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A synergetic organocatalysis for eliminating epimerization in ring-opening polymerizations enables synthesis of stereoregular isotactic polyester

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ABSTRACT: Ring-opening polymerization of *O*-carboxyanhydrides (OCAs) can furnish polyesters with a diversity of functional groups that are traditionally hard to harvest by polymerization of lactones. Typical ring-opening catalysts are subject to unavoidable racemization of most OCA monomers, which hampers the synthesis of highly isotactic crystalline polymers. Here, we describe an effective bifunctional single-molecule organocatalysis for selective ring-opening polymerization of OCAs without epimerization. The close vicinity of both activating groups in the same molecule engenders amplified synergetic effect thus allows for the use of mild bases, thereby leading to minimal epimerization for polymerization. Ring-opening polymerization of *man*OCA monomer (OCA from mandelic acid) mediated by the bifunctional single-molecule organocatalyst yields highly isotactic poly(mandelic acid) (PMA) with controlled molecular weights (up to 19.8 kg mol^{-1}). Mixing of the two enantiomers of PMA generates the first example of crystalline stereocomplex in this area, which displayed distinct T_m values around 150 °C. Remarkably, the bifunctional catalysts are moisture-stable, recyclable, and easy for operation, allowing sustainable and scalable synthesis of stereoregular functional polyester.

INTRODUCTION

Polyesters, including polylactide (PLA), are attractive biodegradable and biocompatible polymers that could provide various applications in biomedicine, agriculture and textile industry.[1-12] Most polyesters, however, lack pendant functionality, which precludes subsequent applications in biomedical research.[13] A promising approach to functionalized polyesters is the ring-opening polymerization (ROP) of *O*-carboxyanhydrides (OCAs), which can be prepared from amino acid or hydroxyl acid precursors that inherently provide rich pendant functionality (Figure 1A).[14] Since 2006,[15] Bourissou, Dove and others have reported OCA monomers deriving from glutamic acid,[16] malic acid,[17] serine,[18] lysine,[19,20] and so on, for the efficient preparation of functionalized polyesters under mild conditions. Among these, OCA prepared from mandelic acid (*man*OCA) is particularly intriguing, because ROP of *man*OCA leads to the synthesis of poly(mandelic acid) (PMA), an aryl analogue of PLA, which exhibits properties comparable to polystyrene, including a high T_g (≈ 100 °C), but is degradable as PLA.[21,22]

Stereocontrol is very significant in polymer science as the stereoregularity is a prerequisite for crystalline polymers, which often possess mechanical performances superior to those of the corresponding atactic polymers.[23] Considering almost endless opportunities of ligand/metal combinations, no surprise that metal-based catalysts have some examples for stereoregular ROP of OCAs.[24-27] For example, Cheng and Tong reported the ROP of OCAs by Zn complex with *β*-diiminate ligands (BDI)Zn resulted in the formation of isotactic polyesters.[24] However, the metal residues and difficulties in operation are accelerating the development of organocatalysts. To today, the stereoregular polymerization of OCAs using organocatalysts is challenging, owing to their strong proneness to racemization under basic condtions, which leads to loss of stereoregularity, and changes in the performances of the resulting polymers.[13,17,18,22,28] More specifically, these challenges are especially difficult to address for *man*OCA, because of its increased C-H acidity.[22,29] Therefore, no example of the crystallization behavior of PMA has been reported until now, regardless of whether they were achieved *via* organic catalysts or organometallic complexes. It has no doubt that design of viable organocatalysts that can lead to highly stereo-controlled ROP of OCAs, in particular, *man*OCA, is of great significance, but is a challenge.

In our attempt to develop a catalyst that can eliminate

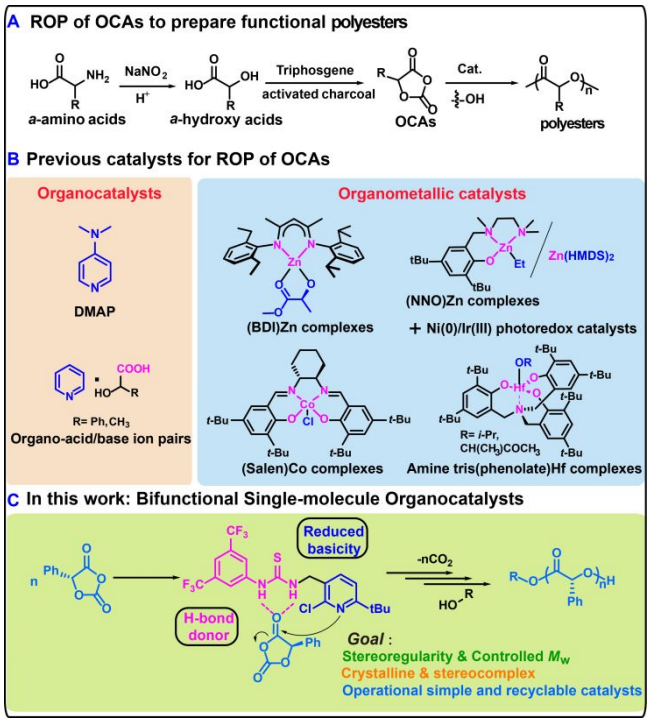

Figure 1. Bifunctional single-molecule organocatalysis for ROP of *O*-carboxyanhydrides (OCAs). (**A**) ROP of OCAs to prepare functional polyesters. (**B**) Previous catalysts for ROP of OCAs. (**C**) Bifunctional single-molecule organocatalysis proposed in this work.

