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Stereoselective Catalysis Achieved through *in Situ* Desymmetrization of an Achiral Iron Catalyst Precursor

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Supporting Information

ABSTRACT: Stereoselective catalysis is described that proceeds with catalyst control but without the need to synthesize preformed chiral catalysts or ligands. Iron-based catalysts were discovered to effect the stereoselective polymerization of lactides starting from a single achiral precursor and the proper choice of an achiral silanol additive. Spectroscopic analysis of the polymer revealed that the stereoselectivity originates from an enantiomorphic site rather than a chain end stereocontrol mechanism. Iron intermediates that are stereogenic at iron are proposed to form *in situ* as a result of desymmetrization that occurs from a change in the metal coordination number. The proposed mechanism is supported by a combination of spectroscopic measurements, model complexes, kinetic measurements, and DFT calculations.

Chiral molecules are important to the pharmaceutical, agrochemical, and polymer industries. Due to their utility, synthetic chemists continue to seek new ways to install stereogenicity in small molecules,[1] or in macromolecular chemistry, to control the assembly of chiral or prochiral monomers to form useful polymeric materials.[2] A contemporary strategy for stereoselective synthesis entails the use of chiral catalysts that engender stereogenicity through steric interactions between the catalyst and the substrate (e.g., catalyst **1**,[3] Figure 1). Although this strategy has been very successful, catalyst optimization often involves synthesis of a variety of chiral catalyst derivatives and, in many cases, the need to purchase expensive chiral precursors.

We envisioned an alternative strategy that involves using easily accessible achiral catalysts, which can promote stereoselective transformations by adopting chiral configurations *in situ*.[1a,4] This strategy is advantageous because it avoids the need for pregenerated chiral precursors, yet rational catalyst modifications can still be made so as to influence stereochemical outcomes. Here, we describe the successful implementation of such a strategy using catalyst **2**, which is formed *in situ* from earth-abundant iron and readily accessible achiral bis(imino)pyridine and siloxide ligands (Figure 1). Complex **2** is formed through a change in ligand coordination number, which promotes the stereoselective polymerization of lactide to form the biodegradable polymer, poly(lactic acid) (PLA, Figure 1).[5] Extending this method to enantioselective reactions will likely require enantiomerically enriched additives in order to bias the system toward forming one enantiomer of the *in situ* formed catalyst. Nevertheless, the method is distinct from diastereoselective reactions where chiral substrates dictate selectivity because the stereogenicity of the catalyst is the stereocontrol element that predominates.

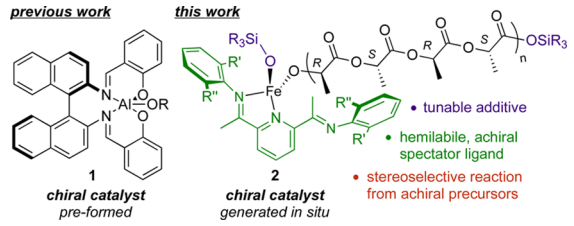

Figure 1. Strategies for catalysts designed to synthesize stereoregular PLA.

Over the past few decades, PLA has become a popular biodegradable alternative to less degradable and oil-derived polymers. PLA is derived from renewable resources and is used in packaging,[6] textiles,[7] dissolvable sutures,[8] and artificial tissue materials.[9] Previous researchers have shown that the physical properties[5] and degradation rates[10] of PLA can be tuned by altering its stereoregularity (i.e., tacticity).[5] Therefore, the development of simple methods to produce PLA with a range of tacticities is desirable, because doing so provides a way to tailor polymer properties in accord with the engineering requirements of the intended application.

Recently, we reported that combining bis(imino)pyridine iron(II) complex, **3**, with aliphatic or aromatic alcohol initiators led to the polymerization of (*rac*)-lactide to form atactic PLA.[11] These iron catalysts are unusual compared to most lactide polymerization catalysts[12] because they can support one or two growing polymer chains per metal center, which is controllable by altering the identity of the alcohol initiator (Scheme 1). We realized that in the instances where one propagating polymer chain prevailed, the alcohol additive serves a dual role to initiate polymerization and to act as an ancillary ligand. Since introduction of a new spectator ligand changes catalyst structure, we reasoned that using different additives could substantially change catalyst performance.

