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In Situ Generation of Carbenes: A General and Versatile Platform for Organocatalytic Living Polymerization

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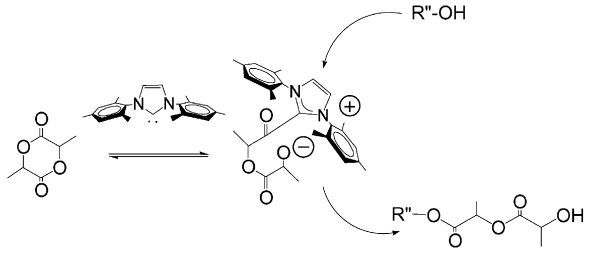
Abstract: A metal-free, organocatalytic approach to living polymerization using *N*-heterocyclic carbenes as nucleophilic catalysts generated and used in situ in a single-pot process is detailed. The *N*-heterocyclic carbene catalyst platform is extremely versatile, as the nature of the substituents has a pronounced effect of catalyst stability and activity toward different substrates. The generation of imidazolium- and thiazaolium-based carbenes was accomplished from the reaction of the corresponding salts with the appropriate bases. This allowed the rapid screening of libraries of catalysts that provided a basic understanding of catalyst structure (sterics, electronics, etc.) with the polymerization rate, control, substrate, and range of molecular weights. The imidazole-based catalysts were significantly more active toward ROP than the thiazolium-based analogues. No appreciable differences between imidazol-2-ylidene and imidazolin-2-ylidene catalysts were observed. Less sterically demanding carbenes were found to be more active toward ring-opening polymerization (ROP) than their sterically encumbered analogues for lactone polymerization. These data prompted the investigation of ionic liquid as a precatalyst reservoir in a phase-transfer polymerization with an immiscible THF solution of monomer and initiator. In situ activation of the ionic liquid generates carbene that migrates to the organic phase effecting living ROP. Precatalyst (ionic liquid) regeneration terminates polymerization. This simple reaction/recycle protocol readily allows repetitive ROPs from the ionic liquid using commercially available materials.

Introduction

Growing trends in asymmetric synthesis for classic reactions that use simple organic molecules as promoters have provided an organocatalytic alternative to traditional organometallic reagents.[1] Simple organic molecules, in enantiomerically pure form, have demonstrated high reactivity and stereospecificity for a number of useful organic transformations.[2] We have recently demonstrated that nucleophilic *N*-heterocyclic carbenes are active catalysts for the living polymerization of cyclic esters and transesterification reactions[3,4] (Scheme 1). These organic catalysts are inexpensive, highly active, and yield polymers of well-defined molecular weight with narrow polydispersities, characteristic of a living polymerization system. As such, they provide an attractive alternative to metal catalysts[5,6] for ring-opening polymerizations (ROPs) for biomedical or microelectronic applications.

Scheme 1



Since the initial description of the synthesis, isolation, and characterization of stable carbenes by Arduengo,[7] the exploration of their versatility and chemical reactivity has become a major

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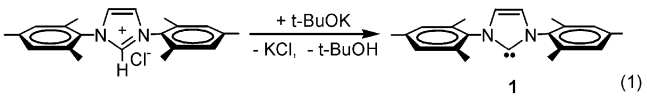
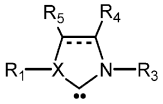
area of research.[8] It has been recognized in organometallic chemistry that the use of *N*-heterocyclic carbenes to replace the electron rich phosphine ligands produces transition metal complexes that manifest enhanced catalytic performances and stability.[9] However, the isolation of *N*-heterocyclic carbenes is complicated by their extreme air and moisture sensitivity. Recent investigations by Grubbs and others demonstrated that free carbenes can be generated in situ and directly used to form *N*-heterocyclic carbene-coordinated catalysts in a greatly simplified process, eq 1.[10] Likewise, the in situ formation of triazolium carbenes from their respective salts have been employed as catalyst for asymmetric Stetter and benzoin condensation reactions.[11]



1 (1)

The high reactivity of the 1,3-bis(2,4,6-trimethylphenyl)-imidazol-2-ylidene, **1**, for the ring-opening polymerization of lactide inspired us to investigate the scope and generality of the carbene-catalyzed ring-opening polymerization reactions. Carbenes can be synthesized with considerable diversity by varying the heteroatom in the ring (X = N or S), the steric arrrangement and electronics of the groups attatched to the imidazole ring ($R_{4,5}$) and the nitrogen(s) ($R_{1,3}$), and the ethylene backbone (i.e., saturated vs unsaturated) (Scheme 2). We envision that the carbene catalyst platform has the potential to become a general methodology for the ROP of a variety of cyclic esters in much the same way that controlled radical polymerization procedures are to vinyl monomers.[12] One of our objectives is to bring this catalyst framework to a level of maturity that would enable semiautomatic or combinatory procedures for materials discovery. We were prompted to examine in situ methods for generating carbene catalysts to avoid the difficulty of isolating sensitive carbene complexes and to facilitate polymerization studies.[10] Herein, we report a general strategy for the ring-opening polymerization of strained cyclic esters by in situ activiation of thiazolium, imidazolium and imidazolinium precursors in solution, along with biphasic phase-transfer polymerization strategy using a recyclable catalyst precursor.

Scheme 2



X = N or S (if S then no R_1)
$R_{4\text{-}5}$ = unsaturated, saturated, electron withdrawing groups
$R_{1,3}$ = optimize steric bulk

Experimental Section

Materials. The L- and D,L-lactide were purchased from Purac and were recrystallized from toluene 3 times prior to use and stored in a glovebox. Benzyl alcohol was refluxed over CaH_2 overnight and then distilled from calcium hydride. Poly(ethylene glycol monomethyl ether) with an average molecular weight of 1900 g/mol was purchased from Polysciences, Inc. and was recrystallized from toluene 3 times prior to use and stored in a glovebox. Toluene was dried by refluxing over sodium/potassium alloy and distilled prior to use. THF was dried by refluxing over sodium and distilled prior to use. 1,3-(2,4,6-trimethylphenyl)imidazolium chloride, 1,3-(2,4,6-trimethylphenyl)imidazolinium chloride, and 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride were prepared according to literature procedures.[13] 1,3,4,5-Tetramethylimidazol-2-ylidene[14] and 1-ethyl-3-methyl-1-*H*-imidazolium tetrafluoroborate[15] were prepared as previously described. 1-Ethyl-3-methyl-1-*H*-imidazolium chloride was purchased from Aldrich and used without further purification.

General Procedure for In Situ Thiazolium-Based Catalyst Formation and Solution Polymerization of L-Lactide. In the glovebox, a vial equipped with a stirbar was charged with 3-methylbenzothiazolium (63 μg, 0.23 μmol), benzyl alcohol (5 mg, 46 μmol), and L-lactide (400 mg, 2.7 mmol) and dissolved in 2 mL of CH_2Cl_2. Triethylamine (1.15 μg, 1.15 μmol) was added, and the solution turned from a light yellow color to a dark orange/red color. The reaction was allowed to proceed for 2 to 4 days, depending on the targeted molecular weight, at room temperature, precipitated in cold hexanes, and dried to a constant weight.

