Macromolecules

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Organocatalytic Precision Synthesis of Poly(ester amide)s with Enhanced Thermal Performance and Programmable Microarchitectures

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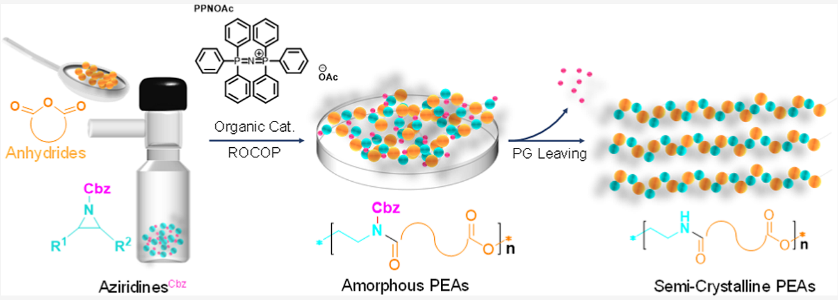
Cite This: *Macromolecules* 2025, 58, 10705−10713

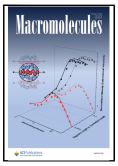


ABSTRACT: Sequence-controlled polymerization, a precision technique enabling programmed arrangement of chemically distinct monomer units during copolymerization, establishes a versatile platform for engineering polymer architectures with tailored functionalities and unlocking unprecedented possibilities in advanced materials development. The ring-opening copolymerization of aziridines with cyclic anhydrides emerges as a particularly promising strategy for synthesizing sequence-regulated polymers through the alternating chain growth mechanism. Herein, we present a novel catalytic system employing organic ammonium salts to mediate the copolymerization of *N*-benzyloxycarbonyl (Cbz)-functionalized aziridines with cyclic anhydrides under mild conditions, yielding linear poly(ester amide)s (PEAs) with exceptional structural control. The electron-withdrawing Cbz-group effectively delocalizes the nitrogen lone pair electrons, suppressing ring-nitrogen nucleophilicity to ensure the formation of perfectly alternating copolymers with narrow molecular weight distributions. Strategic deprotection of the synthesized copolymers yields semicrystalline materials. Capitalizing on inherent monomer reaction activity, we demonstrate architectural control in terpolymer systems through continuous modulation from block-like to random chain sequences. This methodology enables the precise engineering of advanced PEAs through molecular architecture design, featuring programmable sequence control and predictable structure−property relationships that govern material performance characteristics.

■ INTRODUCTION

Polymers with defined sequence, where distinct monomer units are arranged in a precise order that emulate the precision of biopolymers, have emerged as transformative methodologies for developing advanced materials with customized functionalities, such as data storage, anticounterfeiting technologies, microelectronics, and nanomedicine.[1−5] Among various synthetic sequence-controlled polymers, alternating copolymers (poly(A-*alt*-B)s) represent a particularly versatile class that enables precise spatial organization of complementary functional groups (A and B) along polymer backbones.[6] This molecular-level control facilitates the creation of sophisticated microarchitectures that is unattainable through conventional polymerization methods, driving intense cross-disciplinary research efforts from both academic and industrial sectors. Alternating ring-opening copolymerization (ROCOP) has proven to be particularly effective for synthesizing heteroatom-rich copolymers with controlled molecular weights, narrow dispersities, and preserved chain-end functionality. In addition, the ROCOP platform demonstrates exceptional monomer adaptability, enabling programmable control of polymeric architectures through rational comonomer selection. This synthetic versatility is further evidenced by successful implementation across structurally distinct monomer pairs, establishing a robust framework for precision polymer engineering, including epoxides/CO_2 systems for polycarbonates,[7−10] epoxides/CO combinations for polyesters,[11,12] epoxide/anhydride pairs for polyesters,[13−15] and various cyclic anhydride conjugates (e.g., aldehydes/anhydrides,[16] *o*-phtha-

Received: August 4, 2025
Revised: September 24, 2025
Accepted: September 25, 2025
Published: October 1, 2025



