Redox-switchable Ring-opening Polymerization with Ferrocene Derivatives

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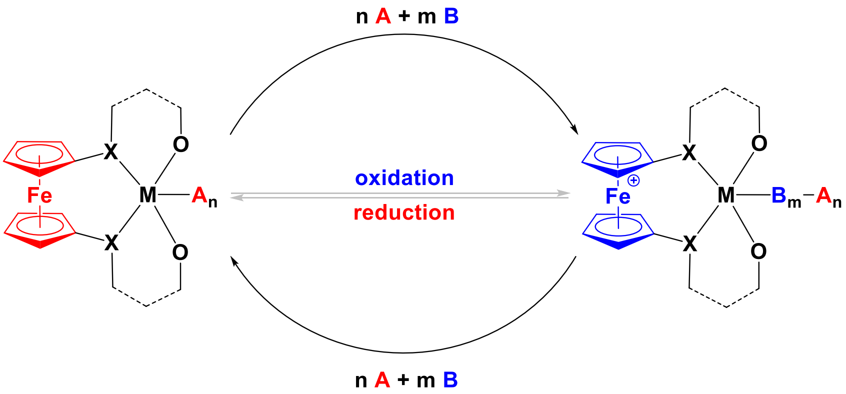
CONSPECTUS: Switchable catalysts incorporate stimuli-responsive features and allow synthetic tasks that are difficult or impossible to accomplish in other ways. They mimic biological processes in that they can provide both spatial and temporal control, unlike most reactions promoted by man-made catalysts that usually occur according to carefully optimized conditions. In the area of switchable catalysis, redox-switchable ring opening polymerization has attracted much attention, emerging as a powerful strategy for the development of environmentally friendly biodegradable copolymers, especially those containing blocks with complementary properties. Controlling the sequence and regularity of each copolymeric building block can affect the material properties significantly since they are directly related to the respective microstructures. Such a control can be exerted with a well-designed redox-switchable catalyst by timing the oxidation and reduction events. In highly selective systems, one form of the catalyst reacts with a monomer until the redox state of the catalyst is altered, when the new catalyst reacts with another monomer. The reaction time may be varied from one cycle to another to generate various designer multiblock copolymers.

The first instance of redox-mediated ring-opening polymerization (ROP) was described by N. Long and coworkers in 2006. This example, as well as many early reported redox-switchable catalysts, could only achieve an on/off switch of activity toward a single monomer or substrate. However, our efforts brought on a general strategy for designing redox-switchable metal complexes that can catalyze different reactions in two oxidation states. In recent years, our contributions to this research field led to the synthesis of several multiblock copolymers prepared from bio-renewable resources.



This Account provides an overview of reported redox-switchable polymerization catalysts that allow for complementary reactivity in different oxidation states, and highlights the potential of this strategy in preparing biodegradable materials. First, we define the field of redox-switchable catalysis and illustrate the design and significance of our ferrocene-chelating ligands, in which the oxidation state of iron in ferrocene can control the reactivity of the resulting metal complexes remotely. Next, we illustrate recent advances in the synthesis of new biodegradable copolymers including (1) how to tune the activity of the ROP catalysts by exploring various metal centers and ferrocene-based ligand combinations; (2) how to synthesize new multiblock copolymers of cyclic esters, epoxides, and carbonates by redox-switchable ROP; (3) how to understand the mechanism of these reactions by discussing both experimental and theoretical investigations. By applying and developing redox-switchable strategies, various novel materials and reactions can be expected in the future.

1. Introduction

Switchable catalysis is an atom-economical method that generates multiple species from a single precursor. The main difference between switchable and other types of catalysis is the use of external triggers that can stop or start a reaction multiple times. It is important to make a distinction between this definition and other uses of the word “switchable” in chemistry since the term has been applied to denote a change in the selectivity of a reaction when different types of conditions are used.

The physical and chemical properties displayed by man-made polymers are directly related to their respective microstructures.[1] By incorporating stimuli-responsive features into artificial catalysts and designing switchable systems, access to various well-defined polymers that are difficult to achieve otherwise is enabled.[2-8] Among such features, redox-active units have attracted much attention because the addition of external redox reagents can alter the chemical reactivity of the corresponding catalyst. While early examples focused on the ability to cycle a polymerization reaction between the on and off states, an ideally designed redox-switchable catalyst should display complementary and orthogonal reactivity of the different states, and allow the selective discrimination of monomers from a mixture (Figure 1).

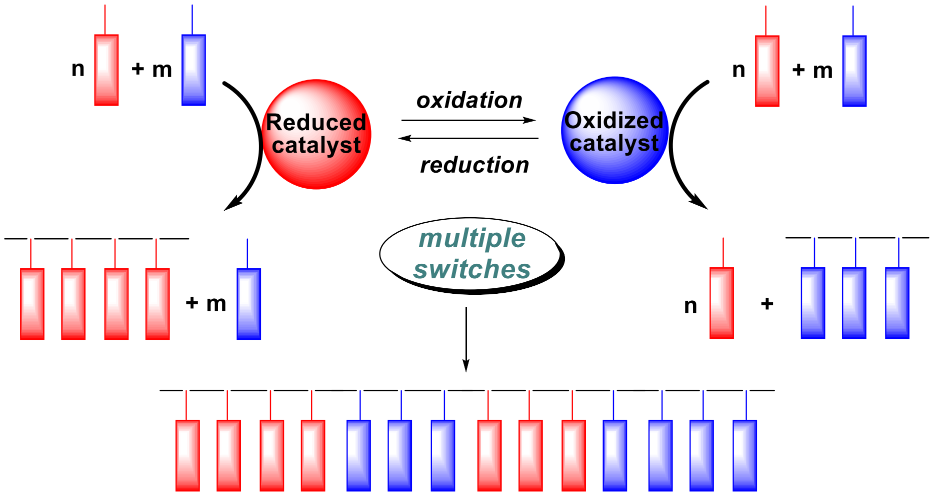


Figure 1. Redox-switchable polymerizations achieved with two monomers in one pot.

Our group has studied the use of ferrocene as a redox switch (Figure 2) for several years.[9-21] The main application of such systems is the formation of biodegrable copolymers. Aliphatic polyesters are a major category of biodegradable polymers, and can be prepared from a variety of natural compounds allowing the use of renewable feedstocks as well as an assortment of various monomers.[22,23] By introducing redox-switchable catalysts into this field, various copolymers of aliphatic esters could be prepared readily.

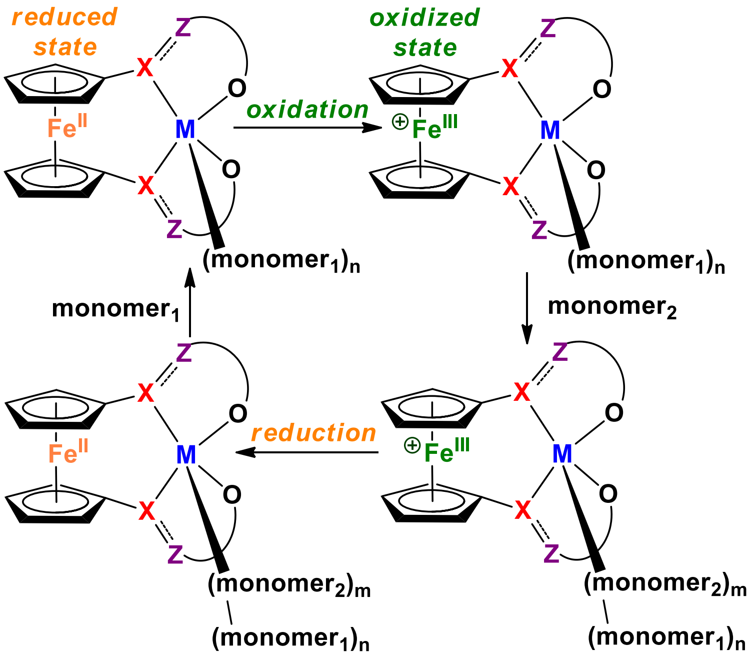


Figure 2. Redox-switchable polymerizations achieved with two monomers in one pot by using ferrocene-derived catalysts.

Although diblock polyesters can usually be synthesized by sequential addition polymerization procedures, the synthesis of multiblock copolymers by a coordination-insertion mechanism is not facile because either the catalytic activity toward the first monomer is quenched after the second monomer is polymerized or transfer agents only transfer the growing polymer chain in one direction.[24] Fortunately, redox-switchable catalysis can provide a novel perspective to solve the problem. This account will summarize the recent progress in unraveling the polymerization of cyclic esters/ethers by utilizing redox-switchable catalysts. Remaining challenges and future opportunities are also considered and discussed.

