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SYNTHESIS OF NOVEL POLYMER MATERIALS VIA ORGANOCATALYTIC
RING-OPENING POLYMERIZATION (ROP) OF CYCLIC LACTONES

BY

U.L.D INUSH KALANA

A DISSERTATION IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

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DOCTOR OF PHILOSOPHY DISSERTATION

OF

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ABSTRACT

The Ring-opening polymerization (ROP) of cyclic lactones has come a long way from 2001 with the aid of organocatalysts. The field of organocatalysts has recent developments to afford precisely tailored biodegradable polyesters via ROP of cyclic esters. However, the organocatalytic ROP of cyclic lactones is still on a laboratory-scale and shows industrial implementation limitations.

A series of conformationally flexible bis(thio)urea was developed to understand the structure-function relationship of the multi H-bonding (thio)ureas in the ring-opening polymerization of lactones. The rates of the ROPs showed a strong dependence upon the length and identity of the tether. The bis(thio)urea with five methylene-unit long tether exhibits the fastest ROP and remains active at low catalyst loadings under solvent-free conditions.

The organocatalytic ROP of (thiono)macrolactones was conducted for the first time. The driving force of the ROPs of (thiono)macrolactones was studied and displayed entropically driven ROPs with minimal or negligible contribution from enthalpy for the ROP yet, retain the characteristics of living polymerization even at elevated temperatures. The polymers of thionomacrolactones showed altered material properties compared to its polylactones. An oxidative crosslinking process was carried out for the poly(thionolactone)s to synthesize a porous, flexible crosslinked polymer that could facilitate the extraction of Au^{3+} from an aqueous solution, demonstrating the synthesized crosslinked polymer's potential to use as a water filter for a host of inorganic materials.

With the discovery of highly efficient and effective multi H-bonding bis-(thio)ureas for the ROPs, a novel series of bis-(thio)urea catalyst was developed as an enantio-selective chiral catalyst for the ROP of *rac*-Lactide. This catalyst shows high stereoselectivity and faster reaction rates at mild conditions for the polymerization of *rac*-LA, forming stereoblock PLA with precise control in molecular weight and enhanced thermal properties.

The ROP of a series of substituted lactones was carried out using a cooperative catalyst system - magnesium salts in the presence of a hyperactive imidate catalyst. This study shows the usage of this mixture of catalysts in performing controlled ROP of substituted 7 membered cyclic lactones which do not polymerize even in the presence of an active imidate H-bonding catalyst systems. A series of block-copolymers were synthesized by switching the catalyst and the temperature.

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I would like to thank the past and present teammates for their help in making this process smooth.

Thank you to the rest of the chemistry graduate community and the Department of Chemistry and Graduate school at the University of Rhode Island for all the support and resources.

- U.L.D Inush Kalana

PREFACE

This dissertation is written in Manuscript Format.

Chapter 1: A review chapter that links to the field of H-bond mediated organocatalysts used for the ring-opening polymerization of cyclic lactones. It is narrowly focused on the superlative organocatalysts for the reaction control and kinetics in ROP of selected strained and less strained cyclic lactones, and challenges still exist for the implementation of organocatalytic ROP at the industrial scale.

Chapter 2: Structure-function relationship, by varying tether lengths of bis-(thio)urea catalysts, has been reported. The relationship between tether lengths of thio-urea catalysts and its activity under solvent free conditions in the ROP of lactones was studied by me. (*Macromolecules*. **2019**, 52(23), 9232-9237).

Chapter 3: For the first time, organocatalytic ring-opening polymerization (ROP) of thiono-macrolactones was studied. Solid, flexible, and porous crosslinked polymers with remarkable material properties were synthesized using poly(thionolactones). Synthesis of new monomers, new polymer materials and Au³⁺ ion recovery studies using the crosslinked polymers were performed by me. (*Polym. Chem.*, **2020**, Advance Article).

Chapter 4: The study reports the development of a novel chiral bis-thiourea catalysts for enantioselective ROP of *rac*-LA. Preliminary catalysts screening was conducted by Oleg Kazakov. The manuscript is in progress.

Chapter 5: The study reports the ROP of substituted 7 membered lactones in the presence of a cooperative magnesium salts - imidate catalyst system. The ROPs for the substituted lactones under solvent free conditions were performed by me. The manuscript is in progress.

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MANUSCRIPT I

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Recent Efforts Focused on the Development of Organocatalysts for Ring-Opening Polymerization (ROP) of lactones

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ABSTRACT

Organocatalysis for ROP has come a long way with recent developments to afford precisely tailored biodegradable polyesters. The field of organocatalysts has developed for a broad monomer scope, easy use, and low cost. However, it is trapped on a laboratory-scale while struggling to get into the industrial level. In this chapter, we discuss the advanced uses of superlative organocatalysts systems for the ROP of selected strains and less strained lactones. This chapter focused on encouraging the polymer community to develop organocatalysts that are capable of resolving existing challenges.

INTRODUCTION

The petroleum-based polymers account for the consumption of ~7% worldwide fossil fuels.¹ It has been a general goal to develop sustainable polymers to mitigate the complications which occurred from petroleum-based polymers.^{2,3} The class of polyesters turns out to be a promising alternative for synthetic plastics since it can be synthesized from renewable monomers.^{1,3,4} Additionally biodegradability, biocompatibility and ability to mimic the characteristics of synthetic polymers are remarkable properties to use as a substitute.^{3,5–10} Hence, polyesters are widely used as bulk commodity materials in a variety of applications including packaging^{11,12}, textile industry^{13,14}, biomedicine^{15–17} and IT field.^{18,19}

In general, the common pathways of extracting monomers from natural sources are 1) fermentation of carbohydrate substrates; (corn and sugar cane)^{3,20}, 2) chemical breakdown of lignocellulose substrates,^{4,21} and 3) transesterification of glycerol in oilseed crops and algae.^{4,20,22} Monomers that are obtainable from those natural sources are diacids, hydroxyl acids, diols, polyols, carbonates, epoxides, and cyclic lactones.^{3,4,20,23} Among those monomers cyclic lactones are one of the most important precursors in the synthesis of polyesters. Most of the commercially available cyclic lactones are derived from natural sources and synthesized from enzymatic routes or platform chemicals through one or multistep synthesis.^{4,24–26}

As the world's interest in the aliphatic polyesters emerges, the ring-opening polymerization (ROP) of cyclic lactones has received tremendous attention over the last

two decades^{27–30}. The ring-opening polymerization is a type of chain-growth polymerization technique where the polymer chain propagates through the addition of cyclic monomers to an active chain end.^{27,31,32} In this process, the initiator opens a cyclic monomer and forms an active center. Depending on the nature of this propagating active center, ROP mechanisms can be illustrated as; cationic, anionic, radical, and covalent.³³ The ROP stands out for end group fidelity, high stereoselectivity and regioselectivity, precise molecular weights and complex polymer architectures.^{33–35} Thus, polyesters synthesized by ROP are chosen for tailor-made drug delivery systems.^{4,5,36} Indeed, to obtain well-defined polymers, catalysis plays a significant role in ROP besides enhancing the rates.³¹ Organometallic catalysts have been used widely in industry; however, metal residues in the final polymer can give detrimental effects on the applications such as biomedicine and microelectronics.^{37,38} Hence, over the last decade understanding of organocatalytic ROP systems has increased and nurtured the need for precisely tailored polyesters.

Organocatalytic ROP has taken place with the aid of a vast variety of organocatalysts such as pyridine-based, N-heterocyclic carbenes (NHCs), guanidine, amidine, phosphazene bases, and thiourea/amine cocatalysts.^{31,33,38–41} Organocatalysts compared to organometallic catalysts are outstanding in its versatility, high selectivity, and the possibility of recovering the catalyst from the end product and easy purification of the final polymer.³⁷ Conceptually, these catalysts activate either monomer or active chain end or both together^{31,33,42,43}. A dual catalyst system can activate both monomer and the chain end which enables the mitigation of side reactions and leads to narrow

molecular weight distribution (polydispersity index-PDI = $M_w/M_n < 1.1$).^{31,38,44} A dual catalyst system can be a unimolecular or bimolecular catalyst system. However, it turned out that using bimolecular dual catalyst system resulted in extremely controlled polymerizations and predictable molecular weights (M_n).^{31,33,38,44–46} The thiourea/base cocatalyst system is an effective bimolecular dual catalyst system which has high tunability, and stability over a wide range of reaction conditions^{47–53}. It exhibits features of a “living” polymerization where no termination is present, which enables to gain controlled molecular weights and highly adorned and precisely tailored polymers.^{27,31} However, in spite of the significant advantages of the organocatalyzed ROP from the viewpoint of material applications, the organocatalyzed ROP of cyclic esters has been insufficiently discussed when compared to the organometallic-catalyzed ROP. Thus, it is important to evaluate the organocatalysts available for the ROP of cyclic esters in order to develop the organocatalyzed polymerization as a new polymer synthetic methodology. Herein, it is narrowly focused on the superlative organocatalysts for the ROP of selected strained and less strained cyclic lactones (Figure 1.1).

Organocatalysts for the ROP of strained lactones

ROP of VL, CL, and LA

Organic acid catalysts. Different types of organic catalysts have been progressively developed to obtain higher molecular weights, higher selectivity, and higher rates for the ROP of lactones (Figure 1.2). The cationic ROP of VL, CL, and LA has been carried out with a wide range of organic acids. The polymerization is catalyzed via electrophilic

monomer activation (Scheme 1.1), where the carbonyl oxygen of the monomer get protonated by the acid catalyst and acts as the activated species which reacts readily with the initiator.²⁷ However, higher reactivity of the protonated monomer can be susceptible to side reactions, which leads to a broader M_w/M_n . The HCl.Et₂O can be used to obtain controlled M_n for ROP of VL and CL with the range of M_w/M_n = 1.10-1.49 in the presence of an alcohol initiator.⁵⁴ A milder acid, tartaric acid, has shown a higher activity towards the ROP of CL over lactic acid, fumaric acid, and citric acid resulting in M_w/M_n ~1.3 with 10 mol% of the catalyst.⁵⁵ The trifluoromethanesulfonic acid (HOTf) in the presence of a protic initiator has shown living ROP of CL and can be used to obtain isotactic L-PLA at room temperature.⁵⁶ However, it is proven that methanesulfonic acid (MSA) is active as HOTf for the ROP of CL while retaining narrow M_w/M_n .⁵⁷ Additionally, the catalytic activity of MSA can be enhanced by a tripodal hydrogen bonds network of methanesulfonic acid-thiophosphoric triamide (MSA-TPTA) complex for the ROP of lactones in a living manner with narrow M_w/M_n (~1.1).⁵⁸ Trifluoromethanesulfonimide (HNTf₂) is another Brønsted acid catalyst which can give living characteristics for the ROP of VL.⁵⁹ Diphenyl phosphate (DPP) is a commercially available, less toxic and a milder catalyst compared to HNTf₂ for the controlled ROP of VL and CL.⁶⁰ Further, a bulky chiral phosphoric acid, 1,10-bis(naphthyl-2,2'-diyl) hydrogen phosphate (BNPH) was used for the ROP of VL and CL in bulk conditions at elevated temperature which could give living and controlled polymerization.⁶¹ Though a wide range of acid catalysts has been used for the ROP of lactones, they still give low to moderate molecular weights and comparatively slow rates. Nevertheless, organic acids considered as the most straightforward class of

catalysts used for the ROP of cyclic lactones in terms of operational simplicity and accessibility.^{31,56}

Phosphazene bases. Phosphazene base is another main category of organocatalysts for ROP (Figure 1.3). It has been found that 2-tert-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP) is an active catalyst over *N'*-tert-butyl-*N,N,N',N',N'',N''*- hexamethylphosphorimidic triamide (P_1 -*t*-Bu) for the ROP of VL and LA in the presence of an initiator which undergoes via chain end activation mechanism (Scheme 1.2). However, The ROP of CL with BEMP is sluggish even at elevated temperature with $M_w/M_n \sim 1.1$.⁶² The ROP of *rac*-lactide catalyzed by BEMP yields a probability of 0.70 isotactic propagation (P_i) at room temperature.⁶² A dimeric phosphazene base (P_2 -*t*-Bu) has been used to obtain highly isotactic polymers ($P_i=0.95$) with *rac*-lactide at -75°C resulting in a minimum epimerization.⁶³ Recently, a study shows CTPB has a decent catalytic activity on ROP of *rac*-lactide at -75°C in terms of rates and isotacticity ($P_i=0.93$).⁶⁴

Pyridine bases. Pyridine bases are widely used for the anionic ROP of LA due to its high nucleophilicity.³¹ The commonly used pyridine bases are 4-(dimethylamino)pyridine (DMAP) and 4-pyrrolidinopyridine (PPY), whereas DMAP outstands in rates over PPY (Figure 1.4).^{31,33,40} In the presence of either primary or secondary alcohol initiator, DMAP can be used to obtain isotactic L-PLA in both solution and melt conditions. Two plausible mechanisms have been proposed for DMAP catalyzed ROPs. Initially, it has been proposed, the monomer activation is taken place through a nucleophilic attack by DMAP on the monomer (Scheme 1.3, a).⁶⁵

However, the chain-end activation mechanism is also supported by computational studies where it proves both pathways are energetically favorable. Thus, in the gas phase and polar aprotic solvents, the H-bonded pathway was proposed to be at a lower energy in the presence of an initiator (Scheme 1.3, b).³¹ Even though, It is declared that controlled ROP of LA can be gained in the presence of a secondary alcohol initiator, the transesterification can be promoted on the PLA backbone specially at elevated temperatures due to the high activity and poor thermal stability of DMAP.⁶⁶ Additionally, DMAP catalyzed ROP of VL and CL were not reported; however, the ROP of LA with DMAP can be considered as sluggish compared to other organocatalysts.

***N*-Heterocyclic carbenes.** *N*-Heterocyclic carbenes (NHCs) are widely used as organocatalysts for the ROP of cyclic lactones (Figure 1.4). It is vastly recognized due to its facile synthesis, tunability of electronic, steric effects and the chemical reactivity.^{67–69} Polymerization rates and selectivities depend on both nature of the carbene and lactone monomer. Besides, It is shown that less sterically hindered NHCs are active for the ROP of lactones than their sterically demanding analogues.^{67,70–72} NHCs can act as nucleophiles; hence nucleophilic monomer activation mechanism was proposed. In addition, computational studies have suggested the H-bonding alcohol activation mechanism from NHCs is also preferable in the presence of an alcohol initiator.³⁹ Recently, it has been found that NHC can activate the alcohol through hydrogen bonding and promotes a nucleophilic attack on to the lactone monomer, that occurs during the polymerization of CL in the presence of methanol as the initiator

which is supported by density functional theory (DFT) calculations (Scheme 1.4 b).⁷³ In the absence of an alcohol initiator, the NHC is capable of forming controlled, high-molecular-weight cyclic polymers such as PLA, PCL, PVL and gradient block PVL-*co*-PCL through ROP, where NHC can act as a catalyst/initiator via zwitterionic ring-opening polymerization (ZROP) (Scheme 1.4 c).^{73–76} Thus, NHC catalysts are extensively studied for the ROP of both linear and cyclic esters. NHC catalysts stand out for LA polymerizations in terms of rates in seconds under low catalyst loadings (0.5 mol%). Additionally, in the presence of an alcohol initiator, it exhibits narrow M_w/M_n (<1.16) and remarkable end group fidelity.^{39,67,69,77} Compared to NHC catalyzed ROP of LA, polymerization rates of VL and CL are much lower, and give broader M_w/M_n (1.16–1.32).³³ Besides its higher catalytic activity, NHCs have been used in the stereoselective polymerization of *rac*-LA at low temperatures and for the formation of heterotactic polylactide from *meso*-lactide. Polymerization of *rac*-LA using sterically hindered, achiral Ph₂IMes catalyst can generate isotactic PLA (P_i = 0.90) at -70°C.⁷⁸ Besides, the ROP of *rac*-LA using sterically hindered chiral (CH(Me)Ph)₂IMes catalyst also formed a highly isotactic PLA at low temperatures. It was suggested that stereo-control is originated from the steric congestion of the active site, rather than by the chirality of the catalyst. The mechanism for ROP of *rac*-LA using either achiral or chiral NHCs catalysts was proposed through the chain-end activation mechanism despite the presence of chiral groups close to the active site.

Unimolecular Bifunctional Catalysts. Another remarkable milestone of the organocatalysts occurred in 2005 with the introduction of Takemoto thiourea for the

ROP of LA (Figure 1.5). Takemoto thiourea acts as a unimolecular bifunctional catalyst which has H-bonding acceptor (thiourea) and H-bonding donor (tertiary amine) moieties. Lactide is activated by the thiourea moiety via H-bonding, and the initiator is activated by the tertiary amine via H-bonding (Scheme 1.5). This dual activation allows for a well-controlled polymerization with a living behavior. Despite its higher selectivity towards the monomer, slothful rates were observed.⁴⁴ Besides, Takemoto thiourea was not active towards the ROP of VL and CL. Takemoto thiourea catalyst shows modest stereoselectivities at room temperature for ROP of *rac*-LA.⁷⁹ Remarkably, it has shown that same activity for the ROP of LA with thiourea (**1-S**) and *N,N*-dimethylcyclohexylamine which proved the bifunctional nature of the catalyst is critical, yet activating units are not required in a single catalyst, it can be a bimolecular system.⁴⁴ This invention marked a key development on the mechanistic perception of organocatalysis.

Highly active, commercially available, a strong guanidine base 1,5,7-triazabicyclo [4.4.0]dec-5-ene (TBD) is a unimolecular bifunctional catalyst for the ROP for lactide (Scheme 1.5), which could increase the rate of polymerization to seconds with a minimum amount of catalyst loading in non-polar solvents. TBD is also able to polymerize VL and CL readily. Interestingly, polymerization of *rac*-lactide with TBD shows a slight isotactic enhancement with a P_i value of 0.58 compared to other organocatalysts at room temperature.³⁸ However, TBD can eventually transesterify the polymer backbone and can lead to poor end group fidelity and broad molecular weight distribution.^{38,80} To mitigate the poor end group fidelity, an acyclic guanidine catalyst

has been designed as less basic than TBD. The ROP of LA with acyclic guanidine shows higher control and end group fidelity despite its low rates.⁸¹ A guanidine base 7-Methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD) and an amidine base 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) are substituted analogues for TBD which are active for the ROP of LA which provided a good selectivity and a narrow M_w/M_n (<1.1). However, the reaction rates are lower and require a higher catalyst loading than TBD. Yet, no significant differences were observed in the selectivity of stereochemistry for the polymerization of *rac*-LA between TBD, DBU, and MTBD.³⁸ Despite the activity of MTBD and DBU towards the ROP of LA, it is reported that those bases are not active for the ROP of VL and CL, but in the presence of **1-S**, MTBD and DBU can promote the ROP of VL and CL.³⁸ Amino-thiazoline is another unimolecular bifunctional catalyst which has been designed for the ROP of LA. This catalyst can give control polymers for the ROP *rac*-LA, though it is sluggish with compared to TBD.⁸²

In 2013, Dixon and co-workers disclosed a novel class of unimolecular bifunctional Iminophosphorane (IPTU-1) catalyst, equipped with a H-bond donor and a Brønsted base for the ROP of lactones. However, for the ROP of CL, an increasing discrepancy between the target molecular weight and M_n was observed as the $[M]_0/[I]_0$ increased.⁸³ Polymerization of *rac*-lactide catalyzed by chiral iminophosphorane catalyst (IPTU-2) gives slight isotactic enhancement ($P_i = 0.64$) at room temperature.⁸³ Recently, the synthesis of bifunctional iminophosphorane thiourea/urea catalysts (IPTU-3 and IPU) has been reported for the ROP of *rac*-LA, which could afford controlled molecular weights, narrow M_w/M_n and well-defined end groups without any undesired side

reactions. The ROP of *rac*-LA catalyzed with IPU has shown a higher stereoselectivity ($P_m = 0.80$) under mild reaction conditions via chain-end control mechanism.⁸⁴ Besides, Chen and Bo-Zhu have newly designed a bifunctional chiral catalyst system incorporating three key elements (β -isocupreidine core, thiourea functionality, and chiral binaphthyl-amine (BINAM)) (β -ICD-TU-BINAM) into a single organic molecule, which is capable of furnishing ROP of *rac*-LA with supreme stereoselectivity factor (k_L/k_D) = 53 and $ee = 91\%$ at 50.6% monomer conversion.⁸⁵ The commercially available chiral version of Takemoto thiourea has been used to form semi-crystalline PLA via isoselective ROP of *rac*-LA. The polymerizations have been carried out at room temperature, and *rac*-LA conversion reached 85% after 238 hours giving expected molecular weight, narrow M_w/M_n and a P_m value of 0.87. Yet, epimerization of *rac*-LA to *meso*-LA was observed due to stereo errors during the ROP process.⁸⁶

H-Bond Donors. Throughout the last decade, a wide range of H-bond donors were explored for the ROP of lactones. Some of the effective H-bond donors are 1) squaramide catalyst(SQA)^{87, 88} 2) amides (A1)⁸⁹, 3) fluorinated alcohols (FA)⁹⁰, 4) sulfonamides (SA)⁹¹ and 5) commercially available phenols (Figure 1.6)⁹². These H-bond donors were utilized with weaker tertiary amine bases for ROP of lactones. Hence, comparatively, these ROP reactions are time-consuming yet, well-controlled. As a remedy (thio)urea catalysts have been developed as H-bond donors with the combination of strong organic bases such as guanidine, amidine and phophazene bases.

(Thio)urea/base Cocatalysts. In the light of above advances of organocatalysts, (thio)urea/ base cocatalyst system was assembled to conduct highly selective ROP of

cyclic lactones, which resulted in precisely tailored polymers with high end group fidelity and narrow molecular weight distributions ($M_w/M_n < 1.1$).³⁸ Despite the high selectivity, this catalyst system suffer from low rates for ROP.^{46,93} In general, thiourea featuring aryl rings with strong electron-withdrawing substituent groups give faster rates, though it is dependent on the reaction conditions.⁴⁷ It is also proven that the high selectivity and activity of ROP of VL are proportional to the magnitude of binding constants of catalysts and the bases. However, when the binding is too strong between base and catalyst, a reduction of the reaction rates was observed.^{93,94}

The synthetic addition of one and two thiourea moieties to **1-S** could increase the rates of the ROP of LA, VL, and CL in non-polar solvents without compromising the high selectivity.^{46,95} Higher activity in **2-S** was explained by *activated thiourea* mechanism supported by computational studies (Figure 1.7). However, the **3-S** catalyst activity was rendered by intramolecular H-bonding network among the thiourea moieties. As a mitigation step of intramolecular H-bonding network, **3-O** was synthesized to have a free urea moiety to activate the monomer which could give remarkable enhanced rate without rendering the selectivity for ROP of VL and CL.⁴⁶ The **3-O**/MTBD cocatalyst system could give markable success over TBD for the ROP of CL and VL in terms of the rate and the selectivity.⁵¹ This renaissance leads to conduct ROP with urea catalysts, which are better H-bond donors than its thiourea analogues in the presence of a base.^{46,47,96} However, The **2-S** catalyst was effective for the ROP of LA than **1-S** and **3-O**.⁹⁵

Recent studies show that the (thio)urea anion ((thio)imidate) which is corresponding to the deprotonation of H-bond donor by a metal hydride or an alkoxide or a strong amine or tetra-*n*-butylammonium hydroxide could give incredible rates and selectivity for the ROP of lactones.^{49,50,52,96,97} It has been computationally and experimentally suggested that (thio)imidate structure can act similarly as TBD where H-bond donor and acceptor are in the same molecule.^{49,50} Thiourea with metal alkoxides such as NaOCH₃ or KOCH₃ makes thioimidate salt and alcohol, which can act as a catalyst/initiator. Hence, for [M]₀/[I]₀= 200 ROP of LA, and 1-10 equiv. of thiourea to alcohol shows higher rates (minutes) and selectivity ($M_w/M_n \sim 1.1$) with lower amounts of thiourea. However, in the absence of excess thiourea, M_w/M_n was broadened to 1.55.⁵⁰ Compared to (thio)urea/alkoxide, (thio)urea/strong organic base shows promising results in reaction control. When (thio)urea mixed with a strong organic base, there can be an equilibrium between classical H-bond mediated ROP and (thio)imidate mediated ROP mechanisms. Hence, it is believed this equilibrium may help to gain reaction control compared to (thio)urea/alkoxide system.^{47,51,52} In addition, it has been found that (thio)imidate mechanism is preferred reaction conditions such as polar solvents, high temperature, high monomer concentration, presence of strong electron-withdrawing groups on the H-bond donor and strong bases.^{47,48,50,52,96,98,99} Moreover, It has shown that more imidate characteristics can attenuate ROP rates in the application of higher acidic (thio)urea, which resulted in the reduction of basicity of formed (thio)imidate structure.^{47,98} A commercially available trichlorocarbene (TCC) has been shown higher activity for the ROP of VL and CL in polar solvents which undergoes through imidate mediated mechanism.⁵² Further, the conformational flexibility between (thio)urea moieties also

has an impact on rates. In recent studies, the **2-O5-O** catalyst has shown astonishing enhanced rates and selectivity for the ROP of VL and CL, due to the stability of the pseudo-7-membered cycle formation of the catalyst through intramolecular H-bonding even in non-polar solvents and under solvent free conditions, whereas **2-S5-O** catalyst shows higher rates for the ROP of LA.⁹⁶ Thiourea catalysts are more effective in the ROP of LA compared to urea catalysts which is contrary to what was observed for VL and CL, since the same structural analogues of thiourea and urea can have different ROP mechanisms. It was revealed that thiourea is more acidic than its identically substituted urea. Thus, it is more favored towards imidate mediated mechanism. A pair of urea and thiourea with an identical pK_a , can undergo the same mechanism during the ROP of LA, whereas the more polar urea, will become the more active H- bond donor while exhibiting higher rates.⁹⁶

Thermal stability of Organocatalysts

The industrial implementation of organocatalyzed polymerizations is limited due to the requirements of high catalyst loading and poor thermal stability.⁶⁶ The standard temperature range for industrial polyester production is 150 °C- 300 °C.¹⁰⁰ Hence, organic acid and base mixtures have been advanced to mitigate the above-mentioned limitations due to its unique ability to form thermally stable complexes (Figure 1.8). One step forward to enhance the green features of organocatalyzed ROP is the use of solvent-less approaches. Hence ROP reactions were attempted under solvent-free conditions. Bulk ROP of LA has been conducted with the stoichiometric mixtures of creatinine + glycolic acid (CR:G) and creatinine + acetic acid (CR:A) at 110 °C and

130 °C. High polymers with a narrow dispersity were obtained, albeit the reactions take days to complete.¹⁰¹ Recently, it was disclosed that DMAP with organic acids (DMAP.HX) could be used to suppress the reactivity of DMAP and overcome thermal instability. The dual activity of the DMAP.HX complex has been proposed through a cooperative activation mechanism (Scheme 1.7).^{102,103} The mixture of DMAP and triflic acid (DMAP:HOTf) displays outstanding catalytic activity over the other tested DMAP.HX systems (X= Cl, OMs) at 130 °C for ROP of L-LA in a living manner.¹⁰⁴ However, at the elevated temperatures, inducement of the racemization reactions was significant. The ROP of VL and CL have attempted with DMAP and it shows meager rates in polymerization. The combining of DMAP with DMAP.HOTf in the presence of an alcohol initiator could increase the rates in the ROP of CL and VL, still, it can be considered as sluggish.¹⁰⁴ Following the same concept, in a recent study DMAP.Saccharin system has been used as a bifunctional catalyst system for the ROP of L-LA and VL. This system shows the adaptability at elevated temperatures (140 °C) with a good controlled polymerization ($M_w/M_n = \sim 1.1$) for low $[M]_0/[I]_0$. Albeit, only up to $[M]_0/[I]_0 = 120$ molecular weights have attempted for the ROP of L-LA.¹⁰² Further, pyridine base (2,2'-bipyridinium) - MSA ionic mixture was used for the ROP of CL at elevated temperature, which resulted in controlled polymerizations, although slight deviation of molecular weights than expected was observed for polymers which are $[M]_0/[I]_0 > 100$ indicating the occurrence of undesirable side reactions.¹⁰⁵ Additionally, MSA and TBD have been used to form either a eutectic or non-eutectic mixture to catalyze the ROP of CL under solvent-free conditions at low temperatures as 37 °C. Although, only low $[M]_0/[I]_0$ were attempted and M_w/M_n was broadened up to ~ 1.5

(Scheme 1.8).¹⁰⁶ However, It has been observed that (thio)urea catalysts are efficient under solvent-free conditions with a minimum amount of catalyst loadings for ROP of lactones while exhibiting excellent weight control from low M_n to high polymers.^{53,96} Further, ROP of lactones can be carried out at elevated temperature (110 °C) using appropriate (thio)urea/base cocatalyst without observing any catalyst degradation.⁴⁸ As we believe, expansion of use and the development of new catalytic strategies will facilitate the path of organocatalysts toward the industrial applications.

