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Thiol-triggered deconstruction of bifunctional silyl ether terpolymers *via* an S_NAr-triggered cascade†

Christopher M. Brown, Da Keith E. L. Husted, Yuyan Wang, Landon J. Kilgallon, Peyton Shieh, Hadiqa Zafar, Da David J. Lundbergab and Jeremiah A. Johnson +*ac

While Si-containing polymers can often be deconstructed using chemical triggers such as fluoride, acids, and bases, they are resistant to cleavage by mild reagents such as biological nucleophiles, thus limiting their end-of-life options and potential environmental degradability. Here, using ring-opening metathesis polymerization, we synthesize terpolymers of (1) a "functional" monomer (e.g., a polyethylene glycol macromonomer or dicyclopentadiene); (2) a monomer containing an electrophilic pentafluorophenyl (PFP) substituent; and (3) a cleavable monomer based on a bifunctional silyl ether ($SiR_2(OR'_2)$). Exposing these polymers to thiols under basic conditions triggers a cascade of nucleophilic aromatic substitution (S_NAr) at the PFP groups, which liberates fluoride ions, followed by cleavage of the backbone Si–O bonds, inducing polymer backbone deconstruction. This method is shown to be effective for deconstruction of polyethylene glycol (PEG) based graft terpolymers in organic or aqueous conditions as well as polydicyclopentadiene (pDCPD) thermosets, significantly expanding upon the versatility of bifunctional silyl ether based functional polymers.

Introduction

Polymers that undergo selective bond cleavage¹ in response to an external trigger have numerous applications, including in drug delivery,²-⁴ sensing,⁵,⁶ transient electronics,⁻,⁶ and recyclable materials.⁰,¹¹⁰ A wide range of functional groups (e.g., azo,¹¹-¹³ dihydrofuran,¹⁴ disulfide,¹⁵,¹⁶ diselenium,¹⁻ ester,¹⁶ ketal,¹⁰ poly(benzyl ether),²⁰ and phosphoramidate²¹) have been employed to enable triggered polymer deconstruction, and various external stimuli such as oxdiation/reduction,²²²,²³ pH,²⁴,²⁵ light,¹² heat,²⁶ nucleophiles,²⁻ and mechanical force²⁶ have been extensively studied. Nevertheless, there is often a trade-off between the introduction of cleavable bonds and polymer stability under use conditions, especially when mild cleavage reagents (e.g., biological triggers), and thus easier-to-cleave bonds, are required.

Bifunctional silyl ethers (SiR₂(OR'₂); "BSEs") are versatile functional groups that have found applications as fluoride- and acid/base-cleavable linkages in, for example, biomaterials,²⁹ controlled release systems,³⁰⁻³² and deconstructable thermosets (Fig. 1A).³³⁻³⁷ BSEs offer a unique combination of synthetic

accessibility, compositional diversity,³⁸ and excellent thermal and oxidative stabilities while providing for highly selective cleavage with rates that can be easily controlled through variation of the Si–R substituents.³⁹ Moreover, cyclic olefins containing BSEs are suitable monomers for the synthesis of deconstructable homopolymers,⁴⁰ copolymers,³⁹ and thermosets *via* ring-opening metathesis polymerization (ROMP).^{35–38,41} Nevertheless, while acid and/or fluoride are convenient triggers for BSE cleavage, there are instances where such stimuli are not compatible with a desired application, leading us to consider alternative methods.

Inspired by advances in radical ring-opening polymerization—where sensitive electrophilic functional groups such as thioesters can be installed within polymer backbones to enable cleavage via nucleophilic attack27,42,43—and with interest in biodegradable polymers, we sought a strategy to facilitate the deconstruction of BSE-based polymers prepared via ROMP through exposure to nucleophiles such as thiols. While BSEs are not sufficiently reactive to undergo cleavage in the presence of thiols under typical conditions, we hypothesized that is would be possible to embed latent, thiol-triggered fluoride sources into BSE-containing polymers to facilitate Si-O bond cleavage following a nucleophilic aromatic substitution (S_NAr) event. S_NAr reactions of pentafluorophenyl (PFP) derivatives⁴⁴ using a range of nucleophiles (e.g., alcohols, 45 amines, 46 phosphites, 47 thiols44,48,49) liberate one equivalent of F per substitution reaction, which we imagined could be utilized as the first step in an S_NAr, fluoride release, and BSE cleavage cascade (Fig. 1B). Additionally, S_NAr reactions of PFP groups are known to be

