Macromolecules
Cite This: Macromolecules XXXX, XXX, XXX−XXX
Article
pubs.acs.org/Macromolecules

Anionic Polymerization of Azidoalkyl Glycidyl Ethers and Post-Polymerization Modification

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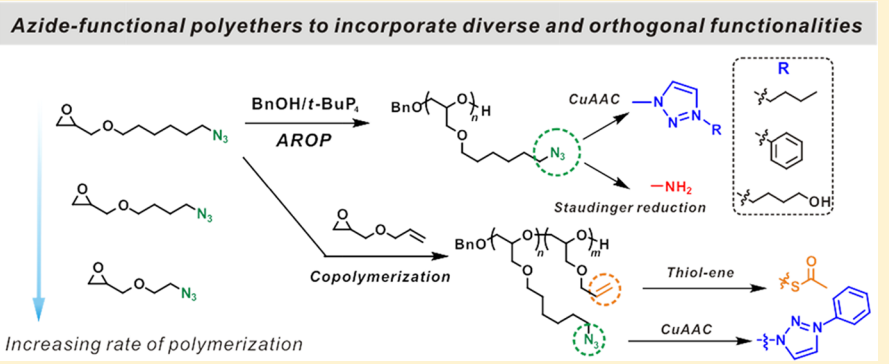
Supporting Information



ABSTRACT: Polyethers like poly(ethylene glycol) have been widely used for a variety of valuable applications, although their functionalization still poses challenges due to the absence of functional handles along the polymer backbone. Herein, a series of novel azide-functionalized glycidyl ether monomers are presented as a universal approach to synthesize functional polyethers by post-polymerization modification. Three azide-functionalized glycidyl ether monomers possessing different alkyl spacers (ethyl, butyl, and hexyl) were designed and synthesized by a simple two-step substitution reaction. Organic superbase-catalyzed anionic ring-opening polymerization can proceed under mild conditions compatible with an azide pendant group, affording well-controlled azide-functionalized polyethers with low dispersity ($Đ$ < 1.2). The azide pendant groups on the resulting polymers were readily modified to a variety of functional groups via copper-catalyzed azide−alkyne cycloaddition reactions and Staudinger reduction. Furthermore, copolymerization of azidohexyl glycidyl ether with allyl glycidyl ether was demonstrated to provide an additional orthogonal functional handle. We anticipate that this work provides a new platform for the preparation of diverse functional polyethers.

INTRODUCTION

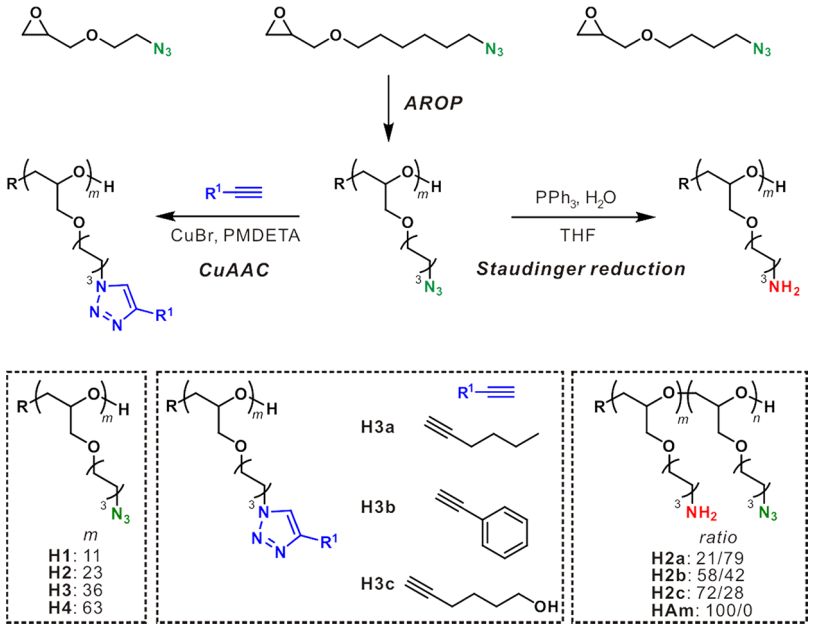
The development of efficient and reliable methods to synthesize functional polymers with diverse properties and architectures is essential to satisfy the demands of various applications in materials science. Many functional polymers have been prepared by direct polymerization of readily polymerizable monomers accompanied by significant advances in controlled polymerization techniques with tolerable functional monomers.[1−3] However, there are still some monomers having reactive functional moieties that are not amenable to direct polymerization.

Alternatively, post-polymerization modification offers an avenue to access multifunctional polymers while circumventing the incompatibility of desirable functional groups with polymerization conditions.[4,5] Many post-polymerization modification strategies are based on the increasing convergence of organic chemistry and polymer synthesis,[6] spearheaded by the introduction of click chemistry by Sharpless and colleagues.[7] For example, post-polymerization modification of many classes of polymers has been achieved through various chemical transformations, including azide−alkyne cycloaddition,[8,9] transesterification,[10] thiol−ene addition,[11] Diels−Alder reactions,[12] Suzuki−Miyaura coupling,[13] and sulfur fluoride exchange.[14] For this strategy, the development of a suitable monomer that is compatible with a polymerization needs to be accompanied. In this manner, BN 2-vinylnaphthalene has been introduced by the Klausen group to prepare poly(vinyl alcohol) derivatives via post-polymerization organoborane oxidation.[15] The Hillmyer group has established a new route to prepare poly(allyl alcohol) by post-polymerization modification of the polymer precursor synthesized from bis(*tert*-butyloxycarbonyl) twisted acrylamide monomer.[16] These strategies highlight the importance of designing a functional monomer suitable for post-polymerization modification to access desired functional polymers that are otherwise inaccessible by direct polymerization.

Received: October 23, 2019
Revised: December 4, 2019

DOI: 10.1021/acs.macromol.9b02236
Macromolecules XXXX, XXX, XXX−XXX

Scheme 1. Post-Polymerization Modification of Azide-Functionalized Polyethers via Copper-Catalyzed Azide−Alkyne Cycloaddition (CuAAC) and Staudinger Reduction



Polyethers like poly(ethylene glycol) (PEG) draw considerable attention as one of the most valuable polymers in biomedical applications by virtue of their excellent biocompatibility and aqueous solubility.[17,18] However, they lack reactive functional handles along their backbone, which limits their implications in broader areas. The typical approach for the preparation of multifunctional PEGs involves anionic ring-opening polymerization (AROP) of functional epoxide monomers.[19,20] Conventional AROP is typically incompatible with most functional groups, such as hydroxyl, carboxylic acid, primary amine, nitrile, and halide groups, due to the highly reactive conditions, leading to undesirable side reactions. An alternative approach such as the activated monomer method has been suggested to avoid such difficulties.[21−23] Nonetheless, the development of epoxide monomers exhibiting functional groups that are tolerable to typical AROP conditions is still necessary to design a convenient post-polymerization modification strategy for polyethers.

To date, several monomers bearing functional groups stable to AROP conditions have been reported.[19] As a representative example, allyl glycidyl ether (AGE) is an epoxide monomer widely used for imparting functionality to PEG. Not only are allyl groups stable under typical AROP conditions but they can also react with functional thiols via the thiol−ene reaction to decorate polyethers with myriad pendant functionalities.[24−26] Intensive studies and various applications of AGE-based polymers by the Hawker and Lynd group have made a significant impact on post-polymerization modification of various polyethers.[27−35] Recently, Frey and co-workers have also developed a novel epoxide monomer, 3,3-dimethoxypropanyl glycidyl ether, for homopolymerization or copolymerization with ethylene oxide to afford PEG, displaying multiple aldehyde functionalities.[36]

Inspired by the advent of click chemistry, the azide functionality is regarded as a good candidate for the post-polymerization modification of polyethers due to its potential to undergo further modification by Cu-catalyzed azide−alkyne cycloaddition (CuAAC) or Staudinger reduction. As a part of our ongoing effort in the development of novel functional glycidyl ether monomer library,[37−43] herein, we introduce a series of new azide-functional glycidyl ether monomers, azidoethyl glycidyl ether (AEGE), azidobutyl glycidyl ether (ABGE), and azidohexyl glycidyl ether (AHGE) that can be polymerizable under organic superbase-catalyzed AROP conditions. The homopolymerization of each monomer was compared using in situ ^{1}H NMR kinetic study. Among them, AHGE was selected as a model monomer for the generation of a modular and versatile synthetic route to post-polymerization modified polyethers (Scheme 1). Polymerization of AHGE provides functional polyethers bearing pendant azide groups, which can be further reacted with functional alkynes to install a broad range of functionalities along the polymer backbone. In addition, Staudinger reduction of the azide group can afford a pendant primary amine group, which is otherwise not tolerable in typical AROP conditions.

