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Using Mechanochemistry to Activate Commodity Plastics as Initiators for Radical Chain Reactions of Small Organic Molecules

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ABSTRACT: Radical initiators such as azo compounds and organic peroxides have been widely used to facilitate numerous transformations of free radicals, which enable the efficient synthesis of structurally complex molecules, natural products, polymers, and functional materials. However, these high-energy reagents are potentially explosive and thus often require special precautions and/or delicate operating conditions. We postulated that a more convenient and safer alternative for the radical-chain initiation could be developed by mechanical activation of thermodynamically stable covalent bonds. Here, we show that commodity plastics such as polyethylene and polyvinyl acetate are capable of acting as efficient initiators for radical chain reactions under solvent-free mechanochemical conditions. In this approach, polymeric mechanoradicals, which are generated by homolytic cleavage of the polymer chains in response to the applied mechanical energy provided by ball milling, react with tris(trimethylsilyl)silane to initiate the radical chain dehalogenation of organic halides. Preliminary calculations support our proposed force-induced radical chain mechanism.

INTRODUCTION

Free radicals are exceptional synthetic intermediates for the preparation of various valuable functional molecules in the fields of pharmaceuticals, polymers, and materials sciences.[1,2] The use of radical initiators such as azo compounds and organic peroxides is an established approach to achieve free-radical-mediated organic transformations (Figure 1A).[3–6] Organometallic reagents such as Et_3B/O_2 and Et_2Zn/O_2 have also been recognized as useful radical initiators, especially for reactions at relatively low temperature (Figure 1A).[7,8] However, these conventional radical initiators are highly sensitive toward photo- or thermal stimuli and are potentially explosive, and thus often require special precautions and/or delicate operating conditions.[3–8] In fact, many accidents involving fires and/or explosions have been caused by azo compounds.[9] Despite the century-long history of research on this class of radical transformations, these safety concerns still represent major drawbacks to their use in radical-based organic chemistry, especially in large-scale and industrial settings.

Since the pioneering studies by Staudinger in the 1930s, it has been well established that mechanically stimulating (e.g., grinding or crushing) polymeric materials causes the homolytic scission of covalent bonds along the polymer backbone to form free radicals, which are known as mechanoradicals (Figure 1B).[10] The direct detection of the generation of such short-lived species using electron spin resonance (ESR) spectroscopy in solution has been reported by Sohma.[11] More recently, Ohtsuka has reported that polymeric mechanoradicals generated by ball milling under solid-state conditions can be successfully detected using a diarylacetonitrile compound as a prefluorescent molecular probe.[12,13] Although the generation of mechanoradicals has been focused upon as a key process of polymer degradation, significant progress has also been made in parallel in mechanical-force-mediated polymer functionalization involving mechanoradical species.[14] Using this "constructive" approach, polymeric mechanoradicals have been shown to react with olefinic monomers to form block copolymers via free-radical polymerization.[15–19] Willis-Fox, Daly, and co-workers have reported that mechanoradicals formed under flow conditions can be trapped by 2,2'-diphenyl-1-picrylhydrazyl to deliver a change in the optical properties of polymethyl methacrylate (PMMA).[20] More recently, our group has reported that radical–radical coupling between polymeric mechanoradicals and a prefluorescent nitroxide-based reagent proceeds under ball-milling conditions to incorporate a luminophore into the polymer main chains via a covalent bond.[21] Although these achievements are remarkable, the use of polymeric materials as the source of radical species for small molecule synthesis has not yet been explored.

Inspired by the utility of radical-based organic syntheses and the generation of polymeric mechanoradicals via mechanical impact, we hypothesized that cheap and abundant plastic materials could be used as thermodynamically stable initiators for free-radical transformations of small organic molecules under mechanochemical conditions (Figure 1B).[22–30] Conventional high-energy radical initiators, such as azo compounds, exothermally generate radical species upon thermal activation and thus pose a risk of explosion (Figure 1B). In contrast, our force-induced approach allows the generation of radical species endothermically via mechanical activation of thermodynamically stable covalent bonds in plastic materials. The generated short-lived mechanoradicals could activate small molecules through hydrogen-atom transfer (HAT) to initiate radical chain reactions, thereby representing a more convenient, safe, and

industrially attractive alternative to potentially explosive radical initiators (Figure 1B).

For a proof-of-concept study, we selected the radical chain dehalogenation of organic halides **1** with tris(trimethylsilyl)silane (**2**) as a model reaction (Figure 1C).[31–33] The key step of this transformation is the HAT from the Si–H bond of **2** to the radical species generated from an initiator. In our postulated mechanism (Figure 1C), the agitation of generic polymers via ball milling generates mechanoradicals in response to mechanical impact. According to previous polymer functionalization studies[15–21], we expected that the thus-formed polymeric mechanoradicals would be sufficiently persistent to undergo HAT with **2**. The generated tris(trimethylsilyl)silyl radical (**I**) would react with an organic halide **1** via halogen-atom transfer (XAT) to form a silyl halide **II** and radical intermediate **III**, which would undergo HAT with **2** to give the desired reduction product (**3**), with concomitant regeneration of **I**.