^aDepartment of Chemistry, Massachusetts Institute of Technology, 77 Massachusetts Avenue, Cambridge, MA 02139, USA. E-mail: jaj2109@mit.edu

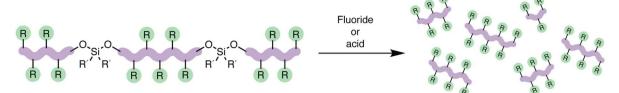
^bDepartment of Chemical Engineering, Massachusetts Institute of Technology, 77 Massachusetts Avenue, Cambridge, MA 02139, USA

David H. Koch Institute for Integrative Cancer Research, Massachusetts Institute of Technology, 77 Massachusetts Avenue, Cambridge, Massachusetts 02139, USA

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Previous work:

A Polymer backbone cleavage triggered by a fluoride salt or acidic conditions

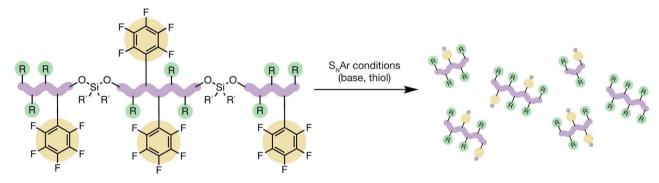


BSE-containing statistical copolymer

Deconstruction products

This work:

B Polymer backbone cleavage *via* S_NAr-induced fluoride release



Statistical terpolymer containing BSE and PFP groups

Deconstruction products

C S_NAr-mediated deconstruction proceeds via a cascade reaction

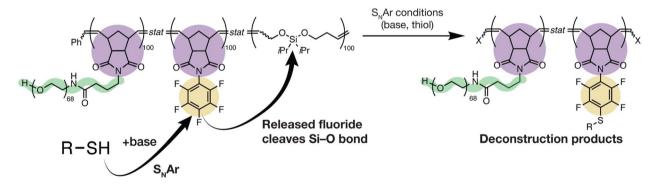


Fig. 1 (A) We have previously reported deconstructable copolymers containing bifunctional silyl ethers (BSEs) where polymer backbone cleavage is initiated by a fluoride source (e.g., tetrabutylammonium fluoride, TBAF) or acidic conditions (e.g., HCl or carboxylic acids), providing oligomeric deconstruction fragments. (B) Here, we describe BSE-containing terpolymers containing pentafluorophenyl (PFP) comonomers, which trigger deconstruction upon exposure to nucleophilic aromatic substitution (S_NAr) conditions (a thiol in the presence of base). (C) The S_NAr -mediated cleavage proceeds via a cascade reaction, where thiolate attacks at the para-position of the PFP ring via S_NAr , releasing a fluoride ion, which in turn cleaves the Si–O bond of the BSE. At full conversion, $X = CH_2CH_2OH$, CH_2OH , Ph or H.

effective reactions for polymer functionalization.⁵⁰⁻⁵⁴ PFPs are compatible with ROMP, and there are many cheap, benign, and/ or biologically-derived thiols that could potentially be used to initiate such a cascade process. Here, we present the realization of this concept, showing that graft and covalently crosslinked thermoset terpolymers with BSE- and PFP-based comonomers

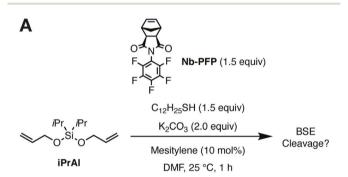
undergo selective backbone cleavage via a thiol-triggered S_N Ar cascade. This work provides a new strategy to enable backbone cleavage of otherwise stable polymeric materials and extends the scope of BSE-based cleavage reactions for responsive materials design.

