



Perfluoro-3-ethyl-2,4-dimethyl-3-pentyl persistent radical: A new reagent for direct, metal-free radical trifluoromethylation and polymer initiation

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ABSTRACT

This review comprehensively profiles perfluoro-3-ethyl-2,4-dimethyl-3-pentyl persistent radical (PPFR) as a new reagent for radical trifluoromethylation, trifluoromethylation/fluorination and polymer initiation. The PPFR is perfectly stable at ambient conditions, but at temperatures above 80 °C undergoes β -scission to generate trifluoromethyl radical. This property can be used to initiate various chain-polymerization or trifluoromethylation reactions. The unique feature of this process, distinguishing it from all other known methods for $\cdot\text{CF}_3$ -radical generation, is that the radical is produced under neutral, inert and additive-free conditions. Hopefully, the mild reaction conditions and commercial availability of PPFR will generate research interest for practical applications of this novel perfluorination reagent for fluorination and polymerization processes.

1. Introduction

Due to the ever-growing impact of fluorine-containing compounds on the progress of chemical, agrochemical and health related industries, the development of new fluorination reagents is an area of most important innovative scientific advances. Currently, fluoro-chemistry is one of the major areas of multidisciplinary research, advancing energy [1], food [2] and health [3] related industries. The properties of fluorine (highest electronegativity; smallest atomic size, after hydrogen; omniphobicity; and stability of C–F bonds) lend unique characteristics for the continuous application of fluorinated compounds in various technical innovations [4,5]. The pace and extension of new practical progress goes alongside developments in synthesis methodology, providing structural and functional variety of fluorine-containing entities to be tested, selected and improved. For example, the recent upsurge of interest in synthesis of fluorine-containing tailor-made amino acids [6–8] stems from the ever-increasing application of this class of compounds in the design of modern pharmaceuticals [3,9], magnetic resonance imaging (MRI) [10], positron emission tomography (PET) using ^{18}F nuclei [11], and peptide/protein engineering [12]. Application of fluorine-containing tailor-made amino acids in probing three-dimensional topographies of peptide/receptor interactions is a particularly exciting area of modern research laying foundation for new

frontiers in medicine.

Among various methodological directions for the synthesis of fluorine-containing compounds [13], the development of new fluorinating reagents is an important area of innovative scientific progresses. For example, Umemoto [14] and Ruppert-Prakash [15] trifluoromethylation reagents have had a momentous impact on the general organic synthesis, accelerating the technological advances enabled by fluorine. Taking advantage of this Special Issue, we would like to emphasize the remarkable contributions of Professor Shibata group to the field of fluorinating reagents [16]. As shown in Fig. 1, over the last decade, a variety of electrophilic fluorination reagents have been successfully developed. These include the following types: fluorination - NFSI 1 [17], axially chiral NFSIs 2 [18], Me-NFSI 3 [19]; trifluoromethylation, 4 (Shibata reagent I) [20], 5 [21], 6 [22] and 7 [23]; monofluoromethylation 8 [24]; difluoromethylation 9 [25], 10 [26] and 11 [27]; trifluoromethylthiolation 12 [28] and 13 (Shibata reagent II) [29] as well as difluoromethylthiolation 14 [30]. Furthermore, nucleophilic mono-fluoromethylation reactions can be performed using reagents FBSM 15 [31] and FBDT 16 [32].

Note that all reagents 1–16 are shelf-stable, can be prepared on a large-scale and some are commercially available.

The major goal of this review article is to familiarize the readers with perfluoro-3-ethyl-2,4-dimethyl-3-pentyl persistent radical (Fig. 2,

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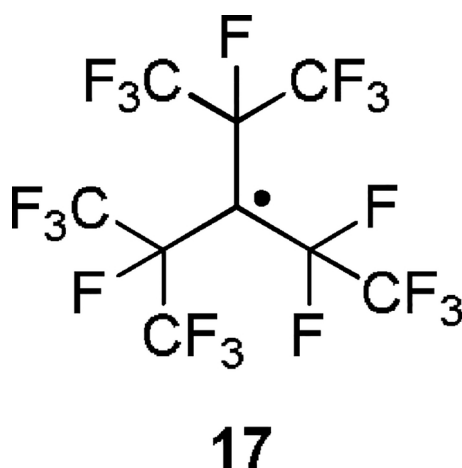
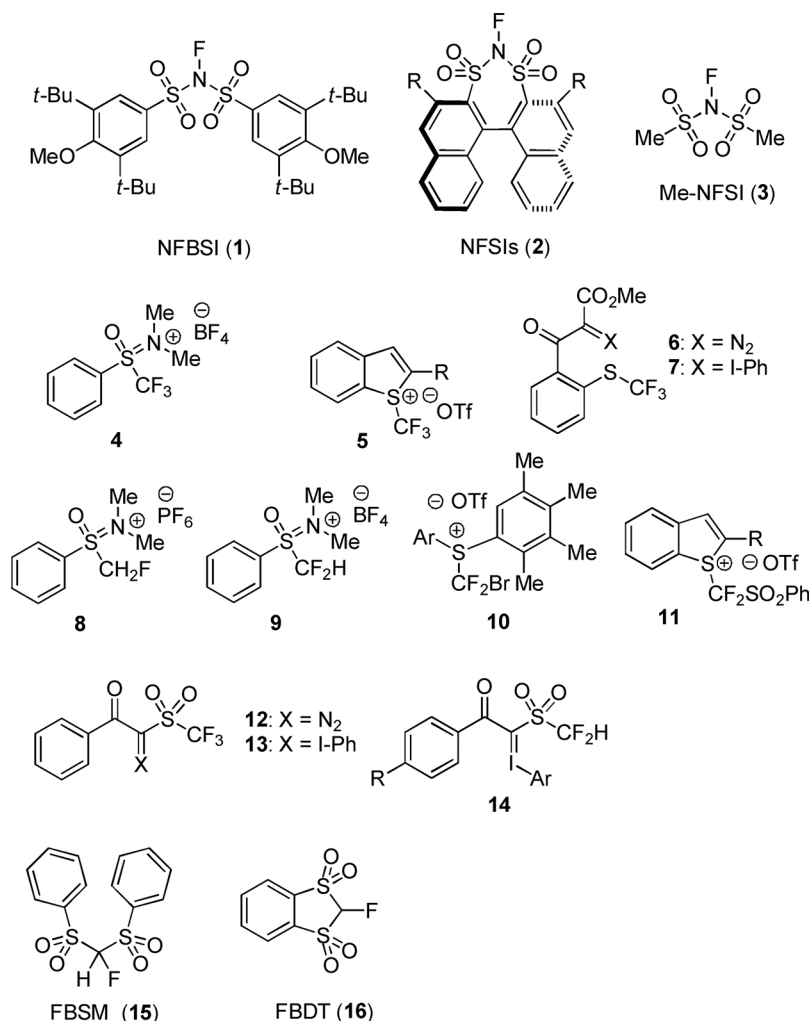


Fig. 2. Structure of perfluoro-3-ethyl-2,4-dimethyl-3-pentyl persistent radical 17.

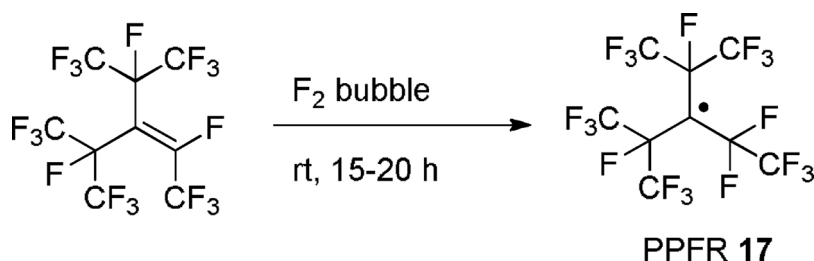
17) as a new reagent for radical trifluoromethylation, polymer initiation and trifluoromethylation-fluorination. We provide a concise summary of its discovery, chemical properties and known synthetic applications.

2. Discovery and physical properties

Persistent perfluoroalkyl radical (PPFR) 17 was discovered by a research group at the University of Southern California in 1985 [33]. It was synthesized by fluorination with perfluoropropylene trimer (Scheme 1). This procedure can be quite easily reproduced on a multi-kilogram scale in good yields (up to ca. 90%) rendering PPFR 17 available on large scale. Considering the established industrial production of both starting hexafluoropropene and fluorine gas, the cost of commercial preparation of PPFR 17 is expected to be relatively low.

Note that PPFR 17 is extraordinary chemically inert as demonstrated by the experiments with F_2 , O_2 , Cl_2 and Br_2 [33]. PPFR 17 is stable at ambient temperature in the open air and does not dimerize. It is also totally inert to aqueous acid or base. This quite unique chemical inertness allows PPFR 17 to be distilled, chromatographed, and detected by gas chromatography or any other analytical technique used for neutral organic compounds. On the other hand, at temperatures over 80 °C, PPFR 17 undergoes β -scission releasing rather chemically inert olefin 18 and, $\cdot CF_3$ radical 19 (Scheme 2).

