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Communication

# Chirality-Directed Regioselectivity: An Approach for the Synthesis of Alternating Poly(Lactic-*co*-Glycolic Acid)

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Cite This: *J. Am. Chem. Soc.* 2021, 143, 4119–4124
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**ABSTRACT:** We report the synthesis of alternating poly(lactic-*co*-glycolic acid) via a regioselective ring-opening polymerization of (*S*)-methyl glycolide. An enantiopure aluminum salen catalyst with binaphthyl backbone facilitates the regioselective ring-opening of this unsymmetrical cyclic diester exclusively at the glycolide acyl−oxygen bond site. This living, chain-growth polymerization is able to reach low dispersities with tailored molecular weights. Quantitative regioselectivity calculations and sequence error analysis have been established for this sequence-controlled polymer.



Polymer sequence control—the precise arrangement of monomer units in a macromolecule—is an important technique for tuning copolymer properties, as well as developing functional materials.[1−4] Among synthetic biomaterials, the random copolymer poly(lactic-*co*-glycolic acid) (PLGA) has garnered significant interest due to its nontoxic hydrolytic degradation pathway *in vivo*, with tunable degradation rates and a $T_g$ that lies just above human body temperature.[5] The utility of PLGA has been demonstrated in a variety of applications, including sustained or targeted drug delivery vehicles, scaffolding for tissue engineering, and bioabsorbable sutures.[6−8] The conventional copolymerization of the cyclic diesters lactide (LA) and glycolide (GA), however, produces a random copolymer with little control over monomer sequence. Thus, it is of great interest to develop a sequence-controlled PLGA and to study the effect of monomer placement on polymer properties.[9]

Alternating PLGA is a particularly attractive sequence variant because this material exhibits distinct degradation properties compared with other microstructures in terms of hydrolysis rates, bulk morphology, and thermal behavior. The Meyer group has demonstrated that, with the same LA/GA composition, higher quantities of G-G linkages (G = glycolic unit) result in faster degradation rates, as they are more susceptible to hydrolysis than L-G or L-L linkages (L = lactic unit).[10] Alternating PLGA, which bears no G-G or L-L linkages, undergoes slow hydrolysis with linear degradation rates and a sustained drug release profile relative to random PLGA 50/50.[11,12] Additionally, the alternating material minimizes sudden local pH changes and *in vivo* inflammatory response associated with acid release.[13] During the degradation of alternating PLGA, the morphology is preserved over a long period of time, without significant swelling or erosion, and its glass transition temperature ($T_g$) remains largely unchanged.[14] This linkage-dependent hydrolytic behavior is also observed for other PLGA derivatives and polyesters.[10,15−17] Block copolymers with alternating PLGA segments also present special properties suitable for thermosensitive hydrogels, controlled drug release, and lithography.[18−20] When self-assembled into micelles, the sequenced structure can further affect the solubility, hydrophilicity, and gel point, offering another approach to tune the gelation properties and drug delivery performance.

PLGA is synthesized by the ring-opening polymerization (ROP) of LA and GA, yielding a random copolymer (Figure 1, bottom left).[21,22] An alternative method is step-growth segmer assembly polymerization (SAP), which produces PLGA with a repeating sequence that depends on the preformed oligomer used.[23] Although this direct polycondensation is reliable for producing high-fidelity alternating PLGA, the SAP method does not allow for molecular weight control, with dispersities ($Đ$) ranging from 1.3 to 2 (Figure 1, top right). ROP of 3-

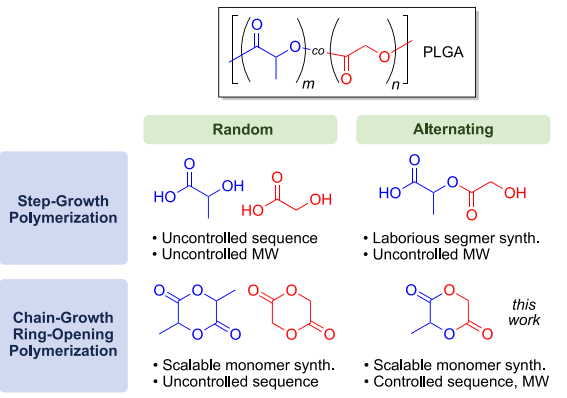
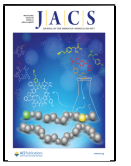



