Supporting Information for

Functionalizable, side chain-immolative poly(benzyl ether)s

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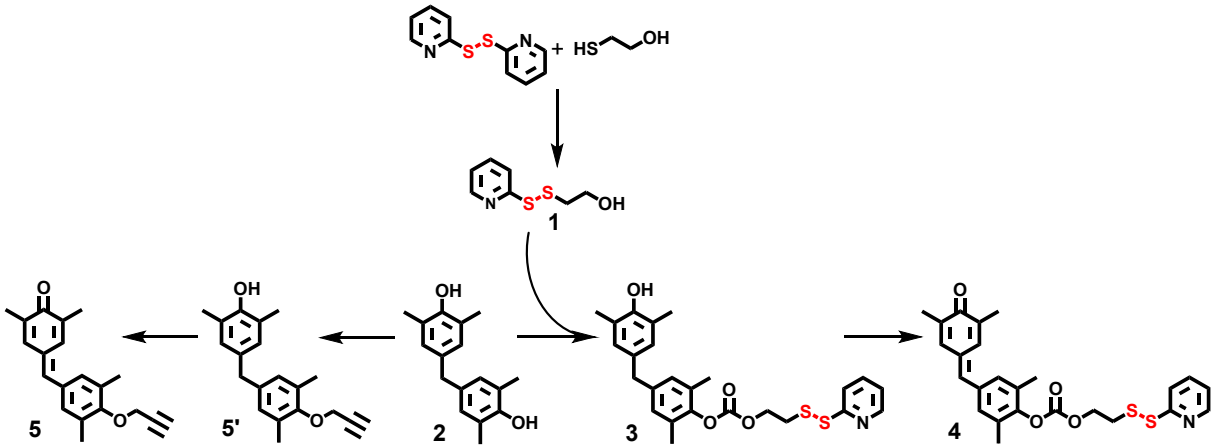
1. Materials and Methods

All reactions were performed in flame-dried glassware under a positive pressure of nitrogen unless otherwise noted. Air- and moisture-sensitive liquids were transferred via syringe in a glovebox. Organic solvents used in column chromatography, including ethyl acetate (EA), dichloromethane (DCM), methanol (MeOH) were of analytical grade and were used as received (Greagent, Shanghai Titan Inc). Super-dry solvents [DCM, THF, *N*,*N*-dimethylformamide (DMF)] were purchased from J&K Scientific Ltd. HPLC-grade DMF and THF were purchased from Oceanpak (Sweden). Mono- and bis-mercapto-terminated poly(ethylene glycol) (HS-PEG) methyl ether (M_n = 2 kDa, PDI = 1.05) were purchased from Shanghai Ponsure Biotech Inc. All other reagents were purchased from J&K Scientific Ltd and used as received unless otherwise noted. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 400 MHz NMR spectrometer. Chemical shifts (δ) were reported in ppm. ESI-MS data was obtained on LCQ-Advantage (USA). THF gel-permeation chromatography (GPC) was performed on a Waters Breeze 2 GPC system (USA) equipped with two PLgel 5 μm MIXED-C, 300×7.5 mm column and refractive index (RI)/2998 photo-diode array (PDA) detectors. HPLC-grade THF was used as the eluent running at a flow rate of 1 mL/min. DMF GPC was carried out on a Waters Breeze 2 GPC system equipped with two PLgel 5 μm MIXED-C, 300×7.5 mm columns and a RI detector. HPLC-grade DMF with 0.1% LiBr was used as the mobile phase, and samples were run at a flow rate of 1 mL/min and 60 °C. The GPC was calibrated using polystyrene (PS) standards (EasiVial PS-M 2 mL) or PEG standards kit (EasiVial PEG/PEO 2 mL) from Agilent Technologies.

2. Synthesis of quinone methides

Compound **1**. 2,2'-Bipyridyl disulfide (3.0 g, 13.6 mmol) was dissolved in 20 mL of MeOH (99.5%) followed by addition of 2-hydroxy-1-ethanethiol (0.54 g, 6.81 mmol, dissolved in 10 mL MeOH) under N_2. The reaction mixture was stirred at room temperature for 12 h. Excess

solvent was then removed under reduced pressure to obtain an oily, bright yellow product. Pure, colorless 2-(pyridin-2-yldisulfanyl)ethanol (**1**) was obtained by column silica gel chromatography using PE/EA (from 4:1 to 2:1, v:v) as the eluent (1.08 g, 85%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.47-8.48 (*d*, *J* = 4.8 Hz, 1H), 7.63-7.69 (*q*, *J* = 8.5 Hz, 4H), 7.11 (*t*, *J* = 6.6 Hz 1H), 3.76 (*t*, *J* = 7.3 Hz, 2H), 3.12 (*t*, *J* = 7.5 Hz, 2H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 159.1, 149.5, 137.3, 122.1, 121.6, 58.4, 42.8. ESI-MS: Calculated for $C_7H_9NOS_2$ ([M]): 187.01; found ([M+H]$^+$): 187.92



Scheme S1. Synthesis of quinone methides (**4** and **5**).

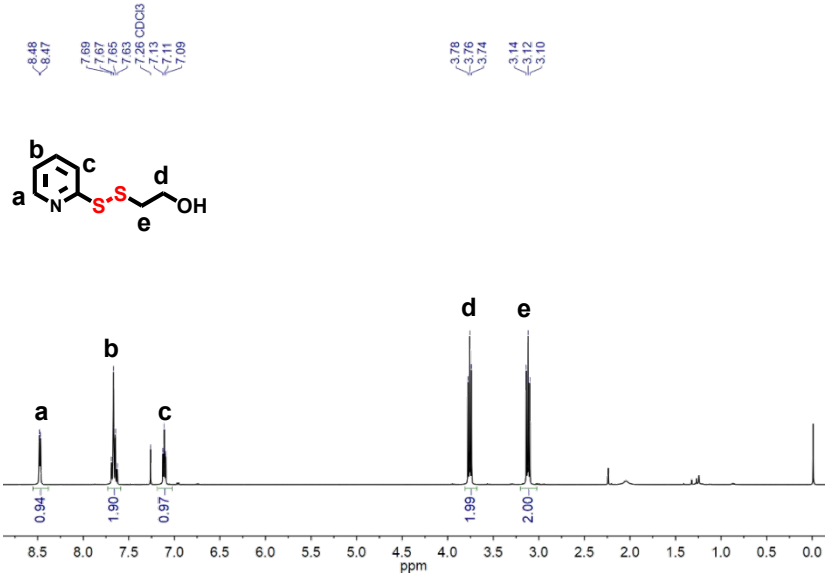


Figure S1. ^{1}H NMR spectrum of compound **1** in $CDCl_3$.