Until very recently this property of PPFR 17 was virtually overlooked, mainly for the following reasons. First, PPFR 17 is very little known to general scientific community, only to the experts in fluorine chemistry working with perfluorinated compounds. Second, while the cost of preparation of PPFR 17 is relatively inexpensive, it can be



Scheme 1. Preparation of persistent perfluoroalkyl radical PPFR.

synthesized only in labs possessing experience of, and the necessary equipment for, working with fluorine gas. Accordingly, very limited recognition and availability prevented the study of unique properties of PPFR 17 and its application in organic chemistry.

The recent upsurge in research activity in fluorine chemistry, and in particular, the search for new fluorinating reagents led to the rediscovery of PPFR 17 as a potentially valuable reagent for radical polymerizations, trifluoromethylation and trifluoromethylation-fluorination. Here we provide a brief description of the reported chemical properties of PPFR 17, showing its clear potential as a new synthetically useful reagent.

2.1. Synthesis

Although the method for the preparation of PPFR 17 via fluorination with F_2 gas could afford the high yield, the handling of F_2 gas was not convenient. In 1996, Ono and co-authors explored an electrochemical fluorination method for the preparation of PPFR 17 with perfluoro-3-isopropyl-4-methylpent-2-ene **20** and perfluoro-3-ethyl-2,4-dimethylpent-2-ene **21** as the starting materials (Scheme 3) [34].

This conventional electrochemical fluorination reaction was carried out in a Monel nickel electrical cell with Ni as electrodes in the presence of HF at the voltage of 5.1–7.5 V without the addition of sodium fluoride. The reaction provided only 2.0% yield of PPFR 17. It should be mentioned that the reaction also generated three by-products (**22–24**) in 17, 41 and 9% yield respectively. Then, they added sodium fluoride into the reaction mixture to increase the conductivity and yield of target product PPFR 17.

The possible mechanism for this electrochemical fluorination reaction was provided in this report (Scheme 4). Initially, the alkenes (**20**, **21**) react with fluoride anion to give the intermediate **25**, which is oxidized at anode to form the corresponding product PPFR 17. At the same time, the formation of the by-products is also proposed. PPFR 17 undergoes reduction hydrogenation to provide the by-product **24**. On the other hand, second anodic oxidation of PPFR 17 generates intermediate **26**. The intermediate **26** reacts with fluoride anion to give by-product **22**. Release of trifluoromethyl cation from intermediate **26** gives olefinic intermediate **18**, which undergoes the sequence of fluorination, anodic oxidation, second anodic oxidation and second fluorination to form the by-product **23**.

2.2. Trifluoromethylation with Ruppert-Prakash reagent

The perfluoroolefins, perfluoro-3-isopropyl-4-methylpent-2-ene **20** and perfluoro-3-ethyl-2,4-dimethylpent-2-ene **21** react with Ruppert-

Prakash (CF_3SiMe_3) reagent to give the highly congested perfluoro compounds. In 2017, Ono developed a KHF_2 -catalyzed trifluoromethylation reaction of olefin **20** with CF_3SiMe_3 as trifluoromethyl source. It should be mentioned that the olefin substrate was about 90%, and contained about 10% **21** [35].

They found that almost no desired product was detected when no KHF_2 was used as additive, and almost all the starting materials remained. A satisfactory result was obtained when 10 mol% of KHF_2 was added, and 68.9% yield of **27** and 31.1% yield of **29** were detected (Scheme 5).

Ono and coworkers also used the high purity olefin **21** (99.7%) as the starting material for this trifluoromethylation reaction with Ruppert-Prakash reagent. In the case of 10 mol% of KHF_2 as additive, almost all the starting material was converted in the product, with 0.4%, 31.9% and 65.7% yield for **27**, **28** and **29** respectively (Scheme 6).

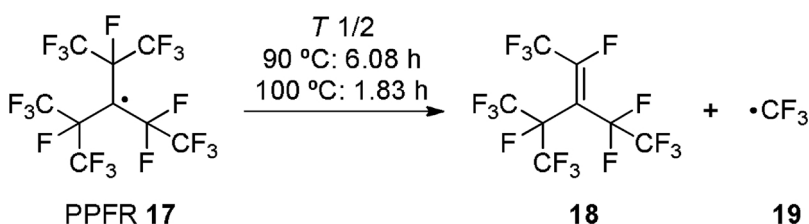
Nishida and co-authors described in 2016 that the two hexafluoropropene trimers (**20** and **21**) reacted with $C_6F_5Si(CH_3)_3$ at room temperature to afford the perfluorinated super-congested compounds [36]. Initially, they used olefin **20** as the starting material for this pentafluorophenyl substitution reaction, which was conducted in DMF as solvent with the addition of KHF_2 for 1 h. The mixture of linear perfluoro (polyphenyl)-substituted products was obtained in moderate yield (Scheme 7). They found the loading amount of $C_6F_5Si(CH_3)_3$ plays an important role in the chemoselectivity of the reaction. When 1.0 and 2.2 equiv of $C_6F_5Si(CH_3)_3$ were used, the resulted mixture mainly contained mono- and bis-perfluorophenyl-substituted compounds, while only 6% of the mono-perfluorophenyl-substituted product **30** was obtained when the amount was increased to 3.1 equiv. At the same time, perfluoro(polyphenyl)-substituted products (**31**, **32** and **33**) were observed in total 76% yields.

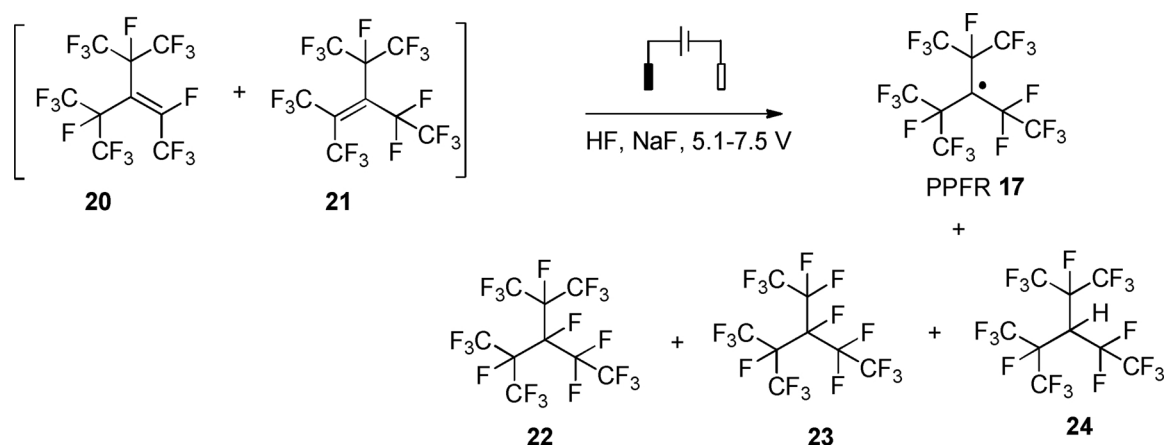
Similar reactions with olefin **21** as the substrate were performed, and interestingly, similar results were obtained on the studies of the addition of $C_6F_5Si(CH_3)_3$ as compared to olefin **20**. It should be mentioned that excellent stereoselectivity was found when 1.4 equiv of $C_6F_5Si(CH_3)_3$ was added. Only the *Z*-isomers were obtained with the total yields of 16% (Scheme 8).

2.3. Properties

In 2009, Ono and co-authors synthesized three PPFR-related super stable fluorocarbon radicals via F_2 fluorination reactions of the corresponding olefins in perfluorohexane (Fig. 3) [37]. After obtaining these radicals, they carried out the fluorine electron nuclear double resonance (ENDOR) of them in solution at room temperature to

Scheme 2. Generation of $\cdot CF_3$ radical.





Scheme 3. Electrochemical fluorination for the synthesis of 17.