epimerization in polymerization, we turned to bifunctional hydrogen-bonding organocatalysts for inspiration.[30-39] These catalysts usually have both a base group and a hydrogen-bond donor group appropriately positioned on a scaffold. Bifunctional hydrogen-bonding organocatalysts have exhibited great versatility and selectivity to promote many transformations, because of their ability for cooperative dual acid and base activation. Among them, the thiourea-amine catalyst has been widely used in many different enantioselective catalytic processes such as the Mannich,[40] and Michael reactions.[41,42] Although the use of bifunctional single-molecule thiourea-amine organocatalysts in the stereocontrolled preparation of small organic compounds has been extensively researched, when we focus on the preparation of polymers, publishing quantity using bifunctional organocatalysts is incomprehensibly diminished.[43-45] Extensive studies have mainly focused on bicomponent thiourea/amine catalyzed controlled ROP of cyclic esters.[46-59] Generally, the close vicinity of both activating groups in the same molecule engenders amplified cooperative effect thus allows for the use of mild bases, thereby leading to high chemoselectivities for ROP.[60] In this sense, bifunctional single-molecule organocatalysis for ROP represents a significant reaction modality and opens new avenues for the development of selective ROP.

An effective approach to overcoming significant epimerization in OCA polymerization is to decrease the basicity of the catalyst. However, the reduced basicity would significantly compromise the catalytic activity. Therefore, we proposed to exploit a bifunctional single-molecule organocatalysis strategy for the ROP of OCA. Our hope was that through the cooperative effects of the H-bond donor and the weaker base, rapid rates of ring-opening with minimal competitive epimerization reactions in challenging organocatalytic OCA polymerization would be obtained.

Herein, we report the first bifunctional single-molecule organocatalysis for selective ROP of OCAs, resulting in highly isotactic polymers with controlled molecular weights (Figure 1C). For that purpose, we prepared bifunctional organocatalyst consisting of a thiourea linked to a pyridine derivative. The premise of our catalyst design was the reduced basicity of the pyridine derivative relative to the DMAP. As the pyridine ring can be modified by various substituent groups, this design could enable the delivering of a series of organocatalysts with basic and/or steric variations. Further changes to the scaffold and the H-bond donor group would considerably increase the diversity of catalysts.

RESULTS AND DISCUSSION

Initially, 3,5-bis(trifluoromethyl)phenyl isothiocyanate was reacted separately with aminopyridine **2a-d** in dry CH_2Cl_2 (Figure S1). After stirring for 2 h, single-molecule thiourea-pyridine organocatalysts **3a-d** were isolated as air-stable solids via filtration and recrystallization (Figure 2). The structures of catalysts **3a-d** was confirmed by NMR spectroscopy, and high resolution mass spectrometry (Figures S14-S21). To demonstrate the potential of the aforementioned organocatalysts, we chose the challenging ROP of enantiomerically pure $_D$-*man*OCA ($_D$-**1**), which was prepared from $_D$-mandelic acid using a simple one-step synthesis (Figures S2-S3).

Catalysts **3a-d** were then tested in the ROP of $_D$-**1** at 25 °C with CH_3OH as the initiator ([$_D$-**1**]/[Catalyst]/[CH_3OH] = 50/2/1). Reactions carried out with the bifunctional organocatalysts, **3a** and **3b**, afforded polymers having low number-average molecular weight ($M_n \leq 3.1$ kg/mol; Table 1, entries 1-2). Neither **3c** nor **3d**, in which thiourea moiety linked to pyridine directly, can catalyze ROP of $_D$-**1** (Table 1, entries 3 and 4). The stereostructures of the resultant polyesters were carefully examined by ^{1}H NMR spectra. As shown in Figure 3, poly($_D$-**1**) produced under DMAP demonstrated substantial racemization and atactic polyester features with broad peaks for the methine moiety, consistent with previous literature reports.[24] Notably, poly($_D$-**1**) mediated by **3a** and **3b** showed partial suppression of the racemization. A dominant singlet signal for the methine moiety in the polyester, attributable to isotactic enrichment of the polyester was seen in ^{1}H NMR spectra. Additionally, ^{13}C NMR spectra further demonstrated stereo-control to some extent (Figure S79A).

In an attempt to further improve the M_n and stereo-control, we decided to expedite screening and prepare a library of bifunctional organocatalysts (**3e-o**) from the corresponding isothiocyanate and aminopyridine (Figure S1, detail procedures for the synthesis of catalysts **3e-o** see SI section). As such, the electronic and steric properties of the two building blocks can easily be adjusted, providing significant flexibility and allowing the properties of the bifunctional organocatalysts to be tuned. This library was evaluated for behaviour in the selective ROP of $_D$-**1** in $CHCl_3$ at 50 °C using CH_3OH as the initiator (Table 1). Pleasingly, extensive screening of the catalysts led us to identify *Ortho*-substituted chloropyridine-derived catalyst **3e** as a superb catalyst for the desired polymerization, furnishing the targeted polymer with M_n (8.8 kDa) close to the theoretical value (6.7 kDa) and with a low $Đ$ ($Đ = M_w/M_n$) of approximately 1.2 (Table 1, entry 5). Most importantly, polymer mediated by **3e** demonstrated

