mL of anhydrous THF. To this solution, **3a** (8.6 mL, 0.042 mmol) was added followed by the addition of benzyl alcohol (2.9 μL, 0.028 mmol). The reaction mixture was sealed and heated to 70 °C for 3 h, and the reaction was terminated by the addition of a drop of water. The polymer was precipitated in methanol and dried to a constant weight. ¹H NMR (CD₃COCD₃, 400 MHz): δ = 1.46–1.56 (m, 3H, CH₃), 5.05–5.25 (m, H, CH).

Transesterification of Dimethyl Terephthalate

A vial equipped with a stir bar was charged with dimethyl terephthalate (0.2 g, 0.001 mol), excess ethylene glycol (1.24 g, 0.02 mol) in THF and reacted at 70 °C (6 h) in the presence of either **3a** (0.05 mmol, 0.011 g) or **4** (0.05 mmol, 0.01 g). Bis(2-hydroxyethyl) terephthalate was isolated in 70 and 72% yield, respectively. ¹H NMR (CDCl₃, 400 MHz): δ = 3.99 (t, *J* = 4.550 Hz, 2H, CH₂), 4.50 (t, *J* = 4.775 Hz, 2H, CH₂), 8.12 (s, 2H, Ar).

Preparation of Methoxybis(dimethylamino)-methane (**3b**)

N,N,N',N'-Tetramethylformamidinium chloride (411 mg, 3 mmol) and sodium methoxide (162 mg, 3 mmol) were measured into a Schlenk flask in a dry-box and 15 mL THF were added. The mixture was stirred at 21 °C overnight and the solution was filtered. 150 μL were diluted with THF-*d*₈ and ¹H NMR revealed the formation of **3b** as a 5:1:1 mixture of **3b**, **4**, and **5b** in THF (0.3 mol/dm³). The solution was used in the ROP of lactide without further purification. ¹H NMR (CDCl₃, 299.947 MHz): δ (**3b**) = 2.24 (s, 12H, NCH₃), 3.34 (s,

3H, OCH₃), 3.55 (s, 1H, CH); 5b δ = 2.19 (s, 6H, NCH₃), 3.21 (s, 6H, OCH₃), 4.30 (s, 1H, CH); 4 δ = 2.29 (s, 18H, NCH₃), 3.22 (s, 1H, CH).

Ring-Opening of Lactide in the Presence of CH₃OD

Tris(dimethylamino)methane (**4**; 17.8 mg, 123 μ mol) and L-lactide (17.7 mg, 123 μ mol) were dissolved in THF-*d*₈ (300 μ L) and CH₃OD (50 μ L, 1.23 mmol) was added. After 10 min ¹H NMR analysis revealed the formation of methyl lactate, a trace amount of methyl dilactate, aminal ester **3b**, amide acetal **5b**, and dimethylamine. Integration of the methine protons of **3b** and **5b** relative to the corresponding methoxy protons revealed approximately 75% and 60% deuterium incorporation into **3b** and **5b**, respectively. ¹H NMR (CDCl₃, 300 MHz): δ (methyl lactate) = 1.28 (d, *J* = 7 Hz, 3H, CH₃), 3.34 (q, *J* = 7 Hz, H, CH); δ (methyl dilactate) = 1.35 (d, *J* = 7 Hz, 3H, CH₃), 1.43 (d, *J* = 7.0 Hz, 3H, CH₃), 4.22 (q, *J* = 7 Hz, 1H, CH), 5.06 (q, *J* = 7 Hz, 1H, CH). The deuterium incorporation was also confirmed by GC-MS.

Thermolysis of Tris(dimethylamino)methane (**4**)

Tris(dimethylamino)methane (0.25 mL, 1.7 mmol) was measured into an NMR tube closed with a J-Young valve and heated to 130 °C. The tube was placed under vacuum briefly every 10 minutes. After an hour, the remaining liquid (~30 μ L) was dissolved in benzene-*d*₆ (0.3 mL) and the ¹H NMR spectrum was recorded. Only **4** was observed. ¹H NMR (C₆D₆, 300 MHz): δ = 2.32 (s, 18H, NCH₃), 3.02 (s, 1H, CH).

Attempted Exchange Reaction between Tris(dimethylamino)methane and Diethylamine

Tris(dimethylamino)methane (42 mg, 0.29 mmol) and diethylamine (41 μ L, 0.29 mmol) were measured into an NMR tube closed with a J-Young valve, dissolved in benzene-*d*₆ (0.3 mL) and heated up to 80 °C. After 30 min the ¹H NMR spectrum was recorded. Only the starting materials were observed.

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