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Tin can milling: low-tech mechanochemical synthesis of plant-based prepolymers incorporating perfluoropyridine

Jason Pulfer,[ab] Miriam Aldom,[a] Maxime Colpaert,[c] Tim Storr[b] and Chadron M. Friesen*[a]

Perfluoropyridine (PFP) is a fluorinated small molecule heterocycle which can undergo a variety of substitutions in the 2-, 4-, and 6-position to afford rationally designed prepolymers. PFP is known to undergo mechanochemical substitutions, however ball mills have a large start-up cost and are bulky, creating a barrier of entry for researchers. We sought to provide a low tech, affordable, reproducible, and space-saving methodology towards general mechanochemistry while retaining the ability to work on gram scale. Herein we report the successful application of tin can milling (TCM) towards the gram scale synthesis of 4-tetrafluoropyridines (24 examples, up to ≥99% conversion) using a tomato paste can, aluminum beads, a rubber stopper, and agitation with a Burrell Wrist Action™ shaker unit. This approach eliminates problems of scalability with a mortar and pestle and provides a clean method to do benchtop-scale mechanochemistry without additional equipment. We further apply this technique towards making natural product-based prepolymers for polymerization by inverse vulcanization as a proof-of-concept for the use of TCM in monomer synthesis.

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1 Introduction

Mechanochemistry is widely recognized as a green, solvent-free methodology that has been applied to C–H bond activation,[1] metal catalysis,[2] polymer degradation and morphology tuning,[3] waste management,[4] hydrometallurgy of sulfides,[5] and supramolecular assemblies.[6] Mechanochemistry is distinct in terms of reactivity and has been observed to produce different products compared to traditional solution state methods, in some cases giving the kinetic product *versus* the thermodynamic product observed in solution.[7] Grinding with a mortar and pestle is one of the first chemical transformations recorded, making mechanochemistry one of the oldest known types of reactions.[8] Mechanochemical transformations in the academic laboratory are typically performed in a planetary ball mill or mixer mill in a hardy milling jar.[9] Twin screw extrusion (TSE) has been applied towards making a "flow"-type reactor, making mechanochemistry viable as a continuous process industrially.[10] TSE has been used by MOF (metal–organic framework) Technologies to achieve mechanochemical synthesis of MOFs at a rate of up to 15 kg h^{-1},[11] and solvent free Michael additions and Knoevenagel condensations have been demonstrated up to 0.5 kg h^{-1}.[12]

Perfluoropyridine (PFP) is a small molecule fluorinated building block which is readily synthesized from commercially available feedstocks.[13,14] PFP exhibits diverse reactivity, acting as a protecting group for alcohols,[15] facilitating amide and ester couplings,[16] cross-coupling chemistry,[17] and hydrodefluorination.[18] PFP is highly regioselective in nucleophilic aromatic substitutions, substituting in the *para* position, followed by further substitution in the *ortho* positions,[19] making it an excellent candidate for thermoset and step-growth networks.[20–23] PFP is known to undergo mechanochemical transformations, as shown by Schumacher *et al.* in the C–N bond coupling of PFP and NH-sulfoximines to form *N*-(tetrafluoropyridyl) sulfoximines in solvent free conditions with KOH at 25 Hz over 90 minutes.[24] Friesen *et al.* discovered that PFP is capable of undergoing nucleophilic aromatic substitution reactions in a ball mill at 80 Hz with a cesium carbonate matrix, attaining substitution in the 2-, 4-, and 6-positions.[25] This technique was used to synthesize prepolymers consisting of PFP with various glycol spacers, which were then polymerized with bisphenols to attain insoluble polymers.

Another type of polymerization which is found to be of interest and viable is inverse vulcanization. It is a method to induce polymerization of a material with elemental sulfur and an unsaturated organic molecule to make copolymers without solvents or radical initiators.[26] Kang *et al.* found that sulfur monochloride could also induce similar inverse vulcanization

[a]*Trinity Western University, 22500 University Drive, V2Y 1Y1, Langley, British Columbia, Canada. E-mail: chad.friesen@twu.ca*

[b]*Simon Fraser University, 8888 University Drive, V5A 1S6, Burnaby, British Columbia, Canada*

[c]*ICGM, Université de Montpellier, CNRS, École Nationale Supérieure de Chimie de Montpellier, Montpellier Cedex 5, 34293 Montpellier, France*

of an unsaturated monomer with two olefin groups to produce linear polychlorosulfides that display optical transparency, low birefringence, and high refractive index (>1.6) in the visible and near-infrared spectrum.[27] Further, oligomerization of natural products such as limonene have been demonstrated with elemental sulfur in a planetary ball mill, affording soluble species without requiring the high heat (>160 °C) of a typical inverse vulcanization reaction.[28]

In exploring mechanochemical substitution of PFP, we determined that there does not exist a generally affordable laboratory scale device to bridge the gap between a mortar and pestle and benchtop mills. As price point can be a deterrent from exploring mechanochemistry, we sought to develop a methodology that is space-saving, low tech, cost effective, and gram scalable for simple mechanical grinding reactions on the bench top. Perfluoropyridine is a useful model for this transformation, is relatively affordable, and has simple ^{19}F NMR patterns to determine substitution. PFP also is useful for polymerization applications due to its 3 active sites, making mechanochemistry a valuable tool for both organic and polymer chemists alike.

2 Results and discussion

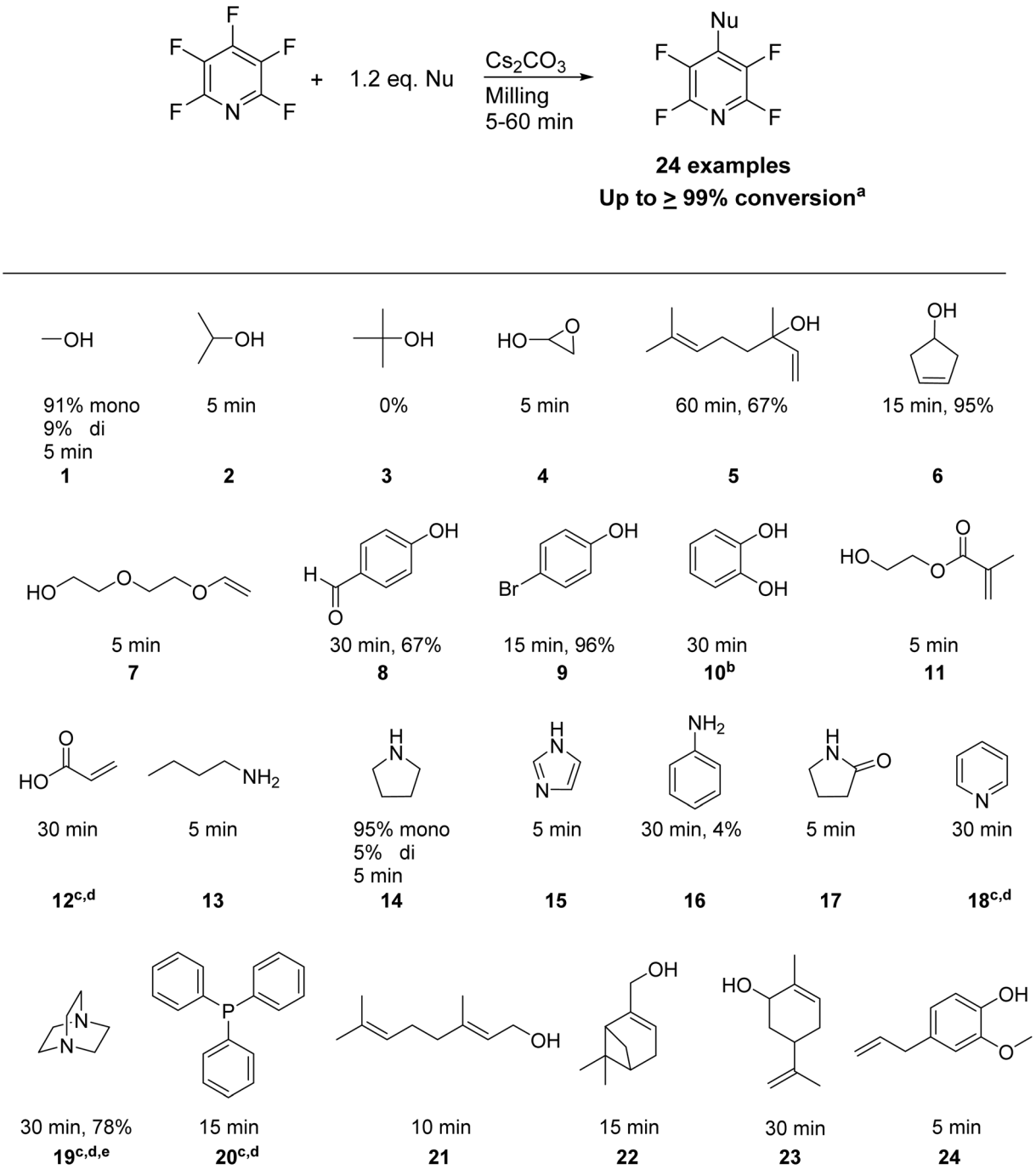
2.1 Reaction scope and synthesis of monomers