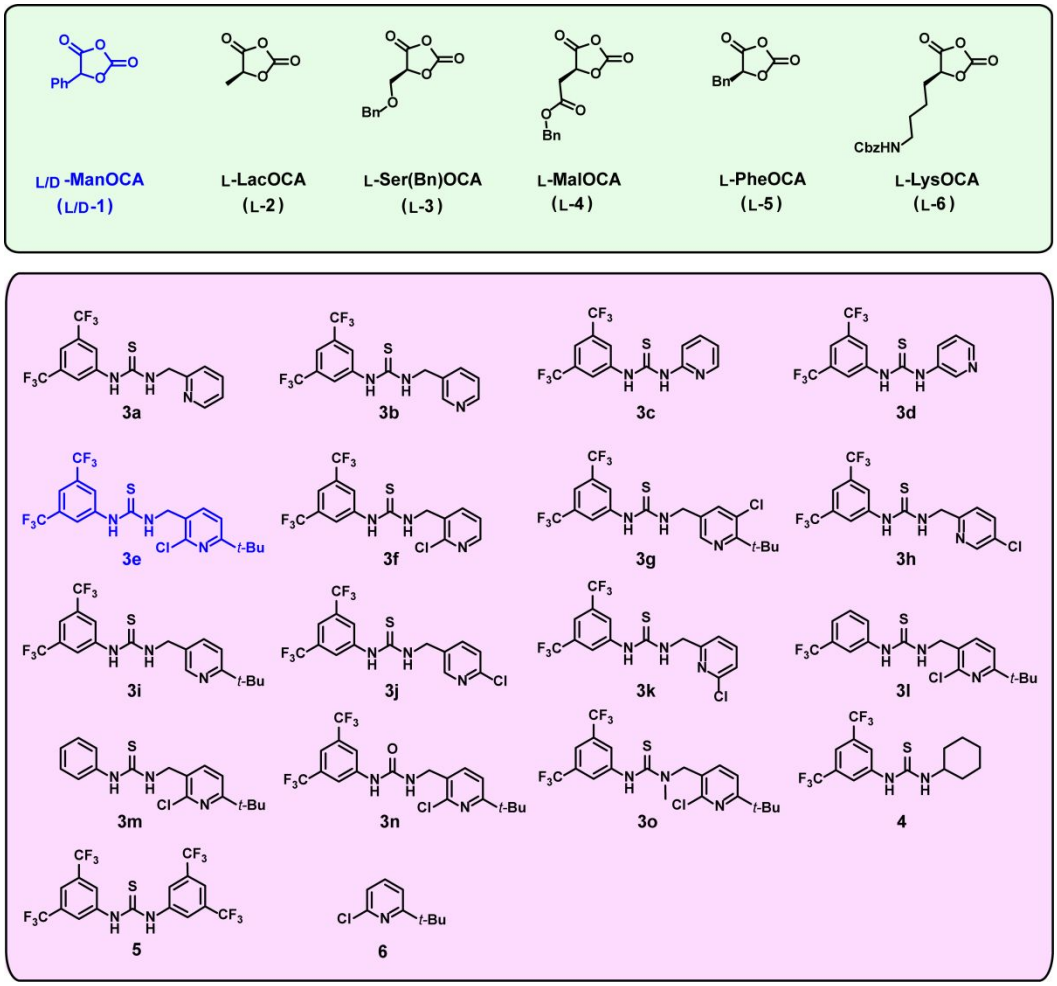

Figure 2. Screening of bifunctional organocatalysts for chemoselective ROP of OCAs.

Table 1. Screening of bifunctional organocatalysts for ROP of $_{D}$-**1** [a]

Entry	Catalysts	[$_{D}$-**1**]/[cat]/[CH_3OH]	Temp. (°C)	Time (h)	Conv.[b] (%)	$M_{n,calcd.}$[c] (kg/mol)	$M_{n,NMR}$[d] (kg/mol)	$M_{n,SEC}$[e] (kg/mol)	$Đ$ (M_w/M_n)[e]	P_m[f]
1	**3a**	50:2:1	25	24	>99	6.7	3.5	3.1	1.08	0.57
2	**3b**	50:2:1	25	24	>99	6.7	3.1	3.0	1.08	nd[g]
3	**3c**	50:2:1	25	48	0	--	--	--	--	--
4	**3d**	50:2:1	25	48	0	--	--	--	--	--
5	**3e**	50:2:1	50	48	>99	6.7	8.3	8.8	1.20	0.90
6	**3f**	50:2:1	50	48	>99	6.7	9.6	10.0	1.30	0.86
7	**3g**	50:2:1	50	48	>99	6.7	3.8	3.4	1.10	nd
8	**3h**	50:2:1	50	48	>99	6.7	5.2	5.4	1.14	0.65
9	**3i**	50:2:1	50	48	>99	6.7	3.6	3.3	1.12	nd
10	**3j**	50:2:1	50	48	0	--	--	--	--	--
11	**3k**	50:2:1	50	48	0	--	--	--	--	--
12	**3l**	50:2:1	50	48	>99	6.7	5.6	5.8	1.21	0.75
13	**3m**	50:2:1	50	48	>99	6.7	5.2	5.6	1.21	0.78
14	**3o**	50:2:1	50	48	>99	6.7	5.7	5.9	1.29	nd
15	**3n**	50:2:1	50	48	0	--	--	--	--	--
16	**4+6**	50:2:1	50	48	0	--	--	--	--	--
17	**5+6**	50:2:1	50	48	>99	6.7	10.0	8.2	1.68	0.66
18	**5+6**	100:2:1	50	96	>99	6.7	12.2	10.9	1.51	0.64
19	**6**	50:2:1	50	48	0	--	--	--	--	--