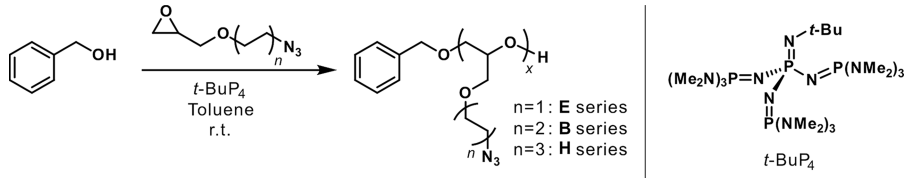
EXPERIMENTAL SECTION

Materials. All reagents and solvents were purchased from Sigma-Aldrich, Alfa Aesar, or Tokyo Chemical Industry and used as received unless otherwise noted. Tetrahydrofuran (THF) and toluene were dried, degassed using a solvent purification system (Vacuum Atmospheres, USA), and collected to use immediately thereafter. $CDCl_3$, DMSO-d_6, toluene-d_8, and D_2O were purchased from Cambridge Isotope Laboratories. AEGE, ABGE, and AHGE were used for polymerization after the distillation over CaH_2.

Characterization. ^{1}H and ^{13}C NMR spectra were recorded on an Agilent 400 MHz spectrometer or Bruker Avance III HD 400 MHz spectrometer at room temperature. Chemical shifts are reported in ppm relative to the signals corresponding to the residual non-deuterated solvents: $CDCl_3$, δH = 7.26 ppm and δC = 77.16 ppm; $(CD_3)_2SO$, δH = 2.50 ppm; D_2O, δH = 4.79 ppm; and C_7D_8, δH = 2.09 ppm. Mass spectrometry was performed on a Bruker 1200 series and HCT basic system using an electrospray ionization (ESI) source. The number- and weight-average molecular weights (M_n and M_w) and molecular weight distributions (M_w/M_n) were measured using size exclusion chromatography (SEC). SEC analyses were performed on an Agilent 1260 Infinity setup with two PLgel 5 μm mixed D columns at 30 °C with either chloroform or THF as the mobile phase. The

DOI: 10.1021/acs.macromol.9b02236
Macromolecules XXXX, XXX, XXX−XXX

Table 1. Characterization Data of Poly(azidoalkyl glycidyl ether)s Prepared in This Study



entry	M_n (target)	M_n (NMR)[a]	M_n (SEC)	$Đ$ (SEC)	conv.[a] (%)	DP (target)	DP[a]
E1	3000	2970	2700[b]	1.13[b]	>99	20	20
E2	3700	3690	3000[b]	1.15[b]	>99	25	25
E3	7300	6700	5600[b]	1.11[b]	>99	50	46
B1	3500	3880	4000[b]	1.08[b]	>99	20	22
B2	8700	9870	7400[b]	1.09[b]	>99	50	57
B3	17,200	17,400	11000[b]	1.13[b]	>99	100	101
H1	2100	2300	3000[c]	1.10[c]	>99	10	11
H2	5100	4690	4900[c]	1.15[c]	>99	25	23
H3	7100	7520	8400[c]	1.21[c]	>99	35	36
H4	13,000	12,660	11600[c]	1.03[c]	>99	65	63

[a]Determined from ^{1}H NMR spectra of resulting polymers. [b]Number-average molecular weight (M_n) and dispersity ($Đ$) were measured by SEC in THF. [c]Number-average molecular weight (M_n) and dispersity ($Đ$) were measured by SEC in $CHCl_3$ with PMMA standard.

columns were calibrated against standard poly(methyl methacrylate) samples (Sigma-Aldrich; M_p, 500−2,700,000). FT-IR spectra were recorded on an Agilent Cary 630 FTIR spectrometer equipped with an ATR module.

Synthesis of Azidoalkyl Glycidyl Ethers. Intermediates 2-azido-1-ethanol (**1b**), 4-azido-1-butanol (**2b**), and 6-azido-1-hexanol (**3b**) were prepared using a method derived by Hawker and co-workers.[44] We describe here a two-step synthesis of azidohexyl glycidyl ether (AHGE) as a representative example.

Synthesis of Azidohexyl Glycidyl Ether (AHGE). *Synthesis of 6-Azido-1-hexanol (**3b**).* A 250 mL round-bottom flask was charged with 6-chloro-1-hexanol (**3a**) (15.0 g, 109.8 mmol), water (22.0 mL), and sodium azide (10.7 g, 164.7 mmol), and then the solution was stirred overnight under reflux conditions. The resulting solution was extracted with ethyl acetate, and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to give **3b** as a yellowish liquid (15.0 g, 98%). The crude product was used for the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.65 (t, J = 6.5 Hz, 2H), 3.27 (t, J = 6.9 Hz, 2H), 1.67−1.53 (m, 4H), 1.49−1.32 (m, J = 4.6, 3.8, 1.8 Hz, 5H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 62.66, 51.42, 32.56, 28.84, 26.56, 25.38.

Synthesis of AHGE. A 40% solution of aqueous KOH was prepared by dissolving 38.18 g of KOH in 57.27 mL of H_2O. Tetrabutylammonium hydrogensulfate ($TBAHSO_4$) (1.17 g, 3.44 mmol) and epichlorohydrin (29.96 mL, 343.85 mmol) were added to the completely dissolved KOH solution at 0 °C. The reaction mixture was stirred for 30 min, and **3b** (9.85 g, 68.77 mmol) was added slowly at 0 °C. The reaction was allowed to proceed for 18 h at room temperature, and reaction progress was monitored by thin-layer chromatography. The mixture was diluted with water and extracted with ethyl acetate (EtOAc). The organic layers were washed with brine, dried over Na_2SO_4, and evaporated to give a crude liquid. The residue was purified by column chromatography (EtOAc/Hexane, 1/3) to give the desired product as a colorless oil (7.59 g, 55%). The product was further purified by vacuum distillation over CaH_2. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.72 (dd, J = 11.5, 3.0 Hz, 1H), 3.58−3.41 (m, 2H), 3.37 (dd, J = 11.5, 5.8 Hz, 1H), 3.27 (t, J = 6.9 Hz, 2H), 3.19−3.08 (m, J = 5.8, 4.1, 2.9 Hz, 1H), 2.80 (dd, J = 5.0, 4.2 Hz, 1H), 2.61 (dd, J = 5.0, 2.7 Hz, 1H), 1.65−1.54 (m, 4H), 1.45−1.34 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 71.57, 71.45, 51.44, 50.94, 44.32, 29.61, 28.85, 26.61, 25.75. ESI-MS (m/z): $[M + Na]^+$ calcd for $C_9H_{17}N_3O_2Na$, 222.12; found, 222.04.

Synthesis of Azidoethyl Glycidyl Ether (AEGE) and Azidobutyl Glycidyl Ether (ABGE). Azidoethyl glycidyl ether (AEGE) and azidobutyl glycidyl ether (ABGE) were prepared from 2-bromo-1-ethanol (**1a**) and 4-chloro-1-butanol (**2a**), respectively, by a two-step substitution reaction, as described in the Synthesis of AHGE.

*Synthesis of 2-Azido-1-ethanol (**1b**).* 2-Azido-1-ethanol was prepared by using 2-bromo-1-ethanol (**1a**) as a starting material, according to the same procedure as described in the synthesis of **3b** in 85% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.78 (dd, J = 10.2, 5.5 Hz, 2H), 3.49−3.39 (m, 2H), 2.44 (t, J = 5.8 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 61.52, 53.59.