Mechanochemical reactions typically make use of a ball mill, twin screw extruder (TSE), or a mortar and pestle. In previous work our group discovered that PFP substitutes quite readily using a mortar and pestle,[29] and Friesen *et al.* successfully demonstrated substitution using a ball mill.[25] Attempts to scale up our mortar and pestle synthesis to gram scale resulted in drastically lower yields compared to millimolar scale. This led to several questions: (1) can low-tech mechanochemistry be done on gram scale, (2) can mechanochemistry be selective for the 4-position of the PFP ring, and (3) is there intermediate technology between a mortar and pestle and a mill which can initiate smaller scale mechanochemical reactions in an affordable manner? In pursuing these questions, we arrived at the elegant solution of a Hunt's tomato paste (2″ diameter × 3 7/16″ height, or 5.1 cm diameter × 8.7 cm height) can as a milling jar fitted with a No. 11 rubber bung (commonly found for home brewing vessels) as a cap (see Fig. 1). We were inspired by the design of a rock crusher apparatus and utilized pea gravel commonly found at home improvement or construction retailers as a grinding medium. Rock dust quickly became an issue, and Lab Armor™ aluminum beads were substituted to mitigate dust formation. Cesium carbonate was chosen as a base due to past literature proving its success in mechanochemical reactions with PFP,[25] and other common bases, such as K_2CO_3 and K_3PO_4, have been found to display low yields in reactions of PFP with sulfonamides.[24]

Marbles or ball bearings are equally suitable replacements as milling balls. Manual shaking was successful in the case of **4** (see Scheme 1) but showed variability between trials dependent on the operator. A Burrel Wrist Action™ shaker unit was used to standardize shaking force and frequency, and a scope of nucleophiles was tested to determine the limits of S_NAr mechanochemistry in tin can milling (TCM) (see Fig. 2).

Samples were milled and tested at the 5, 15, 30, and, in one case 60-minute marks by extracting the deposited reaction mixture off 2–3 of the beads with a suitable deuterated solvent to estimate conversion by ^{19}F NMR. 4-Tetrafluoropyridines

Fig. 1 Tomato paste milling jar after grinding a reaction with eugenol as a nucleophile (left) and solvent extraction of beads with chloroform for analysis of the ether product **28** (right).



Scheme 1 General reaction conditions, scope of nucleophiles and accompanying conversions with reaction time. [a]Yields are quantitative by ^{19}F NMR unless otherwise indicated. [b]Yield represents substitution on both positions of the catechol as excess PFP was used. [c]Yield represents conversion to 4-hydroxytetrafluoropyridine based on past literature.[30] [d]Water-soluble fraction of the aluminum beads used to determine conversion. [e]Yield represents relative to 2 equivalents of PFP used.

show diagnostic peak patterns compared to the starting material (see Fig. 3). PFP shows 3 distinct signals at −86.75 ppm, −132.8 ppm, and −160.98 ppm (referenced to $CFCl_3$ at 0.00 ppm) with a diagnostic 2 : 1 : 2 ratio of integrations. The 4-tetrafluoropyridines show only 2 signals at ∼−90 ppm and ∼−158 ppm with a 1 : 1 integration, and these signals can be used to determine conversion to the desired product.

Most nucleophiles underwent complete conversion to the desired product within 60 minutes, apart from *tert*-butanol which gave 0% conversion (see Scheme 1). Past literature has found that mechanochemical activation of PFP is controllable by stoichiometry to attain mono-, di-, and tri-substituted derivatives,[25] however in our hands we have found that lower frequency milling *via* TCM controls reaction regioselectivity to effectively the mono-substitution only. Methanol and pyrrolidine are the only nucleophiles tested which provide further substitution in the 2-position (9% and 5% conversion to di-substituted product, respectively). Further, all reactions were

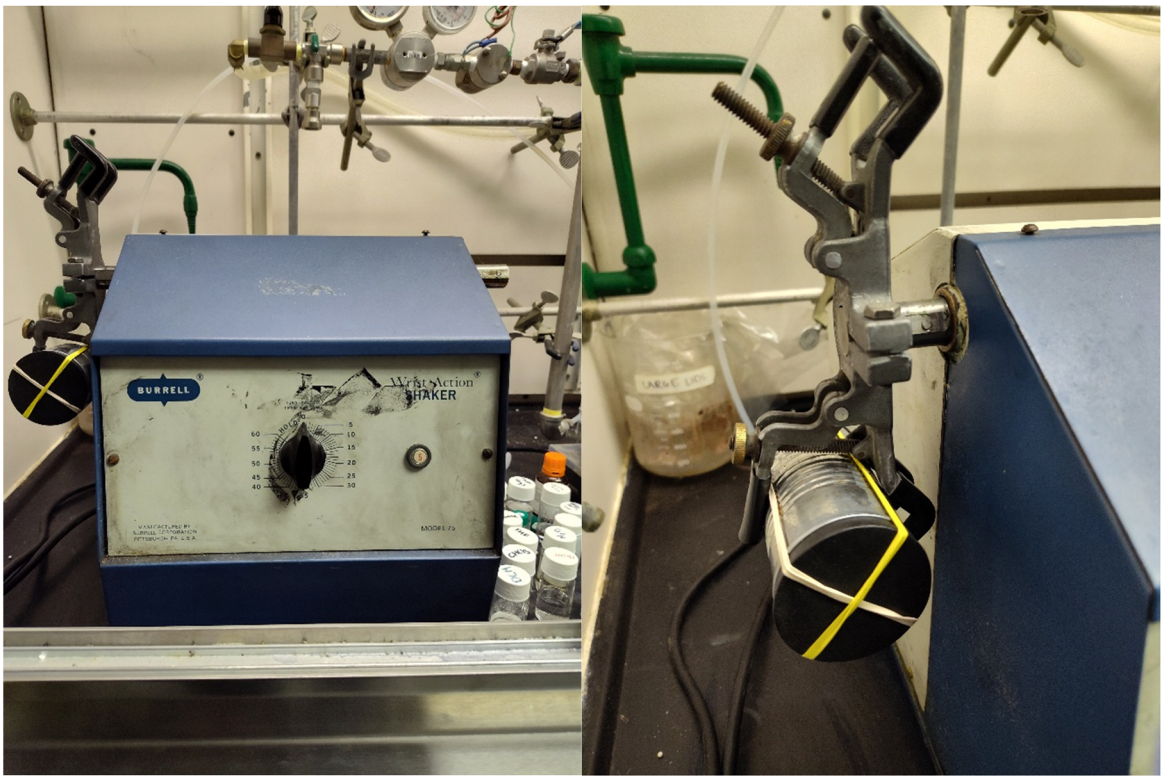


Fig. 2 Burrell Wrist Action™ Shaker unit with variable time dial for application in TCM (left) and close-up of the reactor setup involving a tomato paste can fitted with a No. 11 bung secured with elastic bands.

