Enantioselective Ring-Opening Polymerization of rac-Lactide Dictated by Densely Substituted Aminoacids

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ABSTRACT: Although organometallic catalysts have shown great ability to promote these polymerization reactions, their substantial toxicity and other drawbacks are accelerating the development of organic catalysts. To date, organic catalysts have demonstrated some ability to promote stereocontrolled polymerizations. However, none of them has been able to promote efficiently different stereochemical outcomes depending on the chirality of the organic catalyst. In this work we report for the first time the chirality transfer from catalyst to polymer in the ring-opening polymerization (ROP) of rac-lactide (rac-LA). We have polymerized rac-LA using diastereomeric densely substituted aminoacids (2S,3R,4S,5S)-1-methyl-4-nitro-3,5-diphenylpyrrolidine-2-carboxylic acid (*endo*-**6)** and (2S,3S,4R,5S)-1-methyl-4-nitro-3,5-diphenylpyrrolidine-2-carboxylic acid (*exo*-**6**), combined with 1,8-Diaza-bicyclo[5.4.0]undec-7-ene (DBU) as co-catalyst. Both diastereoisomers not only showed the ability to synthesize enriched isotactic polylactide with a P_m higher than 0.90 at room temperature, but they were also able to preferentially promote the polymerization of one of the isomers (L or D) with respect to the other. Thus, *exo*-**6** preferentially polymerized L-lactide while *endo*-**6** preferred D-lactide as substrate. DFT calculations were conducted to investigate the origins of this unique stereocontrol in the polymerization, providing a mechanistic insight and confirming that the chirality of the catalyst is able to define the stereochemistry of the monomer insertion.

Introduction

Since the discovery of synthetic polymers in the mid 20th century, there has been a continuous search of control over the different aspects of polymerization such as kinetics, stereoregularity, dispersity, sequence distribution, functionality or macromolecular architecture.[1-3] Stereocontrol is very important in polymerization reactions because the stereoregularity is a necessary condition for crystalline polymers which often have an array of mechanical properties superior to those of the corresponding nonstereoregular polymers.[4] Given the excellent performance and almost limitless opportunities of ligand/metal combinations, it is not surprising that transition metals and organometallic catalysts have dominated the field of stereocontrolled polymerizations.[5-8] Stereocontrol polymerization can be performed by two different mechanisms: chain end control and enantiomorphic site control.[1] In the former mechanism, the chirality of the propagating chain end bound to the catalyst regulates the chirality of the next monomer insertion, while in the latter the chirality of the catalyst, and not the chain end, dictates the next monomeric unit insertion.

One of the polymer families where the stereocontrol has attracted great interest is the family of polyesters,[9] specially polylactide (PLA). PLA is nowadays the most popular example of renewable, biocompatible and biodegradable polymer.[2,10,11] Interestingly, PLA´s mechanical properties and biodegradability are linked to its microstructure and hence poly(L-lactide) posses a melting point (T_m) close to 160 °C whereas the atactic one is an amorphous polymer with low mechanical properties.[12] Metal alkoxides and some achiral organometallic catalysts have shown to be efficient to promote the synthesis of stereoregular PLA.[13,14]

Although metal based catalysts are considered much more versatile than non-metal based ones, their substantial toxicity is accelerating the development of organic catalysts.[2,15,16] Some organic catalysts such as N-heterocyclic carbenes,[17,18] phosphazenes[19] or (R)-binaphthol derived phosphoric acids[20] have recently shown the ability to promote the stereocontrolled polymerization of rac-LA. In all these cases the stereocontrol is given *via* chain end control mechanism.[2] Consequently, the catalyst is not able to promote different stereochemical outcomes by modifying the chirality of the catalytic species. More recently the group of Chen have prepared some new bifunctional chiral catalysts based on β-isocupreidine core, thiourea and chiral binaphthyl-amine. They showed the ability to promote different stereochemical outcomes by flipping the chirality of the catalyst. These results showed significant advances to previous works reported in the literature. However, using the S version of the catalyst much inferior kinetic resolution was obtained.[21,] Therefore, the investigation of an organic catalyst family able to dictate the monomer insertion (L-LA or D-LA from the racemic mixture) as a function of the chirality of the catalyst is actively searched.
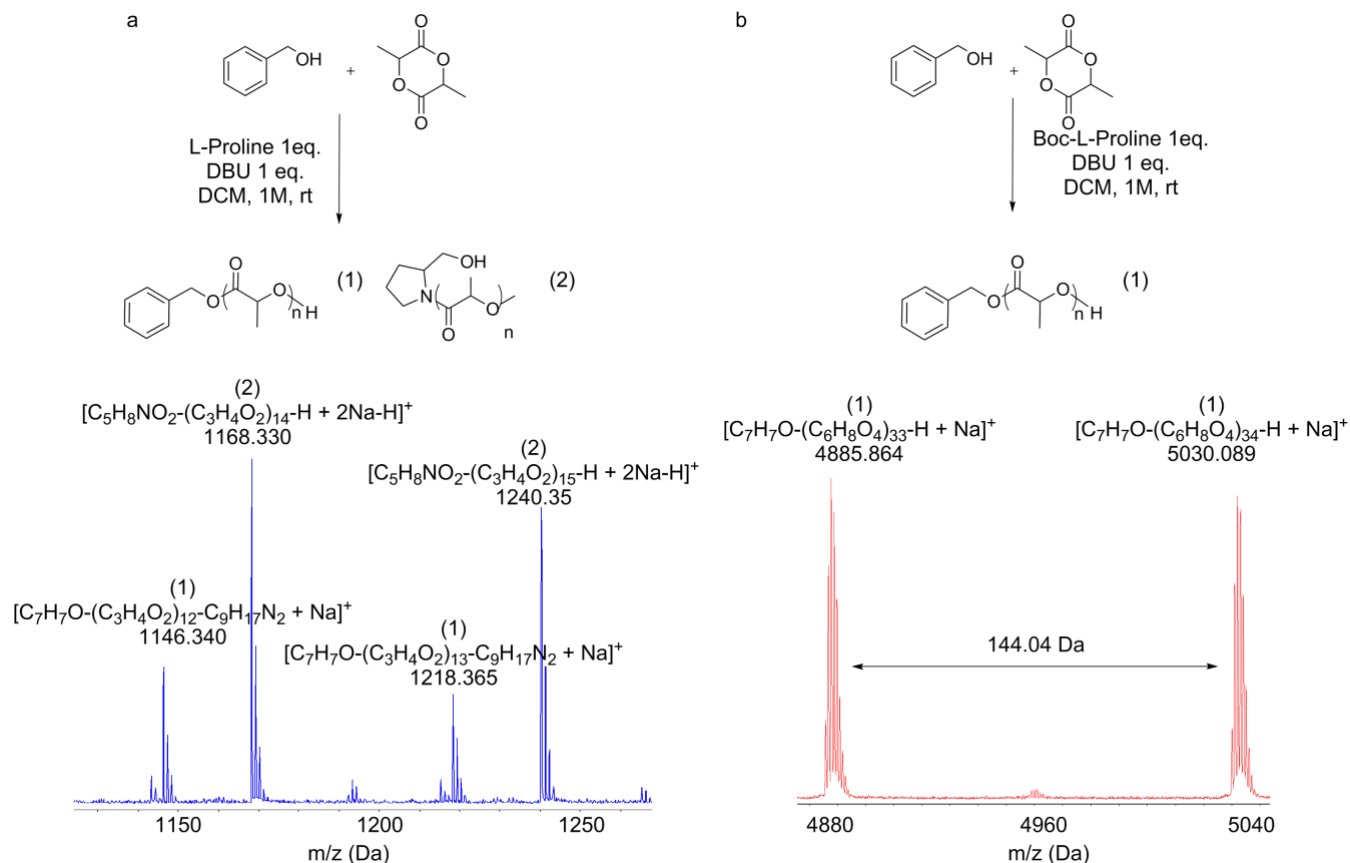
Figure 1. MALDI-TOF spectra enlargements where exact mass and the assigment of each molecule is disclosed for the polymerization of rac-LA using benzyl alcohol as initiator and DBU as co-catalyst a) in the presence of L-proline b) in the presence of Boc-L-proline.