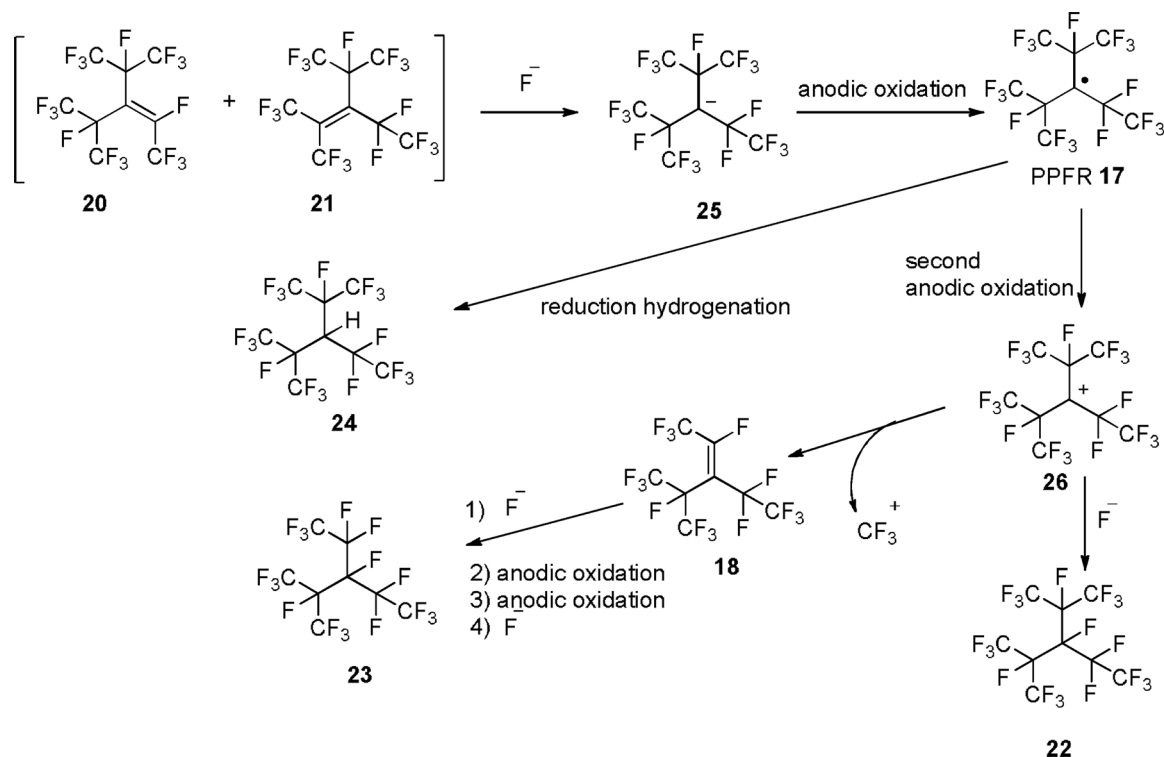
investigate their hyperfine coupling constants. For example, in the ENDOR spectrum of radical **35**, there are two peaks at 17.19 and 17.48 MHz with the intensity ratio of 1:6, which correspond to the F nucleus of β -fluorine and trifluoromethyl groups, respectively. Furthermore, the ^{13}C coupling of 4.3 mT indicates the non-planar structure of radical **35**, which is also confirmed by the *ab initio* calculation.

The same investigations of radicals **17** and **36** were also performed. In the case of radical **17**, the hyperfine coupling is 4.45 mT determined by the ESP spectrum, and its ENDOR spectrum was out of detection. Interestingly, the best ENDOR spectrum was obtained for the radical **36**, which can be found at a higher temperature with a good signal/noise ratio.

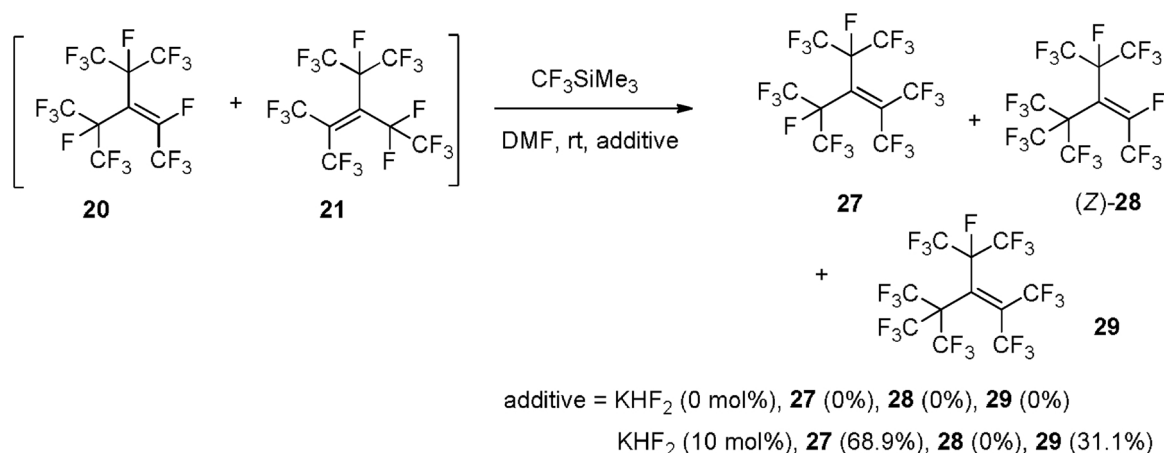
In 1999, Ono and co-authors reported their investigations on the reactivity of the persistent perfluoroalkyl radical, PPFR **17**, by subjecting this compound to the reactions with electron-donating reagents under reductive conditions (Table 1) [38].

It was found that no reaction happened at all under the hydrogen

atmosphere at room temperature without addition of catalyst (entry 1), even when the reaction time was prolonged to seven days. After addition of 5% Pd/C or Pd/BaSO₄ as catalyst, 100% yield of the product **20** was obtained after 30 min (entries 2 and 4) under hydrogen atmosphere. Surprisingly, 25.4% yield of the product **20** was obtained under argon (entry 3). KI/acetone system also could afford the corresponding products **20** and **21** with the ratio of 97:3 (100% yield, entry 5). Lewis bases, including triethylamine, triphenylphosphine and triphenylamine all reacted well with PPFR **17** to give the 100% yields of **20**. The reaction was complete within one minute with triethylamine (entries 7–9). Some other O-containing Lewis bases, such as ether and THF also reacted with PPFR **17** to give the product **20** with obviously lower yields, and also the hydrogenation product **24** was found (entries 10 and 11). As expected, DMF, a non-electron-donating reagent, resulted in no desired product at all with all the starting material remaining (entry 12).



Scheme 4. Proposed mechanism.



Scheme 5. Trifluoromethylation of **20** with CF_3SiMe_3 reagent.

2.4. Charge-transfer complexes

After thorough studies on the preparation and reactivity of this persistent perfluoroalkyl radical, PPFR **17**, Ono and co-authors turned their attentions to the investigations of the charge transfer interaction [39] between this radical and some electron-donating chemicals, including benzene and some of its methyl substituted derivatives, 1-decene and ether [40].

They dissolved the PPFR **17** in benzene, and found no chemical reactions happened at all between them via GC detection. However, the interaction between PPFR **17** with benzene was clearly observed from the UV-vis absorption spectra scanned from 780 to 280 nm with the maximum absorption at 380 nm. As the solvents were changed from benzene to toluene, m-xylene and mesitylene, the solution became a deeper color as the interaction between the radical and the aromatic ring became stronger because of the increase of the π -electron density with substitution of the benzene ring. These results also were quantified and confirmed by the UV-vis absorption spectra. In addition, the red shift in these UV-vis spectra occurred along with the introduction of methyl substitutions to the aromatic ring.

The charge transfer interactions of this radical with 1-decene and ether were also observed, supported by the UV-vis absorption spectra [40].

3. As a reagent for initiation of radical polymerization

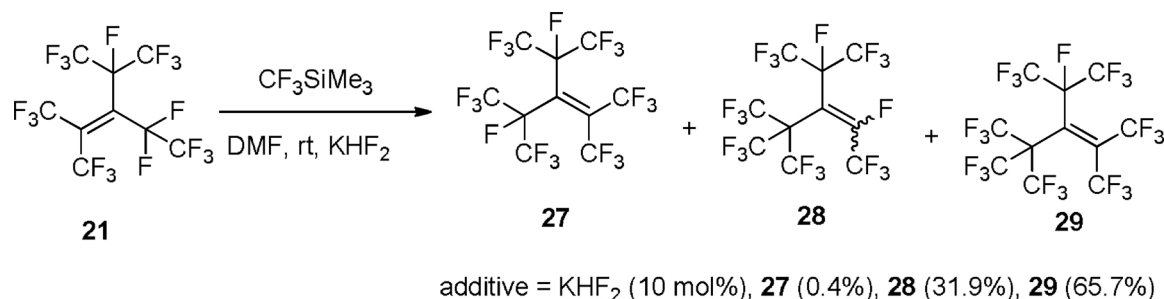
3.1. Importance of fluoropolymers

Fluoropolymers are some of the most prevalent polymeric materials in use in society and in technological development today [41]. These fluorinated macromolecules exhibit unique chemical and physical properties due to the presence of fluorine atoms along the polymer backbone. The highly electronegative fluorine combines with carbon to make the strongest single bond in organic chemistry, which is very