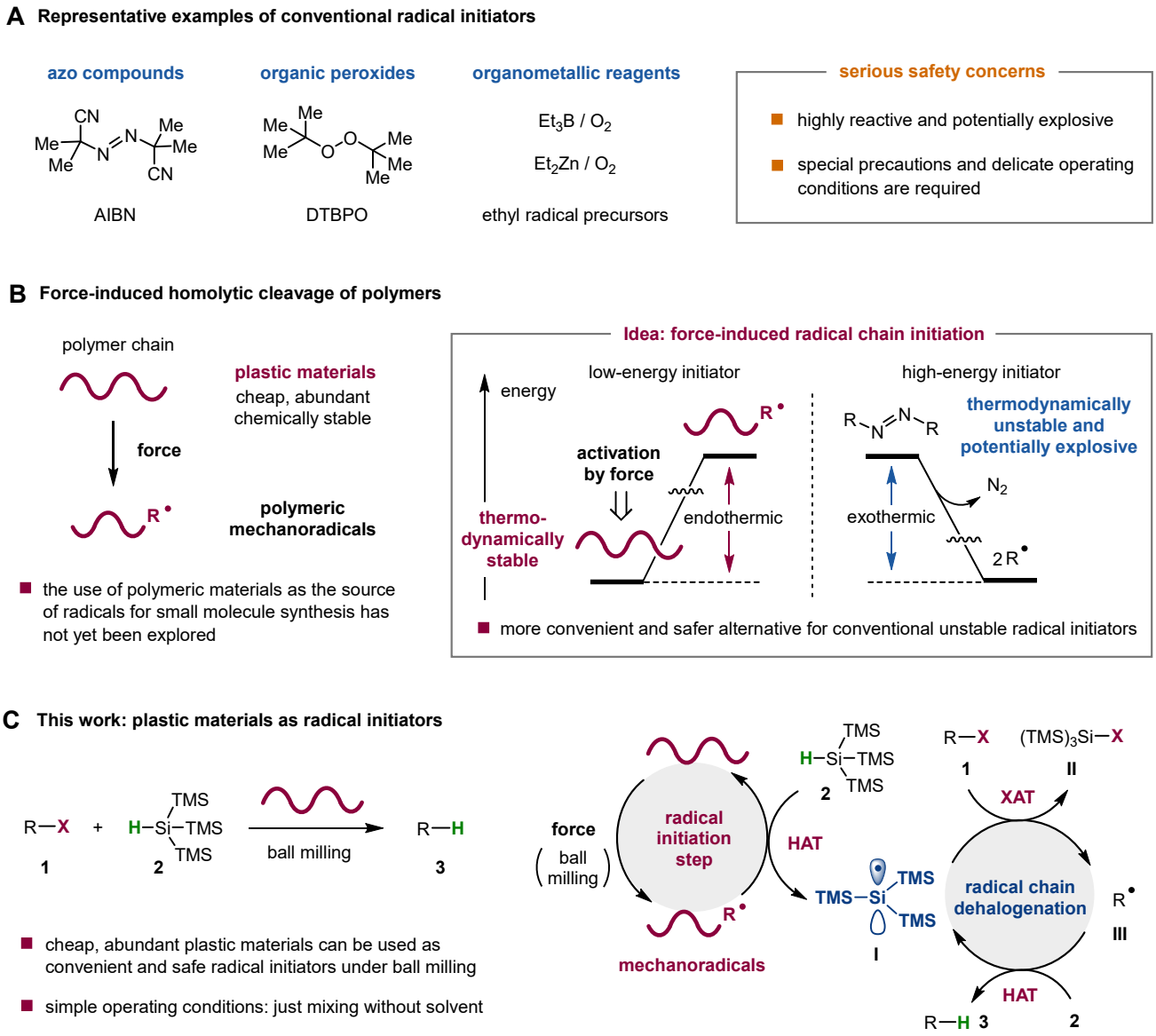

Figure 1. Use of plastic materials as initiators for radical chain reactions under mechanochemical conditions. **A,** Conventional initiators for free-radical chain reactions. **B,** Generation of polymeric mechanoradicals from plastic materials in response to mechanical stimulation. **C,** Use of plastic materials as initiators for radical-based reductive transformations.

RESULTS AND DISCUSSION

All ball-milling experiments were carried out in a Retch MM400 mixer mill (5 mL stainless-steel milling jar and 10 mm diameter stainless-steel balls). To explore the mechanistic hypothesis, we first attempted the proposed radical dehalogenation of 1-bromodecane (**1a**) with **2** (1.2 equiv) in the presence of commercially available polyethylene (ultra-high molecular weight, Aldrich, product no. 434272; 200 mg) (Figure 2). The corresponding reduction product (**3a**) was obtained in 29% yield after milling at 30 Hz for 1 hour slightly above room temperature (35 °C). The temperature inside the mill was confirmed by thermography after opening the jar. A small

