Summer Scholar Report

Toward Branched Polymers via Redox-Switchable Iron Based Catalyst

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Introduction

In the last century, plastics have become widely used in many different applications, such as packages for food, pharmaceuticals, and cosmetics. Many of these plastics are, however, derived from petrochemicals produced from fossil fuels. Although their durability, low cost, and lightweight certainly benefit our daily lives, their lack of biodegradability adds problems in our environment because they decompose very slowly in nature.[1,2] To mitigate this issue, biodegradable alternatives are necessary. A promising biodegradable polymer is poly(lactic) acid (PLA).[3] PLA is produced by the ring-opening polymerization of lactide, which comes from renewable resources such as corn starch, and can degrade through hydrolytic cleavage of ester bonds.[4] Moreover, PLA has been widely utilized in biomedical devices, such as bone substitutes, due to its biocompatibility.[5] However, there are still limitations in using PLA for other applications because of its undesirable properties, such as its brittleness and its poor oxygen barrier. As a result, polymer chemists have begun to explore various polymer compositions and architectures to improve its physical properties and diversify the utility of this biodegradable plastic.[6]

One architecture for PLA that has been underexplored is branched PLA. It has been reported that introducing even a small number of long-chain branches to PLA significantly affects the rheological, thermal, and mechanical properties of the plastic.[7] Historically, there are two general strategies to synthesize branched PLA. The first method, proposed by Knauss and coworkers, was to use $Sn(oct)_2$ as a catalyst to polymerize both lactide and glycidol in bulk at 130 ºC.[8] For the second strategy, Hedrick and coworkers used a hexahydroxy-functional dendrimer based on 1,1,1-tris(4'-hydroxyphenyl) ethane (TFPE) as an initiator for the ring- opening polymerization of lactide in the presence of a tin-based catalyst. To introduce new chains, the hydroxyl end groups are functionalized with benzylidene-protected 2,2-bis(hydroxymethyl) propionic acid (bis-MPA), followed by deprotection through hydrogenation. Lastly, each step was repeated to make this dendritic polymer larger.[9] Although branches are introduced to PLA through these two methods, they have significant disadvantages. The former reaction has a lack of control in making branches because the catalyst does not selectively polymerize the two monomers, so it is very difficult to predict the branching density and consistently produce the polymers with an identical branching density. In comparison to the first method, the second method has more control over the degree of branching, but the iterative steps may cause much of the loss of product through repeated purifications. As

shown by these reactions, there are still many challenges to make branched PLA on a large scale; the focus of this project is to make branched PLA using an alternative strategy that takes advantage of redox-witchable catalysis.[4,11]

In 2013, previous members from the Byers lab have synthesized bis(imino)pyridine iron(II) bis(alkoxide) complexes (**1**) , which were able to polymerize lactide. However, upon in situ oxidation of the catalyst, the ring-opening polymerization completely halted and resumed when the catalyst was reduced.[4] Interestingly, epoxides have an orthogonal reactivity, being active in the iron(III) but not the iron(II) oxidation state as shown in Figure 1.