Synthesis of AEGE. AEGE was prepared by using 2-azido-1-ethanol (**1b**) as a starting material, according to the same procedure as described in the synthesis of AHGE in 45% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.84 (dd, J = 11.6, 2.8 Hz, 1H), 3.77−3.63 (m, 2H), 3.45 (dd, J = 11.6, 5.8 Hz, 1H), 3.41 (t, J = 5.0 Hz, 2H), 3.18 (m, 1H), 2.82 (dd, J = 5.0, 4.2 Hz, 1H), 2.65 (dd, J = 5.0, 2.7 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 71.90, 70.31, 50.90, 50.88, 44.18. ESI-MS (m/z): $[M + Na]^+$ calcd for $C_5H_9N_3O_2Na$, 166.06; found, 166.06.

*Synthesis of 4-Azido-1-butanol (**2b**).* 4-Azido-1-butanol was prepared by using distilled 4-chloro-1-butanol (**2a**) as a starting material, according to the same procedure as described in the synthesis of **3b** in 60% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.65 (t, J = 6.2 Hz, 2H), 3.32 (t, J = 6.6 Hz, 2H), 2.52 (s, 1H), 1.74−1.58 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 62.00, 51.30, 29.73, 25.39.

Synthesis of ABGE. ABGE was prepared by using 4-azido-1-butanol (**2b**) as a starting material, according to the same procedure as described in the Synthesis of AHGE in 41% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.73 (dd, J = 11.5, 2.9 Hz, 1H), 3.59−3.45 (m, 2H), 3.36 (dd, J = 11.5, 5.9 Hz, 1H), 3.33−3.27 (m, 2H), 3.13 (m, 1H), 2.79 (dd, J = 5.0, 4.2 Hz, 1H), 2.60 (dd, J = 5.1, 2.7 Hz, 1H), 1.75−1.60 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 71.45, 70.69, 51.21, 50.77, 44.09, 26.81, 25.68. ESI-MS (m/z): $[M + Na]^+$ calcd for $C_7H_{13}N_3O_2Na$, 194.09; found, 194.16.

Homopolymerization of Azidoalkyl Glycidyl Ethers. The syntheses of all the homopolymers (**E1**−**E3**, **B1**−**B3**, and **H1**−**H4**) were carried out by the Schlenk technique under Ar in flame-dried glass tubes. An exemplary synthetic protocol is described as follows.

*Homopolymerization of AHGE (**H2**).* t-BuP_4 (0.8 M in hexane, 125.5 μL, 0.1 mmol) was added to a solution of benzyl alcohol (10.39 μL, 0.1 mmol) in toluene (0.6 mL) and stirred for 30 min. AHGE (500 mg, 2.51 mmol) was then slowly added to the solution to initiate the polymerization. The reaction was monitored by ^{1}H NMR to determine residual epoxide signals and if the reaction was complete. When reaction completion was determined, an excess amount of benzoic acid was added to terminate the polymerization. The mixture

DOI: 10.1021/acs.macromol.9b02236
Macromolecules XXXX, XXX, XXX−XXX

was passed through a basic alumina pad using THF to remove *t*-BuP$_4$. The polymer solution was concentrated in vacuo to obtain poly(azidohexyl glycidyl ether), P(AHGE) (312 mg, 61%). ^{1}H NMR (**H2**) (400 MHz, $CDCl_3$): δ 7.37−7.33 (m, 5H), 4.56 (s, 2H), 3.70−3.38 (m, 161H), 3.28 (t, J = 6.9 Hz, 46H), 1.69−1.50 (m, 92H), 1.47−1.34 (m, 92H). ^{13}C NMR (**H2**) (101 MHz, $CDCl_3$): δ 79.08, 78.96, 78.82, 71.49, 71.10, 70.25, 70.01, 51.51, 29.76, 29.74, 28.97, 26.75, 25.90. $Đ$ (**H2**) (SEC, $CHCl_3$, PMMA standard) = 1.15. See the Supporting Information for ^{1}H and ^{13}C NMR spectra and SEC trace for **H2** (Table 1, Figures S1−S3).

*Homopolymerization of AEGE (**E2**).* *t*-BuP$_4$ (0.8 M in hexane, 104.7 μL, 0.08 mmol) was added to a solution of benzyl alcohol (8.68 μL, 0.08 mmol) in toluene (0.84 mL) and stirred for 30 min. AEGE (300 mg, 2.1 mmol) was then slowly added to the solution to initiate the polymerization. The reaction was monitored by ^{1}H NMR to determine residual epoxide signals and if the reaction was complete. When reaction completion was determined, an excess amount of benzoic acid was added to terminate the polymerization. The mixture was passed through a basic alumina pad using THF to remove *t*-BuP$_4$. The polymer solution was concentrated in vacuo to obtain poly(azidoethyl glycidyl ether), P(AEGE) (189 mg, 64%). ^{1}H NMR (**E2**) (400 MHz, $CDCl_3$): δ 7.39−7.28 (m, 5H), 4.54 (s, 2H), 3.78−3.49 (m, 175H), 3.42−3.29 (m, 25H). $Đ$ (**E2**) (SEC, THF, PMMA standard) = 1.15 (Table 1).

*Homopolymerization of ABGE (**B2**).* *t*-BuP$_4$ (0.8 M in hexane, 73.01 μL, 0.06 mmol) was added to a solution of benzyl alcohol (6.04 μL, 0.06 mmol) in toluene (1.2 mL) and stirred for 30 min. ABGE (500 mg, 2.92 mmol) was then slowly added to the solution to initiate the polymerization. The reaction was monitored by ^{1}H NMR to determine residual epoxide signals and if the reaction was complete. When reaction completion was determined, an excess amount of benzoic acid was added to terminate the polymerization. The mixture was passed through a basic alumina pad using THF to remove *t*-BuP$_4$. The polymer solution was concentrated in vacuo to obtain poly(azidobutyl glycidyl ether), P(ABGE) (403 mg, 68%). ^{1}H NMR (**B2**) (400 MHz, $CDCl_3$): δ 4.54 (s, 2H), 3.68−3.39 (m, 399H), 3.30 (t, J = 6.4 Hz, 114H), 1.72−1.61 (m, 228H). $Đ$ (**B2**) (SEC, THF, PMMA standard) = 1.09 (Table 1).

In Situ ^{1}H NMR Polymerization Kinetic Experiments. A mixture of benzyl alcohol (1.0 equiv) and monomer (20 equiv) in toluene-d_8 (1.0 M to the monomer) was transferred by a syringe to a conventional NMR tube sealed with a rubber septum. To the NMR tube was added *t*-BuP$_4$ (1.0 equiv), and it was shaken to homogenize the mixture before placing in the NMR spectrometer. The sample temperature was set to 27 °C, and spectra were recorded every 10 min with 16 scans for 4 or 5 h. The integrals of methylene protons of monomer (δ = 2.28 and 2.15 for AEGE, δ = 2.31 and 2.16 for ABGE, and δ = 2.32 and 2.18 for AHGE) were monitored to calculate monomer consumption, referenced to the residual signal of toluene (δ = 2.09 ppm).

Procedures for CuAAC Click Reactions. Click reactions for **H3a**, **H3b**, and **H3c** proceeded using a method derived by Hawker and co-workers.[29] A typical procedure for the click reaction for **H3a** is as follows: **H3** (80 mg, 0.39 mmol of azides, 1.0 equiv) and 5-hexyne (67.8 μL, 0.59 mmol, 1.5 equiv) were dissolved in 3 mL of THF in a 20 mL reaction tube. The solution was degassed by N_2 bubbling for 30 min. CuBr (5.59 mg, 0.039 mmol, 0.10 equiv) and *N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine (PMDETA) (8.14 μL, 0.039 mmol, 0.10 equiv) were added to the mixture, and the solution was stirred for 2 h at room temperature. Saturated ammonium chloride aqueous solution (10 mL) was added to the solution, and then the solution was extracted with dichloromethane (10 mL × 3). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under vacuum to yield 108 mg (99%) of a yellow polymer. See the Supporting Information for ^{1}H NMR spectra for **H3a**, **H3b**, and **H3c**, respectively (Figures S4−S6).

