Episulfide Anionic Ring-Opening Polymerization Initiated by Alcohols and Primary Amines in the Presence of γ-Thiolactones

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Simon Le Luyer, Philippe Guégan* and Nicolas Illy*

Sorbonne Université, CNRS, Institut Parisien de Chimie Moléculaire, Equipe Chimie des Polymères, 4 place Jussieu, F-75005 Paris, France.

Corresponding Author

* philippe.guegan@sorbonne-universite.fr

* nicolas.illy@sorbonne-universite.fr

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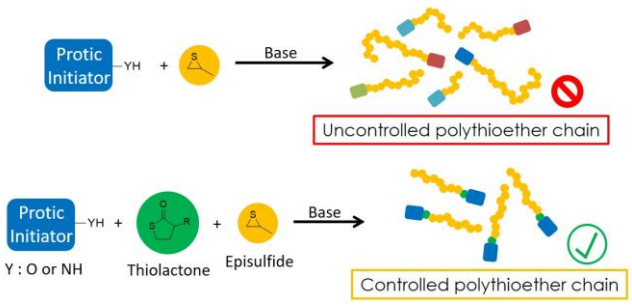

Abstract

Among the sulfur-containing polymers, polythioethers remains very attractive structures due to their high sulfur atom content, making them interesting candidates for various industrial applications, for example in the fields of energy storage or biomedical applications. Although anionic ring-opening polymerization of episulfides is known since decades, only a limited number of efficient initiating systems enable the synthesis of well-defined polymer chains. In this work, a one-pot, two step method was developed in order to efficiently initiate the anionic ring-opening polymerization of propylene sulfide with alcohol or amine moieties using the latent thiol functionality of γ-thiolactones. First, the ring-opening of γ-thiolactones by alcohols or amines was investigated in the presence of various bases (BEMP, DBU, DMAP, *t*BuP$_1$ and *t*BuP$_4$). Then, the polymerization conditions were optimized allowing the synthesis of well-defined α,ω-heterotelechelic poly(propylene sulfide)s with controlled molar mass up to 10 kg.mol^{-1} as evidenced by SEC, ^{1}H, ^{13}C, and 2D NMR and MALDI-TOF mass spectrometry. Depending on the initiating function (alcohol or amine), the initiator and the polythioether chains are connected either by an ester or by an amide bond. The stability of these bonds was studied under basic conditions.

Introduction

Over the last decades, sulfur-containing polymers have generated a persistent interest and various structures were developed, including poly(thioester)s, poly(thioamide)s, poly(thiocarbonate)s, poly(thiourethane)s or poly(thioether)s. In particular, even if they have been known for a long time, polythioethers, also called polysulfides, remain extremely interesting. As a matter of fact, they possess simple and extremely flexible main chains containing very high density of sulfur atoms (thioether functions) giving them valuable properties. They cover a broad range of physicochemical properties, such as high refractivity, heat resistance, heavy metal chelating properties or enhanced dielectrical properties.[1] Therefore, they find applications in a wide range of industrial fields[2-4] ranging from commonly-used adhesives and sealing agents,[5-7] to high tech products, such as optical devices (high refractive index polymers),[8] or self-healing materials.[9, 10] In the field of energy storage, polythioethers, especially poly(ethylene sulfide), have a high potential as solid-state electrolytes to replace poly(ethylene oxide) in lithium-ion batteries.[11] In addition, polysulfides are commonly used as oxidation-responsive or antioxidant materials for biomedical applications due to their up to now unique well-controlled oxidation responsive behavior.[3, 12-14] For example, PPS nanoparticles or PEG-PPS vesicles can be used for oxidation-driven drug-release due to the ability of the hydrophobic PPS to be oxidized *via* chemical or enzymatic oxidation to hydrophilic polysulfoxides and/or polysulfones.[15, 16] In addition, PEG-PPS copolymers were also used to prepare protein repellent layers on implants using the metal affinity of the thioether group.[17]

The anionic ring-opening polymerization (AROP) of episulfides (or thiiranes) is known for many years and allows the formation of various polythioether architectures.[18-21] However, this polymerization is still under-developed in comparison with the one of epoxide monomers. While the advent of organic bases in AROP paved the way to new initiation sites for epoxide

monomers, only few families of nucleophilic molecules enable an efficient initiation and a good control of AROP of thiiranes,.[22-25]

The following initiators were originally used for episulfide polymerization: carbanions (such as naphtalene sodium,[26, 27] carbazyl sodium,[28] or fluorenyl tetrabutylammonium[29]), thiolates (sodium, potassium, zinc, cadmium or quaternary ammonium thiolates),[30-33] or quaternary ammonium dithiobenzoates.[34, 35] Thiolate-zinc complex of *N*-methylporphyrins are effective for the *immortal* polymerization of episulfide.[36, 37] Later, the use of protected thiols (in form of thioacetates) allowed a better control over polythioether molar mass and dispersity, avoiding thiol easy oxidation to disulfide and subsequent errors on the initiator concentration.[38] The thioacetyl group is cleaved *in situ* by methanolysis leading to a thiolate able to initiated the controlled AROP of episulfides.[39-44] Living episulfide polymerizations were also obtained using thiol / 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as initiating system allowing the preparation of various architectures.[11, 19, 20, 42, 45, 46] Except for thiol and thiol-derived compounds, carboxylic acid derivatives have been employed as initiators using (Thio)acyl Group Transfer Polymerization developed by Nishikubo and coll.[47-49]

Alcohol and amine groups are more common chemical moieties and easier to handle than thiol groups. Therefore, it would be greatly advantageous to use them as anchoring point for the episulfide polymerization, without any additional functionalization and purification steps. Previous works reported the use of sodium or potassium alkoxides as initiators but the prepared products were either ill-defined or poorly characterized.[11, 50] In fact, direct initiation with another protic functions, such as an alkoxide, induces transfer reactions to the monomer and the control of the polymerization is therefore impossible.[51] In 2020, the use of histamine primary amine function has been investigated as metal-free initiator for the ring-opening of propylene sulfide under acidic conditions.[52] However, only very short polythioether chains (between 5 and 7 units) were obtained (lower than 700 g/mol). To the best of our knowledge,

controlled AROP of episulfides initiated directly by an alcohol or amine groups have never been reported.

γ-thiolactones can be seen as latent thiols. In the presence of a base, the thiol can be released by nucleophilic aminolysis ring-opening of the cyclic thioester. This interesting feature is commonly used in macromolecular science. For example, *N*-acetyl homocysteine thiolactone (NHTL) is used for the thiolation of proteins and peptides.[53] More recently, one-pot multi-step reactions based on thiolactone chemistry have emerged as powerful tools to synthesize original macromolecular architectures and sequence-defined polymers.[54, 55] It is worth noting that the homopolymerization of monocyclic γ-thiolactone has never been reported. However, we recently carried out the ring-opening copolymerization of thiobutyrolactones and epoxides leading to perfectly alternating poly(ester-*alt*-sulfide) structures, demonstrating the efficiency of the thiolactone ring-opening by alcohol in the presence of a phosphazene base.[56-58]

In this paper, the efficiency of γ-thiolactone with alcohol or amine groups as initiating systems for the anionic ring-opening polymerization of propylene sulfide is investigated (Figure 1). The principle of this new method is to perform a one-pot synthesis in two steps, the first of which is the coupling between alcohol or amine group and thiobutyrolactone in the presence of a strong base. This preliminary functionalization of the initiator induces the formation of a thiolate through the ring-opening of the thiolactone, which can then initiate the controlled polymerization of the propylene sulfide in a second step. Particular attention is given to the nature of the chain ends and the control of the polymerization. The influence of the reaction conditions (solvent, base, nature of the thiolactone and reactant ratio) on the initiation efficiency is assessed. Finally, the stability of the ester or amide groups resulting of the ring-opened thiolactone linker is examined in basic conditions.

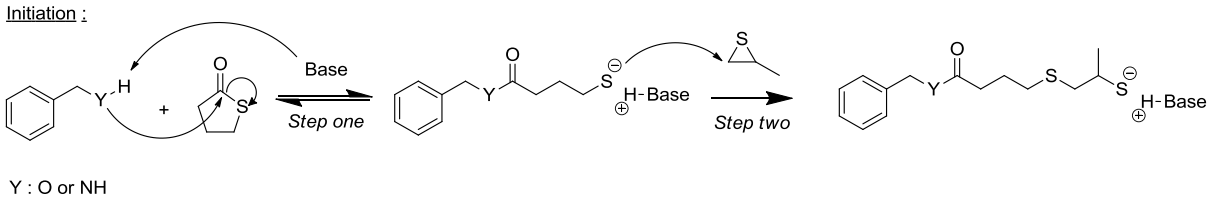

Figure 1. Postulated mechanism of the one-pot, two-step initiation method of the anionic ring-opening polymerization of propylene sulfide by alcohol or amine protic species.

Results and Discussion

The aim of the study is to diversify the range of nucleophilic groups that can efficiently initiate the controlled anionic ring-opening polymerization of episulfides and more specifically propylene sulfide. Hydroxyl functions are abundant in the organic field and their use as initiator remains a real potential for materials and biomaterials development. First part of the study will thus be devoted to the use of alcohol / γ-thiolactone as initiating system for the AROP of propylene sulfide.