Polymerization of thio/thionolactones

Poly(thio/thionoesters) have attracted attention because of their material properties such as higher T_m , higher thermal stability, and lower solubility in organic solvents, which are superior to those of the corresponding polyesters.¹⁰⁷ It has been reported that the homopolymers made from CL have the $T_m \sim 60$ °C, whereas the T_m of poly (ϵ - thiocaprolactone) (PtCL) is (104.5–106 8) °C.¹⁰⁸ Polythioesters have been synthesized via polycondensation of dithiols in the presence of diacid chloride and from the ROP of thiolactones.^{109,110} However, the ROP of thio/thiono lactones are mostly unexplored due to difficult preparation with traditional methods and low stability.

Organocatalytic ROP of ϵ -thiocaprolactone (tCL)

The ROP of tCL was first reported in 1968.¹⁰⁸ The enzymatic and the metallic ROP of tCL has been carried out, but the reported polymerizations were not controlled.^{109,111–113} Few studies have been reported on the organocatalytic ROP of tCL and it is suggested that strong guanidine bases like TBD are effective for the ROP of tCL.¹¹⁴ The ROP of

tCL with TBD in CDCl₃, initiated with octadecylthiol shows rapid reaction rates and gives expected molecular weight with a M_w/M_n of 1.70. The amidine bases MTBD and DBU also provide relatively decent rates, yet controllable ROP of tCL with moderate $M_w/M_n \approx 1.6$ has been observed. It was proposed tCL opened by nucleophilic attack by strong nucleophilic bases. However, a phosphazene base BEMP was not able to perform the ROP of tCL due to its less nucleophilicity and bulkiness. Nevertheless, the addition of an equimolar amount of H-bond donor (1-S) to base (amidine base or phosphazene base) catalyzed ROP of tCL, initiated from octadecylthiol exhibits a marked effect on the rates and the selectivity which leads to a narrow M_w/M_n (1.45). It is suggested the ROP of tCL follows a H-bond mediated mechanism in the presence of an initiator.¹¹⁴

Organocatalytic ROP of ϵ -thionocaprolactone (tnCL)

Anionic ROP. Anionic ROP of tnCL has been carried out with DBU, whereas it acts as a weak nucleophile/initiator. The nucleophile (DBU) attacks to the thiocarbonyl carbon atom of the monomer to result in the alcoholate anion as a propagating species. In contrast, the base can also give a S_N2 nucleophilic attack on to the α -methylene group adjacent to the oxygen atom of the monomer in the initiation process to provide the thiocarboxylate anion which can produce a mix polymer backbone with 89 : 11 unit ratio of thiocarboxylate anion to alcoholate anion units (Scheme 1.9). Additionally, only 25% of the total polymer conversion has been obtained at elevated temperatures in THF after 20 hours. The combination of those two mechanisms provides a copolymer with both the alcoholate and thiocarboxylate anion unit. Albeit, only low $[M]_0/[I]_0$ reactions

were attempted and broad M_w/M_n was observed.¹¹⁰ This S/O scrambling of the polymer occurs simply due to the heating of the reaction.

Cationic ROP. Efficient cationic ROPs of tnCL have been conducted with HOTf, MeOTf, and EtOTf and showed only the formation of polythioester to overcome the formation of scrambled polymer backbone. The thiocarbonyl sulfur of the monomer attacks the electrophile and forms a carbonium cation which leads to the formation of polythioester, whereas the endocyclic oxygen can attack the electrophile to form an oxonium ion. As the carbonium cation is more stabilized due to the resonance effect and lower total energy of the intermediate, the formation of polythioester is more pronounced over polythionoester (Scheme 1.10). The acid-catalyzed cationic ROP of tnCL can afford high polythioesters with targeted molecular weights; however, broad M_w/M_n has been observed ($M_w/M_n=1.95$).¹¹⁵

H-Bond mediated ROP. It is remarkable the retention of the S/O substitution on the polymer backbone allowed by thiourea/amine base cocatalyst system for the ROP of tnCL yet, obtained a controlled polymerization. In the presence of 1-S/DBU co-catalyzed ROP of tnCL has shown a notable impact on the reaction rates at room temperature. In the presence of an alcohol initiator, the 1-S/BEMP co-catalyzed ROP of tnCL in non-polar solvents showed notably enhanced reaction rates and characteristics of living polymerization, yet it retains high selectivity.¹¹⁶ The binding between (thio)thionoester and the H-bond donor is noticeably low compared to the binding between its oxygenated analogues and H-bond donor.^{114,116} However, the reaction rates of tnCL are higher than CL under the same reaction conditions.^{94,116} It is proposed,

though the magnitude of the binding constant of tnCL is low, the 1-S plays a mechanistic role in reaction rates that are not fully understood yet.¹¹⁶

Organocatalysts for the ROP of less-strained lactones

Organocatalytic ROP of macrolactones

Polyesters synthesized from the ROP of macrolactones have attracted much interest over the past few decades due to their mechanical and thermal properties.⁸ ω -pentadecalactone (PDL), and ethylene brassylate (EB) are commonly used macrolactones which are obtainable from natural sources and are widely used in ROP to form polyesters with long aliphatic chains.^{7,117} The polyesters made from PDL, have shown material properties similar to low-density polyethylene (LDPE) and have the potential to be used in biomedical applications.^{7,8} The ROP of macrolactones has been carried out mainly by employing enzyme catalysts, metal catalysts, and organocatalysts.⁶ However, only a handful of studies have been carried out for the organocatalytic ROP of macrolactones.

The ROPs of small lactones are known to be enthalpically driven ROPs resulting in the release of the angular and trans-annular strains. Hence, the polymerization reactions show rapid rates at low or room temperatures.²⁷ However, the ROP of the macrolactones is stated as entropically driven ROPs, since the larger ring size causes a small/less ring-strain and leads to an entropic gain in the polymerization. According to Gibbs free energy equation, the entropy can be increased with the temperature; thus most of the ROPs of macrolactones are carried out at elevated temperatures.

Organocatalytic ROP of PDL and EB

Organic Acids. Only a few studies have been carried out on the organic acid-catalyzed ROP of macrolactones. Dodecylbenzenesulfonic acid (DBSA), DPP, and HOTf are organic acids that have been used for the ROP of PDL in bulk conditions at elevated temperatures (80 °C) in the presence of an alcohol initiator.¹¹⁸ The polymerization reactions catalyzed with DBSA and DPP have taken 24 hours to reach the full conversion and resulted in lower molecular weights than expected.¹¹⁸ However, with HOTf, targeted molecular weights were achieved. Also, organic acid-catalyzed ROP of EB has been carried out with p-toluene sulfonic acid (PTSA), DPP, and DBSA. However, compared to DPP and DBSA, PTSA showed low molecular weight and a broad M_w/M_n .¹¹⁷

Phosphazene Bases. Phosphazene superbases have also been used in the ROP of macrolactones. The ROP of PDL has been carried out with P₂-*t*-Bu, P₄-*t*-Bu and P₄-*t*-Oct bases in the presence of an alcohol initiator in bulk and diluted conditions at 80 °C. Rapid rates of polymerization were observed with P₄-*t*-Bu and P₄-*t*-Oct with decent molecular weights ($M_n \leq 34000$ g mol⁻¹) where P₂-*t*-Bu showed comparatively low rates.¹¹⁹ The ROP of PDL has also been carried out at room temperature under diluted conditions with P₄-*t*-Bu using an alcohol initiator which showed a high conversion with the expected molecular weight though the M_w/M_n was broad ($M_w/M_n = 3.81$).¹¹⁹

H-Bond donors. TBD has been used as the catalyst for the ROP of PDL in bulk and in solvent at 100 °C in the presence of an initiator ($M_n \leq 27100$, $M_w/M_n = 1.3 - 2.1$).^{120,121}

Similarly, TBD has also been used for the ROP of EB in bulk and in diluted conditions at 80 °C, but it took days to reach high conversions.¹¹⁷ Other bases, 1,2,3-tricyclohexylguanidine (TCHG) and 1,2,3-triisopropylguanidine (TIPG) have also been tested on the ROP of EB though higher conversions were limited.¹¹⁷ Additionally, The ROP of PDL has been studied with N-heterocyclic olefins (NHOs) using benzyl alcohol as the initiator in toluene at 110 °C which showed poor conversions and reaction rates.¹²²

The H- bond mediated ROP of macrolactones has been carried out for PDL and EB in the presence of benzyl alcohol as the initiator. The reactions have been carried out in bulk conditions at 80 °C using TCC/BEMP co-catalyst system, which reached high conversions within few hours, resulting in expected molecular weight still, with broader M_w/M_n .⁵³ In general, it has been problematic to obtain narrow M_w/M_n due to the occurrence of transesterification side reactions, which is notable in the ROPs of macrolactones.

CONCLUSION

In this review, we describe the organocatalytic ROP of selected strained and less strained renewable monomers which are capable of synthesizing biodegradable and biocompatible polymers. The field of organocatalysts for the ROP of strained lactones has bloomed significantly in the past two decades, where advanced catalysts provide rapid and precision synthesis of high polymers, which can substitute petroleum-based polymers. Indeed, the higher activity, selectivity, diversity, cost-effectivity, and greener approach of the organocatalytic ROP give viability and advantageous impact in the polymerization field. Organocatalysts have provided new mechanistic insights and new approaches in synthesizing polymers using strained/less strained lactones while affording new types of materials. The organocatalytic ROP of thiono (macro)lactones can yield new families of materials; thus far, they are relatively understudied the polymer community and in the polymer industry.

The ROP of macrolactones has created pathways access to novel polymeric materials featuring long aliphatic polymer backbone. Though organometallic catalysts have been used widely and performed a decent polymerization process of macrolactones, organocatalysts have become an efficient alternative. Most of the organocatalytic ROPs of macrolactones have been carried out at elevated temperatures, yet obtaining higher molecular weights, and narrow distribution have become a challenge. Thus, developments in designing and synthesizing new effective organocatalytic systems are needed.

Despite the significant advances in the organocatalytic ROP of lactones, challenges still exist for the implementation of organocatalytic ROP at the industrial scale. Even if the industrial-scale polyester production is performed at high temperatures, most of the organocatalysts show low thermal stability, and in many cases, those catalysts get deactivated or degraded at high temperatures, which have been drawbacks in the industrial scale. However, organic acid-base mixtures and (thio)urea catalysts have been tested for ROP at elevated temperatures and reported thermal stability.⁴⁸ Nevertheless, only a few studies have been carried out for the use of organocatalysts in ROP at high temperature, and further developments are required to implement of organocatalysts in industry.

The polymers synthesized from LA are commercially important biodegradable and biocompatible polymers that have a wide range of applications. Thus, an adequate amount of studies has been carried out for synthesizing PLA with precise control of molecular weights and narrow M_w/M_n via organocatalytic ROP of L-LA or D-LA. Though, studies on PLAs with different degrees of tacticity are not sufficient to tackle the plausible applications of those polymers.

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Scheme 1.1. Electrophilic Monomer Activation Mechanism for ROP

Scheme 1.2. Chain-End Activation Mechanism for ROP

Scheme 1.3. Proposed Mechanisms for ROP of Lactide with DMAP

Scheme 1.4. Proposed Mechanisms for ROP of lactones with NHC

Scheme 1.5. Bifunctional activation of monomer and initiator/chain end by Takemoto thiourea (a) and by TBD (b)

Scheme 1.6. Equilibrium between imidate mediated mechanism and H-bond mediated mechanism

Scheme 1.7. DMAP/DMAP-HX catalyzed cooperative activation mechanism for the ROP of LA

Scheme 1.8. non-eutectic mixture of TBD: MSA for the ROP of LA

Scheme 1.9 anionic ROP of tnCL

Scheme 1.10 cationic ROP of tnCL

Figure 1.1. a) Some strained lactones b) Some less strained lactones used in organocatalytic ROP

Figure 1.4. Pyridine bases and *N*-Heterocyclic carbenes and olefins for ROP

Figure 1.5. Unimolecular bifunctional catalysts for ROP

Figure 1.6. H-bond donor catalysts for ROP

Figure 1.7. Proposed activated (thio)urea transition state for multi-donors

Figure 1.8. Organic acid base mixtures for ROP

MANUSCRIPT II

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Bisurea and Bisthiourea H-Bonding Organocatalysts for Ring-Opening Polymerization: Cues for the Catalyst Design

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ABSTRACT

A series of conformationally flexible bis(thio)urea H-bond donors plus base cocatalyst were applied to the ring-opening polymerization (ROP) of lactones. The rate of the ROP displays a strong dependence on the length and identity of the tether, where a circa five methylene-unit long tether exhibits the fastest ROP. Any constriction to conformational freedom is deleterious to catalysis. For the ROP of δ -valerolactone (VL) and ϵ -caprolactone (CL), the bisurea H-bond donors are more effective, but for lactide, the bithioureas are more active catalysts. The ROP reactions are rapid and controlled across a wide range of reaction conditions, including solvent-free conditions, exhibiting excellent weight control from low M_n to high polymers. The active mechanism is highly dependent on the identity of the base cocatalyst, and a mechanistic rationale for the observations is discussed. Implications for the design of future generation catalysts are discussed.

INTRODUCTION

H-bonding organocatalysts for ring-opening polymerization (ROP) are a facile means of generating precisely tailored macromolecules.¹⁻³ Among the larger class of H-bonding organocatalysts, (thio)urea H-bond donors stand out for the remarkable level of control they can rendered in polymer synthesis.^{4,5} The thiourea plus base mediated ROP of lactone and carbonate monomers are thought to effect enchainment by H-bond activation of monomer by thiourea and initiating/propagating chain end by base; these catalysts are most active in non-polar solvent.⁵ The urea plus base class of H-bonding catalysts offer no apology in terms of rate and are among the most active catalysts for the ROP of lactones.⁶⁻⁸ Several mechanistic studies by our group and others have shown that (thio)urea/base mediated ROP can proceed by one of two mechanisms: *neutral H-bonding* or *(thio)imideate mediated* ROP (Scheme 2.1).⁷⁻¹⁰ Which mechanism is operative depends largely on reaction conditions (high temperature,¹¹ polar solvent,^{10,12,13} strong electron-withdrawing groups on H-bond donor,¹⁰ early reaction time and strong bases favor imideate)^{7,8} though generally ureas are more active than thioureas and imideate mediated ROP is far more active than neutral H-bonding.³ Remarkably, these ‘hyperactive’ catalysts for ROP remain controlled.

The synthetic addition of one or more (thio)urea H-bond donating arms to the parent (thio)urea has been shown to substantially increase the activity of (thio)urea H-bond donors.^{6,14} Our group first disclosed bis- and tris-(thio)urea H-bond donors for ROP,^{6,14} and other intramolecular Lewis acid donors have been used.¹⁵ In general, the bis-(thio)ureas (**2-O** and **2-S**, Figure 2.1) are more active than mono-(thio)urea (**1-O** and **1-**

S), and ureas are more active than thioureas for the bis-(thio)urea plus base mediated ROP of lactone and carbonate monomers.^{3,6,13} However, this rule of thumb does not apply for the (thio)urea plus base mediated ROP of lactide (LA), where the higher rates are displayed by (bis)-thioureas (versus (bis)-ureas) of like substitution.¹² Again, the high rates exhibited by **2-O** and **2-S** plus base for ROP occur without the reduction of reaction control. Pan *et al.* synthesized bisurea H-bond donors featuring rigid linkers,¹⁶ which were less active for ROP than the flexible 3-carbon tethered **2-O** and **2-S** reported by our group.^{6,14} In the pantheon of conformationally flexible linkers that can be envisaged, only one has been reported.⁶ In light of the recent interest in these catalysts, we disclose here several bisurea and bithiourea H-bond donors for ROP with flexible linkers, most with higher activity and control than the parent **2-X** system. We extend previously proposed mechanisms to the (thio)urea plus alkylamine base mediated ROP of LA to explain why thioureas have been observed to be more effective (versus ureas).

EXPERIMENTAL SECTION

General Considerations. All chemicals were purchased from Fisher Scientific and used as received unless stated otherwise. Benzene- d_6 and chloroform- d were purchased from Cambridge Isotope Laboratories, distilled from calcium hydride and stored under N₂. Acetone- d_6 was purchased from Cambridge Isotope Laboratories, distilled from calcium sulfate and stored under N₂. δ -valerolactone (VL), ϵ -caprolactone (CL) and benzyl alcohol were distilled under high vacuum from calcium hydride prior to use. Dry CH₂Cl₂ was obtained from an Innovative Technology solvent purification system. All experiments were conducted in a stainless-steel glovebox under N₂ unless stated otherwise. NMR experiments were performed on a Bruker Avance III 300 or 400 MHz spectrometer. Urea and thiourea H-bond donors were prepared by established methods.^{17,18}

Mass spectrometry experiments were performed using a Thermo Electron (San Jose, CA, USA) LTQ Orbitrap XL mass spectrometer affixed with electrospray ionization (ESI) interface in a positive ion mode. Collected mass spectra were averaged for at least 50 scans. Tune conditions for infusion experiments (10 μ L/min flow, sample concentration 5 μ g/mL in 50/50 v/v water/ methanol) were as follows: ion spray voltage, 5000 V; capillary temperature, 275^oC; sheath gas (N₂, arbitrary units), 11; auxiliary gas (N₂, arbitrary units), 2; capillary voltage, 21 V; and tube lens, 90 V; multipole 00 offset, -4.25 V; lens 0 voltage, - 5.00; multipole 1 offset, - 8.50 V; Multipole RF Amplitude, 400 V; Ion trap's AGC target settings for Full MS was 3.0e4 and FT's 2.0e5 (with 3 and

2 averaged microscans , respectively). Prior to analysis, the instrument was calibrated for positive ions using Pierce LTQ ESI positive ion calibration solution (lot #PC197784).

Example ROP of VL in benzene- d_6 . To a 7 mL vial, **2-O5** (14.69 mg, 0.024 mmol), VL (100.00 mg, 0.998 mmol) and benzene- d_6 (250 μ L) were added. The contents were stirred until the solution became homogenous. To a second 7 ml vial, benzyl alcohol (2.16 mg, 0.019 mmol), MTBD (3.67 mg, 0.024 mmol) and benzene- d_6 (250 μ L) were added. The contents in the second vial were transferred to the first vial via Pasteur pipette, and the contents were agitated to mix. The reaction solution was then transferred to an NMR tube, and the progress of the reaction monitored by ^1H NMR. The reaction was quenched by the addition of benzoic acid (3.00 mg, 0.024 mmol). Polymer isolated by precipitation with hexanes, and the volatiles were removed under high vacuum before characterization via GPC.

Example solvent-free ROP of VL. A 1.5 mL vial was charged with **2-O5** (12.23 mg, 0.019 mmol), benzyl alcohol (2.15 mg, 0.019 mmol), VL (400.00 mg, 3.99 mmol), magnetic stir bar and stirred until homogeneous. A second vial was charged with MTBD (3.05 mg, 0.019 mmol). The contents of the first vial were transferred to the second vial using a Pasteur pipette, and the solution was stirred. Reaction progress was monitored by taking aliquots of the reaction mixture – either ~ 1.5 μ L solution or a small amount of solid extracted via spatula – at different time intervals and quenched in a solution of benzoic acid in chloroform- d . Conversion was determined via ^1H NMR. The polymer

samples in the aliquots were isolated by precipitating with hexanes, and the volatiles were removed under high vacuum before characterization via GPC.

Synthesis of urea H-bond donors

1,1'-(propane-1,3-diyl)bis(3-(3,5-bis(trifluoromethyl)phenyl)urea) (**2-O3**)- A dried 10 mL Schlenk flask was charged with a stir bar, dichloromethane (7 mL), 3,5-bis(trifluoromethyl)phenyl isocyanate (0.21 g, 0.86 mmol), and 1,3-diaminopropane (0.03 mL, 0.43 mmol) was added dropwise to the Schlenk flask. After stirring overnight, the reaction mixture was filtered via suction filtration and rinsed with 3 portions of cold CH₂Cl₂ to provide a pure white powder that was freed of volatiles under high vacuum. Yield: 97%. Characterization matches literature.⁶

1,1'-(ethane-1,2-diyl)bis(3-(3,5-bis(trifluoromethyl)phenyl)urea) (**2-O2**)- A flame dried 25 mL Schlenk flask was charged with a stir bar, dichloromethane (25 mL), 3,5-bis(trifluoromethyl)phenyl isocyanate (1 g, 3.91 mmol), and ethylenediamine (0.13 mL, 1.95 mmol) was added dropwise to the Schlenk flask. After stirring overnight, the reaction mixture was filtered via suction filtration and rinsed with 3 portions of cold CH₂Cl₂ to provide a pure white powder that was freed of volatiles under high vacuum. Yield: 65%. NMR spectra given below. HRMS: calc. (C₂₀H₁₅F₁₂N₄O₂+H)⁺ = 571.0998; found *m/z* = 571.0998.

1,1'-(butane-1,4-diyl)bis(3-(3,5-bis(trifluoromethyl)phenyl)urea) (**2-O4**)- A flame dried 25 mL Schlenk flask was charged with a stir bar, dichloromethane (25 mL), 3,5-bis(trifluoromethyl)phenyl isocyanate (1 g, 3.91 mmol), and 1,4-diaminobutane (0.20

mL, 1.95 mmol) was added dropwise to the Schlenk flask. After stirring overnight, the reaction mixture was filtered via suction filtration and rinsed with 3 portions of cold CH₂Cl₂ to provide a pure white powder that was freed of volatiles under high vacuum. Yield: 70%. NMR spectra given below. HRMS: calc. (C₂₂H₁₉F₁₂N₄O₂+H)⁺= 599.1238; found *m/z* = 599.1311.

1,1'-(pentane-1,5-diyl)bis(3-(3,5-bis(trifluoromethyl)phenyl)urea) (**2-O5**)- A flame dried 25 ml Schlenk flask was charged with a stir bar, dichloromethane (25 mL), 3,5-bistrifluoromethylphenyl isocyanate (1 g, 3.91 mmol), and 1,5-diaminopentane (0.22 mL, 1.95 mmol) was added dropwise to the Schlenk flask. After stirring overnight, the reaction mixture was filtered via suction filtration and rinsed with 3 portions of cold CH₂Cl₂ to provide a pure white powder that was freed of volatiles under high vacuum. Yield: 74%. NMR spectra given below. HRMS: calc. (C₂₃H₂₁F₁₂N₄O₂+H)⁺= 613.1467; found *m/z* = 613.1467.

1,1'-(hexane-1,6-diyl)bis(3-(3,5-bis(trifluoromethyl)phenyl)urea) (**2-O6**)- A flame dried 25 ml Schlenk flask was charged with a stir bar, dichloromethane (25 mL), 3,5-bistrifluoromethylphenyl isocyanate (1 g, 3.91 mmol), and hexamethylenediamine (0.25 mL, 1.95 mmol) was added dropwise to the Schlenk flask. After stirring overnight, the reaction mixture was filtered via suction filtration and rinsed with 3 portions of cold CH₂Cl₂ to provide a pure white powder that was freed of volatiles under high vacuum. Yield: 80%. NMR spectra given below. HRMS: calc. (C₂₄H₂₃F₁₂N₄O₂+H)⁺= 627.1624; found *m/z* = 627.1624.

1,1'-(dodecane-1,12-diyl)bis(3-(3,5-bis(trifluoromethyl)phenyl)urea) (**2-O12**)- A flame dried 100 ml Schlenk flask was charged with a stir bar, dichloromethane (20 mL), 3,5-bistrifluoromethylphenyl isocyanate (0.63 g, 2.5 mmol), and 1,12-diaminododecane (0.25 g, 1.25 mmol) was added dropwise to the Schlenk flask. After stirring overnight, the reaction mixture was filtered via suction filtration and rinsed with 3 portions of cold CH₂Cl₂ to provide a pure white powder that was freed of volatiles under high vacuum. Yield: 92%. NMR spectra given below. HRMS: calc. (C₃₀H₃₄F₁₂N₄O₂+H)⁺= 711.2382; found *m/z* = 711.2563.

1,1'-((methylazanediyl)bis(ethane-2,1-diyl))bis(3-(3,5-bis(trifluoromethyl)phenyl)urea) (**2-O5-N**)- A flame dried 50 ml Schlenk flask was charged with a stir bar, dichloromethane (20 mL), 3,5-bistrifluoromethylphenyl isocyanate (1.08 g, 4.26 mmol), and N1-(2-aminoethyl)-N1-methylethane-1,2-diamine (0.27 mL, 2.13 mmol) was added dropwise to the Schlenk flask. After stirring overnight, the reaction mixture was filtered and rinsed with 3 portions of cold CH₂Cl₂ to provide a pure white powder that was freed of volatiles under high vacuum. Yield: 47%. NMR spectra given below. HRMS: calc. (C₂₃H₂₁F₁₂N₅O₂+H)⁺= 628.1564; found *m/z* = 628.1594.

1,1'-(oxybis(ethane-2,1-diyl))bis(3-(3,5-bis(trifluoromethyl)phenyl)urea) (**2-O5-O**) - A flame dried 50 ml Schlenk flask was charged with a stir bar, dichloromethane (20 mL), 3,5-bistrifluoromethylphenyl isocyanate (2.2 g, 8.14 mmol), and 2,2'-oxybis(ethan-1-amine) (0.44mL, 4.07 mmol) was added dropwise to the Schlenk flask. After stirring overnight, the reaction mixture was filtered and rinsed with 3 portions of cold CH₂Cl₂

to provide a pure white powder that was freed of volatiles under high vacuum. Yield: 90%. NMR spectra given below. HRMS: calc. $(C_{22}H_{19}F_{12}N_4O_3+H)^+ = 615.1260$; found $m/z = 615.1260$.

1,1'-(2,2-dimethylpropane-1,3-diyl)bis(3-(3,5-bis(trifluoromethyl)phenyl)urea) (**2-O3-diMe**) - A flame dried 50 ml Schlenk flask was charged with a stir bar, dichloromethane (20 mL), 3,5-bis(trifluoromethyl)phenyl isocyanate (0.63 g, 2.5 mmol) 2,2-Dimethyl-1,3-propanediamine and (0.15 mL, 1.25 mmol). After stirring overnight, the reaction mixture was filtered and rinsed with 3 portions of cold CH_2Cl_2 to provide a pure white powder that was freed of volatiles under high vacuum. Yield: 47%. NMR spectra given below. HRMS: calc. $(C_{23}H_{21}F_{12}N_4O_2)^+ = 613.1467$ found $m/z = 613.1467$.

Synthesis of thiourea H-bond donors

1,1'-(ethane-1,2-diyl)bis(3-(3,5-bis(trifluoromethyl)phenyl)thiourea) (**2-S2**) - A flame dried 50 ml Schlenk flask was charged with a stir bar, dichloromethane (20 mL), 3,5-bis(trifluoromethyl)phenyl isothiocyanate (2.1 g, 7.7 mmol), and ethylenediamine (0.26 mL, 3.9 mmol) was added dropwise to the Schlenk flask. After stirring overnight, the reaction mixture was filtered and rinsed with 3 portions of cold CH_2Cl_2 to provide a pure white powder that was freed of volatiles under high vacuum. Yield: 64%. Characterization matches literature.¹⁸

1,1'-(propane-1,3-diyl)bis(3-(3,5-bis(trifluoromethyl)phenyl)thiourea) (**2-S3**) - A flame dried 50 ml Schlenk flask was charged with a stir bar, dichloromethane (20 mL), 3,5-bis(trifluoromethyl)phenyl isothiocyanate (2.0 g, 7.4 mmol), and 1,3-diaminopropane

(0.27 mL, 3.7 mmol) was added dropwise to the Schlenk flask. After stirring overnight, the reaction mixture was filtered via suction filtration and rinsed with 3 portions of cold CH₂Cl₂ to provide a pure white powder that was freed of volatiles under high vacuum. Yield: 58%. Characterization matches literature.⁶

1,1'-(butane-1,4-diyl)bis(trifluoromethyl)phenylthiourea (**2-S4**)- A flame dried 50 ml Schlenk flask was charged with a stir bar, dichloromethane (20 mL), 3,5-bis(trifluoromethyl)phenyl isothiocyanate (1.49 g, 5.5 mmol), and 1,4-diaminobutane (0.27 mL, 2.7 mmol) was added dropwise to the Schlenk flask. After stirring overnight, the reaction mixture was filtered via suction filtration and rinsed with 3 portions of cold CH₂Cl₂ to provide a pure white powder that was freed of volatiles under high vacuum. Yield: 35%. NMR spectra given below. HRMS: calc. (C₂₂H₁₉F₁₂N₄S₂+H)⁺= 631.0845; found *m/z* = 631.0825.

