Organocatalytic Ring-Opening Polymerization

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Contents

1. Introduction

Modern synthetic methods have revolutionized polymer chemistry through the development of new and powerful strategies for the controlled synthesis of complex polymer architectures.[1−5] Many of these developments were spawned by new classes of transition metal catalysts for the synthesis of new polyolefin microstructures,[5] the design of highly efficient families of "living" polymerization strategies for the synthesis of block, graft, and star polymers,[6−12] controlled methods for the synthesis of dendritic macromolecules,[3,13,14] and, recently, strategies for the synthesis of cyclic polyolefins by a metathesis ring-expansion polymerization.[15] Catalysis has proven an enabling science for chemical synthesis, and the development of new classes of well-defined catalysts has proven the enabling science for catalysis.[16]

Given the extraordinary pace of these developments and the rich reactivity patterns engendered by the almost limitless diversity of ligand/metal combinations, it is perhaps not surprising that transition metal and organometallic catalysts have dominated the field of catalysis applied to both fine chemical and macromolecular synthesis. Nevertheless, even a passing familiarity with enzymatic catalysis engenders a sense of awe and deep appreciation for the potential of precisely positioned organic functional groups to catalyze both single and multiple cascade reactions with high rates, selectivities, and energy efficiencies.

As discussed in detail in other reviews in this issue, the field of organocatalysis has undergone a renaissance, particularly for enantioselective catalytic reactions. Some 100 years after Bredig and Fiske's reports of enantioselective cyanohydrin synthesis with quinine alkaloids[17] and Hajos and Parrish's impressive proline-catalyzed Robinson annulations,[18] the field of enantioselective organocatalysis has expanded to encompass an extraordinary diversity of new reactions, catalysts, and processes.[19−26] In this review, we highlight some of the important advances in organocatalytic polymerization reactions and the utility of organocatalytic methods for the synthesis of complex polymer architectures. While extraordinary advances have been made in organometallic catalysts for ring-opening polymerization (ROP) reactions,[27−31] organocatalysts complement transition metal catalysts because of their different mechanisms for effecting bond constructions, as well as benefits that derive from the lack of residual metal contaminants that can compromise the polymer performance in biomedical[32] and microelectronic applications.[33] The primary focus of this review is the ring-opening polymerization of lactones such as lactide (LA), β-butyrolactone (BL), δ-valerolactone (VL), and ϵ-caprolactone (CL), but we also discuss other strained cyclic monomers, such as morpholine-2,6-dione (MDO), trimethylene carbonate (TMC), 2,2,5,5-tetramethyl-1-oxa-2,5-disilacyclopentane (TMOSC), and hexamethylcyclotrisiloxane (D3) (Figure 1). A special emphasis is placed on mechanistic features of novel organocatalysts that enable high reactivity and selectivity for the construction of complex polymer architectures.

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Nahrain E. Kamber (right) was born in 1979 in Baghdad, Iraq. She received her B.A. in 2001 in chemistry from Kalamazoo College (MI) where she did undergraduate research with Professor Thomas J. Smith. She is currently working toward her Ph.D. in chemistry at Stanford University under the supervision of Professor Robert M. Waymouth and Dr. James L. Hedrick. Her current research focuses on the application of *N*-heterocyclic carbenes as organocatalysts for polyester preparation and depolymerization. Upon completion of her Ph.D. studies, she will work as a senior chemist at Dow Chemical in Midland, MI. Wonhee Jeong (left) was born in 1975 in Seoul, Korea. He received his B.S. in 2001 and his M.S. in 2003 in chemistry from Seoul National University (Korea) with Do Y. Yoon. He is currently pursuing his Ph.D. in chemistry at Stanford University under the direction of Robert M. Waymouth and James L. Hedrick. His research interests include *N*-heterocyclic carbenes and their applications to organic and polymer chemistry. Robert M. Waymouth (center) was born in 1960 in Warner Robins, GA. He received bachelor's degrees in mathematics and chemistry from Washington and Lee University and his Ph.D. from the California Institute of Technology in 1987 with Professor Robert H. Grubbs. Following a year of postdoctoral research with the late Professor Pino at the ETH in Zurich, he joined the faculty at Stanford University in 1988, where he is now the Robert Eckles Swain Professor of Chemistry. His research interests are in homogeneous catalysis and polymer chemistry.

Russell C. Pratt (center) received his B.Sc. in Chemistry from the University of British Columbia in 1998, then joined the group of Professor T. Daniel P. Stack at Stanford University to study bioinorganic model compounds, for which he received a Ph.D. in 2004. He subsequently started postdoctoral work cosupervised by Professor Robert M. Waymouth of Stanford University and James L. Hedrick of the IBM Almaden Research Center with a focus on organocatalytic ring-opening polymerization. Bas G. G. Lohmeijer (left) was born in 1977 in Groningen, The Netherlands. He received his M.Sc. in 2000 in chemistry and chemical engineering from Eindhoven University of Technology (The Netherlands) where he did research in the laboratory of Professor E. W. Meijer. He obtained a Ph.D. in 2004 at the same university under the direction of Professor U. S. Schebert, where he studied terpyridine-based metallosupramolecular polymers. After his Ph.D. studies, he completed his postdoctoral training under the supervision of Professor Robert M. Waymouth and Dr. James L. Hedrick while working on organocatalytic ring-opening polymerization. He is currently a scientist at BASF AG in Ludgshafen, Germany, where he works on polymer colloids for coatings. James L. Hedrick (right) was born in 1959 in Blacksburg, Virginia. He received both his B. S. and Ph.D. from the Virginia Tech in 1981 and 1985, respectively, under the mentorship of Dr. James E. McGrath. He is currently a research staff member at IBM's Almaden Research Center in San Jose, CA, and he is also an investigator in the NSF Center for Polymeric Assemblies and Macromolecular Interfaces. He was the recipient of the 2003 American Chemical Society (ACS) Carl S. Marvel Creative Polymer Chemistry Award and the 2006 ACS Industrial Sponsors Award. His research has focused on new synthetic methodologies for microelectronics, nanotechnology, and biocompatible materials using organic catalysis.

The ideal polymer synthesis poses a number of challenges. As highlighted by Wender et al., the ideal for any synthetic reaction is one "*in which the target molecule is prepared from readily available starting materials in one simple, safe, environmentally acceptable, and resource-effective operation that proceeds quickly and in quantitative yield.*"[34] Catalysis

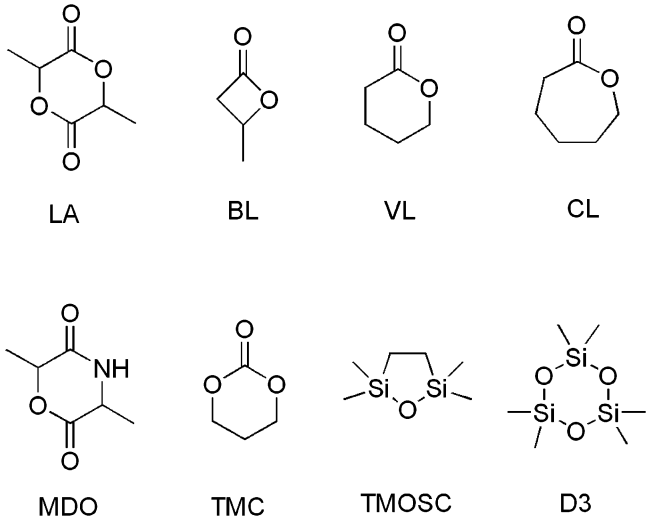
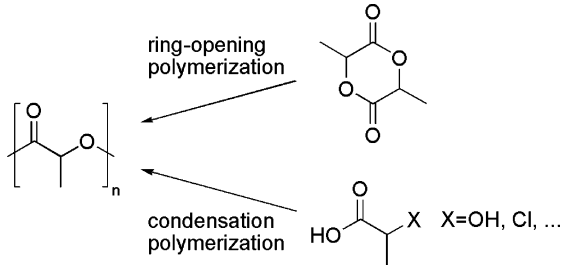


Figure 1. Scope of monomers in this review.

Scheme 1. Synthetic Routes to Poly(lactic acid)

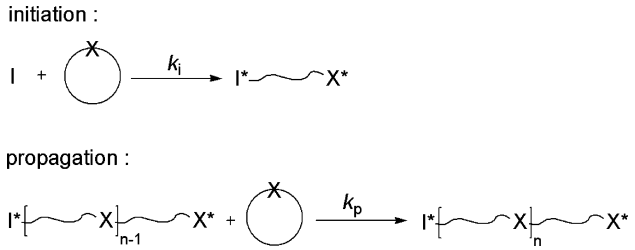


holds the potential to meet this high standard, but there are few synthetic processes that match the exquisite architectural complexity that nature creates in highly coupled, multicomponent catalytic cascades.

Polymerization catalysis, in addition to the general issues of turnover frequency, turnover number, and selectivity (chemo-, regio-, and stereoselectivity), poses additional challenges such as the need to control the molecular weight and the molecular weight distribution of the macromolecules, the nature and number of polymer end groups (end-group fidelity), the topology of the macromolecule (linear, branched, cyclic, concatenated, the presence and/or degree of crosslinking), and the functionality and sequence of monomers along the polymer chain.

Step growth and chain growth represent two general strategies for generating macromolecules.[35] Of the two, chain-growth strategies offer the advantages of providing more precise control over the molecular weight and molecular weight distribution with the advent of "living" polymerization reactions. In addition, as the majority of step-growth polymerizations are mediated by condensation or cross-coupling reactions, they are less atom-economical[36] than typical chain-growth polymerization strategies. For example, poly(lactic acid) (PLA), a biodegradable polymer made from renewable resources, can be made by either ring-opening addition polymerization of LA or condensation polymerization of lactic acid or its derivatives (Scheme 1).[37] In terms of molecular weight control, the living ROP of LA yields a linear relationship between monomer conversion and molecular weight and poly(lactide) (PLA) with a narrow polydispersity (PDI, defined as the ratio between the weight average and number average molecular weights, M_w/M_n). In contrast, the step-growth condensation polymerization limits the practically accessible range of molecular weights and leads to PDIs of 2.[35] The most striking aspect of ROP was theoretically elucidated by Flory; the invariant number of propagating chains in the ROP results in the generation of nearly monodisperse polymers at a high degree of polymerization (DP).[38] The benefits of ROP in conjunction with a "living" method have enabled the controlled synthesis of block, graft, and star polymers,[32] which leads to a present consensus that living ROP is a powerful and versatile addition-polymerization method.

Scheme 2. Gold's Kinetic Scheme for the ROP of Cyclic Monomers



Characteristics of a living chain-growth polymerization include the first-order kinetics in monomer concentration and a linear relationship between molecular weight and monomer conversion (when $k_i \geq k_p$, Figure 2, where k_i = the rate constant of initiation and k_p = the rate constant of propagation; Scheme 2). Deviations from the linear dependence are attributed to the presence of slow initiation or side reactions such as chain transfer and termination reactions.[35] Gold theoretically suggested that addition polymerization with

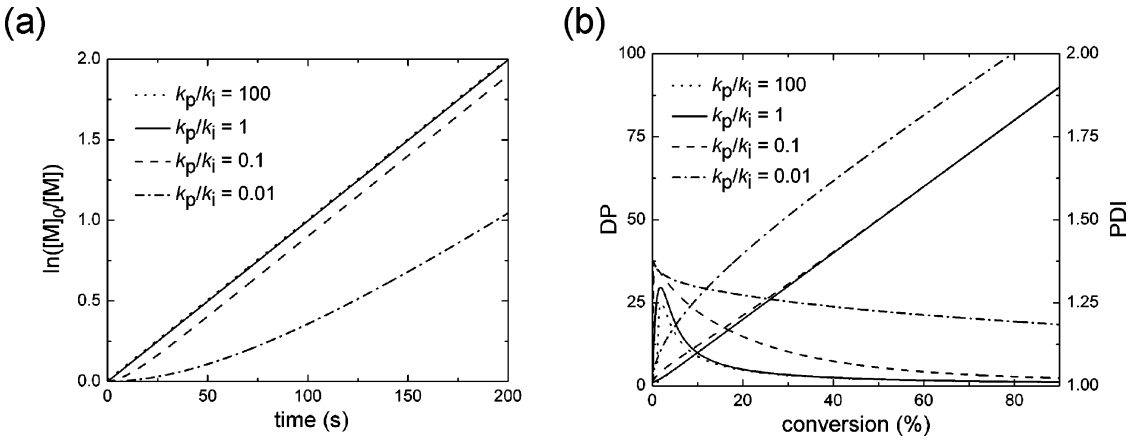


Figure 2. (a) Plots of $\ln([M]_0/[M])$ as a function of time with various k_p/k_i ratios ($[M]_0/[I]_0 = 100$, $k_p = 1\ M^{-1}\ s^{-1}$); (b) plots of DP and PDI as a function of monomer conversion with various k_p/k_i ratios ($[M]_0/[I]_0 = 100$, $k_p = 1\ M^{-1}\ s^{-1}$).

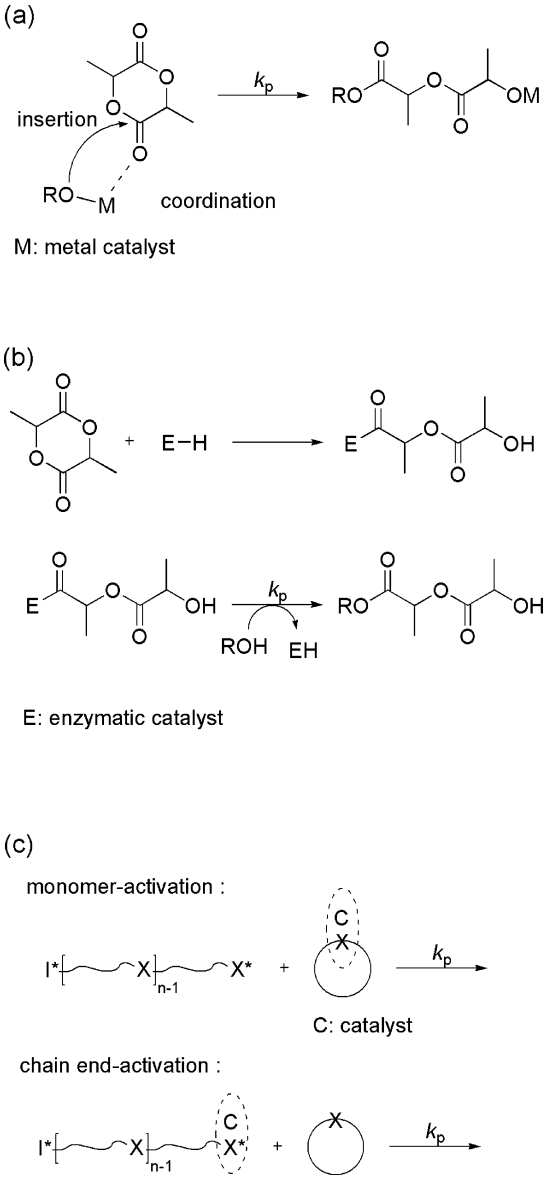
slow initiation could produce polymers with narrow PDI.[39] Experiments have provided abundant evidence supporting the Gold's prediction.[40,41] Figure 2b shows that narrow PDIs (<1.2 at 90% conversion) can be obtained even with $k_p/k_i = 0.01$. In this case, a nonzero intercept in the plot of monomer conversion versus conversion is diagnostic of slow initiation. Side reactions such as intermolecular chain transfer to polymer (reshuffling of active chain ends) and chain termination reactions are typically more responsible for the broadening of molecular size distributions.[42,43] Therefore, controlled polymerization requires catalysts that selectively activate monomers in preference to the propagating chains.

The thermodynamics of ROP is driven by the release of the ring strain of the monomer. The selectivity of the catalyst is critical to facilitate ring-opening relative to transesterification and other side reactions (chain shuffling and termination). Traditional thermal and hydrolytic ROPs are poorly controlled and often induce a great amount of side reactions. Hence, efficient catalysts that accelerate ring-opening of cyclic monomers are needed for controlled ROP.

Conventionally, mechanisms for ROP are divided into cationic and anionic polymerization according to the ionic charge of active propagating species.[35] A special case is zwitterionic polymerization, involving positively and negatively charged groups on the same chain.[35] It is well-established that the metal-catalyzed ROPs of LAs and lactones proceed through a "coordination−insertion" mechanism[29] involving coordination of the monomer to the metal of a catalyst and insertion of the monomer to the metal−oxygen bond (Scheme 3a). The coordination−insertion mechanism differs from cationic and anionic mechanisms involving free ions or ion pairs, in that the charged propagating species and its counterion share a covalent bond.