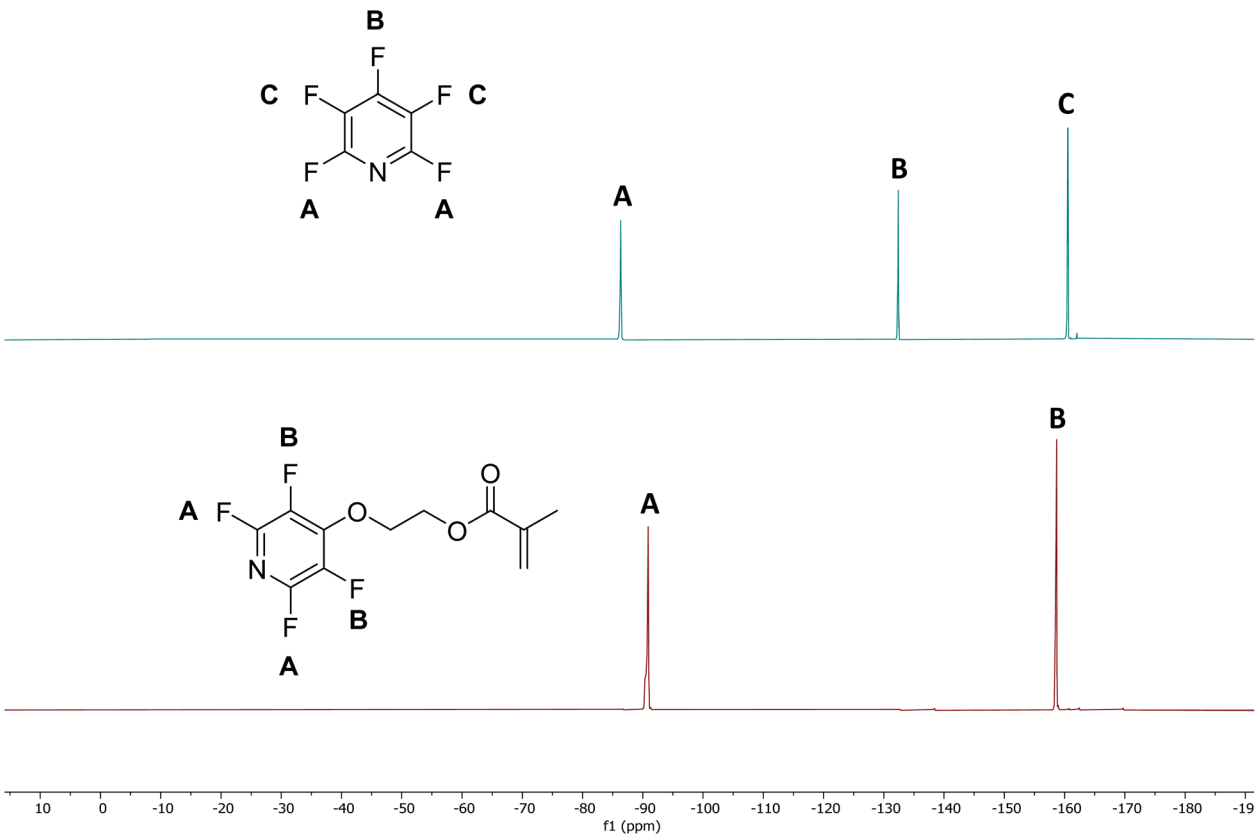


Fig. 3 ^{19}F NMR patterns in $CDCl_3$ of the 4-tetrafluoropyridine methacrylate derivative **11** after TCM (bottom) compared to ^{19}F NMR of PFP (top).

found to be scalable up to 2 grams, providing a facile methodology to create large amounts of substituted PFP with short reaction time. The main advantage to TCM over traditional mechanochemical methods is that it provides similar results to a mortar and pestle, but allows for gram scalability, reproducibility, cost effectiveness, and can be readily employed for reactions which do not require high energy input.

Generally, cyclic structures tend to exhibit lower reactivity than their analogous linear structures. **21** and **22** are primary allylic alcohols, however **22** requires 5 minutes more reaction time. Likewise, **23** requires 30 minutes to reach completion, but **6**, which is less sterically hindered, requires just over 15 minutes. **2** and **4** are also secondary alcohols but can reach completion within 5 minutes, indicating that steric bulk is a significant factor in reducing reactivity. Highly activated aromatic nucleophiles, such as **24**, require only 5 minutes to reach completion, however less activated aromatic nucleophiles require longer reaction time, with **9** reaching completion just after 15 minutes. Deactivated aromatic nucleophiles react very slowly by comparison, with **8** reaching 67% conversion after 30 minutes of shaking.

12 displays substitution through ^{19}F NMR, however the extract was only soluble in water. PFP is known to form acyl fluorides in the presence of organic acids and base *via* ester formation, followed by nucleophilic attack of the fluoride on the ester to release 4-hydroxytetrafluoropyridine and the corresponding acyl fluoride (see Scheme 2).[16] The acyl fluoride is not observed in our hands, likely due to hydrolysis *via* atmospheric water occurring during milling.

Tertiary pnictogens such as **18**, **19**, and **20** all substitute to form water soluble species. **19** displays 78% conversion with 2 equivalents of PFP. **20** shows a distinct pattern of monosubstitution in the ^{19}F NMR in D_2O at −101.5 ppm and −169.9 ppm with a 1 : 1 integration. An additional peak at −122.0 ppm indicates the presence of free fluoride, indicating substitution has occurred (see Fig. 4). Further review shows that **16**, **18**, **19**, and **20** display the same ^{19}F NMR shifts, matching that of **12**, indicating that these species form 4-hydroxytetrafluoropyridine based on ^{19}F NMR in past literature (ref. 15).

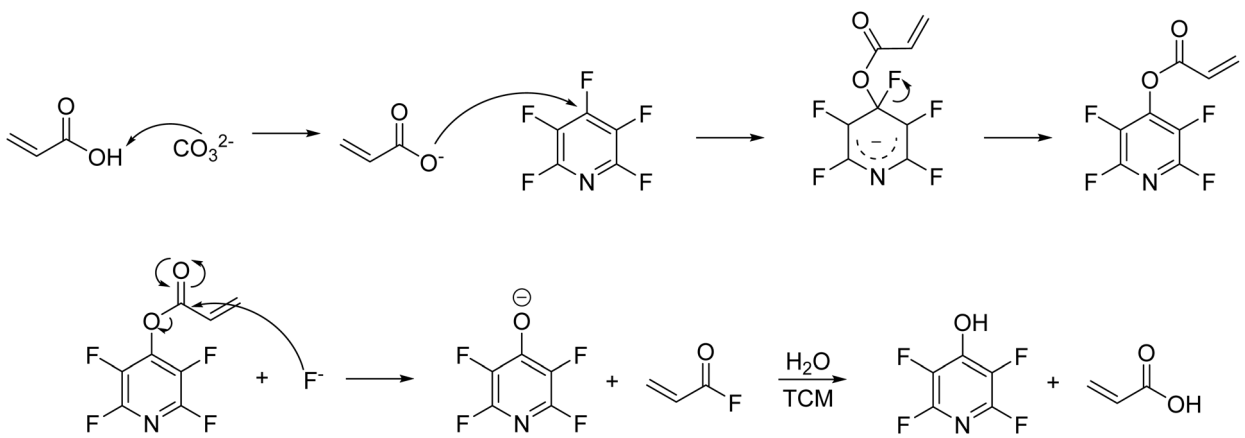
During this work, it was discovered that none of the isolated samples are amendable to classical mass spectrometry (MS) techniques. Of the isolated samples, only **28** was found to provide a MW peak by EI-MS. Samples **25**, **26**, and **27** showed fragmentation patterns by EI-MS, indicating that α,β unsaturated PFP ethers are relatively unstable in by this ionization technique (see Fig. 5).

