

## ACS PRF ANNUAL GRANT REPORT (2017.7-2018.8)

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Project Title: Stereoselective Polymerization of Petroleum-Derived *O*-Carboxy-anhydride

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**AIM 1: Synthesis of new petroleum-derived *O*-carboxyanhydride (OCA) monomer.** We have developed a new method to purify OCA monomers in large quantity. Previously, we have to perform repetitive recrystallization to purify OCA monomers. We found out that a quick flash chromatography using pre-dried silica gels and glassware can minimize the workout step and improve the yield. Gram-scale monomers have been prepared within 2 days. The synthesis of new monomers from petroleum resource is ongoing.

**AIM 2: Controlled polymerization of OCA by organometallic catalysts.** The PI has worked on developing a new polymer chemistry knowledge base. In work published in 2017 (just before receiving PRF) the PI showed that controlled photoredox polymerization of OCAs produces poly( $\alpha$ -hydroxy acids) (including PLA and PLGA) with various side chain functional groups.<sup>1</sup> This new chemistry, which involves Ni/Ir photoredox catalysis and a Zn-alkoxide for efficient ROP at -15 °C, allows both for rapid synthesis of isotactic polyesters with MWs of >140 kDa and  $\bar{D}$  values of <1.1 ( $\bar{D} = M_w/M_n$ ;  $M_n$ , number-average MW;  $M_w$ , weight-average MW). Notably, even for high-MW poly(L-1) ( $M_n = 140.5$  kDa), no epimerization of the  $\alpha$ -methine hydrogen is observed in the homodecoupling <sup>1</sup>H NMR spectrum.<sup>1</sup> The polymerization is first order with respect to L-1, suggesting the living nature of the photoredox ROP.<sup>1</sup>

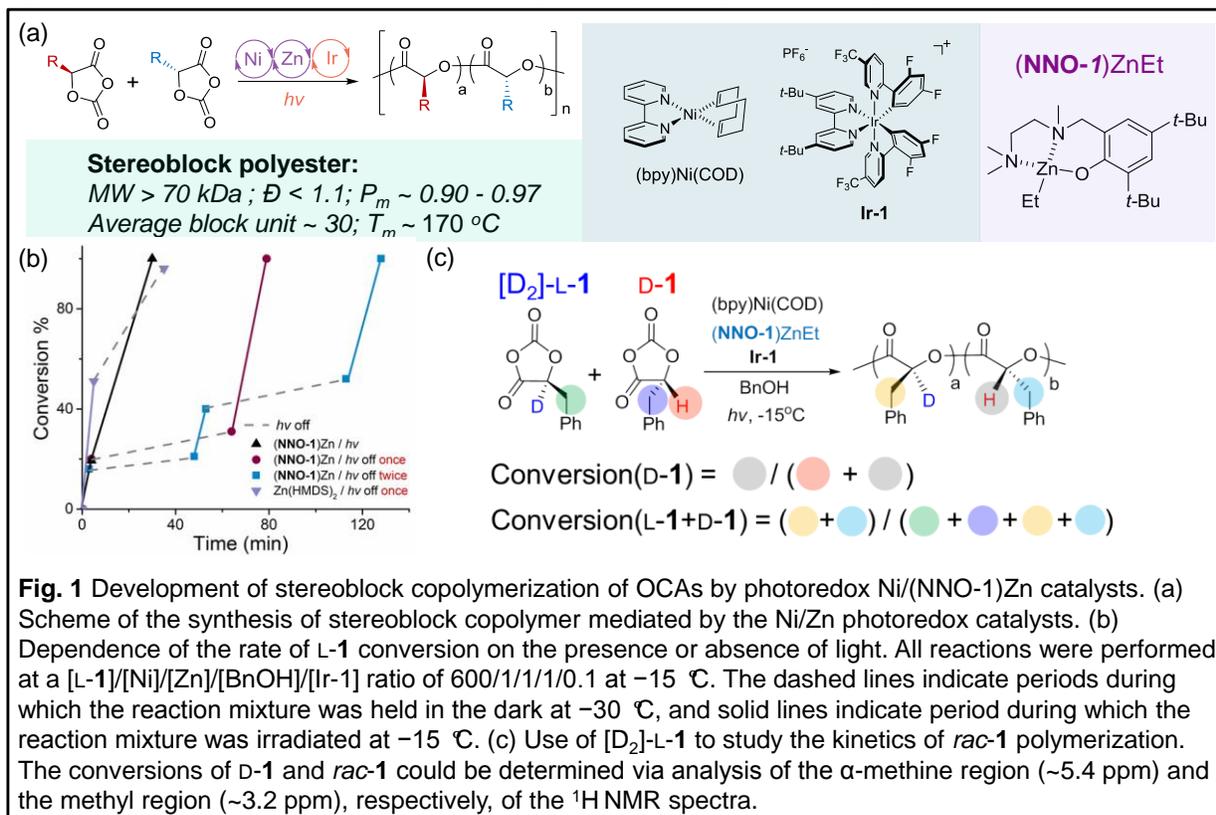
During our polymerization studies using Ni/Zn complexes, we examined various NNO ligand substituents. Reactions carried out with the complexes bearing electron-donating ligands, NNO-1 and NNO-2, afforded polymers with  $M_n$  values close to the expected value (74.1 kDa) and with narrow  $\bar{D}$  values ( $\bar{D} = M_w/M_n$ ) of approximately 1.05, and monomer conversion was quantitative. Uncontrolled polymerization occurred when using Zn complexes bearing electron-withdrawing groups, NNO-3 and NNO-4. When (NNO-1)ZnEt was used for photoredox polymerization,  $M_n$  of the poly(L-1) product increased linearly with initial [L-1]/[Ni]/[Zn]/[Ir-1] ratio up to 1000/1/1/0.1, and the  $\bar{D}$  values of all of the obtained polymers were <1.1, which suggest that chain-breaking reactions did not occur during the ROP (Fig. 1a). Notably, no epimerization of the  $\alpha$ -methine hydrogen was observed in the homodecoupled <sup>1</sup>H NMR spectra, even for high-MW poly(L-1), indicating that the Zn complexes did not affect the chirality of L-1 during the ROP. We also used the (NNO-1)ZnEt complex for photoredox ROP reactions of other OCA monomers (L-2, L-3, and L-4). In all cases, polymerization control was excellent, similar to that for the formation of poly(L-1); the  $M_n$  values of all the obtained polymers were close to the calculated MWs, all the  $\bar{D}$  values were <1.1, and the  $\alpha$ -methine hydrogen did not epimerize.