An alternate classification is common for enzymatic ROPs, which is termed an activated-monomer mechanism, where the enzyme reacts with the monomer and activates it toward enchainment onto the polymer chain end (Scheme 3b).[44,45] Classifying catalytic ROP reactions by either a monomer-activated or chain end-activated mechanism is useful because it defines the primary locus in which catalysts play a role (Scheme 3c). This division enables the clear-cut distinction between two competing mechanisms in generic cationic polymerizations: a monomer-activated mechanism via protonated monomer and a chain-end activated mechanism via cationic oxonium chain ends.[35]

Scheme 3. (a) Coordination−Insertion Mechanism for Metal-Catalyzed ROP of LA; (b) Activated Monomer Mechanism for Enzymatic ROP of LA; (c) Monomer-Activated Mechanism versus Chain End-Activated Mechanism

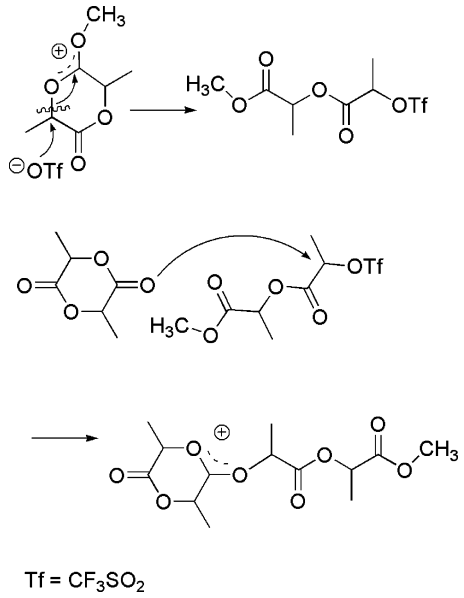


2. Cationic Ring-Opening Polymerization

Cationic polymerization has been applied for the ROP of a variety of cyclic heterocycles.[11] The cationic ROP of lactones has been achieved using alkylating agents, acylating agents, Lewis acids, and protic acids. For example, alkylating agents such as methyl triflate were reported by Kricheldorf and co-workers in a series of papers in the 1980s for the cationic polymerization of various lactones, including β-propiolactone (PL), CL, VL, LA, and glycolide.[46−49] Acylating agents have been reported by Penczek and co-workers for the cationic ROP of CL and PL.[50] A variety of Lewis acids have been screened for the bulk and solution cationic ROP of monomers such as 1,5-dioxepan-2-one (DXO) by Albertsson and Palmgren.[51]

Early attempts reported in 1971 by Dittrich and Schulz to polymerize LA with cationic compounds were unsuccessful.[52] In 1986, Kricheldorf and co-workers screened a variety of acidic compounds, among which trifluoromethanesulfonic acid (triflic acid, HOTf) and methyl triflate (MeOTf) proved to be useful initiators for the cationic ROP of LA.[48,49] Reactions were performed in nitrobenzene for 48 h and at an optimized 50 °C. End-group analysis by ^{1}H NMR indicates methyl ester groups when methyl triflate is used as the initiator, suggesting that the polymerization proceeds by cleavage of the alkyl−oxygen bond rather than the acyl−oxygen bond. Polymerizations of L-LA performed under 100 °C using HOTf and MeOTf initiators resulted in 100% optically active poly(L-LA) (PLLA). A two-step propagation mechanism was proposed involving activation of the monomer by methylation with methyl triflate followed by S_N2 attack of the triflate anion on the positively charged LA ring with inversion of stereochemistry. Propagation was proposed to proceed by nucleophilic attack by LA on the activated cationic chain end with inversion, leading to net retention of the configuration (Scheme 4). Regardless of the monomer-to-initiator ratio (50−400), the reported polymer viscosities were all quite similar, suggesting that the polymerization is not living under the reported optimized conditions.[49]

Scheme 4. Proposed Pathway for Cationic ROP of LA

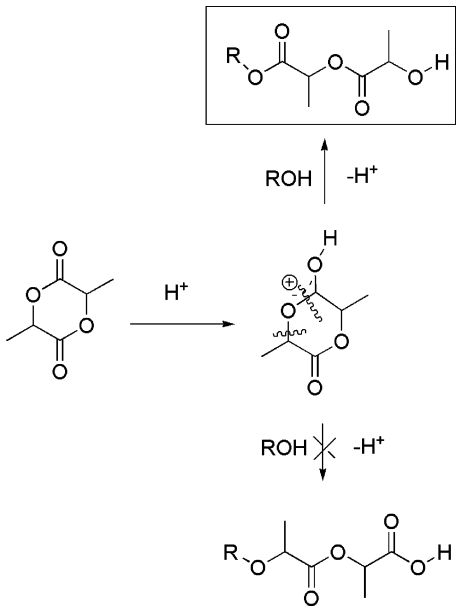


Recently, Bourissou et al. reported the controlled cationic polymerization of LA using a combination of the triflic acid (as the catalyst) and a protic reagent (water or an alcohol) as an initiator.[53] Reactions were performed in CH_2Cl_2 solution at room temperature and required only a few hours for high monomer conversion. In the absence of a protic initiator, monomer conversion reached only 23% after 2 h. Weaker acids such as $HCl{\cdot}Et_2O$ or CF_3COOH were reportedly inactive toward LA polymerization after 2 h under the same conditions. PLAs with molar masses up to 20 000 g/mol with PDIs ranging from 1.13 to 1.48 were obtained using the HOTf catalyst/protic initiator system with quantitative incorporation of the protic initiator confirmed by ^{1}H NMR and ESI mass spectrometry. The controlled character of the polymerization is suggested by the linear relationship of the molecular weight versus monomer conversion and monomer-to-initiator ratio. The controlled cationic ring-opening polymerization is believed to proceed by an "activated cationic polymerization" mechanism as described by Penczek,[11] where the acid would activate the cyclic ester monomer and the alcohol would be the initiator of polymerization. Polymerization is, therefore, thought to proceed by protonation of LA by triflic acid followed by nucleophilic attack by the initiating alcohol or that of the growing polymer chain, as shown in Scheme 5. The presence of isopropyl ester chain ends from the initiating isopropyl alcohol (observed by ^{1}H NMR) suggests that polymerization proceeds by acyl bond cleavage, not by alkyl bond cleavage.

The cationic copolymerization of L-LA with CL using a triflic acid catalyst/protic initiator was recently reported and also suggested to operate by a similar activated-monomer mechanism.[54] Though the rate of homopolymerization of the two monomers is slightly higher for CL, the LA monomer is consumed faster than CL in the copolymerization. The LA preference is likely due to the higher basicity of the LA monomer, leading to a higher concentration of activated LA monomer.

Initial reports using diphenylammonium triflate (DPAT, Figure 3) as an acidic-proton catalyst for the bulk ROP of LA in the presence of ethanol as the alcohol initiator have been reported by Bowden and co-workers.[55] Bulk polymerization at 130 °C using 5 mol % DPAT catalyst relative to

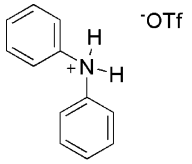
Scheme 5. Proposed Activated Monomer Pathway for Cationic ROP of LA



initiator resulted in molecular weights up to 12 000 g/mol (by gel permeation chromatography (GPC)) and PDIs ranging from 1.24 to 1.51. The high PDIs are likely due to transesterification with prolonged reaction times (>4 days). Similar to the previously described acid-catalyzed ROP of LA, polymerization is thought to proceed through a cationic-activated monomer mechanism. The catalyst has also been applied to the cationic ROP of various lactones including CL, VL, and BL (γ- and β-).[56] For example, the bulk and toluene solution polymerization at 60 °C for the cationic ROP of CL using 1 mol % of DPAT relative to the ethanol initiator resulted in narrow PDIs (<1.34) and good control of molecular weight as predicted by the monomer-to-initiator ratio.

The acid-catalyzed cationic polymerization of lactones such VL or CL can be carried out with $HCl{\cdot}Et_2O$ catalysts. For example, poly(lactone)s with molecular weights up to 10 000 g/mol and narrow PDIs (1.08−1.27) were obtained using the $HCl{\cdot}Et_2O$ catalyst/alcohol initiator system reported by Endo and co-workers for the controlled ROP of CL and VL at room temperature.[57] This catalyst system has been used for the controlled ROP of lactones with the cyclic carbonate, 1,3-dioxepane-2-one, to produce di- and triblock copolymers with controlled molecular weights and narrow PDIs. Similarly, Lee and co-workers synthesized block copolymers of poly(ethylene glycol) (PEG) and poly(caprolactone) (PCL) by the living ROP of CL from a PEG initiator in the presence of the $HCl{\cdot}Et_2O$ catalyst.[58]

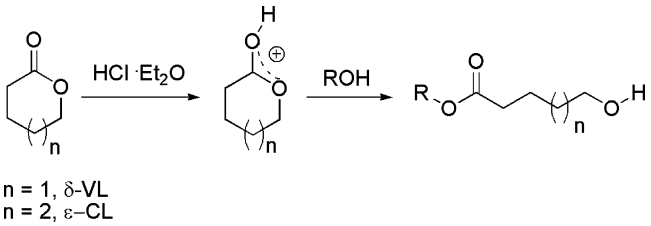
Jerome and co-workers have prepared high molecular weight (M_n up to 50 000 g/mol) poly(valerolactone) (PVL) with very narrow PDIs (~1.05) using the alcohol initiator/



DPAT

Figure 3. Structure of diphenylammonium triflate, DPAT.

Scheme 6. Proposed Activated Monomer Cationic Polymerization of Lactones

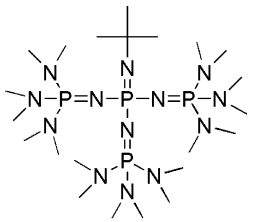


$HCl{\cdot}Et_2O$ system.[59] Reactions were performed with the initial monomer concentration of 4 M in CH_2Cl_2 at 0 and 25 °C for monomer-to-initiator ratios of <300, resulting in high reaction yields in several hours. Unlike for PVL, synthesis of PCL with a molecular weight higher than 15 000 g/mol was unsuccessful under these conditions. A series of α-functional, ω-hydroxylpoly (VL)s was prepared from a series of functionalized alcohols including 9-anthracenemethanol, 2-hydroxyethyl acrylate, 3-buten-1-ol, 2-bromoethanol, and 5-norboernen-2-methanol. The incorporation of the alcohol initiator was confirmed by ^1H NMR and/or GPC using refractive index and UV detectors. In addition, copolymers of poly(ethylene oxide) (PEO)−*b*-poly(VL) di- and triblock polymers were prepared in several hours at 0 °C by ROP of VL using functionalized hydroxyl end-capped polyethers.

Polymerizations of lactones using the $HCl{\cdot}Et_2O$ catalyst are proposed to go through an activated-monomer mechanism where the acid protonates the monomer and facilitates ring-opening by the initiating or propagating alcohol end groups of the growing polymer chain (ROH) in Scheme 6.

Organic and amino acids are also able to catalyze the cationic polymerization of cyclic lactones. The bulk polymerization of CL and VL at 120 °C was performed in 2−7 h using 3 mol % benzyl alcohol and 10 mol % organic acid with catalyst efficiency following the order of tartaric acid > citric acid > lactic acid > proline.[60] A living polymerization was suggested based on the linear relationship between M_n and percent conversion in addition to PDIs (1.29−1.35) for the low molecular weight polymers reported (up to $M_w \approx 2\,700$ g/mol). Terminally carbohydrate-modified PCL has also been obtained using L-lactic acid-catalyzed ROP of CL initiated with β-D-glucopyranoside, sucrose, or raffinose initiators.[61] More recently, lactic acid-catalyzed bulk ROP of CL with the hexahydroxy-functional dendrimer 2,2-bis-(hydroxymethyl)propanoic acid as the initiator was reported.[62]

Polyesters with various polymer architectures have been accessed through cationic acid catalysis. Star polylactones have been synthesized using fumaric acid as the organocatalyst. Endo and co-workers successfully prepared three- and four-armed star PCLs using trimethylpropane and pentaerythritol as initiators, in the presence of fumaric acid catalyst at 90 °C in bulk after 12 h.[63] Room-temperature studies in tetrahydrofuran (THF) or CH_2Cl_2 using the $HCl{\cdot}Et_2O$ catalyst proved relatively unsuccessful, likely due to the low solubility of the pentaerythritol initiator. Similarly, star polymers of VL with M_n's up to 99 000 g/mol were produced by the bulk polymerization of VL at 100 °C after 18 h in the presence of fumaric acid as the catalyst and dipentaerythritol as the multifunctional initiator.[64] The six-arm homopolymers with predictable weight and narrow PDIs were then coupled with α-methoxy-ω-chloroformate PEG to produce star copolymers of poly(VL)-*b*-methoxy PEG.



***t*-ButP$_4$**

Figure 4. Chemical structure of the Schwesinger's phosphazene *t*-BuP_4.

The biocompatibility of these materials was examined through cell viability assays that suggest noncytotoxicity of the copolymers.

In the absence of a protic initiator, amino acids have been shown to initiate the ROP of CL.[65] The polymerization is believed to proceed through cleavage of the acyl−oxygen bond and addition of the amino group of the acid to form the −NHCO− linkage. PCL with M_n up to ∼22 000 g/mol was achieved through bulk ROP of CL at 160 °C for 24−248 h. Evidence of amino acid incorporation was supported by ^1H NMR and titration of the carboxyl group. Though the molecular weight of PCL was dependent on the ratio of monomer to initiator, the PDIs were broad, ranging from 1.50 to 1.89.

Acid catalysts for the cationic ROP of lactones have also been supported on silica for potential catalyst recovery and reuse.[66] In 2004, Jones and Wilson generated polymers with controlled molecular weights and narrow PDIs using *n*-propylsulfonic acid-functionalized porous and nonporous materials. Reaction time for high conversion (up to 90%) was on the order of days, and the supported catalysts were significantly less active than their homogeneous analogues. Furthermore, the catalyst regeneration and reuse was unsuccessful as described, providing little advantage over conventional acid catalysts.

3. Anionic Ring-Opening Polymerization

The anionic polymerization of lactones with Li or K alkoxides is well-known,[67,68] but less work has been done on the anionic ROP of strained heterocycles with organic counterions. Schladd et al.[69] reported the ROP of ethylene oxide using Schwesinger and Schlemper's phosphazene base[70] *t*-BuP_4 (pKa = 30.2 in dimethyl sulfoxide (DMSO), Figure 4). The base, when protonated, acts as a counterion in the metal-free anionic ROP of ethylene oxide and produces PEO with limited molecular weights as reported. Similarly, Rexin and Mülhaupt[71] employed related bulky phosphonium cations for the ROP of propylene oxide to generate low molecular weight polymer. The combination of an alcohol and Schwesinger's phosphazene base has been shown to be a fast initiator for the ROP of cyclic siloxanes such as octamethylcyclotetrasiloxane.[72]

Commercially available phosphazene bases (2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP) **1** ($^{MeCN}pK_{BH}$+ 27.6) and *N*′-*tert*-butyl-*N*,*N*,*N*′,*N*′,*N*″,*N*″-hexamethylphosphorimidic triamide (P_1-*t*-Bu) **2** ($^{MeCN}pK_{BH}$+ 27.6) (Figure 5) have been used for the ROP of cyclic esters including LA and VL.[73]

The catalytic activity of these bases was studied in dry toluene at room temperature for polymerizations with targeted monomer-to-initiator ratios of 100 using 1-pyrene-

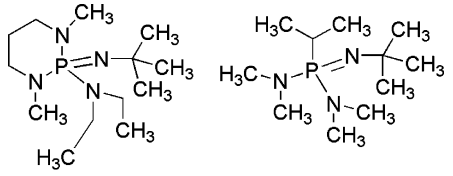


Figure 5. Chemical structure of phosphazene bases, BEMP **1** and P_1-*t*-Bu **2**.

butanol as the initiator. For example, at a 1 mol % catalyst **1**-to-monomer ratio, polymerization of L-LA reached 78% conversion in 23 h to give PLLA with M_n of 13 100 g/mol and a narrow PDI (1.08). A plot of M_n versus monomer conversion showed a linear correlation, characteristic of a living polymerization. The PDI decreases slightly as the conversion approaches 70% and then increases. The increase of molecular weight distribution at high conversion is likely due to the transesterification as the monomer supply is depleted. In an effort to minimize adverse transesterification reactions, the reaction was quenched by the addition of benzoic acid. Polymerization of *rac*-LA yields isotactic-enriched PLA with the probability of isotactic propagation (P_i) equal to 0.70.

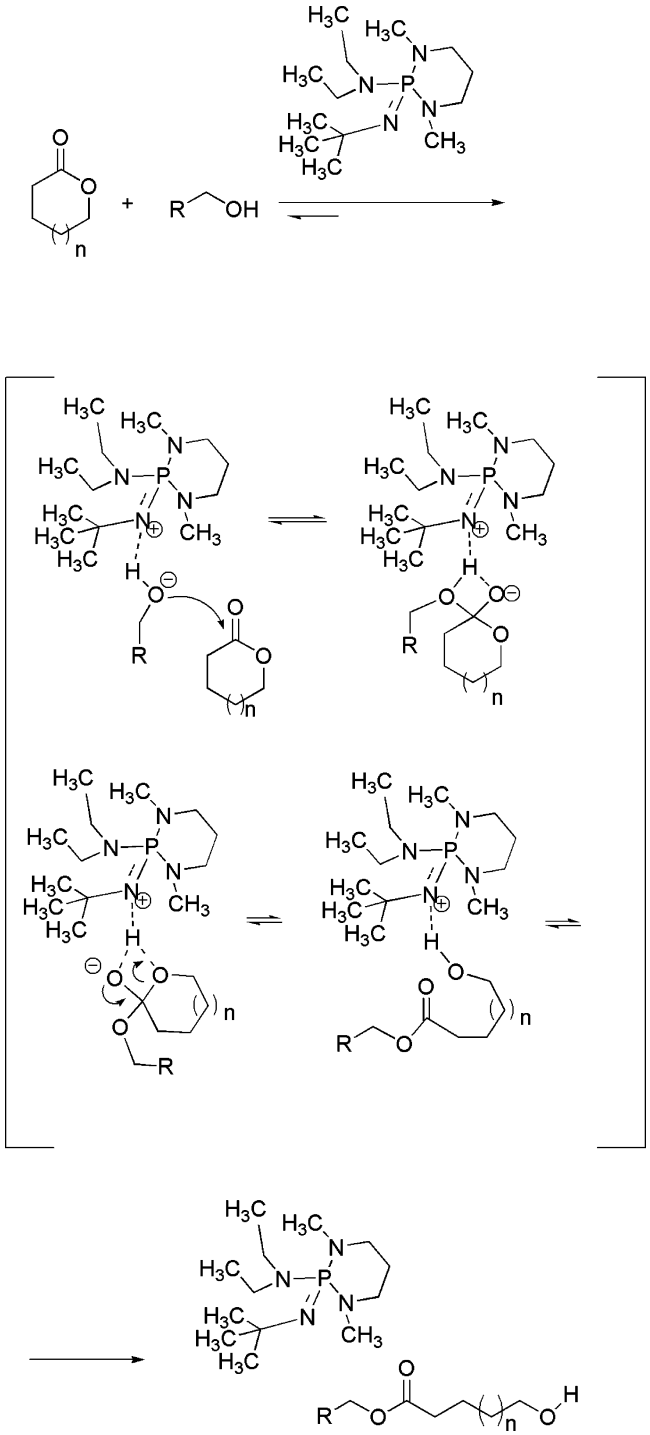
Catalysts **1** and **2** also promoted the ROP of VL. A monomer/initiator/catalyst ratio of 100/1/1 produced PVL in bulk conditions with 70% conversion in 73 h with M_n of 9 200 g/mol and a narrow PDI (1.12). Higher conversions were possible even though the reaction mixture solidified, and the polymer molecular weight was linear with the conversion of the monomer. Mechanistic studies suggest that the intermolecular hydrogen bonding of the alcohol initiator to phosphazene bases activates the alcohol for ROP of cyclic esters, as shown in Scheme 7.

The commercially available compounds, *tert*-butoxybis-(dimethylamino)methane (**3**, also known as Bredereck's reagent) and tris(dimethylamino)methane **4**,[74−79] were investigated for the ROP of LA[80] because they are reminiscent of other protected forms of *N*-heterocyclic carbenes (NHCs)[81−87] and were expected to show similar reactivities. The ROP of LA with commercially available Bredereck-type reagents in the presence of or absence of alcohol initiators is an efficient method for the synthesis of PLAs of controlled molecular weight and narrow PDIs. High monomer conversion was reached after 3 h at 70 °C in THF solution or in several minutes when vacuum was applied. Although these compounds were initially envisioned as precursors to stabilized carbenes, alternative mechanisms involving heterolytic cleavage to alkoxides were proposed, suggesting that these reagents can function as latent anionic initiators for ring-opening polymerization reactions. As shown in Scheme 8, the ring-opening of the LA by the alkoxide provides a propagating anion. This anion can continue to ring open LA through an anionic mechanism. Because 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.