1,1'-(pentane-1,5-diyl)bis(3-(3,5-bis(trifluoromethyl)phenyl)thiourea) (**2-S5**)- A flame dried 50 ml Schlenk flask was charged with a stir bar, dichloromethane (20 mL), 3,5-bis(trifluoromethyl)phenyl isothiocyanate (1.49 g, 5.5 mmol), and 1,5-diaminopentane (0.32 mL, 2.7 mmol) was added dropwise to the Schlenk flask. After stirring overnight, the reaction mixture was filtered via suction filtration and rinsed with 3 portions of cold CH₂Cl₂ to provide a pure white powder that was freed of volatiles under high vacuum. Yield: 57%. NMR spectra given below. HRMS: calc. (C₂₃H₂₁F₁₂N₄S₂+H)⁺= 645.1011; found *m/z* = 645.1016.

1,1'-(hexane-1,6-diyl)bis(3-(3,5-bis(trifluoromethyl)phenyl)thiourea) (**2-S6**)- A flame dried 50 ml Schlenk flask was charged with a stir bar, dichloromethane (20 mL), 3,5-bis(trifluoromethyl)phenyl isothiocyanate (1.87 g, 6.88 mmol), and hexamethylenediamine (0.44 mL, 3.44 mmol) was added dropwise to the Schlenk flask. After stirring overnight, the reaction mixture was filtered via suction filtration and rinsed with 3 portions of cold CH₂Cl₂ to provide a pure white powder that was freed of volatiles under high vacuum. Yield: 76%. NMR spectra given below. HRMS: calc. (C₂₄H₂₃F₁₂N₄S₂+H)⁺= 659.1167; found *m/z* = 659.1148.

1,1'-(dodecane-1,12-diyl)bis(3-(3,5-bis(trifluoromethyl)phenyl)thiourea) (**2-S12**) - A flame dried 50 ml Schlenk flask was charged with a stir bar, dichloromethane (20 mL), 3,5-bis(trifluoromethyl)phenyl isothiocyanate (0.68 g, 2.52 mmol), and 1,12-diaminododecane (0.25 g, 1.25 mmol) was added dropwise to the Schlenk flask. After stirring overnight, the reaction mixture was filtered via suction filtration and rinsed with 3 portions of cold CH₂Cl₂ to provide a pure white powder that was freed of volatiles under high vacuum. Yield: 91%. NMR spectra given below. HRMS: calc. (C₃₀H₃₅F₁₂N₄S₂+H)⁺= 743.2033; found *m/z* = 743.2086.

1,1'-((methylazanediyl)bis(ethane-2,1-diyl))bis(3-(3,5-bis(trifluoromethyl)phenyl)thiourea) (**2-S5-N**)- A flame dried 50 ml Schlenk flask was charged with a stir bar, dichloromethane (20 mL), 3,5-bis(trifluoromethyl)phenyl isothiocyanate (1.48 g, 4.26 mmol), and N1-(2-aminoethyl)-N1-methylethane-1,2-diamine (0.27 mL, 2.13 mmol). After stirring overnight, the reaction mixture was filtered via suction filtration and rinsed with 3 portions of cold CH₂Cl₂ to provide a pure

white powder that was freed of volatiles under high vacuum. Yield: 67%. NMR spectra given below. HRMS: calc. $(\text{C}_{23}\text{H}_{21}\text{F}_{12}\text{N}_5\text{S}_2+\text{H})^+=660.1120$; found $m/z = 660.1120$.

1,1'-(oxybis(ethane-2,1-diyl))bis(3-(3,5-bis(trifluoromethyl)phenyl)thiourea)(2-S5-O)-

A flame dried 50 ml Schlenk flask was charged with a stir bar, dichloromethane (25 mL), 3,5-bis(trifluoromethyl)phenyl isothiocyanate (2.21 g, 8.14 mmol), and 2,2'-oxybis(ethan-1-amine) (0.44 mL, 4.07 mmol). After stirring overnight, the reaction mixture was filtered via suction filtration and rinsed with 3 portions of cold CH_2Cl_2 to provide a pure white powder that was freed of volatiles under high vacuum. Yield: 86%. NMR spectra given below. HRMS: calc. $(\text{C}_{22}\text{H}_{19}\text{F}_{12}\text{N}_4\text{OS}_2+\text{H})^+=647.0803$; found $m/z = 647.0803$.

RESULTS AND DISCUSSION

In the bis(thio)urea plus MTBD cocatalyzed (0.024 mmol) ROP of VL (1.0 mmol, 2 M) from benzyl alcohol (0.02 mmol) in C₆D₆, the bis(thio)ureas featuring a 5-carbon (methylene) tether were most active. Using established procedures,⁶ electron deficient bis(thio)ureas were synthesized featuring linear aliphatic tethers ranging from two to twelve methylene units, bistioureas (**2-Sn**) and bisureas (**2-On**) in Figure 2.1 (n = 2, 3, 4, 5, 6, 12), see Supplemental Information, SI. The **2-O2** H-bond donor was insoluble in solvents relevant for ROP. Especially versus the rigid (thio)urea tethers,¹⁶ our results here suggest that the most effective catalysis arises when the (thio)urea moieties are allowed to interact with one another, lending credence to the originally proposed mechanism whereby bis(thio)urea moieties bring about ROP through an *activated-(thio)urea* mechanism characterized by one (thio)urea stabilizing through internal H-bond activation the (thio)urea which activates the lactone for enchainment, Figure 2.1.^{6,14} We propose that the increased efficacy of **2-S5** and **2-O5** plus MTBD (versus other linker lengths) arises from the stability of the pseudo-7-membered cycle formed by intramolecular H-bonding – the (thio)urea moiety being largely rigid. The enhanced rates displayed by **2-O5** and **2-S5** are enhanced by a factor of two versus their respective ‘parent’ **2-X3** H-bond donor, and this enhanced rate does not result in increased M_w/M_n . The ROP are living in behavior, both **2-S5** and **2-O5** plus MTBD produce linear evolution of M_n versus conversion (Figure 2.2) and M_n that is predictable by $[M]_0/[I]_0$ (Table 2.7). In C₆D₆ (and other non-polar solvents), a H-bond mediated mechanism of

enchainment has been proposed;^{3,6,9} urea plus base mediated ROP have repeatedly been shown to display faster rates than the analogous thiourea.^{6,9}

Bisurea catalysts plus MTBD remain highly active for the ROP of VL in polar solvent and solvent-free conditions. In polar solvent (including solvent-free), the imidate mechanism of enchainment has been shown to be favored.^{7,10,13} This mechanism is characterized by proton transfer from urea to MTBD, forming a highly active urea anion (imidate).⁹ In the bisurea system, the incipient anion would be stabilized via intramolecular hydrogen bonding by the ‘extra’ urea moiety; hence, an *activated-(thio)urea anion mechanism* analogous to the neutral *activated (thio)urea* H-bonding mechanism can be envisaged, Figure 2.3.¹⁴ This mechanism is corroborated by the observation that the five-methylene tether in the **2-O5**/MTBD cocatalyzed ROP of VL produces the most active ROP, just as in the H-bonded system. Reproducing an established experiment,¹³ when **2-O5** is treated with 1 equivalent of MTBD in acetone-*d*₆, an upfield chemical shift is observed, consistent with anion formation and an imidate mechanism (Figure 2.4). The individual urea moieties are indistinguishable, which suggests that the anion/neutral urea exchange is rapid on the NMR timescale (400 MHz). Treatment with an additional equivalent of MTBD (0.096 M MTBD, 0.048 M **2-O5**) does not further shift the bisurea resonances, which suggest that bisimidate is not formed and corroborates previous observations of bis-(thio)ureas operating as a single H-bond donating species. Further, the rate of the **2-O5**/MTBD (0.048 M **2-O5**; 0.096 M MTBD) cocatalyzed ROP of VL under the respective conditions are identical (Figure 2.5), suggesting that the ideal stoichiometry for bisurea/base mediated ROP in an imidate

mechanism is 1:1. Similar relative rates (for the bisureas) are observed under solvent free conditions (Table 2.2) as in acetone- d_6 .

Two bisurea H-bond donors featuring heteroatom-containing tethers were synthesized and indicate a sensitive relationship between cocatalyst geometry and reaction rate. Both of the **2-O5-N** or **2-O5-O** (Figure 2.1) plus MTBD cocatalyzed ROP of VL showed slightly reduced reaction times versus the ‘parent’ **2-O5** under all conditions: benzene- d_6 , acetone- d_6 and solvent-free (Table 2.3). The reactions remained well-controlled, especially solvent-free where $M_w/M_n < 1.03$. The relative reaction times in each of C₆D₆, acetone- d_6 and solvent-free fall in the order **2-O5-O** (fastest) < **2-O5-N** < **2-O5** (slowest). We attribute the subtle changes in reaction time to minute changes in the tether length, where the normal both lengths are C-O < C-N < C-C. This suggests that the most active bis-(thio)urea tether length is somewhere between four and five methylene units long, which may be a useful parameter in the design of advanced H-bond donating catalyst systems. However, these relative rates may be coincidence and could be easily attributed to increased conformational flexibility due to the heteroatom, but these results suggest that there is no stark change in mechanism due to the presence of the heteroatom. As opposed to ROP in solution, bisurea plus MTBD cocatalyzed ROP under solvent-free conditions provide the best weight control (by $[M]_0/[I]_0 \leq 500$), narrowest distributions ($M_w/M_n \leq 1.05$) and access to the highest molecular weights (Table 2.8), consistent with previous observations;¹² the **2-O5-O** H-bond donor is especially active and well controlled. The ROP of CL with these cocatalysts (plus MTBD) exhibit the same relative reaction times and display good control, Table 2.3.

Additionally, we synthesized a symmetric derivative of bisurea **2-O5** featuring a 3,3-dimethyl substitution, **2-O5-diMe**, which is less active as a cocatalyst (with MTBD) for the ROP of VL (C_6D_6 , 90 % conv in 1 hour). This suggests that any steric compression or hindered bond rotation arising from the geminal dimethyl substitution (i.e. Thorpe-Ingold effect)¹⁹ is deleterious to ROP. The bistiourea analogues of these bisurea H-bond donors were also synthesized, but they displayed reduced rates and control versus the bisureas (see Table 2.9). These modified bis-(thio)urea H-bond donors emphasize the sensitive interplay of catalyst structure towards ROP activity.

ROP of Lactide

The most active bis(thio)urea H-bond donors from the VL studies were applied for the ROP of lactide in CH_2Cl_2 and solvent-free with Me_6TREN cocatalyst.²⁰ Low solubility of bisureas under reaction conditions limited all direct comparisons, but this and previous studies¹² show that the bistioureas are more effective than the corresponding bisureas for the ROP of LA (Table 2.4). In the case of lactide, weak alkylamine base cocatalysts are used because stronger imine bases (e.g. MTBD) will polymerize lactide in the absence of H-bond donor in a less-controlled ROP.^{5,20,21} We speculated that the increased rate observed for bistiourea (versus bisurea) plus Me_6TREN mediated ROP of lactide was due to a change in mechanism between the two species. Indeed, the 1H NMR of **2-S5-O** ($acetone-d_6$) shows an upfield shift for the aromatic resonances in **2-S5-O** in the presence (versus absence) of Me_6TREN , suggesting the formation of an imidate species, whereas the chemical shifts for **2-O5-O** with and without Me_6TREN are negligibly different, suggesting H-bonding (see Figure 2.9). The same experiment

when conducted with **1-S** or TCC shows downfield chemical shifts consistent with H-bonding.²² Similar to the acetone-*d*₆ experiment, the ROP results in CH₂Cl₂ (Table 2.4) suggest that the **2-S5-O** plus Me₆TREN mediated ROP of lactide proceeds via an imidate mechanism while **2-O5-O** is an H-bond mediated enchainment.

For identically substituted ureas and thioureas in the ROP of LA, the thiourea is the more active catalyst, and this is attributed to the pK_a of the H-bond donor. The difference in mechanism for the two H-bond donating catalysts presumably arises because any thiourea will be more acidic than its identically substituted (e.g. 3,5-bistrifluoromethyl phenyl) urea.^{23,24} When a pair of mono-H-bond donors (urea or thiourea) of the same pK_a are used as cocatalysts with Me₆TREN for the ROP of lactide, the urea is the more active catalyst, Table 2.5. Having identical pK_a, such a pair of urea and thiourea will effect enchainment by the same mechanism, and hence, the more polar urea (or imidate) is the more active H-bond donor. When a highly acidic H-bond donor is employed (Table 2.5, last entry), the incipient (thio)imidate displays reduced activity arising from its low basicity, as previously observed.^{10,23} These observations are seemingly contrary to the (thio)urea plus strong base mediated ROP of other lactones (e.g. valerolactone or caprolactone).^{7,9,11,23} However, in this latter scenario, the stronger base cocatalyst (versus Me₆TREN) can deprotonate either the urea or thiourea.¹³ In that event, the urea (or resulting imidate) will always be more active than the thiourea (or thioimidate).⁷

CONCLUSION

A series of conformationally flexible bis(thio)urea H-bond donors were applied with the appropriate base cocatalysts for the ROP of lactones. Conformational flexibility is essential for catalyst activity, and the (thio)urea moieties separated by circa five methylene units displays the most rapid ROP. As a summary of our work here and previously, Table 2.6 collects the catalyst systems of this type which we find to be optimal for a given monomer and solvent. Synthetic polymer chemists should hew towards **2-S5-O** for the ROP of lactide; it is readily soluble, easily accessible and is among the most active organocatalysts for the synthesis of polylactide. That bithioureas (versus bisureas) are more active for the ROP of LA is contrary to what is observed for VL and CL, and the higher activity of the thioureas is rendered by the alkylamine cocatalyst, which is unable to deprotonate the (bis)urea catalyst and enter the highly active imidate mediated ROP. For VL and CL, the bisurea **2-O5-O** plus MTBD cocatalyst system is the most active bis(thio)urea examined, and the reaction is well controlled, especially under the easily employable solvent-free conditions. We trust that the results of this study will be informative for the synthesis of advanced H-bond donating catalysts for ROP, and such work is ongoing in our lab.

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H-bond donor (2-Xn)	time (min)	conv. ^b (%)	M_n^c (g/mol)	M_w/M_n^c
2-S2	92	88	8 300	1.06
2-S3	80	89	9 000	1.06
2-S4	53	90	8 200	1.06
2-S5	50	91	9 500	1.05
2-S6	69	89	9 200	1.04
2-S12	250	87	8 200	1.04
2-O3	20	89	8 900	1.07
2-O4	20	92	9 600	1.06
2-O5	12	89	9 500	1.05
2-O6	15	90	9 900	1.06
2-O12	35	90	9 900	1.07

Table 2.1. Bis(thio)Urea and MTBD cocatalyzed ROP of VL in C₆D₆.^a

a. Reaction conditions: VL (1.0 mmol, 1 equiv, 2 M), benzyl alcohol (0.019 mmol), bis(thio)urea/MTBD (0.024 mmol each) in C₆D₆. b. Monomer conversion was monitored via ¹H NMR. c. M_n and M_w/M_n were determined by GPC (CH₂Cl₂) versus polystyrene standards.

solvent	H-bond donor (2-Xn)	time (min)	conv. ^a (%)	M_n^b (g/mol)	M_w/M_n^b
acetone- d_6^c	2-S5	180	90	8 900	1.08
	2-O5	12	84	8 200	1.05
	2-O12	40	84	8 200	1.10
solvent-free ^d	2-O3	20	99	42 300	1.05
	2-O4	22	99	49 600	1.04
	2-O5	12	99	42 300	1.03
	2-O6	19	99	39 400	1.02
	2-O12	29	99	39 200	1.02

Table 2.2. Bis(thio)urea plus MTBD cocatalyzed ROP of VL in acetone- d_6 and solvent-free conditions.

a) Monomer conversion was monitored via ^1H NMR. b) M_n and M_w/M_n were determined by GPC (CH_2Cl_2) versus polystyrene standards c) Reaction conditions: VL (1.0 mmol, 1 equiv, 2 M), benzyl alcohol (0.019 mmol), bis(thio)urea/MTBD (0.024 mmol each) in acetone- d_6 . b) Reaction conditions: VL (3.99 mmol, 1 equiv), benzyl alcohol (0.019 mmol), cocatalyst (0.019 mmol each).

VL or CL	Solvent	H-bond donor (2-O5-N/O)	Time (min)	conv. ^a (%)	M_n^b (g/mol)	M_w/M_n^b
VL	benzene- d_6 ^c	2-O5-N	10	88	8 000	1.05
		2-O5-O	5	90	8 000	1.06
	acetone- d_6 ^c	2-O5-N	8	86	7 800	1.10
		2-O5-O	5	86	7 700	1.11
	solvent-free	2-O5-N^d	5	91	37 500	1.02
		2-O5-O^e	4	99	110 500	1.03
CL	solvent-free ^d	2-O5	30	99	50 500	1.14
		2-O5-N	18	99	51 100	1.20
		2-O5-O	8	99	47 000	1.13

Table 2.3. ROP of VL or CL cocatalyzed by MTBD plus bis-ureas with heteroatom-containing tethers

a) Monomer conversion was monitored via ^1H NMR. b) M_n and M_w/M_n were determined by GPC (CH_2Cl_2) versus polystyrene standards. c) Reaction conditions: VL (1.0 mmol, 1 equiv, 2 M), benzyl alcohol (0.019 mmol), cocatalyst (0.024 mmol each) in C_6D_6 or acetone- d_6 . d) Solvent-free reaction conditions: VL or CL (3.99 mmol, 1 equiv), benzyl alcohol (0.019 mmol), cocatalyst (0.019 mmol each). e) Solvent-free reaction conditions: VL (3.99 mmol, 1 equiv), benzyl alcohol (0.008 mmol), cocatalyst (0.019 mmol each).

solvent	H-bond donor (2-X5-N/O)	Time (min)	conv. ^a (%))	<i>M</i> _n ^b (g/mol)	<i>M</i> _w / <i>M</i> _n ^b
CH ₂ Cl ₂ ^c	2-S5	12	90	17 400	1.05
	2-S5-N	20	90	17 600	1.04
	2-S5-O	5	90	18 800	1.04
solvent-free ^d	2-O5-O	105	90	15 800	1.13
	2-S5-O	15	90	18 500	1.06

Table 2.4. Bis(thio)Urea and Me₆TREN cocatalyzed ROP of L-LA^a

a) Monomer conversion was monitored via ¹H NMR. b) *M*_n and *M*_w/*M*_n were determined by GPC (CH₂Cl₂) versus polystyrene standards. c) Reaction conditions: L-LA (0.693 mmol, 1 equiv, 1 M), benzyl alcohol (0.0069 mmol), cocatalyst (0.017 mmol each) in CH₂Cl₂. d) Solvent-free reaction conditions: L-LA (1.38 mmol, 1 equiv), benzyl alcohol (0.0138 mmol), cocatalyst (0.007 mmol each) at 100 °C

H-bond donor	pK _a ^b	Time (min)	conv. ^c (%)	M _n ^d (g/mol)	M _w /M _n ^d
1	16.8	1440	-	-	-
2	16.1	35	90	17900	1.04
1-S	13.2	48	90	18900	1.07
3	13.8	1	92	19300	1.07
4	8.5	600	90	18100	1.04

Table 2.5. Mono(thio)Urea and Me₆TREN cocatalyzed ROP of L-LA.^a

a) Reaction conditions: L-LA (0.50 mmol, 1 equiv, 1 M), benzyl alcohol (0.005 mmol), cocatalyst (0.025 mmol each) in CH₂Cl₂. b) pK_a values in DMSO²³ c) Monomer conversion was monitored via ¹H NMR. d) M_n and M_w/M_n were determined by GPC (CH₂Cl₂) versus polystyrene standards.

Monomer	Solvent	cocatalyst	Proposed mechanism	refs
VL	$\text{C}_6\text{D}_6^{\text{a}}$	Trisurea/MTBD (16 μmol each)	Neutral H-bonding	6
	acetone- d_6^{a}	2-O5-O/MTBD (24 μmol each)	Imidate mediated	herein
	solvent-free ^b	2-O5-O/MTBD (19 μmol each)	Imidate mediated	herein
CL	$\text{C}_6\text{D}_6^{\text{a}}$	Trisurea/MTBD (16 μmol each)	Neutral H-bonding	6
	solvent-free ^b	2-O5-O/MTBD (19 μmol each)	Imidate mediated	herein
LA	$\text{CH}_2\text{Cl}_2^{\text{c}}$	2-S5-O /ME ₆ TREN (17 μmol each)	Imidate mediated	herein
	solvent-free ^b	2-S5-O/ ME ₆ TREN (7 μmol each)	Imidate mediated	herein

Table 2.6. Optimal (Thio)urea H-Bond Donor Plus Organic Base Cocatalysts for ROP

a) Reaction conditions: Monomer (1.0 mmol, 1 eq. 2 M), benzyl alcohol (0.019 mmol), cocatalyst in C_6D_6 or in acetone- d_6 . b) Solvent-free reaction conditions: VL or CL (3.99 mmol, 1 equiv), benzyl alcohol (0.019 mmol), cocatalyst (0.019 mmol each) c) Reaction conditions: LA (0.693 mmol, 1 equiv, 1 M), benzyl alcohol (0.0069 mmol), cocatalyst (0.017 mmol each) in CH_2Cl_2 . d) Solvent-free reaction conditions: L-LA (1.38 mmol, 1 equiv), benzyl alcohol (0.0138 mmol), cocatalyst (0.007 mmol each) at 100 °

Entry	Solvent	$[M]_o/[I]_o$	M_n^b (g/mol)	M_w/M_n^b
2-05				
1	benzene	50	9500	1.05
2		100	19600	1.05
3		200	30900	1.07
4	acetone	50	9100	1.05
5		100	12000	1.05
6		200	16900	1.15
7	solvent-free ^c	50	10500	1.10
8		100	21500	1.07
9		200	42300	1.03
10		500	96200	1.16
2-05-0				
11	benzene	50	8000	1.06
12		100	20000	1.07
13		200	38700	1.10
14	acetone	50	7700	1.10
15		100	19700	1.04
16		200	35700	1.03
17	solvent-free ^c	50	10500	1.10
18		100	23600	1.10
19		200	43500	1.02
20		500	110500	1.03

Table 2.7. Bis(thio)urea plus MTBD cocatalyzed ROP of VL.^a

a) Reaction conditions: VL (1.0 mmol, 1 equiv, 2 M), cocatalyst (0.024 mmol each) b)

M_n and M_w/M_n were determined by GPC (CH₂Cl₂) versus polystyrene standards. c)

Reaction conditions: VL (3.99 mmol) cocatalyst (0.019 mmol each).

Entry	Solvent	H bond donor (2-Xn)	Time (min)	Conv. ^a (%)	M_n^b (g/mol)	M_w/M_n^b
1	acetone- d_6^c	2-S2	635	88	9500	1.08
2		2-S3	685	85	8700	1.11
3		2-S4	644	89	9100	1.10
4		2-S6	636	88	8900	1.09
5		2-S12	1090	87	6800	1.10
6		2-O3	20	84	7200	1.07
7		2-O4	20	85	7600	1.09
8		2-O6	20	86	7900	1.10
9	solvent-free ^d	2-S2	240	99	35400	1.09
10		2-S3	210	99	40600	1.10
11		2-S4	150	99	41900	1.08
12		2-S5	60	99	45500	1.06
13		2-S6	120	99	42100	1.13
14		2-S12	330	99	39700	1.15

Table 2.8. Different tethered bis(thio)urea and MTBD cocatalyzed ROP of VL.

a) Monomer conversion was monitored via ^1H NMR. b) M_n and M_w/M_n were determined by GPC (CH_2Cl_2) versus polystyrene standards. c) Reaction conditions: VL (1.0 mmol, 1 equiv, 2 M), benzyl alcohol (0.019 mmol), cocatalyst (0.024 mmol each) in acetone- d_6 . d) Solvent free-reaction conditions: VL (3.99 mmol, 1 equiv), benzyl alcohol (0.019 mmol), cocatalyst (0.019 mmol each).

Solvent	H-bond donor (2-S5-N/O)	Time (min)	conv. ^a (%)	M_n^b (g/mol)	M_w/M_n^b
benzene- d_6 ^c	2-S5-N	100	89	8 600	1.05
	2-S5-O	50	90	10 600	1.03
acetone- d_6 ^c	2-S5-N	240	84	7 700	1.07
	2-S5-O	210	83	10 500	1.04
solvent-free ^d	2-S5-N	90	97	42 600	1.06
	2-S5-O	60	99	43 600	1.06

Table 2.9. ROP of VL cocatalyzed by MTBD plus Bisthioureas with Heteroatom-containing Tethers

a) Monomer conversion was monitored via ^1H NMR. e) M_n and M_w/M_n were determined by GPC (CH_2Cl_2) versus polystyrene standards. c) Reaction conditions: VL (1.0 mmol, 1 equiv, 2 M), benzyl alcohol (0.019 mmol), cocatalyst (0.024 mmol each) in C_6D_6 or acetone- d_6 . d) Solvent free-reaction conditions: VL (3.99 mmol, 1 equiv), benzyl alcohol (0.019 mmol), cocatalyst (0.019 mmol each).

Figure 2.1. Mono(thio)urea, bis(thio)urea donors evaluated for the 1-X/2-X plus MTBD and Me₆TREN mediated ROP of VL, CL, L-LA and proposed *activated-thiourea* mode activation for bis-donors.

Figure 2.2. M_n and M_w/M_n versus conversion for the H-bond donor plus MTBD cocatalyzed ROP of VL using (left) **2-S5** and (right) **2-O5**. Reaction conditions: VL (1.0 mmol, 1 equiv, 2 M), benzyl alcohol (0.019 mmol), **2-X5**/MTBD (0.024 mmol each) in C₆D₆.

Figure 2.3. Proposed activated (thio)urea anion mechanism for the bisurea plus MTBD mediated ROP of VL.

Figure 2.4. Downfield portion of ¹H NMR spectra (400 MHz, ppm) of **2-O5** plus MTBD in acetone-*d*₆.

Figure 2.5. First order evolution of VL versus time for the **2-O5**/MTBD catalyzed ring-opening polymerization of VL. Conditions: VL (2 M, 1 mmol), benzyl alcohol (2 mol%, 0.019 mmol), 2-O5 (0.024 mmol), MTBD orange - 0.024 mmol, blue- 0.048 mmol) in acetone- d_6 .

Figure 2.6 M_n and M_w/M_n versus conversion for **2-O5** catalyst. Reaction conditions: VL (1.0 mmol, 1 equiv, 2 M), benzyl alcohol (0.019 mmol), cocatalyst (0.024 mmol each) in acetone- d_6 .

Figure 2.7. M_n and M_w/M_n versus conversion for **2-O5-O** catalyst. Reaction conditions: VL (3.99 mmol, 1 equiv), benzyl alcohol (0.008 mmol), cocatalyst (0.024 mmol each) under solvent free conditions.

Figure 2.8. (left) M_n and M_w/M_n versus conversion for **2-S5**, (right) M_n versus conversion for **2-O5** catalyst. Reaction conditions: VL (3.99 mmol, 1 equiv.), benzyl alcohol (0.019 mmol), cocatalyst (0.019 mmol each) under solvent free conditions.

Figure 2.9. Downfield portion of ^1H NMR spectra (400 MHz, ppm) of **2-O5-O** and **2-S5-O** with and without Me_6TREN in acetone- d_6 .

Figure 2.10. (Upper) ¹H NMR (acetone-*d*₆, 400 MHz, ppm) spectrum of 1,1'-(ethane-1,2-diyl)bis(3-(3,5-bis(trifluoromethyl)phenyl)urea) (**2-O2**), (Lower) ¹³C NMR (acetone-*d*₆, 100 MHz, ppm) spectrum of 1,1'-(ethane-1,2-diyl)bis(3-(3,5-bis(trifluoromethyl)phenyl)urea).

Figure 2.11. (Upper) ¹H NMR (acetone-*d*₆, 400 MHz, ppm) spectrum of 1,1'-(butane-1,4-diyl)bis(3-(3,5-bis(trifluoromethyl)phenyl)urea) (**2-O4**), (Lower) ¹³C NMR (acetone-*d*₆, 100 MHz, ppm) spectrum of 1,1'-(butane-1,4-diyl)bis(3-(3,5-bis(trifluoromethyl)phenyl)urea).

Figure 2.12. (Upper) ¹H NMR (acetone-*d*₆, 400 MHz, ppm) spectrum of 1,1'-(pentane-1,5-diyl)bis(3-(3,5- bis(trifluoromethyl)phenyl)urea)(**2-O5**), (Lower) ¹³C NMR (acetone-*d*₆, 100 MHz, ppm) spectrum of 1,1'- (pentane-1,5-diyl)bis(3-(3,5-bis(trifluoromethyl)phenyl)urea).

Figure 2.13. (Upper) ¹H NMR (acetone-*d*₆, 400 MHz, ppm) spectrum of 1,1'-(hexane-1,6-diyl)bis(3-(3,5-bis(trifluoromethyl)phenyl)urea) (**2-O6**), (Lower) ¹³C NMR (acetone-*d*₆, 100 MHz, ppm) spectrum of 1,1'-(hexane-1,6-diyl)bis(3-(3,5-bis(trifluoromethyl)phenyl)urea).