[a]Polymerization conditions: [$_{D}$-**1**] = 2 M, solvent = $CHCl_3$, initiator = CH_3OH. [b] Determined by ^{1}H NMR analysis of the reaction mixture. [c]$M_{n,calcd.}$=[M(monomer)-M(CO_2)] × [M] / [I] × Conversion (monomer)+M(CH_3OH). [d]Determined from the relative integration of the signals for *a*-H and chain ends by ^{1}H NMR analysis of the polymer samples. [e]Determined by SEC at 50 °C in DMF relative to PMMA standards. [f]P_m is the probability of forming a new isotactic dyad. [g]The tacticities of the atactic polymer samples were difficult to determine from NMR results.

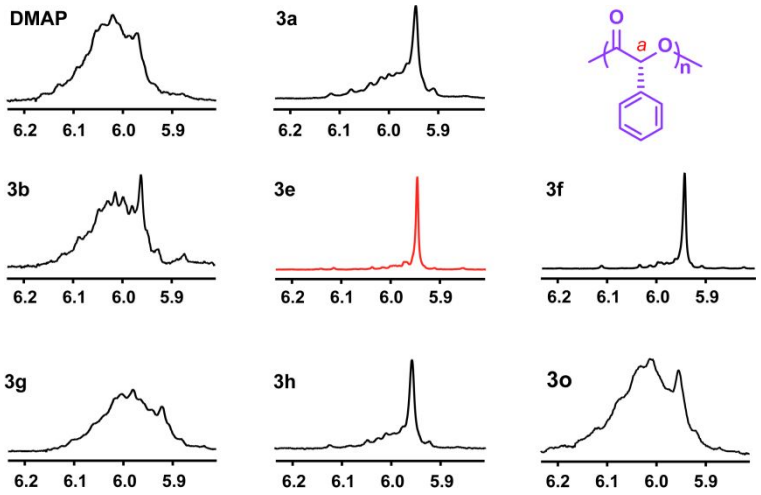

Figure 3. The effect of basicity of catalysts on the methine resonances. The polymerization catalyzed by DMAP showed racemization of the *a*-methine in ^{1}H NMR spectrum of poly($_D$-**1**) while the application of **3e** retained the isotacticity of the polyesters.

excellent isotacticity. A single resonance for *α*-methine region was seen in the ^{1}H NMR spectrum (Figure 3). Meanwhile, ^{13}C NMR spectrum displayed singlet signal corresponding to *a*-carbons, also demonstrating perfect stereo-regulate (Figure 4A). The isotacticity of poly($_D$-**1**) (P_m= 0.90) was evaluated by fitting the tetrad resonances seen in the quantitative ^{13}C NMR spectrum with the values predicted by Bernoullian statistics (Figure S80-S81, Table S2-S5).[61,62]

The use of pyridine with sterically bulkier substituent had a negligible impact on the suppression of the racemization. The polymerization catalyzed by **3f** also gave satisfactory stereo-control but with mediocre molecular weight control (Table 1, entry 6). However, the position and electronic properties of the substituents on the pyridine ring had a significant effect on stereo-structures. More basic *meta*-substituted pyridine derivative (**3g** and **3h**) gave inferior result (Figure 3). Electron-donating group (**3i**) gave only low M_n polymers with atactic structure (Table 1, entry 9, and Figure S79B). The above experiments obviously indicate that the decreased basicity of *ortho*-substituted chloropyridine compared to DMAP is responsible for the significant suppression of the racemization. Furthermore, polymerization with **3j** and **3k** did not proceed, probably due to the even weaker basicity of the pyridine ring (Table 1, entries 10-11, Figure S88). These results again demonstrate that subtle variation of the position of chlorine group in pyridine ring can siginificantly change polymerization efficiency and stereo-structures.

With the best scaffold and base moiety identified, we turned our attention to H-bond donor group. Both **3l** containing one CF_3 substituent and **3m** containing zero CF_3 substituent gave mediocre stereo-control (see Figure S79B) and demonstrated faster polymerization rate than that **3e** (Table 1, entries 12-13, Figure S88). Meanwhile, the role of the N-H in the thiourea appears important, as evidenced by the poor stereo-control exhibited by the methylated thiourea **3o** (Table 1, entry 14, and Figure 3). **3o** also exhibited reaction rate faster than its nonmethylated counterpart **3e** (Figure S89). Furthermore, Polymerization did not occur when using less acidic urea **3n** (Table 1, entry 15). These results illuminate that the H-bond donor group might also contribute to the stereochemical outcome as well as the polymerization rate, and that the 3,5-bis(trifluoromethyl)phenyl thiourea moiety was optimal.