Procedures for Staudinger Reduction. Staudinger reductions for **H2a**−**H2c** and **HAm** proceeded using a method derived by Johnsson and co-workers.[45] A typical procedure for the Staudinger reduction for **H2a** is as follows: **H2** (100 mg, 0.49 mmol of azide, 1.0 equiv) was dissolved in 1 mL of THF, and the solution was degassed by N_2 bubbling for 20 min. PPh_3 (32.26 mg, 0.123 mmol, 0.25 equiv) was completely dissolved in the solution. Water (0.05 mL) was added to the mixture and stirred for 12 h at room temperature. THF was removed under reduced pressure, and 1.0 M HCl solution was added to acidify and dissolve the polymer. The mixture was washed three times with diethyl ether to remove residual triphenylphosphine (TPP) and triphenylphosphine oxide (TPPO). The aqueous phase was lyophilized to give 80 mg of a viscous polymer.

Chain Extension Experiment for Diblock Copolymer Synthesis. The synthesis of the diblock copolymer of AHGE and AGE was carried out by the Schlenk technique under Ar in flame-dried glass tubes. *t*-BuP$_4$ (0.8 M in hexane, 125.5 μL, 0.1 mmol) was added to a solution of benzyl alcohol (10.39 μL, 0.1 mmol) in toluene (1.0 mL) and stirred for 30 min. AHGE (600 mg, 3.0 mmol) was then slowly added to the solution to initiate the polymerization. The reaction was monitored by ^{1}H NMR spectroscopy to determine residual epoxide signals, and once the reaction was completed, a small aliquot of the crude P(AHGE) polymer was taken for SEC analysis. Additional allyl glycidyl ether (AGE) (343.5 mg, 3.01 mmol) was added to the reaction mixture, and the reaction was monitored by ^{1}H NMR to determine residual epoxide signals. When the reaction was determined to be complete, an excess amount of benzoic acid was added to terminate the polymerization. The mixture was passed through a basic alumina pad using THF to remove *t*-BuP$_4$. The polymer solution was concentrated in vacuo to obtain P(AHGE)-*b*-P(AGE) (480 mg). A small aliquot of the crude block copolymer was taken for NMR and SEC analysis to determine the degree of polymerization of each monomer ($M_{n,NMR}$: 10360; M_w/M_n: 1.09; DP_{NMR}: AHGE/AGE = 32/34).

Copolymerization of AHGE and AGE. The synthesis of a statistical copolymer of AHGE and AGE was carried out by the Schlenk technique under Ar in flame-dried glass tubes. *t*-BuP$_4$ (0.8 M in hexane, 375 μL, 0.3 mmol) was added to a solution of benzyl alcohol (31 μL, 0.3 mmol) in toluene (2.4 mL) and stirred for 30 min. A premixed liquid of AHGE (600 mg, 3.0 mmol) and AGE (342 mg, 3.0 mmol) was then slowly added to the solution to initiate the polymerization. The reaction was monitored by ^{1}H NMR to determine residual epoxide signals. When the reaction was determined to be complete, an excess amount of benzoic acid was added to terminate the polymerization. The mixture was passed through a basic alumina pad using THF to remove *t*-BuP$_4$. The polymer solution was concentrated in vacuo to obtain P(AHGE-*co*-AGE) (630 mg). The degree of polymerization of each monomer was determined by ^{1}H NMR analysis ($M_{n,NMR}$: 3330; M_w/M_n: 1.10; DP_{NMR}: AHGE/AGE = 11/9).

Copolymerization Kinetics of AHGE and AGE. A mixture of benzyl alcohol (1.0 equiv) and AHGE and AGE (20 equiv each) in toluene-d_8 (2.5 M to the total amount of monomers) was transferred by a syringe to a conventional NMR tube sealed with a rubber septum. To the NMR tube was added *t*-BuP$_4$ (1.0 equiv), and it was shaken to homogenize the mixture before placing in the NMR spectrometer. The sample temperature was set to 27 °C, and the first spectrum was recorded 21 min after *t*-BuP$_4$ was added and continuously recorded every 16 min with 256 scans for 6 h by an inverse-gated ^{13}C mode. The integrals of methine carbon of each monomer (δ = 50.77 ppm for AHGE and δ = 50.64 ppm for AGE) were monitored to calculate monomer conversion, referenced to the residual signal of toluene (δ = 20.40 ppm).

Orthogonal Functionalization of P(AHGE-*co*-AGE). *CuAAC of Azide Moieties with Phenylacetylene (**H5**).* The CuAAC of P(AHGE-*co*-AGE) was performed by using CuBr and PMDETA in THF as described above for **H3b**. P(AHGE-*co*-AGE) (50 mg, 0.16 mmol of azide, 1.0 equiv) and phenylacetylene (26.3 μL, 0.24 mmol, 1.5 equiv) were dissolved in 1.5 mL of THF in a 10 mL reaction tube. The solution was degassed by N_2 bubbling for 30 min. CuBr (2.3 mg, 0.016 mmol, 0.10 equiv) and PMDETA (3.3 μL, 0.016 mmol, 0.10 equiv) were added to the mixture, and the solution was stirred for 2 h at room temperature. An aqueous solution of saturated ammonium chloride (8 mL) was added to the solution, and the resulting mixture

DOI: 10.1021/acs.macromol.9b02236
Macromolecules XXXX, XXX, XXX−XXX

was extracted with dichloromethane (10 mL × 3). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under vacuum to yield 70 mg of a yellow polymer.

*Thiol−Ene Addition of Allyl Moieties with Thioacetic Acid (**H6**).* Thiol−ene addition of **H5** by using thioacetic acid and 2,2-dimethoxy-2-phenylacetophenone (DMPA) under UV irradiation to give **H6** was proceeded using a method derived by Hawker and co-workers.[34] **H5** (30 mg, 86 μmol of alkene, 1.0 equiv), thioacetic acid (12.3 μL, 4.3 μmol, 0.05 equiv), and DMPA (1.1 mg, 172 μmol, 2.0 equiv) were dissolved in 1.0 mL of THF in a 10 mL reaction tube. The solution was degassed by N_2 bubbling for 30 min. The reaction mixture was stirred under UV light (λ = 365 nm) for 4 h. The reaction was monitored by ^{1}H NMR to determine the complete disappearance of the alkene peaks at 5.22 and 5.91 ppm. The reaction mixture was precipitated in hexane and recovered by dissolving in chloroform. The organic layer was concentrated under vacuum to yield 25 mg of a dark yellow polymer.

RESULTS AND DISCUSSION

Design and Synthesis of Azide-Functionalized Glycidyl Ethers. The simplest glycidyl monomer containing azide functionality for the synthesis of polyethers with multiple azides is glycidyl azide (GA). Initially, we prepared GA as a monomer to demonstrate the versatility of azide-functional polyethers. However, the direct polymerization of simple glycidyl azide under organic superbase-catalyzed highly basic AROP condition was found to suffer from side reactions, such as elimination, in agreement with the previous report (Figure 1a and Figure S7).[46] In this regard, the synthesis of azide-functionalized polyethers has been achieved by the post-polymerization of polyepichlorohydrin that can be converted to the poly(glycidyl azide).[22] Feng et al. recently introduced the direct polymerization of glycidyl azide under the monomer-activated AROP condition only in the presence of an excess amount of triethyl borane.[47] In general, the hydrogens on the β-carbon of the epoxide monomer exhibit a different acidic character in relation to the type of the substituents. Thus, we designed several azide-functional glycidyl ether monomers possessing different lengths of alkyl spacers to avoid such side reactions wherein the alkyl chain and ether linkage reduce the acidity of the β-protons (Figure 1b).

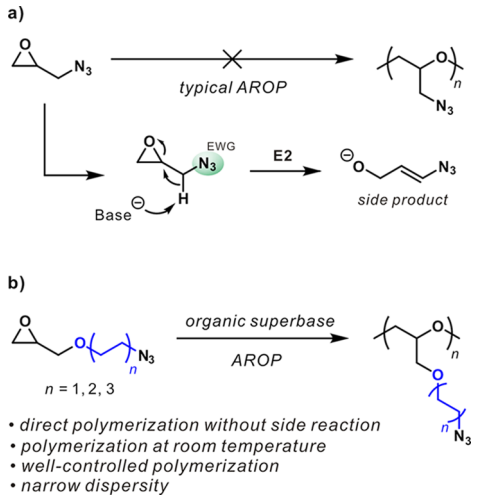


Figure 1. (a) Typical anionic ring-opening polymerization of glycidyl azide suffers from elimination side product. (b) Direct synthesis of azide-functionalized polyethers using a series of azidoalkyl glycidyl ethers.