**Figure 1.** Common routes to synthesize random (left) and alternating (right) PLGA.

**Received:** January 8, 2021
**Published:** March 9, 2021



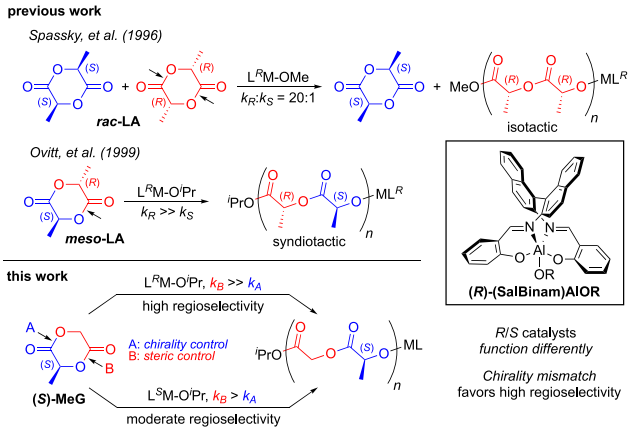



https://dx.doi.org/10.1021/jacs.1c00248
*J. Am. Chem. Soc.* 2021, 143, 4119−4124

methyl glycolide (MeG) has also been used to prepare alternating PLGA, with varying degrees of sequence fidelity.[24−26] In this work, we have been able to achieve a 98% regioselectivity with (*S*)-MeG (Figure 1, bottom right).

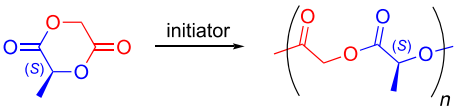
Previous studies on the random copolymerization of GA and LA revealed that the rate of GA incorporation is 10 times that of LA, which is attributed to the steric effect of the methyl substitution.[27] The MeG monomer contains an LA acyl−O bond site (A, Scheme 1) and a GA acyl−O bond site (B, Scheme 1). The ring-opening of MeG intrinsically favors the less hindered GA site, with a reported 84:16 ratio.[24,25] Hillmyer and Vert have reported that ROP of other unsymmetrical cyclic diester monomers proceeds with similar regioselectivity induced by ring-opening at the less hindered site.[28−30] However, near-complete regioselectivity has been achieved in only a few cases using special conditions or monomers with strong steric or electronic bias.[26,31,32] For example, the Satoh group recently developed a phosphazene base-catalyzed ROP of enantiopure MeG with 95% regioselectivity at −78 °C due to the kinetically favored ring-opening at the more electrophilic LA acyl−O site. However, this electronic approach alone was unable to afford this level of regioselectivity at higher monomer loading or at ambient temperature.[26]

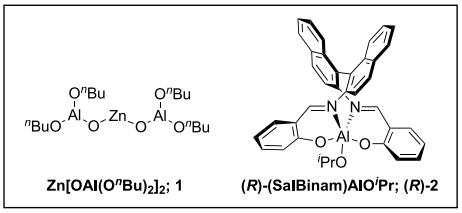
**Scheme 1. Stereo- and Regioselective Ring-Opening Polymerization Using (SalBinam)AlOR**




Inspired by previous work on stereoselective lactide ring-opening, we have developed a completely regioselective MeG polymerization catalyzed by (SalBinam)AlOR (SalBinam = *N*,*N*′-bis(salicylidene)-1,1′-binaphthyl-2,2′-diamine) (Scheme 1). This catalyst is also reactive for lactide copolymerization with lactones or cyclic carbonates.[33−35] Spassky and Ovitt reported that (*R*)-(SalBinam)AlOR preferentially promotes ROP at the carbonyl next to an (*R*)-Me substituent in either *rac*- or *meso*-LA. The relative ROP rates are in the order of (*S*)-MeG > (*R*,*R*)-LA > *meso*-LA > (*S*,*S*)-LA.[36−39] We inferred that (*R*)-(SalBinam)AlOR blocks nucleophilic attack at the chirality-mismatched (*S*)-LA carbonyl of *rac*-LA or *meso*-LA.[40] On the basis of this chirality mismatch, we hypothesized that (*R*)-(SalBinam)AlO$^i$Pr would further discourage ring-opening at the (*S*)-LA site of (*S*)-MeG (Scheme 1). Thus, we theorized that dual steric and chirality control might significantly favor ring-opening at the GA site. Herein, we report the synthesis of alternating PLGA with 98% regioselectivity, high efficiency, tailored molecular weight, and low dispersity.