2. Historical design of redox-switchable catalysts based on ferrocene derivatives

Typically, redox-switchable catalysts are metal complexes containing a separate redox-active group. Examples where the redox-active unit and the metal performing catalysis are the same are also known.[20,25-27] An advantage of the former set might be that the same supporting ligand can be used to coordinate several metals; in this way, a more diverse substrate scope might be achieved than with the latter class. In all cases, these systems have an advantage over a two-catalyst system since only one pre-catalyst is necessary; this provides a method to alter the electronic properties of a metal center without the need for excessive, additional synthetic steps to achieve ligand modifications.[28]

The change between the reduced and oxidized states of iron in a ferrocene framework has been well studied.[29] Due to the synthetic versatility in obtaining ferrocene derivatives, in principle, a plethora of pre-catalyst combinations can be generated allowing fine-tuning of the polymerization activity.

In 2006, N. Long and coworkers reported that the rate of *rac*-lactide ROP could be altered by changing the oxidation state of a ferrocenyl unit in $[(\text{salen})\text{Fc}_2]\text{Ti}(\text{O}^i\text{Pr})_2$ (salen = *N*,*N'*-bis(salicylidene)ethylenediamine, Fc = ferrocenyl, Figure 3).[30] When the ferrocene component was in its reduced, Fe(II) form, the titanium center polymerized *rac*-lactide with an 18% monomer conversion after 8 h at 70 ^{o}C. A significant decrease in reactivity was observed after the oxidation of the ferrocenyl groups by AgOTf. A subsequent reduction of the Fe(III) centers back to Fe(II) with FeCp*_2 (Cp* = pentamethylcyclopentadienyl) restored the catalytic activity. Moreover, the resulting polymer product remained well-controlled even after performing multiple switching events. The authors proposed that the oxidation/reduction of the ferrocene moiety changed the electron density at titanium, affecting the polymerization activity. Although a complete on/off redox-switchable polymerization was not achieved, this report greatly inspired the field of redox-switchable polymerization.

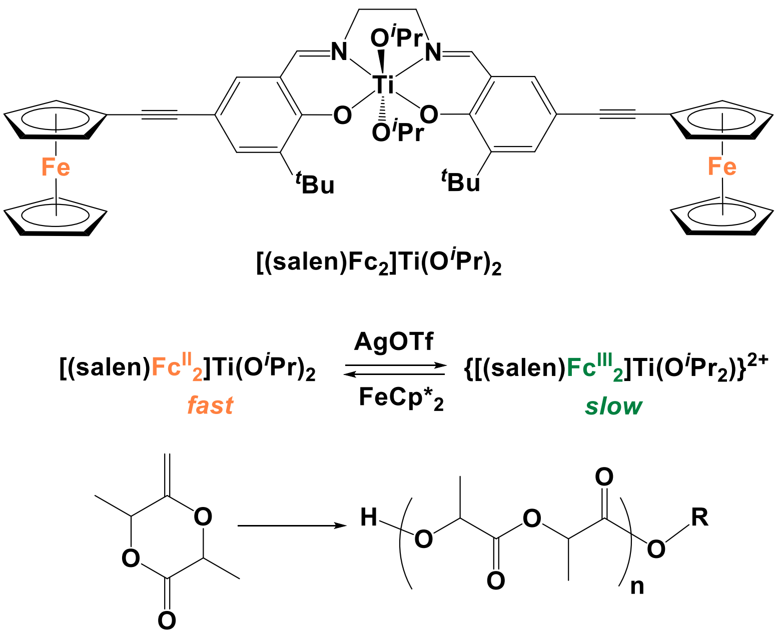


Figure 3. Switchable ROP of *rac*-lactide by [(salen)Fc$_2$]Ti(O^{i}Pr)$_2$. Adapted from ref. 30. Copyright 2006 American Chemical Society.

Our group has been long engaged in the study of 1,1'-disubstituted, ferrocene-chelating ligands.[31-35] In 2011, we employed Ce(phosfen)(O^{t}Bu) (phosfen = 1,1'-di(2-*t*-butyl-6-diphenyl-phosphiniminophenoxy) and Ce(salen')(O^{t}Bu) to test the redox-switchable polymerization of L-lactide (L-LA, Figure 4).[20] Similar to N. Long's results, the less Lewis acidic, Ce(III) complex induced the ROP of L-LA and resulted in PLA with narrow dispersities ($Đ$ = 1.12−1.34). The addition of ferrocenium tetrakis(3,5-bis(trifluoromethyl)phenyl)borate (FcBAr^F) effectively oxidized the catalyst to a cationic derivative, which was inactive toward the polymerization of L-LA.

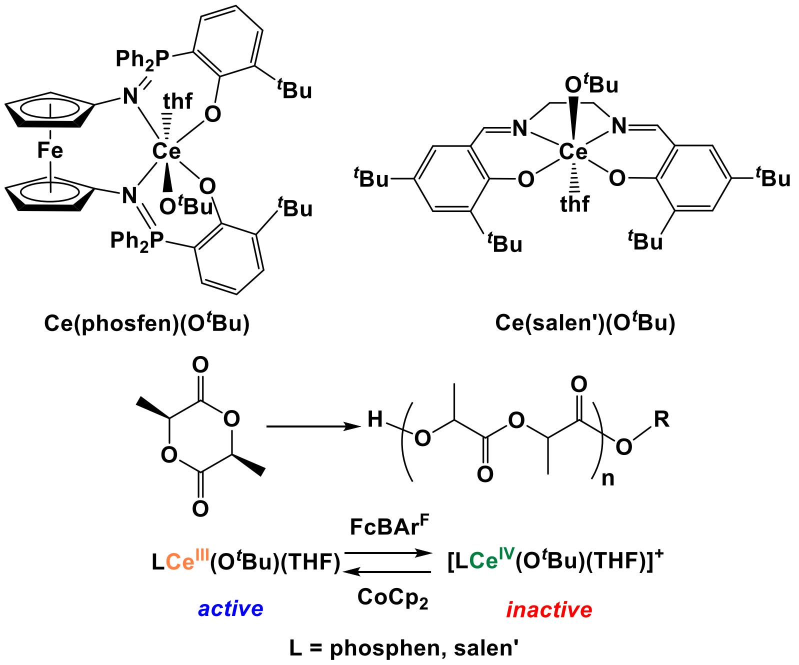


Figure 4. The first example of a metal based switch for the redox controlled polymerization of L-LA. Adapted from ref. 20. Copyright 2011 Royal Society of Chemistry.

Other metal based redox switches for lactide polymerization include Ce(OSSO)$_2$ (OSSO = 1,2-di(2,4-di-*t*-butyl-6-thiophenoxy)ethylene) and 1,2-di(2,4-di-dimethylphenylmethyl-6-thiophenoxy)ethylene) complexes[36] and bis(imino)pyridine iron bis(alkoxides),[26,27] in which cerium and iron, respectively, are used both as the redox switch and the catalytically active center. In all cases, the less Lewis acidic compounds (Ce(III) and Fe(II) complexes) showed activity toward lactide, whereas the Ce(IV) and Fe(III) counterparts did not.

Although metal-based redox switches have shown a great potential in the synthesis of diblock copolymers,[27] their applicability to the synthesis of multiblock copolymers has been restricted. We hypothesized that separating the redox active unit and the metal performing catalysis will improve the control in these systems, and, therefore, looked into the study of appropriate designs. In N. Long's example, [(salen)Fc$_2$]Ti(O^{i}Pr)$_2$, the redox active unit was appended at the periphery of the molecule, and the two ferrocenyl groups communicate with titanium through conjugation, but they are rather apart from it. Since through-space interactions[37] could play an important role in influencing the reactivity of the catalytically active metal, we decided to employ chelating 1,1'-ferrocene derivatives as redox-switchable candidates. This strategy was first used by Wrighton and coworkers when investigating the differential activity of 1,1'-cobaltocenediphosphine rhodium complexes in hydrogenation and hydrosilylation reactions.[38] Using a similar design, the yttrium compound Y(phosfen)(O^{t}Bu) was synthesized and characterized (Figure 5).[19,21] Y(phosfen)(O^{t}Bu) showed activity toward L-LA in the reduced state and no activity after its oxidation by FcBAr^F.[21] By changing the monomer from L-LA to trimethylene carbonate (TMC), the rate of polymerization also decreased when the catalyst was oxidized. However, by changing the central metal to indium, which has a similar ionic radius to yttrium (0.80 *vs.* 0.90 Å), an opposite trend was observed. By using In(phosfen)(OPh), the rate of TMC polymerization increased significantly upon oxidation.[21] Unlike cerium in Ce(phosfen)(O^{t}Bu), yttrium cannot be oxidized. Thus, we hypothesized that the redox switch occurred at iron, a hypothesis confirmed by XANES and Mössbauer spectroscopic studies.