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Results and discussion

Small molecule model studies

First, we sought to determine whether or not BSEs are stable under typical conditions used for S_NAr reactions involving PFP groups, which often involve polar organic solvents and bases such as K₂CO₃, Cs₂CO₃ or 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU).44 PFP-based monomer Nb-PFP (synthesized following a reported procedure⁵⁵) and iPrAl, a BSE mimic of a polymer backbone, were exposed to various conditions relevant to S_NAr (Fig. 2A); gas chromatography-mass spectrometry (GC-MS) was used to monitor iPrAl cleavage (mesitylene was used as an internal standard; see ESI† section "Small Molecule GC-MS Studies" for further information; see ESI† section "Small molecule syntheses" for details). iPrAl remained intact when treated with either 1-dodecanethiol (nucleophile, 1.5 equiv.), K₂CO₃ (base, 2.0 equiv.), Nb-PFP (latent fluoride, 1.5 equiv.), a combination of 1-dodecanethiol and K₂CO₃ (nucleophile and base only), or with a combination of **Nb-PFP** and K₂CO₃ (latent fluoride and base) (Fig. 2B). When iPrAl was exposed to 1dodecanethiol (1.5 equiv.), K₂CO₃ (2.0 equiv.), and Nb-PFP (1.5



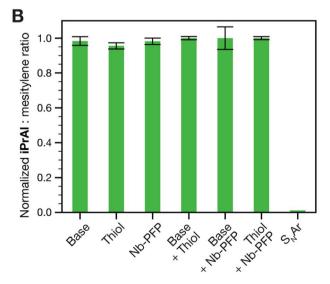


Fig. 2 (A) Scheme showing the methodology for the small molecule GC-MS studies of acyclic BSEiPrAl. (B) Bar chart comparing the ratio of iPrAl to a mesitylene internal standard (10 mol%) from GC-MS runs. iPrAl is treated with either K_2CO_3 (base), Nb-PFP, 1-dodecanethiol (thiol), or combinations of the above in DMF for 1 h at 25 °C. Ratios were calculated using peak integration and averaged over three runs. Error bars show standard deviation.

equiv., *i.e.*, all three reagents critical for S_NAr), however, >98% cleavage was observed after 1 h and no trace of **iPrAl** was seen after 2 h (Fig. S1†). ¹⁹F NMR spectroscopy of the reaction mixture showed a doublet of doublets of doublets and a multiplet with a downfield shift when compared to the parent **Nb-PFP** (Fig. S2A†). This spectrum agrees well with the spectrum obtained for an independently synthesized, authentic sample of the expected *para-1*-dodecanethiol-substituted product **Nb-PFP-SC**₁₂**H**₂₅ (see ESI† section "Small molecule syntheses" for details). Moreover, a ¹⁹F-¹⁹F COSY experiment showed a correlation between the two new ¹⁹F resonances generated under the reaction conditions (Fig. S2B†). Altogether, these results confirm that S_NAr occurs between 1-dodecanethiol and **Nb-PFP** in the presence of K_2CO_3 , and that the resulting fluoride can cleave a model BSE.

Nb-PFP homopolymer model studies

To test the viability of S_NAr in a ROMP-derived PFP-containing polymer, we subjected Nb-PFP (225 equiv.) to Grubbs' 3rd generation bispyridyl initiator (1 equiv.) in 1,4-dioxane, providing polvNb-PFP (Fig. 3A, see ESI† section "Polymer syntheses" for details). The ¹H NMR spectrum of **polyNb-PFP** agrees well with that reported by Tlenkopatchev and coworkers for similar polymers synthesized using Grubbs 1st and 2nd-generation initiators. 56 Complete consumption of Nb-PFP was observed (Fig. S3†). ¹⁹F NMR showed the same three general sets of resonances for polyNb-PFP and Nb-PFP (Fig. S4†). PolyNb-PFP had a low dispersity (D = 1.05) and a number average molecular weight (M_n) of 78 400, close to its theoretical $M_{\rm n}$ of 74 100, as determined by size exclusion chromatography (SEC, CHCl₃ mobile phase) (Fig. 3B, black trace). Exposure of **polyNb-PFP** to C₁₂H₂₅SH (1.2 equiv.) and K₂CO₃ (2.0 equiv.) in DMF at 25 °C (Fig. 3C, see ESI† section "Polymer syntheses" for details) for 1 h gave quantitative conversion to the *para*-substituted S_NAr product as determined by ¹⁹F NMR spectroscopy (Fig. 3D). SEC (CHCl₃ mobile phase) showed a concomitant increase in molecular weight (M_n of 123 800, close to its theoretical M_n of 115 100) and slight increase in dispersity (D = 1.15) (Fig. 3B). A small shoulder is observed, which we attribute to aggregation of the substituted polymer, likely caused by the addition of dodecyl groups to the polymer sidechains.