The AEGE, ABGE, and AHGE monomers were prepared by a two-step reaction from corresponding haloalkanols (Scheme 2). The substitution reaction of haloalkanol with sodium azide under aqueous conditions yielded the azide-functionalized alcohol, which was subsequently coupled with epichlorohydrin to afford AEGE, ABGE, and AHGE after column chromatography purification. Various characterizations including ^{1}H and ^{13}C NMR, ^{1}H−^{1}H correlation spectroscopy (COSY), and ESI-MS supported the successful synthesis of azidoalkyl glycidyl ethers (Figures S8−S24).

Polymerization of Azidoalkyl Glycidyl Ethers. Organic superbase *t*-BuP_4-catalyzed AROP of AEGE, ABGE, and AHGE were conducted using benzyl alcohol as an initiator in toluene at room temperature (Table 1). We employed a commercially available metal-free organic phosphazene as a base due to its high basicity and, most importantly, its facile polymerization at room temperature.[48] For AHGE, monomer conversion was monitored by ^{1}H NMR spectroscopy by observing the reduction of methine and methylene signals of the epoxides at 3.15, 2.80, and 2.60 ppm (Figure 2a). The

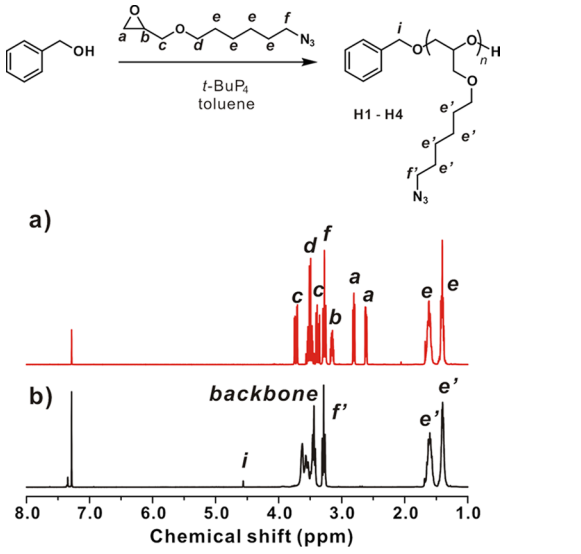
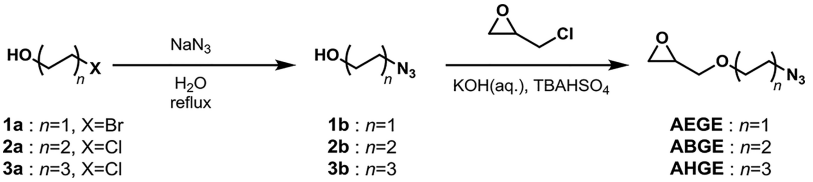


Figure 2. Synthesis of P(AHGE)s by AROP. Representative ^{1}H NMR spectra of (a) AHGE monomer and (b) P(AHGE) (**H4**) in $CDCl_3$ at 25 °C.

Scheme 2. Synthesis of Azidoalkyl Glycidyl Ether Monomers



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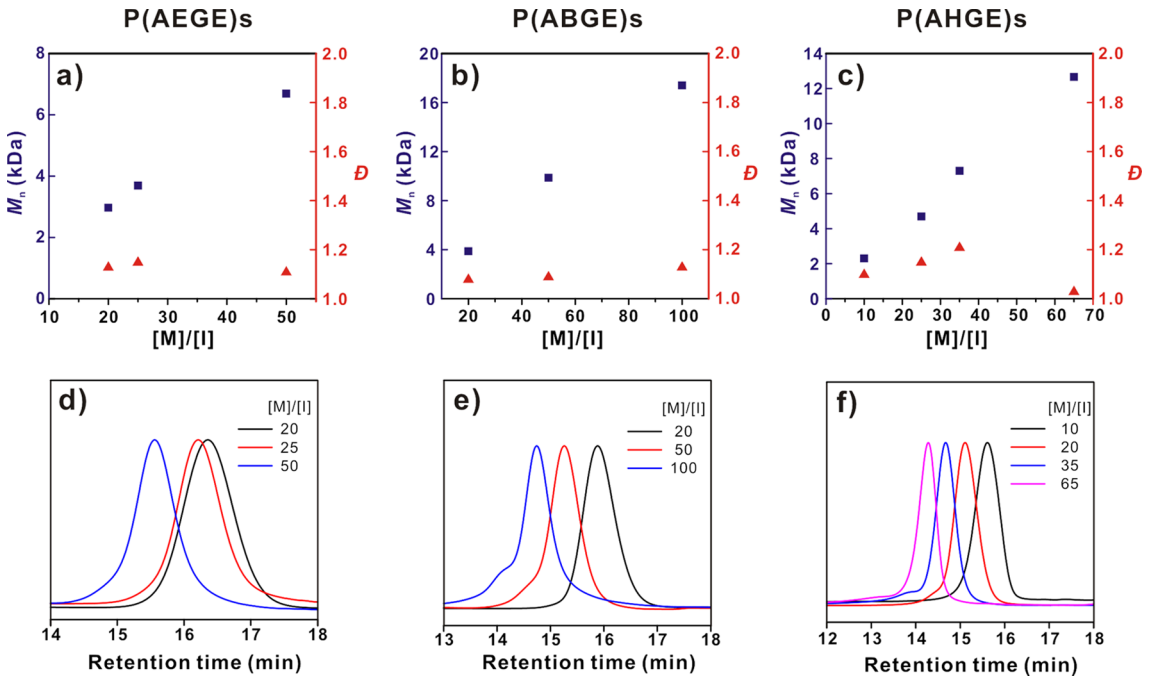

Figure 3. Demonstration of controlled AROP of azidoalkyl glycidyl ethers. (a–c) M_n and $Đ$ of (a) P(AEGE)s, (b) P(ABGE)s, and (c) P(AHGE)s at various monomer-to-initiator ratios, [M]/[I]. (d–f) SEC chromatograms of (d) P(AEGE)s, (e) P(ABGE)s, and (f) P(AHGE)s.

AROP of AHGE (**H4**) proceeded successfully, achieving 99% conversion within 10 h. When the monomer was completely consumed, as evidenced by ^{1}H NMR, the polymerization was quenched by the addition of benzoic acid to protonate the chain end. Filtration through a short pad of basic aluminum oxide was used to remove phosphazene salts. Successful removal of *t*-BuP_4 was confirmed by completely disappeared ^{1}H NMR signals at 2.66 ppm (Figure 2b and Figure S25). According to ^{1}H NMR and FT-IR analyses, the azide groups remained intact after polymerization (Figure S26).

Following this result, we evaluated the stability of the azide group under the polymerization condition. We first prepared a model compound, 1-azido-6-methoxyhexane, to exclude ring opening of epoxide by the nucleophilic attack from alkoxide species. Surprisingly, treatment of 1-azido-6-methoxyhexane (20 equiv) with *t*-BuP_4 (1.0 equiv) in the presence of benzyl alcohol (1.0 equiv) in toluene at room temperature did not result in any changes in the model compound for 3 days (Figure S27 and Table S1). The inertness of the azide group under the AROP condition highlights the compatibility of azidoalkyl glycidyl ether monomers and thus provides the potential to expand the functional polyether platform by attachment of azide moieties in the designer monomer.

We also conducted AROP of AEGE and ABGE under identical reaction conditions, and the resulting polymers were characterized by ^{1}H NMR analysis (Figures S28 and S29). The molecular weights of the homopolymers of AEGE, ABGE, and AHGE (**E1–E3**, **B1–B3**, and **H1–H4**) were well controlled in the range of 2300–17,400 g/mol by adjusting the ratio of monomer to initiator as verified by ^{1}H NMR spectroscopy (Table 1 and Figure 3). Moreover, the azide-functionalized homopolymers exhibited a narrow dispersity ($Đ$) ranging from 1.03 to 1.21, as confirmed by size exclusion chromatography (SEC) (Table 1 and Figure 3). The small shoulder peak observed in the higher molecular weight region possibly originates from chain transfer reactions during anionic polymerization.[47] In general, AROP of certain glycidyl ether monomers is accompanied by a chain transfer reaction due to the abstraction of methylene proton adjacent to the epoxide ring by actively propagating chain end, leading to the formation of allyl alkoxide, which can serve as new initiating species. This phenomenon has been observed in the previous literature for the polymerization of phenyl glycidyl ether, propylene oxide, and ethoxyethyl glycidyl ether.[49,50] Furthermore, monomer purity is another critical consideration in the chain transfer reaction as reported by Lynd group.[33] According to the proven stability of 1-azido-6-methoxyhexane, we assume that the chain transfer is probably not originated from the azide functionality.