**Table 1. Optimization of Reaction Conditions**




| entry | initiator | solvent | $[MeG]_0$:$[init.]_0$ (M:I)[a] | temp (°C) | time (h) | conv (%)[b] | $M_n$ (kDa) theor | $M_n$ (kDa) GPC[c] | $Đ$ ($M_w/M_n$)[c] | regioselectivity (%)[b] |
|---|---|---|---|---|---|---|---|---|---|---|
| 1[d] | **1** | toluene | 131:1 | 90 | 4.5 | >99 | 8.5 | 8.3 | 1.44 | 84 |
| 2 | (*R*)-**2** | toluene | 100:1 | 70 | 19 | 98 | 12.8 | 14.2 | 1.59 | 95 |
| 3 | (*R*)-**2** | toluene | 100:1 | 50 | 17 | 80 | 10.4 | 10.1 | 1.30 | 96 |
| 4 | (*R*)-**2** | toluene | 100:1 | 35 | 21 | 72 | 9.4 | 13.0 | 1.13 | 97 |
| 5 | *rac*-**2** | toluene | 100:1 | 35 | 40 | >99 | 13.0 | 12.6 | 1.20 | 89 |
| 6 | (*S*)-**2** | toluene | 100:1 | 35 | 40 | >99 | 13.0 | 13.8 | 1.27 | 84 |
| 7 | (*R*)-**2** | toluene | 40:1 | 35 | 17 | 98 | 5.1 | 7.1 | 1.18 | 96 |
| 8 | (*R*)-**2** | toluene | 10:1 | 35 | 12 | >99 | 1.3 | 2.0 | 1.29 | 90 |
| 9 | (*R*)-**2** | $CDCl_3$ | 100:1 | 50 | 21 | 97 | 12.7 | 13.6 | 1.15 | 94 |
| 10 | (*R*)-**2** | THF | 100:1 | 50 | 20 | 95 | 12.4 | 12.1 | 1.11 | 96 |
| 11 | (*R*)-**2** | DCM | 100:1 | 35 | 21 | 94 | 12.2 | 15.8 | 1.06 | 98 |
| 12 | (*S*)-**2** | DCM | 100:1 | 35 | 19 | 97 | 12.6 | 16.9 | 1.12 | 78 |
| 13 | (*R*)-**2** | DCM | 200:1[e] | 40 | 48 | 93 | 24.3 | 25.4 | 1.06 | 98 |
| 14 | (*R*)-**2** | DCE | 400:1[f] | 80 | 48 | 73 | 37.9 | 40.0 | 1.09 | 96 |
| 15 | (*R*)-**2** | DCM | 40:1 | 22 | 21 | 99 | 5.1 | 9.0 | 1.05 | 98 |
| 16 | (*R*)-**2** | DCM | 10:1 | 22 | 12 | >99 | 1.3 | 2.1 | 1.10 | 98 |

[a]$[MeG]_0$ = 0.5 M. [b]Determined by $^1$H NMR analysis. [c]Determined by GPC. [d]Data from ref 25. [e]$[MeG]_0$ = 1.0 M. [f]$[MeG]_0$ = 1.5 M.