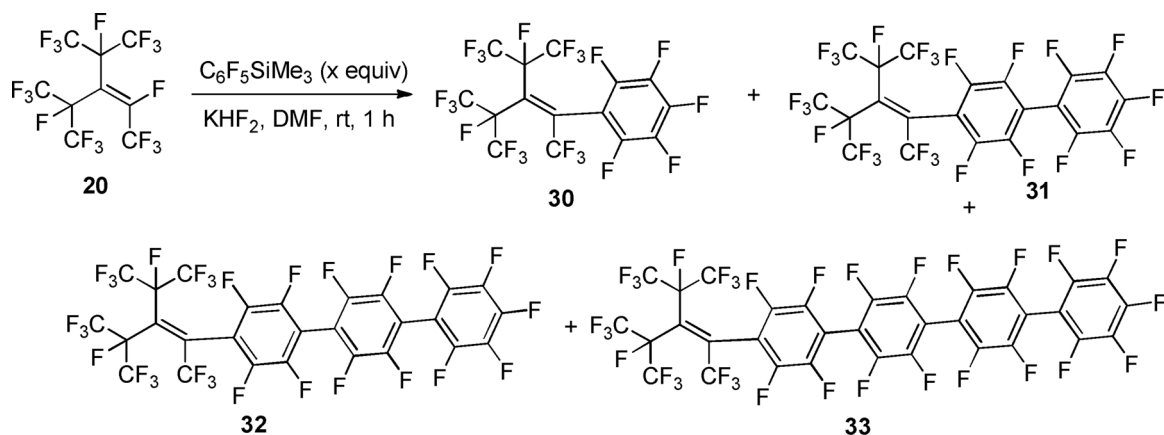
unreactive [42]. This strong C-F bond, along with the added strength of carbon-carbon bonds in the polymer due to nearby influence of fluorine, gives these fluoropolymers high stability and resistance to chemical, temperature, environmental, and thermal extremes. In addition to chemical inertness, fluoropolymers also show other distinct advantages because of the presence of C-F bonds, including strong hydrophobicity, low surface tension, low dielectric constants, and low flammability [42]. The family of fluoropolymers contains innumerable macromolecules from highly crystalline to amorphous in structure for applications in chemically inert reaction equipment, fittings and tubing for harsh conditions, insulation in electrical wiring components, fiber optic cores for communications, protective coatings and surface finishes for transportation, building and clothing, binders and membranes for Lithium-ion batteries and fuel cells, and biomedical apparatus, implants, and sutures [43–47].

3.2. General fluoropolymer synthesis

In the industrial production of fluoropolymers, the choice of monomers and co-monomers, along with synthetic methods, imparts unique melting point, chemical, thermal and electrical properties [42]. Homofluoropolymers, although very useful, have several disadvantages for more general applications. For example in polytetrafluoroethylene (PTFE), the presence of the C-F bond causes the polymer chain to form a helical structure, and leads to crystallization. The highly crystalline PTFE, as with other homofluoropolymers, cannot be dissolved in common organic reagents, and cannot be melt-processed [42]. These disadvantages also affect the characterization of fluoropolymers [48]. The incorporation of co-monomers that contain different fluorinated or non-halogenated moieties changes the properties of the polymer to combine the thermostability, chemical inertness and hydrophobicity of the fluoropolymer with the mechanical properties and functionality of the co-monomer [42,48]. The limitless combinations of monomers and synthetic methods allow for unique fluoropolymer development.



Scheme 6. Trifluoromethylation of **21** with CF_3SiMe_3 .



x = 1.0, **30** (29% yield), **31** (11% yield), **32** (4% yield), **33** (1% yield)
 2.2, **30** (28% yield), **31** (28% yield), **32** (15% yield), **33** (2% yield)
 3.1, **30** (6% yield), **31** (37% yield), **32** (29% yield), **33** (10% yield)

Scheme 7. Pentafluorophenylation reaction of **20** with $\text{C}_6\text{F}_5\text{Si}(\text{CH}_3)_3$.

Most fluoropolymers are synthesized via free radical polymerization of fluoroalkenes from different types of initiators that generate radicals to start the polymerization process. There are three major classes of free radical initiators, named for the chemical conditions under which they release radicals: redox initiators, photoinitiators, and thermal initiators. Overall, the optimal polymerization initiator should be stable at room temperature, but release radicals under specified polymer synthesis conditions [49]. In addition, the radicals are incorporated into the growing polymer, often as the end-groups that may play a role on its properties. Control of these end-groups to give perfluoroalkyl functionality leads to characterization via ^{19}F and ^1H NMR [50].

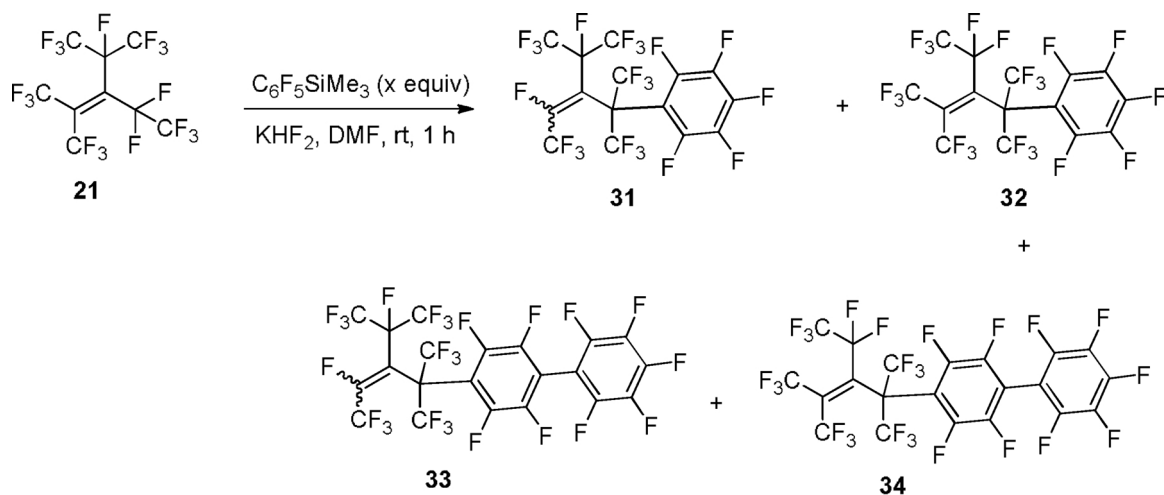
3.3. Persistent perfluoroalkyl radical PPFR: effective thermal initiator for fluoropolymer synthesis

The PPFR **17** has the qualities listed above for an ideal free radical initiator for fluoropolymer synthesis. The PPFR **17** is stable at room temperature and has the potential for use as a thermal initiator for polymerization over 80°C , at which PPFR **17** degrades to release the

$\cdot\text{CF}_3$ radical **19** (Scheme 9). When studying and comparing the synthesis conditions for major fluoropolymers [51], the PPFR **17** offers an interesting choice for polymerization of fluoroalkenes with its stability, safety, commercial availability, and simplicity of handling. The $\cdot\text{CF}_3$ radical incorporates into the polymer to give trifluoromethyl end-groups to add unique properties to the fluoropolymer as well as to aid in the characterization of the polymer [50]. While other fluorinated precursors have been used to generate a trifluoromethyl radical under a variety of conditions, PPFR **17** offers polymer chemists another method that may have benefits when scaled for industrial applications (see references within [50]).

Ameduri and co-authors have shown that this persistent radical is successful in initiating the synthesis of homofluoropolymers and copolymers that cover a wide range of possible applications. In proof of concept, Boshet et al. have been able to synthesize CF_3 -PVDF- CF_3 **37** from the radical polymerization of vinylidene fluoride (VDF) initiated from a $\cdot\text{CF}_3$ radical released from the PPFR **17** at 90°C [50] (Scheme 9).

The CF_3 -PVDF- CF_3 **37** was studied by ^{19}F NMR and ^1H NMR spectroscopy to determine the degree of polymerization and molecular



x = 0.52, **31** (11%), **32** (1%), **33** (8%)
 1.4, (Z)-**31** (5%), (Z)-**33** (11%)

Scheme 8. Reaction of **21** with $\text{C}_6\text{F}_5\text{Si}(\text{CH}_3)_3$.

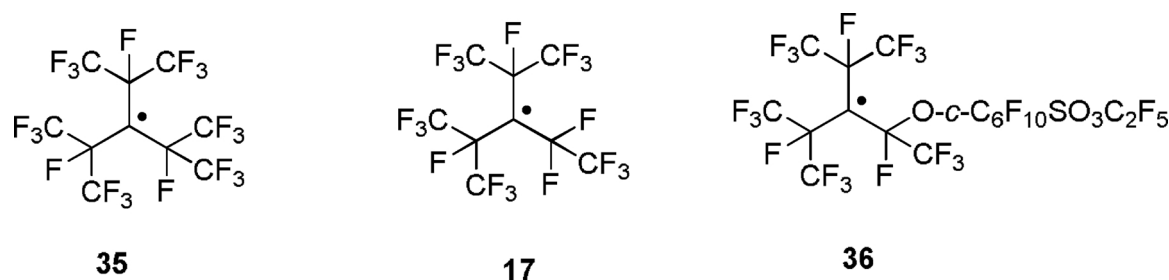


Fig. 3. Structure of perfluoro-alkyl radicals.

weight, as well as the mechanism of the radical polymerization (Table 2). The concentration of the PPFR 17 initiator was increased from five to ten and twenty percent. The number average molecular weights (M_n) of the resultant polymers ranged from 7400 g mol^{-1} to 4200 g mol^{-1} (via ^{19}F NMR) compared to 6100 g mol^{-1} to 2800 g mol^{-1} using size exclusion chromatography (SEC). The structure of the PVDF with $-\text{CF}_3$ as the end-groups was obtained by macromolecular recombination, as proven in the ^{19}F NMR spectra by the absence and presence of certain signals. The $\cdot\text{CF}_3$ radical attacked selectively at the methylene site of the VDF. Thermal properties showed that higher molecular weights were obtained with lower concentrations of PPFR initiator, while the melting (Median T_m of 157°C) and glass transition temperatures for the alpha-form (Median T_g of -14°C) were not as affected. In contrast, the thermostability increased with an increase of initial molar ratios of $[\text{PPFR}]_0/[\text{VDF}]_0$. The use of the PPFR 17 did result in higher crystallinities of the CF_3 -PVDF- CF_3 38 produced as compared to the control PVDF 37, indicating a lower number of polymer backbone defects (tail-to-tail, head-to-head) (Table 2) [50].