https://doi.org/10.1021/acs.macromol.5c02125

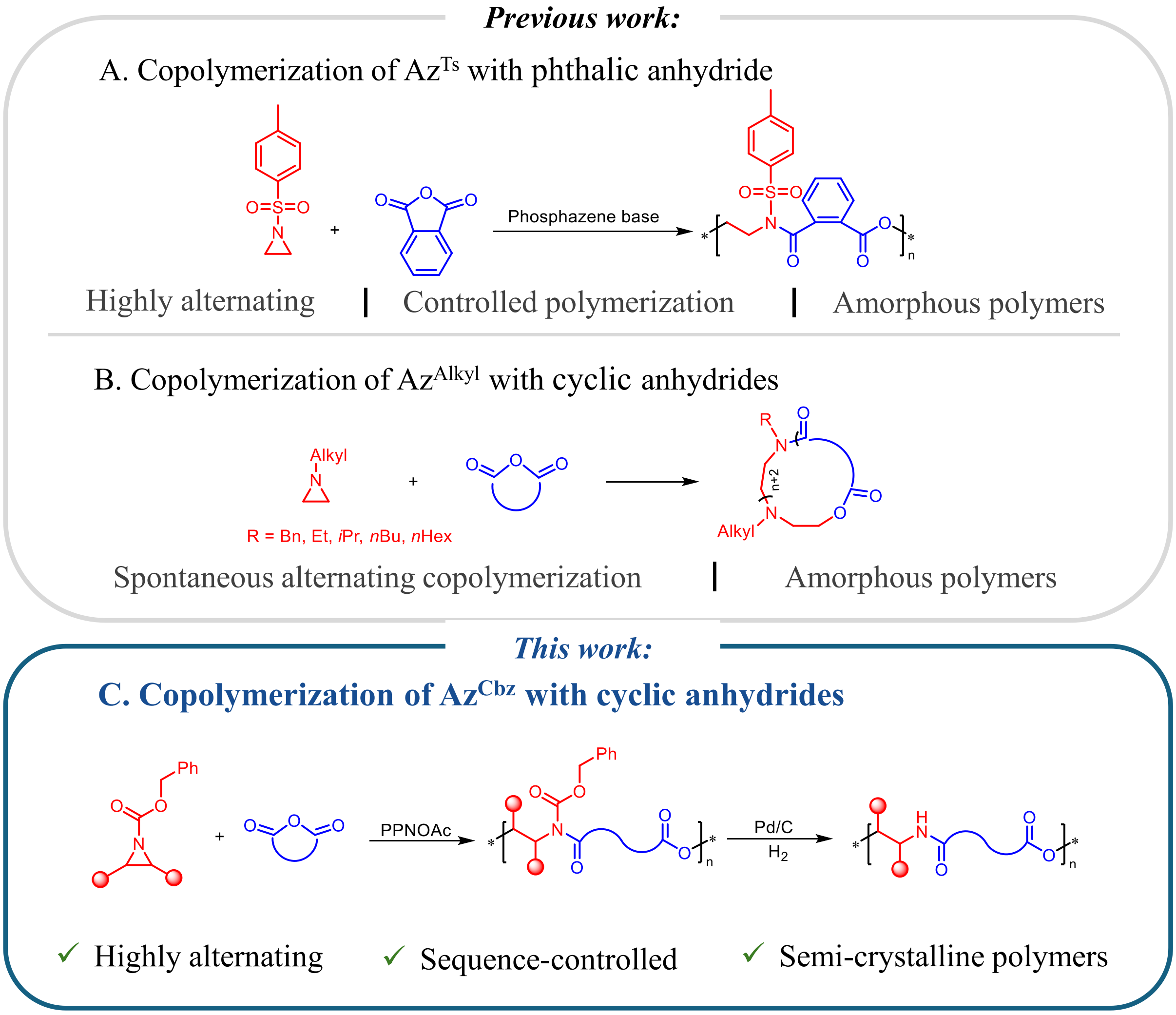


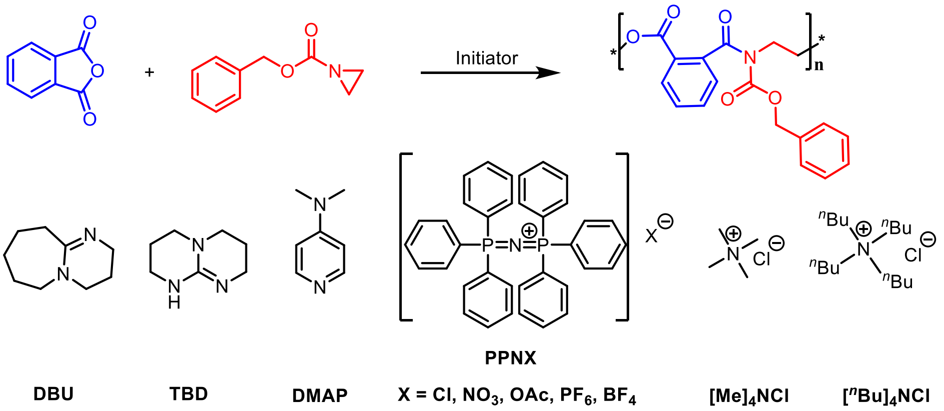
Figure 1. (A) Copolymerization of Az^{Ts} with phthalic anhydride to access poly(ester amide)s. (B) Copolymerization of Az^{Alkyl} with cyclic anhydrides to access cyclic poly(ester amide)s. (C) Copolymerization of Az^{Cbz} with cyclic anhydrides to access poly(ester amide)s.

laldehydes/anhydrides,[17] cyclic acetals/anhydrides[18]) for functional copolymers.

Poly(ester amide)s (PEAs) uniquely combine the degradability of polyesters with the superior thermal stability and mechanical strength characteristic of polyamides. This hybrid property profile has enabled widespread adoption in advanced technological applications, including controlled drug delivery systems, functional hydrogels, advanced packaging solutions, precision 3D printing technologies, composite materials development, and regenerative tissue engineering.[19−24] The ROCOP strategy employing aziridine/cyclic anhydride monomer pairs has emerged as a particularly promising route for PEA synthesis, combining thermodynamic feasibility with exceptional monomer versatility in terms of structural and functional diversity. In 2021, Hadjichristidis' team pioneered controlled ROCOP of *N*-sulfonyl aziridines (Az^{Ts}) with phthalic anhydride (PA) using phosphazene base catalysts, where the electron-withdrawing sulfonyl groups attenuated nitrogen nucleophilicity to enable precise electrophilic monomer activation (Figure 1A).[25] Subsequently, they demonstrated a sophisticated "one-pot/one-step" terpolymerization protocol integrating aziridines, cyclic anhydrides, and epoxides to produce architecturally defined diblock dialternating terpolymers.[26] Almost simultaneously, Ren et al. revealed alternating copolymerization of *N*-benzyl-2-methylaziridine with cyclic anhydrides, where competing zwitterionic pathways resulted in the preferential formation of copolymers with mixed linear and cyclic structures.[27] Very recently, Qin and Tang achieved a breakthrough in catalyst-free copolymerization of *N*-substituted aziridines with phthalic anhydride, yielding high-molecular-weight cyclic copolymers with remarkable alternating selectivity (Figure 1B).[28] Despite considerable progress in this research domain, the resulting poly(ester amide)s (PEAs) predominantly remain in an amorphous state due to the steric and electronic effects of nitrogen-bound substituents. The strategic incorporation of amide linkages (−C═O−NH−) through regioselective nitrogen-deprotection techniques presents a promising pathway for precise polymer engineering. Specifically, developing methodologies to systematically establish intermolecular hydrogen-bonding through controlled deprotection processes, thereby enhancing the crystallinity and structural regularity of PEAs, remains a critical challenge that warrants focused investigation.