In our hands, field-desorption mass spectroscopy (FD-MS) was found to provide exceptionally clean spectra containing the molecular weight peak and is highly recommended by the authors for similar samples which display fragility under conventional EI and ESI ionization techniques (see Fig. 6). **25** and **28** were additionally observed to decompose on the benchtop over the course of 3 months, indicating thermal or photo instability.

2.2 Inverse vulcanization of PFP-containing natural product monomers

Inverse vulcanization is a term for a crosslinked polymer wherein the organic component can be seen as a crosslinking agent to stabilize long sulfur chains. Inverse vulcanized materials are commonly used in energy generation and storage, environmental remediation, optical devices, repairable material development, and mercury capture.[28,31] Such materials have been successfully synthesized on kilogram scale to develop high-capacity polymer electrodes for Li–S batteries with 1,3-diisopropenylbenzene as a comonomer.[32] These sulfur-rich materials have not seen use outside of academic research, however some companies such as ThioTech, Outside the Box Materials, Uberbinder, and Clean Earth Technology have undertaken research in this area to attempt commercial exploitation.[31] Several natural product derivatives of PFP were envisioned to be viable for inverse vulcanization through reaction with elemental sulfur or with sulfur monochloride due to their unsaturated components (see Scheme 3).

The sulfur monochloride product was tested at room temperature and with heating in bulk, with both air and nitrogen atmospheres investigated. Inverse vulcanizations with elemental sulfur were conducted in bulk and were allowed to



Scheme 2 Postulated mechanism of the formation of acyl fluoride and 4-hydroxytetrafluoropyridine.

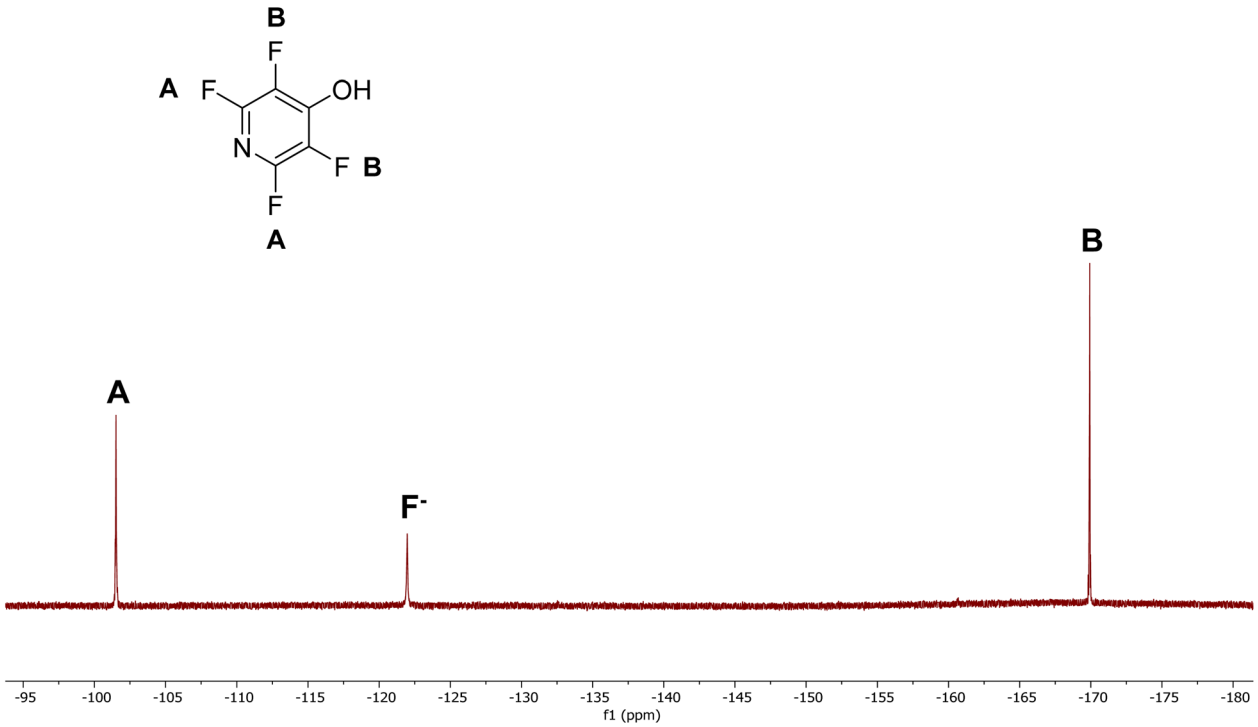


Fig. 4 ^{19}F NMR of 4-hydroxytetrafluoropyridine in D_2O produced from the reactions of **12**, **18**, **19**, and **20**.

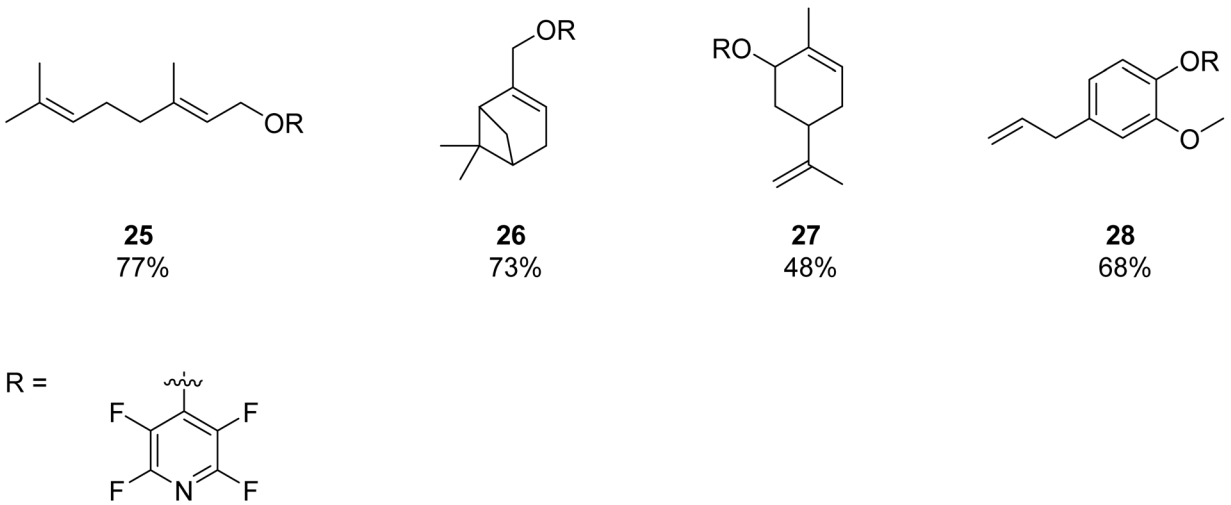


Fig. 5 Candidates for inverse vulcanization of PFP with S_8 and S_2Cl_2 and isolated yields.

proceed until the sample formed a solid at 160 °C, or until 1 week passed, in the case of **28-S$_8$**. The thermal data and gel-permeation chromatography (GPC) results are summarized in Table 1. Yields for the sulfur monochloride reactions are quite low: vulcanization of **25-S$_2$Cl$_2$** in tetrahydrofuran (THF) in atmospheric conditions provided the highest isolated yield of 42%, compared to 4% at 70 °C under nitrogen and 20% at room temperature under air. Conversely, **27-S$_2$Cl$_2$** provides a better yield when cured neat under nitrogen at 70 °C compared to in solution (37% *versus* 12% respectively).

