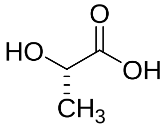
Ring Opening Polymerization of Lactide for The synthesis of Poly (Lactic Acid)

Reported by Keith A. Porter Date 2 March 2006

INTRODUCTION

Poly (lactic acid) (PLA) shows promise as a valuable alternative to petroleum-based polymers for uses as plastics, fibers, and coatings. PLA is produced from renewable resources such as corn and sugar beets, and the material is biodegradable thus making it ideal for industrial use.[1,2] PLA is derived from lactic acid, which exists as two enantiomers: L- and D-lactic acid, **1** and **2**. Lactic acid forms PLA upon polycondensation; however, this is an equilibrium reaction and difficulties completely removing water can limit the maximum molecular weight attained due to hydrolysis of the ester bonds. A solution to this problem is the use of the cyclic dimmer lactide. Lactide undergoes Ring Opening Polymerization (ROP) to give PLA. Since this is not a condensation polymerization, there is no need for the removal of water. Cargill Dow LLC has capitalized on the ROP of lactide to produce about 300 x 10^6 lbs/year of PLA.[3] PLA belongs to a group of polymers known as polyesters, which are among the more versatile of organic polymers. The ROP of lactide is thermodynamically driven by the relief of angle strain and switching from (E) to (Z) ester conformation upon ring opening.[4] There are three stereoisomers of lactide, D-lactide (**3**), L-lactide (**4**), and *meso*-lactide (**5**). This seminar will focus on the stereoselective synthesis of the different PLA microstructures and the properties that arise from stereo-homogeneity.



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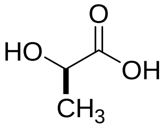

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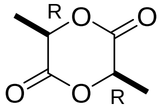

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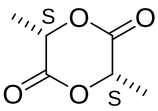

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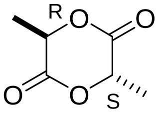

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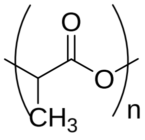
BACKGROUND INFORMATION

PLA is an aliphatic, hydrolyzable polyester (**6**). Upon exposure to heat and water, the polymer breaks down to low molecular weight oligomers.[5] Further degradation can occur by the action of microorganisms in the body and in the environment to produce lactic acid in the former and carbon dioxide and water in the latter. PLA has many properties similar to its petro-chemical based counterparts. PLA is glossy, transparent, and flavor-resistant, and it can be elastic or tough. The polymer has many uses ranging from bottles to high temperature plastic cooking dishes.[6]



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STEREO-HOMOGENEITY OF PLA

Four different stereoisomers of PLA are shown in Figure 1. Isotactic PLA is formed from either pure D- or L-lactide, and the sequential stereogenic carbons have the same absolute configuration. In contrast, syndiotactic PLA has alternating configurations of the sequential stereocenters. Atactic PLA has a random distribution of configurations about the stereocenters while its heterotactic counterpart has regions of stereo-homogeneity.[7] Isotactic stereoblock PLA is similar to isotactic PLA but differs in that *rac*-lactide is used instead of pure L- or D-lactide. Thakur, Munson and co-workers[8] showed that the tacticity can be determined directly by ^{1}H NMR analysis of the methine hydrogen. The most common method for determining the degree of crystallinity is by Differential Scanning Calorimetry (DSC).[9] As stereoregularity increases, so does the overlap between PLA helices, thus increasing the number of stabilizing dipole-dipole interactions.[10] The stronger the intermolecular forces, the greater the mechanical and thermal properties of the polymer.[11] Since the properties arise from the stereochemistry[7], the development of new types of stereocomplexes are vital to make stronger, more durable PLA.