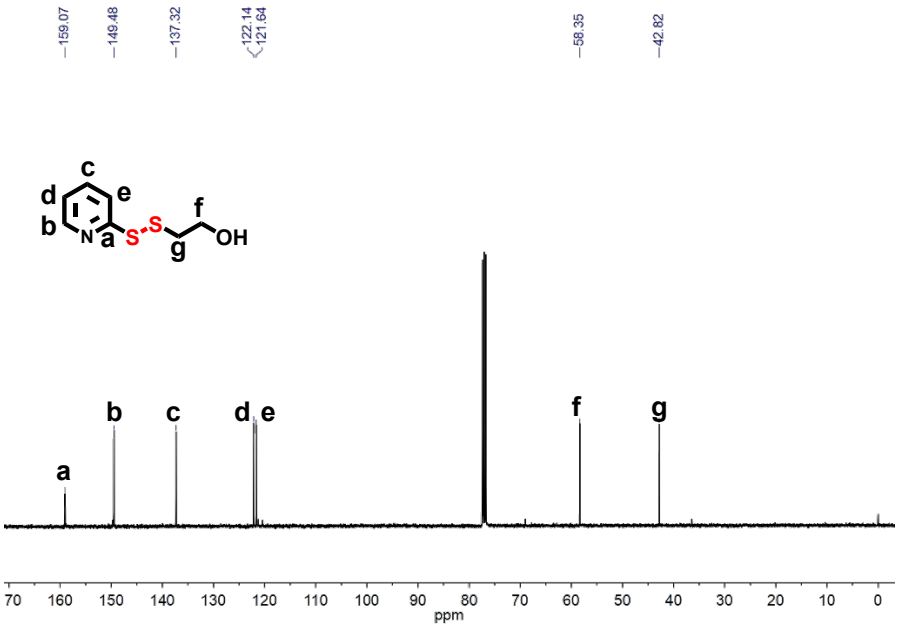


Figure S2. ^{13}C NMR spectrum of compound **1** in $CDCl_3$

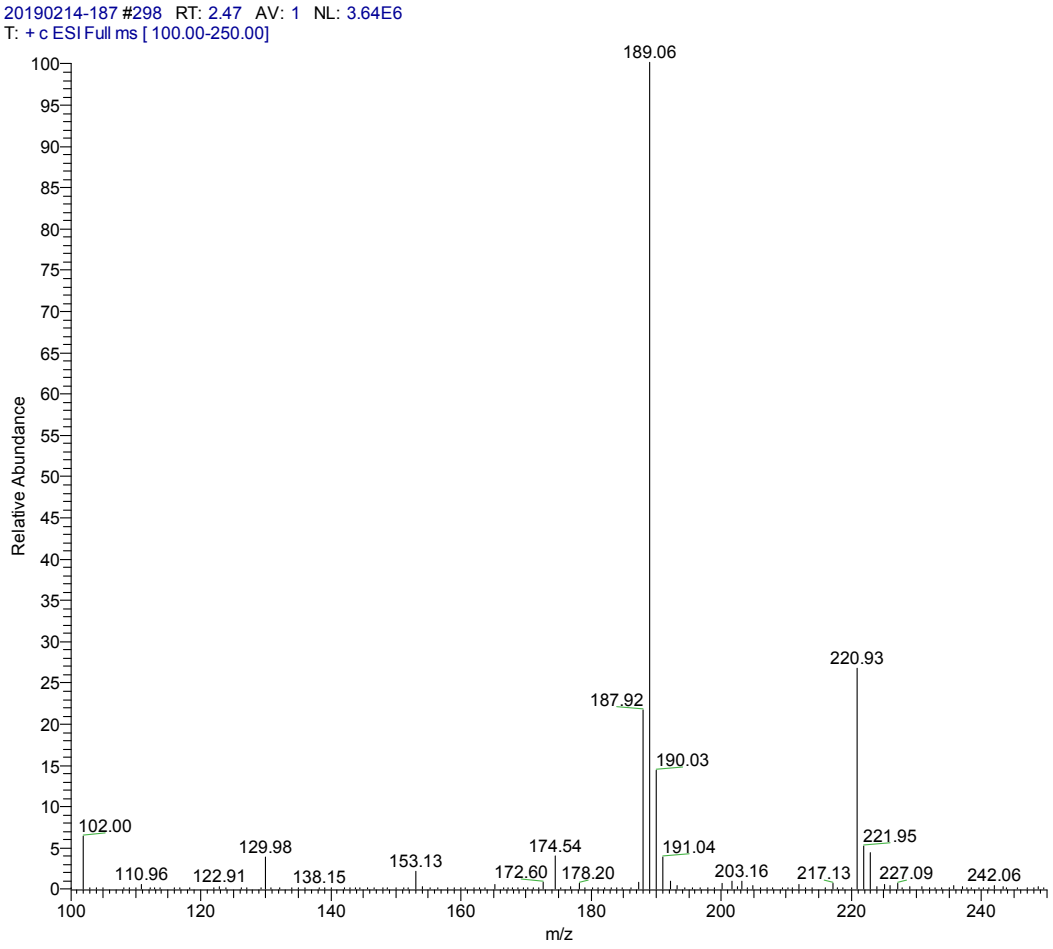


Figure S3. ESI-MS of compound **1**. Calculated: 187.01; found: 187.92.

Compound **2**. 4,4'-methylenebis(2,6-dimethylphenol) was synthesized as previously reported.[1-2] Briefly, concentrated hydrochloric acid (36% w/v, 15 mL) was added dropwise to a biphasic mixture of 2,6-dimethylphenol (10.7 g, 87.6 mmol) in petroleum ether (80 mL) and formaldehyde in water (37% w/v, 16 mL, 198 mmol) over 10 min at room temperature with vigorous stirring in a 250 mL round-bottom flask. White precipitation appeared during the reaction. After 3 h, the mixture was poured into 400 mL of water, mixed well, and filtered through a Buchner funnel to collect a while solid, which was washed with water (300 mL), and dried at 70 °C under vacuum (~1 mmHg) overnight to afford compound **2** without additional purification (11 g, 98%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.79 (*s*, 4H), 4.46 (*s*, 2H), 3.70 (*s*, 2H), 2.20 (*s*, 12H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 150.3, 133.4, 128.9, 122.9, 40.3, 15.9. EI-MS: Calculated for $C_{17}H_{20}O_2$ ([M]): 256.35; found: 256.20

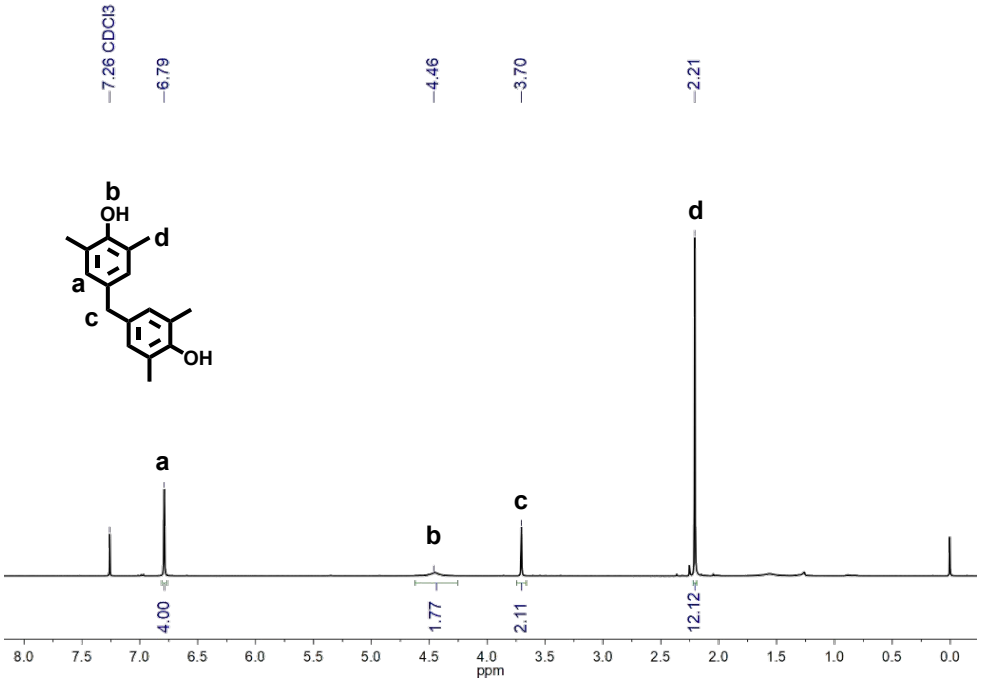


Figure S4. ^{1}H NMR spectrum of compound **2** in $CDCl_3$.

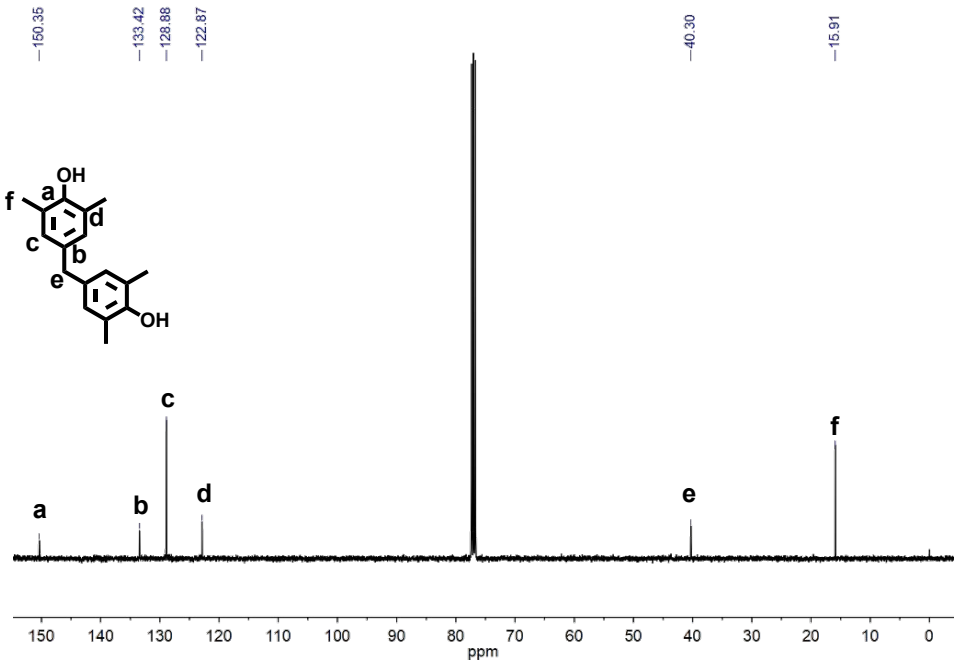


Figure S5. ^{13}C NMR spectrum of compound **2** in $CDCl_3$.