Having identified **3e** as the best catalyst for $_D$-**1**, we further explored this ROP in details. The polymerization of $_D$-**1** by the single-molecule organocatalyst **3e** exhibits several characteristics of controlled polymerization.[63,64] With higher catalyst loading (**3e** of 2 equiv relative to CH_3OH), the M_n values of obtained poly($_D$-**1**) increased linearly with initial [$_D$-**1**]/[CH_3OH] ratios from 25 to 150, along with the unimodal distributions (Figure 4B, C). The determined molecular weights by SEC ($M_{n,SEC}$) and ^{1}H NMR($M_{n,NMR}$) were consistent with $M_{n,calcd}$ calculated from the [$_D$-**1**]$_0$/ [CH_3OH]$_0$ molar ratio and conversion (Figure S94). The methoxy group at the *α*-end of the polymer was clearly seen at δ = 3.78 ppm (Figure S65). Furthermore, the MALDI-TOF-MS of poly($_D$-**1**) consists of an array of peaks separated by a 134 Da interval, which corresponds to the molar masses of the repeating unit (Figure 4D). The MALDI-TOF-MS result also indicated the polymer contained methoxy moiety at the initiating terminal and intact hydroxyl end-group at the capping terminal. Interestingly, the SEC plots of poly($_D$-**1**) after complete monomer consumption and prolonged reaction times showed similar peak shape and elution time, indicative of minimal transesterification of polymer chains (Figure S93). This is similar to other thiourea-based organocatalytic polymerization reported by Waymouth, and co-workers.[52] In addition, other alcohols, such as 3-phenylpropanol, also effectively initiated the polymerization, which proceeded in quantitative yields and afforded polymers having a low $Đ$ ($Đ$ = 1.22; Table 2, entry 4; Figure S91). These results again demonstrate that **3e**-mediated ROP of $_D$-**1** exhibited a controlled feature. However, the polymerizations show some deviations from an ideal "living" behavior.[64] With lower catalyst loading, the observed molecular weights do not correlate to those predicted from the conversion and the ratio [$_D$-**1**]$_0$/[CH_3OH]$_0$ (Table 2, entries 1-2).

To highlight the versatility of our single-molecule organocatalytic system, we used the **3e** for ROP reactions of five other OCA monomers, including methyl ($_L$-LacOCA, $_L$-**2**), benzyl protected hydroxyl ($_L$-Ser(Bn)OCA, $_L$-**3**), benzyl protected carboxyl ($_L$-MalOCA, $_L$-**4**), phenyl ($_L$-PheOCA, $_L$-**5**), and Cbz protected amino groups ($_L$-LysOCA, $_L$-**6**)

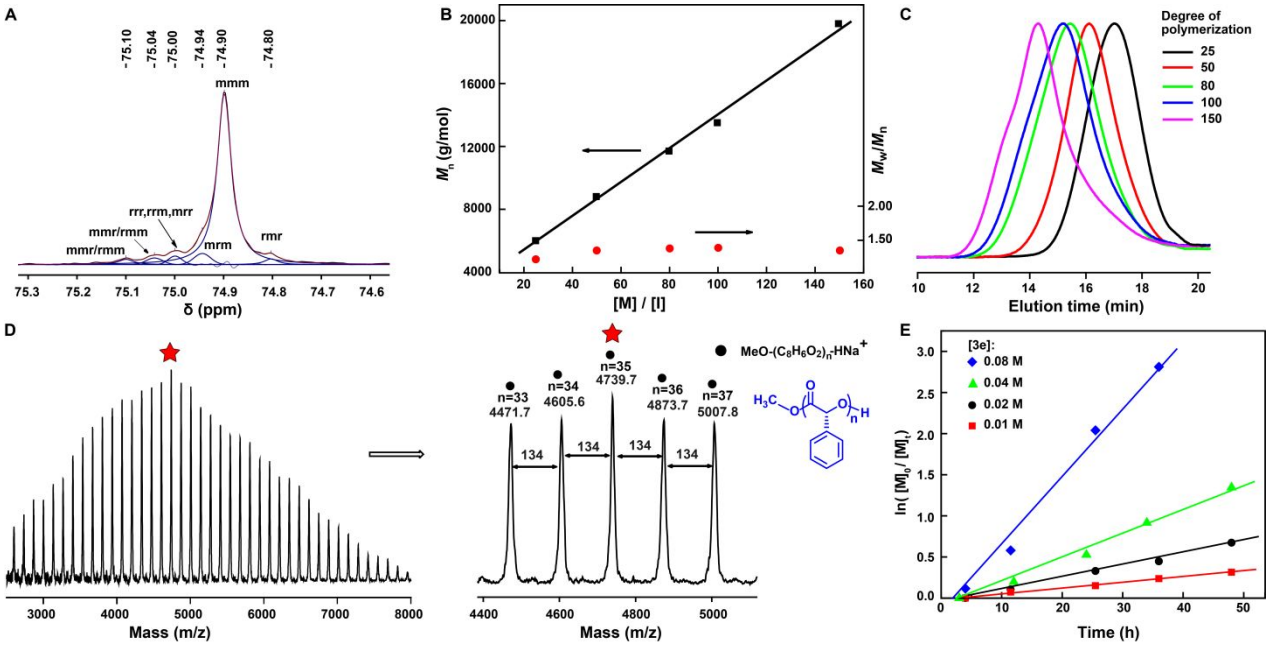

Figure 4. Organocatalytic chemoselective ROP of OCAs. (**A**) Proposed tetrad stereosequence assignments for the methine carbon of ^{13}C NMR spectrum (Quantitative, 150 MHz, $CDCl_3$) of isotactic poly ($_D$-**1**) on the basis of Bernoullian statistics (Table 1, entry 5). (**B**) Plots of M_n (square, black) and $Đ$ (circle, red) versus [M]/[I] ratio (**3e** of 2 equiv relative to CH_3OH). (**C**) Representative SEC traces of poly($_D$-**1**) in panel (**B**). (D) MALDI-TOF-MS of poly($_D$-**1**) prepared by **3e**/CH_3OH. (E) Plot of $_D$-**1** conversion vs. time at various **3e** concentrations. [$_D$-**1**] = 2 M; [$_D$-**1**]/[CH_3OH] =100:1.