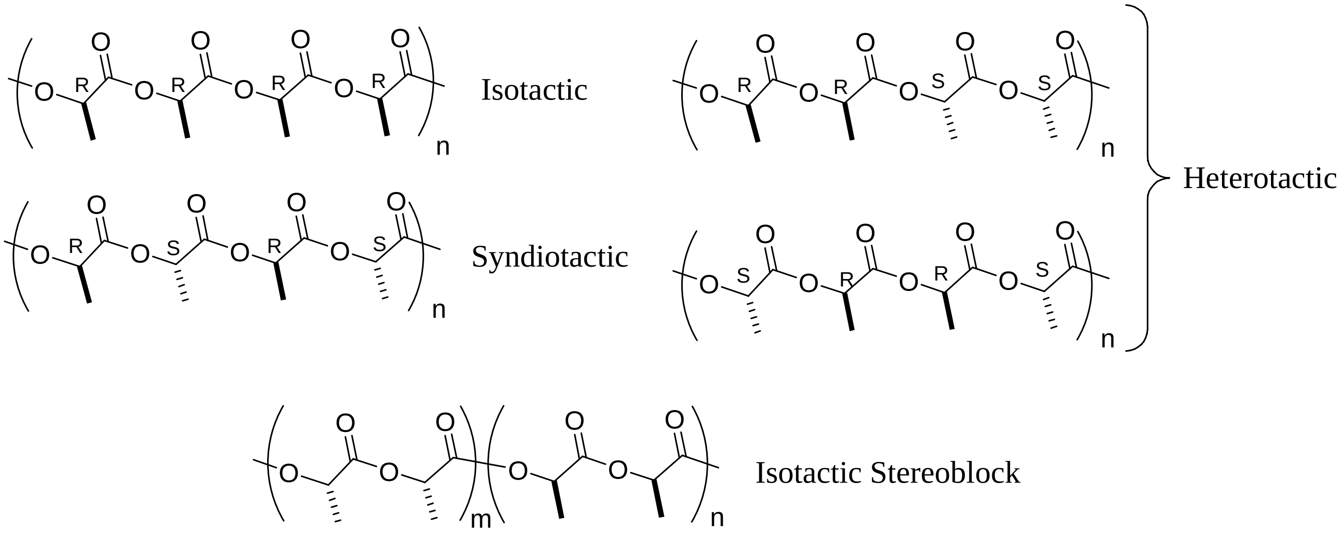


Figure 1. Different microstructures of PLA

SYNTHESIS OF PLA WITH OPTICALLY ACTIVE LACTIDE

Isotactic PLA is formed by the polymerization of either pure L or D-lactide. Several different types of metal catalysts such as zinc (II) and titanium(IV) have been evaluated, but tin (II) 2-ethylhexanoate ($Sn(Oct)_2$) (**7**) has been most widely used because of high reaction rates, the solubility in the monomer melt, and the ability to produce high molecular weights.[1,12] The coordination-insertion mechanism is shown in Figure 2. Molecular modeling suggests that two alcohols (these alcohols can be initiators such as MeOH or iPrOH or the propagating hydrolyzed lactide) exchange with the octoate ligands (**8a**) followed by the coordination of lactide to the metal center (**8b**). Insertion of the alcohol (**8c**) followed by ring-opening (**8d**) generates a linear monomer (**8e**) and starts propagation. The ROP of neat lactide with $Sn(Oct)_2$ gives PLA having molecular weights up to 10^6 g/mol at 140 – 180 ^oC with catalyst concentration of 100-1000 ppm in 2-5 hours.[5] A major drawback of the tin catalyst is the incorporation of the toxic metal on the polymer chain end and the resulting toxicity risk in biomedical applications. Another is the broad polydispersity index ranging from 1.5-2.0. The large range was attributed to the tin complex reacting with impurities in L-lactide to form new initiator species leading to an initiation rate that is slower than the propagation rate.[13]