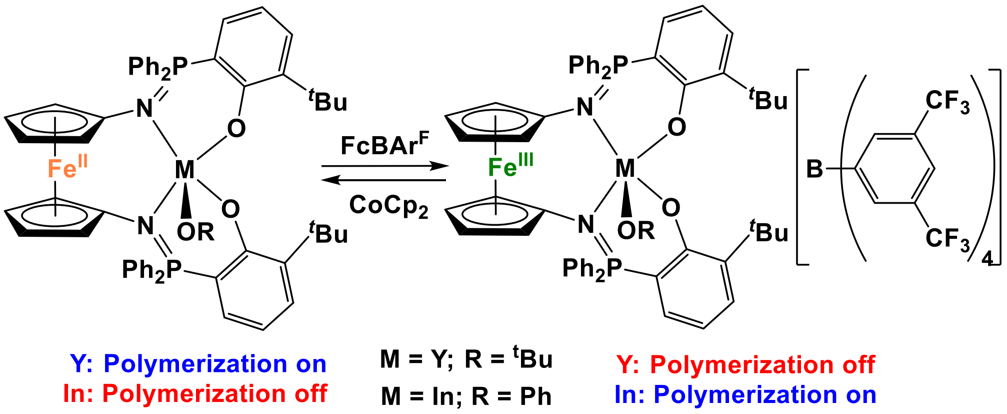


Figure 5. Redox switch of yttrium and indium alkoxides supported by ferrocene derivatives. Adapted with permission from ref. 21. Copyright 2011 American Chemical Society.

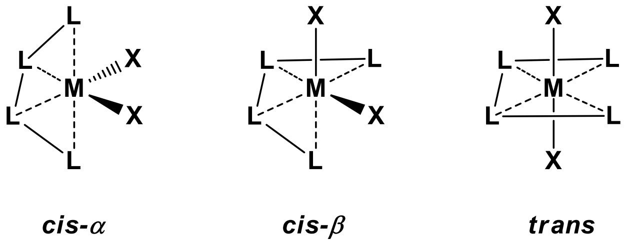


Figure 6. Three possible geometrical isomers in an octahedral coordination environment of tetradentate ligands.

It should be noted that these ferrocene tetradentate ligands can coordinate to the metal center in three different modes, cis-α, cis-β, and trans (Figure 6). The different geometries were found to lead to different activities in ring-opening polymerizations. In 2015, B. Long and co-workers reported a titanium(IV) salfen (salfen = 1,1′- di(2,4-di-*tert*-butyl-6-salicylimine)ferrocene) displaying a cis-β geometry (Figure 7).[39] By comparison, the geometry of the titanium complex reported previously by N. Long and coworkers was trans.[30] Interestingly, in B. Long's paper, the ROP of L-LA with the reduced catalyst was significantly slower than with the oxidized catalyst, which represented an opposite trend in activity as compared with the above mentioned systems. However, if the catalyst was oxidized in the presence of L-LA and then reduced back, the reduced species showed a dramatically increased polymerization rate. Once it was oxidized back in situ, the newly formed compound had no activity toward the ROP of L-LA anymore.

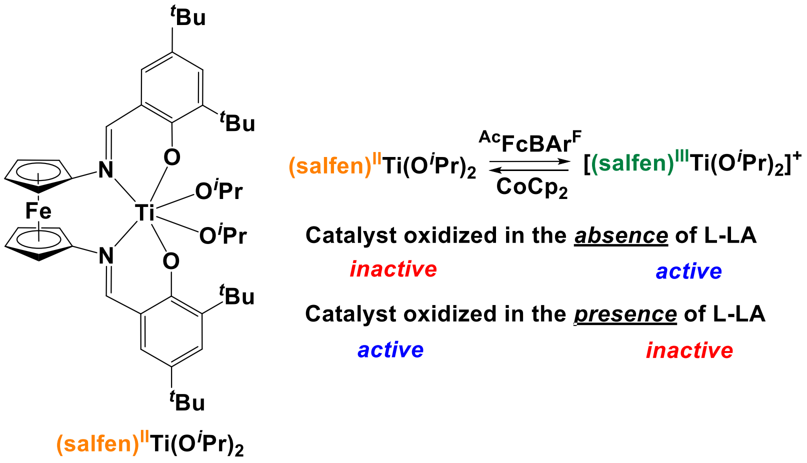


Figure 7. Selective redox-switchable polymerization of L-LA by (salfen)Ti(O^{i}Pr)$_2$. Adapted from ref. 39. Copyright 2015 American Chemical Society.

Although further investigations are needed to explain this phenomenon, based on *in situ* ^1H NMR spectra and cyclic voltammetry (CV) experiments, the authors proposed that the geometry of the catalyst was changed from its original cis-β to a cis-α or trans conformation by using the redox reagents in the presence of L-LA. In the absence of L-LA, the geometry of the catalyst remained cis-β after oxidation. Thus, the authors proposed that when the oxidation and reduction reactions were carried out in the presence/absence of monomers, the polymerization activity was different. These results indicate that the coordination modes of the supporting ligand to the metal can also change the reactivity significantly.

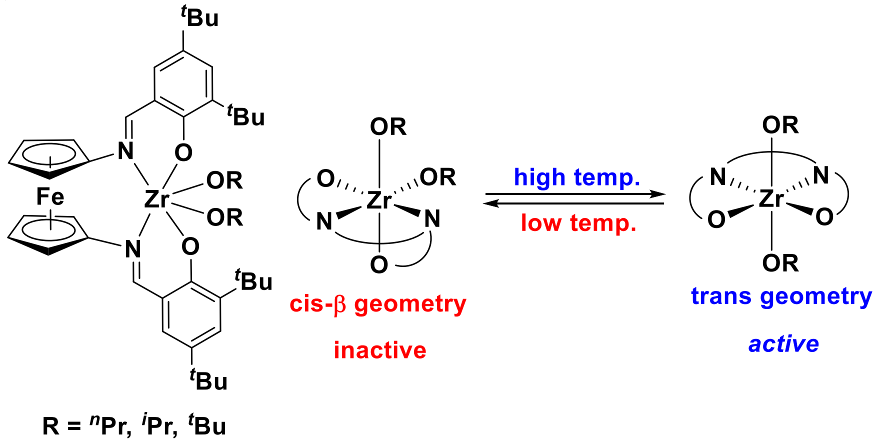


Figure 8. Geometry changes in (salfen)Zr(OR)$_2$ relevant to lactide polymerization. Adapted from ref. 40. Copyright 2018 American Chemical Society.

Interestingly, the zirconium analogues, (salfen)Zr(OR)$_2$ (R = *ⁿ*Pr, *ⁱ*Pr, *ᵗ*Bu), show a somewhat simplified behavior.[40] All three compounds exist as a mixture of cis-β and trans isomers with the isomer featuring a cis-β geometry found majorly in solution. However, an isomerization between the two was observed at ca. 100 °C (Figure 8). This isomerization was also observed in the presence of L-LA. Furthermore, the isolation of a (salfen)Zr(O^{n}Pr)$_2$ lactide intermediate supported the change to the trans coordination geometry necessary for polymerization.[40]

3. Redox-switchable copolymerization reactions

In 2014, our group reported the first redox-switchable copolymerization of L-LA and ε-caprolactone (CL) with a novel titanium(IV) catalyst (Figure 9).[18] In this work, we developed three new supporting ligands, salfan (1,1′-di(2,4-di-*t*-butyl-6-N-methylmethylenephenoxy)ferrocene), thiolfan (1,1′-di(2,4-di-*t*-butyl-6-thiomethylenephenoxy)-ferrocene), and thiolfan* (1,1′-di(2,4-di-*t*-butyl-6-thiophenoxy)ferrocene). Compared with the previous phosfen ligands, which position the auxiliary ligands trans to each other due to their rigid backbone, in salfan and thiolfan, the core metals are well wrapped and the auxiliary ligands are cis. Moreover, the electronic and steric effects can be easily tuned because different groups can be introduced onto both the phenolate and the amine fragment (nitrogen-based variants).