Terpolymer deconstruction using an S_NAr-initiated cascade

After successfully demonstrating S_N Ar of **polyNb-PFP**, we set out to test our hypothesis that an S_N Ar-triggered cascade can enable deconstruction of polymers with backbone BSE groups. **Nb-PFP** was combined with BSE-containing monomer **iPrSi8** (synthesized according to a reported procedure³⁹) and norbornene-terminated 3 kDa polyethylene glycol (PEG) macromonomer⁵⁷ **PEG-MM** in a 1:1:1 molar ratio in 1,4-dioxane and exposed to Grubbs' 3rd-generation bis-pyridyl initiator to generate graft terpolymer **P1** (total monomer: initiator ratio 300:1) (Fig. 4A, see ESI† section "Polymer syntheses" for experimental details). High conversions of **iPrSi8**, **Nb-PFP** and **PEG-MM** were confirmed *via* ¹H NMR (Fig. S5†) and ¹⁹F NMR spectroscopy (Fig. S6†) to yield **P1** with M_n of 636 000 (\pm 18.6%) and D = 1.57 (See ESI† section "Materials and Methods" for

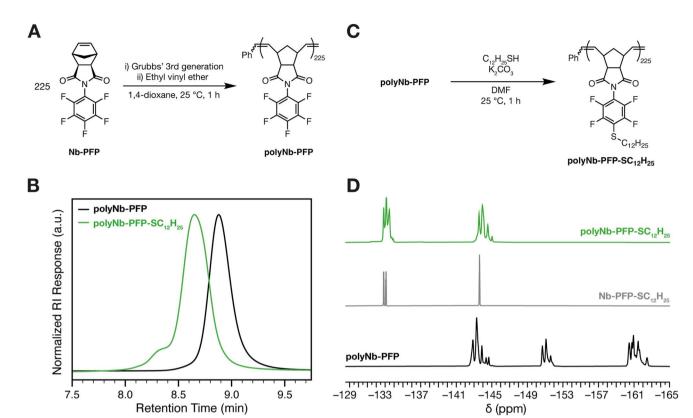


Fig. 3 (A) Synthesis of polyNb-PFP homopolymer. (B) SEC traces (CHCl₃ mobile phase) for polyNb-PFP (black) and S_NAr product polyNb-PFP- $SC_{12}H_{25}$. (C) Synthesis of S_NAr product polyNb-PFP- $SC_{12}H_{25}$. (D) ¹⁹F NMR spectra (565 MHz, CDCl₃, 25 °C) comparing polyNb-PFP (black) to monomer Nb-PFP- $SC_{12}H_{25}$ (grey) and polyNb-PFP- $SC_{12}H_{25}$ (green).

a discussion on M_n calculations). To confirm that BSEs are incorporated into the polymer backbone, **P1** was exposed to 1 M aqueous HCl (see ESI† section "Degradation studies" for experimental details), conditions previously shown to cleave BSEs in norbornene-based terpolymers.³⁹ SEC analysis revealed macromolecular deconstruction products at longer retention times, indicative of polymer backbone cleavage resulting in monomers, dimers, trimers, and higher oligomers³⁹ (Fig. 4B). Moreover, ¹⁹F NMR spectroscopy shows that the PFP group remains unaffected under these conditions (Fig. 4C).