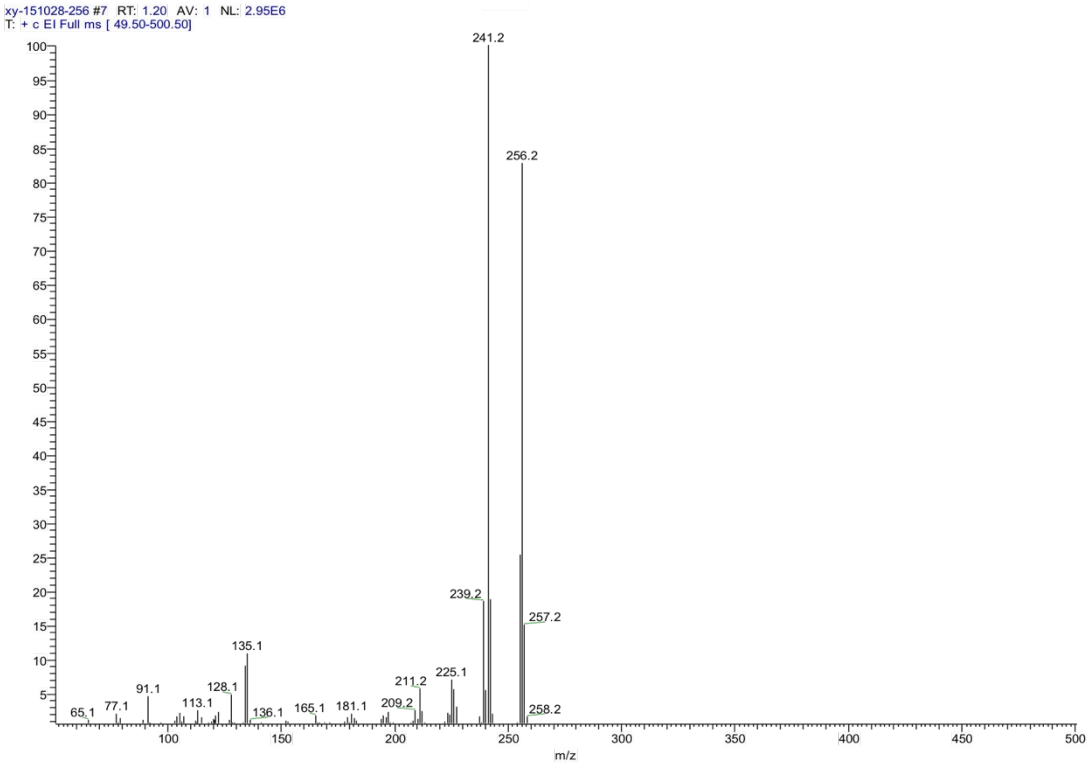


Figure S6. EI-MS of compound **2**. Calculated: 256.35; found: 256.20.

Compound **3**. Compound **1** (200 mg, 1.07 mmol) and triphosgene (159 mg, 0.54 mmol) were dissolved in 8 mL of anhydrous THF. A solution containing triethylamine (TEA, 144 mg,

1.424 mmol) and anhydrous THF (2 mL) was then added dropwise to the mixture under ice cooling and stirring over 15 min. Then the slurry was transferred dropwise to 20 mL of a DCM solution containing compound **2** (320 mg, 1.28 mmol) and TEA (144 mg, 1.424 mmol). The reaction mixture was stirred for 12 h at room temperature and the solvent was removed under reduced pressure. The crude product was purified twice by silica gel column chromatography using PE/EA (from 4:1 to 2:1, v:v) as eluent to give **3** as a viscous, colorless oil (225 mg, 45%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.49 (*d*, *J* = 4.8 Hz, 1H), 7.62-7.70 (*m*, 2H), 7.11 (*t*, *J* = 5.8 Hz, 1H), 6.86 (*s*, 2H), 6.79 (*s*, 2H), 4.51 (*t*, *J* = 6.5 Hz, 2H), 3.74 (*s*, 2H), 3.15 (*t*, *J* = 6.5 Hz, 2H), 2.21 (*s*, 6H), 2.15 (*s*, 6H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 159.4, 159.9, 150.6, 149.7, 146.5, 139.7, 137.2, 132.5, 129.9, 129.1, 123.1, 121.01, 120.03, 66.0, 40.5, 37.1, 15.9. ESI-MS: Calculated for $C_{25}H_{27}NO_4S_2$ ([M]): 469.12; found ([M+H]$^+$): 469.87 found ([M+Na]$^+$): 491.89.

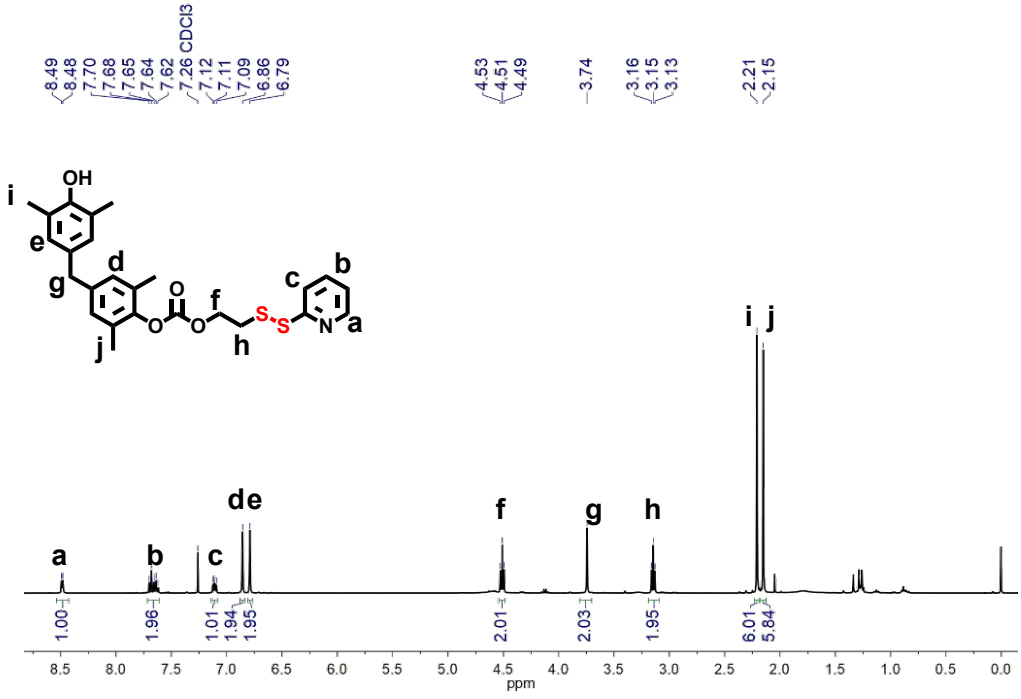


Figure S7. ^{1}H NMR spectrum of compound **3** in $CDCl_3$.

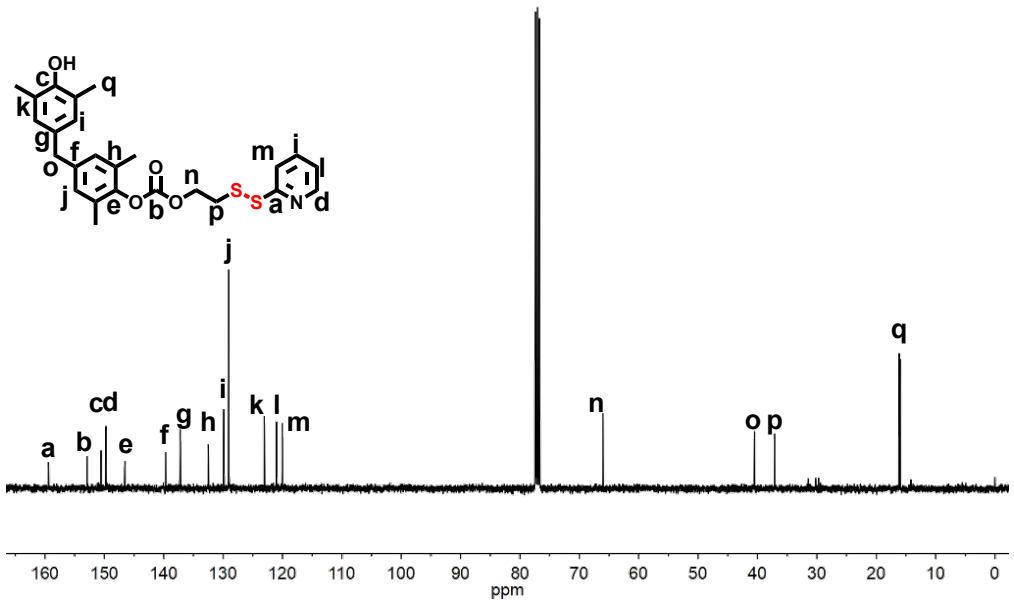


Figure S8. ^{13}C NMR spectrum of compound **3** in $CDCl_3$.

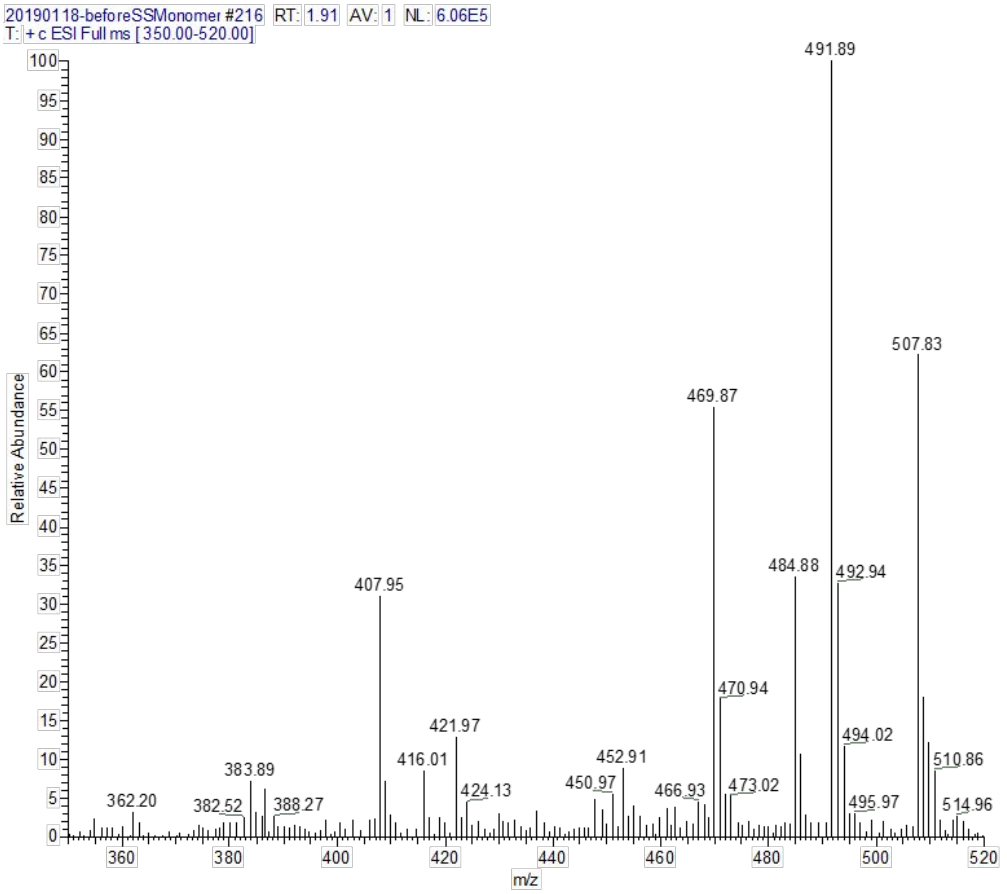


Figure S9. ESI-MS of compound **3**. Calculated: 469.12; found: 469.87.