amount of **3a** was obtained (10% yield) when the reaction was carried out in the presence of polypropylene (M_n = 67 kg/mol). When other commercially available polymers such as polystyrene (M_w = 400 kg/mol), poly(1,4-phenylene sulfide) (M_n = 10 kg/mol), and polymethyl methacrylate (PMMA; M_w = 120 kg/mol) were used, the reactions gave poor results. Interestingly, we found that polyvinyl acetate (M_n = 35 kg/mol) provided a high yield of **3a** (75% yield) under the applied conditions. In the reaction using polyethylene, increasing the reaction temperature (60 °C) using a heat gun (for details, see Supplementary Figure S3) and increasing the amounts of **2** (2.4 equiv) and polyethylene (300 mg) also led to substantial improvement of the product yield (82% yield). The reaction did not proceed in the absence of a polymeric material. Furthermore, no reaction occurred in a test tube with a magnetic stirring bar in the presence of polyethylene. These control experiments suggest that polymeric mechanoradicals generated by ball-milling-induced bond cleavage initiate the radical chain dehalogenation reaction of **1a**. We also confirmed that the radical chain dehalogenation proceeded smoothly even when the reaction was carried out under an argon atmosphere, thus ruling out the possibility of an oxygen-mediated mechanism. Gel-permeation chromatography (GPC) of ball-milled polyethylene and polyvinyl acetate showed that the number-average molecular weight (M_n) decreased, suggesting that homolytic cleavage of covalent bonds occurs to generate mechanoradicals under the applied conditions (for details, see Supplementary Table S1 and S2).

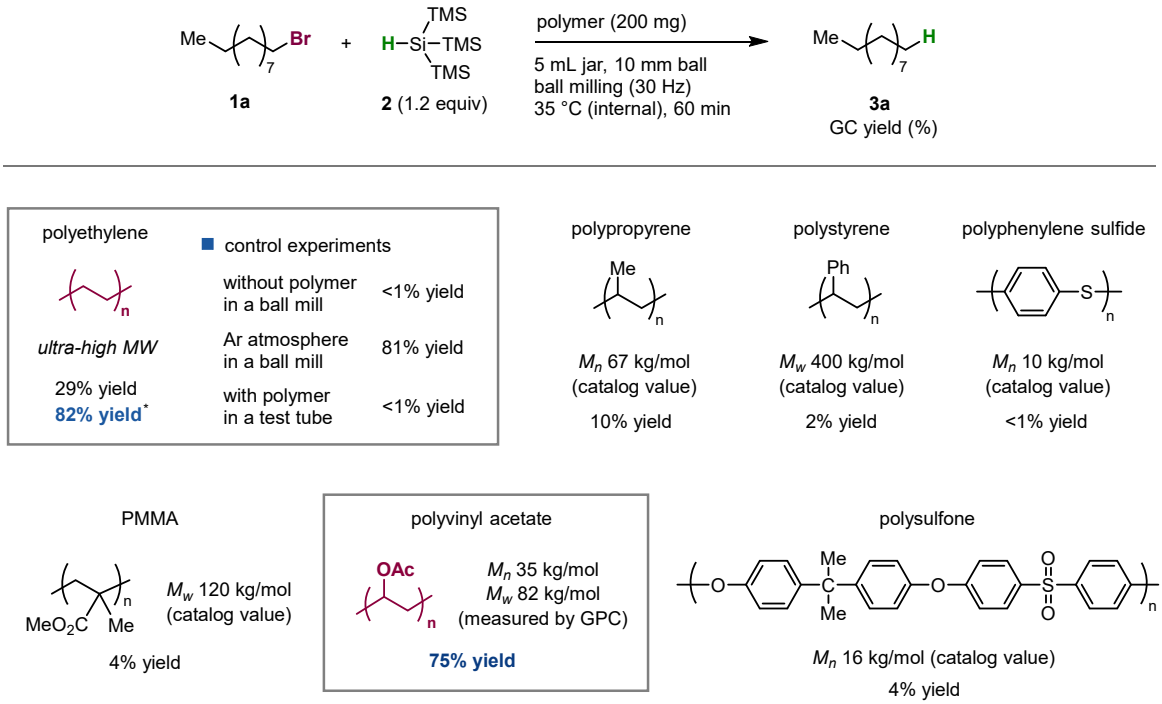

Figure 2. Suitable polymeric materials as radical initiators for dehalogenation under ball-milling conditions. Reactions were conducted with 0.2 mmol of **1a**, 0.24 mmol of **2**, and 200 mg of polymer in a stainless-steel jar (5 mL) with a stainless-steel ball (diameter: 10 mm). Yields were determined by gas chromatography (GC) analysis with an internal standard. *The reaction was conducted with 0.48 mmol of **2** and 300 mg of polyethylene at 60 °C.