Alcohol functionalization:

First, the coupling reaction between benzyl alcohol and γ-thiolactones was extensively investigated, in order to determine which reaction conditions facilitate the ring-opening of the thiolactone. Several reaction parameters were investigated: the nature of the thiolactone, the base, the solvent, the reaction temperature and the molar ratio of the reagents. Two thiolactones were studied: the γ-thiobutyrolactone (TBL) and the *N*-acetyl homocysteine thiobutyrolactone (NHTL). This last compound has the advantage of being bio-based as well as less expensive than TBL. The nucleophilic ring-opening reaction of the thiolactone by the alkoxide is followed by ^{1}H NMR and we observed that an equilibrium is achieved as a function of the operating conditions. Indeed, the ring-opening of the thiolactone and the formation of an ester induce a clear downfield shift of the singlet corresponding to the benzyl

alcohol $-CH_2-$ (Figure S1). The rate of functionalization is calculated according to the equation shown in Figure S1. The functionalization rate was plotted as function of time for the different reaction conditions (Figure 2). The results of all the experiments, the time required to reach the equilibrium and the maximum coupling rate are reported in Table 1.

Table 1. Summary of the conditions and results of the reaction between benzyl alcohol and thiobutyrolactones.

Run	Eq of TBL	Base	Solvent	Temp (°C)	Equilbrium Time (h)	Maximum coupling rate [a] - τ (%)
1	2	*t*BuP$_1$	Toluene	25	2	52
2	2	*t*BuP$_4$	Toluene	25	100	18
3	4	DBU	Toluene	25	35	35
4	2	BEMP	Toluene	25	18	67
5	4	BEMP	Toluene	25	14	81
5'	2+2	BEMP	Toluene	25	24+24	55-76
6	4	DBU	THF	25	30	24
7	4	BEMP	THF	25	30	27
8	2	BEMP	Toluene	50	10	63
9	2	BEMP	Toluene	90	9	55
10	8	BEMP	Toluene	25	20	85
11	4 (NHTL)	BEMP	Toluene	25	12	40
12	4 (NHTL)	BEMP	THF	25	15	41

[a] calculated by ^{1}H NMR spectroscopy (Fig S1).

Four runs were carried out under identical reaction conditions (25°C in toluene) but with different bases to determine their influence on the coupling efficiency (run 1-4, with tert-butylimino-tri(pyrrolidino) phosphorane (*t*BuP$_1$), N‴-(1,1-dimethylethyl)-N,N′,N″-tris[tris(dimethylamino)phosphoranylidene] phosphorimidic triamide (*t*BuP$_4$), DBU and 2-tert-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP), respectively). BEMP shows the highest functionalization rate of 67% (Table 1, run 4). Therefore, the BEMP was selected for the first step of our initiating method. The number of TBL equivalents has a strong effect on the equilibrium: an increase of the number of TBL equivalents to 4 eq. (Table 1, run 5) or 8 eq. (Table 1, run 10) improved the coupling rate from 67% to 81% then to 85%, respectively. However, the difference between the run 5 with 4 equivalents and the run 10 with 8 equivalents is not significant enough to justify to double the amount of TBL at this stage. In addition, run 5' demonstrates the direct influence of the

number of TBL equivalents on the coupling rate. After 24 h of reaction in the presence of 2 eq. of TBL, the coupling rate reached a plateau with a maximum rate of 55%. After the addition of 2 additional equivalents of TBL in the reaction mixture and 24 h reaction, a clear increase of the coupling rate up to 75% was observed (Figure S2). This result is consistent with a chemical equilibrium. The replacement of toluene by THF decreased the efficiency of the coupling (Table 1, run 7). Increasing the temperature did not increase the coupling rate, but only accelerated the reaction (Table 1, run 8 and 9). Finally, the use of the NHTL instead of TBL did not improve the reaction: the functionalization ratio of the alcohol remained limited to a maximum value of ≈ 40% both in toluene (Table 1, run 11) or in THF (Table 1, run 12). Thus, the most convincing results were obtained in toluene at 25°C with 4 equivalents of TBL and using BEMP phosphazene base (Table 1, run 5).

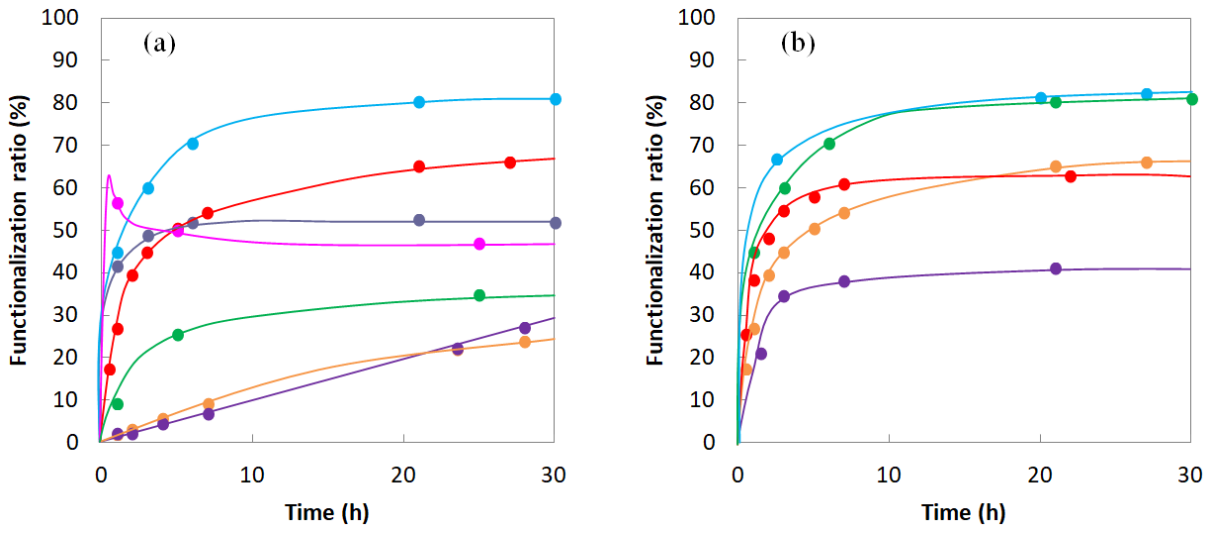

Figure 2. (a) Evolution of the functionalization ratio of the benzyl alcohol by the thiobutyrolactone with time in presence of different base : tBuP1 (run 1 in grey), tBuP4 (run 2 in pink), BEMP (run 4 in red, run 5 in blue, run 7 in purple) and DBU (run 3 in green and run 6 in orange). (b) Evolution of the functionalization ratio of the benzyl alcohol by the thiobutyrolactone with time in presence of the BEMP in toluene with different conditions : temperature (run 4 in orange and run 8 in red), equivalent of TBL (run 5 in green and 10 in blue) and with NHTL (run 11 in purple).

The AROP of propylene sulfide is then investigated using alcohol - γ-thiolactone - BEMP as initiating system according to a one-pot two steps reaction process. According to the results obtained in the previous part, the alcohol-thiolactone coupling step is first carried out in the

presence of an excess of thiolactone and in the absence of monomer at 25°C for at least 20 h. The coupling time and coupling rate are shown in Table 2 for each reaction. Then, the monomer is added according to the conditions reported in Table 2.

Table 2. Experimental conditions and molecular characteristics of propylene sulfide (5M) polymerizations using benzyl alcohol, a thiolactone and different bases as initiating systems.

Run	OH :BEMP :TBL :M	Solvent	Coupling - Time (h)	τ (%)	Time (h)	T (°C)	Cv[a] (%)	Quencher	$M_{n,th}$ (g/mol)	$M_{n,NMR}$[b] (g/mol)	$M_{n,SEC}$ (g/mol)	Dispersity
13	1:1:0:50	Toluene	-	-	2	25	100	BrAcEt	3980	12900	2900	1.88
14	1:1:2:50	Toluene	26	54	2	25	100	BrAcEt	4080	6300	3060	1.74
15	1:1:4:50	Toluene	26	70	2	25	100	BrAcEt	4080	7400	2850	1.50
16	1:1:4:50	DMF	24.5	low	0.25	25	100	BrAcEt	4080	13660	2330	2.02
17	1:1:4:50	THF	26	17	2	25	100	BrAcEt	4080	11700	2190	1.95
18	1:1:0:50	Toluene	-	-	2	-20	28	BrAcEt	1410	4480	2800	1.67
19	1:1:4:50	Toluene	24.5	70	1.5	-20	100	BrAcEt	4080	7150	6000	1.24
20	1:1:4:50	Toluene	24.5	68	0.8	-20	94	Acetic acid	3690	4700	9800	1.14
21	1:1:4:50	Toluene	19.5	70	0.5	-20	74	BrAcEt	3110	4590	3850	1.31
22	1:1:4:50	Toluene	22.5	69	0.5	-20	70	Allyl Br	2970	4990	3290	1.16
23	1:1:4:100	Toluene	24	75	2.3	-20	74	Allyl Br	5814	8480	6870	1.20
24	1 :1 :4 :100°	Toluene	24	75	27	-20	71	Allyl Br	5590	6780	5910	1.26
25	1 :1 :4 :100*°	Toluene	24	72	25	-20	70	Allyl Br	5520	5630	5160	1.17
26	1 :1 :4 :250*°	Toluene	24	77	64	-20	70	Allyl Br	13300	13260	9000	1.45

°: diluted monomer concentration : 2.5M instead of 5M

*: dropwise addition of the monomer at 0.5 mL/h

[a]: monomer conversion calculated by ^{1}H NMR spectroscopy by comparison of the free monomer signal integration with the corresponding polymer chain signal integration

