

Self-Immolative Polymers from Bio-based Monomers via Thiol-Ene Click Chemistry

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ABSTRACT: The use of bio-based polymers is a promising approach to reduce reliance on petrochemicals. In addition, depolymerization is attracting significant attention for the breakdown of polymers at their end-of-life or to achieve specific stimuli-responsive functions. However, the design of polymers incorporating both of these features remains a challenge. Herein, we report a new class of self-immolative polymers based on lignin-derived aldehydes via thiol-ene click polymerization. These polymers can be further used in polymer-polymer coupling to access block copolymers. Moreover, diverse responsive end-caps can be introduced through post-polymerization functionalization from a single polymer precursor. These bio-based self-immolative polymers undergo cascade degradation in response to specific stimuli through alternating 1,6-elimination and cyclization reactions.

Synthetic polymers with extraordinary properties shape our modern life.¹ However, the current production of polymers, mostly derived from fossil resources, follows an unsustainable model, overlooking their adverse outcomes and their end-of-life fate.^{2,3} An immense and growing accumulation of polymer waste is leading to a global plastic pollution crisis, presenting serious health and environmental concerns.^{4,5} While enhanced waste management and recycling can contribute to addressing these pressing challenges, the development of bio-based sustainable polymers derived from renewable resources with intrinsically embedded degradability can also play a crucial role.⁶⁻⁸ Carefully designed degradable polymers have been developed for advanced applications, such as controlled drug delivery, tissue engineering, and chemical recycling.⁹⁻¹¹ To this end, the creation of bio-based polymers whose degradation can be selectively activated by external stimuli is of great significance.¹²⁻¹⁷

Over the past couple of decades, self-immolative polymers (SIPs) that undergo end-to-end depolymerization in response to specific stimuli, have been gaining increasing attention.¹⁸⁻²² Due to their selective and amplified responses to stimuli, SIPs are currently recognized as an emerging class of materials for a range of applications such as sensing,^{18,23} nanolithography,^{24,25} controlled release,²⁶⁻²⁹ and recyclable plastics.^{20,30} Current syntheses of SIPs rely on either step-growth polymerization of precursors containing self-immolative spacers (Figure 1a) or chain-growth polymerization to obtain backbones with low ceiling temperature.^{20,22} With the exception of a recent report from our group,³¹ end-capping has typically been performed *in situ*. Both synthetic approaches involve non-ambient conditions (i.e., high or ultralow temperature), moisture sensitivity, and difficulty in modular end-functionalization.^{20,22} Moreover, the step-growth approach generally necessitates the use of protecting or activating groups within the monomers and thus generates side products, compromising atom economy (Figure 1a).^{20,22} Therefore, it is highly desirable to develop highly efficient strategies to readily access functionalizable SIPs under ambient conditions.