4. Enzymatic Ring-Opening Polymerization

The field of enzyme-catalyzed ring-opening polymerization has grown since the initial application of a lipase catalyst for ring-opening of lactones by the independent groups of Kobayashi[88,89] and Knani.[90] Enzymes exhibit high stereo-, reaction-, and substrate specificity and come from renewable

Scheme 7. Proposed Mechanism for the ROP of Lactones Using Phosphazene Base 1

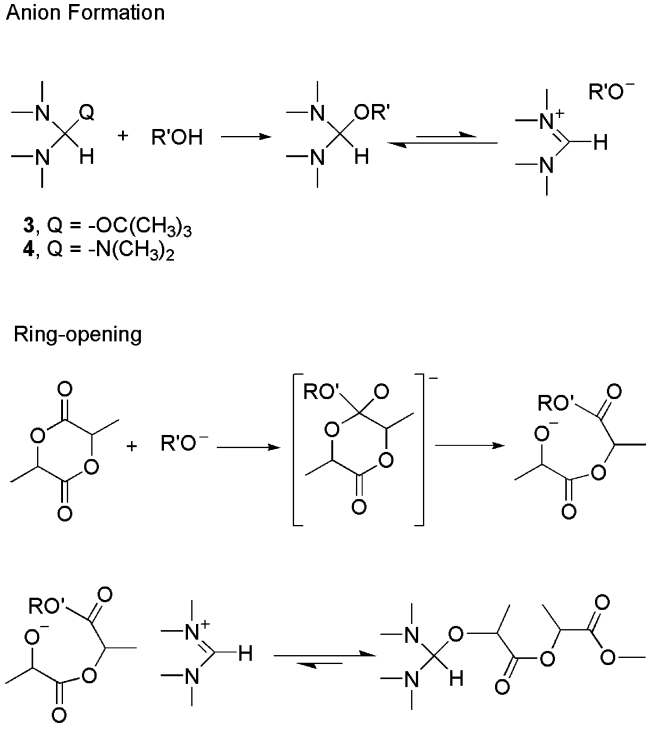


resources that can be easily recycled. Noteworthy advances using enzymes for ROP of various monomers to generate, for example, aliphatic polyesters, polycarbonates, polythioesters, polyphosphates, and polysiloxanes have been made and thoroughly reviewed by Albertsson and co-workers,[32,91] Gross and co-workers,[44,92] Heise and co-workers,[93,94] Kobayashi and co-workers,[45,95] and Matsumura.[96] The reader is referred to these for further discussion.

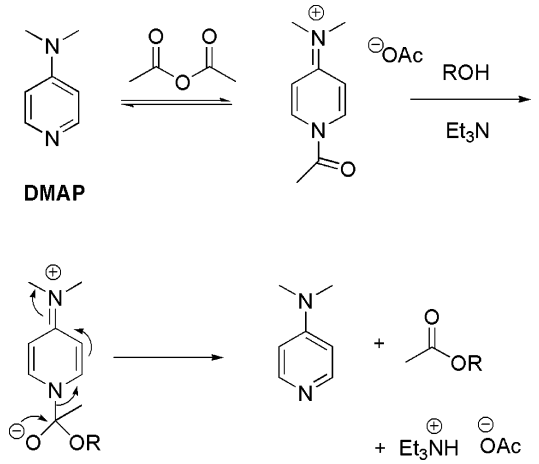
5. Pyridine-Based Organocatalysts

The use of dialkylaminopyridine (DMAP) as a nucleophilic catalyst for the acylation of hindered alcohols was reported

Scheme 8. Proposed Mechanism for LA ROP by 3 and 4



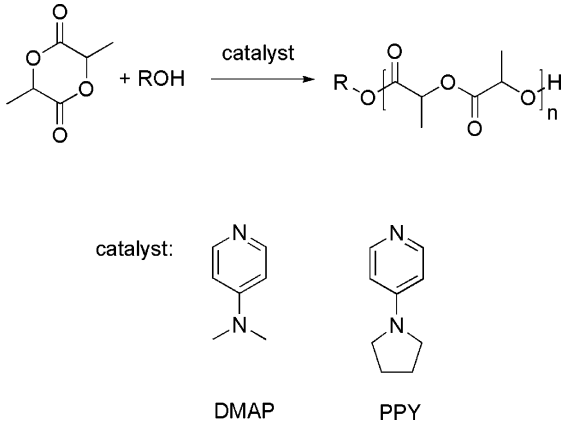
Scheme 9. Proposed Mechanism for a DMAP-Catalyzed Acylation Reaction



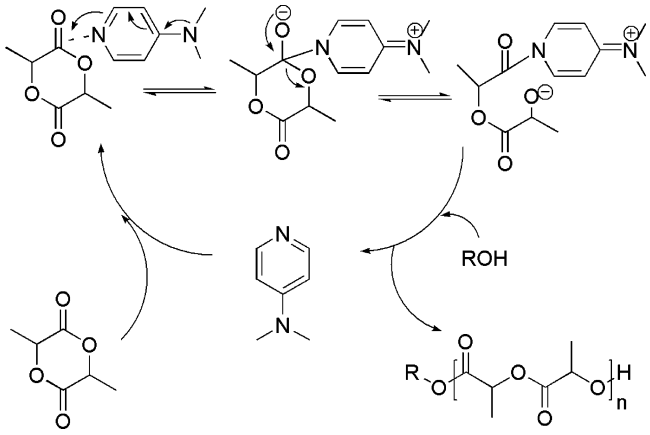
almost 40 years ago by Steglich and Hofle.[97] In later studies by Vorbruggen and co-workers,[98] catalytic amounts of DMAP or 4-pyrrolidinopyridine (PPY) were observed to dramatically enhance yields and reaction rates for the acylation of amines and sterically hindered alcohols. Similarly, the replacement of pyridine by DMAP for the benzoylation of *m*-chloroaniline resulted in 10^4 rate enhancement as observed by Litvinenko and Kirichenko.[99] The commercially available DMAP catalyst is often the common choice for acylation reactions and at times results in high regio- and stereoselectivities.[100] Acylation reactions catalyzed by DMAP are proposed to proceed by a nucleophilic mechanism involving an acyl pyridinium intermediate (Scheme 9).[98,101]

The 4-aminopyridines DMAP and PPY are better catalysts than pyridine.[101] Recently, more potent structural analogues of DMAP/PPY such as bicyclic diaminopyridines and tricylic triaminopyridenes[102] or analogues in which the 4-amino group is conformationally fixed in a ring fused to the pyridine ring[103] have been reported.

Scheme 10. ROP of LA with Amine Catalysts



Scheme 11. Proposed Mechanism for the ROP of LA Using DMAP Catalyst



In addition to acylation, various organic transformations such as alkylations, transesterification, silylations, Baylis−Hillman reactions, nucleophilic substitutions, derivatizations of amines, and others have been catalyzed efficiently by DMAP and have been the subject of several reviews.[98,100,104−106] Chiral versions of DMAP and other nucleophilic amines have been employed as catalysts in various asymmetric transformations and are reviewed elsewhere in this issue.

In 2001, the first organocatalytic approach to the living ROP of LA was reported using Lewis basic amines such as DMAP and PPY as transesterification catalysts (Scheme 10).[107] Using ethanol as an initiator, the amines are effective catalysts for the ROP of LA at 35 °C in CH_2Cl_2 with reaction times ranging from 20 to 96 h. PLAs with narrowly dispersed PDIs with DPs ranging from about 30 to 120 were prepared. High amine concentrations relative to the initiator (1 equiv or greater) proved to be active and highly selective for the ROP of LA in 100% yield. No polymerization was detectable in the absence of the initiator. Bulk polymerizations of D,L- and L-LA at 135 and 185 °C, respectively, using benzyl alcohol as the initiator gave narrowly dispersed polymer in 5−20 min depending on the targeted molecular weight.

The living character of the polymerization was demonstrated by the linear correlation of molecular weight versus monomer conversion in addition to the resulting narrow PDIs and predicted molecular weights based on monomer-to-initiator ratios. Polymerization was proposed to occur through a monomer-activated mechanism, as shown in Scheme 11, but an alcohol-activated mechanism (chain-end activation) cannot be ruled out. The monomer-activation mechanism was

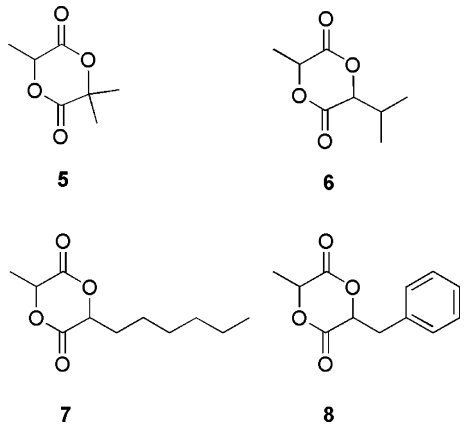


Figure 6. Structure of the substituted LAs **5**−**8** for ROP using DMAP catalyst.

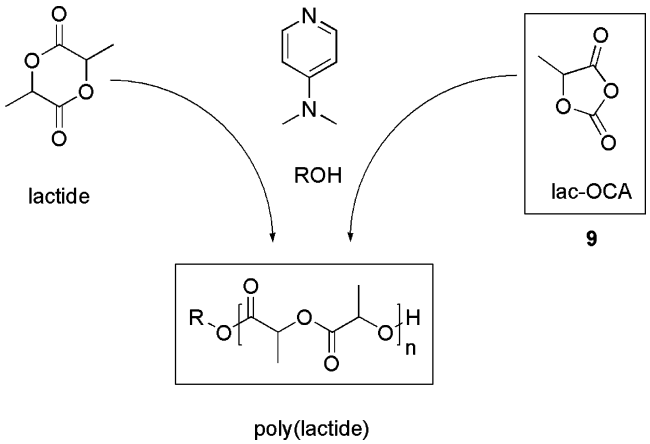
proposed to occur by nucleophilic attack by DMAP on the monomer to generate an alkoxide/acyl pyridinium zwitterion. Subsequent proton transfer from the initiating or propagating alcohol, followed by acylation of the resultant alkoxide, generates the hydroxy-terminated ring-opened monomer. Polymerization proceeds by reaction of the ω-hydroxyl group with the next DMAP−LA intermediate. Studies by ^{1}H NMR spectroscopy confirm the α-chain end of the PLA bears the ester from the initiating alcohol and the ω-chain end bears a hydroxyl group. DMAP is effective for the ring-opening of LA in the presence of either a primary or a secondary alcohol. The resulting propagating species, a secondary alcohol, however, is only active toward the LA monomer and not the polymer chain, minimizing undesirable transesterification reactions.

DMAP was also applied to the depolymerization of PLA with primary alcohols.[108] As primary alcohols undergo transesterification reactions much more rapidly than secondary alcohols, the selective functionalization of PLA chains could be carried out with primary alcohols in the presence of DMAP to selectively introduce end groups onto the PLA chains. DMAP-catalyzed bulk transesterification reactions of commercially available high molecular weight PLA (M_n = 50 000 and 100 000 g/mol) in the presence of various multifunctional alcohols resulted in PLAs with monomodal PDIs and predictable molecular weights consistent with the monomer-to-alcohol initiator ratio. Thus, this new depolymerization strategy based on a transesterification reaction using DMAP provides a facile, single-step route to functionalized polymers with various architectures such as block and star polymers.

DMAP was also shown to catalyze the ROP of L-LA in the presence of a poly(L-lysine) dendron initiator to produce biodegradable poly(L-LA)-*b*-dendritric(L-lysine)s at 55 °C in chloroform with high conversion after 20−80 h.[109]

Moeller and co-workers[110,111] demonstrated that DMAP is an efficient catalyst for the neat ROP of alkyl-substituted LA monomers **5**−**8** shown in Figure 6. Using catalyst concentrations similar to those reported in the previous study[107] (DMAP-to-alcohol initiator ratio of 2), polymerization of LAs **6**−**8** reached 80, 97, and 95% conversion, respectively, after 1 h at 110 °C for targeted DPs of 26−29. Polymerization of D,L-LA at high conversions resulted in polymer with higher PDIs (1.48) relative to polymerizations with the substituted LAs (1.10−1.20). The increase in PDI is likely due to undesirable transesterification or side reactions accessed at the high reaction temperature (110 °C),

Scheme 12. DMAP-Catalyzed Preparation of PLA from the α-Lactone Equivalent *O*-Carboxyanhydride, Lac-OCA 9



as an earlier study[107] reported no broadening in polydispersity when reactions were at lower temperatures (35 °C).

Bourissou recently employed DMAP as an organocatalyst for the ROP of activated equivalents of LA, namely, *O*-carboxyanhydrides, yielding PLAs of controlled molecular weights and PDIs (Scheme 12).[112] The ROP of lac-OCA **9** reaches complete conversion at room temperature in 0.75 M CH_2Cl_2 solution after minutes to hours, depending on the monomer-to-alcohol initiator (*neo*-PentOH) ratio (in the range 10−600) with the initiator-to-catalyst ratio of 1. By comparison, the ROP of L-LA took 4 days at 35 °C in CH_2Cl_2 solution to reach complete conversion for monomer/initiator/catalyst ratio of 10/1/1. Similarly, in previous studies,[107] the ring-opening polymerization L-LA required elevated temperatures and long reaction times (20−96 h). Both primary and secondary alcohols (such as isopropanol) were shown to be good initiators. The living character of the polymerization was demonstrated by linear plot of DP_{NMR} versus monomer conversion, polymers with predictable weights, and a second-feed experiment. Narrow PDIs (<1.3) at high monomer conversions suggested that side transesterification reactions were insignificant. A nucleophilic mechanism was proposed where polymerization proceeds by attack of the DMAP catalyst on the electrophilic carbonyl group of lac-OCA, followed by an exchange reaction with the alcohol initiator or polymer chain and subsequent decarboxylation. The liberation of CO_2 was suggested to be a considerable driving force for the activity difference between lac-OCA and LA.

Attempts by Pohl and co-workers to polymerize BL using DMAP resulted in only oligomers with a DP < 8 at temperatures required for the reaction.[113] Evidence of crotonate end groups formed in terminating steps is given by ^{1}H NMR and MALDI-mass spectrometry. The zwitterionic polymerization of pivalolactone using a variety of amines has been intensively studied.[114] The ROP of pivalolactone by DMAP was recently reinvestigated and shown to proceed by initial nucleophilic attack by DMAP with carbon−oxygen bond cleavage to generate alkylpyridinium end groups and a carboxylate chain end.[115]

The use of DMAP as an organocatalyst has been extended to the graft CL polymerization with a polysaccharide chitosan initiator in the presence of water as the swelling agent.[116] Studies suggest, however, that polymerization is initiated from the amino group, not the hydroxyl group, of the chitosan.

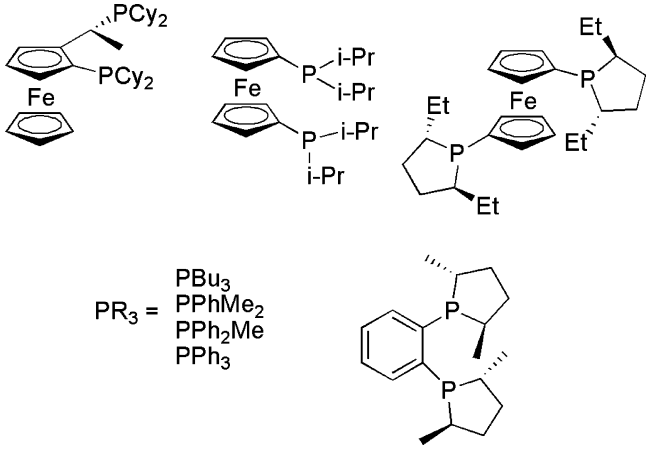


Figure 7. Library of phosphine catalysts for the ROP of LA.

Reaction rate enhancements accompanied at times with a decrease in extraneous transesterification have been observed by the addition of amines such as DMAP and other Lewis bases such as phosphines to traditional organometallic catalysts such as $Sn(Oct)_2$ and $Al(OiPr)_3$ for the ROP of cyclic esters.[117−119] Similar rate enhancement results were obtained when Lewis bases were used as a solvent or additive in LA polymerizations with $Sn(OTf)_2$.[120]

Among the cyclic heterocycles whose polymerization can be catalyzed or initiated by amine nucleophiles such as DMAP, the ROP of α-amino acid *N*-carboxyanhydrides (NCA)s is important because it provides a convenient synthetic route into polypeptides with various architectures and applications. Comprehensive reviews of this area have recently been published by Kricheldorf[121] and Deming.[122]

6. Phosphine Catalysts

Phosphines are commonly recognized as ligands in organometallic chemistry and homogeneous catalysis[123] but are also capable of mediating a variety of organic transformations[124] including acylation reactions.[125,126] A series of tertiary phosphines (Figure 7) were used as transesterification catalysts for the ROP of LA.[127]

In the presence of a benzyl alcohol initiator, phosphines were found to be effective ROP catalysts, generating narrowly dispersed PLA (PDI = 1.11−1.40) with predicted molecular weights (target DPs 30−100). The narrow, monomodal molecular weight distributions suggest minimal transesterification originating from transesterification of the polymer chain. The phosphine-catalyzed polymerizations in CH_2Cl_2 or toluene solution were slower, were less selective, and required higher temperatures (94 °C) than those catalyzed by DMAP. Effective polymerization using these phosphines was performed in bulk. Unlike the amine-catalyzed polymerization, complete LA monomer consumption was not observed when reactions were performed in solution.

Phosphine catalyst activity toward LA polymerization decreased according to the following order: $P(n\text{-}Bu)_3$ > $P(tert\text{-}Bu)_3$ > $PhPMe_2$ > Ph_2PMe > PPh_3 > $P(MeO)_3$ (unreactive). As expected for a proposed nucleophilic mechanism, the more basic and nucleophilic alkyl-substituted phosphines were more effective LA polymerization catalysts than phosphines with one or more aryl groups. Similar results were observed for related $P(Bu)_3$ acylation reactions, which are also suggested to go through a nucleophilic catalyst mechanism.[125,126,128−131]

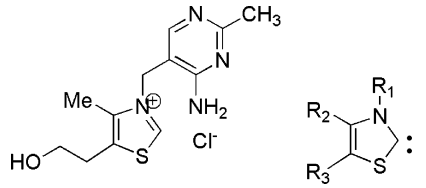
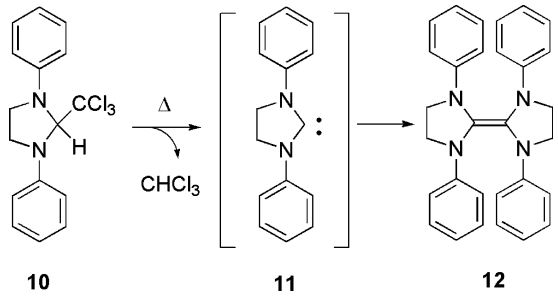


Figure 8. Thiamine (vitamin B_1) and carbene derivative.