With the optimized conditions in hand, we proceeded to investigate the scope and limitations of the mechanoradical-initiated radical dehalogenation of organic halides (Figure 3A). Under the optimized conditions using polyethylene (conditions A), the reactions of primary (**1a**), secondary (**1d**), and tertiary alkyl bromides (**1e**) proceeded smoothly to give the corresponding dehalogenation products (**3a** and **3b**) in good-to-high yield. Alkyl iodides (**1b** and **1f**) also underwent the radical dehalogenation with high efficiency. However, the reactions of alkyl chlorides (**1c** and **1g**), which are less reactive substrates under conventional solution-based conditions[31–33], furnished the corresponding dehalogenation product (**3a** and **3b**) in poor yield under mechanochemical conditions. Next, we investigated the radical dehalogenation of benzyl- and alpha-carbonyl bromides (**1h** and **1i**), and the desired products (**3c** and **3d**) were obtained in good yield. An alkenyl bromide (**1j**) was converted into the dehalogenation product (**3e**) in 32% yield. A brominated sugar derivative (**1k**) afforded the corresponding product (**3f**) in quantitative yield. We also found that the radical dehalogenation of various aryl iodides (**1l**–**1x**) furnished the corresponding products (**3g**–**3r**) in good-to-excellent yield. Similar results were obtained when the radical dehalogenation reactions were carried out under the optimized conditions using polyvinyl acetate (conditions B). Notably, functional groups such as non-protected amine (**1r**), alcohol (**1s**), and alkyne (**1t**) are also compatible under the applied mechanochemical conditions. Furthermore, we found that mechanoradical-initiated radical cyclization of aryl halides that bear an alkene moiety is also feasible (Figure 3B).[34] As examples, indoline, dihydrobenzofuran, and tetrahydrofuran derivatives (**3s**–**3u**) were synthesized via radical cyclization using polyethylene as a radical initiator. The

reaction of 1-iodonaphthalene (**1l**) using tributyltin hydride (n-Bu_3SnH) instead of **2** in the presence of polyvinyl acetate also provided the desired product (**3g**) in 23% yield, suggesting that this strategy has the potential to be applied to a variety of synthetic reagents for radical chain reactions (for details, see Supplementary Figure S8).

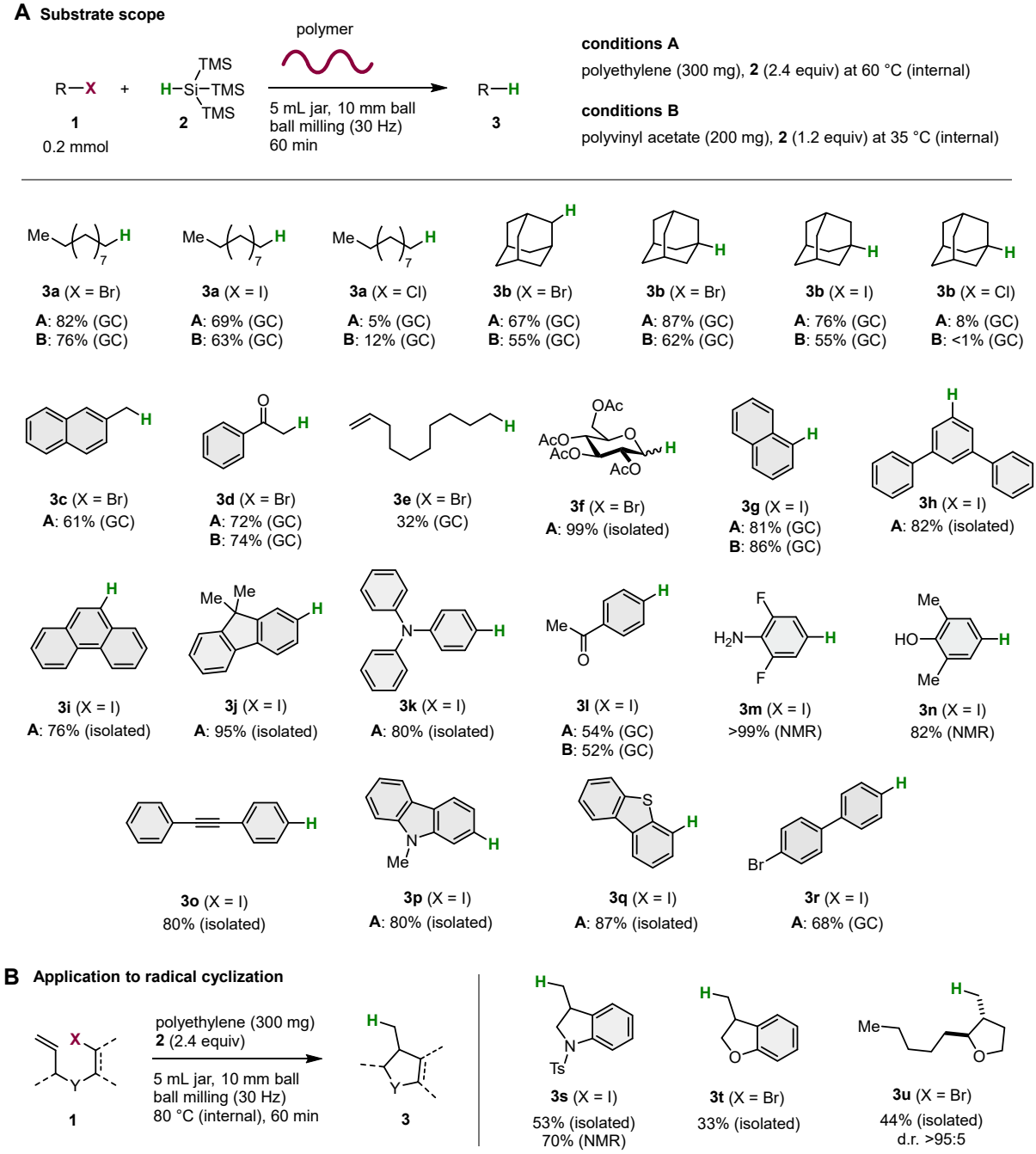

Figure 3. Polymeric-mechanoradical-initiated radical chain dehalogenation. **A,** Substrate scope of polymeric-mechanoradical-initiated reduction of organic halides. **B,** Application to radical cyclization.