General Procedure for In Situ Imidazolium- and Imidazolinium-Based Catalyst Formation and Solution Polymerization of L-Lactide. In the glovebox, a vial equipped with a stirbar was charged with 1,3-

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bis(2,4,6-timethylphenyl)imidazolium chloride salt (8.2 mg, 24 μmol) and potassium *tert*-butoxide (2.4 mg, 21 μmol). THF (2 mL) was added, and the reaction was stirred for 10 min. After 10 min, a light yellow solution was observed. The reaction mixture was filtered through a 10 μm filter. Benzyl alcohol (1.5 mg, 14.4 μmol) was added by microsyringe. To the stirring reaction mixture a solution of L-lactide, (400 mg, 2.7 mmol) dissolved in 3 mL of THF, was added. After completion, the reaction was quenched with a drop of water. The polymer was precipitated from methanol and dried to a constant weight.

General Procedure for In Situ Imidazolium- and Imidazolinium-Based Catalyst Formation and Solution Polymerization of Lactones. In the glovebox, a vial equipped with a stirbar was charged with 1,3-dimethylimidazolium iodide salt (11.0 mg, 50 μmol) and potassium *tert*-butoxide (5 mg, 44 μmol). THF (2 mL) was added, and the reaction was stirred for 10 min. After 10 min, a light yellow solution was observed. The reaction mixture was filtered through a 10 μm filter. Benzyl alcohol (5 mg, 46 μmol) was added by microsyringe. ϵ-Caprolactone (1.05 g, 9.2 mmol) was then added to the stirring catalyst mixture. After completion, the reaction was quenched with a drop of water. The polymer was precipitated from methanol and dried to a constant weight.

General Procedure for Synthesis of Lactone−Lactide Block Copolymers. In the glovebox, 1,3-bis(phenyl)imidazolinium chloride (7.5 mg, 0.029 mmol) and postassium *tert*-butoxide (2.5 mg, 0.022 mmol) were combined with 4 mL of THF in a vial equipped with a stirbar. The reaction was stirred for 10 min and then filtered through a 10 μm filter to yield a clear light yellow solution. Benzyl alcohol (3.1 mg, 0.029 mmol) was then added to the catalyst solution. To the stirring catalyst/alcohol solution was added ϵ-caprolactone (330 mg, 2.9 mmol). The reaction mixture became extremely viscous within 1 min. After 2 h, an aliquot was removed from the reaction vessel and analyzed by ^{1}H NMR and GPC. L-Lactide monomer (389 mg, 2.9 mmol) was then added to the reaction. After 18 h, the reaction was quenched with a drop of water and the polymer was precipitated from cold methanol.

General Procedure for Synthesis of Poly(ethylene glycol)−ϵ-Caprolactone Block Copolymers. In the glovebox, 1,3-dimethylimidazolium iodide salt (25.0 mg, 110 μmol) and potassium *tert*-butoxide (10 mg, 90 μmol) were combined with 2 mL of dry THF in a vial equipped with a stirbar. The reaction was stirred for 20 min and then filtered through a 1.0 μm filter to yield a clear light yellow solution. Poly(ethylene glycol monomethyl ether) (M_n = 1900 av, 150 mg, 0.079 μmol) was then added to the catalyst solution. To the stirring catalyst/PEG-initiator solution was added ϵ-caprolactone (1.13 g, 9.9 mmol). The reaction mixture became extremely viscous within 5 min. After 12 h, the reaction was quenched with a drop of water and the polymer was precipitated from cold methanol. The material was then dried using reduced pressure. Isolated yield 95%. ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) selected assignments (3.99 (t) [2H]; 3.58 (s) [4H, PEG]; 2.24 (t) [2H]; 1.54−1.61 (m) [4H]; 1.27−1.33 (m) [2H]). GPC (THF) M_n = 15 000, PDI = 1.13.

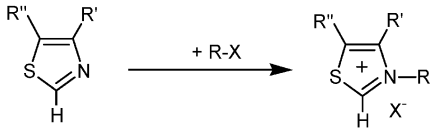
General Procedure for Macromonomer Formation and Graft Copolymerization. In the glovebox, an anhydrous solution of norbornene alcohol (bicyclo-hept[2,2,1]-2-ene-5-methanol) (0.228 g, 0.00 183 mol) in 2 g of THF was added to 0.0025 g (8.27×10^{-6} mol) of 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene to give a yellow colored solution. L-Lactide (2 g, 0.0138 mol, 10 equiv with respect to alcohol) was dissolved in 6 g of THF and then added to the alcohol/catalyst solution. The reaction was stirred for 2 h. The mixture was then taken out of the glovebox, another 5 mL of THF was added, and then the norbornene macromonomer was precipitated from hexanes to give a white material. The material was then dried using reduced pressure. Isolated yield 85%. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 C) selected assignments (6.12 (m), 6.05 (s), 5.89 (m) [2H]), 5.20−5.09 (q, 10H), (4.34−4.31 (q), 3.69−3.73 (q) [2H]), 2.81 (m), 2.32 (m), 2.32 (s), 2.15 (s), 1.82−1.79 (br), 1.58−1.56 (d, 30H), 1.41 (br). GPC M_n = 2500, PDI = 1.12. In a glovebox, the norbornene macromonomer (0.22 g) was dissolved in anhydrous toluene. In a separate vial, commercially available Grubbs catalyst $RuCl_2(PPCy_3)_2$=CHPh (Strem Chemicals) (0.17 g) was dissolved in 2.7 g of toluene. The monomer was added to the catalyst and allowed to stir for 30 min at 50 °C in a sealed reaction flask under an inert atmosphere. The reaction was terminated by the addition of ethyl-vinyl ether. The polymer was precipitated from methanol, filtered, and then dried under reduced pressure. Isolated yield 90%. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 C) selected assignments 5.5−5.2 (br), 5.20−5.09 (br, lactide CH), 4.3−3.7 (br), 1.82−1.79 (br), 1.58−1.56 (br, lactide CH_3), 1.41 (br). GPC M_n = 26 000, PDI = 1.10.

General Procedure for Interfacial/Biphasic L-Lactide Polymerization. In the glovebox, potassium *tert*-butoxide (10 mg, 0.09 mmol) was placed in a 5 mL vial and dissolved in a drop of THF. [emim]-[BF_4] (1.0 g, 5.0 mmol) was placed in the vial and stirred for 30 min. THF (5 mL) and benzyl alcohol (2.3 mg, 0.2 mmol) was added to the vial to form two layers. L-Lactide (610 mg, 4.2 mmol) was then added, and the reaction mixture was stirred for 20 min. The THF layer was noticeably viscous. The reaction mixture was quenched with a small portion of NH_4BF_4, and the THF layer extracted. The ionic layer was extracted 1−2 times with THF. The ionic liquid was then ready to begin another polymerization experiment. No evidence of monomer or polymer was observed in the ^{1}H NMR spectrum of the ionic liquid layer. The polymer was precipitated from cold methanol and dried to a constant weight.