[b]: experimental molar mass determined by ^{1}H NMR spectroscopy of the purified product by comparison of a initiator signal integration with a polymer chain signal integration

First, the polymerization of propylene sulfide was performed in the absence of thiolactone using benzyl alcohol - BEMP as initiating system in order to serve as reference (Table 2, run 13). The direct initiation of propylene sulfide polymerization by an alcohol did not lead to the control of the molar masses. High dispersity is obtained and the experimental molar masses determined by NMR and size exclusion chromatography are not in agreement with the theoretical one. $M_{n,NMR}$ is almost four times higher than $M_{n,th}$ and $M_{n,SEC}$ suggesting both low initiation efficiency and the occurrence of transfer reactions. These assumptions are confirmed by the ^{1}H NMR spectrum of the reaction mixture after quenching by ethyl

bromoacetate, on which almost no ether function could be detected, suggesting that only an extremely limited amount of benzyl alcohol initiated polymer chains (Figure S3). In addition, signals corresponding to allyl end groups as a consequence of transfer to propylene sulfide monomer are detected between 4.95 and 5.10 ppm and between 5.80 and 5.95 ppm. An additional singlet is also visible at 5.24 ppm; we assume that this signal results from the transesterification reaction between non-reacted benzyl alcohol and ethyl acetate end-functionalized polymer chains (Figure S4). The occurrence of the transfer reaction to the monomer and of the final transesterification reaction are confirmed by MALDI-TOF spectrometry, on which four distributions are visible (Figure S5). It should be noted that a minor population corresponding to polymer chains initiated by benzyl alcohol and terminated by ethyl bromoacetate is also visible on the spectrum. A decrease of the reaction temperature to -20°C (in order to reduce side reactions) did not help to improve these results (Table 2, run 18) the polymerization stopped at only 28% monomer conversion. The results were improved by adding 2 or 4 equivalents of TBL as a co-initiator (Table 2, run 14 and 15). On the ^{1}H NMR spectra of the final reaction mixtures after quenching, a peak at 5.16 ppm corresponds to the methylene group of the benzyl alkoxy connected to a ring-opened thiolactone unit (Figure S3). Moreover, no initiation by the alkoxide could be detected and a very strong decrease of the signals corresponding to the side-reactions is noted, especially in the case of 4 equivalents of thiolactones with complete disappearances. Compared to the reaction carried out in the absence of TBL, the number-average molar mass determined by ^{1}H NMR are closer to the M_n determined by SEC (Table 2, runs 14 and 15). However, the experimental M_n are still relatively far away from the theoretical M_n and the dispersities are high. The SEC profile of run 15 shows a tail towards low molar masses, which could results from the presence of undetected transfer reactions (Figure 3).

For Table 2 run 15, the reaction mixtures were analyzed by ^{1}H NMR just before and just after the addition of episulfide. The spectra showed an increase in the rate of functionalization of the benzyl alcohol. Indeed, the functionalization of the thiolate by a growing polysulfide chain induces a Le Chatelier effect on the equilibrium of the benzyl alcohol - TBL coupling (Figure S6).

The use of more polar solvents, namely DMF (Table 2, run 16) or THF (Table 2, run 17), did not improve the results compared to the reactions performed in toluene. In both cases, the solvents are not good promoters for the coupling between TBL and benzyl alcohol, leading to poorly α-functionalized polymer chains ($M_{n,NMR} >> M_{n,SEC}$), high dispersities and broad SEC traces (Figure S7).

In order to minimize the transfer reactions, the polymerization temperature was reduced to -20°C (Table 2, runs 19-22). At this temperature, dispersities are significantly lower (as low as 1.14), suggesting a significant decrease of the secondary reactions during the polymerization. In addition, quenching the reaction before full monomer conversion allowed to greatly reduces the formation of intermolecular disulfide as illustrated by the comparison of the SEC traces of runs 19 and 22 (Figure 3). Indeed, this type of dimerisation reaction occurs mainly at the end of the polymerization.[38] Different quenching agents were tested as reported in Table 2, and the best results were obtained with allyl bromide. A quench with acetic acid (Table 2, run 20) formed only thiols at the end of the chain and promoted the spontaneous formation of disulfides (Figure S8). For the run 22, a good agreement between experimental and theoretical molar masses is observed and the dispersity is narrow with few disulfide formation (Figure 3).

A kinetic study was performed at -40, -20, 0 and 25°C under similar conditions to those of run 22. For all the temperatures, the polymerizations were first order with respect to the monomer over the entire conversion range (Figure 4). These results demonstrates that the

concentrations of active centers remained constant during throughout the polymerizations: no termination reaction or slow initiation steps. Values of 0.161, 0.601, 1.395 and 1.920 $L.mol^{-1}.min^{-1}$ for the rate constants of propagation ($k_{p,app}$) were calculated from the slope of the regression lines for the polymerization performed at -40, -20, 0 and 25°C, respectively.

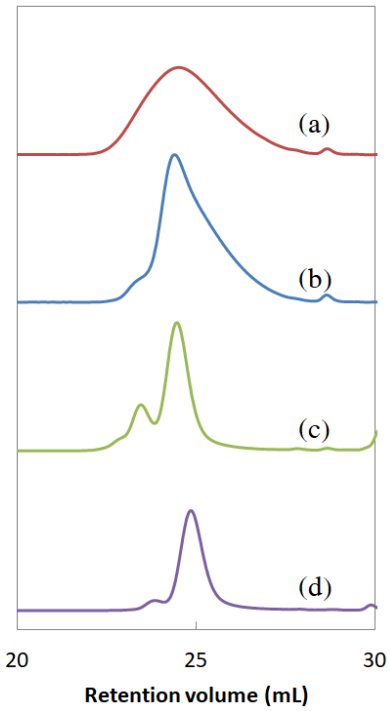

Figure 3. SEC analysis of run 13 (a, in red), 15 (b, in blue), 19 (c, in green) and 22 (d, in purple) in THF.

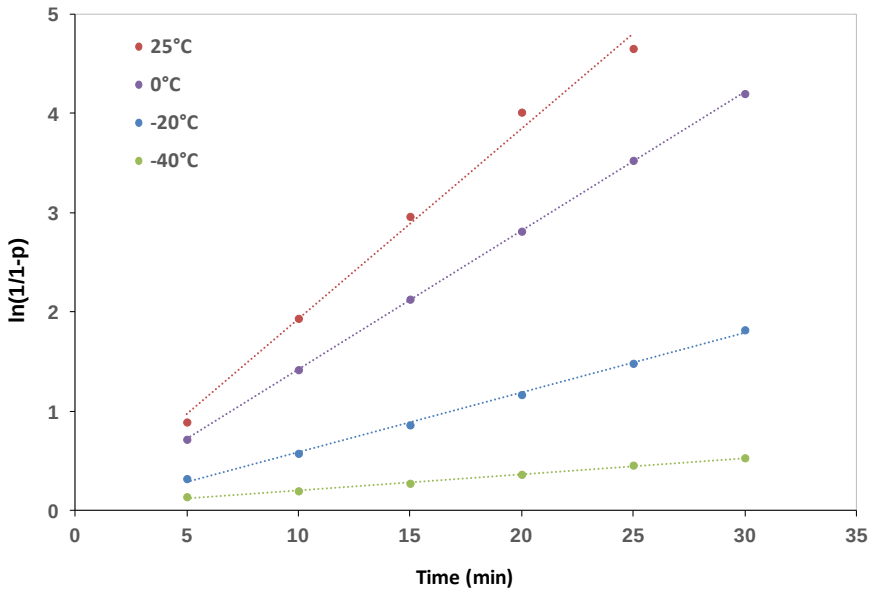

Figure 4. Kinetic study of the propylene sulfide polymerization in toluene using benzyl alcohol-TBL-BEMP as initiating system following time at different temperatures: -40°C (green), -20°C (blue), 0°C (purple), 25°C (red).

Other syntheses were carried out, aiming higher degrees of polymerization. Run 23 was performed using a ratio $[M]_0:[I]_0 = 100:1$. At high monomer conversion, the reaction medium became excessively viscous and the stirring stopped. SEC and NMR analyses witness significant disulfide bond formation (Figure S9). Therefore, the monomer concentration was divided by 2 ($[M]_0 = 2.5$ mol.L^{-1} instead of 5.0 mol.L^{-1}) keeping the same $[M]_0:[I]_0$ ratio. A better agreement between experimental and theoretical molar mass is observed but intermolecular disulfide coupling is still observed (Table 2, run 24). Run 25 was performed under dropwise additions of a monomer solution in toluene. Under these conditions, a very good agreement between experimental and theoretical M_n is observed. SEC trace is depicted in Figure S9: low dispersity is obtained and almost no disulfide formation can be observed at high molar mass. Finally, a degree of polymerization of 250 was targeted in run 26, leading to polythioethers with M_n of almost 10,000 g.mol^{-1}.