In Situ ^{1}H NMR Polymerization Kinetic Study. The homopolymerizations of AEGE, ABGE, and AHGE were investigated by in situ ^{1}H NMR kinetic studies to evaluate the living characteristics and the effect of the monomer structure. The polymerizations were conducted at a monomer concentration of 1.0 M in deuterated toluene. The signals of methylene protons of the monomers were monitored to observe monomer conversion by calculating the integration value in reference to the residual signal of toluene (δ = 2.09 ppm), which remained constant during polymerization (Figures S30–S32). The linear correlation between $\ln([M]_0/[M]_t)$ and the reaction time supported the successful living characteristics of the polymerization of azidoalkyl glycidyl ethers (Figure 4). Interestingly, the kinetic plots obtained by different monomers indicated the increasing order of AHGE, ABGE, and AEGE for the polymerization rate. As the only difference between monomers is the length of alkyl spacer, thus the faster polymerization rate of AEGE can be attributed to the shorter alkyl spacer and larger polarity among three monomers. On the other hand, the longer AHGE monomer showed a lower polymerization rate possibly due to the steric effect of the alkyl chain that might disturb the propagating chain end. Moreover, to explore a correlation between monomer

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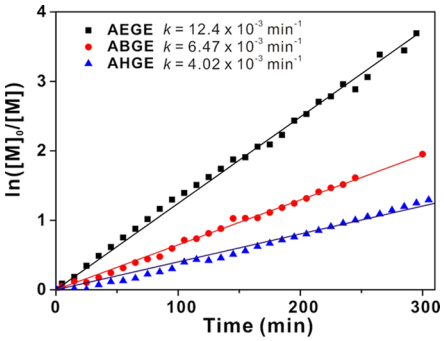

Figure 4. First-order kinetic plots of $\ln([M]_0/[M]_t)$ vs time for the polymerization of AEGE (black square), ABGE (red circle), and AHGE (blue triangle) monomers targeting a degree of polymerization of 20.

hydrophobicity and the polymerization rate, we calculated the octanol/water coefficient (log P) of the monomers using the computational software ALOGPS 2.1 (Table S2).[51,52] The hydrophobicity increased as the length of alkyl spacer increased as expected. Coincidentally, we found that the polymerization rate is inversely proportional to the hydrophobicity of monomer (Figure S33).

Copper-Catalyzed Azide−Alkyne Cycloaddition of P(AHGE). Having synthesized the desired P(AHGE) homopolymers, the potential post-polymerization modification of the pendant azide moieties via CuAAC was demonstrated by the reaction with 1-hexyne, phenylacetylene, and 5-hexyn-1-ol to give the functional polyethers **H3a**, **H3b**, and **H3c**, respectively (Figure 5). ^{1}H NMR confirmed the successful

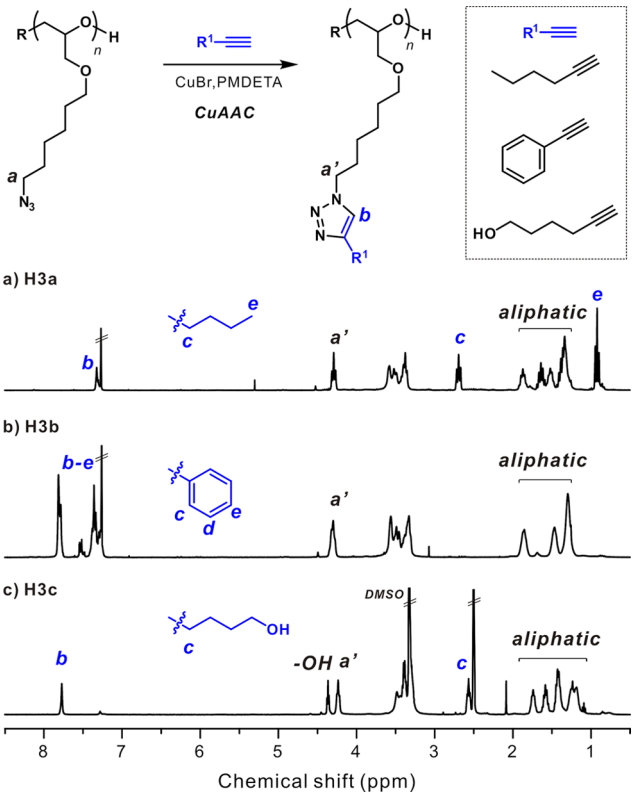

Figure 5. Post-polymerization modification of **H3** via CuAAC with various alkynes. (a−c) ^{1}H NMR spectra after CuAAC of **H3** with (a) 1-hexyne, (b) phenylacetylene, and (c) 5-hexyn-1-ol.

transformation of pendant azide groups into alkyl, phenyl, and hydroxyl functionalities (Figure 5a−c). The protons adjacent to the azide, corresponding to the peak at 3.26 ppm (Figure 2b, peak f′), clearly disappeared, whereas the peak around 4.30 ppm (Figure 5, peak a′) appeared after CuAAC due to the inductive electron-withdrawing character of triazole.[53] The characteristic peak of the triazole proton (Figure 5, peak b) was observed, presenting a clear evidence supporting the successful formation of the triazole group by CuAAC. To further confirm the successful click reaction, FT-IR analysis was conducted (Figure S34). The FT-IR spectra revealed that the characteristic azide peak at 2088 cm^{-1} for **H3** clearly disappeared after the click reactions, in accordance with the ^{1}H NMR analysis.

Staudinger Reduction of P(AHGE). Investigations of the synthesis of the polyethers having pendant primary amine groups along the polymer backbones are limited. Satoh and coworkers demonstrated the synthesis of primary amine-functionalized polyether by t-BuP$_4$-catalyzed AROP of dibenzyl protected monomer, followed by subsequent hydrogenation.[54] Frey and Herzberger reported polymerization by monomer activation of epicyanohydrin that can be converted to amine-functional PEG.[23] However, the drawback of both approaches is a time-consuming deprotection step after polymerization. Alternatively, the Staudinger reduction of azide-functional polyethers can yield pendant amines from the presented azides in this study. We demonstrated Staudinger reduction of **H2** as a representative example (Figure 6). The reaction of **H2** with triphenylphosphine (TPP) and water in THF under ambient conditions resulted in the successfully reduced product, **HAm**, within 12 h. Moreover, the degree of reduction was controlled by the equivalency of TPP used during the reduction to afford polyethers with varying ratios of amine relative to azide, yielding orthogonal pendant groups for post-polymerization modification (**H2a−H2c**). As the equivalency of TPP was increased, the reduced amine to the unreacted azide ratio also increased, correlating well to the relative peak integrations determined by ^{1}H NMR (Figure 6a and Figures S35−S38). FT-IR analyses displayed the disappearance of the characteristic azide peak at 2088 cm^{-1}, providing further evidence supporting the successful reduction (Figure 6b).

Copolymerization of AHGE and AGE. As previously mentioned, AGE is by far the most widely used functional epoxide monomer for post-polymerization modification in polyethers. Thus, we demonstrated the copolymerization of AHGE with AGE to impart a second orthogonal functionality to facilitate further modification. First, the one-pot sequential addition of AGE after the polymerization of P(AHGE) was performed to obtain P(AHGE)-*b*-P(AGE) (Figure 7). The complete shift of the SEC traces to the higher molecular weight diblock copolymer P(AHGE)-*b*-P(AGE) was observed, without the presence of the unreacted chain end of P(AHGE) (Figure 7a). This observation supports the livingness of the propagating chain end of P(AHGE)s. The complete consumption of AGE yielded a well-defined P(AHGE)-*b*-P(AGE), as evidenced by ^{1}H NMR spectrum (Figure S39).