https://dx.doi.org/10.1021/jacs.1c00248
J. Am. Chem. Soc. 2021, 143, 4119−4124

Complex **1** (Table 1) exhibits a regioselectivity of 84% when applied for the ROP of MeG, with baseline monomer-oriented steric control.[25] Following the standard conditions for lactide polymerization reported previously, we examined (*S*)-MeG ROP at 70 °C in toluene with (*R*)-**2**. The dispersity was unexpectedly high, indicating significant transesterification or reversibility. Lowering the temperature to 35 °C helped narrow the dispersity and increase the regioselectivity to 97% (Table 1, entries 2−4). When enantiomeric (*S*)-**2** was used, the regioselectivity dropped from 97% to 84%. As expected, the regioselectivity with *rac*-**2** ranked in between those of its enantiopure counterparts, indicating that while steric preference remained, the catalyst chirality was crucial for enhanced regioselectivity through chirality control (Table 1, entries 4−6). In order to access materials with a wide range of molecular weights, we investigated different ratios of monomer to initiator (M:I). At a low monomer loading, transesterification started to dominate, leading to a high dispersity and low regioselectivity (Table 1, entries 4, 7, and 8).

Polymerizations performed in toluene showed dispersities between 1.1 and 1.3 and limited conversion, likely due to low solubility of the monomer and polymer. Preheating the reaction ensured complete dissolution of monomer at the start of the reaction period, producing PLGA with a slightly lower dispersity. To improve polymer solubility and reduce transesterification at low monomer loading, we screened several solvents with good solubility. $CDCl_3$ exhibited nearly full conversion but lower regioselectivity, likely due to its slight acidity, which can facilitate side reactions. THF also produced high conversion, while other results were similar to those of reactions performed in toluene. DCM was determined to be the optimal solvent, considering solubility, conversion, dispersity, and regioselectivity (Table 1, entries 4, 9−11). Reaction with (*S*)-**2** under the optimal conditions exhibited a reasonably low regioselectivity (Table 1, entry 12). In addition, a higher molecular weight polymer could easily be reached at a prolonged reaction time. Using DCM as solvent also eliminated transesterification at low monomer loading, affording a 98% regioselectivity and $Đ$ as low as 1.05 (Table 1, entries 13−16).

With the possible variations investigated, we sought to design and synthesize a series of polymers with different regioselectivities for future degradation study. At a lower regioselectivity, there are more G-G linkages in the polymer chain, which is expected to have a faster degradation rate. Figure 2 shows a stacking of polymer $^1$H NMR spectra on methine ($\delta$ = 5.2−5.3 ppm) and methylene ($\delta$ = 4.6−4.9 ppm) regions, the regioselectivities of which range from 98% to 84%, in accordance with the reaction conditions in Table 1. At M:I = 100:1, the chain end peaks are almost negligible in the spectra; the minor peaks are therefore assigned to regiodefects. Thus, we could see a clear and gradual increase of regiodefect peaks near the methine quartets and methylene doublets.

Effective sequence error determination, in this case regioselectivity calculation, is a crucial topic for sequence control. Previous studies on ROP of unsymmetrical cyclic diesters reported regioselectivities mostly qualitatively or by end group ratio.[24,25,31,32] In fact, the polymer end group ratio does not necessarily represent the actual regioselectivity of the polymerization, as the two types of chain ends from normal insertion and inverted insertion have different propagation rates. Another calculation method was based on the $^1$H NMR decoupled methine region, but overlapping peaks impeded

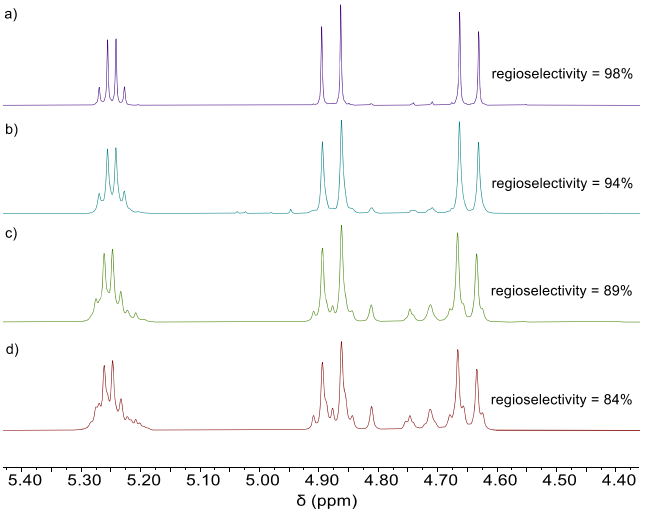



**Figure 2.** Stacked $^1$H NMR spectra of PLGA with different regioselectivities (M:I = 100:1): (a) Table 1, entry 11; (b) Table 1, entry 9; (c) Table 1, entry 5; and (d) Table 1, entry 6.