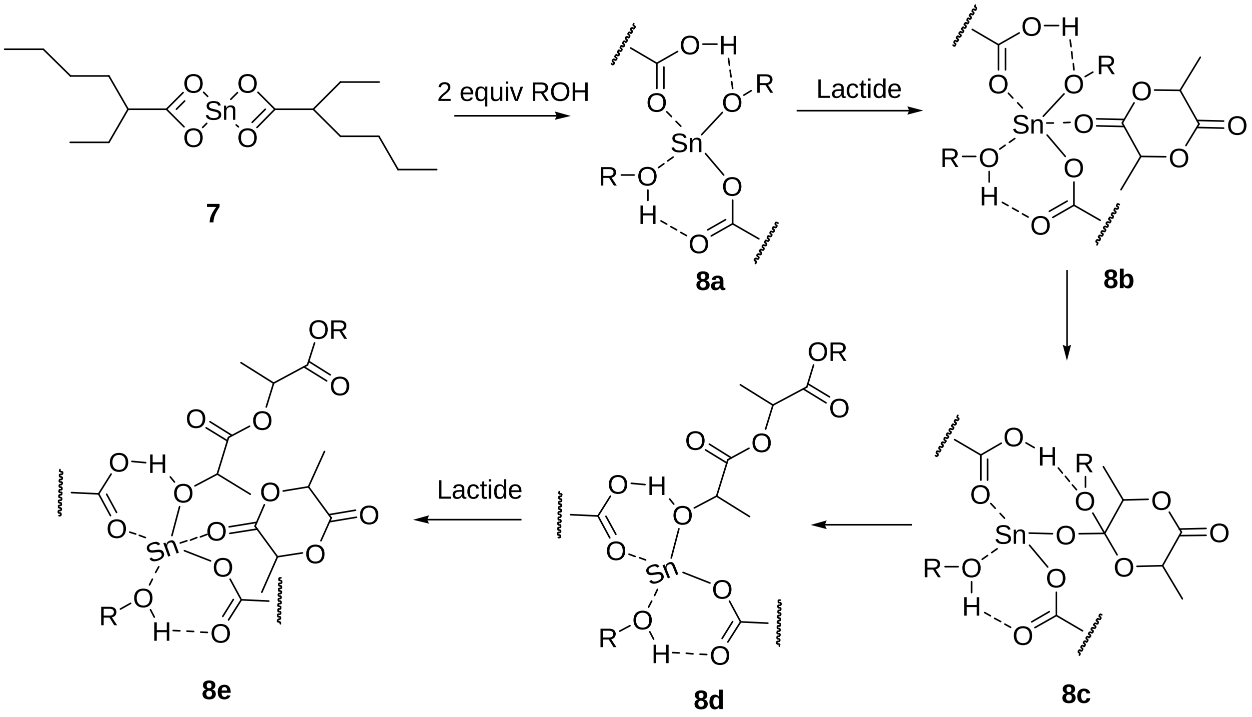


Figure 2. Coordination-insertion mechanism of $Sn(Oct)_2$ catalyzed polymerization of L-lactide.

SYNTHESIS OF PLA WITH *rac*-LACTIDE

Kinetic Resolution of rac-Lactide and the Formation of Isotactic Stereoblocks

The kinetic resolution of *rac*-lactide was accomplished with two different chiral aluminum complexes.[14-16] Spassky and co-workers[14a,b] reported one of the most important discoveries in the stereocontrol of PLA; the use chiral Al(OiPr)[(R)-(SalBinap)] ((*R*)-**9**) catalyst promoted high selectivity in the kinetic resolution of *rac*-lactide. (*R*)-**9** showed a 20:1 preference for the polymerization of D-lactide over L-lactide (Figure 3). This was a major advance in the stereocontrolled polymerization of PLA because the separation of *rac*-lactide to yield enantiopure lactide is expensive and tedious.

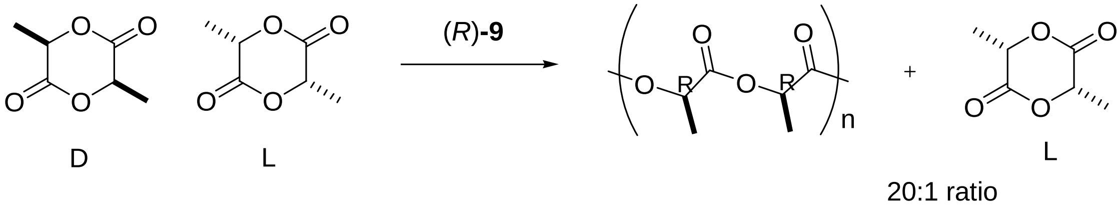
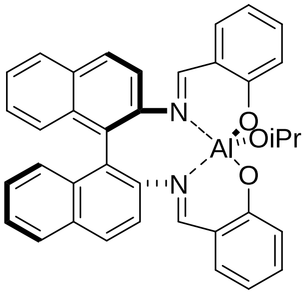