Compound **4**. Potassium ferricyanide (632 mg, 1.92 mmol) was added to a solution of compound **3** (225 mg, 0.48 mmol) in diethyl ether (20 mL) under N_2 atmosphere. Potassium hydroxide (113 mg, 2.01 mmol) in deionized water (5 mL) was added into the mixture, which was then stirred vigorously for 2 h at room temperature and monitored by TLC. After the reaction, the mixture was extracted with diethyl ether (100 mL, 3×) and the combined organic layers were washed with brine (100 mL, 1×) and dried over sodium sulfate. The solids were removed by filtration and the solution was concentrated and dried *in vacuo* to give pure oxidized product **4** as a yellow solid (213 mg, 95%). Of note, compound **4** needs to be stored under a desiccated atmosphere. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.49 (*d*, *J* = 5.2 Hz, 1H), 7.60-7.69 (*m*, 2H), 7.49 (*s*, 1H), 7.16 (*s*, 2H), 7.02-7.13 (*m*, 3H), 4.56 (*t*, *J* = 6.5 Hz, 2H), 3.17 (*t*, *J* = 6.5 Hz, 2H), 2.26 (*s*, 6H), 2.08 (*s*, 6H); ^{13}C NMR (400MHz, $CDCl_3$): δ 187.3, 159.3, 152.5, 149.9, 148.9, 141.8, 138.8, 137.1, 135.7, 133.7, 131.8, 131.2, 130.9, 121.1, 120.1, 66.4, 37.0, 16.9, 16.2. ESI-MS: Calculated for $C_{25}H_{25}NO_4S_2$ ([M]): 467.12; found ([M+H]$^+$): 467.88.

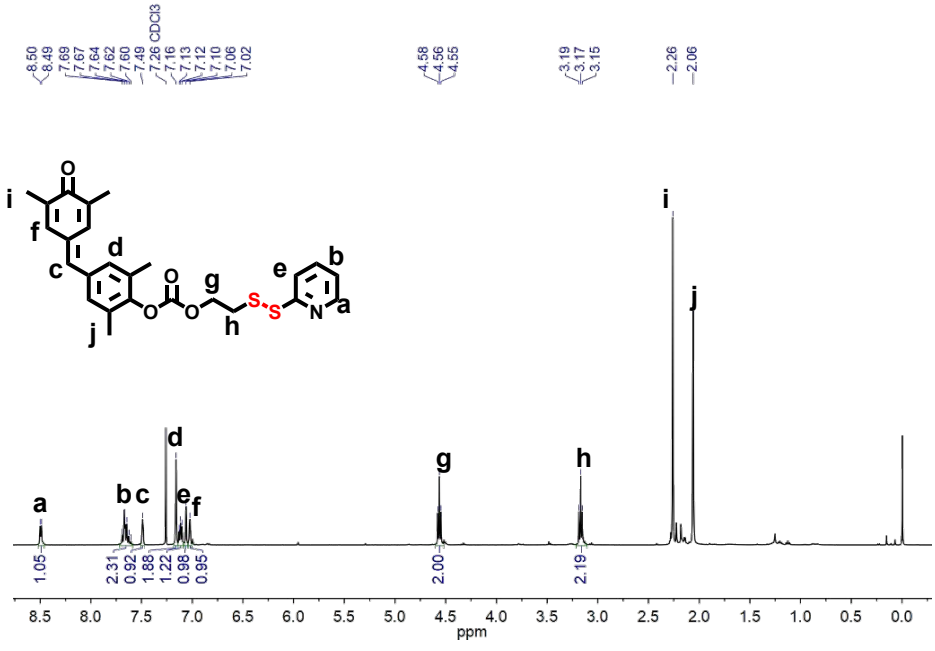


Figure S10. ^{1}H NMR spectrum of compound **4** in $CDCl_3$.

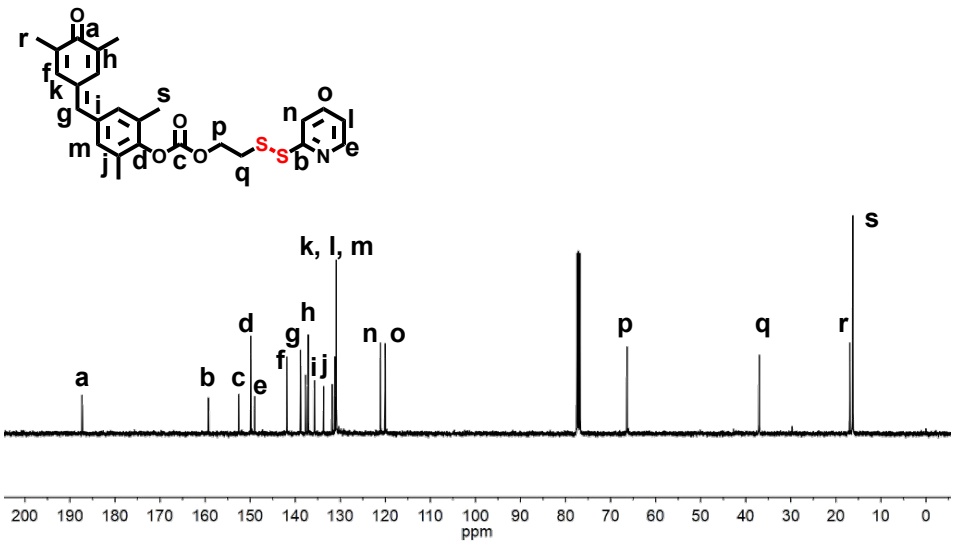


Figure S11. ^{13}C NMR spectrum of compound **4** in $CDCl_3$.

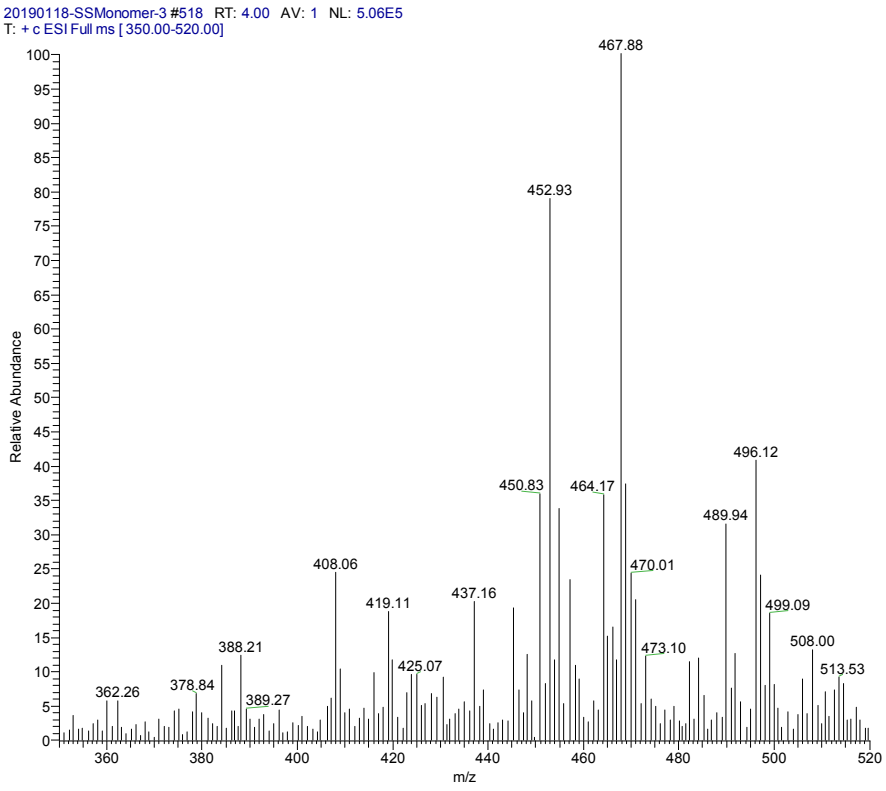


Figure S12. ESI-MS of compound **4**. Calculated: 467.12; found: 467.88.