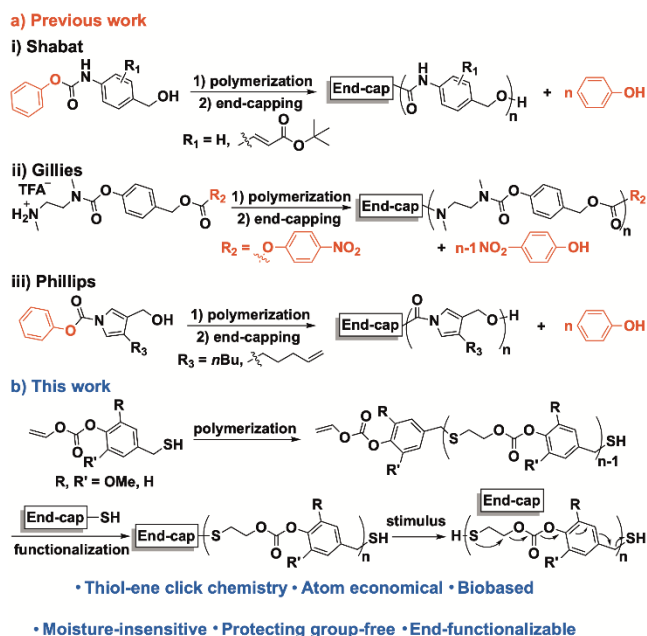
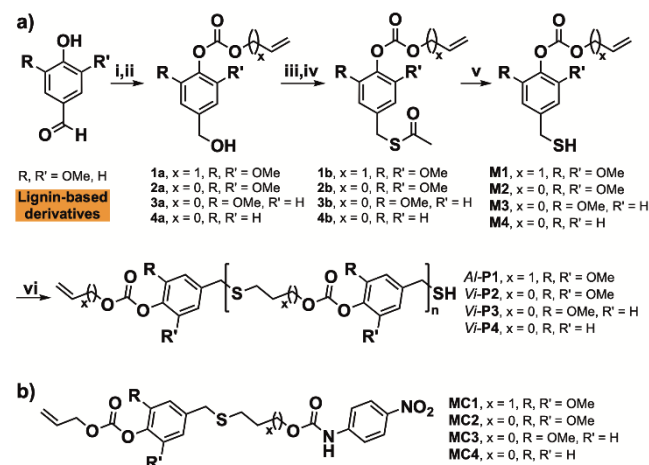


Figure 1. (a) Construction of previously reported SIPs via step-growth polymerization and *in situ* end-capping; (b) bio-based SIPs via thiol-ene click polymerization and post-polymerization thiol-ene functionalization with varying end-caps in this work. After end-cap removal, depolymerization occurs by an alternating 1,6-elimination and cyclization cascade.

The radical-mediated thiol-ene addition reaction has emerged as a versatile click process for surface and polymer functionalization,³² polymer and network synthesis,³³⁻³⁵ and the formation of complex materials and bioconjugates.³⁶⁻³⁸ For example, Hawker et al. described the synthesis of dendrimers using thiol-ene click chemistry to construct the backbone and functionalize the peripheral groups.³⁹ Additionally, polythioethers were effectively constructed via thiol-ene click polyaddition of α,ω -alkylene thiols.⁴⁰⁻⁴² Motivated by these

designs and recent reports on self-immolative elimination to generate thiols,⁴³⁻⁴⁵ we report the synthesis of bio-based SIPs with varying stimuli-sensitive end-caps via thiol-ene click chemistry (Figure 1b). These SIPs exhibit selective depolymerization upon stimuli-mediated end-cap removal.

Scheme 1. (a) Syntheses of monomers M1-M4 and their corresponding polymers^a and (b) Structures of model compounds MC1-MC4.



^a Reagents and conditions: (i) allyl chloroformate or vinyl chloroformate, Et₃N, THF; (ii) NaBH₄, MeOH; (iii) MsCl, Et₃N, THF; (iv) KSAC, acetone; (v) HCl, MeOH, reflux; (vi) DMPA (5 mol%), solvent, UV light.

First, a polymer based on lignin-derived syringaldehyde was prepared, with a three-carbon spacer between the thioether and carbonate. A bifunctional monomer, **M1** with allyloxycarbonyl (Al) and benzyl thiol moieties was synthesized (Scheme 1). Then, UV-actuated thiol-ene polymerization in the presence of photoinitiator 2,2-dimethoxy-2-phenylacetophenone (DMPA) was conducted to generate polymer **Al-P1**, whose chemical structure was confirmed using ¹H and ¹³C NMR spectroscopy (Figure 2a; Figures S9,S10). Size exclusion chromatography (SEC) in THF showed a number average molar mass (*M_n*) of ~5.8 kg/mol and a dispersity (*Đ*) of 2.84, typical for a step-growth polymerization (Figure 2b and Table 1). The high thiol end-group fidelity for **Al-P1** was verified by the successful polymer-polymer coupling with acrylate-terminated poly(ethylene glycol) (PEG-Acrylate) through thiol-Michael addition click reaction⁴⁶ to afford **Al-P1-b-PEG** (Figure 2b; Figure S14).