Recently, Ameduri and coworkers synthesized another homo-fluoropolymer, poly(trifluoroethylene) via the persistent radical mediated polymerization of trifluoroethylene (TrFE) to illustrate why the PPFR generated $\cdot\text{CF}_3$ radical improves selectivity in polymerization. (Scheme 10) While these types of fluoropolymers have important applications due to their electroactive properties, the conventional radical polymerization of trifluoroethylene presents problems due to presence of regioirregular (aregic) polymers in the mix, with 50% or more defects due to head to head: tail to tail addition of monomeric units. The use of PPFR to initiate polymerization of trifluoroethylene significantly reduces the amount of chain defects (seen in dispersity values), to around 14%, as determined by ^{19}F NMR. The $\cdot\text{CF}_3$ radicals are involved

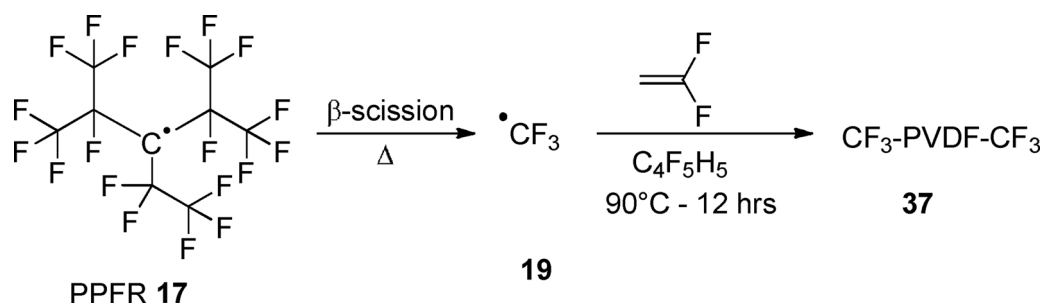
in a partially selective addition (66%) to the less hindered fluoromethylene site of TrFE as shown in the ^{19}F NMR spectrum of CF_3 -PTrFE- CF_3 39 using 2.5 mol % PPFR 17. The polymers had good thermal stability, with decomposition temperatures ranging from 362°C to 428°C , suggesting that the $-\text{CF}_3$ end-groups may offer chemical stability by preventing any unzipping depolymerization seen in many fluoropolymers (Table 2) [52].

Importantly, the α,ω -trifluoromethyl group added onto the end of the polymers acts as an effective label to assess the molecular weights of the resulting copolymers using ^{19}F NMR spectroscopy and the integration values for $-\text{CF}_2$ and $-\text{CF}_3$ signals for the monomers and end-groups. In most polymer molecular weight determinations, chemists use size exclusion chromatography (SEC) with polymethylmethacrylate (PMMA) or polystyrene equivalents. This method does not allow reporting “true” MW values for fluoropolymers, for lack of standards, fluoropolymer solubility and properties. Ameduri and coworkers use the sensitivity of ^{19}F NMR spectroscopy and the wide chemical shift distributions of the polymeric and end-group fluorines to calculate the degree of polymerization and molecular weights of the polymers they synthesize. These new VDF-copolymers allow for the potential creation of new SEC standards for fluoropolymers that can be calibrated by ^{19}F NMR [48,55].

Ameduri, Ono and their group continue to use PPFR 17 to synthesize and study many different fluoropolymer combinations with commercially important co-monomers. This strategy was applied with PPFR 17 to initiate copolymerization reactions with VDF and a common comonomer *tert*-butyl α -trifluoromethacrylate (MAF-TBE) (Scheme 11) [48], used in lithographic materials [56], membranes for fuel cells [57], and Li-ion batteries [58]. NMR studies showed that the synthesis of the resulting poly(VDF-co-MAF-TBE) 40 copolymers was exclusively

Table 1
Investigations on the reactivity of PPFR 17.

entry	conditions	Yield (%)			
		20	21	24	17
1	H_2 , rt, 7 d	–	–	–	100
2	H_2 , 5% Pd/C, rt, 30 min	100	–	–	–
3	Ar, 5% Pd/C, rt, 4.5 h	25.4	–	–	74.6
4	H_2 , 5% Pd/BaSO ₄ , rt, 30 min	100	–	–	–
5	Aq. KI/acetone, 10 min, rt	97.6	2.4	–	–
6	Aq. KBr/acetone, 20 h, rt	–	–	–	100
7	Et_3N , < 1 min, rt	100	–	–	–
8	Ph_3N , 10 min, rt	100	–	–	–
9	Ph_3P , 30 min, rt	100	–	–	–
10	Et_2O , 41 h, rt	37.1	–	28.9	34.0
11	THF, 45 h, rt	46.2	–	45.7	8.1
12	DMF, 48 h, rt	–	–	–	100



Scheme 9. Radical polymerization of vinylidene fluoride (VDF) initiated from a $\cdot\text{CF}_3$ radical released from 17 [50].

initiated by the $\cdot\text{CF}_3$ radical from PPFR decomposition.

During polymerization, the addition of the $\cdot\text{CF}_3$ radical was regioselective with the VDF monomer, leading to the $\text{CF}_3-\text{CH}_2-\text{CF}_2$ radical that further cross-propagated onto the MAF-TBE co-monomer, as seen in the detailed ^{19}F and ^1H NMR spectra. As the initial molar ratios of PPFR and VDF + MAF-TBE decreased ($[\text{PPFR}]_0/([\text{VDF}]_0 + [\text{MAF-TBE}]_0)$), the molecular weights and the thermostability of these original poly(VDF-co-MAF-TBE) 40 copolymers increased, as seen before with the CF_3 -PVDF- CF_3 38 polymers (Table 2) [50]. However, the overall decreased thermal stability of these MAF-TBE copolymers thwarts wide usage due to the isobutylene elimination above 150 °C. To address that issue, Ameduri and coworkers synthesized a 2-trifluoromethacrylate monomer containing a $-\text{C}_6\text{F}_{13}$ side chain, 3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl 2-(trifluoromethyl)acrylate (MAF- C_6F_{13}), and copolymerized it with VDF using a variety of initiators, temperatures and solvents to create poly(VDF-co-MAF- C_6F_{13}) 41 (Scheme 11). Molecular weights and polymerization yields were affected by changes in each of those variables. The optimal conditions were obtained using PPFR as an initiator at 90 °C with $\text{C}_4\text{H}_5\text{F}_3$ /acetonitrile/deionized water as the solvent solution, and the thermostability of the obtained copolymers under

air was significantly improved to that of VDF copolymers containing MAF-TBE (Table 3) [59].

In further studies of copolymerization of VDF with seven different comonomers such as $\text{H}_2\text{C}=\text{CR}^1\text{CF}_3$ (where R^1 stands for H, F, CO_2R ($\text{R} = \text{H}$ or *t*-Butyl) or $\text{F}_2\text{C}=\text{CFR}^2$ (R^2 : H, CF_3 or OCF_3), Patil, Alaaeddine, Ono and Ameduri cement the usefulness of PPFR 17 in initiating the synthesis of a wide range of polymers that could be applied to thermoplastics and fluoroelastomers development (Scheme 12) [55]. In addition, Friesen and Ameduri developed a PPFR initiated radical copolymerization of VDF with oligo(hexafluoropropylene oxide) perfluorovinyl ether macromonomer to obtain a PVDF-g-oligo(HFPO) graft copolymer, expanding the range of types of fluoropolymer architectures synthesized using this initiator [60].

Finally, Ameduri and coworkers have explored using the PPFR 17 as an initiator in iodine transfer polymerization (ITP) for reversible-deactivation radical polymerization (RDRP) of VDF to obtain controlled PVDF polymers with distinct end-groups (Scheme 13). ω -Iodo and telchelic diiodo vinylidene fluoride-containing copolymers were produced using two different iodine chain transfer agents (CTAs) alongside the trifluoromethyl radical from PPFR 17 over a range of solvents and

Table 2

Characteristics of the CF_3 -PVDF- CF_3 38 polymers and CF_3 -PTrFE- CF_3 39 polymers synthesized using PPFR as an initiator.