Furthermore, a well-defined statistical copolymer, P(AHGE-*co*-AGE), was prepared by taking advantage of the living character of AROP with the use of two monomers in a one-pot reaction (Figure 7). The molecular weight and the degree of polymerization of each monomer were characterized by SEC and ^{1}H NMR (Figure 7b and Figure S40). As shown in Figure S33, the characteristic allyl peaks at 5.22 and 5.91 ppm (peaks

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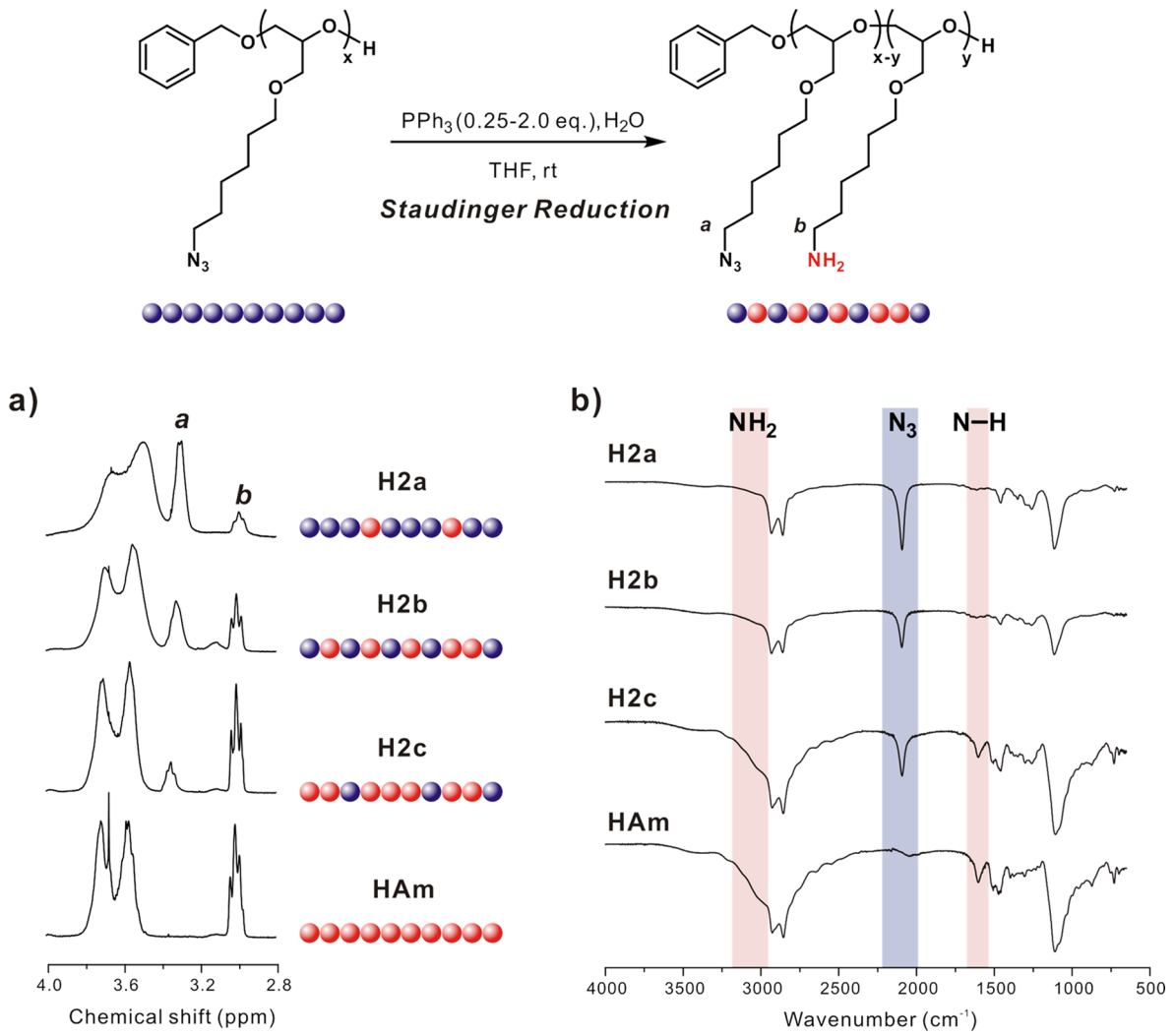

Figure 6. Staudinger reduction of **H2**. (a) ^{1}H NMR spectra of partially reduced polymers (**H2a**–**H2c**) and fully reduced polymer (**HAm**) in D_2O. (b) FT-IR spectra of **H2a**–**H2c** and **HAm**.

b and c) were observed along with the peak corresponding to the proton adjacent to the azide (peak a), indicating successful incorporation of both monomers. Allyl groups often show a tendency toward isomerization under potassium alkoxide base-catalyzed polymerization conditions at high temperature;[28] however, no isomerized alkenes were observed under the organic superbase-catalyzed AROP conditions due to the relatively low reaction temperature. The polymerization of both block and statistical copolymers were conducted in a controlled manner, exhibiting minor deviations from the targeted monomer ratio (Table S3).

To determine the reactivity ratios of AHGE and AGE, we monitored the copolymerization using in situ ^{13}C NMR spectroscopy with inverse-gated decoupling (Figure 8). The copolymerization of AHGE and AGE at a total concentration of 2.5 M in toluene-d_8 was performed in the NMR tube at 27 °C. Both monomer conversions and total conversion as a function of time were measured, and the reactivity ratios of AHGE and AGE were obtained based on the nonterminal model.[55] The methine peaks of AHGE (peak a, 50.77 ppm) and AGE (peak b, 50.64 ppm) were integrated to calculate the monomer conversion using the toluene peak (20.40 ppm) as an internal standard (Figure 8a). The plot of total conversion against monomer conversion was presented to determine reactivity ratios for the pair of monomers: $r_{AHGE} = 0.77 \pm 0.01$ and $r_{AGE} = 1.31 \pm 0.02$ (Figure 8b). As shown in Figure 8b, the copolymerization of AHGE and AGE tends to yield a random statistical microstructure ($r_{AHGE} \times r_{AGE} = 1.01 \pm 0.02$) of the resulting copolymer. A slightly lower reactivity of AHGE compared to AGE is possibly originated from the steric effect of the longer alkyl chain.

Orthogonal Modification of P(AHGE-*co*-AGE). Finally, we demonstrated two selective sequential reactions utilizing the orthogonal azide and allyl functionalities of the copolymer. Using the conditions, we established that for the CuAAC of P(AHGE), the copolymer was first derivatized via the click reaction with phenylacetylene and then was subsequently modified by thiol–ene addition (Figure 9). ^{1}H NMR spectroscopy was used to verify the success of the CuAAC reaction by observing the large downshift of the peak corresponding to the methylene unit adjacent to the azide from 3.26 to 4.3 ppm (Figure 9a, peaks a and a′). The characteristic peaks corresponding to the allyl group (Figure 9a, peaks b–d) were not shifted, suggesting that the orthogonality of CuAAC leaves the allyl groups intact for subsequent modification by thiol–ene addition. To modify the allyl moieties, thiol–ene addition, using thioacetic acid and photoinitiator, proceeded in THF under UV irradiation. ^{1}H