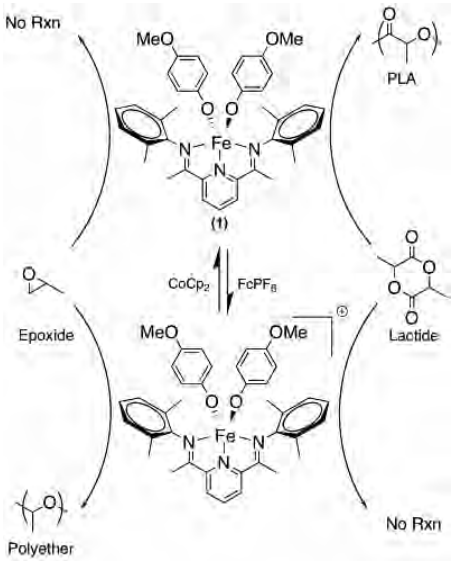
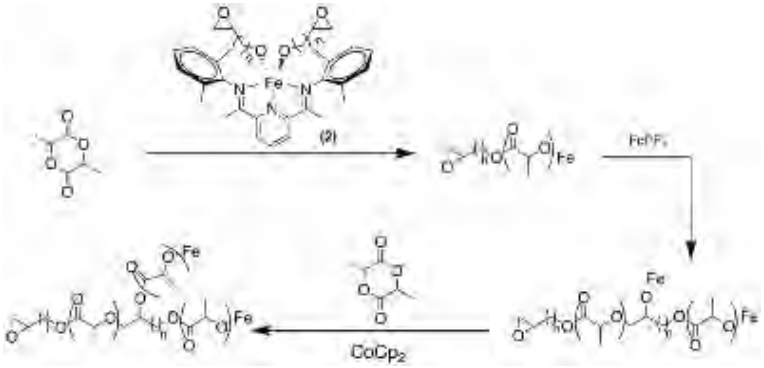


Fig. 1 *Redox Switchable Catalyst*



Scheme 1 *Proposed Synthesis of Branched Polymers).*

With this reactivity, the redox-switchable synthesis of block copolymers and cross-linked polymers was achieved.[10,11] To extend this methodology further, we hypothesize that this unique redox-switchable catalytic system can be used for the synthesis of branched polymers when an epoxy alkoxide is used as an initiator for the iron catalysts (**2**) as shown in Scheme 1. If our proposed method works, branched PLA can be synthesized with a controlled manner because the ironbased catalyst selectively polymerizes the monomers depending on its oxidation state. In addition, the overall reaction is more efficient because the oxidation state of the catalyst can be changed in situ . The goal of this paper is to explore and understand how to make the optimal catalyst for synthesizing the branched polymers.

Result and Discussion

Ligand Synthesis

The methodology for bis(imino) pyridine ligand synthesis was developed by using a templated synthesis strategy using $ZnCl_2$ to pre-coordinate to 2,6-diacetylpyridine as shown in Scheme 2a.[12] $ZnCl_2$ is a Lewis acid that makes tridentate coordination bonds with 2,6 diacetyl pyridine. This ligand synthesis proceeds upon the addition of glacial acetic acid (AcOH) as solvent. Choosing the proton source with a right pKa is very important. Adding a weaker proton source such as ethanol did not complete the reaction and had a trace amount, if not none, of the desired product. Moreover, when cyclohexylamine was used instead of aniline in the ligand synthesis with AcOH, insoluble salts were produced. We hypothesize using AcOH leads to the protonation of the aliphatic amine, which significantly reduces its nucleophilicity. The powerful aspect of this reaction is that once the bis(imino)pyridine zinc complex is formed, it precipitates out from the solvent. The precipitate can then be filtered and washed with cold diethyl ether or hexane to remove excess reagents and unreacted starting materials. The subsequent demetalation of the ligands is obtained by hydrolysis of the zinc complex in a biphasic mixture of dichloromethane and aqueous potassium oxalate. Recrystalization of the ligand from hot methanol results in high yields of the bis(imino)pyridine ligand.