Compounds (salfan)Zr(O^{t}Bu)$_2$, (thiolfan)Zr(O^{t}Bu)$_2$, and (thiolfan*)Ti(O^{t}Bu)$_2$ were synthesized and characterized.[18] Electrochemical studies (E$_{1/2}$= -0.57, 0.07, and 0.02 V vs. ferrocene, respectively) indicated that they can be oxidized by suitable ferrocenium salts. In the reduced (neutral charge) state, all compounds could promote the polymerization of L-LA at 100 °C. The oxidation of the metal complexes with ^{Ac}FcBAr^F (acetylferrocenium tetrakis(3,5-bis(trifluoromethyl)phenyl)borate) would result in no further consumption of L-LA, but the activity could be restored by reduction with CoCp$_2$. Interestingly, the ROP of CL did not occur with (salfan)Zr(O^{t}Bu)$_2$ and (thiolfan*)Ti(O^{i}Pr)$_2$. However, after their oxidation, the resulting cationic complexes could carry it out easily at room temperature.

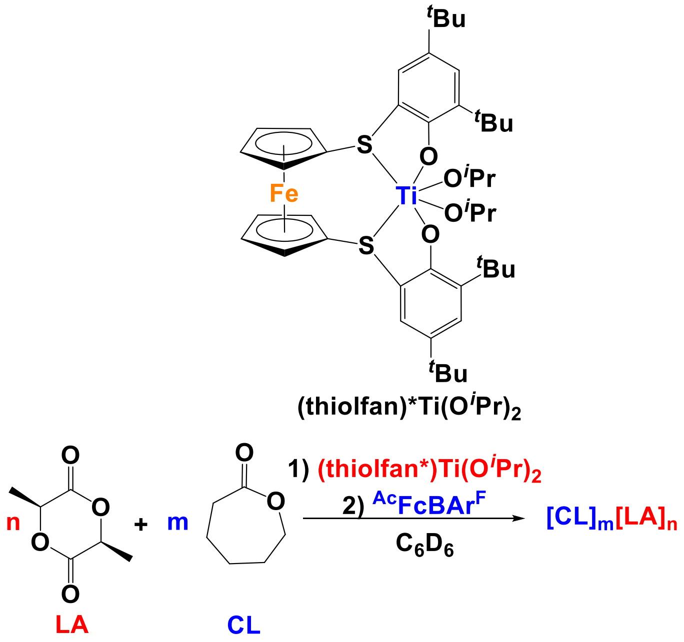


Figure 9. Redox-switchable copolymerization of L-LA and CL in one pot. Adapted from ref. 18. Copyright 2014 American Chemical Society.

The discrimination between the ROP of L-LA and CL enabled the one-pot synthesis of a diblock copolymer (Figure 9). L-LA was polymerized first with 58% conversion by the neutral (thiolfan*)Ti(O^{i}Pr)$_2$ at 100 °C, while almost no conversion of CL was observed. After the addition of the oxidant, ^{Ac}FcBAr^F, at room temperature, CL was then polymerized at 100 °C and ultimately afforded a well-defined ($Đ$ = 1.12) poly(CL-*b*-L-LA) copolymer. As for (salfan)Zr(O^{t}Bu)$_2$, although L-LA could be polymerized by the reduced form of the catalyst, the ROP of CL did not occur after the addition of the ^{Ac}FcBAr^F. Furthermore, (thiolfan)Zr(O^{t}Bu)$_2$, in which the only change versus (salfan)Zr(O^{t}Bu)$_2$ is the use of sulfur instead of nitrogen, showed no big difference in the reactivity of the two redox states toward the ROP of CL.[12] All these results indicated again that the change in reactivity observed as a result of the oxidation state of the ferrocene backbone was strongly affected by both the central metal and the supporting ligand.

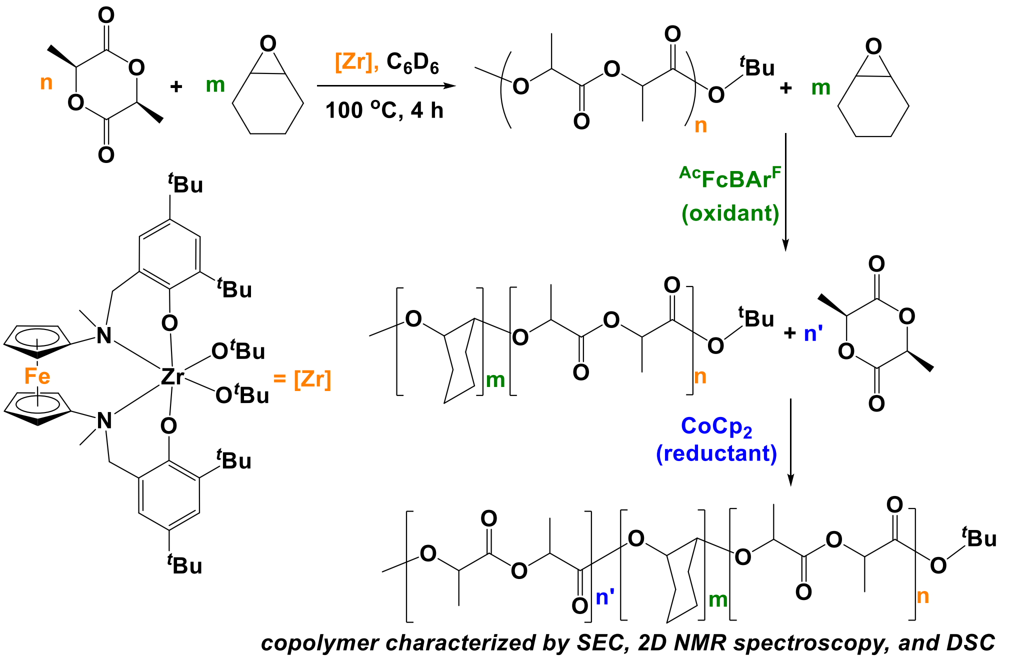


Figure 10. Redox-switchable polymerization of L-lactide and cyclohexene oxide. Adapted from ref. 15. Copyright 2016 American Chemical Society.

In 2016, Byers and coworkers[27] and our group[15] reported another redox controlled block copolymerization, the copolymerization of cyclic esters and epoxides. Byers's iron catalyst (neutral state) could polymerize *rac*-LA, but was inactive toward cyclohexene oxide (CHO). In contrast, the oxidized catalyst showed a reversed activity pattern.[27] Our group found that (salfan)Zr(O^{t}Bu)$_2$ could also be applied to the copolymerization of cyclic esters and epoxides (Figure 10). For example, L-LA and β-butyrolactone were only polymerized by the catalyst in the reduced state, while epoxides were polymerized only with the oxidized catalyst.[15] Thus, the redox-switchable copolymerization of L-lactide/β-butyrolactone and cyclohexene oxide in one pot could be achieved. Various diblock and triblock copolymers were prepared by this strategy and were characterized by size exclusion chromatography (SEC), and 2D and DOSY NMR experiments.

4. Mechanistic studies

Our working hypothesis to explain the shift in reactivity of the catalysts in different oxidation states is that a change in the steric and electronic effects of the supporting ligands will lead to an increased or decreased coordination ability to the metal center. In general, the oxidation process will decrease the electron density of the metal performing the catalysis, making it more electrophilic than its reduced counterpart. However, in order to understand the detailed mechanism of these reactions and move the field forward, there is still much work to be done.

4.1. Computational studies. In this section, we will discuss several explanations to why the redox-switchable organometallic catalysts show different reactivity in ROP. A common coordination-insertion mechanism of cyclic ester ROP is shown in Figure 11, involving monomer coordination, insertion, and ring opening. The driving force of the ROP reaction is the relief of bond-angle strain or steric repulsion within the cyclic monomer.[41]

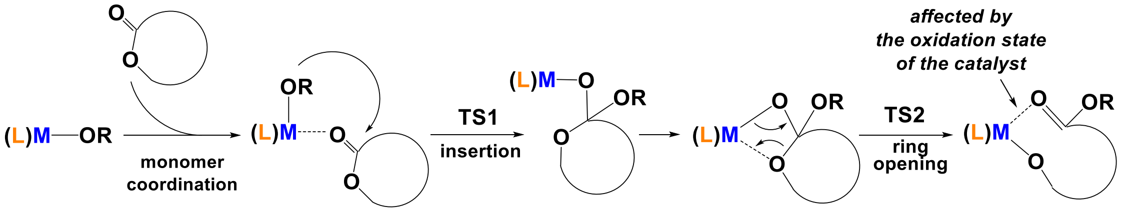


Figure 11. A general mechanism of cyclic ester ROP.

