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Fluoroalkylated hypervalent sulfur fluorides: radical addition of arylchlorotetrafluoro-λ^6-sulfanes to tetrafluoroethylene†

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Fluorinated groups are essential hydrophobic groups in drug design. Combining a carbon-free tetrafluoro-λ^6-sulfanyl (SF_4) group with a polyfluoroalkyl group (R_F) provides SF_4R_F groups, exhibiting high hydrophobicity with a short carbon chain. In this study, various aryltetrafluoro(polyfluoroalkyl)-λ^6-sulfanes ($ArSF_4R_F$) were synthesized through the radical addition of arylchlorotetrafluoro-λ^6-sulfanes ($ArSF_4Cl$) to tetrafluoroethylene. In addition, quantification of hydrophobic constants (π_{Ph}) indicated that the SF_4 group is considerably more hydrophobic than a difluoromethylene (CF_2) group. Further transformation reactions revealed the stabilities and reactivities of these novel fluorinated groups. The high hydrophobicity and synthetic utility of the SF_4R_F group lead to the potential applications of the SF_4R_F group in the pharmaceutical field.

Introduction

Substituents based on hexacoordinated sulfur fluorides have gained significant attention in medicinal and material chemistry.[1] The pentafluoro-λ^6-sulfanyl (SF_5) group has been regarded as a "super-trifluoromethyl" group owing to its enhanced size, electronegativity, hydrolytic stability, and hydrophobicity ($\pi_{Ph}(SF_5)$: 1.23, $\pi_{Ph}(CF_3)$: 0.88).[2] Therefore, researchers have explored various applications of this moiety and dedicated substantial efforts to developing effective synthetic methods for compounds containing the SF_5 group.[2–7] Initial direct fluorination methods require strong oxidants, leading to low yields and poor functional group tolerance because of side reactions, such as overfluorination or C–C/C–S fragmentation.[3] However, recent advancements in the synthesis of aliphatic compounds with the SF_5 group have been achieved through the rapid development of synthetic methods using SF_5X reagents, expanding the accessible range.[2,4] Arylpentafluoro-λ^6-sulfanes ($ArSF_5$) have also gained significant importance in medicinal chemistry attributed to the significant effect of the SF_5 group bound to an aromatic ring on hydrophobicity and metabolic stability.[8] A notable breakthrough in the synthesis of $ArSF_5$ has been the development of two-step routes *via* arylchlorotetrafluoro-λ^6-sulfanes ($ArSF_4Cl$) (Scheme 1A, left).[5,6] These methods have enabled the scalable and inexpensive synthesis of $ArSF_5$ compounds by using less expensive and milder oxidants, such as Cl_2 and trichloroisocyanuric acid (TCICA).

The more hydrophobic SF_4R_F (R_F = polyfluoroalkyl) group is a promising option for the enhancement of biological activity.[9] For instance, the synthesis of aryltetrafluoro(trifluoromethyl)-λ^6-sulfanes ($ArSF_4CF_3$) and the π_{Ph} constant of the SF_4CF_3 group (2.13) were first reported in 2006, demonstrating the high hydrophobicity of the SF_4R_F group (Scheme 1B).[9c] However, direct fluorination is not feasible without deactivating the aromatic ring with a nitro group because of the high reactivity of fluorine gas. Consequently, the synthesis of a wide range of $ArSF_4CF_3$ compounds remains challenging thus far.

Based on this background, we envisioned using $ArSF_4Cl$ compounds in synthesizing $ArSF_4R_F$ compounds. Several radical addition reactions of $ArSF_4Cl$ compounds have been reported thus far (Scheme 1A, right).[5c,10] These synthetic methods are considerably milder than conventional direct fluorination of sulfides and have enabled the preparation of a variety of aromatic compounds with the tetrafluoro-λ^6-sulfanyl (SF_4) moiety. However, radical addition reactions of $ArSF_4Cl$ compounds to fluoroolefins have not been reported. In this study, we discuss radical addition reactions of $ArSF_4Cl$ compounds to tetrafluoroethylene (TFE) as a simple synthetic approach for aryltetrafluoro(polyfluoroethyl)-λ^6-sulfanes (Scheme 1C).[11] The enhanced hydrophobicity of the novel SF_4R_F groups and their reactivities will also be discussed.

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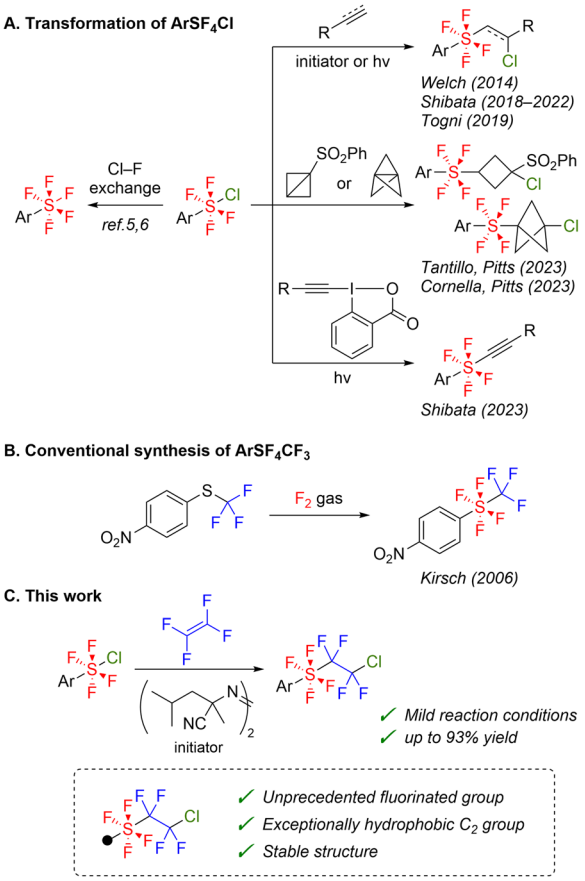