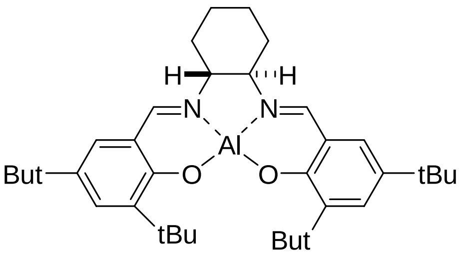
Figure 3. Kinetic resolution of *rac*-lactide.

At 60 % conversion, the product was identified by circular dichroism (CD) as poly(D-lactic acid) with a T_m of 170 ^{o}C. At 100% conversion, the T_m rose to 187 ^{o}C, indicating that eventually, isotactic stereoblock PLA was synthesized.

Feijen and co-worers[16] reported the first neat ROP of *rac*-lactide using a chiral catalyst, (*R, R*) salen-Al catalyst **(10)** in the synthesis of isotactic stereoblock PLA. Aluminum catalyst (*R, R*)-**10** was prefered the ROP of L-lactide over D-lactide by 14:1. The polymer had a T_m of 183.5 which is lower than that of the reported stereoblock complex reported by Spassky. The lower T_m could be attributed to lower stereoselectivity. Catalysts (*R*)-**9** and (*R, R*)-**10** could be used in the synthesis of neat L-lactide; if the polymer reaction were monitored carefully by CD, after polymerization of the reactive lactide (D-lactide is active with **9** and L-lactide is active with **10**), the non-polymerized "left over" could be distilled off under reduced pressure. However no such study has yet been reported.

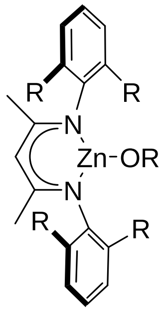


(R)-**9**



(R, R)-**10**

Synthesis of Heterotactic PLA from *rac*-Lactide



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R = iPr

Achiral catalysts are easier to synthesize and generally less expensive than their chiral counterparts; consequently a research priority is to achieve stereocontrolled polymerizations without chiral catalysts. In the polymerization of *rac*-lactide, the bulky nature of achiral catalyst **11** and the nature of the polymer chain-end stereocenter were used to influence the stereochemistry of the last inserted monomer, which determines the enantiomer enchained. If (*R, R*) configuration is enchained, then isotactic PLA is formed, whereas if the chain end attacks (*S, S*), then heterotactic PLA forms. Complex

11 was found to be highly active in the polymerization of *rac*-lactide with 90% of the linkages formed between alternating L and D-lactide. After 20 min at 20 °C, **11** polymerized *rac*-lactide to 95% conversion to PLA with a molecular weight of 37900 g/mol and a polydispersity index of 1.10. This material was also a non-crystalline, amorphous complex with a T_g of 49 °C; however since PLA is mostly used in low temperature environments, heterotactic PLA seems like a cheap alternative to the use of optically pure L or D-lactide.[17-20]

SYNTHESIS OF PLA FROM meso-LACTIDE

Synthesis of Syndiotactic PLA

Syndiotactic polymers often have better properties than their isotactic counterparts, such as increased crystallization rates and higher glass transition temperatures and melting points. Recent studies have thus targeted the synthesis of syndiotactic PLA with efficient seterochemical control and high yields.[15] Previous results by Thakur[21] and Kricheldork[22] have demonstrated low conversion (up to 75 %) of *meso*-lactide to syndiotactic PLA. The two pathways for the stereoselectivity of this polymerization are shown in Figure 4. Consistent attack at the enantiotopic A or B acyl-O bond leads to syndiotactic PLA while alternating attack on B and A leads to heterotactic PLA. Coates and co-workers reported that ***(R)*-9** exhibits a strong preference for opening of *meso*-lactide at the carbonyl group adjacent to the "R" stereogenic center, (Figure 5).