To make it easy to control the polymerization and investigate the mechanism, in 2017, we synthesized and characterized an aluminum complex with only one active alkoxide chain, (thiolfan*)Al(O^{t}Bu).[10] With detailed theoretical and experimental studies, we found out that the chelation of the carbonyl groups to the metal center played an important role during the polymerizations. Before discussing details, it should be mentioned that our computational studies show that most calculated intermediates and transition states preserve six-coordination at the metal by elongating the distance to one or both neutral donors. These elongations have varying degrees ranging from what can be considered a weak interaction (ca. 2.5 Å) to the absence of any interaction (> 5 Å) and rotation of the donor away from the metal center.

In general, the insertion of the first LA is always facile with both reduced and oxidized catalysts (Figure 12). However, after the first insertion of LA, the insertion of a second monomer (such as CL and TMC) is much more difficult. This is due to the carbonyl group of LA chelating to the metal center strongly (forming a five member ring). This chelation results in a slower propagation than initiation rate, leading to a controlled polymerization. We propose that the chelation effects observed with (thiolfan*)Al(O^{t}Bu) also apply to other catalysts active for lactide ROP, explaining the controlled nature of these reactions.

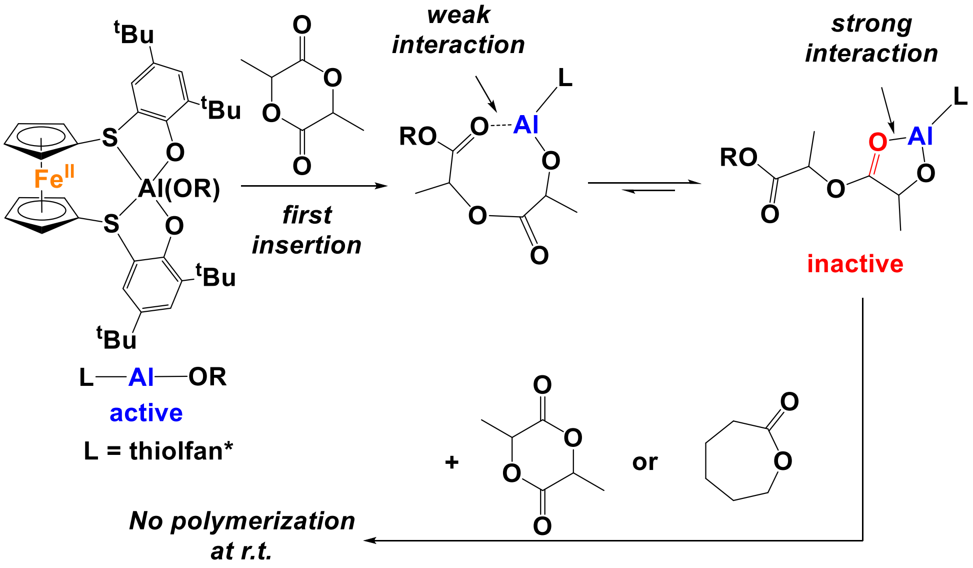


Figure 12. The effect of the first insertion of LA.[10] Reprinted with permission from ref. 10. Copyright 2017 American Chemical Society.

The situation is different for the polymerization of other cyclic esters and carbonates. In the reduced state, the first insertion of CL or TMC usually will not lead to a significant change compared to the next insertion (propagation), as the newly formed product has a similar structure to the original catalyst. However, in the oxidized state, as the metal center is more electron deficient than in the reduced state catalyst, after the insertion of one CL or TMC, the carbonyl group will weakly chelate to the metal center, increasing the nucleophilicity of the alkoxide chain. Thus, the propagation step will be facilitated by the chelation effect, causing a slightly faster propagation than initiation. A faster or similar rate of propagation versus initiation usually translates into a less controlled polymerization, resulting in broad dispersity values and higher molar masses than expected. However, as the energy barriers of the initiation and propagation steps are close, there are more opportunities to tune the polymerizations by modifying the structures of the supporting ligands. We propose that, with different supporting ligands, the ROP of cyclic esters and carbonates could vary from being uncontrolled to controlled.

Understanding these results can help us explain confusing experimental results and design novel catalyst systems. For example, the rate of polymerization of CL is much faster than that of LA with the reduced species. However, if LA and CL are combined in the same pot for copolymerization, LA will be consumed first.[10] The reason the rate of polymerization of LA is slower than that of CL is because, after the first insertion of LA, due to the strong chelating effect of the carbonyl group in LA (forming the five-member ring, Figure 12), the propagation is difficult. However, if LA and CL are together, the insertion of a new LA is always easier than that of a CL molecule (the carbon atom in the carbonyl group of LA is more electron deficient than that in CL). Based on this reasoning, a one-pot procedure for the selective copolymerization of LA and CL could be devised. Even though both LA and CL react with (thiolfan*)Al(O^{t}Bu), the final copolymerization product was the diblock copolymer $(CL)_m(LA)_n$.

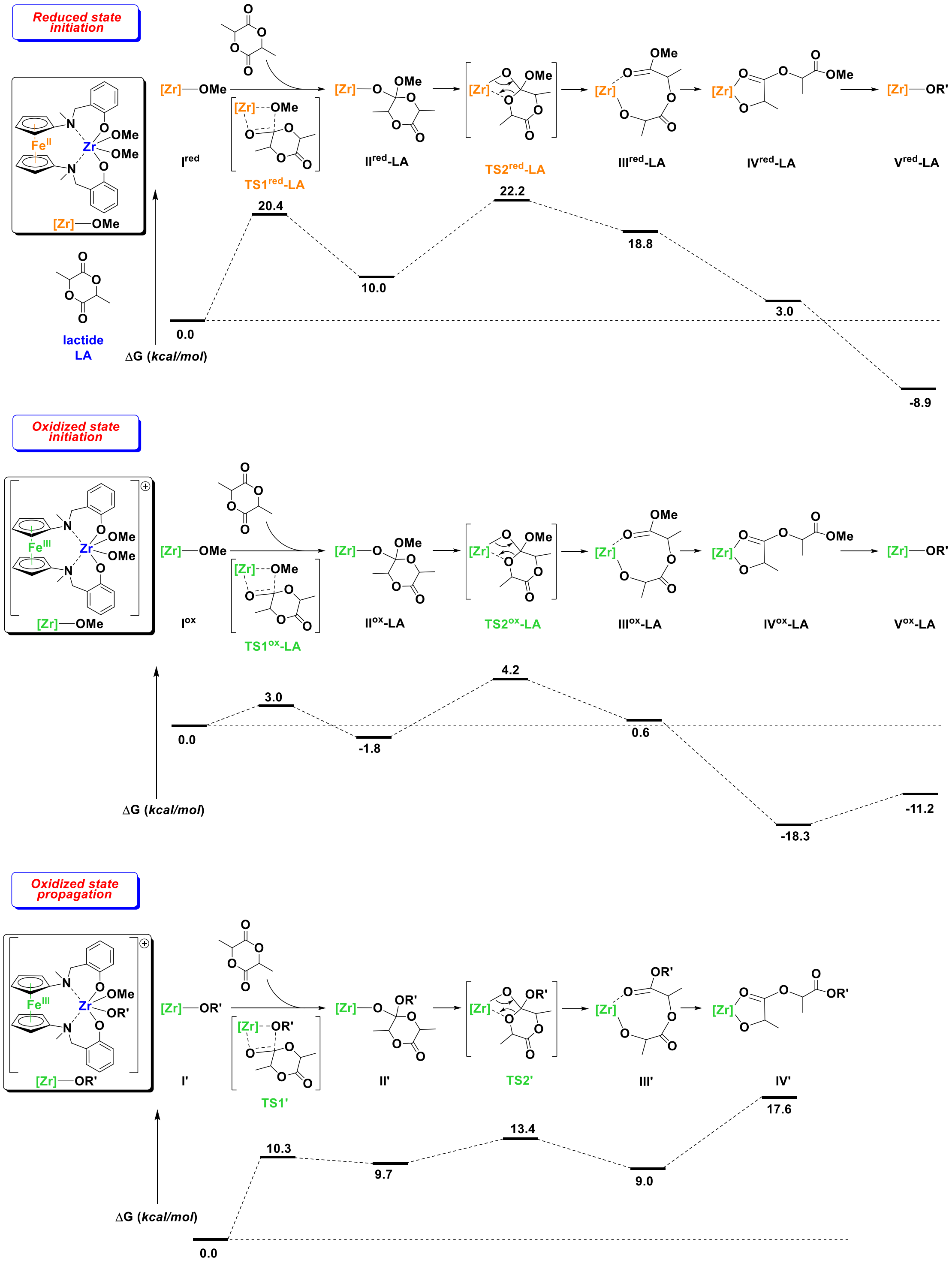


Figure 13. Potential energy surfaces for the ROP of LA by (salfan)Zr(O^{t}Bu)$_2$ (top) and [(salfan)Zr(O^{t}Bu)$_2$][BAr^F] (middle - initiation and bottom - propagation). Reprinted with permission from ref. 11. Copyright 2017 American Chemical Society.