Guided by the above hypothesis, we set out to investigate the effects of alternative initiators on catalytic performance. During these studies, it was found that silanol additives had a profound influence on the reaction (Table 1). When using the same 2,6-

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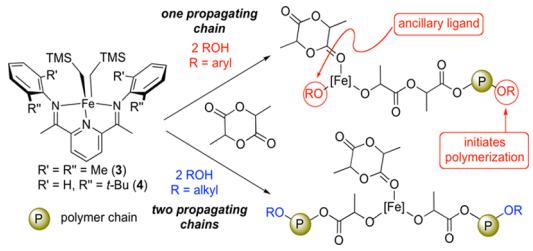
Scheme 1. Bis(imino)pyridine Iron Catalysts for the Polymerization of Lactide via One or Two Propagating Polymer Chains



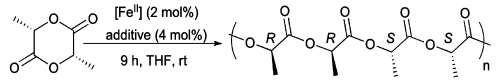
dimethylphenyl bis(imino)pyridine iron precursor **3** as originally reported,[11] the level of stereoselectivity in lactide polymerization was improved when silanols were used as additives, albeit with less control over polymer molecular weight. Compared to atactic polymer produced from reactions initiated with *p*-methoxyphenol (Table 1, entry 1), polymerization of (*rac*)-lactide initiated by a mixture of **3** and Ph_3SiOH led to slightly heterotactic PLA (entry 2).

Models obtained from computational studies (*vide infra*) for the active catalyst revealed possible steric congestion between the siloxide ligand and a methyl substituent on the aromatic ring of the bis(2,6-dimethylphenylimino)pyridine ligand. To alleviate this strain, complex **4** containing bis(2-*tert*-butyl-phenylimino)-pyridine ligand was synthesized and subjected to the reaction conditions. Slightly better stereoselectivities and lower molecular weights were observed compared to **3** (entry 3). Reactions catalyzed by **4** also demonstrated characteristics of a living polymerization, namely a linear relationship between conversion and M_n (Figure S2). Deviation from the theoretical molecular weight was attributed to slow initiation rates as a consequence of the very bulky triphenyl silanol initiator. Supporting this hypothesis were molecular weights that were more consistent with theoretical molecular weights for reactions involving smaller siloxide initiators (entries 4–6, Table 1). The improved behavior of **4** compared to **3** has been attributed to better catalyst stability, which was supported by ^{1}H NMR studies. Both **3** (Table S1) and **4** (Table 1) demonstrated improved stereoselectivity by altering the identity of the silanol initiator with silanols of intermediate size, such as $MePh_2SiOH$, producing the most heterotactic PLA (entry 4).

Next, the generality of this new methodology was explored with the polymerization of (*meso*)-lactide (Table 1, entries 8–12). Unlike (*rac*)-lactide, slightly syndiotactic PLA was obtained when *p*-methoxyphenol was used as a catalyst initiator (entry 8). Nevertheless, polymer tacticity was once again improved when Ph_3SiOH was used as an additive (entry 9). As was observed for (*rac*)-lactide, the identity of the silanol additives influenced the stereoselectivity with Et_3SiOH producing syndiotactic PLA with P_s = 92% (entries 10–12).

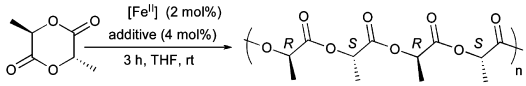
Control experiments ruled out dissociation of the bis(imino)-pyridine ligand and the possibility of a silanol-catalyzed process (see Supporting Information (SI)), thereby reinforcing an iron-catalyzed polymerization reaction that benefits from synergistic effects involving silanol and bis(imino)pyridine ligands bound to iron. Considering that silanols have a similar pK_a as phenols, we reasoned that iron siloxides and iron phenoxides would be similarly nucleophilic and would therefore catalyze polymerization with one propagating polymer chain.[11] That the identity of the silanol initiator had an appreciable effect on polymer tacticity provides further support for one propagating polymer chain. If polymerization were to involve two propagating chains, then polymer tacticity would be minimally impacted by the identity of the initiator since the additives would be far removed from the metal center during propagation.