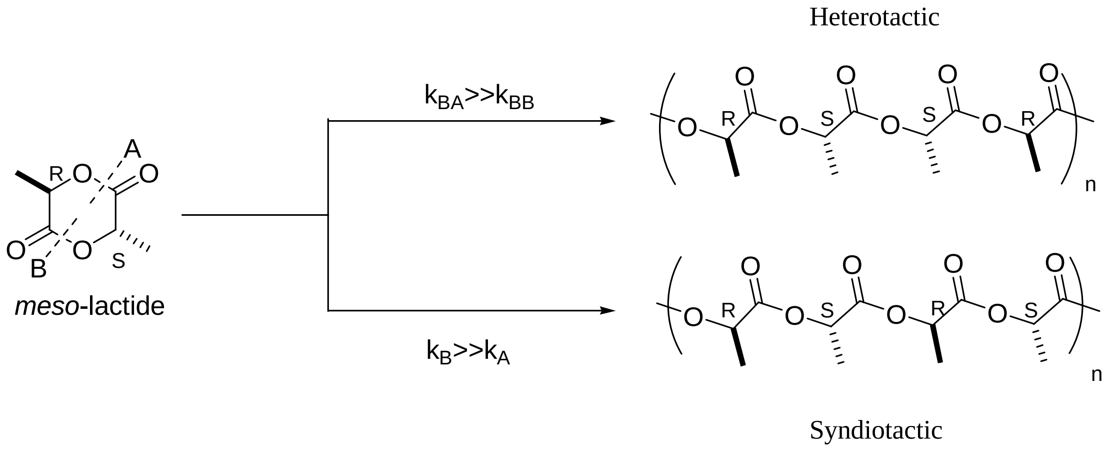


Figure 4. Different types of meso-lactide polymerization

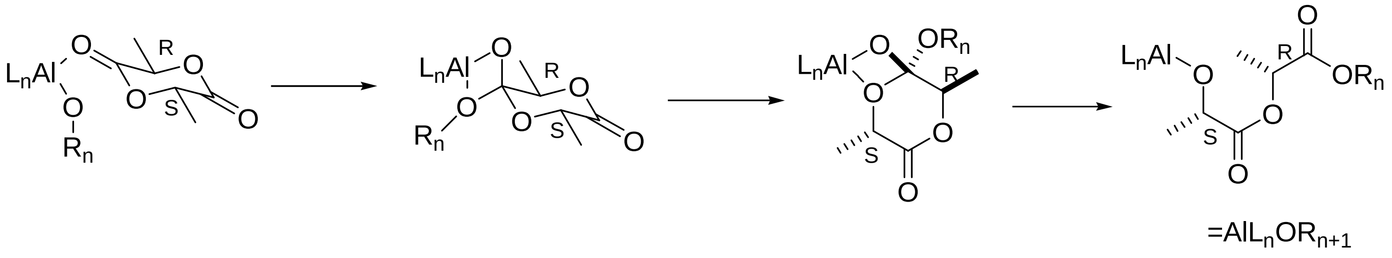


Figure 5. AlL_n-catalyzed polymerization of *meso*-lactide

^{1}H NMR analysis of the polymer proved high syndiotactic content (96%). The polymer had a T_g and T_m of 50.7 and 149 ^oC, respectively, which were lower than the values of isotactic PLA at 60 and 180 ^oC. This deviation was attributed to a lower degree of crystallinity since 96% of monomer was converted to syndiotacic PLA.