Compound **5**. Compound **5** was synthesized as previously reported by our group.[2] Propargyl bromide (1.70 mL, 19.5 mmol) in 15 mL dry DMF was added dropwise to a dry DMF

solution (20 mL) of compound 1 (5.0 g, 19.5 mmol) and potassium carbonate (2.98 g, 21.5 mmol). The reaction mixture was stirred at room temperature for 24 h. The solids were removed by filtration and the solution was concentrated via rotary evaporation at 60 ºC to remove the most of the DMF solvent. The crude product was then diluted by 100 mL of EA and then washed with saturated ammonium chloride solution (100 mL, 1×), water (100 mL, 2×), brine (100 mL, 1×). The combined organic extracts were dried over anhydrous sodium sulfate and the solvent was removed by rotary evaporation. The remaining yellow residue was purified by silica gel column chromatography (gradient elution with 5 – 10% EA in PE), affording compound **5'** a white solid. (1.9 g, 6.45 mmol, 32%). Then potassium ferricyanide (4.48 g, 13.61 mmol, 4 equiv) was added to a solution of compound **5'** (1.0 g, 3.40 mmol) in diethyl ether (90 mL) under N_2 atmosphere. Potassium hydroxide (0.8 g, 14.27 mmol) in deionized water (20 mL) was added into the mixture. The reaction mixture was stirred vigorously for 2 h at room temperature and monitored by TLC. The mixture was then extracted with diethyl ether (100 mL, 3×) and the combined organic layers were washed with brine (100 mL, 1×) and dried over sodium sulfate. The solids were removed by filtration and the solution was concentrated by rotary evaporation to give pure oxidized product as yellow needle-like solid without column purification (0.9 g, 3.08 mmol, 90%). Compound **5** was dried under vacuum for several days and stored in a desiccated atmosphere. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 (*s*, 1H), 7.13 (*s*, 2H), 7.05 (*s*, 1H), 7.01 (*s*, 1H), 4.56 (*s*, 2H), 2.54 (*s*, 1H), 2.36 (*s*, 6H), 2.06 (*d*, *J* = 6.5Hz, 6H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 187.3, 156.5, 142.7, 139.0, 137.4, 135.5, 131.9, 131.2, 78.9, 75.5, 59.9, 16.9, 16.3. EI-MS: Calculated for $C_{20}H_{20}O_2$ ([M]): 292.15; found: 292.10.

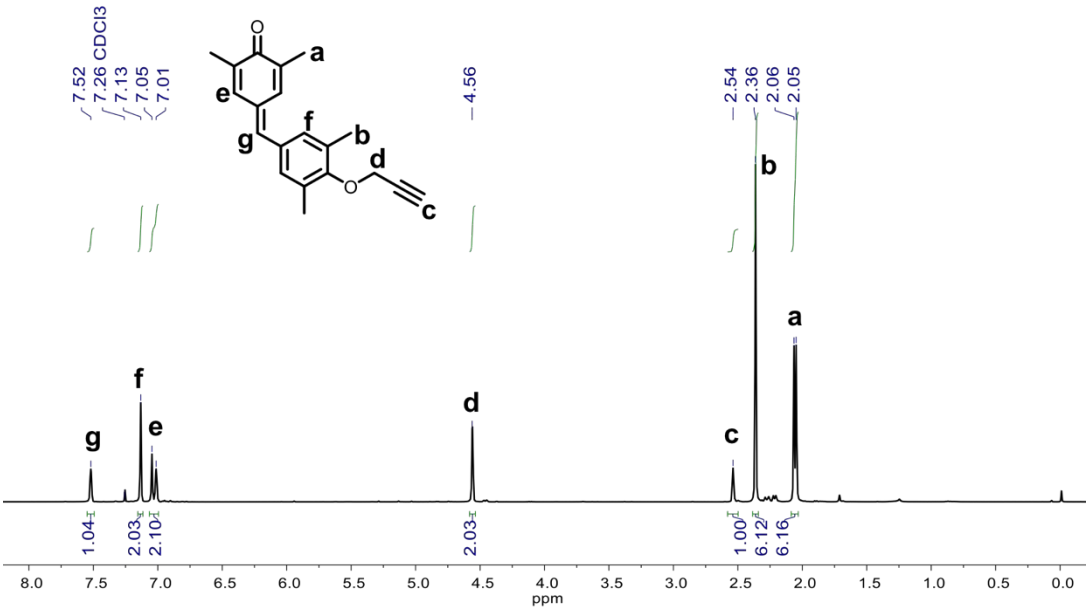


Figure S13. ^{1}H NMR spectrum of compound **5** in $CDCl_3$.

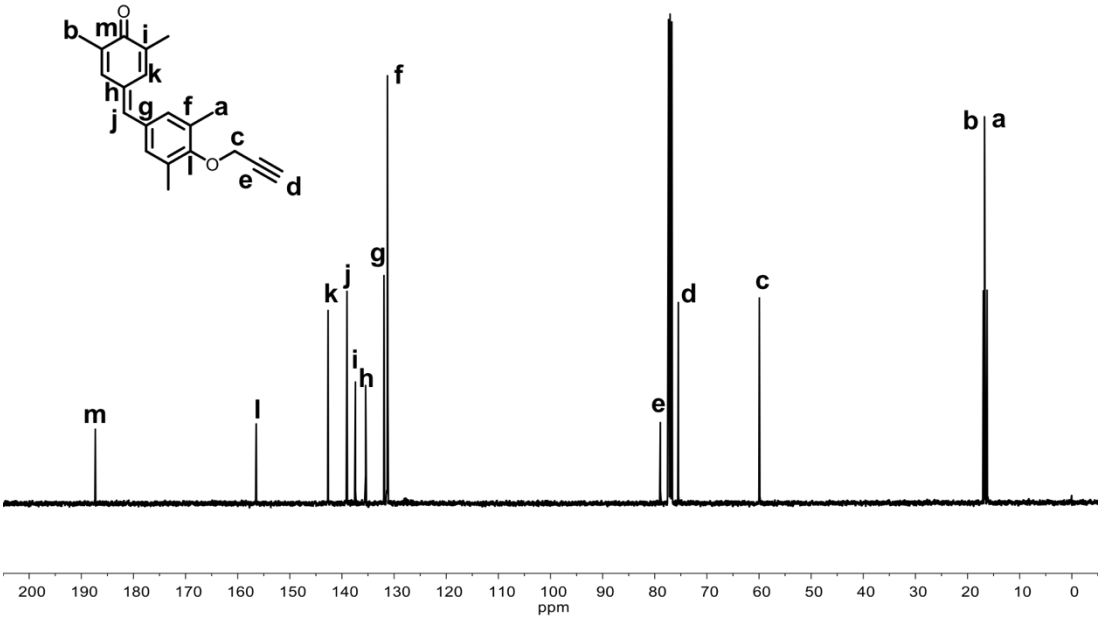


Figure S14. ^{13}C NMR spectrum of compound **5** in $CDCl_3$.

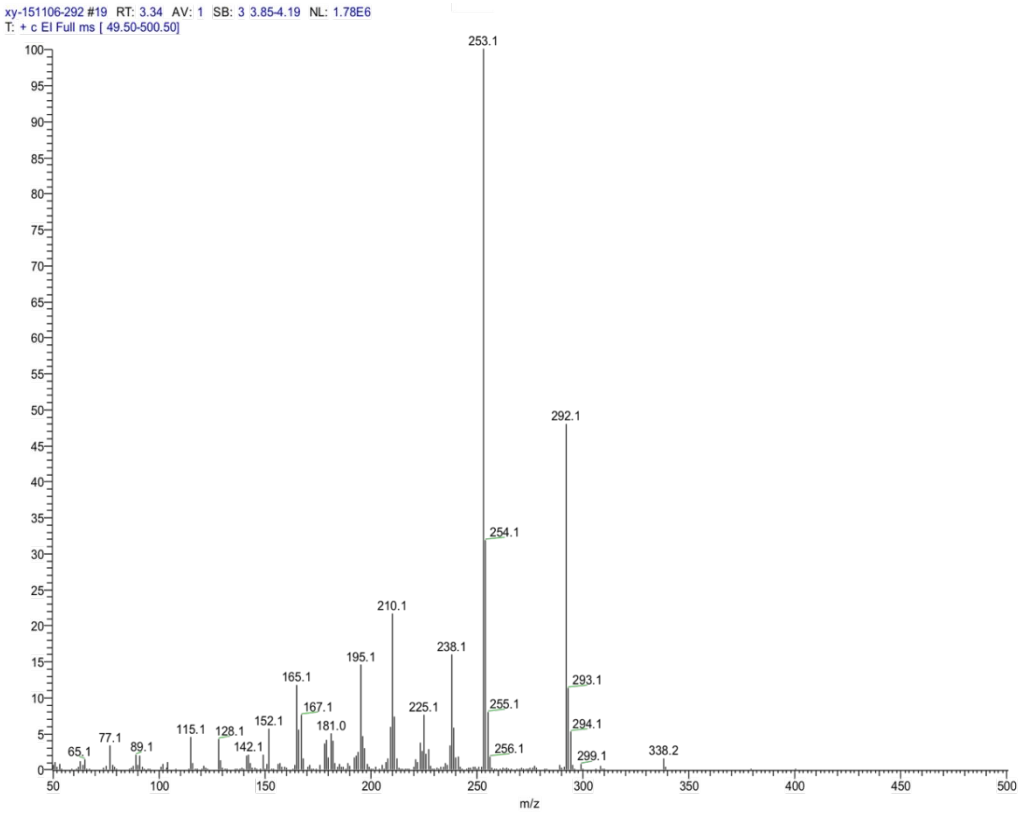
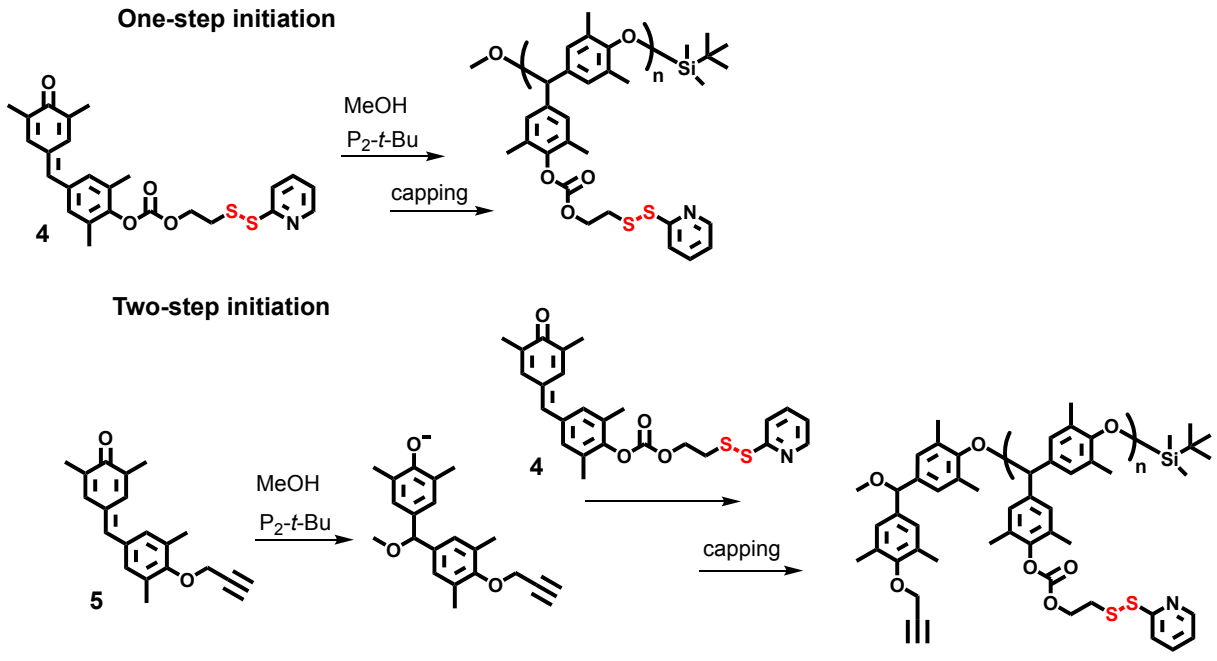