In this work, we present a modular synthetic method for constructing linear poly(ester amide)s through organoammonium-salt-mediated ROCOP of *N*-benzyloxycarbonyl (Cbz)-protected aziridines with cyclic anhydrides under mild conditions. The electron-withdrawing Cbz-group effectively

Table 1. Initiator Screen for Az^{Cbz}/PA Copolymerization[a]



entry	initiator (I)	temp. [°C]	time [h]	conv.[b] [%]	M_n[c] [kDa]	$Đ$[c]
1		120	48			
2	DBU	50	72	69	8.2	1.26
3	TBD	50	23	79	10.0	1.22
4	DMAP	50	23	94	11.2	1.23
5	PPNCl	50	28	93	12.0	1.23
6	PPNOAc	50	5	97	14.2	1.17
7	$PPNNO_3$	50	20	95	13.4	1.25
8	$PPNPF_6$	50	48	12	2.2	1.40
9	$PPNBF_4$	50	48	14	2.3	1.42
10	$[Me]_4NCl$	50	30	76	6.8	1.27
11	$[^nBu]_4NCl$	50	22	94	10.5	1.32
12[d]	PPNOAc	50	3	50	14.6	1.25
13[e]	PPNOAc	80	6	90	37.2	1.28

[a] Reactions were performed with the Az^{Cbz}/PA/initiator/dioxane = 100/100/1/200 in a 10 mL vial unless noted otherwise. [b] Conversion of Az^{Cbz} was calculated using ^1H NMR spectroscopy. [c] Number-average molecular weights (M_n) and dispersity values were determined by size exclusion chromatography (SEC) in THF, calibrated with polystyrene. [d] Reaction was conducted with Az^{Cbz}/PA/initiator/dioxane = 200/100/1/200. [e] Reaction was conducted with Az^{Cbz}/PA/initiator/dioxane = 500/500/1/1000.

delocalizes nitrogen lone pair electrons, strategically modulating monomer nucleophilicity to achieve well-defined alternating copolymers with narrow dispersity. Postpolymerization hydrogenolytic cleavage of the Cbz-protecting group clearly affords semicrystalline PEAs containing amide linkages (−C═O−NH−) with intermolecular hydrogen-bonding. Through precision modulation of monomer reactivity ratios, we further establish a terpolymerization platform enabling precise control over copolymer sequence architecture, spanning from block-like, gradient to random distributions. This methodology addresses the longstanding challenge of incorporating hydrogen-bonding amide functionalities while expanding the toolbox for sequence-controlled polymer synthesis.

■ RESULTS AND DISCUSSION

Well-Controlled ROCOP of Az^{Cbz} with PA. *N*-unsubstituted aziridines typically undergo facile cationic ring-opening polymerization, leading to uncontrolled formation of (hyper)-branched polymeric architectures.[29] Az^{Ts} bearing electron-withdrawing sulfonyl groups on nitrogen atom was demonstrated to enhance aziridine electrophilicity, thereby facilitating well-controlled copolymerization with cyclic anhydrides.[25,30,31] Inspired by the foundation, we hypothesized that introducing an electron-withdrawing Cbz-group into aziridines would delocalize the lone pair electrons of nitrogen atom to suppress nucleophilicity and then afford controlled-PEAs. Furthermore, postpolymerization hydrogenolytic cleavage of the Cbz-protecting group could clearly afford PEAs containing amide (−C═O−NH−) linkages. At the outset, we initially examined the alternating copolymerization of *N*-Cbz-aziridine (Az^{Cbz}) with PA under catalyst-free conditions. No polymerization reactions were proceeded at 120 °C for 24 h according to the signal analysis from ^1H NMR, indicating the spontaneous zwitterionic copolymerization did not proceed, which is different from *N*-alkyl aziridines (Table 1, entry1). Subsequent copolymerization in 1,4-dioxane (Az^{Cbz}/PA/initiator = 100:100:1) was screened with various organic bases, which are effective for the ROCOP of epoxides with cyclic anhydrides.[32] With 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as the initiator, the copolymerization can proceed smoothly at 50 °C, yielding the resulting PEA with perfect alternating structure and narrow distribution (Table 1, entry 2). Similarly, both 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) and 4-dimethylaminopyridine (DMAP) exhibited comparable selectivity and higher activities (Table 1, entries 3−4). Next, we focused on investigating privileged catalyst systems by employing organic ammonium salts for the copolymerization process, which have previously demonstrated exceptional catalytic efficiency in ROCOP of cyclic thioanhydrides with episulfides.[32] At a loading of 1 mol %, all bis-(triphenylphosphoranylidene)ammonium (PPN) salts exhibited remarkable catalytic activity, in which PPNOAc showed the highest reactivity among the series (Table 1, entries 5−9). Notably, the ^1H NMR analysis of the resultant copolymers revealed the absence of detectable signals corresponding to polyamide units, confirming the formation