Figure 2.14. (Upper) ¹H NMR (acetone-*d*₆, 400 MHz, ppm) spectrum of 1,1'-(dodecane-1,12-diyl)bis(3-(3,5-bis(trifluoromethyl)phenyl)urea) (2-O12), (Lower) ¹³C NMR (acetone-*d*₆, 100 MHz, ppm) spectrum of 1,1'-(dodecane-1,12-diyl)bis(3-(3,5-bis(trifluoromethyl)phenyl)urea).

Figure 2.15. (Upper) ¹H NMR (acetone-*d*₆, 400 MHz, ppm) spectrum of 1,1'-((methylazanediyl)bis(ethane-2,1-diyl))bis(3-(3,5-bis(trifluoromethyl)phenyl)urea) (**2-O5-N**), (Lower) ¹³C NMR (acetone-*d*₆, 100 MHz, ppm) spectrum of 1,1'-((methylazanediyl)bis(ethane-2,1-diyl))bis(3-(3,5-bis(trifluoromethyl)phenyl)urea).

Figure 2.16. (Upper) ¹H NMR (acetone-*d*₆, 400 MHz, ppm) spectrum of 1,1'-(oxybis(ethane-2,1-diyl))bis(3-(3,5-bis(trifluoromethyl)phenyl)urea) (**2-O5-O**), (Lower) ¹³C NMR (acetone-*d*₆, 100 MHz, ppm) spectrum of 1,1'-(oxybis(ethane-2,1-diyl))bis(3-(3,5-bis(trifluoromethyl)phenyl)urea).

Figure 2.17. (Upper) ¹H NMR (acetone-*d*₆, 400 MHz, ppm) spectrum of 1,1'-(2,2-dimethylpropane-1,3-diyl)bis(3-(3,5-bis(trifluoromethyl)phenyl)urea) (**2-O3-diMe**) , (Lower) ¹³C NMR (acetone-*d*₆, 100 MHz, ppm) spectrum of 1,1'-(2,2-dimethylpropane-1,3-diyl)bis(3-(3,5-bis(trifluoromethyl)phenyl)urea).

Figure 2.18. (Upper) ¹H NMR (acetone-*d*₆, 400 MHz, ppm) spectrum of 1,1'-(butane-1,4-diyl)bis(3-(3,5-bis(trifluoromethyl)phenyl)thiourea) (**2-S4**), (Lower) ¹³C NMR (acetone-*d*₆, 100 MHz, ppm) spectrum of 1,1'-(butane-1,4-diyl)bis(3-(3,5-bis(trifluoromethyl)phenyl)thiourea).

Figure 2.19. (Upper) ^1H NMR (acetone- d_6 , 400 MHz, ppm) spectrum of 1,1'-(pentane-1,5-diyl)bis(3-(3,5-bis(trifluoromethyl)phenyl)thiourea) (**2-S5**), (Lower) ^{13}C NMR (acetone- d_6 , 100 MHz, ppm) spectrum of 1,1'-(pentane-1,5-diyl)bis(3-(3,5-bis(trifluoromethyl)phenyl)thiourea).

Figure 2.20. (Upper) ¹H NMR (acetone-*d*₆, 400 MHz, ppm) spectrum of 1,1'-(hexane-1,6-diyl)bis(3-(3,5-bis(trifluoromethyl)phenyl)thiourea) (**2-S6**), (Lower) ¹³C NMR (acetone-*d*₆, 100 MHz, ppm) spectrum of 1,1'-(hexane-1,6-diyl)bis(3-(3,5-bis(trifluoromethyl)phenyl)thiourea).

Figure 2.21. (Upper) ^1H NMR (acetone- d_6 , 400 MHz, ppm) spectrum of 1,1'-(dodecane-1,12-diyl)bis(3-(3,5-bis(trifluoromethyl)phenyl)thiourea) (**2-S12**), (Lower) ^{13}C NMR (acetone- d_6 , 100 MHz, ppm) spectrum of 1,1'-(dodecane-1,12-diyl)bis(3-(3,5-bis(trifluoromethyl)phenyl)thiourea).

Figure 2.22. (Upper) ^1H NMR (acetone- d_6 , 400 MHz, ppm) spectrum 1,1'-((methylazanediyl)bis(ethane-2,1-diyl))bis(3-(3,5-bis(trifluoromethyl)phenyl)thiourea) (**(2-S5-N)**), (Lower) ^{13}C NMR (acetone- d_6 , 100 MHz, ppm) spectrum of 1,1'-((methylazanediyl)bis(ethane-2,1-diyl))bis(3-(3,5-bis(trifluoromethyl)phenyl)thiourea)

Figure 2.23. (Upper) ¹H NMR (acetone- *d*₆, 400 MHz, ppm) spectrum 1,1'-(oxybis(ethane-2,1-diyl))bis(3-(3,5-bis(trifluoromethyl)phenyl)thiourea) (**2-S5-O**), (Lower) ¹³C NMR (acetone- *d*₆, 100 MHz, ppm) spectrum of 1,1'-(oxybis(ethane-2,1-diyl))bis(3-(3,5-bis(trifluoromethyl)phenyl)thiourea).

MANUSCRIPT III

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**Organocatalytic Ring-opening Polymerization of Thionolactones: Anything O
Can Do, S Can Do Better**

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ABSTRACT

The H-bond mediated organocatalytic ring-opening polymerizations (ROPs) of four new thionolactone monomers are discussed. The kinetic and thermodynamic behavior of the ROPs is considered in the context of the parent lactone monomers. Organocatalysts facilitate the retention of the S/O substitution as well as the synthesis of copolymers. The thionoester moieties in the polymer backbone serve as a chemical handle for a facile crosslinking reaction, and the porosity of the resulting crosslinked polymer can be tuned by altering the thioester density in the (co)polymer. The crosslinked polymers are shown to be degradable in water, and an Au³⁺ recovery application is demonstrated.

INTRODUCTION

Over the last two decades, organocatalysts for ring-opening polymerization (ROP) are have become firmly established in the community for their ability to synthesize precision macromolecules.¹ The H-bonding class of organocatalysts are notable for their ability to effect highly controlled polymerizations.^{2–5} This class of catalysts, often an H-bond donating (thio)urea plus an H-bond accepting organic base, are believed to effect ROP by H-bond activating a lactone monomer and alcohol chain-end/initiator.^{5,6} More recently, (thio)urea/base mediated ROP have been found to access an alternate mechanism of enchainment whereby proton transfer from (thio)urea to base produces a highly-active (thio)imidate that is among the most active and controlled catalysts for the ROP of lactones, carbonates and other cyclic monomers.^{7–10} Of particular importance here is the highly-controlled aspect of (thio)urea/base mediated ROP, which allows for the polymerization of functionalized and heteroatom containing monomers while retaining polymerization control.

New catalysts and mechanisms of polymer synthesis are one means of begetting new materials. Although the monomer scope has broadened recently, organocatalysts have most frequently been applied to the ROP of lactones, but these same systems have been shown to be effective for the ROP of a thiolactone and a thionolactone.^{11,12} Polythioesters have similar properties to their polyester analogous;^{12–14} however, the altered materials properties of polythionolactones make them an especially enticing synthetic target.¹¹ Versus the corresponding polyesters, polythioesters feature altered physical properties, degradability and novel post polymerization functionalization

abilities.¹¹ In 2016, our group disclosed the H-bond mediated ROP of thionocaprolactone (tnCL).¹¹ Versus earlier studies,^{15,16} the key advance with this report was that H-bond mediated organocatalysts facilitate the retention of the S/O substitution during the ROP. This is vital for accessing the altered materials properties of thionolactones (versus thiolactones), and the organocatalytic methods allow for the synthesis of copolymers.¹¹ Reported here, we believe for the first time, is the ROP of ζ -thionoheptalactone (tnHL), η -thionononalactone (tnNL), ω -thionopentadecalactone (tnPDL), thiono-ethylene brassylate (tnEB) and copolymers.

EXPERIMENTAL SECTION

General Considerations. All chemicals were used as received unless stated otherwise. Hexamethyldisiloxane (HMDO), P_4S_{10} , cycloheptanone, cyclooctanone, 3-chloroperbenzoic acid (*m*-CPBA) and 2-tert-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP) were supplied by Acros Organics. Sodium thiosulfate ($Na_2S_2O_3 \cdot 5H_2O$) was purchased from Allied Chemical. Sigma-Aldrich provided ω -pentadecalactone (PDL). Acetonitrile, potassium carbonate, sodium carbonate, sodium bicarbonate, sodium sulfate, magnesium sulfate, benzyl alcohol, benzoic acid, ethyl acetate, dichloromethane, toluene and hexane were purchased from Fisher Scientific. Acetone- d_6 , chloroform- d and benzene- d_6 were supplied by Cambridge Isotope Laboratories and distilled from CaH_2 under a nitrogen atmosphere. Benzyl alcohol was distilled from CaH_2 under high vacuum. Toluene was dried on an Innovated Technologies solvent purification system with alumina columns and nitrogen working gas. **1** [3,5-bis(trifluoromethyl)phenyl]-3-cyclohexyl-thiourea (CyTU), and **2** 1,1',1''-(nitrilotris(ethane-2,1-diyl))tris(3-(3,5-bis(trifluoromethyl)phenyl)urea (Tris-U2C) were synthesized and purified according to literature procedures.^{5,17} Triclocarban (TCC), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD), and 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) were purchased from Tokyo Chemical Industry (TCI). The syntheses of ζ -heptalactone (HL)¹⁸ and η -nonalactone (NL)¹⁹ were performed according to literature procedures.

All polymerization reactions were performed in an MBRAUN or INERT stainless-steel glovebox equipped with a gas purification system under a nitrogen atmosphere using

glass vials and magnetic stir bars which were baked overnight at 140 °C. NMR experiments were performed on a Bruker Avance III 300 MHz or 400 MHz spectrometer. The chemical shifts for proton (^1H) and carbon (^{13}C) NMR were recorded in parts per million (ppm) relative to a residual solvent. Size exclusion chromatography (SEC) was performed at 30 °C in dichloromethane (DCM) using an Agilent Infinity GPC system equipped with three Agilent PLGel columns 7.5 mm $\times$ 300 mm (pore sizes: 10^3 , 10^4 , and 10^5 Å). M_n and M_w/M_n were determined versus polystyrene standards (500 g/mol – 3,150 kg/mol; Polymer Laboratories). UV-vis were acquired on a Perkin-Elmer Lambda 1050 single beam spectrometer.

Mass spectrometry experiments were performed using a Thermo Electron (San Jose, CA, USA) LTQ Orbitrap XL mass spectrometer affixed with electrospray ionization (ESI) interface in positive ion mode. Collected mass spectra were averaged for at least 50 scans. Tune conditions for infusion experiments (10 $\mu\text{L}/\text{min}$ flow, sample concentration 2 $\mu\text{g}/\text{mL}$ in 50/50 v/v water/methanol) were as follows: ion spray voltage, 4000 V; capillary temperature, 275 °C; sheath gas (N_2 , arbitrary units), 15; auxiliary gas (N_2 , arbitrary units), 2; capillary voltage, 21 V; and tube lens, 90 V; multipole 00 offset, -4.25 V; lens 0 voltage, - 5.00; multipole 1 offset, - 8.50 V; Multipole RF Amplitude, 400 V; Ion trap's AGC target settings for Full MS was 3.0×10^4 and FT's 2.0×10^5 (with 3 and 2 averaged microscans, respectively). Prior to analysis, the instrument was calibrated for positive ions using Pierce LTQ ESI positive ion calibration solution (lot #PC197784). Thermogravimetric analysis (TGA) was performed using a TGA Q500 from TA Instruments under a N_2 atmosphere at a heating rate of 10 °C/min from 25 °C to 600 °C.

The surface analysis of the crosslinked polymer was carried out using a Thermo Scientific Photoelectron Spectrometer (XPS) equipped with a 180° double-focusing hemispherical analyzer and a monochromatized Al K α radiation source. The surface was bombarded with electrons using a flood gun. Binding energy (BE) corrections were done using the position of C-H/C-C at 284.7 eV as a reference. The sample was dried under reduced pressure (10^{-9} – 10^{-10} mbar) overnight before analysis. The sampling spot size was 200 μ m.

Synthesis of ζ -thionoheptalactone (tnHL)

This synthesis of ζ -thionoheptalactone (tnHL) was performed according to literature procedure.²⁰ The crude product mixture was purified by silica-gel column chromatography (3:7 ethyl acetate:hexanes). Characterization matched the literature.²⁰

Synthesis of η -thionononalactone (tnNL)

The synthesis of η -thionononalactone (tnNL) was adapted from a literature procedure.²⁰ NL (3.00 g, 21.11 mmol), HMDO (8.20 mL, 35.25 mmol) and P₄S₁₀ (2.51 g, 5.27 mmol) were dissolved in acetonitrile (23 mL) and stirred at 80 °C for 4 hours. The reaction mixture was cooled in an ice-water bath and quenched with distilled water (2 mL/mmol of P₄S₁₀) and sodium carbonate (8 mmol/mmol of P₄S₁₀) over a period of 30 minutes. The reaction mixture was then vigorously stirred at 0 °C for an additional 30 mins. The reaction mixture was extracted with ethyl acetate (3 x 50 mL) and concentrated in vacuo to yield a yellow-orange oil. Following silica gel column chromatography (1:10 ethyl acetate:hexanes) and Kugelrohr distillation (60 °C, 200 mTorr), a pale yellow oil was obtained (0.67 g, 4.64 mmol, 22 % yield).

Synthesis of ω -thionopentadecalactone (tnPDL)

This synthesis of ω -thionopentadecalactone (tnPDL) was performed according to a literature procedure.²⁰ Following silica-gel column chromatography (1:99 ethyl acetate:hexanes) and Kugelrohr distillation (120 °C, 100 mTorr), the characterization matched the literature.²⁰

Synthesis of thiono-ethylene brassylate (tnEB)

The synthesis of tnEB was adapted from a literature procedure.^{11,21} Ethylene brassylate (13 mL, 50 mmol), HMDO (17 mL, 80 mmol) and P₄S₁₀ (11.11 g, 25 mmol) were dissolved in *o*-xylene (50 mL) and refluxed for 9 hours. The reaction mixture was cooled in an ice-water bath and quenched with distilled water (2 mL/mmol of P₄S₁₀) and sodium carbonate (8 mmol/mmol of P₄S₁₀) over a period of 30 minutes. The reaction mixture was then vigorously stirred at 0 °C for an additional 30 mins. The reaction mixture was extracted with dichloromethane (3 x 100 mL) and concentrated in vacuo to yield a yellow oil. Following silica gel chromatography (ethyl acetate:hexanes 5:95), a yellow oil was obtained (7.54 g, mmol, 25 mmol, 50% yield). HRMS *m/z* calcd (C₁₅H₂₇O₂S₂⁺) 303.1447, found 303.1436. ¹H NMR (400 MHz, CDCl₃) δ 4.72 (s, 4H), 2.75 (t, *J*=7.2, 4H), 1.70 (p, *J*=7.1, 4H), 1.37 – 1.11 (m, 12 H). ¹³C NMR (100 MHz, CDCl₃) δ 25.9, 25.9, 26.0, 26.2, 26.9, 45.9, 68.3, 223.4.

Ring-Opening Polymerization of tnNL

In an N₂-filled glovebox, tnNL (0.100 g, 0.6318 mmol) was added to a 20 mL scintillation vial equipped with a stir bar. TCC (0.0100 g, 0.031 mmol), BEMP (0.008 g, 0.031 mmol) and benzyl alcohol (0.0007 g, 0.006 mmol) were added to another 20 mL scintillation vial in the glovebox. Benzene (0.315 mL, 2 M in tnNL) was divided equally between the two vials. The contents of the vials were stirred for about 2 mins at moderate speed after which the mixture of tnNL in benzene was transferred to the other vial and stirred for 4 hours. The polymer was then precipitated with hexanes. The supernatant was decanted, and remaining volatiles were removed under reduced pressure to yield the polymer (60.8% yield; $M_w/M_n = 1.7$; M_n (GPC) = 24,200; M_n (NMR) = 19,100). ¹³C NMR spectra display characteristic resonances of a polymer with a thionoester repeat at 224 ppm.

Ring-Opening Polymerization of tnPDL

In an N₂-filled glovebox, tnPDL (0.250 g, 0.975 mmol) was added to a 20 mL scintillation vial equipped with a stir bar. TCC (0.015 g, 0.048 mmol), MTBD (0.007 g, 0.048 mmol) and benzyl alcohol (0.001 g, 0.0097 mmol) were added to another 20 mL scintillation vial. Toluene (0.195 mL, 5M in tnPDL) was divided equally between the two vials and stirred to dissolve. The solution of tnPDL was transferred to the other vial via Pasteur pipette and then heated to 100 °C and stirred for 4.5 hours in the glovebox. The polymer was then precipitated with hexanes. The supernatant was decanted, and remaining volatiles were removed under reduced pressure to yield the polymer (62%

yield; $M_w/M_n = 1.8$; M_n (GPC) = 34,400; M_n (NMR) = 21,000). ^{13}C NMR spectra display characteristic resonances of a polymer with a thionoester repeat unit at 224 ppm.

Co-polymerization of tnPDL and PDL

In an N_2 -filled glovebox, PDL (120 mg, 0.50 mmol), tnPDL (128 mg, 0.50 mmol), TCC (0.015 g, 0.050 mmol), BEMP (0.013 g, 0.050 mmol) and benzyl alcohol (0.001 g, 0.01 mmol) were added to a 20 mL scintillation vial with a stir bar. The vial was then heated to 100 °C and stirred for 5 hours in the glovebox. The polymer was then precipitated with hexanes. The supernatant was decanted, and remaining volatiles were removed under reduced pressure to yield the polymer (80% yield; $M_w/M_n = 1.6$; M_n (GPC) = 33,800).

*Synthesis of P(tnPDL-*b*-CL) polymer*

The ROP of tnPDL was carried out as above. After completion, the homopolymer was washed with methanol and volatiles were removed under reduced pressure. The chain extension of PtnPDL was conducted. In one 20 mL vial, PtnPDL (250 mg, 0.975 mmol), TCC (0.015 g, 0.048 mmol), BEMP (0.013 g, 0.048 mmol) were dissolved in CH_2Cl_2 . In a second vial, CL (0.111 g, 0.976 mmol) was dissolved in CH_2Cl_2 (total CH_2Cl_2 volume 1.95 mL), and the contents of the CL vial transferred to the other via Pasteur pipette. The reaction solution as stirred for 9 hours. The polymer was precipitated from hexanes, the supernatant decanted and the product placed under high vacuum (75 % yield; $M_w/M_n = 2.8$; M_n (GPC) = 37,600).

Determination of Thermodynamics of ROP

For HL, tnHL, NL and tnNL:

An NMR tube was loaded with tnHL (e.g., 0.100 g, 0.693 mmol), TBD (0.0048 g, 0.035 mmol), benzyl alcohol (0.0008 g, 0.0069 mmol) in C₆D₆ (1 M in monomer). The [M]_{eq} was measured versus temperature via ¹H NMR from 298 K to 333 K by heating the sample in a variable temperature NMR probe. Data points were taken in duplicate, once while heating and once while cooling, and the [M]_{eq} values are within error of each other. The DH°, DS° and T_{ceiling} for the ROP of tnHL were determined from a van't Hoff plot where the error was calculated from linear regression at 95% confidence interval.

For PDL, tnPDL, EB and tnEB:

In an N₂-filled glovebox, a 20 mL scintillation vial equipped with a stir bar was loaded with tnPDL (e.g., 0.100 g, 0.390 mmol), TCC/BEMP (5 mol% each, 0.0195 mmol), benzyl alcohol (0.0004 g, 0.0039 mmol) in toluene (0.5 M in monomer). The vial was heated to perform the polymerization, and reaction progress was monitored via ¹H NMR by withdrawing aliquots. When the reaction had reached equilibrium, the temperature was increased, and aliquots were withdrawn after the reaction reached equilibrium at different temperatures (from 90 °C to 150 °C) and the [M]_{eq} was analyzed via ¹H NMR. The DH°, DS° and T_{ceiling} for the ROP of tnPDL were determined from a van't Hoff plot of the data where the error was propagated from ¹H NMR integrations (±5%).

Example Synthesis of Cross-Linked Polymers

The polyhomo(thionolactone) or co-polymer was dissolved in CH₂Cl₂, transferred to a 6-8 kDa dialysis bag and stirred in methanol overnight. The purified homopolymer was then dried under reduced pressure. The homopolymer was then weighed (200 mg), transferred to a 100 mL beaker and dissolved in 4 mL of CH₂Cl₂. To the beaker with the dissolved polymer, 20 mL aqueous NaOCl was added (household bleach, 5.25 %). The reaction mixture was then vigorously stirred for 18 hours. A solid white polymer precipitated. The polymer was then filtered and blotted on paper towels to remove excess solvent. The polymer was then washed with water to remove excess NaOCl. The polymer was then dried under reduced pressure. The product recovery was > 99.99 % (200 mg).

Hydrolytic Degradation Studies of PtnPDL-CLP

Polymer samples (approximately 25 mg of the cross-linked polymer) were transferred to empty 20 mL scintillation vials. Each vial was charged with 10 mL of aqueous 0.25 M HCl, aqueous 0.25 M NaOH solution, or distilled water. All vials were vigorously stirred for the duration of the study. Samples were acquired by removing polymer pieces from the solution and blotting to remove the aqueous solution from the surface. Polymer samples were then dried under high vacuum overnight and weighed. The percent mass loss is given by $[\text{mass}]_o - [\text{mass}]_i / [\text{mass}]_o$.¹¹ The same steps were repeated over a ten days period daily.

Determination of Crosslink Density

The crosslink density was determined at room temperature from literature methods.²²

The swelling ratio was calculated using equation 1 where W_d is the pre-immersion weight of the crosslinked polymer, and W_s is the weight after immersion in THF ²³

$$\text{Swelling ratio} = \frac{(W_s - W_d)}{(W_d)} \quad (1)$$

The porosity of the polymer was calculated from equation 2, where V is the volume of the crosslinked polymer disk ($\rho_{THF} = 0.8892 \text{ g/mL}$).²³ Results were averaged of three measurements.

$$\text{Porosity \%} = \frac{(W_s - W_d)}{V\rho} \times 100 \quad (2)$$

For crosslinked densities, the Flory-Huggins polymer-solvent interaction parameter (χ) was calculated using equation 3. δ_1 and δ_2 are the solubility parameters of the solvent (δ_1 (THF) = $18.30 \text{ J}^{1/2} \text{ cm}^{-3/2}$) and the polymer respectively, V_s is the molar volume of the solvent.²⁴ The δ_2 value is estimated from the Hansen solubility parameters of PPDL ($17.5 \text{ J}^{1/2} \text{ cm}^{-3/2}$) and PCL ($19.5 \text{ J}^{1/2} \text{ cm}^{-3/2}$).^{25,26,27} The solubility parameter of PCL was used for PtnCL-CLP and PtnHL-CLP, and that of PPDL for PtnPDL-CLP and P(tnPDL-*b*-CL)-CLP.

$$\chi = \frac{(\delta_1 - \delta_2)^2 V_s}{RT} \quad (3)$$

The crosslinked densities were calculated based on Flory-Rehner equation 4.²⁴

$$-\ln(1 - V_p) + V_p + \chi V_p^2 = V_s n [V_p^{\frac{1}{3}} + \frac{V_p}{2}] \quad (4)$$

V_p is the volume fraction of polymer in the swollen weight, and n is the crosslinked density of the polymer. Errors are taken from the standard deviation of three measurements.

Procedure for Gold Extraction with Varying Amounts of PtnPDL-CLP

A 100 ppm Au^{3+} solution was prepared by dissolving 10 mg of $\text{NaAuCl}_4 \cdot 2\text{H}_2\text{O}$ salt in 50 mL of deionized water. The absorbance was measured for a diluted series of the Au^{3+} solution with different concentrations (5 ppm, 25 ppm, 50 ppm and 75 ppm) using a UV-Vis spectrophotometer to construct a calibration curve. To 10 mL samples of 100 ppm Au^{3+} solution, 25 mg, 50 mg and 100 mg of small PtnPDL-CLP pieces were added. The solutions were stirred for three days and the remaining concentrations of Au^{3+} were measured at different time periods using UV-Vis to calculate the extraction efficiency.

Procedure for Gold Recovery After Heating to 1000 °C

To a 10 mL solution of 100 ppm Au^{3+} solution in deionized water, 50 mg of small PtnPDL-CLP pieces were added and stirred for 3 days. The supernatant was removed, and the polymer was dried under high vacuum at room temperature to afford 53.20 mg solid grey polymer. The polymer was heated in air to 1000 °C and held for 30 minutes to afford 0.45 mg of gold metal. The recovery of extracted gold metal was 99%.

RESULTS AND DISCUSSION

Thermodynamic Studies. The substitution of S for O in thionolactones provides minimal perturbation to the thermodynamics of ROP versus the parent lactone monomers. A slate of lactone monomers from seven to seventeen membered rings and their thionolactones analogues were prepared according to established methods (Figure 3.1, see SI),^{28,29} and their temperature dependent $[M]_{eq}$ were measured by 1H NMR, revealing the entropy and enthalpy of ROP, Table 1. The effect of the S substitution is most prominently seen in the ceiling temperature ($T_{ceiling}$), where tnHL and tnCL have lower $T_{ceiling}$ versus HL and CL, respectively. However, the larger (thiono)lactones (≥ 9) all possess temperature independent equilibria, consistent with the so-called entropically controlled monomers.³⁰ Our observations here are consistent with a previous study which showed thionylation of lactones to primarily alter polymerization kinetics versus thermodynamics.¹¹ d-Thionovalerolactone is known to autopolymerize at low temperature.¹⁴

Organocatalysis. Organocatalysts facilitate the ROP of strained and unstrained thionolactones with retention of S/O substitution. A screen of polymerization conditions was conducted for the lactones and thionolactones shown in Figure 3.1, and the results are shown in Table 2. The full catalyst screen is shown in the SI. Our catalyst screen focused on the H-bonding class of organocatalysts because a previous study from our group demonstrated that strong base catalysts, even strong organic bases (e.g. DBU) in the absence of an H-bond donating cocatalyst, will result in partial switching of the S/O substitution during the ROP to produce a poly(thiono-co-thioester).¹¹ Synthetic

opportunities from this ‘liability’ can be envisaged, but this possibility is left to a future study. For all catalyst systems reported in Table 2, the retention of S/O substitution to form the polythionolactones is confirmed via ^{13}C NMR (see SI). The commercially available TCC plus MTBD or BEMP is a suitable cocatalyst system for the ROP of all (thiono)lactones studied.³² The ROP of NL was sluggish with TCC, and the more active trisurea H-bond donor, **2**, produces a faster and more controlled ROP. In general, the thionolactones are more labile than their lactone analogues, requiring less reaction time or less active cocatalyst system.¹¹ The organocatalytic ROP of macro(thiono)lactones is optimally conducted at elevated temperatures, as previously established.³³

The organocatalytic ROP of thionolactones display the characteristics of living polymerizations and are proposed to be mediated by a neutral H-bonding mechanism. Organocatalysts typically effect ‘living’ ROPs of lactone monomers: first order consumption of monomer, linear evolution of M_n versus conversion and predictable M_n (from $[\text{M}]_0/[\text{I}]_0$).³¹ For strained lactones (≤ 8 membered rings), the ROPs are generally highly controlled with organocatalysts producing very narrow M_w/M_n (<1.1). Unstrained lactones (>9 membered rings) typically experience post-enchainment transesterification that competes substantially with enchainment events, producing broader M_w/M_n , but otherwise these ROP can display ‘living’ behavior.^{5,34–37} Hence, the thionolactones examined here are behaving ‘normally’ where the strained monomers (tnCL¹¹ and tnHL) yield narrowly dispersed polymers, and the unstrained monomers (tnNL in Figure 3.2, tnPDL and tnEB) produced more broadly dispersed polymers. Metal-containing and organic catalysts have previously been shown to produce the ROP of unstrained lactones similar to what is observed here.^{37,3,30,38,33} Our thermodynamic

studies corroborate previous suggestions that NL and tnNL are unstrained lactones,^{39–41} but the TCC/BEMP (0.031 mmol each) cocatalyzed ROP of tnNL (2 M) from 1-pyrenebutanol (0.012 mmol) produces a polymer with overlapping UV and RI traces in the GPC (see SI) further suggesting ‘living’ behavior. The macrothionolactone tnEB displays a high equilibrium monomer concentration ($[M]_{eq} = 0.72$ M, $[2]_o$). The preponderance of evidence from our previous studies suggests that TCC/base mediated ROP in non-polar solvent occurs via a neutral H-bond mediated mechanism. The **1**/BEMP system has been shown to effect H-bond mediated ROP, and TCC is less acidic than **1**.^{7,8,10} The alternate (thio)imide mediated ROP mechanism available to (thio)urea/base cocatalyzed ROP is not readily accessible in non-polar solvent with non-polar lactones (e.g. (tn)PDL and (tn)EB).^{6,9,10,37}

Co-polymerization. Organocatalysts facilitate the one-pot synthesis of copolymers of lactones and thionolactones. As an example, the TCC/BEMP cocatalyzed (5 mol%, 0.0478 mmol each) copolymerization of PDL (2.5 M, 1.0 equiv) and tnPDL (2.5 M, 1.0 equiv) from benzyl alcohol (1 mol%, 0.0097 mmol) in toluene at 100 °C achieved full conversion to polymer in 5 h ($M_n = 34,100$, $M_w/M_n = 1.66$). The two monomers were observed to undergo ROP at similar rates (see SI, $k_{tnPDL}/k_{PDL} = 1.4$), suggesting it forms a random copolymer. The melting points of the polythionolactones are suppressed versus the corresponding polylactones, Table 3. Full analysis of the altered materials properties of polythionolactones will be the subject of future work.