Figure S15. EI-MS of compound **5**. Calculated: 292.15; found: 292.1.

3. Synthesis of ScIPs



Scheme S2. Scheme for one- and two-step initiated polymerization.

One-step initiation. A 10 mL Schlenk flask with a stir bar was flame-dried under vacuum and purged with Ar. The flask was transferred to a glovebox, where compound **4** (80.0 mg, 0.171 mmol, 1 equiv) and super-dry THF (400 μL) was added to the flask. After mixing, the sealed flask was removed from the glovebox, backfilled with Ar, and placed in an ice-salt bath (-20 ºC or 0 ºC). Next, 5 μL of a stock solution containing super-dry MeOH (69 μL) in super-dry THF (2 mL) (also prepared and stored in a glovebox) was added to the reaction mixture (0.0034 mmol MeOH, 0.02 equiv to monomer **4**), immediately followed by the addition of P_2-*t*-Bu phosphazene base solution in THF (13 μL of a 2 M stock solution; 0.0085 mmol, 0.05 equiv to monomer **4**). A fuchsia color was immediately observed. The reaction mixture was left to stir for 1 h, before a capping mix containing *t*-butyldimethylsilyl chloride (TBSCl, 31.0 mg, 0.205 mmol, 1.2 equiv), triethylamine (TEA, 30 μL, 0.205 mmol, 1.2 equiv), and a catalytic amount of 4-(dimethylamino)-pyridine (DMAP) was added to the solution. The solution was then stirred at room temperature for 15 h. The polymer was obtained by precipitation 3× in cold MeOH (60 mL) at -20 ºC followed by drying *in vacuo* as white solids (~15 mg, ~18%).

Two-step initiation. In a glovebox, a 2 mL flame-dried Schlenk flask with a stir bar was charged with compound **5** (29.3 mg, 0.1 mmol, 1 equiv) in super-dry THF (100 μL). Next, super-dry MeOH (2.0 μL, 0.05 mmol) and P_2-t-Bu phosphazene base solution in THF (25 μL, 0.05 mmol) was sequentially added to the flask at room temperature. The solution was stirred for 45 min to yield the initiating solution (a light green color). Separately, in a glovebox, a 10 mL flame-dried Schlenk flask equipped with a stir bar was loaded with compound **4** (80.0 mg, 0.171 mmol) and super-dry THF (400 μL). After mixing, the sealed flask was removed from the glovebox, backfilled with Ar, and placed in an ice-salt bath (-20 ºC or 0 ºC). Then, an 8 μL aliquot of the initiator solution was transferred to the 10 mL Schlenk flask. A fuchsia color was immediately observed. After 1 h, the reaction mixture was quenched with capping mix containing TBSCl (31.0 mg, 0.205 mmol), TEA (30 μL, 0.205 mmol), and a catalytic amount

of DMAP. The reaction was stirred at room temperature for 15 h. The polymer was obtained by precipitation 3× in cold MeOH (60 mL) at -20 ºC followed by drying *in vacuo* as white solids (60.0 mg, 75%).

Table S1. Molecular weight and polydispersity of ScIPs.

Polymerization reaction	Initiator:Monomer (m:m)	T (ºC)	$M_{n,NMR}$[a] (kDa)	$M_{n,GPC}$[b] (kDa)	PDI[b]	DP_n
1[c]	1:50	-20	15.4	17.4	1.8	~33
2[c]	1:50	0	14.1	13.8	1.6	~30
3[d]	1:50	-20	4.7	5.6	1.6	~11
4[d]	1:50	0	4.7	4.3	1.5	~11

[a)] Number-average molecular weight determined by ^{1}H NMR at 27 °C using $CDCl_3$ as solvent; [b)] THF GPC measurement using UV detector and calibration with linear PS standards; [c)] two-step initiated polymerization; [d)] one-step initiated polymerization.

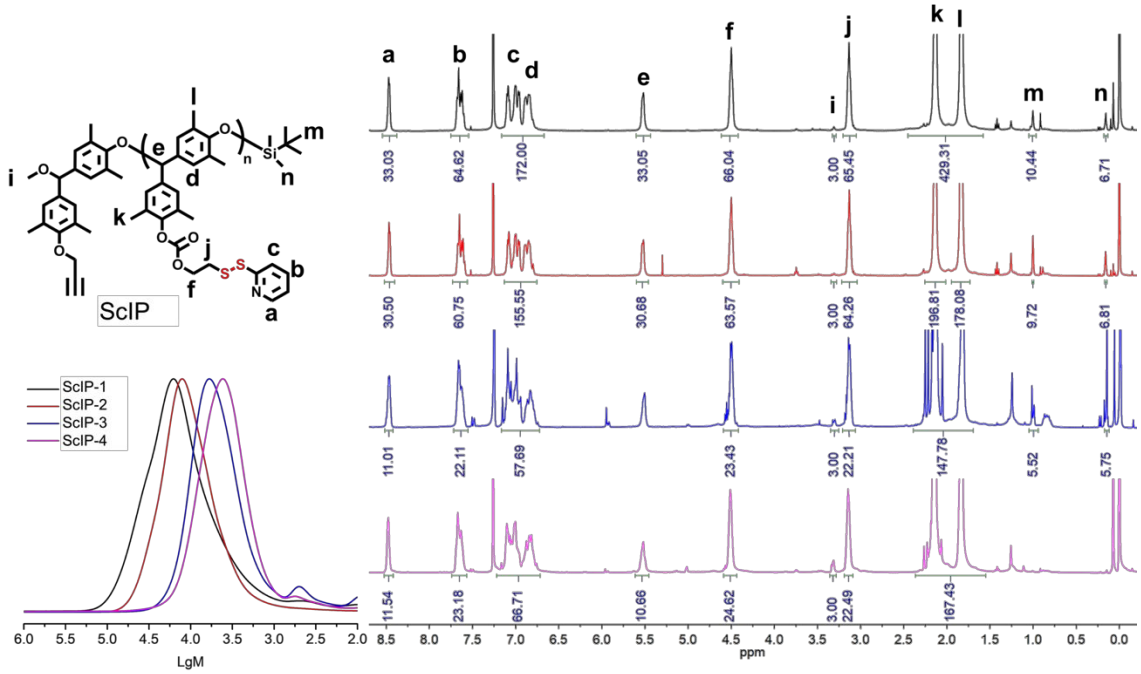
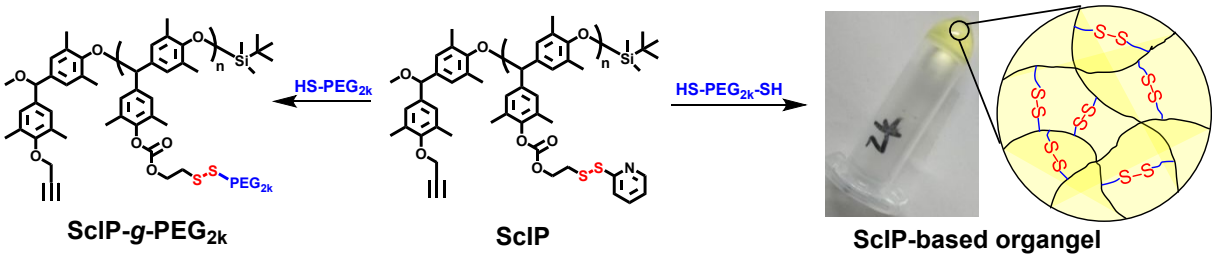


Figure S16. THF GPC and ^{1}H NMR characterization of the ScIPs in Table S1.