In our search to find a catalyst able to promote stereocontrolled polymerizations we turned to nature for inspiration. Nature accomplishes outstandingly enantioselective modifications using macromolecules such as enzymes. Interestingly, Barbas, List and MacMillan, among others, [22-25] showed that enzymes such as aldolases can be reduced to minimalistic analogues such as natural monomeric amino acids without losing the essentials of the catalytic activity.

Among them, proline amino acid is considered one of the most successful catalysts because it promotes many different enantioselective catalytic processes such as the aldol, [26,27] Mannich,[28] Michael,[29,30] and Diels-Alder reactions.[31] Although the use of amino acid based organocatalysts in the stereocontrolled synthesis of small organic molecules has been broadly studied, when we focus on the synthesis of polymers the number of scientific articles using prolines is incomprehensibly diminished. To the best of our knowledge prolines only have shown to be efficient to promote the polyaldol reaction without promoting any stereoregularity.[32-33]

In this paper we report an organic catalyst which shows the ability to transfer the chirality to the polymer and to promote stereocontrolled ROP of lactide. For that purpose, we prepared N-protected densely substituted prolines by means of catalytic asymmetric (3+2) cycloadditions and subsequent transformations. We have investigated how modifying the chirality of two distal centers of these prolines, high stereoselectivity could be promoted in the polymerization of D-lactide or L-lactide starting from a racemic mixture. Density Functional Theory (DFT) calculations were also conducted to provide mechanistic insight into the ROP process in the presence of these densely substituted aminoacids.

Results and Discussion

As a first test, we investigated the commercially available L-proline (L-Pro) aminoacid as potential catalyst for the ROP of rac-LA (Table 1, Entry 1). Although L-proline can act as acid or base catalyst, reaction of rac-LA in the presence of L-Pro and benzyl alcohol as initiator did not lead to polymerization even at elevated temperatures. After this unsuccessful attempt, we envisioned a more efficient ROP, using a co-catalyst inspired by the work of Hedrick et al.[34] The idea relies on forming strong acid / base complexes for the ring opening polymerization of lactide using the carboxylic acid or the amine groups of L-Pro with a base or an acid respectively, without having any negative effect on the polymerization. A variety of co-catalysts were screened together with L-Pro, from strong bases such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to strong acids such as triflic acid (TfOH) (SI section, TableS1).[35] We followed the reaction by ^{1}H NMR and only when L-Pro was combined with DBU full conversion was achieved (Table 1, Entry 2). Nevertheless, the experimental molecular weight (M_n=700 g mol^{-1}) was much lower than the targeted one (M_n=7300 g mol^{-1}). This fact was indicating that besides acting as a catalyst, L-proline / DBU complex might be participating in the initiation process of the polymerization.
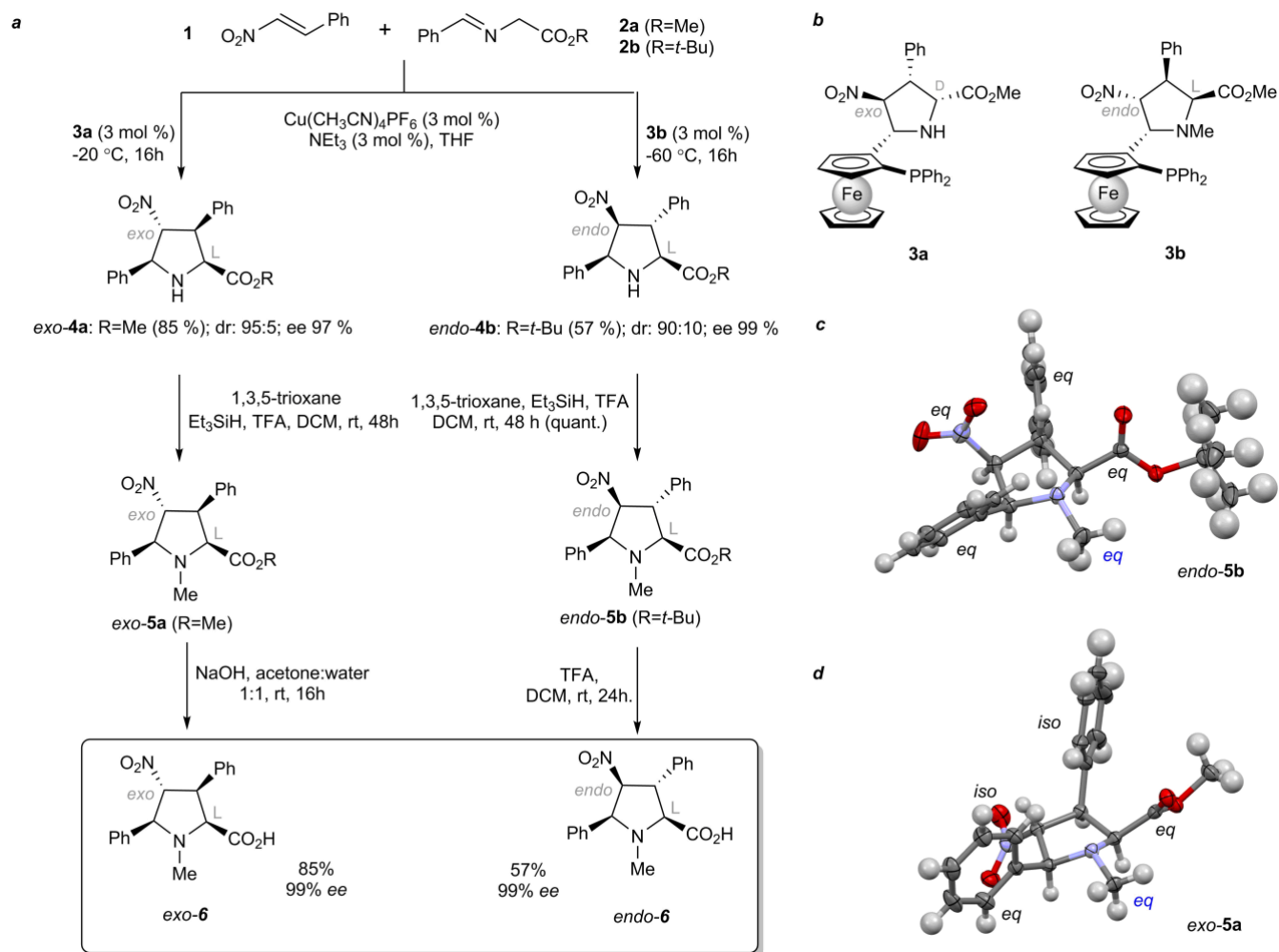
Figure 2. a) Synthesis of unnatural *endo*- and *exo*-N-methylated prolines **6**. b) Chiral ligands 3a,b required for the asymmetric (3+2) cycloaddition between nitroalkene **1** and imines **2a,b** to yield pyrrolidines **4**. c, d) Structures of organocatalysts *exo*-**5a** and *endo*-**5b** as determined by X-ray diffraction analysis**.**

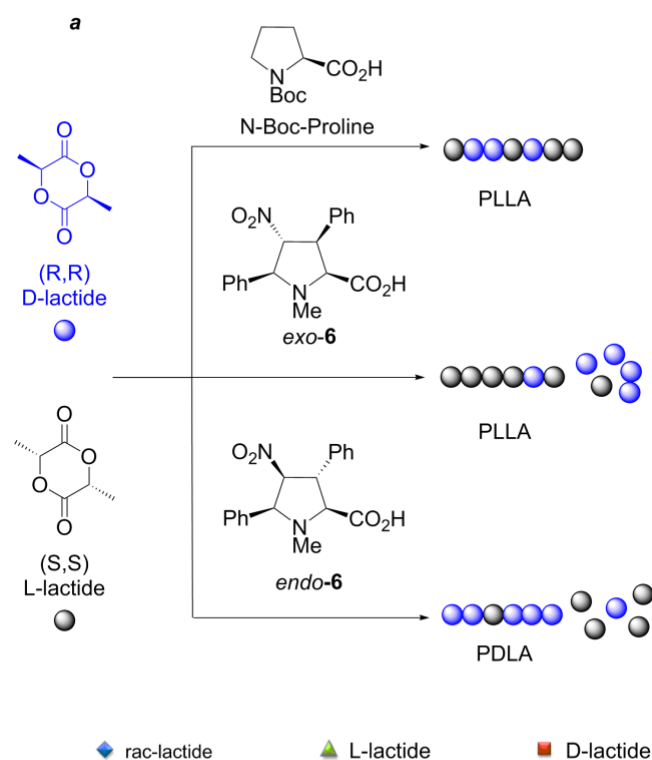Then, the resulting polymer was analyzed by ^{1}H NMR (SI, Figure S8) and MALDI-TOF spectrometry (Figure 1a and SI, Figure S12). As expected, together with the signal attributed to benzyl alcohol chain ends —observed at 7.44 ppm— another set of signals attributed to L-proline protons were observed at 4.45, 3.45 and 2.05 ppm, thus confirming L-proline incorporation into the polymeric chains. Moreover, MALDI-TOF experiments confirmed the presence of two main different initiating species: the benzyl alcohol and the L-proline. These results led us to conclude that the amino group of L-Pro is initiating the ROP of LA as observed before for ε-caprolactone.[33]