Table 1. Polymerization of Lactides Catalyzed by Iron Complexes (3–5) and Various Alcohol Additives



(*rac*)-lactide — heterotactic poly(lactic acid)

	[Fe^{II}]	Additive	Cone angle[13]	M_n (kg/mol)	M_w/M_n	P_s[a] (%)
1[b]	**3**	*p*-MeOC$_6$H$_4$OH	-	9.08	1.42	50
2	**3**	Ph_3SiOH	145	42.9	1.31	66
3	**4**	Ph_3SiOH	145	29.1	1.45	69
4	**4**	$MePh_2SiOH$	136	15.7	1.38	75
5	**4**	Et_3SiOH	132	10.1	1.46	58
6	**4**	$Me_2PhSiOH$	122	9.0	1.50	64
7	**5**	Ph_3SiOH	145	43.1	1.40	73

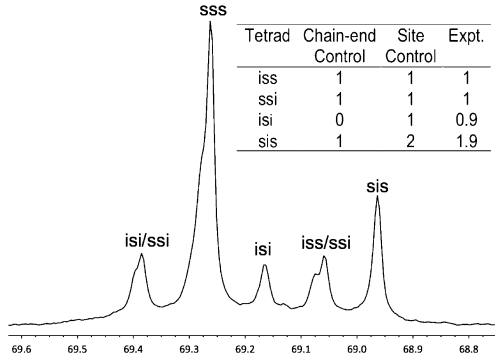


(*meso*)-lactide — syndiotactic poly(lactic acid)

	[Fe^{II}]	Additive	Cone angle[13]	M_n (kg/mol)	M_w/M_n	P_s[a] (%)
8	**4**	*p*-MeOC$_6$H$_4$OH	-	9.04	1.25	67
9	**4**	Ph_3SiOH	145	54.4	1.43	88
10	**4**	$MePh_2SiOH$	136	7.0	1.52	82
11	**4**	Et_3SiOH	132	11.5	1.62	92
12	**4**	$Me_2PhSiOH$	122	8.6	1.40	85
13	**5**	Ph_3SiOH	145	39.2	1.60	70

[a]P_s = probability of inserting a syndiotactic unit.[15] [b]Different than previously reported[11] due to solvent effects.

A requirement to form stereoregular PLA is the involvement of a chiral catalyst, which can operate from an enantiomorphic site[3] or a chain end[14] stereocontrol mechanism (or some combination of the two). A chain end control model seemed likely to explain our results considering that **3** and the silanols were both achiral. Fortunately, the two stereocontrol mechanisms can be distinguished from one another by analyzing $^{13}C\{^1H\}$ or $^1H\{^1H\}$ NMR spectra of the resulting polymer.[5] To our surprise, NMR analysis of PLA produced from the syndiotactic polymerization of (*meso*)-lactide catalyzed by a mixture of **4** and silanols revealed the number and distribution of stereoerrors that was inconsistent with a chain end control mechanism (Figure 2). Instead, the presence of the *isi* stereoerror and the ratio of the *iss*:*ssi*:*isi*:*sis* stereoerrors were more consistent with an



Tetrad	Chain-end Control	Site Control	Expt.
iss	1	1	1
ssi	1	1	1
isi	0	1	0.9
sis	1	2	1.9

Figure 2. $^{13}C\{^1H\}$ NMR spectrum of PLA obtained from Table 1, entry 9. The table contains experimental and predicted distribution of stereoerrors from chain end and enantiomorphic site control mechanisms (*s* = syndiotactic, *i* = isotactic).

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enantiomorphic site control model (see SI).[3,16] Similar analysis of heterotactic PLA obtained from the polymerization of (*rac*)-lactide was less conclusive, but the data were more congruent with an enantiomorphic site rather than a chain end control mechanism (see SI). In order to generate stereoregular PLA from an enantiomorphic site control mechanism, a chiral environment around the iron center must be engendered by the ancillary ligand *in situ*. To satisfy this requirement, we propose that the large siloxide ligands encourage dissociation of one imine arm from the tridentate bis(imino)pyridine ligand, thereby causing the formation of a four-coordinate iron intermediate. Insertion of lactide into one of the iron siloxide bonds destroys the remaining mirror plane symmetry and generates a chiral intermediate that is stereogenic at iron (Figure 3a). Depending on the siloxide into