To demonstrate the synthetic utility of this protocol, we investigated a preliminary scale-up experiment of the radical dehalogenation under the developed mechanochemical conditions, as well as the recycling of polyethylene (Figure 4A and Supplementary Table S5). The reaction of **1e** with **2** in the presence of polyethylene as a radical initiator was carried out on a 2.5 mmol scale in a 5 mL stainless-steel ball-milling jar with one 15 mm diameter stainless-steel ball and provided **3b** in 85% yield (Figure 4A). After separation from the crude reaction mixture and washing, the polyethylene could be reused for the dehalogenation reaction of 1-iodonaphthalene (**1l**) under the

same reaction conditions at least five times (Supplementary Table S5).

Polyhalogenated organic compounds are widely used in industrial applications such as insulating materials and flame retardants.[35] However, due to their high toxicity in even trace amounts, these compounds represent a major class of hazardous waste for the environment. The development of treatment processes for these health-threatening compounds is therefore a high priority in the chemical industry and related areas.[35] To demonstrate the potential utility of the present mechanochemical approach for the dehalogenative detoxification of such polyhalogenated compounds, we investigated the reaction of 1,2,5,6,9,10-hexabromocyclododecane (**1aa**) (Figure 4B), which is known to be a toxic but still widely used as a flame retardant and a curing accelerator for adhesives.[36,37] Pleasingly, the radical debromination of **1aa** proceeded under the developed mechanochemical conditions using polyethylene as an initiator, and the bromine atom content was successfully reduced (Figure 4B).

Furthermore, as part of our great interest in the effective use of plastic waste in organic synthesis, we investigated the mechanochemical dehalogenation reaction using a common plastic bag made of high-density polyethylene (Figure 4C). For that purpose, a commercial plastic bag handed out at a local supermarket was chopped into small pieces, which were then placed in a jar for the dehalogenation of **1l**. After ball milling, the pieces of the plastic bag were converted into a fine powder, and a dark-blue-colored mixture was obtained. Pleasingly, the desired product **3g** was obtained in a promising yield (69%). Although there is room for further improvement, this result is expected to inspire the development of environmentally attractive and sustainable free radical transformations via the utilization of plastic waste as efficient radical initiators.

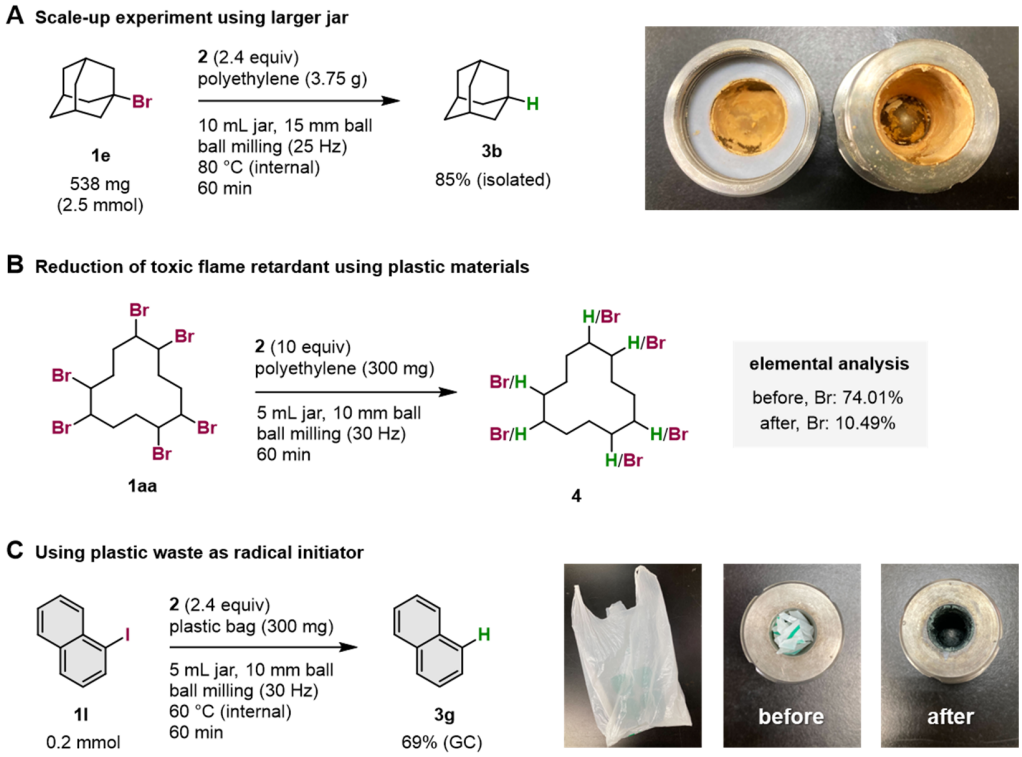

Figure 4. Synthetic applications. **A,** Scale-up reaction of **1e** using a 10 mL ball-milling jar. **B,** Reduction of the toxic flame retardant 1,2,5,6,9,10-hexabromocyclododecane (**1aa**) using polyethylene. **C,** Use of a commercial plastic bag made of high-density polyethylene as an initiator for the radical dehalogenation reaction.