Given the negligible strength of protected amines, we foresaw that N-protected prolines should not initiate the ROP of rac-LA while maintaining its catalytic activity. Thus, L-Pro was replaced by commercially available protected version, Boc-L-Pro for the polymerization of rac-LA (Table 1, Entry 3). Again, the polymerization only occurred in the presence of DBU co-catalyst. In this case, when we measured the molecular weight *vs* conversion (SI section, Figure S6) we found a good relation between the theoretical and experimental. Furthermore, experimental molecular weight (M_n= 8000 g mol^{-1}) was similar to the targeted one (7300 g mol^{-1}) and the dispersity (Đ) was quite narrow, with a measured value of 1.2. To further verify the end-group and the controlled nature of the polymerization, ^{1}H NMR

(SI, Figure S9) and MALDI-TOF experiments were carried out (Figure 1b and SI Figure S13). As expected, only the signals attributed to benzyl alcohol chain ends at 7.44 ppm were observed. These results were confirmed by MALDI-TOF experiments where the corresponding end groups and only one set of peaks or distributions separated by 144 g. mol^{-1} — associated with the lactide monomer unit— were detected. Finally we investigated the potential of this catalyst to prepare higher molecular weight PLA. Therefore we targeted higher polymerization degree (n = 100). We found that experimental molecular weight (M_n= 23000 g mol^{-1}) was similar to the targeted one (Table 1, Entry 14 and SI, Figure S21).

Although the Boc protected L-Pro / DBU complex exhibited the ability to promote the controlled ROP of rac-LA, the main goal of our study was to promote stereocontrolled polymerizations. Thus, the microstructures of the PLA samples produced using rac-LA were determined by analyzing ^{13}C NMR signal intensities of the methine region using Bernoullian statistics.[20] According to the data shown in Table 1, Boc-L-Pro/DBU complex exhibited some isotactic selectivity (P_m=0.65) while DBU alone did not exert any significant stereocontrol and an essentially atactic material was obtained (P_m=0.50) (Table 1, Entry 4). On the other hand, using the method of Coudane et al.[36] the average of the enantiomerically pure repeating units along the polymer chain was found to be 6

using Boc-L-Pro. These stereoselectivity values are promising but still far from those observed in other stereocontrolled polymerizations, which show P_m values higher than 0.85.[2]
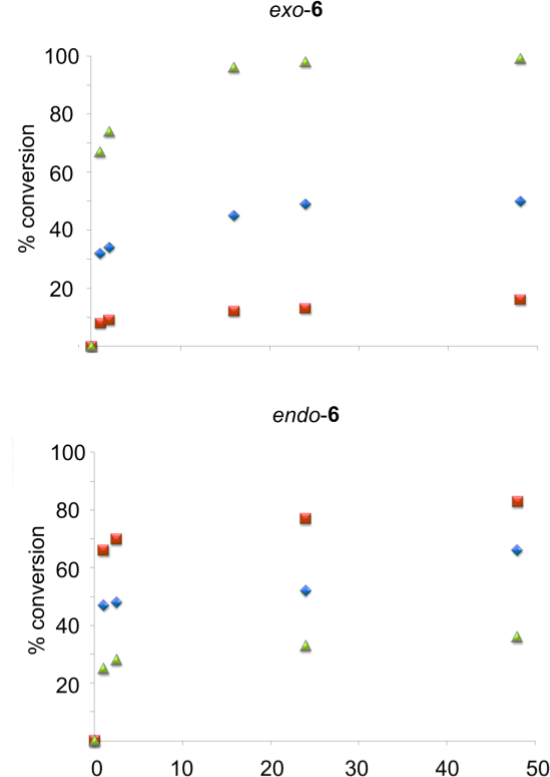
Figure 3.a) Schematic representation of the rac-LA polymerization in the presence of the 3 different N-protected prolines used in this study in DCM at r.t using DBU as co-catalyst and BnOH as initiator. Polymerization kinetics of L, D and rac-LA monomers in the presence of b) *exo*-**6** or c) *endo*-**6** in DCM at r.t using DBU as co-catalyst and BnOH as initiator.

In view of these results, we decided to prepare and explore densely substituted prolines for the enantioselective polymerization of rac-LA. These unnatural amino acid derivatives can incorporate up to four chiral centers in the pyrrolidine ring while commercially available prolines could have only one or two.[27] This high number of chiral centers in a reduced molecular volume could permit to concentrate many chiral induction effects in the neighborhood of the LA unit participating in one given polymerization step. This strong chiral induction was utilized by some of us in aldol reactions to yield opposite enantiomers, promoted by remote effects.[37] This anticipated the potential to obtain enhanced stereochemical outcomes by modifying the chirality and the nature of the substituents at the different positions of the corresponding organocatalyst. In order to synthesize *endo*- and *exo*-N-substituted densely substituted prolines **6** gathered in Figure 2a, we first obtained (3+2) cycloadducts **4** by 1,3-dipolar reactions between imines **2a,b** and nitroalkene **1**, catalyzed by Cu(I) complexes derived from enantiopure ligands **3a,b** (Figure 2b). N-methylation of these densely substituted pyrrolidines was carried out in the presence of trifluoroacetic acid and triethylsilane. The structures of *endo*- and *exo*-N-methylated esters **5a,b** was confirmed by X-ray diffraction analysis (Figures 2c,d). Finally, basic or acidic cleavage of the ester moieties yielded organocalysts *exo*-**6** and *endo*-**6**, respectively. Full details about the preparation and characterization of these catalysts are given in the SI section.

Next, the catalytic activity of these unnatural *endo*- and *exo*-N-substituted prolines was investigated for the ROP of L-Lactide (L-LA), D-Lactide and racemic lactide (rac-LA here after) in di-chloromethane (DCM) at room temperature using benzyl alcohol as the initiator (Figure 3a). First we explored the catalytic activity of *exo*-**6** for the polymerization of L-LA. As expected, the polymerization did not occur when *exo*-**6** was used as the sole catalyst (SI section, Table S1) and only when DBU co-catalyst was added we were able to promote the polymerization (Table 1, Entry 5).

The ROP conditions for L-LA were surveyed by varying catalyst concentration and solvent and we found that using a monomer/initiator/catalyst ratio of 50/1/1 we were able to reach full conversion in 24 h at room temperature (Table 1, Entry 6). As in the previous case, *exo*-**6**/DBU complex exhibited the ability to promote the controlled ROP of L-LA as observed by the end-group fidelity confirmed by ^{1}H NMR and MALDI-TOF experiments (SI section, Figure S14). Furthermore, an experimental molecular weight Mn= 8300 g mol^{-1} was observed, which was similar to the targeted one (Mn = 7300 g mol^{-1}). In addition, the dispersity (Đ) was narrow again showing a value of 1.2.