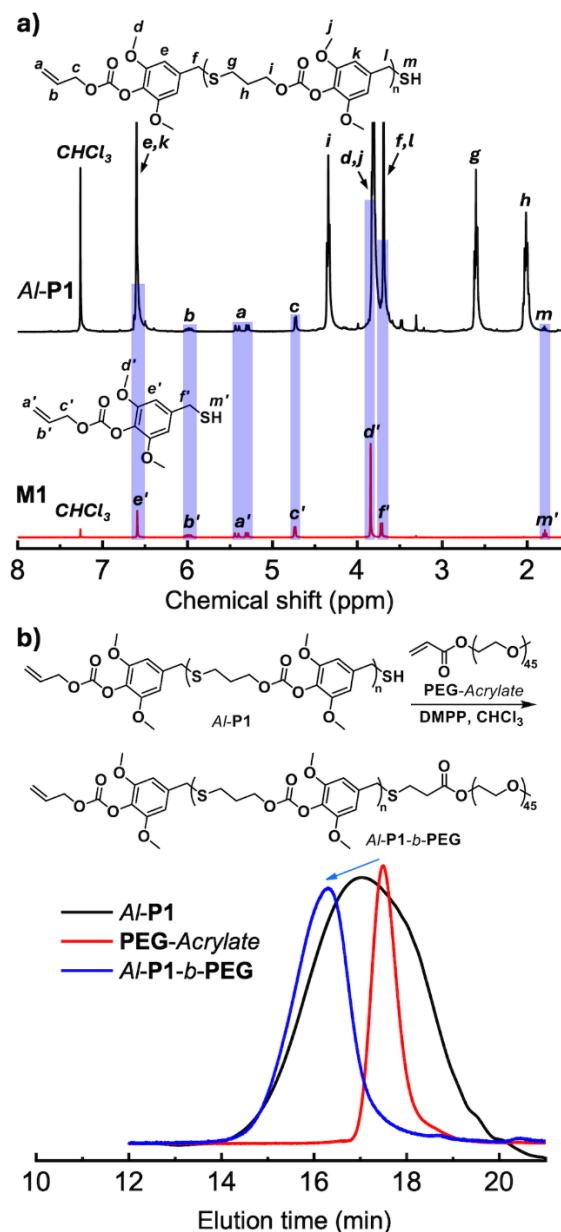


Figure 2. (a) Stacked ¹H NMR spectra of monomer **M1** and **Al-P1**. (b) Thiol-Michael addition click reaction between **Al-P1** and **PEG-Acrylate** afforded block copolymer **Al-P1-b-PEG**.

Table 1. Reaction conditions and molar mass data for thiol-ene polymerizations of M1 – M4^a

Entry	Monomer	Solvent	[M] ₀ (mol/L)	Time (h)	Polymer	<i>M_n</i> (kg/mol) ^b	<i>Đ</i> ^b
1	M1	CHCl ₃	2.0	1	Al-P1	5.8	2.84
2	M2	THF	1.0	4	Vi-P2_a	9.7	3.43
3	M2	MeCN	1.0	4	Vi-P2_b	5.9	2.44
4	M2	DMSO	1.0	4	Vi-P2_c	4.1	2.41
5	M2	THF	2.0	4	Vi-P2_d	10.3	3.26
6	M3	THF	1.0	4	Vi-P3	7.7	5.20
7	M4	THF	1.0	4	Vi-P4	IS ^c	/

^a DMPA was used as an initiator (5 mol% relative to monomer) under UV light at 25 °C. ^b Determined by THF SEC calibrated using poly(methyl methacrylate) (PMMA) standards. ^c IS denotes insoluble.