Gratifyingly, exposure of P1 to S_NAr conditions—K₂CO₃ (2.0 equiv. w.r.t. Nb-PFP in the terpolymer) and 1-dodecanethiol (1.5 equiv. w.r.t. Nb-PFP in the terpolymer) in DMF-for 30 min at 25 °C led to backbone deconstruction and a nearly identical SEC trace to that for HCl-induced deconstruction (Fig. 4B, purple trace; see ESI† section "Deconstruction studies" for experimental details). ¹⁹F NMR spectroscopy confirms formation of the expected S_NAr product, suggesting that deconstruction is triggered by S_NAr (Fig. 4C). Notably, exposing the polymer to K₂CO₃ alone (in DMF at room temperature) for the same time period does not lead to any polymer cleavage by SEC (Fig. 4B, green trace, $M_{\rm p}=$ 536 000 ($\pm 17.1\%$), D = 1.53); exposing the polymer to 1-dodacenethiol in the absence of base leads to a small shift in the SEC peak to a longer retention time, suggesting a small amount of decomposition likely due to background S_NAr (Fig. 4B, yellow trace, $M_{\rm n}=268\,000~(\pm 14.6\%),\, D=1.57)$.

PEG-based graft terpolymer deconstruction under aqueous conditions

We initially designed iPrSi8 and related monomers39 for the purpose of enabling the deconstruction of PEG-based graft terpolymers under aqueous conditions that may be translatable to applications in drug delivery and biological imaging.58-62 Delaittre and coworkers reported thiol-mediated S_NAr of PFP-containing poly(N,N-dimethylacrylamide) in alkaline water (pH ≥ 11),63 which inspired us to investigate backbone deconstruction of P1 under similar conditions. First, we exposed the polymer to Na₂HPO₄/NaOH buffer solution (pH = 12; see ESI† section "Degradation studies" for full experimental details) for 30 min at 25 °C; very little change was observed by SEC following this treatment, suggesting that the polymer is stable in aqueous alkaline buffer (Fig. S7†). When 2mercaptoethanol (1.5 equiv. per PFP group) was added to this solution, which is sufficiently basic to generate the corresponding thiolate (p K_a of 2-mercaptoethanol = 9.72),⁶⁴ complete polymer deconstruction was observed in 30 min at room temperature (Fig. 5). 19F NMR spectroscopy confirms the formation of S_NAr products, consistent with S_NAr-induced fluoride release and BSE cleavage (Fig. S8†). The efficiency of this reaction is notable; previous work suggested that elevated temperatures (e.g., 40 °C), extend reaction times (e.g., 72 h), and large excesses of thiols (e.g., 10-20 equiv.) are needed to induce S_NAr of polymeric PFP groups under aqueous conditions.63 Here, deconstruction may be facilitated by the