Table 2 run 22 and 25 polymers have been carefully characterized by ^{1}H, ^{13}C, COSY and HSQC NMR and MALDI-TOF spectrometry (Figures 5-6 and S10-S14). On the ^{1}H NMR and ^{13}C NMR spectra (Figures 5, S10 and S13), all signals could be attributed to the expected α,ω-heterotelechelic polymer, bearing one benzyloxy ring-opened thiolactone and one allyl end groups. It is worth noting that in the case of Table 2 run 25, only the expected α,ω-heterotelechelic poly(propylene sulfide) population is visible on the MALDI-TOF spectrum shown in Figure 6. However, in the case of Table 2 run 22, one major and two very minor distributions could be identified on the MALDI-TOF spectrum (Figure S14). For all the distributions, the molar mass difference between two peaks is strictly equal to the molar mass of one propylene sulfide repeating unit (74.02 mass unit) and all the three populations were identified. The main distribution corresponds to the expected poly(propylene sulfide) cationized by a sodium ion and end-terminated by a benzyloxy ring-opened thiolactone group

at one end and by an allyl group at the other end. The two minor populations can be attributed to poly(propylene sulfide) chains initiated by moisture traces or resulting from transfer reaction to the monomer.

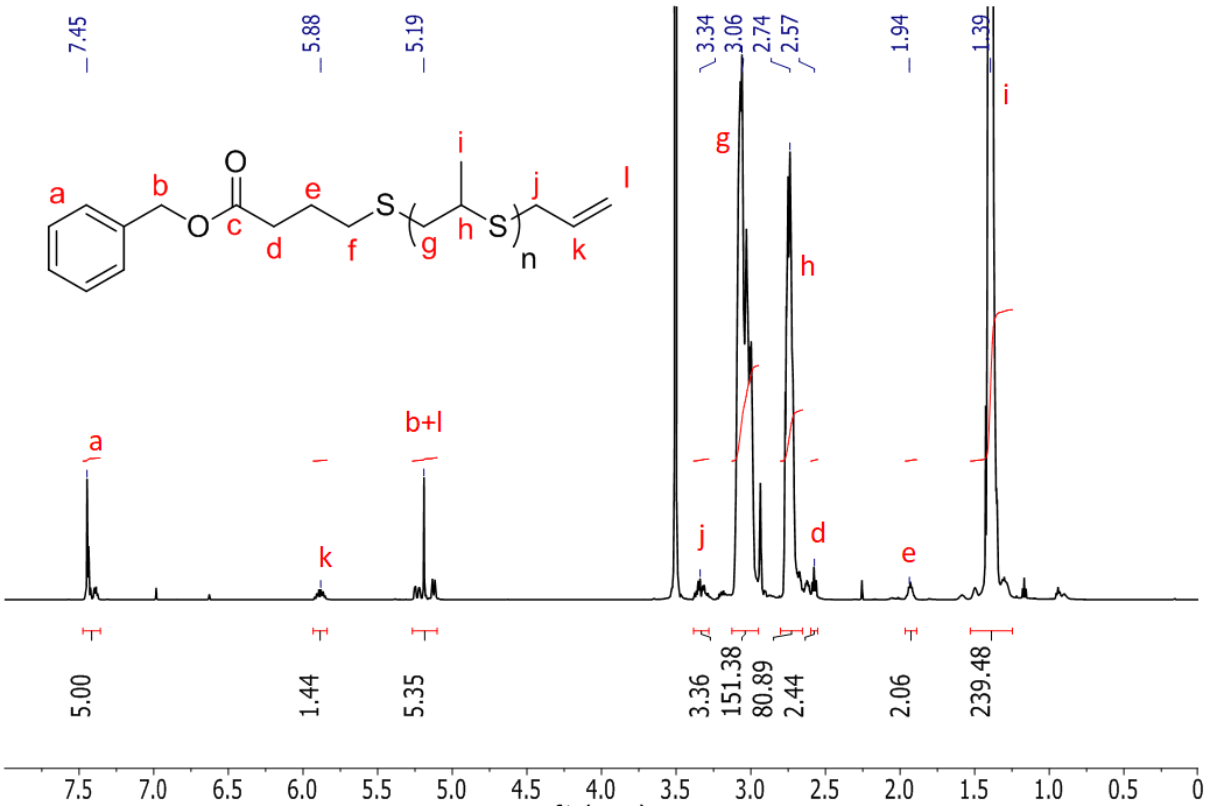

Figure 5. ^{1}H NMR spectrum of run 25 in DMF-d_7 at 25°C.

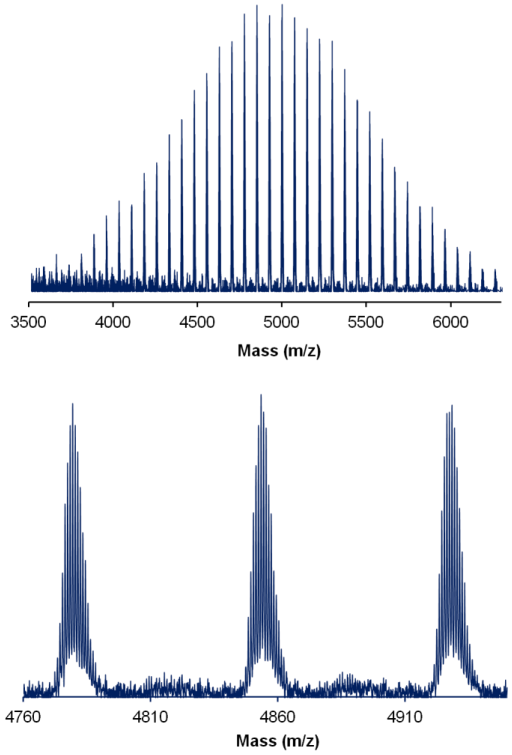

Figure 6. MALDI-TOF spectrum (reflectron mode) of a poly(propylene sulfide) synthesized using benzyl alcohol-thiobutyrolactone-BEMP as initiating system at -20 °C (Table 2, run 25).

This two-step initiation method allows functionalizing alcohols protic groups by AROP of episulfides in a controlled way. But it also induces the presence of an ester function between the initiator and the polymer chain. An hydrolysis was carried out on one α,ω-heterotelechelic poly(propylene sulfide) to evaluate the cleavability of this ester group. Table 2 run 22 polymer was analyzed by ^{1}H NMR before and after a simple treatment with sodium hydroxide at 0.1 mol.L^{-1} in a THF-methanol mixture (50% volume each). A shift of the methylene protons in alpha position of the aromatic ring from 5.19 ppm to 4.73 ppm is observed, proving the hydrolysis of the ester function and the cleavage of the benzyloxy during the treatment (Figure S15). In addition, after dialysis of the hydrolyzed product (1kDa cut-off), the signals corresponding to the benzyl alcohol are not present anymore while the signals of the polymer chain are still visible (Figure 7). The hydrolyzed polymer is also analyzed by SEC, demonstrating the integrity of the polymer chains (Figure S16).

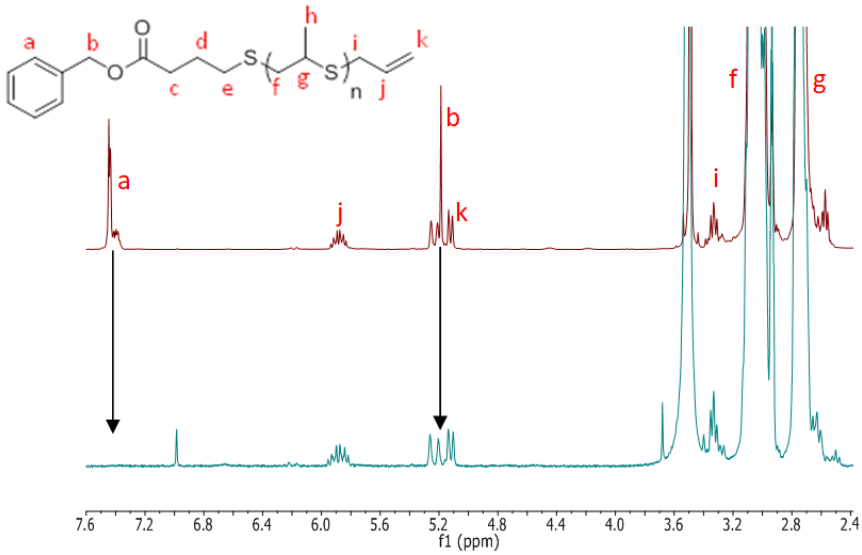

Figure 7. ^{1}H NMR spectrum (in DMF-d_7 at 25 °C) of run 22 before (in red) and after (in green) basic hydrolysis followed by dialysis against THF.

Amine functionalization:

In order to further extend the scope of the nucleophilic compounds that can be used as initiators for episulfide AROP, similar investigations were performed using benzylamine. As previously, preliminary studies have been performed to investigate the thiolactone-amine equilibrium. The results of this study are summarized in Table 3 and in Figure S17.

Table 3. Summary of the conditions and results of the reaction between benzylamine and thiobutyrolactones.

Run	Eq of thiolactone	Base	Solvent	Temp (°C)	Equilbrium Time (h)	Maximum coupling[a] rate (%)
27	4 (TBL)	BEMP	Toluene	25	2	6.5
28	4 (TBL)	BEMP	THF	25	2	7
29	2 (NHTL)	BEMP	THF	25	11	100
30	4 (NHTL)	BEMP	THF	25	3.3	100
31	4 (NHTL)	BEMP	THF	50	2.5	100
32	4 (NHTL)	BEMP	Toluene	25	3	100
33	4 (NHTL)	DMAP	THF	25	20	100
34	4 (NHTL)	*t*BuP$_4$	THF	25	2.75	100
35	4 (NHTL)	DBU	THF	25	0.75	100

[a]: calculated by ^{1}H NMR spectroscopy (Figure S18).