We found that the presence of NNO-1 ligand in the Zn complex allowed us to modify the polymerization kinetics by turning the light on or off (Fig. 1b).<sup>5</sup> Specifically, in the presence of (NNO-1)ZnEt at a DP of 600, irradiation of the reaction solution for 4 min resulted in 22% conversion of L-1. If the reaction mixture was then placed in the dark at -30 °C for 60 min, conversion of L-1 increased only slightly, to 31%; but once irradiation was resumed, L-1 was rapidly consumed, within 15 min. In contrast, in a similar reaction mediated by Zn(HMDS)<sub>2</sub>, consumption of L-1 continued even after the light was turned off at -30 °C. In the presence of (NNO-1)ZnEt, the photoredox ROP could be slowed down and speeded up multiple times: each time the light was turned off, the ROP almost stopped, and it again proceeded rapidly when irradiation was resumed. This phenomenon would allow us to monitor the reaction kinetics and analyze intermediates using NMR by temporarily quenching the polymerization in the dark at low temperature.

**AIM 3: Stereoselective ROP of OCA.** We discovered that within 4 h of irradiation at -15 °C, photoredox ROP mediated by (NNO-1)ZnEt ([L-1]/[D-1]/[Zn]/[Ni]/[BnOH]/[Ir-1] = 150/150/1/1/1/0.1) resulted in a product with a  $M_n$  of 45.7 kDa, which was close to the expected MW (44.5 kDa), and a narrow  $\bar{D}$  (1.06). Homodecoupled <sup>1</sup>H NMR analysis of the microstructure of the obtained polymer revealed a high degree of isotacticity, as evidenced by the large *mmm* tetrad peak (*m*-dyad represents two identically oriented units [*meso*]) in the methine region ( $\delta \approx 5.2$  ppm). The highest probability of *meso* dyad formation ( $P_m$ , i.e., isotactic enchainment) was 0.97, as calculated by analysis of the methine region in the homodecoupled <sup>1</sup>H NMR spectrum, which was also confirmed by analysis of the <sup>13</sup>C NMR spectrum of the methine region ( $\delta \approx 73.4$  ppm). In contrast, Zn(HMDS)<sub>2</sub>-mediated photoredox polymerization of *rac*-1 afforded an atactic polymer, confirming that the NNO-1 ligand influenced the stereoselectivity of OCA polymerization.