Characterization. ^{1}H NMR spectra were recorded in either $CDCl_3$ or acetone-d_6 with a Bruker Avance 2000 (400 MHz) spectrometer with the solvent proton signal as an internal standard. ^{13}C NMR spectra were recorded at 100 MHz on a Bruker Avance 2000 spectrometer with the solvent carbon signal as internal standard. Gel permeation chromatography (GPC) or size exclusion chromatography (SEC) were carried out on a Waters chromatography instrument connected to a Waters 410 differential refractometer. Polystyrene samples of known molecular weight were used as calibration standards. Four 5 μm Waters columns (300 × 7.7 mm) connected in series in order of increasing pore size (100, 1000, 10^5, 10^6) were used with THF as a solvent.

Results and Discussion

Thiazole Carbene Catalysts. It is well established that thiazole carbenes are catalysts for a number of biologically important transformations.[16] For example, the pioneering work of Breslow illuminated the role of thiamine cofactors in the benzoin condensation.[17−19] To investigate the activity of thiazole carbenes for ring-opening polymerization reactions, we investigated the polymerization of lactide with thiazolium precursors in the presence of triethylamine. Many thiazolium precursors are commercially available (Table 1, entries 1,2,4) or readily synthesized from commercial materials.[19] Thiazolium salts were readily synthesized, via alkylation of the appropriate thiazole precursor, eq 2, and examined as precursors for ROP catalysis (Table 1).



(2)

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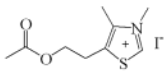
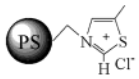
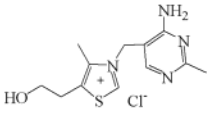
Table 1. Characteristics of Selected Polylactides Prepared from Thiazolium Precatalysts and Triethylamine[a]

no.	Precatalyst	Time (h)	Temp(°C)	Conv.(%)	[M/[I]	DP(^{1}H NMR)	PDI
1		48	25	83	60	52	1.10
2		72	25	83	120	100	1.08
3		48	25	80	60	48	1.07
4		48	38	85	60	50	1.35

[a]Benzyl alcohol was the initiator for all entries except entry 2, where 1-pyrene-butanol was the initiator.

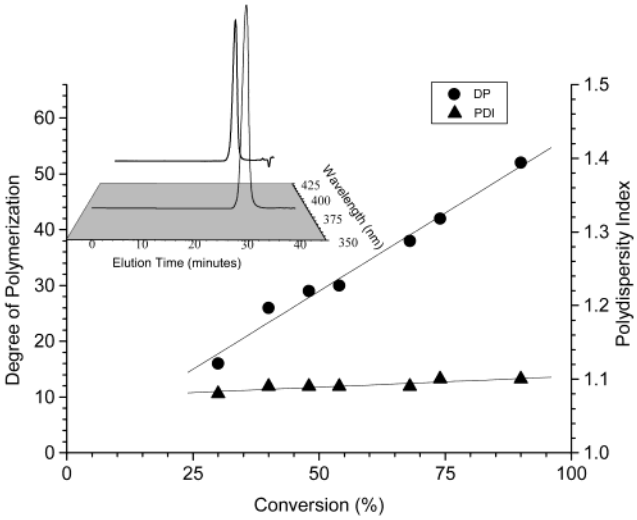


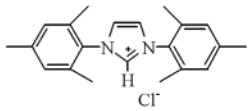
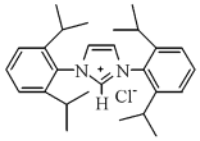
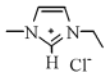
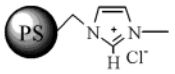
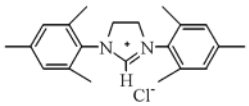
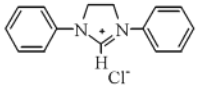
Figure 1. DP and PDI versus conversion for the ROP of lactide initiated from pyrene butanol in the presence of entry 1 from Table 1 together with the GPC results using both the RI (410 nm) and UV (350 nm) detectors.

Polymer supported thiazolium precatalysts can be readily prepared (Table 1, entry 3).[20] The addition of triethylamine to a solution of thiazolium salt and monomer resulted in an immediate change in color from light yellow to dark red/brown, consistent with the dimerization of the thiazole carbene.[18] In the presence of a benzyl alcohol initiator, the ring-opening polymerization of lactide polymerization was achieved with the thiazolium salts and triethylamine.[21] A ratio of 2−5 equiv of triethylamine per thiazolium salt, in CH_2Cl_2, was required for optimal catalytic performance.[22] The rate of polymerization showed little dependence on catalysts concentration and monomer conversion when the triethylamine, thiazolium salt, and initiator were held in a 5:2:1 ratio. The polymerizations generated low polydispersities and molecular weights that closely tracked the monomer-to-initiator ratio for low molecular weight polymers (i.e., DP ≈ 60), irrespective of the catalyst. However, because of the limited solubility of thiamine in CH_2Cl_2 (Table 1, entry 4), it was difficult to achieve polydispersities less than 1.1. A plot of the molecular weight and polydispersity versus conversion for the thiazolium catalyzed ROP was linear, consistent with a living polymerization (Figure 1). The GPC traces of polylactide initiated from pyrene butanol using both the refractive index and UV detectors (410 and 350 nm, respectively) are also included in Figure 1. These data clearly show the distribution of pyrene throughout the sample and corroborate ^{1}H NMR studies that indicate the presence of one initiator per polymer chain. Efforts to generate higher molecular weight polylactides were less successful: monomer conversions in excess of 85% for targeted DPs of 90 and above were difficult to achieve even with extended reaction times (48−72 h) (Table 1).

Imidazol-2-ylidene Carbene Catalysts. Imidazolium salts were synthesized according to established procedures, Scheme 3.[13] Imidazol-2-ylidene catalysts,[23] prepared in situ,[24] were significantly more active ROP catalysts than the thiazole carbene catalysts. Catalytic activity showed little solvent dependence; rates of lactide polymerization were indistinguishable in THF or toluene. High molecular weight polylactides (M_n > 25 000 g/mol) were readily synthesized within 10 min at room temperature (Table 2, entries 1,2). That catalytic activity was also observed at temperatures below 0 °C further demonstrates the efficiency of these catalysts toward lactide ROP. Catalyst ratios of 0.25−1.5 equiv relative to initiating alcohol for targeted DPs of >100 produced narrowly dispersed polylactides in 1−2