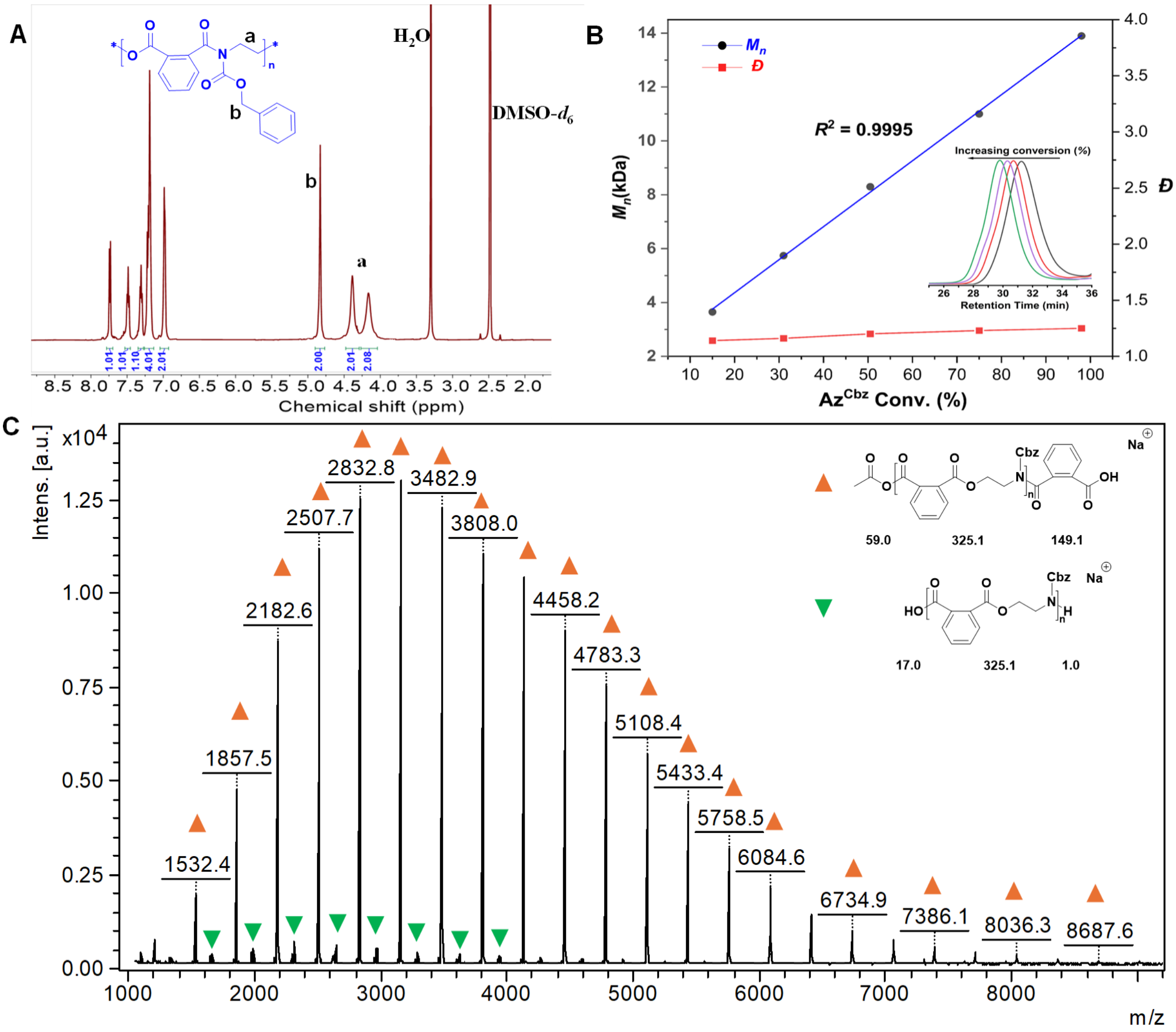


Figure 2. (A) ^{1}H NMR spectrum (400 MHz, DMSO-d_6) of poly(Az^{Cbz}-*alt*-PA) resulting from the conditions: PPNOAc/Az^{Cbz}/PA/dioxane = 1/100/100/200 (molar ratio) at 50 °C. (B) M_n (kDa) and $Đ$ versus conversion of poly(Az^{Cbz}-*alt*-PA) and SEC traces of copolymers with increasing monomer conversion, calibrated relative to monodisperse polystyrene standards. (C) MALDI-TOF mass spectrum of poly(Az^{Cbz}-*alt*-PA).

of the perfectly alternating structure (Figure 2A). Systematic evaluation of the initiator ionic components revealed significant cation/anion effects on polymerization efficiency. Replacement of the nucleophilic PPNOAc with non-nucleophilic counterparts (PPNPF$_6$ and PPNBF$_4$) decelerated the reaction activity and afforded polymers with lower molecular weight (M_n) (Table 1, entries 8−9). Similarly, substitution of PPNCl with [^{n}Bu$_4$N]Cl or [Me$_4$N]Cl resulted in substantial reductions in polymerization rates (Table 1, entries 10−11). Notably, employing an excess of Az^{Cbz} significantly accelerated the ROCOP process, achieving complete PA conversion within 3 h while effectively suppressing undesirable Az^{Cbz} homopolymerization following PA depletion. This characteristic behavior contrasts markedly with the *N*-sulfonyl aziridine/anhydride copolymerization system, where substantial homopolymerization typically occurs after monomer consumption (Table 1, entry 12).[25] Strikingly, reducing the PPNOAc loading to 0.2 mol % enabled successful synthesis of PEA with controlled molecular characteristics, achieving a high M_n of 37.2 kDa and narrow dispersity ($Đ$ = 1.28) (Table 1, entry 13).

The structural characteristics of resultant copolymers were systematically investigated through comprehensive spectroscopic analyses, including ^{1}H NMR, ^{13}C NMR, and matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS). According to the ^{1}H NMR, the methylene protons exhibited a marked downfield shift (from 2.23 ppm to 4.20−4.60 ppm) as a consequence of ester/amide bond formation, consistent with enhanced electron withdrawal effects (Figures 2A and S6). Notably, the absence of polyamine-specific proton signals in the spectra strongly supported the formation of a strictly alternating copolymer architecture. A linear correlation between molecular weight and monomer conversion and consistently narrow, monomodal molecular weight distributions ($Đ$ = 1.16−1.25) revealed that the copolymerization exhibited controlled characteristics (Figures 2B and S54). Furthermore, the structural regularity was further corroborated by MALDI-TOF MS data, which exhibited a periodic peak pattern with uniform mass intervals of 325.1 Da. Crucially, the mass spectra revealed no detectable signals corresponding to branched or cyclic byproducts from inter/intramolecular nucleophilic side reactions, confirming the efficient suppression of competitive