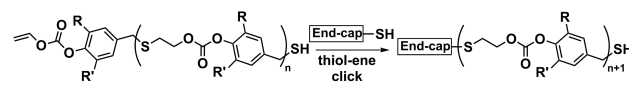
With both **Al-P1** and **Al-P1-b-PEG** in hand, their degradation profiles were evaluated upon end-cap cleavage of the allyloxycarbonyl with tetrakis(triphenylphosphine)palladium(0) (Pd(0)) under different conditions in the presence of *N*-methylaniline (NMA) as the allyl group scavenger⁴⁷ and the base 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to promote the deprotonation of generated thiol moieties. Note that nucleophilic NMA can also trap the reactive quinone methides generated during 1,6-elimination. However, the degradation of these polymers discontinued after removal of *Al* and only one 1,6-elimination with generation of one new thiol moiety, as revealed by ¹H NMR spectroscopy, regardless of the conditions (i.e., different fractions of D₂O in DMSO-*d*₆; Figures S15-S19). These results indicated that the cyclization reaction of the thiol group on the carbonate to obtain a six-membered ring product was unfavorable,⁴⁸ impeding further depolymerization. Motivated by this observation and previous reports on self-immolative linkers,^{48, 49} we synthesized small molecule model compounds with two- and three-carbon spacers between sulfur and the carbonyl group (Scheme 1b) to elucidate the effect of spacer length on the cyclization reaction.

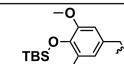
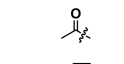
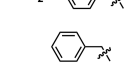
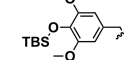
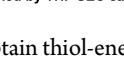
Model compounds **MC1** and **MC2** with three- and two-carbon spacers between sulfur and carbonyl moiety, respectively, were synthesized (Schemes 1b, S3; note: 4-nitrophenyl carbamate is more stable than 4-nitrophenyl carbonate, which allows monitoring of the degradation using NMR spectroscopy). When **MC1** was subjected to Pd(0) in the presence of NMA and DBU, only the thiol intermediate was formed without generating reporter molecule 4-nitroaniline, even 7 days (Figure S28). In contrast, **MC2** showed complete degradation, generating 4-nitroaniline quantitatively after 24 h under identical conditions (Figure S30). These results confirmed that the spacer length determines the propensity of cyclization and that the elimination-cyclization sequence proceeded efficiently for **MC2**. Cyclization presumably occurs much more rapidly with the two-carbon spacer due to the formation of the three-membered thiirane, in agreement with previous work (Scheme S10).⁴⁸ Encouraged by these results, two additional model compounds **MC3** and **MC4** from lignin-derived vanillin and 4-hydroxybenzaldehyde, respectively, were prepared to probe the electronic effects on the elimination reactions (Schemes 1b, S4). The relative rates of liberation of 4-nitroaniline after Pd(0) triggering followed the order **MC2**>**MC3**>**MC4** (Figures S30,S44,S46,S48), suggesting an acceleration effect from electron-donating methoxy substituents, which could be explained by more favorable dearomatization to facilitate the 1,6-elimination.⁵⁰⁻⁵² Favorably, **MC2** and **MC1** with two methoxy substituents also exhibited the highest stability in the absence of Pd(0), which can be explained by the strong steric hindrance around the carbonate linkage (Figures S29,S31,S45,S47,S48).

We then sought to prepare a new class of SIPs containing the same structural units as **MC2-MC4** to evaluate their depolymerization performance. Thus, three monomers, **M2-M4** containing vinyloxycarbonyl (*Vi*) and benzyl thiol moieties were designed and synthesized (Scheme 1). Subsequently, photo-initiated thiol-ene click polymerization was conducted to generate polymers (Scheme 1). Taking the polymerization of **M2** as an example, different solvents and monomer concentrations were screened. THF was a good solvent to afford **Vi-P2_a** with a *M_n* of 9.7 kg/mol when the initial concentration of **M2** was 1.0 M (Table 1). A higher initial concentration of **M2** (2.0 M) in THF led to formation of **Vi-P2_a** with a slightly higher *M_n* of 10.3 kg/mol, which is characteristic of step-growth polymerization (Figures S81-S83). The thermal properties of **Vi-P2_a** were assessed by thermogravimetric analysis