Scheme 13. Preparation of Wanzlick's Carbene



The ^1H NMR spectrum of PLA initiated with 1-pyrenebutanol with $P(Bu)_3$ as the catalyst shows the resonances associated with the butyl ester and the hydroxyl group. GPC traces of PLA initiated from 1-pyrenebutanol using both the refractive index and UV detectors (410 and 350 nm, respectively) show a statistical distribution of pyrene throughout the sample. Coupled with ^1H NMR studies, the results indicate the presence of one initiator alcohol per chain.

7. *N*-Heterocyclic Carbenes (NHC)s

The possibility that stabilized singlet carbenes could function as nucleophilic catalysts was first indicated in Breslow's pioneering studies in 1958 on the mechanism of action of the coenzyme thiamine (vitamin B_1, a naturally occurring thioazolium salt, Figure 8).[132] Breslow demonstrated that both thiazolium salts and imidazolium salts catalyze the benzoin condensation by a mechanism involving deprotonation of the thiazolium and nucleophilic attack on the aldehyde by a process analogous to the catalytic activity of cyanide.[133] This seminal work established the general concept that deprotonated thiazolium or imidazolium salts can act as nucleophilic catalysts.

Soon after Breslow's studies, Wanzlick and co-workers carried out a series of investigations on NHCs based on imidazolin-2-ylidenes[134−138] and proposed that the deprotonated thiazolium and imidazolium salts fall into a general class of heteroatom-stabilized nucleophilic carbenes.[137] The bis-1,3-diphenyl imidazolin-2-ylidenes **11** were initially generated by elimination of chloroform from the imidazoline **10** (Scheme 13) but could also be prepared by the depronon-ation of the imidazolium salts.[134,135−138] At the time, these carbenes were not isolated but could be identified by trapping reactions with oxygen, water, hydrochloric acid, and cyclopentanone—indirect evidence for the nucleophilic character of the carbene species. In the absence of trapping agents, the bis-1,3-diphenyl imidazolin-2-ylidene dimerizes readily to the tetraamino olefin **12** (Wanzlick dimer). Wanzlick's controversial proposal[137] that the tetramino olefin **12** was in equilibrium with the free carbene[139,140] was later shown to be true only for specifically substituted carbenes.[141,142]

Substantial progress in the chemistry of heteroatom-stabilized singlet carbenes was achieved almost 20 years later

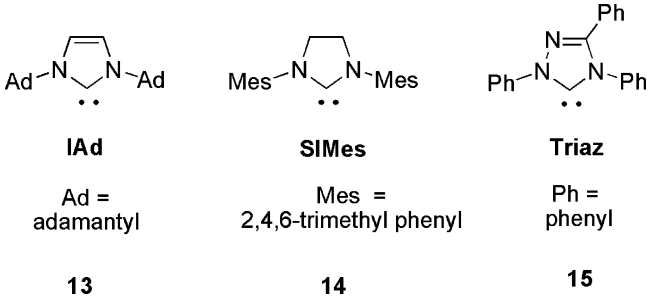


Figure 9. Chemical structure of Arduengo's and Enders's carbene.

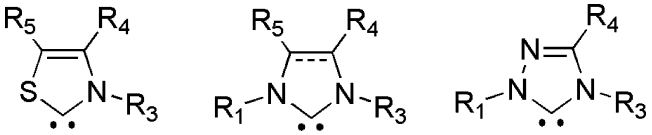


Figure 10. Steric and electronic diversity of NHCs.

with Arduengo and co-workers's[143,144] and Bertrand et al.'s[145] studies on the preparation of stable heteroatom-stabilized carbenes. Arduengo and co-workers prepared, isolated, and characterized, in 1991, the imidazol-2-ylidene **13**,[143,144] a crystalline solid at room temperature, and later in 1995, the saturated imidazolin-2-ylidene **14** (Figure 9).[146] Enders et al. synthesized and isolated the free triazol-5-ylidene **15**[147] that was shown to be stable to high temperatures (up to 150 °C) in the absence of air and water.

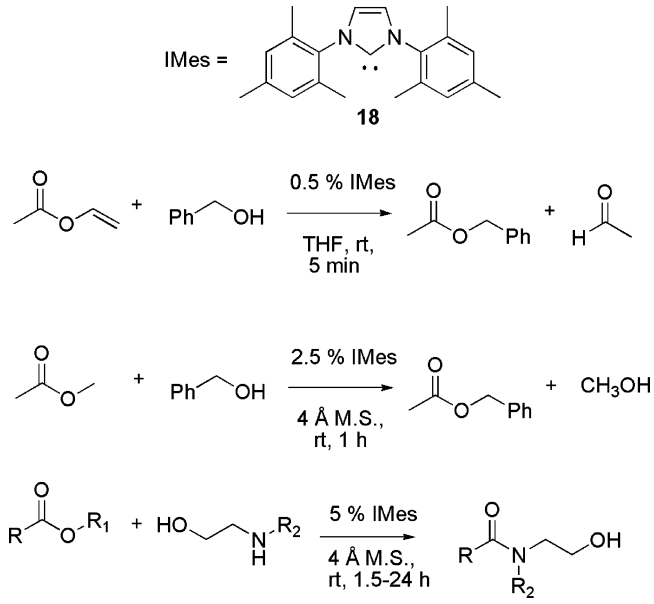
The isolation of these stable carbenes in the 1990s stimulated extensive studies on NHC preparation and application. NHCs can be synthesized with considerable diversity by varying the heteroatom in the ring, the steric and electronics of the substituents attached to the nitrogen (or heteroatom) (R_1, R_3), the imidazole ring (R_4, R_5), and the ethylene backbone (i.e., saturated versus unsaturated) (Figure 10).

Several excellent reviews have appeared on different aspects of this highly dynamic research area.[21,145,148−154] As potent sigma-donors, NHCs have been extensively investigated as alternatives to the well-established phosphine ligands in organometallic compounds. Noteworthy examples include Ru-catalyzed alkene metathesis[155,156] and Pd-catalyzed C−C coupling such as Suzuki−Miyraua and Heck reactions.[157,158]

7.1. Organocatalysis Using NHCs

Breslow's studies stimulated several groups to investigate the use of stabilized carbenes as nucleophilic organic catalysts. Stetter demonstrated the use of thiazolium salts for the addition of aliphatic aldehydes to α,β-unsaturated ketones.[159] The formoin condensation converting formaldehyde to glycolaldehyde is catalyzed by carbenes derived from imidazolium, thiazolium, and triazolium salts.[160] NHCs are also capable of mediating asymmetric variants of these transformations.[21,161] Early studies by Sheehan and Hunneman in 1966[161] were extended significantly by Enders and Kallfass[162] and Knight and Leeper,[163] employing chiral triazolium and thiazolium salts for asymmetric benzoin condensation reactions utilizing NHC salts with high yields and enantioselectivities. Enders et al.[164] and Rovis and co-workers[165] have reported that chiral triazole carbenes are effective catalysts for asymmetric intramolecular Stetter reactions. Along similar lines, Murry et al. have reported the stereoselective thiazolium-catalyzed intermolecular aldehyde−imine cross-coupling.[166] Bode and co-workers,[167]

Scheme 14. NHC-Catalyzed Transesterification



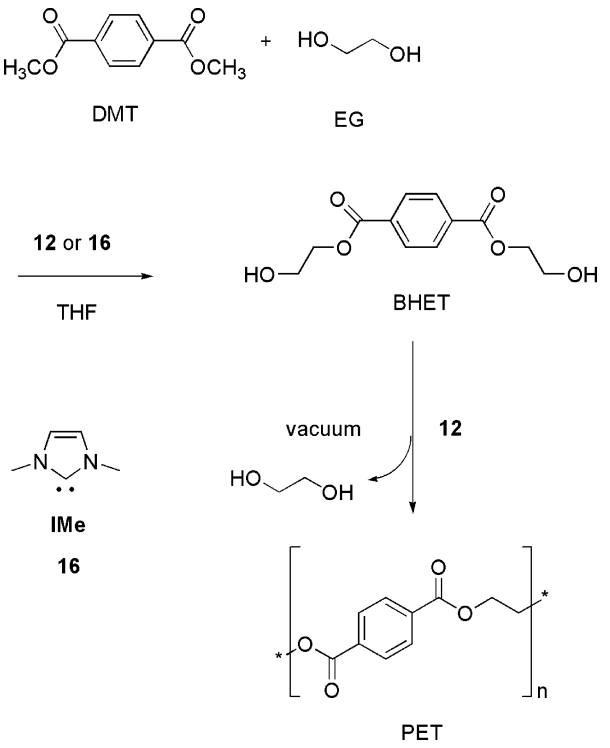
Rovis and co-workers,[168] Chan and Scheidt,[169] and Burstein and Glorius[170] have developed clever cascade nucleophilic acylation reactions from reactions of *N*-heterocyclic carbenes with aldehydes or enals.

N-heterocyclic carbenes are also highly efficient transesterification catalysts for a variety of carboxylic acid esters[154,171−174] and phosphorus esters.[175] Transesterification reactions are sensitive to the natures of both the carbene and the alcohol. The *N*-alkyl substituted carbenes are more effective than the *N*-aryl carbenes, particularly for secondary alcohols,[171−173] but the strongly basic IAd carbene **13** can also enolize methyl acetate.[176] The diaryl carbene IMes as well as the less sterically hindered 1,3-bis(dimethyl)imidazol-2-ylidene (IMe) **16** and 1,3-bis(methyl,ethyl)imidazol-2-ylidene (IEtMe) **17** (generated in situ from the imidazolium salts) catalyze the transesterification of methylbenzoate with excess ethanol to 80% conversion in 1 h (4 mol % catalyst), but with secondary alcohols, the less sterically hindered carbenes IMe **16** and IEtMe **17** are more effective.[171] The use of molecular sieves enables the facile transesterification of methyl esters with stoichiometric amounts of alcohols in the presence of 0.5 mol % NHC catalysts (Scheme 14). Vinyl esters are particularly effective for acylation of secondary alcohols,[154,172−174] which enabled the kinetic resolution of secondary alcohols in the presence of chiral carbenes with moderate (0−25 °C)[177,178] to high selectivities (−78 °C).[179] The carbene IMes **18** also catalyzes the amidation of esters with amino alcohols.[180]

The high reactivity of *N*-heterocyclic carbenes for transesterification reactions has been exploited for the step-growth polycondensation reactions[171] and depolymerization reactions[181] of engineering thermoplastics. High molecular weight polyesters PCL and poly(glycolide) were prepared using NHC-catalyzed self-condensations of ethyl 6-hydroxyhexanoate and ethyl glycolate, respectively, in bulk at 60 °C under vacuum for 24 h.

The commercially important polyester poly(ethylene terephthalate) (PET) has been prepared by the NHC-catalyzed process. PET is generally prepared in a two-step process: the condensation of dimethyl terephthalate (DMT) with excess ethylene glycol (EG) in THF at room temperature to generate bis(2-hydroxylethyl terephthalate) (BHET), followed

Scheme 15. Formation of PET by NHC-Catalyzed Transesterification



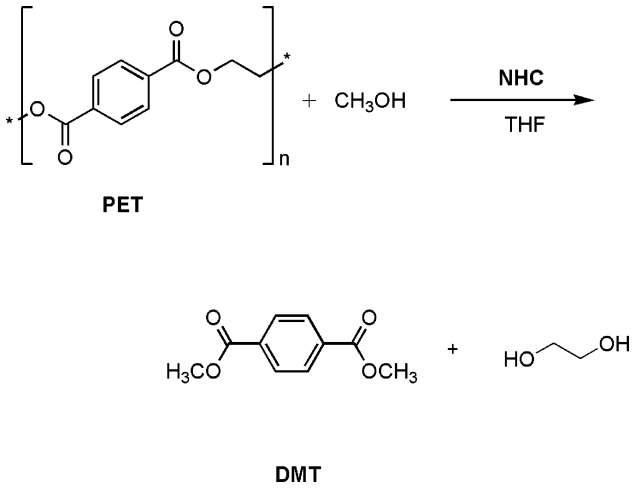
by the self-condensation of BHET at high temperatures (270−290 °C) in the presence of organometallic catalysts. Using an alternative metal-free approach, the tetraamino olefin **12** and carbene **16** were employed to catalyze condensation of DMT with excess EG (Scheme 15). Complete conversion of DMT to BHET was realized in 1 h for both carbenes. An ionic liquid media based on an imidazolium salt, in the presence of a base, also proved to be efficient for this NHC-catalyzed process to form BHET, which could easily be isolated from solvent extraction or precipitation. The melt condensation of BHET was formed in the presence of the tetraamino olefin **12** using a slow heating ramp to 280 °C under vacuum to generated PET. Importantly, the NMR spectra and melting point of the produced polymer were identical to the commercial PET. Tam and Williamson have also reported the polymerization of macrocyclic polyester oligomers to produce linear polyesters in the presence of NHCs.[182]

NHCs effectively catalyze the depolymerization of polyesters.[181] For example, the transesterification reaction of PET with methanol in the presence of a NHC catalyst yields DMT and ethylene glycol (Scheme 16). This depolymerization method is performed under relatively mild conditions (typically at 80 °C or less) and provides an approach to chemical recycling of commercial polymers such as PET.

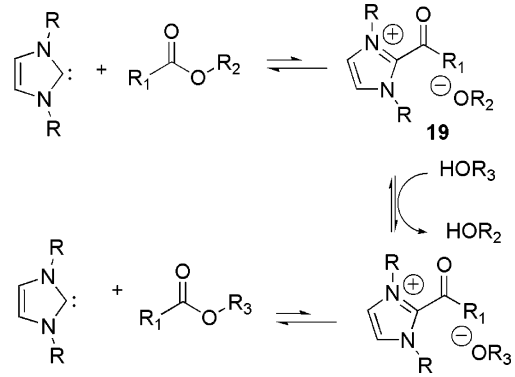
Two mechanisms have been proposed for the NHC-catalyzed transesterification reactions: a nucleophilic mechanism to generate acyl imidazolium intermediates **19** (Scheme 17)[171] and an alcohol-activation mechanism where hydrogen-bonding between the carbene and the alcohol activates the alcohol toward nucleophilic attack[180] and stabilizes the tetrahedral intermediate **20** (Scheme 18).[183]

Indirect evidence for a nucleophilic mechanism in carbene-mediated transesterification reactions was provided by independent generation of an acyl imidazolium intermediate from benzoyl chloride and IMes.[184] Treatment of this

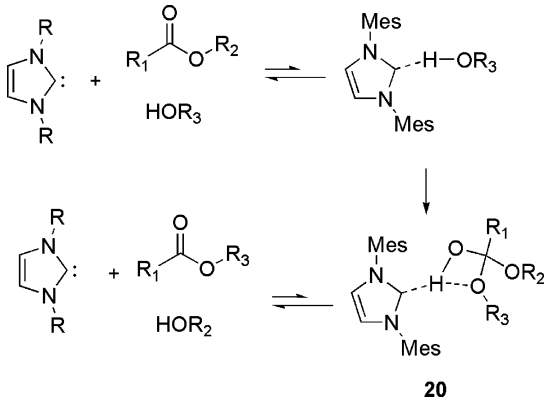
Scheme 16. NHC-Catalyzed Depolymerization of PET



Scheme 17. Nucleophilic Mechanism for Transesterification

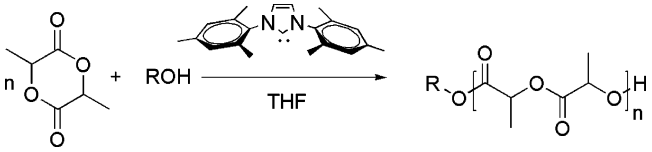


Scheme 18. Alcohol-Activation Mechanism for Transesterification



intermediate with sodium methoxide cleanly generated methyl benzoate, indicating that acylimidazolium species are chemically competent intermediates in transesterification reactions. Evidence for the alcohol-activation mechanism was provided by the isolation and crystal structure of a hydrogen-bonded adduct between IMes and methanol[180] and theoretical studies that suggest that the hydrogen-bonded tetrahedral intermediate and transition states are lower in energy than the acyl imidazolium intermediate.[183] Nevertheless, NHC-catalyzed transesterification reactions have not yet been subject to the detailed mechanistic studies that have helped illuminate the DMAP-catalyzed acylation reactions, for which a nucleophilic mechanism has been invoked.[101]

Scheme 19. ROP of LA with IMes



7.2. Application of NHCs as Ring-Opening Polymerization Catalysts

The high reactivity of *N*-heterocyclic carbenes for transesterification reactions is manifested in their ability to catalyze the ROP of lactones.[153] In 2001, the carbene IMes was shown to catalyze the living ROP of lactones to generate polylactones of defined molecular weight and narrow polydispersity (Scheme 19).[185]

Since this first report, extensive work has been carried out to exploit the wide structural and electronic diversity of *N*-heterocyclic carbenes for the ROP of different monomers including LA,[185−188] lactones,[186] carbonates,[189] and silyl ethers.[190] A wide range of diverse NHCs based on thiazolylidene carbenes, unsaturated imidazolylidene carbenes, saturated imidazolinylidene carbenes, and triazolylidene carbenes have been shown to be effective for ROP (Figure 11), and the activities and selectivities of these polymerizations depend sensitively on the nature of the carbene and the monomer (vida infra).