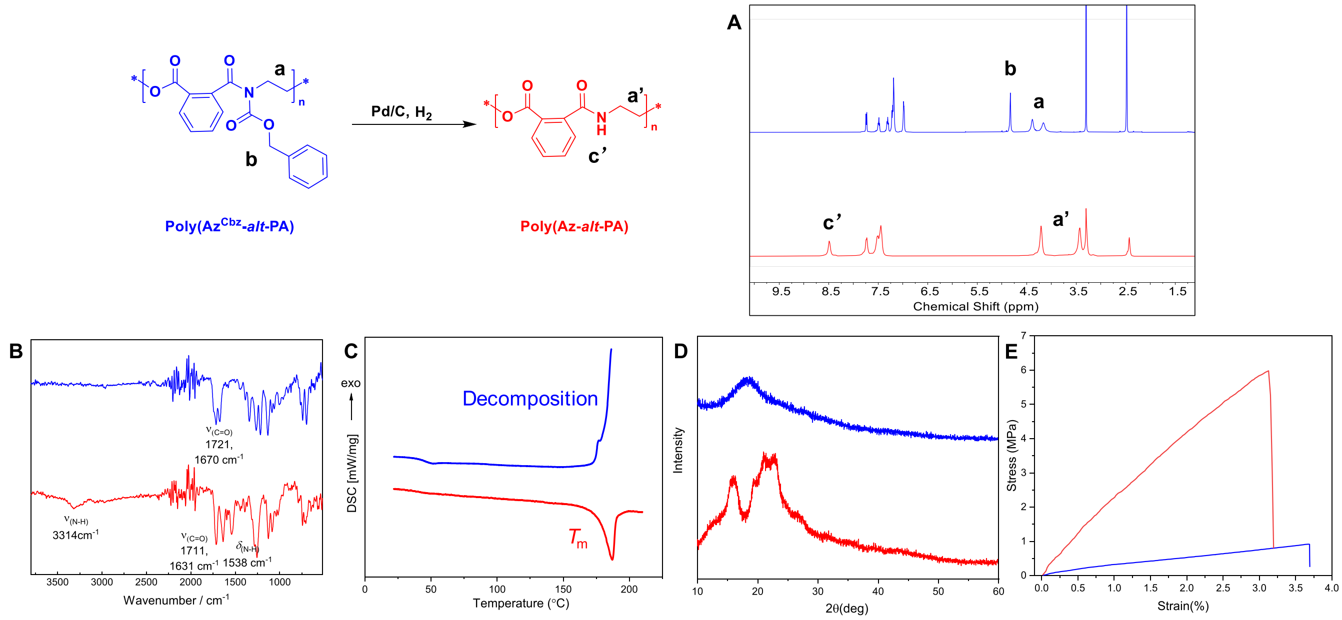
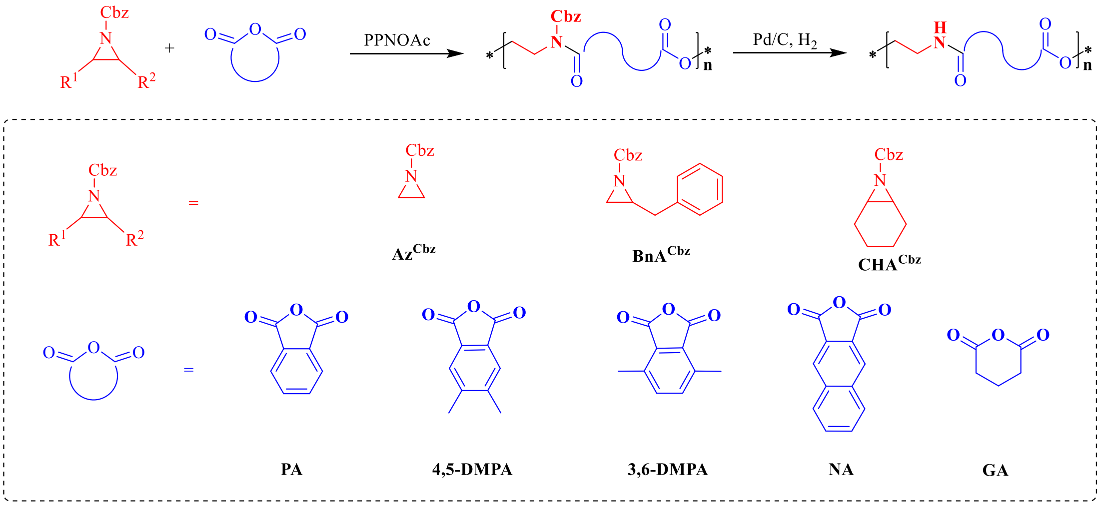


Figure 3. (A) ^{1}H NMR spectrum (400 MHz, DMSO-d_6) of poly(Az^{Cbz}-*alt*-PA) and deprotection poly(Az-*alt*-PA). (B) FT-IR spectra of poly(Az^{Cbz}-*alt*-PA) and deprotection poly(Az-*alt*-PA). (C) DSC thermograms of poly(Az^{Cbz}-*alt*-PA) and deprotection poly(Az-*alt*-PA). (D) WAXD profiles of poly(Az^{Cbz}-*alt*-PA) and deprotection poly(Az-*alt*-PA). (E) Stress–strain curves of poly(Az^{Cbz}-*alt*-PA) and deprotected poly(Az-*alt*-PA).

side reactions (Figure 2C). Notably, the predominant end-group composition of these polymers suggested that chain initiation occurred predominantly through PA ring-opening initiated by an acetate anion rather than aziridine Az^{Cbz} (derived from PPNOAc). To elucidate the initiation mechanism, treatment of PPNOAc (0.02 M in $CDCl_3$) with excess Az^{Cbz} (3.0 equiv) at 50 °C over 1 h showed no detectable reaction. In contrast, the subsequent mixing of PPNOAc (0.02 M in $CDCl_3$) with PA (1.0 equiv) generated anhydride end groups within minutes (Figures S2 and S3). To rationalize these findings, two distinct initiation pathways were systematically investigated through density functional theory (DFT) calculations. For computational efficiency, the acetate anion was employed as a simplified model of PPNOAc. The calculated Gibbs free energy profiles reveal a striking contrast: nucleophilic attack by the acetate anion occurs with an activation barrier of 4.37 kcal/mol for PA versus 25.70 kcal/mol for Az^{Cbz} (Figure S83, orange and red lines). This significant energy difference ($\Delta\Delta G^\ddagger$ = 21.33 kcal/mol) conclusively demonstrates the preferential reactivity of PPNOAc toward PA, thereby establishing it as the dominant initiation pathway for polymerization.