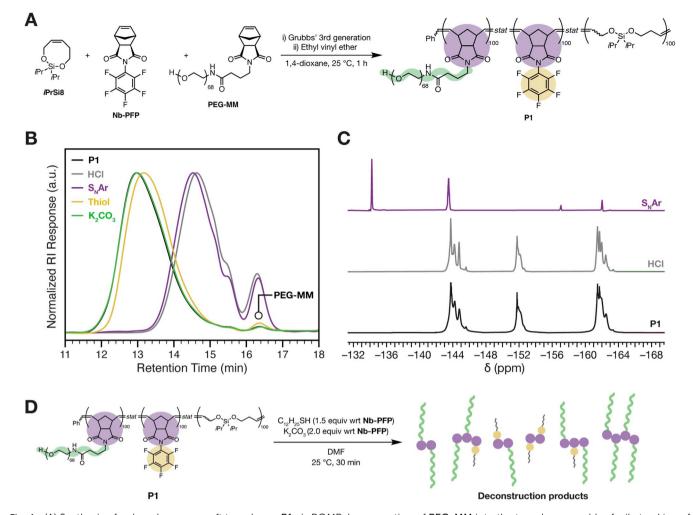


Fig. 4 (A) Synthesis of polynorbornene graft terpolymer P1 via ROMP. Incorporation of PEG-MM into the terpolymer enables facile tracking of subsequent deconstruction. (B) SEC traces (DMF mobile phase) showing polymer P1 (black), the control deconstruction of P1 using HCl (grey), the control deconstruction of P1 using K₂CO₃ (green), the control deconstruction of P1 using 1-dodecanethiol (thiol, yellow) and the deconstruction of P1 using the S_NAr conditions of 1-dodecanethiol and K_2CO_3 (purple). (C) ^{19}F NMR spectra (565 MHz, CDCl₃, 25 °C) comparing the parent terpolymer P1 (black), to the deconstruction products using HCl (grey), or S_NAr conditions (purple). (D) Schematic showing the deconstruction of P1 using S_NAr conditions.

hydrophobic local environment of P1, where the PFP and BSE groups reside, which may elevate the local concentration of thiol and/or stabilize the S_NAr transition state.

Thiol-triggered cascade deconstruction of polydicyclopentadiene thermosets

We have shown that BSE-containing monomers such as iPrSi8 can be copolymerized with dicyclopentadiene (DCPD) to deconstructable38,41 remoldable35 and dicyclopentadiene (pDCPD) thermosets and composites, offering a new end-of-life strategy for this high-performance engineering material.65 Nevertheless, in these studies we have used 1 M TBAF, 1 M HCl, or high-temperature treatment with octanoic acid as deconstruction triggers; we hypothesized that the S_NAr-triggered cascade process introduced here could serve as an alternative method for pDCPD deconstruction.

To test this hypothesis, we prepared two thermosets: the first—thermoset T1 (Fig. 6A)—was prepared by curing a liquid

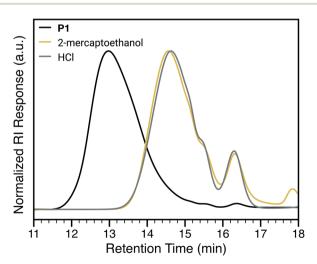
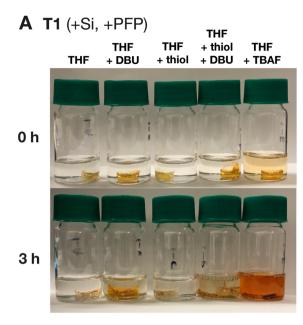


Fig. 5 Deconstruction of P1 in pH 12 buffer. SEC traces (DMF mobile phase) of the parent terpolymer (black), HCl-deconstructed material (grey), and P1 exposed to 2-mercaptoethanol in pH 12 Na₂HPO₄/ NaOH buffer solution (yellow).



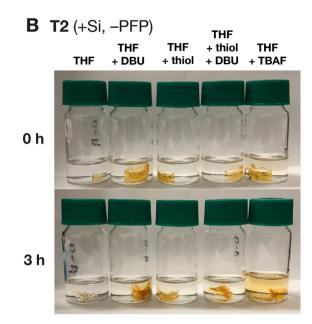


Fig. 6 Deconstruction of BSE-containing pDCPD thermoset materials. (A) Thermoset T1 (+Si, +PFP) prepared using pDCPD, iPrSi8 (10% v/v) and Nb-PFP (2.0 equiv. w.r.t. iPrSi8) in solutions of: THF; THF and DBU; THF and 1-dodecanethiol (thiol); THF, thiol, and DBU; THF and TBAF at 25 °C, after 0 and 3 h. (B) Control thermoset T2 (+Si, -PFP) prepared using pDCPD and iPrSi8 (10% v/v) in solutions of: THF; THF and DBU; THF and 1-dodecanethiol (thiol); THF, thiol, and DBU; THF and TBAF at 25 °C, after 0 and 3 h.