Besides the polymerization of L-LA, we carried out the polymerization of rac-LA (mixture of L-LA and D-LA) in the presence of *exo*-**6** using the same monomer/initiator/catalyst ratio of 50/1/1 (Table 1, Entry 7). At the initial stages of the ROP, the rac-LA proceeded selectively to polymer derived from L-LA, but beyond a conversion of 40 % the polymerization substantially slowed down, and the reaction stopped around 50 % conversion

(Figure 3b). It seemed that *exo*-**6** had preference towards one of the isomers showing enantiomeric selectivity during the polymerization. To confirm this fact, we performed the same polymerization but using D-LA (Table 1, Entry 8). Surprisingly, the polymerization

Table 1. Polymerization of lactide (LA) with different catalysts (Cat.) at r.t.

entry	Monomer	Catalyst	[LA]/[BnOH]/[Cat]	Conv.(%)[a]	M_n(SEC) (g.mol^{-1})[b]	PDI[c]	P_m[d]
1	rac- LA	L-Pro	-	-	-	-	-
2	rac- LA	L-Pro/DBU	50/1/5	<98	700	1.5	-
3	rac- LA	Boc-L-Pro/DBU	50/1/5	<98	8000	1.2	0.65
4	rac- LA	DBU	50/1/5	<98	12200	2.1	0.50
5	L-LA	*exo*-**6**/ DBU	50/1/5	100	6100	1.4	1.00
6	L-LA	*exo*-**6**/ DBU	50/1/1	100	8300	1.2	1.00
7	rac- LA	*exo*-**6**/DBU	50/1/1	50	3300	1.1	0.96
8	D-LA	*exo*-**6**/ DBU	50/1/1	20	-	-	1.00
9	rac- LA	*endo*-**6**/ DBU	50/1/1	51	3100	1.2	0.90
10	D-LA	*endo*-**6**/ DBU	50/1/1	83	3900	1.2	1.00
11	L-LA	*endo*-**6**/ DBU	50/1/1	36	1900	1.4	1.00
12	rac- LA	*exo*-**6**/DBU	100/1/2	58	7500	1.2	0.87
13	rac- LA	*exo*-**6**/*endo*-**6**/DBU	50/1/1	<98	10200	1.2	0.60
14	L-LA	Boc-L-Pro/DBU	100/1/2	<98	23000	1.3	1.00

[a] *As determined by* ^{1}*H NMR in CDCl$_3$.*

[b,c] *As determined by size exclusion chromatography (SEC) in THF according to PS standards.*

[d] P_m *is the probability of meso linkage between monomer units and was calculated from the methine region of* ^{13}*C NMR spectrum:* $[mmm] = P_m(P_m+1)/2$; $[mmr] = P_m(1-P_m)/2$; $[rmm] = P_m(1-P_m)/2$; $[rmr] = (1-P_m)^2/2$; $[mrm] = (1-P_m)/2.$[2]

was much slower and after 48 h we were able to reach only 20 % conversion (Figure 3b), being unable to get high molecular weight polymer (Table 1, entry 8). These results are congruent with the fact that the catalyst dictates the entrance of the next monomeric unit and suggested that the chirality of the catalyst is the dominating factor determining the stereocontrol. To further investigate the mechanism, we performed the same experiments using the analogous *endo*-**6**. Interestingly, the opposite behavior was observed (Table 1, Entry 9, 10 & 11). In this case, *endo*-**6** showed much higher preference towards D-LA rather than towards L-LA (Figure 3c).

To further confirm and quantify the ability of our organic catalysts to promote stereocontrolled ROP processes, the different reaction mixtures were analyzed. To this end, the corresponding crude polymeric material was precipitated in cold methanol and the residual monomer was recovered to analyze the unreacted monomer using chiral HPLC measurements. The HPLC chromatograms showed that in the presence of *exo*-**6**, L-LA was preferentially polymerized due to the disappearance of the signal associated to this (S,S) monomer. Meanwhile, in the case of *endo*-**6**, the opposite behavior was observed (SI, Figure S24-S28). Figure 3 shows a schematic representation of the polymerization process. As observed in the presence of a racemic mixture of D-LA and L-LA, *exo*-**6** promoted the polymerization of L-LA obtaining highly stereoregular poly(L-lactide) (PLLA), while in the case of *endo*-**6** highly stereoregular poly(D-lactide) (PDLA) could be achieved (Figure 3). Apparently, *endo*- and *exo*-N-methylated prolines were able to preferentially promote the polymerization of one of the enantiomers with respect to the other.

Nevertheless, we wanted to compare our results with other enantioselective polymerizations of rac-LA. For that purpose we analyzed the ^{13}C NMR signal intensities of the carbonyl region and methine region using Bernoullian statistics (Figure 4) of the obtained polymers. According to the data shown in Figure 4 and Table 1, both *endo*- and *exo*-N-methylated prolines showed excellent isotactic selectivities, with $P_m=0.90$ and $P_m=0.96$, respectively for rac-LA (Figure 4, SI, Figure S10). Moreover, in order to definitely assign the P_m values of the obtained polymers the analysis of the homonuclear ^{1}H NMR spectra of the methine region was carried out (SI, Figure S11) and confirmed the excellent control of the polymerization. According to the data shown in Figure 4, SI section and Table 1, both *endo*- and *exo*-N-methylated prolines showed excellent isotactic selectivities, with $P_m=0.90$ and $P_m=0.96$, respectively for rac-LA. It is worth noting that these are the highest values reported in the literature for organic catalysts at room temperature. Previous organic catalysts such as N-heterocyclic carbenes [17,18] showed a $P_m=0.59$, phosphazenes [19] a $P_m=0.72$ or (R)-binaphthol derived phosphoric acids a $P_m=0.86$.[20] Most importantly, most of the previous examples incorporated preferentially L-LA. In our case we were able to show for the first time high selectivity towards both L-lactide but also D-lactide just by switching the chirality of the distal centers of the catalyst. We found that using *exo*-**6,** the stereocontrol ($P_m=0.96$) was slightly better than when using *endo*-**6** ($P_m=0.90$). These observation is in good agreement with previous results where *exo*-**6** showed higher kinetic resolution than *endo*-**6** in aldol reactions.[27] Finally we performed the polymerization of rac-LA in the presence of *exo*-**6** and *endo*-**6** (Table 1, entry 13). In this case we were able to get a good control over the polymerization but the isotactic selectivity was much lower than in previous cases.

To further confirm the excellent stereocontrol observed in the ROP processes, the specific rotations values [α] and the thermal properties of the synthesized PLA were investigated.[38] Hence, starting from racemic lactide (rac-LA) when proline *endo-6* is used as catalyst (Table 1, entry 9), the value of the obtained polymers is [α]$_D$ = 75.9 (Figure 4). This value is in good agreement with that of the PDLA polymer (Table 1, entry 10). Meanwhile using the diastereoisomeric proline *exo-6* the α value is [α]$_D$= -79.6 in agreement with the values measured for PLLA and confirming the ability of obtaining opposite outcomes switching the *endo/exo* diastereomeric nature of the catalyst. Furthermore, differential scanning calorimetry (DSC) analyses confirmed the crystalline character of the polymer obtained from rac-LA. For instance, the PLLA (Table 1, entry 12) showed a melting temperature of 165 °C, and enthalpy values of 31 J/g similar to the ones reported in the literature for isotactic PLLA.[15]
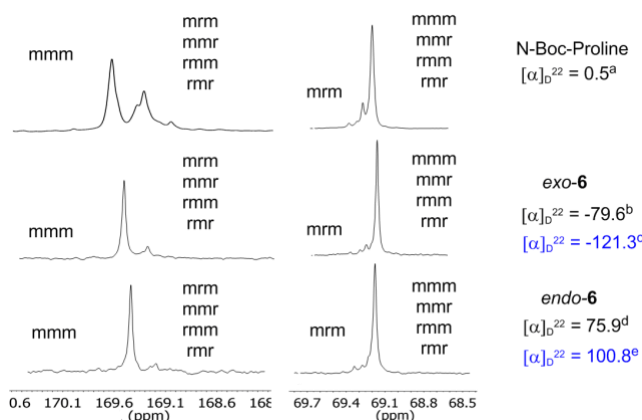
Figure 4. Carbonyl region (170-168 ppm) and methine region (70-67 ppm) of ^{13}C NMR spectra of poly(rac-LA) obtained using 3 different prolines as catalyst showing the different tetrads and specific rotation values [α] for the polymers obtained in Table 1 ([a] corresponds to Entry 3, [b] corresponds to Entry 7, [c] corresponds to Entry 6, [d] corresponds to Entry 9 and [e] corresponds to Entry 10).[39]

All these results confirmed that our highly substituted prolines not only provided polymers with low dispersities and molecular weights that closely track the monomer-to-initiator ratio, but also that depending on the remote substituent chirality, different polymeric stereochemical outcomes could be promoted.