Oxidative Crosslinking of Polythionolactones. The oxidation of polythionolactones yields a degradable, crosslinked foam with controllable porosity. We sought to demonstrate the unique chemistry of thionolactones via an example oxidation reaction. Treatment of a CH₂Cl₂ solution (4 mL) of 200 mg of PtnCL (pre-crosslink Mn =20,600) with 20 mL commercial bleach solution (20 mL) yields a flexible, opaque, spongy disk that is intractable in any solvent examined. This solid is swellable in organic solvents, suggesting a lightly crosslinked polymer, PtnCL-CLP. Repeating this experiment with homo-PtnHL, homo-PtnPDL and a PtnPDL-block-PCL copolymer revealed crosslinked polymers (CLPs) with progressively larger pores under optical microscopy, Figure 3.3. The porosity and crosslink density of the several crosslinked polymers was measured with a swelling test in THF (see SI) revealing a progressive attenuation of the crosslink density and progressive augmentation of the porosity with decreasing thionoester moiety content, Table 4. As expected, the PtnPDL-block-PCL-CLP has the largest porosity and lowest crosslink density of the studied samples, and this CLP becomes optically transparent when swollen, see SI. In total, this suggests that the polythionolactone platform provides a means of generating crosslinked polymers with easily tunable porosity.

The crosslinked polythionolactones are degradable in aqueous solutions. The low crosslink density of the examined CLPs suggests that most of the thionolactones linkages remain unaltered from the oxidation procedures, and solid-state IR spectroscopy corroborates this suggestion (see SI). XPS analysis of PtnPDL-CLP at the C 1s core and S 2p core regions suggest the presence of C=S, disulfide and sulfone groups (see SI). This suggests that some thionolactones are converted to disulfide and

sulfone groups during the oxidation. This observation is reminiscent of the NaOCl mediated oxidation/dimerization of thioketones whereby two thioketones are oxidized to the respective S-oxides and undergo a [4+2] cycloaddition and rearrangement.⁴⁴ Regardless, previous studies from our group suggest that if the majority of the thionolactones moieties were intact, the crosslinked polymers should degrade in water.¹¹ PtnPDL-CLP samples were submerged in aqueous 0.25 M HCl, aqueous 0.25 M NaOH and deionized water, and the weight of the samples monitored over days. In the basic solution, PtnPDL-CLP degraded to less than half of its original mass in 10 days. The sample was more stable (<10% mass loss in 10 days) in neutral and acidic media (see SI), consistent with previous studies.¹¹ Despite being easily degradable via hydrolysis, the CLPs are thermally stable. Thermal gravimetric analysis of PtnPDL-CLP under N₂ revealed onset of decomposition (T_d) at 421 °C. The chemical nature of the crosslink will be the subject of future studies.

Crosslinked Polythionolactone as Gold Binding Agent. Recent reports of waste gold recovery mediated by polymer bound thiocarbonyls inspired us to apply our crosslinked polythionolactones to this challenge.^{45,46} More than 25% of the annual demand for metallic gold is satisfied through recycling, especially electronic waste.^{47,46} Traditional solution-based, batch process, methods often employ stoichiometric reagents.^{46,48,49} PtnPDL-CLP (100 mg) was cut into small pieces (~5 mm) and added to an aqueous solution of NaAuCl₄ (100 mg/L in Au³⁺, 10 mL), and the amount of Au³⁺ in remaining solution over time was determined via UV-vis, analogous to established methods.^{45,46} After 3 days, the once yellow solution appeared colorless, and the UV-vis signal (Au³⁺) was 12% the starting intensity, suggesting 88% extraction efficiency. Isolation of the

PtnPDL-CLP followed by obliteration of the organic portion by heating in air (1000°C) revealed 0.85 mg of a lustrous gold-colored metal (97% yield for Au⁰), Figure 3.4. Recent studies have shown that sulfur-containing polymers are also capable of extracting toxic heavy metals.^{45,46} A flow through version of this batch process can be envisaged.

CONCLUSION

Organocatalysts previously developed for the ROP of lactones were applied to the ROP of thionolactones. The highly controlled urea/base cocatalysts facilitated the synthesis of polythionolactones and their copolymers via a proposed H-bond mediated mechanism. These mild catalysts are essential to preserve the S/O substitution which renders the thionoester chemical handle in the polythionolactones. The mild and facile oxidative crosslinking of polythionolactones forms a degradable polymeric foam. Again, the highly general nature of (thio)urea/base mediated ROP toward cyclic monomers, broadly considered, facilitates the synthesis of a host of copolymers which renders tunable the porosity of the subsequent crosslinked system. Catalytic advances directly facilitate the synthesis of new materials; fundamental, mechanistic chemistry begets new applications.

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entry	monomer	ΔH_p° (kcal/mol)	ΔS_p° (cal/mol K)	T_{ceiling}° (°C)	ref
1	CL	-5.90 ± 0.05	-8 ± 10	503	--
2	tnCL	-5.79 ± 0.32	-13 ± 1	156	11
3	HL	-4.60 ± 0.75	-8 ± 2	332	--
4	tnHL	-5.14 ± 0.43	-11 ± 1	193	--
5	NL	0 ± 2.5	7 ± 1	--	--
6	tnNL	0 ± 2.5	9 ± 1	--	--
7	PDL	0.7	6	--	31
8	tnPDL	0 ± 2.6	8 ± 1	--	--
9	EB	0 ± 2.6	15 ± 1	--	--
10	tnEB	0 ± 2.9	0.8 ± 1.1	--	--

Table 3.1. Thermodynamics of Ring-Opening Polymerization^a

a. Determined by measuring $[M]_{\text{eq}}$ versus temperature in solution, see SI for full experimental details.

<div style="display: flex; align-items: center; justify-content: center;"> <div style="text-align: center;"> THIONOLACTONE -or- LACTONE (1 equiv) </div> <div style="margin: 0 10px;">+</div> <div style="text-align: center;"> $[I]_0/[M]_0$ equiv. </div> <div style="margin-left: 20px;"> $\xrightarrow[\text{solvent or solvent-free}]{\text{ORGANOCATS. (<5 mol\% each)}}_{\text{r.t. - 100}^\circ\text{C}}$ </div> <div style="text-align: center;"> POLY(THIONO)LACTONE </div> </div>									
entry	monomer ([M] ₀)	cocatalysts	solvent	[M] ₀ /[I] ₀	temp. (°C)	Time (h)	conv. (%) ^a	M_n^b (g/mol)	M_w/M_n^b
1	HL (2 M)	TCC/MTBD (5 mol%)	C ₆ D ₆	100	r.t.	5	90	19,200	1.02
2	tnHL (2 M)	TCC/MTBD (5 mol%)	C ₆ D ₆	100	r.t.	4	90	16,200	1.03
3	NL (2 M)	2 /BEMP (1.67 mol%)	C ₆ D ₆	100	r.t.	10	90	23,200	1.30
4	tnNL (2 M)	TCC/BEMP (5 mol%)	C ₆ D ₆	100	r.t.	4	99	24,200	1.70
5	PDL (5 M)	TCC/MTBD (5 mol%)	toluene	100	100	9.8	88	34,200	1.60
6	tnPDL (5 M)	TCC/MTBD (5 mol%)	toluene	100	100	4.5	90	34,400	1.80
7 ^c	EB (4 M)	TCC/BEMP (2 mol%)	solvent- free	100	80	2	92	43,000	1.30
8	tnEB (2 M)	TCC/BEMP (5 mol%)	toluene	100	80	4.5	64	10,600	1.90

Table 3.2 Organocatalytic ROP of (thiono)lactones^a

a. Monomer conversion was monitored via ¹H NMR. b. M_n and M_w/M_n were determined by GPC (CH₂Cl₂) versus polystyrene standards. c. EB (2.95 mmol, 1 equiv).

Polymer	M_n (g/mol)	M_w/M_n	T_m (°C)	ref
PHL	17,100	1.02	61	--
PtnHL	14,900	1.19	18	--
PNL	25,500	1.48	66	--
PtnNL	24,200	1.70	0	--
PPDL	64,500	2.00	97	42
PtnPDL	34,400	1.80	60	--
PEB	55,100	1.50	78	43
PtnEB	10,600	1.90	70	--

Table 3.3. Melting Points of the Poly(thiono)lactones^a

a. M_n and M_w/M_n were determined by GPC (CH₂Cl₂) versus polystyrene standards.

Crosslinked polythionolactone	Pre-crosslink M_n (M_w/M_n)	swelling ratio	porosity%	crosslinked density(n) (mmol.cm ⁻³)
PtnCL-CLP	20,600 (1.42)	4.60 ± 0.01	38.9 ± 0.1	6.47 ± 0.01
PtnHL-CLP	12,700 (1.47)	5.16 ± 0.02	47.4 ± 0.2	3.95 ± 0.02
PtnPDL-CLP	28,800 (1.68)	9.40 ± 0.03	54.6 ± 0.2	3.00 ± 0.01
P(tnPDL- <i>b</i> -CL)-CLP	31,000 (2.08)	9.72 ± 0.25	82.3 ± 0.9	0.45 ± 0.00

Table 3.4 Calculated crosslinked densities and porosity% of the CLPs^a

a. Swelling tests were carried out in THF at room temperature. Swelling ratios, porosity%, and the crosslinked densities (n) were calculated using equation (1), (2), and (4), respectively.

entry	base	cocatalyst	[M] _o /[I] _o	conv. ^b (%)	time (h)	<i>M_n</i> ^c (g/mol)	<i>M_w</i> / <i>M_n</i> ^c
1 ^d	TBD	-	100	93	2	24,600	1.59
2	BEMP	TCC	100	88	0.06	12,600	1.04
3	MTBD	TCC	200	90	8.5	32,100	1.02
4	MTBD	TCC	100	90	5	19,200	1.02
5	MTBD	TCC	50	91	2	11,500	1.03
6	MTBD	TCC	25	90	1	6,100	1.04
7	DBU	TCC	100	89	21	18,200	1.03
8 ^e	BEMP	2	100	98	0.83	23,800	1.13
9 ^e	MTBD	2	100	89	2	24,300	1.13
10 ^e	DBU	2	100	89	18	17,800	1.03

Table 3.5. ROP of HL with urea/base cocatalyst system.^a

a. Reaction conditions: HL (2 M, 0.78 mmol, 1 equiv), benzyl alcohol initiator (I), TCC/base (5 mol %, 0.039 mmol each) in C₆D₆. b. Monomer conversion was monitored via ¹H NMR. c. *M_n* and *M_w*/*M_n* were determined by GPC (CH₂Cl₂) versus polystyrene standards. d. TBD (1 mol %, 0.0078 mmol). e. **2**/base (1.67 mol %, 0.013 mmol each).

Entry	Base	Cocatalyst	[M] ₀ /[I] ₀	Conv. ^b (%)	Time (h)	<i>M_n</i> ^c (g/mol)	<i>M_w</i> / <i>M_n</i> ^c
1	BEMP	TCC	100	92	0.63	14,700	1.19
2	MTBD	TCC	200	89	6.75	28,700	1.14
3	MTBD	TCC	100	90	4	16,200	1.03
4	MTBD	TCC	50	88	2.25	8,700	1.03
5	MTBD	TCC	25	90	1	4,900	1.02
6 ^d	MTBD	2	100	85	12	11,700	1.19
7 ^e	TBD	-	100	89	0.35	19,400	1.13

Table 3.6. ROP of tnHL with urea/base cocatalyst system ^a

a. Reaction conditions: tnHL (2 M, 1.04 mmol, 1 eq), benzyl alcohol as initiator, TCC/base (5 mol %, 0.052 mmol each) in C₆D₆. b. Monomer conversion was monitored via ¹H NMR. c. *M_n* and *M_w*/*M_n* were determined by GPC (CH₂Cl₂) versus polystyrene standards. d. **2**/base (1.67 mol %, 0.017 mmol each). e. TBD (1 mol %, 0.010 mmol).

Entry	Base	Cocatalyst	conv. ^b (%)	time (h)	M_n^c (g/mol)	M_w/M_n^c
1 ^d	TBD	-	85	6	35,000	1.93
2	BEMP	TCC	90	5	35,800	1.80
3	MTBD	TCC	93	4.5	34,400	1.80

Table 3.7. ROP of tnPDL with urea/base cocatalyst system ^a

a. Reaction conditions: tnPDL (5 M, 0.974 mmol, 1 eq), benzyl alcohol (1 mol %, 0.0097 mmol) TCC/base (5 mol %, 0.0478 mmol each) in toluene at 100 °C. b. Monomer conversions were monitored via ¹H NMR. c. M_n and M_w/M_n were determined by GPC (CH₂Cl₂) versus polystyrene standards. d. TBD (2 mol%, 0.0194 mmol).

Entry	Base	Cocatalyst	Conv. ^b (%)	Time(h)	M_n^c (g/mol)	M_w/M_n^c
1	BEMP	TCC	64	4.5	10,600	1.90
2	MTBD	TCC	67	8	8,900	1.80
3 ^d	BEMP	2	6	77	-	-
4 ^d	MTBD	2	29	77	-	-

Table 3.8. ROP of tnEB with urea/base cocatalyst system^a

a. Reaction conditions: tnEB (2 M, 1.32 mmol, 1 eq), benzyl alcohol (1 mol %, 0.0132 mmol), TCC/base (5 mol%, 0.0661 mmol each) in toluene at 80 °C. b. Monomer conversion were monitored via ¹H NMR. c. M_n and M_w/M_n were determined by GPC (CH₂Cl₂) versus polystyrene standards. d. **2**/base (1.67 mol%, 0.022 mmol each).

entry	Base	Cocatalyst	Solvent	$[\text{M}]_0/[\text{I}]_0$	Conv. ^b (%)	Time (h)	M_n^c (g/mol)	M_w/M_n^c
1 ^d	TBD	-	toluene	100	85	76	12,100	1.68
2	BEMP	TCC	acetone- <i>d</i> ₆	100	96	25	18,000	1.80
3	MTBD	TCC	acetone- <i>d</i> ₆	100	27	24	9,200	1.31
5	BEMP	TCC	benzene- <i>d</i> ₆	100	80	48	22,000	1.57
6 ^e	BEMP	2	benzene- <i>d</i> ₆	200	84	22	27,600	1.50
7 ^e	BEMP	2	benzene- <i>d</i> ₆	100	90	10	23,200	1.30
8 ^e	BEMP	2	benzene- <i>d</i> ₆	50	87	5.5	11,300	1.50
9 ^f	BEMP	2	toluene	100	97	3	29,000	1.55

Table 3.9. ROP of NL with urea base cocatalyst system^a

a. Reaction conditions: NL (2 M, 0.703 mmol, 1 eq), benzyl alcohol as initiator TCC/base (5 mol %, 0.0351 mmol each), b. Monomer conversions were monitored via ¹H NMR. c. M_n and M_w/M_n were determined by GPC (CH₂Cl₂) versus polystyrene standards d. TBD (5 mol %, 0.0351 mmol) e. **2**/base (1.67 mol %, 0.0117 mmol each) f. **2**/base (1.67 mol%, 0.0117 mmol each) in toluene at 80°C.

entry	Base	Cocatalyst	Solvent	[M] ₀ /[I] ₀	Conv. ^b (%)	Time (h)	M _n ^c (g/mol)	M _w /M _n ^c
1	BEMP	TCC	acetone- <i>d</i> ₆	100	95	4	23,500	1.81
2	MTBD	TCC	acetone- <i>d</i> ₆	100	75	48	14,800	1.73
3	BEMP	TCC	benzene- <i>d</i> ₆	200	94	7.75	26,400	1.50
4	BEMP	TCC	benzene- <i>d</i> ₆	100	99	4	24,200	1.70
5	BEMP	TCC	benzene- <i>d</i> ₆	50	93	2.5	12,500	1.50

Table 3.10. ROP of tnNL with urea/base cocatalyst system^a

a. Reaction conditions: tnNL (2 M, 0.632 mmol, 1 eq), benzyl alcohol as initiator, TCC/base (5 mol %, 0.0315 mmol each), b. Monomer conversion were monitored via ¹H NMR. c. *M_n* and *M_w/M_n* were determined by GPC (CH₂Cl₂) versus polystyrene standards.

Figure 3.1. Monomers and (co)catalysts used herein.

Figure 3.2. (Left) M_n versus conversion, and (Right) First order evolution of [tnNL] versus time. Reaction conditions: tnNL (2 M, 0.632 mmol, 1 equiv), benzyl alcohol (1 mol%, 0.0063 mmol) catalyzed by TCC/BEMP (5 mol%, 0.0315 mmol each) in C_6D_6 .

Figure 3.3. (a) Image of PtnPDL-CLP flexible polymer. (b) Images of PtnCL, PtnHL, and P(tnPDL-*b*-CL) CLPs (c) cross sectional morphology of crosslinked polymers with optical microscopic; magnification X 10.

Figure 3.4. Visual progress of $\text{Au}^{3+}_{(\text{aq})}$ extraction and Au^0 recovery mediated by 100 mg of PtnPDL-CLP. $[\text{Au}^{3+}]_0 = 100 \text{ ppm}$, Au^{3+} volume = 10 mL.

Figure 3.5. RI and UV GPC traces of the ROP initiated from pyrenebutanol for tnNL. Conditions: tnNL (0.631 mmol, 2 M in acetone- d_6), 1-pyrenebutanol (2 mol %, 0.012 mmol), TCC/BEMP (5 mol %, 0.0315 mmol each) in acetone- d_6 .

Figure 3.6. (Left) M_n versus conversion. (Right) First order evolution of $[HL]$ versus time; Reaction conditions: HL (0.78 mmol, 2M in C_6D_6), benzyl alcohol (1 mol %, 0.0078 mmol) catalyzed by TCC/MTBD (5 mol %, 0.039 mmol each) in C_6D_6 .

Figure 3.7. (Left) M_n versus conversion. (Right) First order evolution of [tnHL] versus time. Reaction conditions: tnHL (1.04 mmol, 2M in C_6D_6), benzyl alcohol (1 mol %, 0.010 mmol), TCC/MTBD (5 mol %, 0.034 mmol each) in C_6D_6

Figure 3.8. (Left) M_n versus conversion. (Right) First order evolution of [tnPDL] versus time. Reaction conditions: tnPDL (0.974 mmol, 5M in toluene), benzyl alcohol (1 mol %, 0.0097 mmol) catalyzed by TCC/MTBD (5 mol %, 0.0478 mmol each) in toluene at 100 °C.

Figure 3.9. (Left) M_n versus conversion. (Right) First order evolution of [PDL] versus time. Reaction conditions: PDL (1.05 mmol, 5M in toluene), benzyl alcohol (1 mol%, 0.0105 mmol) catalyzed by TCC/MTBD (5 mol %, 0.0525 mmol each) in toluene at 100 °C

Figure 3.10. (Left) M_n versus conversion. (Right) First order evolution of [tnEB] versus time. Reaction conditions: tnEB (1.32 mmol, 2M in toluene), benzyl alcohol (1 mol %, 0.0132 mmol) catalyzed by TCC/BEMP (5 mol %, 0.0661 mmol each) in toluene at 80 °C.

Figure 3.11. (Left) M_n versus conversion. (Right) First order evolution of [EB] versus time. Reaction conditions: EB (2.95 mmol), benzyl alcohol (1 mol %, 0.0295 mmol) catalyzed by TCC/BEMP (2 mol %, 0.0590 mmol each) at 80 °C under solvent-free conditions.

Figure 3.12. (Left) M_n versus conversion. (Right) First order evolution of [NL] versus time. Reaction conditions: NL (0.703 mmol, 2M in C_6D_6), benzyl alcohol (1 mol %, 0.00703 mmol) catalyzed by **2**/BEMP (1.67 mol %, 0.0117 mmol each) in C_6D_6 .

Figure 3.13. (Left) Van't Hoff plot for the ROP of HL (0.780 mmol, 0.5M in C_6D_6) from benzyl alcohol (1 mol %, 0.0078 mmol) catalyzed by TBD (5 mol %, 0.039 mmol). (Right) Van't Hoff plot for the ROP of tnHL (0.694 mmol, 1M in C_6D_6) from benzyl alcohol (1 mol %, 0.0069 mmol) catalyzed by TBD (5 mol %, 0.039 mmol).

Figure 3.14. (Left) Van't Hoff plot for the ROP of NL (0.703 mmol, 0.5M in C_6D_6) from benzyl alcohol (1 mol %, 0.0070 mmol) catalyzed by TCC/BEMP (5 mol %, 0.0352 mmol each). (Right) Van't Hoff plot for the ROP of tnNL (0.632 mmol, 0.5M in C_6D_6) from benzyl alcohol (1 mol %, 0.0063 mmol) catalyzed by TCC/BEMP (5 mol %, 0.0315 mmol each).

Figure 3.15. Van't Hoff plot for the ROP of tnPDL(0.390 mmol, 0.5 M in toluene) from benzyl alcohol (1 mol %, 0.0039 mmol) catalyzed by TCC/BEMP (5 mol% each, 0.0195 mmol each).

Figure 3.16. (Left) Van't Hoff plot for the ROP of EB (0.370 mmol, 0.5 M in toluene) from benzyl alcohol (1 mol %, 0.0037 mmol) catalyzed by TCC/BEMP (5 mol %, 0.0185 mmol each). (Right) Van't Hoff plot for the ROP of tnEB (1.32 mmol, 2 M in toluene) from benzyl alcohol (1 mol% 0.013 mmol) catalyzed by TCC/BEMP (5 mol%, 0.066 mmol each)

Figure 3.17. First order evolution of monomer concentrations versus time for the one-pot copolymerization of tnPDL and PDL. Reaction conditions: tnPDL and PDL (0.50 mmol each), benzyl alcohol (0.010 mmol) catalyzed by TCC/BEMP (0.0504 mmol each) in toluene (0.200 mL) at 100 °C.

Figure 3.18. MALDI-ToF mass spectrum of PtnHL homopolymer ($[M]_0/[I]_0=25$)

Figure 3.19. MALDI-ToF mass spectrum of PtnNL homopolymer ($[M]_0/[I]_0=25$)

Figure 3.20. Differential scanning calorimetry spectrum of PHL homopolymer

Figure 3.21. Differential scanning calorimetry spectrum of PtnHL homopolymer

Figure 3.22. Differential scanning calorimetry spectrum of PNL homopolymer

Figure 3.23. Differential scanning calorimetry spectrum of PtnNL homopolymer

Figure 3.24. Differential scanning calorimetry spectrum of PtnPDL homopolymer

Figure 3.25. Differential scanning calorimetry spectrum of PtnEB homopolymer

Figure 3.26. Differential scanning calorimetry spectrum of P(tnPDL-co-PDL) copolymer

Figure 3.27. Swelling ratios of crosslinked polymers in THF

Figure 3.28. Dependence of porosity on cross-linked density of CLPs

Figure 3.29. Images of the transparent P(tnPDL-*b*-CL)-CLP after immersed in THF

Figure 3.30. (a) XPS spectrum for the C 1s (b) XPS spectrum for the S 2p

Figure 3.31. Percent mass loss for PtnPDL-CLP in acidic (0.25 M HCl), basic (0.25 M NaOH), and neutral (distilled water) conditions versus time. The results shown are an average of three replicates.

Figure 3.32. Solid-state IR spectrum of PtnPDL.

Figure 3.33. Solid-state IR spectrum of the crosslinked polymer (PtnPDL-CPL).

Figure 3.34. UV-vis spectrum for the Au³⁺ (100 ppm aqueous solution) extraction with PtnPDL-CLP (100 mg).

Figure 3.35. (Upper) ^1H NMR (CDCl_3 , 300 MHz, ppm) spectrum of tnHL. (Lower) ^{13}C NMR (CDCl_3 , 100 MHz, ppm) spectrum of tnHL.

Figure 3.36. (Upper) ^1H NMR (CDCl_3 , 300 MHz, ppm) spectrum of tnNL. (Lower) ^{13}C NMR (CDCl_3 , 100 MHz, ppm) spectrum of tnNL.

Figure 3.37. (Upper) ^1H NMR (CDCl_3 , 300 MHz, ppm) spectrum of tnPDL. (Lower) ^{13}C NMR (CDCl_3 , 100 MHz, ppm) spectrum of tnPDL.

Figure 3.38. (Upper) ^1H NMR (CDCl_3 , 300 MHz, ppm) spectrum of tnEB. (Lower) ^{13}C NMR (CDCl_3 , 100 MHz, ppm) spectrum of tnEB.

Figure 3.39 (Upper) ^1H NMR (CDCl_3 , 400 MHz, ppm) spectrum of PtnHL. (Lower) ^{13}C (75 MHz, CDCl_3) spectrum of PtnHL

Figure 3.40. (Upper) ^1H NMR (CDCl_3 , 400 MHz, ppm) spectrum of PtnNL. (Lower) ^{13}C NMR (100 MHz, CDCl_3) spectrum of PtnNL.

Figure 3.41. (Upper) ^1H NMR (CDCl_3 , 400 MHz, ppm) spectrum of PtnPDL. (Lower) ^{13}C NMR (100 MHz, CDCl_3) spectrum of PtnPDL.

Figure 3.42 (Upper) ^1H NMR (CDCl_3 , 400 MHz, ppm) spectrum of PtnEB. (Lower) ^{13}C NMR (75 MHz, CDCl_3) spectrum of PtnEB.

Figure 3.43. (Upper) ^1H NMR (CDCl_3 , 400 MHz, ppm) spectrum of $\text{P}(\text{tnPDL-co-PDL})$ (1:1). (Lower) ^{13}C NMR (100 MHz, CDCl_3) spectrum of $\text{P}(\text{tnPDL-co-PDL})$ (1:1)

Figure 3.44. (Upper) ^1H NMR (CDCl_3 , 400 MHz, ppm) spectrum of P(tnPDL-*b*-CL) (1:1). (Lower) ^{13}C NMR (100 MHz, CDCl_3) spectrum of P(tnPDL-*b*-CL) (1:1).

MANUSCRIPT IV

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Stereoselective Ring Opening Polymerization of *rac*-lactide using Chiral Bis-thiourea Catalysts

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ABSTRACT

Poly(lactide (PLA) is derived from biorenewable sources and is an attractive polymer due to its biocompatibility, biodegradability and the ability for it to show drastically variable physical and mechanical properties depending on its tacticity. The properties of PLA can be significantly enhanced (T_m , 230-240 °C) by forming stereocomplexes of PLA. One method of achieving this is by stereoselective polymerization of *rac*-lactide. In this study we developed an enantio-selective chiral bis-thiourea catalysts that not only shows high stereoselectivity at mild conditions, but also show faster rates of polymer formation with precise control in molecular weight. We believe this system follows a mixed mechanism of stereoselectivity with a higher inclination towards ESC mechanisms and catalyzes the reaction via an imidate mediated H-bonding mechanism.