Three different microstructures may have contributed to the high  $P_m$ . Considering the difficulty of distinguishing L-1 from D-1 by either FTIR or NMR spectroscopy, we first prepared deuterated [D<sub>2</sub>]-L-1 from [D<sub>2</sub>]-L-phenylalanine because the methine deuterium in [D<sub>2</sub>]-L-1 does not show up in the <sup>1</sup>H NMR spectrum to analyze

the high isotacticity of poly(*rac*-**1**) obtained from the reaction mediated by (NNO-**1**)ZnEt (**Fig. 1c**). We then studied the kinetics of the photoredox ROP of poly(*rac*-**1**) by mixing [D<sub>2</sub>]-L-**1** and D-**1** at a 1/1 molar ratio ([D<sub>2</sub>]-L-**1**]/[D-**1**]/[Ni]/[Zn]/[BnOH]/[Ir-**1**] = 150/150/1/1/1/0.1) at -20 °C. After reaction for 18 min, 39.5% of the D-**1** had been converted, as determined by integration of the methine region (~5.2 ppm) in the <sup>1</sup>H NMR spectrum; whereas total enantiomer conversion was 36.7%, as determined by integration of the methylene region (~3.2 ppm) in the <sup>1</sup>H NMR spectrum. In comparison, at the same time point, 41.5% of both enantiomers had been converted (as indicated by <sup>1</sup>H NMR spectroscopy) in a reaction in which [D<sub>2</sub>]-L-**1** was replaced with L-**1**. These results suggest that the polymer chain end did not have a kinetic preference for a specific enantiomer in the (NNO-**1**)ZnEt-mediated photoredox copolymerization of *rac*-**1** and, therefore, that the possibility of a tapered block copolymer can be excluded.



**Fig. 1** Development of stereoblock copolymerization of OCAs by photoredox Ni/(NNO-**1**)Zn catalysts. (a) Scheme of the synthesis of stereoblock copolymer mediated by the Ni/Zn photoredox catalysts. (b) Dependence of the rate of L-**1** conversion on the presence or absence of light. All reactions were performed at a [L-**1**]/[Ni]/[Zn]/[BnOH]/[Ir-**1**] ratio of 600/1/1/1/0.1 at -15 °C. The dashed lines indicate periods during which the reaction mixture was held in the dark at -30 °C, and solid lines indicate period during which the reaction mixture was irradiated at -15 °C. (c) Use of [D<sub>2</sub>]-L-**1** to study the kinetics of *rac*-**1** polymerization. The conversions of D-**1** and *rac*-**1** could be determined via analysis of the  $\alpha$ -methine region (~5.4 ppm) and the methyl region (~3.2 ppm), respectively, of the <sup>1</sup>H NMR spectra.

In addition, because the copolymerization of *rac*-**1** was much slower than the copolymerization of either enantiomer separately at the same [I]/[Zn] ratio under the same reaction conditions (at a [I]/[Zn] ratio of 300, the polymerization rate constant of L-**1** was 54.9-times higher than that of *rac*-**1**), it is unlikely that two isotactic polymers, poly(L-**1**) and poly(D-**1**), formed separately, which also excludes the possibility of enantiomeric-site-control mechanism for this isospecific polymerization. Note that changing the [L-**1**]/[D-**1**] ratio from 1/1 to 2/1 did not markedly affect the MW,  $\mathcal{D}$ , or  $P_m$ , a result that suggests that the two enantiomers were copolymerized into one polymer. Taken together, the results of this series of experiments are completely consistent with the formation of a stereoblock copolymer (**Fig. 1a**).

**IMPACT.** This PRF grant substantially supports my research in the living polymerization of *O*-carboxyanhydrides. During the first year, we have published the Nature Communications paper based on our research progress (reference # 2). The PI truly appreciates the support from this grant to help the start of his early career. During the first year, three graduate students were supported by this grant. They also traveled to the ACS national conference to present the research.

## REFERENCE

- (1) Feng, Q.; Tong, R. Controlled Photoredox Ring-Opening Polymerization of *O*-Carboxyanhydrides. *J. Am. Chem. Soc.* **2017**, *139*, 6177-6182.
- (2) Feng, Q.; Yang, L.; Zhong, Y.; Guo, D.; Liu, G.; Xie, L.; Huang, W.; Tong, R. Stereoselective photoredox ring-opening polymerization of *O*-carboxyanhydrides. *Nat. Commun.* **2018**, *9*, 1559.