These results indicate that the chirality of the catalyst can be transferred in an efficient way to the polymer. In order to gain a better understanding of the origins of this transfer, we performed experimental and computational studies on the nature of the reactants and their interactions before and during the polymerization process. We first analyzed the structure and dynamics of *exo-6* by ^{1}H NMR diffusion ordered spectroscopy[40-42] (DOSY) experiments. The DOSY spectra of *exo-6* at 0.25M and 1M concentrations (Figure 5a) showed different diffusion coefficients, thus indicating aggregation phenomena. At 1M concentration of *exo-6*, the measured D_{1M} value resulted to be associated with a heavier species, whereas the $D_{0.25M}$ coefficient corresponded to a more mobile smaller structure. According to the Stokes-Einstein equation[40] and assuming similar shape parameters for both species, we obtained the following ratio between the respective hydrodynamic radii of *exo-6* at both concentrations:

$$\frac{D_{0.25M}}{D_{1M}} \gg \frac{r_{1M}}{r_{0.25M}} = 2.08 \tag{1}$$

This result suggested that if the dominant species at 0.25 M concentration is monomeric *exo-6*, the major aggregate at 1M is the dimer. We analyzed this result by computational methods. Density functional theory (DFT) calculations performed in dichloromethane at the M062X(PCM)/6-31+G(d,p) level of theory[43-46] showed that formation of dimer **d1** from *exo-6* is an almost energetically degenerated process with ΔE=-0.02 kcal/mol:

$$\tag{2}$$
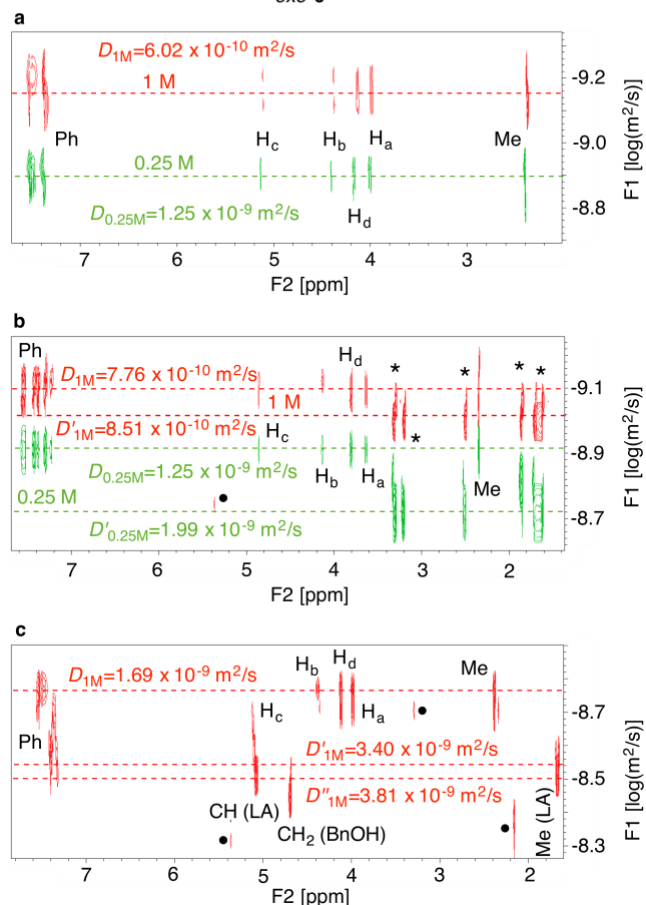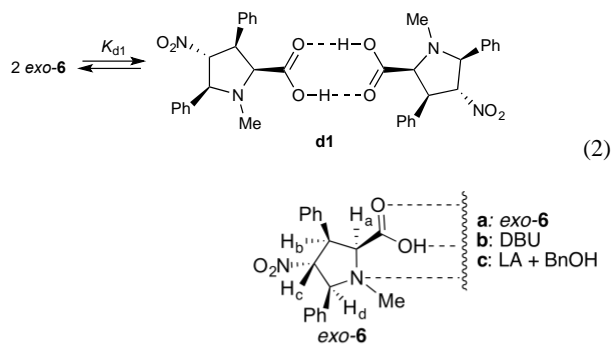
Figure 5. DOSY spectra of (a) *exo-6* at 1M (red) and 0.25 M (green) concentrations in deuterated dichloromethane; (b) *exo-6* and DBU mixtures at the same concentrations; and (c) *exo-6*, lactide (LA) and benzyl alcohol (BnOH). The DOSY signals associated with DBU are indicated as asterisks. The residual signals corresponding to other solvents such as non-deuterated dichloromethane, acetone and water are highlighted as dots. The diffusion coefficients D (in m^2/s) are indicated for each component.

We next measured the effect of DBU on the behavior of *exo-6*. Figure 5b shows the DOSY spectra of the *exo-6*/DBU pairs at 1M and 0.25 concentrations. Our results indicate that the

interaction of DBU with *exo*-**6** is weaker since both species diffuse closely but not as a unique complex. Thus, the D_{1M} value of *exo*-**6** is close to (but larger than) that measured in the previous experiments. However, at the concentration of 0.25M the $D_{0.25}$ value of *exo*-**6** is identical to that found in the absence of DBU (vide supra). As far as DBU is concerned, the corresponding D_{1M} value was found to be lower than $D_{0.25}$. This latter value was almost identical to that measured for free DBU ($D_{DBU}=1.66 \times 10^{-9}$ m^2/s). DFT calculations permitted the characterization of a weak *exo*-**6**/DBU complex **d2** (eq. 2), whose associated equilibrium constant was calculated to be close to that corresponding to an isoenergetic transient-complexation process ($K_{d2}=0.93$ M^{-1}):

$$\textit{d1/exo-}\mathbf{6} + \text{DBU} \underset{}{\overset{K_{d2}}{\rightleftharpoons}} \mathbf{d2} \tag{3}$$
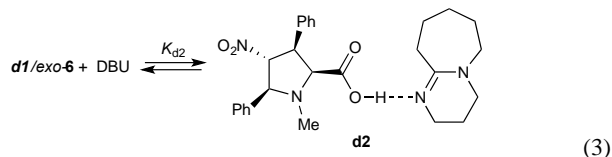
This result is compatible with the loose interaction between *exo*-**6** and DBU detected by the DOSY experiments. The possibility of an ionic pair **d3** formed by the acid/base interaction between both components was also analyzed (eq. 4):

$$\mathbf{d2} \underset{}{\overset{K_{d3}}{\rightleftharpoons}} \mathbf{d3} \tag{4}$$
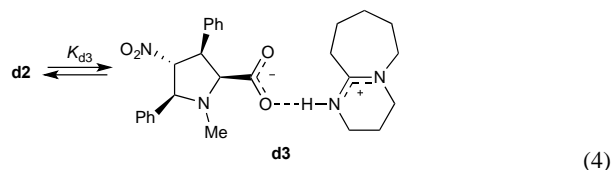
Our calculations indicated that in dichloromethane solution both pairs are almost isoenergetic with $K_{d3}=0.95$, in which **d2** is the major species. In fact, ionic pair **d3** should result in a tighter complex, thus promoting a more coherent diffusion, which was not suggested by the DOSY experiments.

From these results we concluded that the presence of DBU can modify the dimeric structure of *exo*-**6** at a concentration of 1M in dichloromethane, but it does not alter significantly the ability of *exo*-**6** to participate in the catalytic cycle associated with the polymerization process. Actually, DOSY experiments including a mixture of *exo*-**6**, lactide and benzyl alcohol (total concentration: 1M) showed a slight modification in the dynamic behavior of *exo*-**6** (Figure 5c). Although on average the three components of the mixture moved separately, the D_{1M} value for *exo*-**6** corresponds to a lighter monomeric species that can interact with the reactants to trigger the polymerization process. Therefore, this latter neutral *N*-methyl amino acid can be considered explicitly as the active chiral organocatalyst in the polymerization process.