precise integration, especially at near-perfect regioselectivities. We developed a quantitative method based on integrations of accumulative repeating units using the most sensitive $^1$H NMR methylene region. The heteronuclear single quantum coherence (HSQC) spectrum (Figure 3a, top) shows three sets of minor $CH_2$ doublets resulting from one regiodefect (GLLGGL). Among these three minor $CH_2$ groups, one is directly derived from the inverted insertion (GLLGGL), while the other two are adjacent to the regiodefect under normal insertion (GLLGGL and GLLGGL). From the sequence structure, only the actual regiodefect $CH_2$ group (GLLGGL) would not have a three-bond correlation with an L carbonyl in the heteronuclear multiple bond correlation (HMBC) spectrum (Figure 3a, bottom). Based on this, we could assign all three sets of minor $CH_2$ groups to the sequence in Figure 3b. Notably, half of this regiodefect $CH_2$ group (GLLGGL) ($\delta$ = 4.80−4.85 ppm) can be integrated separately without any overlap, while the other half ($\delta$ = 4.71−4.76 ppm) is overlapped and split due to the influence of an adjacent regiodefect in a row. Hence, precise NMR integration on half of the regiodefect $CH_2$ group ($\delta$ = 4.80−4.85 ppm) and the overall $CH_2$ group ($\delta$ = 4.50−4.92 ppm) allows us to accurately and reproducibly calculate the regioselectivity representative of the whole polymer (Figure 3b).

The previous hypothesis is that ring-opening occurs preferentially at the less hindered GA site under steric control and is disfavored at the (*S*)-LA site with a mismatched catalyst under chirality control. In order to prove this idea, we conducted a $[MeG]_0$:$[Initiator]_0$ = 1:1 experiment and investigated the initial ring-opened adducts. The ratio of the resulting lactyl and glycolyl chain ends was used as an indication of regioselectivity. As a control experiment, $^i$PrOH was used to open (*S*)-MeG, generating products in a 60:40 ratio (lactyl:glycolyl chain ends; Scheme 2a). Using (*R*)-**2**, the lactyl-terminated product was formed in a 97% yield, indicating that nucleophilic attack occurred almost exclusively at the less hindered GA acyl−O bond site (Scheme 2b). As mentioned previously, (*R*)-**2** preferentially promotes ring-opening at the (*R*)-LA site. When using (*S*)-MeG, a chirality mismatch with (*R*)-**2** prevents the opening at the (*S*)-LA site, further