Table 2. Controlled ROP of OCAs mediated by **3e** [a]

Entry	OCA	[M]/[**3e**] /[I]	Conv.[b] (%)	$M_{n,calcd.}$[c] (kg/mol)	$M_{n,NMR}$[d] (kg/mol)	$M_{n,SEC}$[e] (kg/mol)	$Đ$ (M_w/M_n)[e]	P_m[g]
1	$_D$-**1**	50:0.5:1	47	3.2	6.5	7.9	1.21	0.88
2	$_D$-**1**	50:1:1	73	4.9	8.1	8.9	1.25	0.89
3	$_D$-**1**	50:2:1	>99	6.7	8.3	8.8	1.20	0.90
4[f]	$_D$-**1**	50:2:1	>99	6.8	6.9	7.9	1.22	0.90
5	$_L$-**1**	50:2:1	>99	6.7	8.5	9.1	1.26	0.84
6	$_L$-**2**	50:2:1	>99	3.6	3.7	3.9	1.22	>0.99
7	$_L$-**3**	50:2:1	>99	8.9	8.4	7.1	1.29	>0.99
8	$_L$-**4**	50:2:1	>99	10.3	8.7	6.9	1.29	>0.99
9	$_L$-**5**	50:2:1	>99	7.4	7.5	5.2	1.22	>0.99
10	$_L$-**6**	50:2:1	>99	13.1	9.6	5.4	1.21	>0.99

[a]Polymerization conditions: [OCA] = 2 M, solvent = $CHCl_3$, initiator = CH_3OH, temperature = 50 °C, time = 48h.[b] Determined by ^1H NMR analysis of the reaction mixture. [c]$M_{n,calcd.}$=[M(monomer)-M(CO_2)] × [M] / [I] × Conversion (monomer)+M(initiator). [d]Determined from the relative integration of the signals for a-H and chain ends by ^1H NMR analysis of the polymer samples. [e]Determined by SEC at 50 °C in DMF relative to PMMA standards. [f]initiator = $PhCH_2CH_2CH_2OH$. [g]P_m is the probability of forming a new isotactic dyad.

(Figure 2,Table 2, entries 6-10, detail procedures for the synthesis of monomers see SI section). In all cases, polymerization control was excellent, similar to that for the formation of poly($_D$-**1**); all the $Đ$ values were < 1.3, and the α-methine region did not epimerize (Figure S69-78).

A notable feature of single-molecule organocatalyst **3e** is that it can be recycled and reused with negligible loss of activity and controllability (Table S1, entry 6). Recovered **3e** remained structurally intact, as evidenced by ^1H NMR and ESI-MS (Figure S96-S97).

To obtain an insight into the polymerization mechanism catalyzed by **3e**, we firstly carried out the kinetic experiments to determine reaction orders of $_D$-**1** and **3e**. Analysis of a plot of ln([M]$_0$/[M]) vs. time indicated that the polymerization was first-order with respect to the OCA concentration (Figure 4E). The reaction orders with respect to **3e** were 1.21 ± 0.05 (Figure 4E and Figure S90C), whereas the reaction was zero-order with respect to CH_3OH (Figure S90D). These experiments demonstrated that the propagation rate was independent of CH_3OH. In additional, these results indicated that the overall rate law can be described as follows:

$$-d[_D\text{-}\mathbf{1}]/dt = k_p\,[\mathbf{3e}]^{1.21}[_D\text{-}\mathbf{1}] \quad (1)$$

where k_p is the propagation rate constant.

We have further investigated the hydrogen bonding between **3e**, $_D$-**1** and CH_3OH in $CDCl_3$ *via* ^1H NMR spectra. At **3e**/$_D$-**1** = 1/1, the H-bond interaction was obviously demonstrated by shift of peaks attributed to NH groups from 6.69/7.87 to 6.76/8.25 ppm (Figure 5 and Figure S95). Conversely, the ^1H NMR spectrum of a mixture of **3e** and CH_3OH revealed the

activation of CH_3OH by chloropyridine moiety could be too weak to be realistic (Figure S82).[48] Meanwhile, DFT calculations and ^{1}H-^{1}H NOESY studies indicated that thiourea moiety was found to preferentially interact with C5-carbonyl of OCA (Figures S98-S99). Of interest, the ^{1}H NMR spectrum of **3e** by mixing with $_D$-**1** at 50 °C after 0.5 h(shift of the proton signal of chloropyridine moiety from 7.85/7.27 to 7.59/7.38 ppm, shift of the proton signal of NH group from 6.69/7.87 to 13.07/11.70 ppm, Figure 5B and 5D) revealed some information about the nucleophilic ring-opening of activated monomer $_D$-**1** by chloropyridine moiety, leading to acylpyridinium intermediate, which was stabilized by dual hydrogen bonding to the thiourea.[36,37] The structure of acylpyridinium intermediate was also confirmed by FTIR and ^{13}C NMR (Figure S83-S84). On the other hand, neither monofunctional analogue **6** nor thiourea/base bicomponent system **4**+**6**, could react with $_D$-**1** under the same conditions (Table 1, entries 16 and 19, Figure S85). When using strong thiourea/base bicomponent system **5**+**6**, uncontrolled polymerization occurred, affording polymer with bimodal molecular weight distribution (Table 1, entries 17-18 and Figure S91). These results indicated that the close vicinity of thiourea moiety and pyridine in the same molecule resulted in significantly magnified synergistic effect thus allows for the use of mild bases, thereby minimizing unexpected side reactions and leading to high chemoselectivities for ROP. Conversely, this cooperative effect was entropically disfavored for thiourea/pyridine bicomponent system in solution.[65] It should also be noted that the thiourea/strong base (e.g.: phosphazene, and guanidine) bicomponent system offered obvious synergistic effect,[51,56,57,66] suggesting the significant differences in catalytic pathways in these related processes.