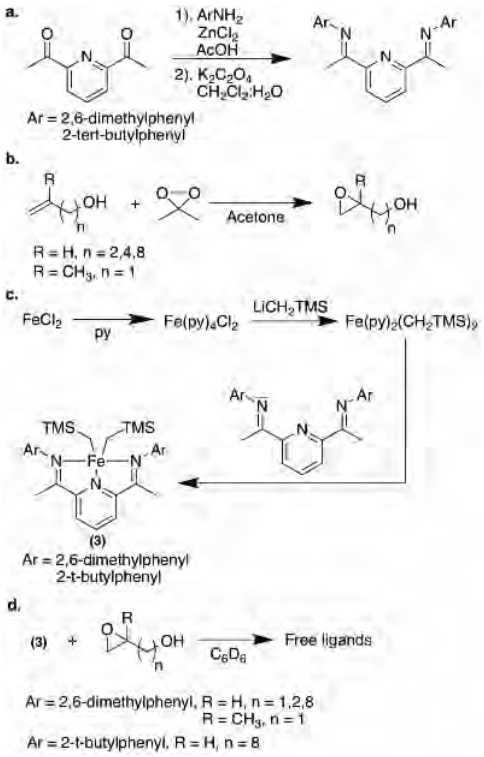
Epoxy Alcohol Synthesis

meta-Chloroperoxybenzoic acid (m-CPBA) is known as a powerful oxidizing agent to synthesize epoxides from alkenes. However, m-CPBA not only is toxic but also generates a stoichiometric amount of byproduct, which is m-chlorobenzoic acid. In this project, dimethyldioxirane (DMDO) was used instead to make epoxy alcohols. Since acetone is produced when DMDO reacts with the alkeneols, no aqueous work up is necessary and simple evaporation of solvent leads to the crude product, which is purified by column chromatography to give the epoxy alcohols (Scheme 2b). This procedure led to clean product for most epoxy alcohols, but the epoxy alcohol derived from 4-penten-1-ol was

not obtainable using this procedure. Instead, the epoxy alcohol product undergoes kinetically favored 5-exo cyclization to make a tetrahydrofuran product. To avoid this cyclization reaction, the alcohol group should be protected before epoxidation. 6-exo cyclization also occurred upon oxidation of 5-hexen-1-ol with DMDO, but since 6-exo cyclization is not as fast as 5-exo cyclizations, the desired epoxy alcohol could be isolated. The competing cyclization reaction was not a problem for small alkeneols like 4-buten-1-ol as well as for large ones such as 9-decen-1-ol, and high yields of the corresponding epoxyalcohols could be obtained.

Iron Complex Synthesis

The Fe(PDI)(CH_2 TMS)$_2$ (**3**) synthesis was accomplished following literature precedence (Scheme 2c).[4,14] First, $FeCl_2$ was stirred in pyridine solvent to give $Fe(py)_4Cl_2$. Alkylation of $Fe(py)_4Cl_2$ was then achieved using two equivalences of $LiCH_2TMS$ to give $Fe(py)_2(CH_2TMS)_2$ as a red oil. $Fe(py)_2$ $(CH_2TMS)_2$ decomposes within a week even if it is stored in a freezer, so, it must be used as early as possible or stored at low temperatures in a frozen benzene solution. The labile property of pyridine allow the pyridine ligands of $Fe(py)_2(CH_2TMS)_2$ to be replaced by bis(imino)pyridine ligands, which affords the bis(imino)pyridine iron alkyl complex (**3**) as a purple solid. Previously, the last step to make the iron based catalyst for lactide polymerization was protonolysis



Scheme 2 *Synthetic route for the catalyst*

of the iron alkyl to make discrete iron alkoxide complexes. Thus, attempts to carry out the protonolysis of the alkyl iron complex with epoxy alcohols were made to synthesize the desired epoxy alkoxide iron complex. However, when (**3**) with 2,6-dimethylphenyl group and glycidol were mixed in deuterated benzene, the resulting NMR spectrum did not demonstrate any evidence for paramagnetic peaks and only showed evidence for the free bis(imino)pyridine ligand. We hypothesized that even though alcohol group from epoxy alcohol might ligate to the iron center, the epoxide group might also chelate. In such an instance, the epoxide group could liberate the bis(imno)pyridine ligand.