Polymer ^a	%PPFR [%]	Yield [%]	M_n^b , NMR	M_n^c , SEC	\bar{D}^c	$T_d^{10\%}$ [°C]	T_g^e [°C]	T_m^e [°C] α/β^f	χ^f [%]	% Defect ^g (both H-H and T-T)
37a PVDF	0	17	–	18 400	1.45	454	–30	159/165 [†]	34	13.0
38-1 CF3-PVDF-CF3	5	72	7400	6100	2.00	422	–14	158/166 [†]	49	10.4
38-2 CF3-PVDF-CF3	10	58	5300	3700	2.37	402	–14	156/164 [†]	52	10.1
38-3 CF3-PVDF-CF3	20	41	4200	2800	1.87	381	–12	154/162 [†]	58	9.8
39-1 CF3-PTrFE-CF3	5	86	24 400	11 400	3.28	428	*	192	36	14.0
39-2 CF3-PTrFE-CF3	15	76	13 800	9400	2.76	362	*	185	36	14.3
39-3 CF3-PTrFE-CF3	20	87	15 500	7700	2.84	362	*	187	37	14.8

^a initiated by tert-butyl peroxyppivalate.

Acronyms: PVDF: polyvinylidene fluoride; PTrFE: polytrifluoroethylene; PPFR: perfluoro-3-ethyl-2,4-dimethyl-3-pentyl persistent radical; PFB: 1,1,1,3,3-pentafluorobutane.

* Lee et al. [53] published the differential scanning calorimetry (DSC) thermograms of PTrFE and showed they do not have any inflection point assigned to the glass transition temperature, see [52] for details.

[†]For PVDF, there are two melting temperatures in the DSC thermograms corresponding to the α - and β - forms as previously observed [54].

^a Polymerization condition of 37: 1.04 g VDF + 2,5-bis(tert-butylperoxy)-2,5-dimethyl hexane (5 mol %) as control. This 37 polymer serves as a control to compare with use of the PPFR as an initiator. Polymerization conditions of 38-1, 38-2 and 38-3 - 1.04 g of VDF + PPFR for 12 h at 90 °C in PFB. Polymerization conditions of 39-1, 39-2 and 39-3 - 5.50 g (67.1 mmol) of TrFE + PPFR for 18 h at 83 °C in PFB. See references [50] and [52], respectively for other details.

^b Molar masses (M_n 's) were determined by ^{19}F NMR with equations in [50,52].

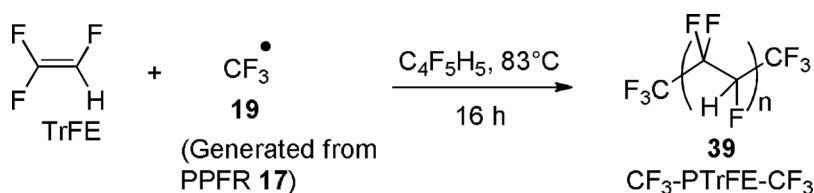
^c Number average molar masses (M_n 's) and dispersities (\bar{D} 's) were estimated by SEC with either poly(methyl methacrylate) standards in DMF/LiCl for 38-1, 38-2 and 38-3 or polystyrene standards in THF for 39-1, 39-2 and 39-3.

^d Measured by thermogravimetric analysis (TGA) under air, T_d being the temperature at which 10% of the polymer is degraded.

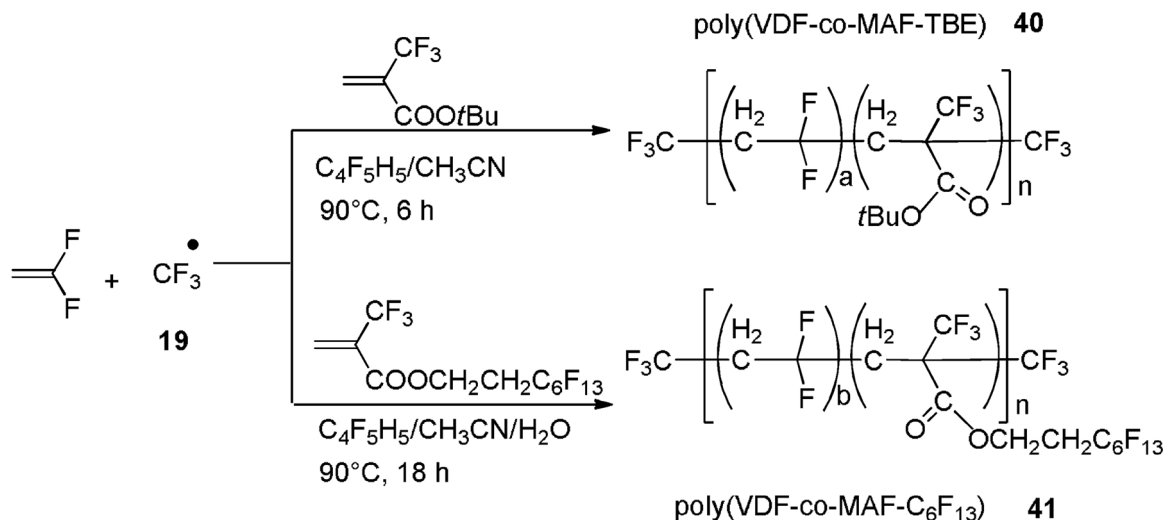
^e T_g and T_m stand for glass transition temperature and melting temperature, respectively, determined by differential scanning calorimetry corresponding to the value at the peak(s).

^f Degree of crystallinity determined by equations in [50,52] using melting enthalpies.

^g Chain defects calculated using equations with data acquired through ^{19}F NMR and ^1H NMR, see references [50,52] for experimental details.



Scheme 10. Radical polymerization of Trifluoroethylene (TrFE) initiated from a $\cdot\text{CF}_3$ radical 19 released from 17 using 1,1,1,3,3-pentafluorobutane as the reaction solvent [52].



Scheme 11. Radical copolymerizations of VDF with MAF-TBE and VDF with MAF- C_6F_{13} with PPFR as a free radical initiator [48,59].

Table 3

Comparison of poly(VDF-co-MAF-TBE) 40 and poly(VDF-co-MAF- C_6F_{13}) 41, both synthesized using PPFR as a radical initiator for polymerization.

Polymer ^a	PPFR [mol %]	Yield [%]	VDF [mol%]		M_n^c NMR	D^d	T_d^e , 10% [$^\circ\text{C}$]	T_g^f [$^\circ\text{C}$]
			feed	Copolymers ^b				
Poly(VDF-co-MAF-TBE) 40	1.0	48	80	49	49 900	1.6	177	7
Poly(VDF-co-MAF- C_6F_{13}) 41	0.9	57	94	78	61 700	*	369	26

* Molecular weight distribution could not be determined for the poly(VDF-MAF- C_6F_{13}) due to the difficulty in performing SEC of these types of copolymers.

^a Reaction conditions are as follows: For poly(VDF-co-MAF-TBE), VDF/MAF-TBE in feed 80:20 mol % ratio, solvent used: $\text{C}_4\text{F}_5\text{H}_5$ + CH_3CN = 60 mL; reaction temperature: 90 $^\circ\text{C}$; reaction time = 6 h (see ref. [48] for further details.) For poly(VDF-MAF- C_6F_{13}), VDF/MAF- C_6F_{13} feed of 94:6 mol % ratio; solvent used: $\text{C}_4\text{F}_5\text{H}_5$ + CH_3CN + deionized water; reaction temperature: 90 $^\circ\text{C}$; reaction time = 18 h.

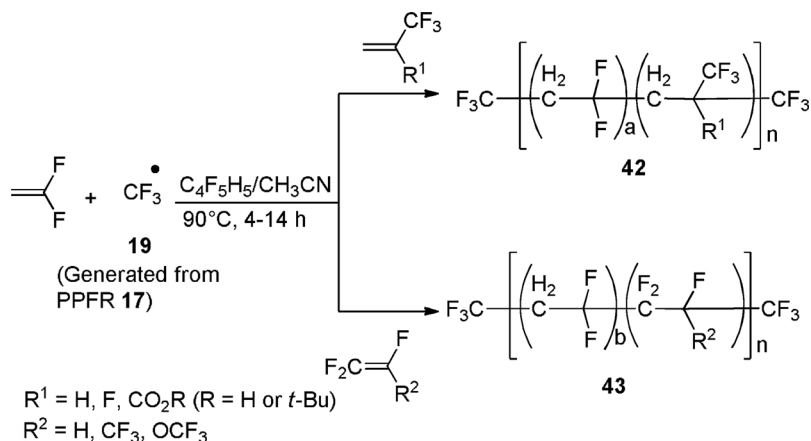
^b Copolymer compositions were analyzed by ^{19}F NMR spectroscopy.

^c In g/mol; determined from ^{19}F NMR spectroscopy using previously published formula.