https://dx.doi.org/10.1021/jacs.1c00248
J. Am. Chem. Soc. 2021, 143, 4119−4124

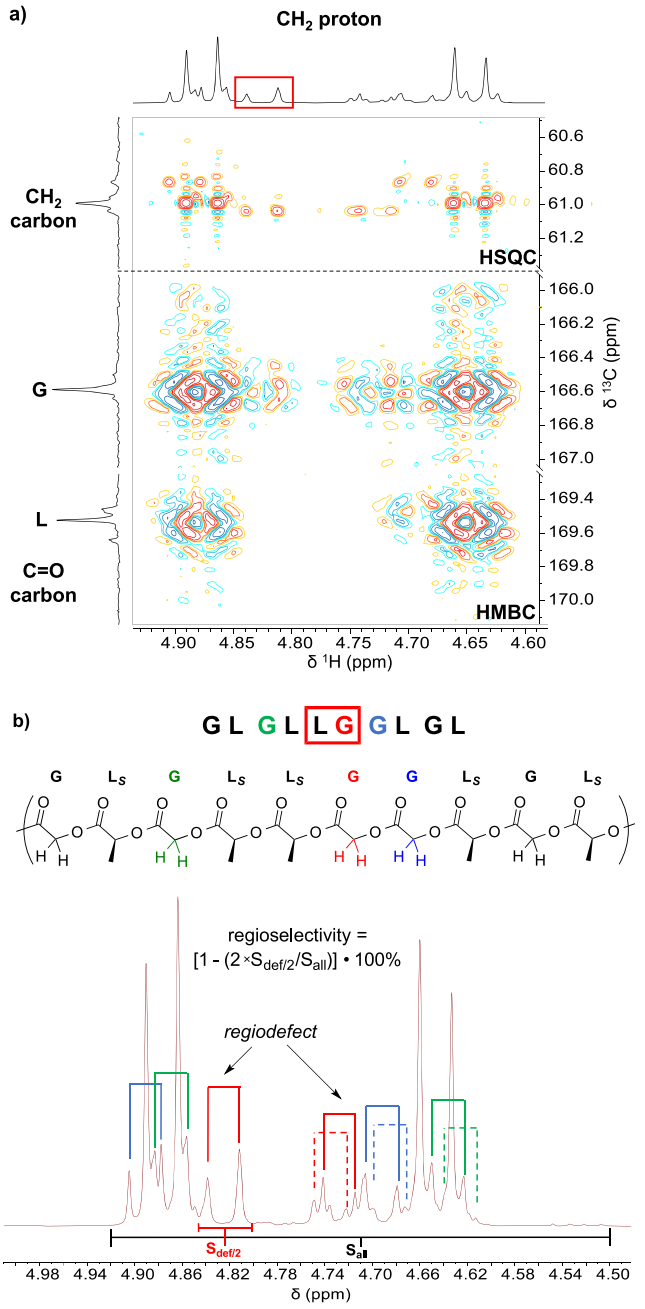
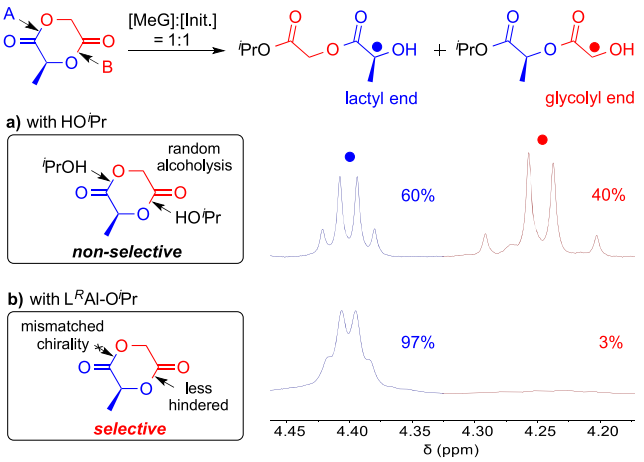



**Figure 3.** NMR spectra used for the regioselectivity calculation. (a) HSQC (top) and HMBC (bottom) spectra showing the methylene and carbonyl regions. (b) $^{1}$H NMR spectrum of the methylene region.

improving regioselectivity. Moreover, the polymer NMR also displays exclusively lactyl chain ends. These results suggest that the ROP of (*S*)-MeG undergoes a site-controlled coordination−insertion mechanism, with near-exclusive ring-opening at the GA acyl−O bond site.

In conclusion, we have developed a chirality-directed regioselective approach for the sequence-controlled synthesis of PLGA. This process produces alternating PLGA under living chain growth conditions. Quantitative regioselectivity determination has been established for a precise sequence error determination. A degradation study on polymers with varied regioselectivities is currently in progress. The effect of sequence on polymer hydrolysis behavior, together with kinetic and mechanistic studies, will be explored in depth in a future report.

**Scheme 2. Ring-Opening Site Determination**




## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c00248.

Experimental procedures, material characterization, and spectral data (PDF)

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### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

This research was supported by the Center for Sustainable Polymers, a National Science Foundation (NSF) Center for Chemical Innovation (CHE-1901635), and Cornell University. The authors also acknowledge the NSF for financial support under the award CHE-1709144. This work made use of the NMR Facility at Cornell University, which is supported, in



https://dx.doi.org/10.1021/jacs.1c00248
J. Am. Chem. Soc. 2021, 143, 4119−4124

part, by the NSF under the award CHE-1531632. We thank Dr. Ivan Keresztes for assistance with NMR analysis.

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*J. Am. Chem. Soc.* 2021, 143, 4119−4124