To prevent this chelation, we increased the number of carbon between the epoxide functionality and the alcohol functionality in the epoxy alcohol. However, when 3,4-epoxy-1-butanol was used for the protonolysis reaction, the resulting NMR spectrum once again only showed evidence for free ligand. At this stage in our investigations, we had two different ways to approach this problem. First, we hypothesized that epoxy alcohol with 2, 3, and 4 methylene spacers could chelate to the iron center to make a thermodynamically stable ring. As a result, we pursued 9,10-epoxy-1-decenol for the protonolysis reaction because this epoxy alcohol has 8 methylene units, which would be too long to form a stable chelate. Second, we hypothesized that using a more sterically hindered epoxide would prevent chelation. With this rationale, 2, 3-epoxy-2-methyl-1-propanol was synthesized to test if our hypothesis was correct. Unfortunately, both 9,10-epoxy-1-decenol and 2,3-epoxy-2-methyl-1-propanol failed to ligate with the iron complex because all the paramagnetic peaks were lost. Moreover, Fe(PDI)$(CH_2TMS)_2$ with tert-butylphenyl group was mixed with 9,10-epoxy-1-decenol to see if changing the 2,6-dimethyl groups to a 2-*t*-butyl group would affect the reaction. However, once again, the mixture only showed the free ligands in the NMR spectrum.

Conclusion

Even though the synthesized epoxy alcohols were not effective to create the desired iron complex needed to synthesize the branched PLA, there are still many directions to explore. For example, aromatic epoxy alcohols have yet to be investigated. Since para-methoxylphenol undergoes protonolysis with the alkyl iron complex, we believe that compounds like epoxy phenol would be able to make the epoxy alkoxide iron complex. Moreover, the steric environment about the epoxide has not been explored extensively. Lastly, modification of the bis(imino)pyridine ligand may also lead to productive results. We have primarily used Fe(PDI)$(CH_2TMS)_2$ with 2,6 dimethylphenyl group thus far, but different ligands such as those derived from 2-t-butyl-aniline or with cyclohexylamine have not been extensively explored. We expect that changing the steric environment of the ligand will affect the interaction between the iron complex and the epoxy alcohol so that the discrete iron alkoxides required for lactide polymerization are formed.

Experimental Section

General Considerations

All reactions were carried out in open air in the fume hood, except for the synthesis of iron complex, which were carried out in an inert atmosphere glove box. Nuclear magnetic resonance (NMR) spectra were recorded at ambient temperature on a Varian spectrometer (^{1}H 500 MHz) in $CDCl_3$ or C_6D_6 and are referenced versus chemical shifts of residual protic solvent impurities. The line listing for the ^{1}H NMR spectra are reported as: chemical shift in ppm (multiplicity, number of protons, coupling constant in Hz). Deuterated solvents were obtained from Cambridge Isotopes Laboratories and used without further purification. All synthesized compounds that were made previously matched the reported spectra in the literature. Reactions were monitored by thin layer chromatography (TLC). TLC was carried out using Merck TLC Silica gel 60 F254 glass plates and stained with cerium ammonium molybdate stain (CAM) and UV light. Flash column chromatography was carried out using 40-63μm (230 x 400 mesh) sized silica.

General Procedure for Bis(imino) Pyridine Ligand (PDI) Synthesis[12]

A 250 mL round bottom flask was dried in an oven. 2,6-diacetyl pyridine (0.500 g, 3.06 mmol, 1 equiv.), acetic acid(30 mL), and $ZnCl_2$ (0.500g, 3.67 mmol, 1.1 equiv.) were added in the round bottom flask. While stirring, the corresponding aniline (2.4 equiv.) was added to the reaction mixture. The reaction was refluxed for 40 min and then cooled down to room temperature. The yellow precipitates were filtered and washed with cold acetic acid and diethyl ether or hexane. The solid was suspended in CH_2Cl_2 (125 mL) and potassium oxalate (5.00 g, 30.1 mmol, 10 equiv.) in water (50.0 mL). The mixture was stirred for 5 min at room temperature. The organic layer was separated and the aqueous layer was washed with CH_2Cl_2 (3 x 7.5 mL). All collected organic layer was dried with Na_2SO_4 , and the solvent was removed *in vacuo* , which would give yellow solid products.