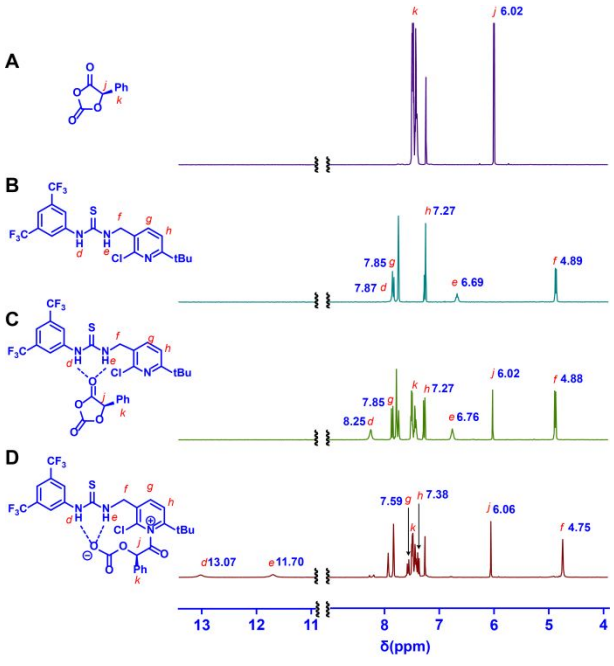

Figure 5. The activation of bifunctional organocatalyst **3e** to OCA *via* hydrogen-bonding interaction, and the formation of acylpyridinium intermediate cooperatively. (**A**) ^{1}H NMR spectrum of $_D$-**1**. (**B**) ^{1}H NMR spectrum of **3e**. (**C**) ^{1}H NMR spectrum of **3e**/$_D$-**1** (1/1). (**D**) ^{1}H NMR spectrum of **3e** by mixing with $_D$-**1** (1:1) at 50 °C after 0.5 h in $CDCl_3$.

^{1}H NMR spectra of a mixture of **3e**, $_D$-**1** and CH_3OH (1 equiv of each) were measured in $CDCl_3$ at 50 °C by varying the time (Figure S86). In the presence of CH_3OH, all of acylpyridinium intermediates gradually converted into methyl mandelate within 12 hours through decarboxylation process and substitution with CH_3OH (Figure S86C). This resulted in the formation of the end -OCH_3 group of poly($_D$-**1**), as clearly illuminated by MALDI-TOF MS (Figure 4D). Increasing the monomer amount to 5 equiv (**3e**/$_D$-**1**/CH_3OH = 5/1/1), the substitution with CH_3OH was completed in 4 hours (Figure S87). In the actual polymerization process, the existence of excess monomers allowed the substitution reaction to occur more quickly, which was confirmed by the regulation of M_n *via* [$_D$-**1**]/[CH_3OH] ratios (Figure 4B).

Based on the aforementioned findings, we therefore postulate a polymerization mechanism mediated by **3e** (Figure 6). The polymerization starts with the activation of $_D$-**1** to the thiourea moiety of **3e** (***a***). In this premise, nucleophilic ring-opening by chloropyridine moiety in the same molecule occurs with the formation of acylpyridinium intermediate (***b***) cooperatively, followed by decarboxylation process, and substitution with either the alcohol or the growing polymer chain (***c***), keeping the configuration at the α-methine carbon. The coordination of the incoming monomer to **3e**, facilitates decarboxylation and substitution process. Zero-order reaction kinetics for alcohol (Figure S90D) implied that the rate-determining step in the propagation was the nucleophilic attack of **3e** on the monomer, further corroborating this hydrogen bonding assisted nucleophilic monomer activation mechanism. Remarkably, significant synergistic effect of both thiourea and pyridine groups in the same molecule, allowed control over the polymerization of OCA as shown by the controlled molecular weights and the low molecular weight distributions.

Additionally, it should be noted that a distinct induction period was observed for the **3e**-mediated ROP of $_D$-**1** (Figure 4E**).** Similar induction periods were observed in the zwitterionic ROP of lactones reported by Hedrick, Waymouth, and co-workers, and is attributed to slow initiation behavior.[47,67,68] It is also postulated that the slow initiation accounts for the deviation from the ideal "living" behavior in our system.[69]