SYNTHESIS OF HETEROTACTIC PLA

Coates and co-workers were interested in determining if syndiotactic PLA could be synthesized with an optically impure catalyst, *rac*-**9**. They found that the reaction gave amorphous heterotactic polymer with a T_g = 43.2 ^oC (Figure 6). The ^{1}H NMR spectrum revealed heterotactic PLA. The authors have previously reported that (*R*)**-9** prefers to attack the carbonyl closest to the "R" stereocenter. After initiation, the polymer chains switch enantiomeric aluminum catalyst before insertion into the next monomer site. Molecular modeling suggests that (*R*)**-9** prefers the "R" center and (*S*)**-9** prefers the "S" center.

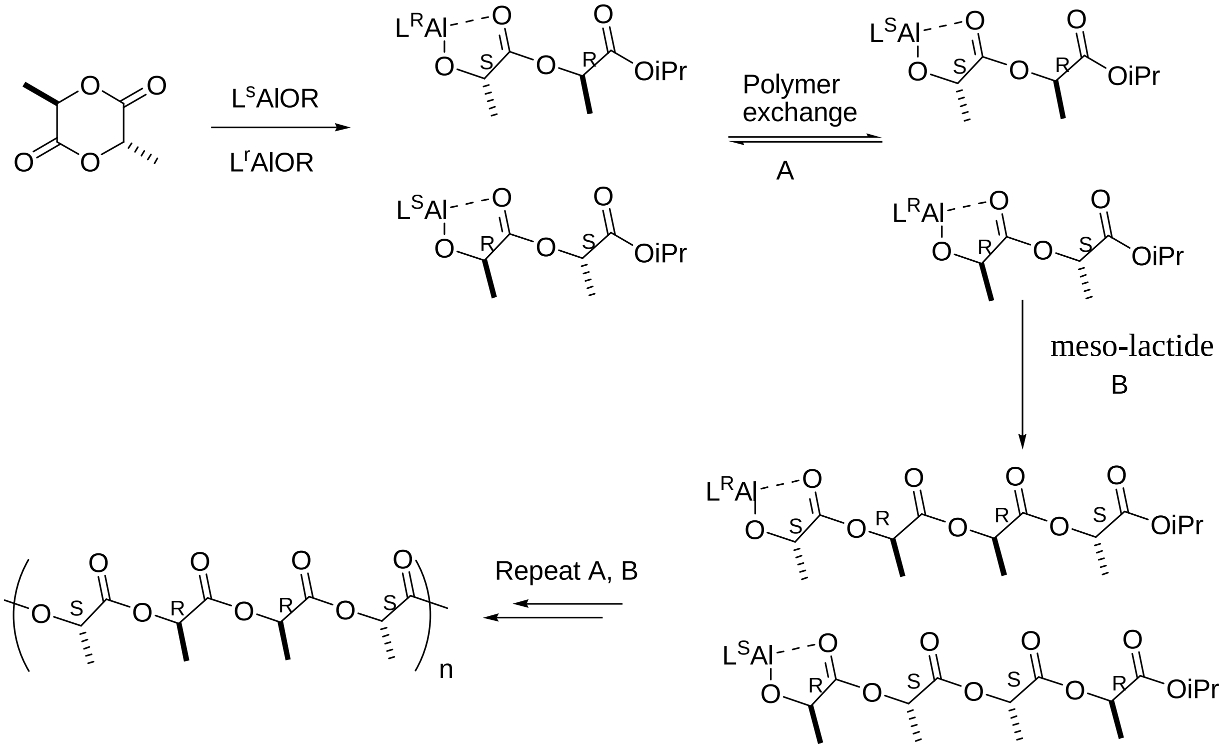
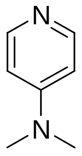