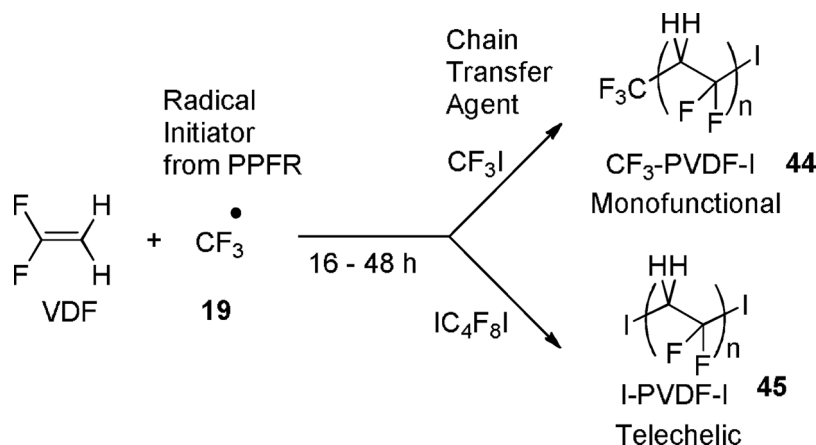
^d Characterized by SEC calibrated with polystyrene standards.

^e Measured by thermogravimetric analysis under air at 10 $^\circ\text{C}/\text{min}$.

^f Determined by differential scanning calorimetry.



Scheme 12. Radical copolymerizations of vinylidene fluoride (VDF) with $\text{H}_2\text{C}=\text{CR}_A\text{CF}_3$ (where R_A stands for H, F, CO_2R (R = H or $t\text{Bu}$) or with $\text{F}_2\text{C}=\text{CFR}_B$ (R_B : H, CF_3 , OCF_3) initiated by $\cdot\text{CF}_3$ radical generated from PPFR at 90 $^\circ\text{C}$. Reactions time dependent on different co-monomers.

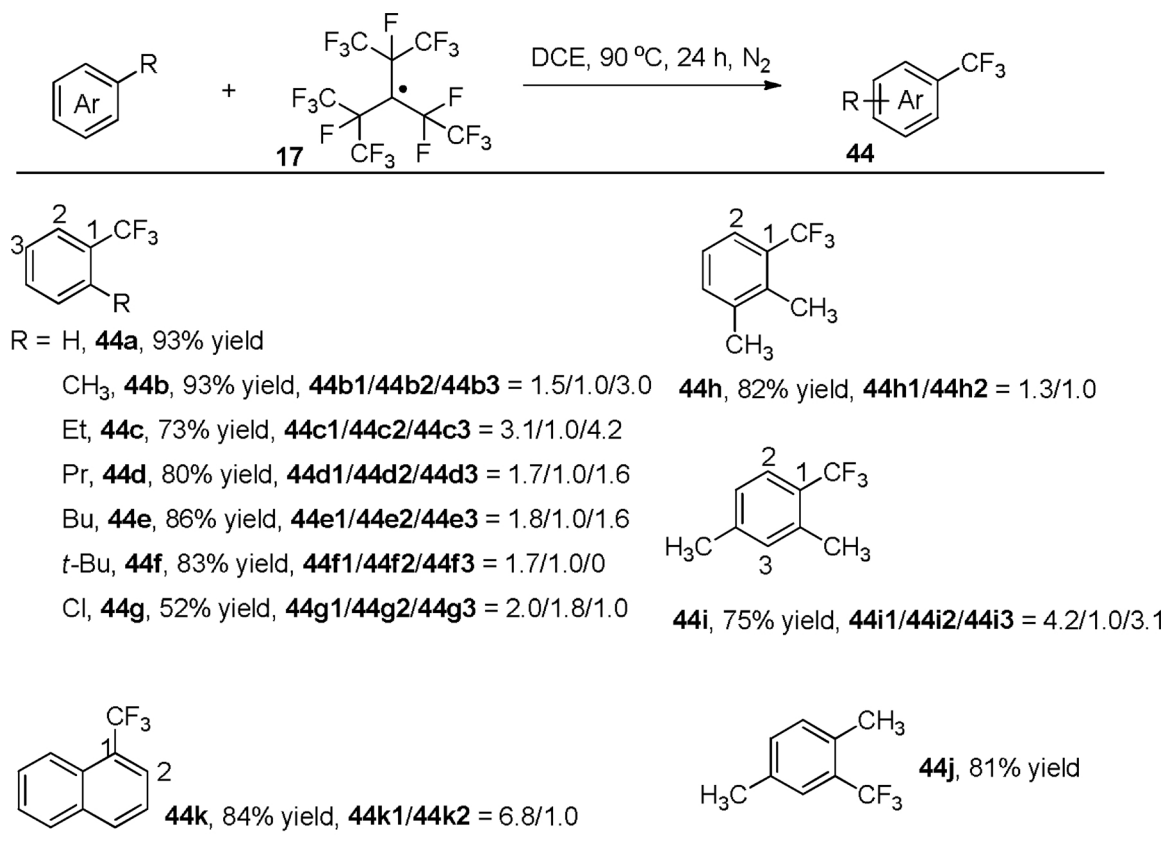


Scheme 13. Polymerization of VDF using iododifluorinated chain transfer agents from a ·CF₃ radical released by PPFR.

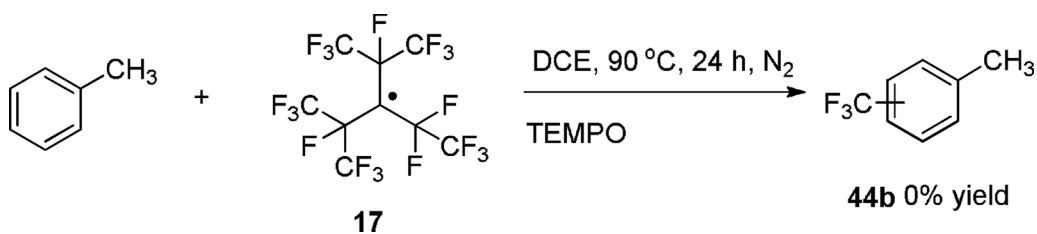
Table 4

Representative results of optimization of reaction conditions.

entry	PPFR (equiv)	atmosphere	time (h)	yield (%)	isomer ratio (<i>para:meta:ortho</i>)
1	2.0	N ₂	24	59	2.4:1.0:1.7
2	3.0	N ₂	24	94	3.0:1.0:1.5
3	3.0	O ₂	24	56	3.0:1.0:1.5
4	2.0	N ₂	48	88	2.3:1.0:1.2



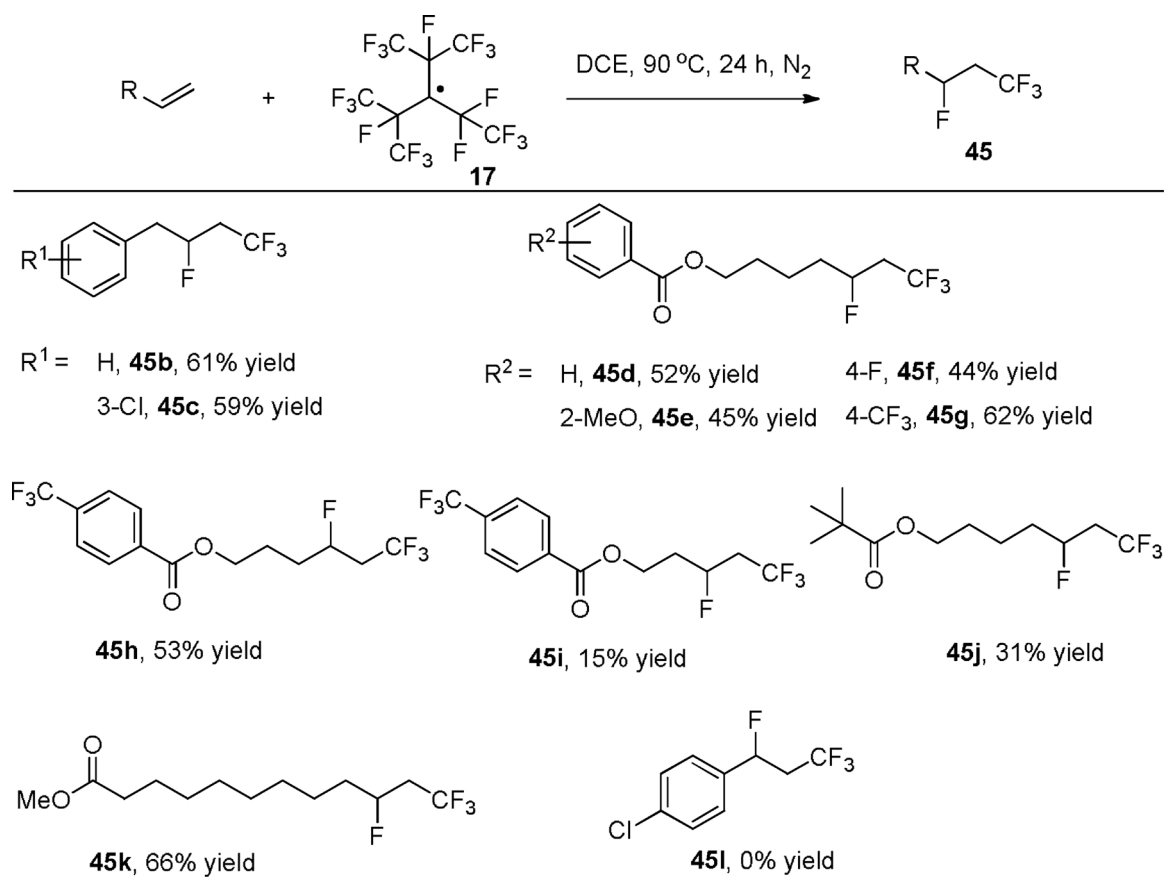
Scheme 14. Substrate generality of the radical trifluoromethylation reaction.