resin containing DCPD (14.4 equiv.) with 10% v/v of iPrSi8 (1.0 equiv.) and Nb-PFP (2.0 equiv.); the second—thermoset T2 (Fig. 6B)—was prepared by curing a resin containing DCPD with 10% v/v of iPrSi8 only (see ESI† section "Thermoset materials" for full experimental details). Two equivalents of Nb-PFP with respsect to iPrSi8 were chosen to facilitate full material deconstruction; as there are 2 Si-O bonds per BSE, 2 equiv. of fluoride are required to achieve complete Si-O bond cleavage. Dynamic mechanical analysis (DMA, Fig. S9 and Table S1†) showed that the glass transition temperature ($T_{\rm g}$) of T1 ($T_{\rm g}=67$ °C) was highly depressed compared to T2 ($T_g = 134$ °C), which is likely due to dilution of the thermoset crosslink density through incorporation of Nb-PFP. Nevertheless, thermogravimetric analysis (TGA, Fig. S10 and Table S2†) showed that the decomposition temperatures (T_d) of T1 $(T_d = 458 \text{ °C (plus }))$ a secondary shoulder at 550 °C due to addition of Nb-PFP)) and T2 ($T_{\rm d} = 464$ °C) were similar, suggesting that the addition of **Nb-PFP** does not have a major negative impact on the stability of these two thermoset materials. The storage moduli (E') and loss moduli (E'') of the thermosets were determined by DMA (Fig. S11 and S12, \dagger respectively). **T1** and **T2** displayed similar E'at 30 °C (well below their respective $T_{\rm g}$ values) when compared to a neat pDCPD sample. Lower rubbery moduli (i.e., moduli collected above T_{σ}) were observed for Nb-PFP-containing T1 when compared to T2 or neat pDCPD, which is also consistent with a reduced crosslink density.35

Both thermosets were exposed to S_N Ar conditions,⁴⁴ in this case using 1-dodecanethiol (2.0 equiv. w.r.t. PFP groups) and the organic base 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU, 2.0 equiv.) in tetrahydrofuran (THF) solvent, which facilitates swelling of the materials. In line with our hypothesis, **T1** was almost completely deconstructed (8% residual mass) to form soluble products

under these conditions (Fig. 6A) while T2 remained intact (Fig. 6B). Both thermosets were dissolved in 1 M TBAF in THF (4% residual mass), confirming that the stability of T2 under S_NAr conditions is due to a lack of latent fluoride groups. Moreover, T1 did not dissolve in the presence of 1-dodecanethiol or DBU alone (Fig. S13–S16†). ^{19}F NMR analysis of the soluble fragments of T1 deconstruction showed that under TBAF conditions (Fig. S17†), the three sets of resonances corresponding to the PFP group are retained and additional ^{19}F resonances consistent with difluor-osilane cleavage products are observed, 36 in line with direct cleavage of the Si–O bond by TBAF. By contrast, fragments from S_NAr conditions show two downfield ^{19}F resonances (Fig. S18†), which is consistent with S_NAr of the PFP groups.

Conclusions

In summary, we describe a new method to deconstruct BSE-containing macromolecules using thiol-mediated S_N Ar of PFP groups, which liberates fluoride and induces Si–O bond cleavage. The method is shown to be applicable to soluble graft terpolymers and insoluble thermosets, and it works in organic (DMF and THF) solvents or water with an appropriate base (K_2 CO₃, DBU, and phosphate buffer) and nucleophile (1-dodecanethiol and 2-mercaptoethanol). This approach expands the scope of BSE chemistry and may provide new ways to couple chemical triggers (*e.g.*, thiols) with polymer deconstruction to achieve novel functions and end-of-life options.

Author contributions

CMB synthesized starting materials and polymers, performed GC-MS studies, and organic and aqueous degradation studies.

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KELH and YW performed thermoset experiments. YW conducted DMA experiments, LJK synthesized flourinated silvl ether analogues, PS synthesized iPrSi8, HZ performed GC-MS experiments, and DJL synthesized PEG-MM. CMB, PS and JAJ conceived of the project. CMB and JAJ wrote the manuscript.

Conflicts of interest

CMB, PS and JAJ are named inventors on a patent application (US provisional application no. 63/195259) filed by the Massachusetts Institute of Technology on the monomers and copolymers in this work.

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