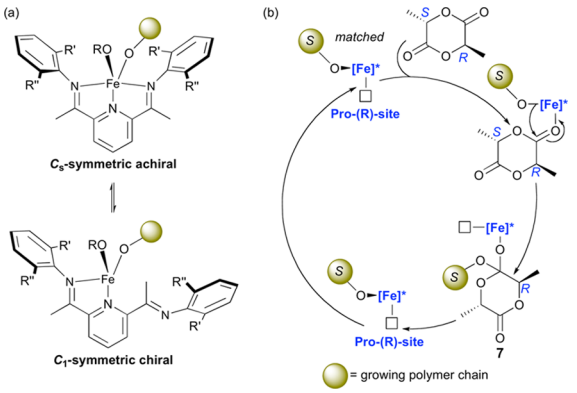

Figure 3. (a) Proposed origin of stereogenic iron centers and (b) mechanism for syndiotactic polymerization of (*meso*)-lactide. The Cahn–Ingold–Prelog designation in the polymer chain represents the stereocenter proximal to metal.

which the lactide inserts, diastereomeric sites are created that favor insertion of lactide monomers with either (*R*) or (*S*) stereocenters proximal to the metal center (pro-(*R*) or pro-(*S*) sites, respectively).

To test the viability of this mechanistic hypothesis, insight into the structure of the active catalyst species was needed. Unfortunately, the high solubility of the product resulting from mixing **4** with Ph_3SiOH precluded structure determination by X-ray crystallography. Nevertheless, information about the identity of the complex was obtainable using UV–vis and ^{1}H NMR spectroscopies. By ^{1}H NMR spectroscopy, reaction between **4** and Ph_3SiOH proceeded in a similar fashion as previously described for reactions between **3** and other alcohols,[11] cleanly affording a single new paramagnetic species with C_{2v} symmetry (Figure S9). Contrasting this behavior, the UV–vis spectrum of the teal complex resulting from mixing **4** with Ph_3SiOH (λ_{max} = 608 nm, ε = 118 M^{-1} cm^{-1}) was substantially different compared to the deep burgundy bis(imino)pyridine iron bis-aryl or bis-alkyl alkoxides (λ_{max} = 560 nm, ε = 1644 M^{-1} cm^{-1}, Figure S7). In order to rectify these results, we posit that the iron species formed *in situ* between **4** and the silanols are four-coordinate on the UV–vis time scale but are in dynamic equilibrium with a five-coordinate iron species on the NMR time scale.

As a model for the κ^2-coordination mode of the bis(imino)-pyridine ligand, an iron bis(siloxide) complex (**5**) containing a bidentate iminopyridine ligand was synthesized and characterized by X-ray crystallography (Figure 4). Iron complex **5** took on a teal hue (λ_{max} = 635 cm^{-1}, ε = 127) similar to the color observed when mixing **4** with silanols. The UV–vis spectra for **5**

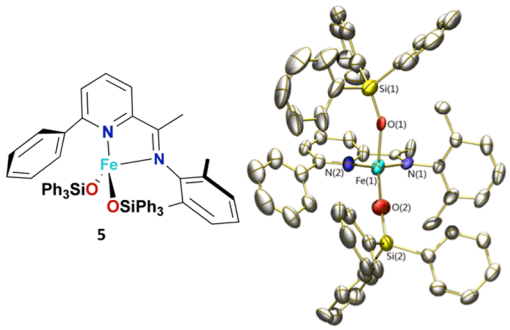

Figure 4. X-ray crystal structure for **5**. Thermal ellipsoids shown at the 50% probability level.

and the iron complex resulting from mixing **4** with Ph_3SiOH were similar to one another (Figure S8). Both spectra contained two weakly absorbing bands between 550 and 800 nm that are likely due to d–d transitions. In contrast, the UV–vis spectrum of bis(imino)pyridine iron bis(4-methoxy-phenoxide) complex **6** was dominated by a strongly absorbing charge-transfer band at 560 nm and contained a weakly absorbing d–d transition at 720 nm (Figure S7). The UV–vis spectrum for **6** is typical for five-coordinate iron complexes bearing tridentate bis(imino)pyridine ligands.[17]

The reactivity of **5** provided further support for the involvement of an active catalyst containing a bidentate bis(imino)pyridine ligand. As was the case for reactions catalyzed by combining **4** and silanols, complex **5** catalyzed (*rac*)-lactide polymerization to form heterotactic polymer (Table 1, entry 7) and (*meso*)-lactide polymerization to form syndiotactic polymer (Table 1, entry 13). The polymerization reactions catalyzed by **5** were slower, and the stereoselectivities obtained were different compared to reactions catalyzed by mixing **4** with Ph_3SiOH, but NMR analysis of the PLA produced using **5** as the catalyst once again supported an enantiomorphic site stereocontrol model (Figure S24). The differences in stereoselectivity observed between **5** and the catalyst resulting from mixing **4** with Ph_3SiOH are likely due to the different steric environments imparted by the aminopyridine and κ^2-bis(imino)pyridine ligands.