2.3 Gel permeation chromatography (GPC) and thermal analysis of the polymers

25 was chosen to examine various conditions for bulk sulfur monochloride vulcanization and generally forms lower molecular weight oligomers at room temperature and elevated temperature under nitrogen. The best conditions for this reaction appear to be under nitrogen at 70 °C, which gives the highest M_N value of 1677 g mol^{-1} and a PDI of 1.46. Oddly, room temperature vulcanization of **25** under ambient atmosphere provides 2 peaks in the chromatogram, with an M_N at 45 399 g

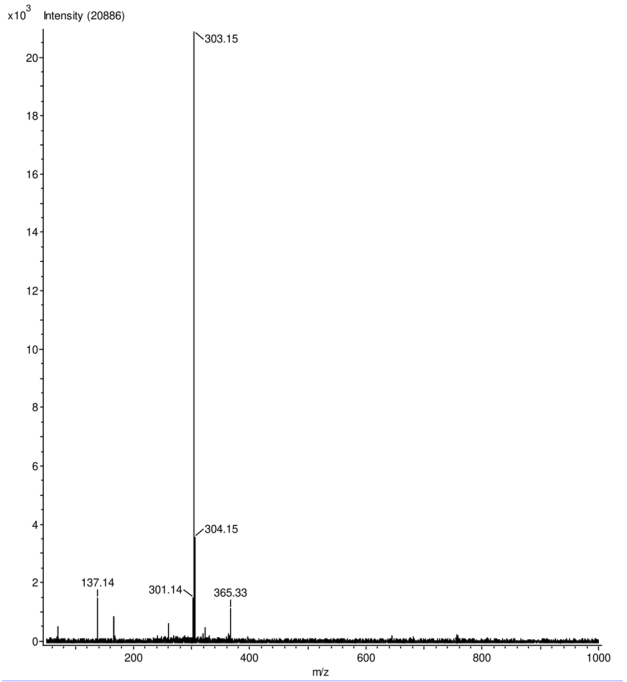
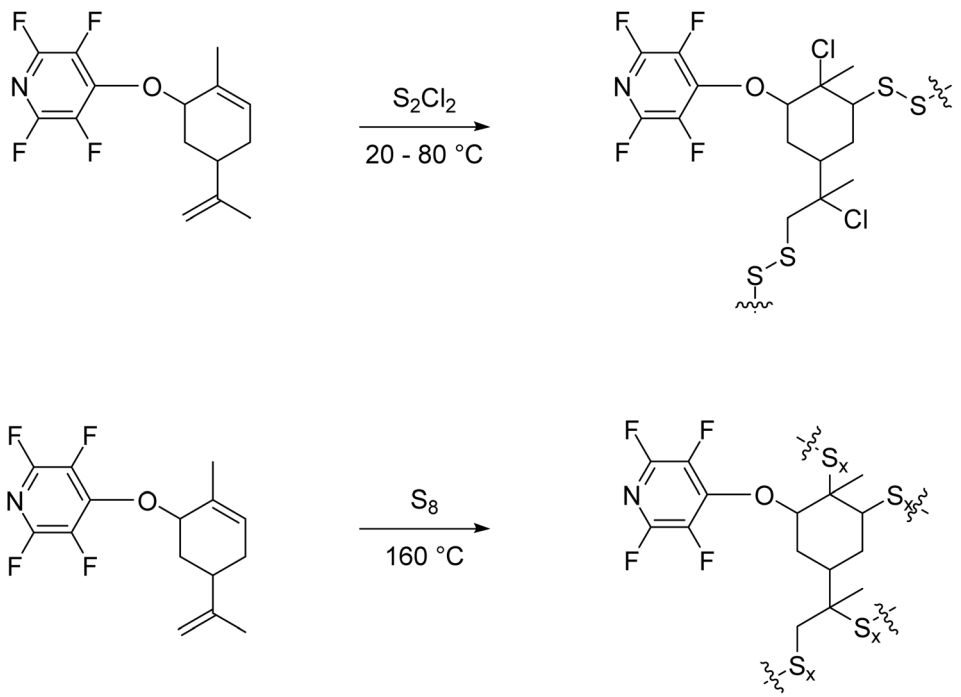


Fig. 6 Sample FD-MS spectrum of **25** with MW 303.15 g mol^{-1} (see Fig. 6).

mol^{-1} and a PDI of 1.07 as the minor peak (25% by UV detector peak area), indicating the material can undergo significant polymerization to make longer chains given appropriate conditions. **27** mainly produces low molecular weight oligomer (400–1200 g mol^{-1}), likely due to steric bulk of the ring.

The T_{onset} (temperature of onset of degradation measured as the intersection of the baseline weight and tangent of the point of maximum gradient of the curve)[33] (see Table 1) of S_8 crosslinked materials are consistent at 205–230 °C, with **25-S_8** showing slightly higher T_{onset} values of ~228 °C in air. Sulfur monochloride vulcanized material gives similar results between air and nitrogen, and **27-S_2Cl_2** showing the highest thermal stability when vulcanized at 70 °C under nitrogen (~201 °C). Compared to **25-S_2Cl_2** crosslinked under the same conditions, **27-S_2Cl_2** has a ~40 °C increase in T_{onset} at a lower molecular weight (1071 g mol^{-1} compared to 1677 g mol^{-1}), indicating higher stability of the carveol group. Glass transition temperatures (T_g) vary across polymer classes, with S_8 vulcanized material ranging from −2–61 °C, and sulfur monochloride vulcanized material ranging from 0.6–53.3 °C. In our hands **25-S_8** does not present a T_g in the DSC, however, PFP with alkyl units such as **26-S_8** and **27-S_8** give low T_g values of −2 °C and −5 °C respectively, compared to 61 °C for **28-S_8**. This is hypothesized to be due to the rigid nature of the eugenol substituent, indicating that T_g can be readily modulated in S_8-vulcanized material, allowing for the production of glassy or more flexible material based on the comonomer. As inverse vulcanized materials are hypothesized to have application in Li–S batteries, materials with highly fluorinated aromatics could be a potential route to lower T_g values and produce battery films that are capable of low temperature applications.[32] Materials undergoing S_2Cl_2 inverse vulcanization demonstrate an increase of T_g when vulcanized under N_2 (42 and 53 °C for **25-S_2Cl_2** and **27-S_2Cl_2** respectively) compared to normal atmosphere (10 and 20 °C for **25-S_2Cl_2** and **27-S_2Cl_2** respectively), indicating that higher molecular weight increases the glass transition temperatures, and these materials could have potential use in flexible optical films or as low birefringence materials, similar to those developed by Kang *et al.*[27]



Scheme 3 General scheme of the vulcanized materials.

Table 1 Thermal data and GPC of the inverse vulcanized polymers produced with **25**, **26**, **27** and **28**

Sample	T_{onset} air (°C)	T_{onset} N_2 (°C)	T_g (°C)	M_N (g mol^{-1})	M_W (g mol^{-1})	PDI
25-S$_8$	207	209	—	—	—	—
26-S$_8$	228	217	−2	—	—	—
27-S$_8$	208	206	−5	—	—	—
28-S$_8$	227	241	61	—	—	—
25-S$_2$Cl$_2$ (20 °C, air)	142	143	1	1363[a]	2038[a]	1.5
				45 399[b]	48 252[b]	1.1
25-S$_2$Cl$_2$ (65 °C, THF air)	168	168	10	842	1983	2.4
25-S$_2$Cl$_2$ (70 °C, N_2)	172	173	42	1677	2456	1.5
27-S$_2$Cl$_2$ (65 °C, THF, air)	162	184	20	457	872	1.9
27-S$_2$Cl$_2$ (70 °C, N_2)	202	202	53	1071	2548	2.4

[a] Low molecular weight distribution peak from GPC. [b] High molecular weight distribution peak from GPC.