Cbz-groups are commonly transformed into the corresponding amines by Pd/C-catalyzed hydrogenolysis. More specifically, the copolymer poly(Az^{Cbz}-*alt*-PA) (Table 1, entry 6) was dissolved in 1:1 DCM/methanol with Pd/C (20% catalyst loading based on Pd) and pressurized to 1.0 MPa of H_2 for 24 h. Following isolation of the polymer, ^{1}H NMR analysis confirmed that the methylene in the Cbz-groups at 4.89 ppm disappeared, verifying the loss of the Cbz-group from the polymer. Additionally, the aliphatic proton signals of the methylene protons in the polymer backbone shifted from the range of 4.60–4.20 ppm to specific peaks at 4.25 and 3.50 ppm (Figure 3A). To further demonstrate the successful synthesis of the copolymer poly(Az-*alt*-PA), Fourier transform infrared spectroscopy (FT-IR) was employed. The original polymer, poly(Az^{Cbz}-*alt*-PA), exhibited absorption peaks at 1721 cm^{-1} and 1670 cm^{-1}, corresponding to the stretching vibrations of C═O bonds in esters and amides, respectively. In contrast, the FT-IR spectrum of poly(Az-*alt*-PA) displayed distinct C═O stretching peaks at 1711 cm^{-1} and 1631 cm^{-1}. Notably, new peaks attributed to N–H bending vibration at 1538 cm^{-1} and the N–H stretching vibration peak at 3314 cm^{-1} emerged in the FT-IR spectrum, confirming the formation of amide (–C═O–NH–) bonds in the polymer structure (Figure 3B). Additionally, the proposed structure was also supported by size-exclusion chromatography (SEC) analysis. With the poly(Az^{Cbz}-*alt*-PA) as the reactant (M_n = 14.2 kDa, $Đ$ = 1.17, Table 1, entry 6), the resulting copolymer poly(Az-*alt*-PA) exhibited a molecular weight of 8.1 kDa and a polydispersity index of 1.20, consistent with the expected structural changes (Figure S55). In terms of solubility, the deprotected copolymer demonstrated limited solubility in common organic solvents such as DCM but showed slight solubility in DMF and DMSO. The thermal properties of the deprotected copolymer poly(Az-*alt*-PA) were significantly enhanced compared to the pristine poly(Az^{Cbz}-*alt*-PA). Differential scanning calorimetry (DSC) thermogram of poly(Az^{Cbz}-*alt*-PA) featured a glass transition of around 48 °C (Figure 3C, blue line). In contrast, the deprotected copolymer poly(Az-*alt*-PA) exhibited a distinct melting endothermic peak at 187 °C, with a heat of fusion (ΔH_m) of 26.72 J/g, indicative of a semicrystalline material (Figure 3C, red line). Powder X-ray diffraction (PXRD) analysis further corroborated the structural changes. While poly(Az^{Cbz}-*alt*-PA) showed no diffraction signals, attesting its amorphous nature, the deprotected copolymer poly(Az-*alt*-PA) exhibited characteristic diffraction peaks at 2θ angles of 15.9°, 19.3°, 21.3°, and 22.7°, consistent with a semicrystalline material (Figure 3D). Tensile testing studies using polymer films illustrated that poly(Az^{Cbz}-*alt*-PA) showed a lower strength with σ_B = 0.94 MPa. In contrast, poly(Az-*alt*-PA) exhibited mechanical properties with a

Table 2. Aziridines/Cyclic Anhydrides Copolymerization Scope[a]



entry	monomers	temp. [°C]	time [h]	conv.[b] [%]	M_n[c] [kDa]	$Đ$[c]	T_g[d] [°C]	T_g/T_m[e] [°C]
1	Az^{Cbz}/PA	50	5	97	14.2	1.17	48.0	--/187.0
2	Az^{Cbz}/4,5-DMPA	50	5	93	10.5	1.25	83.2	87.9/--
3	Az^{Cbz}/3,6-DMPA	50	24	87	8.55	1.27	58.7	74.3/--
4	Az^{Cbz}/NA	70	5	99	9.36	1.32	75.0	118.0/197.0
5	Az^{Cbz}/GA	70	24	33	2.3	1.37	34.0	
6	(*R*)-BnA^{Cbz}/PA	80	6	99	9.17	1.20	72.1	104.0/--
7	(*S*)-BnA^{Cbz}/PA	80	6	94	9.20	1.26	73.0	105.4/--
8[f]	CHA^{Cbz}/PA	50	24	83	6.72	1.47	62.9	105.0/--
9[f]	CHA^{Cbz}/NA	70	15	92	9.32	1.20	141.0	175.2/--

[a] Reactions were performed with aziridine/cyclic anhydride/initiator/dioxane = 100/100/1/200 in a 10 mL vial unless noted otherwise. [b] Conversion of aziridine was calculated using ^{1}H NMR spectroscopy. [c] Number average molecular weights (M_n) and dispersity ($Đ$) values were determined by size exclusion chromatography (SEC) in THF, calibrated with polystyrene. [d] Measured using DSC, the T_g values reported are from the second heat. [e] Measured using DSC for copolymers without the Cbz-protecting group. [f] SalenAl(III)Cl complexes were added as catalysts. Reactions were conducted with Aziridine/PA/SalenAl(III)Cl/Initiator/Dioxane = 100/100/1/1/200.

relatively moderate tensile strength with σ_B = 5.96 MPa with an elongation at break (ε_B) < 5%, representing a brittle material (Figure 3E).

Substrate Scope of Aziridines with Cyclic Anhydrides. With an efficient copolymerization initiator PPNOAc in hand, we investigated the substrate scope of the aziridines/anhydrides copolymerization to establish a library of novel poly(ester amide)s. Using Az^{Cbz} as a model, several anhydrides, including 4,5-dimethylphthalic anhydride (4,5-DMPA), 3,6-dimethylphthalic anhydride (3,6-DMPA), and naphthyl anhydride (NA), were tested under mild conditions, yielding copolymers with glass transition temperatures (T_g) of 83.2 °C, 58.7 °C, and 75.0 °C, respectively (Table 2, entries 2–4). While Az^{Cbz} demonstrated effective copolymerization with aromatic anhydrides to produce PEAs with high molecular weights, aliphatic counterparts such as glutaric anhydride (GA) showed significantly diminished reactivity (Table 2, entry 5). This disparity might potentially be attributed to inadequate catalytic activation, in which the sluggish ring-opening step of aliphatic cyclic anhydrides ($\Delta\Delta G^{\ddagger}$ = 25.70 kcal/mol) compared to that of their aromatic counterpart ($\Delta\Delta G^{\ddagger}$ = 16.93 kcal/mol) cause the low molecular weights of resultant polymers (Figures S85 and S86). The initiator demonstrated compatibility with various substituted aziridines, including chiral monomers such as (*R*)- or (*S*)-BnA^{Cbz}, which copolymerized with PA to produce isotactic poly(ester amide)s with a T_g of approximately 72.1 °C with high regioselectivities (Table 2, entries 6–7, Figures S51 and S61). Disubstituted aziridine, CHA^{Cbz}, was employed to copolymerize with PA and NA in the presence of the salenAl(III)Cl/PPNOAc system to yield poly(ester amide)s with T_g values of approximately 62.9 and 141.0 °C (Table 2, entries 8–9). Of particular interest, deprotecting the Cbz-group significantly enhanced the thermal properties of the copolymers due to the intermolecular hydrogen bonding. For instance, deprotected copolymers derived from Az^{Cbz}/NA exhibited melting temperatures of 197 °C (Figure S58). Furthermore, copolymers without the Cbz-group, such as those from CHA^{Cbz}/PA and CHA^{Cbz}/NA, displayed exceptionally high glass transition temperatures (T_g) of 105 and 175 °C, representing an increase of 42 and 34 °C, respectively, and exhibited outstanding thermal stability (Figures S62 and S63).