Poly(mandelic acid) (PMA) is an aryl analogue of poly(lactic acid) (PLA) and a biodegradable analogue of polystyrene. Unfortunately, all of the previously reported PMAs are amorphous,[21,22] limiting possible commodity and biomedical applications. Physical blending of enantiomers of chiral polymers in a stoichiometric ratio allows the formation of crystalline stereocomplexed materials that often display improved properties.[69] In this context, a stereocomplex from the 1:1 mixture of ($_D$)-PMA (M_n =13.5 kg mol^{-1}, PDI=1.27) and ($_L$)-PMA (M_n =13.4 kg mol^{-1}, PDI=1.28) was analyzed by DSC and the thermal properties were compared to the enantiopure polymers (Figure 7). In the second heating scans (after cooling at 10°C/min) the enantiomeric polymers displayed only a glass transition temperature T_g of ~100°C. On the other hand, we were delighted to find that the stereocomplex was semicrystalline, and DSC profile displayed a melting peak of T_m = 150 °C (T_c = 118°C). Such obvious melting and crystallization behaviors of PMA have not been observed in the previous report. Both the highly isotactic structures coupled with the stereocomplexation between two opposite enantiomeric polymers are responsible for the crystallization behavior we observed. The promotion of crystallization by stereocomplexation was also confirmed by Coate, Chen and other's paper.[27,70-72]

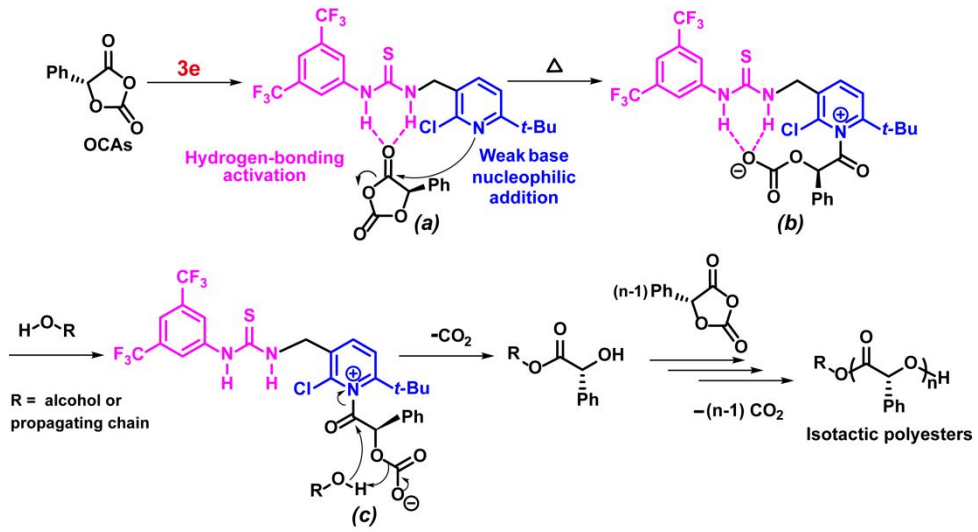

Figure 6. Proposed polymerization mechanism for ROP of OCA. Chain initiation and growth routes are presented upon the cooperative catalysis of bifunctional organocatalyst **3e** in the presence of alcohol. Species (***a***)-(***c***) were revealed by Figure 5 and Figure S82-S87.

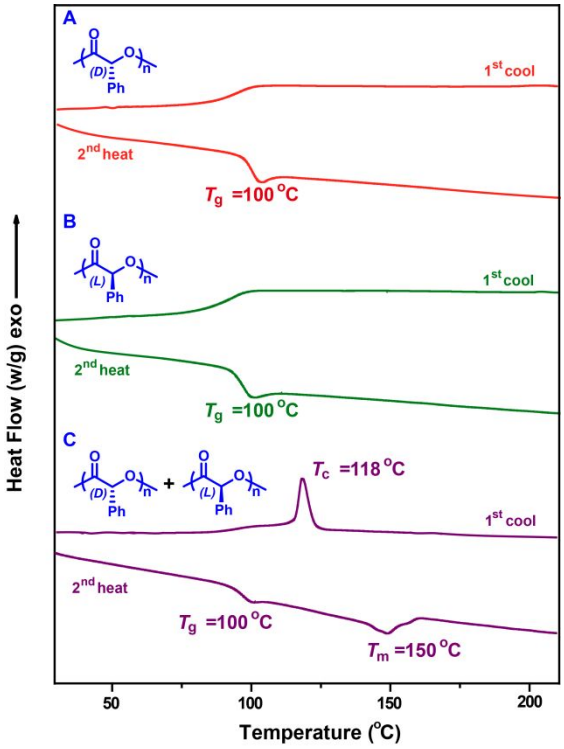

Figure 7. DSC thermograms of (**A**) isotactic ($_D$)-PMA, (**B**) isotactic ($_L$)-PMA, and (**C**) the stereocomplexed mixture of both polymers. Heating rate 10°C/min for ($_D$)-PMA and ($_L$)-PMA or 5 °C/min for stereocomplex.

CONCLUSION

In summary, we report a bifunctional single-molecule organocatalytic system for the chemoselective polymerization of OCAs without epimerization, affording stereoregular polyesters bearing various functional side chain groups. Of importance, mixing of the two enantiomers of poly(mandelic acid) (PMA) generates the first example of crystalline stereocomplex in this area. The mechanistic study highlighted the key roles played by the close vicinity of both the thiourea moiety and *Ortho*-substituted chloropyridine group in the same molecule for achieving this degree of control. We anticipate that the operational simplicity of these organocatalysts, together with their recyclability and capability to impart exquisite control on ROP will make them valuable to the chemistry community. More generally, the concept of using the synergistic effects between the weaker base and the H-bond donor to minimize epimerization and to improve the catalytic activity is general and should prove useful for various catalytic reactions.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge *via* the Internet at http://pubs.acs.org.

Details on materials and methods, experimental procedures, characterization data.

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NOTES

The authors declare no competing financial interests.

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