The optimized coupling conditions determined in the case of alcohol groups were applied to the functionalization of amine group with TBL in toluene or in THF providing very limited coupling rates (Table 3 runs 27 and 28). Du Prez et al. showed that the coupling between

NHTL and an amine in the presence of DMAP is quantitative,[36] therefore we chose to replace TBL by NHTL (Table 3, runs 29-35). Unlike the reaction between TBL and benzyl alcohol where the functionalization rate did not exceed 85%, the coupling of benzylamine with NHTL was fast and quantitative under all the tested conditions.

The AROP of propylene sulfide is then investigated using benzyl amine / NHTL / BEMP as initiating system according to a one pot two-step reaction process. The different reaction conditions are summarized in the table 4.

Table 4. Experimental conditions and molecular characteristics of poly(propylene sulfide) samples synthesized using benzylamine, a thiolactone and different bases as initiating systems.

Run	NH_2:BEMP: TBL:M	Thiolactone	Solvent	T (°C)	Coupling - Time (h)	τ (%)	Polym - Time (h)	Cv[a] (%)	$M_{n,th}$ (g/mol)	$M_{n,NMR}$[b] (g/mol)	$M_{n,SEC}$ (g/mol)	Dispersity
36	1:1:0:50	-	THF	-20	-	-	2	75	3000	61270	10170	1.53
37	1:1:4:50	TBL	Toluene	-20	27	7	0.7	36	1440	2490	6880	1.28
38	1:1:4:50	NHTL	Toluene	-20	25	100	0.7	21	1020	1890	2840	1.37
39	1:1:4:50	NHTL	THF	-20	24	100	1.25	100	4100	4380	4150	1.25
40	1:1:4:100*°	NHTL	THF	-20	3.5	100	19.5	100	7720	7410	6360	1.15

°: diluted monomer concentration: 2.5M instead of 5M

*: dropwise addition of the monomer at 0.5 mL/h

[a]: monomer conversion calculated by ^{1}H NMR spectroscopy by comparison of the free monomer signal integration with the corresponding polymer chain signal integration

[b]: experimental molar mass determined by ^{1}H NMR spectroscopy of the purified product by comparison of a initiator signal integration with a polymer chain signal integration

A first control experiment was conducted in THF with one equivalent of BEMP but without thiolactone (Table 4, run 36). The experimental number-average molar masses determined by SEC and ^{1}H NMR are much higher than the theoretical one, suggesting a poor efficiency of amine groups as direct initiator for the polymerization of episulfides. In addition in SEC, the resulting polymer exhibits a high molar mass distribution ($Đ$ = 1.56) with low-molar-mass tailing. A second control polymerization was carried out under the experimental conditions that had been optimized for benzyl alcohol initiator, i.e. in toluene in the presence of 1 eq. of BEMP and 4 eq. of γ-thiolactone (Table 4, run 37). Due to the low coupling rate (7%), the M_n

is not controlled and the polymerization rate is slow compared to those of the polymerizations using alcohol-γ-thiolactone as initiating system.

As expected, the use of NHTL as a co-initiator greatly improved the results, especially when the reaction is performed in THF (Table 4, run 39). In this case, the coupling of benzylamine with NHTL is quantitative and a very good agreement is observed between the experimental M_n and $M_{n,th}$. In addition, a dispersity value equal to 1.25 was measured by SEC with a limited formation of disulfides (Figure S19). Eventually, a well-defined polymer with a higher *Mn* (6360 g.mol^{-1}) and a low dispersity (Đ = 1.15) was synthesized using a monomer dropwise addition of the monomer (Table 4, run 40). The last polymers were carefully characterized by SEC, NMR and MALDI-TOF spectroscopy (Figures 8-9 and S20-S24). All the ^{1}H and ^{13}C NMR signals could be attributed to the expected structure (Figures 8 and S23). These results are confirmed by MALDI-TOF spectroscopy where, in the case of run 40, only the population corresponding to poly(propylene sulfide) chains, terminated by allylbromide and initiated by the benzylamine linked to one unit of NHTL, could be evidenced (Figure 9). It may be noted that two minor populations are visible on the MALDI-TOF spectrum of run 39 and correspond to moisture-initiated chains and transfer to the monomer (Figure S24).

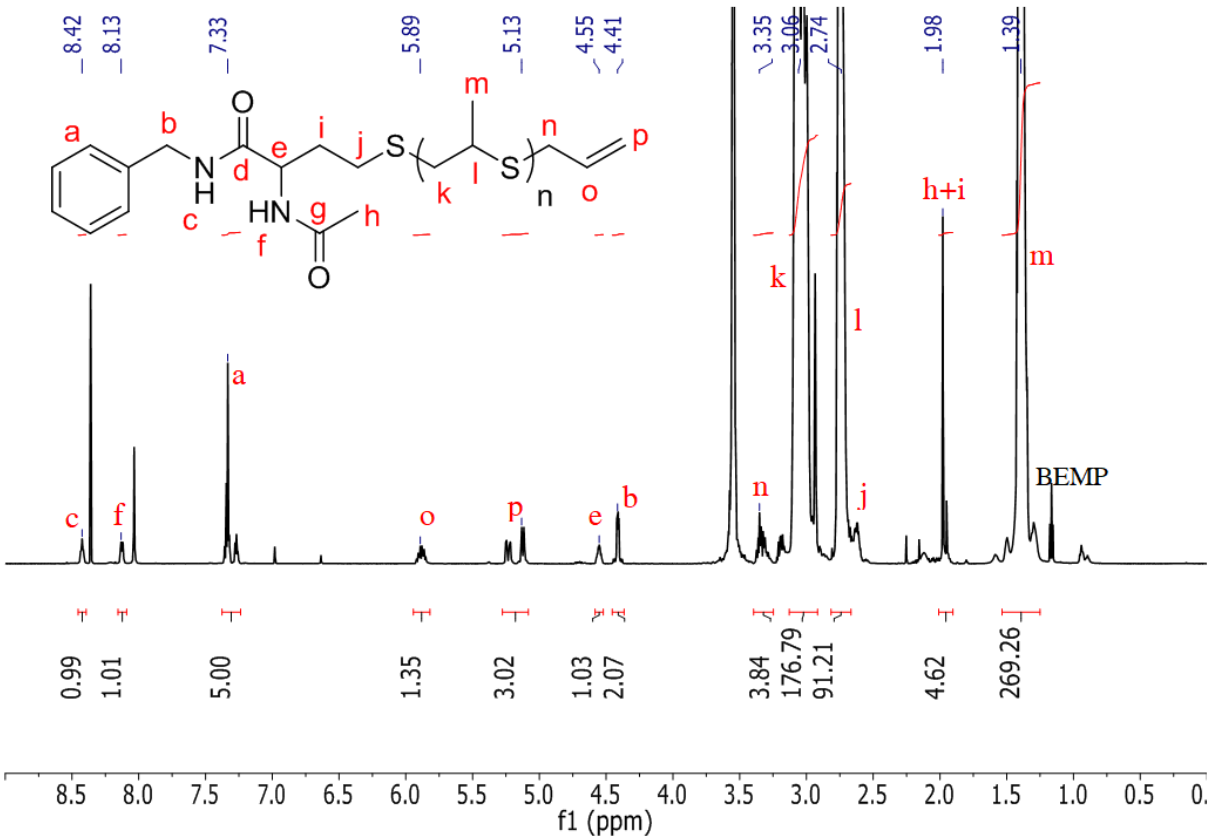

Figure 8. ^{1}H NMR spectrum of run 40 in DMF-d_7 at 25°C.

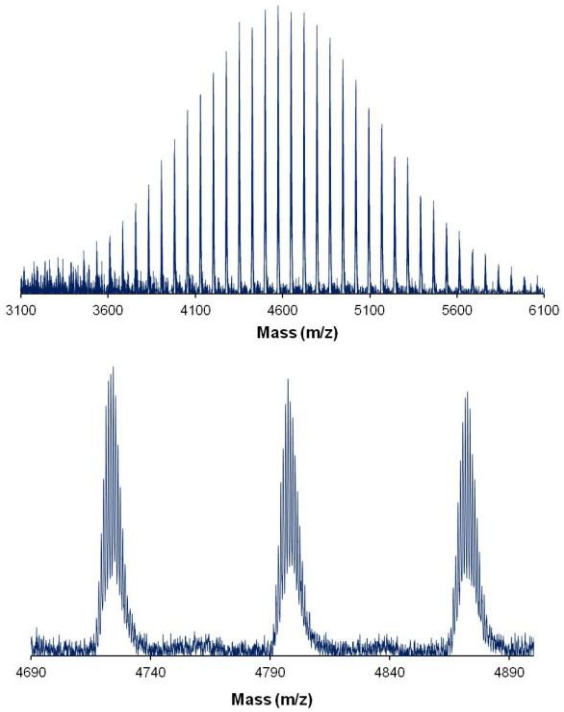

Figure 9. MALDI-TOF spectrum (reflectron mode) of a poly(propylene sulfide) synthesized using benzyl alcohol-thiobutyrolactone-BEMP as initiating system at -20 °C (Table 4, run 40).

A kinetic study was performed at -40, -20, 0 and 25 °C under the conditions of run 39. At 0 and 25°C, the polymerization were very fast and full monomer conversions were reached in less than 5 minutes. For the polymerizations at 0 and 25 °C, kinetic data could be fitted according to a first-order equation showing that the concentrations of the propagating species were constant and no termination reaction occurred over time (Figure S25). Values of 0.019 and 0.643 $L.mol^{-1}.min^{-1}$ for the rate constants of propagation ($k_{p,app}$) were determined.