2,6-Bis(1-((2,6-dimethylphenyl)imino)ethyl)-pyridine.

Yield: 70%. ^{1}H NMR (500 MHz, $CDCl_3$): 2.06 (s, 12H), 2.24(s, 6H), 6.95(t, J = 7.5 Hz, 2H), 7.08(d, J = 7.5 Hz, 4H), 7.92(t, J = 7.9 Hz, 1H), 8.48(d, J = 7.8 Hz, 2H).

2,6-Bis(1-((2-tert-butylphenyl)imino)ethyl)-pyridine.

Yield: 80%. ^{1}H NMR (500 MHz, CDCl3): 1.37(s, 18H), 2.41(s, 6H), 6.54(d, J = 7.6 Hz, 2H), 7.08(t, J = 7.6 Hz, 2H), 7.20(t, J = 7.5 Hz, 2H), 7.43(d, J = 8.0 Hz, 2H), 7.93(t, J = 7.8 Hz, 1H), 8.40(d, J = 7.8 Hz, 2H).

Synthesis of Dimethydioxirane[13]

In a 1 L round bottom flask, water (20.0 mL, 1110 mmol, 2.7 equiv.) was added and put at 0 ºC in an ice bath. Acetone (30.0 mL, 408 mmol, 1 equiv.) was added to water, followed by NaHCO3 (24.0 g, 285 mmol, 0.7 equiv.). The reaction mixture was stirred for 20 min. The stirring was halted, and Oxone (25.0 g, 41 mmol, 0.1 equiv.) was added slowly. The reaction mixture was stirred for another 15 min. The mixture was distilled using a rotovap with the same procedure as the literature.13 The collected faint yellow solution was dried with Na2 SO4 and decanted to a graduated cylinder. Less than 10 mL of Acetone was used to rinse and poured into the graduated cylinder. The product solution was poured into a 40 mL vial covered with aluminum foil and stored in a fridge for the following epoxidation reaction. The total volume was about 35 mL and the molarity varied from 0.04-0.07.

General Procedure for Epoxy Alcohol Synthesis

In a 100 mL round bottom flask, corresponding olefin alcohols (0.9 equiv.) was added and put at 0 ºC in an ice bath. DMDO diluted in Acetone (35 mL, 1 equiv.) was added to the flask and stirred for 2 hours. The Acetone solvent was removed using a rotovap and the crude product was passed through column with the Hexane : Ethyl acetate (7:3) eluent. This gave a colorless clear oil.

2,3-Epoxy-2-Methyl 1-propanol. Yield: 66%. ^{1}H NMR (500 MHz, $CDCl_3$): 1.36(s, 3H), 2.66 d, J= 5.8 Hz, 1H), 2.92 (d, J = 4.6 Hz, 1H), 3.62(d, J = 11.9 Hz, 1H), 3.73(d, J = 12.3 Hz, 1H).

3,4-Epoxy-1-butanol. Yield: 52%. ^{1}H NMR (500 MHz, $CDCl_3$): 1.72(m, 1H), 1.92(m, 1H), 2.60(dd, J = 4.8, 2.8 Hz, 1H), 2.81(t, J = 4.4 Hz, 1H), 3.10 (m, 1H), 3.82 (t, J = 6.0 Hz, 2H).

5,6-Epoxy-1-hexanol. Yield: 25%. ^{1}H NMR (500 MHz, $CDCl_3$): 1.29 (br, 1H), 1.52-1.67 (m, 6 H), 2.48(dd, J = 5.0, 2.7 Hz, 1H), 2.76(t, J = 4.5 Hz, 1H), 2.92(m, 1H), 3.67(t, J = 6.2 Hz, 2H).

9,10-Epoxy-1-decanol. Yield: 57%. ^{1}H NMR (500 MHz, $CDCl_3$): 1.32 (br, 8H), 1.48-1.60 (m, 6H), 2.46 (dd, J = 5.1, 2.7 Hz, 1H), 2.75(t, J = 4.5 Hz, 1H), 2.90 (m, 1H), 3.64 (t, J = 6.6 Hz, 2H).