4. Synthesis of ScIP-backboned graft copolymer and ScIP-based organogel

ScIP-*g*- PEG_{2k}. The thiol-disulfide exchange reaction between HS-PEG_{2k} (90.0 mg, 0.045 mmol HS-) and ScIP (14.0 mg, 0.03 mmol pyridine disulfide side chain group) were

conducted in a 10 mL Schlenk flask with 2 mL THF as the solvent. The reagents were mixed and stirred at room temperature under Ar overnight. Thereafter, the reaction mixture was purified by THF GPC to remove the unreacted PEG and other small molecules residues. The fraction for the conjugates were collected, combined, and dried *in vacuo*.



Scheme S3. Synthesis of ScIP-*g*-PEG_{2k} graft polymer (left) and ScIP-based organogel (right).

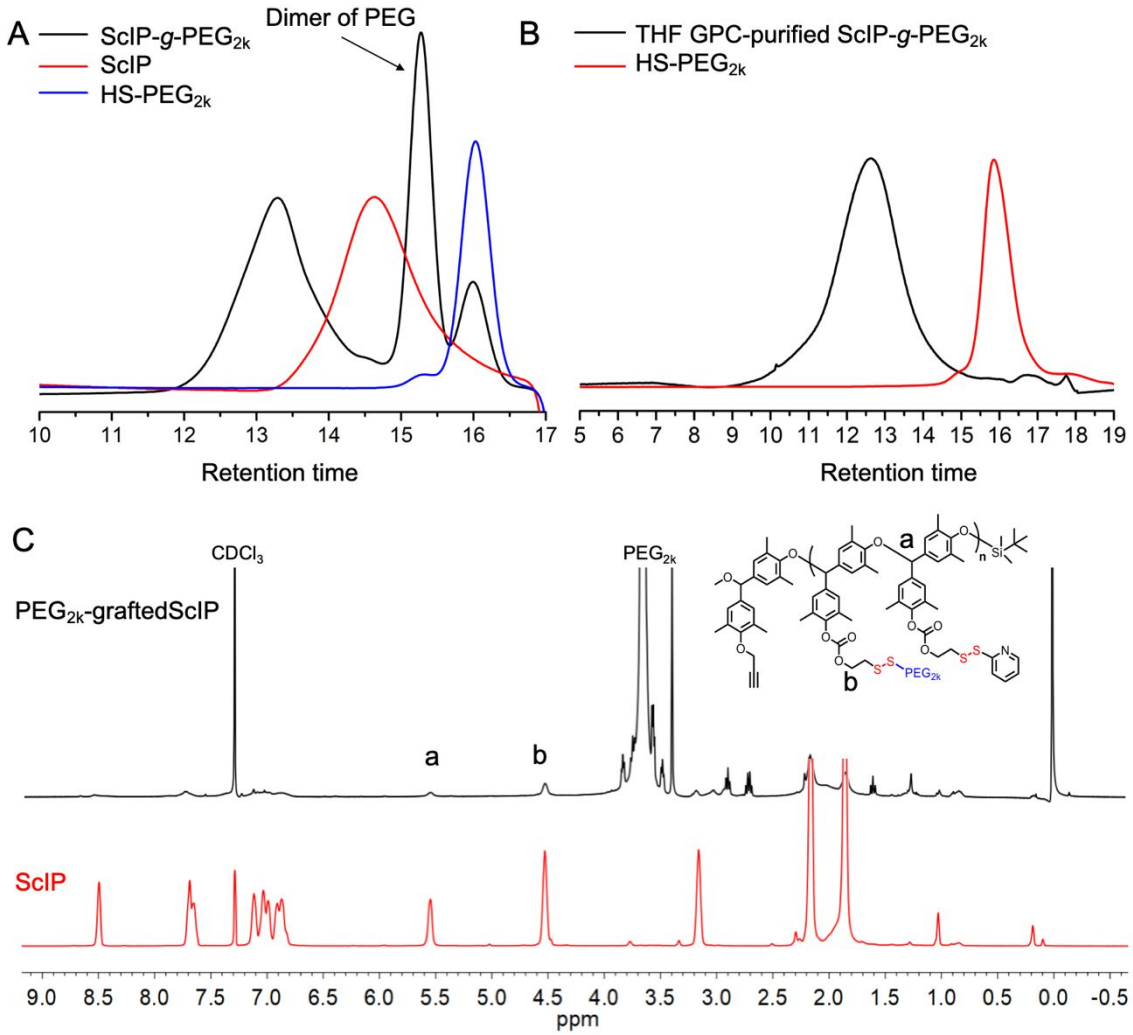


Figure S17. (A). DMF GPC chromatograms of unpurified ScIP-*g*-PEG_{2k} and its synthetic components. (B). Purification of ScIP-*g*-PEG_{2k} using THF GPC. (C) ^{1}H NMR spectra of ScIP-*g*-PEG_{2k} and ScIP in $CDCl_3$.

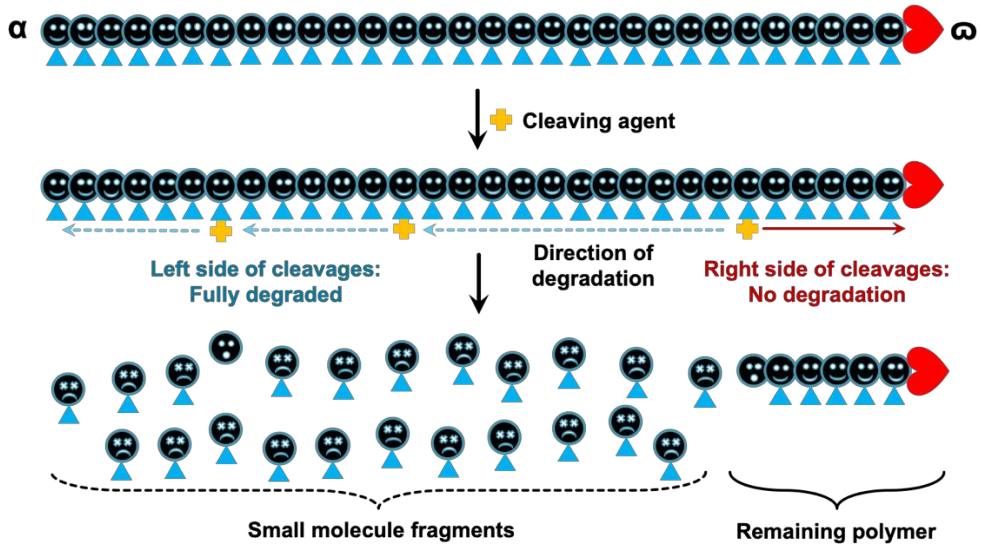
ScIP-based organogel. In a 2 mL centrifuge tube was placed ScIP (9.6 mg, 0.04 mmol pyridine disulfide side chain group) and a saturated DMF solution containing HS-PEG_{2k}-SH (40.0 mg, 0.02 mmol thiol). The centrifuge tube was then placed on an Eppendorf shaker to gently shake at room temperature. After 1 h the solution became slightly yellow (due to the side product of pyridine thiol) and highly viscous. Gelation occurred overnight and the yellow color no longer increased after 24 h. In order to determine the gel content, two pieces of the organogel (~30 mg) were placed in pre-weighed vials. One vial was subjected to a brief rinse with THF to remove the yellow pyridine thiol contained within the gel. To the second vial, 5 mL of dichloromethane (DCM) was added, and the vial was gently shaken on a shaker at room temperature. The DCM was replaced 10 times over a period of 36 h. Thereafter, both vials were dried under vacuum, and 2 mL of water was added to each vial to hydrate the gel. The water were then removed by lyophilization. The weight of the dried gels were compared to determine the gel content. The experiment was performed in triplicate.

5. Degradation of ScIPs

Solution-phase degradation of unmodified ScIP and ScIP-*g*-PEG. In a typical degradation experiment, the polymer (0.0043 mmol pyridine disulfides) was dissolved in THF (600 μL), to which a THF solution of DTT (0.1-1 equiv to pyridine disulfide, 200 μL) and DBU (0.4-4 equiv to pyridine disulfide) were added. The reaction mixture was allowed to gently shake on an Eppendorf shaker for 20 min, before being analyzed by THF GPC. For NMR monitoring, deuterated THF-d_8 was used instead.

Solid-state degradation of unmodified ScIP pellets. Pellets were prepared in 1.5 mL centrifuge tubes by precipitating the ScIP THF solution in cold MeOH, followed by centrifugation at 14,000 rpm for 20 minutes to collect the solids. The pellets were dried for 24 h *in vacuo* before use. For degradation, the ScIP pellet was suspend in acetonitrile (1 mL) containing 0.8 mM DBU and 0.2 mM DTT in a 5 mL glass vial. DBU, DTT, and TBAF (0.2 mM) were also separately used as controls. The reactions were monitored by photography.