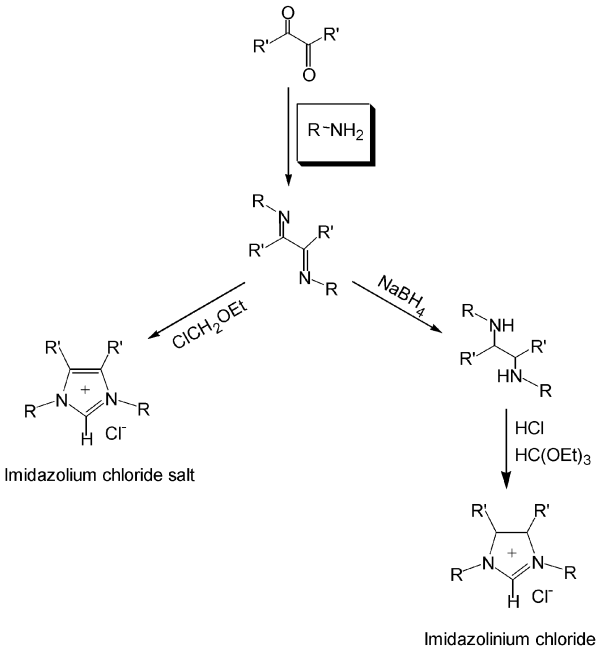
(20) Polymer supported catalysts were synthesized by reacting Merrifield resin with thiazole in 2-propanol at 60 °C for 3 days.
(21) It was determined by control experiments that triethylamine does not catalyze the polymerization of lactide.
(22) These conditions are consistent with a recent report of thiazolium catalyzed synthesis of α-amido ketones. For example, see: Murry, J. A.; Frantz, D. E.; Soheili, A.; Tillyer, R.; Grabowski, E. J. J.; Reider, P. J. *J. Am. Chem. Soc.* **2001**, *123*, 9696.
(23) (a) Arduengo, A. J. *Acc. Chem. Res.* **1999**, *32*, 913. (b) Arduengo, A. J.; Krfczyk, R. *Chem. Z.* **1998**, *32*, 6. (c) Bourissou, D.; Guerret, O.; Gabbai, F. P.; Bertrand, G. *Chem. Rev.* **2000**, *100*, 39. (d) Herrmann, W.; Kocher, C. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2162. (e) Scholl, M.; Trnka, T. M.; Morgan, J. P.; Grubbs, R. H. *Tetrahedron Lett.* **1999**, *40*, 2247. (f) Huang, J.; Stevens, E. D.; Nolan, S. P. Petersen, J. L. *J. Am. Chem. Soc.* **1999**, *121*, 2674. (g) Weskamp, T.; Schattenmann, W. C.; Spiegler, M.; Herrmann, W. A. *Angew. Chem., Int. Ed.* **1998**, *37*, 2490. (h) Herrmann, W. A.; Elison, M.; Fisher, J.; Kocher, C.; Artus, G. J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2371. (i) Herrmann, W. A.; Goossen, L.; Kocher, C.; Artus, G. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2805. (j) Lappert, M. *J. Organomet. Chem.* **1988**, *358*, 185. (k) Enders, D.; Breuer, K.; Raabe, G.; Runsink, J.; Henrique, T.; Melder, J.-P.; Ebel, K.; Brode, S. *Angew. Chem., Int. Ed. Engl.* **1995**, 34, 1021.
(24) Since potassium *tert*-butoxide initiates polymerization of cyclic esters, we used 1.2−1.5 equiv of imidazolium or imidazolinium salt to 1 equiv of potassium *tert*-butoxide stoichiometry to ensure complete consumption of alkoxide. ^{1}H NMR spectra of the in situ catalysts were identical to values reported in the literature. Although *tert*-butyl alcohol is a byproduct of these reactions, we have seen no evidence of initiation of polymerization by *tert*-butyl alcohol.

Table 2. Characteristics of Selected Polylactides Prepared from Imidazolium and Imidazolinium Precatalysts and Potassium *tert*-Butoxide[a]

no.	Precatalyst	Time(h)	Conv.(%)	[M]/[I]	DP(^{1}H NMR)	PDI
1		0.25	85	200	173	1.18
2		0.25	92	200	185	1.18
3		1.0	60	200	123	1.16
4		0.25	97	200	194	1.31
5		1.0	95	200	190	1.52
6		0.25	99	200	190	1.23
7		0.25	99	200	197	1.46

[a] Benzyl alcohol was the initiator for all entries. A catalyst/initiator ratio of 1.5 was used for all entries except entry 3, where a catalyst/initiator ratio of 0.25.

Scheme 3



M THF lactide solutions (Table 2, entries 1−3). Higher monomer concentrations or catalyst/initiator ratios resulted in polymer polydispersities greater than 1.2. Significant reduction of the catalyst/initiator/monomer ratio was necessary to achieve narrowly dispersed oligomers (DP = 10) (Figure 2). The narrowest polydispersity was achieved when a 1200:80:1 monomer/initiator/catalyst ratio was used.

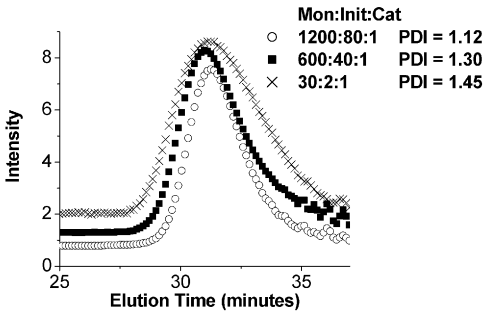
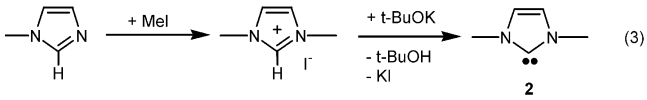


Figure 2. GPC traces of L-lactide oligomers (DP = 10), catalyzed by 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene, with different momoner/initiator/catalyst ratios.

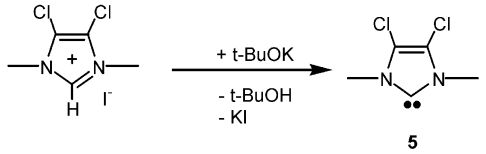
We were interested in exploring the effect of replacing bulky mesityl and 2,6-diisopropylphenyl groups with smaller substituents at the 1,3 positions. Alkylation of 1-methylimidazole with methyl iodide, eq 3, provides a convenient synthesis of 1,3-dimethylimidazolium iodide salt precursor (Table 2, entry 3) which can subsequently be deprotonated to yield 1,3-dimethylimidazol-2-ylidene, **2**. In addition, 1-ethyl-3-methylimidazol-2-ylidene, **3**, can be synthesized from 1-ethyl-3-methylimidazolium chloride, which is commercially available (Table 2, entry 4). Arduengo has reported that the less sterically demanding



(3)

carbenes **2** and **3** are only modestly stable oils when isolated but are significantly more stable in solution.[25] Carbenes **2** and **3** were extremely active toward lactide polymerization generating narrowly dispersed products of predictable molecular weight, but they were more difficult to control than **1**. Catalyst/initiator ratios of less than 0.5:1 were required to obtain controlled lactide polymerization reactions with monomer concentrations of ≤ 1 M, which were necessary to obtain narrowly dispersed polymers. Methylimidazole reacts with Merrifield resin to afford a solid supported precatalyst, **4**, (Table 2, entry 5).[26] Lactide polymerizations with activated precatalyst **4** resulted in high molecular weight polylactide with relatively broad polydispersities, which may be attributed to the lack of solubility of the polymer supported catalyst in THF.