Then, the stability of the amide function between the initiator and the polythioether chain was tested on the polymer prepared in run 39 under basic conditions ($[NaOH]_0$ = 0.1 mol/L in THF:methanol 50:50 in volume). ^{1}H NMR analyses before and after hydrolysis demonstrate the stability of the amide, which is not hydrolyzed under these conditions contrary to the ester groups in the previous part of this work (Figure S26).

Conclusion

In conclusion, a one pot - two steps method has been developed in order to efficiently initiate the controlled AROP of propylene sulfide with alcohol or amine groups without any preliminary functional modification reaction. This could be achieved due to the latent thiol nature of thiolactones and to the study of their ring-opening by primary alcohols and amines generating thiolates in the presence of different organic bases and under different reaction conditions. Well-defined α-ω-heterotelechelic poly(propylene sulfide)s were synthesized with molar masses up to 10 $kg.mol^{-1}$. In the case of alcohol moieties, the best results were obtained for reactions in toluene using TBL, while in the case of amine moieties, reaction should preferably be performed in THF using NHTL. Depending on the initiating function, the thiolactone linker unit inserts an ester or an amide bond between the initiating compound and the polythioether chain. The stability of these bonds were investigated under basic conditions.

Ester bond were hydrolyzed under the tested conditions and benzyl alcohol was released opening the way to prodrug synthesis strategy. It is noteworthy that the termination step is crucial to control the chain ends and to limit the formation of disulfides. A quench at low conversion was used to greatly limit these intermolecular couplings at the end of the polymerization. The possibility to use very common functional groups, such as alcohols or amines, as nucleophilic initiators for AROP of episulfides is expected to lead to new synthetic strategies for macromolecular engineering and to easier grafting-from polymerization reaction of polythioether chains on various functional (macro)molecules.

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EXPERIMENTAL SECTION

Materials. 2-*tert*-Butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine solution (BEMP, 1.0 mol.L^{-1} in hexane, Sigma-Aldrich), *N‴*-(1,1-Dimethylethyl)-*N*,*N′*,*N″*-tris[tris(dimethylamino)phosphoranylidene]phosphorimidic triamide solution (*t*BuP_4, 0.8 mol.L^{-1} in hexane, Sigma-Aldrich), tert-Butylimino-tri(pyrrolidino)phosphorane (*t*BuP_1, >97%, Sigma-Aldrich), 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU, >99%, Sigma-Aldrich), CaH_2 (93%, 0-2 mm grain size, Acros Organics), benzyl alcohol (99.8% anhydrous, Sigma-Aldrich), benzylamine (99,5%, Acros Organics), N-acetyl-DL-homocysteine thiolactone (NHTL, >99%, Sigma-Aldrich), allyl bromide (99%, Alfa-Aesar) and ethyl bromoacetate (98%, Alfa-Aesar) were used as received. Propylene sulfide (98%, TCI-Chemicals) and γ-thiobutyrolactone (TBL, 98%, Sigma-Aldrich) were cryo-distilled over CaH_2 twice prior use. Toluene and THF were dried with an MBRAUN MB SPS-800 solvent purification system under nitrogen.

Instruments. *^{1}H and ^{13}C NMR spectra* were recorded in $CDCl_3$ or DMF-d7 using a Bruker 400 MHz NMR spectrometer. Size Exclusion Chromatography Experiment (SEC) were carried out on three PL gel Mixed-C 5µm columns (7,5 × 300 mm; separation limits: 0,2 to 2000 kg.mol^{-1}) maintained at 40°C and sample Viscotek GPCmax delivery module and 2 modular detectors: a Viscoteck 3580 differential refractive index (RI) detector and a Shimadzu SPD20-AV diode array UV detector. THF was used as the mobile phase at a flow rate of 1 mL.min^{-1}, toluene was used as a flow rate marker. All polymers were injected (50 µL) at a concentration of 5 mg.mL^{-1} after filtration through a 0.45 µm pore-size membrane. The OmniSEC 4.6.2 software was used for data acquisition and analysis. Number-average molar masses (M_n), weight-average molar masses (M_w) and dispersities were determined by SEC with a calibration curve based on poly(methyl methacrylate) standard, using the RI detector.

Matrix-Assisted Laser Desorption and Ionization Time-of-Flight Mass Spectrometry (MALDI−TOF MS). Mass spectra were recorded by MALDI-TOF MS using dithranol as a matrix and NaI as cationizing agent using a Bruker Autoflex Speed mass spectrometer, equipped with a laser that produces pulses at 337 nm or using an Applied Biosystems 4700 Proteomics Analyzer instrument. Spectra were recorded in reflectron mode at an accelerating potential of 20 kV. Samples were prepared by dissolving the polymer in THF at a concentration of 5 mg.mL^{-1}. A 10 µL aliquot of this solution was mixed with 20 µL of matrix solution and 10 µL of NaI solution (both at 20 mg.mL^{-1} in THF). Poly(ethylene oxide) standards (Polymer Standards Service) of known structures, Mn =1500 g·mol^{-1} were used to calibrate the mass scale. In all cases, to determine m/z, the molar mass of the sodium cation was added.

Typical procedures for the study of the benzyl alcohol / γ-thiolactone equilibrium. In a glove box, 1mL of toluene, 25µL of benzyl alcohol (0.242 mmol, 1eq) and 42µL (0.484mmol, 2eq), 84µL (0.968mmol, 4eq) or 168µL (1.936 mmol, 8eq) of thiobutyrolactone are introduced in a reaction tube. 240µL of 1M BEMP solution (0.240 mmol, 1eq) is then added. The tube is placed under stirring in an oil bath at the studied temperature. Samples are taken with a syringe through the septum to perform a ^{1}H NMR analysis of the reaction medium. The functionalization rate of the benzylic initiator is then calculated by the integration ratio of the signals of the aliphatic proton of the initiator between its alcohol form and the ester form (Fig S1). A similar protocol has been used with benzyl amine instead of benzyl alcohol as initiator.

General polymerization procedure. The polymerization was carried out according to the following typical procedure (Table 2, run 22). In a glove box, 1 mL of solvent (toluene or THF), 25 µL of benzyl alcohol (0.242 mmol) and 84 µL of thiolactone (4eq., 0.968 mmol) are introduced in a reaction tube. 240 µL of the 1M BEMP solution (1eq., 0.242 mmol) is then added using a microsyringe. The tube is placed under stirring in an oil bath at 25°C. After 20h of equilibrium for the coupling, the reaction tube is placed in an isopropanol bath thermostated at -20°C. After 20-30 min (when the reaction medium cooled at -20°C), 1 mL of propylene sulfide (50 eq., 12.1 mmol) is added dropwise through the septum (within 5 min of time to limit the temperature increase of the reaction mixture).

A small portion of the reaction mixture was sampled through a septum at different times for ^{1}H NMR analysis. The monomer conversion is determined by comparing the signals corresponding to the $-CH_3$ of both monomer and polymer. After 70% of monomer conversion, an excess of terminating agent (0.1 mL of allyl bromide, 1.21 mmol, 5 eq.) is then added to quench the polymerization and let to react overnight. Then, the final reaction mixture is placed in the rotary evaporator to remove the solvents and the remaining volatile monomers. The resulting crude product is then analyzed by SEC in THF using PMMA

standard to determine the molar masses and then, dialyzed in cellulose ester membrane (Repligen Spectra/Por 6 dialysis tubing, flat width = 45 mm, molecular cutoff = 1 kDa) against THF for 24 h with 3 solvent changes. After removing the solvent under rotary evaporation, the product is dried under vacuum at 50 °C overnight. A colorless oil is obtained (yield = 80%) and analyzed by ^{1}H, ^{13}C, COSY, HSQC NMR and MALDI-TOF. Deviations from this general procedure are summarized in Tables 2 and 4.

Typical procedures for hydrolysis. In a tube reaction, 100 mg of polymer is dissolved in 1mL of NaOH solution (0.1 $mol.L^{-1}$) in a mixture of methanol and tetrahydrofurane (50:50 volume ratio). The tube is placed under stirring in an oil bath at 37°C. Samples are taken with a syringe through the septum to perform a ^{1}H NMR analysis of the reaction medium. The functionalization rate of the benzylic initiator is then calculated by the integration ratio of the signals of the aliphatic proton of the initiator between its alcohol form and the ester form (Fig S1). After 17h of reaction (overnight), the reaction medium is neutralized with HCl. A liquid-liquid extraction is performed with water and chloroform. The organic layers is recovered and dryied over $MgSO_4$. After removing the solvent under rotary evaporation, the product is dialyzed in cellulose ester membrane (Repligen Spectra/Por 6 dialysis tubing, flat width = 45 mm, molecular cutoff = 1 kDa) against THF for 24 h with 3 solvent changes. After removing the solvent under rotary evaporation, the product is dried under vacuum at 50 °C overnight. A colorless oil is obtained (yield = 70%) and analyzed by ^{1}H NMR and SEC in THF using PMMA standard to determine the molar masses.

Supporting Information. NMR spectra of reaction mixtures and polymers, MALDI-TOF spectra and SEC traces.

References

(1) Zhang, X. H.; Theato, P. *Sulfur-Containing Polymers: From Synthesis to Functional Materials*; Wiley, 2021.