Additional DFT calculations were conducted to investigate the origin of the enantiomeric site control of the polymerization process. Although different proposals for organocatalytic ROP reactions have been reported,[47,48] no precedent exists for our catalytic system. On the basis of computational studies for related transesterification processes[34,49,50] as well as on the previous DOSY and computational experiments (vide supra), the catalytic cycle gathered in Figure 6 can be proposed, which relies on the preferential coordination of D-LA or L-LA with catalysts **6** (vide supra). Since chiral discrimination is required to promote the reaction of LA with an alcohol (benzyl alcohol in the first catalytic cycle, see Figure 5a), interaction of LA with the acidic part of organocatalysts **6** results in LUMO activation that enhances the electrophilicity of the substrate. In addition, the alcohol can be activated by increasing the energy of its HOMO by

means of the interaction of the hydroxy group with the tertiary amine moiety of **6** (Figure 6). Of course, DBU can move around the active sites of catalysts **6**. However, as demonstrated in the previous DOSY and computational experiments, interaction of monomeric neutral organocatalysts **6** with LA and MeOH captures the essential aspects of the origins of the stereocontrol.

Dual activation of **INT1** results in the formation of intermediate **INT2**, in which the tetrahedral intermediate derived from the nucleophilic attack of the alcohol on LA is stabilized by hydrogen bonding with the zwitterionic tautomer of organocatalyst **6** (Figure 6a). Intermediate **INT2** is converted into alcohol **INT3** with the assistance of DBU or the **6**/DBU pair. This latter intermediate enters the next catalytic cycle to proceed with the polymerization process. Iteration of this cycle results in the elongation of the polymeric chiral chain. This mechanism requires chiral discrimination only at the **INT1** → **INT2** step. Therefore, the interaction between catalysts **6** and D-LA or L-LA will determine the stereo regularity of the corresponding polymers. DFT calculations at the MO6-2X(PCM)/6-31+G(d,p)//B3LYP/6-31G(d) level of theory[43,46] using methanol as model nucleophilic alcohol were carried out in order to get a better understanding of the origins of the stereoselection between L-LA and D-LA by *exo*-**6** and *endo*-**6**, respectively. Since the pyrrolidine ring of both organocatalysts can adopt different conformations, all the possible energetically available conformers of *endo*-**6** and *exo*-**6** compounds were explored. In particular, we found that whereas the most stable conformations included both carboxy and 5-phenyl moieties in equatorial disposition, the *N*-methyl group can be either in equatorial or axial orientations with respect to the carboxy group, denoted in Figure 5b as *anti* and *syn* conformations, respectively. The above mentioned interactions of the amino and carboxy groups with the alcohol and the lactide lead to quite different geometries for the respective complexes **INT1**, transition structures, and addition products **INT2** (see the SI for further details). In particular, our calculations showed that **INT2** regenerates catalyst *exo*-**6** in its neutral form, an energetically favoured process (see Figure S44 of the SI).

In the case of *exo*-**6,** the saddle point of lowest energy, denoted as *exo,anti*-**TS** in Figure 6c, exhibited an equatorial *N*-methyl group with a preference for L-LA of 0.9 kcal/mol in terms of Gibbs energy with respect to D-LA. This difference in free energy corresponds to a (*S,S*):(*R,R*) discrimination ratio of 83:17, a value in excellent agreement with the experimentally found value of 86:14 (see the SI for further information). In contrast, when the reaction coordinate of *endo*-**6** was studied, it was found that saddle point *endo, syn*-**TS** with an axial *N*-methyl group, and D-LA as substrate, was the less energetic one, the *endo,anti*-**TS** with L-LA as substrate being 0.30 kcal/mol higher in energy. This value corresponds to a (*S,S*):(*R,R*) discrimination ratio of 38:62, also in good agreement with the experimentally found value of 30:70 (Figure 3b,c). These results are compatible with the mechanistic proposal consisting of a nucleophilic attack of the activated alcohol on the corresponding chiral LA, whose electrophilicity is enhanced by the chiral carboxy group of the organocatalysts. These attacks are quite synchronous (Figure 6c) in terms of formation of the new C-C bond and proton motion from the alcohol to the catalyst and from the carboxy group to the lactide. This high density of chiral an prochiral centres results in a high selectivities of *exo*-**6** and *endo*-**6** towards L-LA and D-LA, respectively. In addition, our calculations reproduce correctly two relevant experimental findings: (i) both catalysts *exo*-**6** and *endo*-**6** give rise to opposite stereochemical outcomes; and (ii) *exo*-**6** is more stereoselective than its *endo* congener.

Conclusions

In summary, we report a highly efficient organic catalytic

system for the stereocontrolled ROP of rac-LA. We have found that by switching from *endo* to *exo* configuration in unnatural densely substituted proline **6**, the chirality of the catalyst is transferred efficiently to the polymer, thus obtaining different stereochemical outcomes. Hence, when *endo*-**6** was used, it preferentially promoted the polymerization of D-LA, whereas *exo*-**6** polymerized preferentially L-LA from a racemic mixture of L- and D- stereoisomers. Mechanistic and computational studies reveal the importance of the configuration of the densely substituted aminoacids to
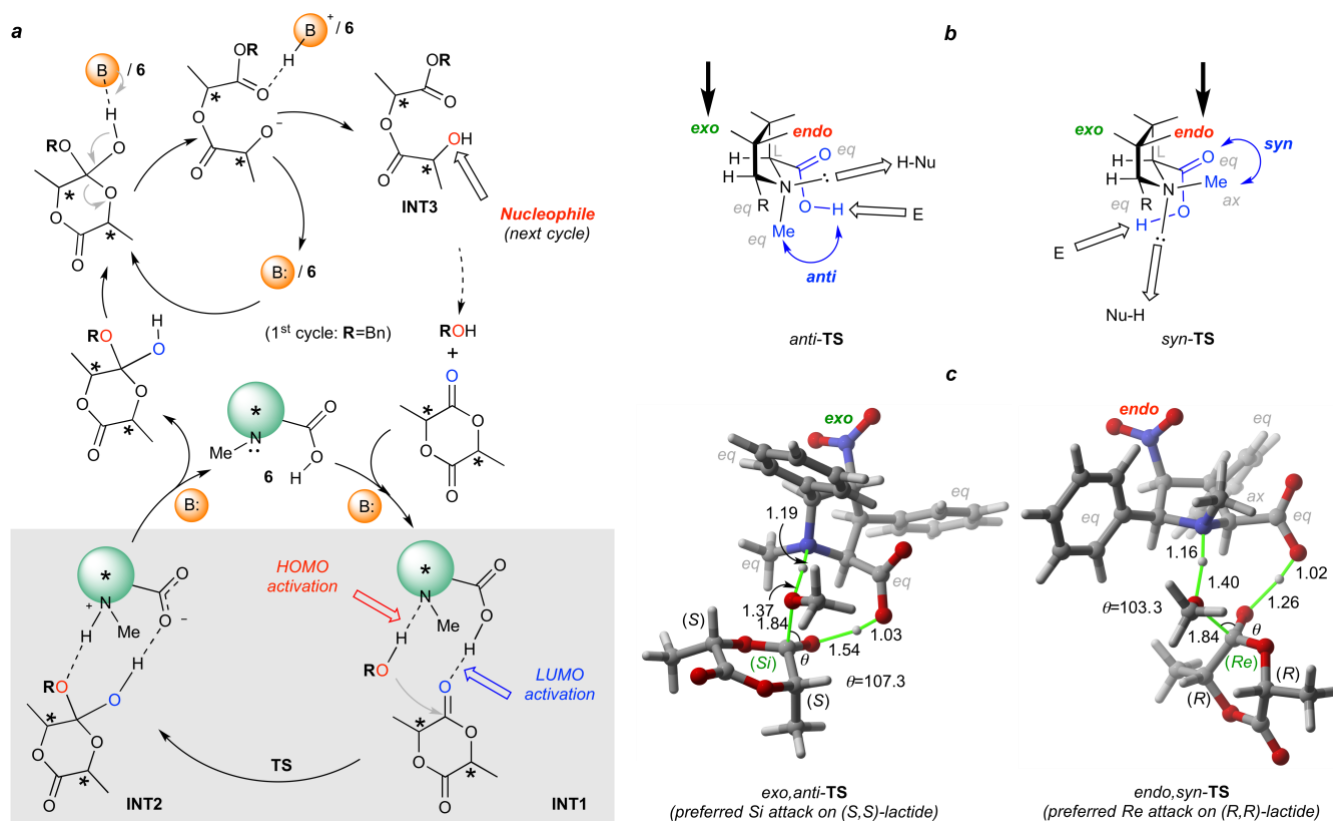
Figure 6. a) Proposed catalytic cycle for the ROP of (*R,R*)-D-lactide and (*S,S*)-L-lactide. Notice the dual activation of the nucleophilic alcohol and electrophilic lactide, as well as the chiral discrimination induced by catalysts **6**. b) Possible interaction patterns depending upon the syn/anti relationship between the carboxylic acid (in equatorial disposition) and *N*-methyl group (in axial or equatorial dispositions) of organocatalysts **6**. c) Optimized geometries (B3LYP/6-31G(d) level of theory) of preferred transition structures **TS** associated with the interaction between methanol (as a model primary alcohol) and lactide in the presence of *exo*-**6** (*exo, anti*-**TS**) and *endo*-**6** (*endo, syn*-**TS**). Distances and angles given in Å and deg. respectively. Relative energies were computed at the M062X(PCM)/6-31+G(d,p)//B3LYP/6-31G(d) level of theory, in which dichloromethane was included in the PCM calculations