The ROP of lactones by NHCs exhibit several notable features. Reaction rates can be extremely high. The IMes carbene **18** catalyzes the ROP of LA in the presence of an alcohol initiator within seconds at room temperature (turnover frequency TOF = 18 s^{-1}) with catalyst loadings as low as 0.5 mol %.[191] These rates are comparable to those of the most active metal catalysts reported for ROP of LA.[31,192,193] In addition to the rapid rate of polymerization, the ROP of LA mediated by NHCs is remarkably well-controlled and exhibits many of the features of a living polymerization. The polymerization of LA using the IMes carbene **18** in the presence of an alcohol initiator at room temperature generated PLAs with narrow PDIs (<1.16) with high end-group fidelity (the alcohol initiator is incorporated onto every polymer

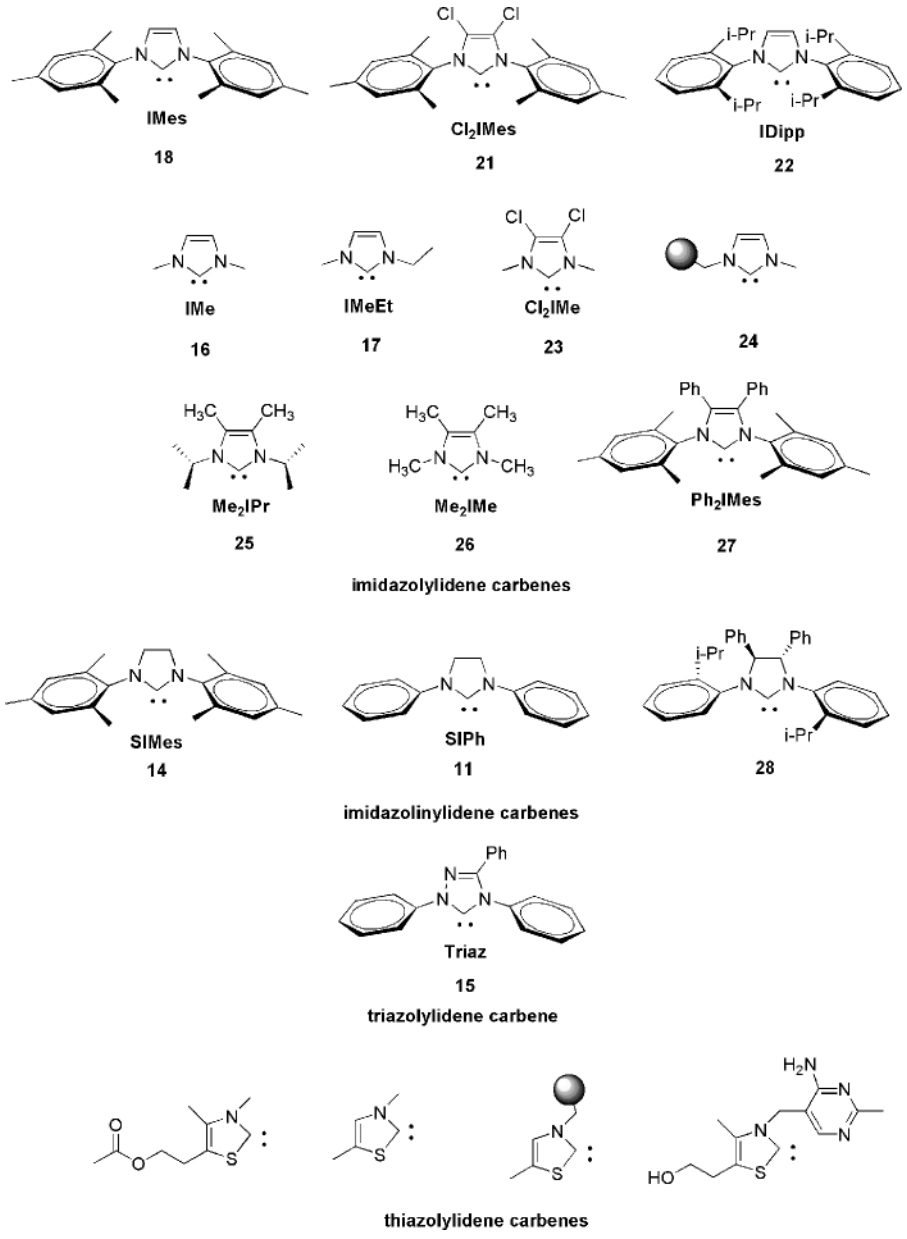
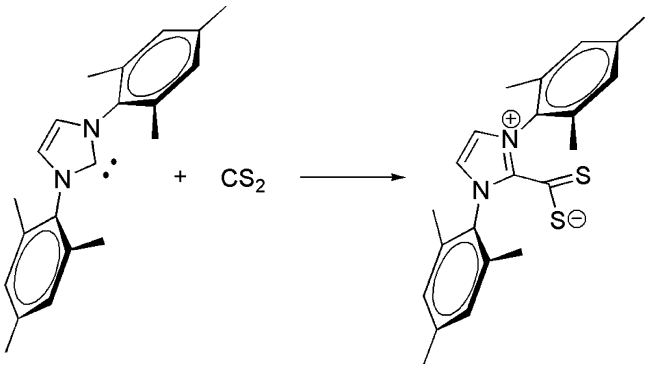


Figure 11. Library of NHCs for ROP.

Scheme 20. Formation of the Zwitterionic Species by Trapping of the IMes Carbene 18



chain). Living polymerization was demonstrated by the linear relationship between molecular weight and conversion, the chain-extension experiments by incorporation of additional monomer, and the synthesis of block copolymers. Polymerizations can be terminated by deactivation of the carbene with the addition of acetic acid, CO_2, or CS_2, the latter of which forms a zwitterionic species[194,195] that is easily removed from the polymer upon precipitation (Scheme 20).

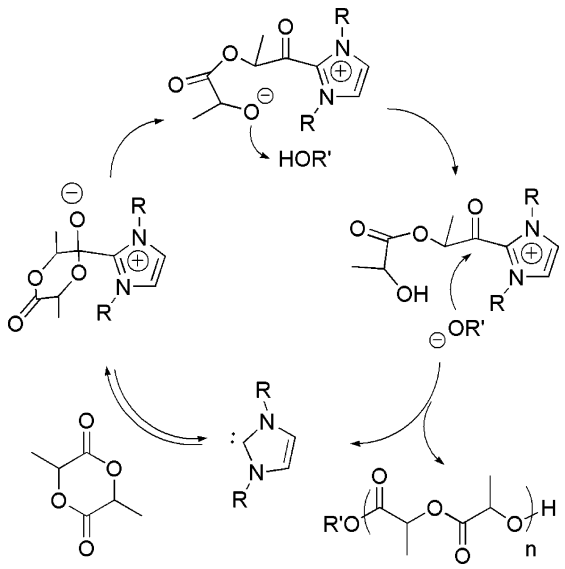
Relative to the polymerization of LA, the ROP of cyclic lactones required longer polymerization times and generally resulted in broader PDIs with the IMes catalyst. Less sterically demanding and more basic carbenes such as **16** and **17** effectively polymerized CL, VL, and BL at room temperature to give polymers with narrower PDIs (1.16−1.32). Recent studies indicate that CL polymerization using NHCs can be complete in minutes.[191,196] Imidazolylidene carbenes were also shown to be effective catalysts for the ROP of CL, VL, and BL.[185,186] The wide steric and electronic diversity of NHCs merits further optimization studies to match the appropriate carbene for the ROP of the respective lactone.

Block copolymers of LA and CL were successfully prepared using the unsaturated carbenes. In addition, amphiphilic block copolymers with M_n up to 25 000 g/mol and narrow PDIs (1.22−1.30) were prepared using monohydroxyl functional PEO oligomers as macroinitiators for the ROP of CL using carbene **16**.[186]

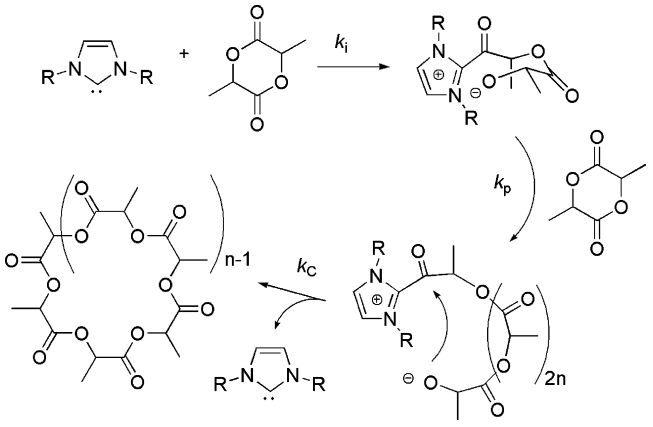
7.2.1. Mechanism of NHC Catalyzed Ring-Opening Polymerization

The ROP of LA mediated by NHCs exhibits many of the features of those catalyzed by DMAP, but it is much faster. The higher nucleophilicity and high basicity of NHCs relative to DMAP is likely responsible for the faster rates. A further advantage of the NHC catalysts is the ability to tune the nucleophilicity and basicity of the NHCs by both electronic and steric effects.[186] Because the ROP is fundamentally a transesterification reaction, two possible mechanisms can be envisaged (Schemes 17 and 18): a monomer-activated mechanism mediated by the nucleophilic attack of the carbene on the lactone and a chain-end-activated mechanism whereby the carbene activates the alcohol toward nucleophilic attack. In their early report, Hedrick and co-workers proposed a nucleophilic mechanism in analogy to the known behavior of pyridine derivatives in acylation reactions[101] and Breslow's proposed nucleophilic mechanism for the benzoin and formoin condensation reactions.[132] The nucleophilic mechanism was favored as it was argued on the basis of relative pKa's that the alcohol was unlikely to protonate the

Scheme 21. Nucleophilic Monomer-Activated Mechanism for ROP



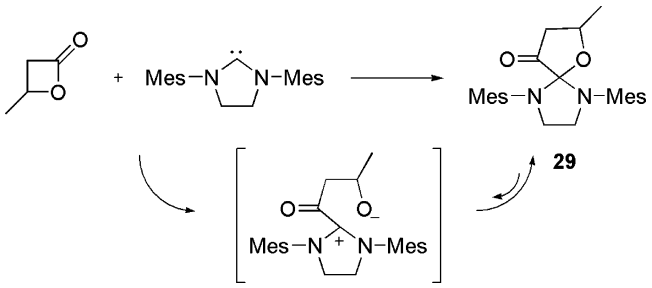
Scheme 22. Zwitterionic Polymerization of LA to Cyclic PLAs



carbene IMes to initiate an anionic polymerization from the alkoxide.[185] Subsequently, it was proposed that hydrogen-bonding between the carbene and the alcohol could activate the alcohol toward nucleophilic attack.[180,183] For the ROP, this would correspond to a chain-end activation mechanism.

A key feature of the nucleophilic mechanism is the formation of a zwitterionic intermediate generated from nucleophilic attack of the carbene on the lactone followed by ring-opening of the tetrahedral intermediate to generate the acylimidazolium alkoxide zwitterions (Scheme 21). Protonation of the alkoxide of the zwitterion by the initiating or chain-end terminated alcohol generates an alkoxide that esterifies the acylimidazolium to generate the open-chain ester and the carbene. Once the initiating alcohol is consumed, the activated monomer (in the form of the zwitterion) appends the activated monomer to the growing polymer chain. Because every growing chain has an equal probability of accepting the activated monomer, all chains would grow at the same rate, a kinetic characteristic of living polymerization reactions. Compelling evidence for the nucleophilic mechanism in the ROP of LA was provided in studies to attempt to generate zwitterions from NHCs and LA in the absence of alcohol initiators.[197] These mechanistic investigations led to a new strategy for generating cyclic polyesters (Scheme 22).

Scheme 23. Formation of Spirocycles from BL and Saturated Carbenes



7.2.2. Zwitterionic Polymerization of LA to Generate Cyclic Polyesters

To assess the role of zwitterionic intermediates in these polymerizations, the polymerization of LA was carried out in the absence of alcohol initiators. Remarkably, these conditions led to the formation of cyclic PLAs of defined molecular weight, even at relatively high monomer concentrations (0.6−1.0 M in THF).[197] The polymerization of *rac*-LA with IMes occurs rapidly (5−900 s) at room temperature to yield cyclic PLAs with molecular weights of 7 000−26 000 g/mol with narrow PDIs. The cyclic structure of the products was determined by a combination of techniques, including the absence of end groups by ^{1}H nuclear magnetic resonance (NMR) spectroscopy, MALDI-TOF mass spectrometry, and the lower solution viscosities of the cyclic polymers relative to their linear congeners.

Notably, these NHC-mediated zwitterionic polymerizations display a remarkable degree of control and exhibit features of living polymerizations. Plots of molecular weight (M_n) against monomer conversion are linear, and PDIs are <1.3 for polymerizations with conversions < 90%. In contrast to other known zwitterionic polymerizations,[35,114,198] high molecular weight cyclic polymers are generated with high selectivities. Polymerization of optically pure L-LA with IMes generated crystalline cyclic PLLA, indicating that the polymerization proceeds with retention of stereochemistry. The selectivity for the formation of high molecular weight macrolactones, even at relatively high monomer concentrations, was proposed to be a consequence of the enforced proximity of the zwitterionic chain ends.[114]

Further evidence for the intermediacy of zwitterions was provided by the reaction of the saturated carbene SIMes **14** with lactones (Scheme 23).[199] Treatment of SIMes **14** with 1 equiv of BL generated a novel spirocycle **29** (Scheme 23). In this case, generation of the zwitterion by nucleophilic attack of the carbene on BL is followed by collapse of the zwitterion to the spirocycle. The spirocycle was shown to be a competent initiator for the ROP of PL. The formation of cyclic PLAs and spirocycles from NHCs and lactones provides compelling indirect support for the viability of the nucleophilic monomer-activated mechanism for the ROP of lactones. Moreover, the formation of large cyclic polyesters highlights the utility of organocatalysts for the construction of novel architectures.

While the foregoing mechanistic studies provide evidence for the viability of a monomer-activated nucleophilic mechanism, they do not rule out an alcohol-activation mechanism. In fact, as discussed elsewhere in this review, the use of strong neutral bases to activate alcohol nucleophiles for ring-opening reactions is a viable and useful strategy for mediating ROP and could well be a competitive process for the ROP of lactones in the presence of NHCs.

A further issue associated with the potent basicity of NHCs[200−202] is the possibility of epimerization of either the PLAs or the LA monomer in competition with ring-opening.[203] To assess the role of epimerization in ring-opening reactions mediated by carbenes, mechanistic studies carried out with excess CH_3OD and LA in the presence of IMes revealed that the ring-opening of LA to methyl dilactate and methyl lactate is much faster than the epimerization of either LA or the opened methyl lactates.[184] Ring-opening of LA with 1 equiv of IMes **18** in the presence of 10 equiv of CH_3OD generated methyl lactate within 10 min. Analysis by ^{1}H NMR provided no evidence for incorporation of deuterium at the alpha-carbon of methyl lactate, indicating that enolization of methyl lactate or LA is not competitive with ring-opening. However, after 3 days at room temperature, ∼50% of the alpha hydrogens were substituted with deuterium, indicating that the carbene is capable of enolizing methyl lactate, but at a rate that is much slower than ring-opening.

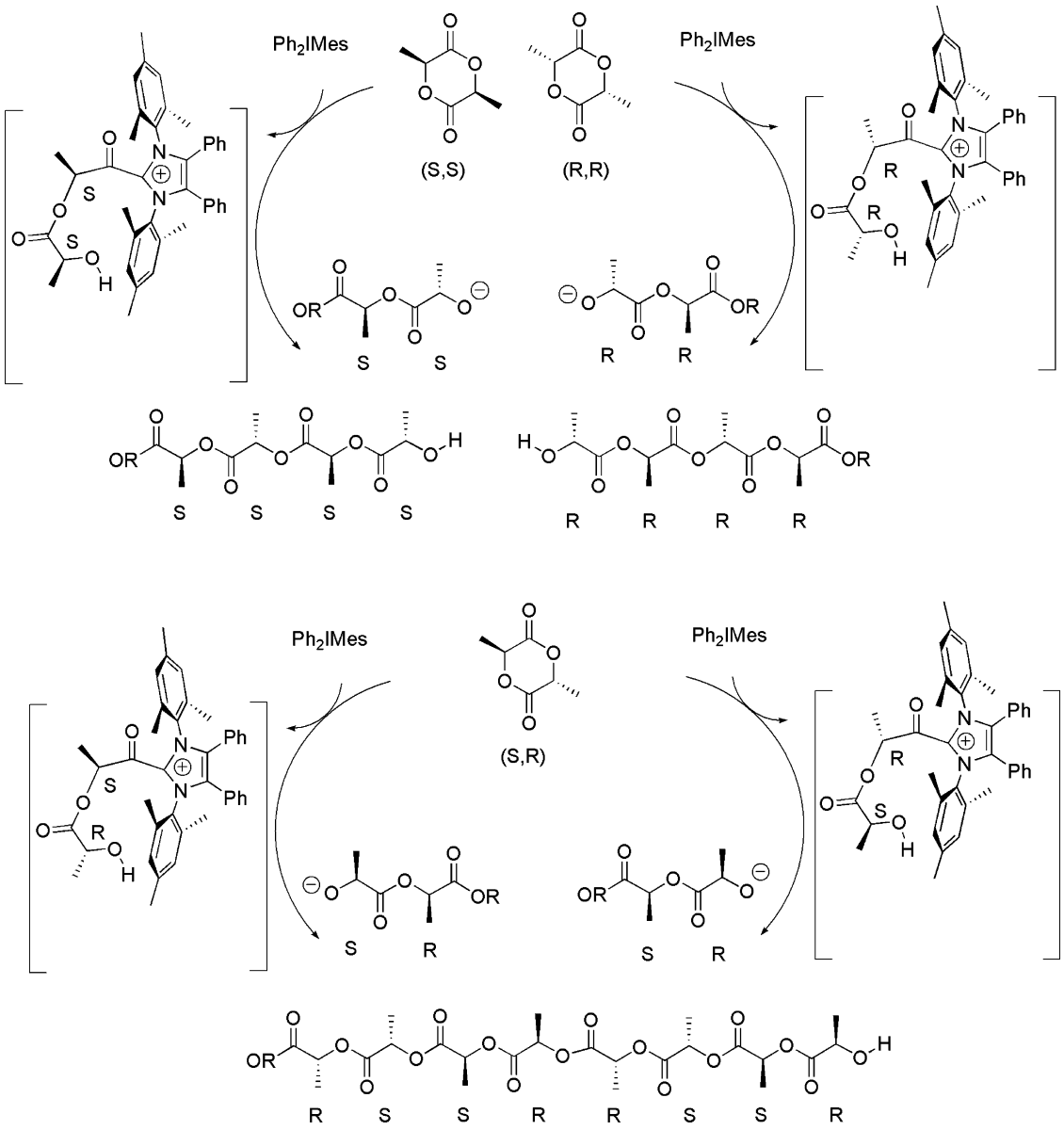
As a consequence of the slow rate of enolization, the ROP of optically pure L-LA by IMes at room temperature is stereospecific and provides a route to both linear and cyclic crystalline, isotactic PLLA. For example, polymerization of L-LA (0.63 M) with methanol as the initiator in the presence of IMes ($[M]_0/[I]_0/[IMes]_0 = 100/1/1$) for 6 s proceeded to 84% conversion to generate isotactic PLLA with an optical rotation of −122° ($CHCl_3$ c = 9 mg/mL, 24.6 °C) and a melting point of 158 °C. Polymerization of L-LA (0.63 M) with IMes ($[M]_0/[IMes]_0 = 100/1$) in the absence of alcohols generated a crystalline cyclic PLLA (M_n = 32 000 g/mol, PDI = 1.16, T_m = 133, 143 °C, ΔH_f = 22.7 J/g, $[\alpha]_D$ = −118°).[197] The slightly lower melting points and optical rotations observed (lit. T_m = 181 °C, ΔH_f = 85 J/g, $[\alpha]_D$ = −156°)[37,204] suggest that a small degree of epimerization occurs under these conditions.

The extraordinarily high activity of the carbenes for ROP enables the stereoselective polymerization of *rac*- and *meso*-LA at low temperatures.[205,206] For example, polymerization of *rac*-LA with the sterically encumbered carbene Ph_2IMes **27** in CH_2Cl_2 at −70 °C for 2 h (91% conversion) yielded a crystalline PLA (likely a stereoblock structure of L- and D-LA) with a melting point of 153.3 °C (ΔH_f = 13 J/g). This result was interpreted in terms of a chain-end control mechanism where the stereogenic terminal alkoxide of the growing chain selectively attacks the acyl imidazolium of the same relative stereochemistry, leading to preferential isotactic enchainments (probability of isotactic placement P_i = 0.90). This hypothesis was supported by the stereoselective polymerization of *meso*-LA with Ph_2IMes at −40 °C to yield a heterotactic PLA with a P_i = 0.83 (Scheme 24).