Synthesis of $Fe(py)_4Cl_2$[4,14]

In a glovebox, FeCl2 (10.0 g, 78.9 mmol) was added to a two-neck round bottom flask equipped with a septum and a 180º joint. The round bottom flask was taken out from the glove box, cooled to -20.0C in an ethylene glycol dry ice bath under Nitrogen from the schlenk line. Freshly distilled pyridine (100 mL) was added dropwise to the flask while stirring the reaction mixture. After the addition of pyridine, the reaction was stirred for 4 hours. Flask smoked, and yellow solid appeared. After all pyridine was pumped into the

secondary trap, the flask was tightly sealed and brought to the glovebox. The solid was washed on a frit with copious amount of pentane. The yellow powder was dried *in vacuo* overnight. Yield: 94% ^{1}H NMR (500 MHz, C_6D_6): 3.30, 4.97, 7.99.

Synthesis of $Fe(py)_2(CH_2TMS)_2$[4,14]

In a glovebox, $Fe(py)_4Cl_2$ (0.600 g, 1.35 mmol, 1 equiv.) was suspended in a vial with pentane (4.00 mL) and put in a freezer for 30 min. $LiCH_2TMS$ (0.255 g, 2.71 mmol, 2 equiv.) was dissolved in pentane (3.00 mL). The iron solution was taken out from the freezer and stirred at room temperature. Then, $LiCH_2TMS$ solution was slowly added to the iron solution, changing the color from yellow to red. The reaction mixture was stirred for an hour. The crude product was run through a frit with celite with a copious amount of pentane. Pentane was evaporated *in vacuo*. The product was a red oil and yielded 89%. ^{1}H NMR (500 MHz, C_6D_6): 10.85, 16.07, 36.85.

Synthesis of Fe(PDI)2,6-dimethyl$(CH_2TMS)_2$[4,14]

In a glovebox, Fe(py)2 (CH2 TMS)2 (0.385 g, 0.991 mmol, 1 equiv.) was added in a vial and dissolved in pentane (3 mL). 2,6-Bis(1-((2,6-dimethylphenyl)imino)ethyl)-pyridine (0.319 g, 0.864 mmol, 0.87 equiv.) was added in a vial and suspended in pentane (3.00 mL). The iron complex solution was added to the vial with the pyridine ligand. The reaction mixture was stirred for a few seconds, and the color of the solution changed from red to purple. The reaction mixture was passed through a frit with celite and pentane was used to wash. Pentane was dried *in vacuo*. The product was put at a minimum amount of pentane for recrystallization overnight in a freezer. The product was a purple solid and yielded 75%. ^{1}H NMR (500 MHz,C6 D6): -147.32, -16.28, 11.55, 12.89, 22.80, 57.80.

Synthesis of Fe(PDI)2-t-butyl$(CH2TMS)_2$[4,14]

In a glovebox, $Fe(py)_2(CH_2TMS)_2$ (0.167 g, 0.431 mmol, 1 equiv.) was added in a vial and dissolved in toluene (2 mL). 2,6-Bis(1-((2-tert-butylphenyl)imino)ethyl)-pyridine (0.157 g, 0.369 mmol, 0.86 equiv.) was added in a vial and dissolved in toluene (2 mL). The iron complex solution was added to the vial with the pyridine ligand. The reaction mixture was stirred for a few seconds, and the color of the solution changed from red to purple. The solvent was removed *in vacuo* and dissolved in pentane. The reaction mixture was passed through a frit with celite and pentane was used to wash. Pentane was dried *in vacuo*. The product was put at a minimum amount of pentane for recrystallization overnight in a freezer. The product was purple and yielded 73%. ^{1}H NMR (500 MHz, C_6 D_6): -151.35, -43.54, -16.99, 12.14, 18.50, 52.21.

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