promote the stereocontrolled polymerization. This strategy of using combined enantiopure unnatural organocatalyst/organic base pairs could be readily extended to other stereocontrolled metal-free polymerization processes.

Experimental Section

Preparation of *exo*-**6**. A solution of chiral ligand NMe-D-EhuPhos-**3b** (0.03 mmol) and Cu(CH₃CN₄)PF₆ (0.03 mmol) in 2.0 mL of dry THF was stirred at -20 °C for 20 minutes. Then, a solution of imine **2a** (0.9 mmol) in 3 mL of solvent, triethylamine (7 mL, 0.05 mmol) and trans-β-nitrostyrene **1**(1 mmol) in 3 mL of solvent were consecutively added. After reaction completion, the mixture was filtered through a celite pad and the filtrate was concentrated under reduced pressure and purified by silica gel flash column chromatography. The corresponding *exo*-**5b** cycloadduct (1.50 mmol) and 1,3,5-trioxane (4.50 mmol) were dissolved in 2.5 mL of dry dichlorometane and trifluoroacetic acid

(1.2 mL) and Et₃SiH (2.44 mL, 15.0 mmol) were added subsequently. The mixture was stirred at room temperature for 48h. The, water was added and the mixture was extracted three times with CH₂Cl₂. The combined organic layers were dried and concentrated under reduced pressure to yield crude *exo*-**5a**. Finally, to a solution of *exo*-**5a** (1.45 mmol) in acetone (4.5 mL) stirred at room temperature a solution of sodium hydroxide (3.12 mmol) in water (4.5 mL) was added. The reaction mixture was stirred for 16h and acidified with 2N HCl to pH ≈ 2. A solid precipitated from the solution and was filtered, washed with water and dried under vacuum to afford the desired product *exo*-**6**. Yield: 85%. Yellow syrup. $[\alpha]_D^{25}$ = +48.6 (*c* 0.33, acetone). FTIR (neat, cm⁻¹): 1550, 700. ¹H NMR (400 MHz, Acetone-*d₆*) δ 7.61 (d, *J* = 7.4 Hz, 2H), 7.47 (ddd, *J* = 19.5, 14.4, 7.0 Hz, 6H), 7.32 (q, *J* = 7.1 Hz, 2H), 5.19 (t, *J* = 7.6 Hz, 1H), 4.44 (dd, *J* = 9.5, 6.9 Hz, 1H), 4.23 (d, *J* = 8.4 Hz, 1H), 4.14 (d, *J* = 9.5 Hz, 1H), 2.41 (s, 3H). HRMS (ESI) for C₁₈H₁₈N₂O₄ calculated [M + H]⁺: 327.1267. Found: 327.1338.

Preparation of *endo*-**6.** A solution of chiral ligand NMe-L-EhuPhos-**3a** (0.03 mmol) and Cu(CH$_3$CN)$_4$PF$_6$ (0.03 mmol) in 2.0 mL of dry THF was stirred at -60 ºC for 15 minutes. Then, a solution of imine **2b** (0.9 mmol) in 3.0 mL of solvent, triethylamine (7 ml, 0.05 mmol) and the corresponding nitroalkene **1** (0.50 mmol) in 1.0 mL of solvent were successively added. After reaction completion, the mixture was filtered through a celite pad and the filtrate was concentrated under reduced pressure and purified by silica gel flash column chromatography. The corresponding *endo*-**5b** cycloadduct (1.50 mmol) and 1,3,5-trioxane (4.50 mmol) were dissolved in 2.5 mL of dry dichlorometane and trifluoroacetic acid (1.2 mL) and Et$_3$SiH (2.44 mL, 15.0 mmol) were added subsequently. The mixture was stirred at room temperature for 48h. Then, TFA (11 mL) was added. After 16h water was added and the mixture was extracted three times with CH$_2$Cl$_2$. The combined organic layers were dried and concentrated under reduced pressure. The crude mixture was purified by precipitation with Et$_2$O to obtain *endo*-**6**. Yield: 57%. Pale yellow syrup. [α]$_D^{25}$ = +20.81 (*c* 0.85, acetone). FTIR (neat, cm^{-1}): 3055, 2925, 2854, 1719, 1554, 1264, 732, 700. ^{1}H NMR (400 MHz, Acetone-*d$_6$*) δ 7.52 (d, *J* = 7.2 Hz, 2H), 7.46 (d, *J* = 7.6 Hz, 2H), 7.36 (dt, *J* = 20.0, 7.4 Hz, 6H), 5.64 – 5.54 (t, *J* = 8.1 Hz, 1H), 4.52 (d, *J* = 8.7 Hz, 1H), 4.50 – 4.47 (m, 1H), 3.61 (d, *J* = 9.5 Hz, 1H), 2.37 (s, 3H). HRMS (ESI) for C$_{18}$H$_{18}$N$_2$O$_4$ calculated [M + H]$^+$: 327.1267. Found: 327.1345.

Polymerization of rac-lactide (rac-LA). Polymerizations were carried out in nitrogen filled glove box. In a typical procedure, rac-lactide was polymerized using a mixture of the densely substituted proline *exo*-**6** or *endo*-**6** and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) co-catalyst. In brief, rac-lactide (0.3 g, 2.08 mmol, 50 equiv) benzyl alcohol (4.4 µL, 0.042 mmol, 1 equiv) (for a degree of polymerization of 50) were charged in a 20 mL vial. Afterwards, dicloromethane was added and the concentration was adjusted to 1 M. To initiate the polymerization, densely substituted proline (0.014 g, 0.042 mmol, 1 equiv) and DBU (0.0063 g, 0.042 mmol, 1 equiv) were added. After 24h, the polymerization was quenched with excess of benzoic acid and the crude product was precipitated in cold methanol. The collected polymer was dried under vacuum at 35 ºC until a constant weigh was reached. Yield, 0.14 g (45%). Size exclusion chromatography (SEC): Mn = 3300 g/mol, dispersity (Đ) = 1.10, ^{1}H NMR (CDCl$_3$) 7.35 (ArH, Initiator) 5.21 (CH, 2H), 1.42 (CH$_3$, 6H).

ASSOCIATED CONTENT

Supporting Information

Experimental procedure and characterization of compounds, ORTEP diagrams and computational details. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interests.