With the nature of the active species established, what remains is an explanation for the stereochemical course of the polymerization reactions. We submit that polymer propagation occurs by means of a coordination–insertion mechanism involving the formation and destruction of the tetrahedral intermediate **7** (Figure 3). Collapse of **7** results in lactide enchainment and the regeneration of an iron bis(alkoxide) intermediate that occurs without epimerization of the iron stereogenic center. This mechanism explains the stereochemical outcome observed using (*meso*)-lactide, because the production of syndiotactic polymer requires consecutive lactide insertions from the same diastereomeric site (illustrated in Figure 3 for the pro-(*R*) sites). This hypothesis was further corroborated with DFT calculations, which not only predicted energy differences between pro-(*S*) and pro-(*R*) insertions but also supported an enantiomorphic site stereocontrol mechanism (see SI).

A different mechanism is needed to explain the heterotactic PLA obtained from (*rac*)-lactide because heterotactic PLA requires the catalyst to alternate between pro-(*R*) and pro-(*S*) diastereomeric sites. To accommodate this requirement, we propose that epimerization of the iron stereogenic center occurs after every inserted (*rac*)-lactide monomer (Figure 5). The mechanism for this site epimerization is unclear, but several

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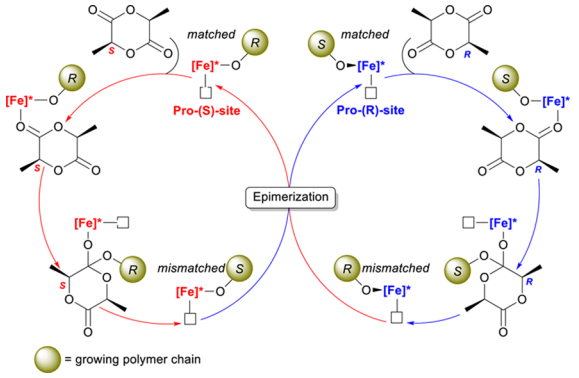

Figure 5. Mechanism for heterotactic polymerization of (*rac*)-lactide. The Cahn–Ingold–Prelog designation in the polymer chain represents the stereocenter proximal to metal.

possibilities are presented in the SI. To explain why site epimerization occurs in preference to consecutive lactide enchainments for (*rac*)-lactide but not (*meso*)-lactide, a diastereomeric matched-mismatched situation is proposed.[18] We hypothesize that insertion of (*rac*)-lactide leads to a chiral intermediate whose stereogencity at the polymer chain end is mismatched with the stereogenicity at iron (Figure 5). To alleviate this energetically unfavorable situation, site epimerization occurs in preference to insertion of a lactide monomer. As a result, insertion alternates with site epimerization and heterotactic PLA is formed.

In conclusion, we have demonstrated a novel approach to form stereoregular PLA, which is based on the *in situ* generation of a chiral catalyst. The catalyst precursors are achiral, and the methods for their preparation neither require laborious synthetic sequences nor the purchase of expensive chiral starting materials. This method is conceptually similar to work from Walsh, who has shown that enantiomerically enriched additives can enhance stereoselectivity in several reactions.[1a] It also shares features with work from Okuda, who has utilized achiral ligands that adopt chiral configurations when bound to a metal so as to affect high levels of stereocontrol in lactide polymerization.[4] What distinguishes our strategy from these examples is that the predominate stereochemical control element arises from stereogenicity that is generated *in situ* rather than from being introduced by chiral additives or that is inherent to the binding mode of an ancillary ligand. In this way, the stereoregularity of the polymer formed can be controlled with the appropriate choice of silanol additive. While this strategy has been demonstrated using lactide polymerization, we envision similar strategies being applicable to other stereoselective processes in chemical synthesis. Future work will be focused on exploring these avenues, improving PLA tacticity through catalyst design, and combining this feature with other properties of the catalyst to further diversify the properties of degradable polymers.

■ ASSOCIATED CONTENT

Supporting Information

Full experimental procedures, DFT calculations, and further discussion of stereocontrol mechanism. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b09966.

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Notes

The authors declare no competing financial interest.

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