(2) Mutlu, H.; Ceper, E. B.; Li, X.; Yang, J.; Dong, W.; Ozmen, M. M.; Theato, P. Sulfur Chemistry in Polymer and Materials Science. *Macromolecular Rapid Communications* **2019**, *40* (1), 1800650. DOI: 10.1002/marc.201800650.
(3) Vo, C. D.; Kilcher, G.; Tirelli, N. Polymers and Sulfur: what are Organic Polysulfides Good For? Preparative Strategies and Biological Applications. *Macromolecular Rapid Communications* **2009**, *30* (4-5), 299-315. DOI: https://doi.org/10.1002/marc.200800740.
(4) Worthington, M. J. H.; Kucera, R. L.; Chalker, J. M. Green chemistry and polymers made from sulfur. *Green Chem.* **2017**, *19* (12), 2748-2761, 10.1039/C7GC00014F. DOI: 10.1039/c7gc00014f.
(5) Lv, J.; Liu, Z.; Zhang, J.; Huo, J.; Yu, Y. Bio-based episulfide composed of cardanol/cardol for anti-corrosion coating applications. *Polymer* **2017**, *121*, 286-296. DOI: https://doi.org/10.1016/j.polymer.2017.06.036.
(6) Pirayesh, A.; Salami-Kalajahi, M.; Roghani-Mamaqani, H.; Najafi, F. Polysulfide Polymers: Synthesis, Blending, Nanocomposites, and Applications. *Polymer Reviews* **2019**, *59* (1), 124-148. DOI: 10.1080/15583724.2018.1492616.
(7) Syao, O.; Malysheva, G. V. Properties and application of rubber-based sealants. *Polymer Science Series D* **2014**, *7* (3), 222-227. DOI: 10.1134/s1995421214030150.
(8) Higashihara, T.; Ueda, M. Recent Progress in High Refractive Index Polymers. *Macromolecules* **2015**, *48* (7), 1915-1929. DOI: 10.1021/ma502569r.
(9) He, L.; Szopinski, D.; Wu, Y.; Luinstra, G. A.; Theato, P. Toward Self-Healing Hydrogels Using One-Pot Thiol–Ene Click and Borax-Diol Chemistry. *ACS Macro Letters* **2015**, *4* (7), 673-678. DOI: 10.1021/acsmacrolett.5b00336.
(10) Pepels, M.; Filot, I.; Klumperman, B.; Goossens, H. Self-healing systems based on disulfide–thiol exchange reactions. *Polymer Chemistry* **2013**, *4* (18), 4955-4965, 10.1039/C3PY00087G. DOI: 10.1039/c3py00087g.
(11) Hatakeyama-Sato, K.; Wakamatsu, H.; Matsumoto, S.; Sadakuni, K.; Matsuoka, K.; Nagatsuka, T.; Oyaizu, K. TEMPO-Substituted Poly(ethylene sulfide) for Solid-State Electro-Chemical Charge Storage. *Macromolecular Rapid Communications* **2021**, *42* (4), 2000607. DOI: https://doi.org/10.1002/marc.202000607.
(12) Carampin, P.; Lallana, E.; Laliturai, J.; Carroccio, S. C.; Puglisi, C.; Tirelli, N. Oxidant-Dependent REDOX Responsiveness of Polysulfides. *Macromol. Chem. Phys.* **2012**, *213* (19), 2052-2061. DOI: https://doi.org/10.1002/macp.201200264.
(13) Lallana, E.; Tirelli, N. Oxidation-Responsive Polymers: Which Groups to Use, How to Make Them, What to Expect From Them (Biomedical Applications). *Macromol. Chem. Phys.* **2013**, *214* (2), 143-158. DOI: https://doi.org/10.1002/macp.201200502.
(14) El Mohtadi, F.; d'Arcy, R.; Yang, X.; Turhan, Z. Y.; Alshamsan, A.; Tirelli, N. Main Chain Polysulfoxides as Active 'Stealth' Polymers with Additional Antioxidant and Anti-Inflammatory Behaviour. *International Journal of Molecular Sciences* **2019**, *20* (18), 4583.
(15) Allen, B. L.; Johnson, J. D.; Walker, J. P. Encapsulation and Enzyme-Mediated Release of Molecular Cargo in Polysulfide Nanoparticles. *ACS Nano* **2011**, *5* (6), 5263-5272. DOI: 10.1021/nn201477y.
(16) Napoli, A.; Valentini, M.; Tirelli, N.; Müller, M.; Hubbell, J. A. Oxidation-responsive polymeric vesicles. *Nature Materials* **2004**, *3* (3), 183-189. DOI: 10.1038/nmat1081.
(17) Feller, L. M.; Cerritelli, S.; Textor, M.; Hubbell, J. A.; Tosatti, S. G. P. Influence of Poly(propylene sulfide-block-ethylene glycol) Di- and Triblock Copolymer Architecture on the Formation of Molecular Adlayers on Gold Surfaces and Their Effect on Protein Resistance: A Candidate for Surface Modification in Biosensor Research. *Macromolecules* **2005**, *38* (25), 10503-10510. DOI: 10.1021/ma051424m.

(18) Boileau, S. Anionic ring-opening polymerization: epoxides and episulfides. *Pergamon Press plc, Comprehensive Polymer Science: the Synthesis, Characterization, Reactions & Applications of Polymers*. **1989**, *3*, 467-487.
(19) Nicol, E.; Bonnans-Plaisance, C.; Levesque, G. A New Initiator System for the Living Thiiranes Ring-Opening Polymerization: A Way toward Star-Shaped Polythiiranes. *Macromolecules* **1999**, *32* (13), 4485-4487. DOI: 10.1021/ma9900434.
(20) Kuhlmann, M.; Singh, S.; Groll, J. Controlled Ring-Opening Polymerization of Substituted Episulfides for Side-Chain Functional Polysulfide-Based Amphiphiles. *Macromolecular Rapid Communications* **2012**, *33* (17), 1482-1486. DOI: https://doi.org/10.1002/marc.201200297.
(21) Takahashi, A.; Yuzaki, R.; Ishida, Y.; Kameyama, A. Controlled ring-expansion polymerization of thiiranes based on cyclic aromatic thiourethane initiator. *Journal of Polymer Science Part A: Polymer Chemistry* **2019**, *57* (24), 2442-2449. DOI: https://doi.org/10.1002/pola.29490.
(22) Dentzer, L.; Bray, C.; Noinville, S.; Illy, N.; Guégan, P. Phosphazene-Promoted Metal-Free Ring-Opening Polymerization of 1,2-Epoxybutane Initiated by Secondary Amides. *Macromolecules* **2015**, *48* (21), 7755-7764. DOI: 10.1021/acs.macromol.5b01638.
(23) Zhao, J.; Schlaad, H. Controlled Anionic Graft Polymerization of Ethylene Oxide Directly from Poly(N-isopropylacrylamide). *Macromolecules* **2011**, *44* (15), 5861-5864. DOI: 10.1021/ma2012392.
(24) Hassouna, L.; Illy, N.; Guegan, P. Phosphazene/triisobutylaluminum-promoted anionic ring-opening polymerization of 1,2-epoxybutane initiated by secondary carbamates. *Polymer Chemistry* **2017**, *8* (27), 4005-4013, 10.1039/C7PY00675F. DOI: 10.1039/c7py00675f.
(25) Tezgel, Ö.; Noinville, S.; Bennevault, V.; Illy, N.; Guégan, P. An alternative approach to create N-substituted cyclic dipeptides. *Polymer Chemistry* **2019**, *10* (6), 776-785, 10.1039/C8PY01552J. DOI: 10.1039/c8py01552j.
(26) Favier, J. C.; Boileau, S.; Sigwalt, P. Etude cinetique de la polymerisation anionique du sulfure de propylene dans: Polymeres bifonctionnels dans le cas d'un contre-ion sodium A −30°. *European Polymer Journal* **1968**, *4* (1), 3-12. DOI: https://doi.org/10.1016/0014-3057(68)90002-5.
(27) Boileau, S.; Champetier, G.; Sigwalt, P. Polymérisation anionique du sulfure de propylène. *Die Makromolekulare Chemie* **1963**, *69* (1), 180-192. DOI: https://doi.org/10.1002/macp.1963.020690114.
(28) Hemery, P.; Boileau, S.; Sigwalt, P. Etude cinetique de la polymerisation du sulfure de propylene dans le tetrahydrofuranne dans le cas d'un contre-ion sodium—IV. Influence de la temperature. Determination des energies d'activation sur les paires d'ions et sur les ions libres. *European Polymer Journal* **1971**, *7* (11), 1581-1593. DOI: https://doi.org/10.1016/0014-3057(71)90027-9.
(29) Tersac, G.; Boileau, S.; Sigwalt, P. Etude cinétique de la polymérisation anionique du sulfure de propylène amorcée par des sels d'ammonium quaternaire. *Die Makromolekulare Chemie* **1971**, *149* (1), 153-167. DOI: https://doi.org/10.1002/macp.1971.021490112.
(30) Cooper, W.; Morgan, D. R.; Wragg, R. T. Initiators for the polymerization of propylene sulphide. *European Polymer Journal* **1969**, *5* (1), 71-77. DOI: https://doi.org/10.1016/0014-3057(69)90105-0.
(31) Guerin, P.; Boileau, S.; Sigwalt, P. Polymerisation stereospecifique du sulfure de propylene en phase homogene. *European Polymer Journal* **1974**, *10* (1), 13-18. DOI: https://doi.org/10.1016/0014-3057(74)90043-3.
(32) Dumas, P.; Sigwalt, P. Living enantiosymmetric and enantioasymmetric polymerization of methylthiirane in homogeneous phase. *Chirality* **1991**, *3* (6), 484-491. DOI: https://doi.org/10.1002/chir.530030614.