INTRODUCTION

Poly(lactide) (PLA) which is derived from bio-renewable sources has surfaced as an attractive polymer due to its biocompatibility and biodegradability.^{1,2} PLA can be synthesized by either polycondensation of lactic acid or ring opening polymerization (ROP) of lactide (LA).¹ ROP has been reported to produce polymers with precise control over molecular weight, which leads to polymer samples with narrow molecular weight distribution compared to polycondensation reactions.³⁻⁵ Lactide due to its two stereo- centers can be found in three forms of diastereomers, D-LA (RR), L-LA (SS) and (RS) meso- lactide.^{1,6} D-LA, L-LA isomers are commercially available more commonly as racemic mixture (rac-LA). ROP of rac-LA can result in a range of polymer microstructures depending on the arrangement of chiral centers along the polymer chain (Figure 4.1).^{1,2,6} Different microstructures of PLA give rise to polymers with different degrees of tacticity. Polymers exhibiting different degrees of tacticity show different physical and mechanical properties.⁶ Atactic PLA with random distribution of chiral centers is an amorphous polymer that show no melting temperature, isotactic PLLA possesses a $T_m = 180\text{ }^{\circ}\text{C}$, heterotactic PLA ($T_m\ 130\text{ }^{\circ}\text{C}$) and an equimolar mixture of PLLA and PDLA show a significantly high melting temperature ($T_m\ 230\text{ }^{\circ}\text{C}$) due to stereo-complexation.^{1,2,6,7} High melting PLA can also be obtained by the formation of stereo-block polymers by the ROP of rac-LA as a result of the two portions of PLLA and PDLA of a single polymer sample packing together forming a crystalline polymer.^{2,7} A method of achieving stereo-block PLA is by stereoselective ring opening polymerization of rac-lactide (sROP).^{2,6} Stereo- controlled ROP can follow two main mechanisms depending on the catalysts used. In the presence of bulky catalysts sROP

occurs via chain end-controlled mechanism (CEC) where the initial monomer insertion happens in a random manner and thereafter monomer preference is dependent on the chirality of the chain end (Figure 4.2a).^{1,2,7-9} These types of reactions are fast but are limited to cold reaction temperatures in order to minimize stereo error.⁷⁻⁹ In contrast to CEC mechanism, enantio-site control (ESC) mechanism follows a more controlled pathway where a chiral catalyst selectively activates one diastereomer over the other for polymerization and doesn't require harsh temperatures to maintain stereo selectivity (Figure 4.2b).^{1,2,10,11} Although numerous studies have been reported for sROP of rac-lactide that deliver high degree of stereoselectivity, these systems still suffer from low reaction rates (days to achieve high conversions) or require harsh conditions (high to low temperatures).⁷⁻¹⁰ Thiourea organocatalysts have had great success in producing PLA with highly controlled properties due to their high monomer selectivity.^{3-5,10,12} However, only a handful of studies report the use of thiourea for sROP of rac-lactide and the reported studies suffer similar drawbacks in terms of rate and/or rigorous conditions of polymerization.^{7,10,13} Our group has successfully designed bis, tris-thiourea catalysts that have revolutionized the field of ROP of lactones by converting cyclic monomers to polymers with high control in merely minutes.^{4,12,14,15} Our motivation is to translate our knowledge of bis-thioureas to design novel chiral catalysts by introducing chirality via insertion of chiral amino acid derivatives that will enable the production of crystalline PLAs at faster rates under mild conditions.

EXPERIMENTAL SECTION

All chemicals were purchased from Acros organics and used as received unless stated otherwise. chloroform-d and acetone-d6 were purchased from Cambridge Isotope Laboratories, distilled from calcium hydride and calcium sulfate respectively and stored under N₂. Benzyl alcohol was distilled under high vacuum from calcium hydride prior to use. Dry CH₂Cl₂ was obtained from an Innovative Technology solvent purification system. 4-nitrophenyl isothiocyanate, 3,5-bis(trifluoromethyl)phenyl isothiocyanate, 3,5-dimethyl isothiocyanate was purchased from Sigma Aldrich and used as it is. L-lactide, D-lactide was obtained from Carbion and rac-lactide was obtained from Acros Organics and recrystallized from dry toluene prior to use. All experiments were conducted in a stainless- steel glovebox under N₂ unless stated otherwise. NMR experiments were performed on a Bruker Avance III 300 or 400 MHz spectrometer. Decoupled experiments were performed on a Varian 500 MHz NMR spectrometer in the department of pharmacy at the University of Rhode Island. Mass spectrometry experiments were performed using a Thermo Electron (San Jose, CA, USA) LTQ Orbitrap XL mass spectrometer affixed with electrospray ionization (ESI) interface in a positive ion mode. Collected mass spectra were averaged for at least 50 scans. Tune conditions for infusion experiments (10 µL/min flow, sample concentration 5 µg/mL in 50/50 v/v water/ methanol) were as follows: ion spray voltage, 5000 V; capillary temperature, 275 °C; sheath gas (N₂, arbitrary units), 11; auxiliary gas (N₂, arbitrary units), 2; capillary voltage, 21 V; and tube lens, 90 V; multipole 00 offset, -

4.25 V; lens 0 voltage, - 5.00; multipole 1 offset, - 8.50 V; Multipole RF Amplitude, 400 V; Ion trap's AGC target settings for Full MS was 3.0e4 and FT's 2.0e5 (with 3 and 2 averaged microscans , respectively). Prior to analysis, the instrument was calibrated for positive ions using Pierce LTQ ESI positive ion calibration solution (lot #PC197784).

Determination of thermal properties.

Melting temperatures (T_m) of PLA synthesized in this study were determined by differential scanning calorimetry (DSC) using a shimadzu differential scanning calorimeter 60 plus that has been calibrated using high purity indium at a heating rate of 5 °C/min. Polymer sample (5 mg) was first heated to 180 °C at 5 °C/min, held at this temperature for 15 h to anneal the sample. The sample was cooled to 25 °C at 5 °C/min, held for 10 min, and reheated to 250 °C at 5 °C/min. All thermal data was obtained from the second cycle.

Determination of P_m .

An NMR sample of purified polymer (1mg/ml) was prepared in chloroform-d and analyzed by ^1H - homo decoupled NMR at 50 °C. The procedure for determining P_m was followed as reported.^{16,17}

HPLC measurement.

The unreacted monomer at 50 % monomer conversion from the quenched reaction was isolated by washing the reaction with isopropanol: hexane 1: 1 and the soluble portion was extracted and concentrated under vacuum. Further purification by column

chromatography was done to purify the unreacted monomer and to remove traces of catalysts. Isolated monomer was then analyzed by chiral HPLC using hexane/isopropanol (7/3). The selectivity factor (k_D/k_L) was determined by $k_D/k_L = \{\ln[(1 - \text{conv.})(1 - ee)]\} / \{\ln[(1 - \text{conv.})(1 + ee)]\}$.¹¹

Example ROP of rac-LA at room temperature.

A 7 mL vial was charged with **1** (7.0 mg, 0.005 mmol), rac-LA (70 mg, 0.475 mmol) and CH₂Cl₂ (480 μL) and agitated to make a homogeneous solution. A stock solution of benzyl alcohol (0.5 M) was prepared using benzyl alcohol (5.4 mg, 0.05 mmol) in CH₂Cl₂ (100 μL) and 9.5 μL from the stock solution was transferred to the vial and the content shaken to mix well. A stock solution of Tris[2-(dimethylamino)ethyl]amine (Me6TREN) (0.5 M) was prepared using Me6TREN (11.5 mg, 0.05 mmol) in CH₂Cl₂ (100 μL) and 19.0 μL from the stock solution was transferred to the vial to start the reaction. The content was transferred to an NMR tube and the reaction monitored using ¹H NMR and locked using a DMSO capillary. When the desired conversion was achieved, the reaction was quenched with at least 2 equivalents of benzoic acid to the amount of Me6TREN. The reaction was then concentrated under vacuum. The dried polymer was purified using a methanol wash and subjected to high vacuum. The purified polymer was characterized using NMR, DSC and GPC.

Example ROP of rac-LA at -15 °C.

A 7 mL vial was charged with **1** (7.0 mg, 0.005 mmol), rac-LA (70 mg, 0.475 mmol) and CH₂Cl₂ (480 μL) and agitated to make a homogeneous solution. A stock solution of benzyl alcohol (0.5 M) was prepared using benzyl alcohol (5.4 mg, 0.05 mmol) in

CH₂Cl₂ (100 μ L) and 9.5 μ L from the stock solution was transferred to the vial and the content shaken to mix well. The content in the vial was allowed to equilibrate at -15 $^{\circ}$ C for 30 min. A stock solution of Tris[2- (dimethylamino)ethyl]amine (Me6TREN) (0.5 M) was prepared using Me6TREN (11.5 mg, 0.05 mmol) in CH₂Cl₂ (100 μ L) and the stock solution was also allowed to equilibrate at - 15 $^{\circ}$ C for 30 min and 19.0 μ L from the stock solution was transferred to the vial to start the reaction post equilibration. The reaction was monitored by obtaining aliquots. When the desired conversion was achieved, the reaction was quenched with at least 2 equivalents of benzoic acid to the amount of Me6TREN dissolved in cold DCM. The reaction was then concentrated under vacuum. The dried polymer was purified using a methanol wash and subjected to high vacuum. The purified polymer was characterized using NMR, DSC and GPC.

Synthesis of bis thiourea H-bond donor TU 1-3.

Intermediate product **I 1.1** was synthesized according to an adapted literature procedure.¹⁸ A 25 mL flame-dried Schlenk flask was charged with dry DCM (10 mL). N-Boc-L-tert- leucine (Boc-L-Leu) (100 mg, 0.43 mmol), N,N,N',N'-Tetramethyl-O- (1H-benzotriazol-1- yl)uronium hexafluorophosphate (HBTU) (163.1 mg, 0.43 mmol), and N,N- Diisopropylethylamine (DIPEA) (0.23 mL, 1.29 mmol) was added to the flask and the reaction was stirred under nitrogen. N-Boc-1,3-propanediamine (Boc-DAP) was then added (0.082 mL, 0.47 mmol) to the flask. The reaction was allowed to stir under

nitrogen overnight. Afterwards, the reaction mixture was concentrated under vacuum. The residue was purified with column chromatography on silica gel using ethyl acetate / hexanes (1:1).

A round bottom flask was charged with 4 N HCl in 1,4-dioxane (1.40 mL, 5.59 mmol of HCl), followed by the addition of **11.1** (166 mg, 0.43 mmol). The content was stirred for 2 hours. Next, the volatiles were removed via vacuum transfer. The residue was subjected to high vacuum.

A flame-dried Schlenk flask was charged with dry THF, then **11.2** (112 mg, 0.43 mmol) was added followed by Triethylamine (TEA) (0.35 mL, 2.6 mmol). The mixture was stirred under nitrogen for about 10 minutes and Isothiocyanate (ITC) (0.16 mL, 0.86 mmol) was added dropwise. The reaction mixture was allowed to react at ambient temperature under nitrogen overnight. The solvent was removed using a rotavap and the residue was purified with column chromatography on silica gel using ethyl acetate / hexanes (1:1) for **TU 1** and **TU 3** and 100 % ethyl acetate for **TU 2**. **TU 1**, white powder. yield: 60 %. **TU 2**, a yellow powder. Yield: 55%. **TU 3** a white powder. Yield 50%. NMR spectra given below. HRMS: **TU 1** calc. (C₂₇H₂₇F₁₂N₅OS₂+H)⁺= 730.15;

found $m/z = 730.15$. **TU 2** calc. $(C_{23}H_{29}N_7O_5S_2+H)^+ = 547.65$; found $m/z = 547.16$.

TU 3 calc. $(C_{27}H_{39}N_5OS_2 + H)^+ = 513.76$; found $m/z = 513.25$.

Synthesis of bis thiourea H-bond donor TU 4.

A flame-dried Schlenk flask was charged with dry DCM, then 1,3-Diaminopropane (100 mg, 1.34 mmol), was added to the flask. The mixture was stirred under nitrogen and ITC (0.15 mL, 1.34 mmol) was added dropwise. The reaction mixture was allowed to react at ambient temperature under nitrogen overnight. The solvent was removed using a rotavap and the residue was purified with column chromatography on silica gel using DCM/Methanol (9:1).

A 25 mL flame-dried Schlenk flask was charged with dry THF (20 mL). N-Boc-L-tert-leucine (Boc-L-Leu) (309 mg, 1.34 mmol), Benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate (PyBOP) (572.3 mg, 1.10 mmol), and N,N-Diisopropylethylamine (DIPEA) (0.70 mL, 4.02 mmol) was added to the flask and the reaction was stirred under nitrogen. **14.1** was then added (317.7 mg, 1.34 mmol) to the flask. The reaction was allowed to stir under nitrogen overnight. Afterwards, the

reaction mixture was concentrated under vacuum. The residue was used as it is for the next step.

A round bottom flask was charged with 4 N HCl in 1,4-dioxane (2.10 mL, 8.71 mmol of HCl), followed by the addition of **I 4.2** (603.4 mg, 1.34 mmol). The content was stirred for 2 hours. Next, the volatiles were removed via vacuum transfer. The residue was subjected to high vacuum.

A flame-dried Schlenk flask was charged with dry THF, then **I 4.3** (518.5 mg, 1.34 mmol) was added followed by TEA (0.6 mL, 4.02 mmol). The mixture was stirred under nitrogen for about 10 minutes and ITC (0.5 mL, 2.71 mmol) was added dropwise. The reaction mixture was allowed to react at ambient temperature under nitrogen overnight. The solvent was removed using a rotavap and the residue was purified with column chromatography on silica gel using ethyl acetate / hexanes (1:1). **TU 4**, yellow white powder. yield: 60 %. NMR spectra given below. HRMS: calc. (C₂₇H₃₃F₆N₅OS₂+H)⁺= 622.20; found m/z = 622.20.

Synthesis of bis thiourea H-bond donor TU 5.

A flame-dried Schlenk flask was charged with dry DCM, then 1,3-Diaminopropane (100 mg, 1.34 mmol), was added to the flask. The mixture was stirred under nitrogen and ITC (0.25 mL, 1.34 mmol) was added dropwise. The reaction mixture was allowed to react at ambient temperature under nitrogen overnight. **5.1** was precipitated at 0°C then filtered and washed with cold DCM and dried under vacuum.

A 25 mL flame-dried Schlenk flask was charged with dry THF (20 mL). *N*-Boc-L-tert-leucine (Boc-L-Leu) (309 mg, 1.34 mmol), *N,N,N',N'*-Tetramethyl-*O*-(1*H*-benzotriazol-1-yl)uronium hexafluorophosphate (HBTU) (417.2 mg, 1.10 mmol), and *N,N*-Diisopropylethylamine (DIPEA) (0.70 mL, 4.02 mmol) was added to the flask and the reaction was stirred under nitrogen. **5.1** was then added (462.7 mg, 1.34 mmol) to the flask. The reaction was allowed to stir under nitrogen overnight. Afterwards, the reaction mixture was concentrated under vacuum. The residue purified with column chromatography on silica gel using ethyl acetate/hexane (3:7).

A round bottom flask was charged with 4 N HCl in 1,4-dioxane (2.10 mL, 8.71 mmol of HCl), followed by the addition of **15.2** (748.5 mg, 1.34 mmol). The content was stirred for 2 hours. Next, the volatiles were removed via vacuum transfer. The residue was subjected to high vacuum.

A flame-dried Schlenk flask was charged with dry THF, then **15.3** (663.2 mg, 1.34 mmol) was added followed by TEA (0.6 mL, 4.02 mmol). The mixture was stirred under nitrogen for about 10 minutes and ITC (0.5 mL, 2.71 mmol) was added dropwise. The reaction mixture was allowed to react at ambient temperature under nitrogen overnight. The TEA salt was filtered and the solvent was removed using a rotavap and the residue was purified with column chromatography on silica gel using ethyl acetate / hexanes (1:1). **TU 5**, white powder. yield: 60 %. NMR spectra given below. HRMS: calc. (C₂₇H₃₃F₆N₅OS₂+H)⁺= 622.21; found *m/z* = 622.21

Synthesis of bis thiourea H-bond donor TU 6.

Intermediate product **I 6.1** was synthesized according to an adapted literature procedure. A 25 mL flame-dried Schlenk flask was charged with dry DCM (10 mL). *N*-Boc-L-tert-leucine (Boc-L-Leu) (100 mg, 0.43 mmol), *N,N,N',N'*-Tetramethyl-*O*-(1*H*-benzotriazol-1-yl)uronium hexafluorophosphate (HBTU) (163.1 mg, 0.43 mmol), and *N,N*-Diisopropylethylamine (DIPEA) (0.23 mL, 1.29 mmol) was added to the flask and the reaction was stirred under nitrogen. *N*-Boc-1,2-diaminoethane (Boc-DAE) was then added (75 mg, 0.47 mmol) to the flask. The reaction was allowed to stir under nitrogen overnight. Afterwards, the reaction mixture was concentrated under vacuum. The product was deprotected as it is.

A round bottom flask was charged with 4 N HCl in 1,4-dioxane (1.39 mL, 5.59 mmol of HCl), followed by the addition of **I 6.1** (160.5 mg, 0.43 mmol). The content was stirred for 2 hours. Next, the volatiles were removed via vacuum transfer. The residue was subjected to high vacuum.

A round bottom flask was charged with 4 N HCl in 1,4-dioxane (0.8 mL, 3.05 mmol of HCl), followed by the addition of **I 7.1** (123.0 mg, 0.43 mmol). The content was stirred for 2 hours. Next, the volatiles were removed via vacuum transfer. The residue was subjected to high vacuum.

A flame-dried Schlenk flask was charged with dry THF, then **I 7.2** (95.5 mg, 0.43 mmol) was added followed by TEA (0.18 mL, 1.29 mmol). The mixture was stirred under nitrogen for about 10 minutes and ITC (0.08 mL, 0.43 mmol) was added dropwise. The reaction mixture was allowed to react at ambient temperature under nitrogen overnight. The solvent was removed using a rotavap and the residue was purified using column chromatography using ethyl acetate / hexanes (1:2) as an eluant for **TU 7**. **TU 6**, yellow white powder. yield: 57 %. NMR spectra given below. HRMS: calc. ($\text{C}_{19}\text{H}_{25}\text{F}_6\text{N}_3\text{OS}+\text{H}$) $\pm$ 458.16; found m/z = 458.16.

Synthesis of bis thiourea H-bond donor TU 9.

Intermediate product **I 9.1** was synthesized according to an adapted literature procedure. A 25 mL flame-dried Schlenk flask was charged with dry DCM (10 mL). Boc-L- α -phenylglycine (108 mg, 0.43 mmol), *N,N,N',N'*-Tetramethyl-*O*-(1*H*-benzotriazol-1-yl)uronium hexafluorophosphate (HBTU) (163.1 mg, 0.43 mmol), and *N,N*-

Diisopropylethylamine (DIPEA) (0.23 mL, 1.29 mmol) was added to the flask and the reaction was stirred under nitrogen. *N*-Boc-1,3-propanediamine (Boc-DAP) was then added (0.082 mL, 0.47 mmol) to the flask. The reaction was allowed to stir under nitrogen overnight. Afterwards, the reaction mixture was concentrated under vacuum. The residue was purified with column chromatography on silica gel using ethyl acetate.

A round bottom flask was charged with 4 N HCl in 1,4-dioxane (1.40 mL, 5.59 mmol of HCl), followed by the addition of **19.2** (175 mg, 0.43 mmol). The content was stirred for 2 hours. Next, the volatiles were removed via vacuum transfer. The residue was subjected to high vacuum.

A flame-dried Schlenk flask was charged with dry THF, then **19.2** (89 mg, 0.43 mmol) was added followed by TEA (0.35 mL, 2.6 mmol). The mixture was stirred under nitrogen for about 10 minutes and Isothiocyanate (ITC) (0.16 mL, 0.86 mmol) was added dropwise. The reaction mixture was allowed to react at ambient temperature under nitrogen overnight. The solvent was removed using a rotavap and the residue was purified with column chromatography on silica gel using ethyl acetate / hexanes (1:1).

TU 9, white powder. yield: 41 %. NMR spectra given below. HRMS: calc. ($C_{29}H_{23}F_{12}N_5OS_2+H$) $^{+}= 750.12$; found $m/z = 749.12$.

Synthesis of bis thiourea H-bond donor TU 10.

Intermediate product **I 10.1** was synthesized according to an adapted literature procedure. A 25 mL flame-dried Schlenk flask was charged with dry DCM (10 mL). **Boc-l-proline** (108 mg, 0.43 mmol), *N,N,N',N'*-Tetramethyl-*O*-(1*H*-benzotriazol-1-yl)uronium hexafluorophosphate (HBTU) (163.1 mg, 0.43 mmol), and *N,N*-Diisopropylethylamine (DIPEA) (0.23 mL, 1.29 mmol) was added to the flask and the reaction was stirred under nitrogen. *N*-Boc-1,3-propanediamine (Boc-DAP) was then added (0.082 mL, 0.47 mmol) to the flask. The reaction was allowed to stir under nitrogen overnight. Afterwards, the reaction mixture was washed with water (3x 20mL), dried then concentrated under vacuum.

A round bottom flask was charged with 4 N HCl in 1,4-dioxane (1.40 mL, 5.59 mmol of HCl), followed by the addition of **I 10.2** (175 mg, 0.43 mmol). The content was stirred for 2 hours. Next, the volatiles were removed via vacuum transfer. The residue was subjected to high vacuum.

A flame-dried Schlenk flask was charged with dry THF, then **I 9.2** (89 mg, 0.43 mmol) was added followed by TEA (0.35 mL, 2.6 mmol). The mixture was stirred under nitrogen for about 10 minutes and ITC (0.16 mL, 0.86 mmol) was added dropwise. The reaction mixture was allowed to react at ambient temperature under nitrogen overnight. The TEA salt was filtered and the solvent was removed using a rotavap and the residue was purified with column chromatography on silica gel using ethyl acetate / hexanes (1:1). **TU 10**, white powder. yield: 45.8 %. NMR spectra given below. HRMS: calc. (C₂₈H₂₂F₁₂N₅OS₂+H)⁺= 737.11; found *m/z* = 737.11.

RESULTS AND DISCUSSIONS

A leucine derivatized chiral bis thiourea, **TU1**, (Figure 4.3) was studied for the stereo-controlled ring-opening polymerization (sROP) of *rac*-LA. To investigate the polymerization characteristics of **TU1** as stereoselective catalysts for ROP, Me6TREN (0.0095 mmol) was dissolved in dichloromethane (DCM) and added to a solution of DCM containing **TU1** (0.0095 mmol), *rac*-LA (0.475 mmol, 0.95 M) and benzyl alcohol (BnOH) (0.0048 mmol) at room temperature in a glovebox. Under these conditions, 90% of the monomer was converted in less than 5 h producing crystalline poly(lactide) (PLA), with predictable number average molar mass $M_n = 17.5$ kg/mol consistent with the monomer to initiator ratio $[M]_0/[I]_0$ and narrow molecular weight distribution, $M_w/M_n = 1.05$; (Table 4.1, entry 1). This system produces polymers with high chain-end fidelity confirmed by Gel permeation chromatography (GPC) (Figure 4.6). The polymerization exhibits “living” character showing linear increment of molecular weight with conversion (Figure 4.7) and possess the ability to produce polymers with predictable molecular weights and narrow $M_w/M_n \leq 1.05$ upto $[M]_0/[I]_0 = 200$ (Table 4.1). Analysis of a sample prepared under similar conditions described above by MALDI-TOF mass spectrometry showed a single series of ions separated by m/z 144, revealing no to minimal transesterification of the polymer backbone (Figure 4.8) suggesting high selectivity of the catalyst towards the monomer vs the polymer.

Since the main goal of this work was to establish a stereo-selective catalyst for ROP of *rac*-LA, the microstructure of the PLA produced using *rac*-LA with our catalyst system was investigated. This was determined by ^1H homonuclear decoupled NMR spectroscopy conducted at 50°C by analyzing the methine region of PLA and calculating

the probability of forming meso dyads (P_m); $P_{m(ESC)} = 0.87$ using ESC statistical model and $P_{m(CEC)} = 0.80$ using CEC statistical model using non-Bernoullian statistics and Bernoullian statistics as reported elsewhere (Figures 4.9).^{1,16,17} Analysis of the polymer produced using differential scanning calorimetry (DSC) ($T_m = 168\text{ }^{\circ}\text{C}$) (Figures 4.10) indicate characteristics of an isotactic crystalline polymer. Associating the information obtained from DSC and the calculated P_m values the mechanism of stereoselectivity with our catalyst system demonstrates a higher inclination towards an ESC mechanism rather than a CEC mechanism. This deduction was reached due to the high T_m of our polymer (Table 4.1, entry 1) usually shown by PLA with $P_m \geq 0.81$.^{2,7,19} The stereoselectivity factor ($s = k_D/k_L = 1.8$) of the polymerization in the presence of **TU1**/Me₆TREN, was determined by analyzing the unreacted monomer at 47% monomer conversion using chiral HPLC (figure 4.12). The analysis revealed that in the presence of **TU1**, D-LA was favored, as displayed by the reduction of the signal associated with D-LA.

A kinetic experiment was then conducted to confirm this observation by polymerizing D-LA, L-LA and *rac*-LA separately with **TU1**/Me₆TREN. The first order plot for the polymerization of D-LA, L-LA and *rac*-LA (figure 4.4a) show preferential rate acceleration of the polymerization of D-LA vs L-LA and *rac*-LA, consistent with the chiral HPLC analysis. However, the selectivity factor obtained using corresponding k_{obs} from the first order plots ($s = k_{obs\text{ D-LA}}/k_{obs\text{ L-LA}} = 3.4$) is higher than what was obtained using chiral HPLC. Interestingly, the first order plot for the ROP of *rac*-LA exhibits two discrete slopes (figure 4.4a) ($k_{obs1} = 0.009$, $k_{obs2} = 0.006$), selectivity factor calculated using these k_{obs} values ($s = k_{obs1}/k_{obs2} = 1.5$) is more similar to that obtained from chiral

HPLC analysis, indicating that in the case of *rac*-LA that comprises of 1:1 ratio of D-LA and L-LA, when **TU1**/Me6TREN cocatalyst system is used initially the more selective monomer (D-LA) is consumed, but when the D-LA concentration is reduced in the course of the polymerization there is a strong competition between D-LA and L-LA to bind to the catalyst and hence we observe a decline in selectivity.

To determine the effect of H-bond donor : H-bond acceptor ratio in stereoselective ROP, *rac*-LA was polymerized with **TU1**/Me6TREN, where the ratio between thiourea and base was changed from 1:1 to 2:1 and 3:1 respectively, no significant change was seen in the former instance (Table 4.1, entry 2). However, a slight enhancement in T_m and P_m and a decline in rate of polymerization was observed in the latter case when the **TU1**/Me6TREN ratio was changed to 3:1 (Table 4.1, entry 3) indicating 1:1 ratio of thiourea and base to be ideal with respect to maintaining stereoselectivity and enhancing rates. Despite these observations it is worth to note that chiral bis-thiourea **TU1** reported here in, show significantly faster rates compared to other organocatalysts reported thus far that show similar stereoselectivity and follow ESC controlled sROP at room temperature.^{10,13}

With the motivation of further optimizing the stereoselectivity and enhancing the rate of reaction, a variety of bases from weak to strong in combination with **TU1** were screened at room temperature (Table 4.1) and at cold temperatures (-15°C) (Table 4.2). When the polymerizations were conducted at room temperature with **TU1** and t-TACN or PMDTA, an enhanced rate was seen in the presence of t-TACN (Table 4.11 , entry 6), and with PMDTA the reaction slowed down than in the presence of Me6TREN and reached equilibrium at 75% monomer conversion (Table 4.1 , entry 7). However, in both

cases there was no observed enhancement in stereoselectivity, as indicated by the Pm values and the Tm of the produced PLA.

Conducting reactions at cold temperatures (-75°C) is another technique used to enhance selectivity in sROP. We decided to make use of this approach but at much milder conditions compared to temperatures reported thus far. Since our catalyst system already showed a moderately good stereoselectivity at room temperature, we analyzed our polymerization system at -15°C. In the presence of Me6TREN and t-TACN (relatively weak bases) the polymerization rates diminished, but still could be considered faster than other reported organocatalysts that follow ESC mechanism at room temperature,^{10,13} but the stereoselectivity enhanced significantly (Table 4.2, entry 1,2) compared to that at room temperature. When these reactions were performed with **TU1** in the presence of stronger bases like BEMP and MTBD, the polymerization reached 90 % conversion in 90 min and 60 min respectively, producing highly isotactic polymers with good control over M_n and M_w/M_n (Table 4.2, entry 3,4). Previous studies report BEMP by itself as a successful catalyst for sROP of *rac*-LA to produce highly isotactic PLA within few minutes. However, the reports indicate limitations with respect to requirement of harsh conditions of reaction temperatures (-75°C) to achieve high stereoselectivity.⁸ This was also seen in our work, when the polymerization was conducted with BEMP in the absence of **TU1** at -15°C 90 % monomer conversion was achieved in 5 min, but the resulting polymer showed no melting peak, indicating the formation of atactic amorphous PLA. This observation indicated that the presence of **TU1** is crucial in producing isotactic polymer at less harsh conditions of -15°C or room temperature. In contrast to weak bases in the presence of strong bases, we believe the

polymerization proceeds preferentially via CEC mechanism. This was depicted by the first order plots for the polymerization D-LA and L-LA with **TU1**/BEMP (Figure 4.5) where no significant difference between the k_{obs} values were observed like in the case of weak bases.