To validate the reaction mechanism proposed in Figure 1D, density functional theory (DFT) calculations were conducted (Figure 5). We confirmed that once the tris(trimethylsilyl)silyl radical is formed, the subsequent radical chain dehalogenation is a self-sustainable reaction due to the extremely low barrier and the relatively large exergonicity (Supplementary Figure S10). Accordingly, the success of the reaction can be determined exclusively by the radical initiation step. First, we investigated the generation of mechanoradicals under ball-milling conditions. The simulation of C–C bond cleavage under force for three different polymer surrogates (polyethylene, polyvinyl acetate, and polystyrene) is shown in Figure 5A. The construction of the force-modified potential surface was successfully realized using the Artificial Force Induced Reaction (AFIR) method.[21, 38–42] Considering the timescale of our reactions, the effective barrier of covalent bond cleavage was set to 90.0 $kJ \cdot mol^{-1}$. To lower the barrier to this level, the fracture forces for polyethylene, isotactic polyvinyl acetate, and isotactic polystyrene should reach 3660, 3520, and 2980 pico-Newtons, respectively. The calculations revealed that polyethylene gave a primary carbon radical (**PE_r**), while polyvinyl acetate and polystyrene gave both primary (**PVAc_r1** and **PS_r1**, respectively) and secondary carbon radicals (**PVAc_r2** and **PS_r1**, respectively) via homolytic cleavage of the C–C bond under force. Moreover, we found that the fracture force of polyvinyl acetate is slightly lower than that of polyethylene, while that of polystyrene is the lowest. Based on these results, polystyrene is clearly the most reactive under force, and would be expected to generate the largest amount of mechanoradicals under

mechanochemical conditions. However, our experimental results showed a contradictory result, as the yield of the desired dehalogenation product was very low (2%) when polystyrene was used for the reaction. This puzzling situation encouraged us to further study the reactivity of the mechanoradicals in the radical initiation step via HAT.