REFERENCES

(1)   Coates, G. W. *Chem. Rev.* **2000**, *100*, 1223.
(2)   Stanford, M. J.; Dove, A. P. *Chem. Soc. Rev.* **2010**, *39*, 486.
(3)   Hawker J.C.; Wooley K.L. *Science.* **2005**, 5738,1200.
(4)   Natta, G.; Pino, P.; Corradini, P.; Danusso, F.; Mantica, E.; Mazzanti, G.; Moraglio, G. *J. Am. Chem. Soc.* **1955**, *77*, 1708.
(5)   Ovitt, T. M.; Coates, G. W. *J. Am. Chem. Soc.* **2002**, *124*, 1316.
(6)   Jensen, T. R.; Breyfogle, L. E.; Hillmyer, M. A.; Tolman, W. B. *Chem. Commun.* **2004**, 2504.
(7)   Mou, Z.; Liu, B.; Liu, X.; Xie, H.; Rong, W.; Li, L.; Li, S.; Cui, D. *Macromolecules.* **2014**, *47*, 2233.
(8)   Carpentier, J.-F. *Macromol. Rapid Commun.* **2010**, *31*, 1696.
(9)   Lecomte, P.; Jérôme, C. In *Synthetic Biodegradable Polymers*; Rieger, B., Künkel, A., Coates, W. G., Reichardt, R., Dinjus, E., Zevaco, A. T., Eds.; SpringerBerlin Heidelberg: Berlin, Heidelberg, 2012, p 173.
(10)   Zhang, X.; Jones, G. O.; Hedrick, J. L.; Waymouth, R. M. *Nat. Chem.* **2016**, *8*, 1047.
(11)   Thomas, C. M. *Chem. Soc. Rev.* **2010**, *39*, 165.
(12)   Miyake, G. M.; Chen, E. Y. X. *Macromolecules.* **2011**, *44*, 4116.
(13)   Zhong, Z.; Dijkstra, P. J.; Feijen, J. *J. Am. Chem. Soc.* **2003**, *125*, 11291.
(14)   Dechy-Cabaret, O.; Martin-Vaca, B.; Bourissou, D. *Chem. Rev.* **2004**, *104*, 6147.
(15)   Ottou, W. N.; Sardon, H.; Mecerreyes, D.; Vignolle, J.; Taton, D. *Prog. Polym. Sci.* **2016**, *56*, 64.
(16)   Kiesewetter, M. K.; Shin, E. J.; Hedrick, J. L.; Waymouth, R. M. *Macromolecules.* **2010**, *43*, 2093.
(17)   Dove, A. P.; Li, H.; Pratt, R. C.; Lohmeijer, B. G. G.; Culkin, D. A.; Waymouth, R. M.; Hedrick, J. L. *Chem. Commun.* **2006**, 2881.
(18)   Fevre, M.; Pinaud, J.; Gnanou, Y.; Vignolle, J.; Taton, D. *Chem. Soc. Rev.* **2013**, *42*, 2142.
(19)   Zhang, L.; Nederberg, F.; Messman, J. M.; Pratt, R. C.; Hedrick, J. L.; Wade, C. G. *J. Am. Chem. Soc.* **2007**, *129*, 12610.
(20)   Makiguchi, K.; Yamanaka, T.; Kakuchi, T.; Terada, M.; Satoh, T. *Chem. Commun.* **2014**, *50*, 2883.
(21)   Zhu, J. B.; Chen, E. Y. X. *J. Am. Chem. Soc.* **2015**, *137*, 12506.
(22)   Ahrendt, K. A.; Borths, C. J; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243.
(23)   Jarvo, E. R. & Miller, S. J. *Tetrahedron.* **2002**, *58*, 2481.
(24)   List, B. *Tetrahedron.* **2002**, 58, 5573.
(25)   List, B., Lerner, R. A. & Barbas, C. F. *J. Am. Chem. Soc.* **2000**, 122, 2395.
(26)   Ruiz-Olalla, A.; Retamosa, M. d. G.; Cossío, F. P. *J. Org. Chem.* **2015**, *80*, 5588.
(27)   Conde, E.; Bello, D.; de Cozar, A.; Sanchez, M.; Vazquez, M. A.; Cossio, F. P. *Chemical Science.* **2012**, *3*, 1486.
(28)   Yang, J. W.; Chandler, C.; Stadler, M.; Kampen, D.; List, B. *Nature.* **2008**, *452*, 453.
(29)   Palomo, C.; Vera, S.; Mielgo, A.; Gómez-Bengoa, E. *Angew. Chem. Int. Ed.* **2006**, *45*, 5984.
(30)   List, B.; Pojarliev, P.; Martin, H. J. *Org. Lett.* **2001**, *3*, 2423.
(31)   Ramachary, D. B.; Chowdari, N. S.; Barbas, C. F. *Angew. Chem. Int. Ed.* **2003**, *42*, 4233.

(32)   Liu, N.; Martin, A.; Robert, F.; Vincent, J.-M.; Landais, Y.; Vignolle, J.; Cramail, H.; Taton, D. *Macromolecules*. **2014**, *47*, 525.

(33)   Liu, J.; Liu, L. *Macromolecules*. **2004**, *37*, 2674.

(34)   Coady, D. J.; Fukushima, K.; Horn, H. W.; Rice, J. E.; Hedrick, J. L. *Chem. Commun*.**2011**, *47*, 3105.

(35)   It is worth nothing that after the conditions for the polymerization were surveyed in terms of different solvents (DCM, THF and DMF) and differen tcatalyst concentrations (1, 5, 10, 20 mol % respect to the initiator), the best results in terms of end-group fidelity were obtained using DCM and initial initiator-to-catalyst ratio of 5 mol % (Table S2).

(36)   Coudane, J.; Ustariz-Peyret, C.; Schwach, G.; Vert, M. *J. Polym. Sci., Part A: Polym. Chem.***1997**, *35*, 1651.

(37)   de Gracia Retamosa, M.; de Cózar, A.; Sánchez, M.; Miranda, J. I.; Sansano, J. M.; Castelló, L. M.; Nájera, C.; Jiménez, A. I.; Sayago, F. J.; Cativiela, C.; Cossío, F. P. *Eur. J. Org. Chem.* **2015**, *2015*, 2503.

(38)   Wisniewski, M.; Borgne, A. L.; Spassky, N. *Macromol. Chem. Phys.***1997**, *198*, 1227.

(39)   exchanging R by S same tetrads will be obtained.

(40)   Macchioni, A.; Ciancaleoni, G. Z.; Zuccaccia, C.; Zuccaccia, D. *Chem. Soc. Rev.* **2008**, *37*, 479.

(41)   Li, D.; Keresztes, I.; Hopson, R.; Williard, P. G. *Acc. Chem. Res.* **2009**, *42*, 270.

(42)   Pregosin, P. S. *Pure Appl. Chem.* **2009**, *81*, 615.

(43)   (a) Zhao, Y.; Truhlar, D. G. *Theor. Chem. Acc.***2008**, *119*, 525. (b) (Zhao, Y.; Truhlar, D. G. Theor. Chem. Acc. **2008**, *120*, 215. (b) Zhao, Y.; Truhlar, D. G. *Acc. Chem. Res*. **2008**, *41*, 157.

(44)   (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1998**, *37*, 785. (c) Vosko, S. H.; Wilk, L.; Nusair, M. *Can. J. Phys.* **1980**, *58*, 1200.

(45)   Cammi, R.; Mennucci, B.; Tomasi, *J. J. Phys. Chem. A*. ***2000, 104,*** 5631.

(46)   Gaussian 09, Revision D.01; Gaussian, Inc., Wallingford, CT, 2009.

(47)   Fastnacht, K. V.; Spink, S. S.; Dharmaratne, N. U.; Pothupitiya, J. U.; Datta, P. P.; Kiesewetter, E. T.; Kiesewetter, M. K. *ACS Macro Lett.***2016**, 5, 982.

(48)   Kadota, J.; Pavlović, D.; Desvergne, J.-P.; Bibal, B.; Peruch, F.; Deffieux, A. *Macromolecules*.**2010**, *43*, 8874.

(49)   Horn, H. W.; Jones, G. O.; Wei, D. S.; Fukushima, K.; Lecuyer, J. M.; Coady, D. J.; Hedrick, J. L.; Rice, J. E. *J. Phys. Chem. A*.**2012**, *116*, 12389.

(50)   Bonduelle, C.; Martín-Vaca, B.; Cossío, F. P.; Bourissou, D. *Chem. Eur. J*.**2008**, *14*, 5304.

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