Degradation test of ScIP-based organogel. The organogel was first incubated in acetonitrile or THF overnight to displace the DMF inside the gel. Then, a small piece of gel was cut with knife and placed in a recrystallization dish containing 2 mL acetonitrile or THF. Next, 0.2 mM DTT and 0.8 mM DBU was introduced into the dish and the reaction progress was monitored by photography. In separate dishes, DBU and DTT were used alone as controls.



Scheme S4. Schematic illustration of the side-chain immolative process.

Prediction of degradation product molecular weight distribution. The side chain-immolation process for ScIP was modeled as a stochastic event, i.e. all disulfides have a random and equal chance of being cleaved. At the beginning of the simulation, a group of polymers (~2000 chains, with a distribution profile mapped to experimental GPC data) was generated. A certain

percentage of the disulfides were then "cleaved", resulting in monomer fragments and a non-degraded section at the ω end (see Scheme S4). After these operations, the resulting fragments were sorted and their MW distribution were obtained. The Python script that implements this process is available upon request.

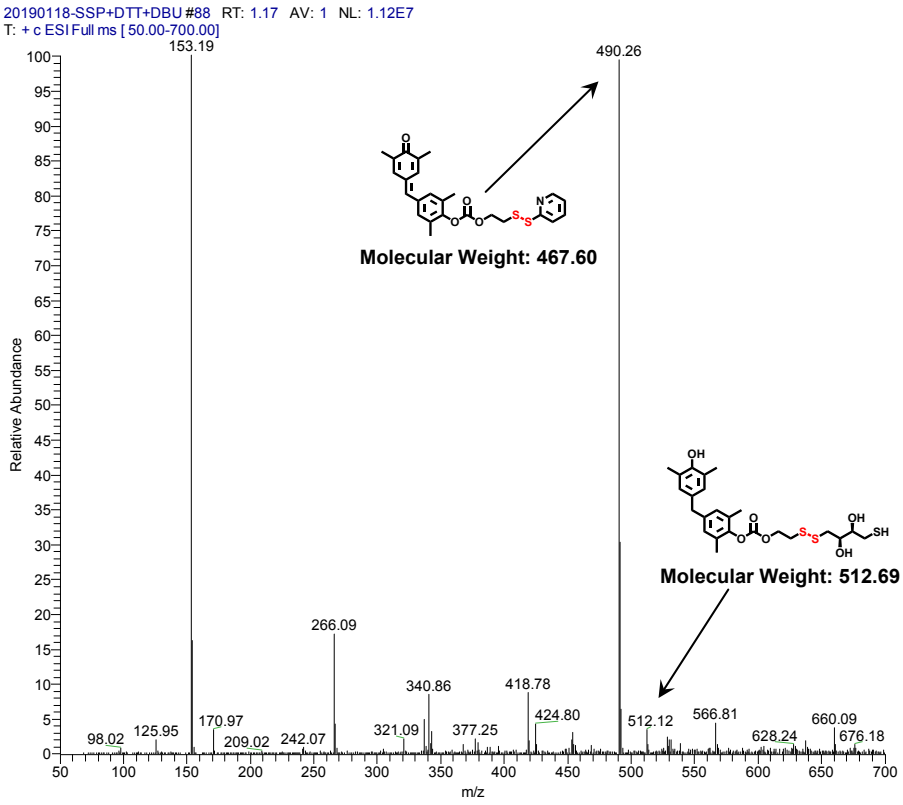


Figure S18. ESI-MS (positive mode) of degraded products.

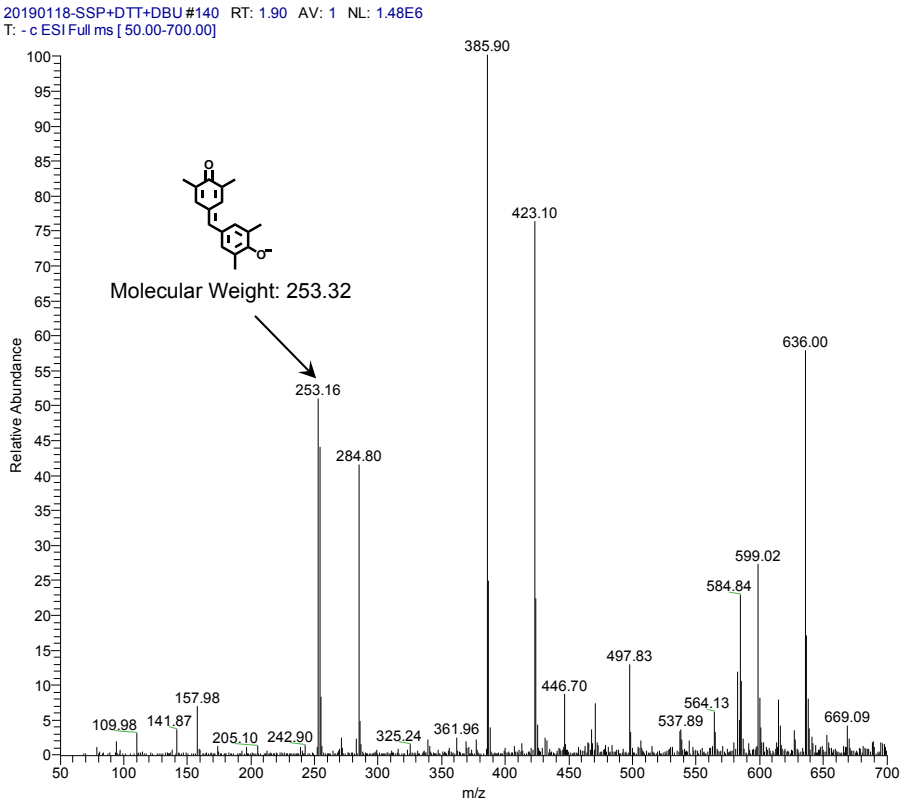


Figure S19. ESI-MS (negative mode) of degraded products.

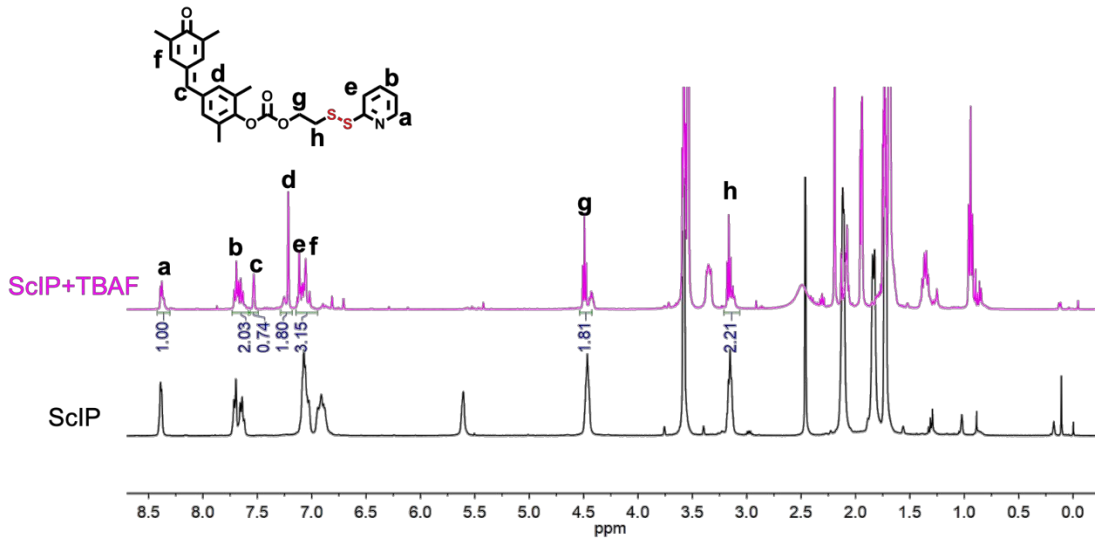


Figure S20. ^{1}HNMR spectra for the unmodified ScIP and end cap-initiated degradation products when treated with TBAF in THF-d_8.

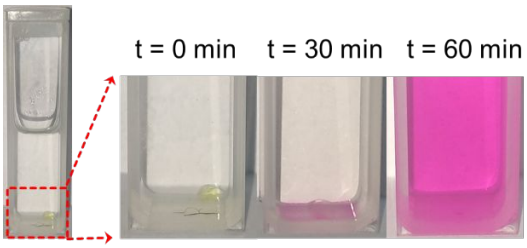


Figure S21. Photographs showing the degradation of ScIP organogel in THF containing 0.2 mM DTT and 0.8 mM DBU.

References:.

(1). Yeung, K.; Kim, H.; Mohapatra, H.; Phillips, S. T., Surface-accessible detection units in self-immolative polymers enable translation of selective molecular detection events into amplified responses in macroscopic, solid-state plastics. *J. Am. Chem. Soc.* **2015,** *137* (16), 5324-5327.
(2). Xiao, Y.; Li, H.; Zhang, B.; Cheng, Z.; Li, Y.; Tan, X.; Zhang, K., Modulating the Depolymerization of Self-Immolative Brush Polymers with Poly(benzyl ether) Backbones. *Macromolecules* **2018,** *51* (8), 2899-2905.