7.3. Methods of Carbene Delivery

The wide utility of NHCs as ligands in organometallic chemistry and as organic catalysts has motivated efforts to generate these active intermediates in situ. While a variety of NHCs are isolable, the synthesis of these reactive species is not always straightforward to the uninitiated. The stability and air and moisture sensitivity of the reactive species depends sensitively on the structure of the carbene. A variety of techniques have been reported for the generation of carbenes from more readily available precursors; the choice among various methods depends on the nature of the carbene as well as the compatibility of the generation method to the reaction of interest.

Scheme 24. Stereoselective Polymerization of *rac*- and *meso*-LA with Ph_2IMes 27

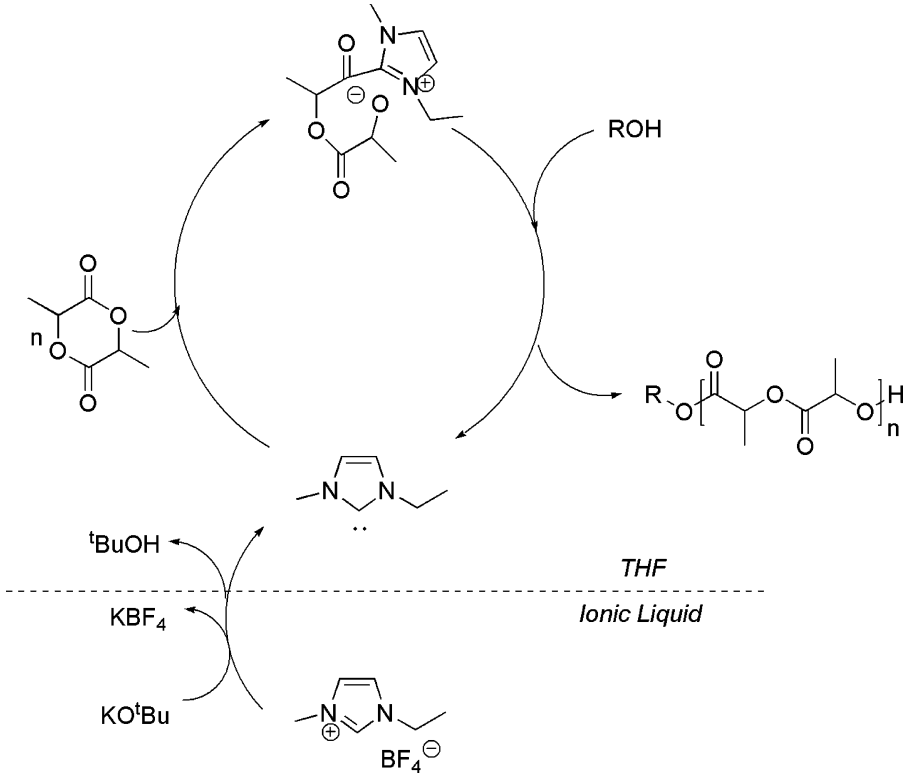


7.3.1. In situ Deprotonation of Imidazolium and Triazolium Salts

The deprotonation of thiazolium, imidazolium, or triazolium salts is a common method for generating carbenes. The in situ deprotonation of imidazolium salts with substoichiometric amounts of *tert*-butoxide prior to the addition of substrates leads to similar activities and yields for transesterification[173] and ROP reactions.[153,186] This procedure enabled the rapid screening of a variety of carbenes (some of which are too reactive to isolate) for the ROP of cyclic esters. High molecular weight PLAs (M_n > 25 000 g/mol) were synthesized within 10 min at room temperature using carbenes generated from the imidazolium salts of the IMeEt **17**, IMes **18**, and IDipp **22** carbenes. LA polymerization was performed in THF or toluene with catalytic activity showing little solvent dependence. Catalyst ratios of 0.25−1.5 equiv relative to the initiating alcohol (benzyl alcohol) for target DPs > 100 produced narrowly dispersed PLA in 1−2 M THF LA solutions. Higher monomer concentrations or catalyst-to-initiator ratios resulted in broadened PDIs (>1.2). The preparation of narrowly dispersed oligomers could be achieved with a significant reduction in catalyst/initiator/LA ratio. Controlled polymerizations could be achieved with catalyst/initiator/LA ratios as low as 1/80/1200.

An extension of this methodology involves the use of imidazolium-derived ionic liquids[207−210] both as catalyst reservoirs and solvents for transesterification and ROP.[186] Polymerizations using ionic liquids have been performed using two different approaches. In the first method, the polymerization was performed in neat ionic liquid, which serves as both the solvent and catalyst source. LA polymerization was performed in neat 1-ethyl-3-methylimidazalium tetrafluoroborate activated with the base potassium *tert*-butoxide and benzyl alcohol as the initiator. Under these conditions, the reaction proceeded to 50% conversion in 10 min before polymer precipitation occurred from the ionic liquid. An alternative method utilized a THF/ionic liquid mixture, resulting in a biphasic polymerization in which the ionic liquid served as a catalyst reservoir (Scheme 25). Migration of the generated NHC to the organic phase effectively leads to the ROP of LA to produce high molecular weight PLAs (M_n > 24 000 g/mol) with PDIs of 1.4. Polymerizations were terminated by the addition of acid to regenerate the imidazolium precursor, and the resulting

Scheme 25. LA Polymerization Using a Biphasic Ionic Liquid−NHC System

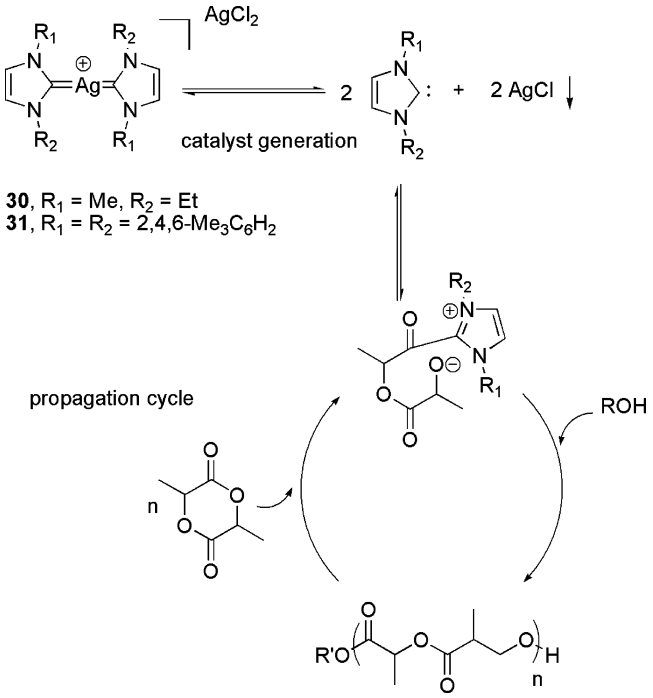


polymer was readily extracted by removal of the THF layer. The same liquid reservoir was reused for subsequent polymerization, thus demonstrating a reaction/recycle protocol.

7.3.2. Silver(I) NHC Complexes

Silver(I) NHC complexes are commonly employed as transmetallating agents to generate other transition metal carbene complexes.[211] As these silver complexes are readily prepared from imidazolium salts and Ag_2O,[212] many structurally diverse Ag−NHC complexes have been synthesized and characterized. The catalytic application of Ag−NHCs has been relatively unexplored.[211] These silver Ag−NHCs can be used directly as catalyst precursors for transesterification and ROP reactions.[213,214] The thermal stability of the silver carbene complexes **30** and **31** (Scheme 26) was studied by DSC and thermogravimetric analysis (TGA). Compound **31** was found to be stable below 250 °C, while **30** showed thermal decomposition at 89.2 °C. Upon heating compound **30** at 60 °C with carbon disulfide in THF, a zwitterionic carbon disulfide species is formed, implicating the formation of the free carbene. The polymerization of L-LA catalyzed by **30** in the presence of the 1-pyrenebutanol as the initiator at 60 °C is significantly slower than the analogous IMeEt **17** carbene generated in situ from the imidazolium salt[186] (90% conversion after 12 h), generating PLA with a molecular weight M_n of 26 000 g/mol and PDI of 1.12 by GPC with no racemization of LA observed. Though compound **31** showed no strong thermal transitions at 100 °C, it is capable of catalyzing the polymerization of L-LA at a much slower rate (95% conversion after 72 h at 100 °C) to yield PLA with a narrow PDI (1.17). The resulting catalytic activity is likely due to the small concentration of free carbene in solution that is able to polymerize LA. Alternatively, the silver carbene complex may be able to polymerize LA directly, as recently established for Zn carbene complexes.[206] More studies are warranted to address the nature

Scheme 26. Catalyst Generation and ROP of LA from Silver(I) Carbene Complexes

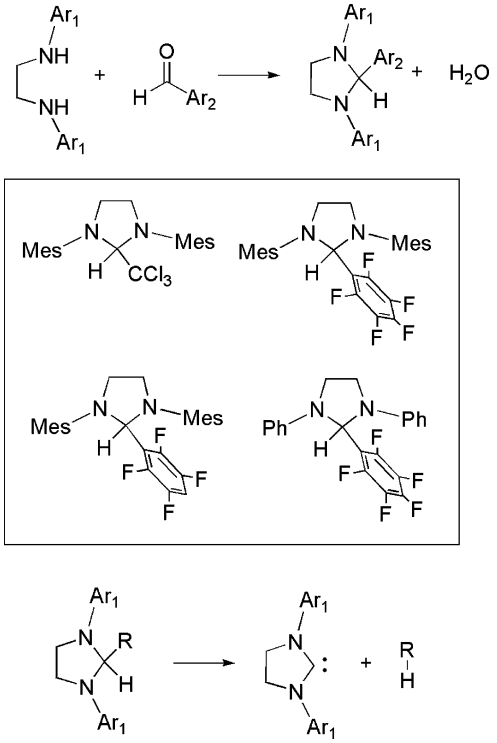


of the catalytic species. Silver carbene complexes are also active catalysts for the ROP of L-LA at 160 °C in the bulk in 4 h with high conversion, but relatively broad PDIs (1.22−1.47) are obtained under these conditions.[215]

7.3.3. Adducts Derived from Insertion Carbenes into Acidic C–H, O–H, and N–H Bonds

Wanzlick has shown that NHCs will undergo insertion into acidic C−H and O−H bonds.[137] Subsequent studies demonstrated that the saturated imidazol-2-ylidene carbene **14**

Scheme 27. Various Chloroform and Fluoro-substituted Arene NHC Adducts and Their Preparation

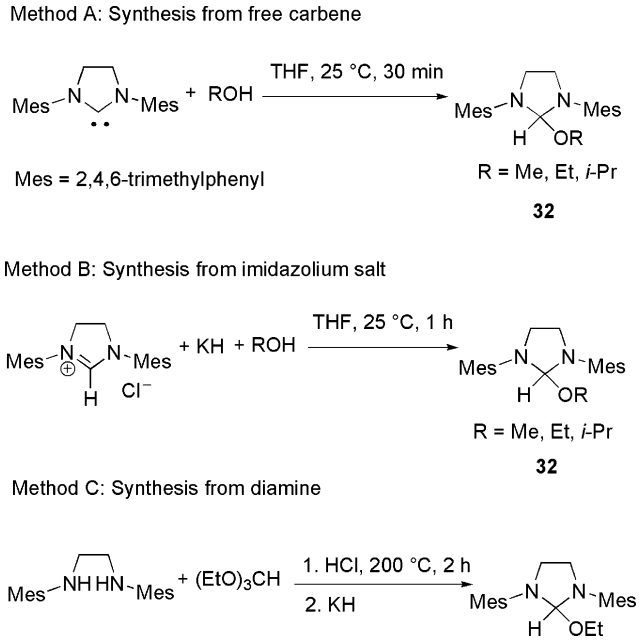


cleanly undergoes insertion with compounds containing acidic C−H bonds to form stable imidazolines (subsequently referred to as alkane adducts of NHCs), whereas corresponding unsaturated carbenes lead to a complicated mixture of products.[216−219]

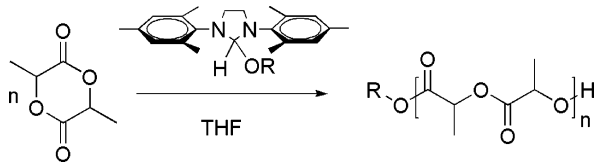
Following a strategy devised by Wanzlick and Loechel in 1953,[220] the synthesis of NHC adducts by an acid-catalyzed condensation of diamines with various substituted benzaldehydes has been described (Scheme 27).[87] At elevated temperatures, the carbene−adduct bond is cleaved and the free carbene is released into solution. The thermoloysis of these stable chloroform and fluoro-substituted arene adducts was found to be highly dependent on the nature of the substituents on the carbene and adduct, providing a convenient way for tuning the rate of generation of the saturated carbenes in situ.

Comparisons of the first-order rate constants of elimination of the haloalkane or arene from the adducts ($k_{obs}(CHCl_3) = 1.86 \times 10^{-5}$ s^{-1}, $k_{obs}(C_6F_5H) = 8.39 \times 10^{-5}$ s^{-1} at 39 °C) revealed that the rate of generation of the carbene was quite sensitive to the nature of the adduct. These adducts were found to be effective catalyst precursors for the ROP of L-LA (as well as useful sources of carbenes as ligands for transition metal complexes).[87] Reactions were performed in the presence of a benzyl alcohol initiator and 1.5 equiv of NHC adduct (parts a−d of Scheme 27) relative to the initiator in 1−2 M THF or toluene solution. End-group fidelity was demonstrated by both ^{1}H NMR and UV−GPC. The effectiveness of these adducts for the ROP of LA depends on the nature of both the alkane liberated and the *N*-aryl substituent on the imidazoline. The chloroform and perfluorophenyl adducts of SIMes catalyze the ROP of LA at 65 °C to high monomer conversion after 3 h, while the tetrafluorophenyl adduct was less active, polymerizing LA to modest monomer conversion after 24 h under the same conditions (PDI = 1.10−1.15). The 1,3-diphenylimidazoline

Scheme 28. Preparation of NHC−Alcohol Adducts



Scheme 29. Polymerization of LA with Alcohol Adducts of Saturated Carbenes



adducts were much less active, even at 144 °C, and led to less well-controlled polymerization, resulting in broader PDIs (1.52). The differences in catalytic activity were attributed to the relative stabilities of the alkane adducts.

7.3.4. Single-Component Catalyst/Initiators

The imidazolin-2-ylidene carbenes were shown by Lachmann and Wanzlick to insert into O−H bonds to generate alcohol adducts (ester aminals) **32**,[221] structurally analogous to the Brederick reagent $(Me_2N)_2CH(Ot\text{-}Bu)$.[77,79] Grubbs and co-workers,[84,86,222] Blechert and co-workers[223] have utilized these alcohol adducts to deliver NHCs to transition metal complexes. The *tert*-butanol adduct of SIMes **32** (where R = *t*-Bu) reacts with transition metals at room temperature,[86] to generate transition metal−carbene complexes. Alcohol adducts of SIMes **32** can be prepared by several routes (Scheme 28), and the methanol adduct was structurally characterized.[188] These adducts readily eliminates alcohol at room temperature to generate the free carbene, as established by trapping studies with CS_2.

These carbene adducts function as single-component catalyst/initiators for the ROP of LA at room temperature.[188] Polymerizations using these adducts (Scheme 29) were performed in THF with a monomer-to-adduct ratio of 100, resulting in polymers with controlled molecular weights and PDIs (1.18−1.34) in 10 min at room temperature. End-group fidelity was observed by ^{1}H NMR and UV-GPC analysis. Slight increases in PDIs with increased reaction time suggest that the adducts also catalyze transesterification reactions at high monomer conversion. To further demonstrate the versatility of this system, various multifunctional adducts (Figure 12) were prepared and used for LA polymerization

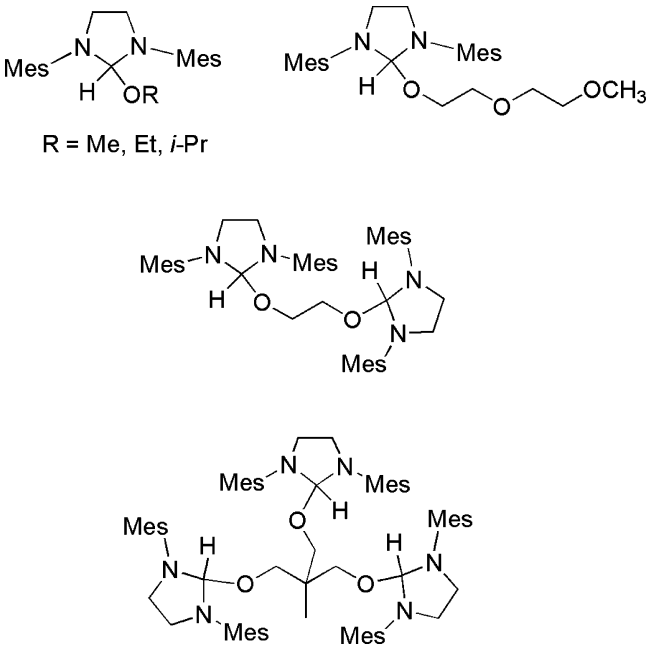
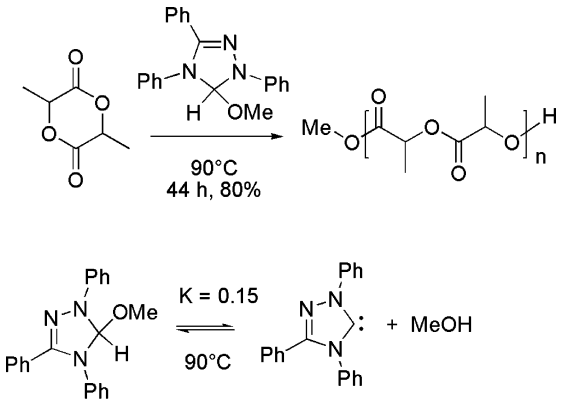


Figure 12. Various NHC alcohol adducts for the ROP of LA.