(33) Machon, J. P.; Nicco, A. Preparation d'homopolymeres du thietanne de masses moléculaires determinees. *European Polymer Journal* **1971**, *7* (4), 353-361. DOI: https://doi.org/10.1016/0014-3057(71)90006-1.
(34) Bonnans-Plaisance, C.; Levesque, G. Homo- and copolymerization of unprotected 2-(hydroxymethyl)thiirane initiated by quaternary ammonium salts of dithiocarboxylic acids. *Macromolecules* **1989**, *22* (4), 2020-2023. DOI: 10.1021/ma00194a088.
(35) Bonnans-Plaisance, C.; Levesque, G.; Midrak, A. Polymerisation du methylthiirane par les sels d'ammonium quaternaire des (di)thioacides: Etude cinetique dans le THF. *European Polymer Journal* **1994**, *30* (2), 239-244. DOI: https://doi.org/10.1016/0014-3057(94)90166-X.
(36) Aida, T.; Kawaguchi, K.; Inoue, S. Zinc N-substituted porphyrins as novel initiators for the living and immortal polymerizations of episulfide. *Macromolecules* **1990**, *23* (17), 3887-3892. DOI: 10.1021/ma00219a004.
(37) Watanabe, Y.; Aida, T.; Inoue, S. Visible-light-mediated living and immortal polymerizations of epoxides initiated with zinc complexes of N-substituted porphyrins. *Macromolecules* **1990**, *23* (10), 2612-2617. DOI: 10.1021/ma00212a003.
(38) Wang, L.; Kilcher, G.; Tirelli, N. Avoiding Disulfides: Improvement of Initiation and End-Capping Reactions in the Synthesis of Polysulfide Block Copolymers. *Macromol. Chem. Phys.* **2009**, *210* (6), 447-456. DOI: https://doi.org/10.1002/macp.200800466.
(39) Velluto, D.; Demurtas, D.; Hubbell, J. A. PEG-b-PPS Diblock Copolymer Aggregates for Hydrophobic Drug Solubilization and Release: Cyclosporin A as an Example. *Molecular Pharmaceutics* **2008**, *5* (4), 632-642. DOI: 10.1021/mp7001297.
(40) Napoli, A.; Tirelli, N.; Kilcher, G.; Hubbell, A. New Synthetic Methodologies for Amphiphilic Multiblock Copolymers of Ethylene Glycol and Propylene Sulfide. *Macromolecules* **2001**, *34* (26), 8913-8917. DOI: 10.1021/ma0108057.
(41) Brubaker, C. E.; Velluto, D.; Demurtas, D.; Phelps, E. A.; Hubbell, J. A. Crystalline Oligo(ethylene sulfide) Domains Define Highly Stable Supramolecular Block Copolymer Assemblies. *ACS Nano* **2015**, *9* (7), 6872-6881. DOI: 10.1021/acsnano.5b02937.
(42) Rehor, A.; Tirelli, N.; Hubbell, J. A. A New Living Emulsion Polymerization Mechanism: Episulfide Anionic Polymerization. *Macromolecules* **2002**, *35* (23), 8688-8693. DOI: 10.1021/ma0211378.
(43) Wang, L.; Kilcher, G.; Tirelli, N. Synthesis and Properties of Amphiphilic Star Polysulfides. *Macromolecular Bioscience* **2007**, *7* (8), 987-998. DOI: https://doi.org/10.1002/mabi.200700109.
(44) d'Arcy, R.; Gennari, A.; Donno, R.; Tirelli, N. Linear, Star, and Comb Oxidation-Responsive Polymers: Effect of Branching Degree and Topology on Aggregation and Responsiveness. *Macromolecular Rapid Communications* **2016**, *37* (23), 1918-1925. DOI: https://doi.org/10.1002/marc.201600481.
(45) Jeanmaire, D.; Laliturai, J.; Almalik, A.; Carampin, P.; Richard, d. A.; Lallana, E.; Evans, R.; Winpenny, R. E. P.; Tirelli, N. Chemical specificity in REDOX-responsive materials: the diverse effects of different Reactive Oxygen Species (ROS) on polysulfide nanoparticles. *Polymer Chemistry* **2014**, *5* (4), 1393-1404, 10.1039/C3PY01475D. DOI: 10.1039/c3py01475d.
(46) Vo, C.-D.; Cadman, C. J.; Donno, R.; Goos, J. A. C. M.; Tirelli, N. Combination of Episulfide Ring-Opening Polymerization With ATRP for the Preparation of Amphiphilic Block Copolymers. *Macromolecular Rapid Communications* **2013**, *34* (2), 156-162. DOI: https://doi.org/10.1002/marc.201200636.
(47) Nagai, A.; Koike, N.; Kudo, H.; Nishikubo, T. Controlled Thioacyl Group Transfer (TAGT) Polymerization of Cyclic Sulfide: Novel Approach to AB Diblock Copolymers by

the Combination of RAFT and TAGT Polymerizations. *Macromolecules* **2007**, *40* (23), 8129-8131. DOI: 10.1021/ma071533w.
(48) Kudo, H.; Makino, S.; Kameyama, A.; Nishikubo, T. Synthesis of Cyclic Polymers: Ring-Expansion Reaction of Cyclic S-Dithioester with Thiiranes. *Macromolecules* **2005**, *38* (14), 5964-5969. DOI: 10.1021/ma047642h.
(49) Kameyama, A.; Shimotsuma, K.; Nishikubo, T. Acyl group transfer polymerization of thiiranes with carboxylic acid derivatives. *Macromolecular Rapid Communications* **1994**, *15* (4), 335-342. DOI: https://doi.org/10.1002/marc.1994.030150406.
(50) Swinarew, A.; Stolarzewicz, A.; Grobelny, Z.; Swinarew, B.; Grazulevicius, J. V.; Simokaitiene, J.; Andrikaityte, E. Star-shaped poly(2-(9-carbazolyl)methylthiirane): Synthesis, analysis and photoluminescencent properties. *Journal of Molecular Structure* **2011**, *1005* (1), 129-133. DOI: https://doi.org/10.1016/j.molstruc.2011.08.035.
(51) Boileau, S.; Sigwalt, P. Copolymères séquencés de l'époxyéthane avec les épithioalcanes. *Die Makromolekulare Chemie* **1973**, *171* (1), 11-18. DOI: https://doi.org/10.1002/macp.1973.021710102.
(52) Cabrera-García, A.; Blay-Roger, R.; Blay, V.; Ravelo, Á. G.; Martín-Zarza, P. Histamine, an effective initiator for the synthesis of polysulfides. *Reaction Chemistry & Engineering* **2020**, *5* (2), 258-262, 10.1039/C9RE00411D. DOI: 10.1039/c9re00411d.
(53) Jiang, S.-Y.; Hsieh, W.-T.; Chen, W.-S.; Liao, J.-S.; Chiang, P.-Y.; Lin, Y. A. Synthesis of Thiol-Containing Oligopeptides via Tandem Activation of γ-Thiolactones by Silver-DABCO Pair. *Asian Journal of Organic Chemistry* **2020**, *9* (10), 1638-1649. DOI: https://doi.org/10.1002/ajoc.202000310.
(54) Espeel, P.; Du Prez, F. E. One-pot multi-step reactions based on thiolactone chemistry: A powerful synthetic tool in polymer science. *European Polymer Journal* **2015**, *62*, 247-272. DOI: https://doi.org/10.1016/j.eurpolymj.2014.07.008.
(55) Martens, S.; Landuyt, A.; Espeel, P.; Devreese, B.; Dawyndt, P.; Du Prez, F. Multifunctional sequence-defined macromolecules for chemical data storage. *Nature Communications* **2018**, *9* (1), 4451. DOI: 10.1038/s41467-018-06926-3.
(56) Puchelle, V.; Latreyte, Y.; Girardot, M.; Garnotel, L.; Levesque, L.; Coutelier, O.; Destarac, M.; Guégan, P.; Illy, N. Functional Poly(ester-alt-sulfide)s Synthesized by Organo-Catalyzed Anionic Ring-Opening Alternating Copolymerization of Oxiranes and γ-Thiobutyrolactones. *Macromolecules* **2020**, *53* (13), 5188-5198. DOI: 10.1021/acs.macromol.0c00261.
(57) Illy, N.; Puchelle, V.; Le Luyer, S.; Guégan, P. Alternating Copolymerization of Bio-based N-acetylhomocysteine Thiolactone and Epoxides. *European Polymer Journal* **2021**, 110490. DOI: https://doi.org/10.1016/j.eurpolymj.2021.110490.
(58) Le Luyer, S.; Quienne, B.; Bouzaid, M.; Guégan, P.; Caillol, S.; Illy, N. Bio-based poly(ester-alt-thioether)s synthesized by organo-catalyzed ring-opening copolymerizations of eugenol-based epoxides and N-acetyl homocysteine thiolactone. *Green Chem.* **2021**, *23* (19), 7743-7750, 10.1039/D1GC02138A. DOI: 10.1039/d1gc02138a.