(TGA) and differential scanning calorimetry (DSC). **Vi-P2_a** had relatively high thermal stability with a decomposition temperature (*T_d*, 5% weight loss) above 220 °C (Figure S87a) and a glass transition temperature (*T_g*) around 64 °C (Figure S87b). Thiol-ene polymerization of **M3** in THF generated **Vi-P3** with a *M_n* of 7.7 kg/mol (Figures S84-S86). Multiple attempts to obtain thiol-ene polymer from **M4** failed as only insoluble product was obtained, for reasons that are not clear at this time. A one-pot synthesis of a block copolymer was also attempted via thiol-ene polymerization of **M2** in the presence of allyl ether-terminated PEG (**PEG-Allyl ether**),⁴² successfully producing **Vi-P2_e-b-PEG** as confirmed by both ¹H NMR and SEC characterization (Figures S90,S91).

Scheme 2. Thiol-ene click end-functionalization toward various triggerable self-immolative polymers.



Polymer	End-cap	Target signal	R, R' group	<i>M_n</i> (kg/mol) ^a	<i>D_n</i> ^a
TBS-P2		F	R, R' = OMe	5.7	4.09
TA-P2		βME	R, R' = OMe	6.3	4.05
NB-P2		Zn/AcOH	R, R' = OMe	6.0	4.02
Bn-P2		control	R, R' = OMe	6.7	4.56
TBS-P3		F	R = OMe, R' = H	7.1	4.92

^a Determined by THF SEC calibrated using PMMA standards.

To obtain thiol-ene polymers from **M2** and **M3** with stimuli-responsive depolymerization capabilities, post-polymerization thiol-ene modification was performed (Scheme 2). A fluoride ion-sensitive *tert*-butyldimethylsilyl (TBS) ether end-cap was efficiently incorporated into both **Vi-P2_b** and **Vi-P3**, affording **TBS-P2** and **TBS-P3**, respectively. In addition, thiol-sensitive thioacetate (TA), reduction-sensitive 4-nitrobenzyl thioether (NB), and non-responsive control benzyl thioether (Bn) end-caps were also introduced onto **Vi-P2_b** to produce **TA-P2**, **NB-P2**, and **Bn-P2** respectively, suggesting the generalizability of this post-polymerization functionalization method. ¹H NMR spectroscopy and SEC analyses confirmed the resulting polymer structures (Figures S92 - S101).

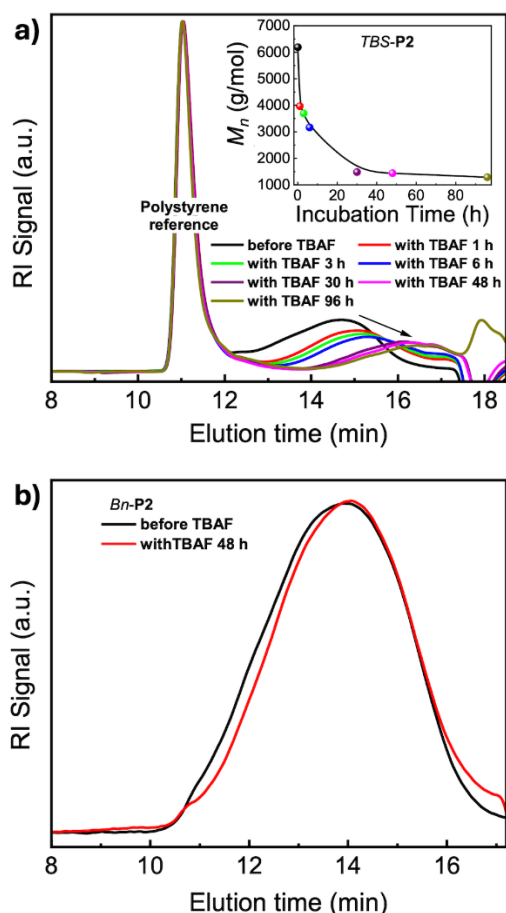


Figure 3. DMF SEC traces for (a) *TBS-P2* and (b) *Bn-P2* upon incubation with TBAF (3 equiv. relative to end-cap), DBU (3 equiv. relative to repeating units), and NMA (3 equiv. relative to repeating units) in DMF at 25 °C. The inset in (a) shows the reduction of M_n for *TBS-P2* in the presence of TBAF, DBU, and NMA. A polystyrene standard with M_n of 179 kg/mol was used as an inert reference for SEC analysis.