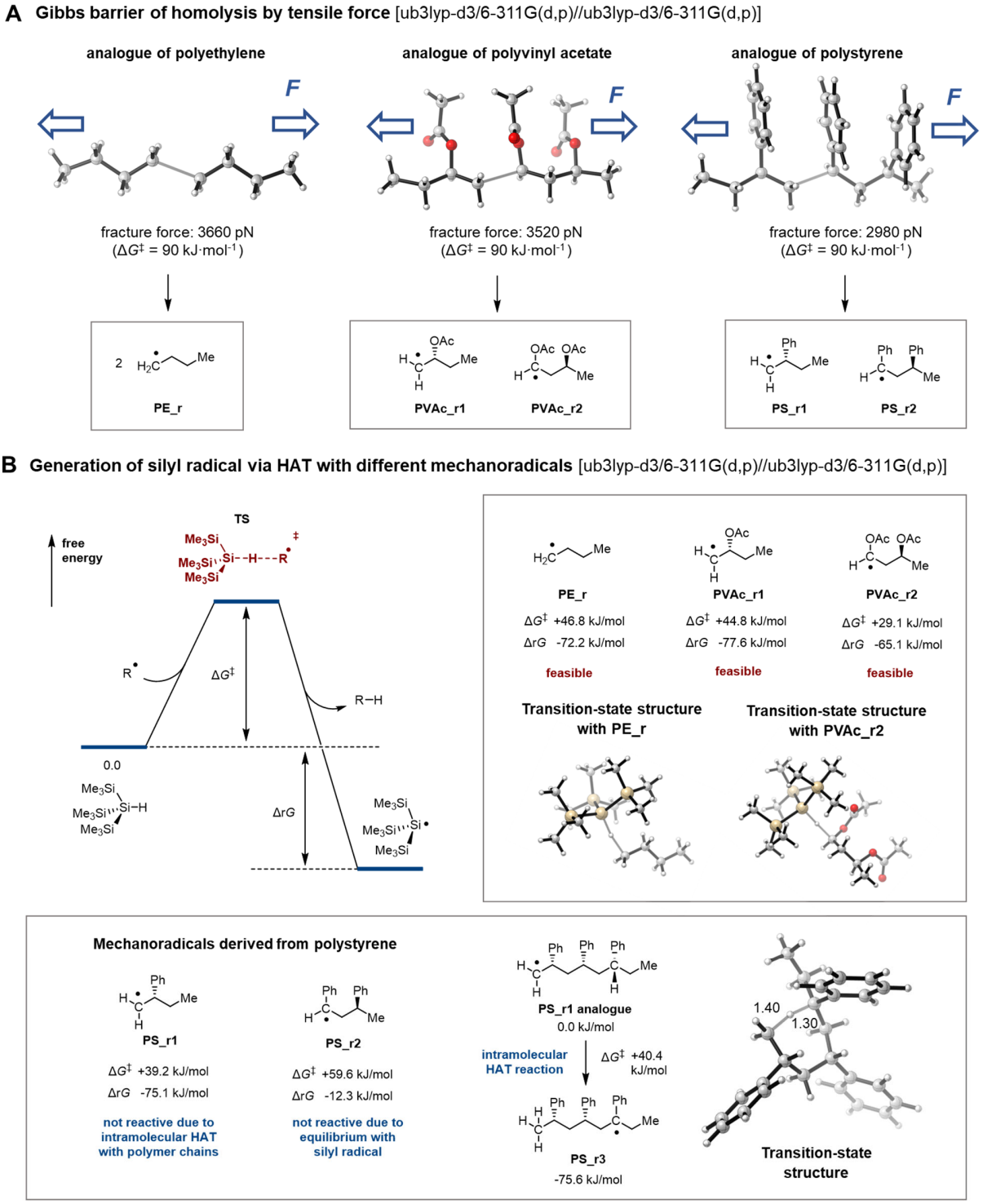

Figure 5. Computational study. **A,** Relative Gibbs energies ($\Delta G^{\ddagger}$) calculated at the ub3lyp-d3/6-311G(d,p)//ub3lyp-d3/6-311G(d,p) level (in kJ/mol) are given for the homolytic C–C bond cleavage by tensile force. **B,** Silyl-radical-generation step calculated at the ub3lyp-d3/6-311G(d,p)//ub3lyp-d3/6-311G(d,p) level.

The energy profile for the HAT reaction between the mechanoradicals and tris(trimethylsilyl)silane is shown in Figure 5B. Our calculations revealed that the primary alkyl radicals (**PE_r**, **PVAc_r1**, and **PS_r1**) and the secondary alkyl radical (**PVAc_r2**) are all sufficiently reactive to abstract the H atom from tris(trimethylsilyl)silane to generate a

tris(trimethylsilyl)silyl radical, which can initiate the radical dehalogenation reaction. However, importantly, we then noticed that **PS_r1** analogue, whose structure is similar to that of **PS_r1**, can undergo an intramolecular HAT reaction by extracting the H-atom from the middle of the polymer chain to form the more stable migrated secondary benzylic alkyl radical **PS_r3**; the barrier for this process is comparable to that of the HAT of tris(trimethylsilyl)silane by **PS_r1** (Figure 5B). The $\Delta_r G$ value for the HAT of tris(trimethylsilyl)silane by the migrated benzylic radical **PS_r3** is only –5.2 kJ/mol, suggesting that this HAT involves a fast equilibrium between the benzylic radical and the silyl radical, and therefore it is unable to generate sufficient silyl radicals for an efficient dehalogenation reaction. Similar reactivity was also suggested for the secondary benzylic radical (**PS_r2**) generated from polystyrene (see Figure 5B). For the primary alkyl radicals (**PE_r** and **PVAc_r1**) derived from polyethylene and polyvinyl acetate, such migrated radicals are still reactive for the HAT from tris(trimethylsilyl)silane (for calculation details, see the Supplementary Material). Overall, the observed reactivity differences among these polymeric materials could be explained by these intramolecular HAT reactions of the polymer chains, which lead to radicals with different reactivity toward the HAT process. The reactivity profile suggested by the calculations is consistent with our experimental results.

To demonstrate the broad applicability of this force-induced strategy, we also investigated a mechanoradical-initiated sp^3C–H fluorination reaction using the polymer-grinding system (Figure 6A),[43,44] which is of significant importance in contemporary synthetic organic chemistry and pharmaceutical research because the introduction of fluorine atoms into organic molecules often leads to compounds with unique properties and enhanced biological activity.[43,44] The original solution-based protocol using Et_3B/O_2 as a radical initiator was reported by Lectka and co-workers.[45] The key step of this transformation is the fluoride-atom transfer from Selectfluor (**5**) to the radical species generated from an initiator molecule. In our postulated mechanism shown in Figure 6B, the generated mechanoradicals from plastic materials under ball-milling conditions undergo the fluoride-atom transfer with Selectfluor (**5**). The generated nitrogen-based radical species **IV** would then react with aliphatic compound **6** via HAT to form radical intermediate **VI**, which could then undergo the fluoride-atom transfer with **5** to give the desired radical sp^3C–H fluorination product (**7**) with concomitant regeneration of **IV**.