Scheme 30. ROP of LA Using the Triaz 15 Carbene



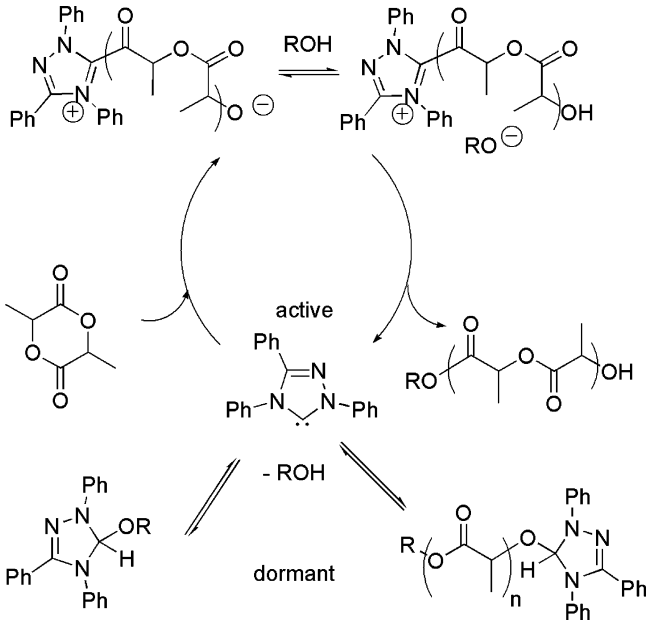
33

to produce block copolymers, telechelic polymers, and star polymers.[188] The alcohol adducts of SIMes show comparable behavior to the isolated SIMes **14** carbene or SIMes **14** generated in situ from the imidazolium salt for the ROP of LA.[186]

The commercially available triazolylidene Triaz **15** is much less active for ROP than the analogous imidazol-2-ylidenes such as IMes **18** or the imidazolin-2-ylidenes such as SIMes **14**. Mechanistic studies indicate that the attenuated activities of the triazole carbene **15** are due to the formation of alcohol adducts, which, in contrast to those derived from the saturated imidazolinylidene SIMes **14**, are much more thermally stable and essentially inactive as polymerization catalysts at room temperature. Enders et al. had shown that, at room temperature, the triazole carbene **15** reacts rapidly with methanol to generate the methoxytriazoline **33**.[147] This adduct is stable at room temperature but dissociates at 90 °C to the methanol adduct with an equilibrium constant of $K = 0.15$ (Scheme 30).[187,224]

The ROP of LA at 90 °C with either the adduct or with the triazole carbene in the presence of alcohol initiators is slower than that with IMes **18**, but at a monomer-to-initiator ratio of 100 proceeds with high conversion in 50 h to

Scheme 31. Proposed Mechanism for ROP with Reversible Activation and Deactivation of Alcohol End Groups

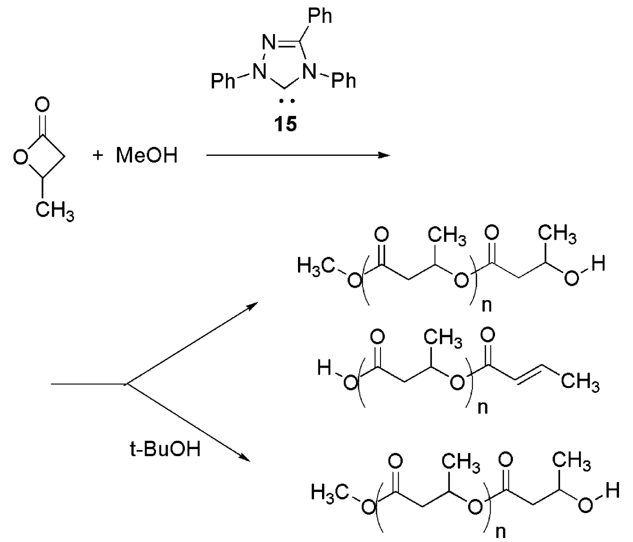


generate PLAs with narrow PDIs (1.09). These polymerizations are very well-controlled under these conditions, proceeding with first-order kinetics and exhibiting a linear correlation between molecular weight and conversion. Attractive features of this system are that the polymerization can be reversibly terminated simply by modulating the temperature—at room temperature, polymerization ceases; increasing the temperature to 90 °C reinitiates the polymerization. Moreover, in contrast to behavior observed with IMes **18** or SIMes **14**, very little transesterification is observed at high monomer conversion, as evidenced by the negligible increase in PDIs (1.13−1.29) upon heating the polymer sample for 12 h at 90 °C.[187,224]

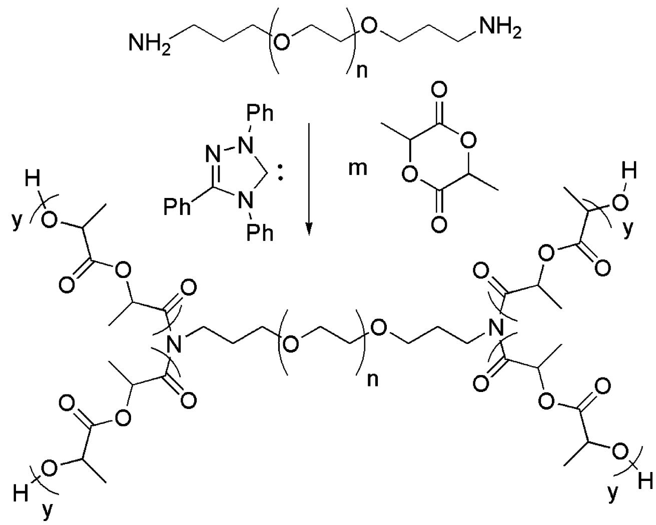
The exceptional control observed in this system is attributed to the reversible formation of a dormant alkoxyl triazoline, which keeps both the free carbene and the alcohol chain ends at a low concentration, thereby minimizing the rate of transesterification of the polymer (Scheme 31). This reversible interconversion between dormant and active sites (which in this case is tunable by modulating the temperature) is a common feature of many living polymerization systems, such as modern controlled radical polymerization reactions.[225] The reversible formation of a "dormant" alcohol adduct by combination of the free carbene with the propagating alcohol chain end leads to reversible deactivation, thus maintaining a low concentration of catalyst in solution.

The extraordinary selectivity of Triaz **15** also enabled the controlled ROP of BL to poly(hydroxybutyrate)s (PHB)s. The ROP of BL is of particular importance because it provides a synthetic entry to poly(hydroxyalkanoates), an important class of biomacromolecules that are produced by microorganisms.[226,227] The ROP of BL is challenging in that ring-opening can proceed by bond breaking either between the carbonyl carbon and oxygen atom of the β-lactone ring (acyl cleavage), resulting in retention in stereochemistry, or between the β-carbon and oxygen atom (alkyl cleavage), leading to inversion of configuration and loss of end-group fidelity.[228,229] An additional complication is that poly(hydroxyalkanoates) are extraordinarily base-sensitive and are readily deprotonated by bases to eliminate crotonates and

Scheme 32. Ring-Opening Polymerization of BL Using Triaz 15



Scheme 33. Synthesis of H-shaped Block Copolymers by Initiation from Telechelic Diamine Macromonomers



carboxylates.[230−237] The resultant carboxylates are themselves initiators for polymerization of BL by alkyl cleavage, leading to loss of control and end-group fidelity.

The polymerization of *rac*-BL initiated from methanol and Triaz **15** was performed at 80 °C in toluene with and without *tert*-butanol as an additive as shown in Scheme 32. The addition of *tert*-butanol was expected to tie up the reactive carbene as a reversible adduct. End-group fidelity and predictable molecular weights, particularly for targeted DPs of 200 or less, were demonstrated for the polymerizations with the *tert*-butanol additive. However, polymerization targeting higher molecular weights (DPs ranging from 250 to 450), generally accompanied by long reaction times, showed broadening in the PDIs (1.10−1.15). Moreover, for these high molecular weights, a small amount of crotonate was observed (∼25% of total chain ends), consistent with a second mode of polymerization. The loss of control and end-group fidelity at the high molecular weights is consistent with that observed by Coates and co-workers.[237]

7.3.5. Amino-Adducts: Initiation from Primary Amines

Because saturated imidazolinylidenes and triazolylidenes also undergo N−H insertion reactions with amines to yield amino adducts,[147,238,239] primary amines were investigated as initiators for the ROP of LA. Remarkably, primary amines act as bifunctional initiators to generate two chains per initiating amine, enabling the facile construction of branched block copolymers from amine-terminated macromonomers. Polymerization of LA from bis(3-aminopropyl)PEG (M_n = 3 400 g/mol) in the presence the triazole carbene yielded the H-shaped block copolymer (M_n = 9 600 g/mol, PDI = 1.09) after 71 h at 90 °C (Scheme 33).[240] This result is in marked contrast to organometallic promotors where only one chain is initiated from primary amines, generating an amide end group.[241]

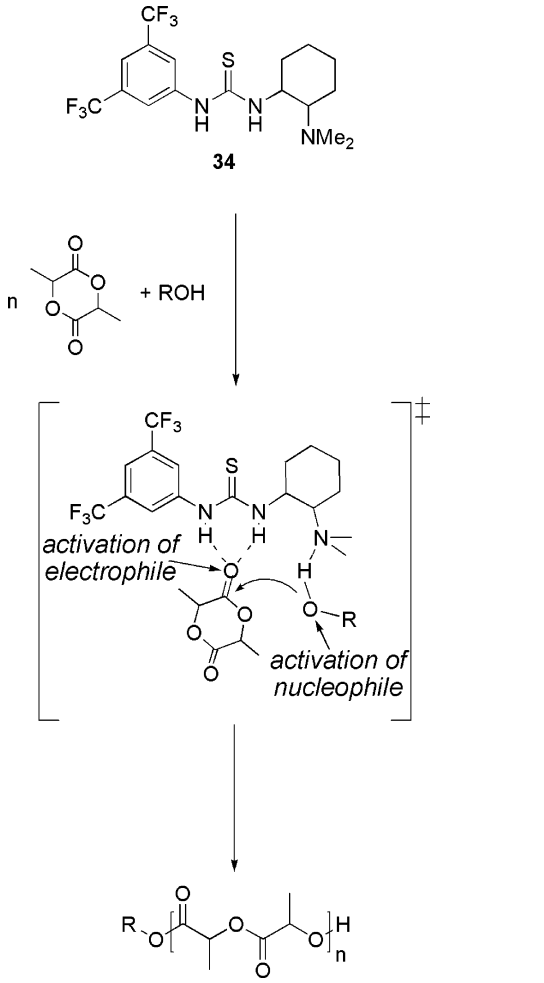
8. Bifunctional Organocatalysis Using H-Bonding Thioureas

The increased activity of NHCs versus DMAP for ROP of lactones is a result of the increased nucleophilicity and/or basicity of the NHCs. However, ROP involves both a nucleophilic component in the form of the initiating or propagating alcohol as well as an electrophilic component in the form of the cyclic monomer. The classic coordination/insertion mechanism primarily involves electrophilic activation of the monomer by Lewis acidic metal cations such as Sn(II).[242] Development of small-molecule ROP organocatalysts by including organic Lewis acids therefore provides a complementary path to accelerate or control ROP. As described elsewhere in this issue, ureas and thioureas are being intensely studied as organocatalysts for a number of small-molecule transformations.[25,243] A transformation particularly relevant to ROP is the dynamic kinetic resolution of azlactones by selective ring-opening of the appropriate enantiomer reported by Berkessel and co-workers.[244−246] The bifunctional catalysts used, including some originally described by Takemoto and co-workers for other small-molecule transformations,[247−249] depend on the presence of both of an electrophile-activating thiourea and a nucleophile-activating amine, making them suitable for dual activation of an electrophilic lactone and nucleophilic alcohol in ROP.

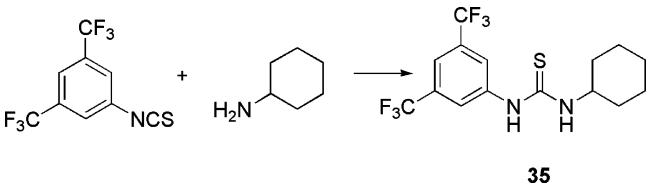
A bifunctional thiourea−amine **34** was tested for solution ROP of LA and provided PLA with controlled molecular weights, end-groups defined by the added initiating alcohols, and low PDIs (Scheme 34).[250] While the rate of polymerization is significantly slower (reaction time of 48−72 h under typical conditions) than that found for NHC catalysts, an interesting feature of the thiourea-catalyzed polymerization is that prolonged reaction times led to negligible broadening of the PDI even at near-complete conversion, indicating that little transesterification of the linear polymer occurs. Chain extension of the PLA could be achieved simply by addition of more monomer; in parallel, initiation from monohydroxy-terminated macroinitiators gives well-defined block copolymers (vide infra).

Mechanistic and theoretical studies support a bifunctional mechanism involving activation of both the LA monomer and the alcohol nucleophile.[250] Moreover, a mixture of the thiourea **35** (Scheme 35) and a tertiary amine is also effective for the ROP of lactones.[250] Screening studies demonstrated that a variety of thiourea−amine combinations were found to be catalytically active for ROP of LA.[251] Electron-withdrawing groups on the aryl group of the thiourea generate higher rates of catalysis, in agreement with the thiourea's proposed role as a H-bonding activator for activating the monomer.[25] Similarly, increased basicity of the amine

Scheme 34. Proposed Activation Pathway for LA ROP Using a Bifunctional Thiourea Catalyst



Scheme 35. Synthesis of Thiourea Catalyst 35



component accelerated polymerization, presumably due to basic activation of the propagating alcoholic chain end. Though the structural possibilities have not been explored exhaustively, the most active thiourea−amine cocatalyst system found so far consists of thiourea **35** in combination with the natural product (−)-sparteine.

The interactions of the thiourea cocatalyst **35** with cyclic versus linear esters were studied by ^{1}H NMR.[252] Titration studies indicated that the association constants for the binding of lactones to the thioureas were ∼40. In contrast, the association constants for linear esters were too low to be estimated by NMR methods. The higher affinity of the thiourea for the cyclic ester monomer relative to the linear ester polymer is likely the origin of the exquisite specificity of this catalyst system for ring-opening relative to transesterification. The thiourea is not inhibited by associating with the polymer, and transesterification of the polymer chain is minimized because its ester linkages are poor substrates for activation by the thiourea.

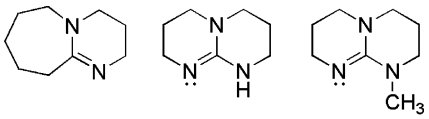


Figure 13. Chemical structures of DBU, TBD, and MTBD.

Trimethylene carbonate (TMC) can be polymerized by thiourea−amine catalysts with control similar to that found when polymerizing LA.[189] ^{1}H NMR studies paralleling those performed with cyclic esters again show that the thiourea associates more strongly with cyclic carbonate when compared to a linear carbonate, providing support for a similar rationale for the lack of polymer scrambling observed. The thiourea−amine catalysts were found to be ineffective for polymerization of cyclic esters other than LA and glycolide, such as VL or caprolactone; more basic amines are necessary (vide infra).

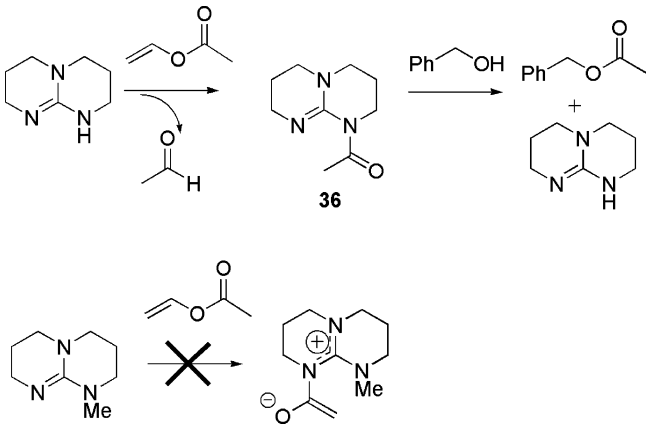
9. Amidine and Guanidine Organocatalysis

The acceleration of ROP found when substituting more basic (−)-sparteine for other tertiary amines in the thiourea−amine cocatalysts can be extrapolated to the use of even stronger bases as cocatalysts: the so-called "superbases", such as amidines, guanidines, and phosphazenes. These compounds have been investigated as small-molecule transesterification catalysts.[173,253] The use of the superbasic guanidine 1,4,7-triazabicyclodecene (TBD) under melt conditions to polymerize various lactones has been described; variable molecular weights and high PDIs were observed.[254,255] Similarly, the amidine 1,8-diazabicycloundec-7-ene (DBU) has been used for ROP of cyclic carbonate and lactone monomers in the melt.[256,257] Studies by mass spectrometry showed incorporation of DBU into the polycarbonate, suggesting a dual role as a pseudo-anionic catalyst and as an initiator.

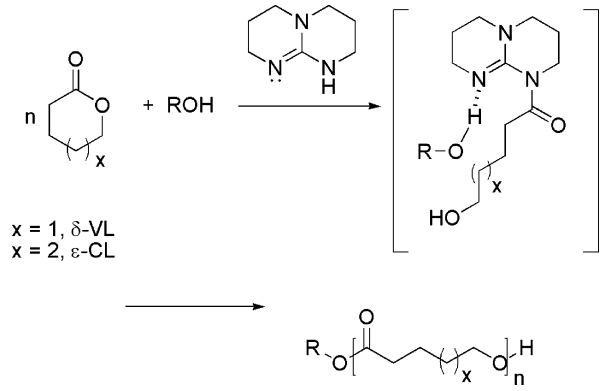
Screening studies showed that DBU, TBD, and *N*-methyl TBD (MTBD) (Figure 13) are highly active catalysts for solution-phase ROP of LA in nonpolar solvents. In contrast to the thiourea−amine systems, their basicities are such that the thiourea is unnecessary for LA polymerization, and complete conversions are reached significantly faster than even with the thiourea−sparteine cocatalyst system.[258] Cyclic esters such as VL and CL can be polymerized by TBD alone; both DBU and MTBD can only polymerize these monomers in the presence of the thiourea cocatalyst **35**.[252] In contrast to the melt polymerization results, no catalyst is incorporated into the polymer, with the end group defined by added alcoholic initiators.

The heightened activity of TBD in comparison to the other superbases is striking and approaches that of the NHC catalysts. ^{1}H NMR experiments show that TBD is the most basic of the aforementioned superbases.[259] However, the difference in pKa between TBD and MTBD is not much more than the difference between MTBD and DBU. A key structural difference in TBD is that it contains two accessible nitrogen atoms, while MTBD and DBU are essentially monofunctional. The enhanced functionality of TBD was demonstrated by a model reaction in which TBD was acylated by a reactive vinyl ester, forming a stable acyl−TBD intermediate **36** (Scheme 36).[258] In the presence of excess alcohol, the acyl−TBD intermediate **36** acylates the alcohol regenerating TBD and the ester.

Scheme 36. Model Acyl Transfer Reaction



Scheme 37. Proposed Dual Activation of Monomer and Initiator for ROP of Lactones



In contrast, DBU and MTBD showed no reactivity with vinyl acetate. These studies suggest a novel monomer-activated mechanism for the ring-opening by TBD involving acylation of TBD by the lactone, followed by displacement of the acylated TBD to the chain-end alcohol (Scheme 37). Isolation and characterization of a ring-opened intermediate resulting from the reaction of TBD with BL provides support for this proposed mechanism.[252] An alternative mechanistic possibility more closely related to the proposed mechanism of the thiourea−amine systems is that TBD behaves simultaneously as both a hydrogen-bond donor to the monomer via the N−H site and also a hydrogen-bond acceptor to the hydroxylic proton of the propagating alcohol, achieving activation of both the electrophile and the nucleophile. Literature reports of reactions catalyzed either by thiourea−amine bifunctional catalysts or by TBD alone lend credence to the latter mechanism.[260,261] Computational studies are underway to distinguish the two mechanisms.