A similar computational study performed with a model of (salfan)Zr(O^tBu)$_2$, (salfan)Zr(OMe)$_2$ (Figure 13), reinforced the conclusions discussed in the previous paragraphs.[11] For example, when the energy barriers for the polymerization of LA catalyzed by the two oxidation states of (salfan)Zr(OMe)$_2$ were calculated, it was found that the coordination of the carbonyl group is the major factor in determining the observed behavior. For the reduced catalyst, the first insertion of LA is favorable. The final product **V^{red}-LA** has a similar structure to the initial catalyst **I^{red}-LA** and is more stable by 8.9 kcal/mol. Therefore, the propagation step should have a similar energy barrier as the initiation step and LA polymerization should proceed smoothly, as observed experimentally.

For the oxidized catalyst, however, after the insertion of LA, the carbonyl group coordinates to zirconium tightly, making the five-member ring structure **IV^{ox}-LA** the favored product. The product **V^{ox}-LA** is less stable by 7.1 kcal/mol than **IV^{ox}-LA**, making the following propagation thermodynamically unfavorable.

Finally, from natural bond order (NBO) studies performed during the aluminum study,[10] we realized that the interactions between the metal center and the carbonyl groups can be roughly predicted by electrostatic effects. In general, in the oxidized compounds, the metal center is more electron deficient than in the reduced state. Thus, the interactions between the metal center and the carbonyl group in the oxidized complexes are stronger than in the reduced complexes. On one hand, the chelating effect of the carbonyl group will increase the steric hindrance effect, which makes the coordination of the monomer more difficult and thus slow down the propagation. On the other hand, the interactions between the metal center and the carbonyl group will increase the electron density around the metal, which facilities the nucleophilic attack of the propagation. As mentioned above in section 3.1, and observed with other classes of metal complexes,[9,13,16,17,42] the coordination mode of the ferrocene tetradentate ligands to the metal center can also affect the activities strongly. Since during the oxidation/reduction reaction a change in the coordination mode of the supporting ligand is possible, small changes in the central metals and the ligands will affect the redox-switchable ROP significantly.

4.2. System effects. During mechanistic studies carried out with (salfan)Zr(O^{t}Bu)$_2$ and lactide/cyclohexene oxide,[11] we noticed that one monomer has a rather large influence on the polymerization of the other (Figure 14). Therefore, we decided to study the different conversion times of LA and CHO as a function of the block identity, i.e., whether the switchable polymerization starts with LA or with CHO. In those experiments, LA is polymerized more quickly in the presence of CHO, while CHO is polymerized more slowly when LA is present (Figure 14). These relative changes occurred regardless of monomer concentration or number of equivalents and correlated with the amount of leftover monomer in solution from the synthesis of the previous block.[11]

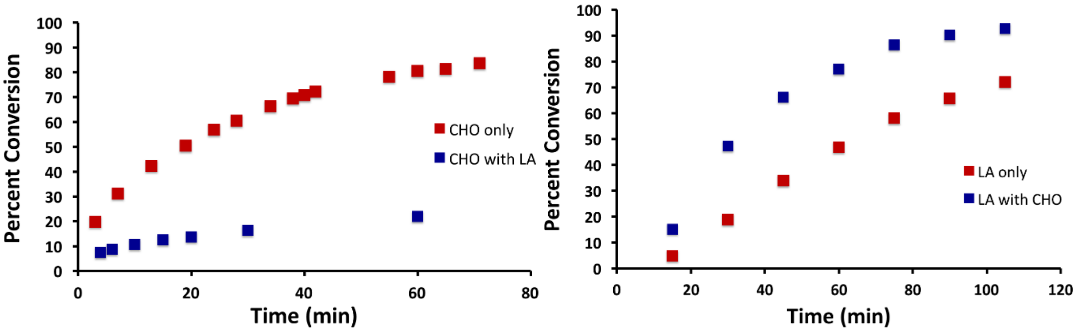


Figure 14. Comparison of polymerization rates of CHO by (salfan)Zr(O^{t}Bu)$_2$ (left) and L-LA by in situ generated [(salfan)Zr(O^{t}Bu)$_2$][BAr^F] (right) with and without the presence of the other monomer. Reprinted with permission from ref. 11. Copyright 2017 American Chemical Society.

Similar observations were made with (thiolfan*)Ti(O^{i}Pr)$_2$ when copolymers of lactide and ε-caprolactone (CL) were attempted.[12] Although [(thiolfan*)Ti(O^{i}Pr)$_2$][BAr^F] does not react with LA, a one-pot reaction with L-lactide and ε-caprolactone showed 62% LA and 36% CL conversion in 14 hours (Figure 15). Even though the oxidized titanium species shows virtually no activity with L-lactide by itself, a significant activity was observed when L-lactide was in the presence of ε-caprolactone. Furthermore, although the activity of (thiolfan*)Ti(O^{i}Pr)$_2$

toward L-lactide is not modified by the presence of ε-caprolactone, the reverse is not true: the conversion of CL was slowed down from 83% to ca 15% after 28 h at 100 ºC (Figure 15).[12]

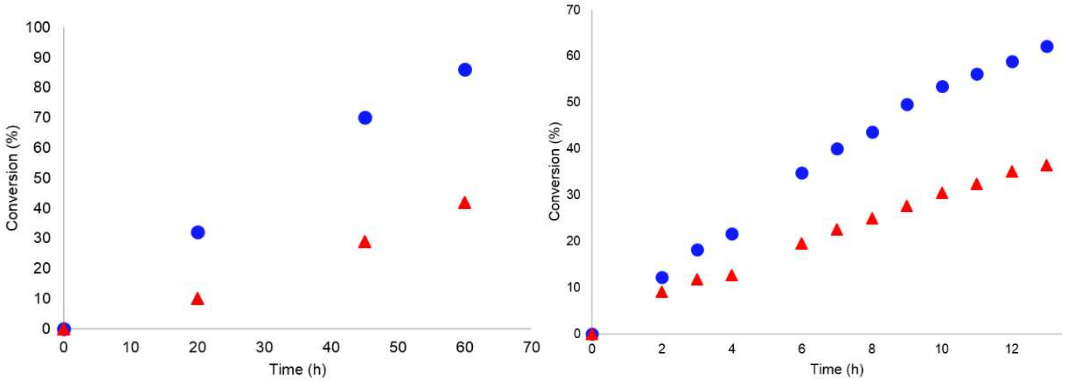


Figure 15. One-pot polymerization of LA (blue circles) and CL (red triangles) with (thiolfan*)Ti(O^{i}Pr)$_2$ (left) and [(thiolfan*)Ti(O^{i}Pr)$_2$][BAr^F] (right) at 100 ºC. Reproduced from ref. 12 with permission from the Royal Society of Chemistry.

5. Conclusions and Outlook

In this Account, we discussed the recent progress in applications of ferrocene derivatives to redox-switchable ring-opening polymerization. Both homopolymerizations and copolymerizations were illustrated. Although many of the reported examples only show the "on-off" switching of one monomer, we applied and expanded this strategy to the synthesis of multiblock copolymers; the main technique used is the selective polymerization of a specific monomer from various mixtures of different monomers in one pot.

A consideration of possible mechanistic issues brings an understanding of the origin of this selectivity. However, many other aspects remain relatively unexplored, especially those related to the prediction of catalysts capable of showing both high activity and high selectivity[9] and of new designs for compounds capable of performing other types of redox-switchable reactions.[14,43-47] Five years ago, there were no examples of switchable catalysts that can carry out selective copolymerizations of cyclic esters/ethers or capable of combining any two orthogonal reactions; at the present, in addition to the two types of redox-switchable systems discussed above, a chemically switchable system can be used for the synthesis of up to pentablock copolymers[48,49] and a light switchable system can be used for the synthesis of diblock copolymers.[50] Despite these achievements, a lot of the past work was based on chemical intuition and trial and error. Given the fact that these systems are relatively complicated and require a certain amount of synthesis, progress in discovering new designs has been slow.