To explore this mechanistic hypothesis, we attempted the proposed radical sp^3C–H fluorination of adamantane (**6a**) with **5** (2.2 equiv) in the presence of commercially available polymers (300 mg) and MeCN (0.5 μL/mg) as a liquid-assisted-griding (LAG) additive under ball-milling conditions for 60 min at 60 ℃. We found that polystyrene (M_w = 350 kg/mol) can serve as an efficient initiator for the radical chain sp^3C–H fluorination reaction to give the fluorinated products (**7a** and **7b**) in 47% and 11% yield, respectively (total yield: 58%; **7a**:**7b** = 81:19). This result is comparable to Lectka's solution-based conditions using Et_3B/O_2 (total yield: 50%; **7a**:**7b** = 84:16).[45] Importantly, these fluorinated products (**7a** and **7b**) are generated in a very low yield (total yield: 4%; **7a**:**7b** = >99:1) in the absence of a polymeric material, suggesting that polymeric mechanoradicals initiate the radical sp^3C–H fluorination. The use of polyethylene (ultra-high molecular weight) and polyvinyl acetate (M_n = 35 kg/mol), which are good initiators for the radical chain-dehalogenation reaction, provided no or a very low yield of product (for details, see the Supporting Information). Under the developed mechanochemical conditions using polystyrene as a radical initiator, other adamantane derivatives (**6b** and **6c**) and cyclooctane (**6d**) were also fluorinated to give the corresponding products (**7c**–**7g**) in low to moderate yield (35%, 26%, and 17%, respectively). Further experimental and theoretical mechanistic studies will be carried out in order to improve the efficiency and explain the observed reactivity differences among these polymeric materials for the mechanoradical-initiated sp^3C–H fluorination.

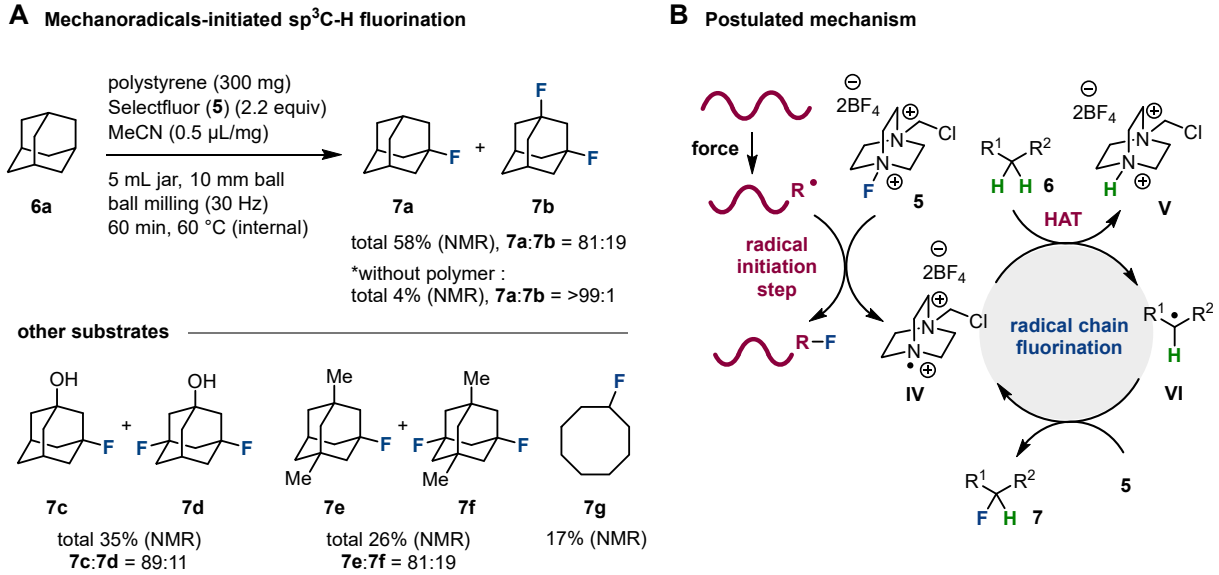

Figure 6. Use of plastic materials as initiators for radical chain sp^3C–H fluorination reactions under mechanochemical conditions. **A**, Preliminary substrate scope. **B**, Postulated mechanoradical-initiated mechanism.

CONCLUSION

We have demonstrated that a mechanochemical approach allows using cheap and abundant plastic materials as thermodynamically stable initiators for free-radical reactions of small organic molecules. The developed mechanochemical conditions can be carried out without the use of large amounts of dry and degassed organic solvents in air, and special operating conditions and precautions are not required. Considering the potential hazards of conventional high-energy radical initiators such as azo compounds, organic peroxides, and organometallic reagents, as well as the serious issues associated with solvent waste in conventional methods, we expect that this operationally simple and solvent-free mechanochemical protocol using commodity plastics will inspire the development of more convenient, safe, sustainable, and industrially attractive free-radical reactions.

ASSOCIATED CONTENT

Supporting Information

Supporting Information is available free of charge via the Inter-net at http://pubs.acs.org. Materials and methods, experimental procedures, compound characterization data, NMR spectra (PDF).

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Notes

The authors declare no competing financial interests.

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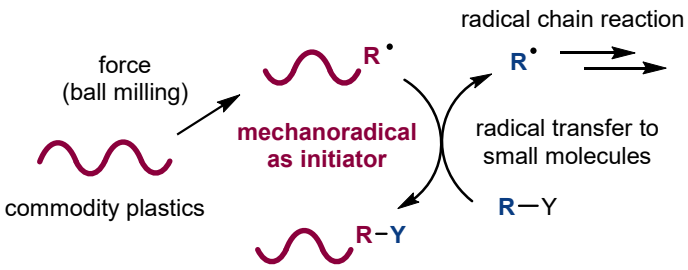
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