3 Conclusion

Perfluoropyridine was found to undergo mechanochemical substitution in up to quantitative conversion through simple, low tech mechanochemistry in a tomato paste can with commonplace grinding media. The approach is gram scalable, cheap, and highly regioselective to the 4-position of the ring. The natural product derivatives of PFP were demonstrated to undergo inverse vulcanization with elemental sulfur and sulfur monochloride, showing utility of the methodology towards prepolymer design and synthesis. Future work will focus on low tech methodologies to rival commercial ball mills using common equipment from the laboratory or hardware store.

4 Experimental

4.1 Materials

Chemicals were used as received unless otherwise noted. Geraniol (≥97%), eugenol (99%), (−)-carveol (mixture of isomers, 97%), myrtenol (≥95%), pyrrolidine (≥99.0%), pyridine (99.8%), methanol (≥99.6%), isopropanol (≥99.5%), 1,4-diazabicyclo [2.2.2]octane (DABCO) (≥99%), imidazole (≥99.5%), 2-pyrrolidinone (99%), 4-bromophenol (99%), 4-hydroxybenzaldehyde (98%), acrylic acid (≥99.0), glycidol (96%), 2-hydroxyethylmethacrylate (97%), hexanes (mixture of isomers, ≥98.5%), diethyl ether (≥99.0%), ethyl acetate (≥99.5%), chloroform (≥99.8%), dichloromethane (≥99.8%), tetrahydrofuran (≥99.0%), catechol (≥99%), alumina (80–200 mesh, chromatographic grade) and silica (70–230 mesh, 60 Å, for column chromatography) all came from Sigma-Aldrich. Sulfur monochloride (98%) obtained from Sigma-Aldrich and distilled before use, giving an orange liquid. Perfluoropyridine (PFP) (99%), cesium carbonate (99.9%), 3-cyclopenten-1-ol (98%) and diethylene glycol monovinyl ether (98%) were obtained from AK Scientific. Triphenylphosphine (powder, 99%) and sulfur (powder, 325 mesh, 99.5%) came from Alfa Aesar. *tert*-Butanol was obtained from Fischer Scientific. Butylamine (98%) was obtained from EM Scientific. Aniline (99%) was obtained from Anachemia.

4.2 Characterization

4.2.1 Spectroscopy. NMR spectra were collected on a Bruker ASCEND III 400 MHz NMR with a Bruker AVANCE III 400 MHz running TopSpin 3.1.6 and processed with MestReNova or TopSpin. ^{1}H (400 MHz) and ^{13}C NMR (101 MHz) spectra were referenced to an internal standard or $CDCl_3$ (7.26 ppm) and ^{19}F NMR (376 MHz) spectra were to CCl_3F (0.00 ppm). Chemical shifts were reported in parts per million (ppm) and coupling constants are reported in Herz to the nearest 0.01 Hz. NMR data is reported as: chemical shift, multiplicity (s, d, t, q, pent, and sext stand for singlet, doublet, triplet, quartet, pentet, and sextet, respectively), coupling constants (Hz), integration, and identity. ^{19}F NMR parameters are as follows: 64 scans, acquisition time 1.467 s, relaxation delay 2 s, −43.56 ppm offset, and 237.165 ppm sweep width. Field desorption mass spectroscopy (FD-MS) was conducted on a Jeol JMS-T100GCV AccuTOF GCv 4 g equipped with a field desorption source. Attenuated total reflectance Fourier transform infrared spectroscopy (ATR-FTIR) was performed on a ThermoFisher Nicolet 6700 spectrometer fitted with a Smart iTR sampling accessory and reported in reciprocal centimeters (cm^{-1}).

4.2.2 Differential scanning calorimetry (DSC). Analysis was carried out using a NETZSCH DSC200F3 calorimeter. The calibration was performed using adamantane, biphenyl, indium, tin, bismuth and zinc standards. Nitrogen was used as purge gas. Approximately 10 mg of sample were placed in perforated aluminum pans and the thermal properties were recorded. Data was analyzed using Proteus 8.1 and OriginPro 2021.

4.2.3 Thermal gravimetric analysis (TGA). Measurements were conducted on a TGA Q50 from TA analysis. Samples were placed in 30 μL aluminum crucibles and heated from 25 to 500 °C at 10 °C min^{-1} under nitrogen or air flow (60 mL min^{-1}). Data was analyzed with Origin Pro 2021. T_{onset} was defined as the temperature of onset of degradation measured as the intersection of the baseline weight and tangent of the point of maximum gradient of the curve.

4.2.4 Size-exclusion chromatography (SEC). Analyses of polymers were conducted on a system composed of an Agilent Infinity I pump degasser, oven and detector 1260 VWD G1314F and a Varian 390-LC Multi detector suite fitted with differential refractive index, light scattering, and viscosimeter. The system was equipped with a guard column (Agilent Mesopore, 50 × 7.5 mm) and two columns (Agilent Mesopore and Resipore, 300 × 7.5 mm). The mobile phase was tetrahydrofuran (THF) at a flow rate of 1.0 mL min^{-1}. Toluene was added to the samples as

a flow marker and samples (typical concentration: 5 mg mL^{-1} and injection 100 μm) were filtered prior to analysis (0.20 μm PTFE filter) and results were calibrated with and poly(methyl methacrylate) (PMMA) standards (550–2 210 000 g mol^{-1}) or polystyrene standards (162–371 000 g mol^{-1}) using Agilent GPC/SEC v1.2 software.

4.3 Preparation

4.3.1 General TCM reaction procedure. For production of mono-substituted perfluoropyridine in the 4-position, ~95 g of Lab Armor™ aluminum beads were placed in a Hunt's tomato paste can, along with Cs_2CO_3 (1.3 eq., 2.390 g, 7.34 mmol), PFP (1.2 eq., 1.098 g, 6.50 mmol), and nucleophile (for geraniol ex. 1 eq., 0.846 g, 5.48 mmol). The reactor was then agitated using a Burrell Wrist Action™ Shaker and monitored using ^{19}FNMR at the 5-, 15-, 30-, and 60-minute mark. Reactions were isolated by filtration through a cotton plug and alumina to afford the product as an oil. Reactions for the scope were performed with slight excess of nucleophile (1.2 eq.) to ensure conversion and determine if secondary substitution occurred. Isolated materials were performed with a slight excess of PFP (1.2 eq.) to ensure ease of purification. Note: filtration of the aluminum beads through a glass frit or a glass frit with a Celite plug under nitrogen pressure was unilaterally observed to induce clogging, thereby making filtrations long and tedious. The authors recommend vacuum filtration through a glass funnel with a cotton plug and alumina to ensure a smooth, simple work-up. Prior to the use of a tomato paste can as a milling jar, the can must be washed thoroughly with soap and water, followed by soaking and rinsing with dichloromethane at least 5 times to remove the plastic lining.

*4.3.1.1 Synthesis of **25**.* PFP (1.098 g, 6.50 mmol, 1.2 eq.) was placed in a tomato paste can containing aluminum beads, along with Cs_2CO_3 (2.390 g, 7.34 mmol, 1.3 eq.), and geraniol (0.846 g, 5.48 mmol, 1.0 eq.). Quantitative conversion was shown by ^{19}F NMR after 10 minutes of agitation. The product was extracted with 3 × 50 mL of chloroform, vacuum filtered through alumina and a cotton plug in a glass funnel, and concentrated to a golden yellow oil (88% isolated yield).

^{19}F NMR ($CDCl_3$, 376 MHz, CCl_3F) δ: −91.6 (m, 2F, 2,6-position C_5F_4N), −159.0 (m, 2F, 3,5-position C_5F_4N).