Mechanistic studies also point to some of the complications that can arise in these systems, where orthogonal reactions are combined. As described above (Section 4.2), even though a switchable catalyst shows orthogonal activity in the two oxidation states toward different monomers, the presence of one monomer can greatly influence the catalyst response toward the other. These effects are related to the fact that during the polymerization reactions, different species than the precatalyst are present, and those have a different reactivity toward the monomers. These results show that in these complimentary catalytic cycles subtle effects are responsible for the observed reactivity and that it would be valuable to predict them.

Another possible complication of using redox reagents as switches is the accumulation of byproducts that, eventually, reach critical concentrations and interfere with the reactions of interest. A possible alternative is the use of an electrochemical setup, although, as recently reported,[51] this new area of exploration brings certain challenges as well. Nonetheless, the chemical and electrochemical setups may prove to be useful for complementary applications.

Other challenges are also apparent. For instance, only a limited number of block copolymers has been achieved. Several avenues are being currently pursued. With respect to redox-switchable ring-opening polymerization, it should be possible to introduce carbon dioxide into the copolymerization of lactide and epoxides. In the same vein, the creation of block copolymers between cyclic anhydrides and a variety of other substrates via redox-switchable polymerization needs to be explored.

Furthermore, other possibilities of copolymerization need to be investigated in detail. For example, the combination of two different mechanisms for polymerization is really important. In this area, methods to pair radical and cationic mechanisms for the copolymerization of vinyl ethers and acrylates have been developed.[52-54] These efforts culminated recently in the synthesis of tetrablock copolymers by using two external stimuli: a cationic polymerization was controlled by a chemical stimulus that was both orthogonal and compatible with a photocontrolled radical polymerization.[55]

Finally, the development of novel redox-switchable catalysts that can be shuttled among multi-states (more than two) also needs to be considered. An example with applications in olefin polymerization has been recently reported.[56] This could lead to an enhanced level of on/off control over polymer architecture by involving more monomers. Moreover, in some cases, the organic framework of the supporting ligands is oxidized/reduced instead of the iron metal during the redox switch.[9] The role of these non-innocent ligands also needs to be studied further, since it might guide the design of the next generations of redox-switchable catalysts. We hope the nascent development of redox-switchable polymerizations will be a useful method to facilitate the synthesis of new polymeric materials that are challenging or impossible to be prepared by other techniques.

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REFERENCES

(1) Moughton, A. O.; Hillmyer, M. A.; Lodge, T. P. Multicompartment Block Polymer Micelles. *Macromolecules* **2012**, *45*, 2-19.

(2) Blanco, V.; Leigh, D. A.; Marcos, V. Artificial switchable catalysts. *Chem. Soc. Rev.* **2015**, *44*, 5341-5370.

(3) Teator, A. J.; Lastovickova, D. N.; Bielawski, C. W. Switchable Polymerization Catalysts. *Chem. Rev.* **2016**, *116*, 1969-1992.

(4) Guillaume, S. M.; Kirillov, E.; Sarazin, Y.; Carpentier, J.-F. Beyond Stereoselectivity, Switchable Catalysis: Some of the Last Frontier Challenges in Ring-Opening Polymerization of Cyclic Esters. *Chem. Eur. J.* **2015**, *21*, 7988-8003.

(5) Leibfarth, F. A.; Mattson, K. M.; Fors, B. P.; Collins, H. A.; Hawker, C. J. External Regulation of Controlled Polymerizations. *Angew. Chem. Int. Ed.* **2013**, *52*, 199-210.

(6) Chen, C. Redox-Controlled Polymerization and Copolymerization. *ACS Catal.* **2018**, *8*, 5506-5514.

(7) Kaiser, J. M.; Long, B. K. Recent developments in redox-active olefin polymerization catalysts. *Coord. Chem. Rev.* **2018**, *372*, 141-152.

(8) Stößer, T.; Chen, T. T. D.; Zhu, Y.; Williams, C. K. ‘Switch’ catalysis: from monomer mixtures to sequence-controlled block copolymers. *Philos. Trans. Royal Soc. A* **2018**, *376*.

(9) Abubekerov, M.; Vlček, V.; Wei, J.; Miehlich, M. E.; Quan, S. M.; Meyer, K.; Neuhauser, D.; Diaconescu, P. L. Exploring Oxidation State-Dependent Selectivity in Polymerization of Cyclic Esters and Carbonates with Zinc(II) Complexes. *iScience* **2018**, *7*, 120-131.

(10) Wei, J.; Riffel, M. N.; Diaconescu, P. L. Redox Control of Aluminum Ring-Opening Polymerization: A Combined Experimental and DFT Investigation. *Macromolecules* **2017**, *50*, 1847-1861.

(11) Quan, S. M.; Wei, J.; Diaconescu, P. L. Mechanistic Studies of Redox-Switchable Copolymerization of Lactide and Cyclohexene Oxide by a Zirconium Complex. *Organometallics* **2017**, *36*, 4451-4457.

(12) Lowe, M. Y.; Shu, S.; Quan, S. M.; Diaconescu, P. L. Investigation of redox switchable titanium and zirconium catalysts for the ring opening polymerization of cyclic esters and epoxides. *Inorg. Chem. Front.* **2017**, *4*, 1798-1805.

(13) Abubekerov, M.; Khan, S. I.; Diaconescu, P. L. Ferrocene-bis(phosphinimine) Nickel(II) and Palladium(II) Alkyl Complexes: Influence of the Fe–M (M = Ni and Pd) Interaction on Redox Activity and Olefin Coordination. *Organometallics* **2017**, *36*, 4394-4402.

(14) Shepard, S. M.; Diaconescu, P. L. Redox-Switchable Hydroelementation of a Cobalt Complex Supported by a Ferrocene-Based Ligand. *Organometallics* **2016**, *35*, 2446–2453.

(15) Quan, S. M.; Wang, X.; Zhang, R.; Diaconescu, P. L. Redox Switchable Copolymerization of Cyclic Esters and Epoxides by a Zirconium Complex. *Macromolecules* **2016**, *49*, 6768-6778.

(16) Abubekerov, M.; Shepard, S. M.; Diaconescu, P. L. Switchable Polymerization of Norbornene Derivatives by a Ferrocene-Palladium(II) Heteroscorpionate Complex. *Eur. J. Inorg. Chem.* **2016**, *2016*, 2634-2640.

(17) Abubekerov, M.; Diaconescu, P. L. Synthesis and Characterization of Ferrocene-Chelating Heteroscorpionate Complexes of Nickel(II) and Zinc(II). *Inorg. Chem.* **2015**, *54*, 1778–1784.

(18) Wang, X.; Thevenon, A.; Brosmer, J. L.; Yu, I.; Khan, S. I.; Mehrkhodavandi, P.; Diaconescu, P. L. Redox Control of Group 4 Metal Ring-Opening Polymerization Activity toward l-Lactide and ε-Caprolactone. *J. Am. Chem. Soc.* **2014**, *136*, 11264-11267.

(19) Broderick, E. M.; Thuy-Boun, P. S.; Guo, N.; Vogel, C. S.; Sutter, J.; Miller, J. T.; Meyer, K.; Diaconescu, P. L. Synthesis and Characterization of Cerium and Yttrium Alkoxide Complexes Supported by Ferrocene-Based Chelating Ligands. *Inorg. Chem.* **2011**, *50*, 2870-2877.

(20) Broderick, E. M.; Guo, N.; Wu, T.; Vogel, C. S.; Xu, C.; Sutter, J.; Miller, J. T.; Meyer, K.; Cantat, T.; Diaconescu, P. L. Redox control of a polymerization catalyst by changing the oxidation state of the metal center. *Chem. Commun.* **2011**, *47*, 9897-9899.

(21) Broderick, E. M.; Guo, N.; Vogel, C. S.; Xu, C.; Sutter, J.; Miller, J. T.; Meyer, K.; Mehrkhodavandi, P.; Diaconescu, P. L. Redox Control of a Ring-Opening Polymerization Catalyst. *J. Am. Chem. Soc.* **2011**, *133*, 9278–9281.

(22) Zhu, Y.; Romain, C.; Williams, C. K. Sustainable polymers from renewable resources. *Nature* **2016**, *540*, 354-362.

(23) Hong, M.; Chen, E. Y. X. Chemically recyclable polymers: a circular economy approach to sustainability. *Green Chem.* **2017**, *19*, 3692-3706.

(24) Hillmyer, M. A.; Tolman, W. B. Aliphatic Polyester Block Polymers: Renewable, Degradable, and Sustainable. *Acc. Chem. Res.* **2014**, *47*, 2390-2396.