We next sought to evaluate the triggered depolymerization profiles of the SIPs. SEC was first employed to probe the degradation of *TBS-P2* in DMF upon treatment with tetra-*n*-butylammonium fluoride (TBAF) in the presence of DBU and NMA. A progressive shift from high to low molar mass was observed, and the M_n decreased to ~1.4 kg/mol after 48 h from the initial ~6.2 kg/mol (Figure 3a). The controlled degradation of *TBS-P2* upon exposure to TBAF was also supported by ^1H NMR analysis in $\text{DMF-}d_7$ (Figure S102). Moreover, the proposed degradation product was clearly observed by ESI-MS analysis, showing a peak corresponding to NMA-trapped quinone methide (Figure S103). To further confirm the effect of spacer length between sulfur and the carbonyl moieties on the depolymerization, *TBS-P2* was dissolved in a mixture of $\text{DMSO-}d_6$ and D_2O (10/1, v/v) and then treated with TBAF in the presence of NMA and DBU. With the exception of the stimulus, these are the same conditions that had been used initially to evaluate the depolymerization of *Al-P1*. ^1H NMR spectroscopic monitoring of the *TBS-P2* depolymerization under these conditions clearly showed a decrease of backbone methylene signals and concomitant increase of small molecule products generated by trapping of the reactive quinone methide with NMA and

water (Figure S104, see full details in the Supporting Information). This result contrasted with the hindered degradation of *Al-P1* after triggering (Figures S15,S16), confirming the importance of the linker length.

The desired degradation response is important, but the absence of nonspecific degradation is equally crucial. Thus, control polymer *Bn-P2* was exposed to TBAF in the presence of DBU and NMA in DMF. No degradation was detected after 48 h (Figure 3b), corroborating the specific depolymerization imparted by the reactivity of the end-cap. In addition, *TA-P2* and *NB-P2* showed similar degradation profiles as *TBS-P2* when actuated by β -mercaptoethanol (βME) and reduction (Zn/HOAc), respectively (Figures S105-S107). *TBS-P3* underwent rapid degradation under the conditions used to depolymerize *TBS-P2* (Figure S108a). However, a very significant background degradation was also observed for the corresponding non-responsive control *Vi-P3* (Figure S108a). These degradation results clearly highlight the importance of strong steric hindrance in stabilizing the syringaldehyde-derived SIPs (**P2**) against undesired background degradation, without compromising their desired stimuli-responsive depolymerization.

In summary, bio-based polymers were synthesized via thiol-ene click polymerization of monomers derived from lignin-derived aldehydes. These polymers were used in polymer-polymer coupling to efficiently access block copolymers via thiol-Michael addition click reaction. Moreover, diverse thiol-containing stimuli-reactive end-caps were readily introduced into a single bio-based polymer precursor via thiol-ene click reaction, providing a general approach to access triggerable SIPs. The syringaldehyde-derived SIPs in particular underwent cascade depolymerization through alternating 1,6-elimination and cyclization reactions upon selective removal of their end-caps, while exhibiting high stability in the absence of stimuli. Overall, this work opens a new avenue for designing bio-based polymers with stimuli-triggered degradability via highly efficient click reactions. The exploration of applications of these bio-based SIPs are underway in our lab.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge via the Internet at <https://pubs.acs.org/doi/10.1021/jacs>.

Experimental procedures, additional schemes, NMR and SEC characterization data, additional depolymerization data (PDF)

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Author Contributions

All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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