Scheme 15. Control experiment with the addition of TEMPO.

Table 5
Representative results of optimization of reaction conditions.

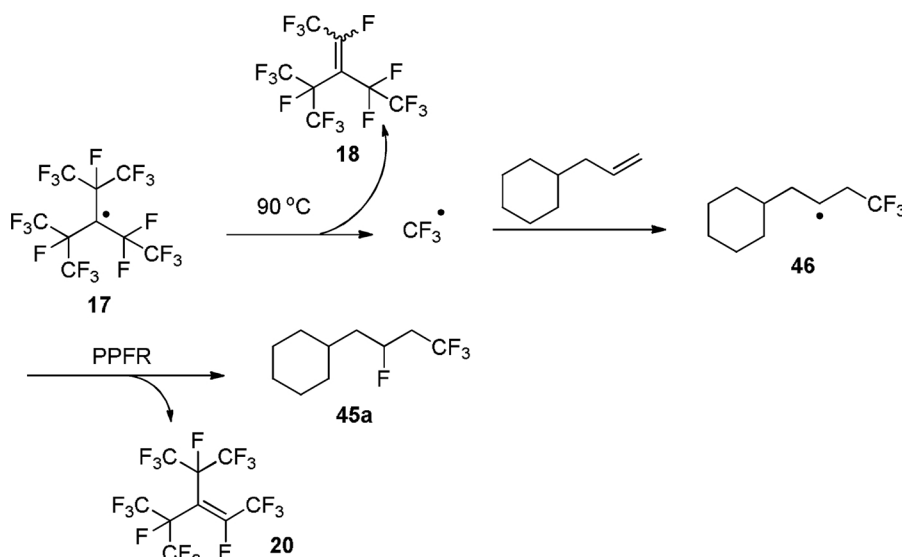
17			
45a			
entry	PPFR (equiv)	solvent	yield (%)
1	3.0	DCE	82 (¹⁹ F NMR)
2	1.0	DCE	45 (¹⁹ F NMR)
3	2.0	DCE	84 (Isolated)
4	2.1	CHCl ₃	52 (¹⁹ F NMR)
5	2.0	CCl ₄	0 (¹⁹ F NMR)



Scheme 16. Substrate generality of this reaction.

initial molar ratios of initiators. The diiodo chain transfer agent 1,4-Diiodooctadecylfluorobutane, IC₄F₈I, was more efficient and reactive than the monoiodide, Trifluoriodomethane, CF₃I. All of the resulting iodinated PVDFs had highly regulated number average molecular weights, as well as dispersity values, and exhibited low defects in the polymer

chain as seen in NMR spectra. These PVDFs have high melting temperatures (161–172 °C) as well as good thermal stability (values reaching 270 °C under air). The resulting PVDF-I **44** or I-PVDF-I **45** polymers, using mono- or diiodo chain transfer agents (CTAs) are precursors of diblock and triblock copolymers, respectively, which offer a



Scheme 17. Proposed mechanism for the trifluoromethyl-fluorination reaction.

range of possibilities for post-polymerization modification. PPFR provides a unique thermal radical initiator for ITP, with more predictable polymerization results than other conventional industrial polymerization processes [61].

4. As reagent for fluorination

4.1. Radical trifluoromethylation

In 2015, Soloshonok from University of Basque Country and co-authors developed PPFR 17 as a new trifluoromethylation reagent for the introduction of trifluoromethyl into aromatic compounds [62]. Detailed preliminary studies revealed that PPFR 17 could be converted into trifluoromethyl radical via heating at 90 °C. They also did the thorough conditions optimization for the reaction between toluene and PPFR 17, with the representative results shown in Table 4. The reaction was conducted under transition-metal-free conditions with dichloroethane (DCE) as solvent under nitrogen atmosphere, affording the desired product **44b** in 59% yield (entry 1). It was found that increasing the loading amount of PPFR to 3.0 equiv resulted in dramatically increased yield (94%) along with slightly improved chemoselectivity (3.0:1.0:1.5, entry 2). The inert reaction atmosphere was essential for this transformation, and only 56% yield was observed when the reaction was performed under oxygen (entry 3). They also found that decreasing the amount of PPFR afforded the same level of yield if the reaction time was prolonged to 48 h, but with slightly lower chemoselectivity (entry 4).

Soloshonok and co-authors also carried out the detailed studies on substrate scope via employing varieties of benzene derivatives in this reaction (Scheme 14). It was found that substrates bearing different alkyl substitutions could all be well tolerated in this system and provided the corresponding product in excellent yields (**44a-f**). The variation of length of the alkyl chain showed no effect on the reaction outcome. In sharp contrast, reaction of the benzene containing an electron-withdrawing group ($R = \text{Cl}$) afforded the obviously decreased yield (**44g**). The bis-substituted benzenes and naphthalene were also good substrates and provided the desired products in good yields (75–82%, **44h-j**). It should be mentioned that better yields were found from the reactions of PPFR comparing with those of trifluoroacetic acid [63] and TMSCF_3 [64].

They also carried out a control experiment to get insight into the reaction mechanism (Scheme 15). The reaction did not happen and no desired product was observed when a radical inhibitor TEMPO was

added to the reaction under the standard reaction conditions. Although they did not mention what intermediate was trapped by TEMPO, this result clearly indicates this is a radical process.

4.2. Radical trifluoromethylation-fluorination

After the development of the trifluoromethylation of arenes with this new reagent, the group of Soloshonok recently reported a trifluoromethyl-fluorination difunctionalization of alkenes with PPFR without use of any catalyst or additive. Interestingly, PPFR 17 was used as both the trifluoromethyl and fluorine sources. After careful screening of the reaction conditions, the loading amount of PPFR showed an obvious effect on the chemical yield (entries 1–3, Table 5). The use of 2.0 equiv of PPFR resulted in the highest yield of the desired product **45a** in 84% isolated yield. Solvent also played an important role in this system. For example, no product **45a** was obtained at all when the reaction was conducted in CCl_4 , while reaction in CHCl_3 could provide the product **45a** in 52% yield determined by ^{19}F NMR.

This trifluoromethyl-fluorination difunctionalization reaction exhibited a broad substrate scope, and several types of terminal alkene could be tolerated in this system with moderate yields (Scheme 16). Benzyl substituted alkenes were found to work well affording the products **45b** and **45c** with 61% and 59% yield respectively. Then, δ -ester substituted alkenes were examined with yield ranging from 44% to 62%. It was clear that the substrate bearing the electron-withdrawing group ($R = 4\text{-CF}_3$) substituted benzoic acid ester gave a better yield (**45g**). The length of alkyl chain was also investigated, and the yield decreased as the chain length decreased (**45g-k**). In particular, the best yield was observed from the reaction of methyl undec-10-enoate (66%, **45k**). Styrene substrate also was tried to be as substrate for this reaction, however, no desired product was obtained at all (**45l**).

The authors proposed a possible radical mechanism for this trifluoromethyl-fluorination reaction (Scheme 17). The initial step was the generation of trifluoromethyl radical via heating PPFR under nitrogen with the release of olefin 18.[33] Then, addition of trifluoromethyl radical to alkene gave the radical intermediate **46**, which underwent the fluorination reaction by treatment of the second equiv of PPFR to afford the target product **45a** as well as the olefin 20.

5. Conclusions

Reviewing the presented above data, one can conclude that persistent radical PPFR 17 has exceptionally high synthetic and practical

potential as fluorination and radical initiation reagent. The reported results are still of the preliminary value and the true potential of PPRF 17 still remains virtually unexplored. It is expected that dissemination of these results and commercial availability of PPRF 17 will generate high interest in research activity discovering yet unknown properties and practical applications of this novel perfluorinated reagent. One exciting trend that is emerging from the reported results is that the reactivity of the PPRF-generated trifluoromethyl radical is somehow different from literature data on the radical trifluoromethylation reactions. One of the reasons may be that PPRF-generated trifluoromethyl radical is released under inert, neutral and any additive-free conditions allowing to display its unhindered reactivity. Therefore, besides the synthetic application, the chemistry of PPRF may have important theoretical impact for deeper and more precise understanding the innate reactivity of a trifluoromethyl radical.

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