Finally, we examined the effect of introducing electron withdrawing subtituents at the 4,5 positions of the imidazole ring. Arduengo and co-workers have demonstrated that the stability of **1** was significantly enhanced upon chlorination of the olefin backbone, suggesting that *N*-heterocyclic carbene reactivity may be "electronically" tunable. Therefore, we synthesized 4,5-dichloro-1,3-dimethylimidazol-2-ylidene, **5**, eq 4, and compared the reactivity with **2**. A plot of the conversion



(4)

to polylactide versus time for L-lactide ROP is shown in Figure 3. While 97% conversion is achieved within 5 min with catalyst **2**, only 85% conversion is observed with catalyst **5** under identical conditions. Clearly, the chloride substituents have a pronounced effect on carbene reactivity. This also suggests that a considerable amount of control can be achieved by the judicious choice of substituents on the imidazole ring.

Imidazolin-2-ylidene Carbene Catalysts. Imidazolin-2-ylidene carbene catalysts were synthesized according to published procedures (Scheme 3).[13] Saturation of the *N*-heterocyclic carbene backbone (imidazolin-2-ylidene carbenes) gives rise to distinct differences relative to unsaturated imidazol-2-ylidene carbenes. For example, unlike imidazol-2-ylidenes, imidazolin-2-ylidene carbenes readily dimerize if bulky substituents are not introduced at the 1,3 positions to provide kinetic stability.[27] Grubbs and co-workers have also reported differences in reactivity of *N*-heterocyclic carbene Ru alkylidene catalysts, where only the backbone of the *N*-heterocyclic carbene has been changed from unsaturated to saturated.[28] We were interested in determining how these differences effect lactide polymerization. **1** and 1,3-bis(2,4,6-trimethylphenyl)imidzolin-2-ylidene, **6**, provide a direct comparison. **6**, synthesized in situ from the appropriate salt precursor (Table 2, entry 6), was an extremely

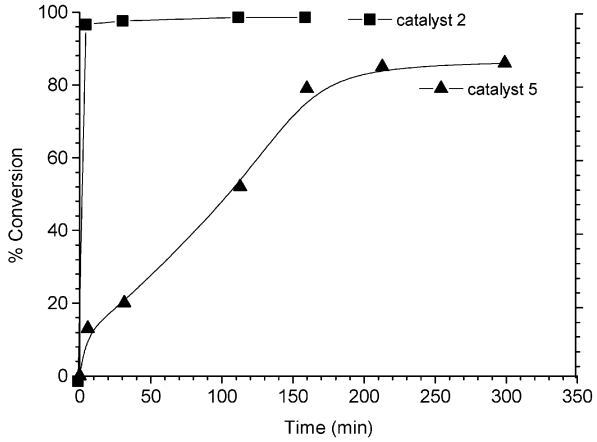
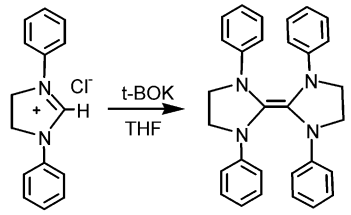


Figure 3. L-Lactide ROP: conversion to polylactide vs time with catalysts **2** and **5**.

active lactide polymerization catalyst and produced high molecular weight polylactides at room temperature <10 min. However, no significant differences in ROP reactivity between **1** and **6** were observed. Like **1**, polymerization reactions with **6** require attention to catalyst and monomer concentrations to obtain narrowly dispersed polymers. Catalyst/initiator ratios of 0.5−1:1 in ≤ 1 M solutions of lactide monomer routinely resulted in controlled polymerization reactions.

Although the imidazolin-2-ylidene carbenes are prone to dimerize, in the absence of bulky groups at the 1,3 positions, Wanzlick's original work demonstrated that tetraaminoethylene complexes have a reactivity characteristic of nucleophilic carbenes, eq 5.[29] To further investigate the scope of imidazolin-



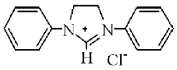
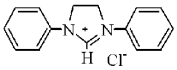
(5)

2-ylidene nucleophilic catalysts, we were prompted to explore the utility of "Wanzlick" carbenes as potential polymerization catalysts. Bis(1,3-diphenyl)imidazolin-2-ylidene, **7**, prepared in situ from its salt precursor (Table 2, entry 7), was indeed a potent lactide polymerization catalyst. Controlled polymerizations were difficult to achieve with these catalysts which usually resulted in polymers with broad polydispersities (PDI = 1.5−1.6).

ϵ-Caprolactone Polymerizations. In our initial report, **1** catalyzed the ROP of neat lactone at elevated temperatures in 24 h but only for modest molecular weights under specific polymerization conditions. In contrast to lactide polymerization, polymerizations of ϵ-lactone with **1** or **6**, in THF or toluene, were extremely sluggish at room temperature and typically resulted in little or no polymer after 48−72 h. X-ray crystallographic data of lactide show an irregular skewed-boat confomation with appropriate C_2 symmetry in which the two ester groups adopt planar conformations.[30] Use of a sterically

(25) Arduengo, A. J.; Davidson, F.; Dias, H. V. R.; Goerlich, J. R.; Khasnis, D.; Marshall, W. J.; Prakasha, T. K. *J. Am. Chem. Soc.* **1997**, *119*, 12742.
(26) See ref 20 for reaction conditions.
(27) Arduengo, A. J., III; Goerlich, J. R.; Marshall, W. J. *J. Am. Chem. Soc.* **1995**, *117*, 11027.
(28) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18.
(29) (a) Wanzlick, H.-W.; Kleiner, H.-J *Angew. Chem.* **1961**, *73*, 493. (b) Wanzlick, H.-W. *Angew. Chem.* **1962**, *74*, 128. (c) Wanzlick, H.-W.; Kleiner, H.-J. *Chem. Ber.* **1963**, *96*, 3024.
(30) Van Hummel, G. J.; Harkema, S.; Kohn, F. E.; Feijen, *Acta Crystallogr., Sect. B* **1982**, *38*, 1679.

Table 3. Characteristics of Selected Polylactones Prepared from Imidazolium and Imidazolinium Precatalysts and Potassium *tert*-Butoxide[a]

no.	Precatalyst	Monomer	Time(h)	Conv.(%)	[M]/[I]	DP(^{1}H NMR)	PDI
1		β-Butyrolactone	3	100	200	192	1.04
2		δ-Valerolactone	3	98	200	185	1.32
3		ε-Caprolactone	6	98	200	188	1.16
4		ε-Caprolactone	6	99	200	194	1.40
5		ε-Caprolactone	0.5	99	100	98	1.55
6		δ-Valerolactone	0.5	99	108	105	1.52
7		ε-Caprolactone	2	100	20	20	1.32
8		ε-Caprolactone	1	100	20	20	1.28

[a] Benzyl alcohol was the initiator for all entries. Catalyst 8 in entry 4 and 8 was prepared according to literature procedures.[14]

encumbered catalyst, such as **1**, may preclude activation of ϵ-caprolactone, since the seven-member ring is expected to have a more skewed conformation.