Figure 6. Synthesis of heterotactic PLA from *meso*-lactide using *rac*-**8**

ORGANIC CATALYST FOR ROP OF LACTIDE

An important consideration in the polymerization of lactide is the removal of metal contaminants, bound to the chain end before application in resorbable biomaterials.[23] The application of organocatalysts to controlled lactide polymerization would be a highly viable alternative to organometallic approaches. Several organic compounds have demonstrated high activity and enantioselectivity in a number of common organic transformations. Hedrick and co-workers were the first to report the use of first organic catalyst 4-(dimethylamino)pyridine (DMAP), **12**, in the ROP of lactide.[23] The catalytic cycle for **12** (Scheme 1a) and N-Heterocyclic carbene (NHC) **13** (Scheme 1b) are shown. Initiation occurs when an alcohol reacts with the lactide-organic catalyst complex, leaving a terminal ω-hydroxyl group to act as a nucleophile to react with additional lactide monomer. High conversions of up to 99% in two hours were obtained with NHC **13**. Thiourea-amine catalyst **14** has also been used but the ROP occurs by a different catalytic mechanism. Thiourea-amine **14** H-bonds to the carbonyl oxygen through the thiourea and the alcohol initiator is directed to attack the acyl-oxygen bond by the tertiary amine.[25]



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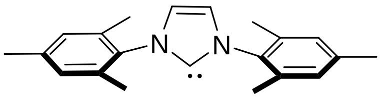

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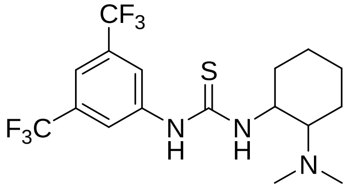

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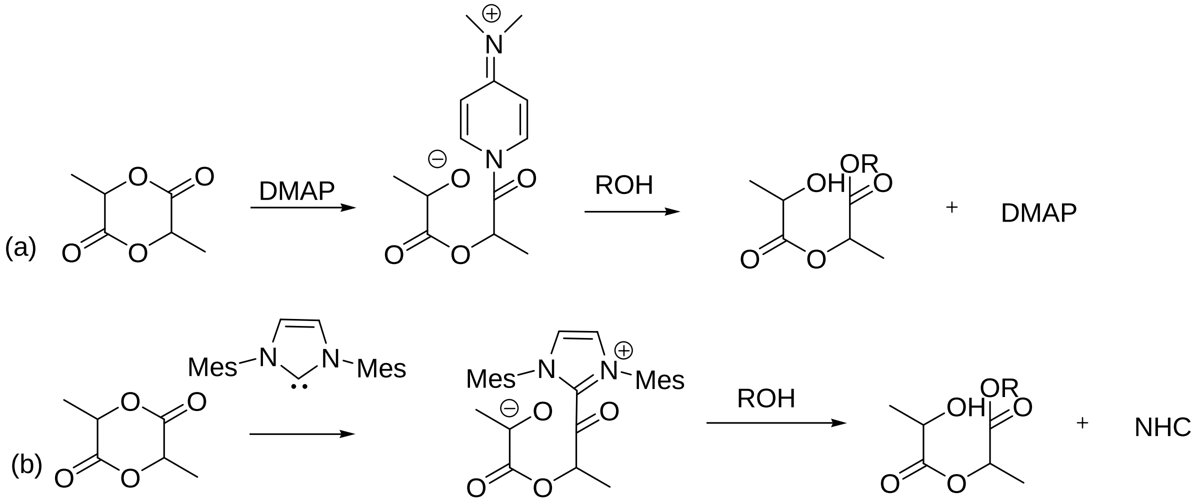
Scheme 1. Proposed mechanism of ROP of Lactide with **12** and **13**.



These organic catalysts are relatively inexpensive and highly active, and they yield PLA with low PDI because they are living polymerizations.[23] Organocatalysts provide attractive substitutes for the ROP of lactide for biomedical and environmental applications.[26]

CONCLUSION AND FUTURE WORK

PLA has recently attracted much attention as a biodegradable polymer for the replacement of oil-based material. Several different types of PLA have been synthesized with high stereoregularity and in high yield. More recent work has been devoted to the synthesis of organocatalysts because they are less toxic than metal catalysts. Hedrick has prepared a series of organocatalysts that have been highly reactive for the ROP of lactide. However, so far they have not shown as high stereocontrol or high molecular weights as the metal catalysts have. No doubt, new organocatalysts will be synthesized that will withstand the high temperature of the lactide melt while maintaining stereocontrol ability.

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