Taking the observation thus far in to consideration Me6TREN was used as the base for the rest of the study. To comprehend the relationship between the electronics of chiral bis thioureas and its activity in sROP, a variety of thioureas (Figure 4.3) were studied using Me6TREN as a base at room temperature. When the polymerization was conducted with achiral thiourea **TU8**/Me6TREN, atactic PLA was produced (suggested by DSC analysis) where no melting peak was observed, and the catalyst showed no preference towards L-LA or D-LA (Figure 4.4b), indicating that the chiral moiety is an essential component for its activity as a stereoselective catalyst. Catalyst **TU9** and **TU10** was synthesized bearing slightly different chiral moieties. In the presence of **TU9** *rac*-LA was rapidly converted to polymer, but the transformation lacks stereoselectivity. **TU10** carrying a proline group produced highly isotactic PLA, However, the transformation was much slower than with **TU1** under similar reaction conditions. When **TU2** with a strong electron withdrawing (EW) group on para position was studied (Table 4.1, entry 10), the reaction reached 90% monomer conversion at a slightly slower rate than **TU1** and exhibited less stereo control. Polymerization conducted with **TU3** where the EW CF₃ groups were replaced by electron donating (ED) CH₃ groups, there was no observed conversion in 24 h, this phenomenon is likely a consequence of the diminished polarity of thiourea making it a poor H-bond donor.^{15,20} Making use of these observations we then designed catalyst **TU4** with EW groups closer to the chiral center

and ED groups away from the chiral center with the intention of forcing the monomer to selectively bind to the thiourea moiety close to the sterically hindered chiral center. In the presence of **TU4** 23 % of monomer was converted to polymer in 14 h and the reaction reached equilibrium thereafter. In the presence of **TU5** an analogous structure to **TU4** the polymerization reaches 42 % conversion in 18 h and no further conversion was observed. We believe the reason for low conversion with **TU4** & **TU5** is lack of internal activation of the thiourea moiety making it function more like a mono thiourea rather than a bis thiourea suggested by NMR binding studies (Figure 4.9). The difference in conversion with **TU4** vs **TU5** could be a consequence of position of the bulky group on the catalyst. To confirm this observation chiral mono thiourea **TU7** was synthesized and studied with Me6TREN as a base, the polymerization reaches equilibrium at 20% monomer conversion in 24 h corroborating our observation.

With the aim of further enhancing the rate by manipulating the thiourea catalyst and taking advantage of a recent discovery by our group where the 5 atom linkers between thiourea moieties showed the fastest rates in bis-thiourea systems,¹⁵ we synthesized **TU6**, a leucine functionalized chiral thiourea with only 5 atoms between the thiourea moieties. As anticipated in the presence of **TU6**/Me6TREN, fastest rates were observed (Table 4.1, entry 13), yet the polymerization lack stereo control making it unfit to function as a stereoselective catalyst for this transformation.

Understanding the mode of monomer activation is critical in comprehending the mechanism of stereoselectivity. Thiourea catalyst in the presence of weak bases are known to catalyze ROP of LA via neutral H-bonding mechanism, where LA was activated by the internally activated bis-thiourea, and the chain end by the base (scheme

8.1).¹² Our group revealed that even in the presence of weak bases ROP of LA can proceed through an imidate H-bonding mechanism depending on the acidity of the thiourea.¹⁵ Therefore, grasping the mechanism of catalyst activation is crucial to explain the rate enhancement by some thioureas, and why in the presence of others no enhancement of rates or stereoselectivity was observed. Replicating an NMR experiment to determine imidate or neutral H-bonding mechanism, thioureas **TU1-TU5**, with and without base was compared.³ **TU1** and **TU2**, both show convergence of the aromatic and NH peaks (Figures 4.13) suggesting an imidate nature.^{3,20} Lack of polymerization in the presence of **TU3**, corroborates with the NMR experiment, where no to minimal peak shifts were observed in the downfield region, suggesting minimum interaction between the base and **TU3**. In the presence of Me6TREN, **TU4** and **TU5**, exhibit broadening of NH peaks associated with the thiourea moiety and show a slight downfield shift of the ortho protons indicating neutral H-bonding mechanism.²⁰ Accordingly, our observations revealed that bis-thiourea chiral catalyst that follow imidate mediated H-bonding ROP show enhanced rates and better stereo-control than the slower catalysts that follow neutral H-bonding mechanism. To further understand the mechanism of stereoselectivity, ratio between the peak intensities of the methine region of the ¹H homonuclear decoupled NMR was determined. Previous reports indicate that if the polymerization followed CEC mechanism relative tetrad intensities would be [mrm] : [mrm] : [rmm] 1:1:1 and if it followed ESC [rmr] : [mmr] : [rmm] : [mrm] 1:1:1:2.² However, after close analysis of the polymer produced in the presence of **TU1**/Me6TREN (Table 4.1, entry 1) at room temperature, the relative tetrad intensities (Figure 4.8) do not follow either one of the above patterns, suggesting both

mechanisms prevail in the polymerization under the conditions reported here in. However, a higher inclination towards ESC mechanism is seen when we associate the P_m values with the T_m obtained for PLA and by considering the kinetic resolution seen when D-LA and L- LA was polymerized using **TU1**. Apart from the reduced stereoselectivity of the transformation, a major contributor of stereo-error during the course of polymerization is epimerization of rac-LA that can occur in the presence of bases.² Close monitoring of the ROP of rac-LA at room temperature at 90% monomer conversion revealed no to minimum epimerization, suggesting negligible contribution towards depressing of the P_m .

CONCLUSION

In summary, the bis-chiral thiourea bearing a tert-butyl leucine derivative (**TU1**) has been shown to be a highly effective enantio-selective catalysts that promotes fast stereo-selective ROP of *rac*-LA at room temperature in the presence of Me6TREN and at cold temperatures (-15 °C) with BEMP. The co-catalysts system not only shows high enantio-selectivity but also exhibits living behavior and produces polymers with precise control of molecular weight and narrow molecular weight distribution. Even though the catalysts system doesn't produce perfectly isotactic PLA, to our knowledge the system reported herein show faster rates and comparable stereoselectivity at milder conditions compared to other organo-catalysts that have been reported thus far. We also believe there is potential for further manipulation of the catalysts design to improve the stereo-selectivity of these bis- chiral thiourea catalysts systems and build a library of chiral catalysts for the polymerization of other cyclic monomers bearing chiral functionality.

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entry	TU/base	[LA]/[BnOH]/[cat]/[base]	Time (min)	Conv. %	M _n (g/mol)	M _w /M _n	P _m		T _m
							ESC	CEC	
1	TU1/Me ₆ TREN	100/1/2/2	281	90	17,500	1.05	0.87	0.80	168
2	TU1/Me ₆ TREN	100/1/2/1	354	90	17,600	1.05	0.87	0.81	168
3	TU1/Me ₆ TREN	100/1/3/1	200	90	18,500	1.05	0.89	0.83	169
4	TU1/Me ₆ TREN	100/2/2/2	90	91	9,500	1.04	0.86	0.80	161
5	TU1/Me ₆ TREN	100/0.5/2/2	605	90	3,8000	1.04	0.88	0.81	159
6	TU1/t-TACN	100/1/2/2	165	90	19,000	1.04	0.85	0.77	156
7	TU1/PMDTA	100/1/2/2	1020	75	15,000	1.05	0.84	0.76	151
8	TU9/ Me ₆ TREN	100/1/2/2	120	90	16,800	1.04	0.82	0.73	140
9	TU10/ Me ₆ TREN	100/1/2/2	1140	84			0.88	0.80	
10	TU2/Me ₆ TREN	100/1/2/2	315	90	17,700	1.06	0.86	0.78	151
11	TU4/Me ₆ TREN	100/1/2/2	840	23	6,000	1.34	0.85	0.77	-
12	TU5/Me ₆ TREN	100/1/2/2	960	51	14,600	1.03	0.88	0.70	141
13	TU6/Me ₆ TREN	100/1/2/2	175	90	19,700	1.06	0.83	0.74	132

Table 4.1. Polymerization of *rac*-LA at room temperature. Reaction conditions: *rac*-LA (0.475 mmol, 0.95M), benzyl alcohol (2 mol%), DCM. monomer conversion was determined via ¹H NMR. *M_n* and *M_w/M_n* were determined by GPC (CH₂Cl₂) versus polystyrene standards. P_m determined by ¹H homonuclear decoupled NMR at 50 °C. T_m determined by DSC.

entry	TU/base	[LA]/[BnOH]/[cat] /[base]	Time (min)	Conv. %	M _n (g/mol)	M _w /M _n	P _m		T _m
							ESC	CEC	
1	TU1/Me ₆ TREN	100/1/2/2	480	90	17,700	1.06	0.92	0.87	184
2	TU1/t-TACN	100/1/2/2	240	89	17,600	1.05	0.92	0.88	183
3	TU1/BEMP	100/1/2/2	90	90	16,700	1.07	0.91	0.86	186
4	TU1/MTBD	100/1/2/2	60	91	16,600	1.08	0.90	0.86	184
5 ^e	BEMP	100/1/2/2	5	90	17,200	1.06	0.79	0.74	-

Table 4.2. Polymerization of *rac*-LA at -15° C. Reaction conditions: *rac*-LA (0.475 mmol, 0.95M), benzyl alcohol (2 mol%), DCM. monomer conversion was determined via ¹H NMR. *M_n* and *M_w/M_n* were determined by GPC (CH₂Cl₂) versus polystyrene standards. P_m determined by ¹H homonuclear decoupled NMR at 50 °C. T_m determined by DSC.

Scheme 4.1. a. Neutral H-bonding mediated ROP of LA. b. Imidate H-bonding mediated ROP of LA

Figure 4.1. Microstructures of PLA formed by the polymerization of *rac*-LA

a. Chain end-control mechanism

b. Enantio-site control mechanism

Figure 4.2. Mechanisms of stereocontrolled ROP

Figure 4.3. H-bond donors and acceptors used in this study.

Figure 4.4. a. First order plots for the polymerization of D-LA, rac-LA and L-LA respectively with **TU1**/ Me6TREN. b. First order plots for the polymerization of L-LA, D- LA and rac-LA respectively with **TU8**/ Me6TREN.

Figure 4.5. First order plots for the polymerization of D-LA, *rac*-LA and L-LA respectively with **TU1**/ BEMP.

Figure 4.6. RI and UV GPC traces of the PLA initiated by 1-pyrenebutanol. Conditions: rac-LA (0.95 M, 0.475 mmol), 1-pyrenebutanol (2mol%, 0.02mmol), TU1 (2mol%, 0.05 mmol), Me6TREN (5 mol%, 0.05 mmol) in CH_2Cl_2 .

Figure 4.7. M_n (blue) and M_w/M_n (orange) catalyzed ring-opening polymerization of rac-LA. Conditions: rac-LA (0.95 M, 0.95 mmol), benzyl alcohol (1mol%, 0.0095 mmol), TU1 (2mol%, 0.019 mmol), Me6TREN (2mol%, 0.019 mmol) in CH_2Cl_2 .

Figure 4.8. MALDI-TOF of the PLA resulting from TU1/Me6TREN cocatalyzed ROP of rac-LA. The peaks represent the whole repeat units $m/z = (\text{Na}^+ + \text{benzyl alcohol} + n \cdot \text{LA})$.

Figure 4.9. Homonuclear decoupled ^1H NMR spectrum (400 MHz, CDCl_3) of the methine region of PLA obtained from **TU1** at 50 °C NMR (Table 4.1, entry 1)

Figure 4.10. DSC thermograms of PLA obtained at a heating and cooling rate of 5°C/min (2nd scan after annealing sample at 170 °C for 15 h), PLA produced by ROP at r.t (Table 4.1, entry 1).

Figure 4.11. DSC thermograms of PLA obtained at a heating and cooling rate of 5°C/min (2nd scan after annealing sample at 170 °C for 15 h), PLA produced by ROP at -15°C (Table 4.2, entry 1).

Figure 4.12. HPLC chromatograms of (run a) L-LA, (run b) D-LA (run c), rac-LA as a reference (run d) and the unreacted monomer at 47 % monomer conversion determined using a UV (254 nm) detector (Flow rate, 0.5 mL min⁻¹; eluent, hexane/isopropanol = 7/3; temperature; 25 °C.).

Figure 4.13. Downfield portion of ¹H NMR spectra (400 MHz, ppm) of **TU1-TU4** with and without Me6TREN in CH₂Cl₂ using a DMSO-*d*₆ capillary.

Figure 4.14. (Upper) ¹H NMR (CDCl₃, 400 MHz, ppm), (Lower) ¹³C NMR (CDCl₃ 100 MHz, ppm) spectrum of **TU1**

Figure 4.15. (Upper) ¹H NMR (DMSO-*d*₆, 400 MHz, ppm), (Lower) ¹³C NMR (DMSO-*d*₆ 100 MHz, ppm) spectrum of **TU2**.

Figure 4.16. (Upper) ¹H NMR (DMSO-*d*₆, 400 MHz, ppm), (Lower) ¹³C NMR (DMSO-*d*₆ 100 MHz, ppm) spectrum of **TU3**.

Figure 4.17. (Upper) ¹H NMR (CDCl₃, 400 MHz, ppm), (Lower) ¹³C NMR (CDCl₃ 100 MHz, ppm) spectrum of **TU4**

Figure 4.18. (Upper) ^1H NMR (CDCl₃, 400 MHz, ppm), (Lower) ^{13}C NMR (CDCl₃ 100 MHz, ppm) spectrum of **TU5**

Figure 4.19. (Upper) ¹H NMR (CDCl₃, 400 MHz, ppm), (Lower) ¹³C NMR (CDCl₃ 100 MHz, ppm) spectrum of **TU 6**.

Figure 4.20. (Upper) ¹H NMR (CDCl₃, 400 MHz, ppm), (Lower) ¹³C NMR (CDCl₃ 100 MHz, ppm) spectrum of **TU 7**.

Figure 4.21. (Upper) ^1H NMR (CDCl_3 , 400 MHz, ppm), (Lower) ^{13}C NMR (CDCl_3 100 MHz, ppm) spectrum of **TU 9**

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Ring-Opening Polymerization of a series of monomers with a cooperative salty cocktail of H-bonding co-catalysts.

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ABSTRACT

Here in is an illustration the use of a cooperative catalyst system - magnesium salts in the presence of a hyperactive imidate catalyst to polymerize monomers. This is shown to be a good approach in the polymerization of monomers that does not open up in the presence of some of the most active imidate H-bonding catalyst systems. This study shows the usage of this mixture of catalysts in performing controlled ROP of 7 membered cyclic lactones such as ϵ -caprolactone, 6-methyl caprolactone and ($\pm$) menthide. A series of block copolymers were synthesized with the use of a catalyst switch and temperature switch approach to design new polymer architecture shown in this study.

INTRODUCTION

The extensive use of non-biodegradable polymeric materials has been a growing threat to the environment.^{1,2,3} Attention has been greatly focused by many research groups on monomers derived from sustainable sources in the development of biodegradable polyesters, which would have less harmful impact on nature.^{4,5} Precisely tailoring polymers with complex architecture and similar functionality to macromolecules found in nature has been a daunting challenge for scientists around the world. Ring-opening polymerization (ROP) of cyclic lactone monomers is one approach towards making well defined, structurally complex, and biodegradable macromolecules.^{6–13} Lately, great advances in catalyst design to obtain efficient transformations, and monomer designs for the development of degradable and sustainable polymers are constantly being reported.^{7,11,14–17} Metal catalyst systems such as Mg(II), Sn(IV), Zn(II) and Al(III) containing compounds have been widely used in ROP of cyclic lactones.^{12,18–22} Such catalysts have shown favorable rates of monomer conversion (at ambient and high temperatures) via coordination insertion mechanism.^{12,18–20} Albeit, compromising polymer weight control and polydispersity indices (PDI), due to lack of solubility and extremely high post polymerization transesterification.^{7,9,11} Utilization of organocatalysts to overcome such drawbacks are a suitable approach,^{7,9,11} as these systems have evolved to become equally effective and efficient to conventional metal catalysts.^{17,23,24} Single molecular catalysis with catalysts such as 1,5,7-triazabicyclo[4.4.0]dec-5ene (TBD); and dual molecular catalysis using thio(urea) and base cocatalyst systems are some of the more common organocatalyst systems

studied.^{7,11,16,23–28} ROP of lactones in the presence of such H-bonding catalysts show two possible mechanisms: The H-bonding imidate, and conventional H-bonding path.^{8,23,25} The mechanism governing the catalysis of ROP is dependent upon the pK_a of the thio(urea) and base used, and solvent the reaction is carried out in.^{8,23,25} The hyperactive H-bonding imidate mechanism is active in the presence of highly acidic thio(urea) and strong bases. Which has been proven to be effective for ROP lactones which were previously inaccessible.

Studies performed for the ROP of substituted monomers such as menthide and 6-methyl caprolactone (6-MeCL) with thio(urea)/base cocatalyst systems have shown to be ineffective. However, recent studies introduced by Dove and Coworkers have introduced magnesium salts as Lewis acids in the presence of guanidine, amidine bases, and NHCs to perform ROP in solvent systems.²⁹ The order of activity during ROP of all lactones was MgI₂>MgBr₂>MgCl₂.²⁹ The combination of the bifunctional imidate cocatalyst with a magnesium salt seems to be a sufficient combination of active species to catalyze ROP. Similar studies have been conducted to show the use of simple Lewis acids to perform the ROP of cyclic lactones.^{30,31} Recently many groups have shown a great deal of interest in the usage of this cooperative mix of catalyst systems to perform ROP of cyclic lactones.^{31,32} Inspired by such studies, our focus shifted towards the use of readily available and easily accessible metal catalyst systems in the presence of the urea/base systems which we believe would equally active to perform ROP of monomers. A comprehensive study of the performance of dual-organic catalysts for the ROP in solvent and solvent-free conditions in a range of temperatures has been carried out. We

believe this study could be beneficial for the synthesis of a variety sustainable polymers for use in numerous applications in the future.

EXPERIMENTAL SECTION

General Considerations. All manipulations were performed in an MBRAUN stainless steel glovebox equipped with a gas purification system or using Schlenk technique under nitrogen atmosphere. All chemicals were purchased from Fischer Scientific and used as received unless stated otherwise. Tetrahydrofuran and dichloromethane were dried on an Innovative Technologies solvent purification system with alumina columns and nitrogen working gas. Benzene-*d*₆, chloroform-*d*, and Acetone-*d*₆ were purchased from Cambridge Isotope Laboratories and distilled from CaH₂ under a nitrogen atmosphere. δ -valerolactone (VL; 99%), ϵ -caprolactone (CL; 99%) and benzyl alcohol were distilled from CaH₂ under reduced pressure. 3,5- bis(trifluoromethyl)phenyl isocyanate, and 2-tert-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine, and *m*-chloroperbenzoic Acid were purchased from Acros Organics. 3,5- bis(trifluoromethyl)phenyl aniline was purchased from Oakwood Products. 7-methyl-1,5,7-triazabicyclo[4,4,0]dec-5-ene (MTBD), δ -hexanolactone, and 3,4,4'-trichlorocarbanilide (TCC) were purchased from TCI. Tris(2-aminoethyl) amine, menthone, and 2-methyl cyclohexanone were purchased from Alpha Aesar. The H-bond donors, 2-O and 3-O were prepared according to published procedures.¹⁻⁵ All NMR experiments were done using Bruker Avance III 300 MHz or 400 MHz spectrometers. Size exclusion chromatography (SEC) was done at 40 °C using dichloromethane eluent on an Agilent Infinity GPC system equipped with three Agilent PLGel columns 7.5 mm $\times$ 300 mm (5 μ m, pore sizes: 103, 104 , 105 Å). Mn and Mw/Mn were determined vs. PS standards (500 g/mol-3150 kg/mol, Polymer Laboratories).

Synthesis of Cyclic Lactone Monomers

Menthide [(±)-4-methyl-7-(1-methylethyl)oxepan-2-one]: A 600 mL beaker was charged with meta-chloroperbenzoic acid (17.25 g, 0.1035 mol) and dichloromethane (150 mL). Separately, a 500 mL dried Round Bottom Flask was charged with a stir bar, dichloromethane (10 mL), and menthone [(±)-p-menthan-3-one, (2S,5R)-2-isopropyl-5-methylcyclohexanone] (4.47 g, 0.0345 mol). The round bottom flask was then combined with the contents of the beaker. The solution was allowed to stir overnight for 20 hours, conversion was determined through ¹H NMR (300MHz, Chloroform-d). The solution was filtered and purified through extraction (2x 10 % sodium thiosulfate, 3x Sat. sodium carbonate, 3x Sat. sodium chloride). Excess solvent was removed under reduced pressure. The resulting liquid was further purified through silica gel column chromatography with 50:50 ethyl acetate: Hexanes mobile phase. Resulting liquid further purified in a basic alumina column chromatography with no mobile phase. Yield: 3.766 g, 76%. Product Characterized through ¹H NMR (300MHz, Chloroform-d).

6-methyl-ε-caprolactone: A 600 mL beaker was charged with *m*-chloroperbenzoic acid (21.2 g, 0.123 mol) and dichloromethane (150 mL). Separately, a 500 mL dried Round Bottom Flask was charged with a stir bar, dichloromethane (10 mL), and 2-methyl cyclohexanone (4.62 g, 0.041 mol). The round bottom flask was then combined with the contents of the beaker. The solution was allowed to stir overnight for 20 hours, conversion was determined through ¹H NMR (300MHz, chloroform-d). The solution was filtered and purified through extraction (2x 10 % sodium thiosulfate, 3x Sat. sodium carbonate, 3x Sat. sodium chloride). Excess solvent was removed under reduced

pressure. The resulting liquid was further purified using basic alumina column chromatography with no mobile phase. Yield: 3.744 g, 76%. Product Characterized through ^1H NMR (300MHz, Chloroform-d).

Example of ROP of ϵ -Caprolactone in solvent

A 7 mL vial was charged with benzyl alcohol (2.84 mg, 0.026 mmol) and THF (1314 μL) to make a stock solution. A separate 7 mL vial was charged with a stir bar, MgI_2 (12.2 mg, 0.0438 mmol) crushed to a powder, and MTBD (6.7 mg, 0.0438 mmol), and was set on a hot plate set to 60°C. A separate 7 mL vial was charged with TCC (13.8 mg, 0.0438 mmol), ϵ -caprolactone (100 mg, 0.876 mmol), and the contents of the vial containing the stock solution (439 μL), and was set on a hot plate set to 60°C. The contents of the second vial were transferred to the first vial via Pasteur Pipette, and allowed to proceed on the hot plate. Aliquots of 10 μL of reaction was quenched in solutions of benzoic acid in dry DCM. These aliquot solutions were dried under reduced pressure and percentage conversion was monitored by dissolving the contents in CDCl_3 and analysis via ^1H -NMR.

Example of ROP of Menthide in solvent

A 7 mL vial was charged with benzyl alcohol (1.89 mg, 0.017 mmol) and THF (880.5 μL) to make a stock solution. A separate 7 mL vial was charged with a stir bar, MgI_2 (8.1 mg, 0.029 mmol) crushed to a powder, and MTBD (4.4 mg, 0.029 mol), and was set on a hot plate set to 60°C. A separate 7 mL vial was charged with TCC (9.2 mg, 0.029 mmol), menthide (100 mg, 0.587 mmol), and the contents of the vial containing

the stock solution (294 μL), and was set on a hot plate set to 60°C. The contents of the second vial were transferred to the first vial via Pasteur Pipette, and allowed to proceed on the hot plate. Aliquots of 10 μL of reaction was quenched in solutions of benzoic acid in dry DCM. These aliquot solutions were dried under reduced pressure and percentage conversion was monitored by dissolving the contents in CDCl_3 and analysis via $^1\text{H-NMR}$.

Example of ROP of 6-MeCL in solvent

A 7 mL vial was charged with benzyl alcohol (5.07 mg, 0.047 mmol) and THF (1170 μL) to make a stock solution. A separate 7 mL vial was charged with a stir bar, MgI_2 (10.9 mg, 0.039 mmol) crushed to a powder, and MTBD (6.0 mg, 0.039 mmol), and was set on a hot plate set to 60°C. A separate 7 mL vial was charged with TCC (12.3 mg, 0.039 mmol), 6-MeCL (100 mg, 0.78 mmol), and the contents of the vial containing the stock solution (391 μL), and was set on a hot plate set to 60°C. The contents of the second vial were transferred to the first vial via Pasteur Pipette, and allowed to proceed on the hot plate. Aliquots of 10 μL of reaction was quenched in solutions of benzoic acid in dry DCM. These aliquot solutions were dried under reduced pressure and percentage conversion was monitored by dissolving the contents in CDCl_3 and analysis via $^1\text{H-NMR}$.

Example of ROP of ϵ -Caprolactone under solvent-free conditions

A separate 1 mL vial was charged with a stir bar, MgI_2 (3.65mg, 0.013 mmol) crushed to a powder, and BEMP (3.59 mg, 0.013mmol), and was set on a hot plate set to 60°C. A separate 7 mL vial was charged with TCC (4.13 mg, 0.013 mmol), ϵ -caprolactone (300 mg, 2.63 mmol), and benzyl alcohol (2.84mg, 0.026mmol) and was set on a hot plate set to 60°C. The contents of the second vial were transferred to the first vial via Pasteur Pipette, and allowed to proceed on the hot plate. Aliquots of 10 μL of reaction was quenched in solutions of benzoic acid in dry DCM. These aliquot solutions were dried under reduced pressure and percentage conversion was monitored by dissolving the contents in CDCl_3 and analysis via $^1\text{H-NMR}$.

Example of ROP of Menthide under solvent-free conditions

A separate 1 mL vial was charged with a stir bar, MgI_2 (2.45mg, 0.00881 mmol) crushed to a powder, and BEMP (2.41 mg, 0.00881mmol), and was set on a hot plate set to 60°C. A separate 7 mL vial was charged with TCC (2.78 mg, 0.00881mmol), menthide (300 mg, 1.76 mmol), and benzyl alcohol(1.91mg, 0.017mmol) and was set on a hot plate set to 60°C. The contents of the second vial were transferred to the first vial via Pasteur Pipette, and allowed to proceed on the hot plate. Aliquots of 10 μL of reaction was quenched in solutions of benzoic acid in dry DCM. These aliquot solutions were dried under reduced pressure and percentage conversion was monitored by dissolving the contents in CDCl_3 and analysis via $^1\text{H-NMR}$.

Example of ROP of 6-MeCL under solvent-free conditions

A separate 1 mL vial was charged with a stir bar, MgI_2 (3.21 mg, 0.0117 mmol) crushed to a powder, and BEMP (3.25 mg, 0.0117 mmol), and was set on a hot plate set to 60°C. A separate 7 mL vial was charged with TCC (3.69 mg, 0.0117 mmol), 6-MeCL (300 mg, 2.34 mmol), and benzyl alcohol (2.53 mg, 0.0234 mmol), and was set on a hot plate set to 60°C. The contents of the second vial were transferred to the first vial via Pasteur Pipette, and allowed to proceed on the hot plate. Aliquots of 10 μL of reaction was quenched in solutions of benzoic acid in dry DCM. These aliquot solutions were dried under reduced pressure and percentage conversion was monitored by dissolving the contents in CDCl_3 and analysis via $^1\text{H-NMR}$.

Example of Block Copolymerization of caprolactone and 6-MeCL (catalyst switch)

A 7 mL vial was charged with a stir bar, MgI_2 (4.25 mg, 0.015 mmol) crushed to a powder and BEMP (4.20 mg, 0.015 mmol) and was set on a hot plate set to 60°C. Another 7 mL vial was charged with TCC (4.84 mg, 0.015 mmol), caprolactone (100 mg, 0.876 mmol) and 6-MeCL (112.3 mg, 0.876 mmol) and benzyl alcohol (0.947 mg, 0.91 mmol) and 438 μL of THF was added and mixed well and left to polymerize at room temperature. The contents of the second vial were transferred to the first vial via Pasteur Pipette, and the reaction was allowed to proceed on a hot plate at 60°C. Aliquots of 10 μL of reaction was quenched in solutions of benzoic acid in dry DCM. These aliquot solutions were dried under reduced pressure and percentage conversion was monitored by dissolving the contents in CDCl_3 and analysis via $^1\text{H-NMR}$.

Example of Block Copolymerization of caprolactone and Menthide

A 7 mL vial was charged with a stir bar, MgI_2 (4.25 mg, 0.015 mmol) crushed to a powder and BEMP (4.20 mg, 0.015 mmol) and was set on a hot plate set to 60°C. Another 7 mL vial was charged with TCC (4.84 mg, 0.015 mmol), caprolactone (100 mg, 0.876 mmol) and menthide (112.3 mg, 0.876 mmol) and benzyl alcohol (0.947 mg, 0.91 mmol) and 438 μL of THF was added and mixed well set on a hot plate set to 60°C. The contents of the second vial were transferred to the first vial via Pasteur Pipette, and the reaction was allowed to proceed on the hot plate. Aliquots of 10 μL of reaction was quenched in solutions of benzoic acid in dry DCM. These aliquot solutions were dried under reduced pressure and percentage conversion was monitored by dissolving the contents in CDCl_3 and analysis via $^1\text{H-NMR}$.