To test this hypothesis, two less sterically demanding catalysts were surveryed for the ROP of lactone: 1,3-dimethylimidazol-2-ylidene, **3**, and tetramethylimidazol-2-ylidene, **8**.[25] Effective ROP of ϵ-caprolactone was accomplished with **3** and **8** in the presence of benzyl alcohol; however, the polymerization kinetics and subsequent control was strongly dependent on the polymerization conditions including catalyst and monomer concentrations. For example, shown in Figure 4 are conversion versus time plots for the ROP of ϵ-caprolactone using **3**, generated in situ, as the catalyst, where the solvent to monomer content (S/M) was varied from 1−10 and the catalyst concentration ranged from 0.1 to 10 equiv relative to that of initiator for a targeted DP of 200. Facile polymerization (1−6 h) was observed for high monomer content for catalyts/initiator ratios of 0.5−10. The higher catalysts concentrations tended to give broadly dispersed products (1.5−1.8), whereas the lower catalyst/initiator ratios (0.5−1.0) gave the narrowest distributions (Table 3). Lower monomer concentrations further enhanced polymerization control in reasonable times. Catalyst **8** was extemely active, and to avoid broad polydispersities and loss of polymerization control, catalyst/monomer ratios of 0.5−1.0 at 50−10% monomer, respectively, were required (Table 3). A plot of molecular weight versus conversion for the ROP of ϵ-caprolactone initiated from benzyl alcohol in the presence of either **3** or **8** shows a

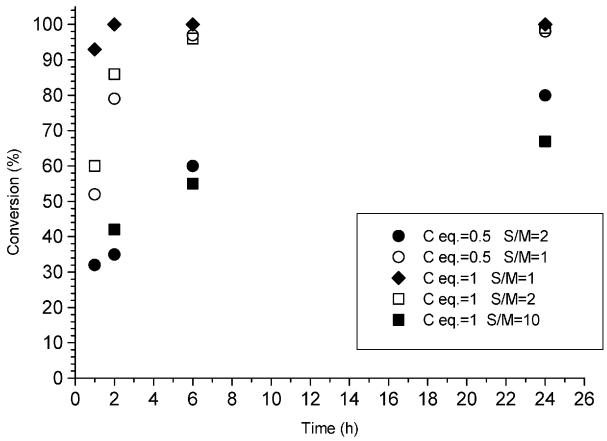
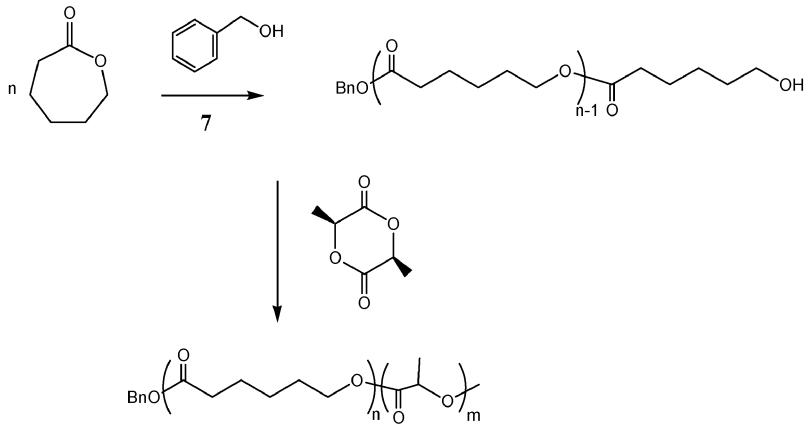


Figure 4. Conversion versus time for different catalyst equivalents to initiator (C eq.) and solvent (mL) to monomer (g) ratios (S/M).

correlation characteristic of a living polymerization (Figure 5). However, prolonged reaction times after monomer consumption often broadened the polydispersity, possibly because of adverse transesterification side reactions. Interestingly, **6**, an analogue of **3** and **8**, does not polymerize ϵ-caprolactone under the same conditions.

We then investigated the reactivity of imidazolin-2-ylidene catalysts toward caprolactone polymerization. Like **1**, **6** did not polymerize caprolactone at 25 °C in THF or toluene. However, **7** does readily polymerize caprolactone under the same condi-

Scheme 4



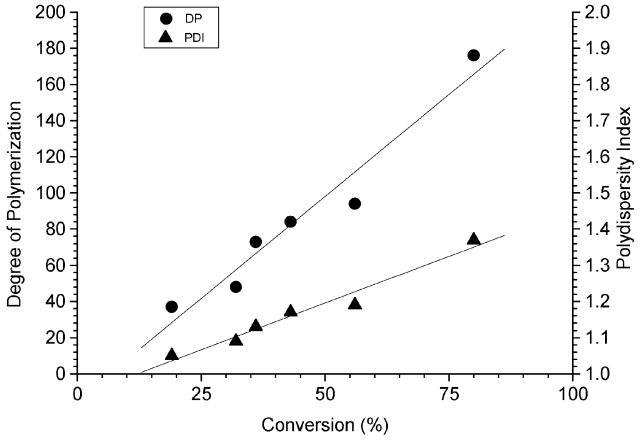


Figure 5. Degree of polymerization and polydispersity index versus time for the ROP of lactone using catalyst **3**. The reaction was deliberately slowed by minimizing catalyst and by solvent dilution (0.5 equiv of catalyst/initiator and 2 mL of solvent/g of monomer) in order to follow the polymerization.

tions (Table 3, entry 5). Apparently, removal of the methyl groups at the 2,4,6 positions of the phenyl ring greatly increases the reactivity of carbene catalyst toward lactone polymerization, suggesting that the sterics of the carbene catalysts can be tailored to optimize reactivity.

Finally, to demonstrate the versatility and generality of the catalysts toward lactone polymerization, β-butyrolactone, δ-valerolactone, and oxotridecane-2-one were investigated as substrates. Facile and controlled polymerization of the small cyclic esters was observed, but the larger ring did not polymerize, consistent with ring strain (Table 3). These less sterically demanding carbenes have comparable turnovers and selectivity to those the most advanced organometallic promoters for the ROP of lactone; however, unlike biocatalysts,[31] they are not able to polymerize larger cyclic esters.

Block Copolymers. Biocompatible and biodegradable polymers for biomedical applications have been an area of intense research interest.[32−34] We decided to examine the feasibility of these catalysts to create well-defined block copolymers. Caprolactone monomer was added to a solution of **7** and benzyl alcohol to synthesize the first block of the polymer (Scheme 4). After 2 h, complete consumption of monomer had occurred, as determined by ^{1}H NMR. The molecular weight of the polycaprolactone block was determined by GPC (M_n = 9000). L-Lactide monomer was then added to the polylactone/catalyst mixture. After 12 h, the reaction was quenched and the polymer was precipitated from methanol. One elution peak was observed in the gel permeation chromatogram of the precipitated polymer with M_n = 30 000 and PDI = 1.38. In addition, transesterification appears to be insignificant, since only two signals in the carbonyl region are observed in the ^{13}C NMR (Figure 6) spectrum.[34,35] Attempts to grow polycaprolactone from polylactide were unsuccessful.