10. Block Copolymers

Block copolymers display remarkable phase behavior and are industrially important as thermoplastic elastomers,[262] impact modifiers,[263] compatibilization agents,[264] and surfactants.[265] The novel properties that arise in block copolymers when compared to random copolymers result from microphase separation of the components. A generally recognized prerequisite for well-defined phase behavior is to have low PDIs for each of the blocks (generally PDI < 1.3), and especially precise synthetic techniques are required for control of molecular weight and PDI. In particular, anionic polymerization has been successfully applied for block copolymer synthesis.[10] Several other routes have been realized as well, including controlled radical polymerization,[9,12,266,267] living cationic polymerization,[8,268,269] group transfer,[270−272] metathesis polymerization,[273,274] ring-opening polymerization,[275−277] or combinations of these techniques.

Recently, block copolymers and, in particular, block co-(polyesters) have shown great promise in both nanoscale patterning of microelectronics and biomedical applications, due to the variety of two- and three-dimensional morphologies that can be constructed and the (bio)degradability of polyester segments. Organocatalytic strategies that avoid introducing any metallic catalysts appear highly advantageous.

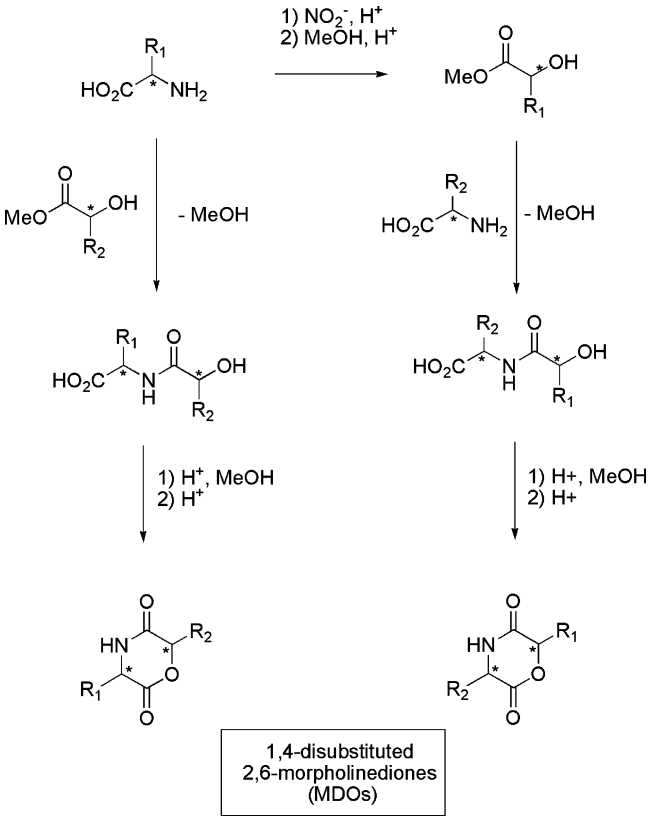
The significant rate differences observed when different cyclic esters are homopolymerized using organocatalysts (LA ≫ VL > CL) are reflected when random copolymerizations are attempted.[251,252] For example, when an equimolar mixture of LA and CL was subjected to superbasic organocatalytic ROP conditions at room temperature, the fastest propagating monomer (LA) polymerized first to >95% conversion. Subsequently, the so-formed PLA backbone began to transesterify, leading to broadening PDIs, and ring-opening of CL was negligible. Similarly, if LA was homopolymerized first and CL was added afterward, the PDI increased and little CL polymerized. Organocatalysts, therefore, appear unsuitable for the synthesis of random copolyesters, unless the reactants can be allowed to thoroughly transesterify and the resulting high PDIs are tolerable.

Block copolyesters of LA, VL, and/or CL have been synthesized using superbasic organocatalysts by sequential addition of two different cyclic ester monomers.[251,252] Control was achieved by first ring-opening the slower-propagating monomer (e.g., CL or VL) to 70% conversion, then adding the faster-propagating monomer (e.g., VL or LA), and finally quenching the reaction after 95% conversion of the second monomer. Clean chain extensions were observed when this procedure was followed and the PDIs of the final block copolymers remained narrow, indicating efficient crossover reactions. Importantly, integration of the NMR signal from monomer left over from the first stage does not change during the course of polymerization of the second monomer, demonstrating the consistent selectivity of the organocatalysts. Interestingly, TBD alone, DBU/thiourea, and MTBD/thiourea show similar copolymerization behaviors in ROP. The reaction time for a DP of 100 in each of the blocks is much shorter for TBD, and lower catalyst loadings are required.

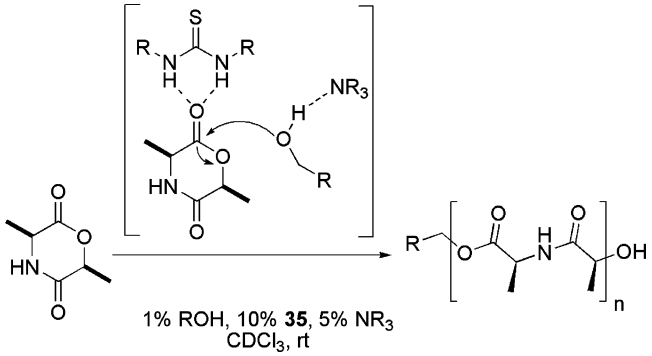
11. Extension to Other Strained Cyclic Heterocyclic Monomers

The successful pursuit of organocatalytic methods for the ROP of LA and the basic understanding of the polymerization mechanism has motivated the synthesis of other strained heterocyclic monomers. For instance, the incorporation of reactive functional groups into polyesters would allow for covalent attachment of moieties suitable for a variety of purposes, such as the growth of polymer brushes or the attachment of bioactive molecules for drug delivery. A route to functionalized polymers more amenable than LA derivatives is to use structurally similar morpholine-2,6-dione (MDO) monomers. These cyclic esters resemble LA, but one of the cyclic esters is replaced with a cyclic amide. As shown in Scheme 38, retrosyntheses of MDOs show that they are derived from an α-hydroxy acid and an α-amino acid, and

Scheme 38. Preparation of MDOs



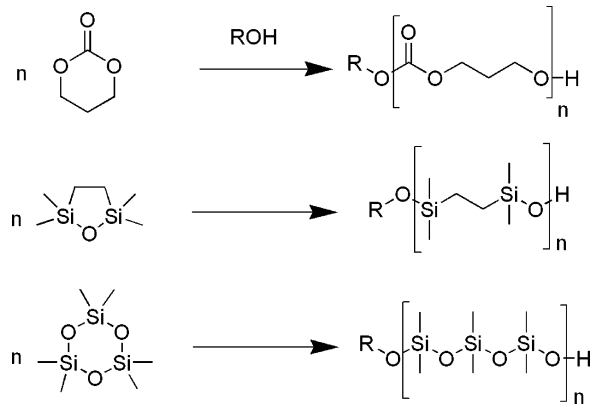
Scheme 39. ROP of MDO Using Thiourea−Amine Catalyst System



a procedure for MDO synthesis based on these synthons using no covalent protecting groups is available. Clearly, the ready commercial availability of a wide range of natural and non-natural α-amino acids should allow for a selection of functional groups to be incorporated into MDO monomers.

The polymerization of MDO monomers using organometallic complexes has met with varying success.[278−282] Polymerization using NHCs resulted in low molecular weight polymer with no control, presumably since the amides can initiate polymerization in the presence of NHC. In previous studies of LA polymerization using thiourea−amine catalyst systems, the thiourea **35** with (−)-sparteine (NR_3 in Scheme 39) as the amine gave the most rapid rate of ROP, without causing detrimental transesterification of the polymer chains. This catalyst system was subsequently used to successfully polymerize MDO.[283] Polymerization of the MDOs was found to be significantly slower in comparison to LA: while LA polymerizations reached near-quantitative conversions in 2 h, under the same conditions, MDOs failed to reach complete conversion after 48 h. Narrowly dispersed products were obtained with end-group fidelity.

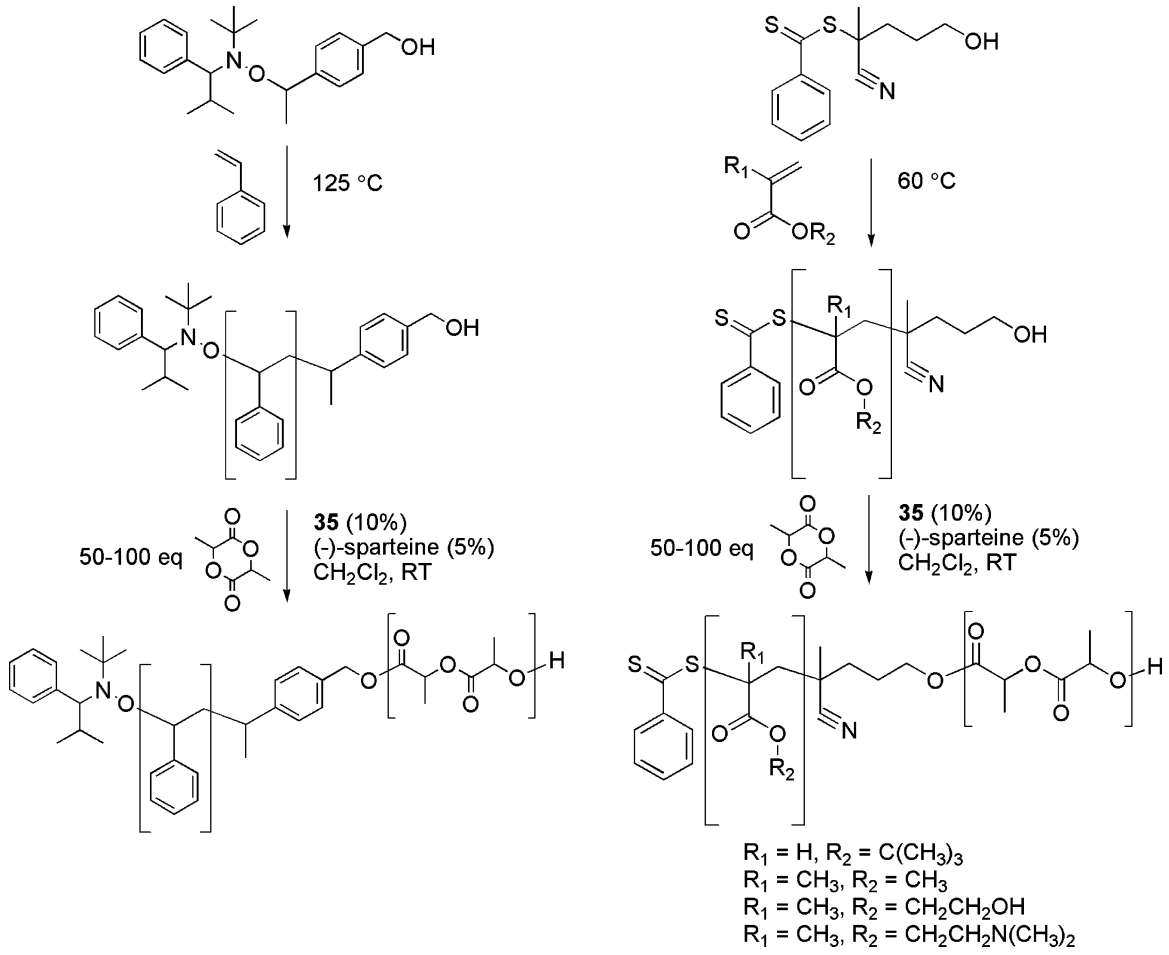
Scheme 40. ROP of Various Monomers Using NHC Catalysts



Organocatalytic methods to effect the ROP of TMC and substituted analogs of TMC, the effect of substituents on polymerization kinetics, and attempts to build block and random carbonate copolymers have been investigated.[189] Well-controlled polymerization of TMC using a variety of organocatalysts including NHCs resulted in polycarbonates with molecular weights up to 50 000 g/mol with narrow PDIs (<1.08) and good end-group fidelity (Scheme 40). Polymerizations were performed in a 2.0 M solution of CH_2Cl_2 using benzyl alcohol as the initiator with a targeted DO of 50. Reaction times were dependent on the type of NHC employed. For example, carbene Me_2IPr **25** was able to polymerize TMC in seconds, but led to broadened PDIs (>2). The high reactivity is likely due to the high basicity of the alkyl-substituted carbene. Polymerizations with the more sterically encumbered and less basic carbene IDipp **22** resulted in a higher degree of control, as exhibited by a narrower PDI of 1.06 after 30 min. Among the other organocatalysts surveyed for TMC polymerization, TBD exhibited activities as high as that of the carbenes, with slight broadening in PDIs (∼1.3), but could be employed to achieve DP as high as 420. MTBD and DBU had moderate activities with greater control over PDIs (1.28 and 1.04, respectively). Thiourea−amine catalysts are also effective, though significantly slower, achieving >90% conversions in hours to days. Despite the long reaction times, PDIs remain low (<1.09), indicating that little scrambling takes place. A brief ^{1}H NMR study of the thiourea−carbonate interaction showed that linear carbonates bind to the thiourea cocatalyst with much lower affinity than seen for the cyclic carbonate, paralleling results seen for linear versus cyclic esters (vide supra).

An organocatalytic route to narrowly dispersed poly(siloxanes) and poly(carbosiloxanes) of predictable molecular weights and end-group fidelity has been described.[190] Among the various organocatalysts employed, NHCs efficiently catalyze the ring-opening of cyclic silylethers. Polymerization of TMOSC (2 M toluene solution) with a primary alcohol initiator in the presence of NHC catalyst produced polymers with M_n up to 10 000 g/mol and narrow PDIs (1.14−1.19) (Scheme 40). Reactions with IMes **18** carbene reached complete conversion within 1 h, whereas polymerizations using carbene Me_2IPr **25** were essentially complete in 1 min, implying that the more basic carbene Me_2IPr **25** is the more-efficient catalyst. However, high activities do not appear to be solely the consequence of high basicity. When TBD and MTBD were screened for the ROP of TMOSC, only the

Scheme 41. Bifunctional Initiators Capable of Both ROP Using the Hydroxyl Group as Initiator and CRP Using the Alkoxyamine for NMP and the Dithioester Group for RAFT



former was an active catalyst. The use of TBD for the ROP of TMOSC required longer reaction times but with the benefits of slightly better control (PDI < 1.05), and minimal transetherification was noted even after complete monomer conversion. When compared to mechanisms proposed for polymerization of cyclic ethers, monomer transfer to the catalyst seems unlikely for the silyl ethers, leaving hydrogen-bonding activation of the initiating alcohol or propagating silanol to the NHC or TBD as the most likely mechanism.

The ROP of D3[190] (Scheme 40) and other cyclic siloxanes[284] can also be carried out with organic catalysts. Compared with the ROP of TMOSC, the ROP of D3 using NHCs proceeded with less control as shown by broader molecular weight distributions (PDI > 1.4). The lack of control was circumvented by using the slightly less active TBD catalyst, which could produce polymer from D3 with narrow molecular weight distributions (PDI < 1.2).

12. Disparate Polymerization Techniques

Modern controlled radical polymerizations are capable of producing polyvinylic materials with the controlled molecular weights and PDIs necessary for good microphase separation. Two methods, nitroxide-mediated polymerization (NMP) and radical addition fragmentation and chain transfer (RAFT), rely on living organic radicals and, therefore, avoid the introduction of metallic reagents. Moreover, these radical reactions are orthogonal in nature to the functionalities associated with ROP. Bifunctional initiators were found to be highly suitable for sequential growth of block copolymer segments by combining controlled radical polymerization (CRP) and ROP techniques (Scheme 41).[285,286] Macroinitiators prepared by established NMP or RAFT procedures were successfully chain-extended by organocatalytic ROP of LA,[224,251] VL, CL, TMC,[189] D3, and TMOSC.[190] The polyvinylic macroinitiators used include hydroxyfunctional polystyrene (PS) and poly(*N*,*N*-dimethylacrylamide) (PDMA) prepared by NMP and hydroxyfunctional poly(methyl methacrylate) (PMMA), poly(*t*-butyl acrylate) (PtBA), poly(*N*,*N*-dimethylaminoethylmethacrylate) (PDMAEMA), poly(2-vinylpyridine) (P2VP),[287,288] and polystyrene-*block*-poly(methyl methacrylate) (PS-*b*-PMMA) prepared by RAFT.[251]

Differences are observed when using different ROP organocatalysts for these sequential CRP/ROP syntheses, making judicious choice of the catalyst important. For instance, when LA was polymerized using PDMAEMA or P2VP macroinitiators generated by RAFT using the triazolylidene carbene as catalyst at 90 °C, the RAFT end group was lost during the process. Moreover, PDIs broadened and the length of the second block remained relatively short before control was lost.[224] For PS and PDMA macroinitiators, the triazolylidene catalyst was again inappropriate: in toluene, the preferred solvent, it is believed that micelles formed with vitrified PLA cores, hampering further polymerization and limiting conversion. When using thiourea−tertiary amine cocatalyst systems, much better control over the second block was observed for LA chain extension. The sensitive RAFT thioester end group was retained in these

cases, highlighting the mildness of the thiourea−amine-catalyzed ROP conditions. When using the superbasic catalysts TBD, DBU, and MTBD, RAFT end groups on the macroinitiators were again unstable. Nevertheless, when using TBD, DBU/thiourea, and MTBD/thiourea, PS and PDMA macroinitiators were successful in the growth by ROP of LA, VL, CL, TMC, and TMOSC segmented block copolymers. Commercially available monohydroxy-functionalized PEO could also be successfully chain-extended using the appropriate ROP organocatalysts.[186,251]

13. Conclusions

The ring-opening polymerization of lactones and other strained cyclic monomers provides an efficient route to thermoplastics derived from renewable resources.[37] Organocatalytic methods for ROP provide a complementary approach to those mediated by metal alkoxides[27−31] or enzymes.[32,44,45,91−96] The rates and selectivities of organocatalysts can be competitive with the most active and selective metal-based or enzyme catalysts. Moreover, the different mechanisms of enchainment engendered by the different classes of organocatalysts provide new opportunities for the controlled synthesis of macromolecules. For example, the thiourea-based catalysts exhibit remarkable selectivities for ring-opening relative to transesterification (section 8), and the carbene-derived catalysts enable the facile synthesis of novel polymer architectures such as cyclic polyesters (section 7.2.2) or H-shaped triblock copolymers (section 7.3.5). These advances, coupled with those from enzymatic and metal-based methods for ring-opening, provide the synthetic chemist with a powerful class of strategies to challenge nature's monopoly on the construction of macromolecules with well-defined structure and function.

14. Acknowledgements

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