Sequence-Controlled Terpolymerization of Aziridines with Cyclic Anhydrides. The synthesis of sequence-defined polymers, where monomer units of differing chemical natures are arranged in an ordered manner, has fascinated chemists due to their unique macroscopic properties. By strategically tuning the reactivity ratios of comonomer pairs, researchers engineer high-performance polymeric materials with precisely controlled microarchitectures (e.g., block, gradient, or alternating sequences), thereby enabling structure-driven property optimization for targeted applications.[32,33] In this study, we orchestrated the terpolymerization of aziridines and cyclic anhydrides by a one-step/one-pot method, achieving excellent control over monomer sequencing. This sequence-directed polymerization strategy enables

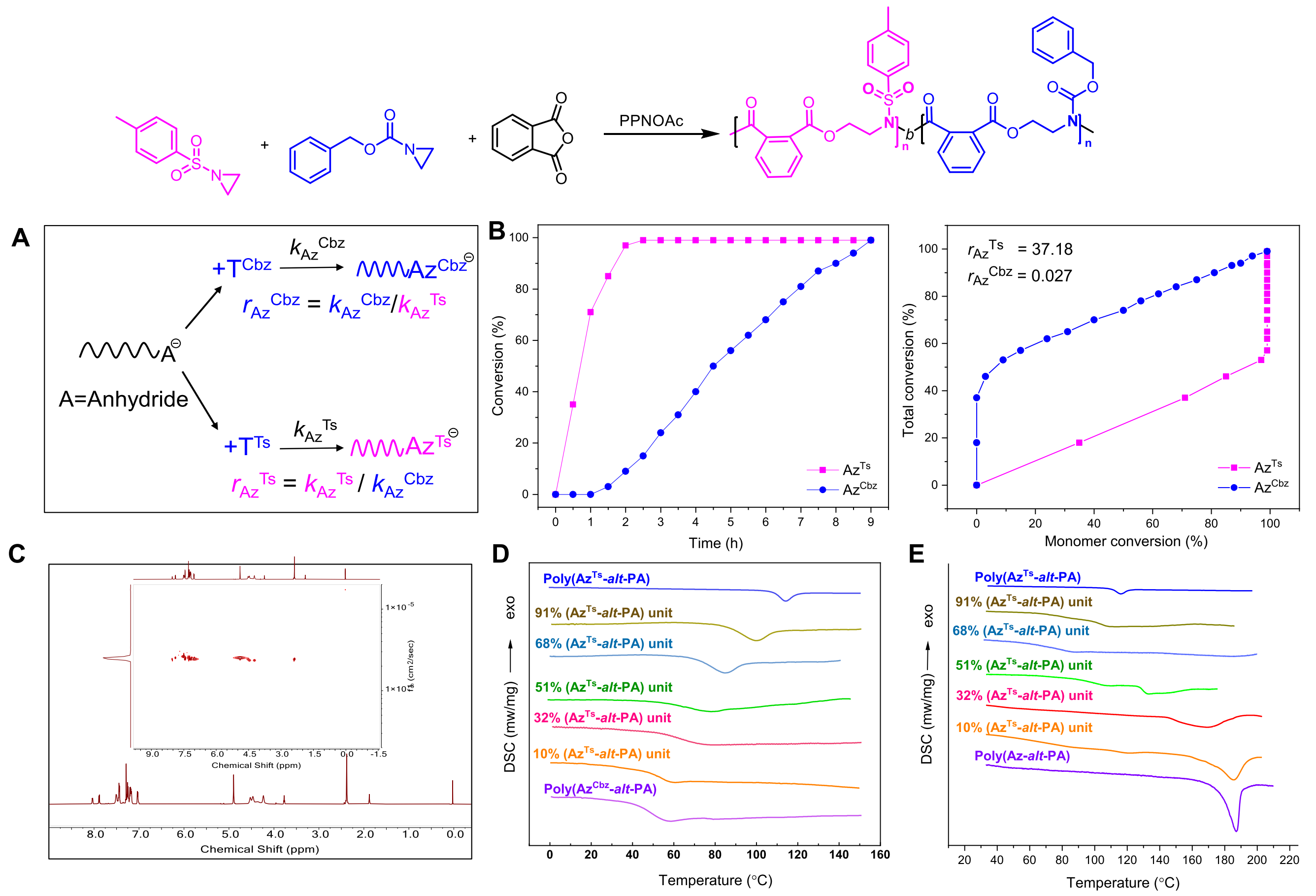
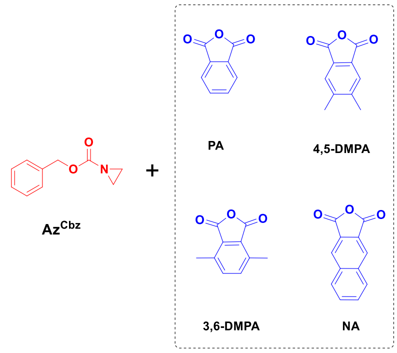


Figure 4. (A) Definition of reactivity ratios based on the Beckingham−Sanoja−Lynd model. (B) Reactivity ratios of Az^{Cbz} and Az^{Ts} in terpolymerization. (C) ^1H NMR spectra of poly(Az^{Ts}-*alt*-PA)-*b*-poly(Az^{Cbz}-*alt*-PA). (D) DSC profiles of block-like Az^{Ts}/Az^{Cbz}/PA terpolymers. (E) DSC profiles of the block-like Az^{Ts}/Az/PA terpolymers through postpolymerization hydrogenolytic cleavage of the Cbz-protecting group.