In another example, amphiphilic block copolymers were prepared using monohydroxyl functional poly(ethylene oxide) oligomers as macroinitiators for the ROP of lactone in the presence of **2** in THF (Scheme 5). Catalyst **2** was generatedl.[34,36] from the respective salt in situ in a THF solution, filtered to remove salt side products, and stirred with the macroinitiator. The macroinitiator had a molecular weight of 1900 g/mol by GPC, relative to polystyrene standards, with a polydispersity of 1.08. Polymerization of ϵ-caprolactone was accomplished in 20 h with targeted DPs of 100, 150, and 200. Each of the polymers showed the expected increase in molecular weight by GPC using polystyrene strandards with narrow polydispersities (1.22, 1.30, and 1.24, respectively) with molecular weights of 22 000, 24 000, and 25 000 g/mol, respectively, by GPC. Monomodal polydispersities were obtained for the diblocks with no evidence of the macroinitiator, further demonstrating the efficiency of the catalyst and initiation.

To further demonstrate the efficiency and versatility of the catalysts, norobornene functional lactide macromonomers were prepared and polymerized to form well-defined graft copolymers. The macromonomers were prepared using norbornene alcohol (bicyclohept[2,2,1]-2-ene-5-methanol) as an initiator for the ROP of lactide in the presence of the mesityl carbene (Scheme 6). Narrowly dispersed (∼1.1) macromonomers were obtained with molecular weights that closely tracked the lactide

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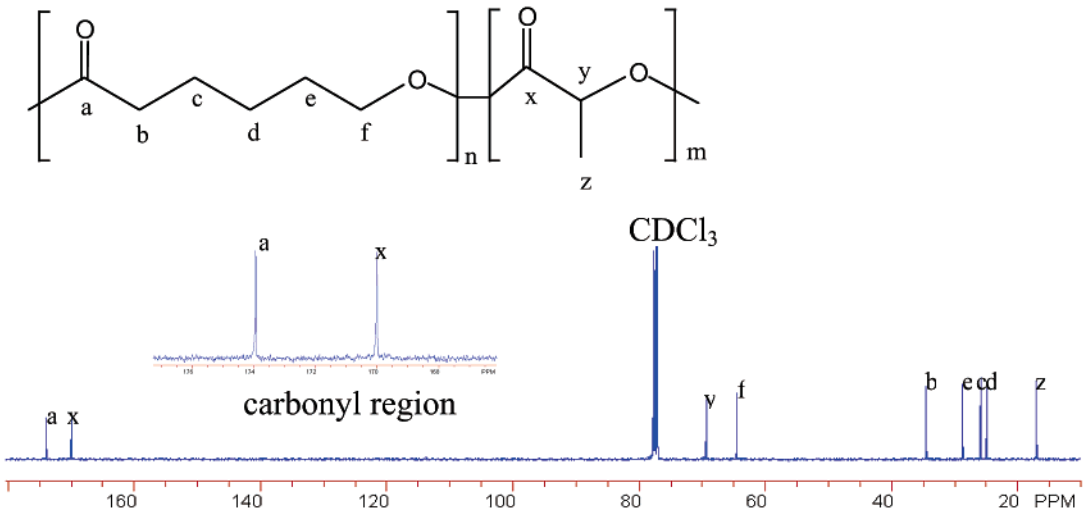
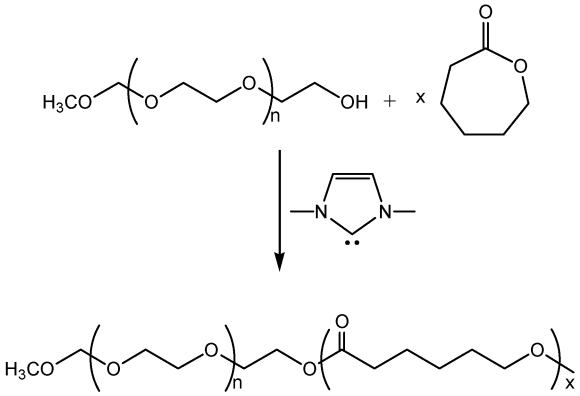


Figure 6. ^{13}C NMR of poly(caprolactone−lactide) copolymer.

Scheme 5



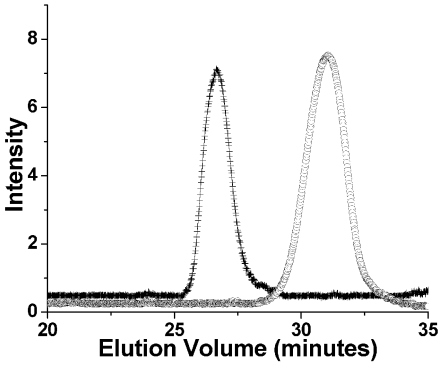
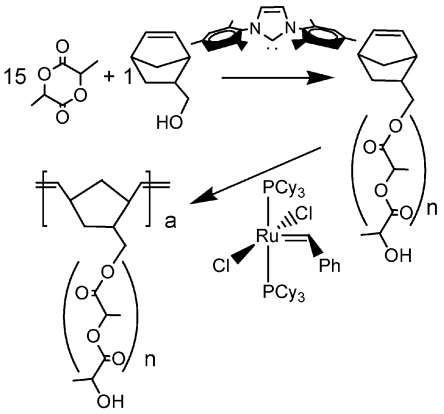


Figure 7. GPC chromatograms of lactide macromonomer (○) and graft copolymer (+).

Scheme 6



to norobornene alcohol ratio. The α-(norobornenyl ester) and ω-(hydroxy) functional end groups were readily observed by ^{1}H NMR and were used to determine the number average molecular weights. The macromonomers were polymerized by ring-opening metathesis polymerization using Grubb's catalysts to form a graft copolymer. Shown in Figure 7 are the GPC chromatograms of the macromonomer and the graft copolymers. Quantitative comsumption of macromonomer is observed generating a narrowly dispersed polymer, further demonstrating the capability of the carbene catalyst platform to prepare well-defined functional materials.

Ionic Liquids. The above data clearly demonstrate that in situ generation of thiazolium and imidazolium catalysts is a convenient and effective strategy to prepare polyesters of controlled molecular weight. The success of this strategy prompted us to investigate the use of the corresponding ionic liquid directly as a reactive media for the ring-opening polymerization of lactide and lactones.[37,38] Although there are numerous examples of ionic liquids used as solvents in catalysis,[39] the use of ionic liquids as a reactive media has largely been confined to Lewis- or Bronsted-acid-catalyzed reactions.[40]

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(38) For example, see: (a) Carmichael, A. J.; Haddleton, D. M.; Bon, S. A.; Seddon, K. *Chem. Commun.* **2000**, 1237. (b) Carlin, R. T.; Wilkes, J. S. *J. Mol. Catal.* **1990**, *63*, 125.