Example of gradient copolymer of caprolactone and 6-MeCL

A 7 mL vial was charged with a stir bar, MgI_2 (4.25 mg, 0.015 mmol) crushed to a powder and BEMP (4.20 mg, 0.015 mmol) and was set on a hot plate set to 60°C. Another 7 mL vial was charged with TCC (4.84 mg, 0.015 mmol), caprolactone (100 mg, 0.876 mmol) and 6-MeCL (112.3 mg, 0.876 mmol) and benzyl alcohol (0.947 mg, 0.91 mmol) and 438 μL of THF was added and mixed well set on a hot plate set to 60°C. The contents of the second vial were transferred to the first vial via Pasteur Pipette, and the reaction was allowed to proceed on the hot plate. Aliquots of 10 μL of reaction was quenched in solutions of benzoic acid in dry DCM. These aliquot solutions were dried under reduced pressure and percentage conversion was monitored by dissolving the contents in CDCl_3 and analysis via $^1\text{H-NMR}$.

RESULTS AND DISCUSSION

ROP of CL. The ROP of caprolactone in the presence of the TCC/base has extensively been studied previously by our group and has been shown to be very efficient in the ROP of similar lactones.^{15,23} Thus, we believed ROP of CL in the presence of imidate cocatalyst and MgI₂ was an appropriate approach to tap into ROP of monomers for which the hyper active imidate type catalysts are unsuccessful.

When the polymerization of CL was carried out in the presence of the dual cocatalysts we observe living polymerization characteristics in solvent and neat conditions. Figure 5.2 shows the linear evolution of monomer and linear M_n vs percentage conversion. A DP study was performed under solvent-free conditions as shown in Table 5.1. Predictable M_n values were attainable under solvent-free conditions. This trend does not hold true for ROP in THF and toluene, where molecular weight control was only achievable up to a target DP of 100, (see Table 5.6 and Table 5.7). The polymerizations in the presence of 3-O and 2-O with MTBD and MgI₂ also showed living polymerization characteristics while reaching 90 % conversion in 5 mins and acceptable control over the molecular weight distribution, (see Table 5.6). Previous studies have shown the polymerizations in the presence of the cocatalyst system TCC and MTBD showed much better control compared to the polymerizations with the MgI₂.¹⁵ This lack of selectivity with the cooperative catalyst system may be related to – post polymerization transesterification - high activity of the catalyst which causes the broadening of the molecular weight distribution at higher conversions. This could be further illustrated by the broadening of M_w/M_n values with time after reaching completion. Polymerization

of CL was also successfully carried out in the presence of MgCl₂ and MgSO₄, (see Table 5.8).

ROP of 6-Me-CL. Preliminary studies carried out showed that ROP of 6-Me-CL at room temperature in the presence of TCC and 2-*tert*-Butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP) was very slow and uncontrolled. This catalyst system is extremely active for the ROP of CL. We believe this reduced activity of the TCC/BEMP system with 6-Me-CL is due to the presence of a methyl group in the 'ε' position of the ring, which sterically hinders the activation of the monomer. The polymerization of 6-Me-CL (0.78 mmol, 2 M) in the presence of TCC and DBU (0.020 mmol, each), and benzyl alcohol (0.008 mmol) in THF at 60°C was conducted. The progress of reaction was extremely slow, 21% conversion in 6 days, (see Table 5.9). In the presence of MgI₂ we observe an increase in the rate of polymerization along with better control over molecular weight - M_n value of 20,300 g/mol and M_w/M_n of 1.05, see Entry 1 Table 5.2. The reaction conducted with 6-Me-CL (0.78 mmol, 2 M) was observed in the presence of DBU and MgI₂ (0.020 mmol, each), and benzyl alcohol (0.008 mmol) in THF at 60°C. These results show similar rates but low control in M_n and M_w/M_n values as shown in Table 5.2.

An enhancement for the rate of polymerization of 6-MeCL was observed in the presence of TCC and BEMP (0.02 mmol, each) compared to the reactions conducted in the presence of DBU. ROP conducted in the absence of the urea donor showed low control over the polymerization with M_n values lower than predicted and broad M_w/M_n values at a target DP of 100 in THF at 2M monomer concentration. A degree of polymerization

study conducted showed that control of molecular weights above a target DP of 100 was unachievable in solvent, (See Table 5.10). This could be due to solvent molecules at high conversions competing with monomer that might limit enchainment of monomer to the polymer backbone. However, these polymerizations showed linear first order evolution plots and linear molecular weight vs percentage conversion plots which illustrates the living character for the polymerization of 6-MeCL in solvent as in Figure 5.3.

ROP of 6-MeCL under solvent free conditions demonstrated living characteristics and better control in the presence of the dual catalyst system containing TCC/base and MgI_2 . This polymerization with 6-MeCL (0.78 mmol, 2M) and TCC, MTBD, and MgI_2 (0.039 mmol, each) at 60°C reached 96% conversion in 40 minutes with a M_n of 25,000 g/mol and M_w/M_n of 1.04. A degree of polymerization study carried out solvent-free conditions show better control over molecular weights can be achieved compared to that in solvents such as THF or toluene, (See Table 5.6). The linear evolution of monomer and linear evolution of M_n vs percentage conversion shows that this polymerization is living in nature.

ROP of Menthide. The ROP of ($\pm$) menthide was performed in the presence of an H-bonding organic catalyst. The ROP of ($\pm$) menthide (1.76 mmol), benzyl alcohol (0.018 mmol) with TCC (0.009 mmol) and BEMP (0.009 mmol) under solvent-free conditions did not proceed when performed at a temperature of 60°C. We believe the polymerization does not proceed due to lack of activation of the monomer, which arises by steric hindrance caused by the bulky isopropyl group in the 'ε' position of the ring.

However, in the presence of TCC/BEMP/MgI₂ (0.009 mmol) with menthine (1.76 mol) and benzyl alcohol (0.018 mmol) at 60°C we observed 90% conversion in 13 hours, M_n of 17,700 g/mol and M_w/M_n of 1.03. This reaction is controlled compared to other catalyst systems that have been previously studied for the ROP of menthine such as Zinc alkoxide catalyst.²² The first-order evolution plot is linear and also shows linear molecular weight increase vs percent conversion, which provide evidence for the living character of these polymerizations, see Figure 5.4.

The effect of Mg salt for the ROP of menthine is believed to be due to the strong interaction between the carbonyl group of the monomer and the MgI₂ as shown in Scheme 5.1. A DP screen conducted in the presence of this catalyst system showed good control over molecular weights under solvent-free conditions suggesting that this system is highly efficient in the ROP of menthine, (see Table 5.12). Studies conducted in the presence of MgCl₂ and Mg(SO₄) as Lewis acids showed no conversion of menthine to polymer even though MgCl₂ was seen to completely dissolve in the reaction mixture unlike Mg(SO₄) which was less soluble, (see Table 5.13).

The ROP of menthine (0.587 mmol, 2M), benzyl alcohol (0.006 mmol) with TCC and BEMP (0.029 mmol each) in THF is slow with only 24% conversion after 7 days of heating the reaction at 60°C. In THF with the presence, TCC and BEMP with MgI₂ showed living character with low control of molecular weight distribution. A conversion of 91% in 12 hours, M_n of 12,600 g/mol and M_w/M_n value of 1.31 was observed with menthine (0.587 mmol), benzyl alcohol (0.006 mmol) with TCC, BEMP,

and MgI_2 (0.029 mmol each) in THF at 60°C . ROP in the presence of the 3-O catalyst donor did not progress to form polymer, which we believe is due to the steric hindrance.

A degree of polymerization (DP) study carried out showed no control of molecular weight was achievable above a target DP of 100, (See Table 5.11). The polymerization conducted with menthide in the presence of benzyl alcohol as the initiator showed the refractive index peak and the UV trace from the GPC chromatogram overlap. This suggests the polymerization of menthide initiates from the alcohol initiator the RI and UV traces has been provided in the supporting information, (See Figure 5.9). The reaction conducted in toluene at 60°C showed higher M_n (20,000 g/mol) and M_w/M_n of 1.10 but slower rates of conversion. However, control of molecular weight with increase in the target DP was seen under solvent-free conditions like CL and 6-MeCL, (see Table 5.12). This demonstrates that interference of the solvent in the activity of the cooperative catalyst system causes this lack of control.

Further understanding the cooperative catalytic activity and mechanism. Studies to evaluate the most probable mechanism was carried out using ^1H -NMR. ^1H -NMR studies (See Figure 5.11) were carried out with the components used for the polymerization to propose a feasible mechanism by which this mixture of catalysts may be active during the polymerization. We believe the results indicate a complicated interplay between imidate – neutral H-bonding and Lewis acid catalyzed polymerization (Scheme 5.1). NMR studies show a downfield shift of the monomer (CL) peaks in the presence of MgI_2 and TCC/base suggesting activation of the monomer occurs in the presence of the cooperative catalyst compared to that of just TCC/base. The peaks of

TCC and base in the presence of MgI_2 broadens out probably due to the lack of solubility of the catalyst system in the absence of monomer. However, we would like to propose the mechanism based on the studies conducted where we believe the possibility of 3 transition states in equilibrium with each other. Scheme 5.1 shows the proposed mechanism based on ^1H -NMR studies and ROPs carried out to understand the catalytic activity.

Studies carried out for the ROP of cyclic lactones in the presence of H-bonding catalyst systems. The reactions conducted in the presence of TCC and Base (0.015 mmol), CL (0.876 mmol), menthide (0.876 mmol) and benzyl alcohol (0.0009 mmol) in THF. The reaction mixture was stirred at room temperature for 24 hours. The monomer conversion was obtained using NMR and this reaction mixture was transferred to a vial containing MgI_2 (0.015 mmol). CL monomer had converted to polymer. Thereafter, this reaction was kept on a hot plate at 60°C and the progress of the reaction was monitored. The menthide converted to polymer once heating of the reaction mixture started. The resulting polymer had M_n of 21,000 g/mol and PDI of 1.7. The H-NMR spectra of the aliquots taken during progress of the reaction clearly show the incorporation of menthide to the CL polymer.

Similarly, the copolymerization of CL and 6-MeCL was conducted. The reaction was conducted with TCC and BEMP (0.015 mmol), CL (0.876 mmol), 6-MeCL (0.876 mmol) and benzyl alcohol (0.0009 mmol) in THF in a vial. The reaction mixture was stirred at room temperature for 4.5 hours. CL polymerized faster than 6-MeCL at room temperature in the absence of MgI_2 . Once the reaction mixture was transferred to a vial

containing MgI_2 (0.015 mmol) 6-MeCL was polymerized from the PCL macro-initiator to obtain a gradient block copolymer of CL and 6-MeCL with an M_n of 40,000g/mol and PDI of 1.75. $^1\text{H-NMR}$ data of aliquots obtained show gradual progress of the reaction and monomer switch with addition of MgI_2 . The addition of urea/base and MgI_2 (0.015mmol each) mixture in the presence of CL and 6-MeCL (0.88 mmol each) and benzyl alcohol (0.009 mmol) yielded a gradient copolymer. This can be observed clearly using the linear first order evolution plots of the respective monomer enchainment by H-NMR. The ratio of rates of polymerization of each monomer $k_{\text{obs}(\text{CL})}/k_{\text{obs}(6\text{-MeCL})} \sim 2$ suggests that a gradient copolymer is formed. H-NMR spectra of the polymers show evidence of both monomers being enchainned to the polymer backbone. All copolymers synthesized using 6-MeCL with CL were semi-solid while Menthide and CL were gels.

CONCLUSION

The rates of polymerization showed in the presence of TCC/base/MgI₂ showed a trend of CL > 6-MeCL > menthide in solvent at 2M with THF as solvent and solvent-free conditions. Highly polar solvents such as acetone showed no conversions in the presence of Mg salts due to inactivation of catalyst likely due to solvent binding strongly to the Lewis acid. Solvent-free polymerization showed the best control under these conditions with greater control over degree of polymerization and molecular weight distribution. We were also able to propose a mechanism by which this cooperative catalyst system may catalyze the polymerization of these lactones. Structurally complex copolymers may be synthesized using catalyst switch approach to design and develop new polymeric materials with probable future applications.

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Entry	[M] ₀ /[I]	Time (min)	Conv. (%) ^a	(g mol ⁻¹) ^b	<i>M_w</i> / <i>M_n</i> ^b
1	25	2	96	5 500	1.10
2	50	2	97	11 600	1.15
3	100	5	94	25 900	1.10
4	200	7	98	68 800	1.40

Table 5.1. DP Screen for TCC/MTBD/MgI₂ cocatalyzed ROP of ε-Caprolactone (Solvent-free)

Reaction Conditions: ε-Caprolactone (2.63 mmol) and TCC, MTBD, and MgI₂ (0.013 mmol, each) at 60°C. a. Percentage conversion determined by ¹H-NMR. b. *M_n* and *M_w*/*M_n* determined by GPC.

Entry	donor	base	time (min)	Conv. (%) ^c	M _n (g mol ⁻¹) ^d	M _w /M _n ^d
1 ^a	TCC	DBU	19	83	20 300	1.05
2 ^a	TCC	MTBD	18	80	16 300	1.07
3 ^a	TCC	BEMP	20	86	20 600	1.05
4 ^b	3-O	DBU	201	89	19 000	1.07
5 ^b	3-O	MTBD	122	93	19 800	1.07
6 ^b	3-O	BEMP	90	91	20 700	1.07
7 ^e	N/A	BEMP	15	91	21 000	1.28
8 ^e	N/A	MTBD	22	94	22 500	1.29
9 ^e	N/A	DBU	20	90	14 000	1.10
10 ^e	N/A	TBD	20	95	11 000	1.27
11 ^f	TCC	BEMP	2 days	84	7 200	1.74

Table 5.2. H-bond donor and base screen for 6-MeCL.

Reaction conditions: a. 6-Me-CL (0.78 mmol, 2M) TCC, Base, MgI₂ (0.020 mmol, each), and benzyl alcohol (0.008 mmol) in THF at 60°C. b. 6-Me-CL (0.78 mmol, 2M) and 3-O and Base (0.013 mmol, each), and benzyl alcohol (0.008 mmol) in THF at 60°C. c. Percentage conversions determined by ¹H-NMR. d. *M_n* and *M_w/M_n* determined by GPC. e. 6-MeCL (0.78 mmol, 2M) and Base and MgI₂ (0.039 mmol, each) and benzyl alcohol (0.0078mmol) in THF at 60°C. ^f 6-Me-CL (0.78 mmol, 2M) TCC and BEMP (0.03 mmol and 0.015 mmol respectively), and benzyl alcohol (0.008 mmol) in THF at 60°C.

Entry	[M] ₀ /[I]	time (min)	Conv. (%) ^a	M _n (g mol ⁻¹) ^b	M _w /M _n ^b
1	25	50	75	3 800	1.06
2	50	175	91	8 440	1.06
3	100	95	85	18 200	1.04
4	200	92	87	31 900	1.05

Table 5.3. DP screen for TCC/MTBD/MgI₂ cocatalyzed ROP of 6-MeCL

Reaction Conditions: 6-MeCL (2.63 mmol) and TCC, MTBD, and MgI₂ (0.013 mmol, each) at 60°C. a. Percentage conversion determined by ¹H-NMR. b. *M_n* and *M_w/M_n* determined by GPC.

Entry	donor	base	time (hrs)	Conv. (%) ^c	M _n (g mol ⁻¹) ^d	M _w /M _n ^d
1 ^a	TCC	BEMP	12	91	12 600	1.31
2 ^a	TCC	MTBD	15	88	9 000	1.40
3 ^a	TCC	DBU	15	89	11 750	1.26
4 ^b	2-O	BEMP	18	83	9 100	1.16
5 ^b	2-O	MTBD	13	60	8 000	1.11
6 ^b	2-O	DBU	18	73	7 700	1.11
7 ^e	N/A	BEMP	7	91	11 000	1.38
8 ^f	TCC	BEMP	24	0	-	-
9 ^f	3-O	BEMP	24	0	-	-

Table 5.4. H-bond donor screen for H-Bond Donor/Base/MgI₂ cocatalyzed ROP of Menthide.

Reaction Conditions: a. Menthide (0.587 mmol, 2M) and TCC and Base (0.020 mmol, each), and benzyl alcohol (0.006 mmol) in THF at 60°C. b. Menthide (0.587 mmol, 2M) and TCC, Base, and MgI₂ (0.013 mmol, each), and benzyl alcohol (0.006 mmol) in THF at 60°C. c. Percentage conversions determined by ¹H-NMR. d. *M_n* and *M_w/M_n* determined by GPC, (CH₂Cl₂) vs. Polystyrene Standards. e. No TCC was used. ^f No MgI₂ was used.

Entry	[M] ₀ /[I]	Time (min)	Conv. (%) ^a	(g mol ⁻¹) ^b	<i>M_w</i> / <i>M_n</i> ^b
1	25	5	97	6 900	1.17
2	50	5	86	12 300	1.14
3	100	6	84	22 700	1.40
4	200	6	90	51 000	1.31

Table 5.5. DP Screen for TCC/DBU/MgI₂ cocatalyzed ROP of ϵ -Caprolactone (Solvent-free)

Reaction Conditions: ϵ -caprolactone (2.63 mmol) and TCC, DBU, and MgI₂ (0.013 mmol, each) at 60°C. a. Percentage conversion determined by ¹H-NMR. b. *M_n* and *M_w*/*M_n* determined by GPC.

Entry	[M] ₀ /[I]	Time (min)	Conv. (%) ^a	<i>M_n</i> (g mol ⁻¹) ^b	<i>M_w</i> / <i>M_n</i> ^b
1	25	2	94	4 600	1.13
2	50	2	96	9 600	1.11
3	100	8	91	22 700	1.51
4	200	20	100	19 700	1.65

Table 5.6. DP Screen for TCC/MTBD/MgI₂ cocatalyzed ROP of ϵ -Caprolactone (THF)

Reaction Conditions: ϵ -caprolactone (0.876 mmol, 2M) and TCC, MTBD, and MgI₂ (0.0438 mmol, each) in THF. a. Percentage conversion determined by ¹H-NMR. b. *M_n* and *M_w*/*M_n* determined by GPC.

Entry	[M] ₀ /[I]	Time (min)	Conv. (%) ^a	<i>M_n</i> (g mol ⁻¹) ^b	<i>M_w</i> / <i>M_n</i> ^b
1	25	2	93	5 300	1.08
2	50	5	83	11 900	1.04
3	100	40	100	18 100	1.57
4	200	45	89	9 200	1.65

Table 5.7. DP Screen for TCC/MTBD/MgI₂ cocatalyzed ROP of ε-Caprolactone (Toluene)

Reaction Conditions: ε-Caprolactone (0.876 mmol, 2M) and TCC, MTBD, and MgI₂ (0.0438 mmol, each) in toluene. a. Percentage conversion determined by ¹H-NMR. b. *M_n* and *M_w*/*M_n* determined by GPC.

Entry	Magnesium Salt	Monomer	Temperature (°C)	time (min)	Conv. (%) ^c	<i>M_n</i> (g mol ⁻¹) ^b	<i>M_w</i> / <i>M_n</i> ^b
1	MgI ₂	CL	25	180	96	18 000	1.22
2	MgI ₂	CL	60	8	91	22 600	1.51
3	MgCl ₂	CL	60	15	100	24 000	1.31
4	MgSO ₄	CL	60	45	88	17 000	1.10

Table 5.8. Magnesium Salt Screen for ε-Caprolactone (THF)^a.

Reaction Conditions: a. TCC, MTBD, and MgX (0.0438 mmol, each) in THF at 60 °C. ε-Caprolactone (0.876 mmol, 2M). c. Percentage conversion determined by ¹H-NMR. b. *M_n* and *M_w*/*M_n* determined by GPC.

Entry	base	time (days)	Conv. (%) ^a	M_n (g mol ⁻¹) ^b	M_w/M_n ^b
1	DBU	6	21	-	-
2	MTBD	6	71	-	-
3	BEMP	1	74	-	-

Table 5.9. Base screen for TCC/BASE/MgI₂ cocatalyzed ROP of 6-MeCL (THF)

Reaction Conditions: 6-MeCL (0.78 mmol, 2M) and TCC, Base (0.039 mmol, each) and benzyl alcohol (0.0078mmol) in THF at 60°C. a. Percentage conversion determined by ¹H-NMR. b. M_n and M_w/M_n determined by GPC.

Entry	[M] ₀ /[I]	time (min)	Conv. (%) ^a	M_n (g mol ⁻¹) ^b	M_w/M_n ^b
1	25	17	93	5 400	1.10
2	50	10	91	11 850	1.06
3	100	18	80	16 300	1.07
4	200	23	91	16 600	1.20
5	500	59	93	21 000	1.14

Table 5.10. DP screen for TCC/MTBD/MgI₂ cocatalyzed ROP of 6-MeCL (THF)

Reaction Conditions: 6-MeCL (0.78 mmol, 2M) and TCC, MTBD, and MgI₂ (0.039 mmol, each) in THF at 60°C. a. Percentage conversion determined by ¹H-NMR. b. M_n and M_w/M_n determined by GPC.

Entry	[M] ₀ /[I]	time (hrs)	Conv. (%) ^a	<i>M_n</i> (gmol ⁻¹) ^b	<i>M_w</i> / <i>M_n</i> ^b
1	25	25	91	6 000	1.16
2	50	19	88	11 900	1.21
3	100	15	88	9 000	1.40
4	200	19	86	11 600	1.51
5	500	19	87	10 100	1.65

Table 5.11. DP screen for TCC/MTBD/MgI₂ cocatalyzed ROP of Menthide (THF)

Reaction Conditions: Menthide (0.587 mmol, 2M) and TCC, MTBD, and MgI₂ (0.029 mmol, each) in THF at 60°C. a. Percentage conversion determined by ¹H-NMR. b. *M_n* and *M_w*/*M_n* determined by GPC.

Entry	[M] ₀ /[I]	time (hrs)	Conv. (%) ^a	<i>M_n</i> (gmol ⁻¹) ^b	<i>M_w</i> / <i>M_n</i> ^b
1	25	30	85	5 400	1.08
2	50	25	83	9 900	1.03
3	100	13	90	17 700	1.03
4	200	23	64	31 400	1.02

Table 5.12. DP screen for TCC/MTBD/MgI₂ cocatalyzed ROP of Menthide (solvent-free)

Reaction Conditions: Menthide (1.762 mmol, 300mg) and TCC, BEMP, MgI₂ (0.0881 mmol each) at 60°C. a. Percentage conversion determined by ¹H-NMR. b. *M_n* and *M_w*/*M_n* determined by GPC.

Entry	Magnesium Salt	Monomer	time (min)	Conv. (%) ^a	M _n (gmol ⁻¹) ^b	M _w /M _n ^b
1	MgI ₂	CL	12	93	26 600	1.14
2	MgI ₂ ^c	CL	315	90	20 000	1.84
3	MgCl ₂	CL	20	91	22 200	1.44
4	MgI ₂	menthide	780	90	17 700	1.03
5	MgI ₂ ^c	menthide	1440	0	-	-
6	MgCl ₂	menthide	1440	0	-	-
7	MgSO ₄	menthide	1440	0	-	-
8	MgI ₂	6-MeCL	40	96	25 000	1.04
9	MgI ₂ ^c	6-MeCL	60	95	24 000	1.04

Table 5.13. Magnesium salts and Monomer Screen (Solvent-free)

Reaction Conditions: TCC, BEMP, and MgX (0.0438 mmol, each) under neat conditions at 60°C. a. Percentage conversion determined by ¹H-NMR. b. *M_n* and *M_w/M_n* determined by GPC. c. No trichlorocarbene (TCC) was used.

Entry	Solvent	Time (Hours)	Conv. (%) ^a	M_n (g·mol ⁻¹) ^b	M_w/M_n ^b
1	THF	15	88	9 000	1.21
2	toluene	20	90	20 000	1.10
3	acetone	15	-	-	-

Table 5.14 Solvent Screen for TCC/MTBD/MgI₂ cocatalyzed ROP of Menthide

Conditions: Menthide (0.587 mmol, 2M) and TCC, MTBD, and MgI₂ (0.029 mmol, each) in solvent at 60°C. a. Percentage conversion determined by ¹H-NMR. b. M_n and M_w/M_n determined by GPC.

Entry	H-Bond Donor	Time (Minutes)	Conv. (%) ^a	M_n (g·mol ⁻¹) ^b	M_w/M_n ^b
1 ^c	TCC	8	91	22 700	1.51
2 ^d	2-O	5	90	13 200	1.22
3 ^e	3-O	5	90	15 400	1.09

Table 5.15 H-Bond Donor Screen for H-Bond Donor/MTBD/MgI₂ cocatalyzed ROP of CL

Reaction conditions: ε-Caprolactone (0.876mmol, 2M), and Benzyl alcohol (0.009 mmol). c.TCC, MTBD, and MgI₂ (0.0438 mmol, each) in THF at 60°C. d. 2-O, MTBD, MgI₂ (0.0219 mmol, each) in THF at 60°C. e.3-O, MTBD, MgI₂ (0.0146 mmol each) in THF at 60°C. a. Percentage conversion determined by ¹H-NMR. b. M_n and M_w/M_n determined by GPC.

Scheme 5.1: Proposed cooperative Mg salt and imidate H-bonding mediated mechanism for ROP of cyclic lactones.

Figure 5.1. Monomers and organocatalysts used in this study

Figure 5.2. (Left) First order evolution plot. (Right) M_n and M_w/M_n vs % Conversion for the TCC/MTBD/MgI₂ cocatalyzed ROP of CL. conditions: CL (3.50 mmol), TCC, MTBD, and MgI₂ (0.0175 mmol, each), and Benzyl Alcohol (0.035 mmol) solvent-free, at 60°C.

Figure 5.3. (Left) First order evolution of [6-MeCL] vs. time. (Right) M_n and M_w/M_n vs % Conversion for the TCC/MTBD/MgI₂ cocatalyzed ROP of 6-MeCL. conditions: 6MeCL (0.78 mmol, 2M), TCC, MTBD, and MgI₂ (0.039mmol each), and Benzyl Alcohol (0.0078 mmol) in THF at 60°C.

Figure 5.4 (Left) First order plot of menthide solvent-free, (Right) M_n vs M_w/M_n for ROP of menthide solvent-free. Conditions: Menthide (1.76 mmol), benzyl alcohol (0.018 mmol) and TCC/BEMP/MgI₂ (0.009 mmol) at 60°C.

Figure 5.5 (Left) First order evolution of [CL] vs. time. (Right) M_n and M_w/M_n vs % Conversion for the TCC/MTBD/MgI₂ cocatalyzed ROP of CL. conditions: CL (0.876 mmol, 2M), TCC, MTBD, and MgI₂ (0.044 mmol, each), and Benzyl Alcohol (0.009 mmol) in THF at 60°C.

Figure 5.6. (Left) First-order evolution of [monomer] vs time and (Right) M_n and M_w/M_n vs conversion for the TCC/DBU cocatalyzed ROP of CL. conditions: CL (0.876 mmol, 2M) and TCC and DBU (0.044 mmol, each), and benzyl alcohol (0.008 mmol) at 60°C.

Figure 5.7. (Left) First-order evolution of [monomer] vs time and (Right) M_n and M_w/M_n vs % conversion for the 3-O/BEMP/ MgI_2 cocatalyzed ROP of 6-MeCL. conditions: 6-Me-CL (0.78 mmol, 2M) and 3-O, BEMP, MgI_2 (0.013 mmol, each), and benzyl alcohol (0.008 mmol) in THF at 60°C.

Figure 5.8. (Left) First-order evolution of [Menthide] vs time and (Right) M_n and M_w/M_n vs conversion for the TCC/BEMP/MgI₂ cocatalyzed ROP of Menthide. conditions: Menthide (0.59 mmol, 2M) and TCC, BEMP, MgI₂ (0.014 mmol, each), and benzyl alcohol (0.006 mmol) in THF at 60°C.

Figure 5.9. GPC Spectrum of the ROP of menthilde

Reaction Conditions: Menthide (1.762 mmol, 300mg) and TCC, BEMP, MgI₂ (0.0881 mmol each), and benzyl alcohol (0.035 mmol) in THF at 60°C. Blue line represents RI trace, orange line represents 250nm UV trace.

Figure 5.10 First-order evolution of Gradient copolymerization of ϵ -caprolactone and 6-methyl caprolactone

Reaction Conditions: Caprolactone (0.88mmol, 2M) 6-MeCL (0.88mmol, 2M) TCC, BEMP, and MgI_2 (0.015mmol, each) and benzyl alcohol (0.009 mmol) in THF at 60°C. Percentage Conversion determined by 1H -NMR (400 MHz)

Figure 5.11. ^1H -NMR study using CL/TCC/BEMP/ MgI_2 in $\text{Acetone-}d_6$

Reaction Conditions: CL, TCC, BEMP and MgI_2 (0.03 mmol, each) in 450 μL of $\text{Acetone-}d_6$ at room temperature

Figure 5.12. (Top) ^1H -NMR and (bottom) ^{13}C NMR of Copolymers