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 5.47 (t, ^{3}J = 6.94 Hz, 1H, –O–CH_2–**CH**=C–), 5.02 (s, 1H, –**CH**=$C(CH_3)_2$), 5.00 (s, 2H, –O–**CH_2**–CH=), 2.08 (s, 4H, –**CH_2CH_2**–CH=C–), 1.74 (s, 3H, –O–CH_2–CH=C–**CH_3**), 1.66 (s, 3H, –C–(**CH_3**)$_2$), 1.59 (s, 3H –C–(**CH_3**)$_2$).

^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 147.2 (m, 4-position C_5F_4N), 146.1 (s, –CH=**C**(CH_3)–CH_2–), 144.3 (dm, ^{1}J = 242 Hz, 3,5-position C_5F_4N), 135.5 (dm, ^{1}J = 256 Hz, 2,6-position C_5F_4N), 132.3 (s, –CH=**C**$(CH_3)_2$), 123.4 (s, –**CH**=$C(CH_3)_2$), 117.6 (s, –CH_2–**CH**=(CH_3)–CH_2–), 70.9 (t, ^{4}J = 4.3 Hz, –O–**CH_2**–CH=,), 39.6 (s, =$C(CH_3)$–**CH_2**–), 26.3 (s, =$C(CH_3)$–CH_2–**CH_2**–), 25.7 (s, =C(**CH_3**)–CH_3), 17.8 (s, =$C(CH_3)$–**CH_3**), 16.8 (s, =C(**CH_3**)–CH_2–).

FD-MS *m*/*z*: 303.15, 304.15.

Calc. *m*/*z*: 303.12, 304.13, 305.13.

*4.3.1.2 Synthesis of **26**.* PFP (1.092 g, 6.46 mmol, 1.3 eq.) was placed in a tomato paste can containing aluminum beads, along with Cs_2CO_3 (2.418 g, 7.42 mmol, 1.5 eq.), and myrtenol (0.740 g, 4.86 mmol, 1.0 eq.). Quantitative conversion was shown by ^{19}F NMR after 15 minutes of agitation. The product was extracted with 3 × 50 mL of chloroform, vacuum filtered through alumina and a cotton plug in a glass funnel, and concentrated to a golden yellow oil (92% isolated yield).

^{19}F NMR ($CDCl_3$, 376 MHz, CCl_3F) δ: −91.6 (m, 2F 2,6-position C_5F_4N), −158.3 (m, 2F 3,5-position C_5F_4N).

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 5.72 (s, 1H, –C=**CH**–), 4.86 (dd, ^{4}J = 11.90 Hz, ^{5}J = 19.99 Hz, 2H –O–**CH_2**–), 2.41 (dt, ^{3}J = 5.59 Hz, ^{4}J = 8.80 Hz, 1H, –O–C–**CH**–C$(CH_3)_2$–), 2.28 (m, 2H, =CH–**CH_2**–CH), 2.10 (s, 3H, –**CH**–CH_2–CH= and –CH–**CH_2**–CH–), 1.30 (s, –C(**CH_3**)–CH_3), 1.02 (d, ^{3}J = 6.56 Hz, 1H, –CH–**CH_2**–CH–), 0.75 (s, 3H, –C(CH_3)–**CH_3**).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 147.2 (m, 4-position C_5F_4N), 144.3 (dm, ^{1}J = 242 Hz, 3,5-position C_5F_4N), 142.7 (s, –O–CH_2–**C**=), 135.5 (dm, ^{1}J = 257 Hz, 2,6-position C_5F_4N), 124.9 (s, –C=**CH**–CH_2), 77.0 (t, ^{4}J = 4.40, –O–**CH_2**–), 43.3 (s, –CH=C–**CH**–), 40.7 (s, –C$(CH_3)_2$–**CH**–CH_2–CH=), 38.2 (s, –CH–**C**$(CH_3)_2$–CH–), 31.6 (s, =CH–**CH_2**–CH–), 31.5 (s, =C–CH–**CH_2**–CH–), 26.1 (s, –C(**CH_3**)$_2$–), 21.0 (s, –C(**CH_3**)$_2$–).

FD-MS *m*/*z*: 301.13, 302.13, 303.13.

Calc. *m*/*z*: 301.11, 302.11, 303.12.

*4.3.1.3 Synthesis of **27**.* PFP (1.101 g, 6.51 mmol, 1.3 eq.) was placed in a tomato paste can containing aluminum beads, along with Cs_2CO_3 (2.542 g, 7.80 mmol, 1.5 eq.), and (−)-carveol (0.774 g, 5.08 mmol, 1 eq.). Quantitative conversion was shown by ^{19}F NMR after 30 minutes of agitation. The product was extracted with 3 × 50 mL of chloroform, vacuum filtered through alumina and a cotton plug in a glass funnel to yield a grey oil. This oil was filtered over silica and concentrated to a golden yellow oil (77% isolated yield).

^{19}F NMR ($CDCl_3$, 376 MHz, CCl_3F) δ: −91.0 (m, 2F, 2,6-position C_5F_4N), −157.7 (m, 2F, 3,5-position C_5F_4N).

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 5.86 (m, 2H, –C(CH3)=**CH**–), 5.69 (m, 1H, –C(CH_3)=**CH**–), 5.26 (s, 1H, –O–**CH**–), 4.97 (s, 2H, –O–**CH**–), 4.76 (s, 4H, –C=**CH_2**), 4.73 (s, 2H, –C=**CH_2**), 2.51 (t, ^{3}J = 5.52 Hz, 2H, –CH–C(**CH_3**)=CH_2), 2.36–1.90 (m, 13H, –**CH_2**–**C**($C(CH_3)$=CH_2)–**CH_2**), 1.86 (s, 6H, –C(**CH_3**)=CH_2), 1.82 (s, 3H, –C(**CH_3**)=CH_2), 1.73 (s, 9H, –O–CH–C(**CH_3**)=).

^{13}C NMR ($CDCl_3$, 101 MHz) δ: 148.2 and 147.8 (s, –**C**(CH_3)=CH_2), 147.4 (m, 4-position C_5F_4N), 144.4 (dm, ^{1}J = 242 Hz, 3,5-position C_5F_4N), 135.5 (dm, ^{1}J = 257 Hz, 2,6-position C_5F_4N), 132.5 and 130.4 (s, –O–CH–**C**(CH_3)=CH–), 129.6 and 127.3 (s, –CH–C(CH_3)=**CH**–), 110.0 and 109.8 (s, –C(CH_3)=**CH_2**), 84.8 (t, ^{4}J = 3.43 Hz, –O–**CH**–), 82.8 (t, ^{4}J = 4.10 Hz, –O–**CH**–), 40.5 and 35.2 (s, –CH_2–**CH**(C(CH_3)=CH_2)–CH_2–), 34.8 and 33.8 (s, –**CH_2**–CH(C(CH_3)=CH_2)–CH_2–), 31.0 and 30.9 (s, –CH_2–CH(C(CH_3)=CH_2)–**CH_2**–), 20.8 (s, –O–CH–C(**CH_3**)=CH–), 20.4 and 18.3 (s, –C(**CH_3**)=CH_2).

FD-MS *m*/*z*: 301.14, 302.15.

Calc. m/*z* 301.11, 302.11, 303.12.

*4.3.1.4 Synthesis of **28**.* PFP (1.084 g, 6.41 mmol, 1.0 eq.) was placed in a tomato paste can containing aluminum beads,

along with Cs_2CO_3 (2.346 g, 7.20 mmol, 1.1 eq.), and eugenol (1.158 g, 7.05 mmol, 1.1 eq.). Quantitative conversion was shown by ^{19}F NMR after 5 minutes of agitation. The product was extracted with 3 × 50 mL of chloroform, vacuum filtered through alumina and a cotton plug in a glass funnel and concentrated to a golden yellow oil (≥99% isolated yield).