(39) For a few examples, see: (a) Chauvin, Y.; Mussman, L.; Olivier, H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2698. (b) Tucker, C. E.; Jaeger, D. A. *Tetrahedron Lett.* **1989**, *30*, 1785. (c) Kaufmann, D. E.; Nouroozian, M.; Henze, H. *Synlett* **1996**, 1091. (d) Carlin, R. T.; Wilkes, J. S. *J. Mol. Catal.* **1990**, *63*, 125. (e) Chauvin, Y.; Einloft, S.; Olivier, H. *Ind. Eng. Chem. Res.* **1995**, *34*, 1149. (f) Suarez, P. A. Z.; Dullius, J. E. L.; Einloft, S.; de Souza, R. F.; Dupont, J. *Polyhedron* **1996**, *15*, 1217. (g) Carmichael, A. J.; Haddleton, D. M; Bon, S. A. F.; Seddon, K. R. *Chem. Commun.* **2000**, 1237.

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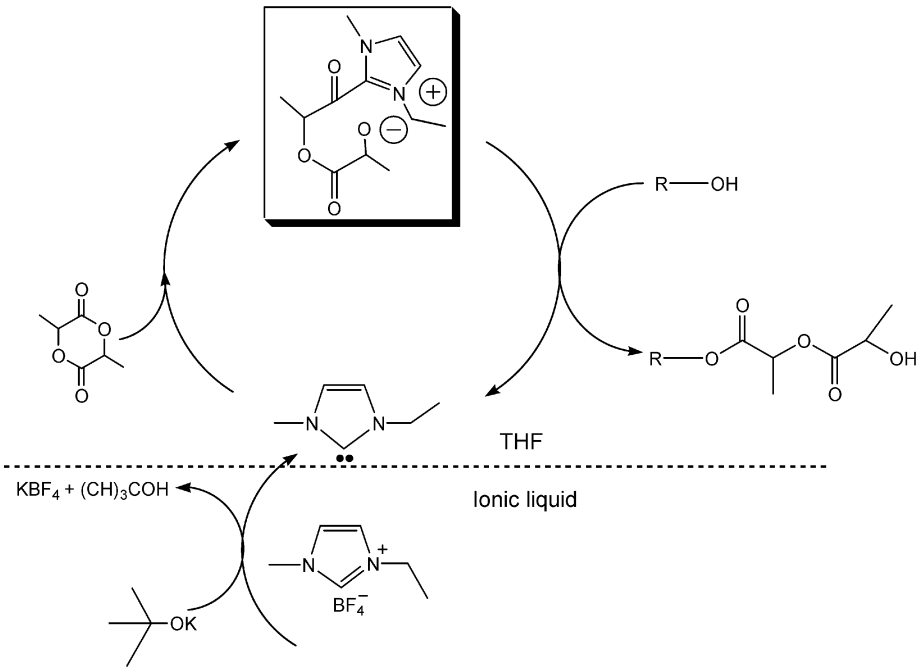
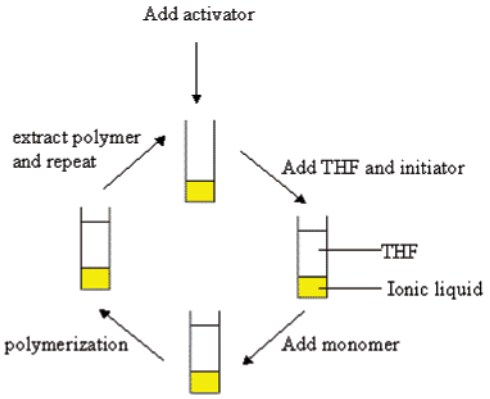
Scheme 7

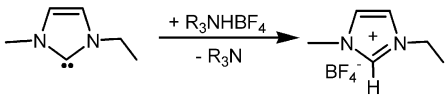


Scheme 8



Attempts to polymerize lactide with the thiazolium-based ionic liquid, 3-butyl-5-methylthiazolium tetrafluoroborate[41] in the presence of triethylamine, did not produce satisfactory results. In contrast, the room temperature ionic liquid 1-ethyl-3-methylimidazolium tetrafluroborate salts [emim][BF_4], **9**, proved an outstanding medium for ring-opening polymerization. This ionic liquid is readily synthesized by the methathesis of commercially available precursors [emim][Cl] and NH_4BF_4 in acetone.[42] Polymerization reactions were conducted with ionic liquids using two different approaches: (1) neat **9** and (2) a biphasic system comprised of **9** and THF. Lactide polymerizations initiated from benzyl alcohol in neat **9**, activated with potassium *tert*-butoxide, dissolved in a drop of THF proceeded to 50% conversion (DP = 150, PDI = 1.4) within 10 min to form a plug of polymer. In addition, ϵ-caprolactone was also readily polymerized under these conditions in high yield to afford high molecular weight polycaprolactone (22 000 g/mol, PDI = 1.6).

The success of these experiments prompted us to investigate a biphasic polymerization in an immiscible mixture of **9** and THF. In situ activation of **9** with potassium *tert*-butoxide generates the carbene catalyst, which is then extracted into the organic phase to begin ROP catalysis (Scheme 7. High molecular weight polylactides (M_n > 24 000 g/mol) with relatively narrow polydispersities (PDI = 1.4) were routinely achieved in greater than 95% yield within 10 min. This reaction constitutes a phase-transfer catalytic ring-opening polymerization where the reactive carbene is generated in situ in the ionic liquid, migrates to the organic phase, and induces ring-opening polymerization. The polymerization reaction is readily terminated by the addition of [R_3NH][BF_4], which regenerates the imidazolium precursor, eq 6. Since neither the residual monomer



(6)

nor polymer could be detected in the ionic liquid phase, the polymer could be readily separated from the ionic liquid phase and the ionic liquid could be reused for a subsequent polymerization. Four successive biphasic lactide polymerization experiments were carried out in the same reaction vessel with the same ionic liquid reservoir in a reaction/recycle protocol, as outlined Scheme 8.

Conclusion

The in situ generation of the *N*-heterocyclic carbene catalysts directly from their respective salts allowed the rapid screening of libraries of catalysts for the ROP of both lactide and lactone. The direct comparison to the in situ generation of thiazolium-based carbenes, known to catalyze a variety of transformations, allowed us to further assess the efficiency of the imidazole-based carbenes. No appreciable differences between imidazol-2-ylidene and imidazolin-2-ylidene catalysts were observed with lactide. However, less sterically demanding carbenes were found to be more active toward ROP than their sterically encumbered analogues for lactone polymerization. Extension to commercially

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available materials and solid supported catalysts were demonstrated as the ultimate goals in providing a universal catalyst platform: in most cases, narrowly dispersed products with predictable molecular weights from the monomer-to-initiator ratio. Block and graft copolymers, macromonomers, and functional oligomers were demonstrated. An interfacial biphasic polymerizaton using ionic liquid as a catalyst reservoir allowed rapid and repetitive polymerizations. Current efforts focus on extending the catalyst pool to protected carbenes to enable bulk polymerizations and chiral carbene catalysts to elaborate enantioselective complex targets including asymmetric synthesis and stereochemically controlled polymerization.

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