Monomer Combinations	$r_{\text{anhydride-1}}$	$r_{\text{anhydride-2}}$	Distribution
Az^{Cbz} / PA / 4,5-DMPA	9.87	0.101	Gradient
Az^{Cbz} / PA / 3,6-DMPA	13.4	0.0748	Gradient
Az^{Cbz} / PA / NA	7.24	0.135	Gradient
Az^{Cbz} / 4,5-DMPA / 3,6-DMPA	1.23	0.81	Random
Az^{Cbz} / NA/3,6-DMPA	1.74	0.576	Random
Az^{Cbz} / NA/4,5-DMPA	0.741	1.35	Random

Figure 5. Reactivity ratio of various cyclic anhydrides under Az^{Cbz}/anhydride-1/anhydride-2 ROCOP with different combinations.

the synthesis of copolymers with programmable architectural diversity, where monomer positioning engineering directly dictates chain organization—spanning block-like, gradient, and random configurations.

At the outset, the terpolymerization of Az^{Cbz}, Az^{Ts}, and PA was performed at 50 °C initiated by PPNOAc (1.0 mol %). The relative compositions of two kinds of ester amide units in the resulting terpolymers could be easily tuned by varying the aziridine ratios in the feedstock. As the nucleophilic attack of the carboxylate anion on Az^{Cbz} or Az^{Ts} is considered as an independent step, the nonterminal Beckingham−Sanoja−Lynd copolymerization formalism was implemented for the precise determination of monomer reactivity ratios (r_{Az}^{Ts} and r_{Az}^{Cbz}).[33]

The reactivity ratios revealed that Az^{Ts} has a significantly higher reactivity (r_{Az}^{Ts} = 37.18) compared to Az^{Cbz} (r_{Az}^{Cbz} = 0.027) (Figure 4A and B, Table S3). This disparity in reactivity indicated a block-like distribution of monomers in the polymer chain, where (Az^{Ts}-*alt*-PA) units are more prevalent initially, followed by an increase in (Az^{Cbz}-*alt*-PA) units as the reaction progressed. Diffusion-ordered spectroscopy (DOSY) NMR analysis provided critical insights into the copolymers' architectures. The block-like copolymer exhibits a single diffusion coefficient, indicating a uniform structure (Figure 4C). In contrast, physical blending of (Az^{Ts}-*alt*-PA) and (Az^{Cbz}-*alt*-PA) shows two diffusion coefficients, suggesting a more heterogeneous structure (Figures S69 and S70). The thermal properties of the terpolymers are directly affected by the composition of the polymers. As the (Az^{Ts}-*alt*-PA) unit content decreases, the T_g of terpolymers decreases from 114 to 48 °C (Figure 4D). Conversely, the removal of the Cbz-protection group reveals the underlying structure, and when the content of (Az^{Ts}-*alt*-PA) units decreases, the melting temperature (T_m) of poly(Az-*alt*-PA) gradually becomes more apparent (Figure 4E). For instance, at 50% (Az^{Ts}-*alt*-PA) content, the terpolymer exhibits *semi*-crystalline behavior with a T_m of 133 °C and a T_g of 99 °C. Furthermore, upon increasing the (Az-*alt*-PA) ester unit content to 90%, only a T_m of 185 °C was detected, and this value is close to that of the pure poly(Az-*alt*-PA) copolymer.

Based on the achievement of precise monomer sequence control in the terpolymerization of Az^{Ts}/Az^{Cbz}/PA using PPNOAc, this study was extended to explore a broader range of monomers. By retention of Az^{Cbz} as the aziridine component, six distinct monomer combinations were systematically evaluated with four different cyclic anhydrides: PA, 4,5-DMPA, 3,6-DMPA, and NA (see Figure 5). This approach enabled a thorough investigation of the effects of varying monomeric components while maintaining key structural elements constant (Figures S71−S82). For example, involving the terpolymerization of Az^{Cbz}/PA/4,5-DMPA at 70 °C (1 mol %), the reactivity ratios reveal that PA has a significantly higher reactivity (r_{PA} = 9.87) compared to 4,5-DMPA ($r_{4,5\text{-DMPA}}$ = 0.101), indicating a gradient distribution. Similarly, the other two combinations—Az^{Cbz}/PA/3,6-DMPA, Az^{Cbz}/PA/NA—displayed gradient distributions as well. Notably, three random-like terpolymers were obtained from the combinations of Az^{Cbz}/4,5-DMPA/3,6-DMPA, Az^{Cbz}/NA/3,6-DMPA, and Az^{Cbz}/NA/4,5-DMPA, thereby leading to the production of statistical terpolymers, in which two kinds of ester units are distributed in the main chain with probability.

■ CONCLUSION

In summary, we present a robust strategy for synthesizing sequence-defined linear poly(ester amide)s (PEAs) via organocatalytic copolymerization of *N*-carbobenzyloxy (Cbz)-substituted aziridines with cyclic anhydrides using PPNOAc as initiators under mild conditions. The electron-withdrawing Cbz-group effectively delocalizes nitrogen lone pair electrons, thereby enabling the precise modulation of monomer electrophilicity/nucleophilicity balance to produce alternating copolymers with controlled molecular weights and narrow dispersity. Postpolymerization hydrogenolytic cleavage of the Cbz-protecting group clearly yields semicrystalline PEAs containing amide linkages (−C═O−NH−). Through systematic manipulation of monomer reactivity ratios, we further establish a terpolymerization paradigm permitting precise control over copolymer sequence architecture, spanning from block-like, gradient to random configurations. This methodology provides a tunable platform for providing sequence-controlled PEA materials with tailorable thermal properties and hydrolytic degradation profiles. Further investigation will focus on expanding their potential in sustainable polymer applications.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.macromol.5c02125.

Synthetic procedures of all new compounds, supplementary characterization data including ^{1}H NMR and ^{13}C NMR spectra, and DSC and XRD data of various copolymers (PDF)

Accession Codes

Accession Codes Deposition Numbers 2425195 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via the joint Cambridge Crystallographic Data Centre (CCDC) and Fachinformationszentrum Karlsruhe Access Structure service.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the National Natural Science Foundation of China (NSFC, Nos. 22275148 and 22301243) and the Fundamental Research Funds for the Central Universities (D5000230135).

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