(25) Sauer, A.; Buffet, J.-C.; Spaniol, T. P.; Nagae, H.; Mashima, K.; Okuda, J. Switching the Lactide Polymerization Activity of a Cerium Complex by Redox Reactions. *ChemCatChem* **2013**, *5*, 1088-1091.

(26) Biernesser, A. B.; Li, B.; Byers, J. A. Redox-Controlled Polymerization of Lactide Catalyzed by Bis(imino)pyridine Iron Bis(alkoxide) Complexes. *J. Am. Chem. Soc.* **2013**, *135*,

16553-16560.

(27) Biernesser, A. B.; Delle Chiaie, K. R.; Curley, J. B.; Byers, J. A. Block Copolymerization of Lactide and an Epoxide Facilitated by a Redox Switchable Iron-Based Catalyst. *Angew. Chem. Int. Ed.* **2016**, *55*, 5251–5254.

(28) Allgeier, A. M.; Mirkin, C. A. Ligand Design for Electrochemically Controlling Stoichiometric and Catalytic Reactivity of Transition Metals. *Angew. Chem. Int. Ed.* **1998**, *37*, 894-908.

(29) Štěpnička, P.: *Ferrocenes: Ligands, Materials and Biomolecules*; Wiley: West Sussex, 2008.

(30) Gregson, C. K. A.; Gibson, V. C.; Long, N. J.; Marshall, E. L.; Oxford, P. J.; White, A. J. P. Redox Control within Single-Site Polymerization Catalysts. *J. Am. Chem. Soc.* **2006**, *128*, 7410-7411.

(31) Huang, W.; Diaconescu, P. L. Reactivity and Properties of Metal Complexes Enabled by Flexible and Redox-Active Ligands with a Ferrocene Backbone. *Inorg. Chem.* **2016**, *55*, 10013–10023.

(32) Diaconescu, P. L. Reactions of Aromatic N-Heterocycles with d^0f^n-Metal Alkyl Complexes Supported by Chelating Diamide Ligands. *Acc. Chem. Res.* **2010**, *43*, 1352-1363.

(33) Huang, W.; Diaconescu, P. L.: C-H Bond Activation of Hydrocarbons Mediated by Rare-Earth Metals and Actinides: Beyond σ-Bond Metathesis and 1,2-Addition. In *Advances in Organometallic Chemistry*; Pérez, P. J., Ed.; Academic Press: UK, 2015; Vol. 64; pp 41-75.

(34) Huang, W.; Diaconescu, P. L. Rare-earth metal π-complexes of reduced arenes, alkenes, and alkynes: bonding, electronic structure, and comparison with actinides and other electropositive metals. *Dalton Trans.* **2015**, *44*, 15360-15371.

(35) Huang, W.; Diaconescu, P. L.: Rare Earth Arene-bridged Complexes Obtained by Reduction of Organometallic Precursors. In *Handbook on the Physics and Chemistry of Rare Earths*; Bünzli, J.-C., Pecharsky, V., Eds.; Elsevier: Amsterdam, The Netherlands, 2014; Vol. 45; pp 261-329.

(36) Sauer, A.; Buffet, J.-C.; Spaniol, T. P.; Nagae, H.; Mashima, K.; Okuda, J. Synthesis, Characterization, and Lactide Polymerization Activity of Group 4 Metal Complexes Containing Two Bis(phenolate) Ligands. *Inorg. Chem.* **2012**, *51*, 5764-5770.

(37) Hoffmann, R. Interaction of orbitals through space and through bonds. *Acc. Chem. Res.* **1971**, *4*, 1-9.

(38) Lorkovic, I. M.; Duff, R. R.; Wrighton, M. S. Use of the Redox-Active Ligand 1,1'-Bis(diphenylphosphino)cobaltocene To Reversibly Alter the Rate of the Rhodium(I)-Catalyzed Reduction and Isomerization of Ketones and Alkenes. *J. Am. Chem. Soc.* **1995**, *117*, 3617-3618.

(39) Brown, L. A.; Rhinehart, J. L.; Long, B. K. Effects of Ferrocenyl Proximity and Monomer Presence during Oxidation for the Redox-Switchable Polymerization of l-Lactide. *ACS Catal.* **2015**, *5*, 6057-6060.

(40) Dai, R.; Lai, A.; Alexandrova, A. N.; Diaconescu, P. L. Geometry Change in a Series of Zirconium Compounds during Lactide Ring-Opening Polymerization. *Organometallics*

2018, *37*, 4040-4047.

(41) Dubois, P.; Coulembier, O.; Raquez, J.-M.: *Handbook of Ring-Opening Polymerization*; Wiley-VCH: Weinheim, Germany, 2009.

(42) Abubekerov, M.; Wei, J.; Swartz, K. R.; Xie, Z.; Pei, Q.; Diaconescu, P. L. Preparation of multiblock copolymers via step-wise addition of l-lactide and trimethylene carbonate. *Chem. Sci.* **2018**, *9*, 2168-2178.

(43) Klenk, S.; Rupf, S.; Suntrup, L.; van der Meer, M.; Sarkar, B. The Power of Ferrocene, Mesoionic Carbenes, and Gold: Redox-Switchable Catalysis. *Organometallics* **2017**, *36*, 2026-2035.

(44) Feyrer, A.; Breher, F. Palladium complexes of ferrocene-based phosphine ligands as redox-switchable catalysts in Buchwald-Hartwig cross-coupling reactions. *Inorg. Chem. Front.* **2017**, *4*, 1125-1134.

(45) Lastovickova, D. N.; Teator, A. J.; Shao, H.; Liu, P.; Bielawski, C. W. A redox-switchable ring-closing metathesis catalyst. *Inorg. Chem. Front.* **2017**, *4*, 1525-1532.

(46) Tennyson, A. G.; Lynch, V. M.; Bielawski, C. W. Arrested Catalysis: Controlling Kumada Coupling Activity via a Redox-Active N-Heterocyclic Carbene. *J. Am. Chem. Soc.* **2010**, *132*, 9420-9429.

(47) Ibáñez, S.; Poyatos, M.; Dawe, L. N.; Gusev, D.; Peris, E. Ferrocenyl-Imidazolylidene Ligand for Redox-Switchable Gold-Based Catalysis. A Detailed Study on the Redox-Switching Abilities of the Ligand. *Organometallics* **2016**, *35*, 2747-2758.

(48) Chen, T. T. D.; Zhu, Y.; Williams, C. K. Pentablock Copolymer from Tetracomponent Monomer Mixture Using a Switchable Dizinc Catalyst. *Macromolecules* **2018**, *51*, 5346-5351.

(49) Romain, C.; Williams, C. K. Chemoselective Polymerization Control: From Mixed-Monomer Feedstock to Copolymers. *Angew. Chem. Int. Ed.* **2014**, *53*, 1607-1610.

(50) Eisenreich, F.; Kathan, M.; Dallmann, A.; Ihrig, S. P.; Schwaar, T.; Schmidt, B. M.; Hecht, S. A photoswitchable catalyst system for remote-controlled (co)polymerization in situ. *Nat. Catal.* **2018**, *1*, 516-522.

(51) Qi, M.; Dong, Q.; Wang, D.; Byers, J. A. Electrochemically Switchable Ring-Opening Polymerization of Lactide and Cyclohexene Oxide. *J. Am. Chem. Soc.* **2018**, *140*, 5686-5690.

(52) Kottisch, V.; Michaudel, Q.; Fors, B. P. Photocontrolled Interconversion of Cationic and Radical Polymerizations. *J. Am. Chem. Soc.* **2017**, *139*, 10665-10668.

(53) Satoh, K.; Hashimoto, H.; Kumagai, S.; Aoshima, H.; Uchiyama, M.; Ishibashi, R.; Fujiki, Y.; Kamigaito, M. One-shot controlled/living copolymerization for various comonomer sequence distributions via dual radical and cationic active species from RAFT terminals. *Polym. Chem.* **2017**, *8*, 5002-5011.

(54) Aoshima, H.; Uchiyama, M.; Satoh, K.; Kamigaito, M. Interconvertible Living Radical and Cationic Polymerization through Reversible Activation of Dormant Species with Dual Activity. *Angew. Chem. Int. Ed.* **2014**, *53*, 10932-10936.

(55) Peterson, B. M.; Kottisch, V.; Supej, M. J.; Fors, B. P. On Demand Switching of Polymerization Mechanism and Monomer Selectivity with Orthogonal Stimuli. *ACS Cent. Sci.* **2018**, *4*, 1228-1234.

(56) Zhao, M.; Chen, C. Accessing Multiple Catalytically Active States in Redox-Controlled Olefin Polymerization. *ACS Catal.* **2017**, *7*, 7490-7494.