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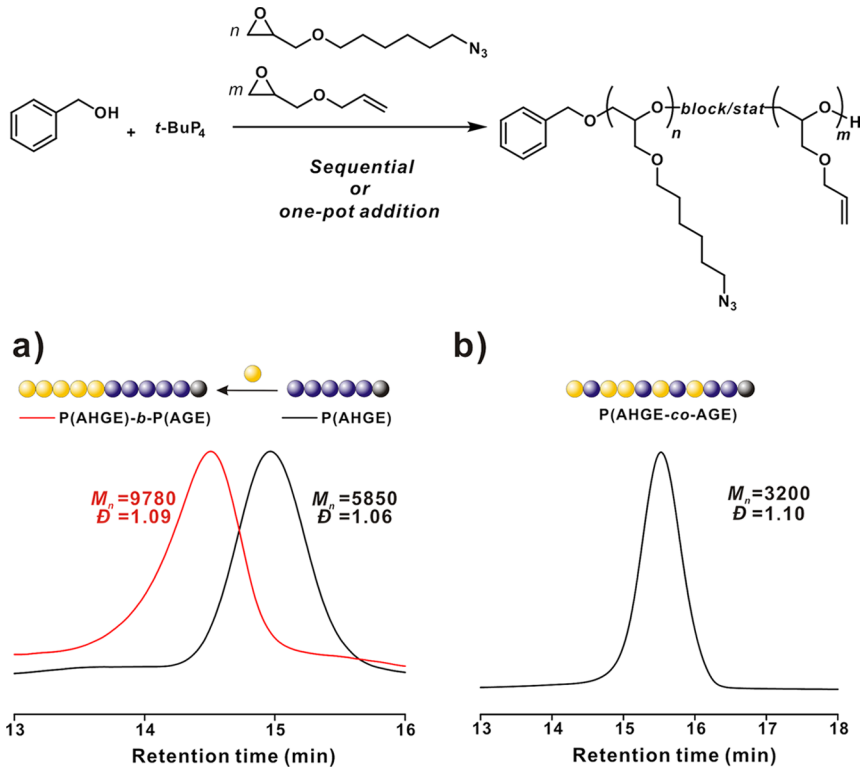

Figure 7. Synthesis of P(AHGE)-*b*-P(AGE) or P(AHGE-*co*-AGE) by sequential or one-pot monomer addition, respectively. SEC chromatograms of (a) P(AHGE) (black) and P(AHGE)-*b*-P(AGE) (red) and (b) P(AHGE-*co*-AGE) measured in $CHCl_3$.

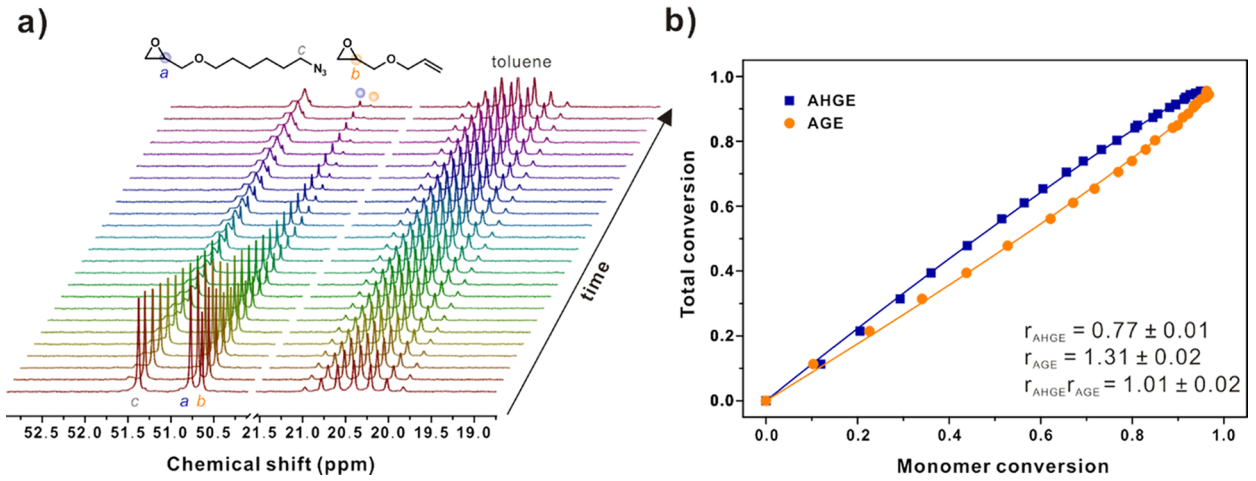

Figure 8. (a) Time-resolved ^{13}C NMR spectra of copolymerization of AHGE and AGE in toluene-d_8 under polymerization conditions. (b) Total polymerization conversion versus monomer conversion for the copolymerization of AHGE (blue square) and AGE (orange circle). The initial compositions: n_{AHGE} = 0.58 and n_{AGE} = 0.42.

NMR observation of the complete disappearance of the signals corresponding to the allyl group and the appearance of the new signal at 2.29 ppm (peak f) corresponding to the methyl group of the thioester confirmed the successful functionalization of the allyl groups.

FT-IR analysis indicated the smooth progress of the sequential reactions, evidenced by the disappearance of the band corresponding to the azide (2088 cm^{-1}) and the appearance of a new band at 1691 cm^{-1} corresponding to the thioester group (Figure 9b). These results suggested that azide and alkene can be orthogonally functionalized without any cross-reactivity. There are many reports demonstrating multifunctional polyethers;[19] however, synthesis and post-polymerization modification of polyethers with both azide and alkene pendant groups along the polymer backbone have not been introduced to date. These systems present a unique avenue for orthogonal post-polymerization modification, which is the subject of our ongoing research endeavor.

CONCLUSIONS

In conclusion, a series of azide-functionalized glycidyl monomers with different alkyl spacers have been introduced, including AEGE, ABGE, and AHGE. Interestingly, azide moieties of azidoalkyl glycidyl ethers were intact under the highly basic AROP condition, which were not in the case of

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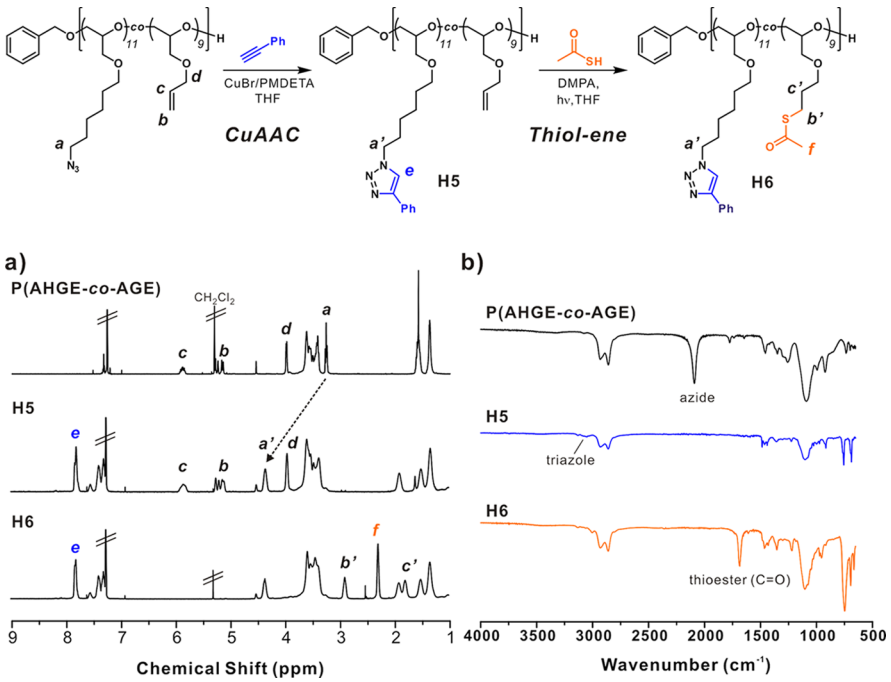

Figure 9. Orthogonal modification of P(AHGE-*co*-AGE) via sequential CuAAC and thiol−ene addition. (a) ^{1}H NMR and (b) FT-IR spectra of P(AHGE-*co*-AGE), **H5**, and **H6**.

glycidyl azide. The investigation on polymerization kinetics of the monomers revealed that the AEGE shows a much faster reaction rate than those of ABGE and AHGE. Using AHGE as a model monomer, versatile multifunctional polyethers were synthesized and primed for post-polymerization modification. Azide pendant groups appended to the polyether backbone enable diverse chemical modification to afford a variety of functionalities via CuAAC and Staudinger reduction. Copolymerization with other epoxide monomers, such as AGE, was used to access a variety of combinations of orthogonal functionalities. The introduction of the azide-functionalized epoxide monomer further diversifies the library of functional epoxide monomers, increasing the potential to develop new multifunctional polyethers.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.macromol.9b02236.

Additional experimental procedures, ^{1}H and ^{13}C NMR, FT-IR, ESI-MS, and SEC data (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the National Research Foundation of Korea (NRF-2017R1A2B3012148 and NRF-2018R1A5A1025208).

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