^{19}F-NMR ($CDCl_3$, 376 MHz, CCl_3F) δ: −91.0 (m, 2,6 position C_5F_4N, 2F), −158.3 (m, 3,5 position C_5F_4N, 2F).

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.08 (d, ^3J = 8.12 Hz, 1H, –O–Ar (position 5)–), 6.80 (d, ^4J = 1.36 Hz, 1H, –O–Ar (position 3)–), 6.77 (dd, ^3J = 8.10 Hz, ^4J = 2.01 Hz, 1H, –O–Ar (position 6)–), 5.97 (m, 1H, –CH_2–**CH**=CH_2), 5.10 (m, 2H, –CH=**CH_2**), 3.79 (s, 3H, –O–CH_3), 3.40 (d, ^3J = 6.56 Hz, 2H, –Ar–CH_2–CH=).

^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 150.1 (s, –O–Ar(1 position)–O–CH_3), 146.2 (m, 4-position C_5F_4N), 144.0 (dm, ^1J = 242 Hz, 3,5-position C_5F_4N), 142.6 (s, –O–Ar (2 position)–O–CH_3), 139.1 (s, –CH_2–**CH**=CH_2), 136.9 (s, –O–Ar (4 position)–O–CH_3), 135.1 (dm, ^1J = 260 Hz, 2,6-position C_5F_4N), 120.9 (s, –O–Ar (6 position)–O–CH_3), 119.6 (s, –O–Ar (5 position)–O–CH_3), 116.5 (s, –CH=**CH_2**), 113.0 (s, –O–Ar (3 position)–O–CH_3), 56.0 (s, –O–**CH_3**), 40.0 (s, –Ar–**CH_2**–CH=CH_2).

GC-EI/MS *m*/*z*: 313.1 (100%), 314.1 (15.4%), 315.1 (1.6%).

Calc. *m*/*z*: 313.07 (100%), 314.08 (16.4%), 315.08 (1.7%).

4.3.2 General procedure for inverse vulcanization of natural product monomers with S_8. Polymers were prepared using 25% by weight of the desired monomer and 75% by weight sulfur powder. The solutions were heated while stirring to 160 °C under atmospheric conditions until solid. The bulk material underwent TGA and DSC analysis without further purification.

*4.3.2.1 Inverse vulcanization of **25** with S_8.* 0.528 g of **25** (25% wt.) and 1.543 g of sulfur powder (75% wt.) were combined and left to stir at 160 °C for 71 hours, upon which a solid was formed and the product was removed from heat and cooled to form a dark brown solid (1.683 g isolated yield).

*4.3.2.2 Inverse vulcanization of **26** with S_8.* 0.540 g of **26** (27% wt) were added to 1.425 g of sulfur powder (73% wt). The solution was left to stir at 160 °C until the solution solidified (71 hours) to form a dark brown solid (1.161 g isolated yield).

*4.3.2.3 Inverse vulcanization of **27** with S_8.* 0.532 g of **27** perfluoropyridine (26% wt), and 1.487 g of sulfur powder (74% wt) were combined, and allowed to stir until a solid was formed after 144 hours. The polymer formed was a dark brown solid (1.109 g isolated yield).

*4.3.2.4 Inverse vulcanization of **28** with S_8.* 0.512 g of **28** (26% wt) and 1.480 g of sulfur powder (74% wt) were left to stir at 160 °C for 1 week. A viscous red solution was formed that solidified to a red-brown solid upon cooling to room temperature (1.459 g isolated yield).

4.3.3 General procedure for inverse vulcanization of natural product monomers with S_2Cl_2. The prepolymer (1 eq.) was introduced into a clean dram vial with stirring and freshly distilled S_2Cl_2 (1 eq.) was added. The mixture was stirred under air or a N_2 atmosphere, left to cure at 20 °C or 70 °C overnight for 20–24 hours. The mixture was precipitated into methanol, aged until solid, and filtered to afford the product as a powder.

*4.3.3.1 Inverse vulcanization of **25** with S_2Cl_2 at room temperature.* Sulfur monochloride (0.394 g, 2.9 mmol, 1.4 eq.) was added to **25** (0.655 g, 2.2 mmol, 1 eq.) with stirring at room temperature for 24 hours. A dark, viscous oil was formed. This was dissolved in DCM and precipitated in methanol. The purified polymer was a solid and gave a final yield of 0.192 g, (20%).

*4.3.3.2 Inverse vulcanization of **25** with S_2Cl_2 in THF at 65 °C.* Sulfur monochloride (0.13 mL, 0.220 g, 1.63 mmol, 1.4 eq.) was added to **25** (0.542 g, 1.79 mmol, 1.1 eq.) in 1 mL THF with stirring at 65 °C for 24 hours to form a yellow solution. This was dissolved in DCM and precipitated in methanol. The purified polymer was a light brown solid and gave a final yield of 0.322 g, (42%).

*4.3.3.3 Inverse vulcanization of **25** with S_2Cl_2 at 70 °C under N_2.* Sulfur monochloride (0.08 mL, 0.135 g, 1.00 mmol, 1.06 eq.) was added to **25** (0.286 g, 0.94 mmol, 1 eq.) with stirring at room temperature under a nitrogen blanket for 10 minutes, followed by heating at 70 °C for 22 hours to afford a dark solid. This was dissolved in THF and precipitated in methanol to give a brown powder with a final yield of 0.017 g (4%).

*4.3.3.4 Inverse vulcanization of **27** with S_2Cl_2 in THF at 65 °C.* Sulfur monochloride (0.13 mL, 0.220 g, 1.63 mmol, 1.01 eq.), was added to **27** (0.486 g, 1.61 mmol, 1 eq.) in 1 mL of THF and heated at 65 °C for 22 hours to form an orange solution. The solution precipitated in excess methanol. The isolated polymer was a light brown solid, with a yield of 0.087 g (12%).

*4.3.3.5 Inverse vulcanization of **27** with S_2Cl_2 at 70 °C under N_2.* Sulfur monochloride (0.07 mL, 0.118 g, 0.876 mmol, 1 eq.), was added to **27** (0.275 g, 0.913 mmol, 1.04 eq.) and allowed to stir for ten minutes before heating to 70 °C for 22 hours, and a red solid was formed. This was dissolved in THF and precipitated in methanol. The isolated polymer was a light brown solid, with a yield of 0.146 g (37%).

Abbreviations

ATR	attenuated total reflectance
DABCO	1,4-diazabicyclo[2.2.2]octane
DSC	differential scanning calorimetry
EI	Electron impact
ESI	Electrospray ionization
FD	Field desorption
FTIR	Fourier transform infrared spectroscopy
GPC	gel permeation chromatography
MOF	Metal-organic framework
MS	mass spectrometry
MW	molecular weight
NMR	nuclear magnetic resonance
PDI	polydispersity index
PFP	pentafluoropyridine
PMMA	poly(methyl methacrylate)
PTFE	poly(tetrafluoroethylene)
SEC	size-exclusion chromatography
TCM	tin can milling
TGA	thermal gravimetric analysis

THF	tetrahydrofuran
TSE	twin screw extrusion
UV	ultraviolet

Author contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript. The conceptual ideas for the manuscript came from Jason Pulfer and Chadron Friesen. The experimental work was performed by Jason Pulfer and Miriam Aldom. GPC, TGA, and DSC analysis was provided by Maxime Colpaert.

Conflicts of interest

The authors declare no competing financial interest.

Data availability

The data supporting this article have been included as part of the SI.

Supplementary information is available: details on the synthesis and structural characterization of monomers by ^{19}F NMR, ^{1}H NMR, ^{13}C NMR, GC-MS, and FD-MS. See DOI: **https://doi.org/10.1039/d5ra03019f**.

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