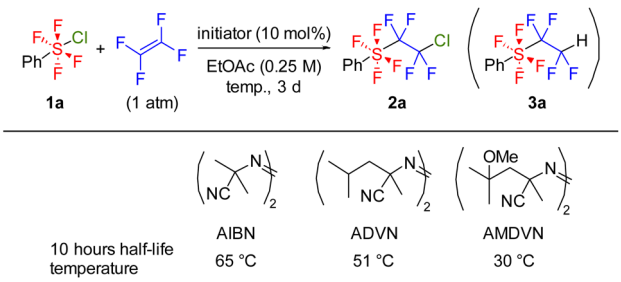
Scheme 1 Synthetic methods for the aromatic compounds with sulfur–fluorine functional groups. (A) Chlorine–fluorine exchange reactions and radical addition reactions of $ArSF_4Cl$ compounds. (B) Conventional synthesis of $ArSF_4CF_3$ compounds through direct fluorination. (C) This work: radical addition reactions of $ArSF_4Cl$ compounds to tetrafluoroethylene.

Results and discussion

Radical addition of arylchlorotetrafluoro-λ^6-sulfanes to tetrafluoroethylene

We synthesized chlorotetrafluoro(phenyl)-λ^6-sulfane **1a** using the optimized conditions involving TCICA/KF,[5c,d] and then the radical addition reaction of **1a** to TFE was examined by exploring various radical initiators (Table 1). Although triethylborane effectively catalyzed the addition reaction of $ArSF_4Cl$ compounds to terminal alkynes and alkenes,[10a–c] a low yield was obtained in the reaction with TFE (entry 1). Irradiation with a blue LED, known as the activation method for $ArSF_4Cl$ compounds,[10b,d] afforded the adduct **2a** in 49% yield (entry 2). A higher yield was obtained when BDK (2,2-dimethoxy-2-phenylacetophenone) was used as the photoinitiator (entry 3). Subsequently, we examined several thermal initiators, such as AIBN, ADVN, and AMDVN, each requiring different initiation temperatures (entries 4–6). Azo-type initiators exhibited good yields, with ADVN demonstrating the best performance and affording **2a** in 88% yield (entry 5). Reducing the reaction time to 20 h resulted in incomplete substrate conversion (entry 7).

Table 1 Effect of radical initiators on the radical addition reaction of **1a** to tetrafluoroethylene

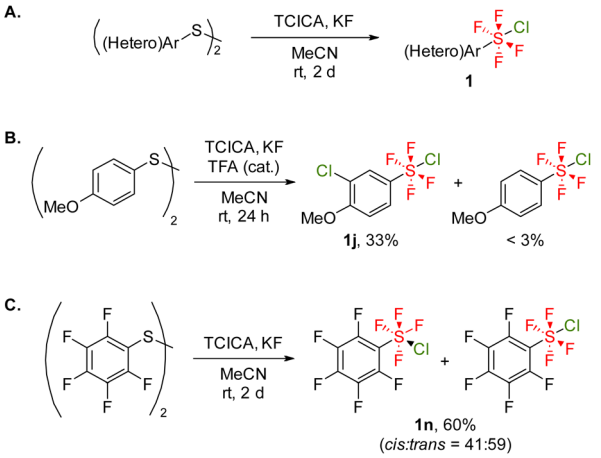


Entry	Initiator	Temp.	Yield[a] (%)
1	BEt_3	rt	5
2[b]	—	rt	49
3[b]	BDK	rt	68
4	AIBN	60 °C	80
5	ADVN	40 °C	88 (77[f])
6	AMDVN	25 °C	72
7[c]	ADVN	40 °C	23
8[c,d]	ADVN	40 °C	75
9[c]	ADVN	60 °C	65
10[e]	ADVN	40 °C	38[g]

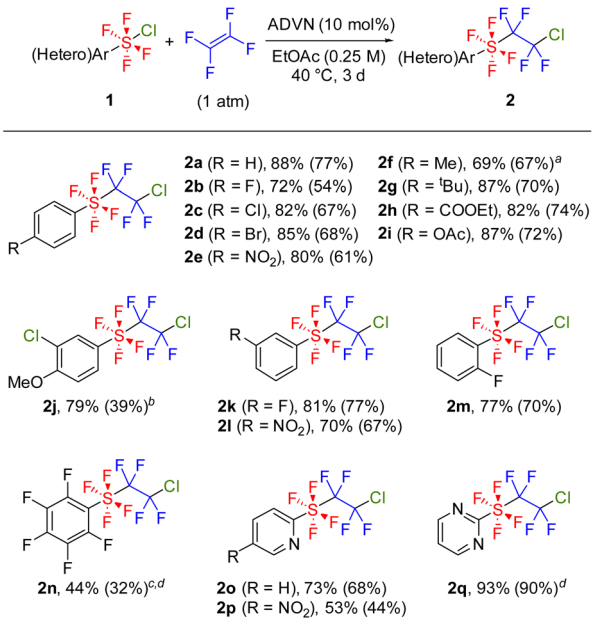
[a] Determined by ^{19}F NMR analysis of the crude mixture relative to an internal standard (1,4-bis(trifluoromethyl)benzene). [b] Irradiated with blue LED. [c] 20 h. [d] 30 mol% initiator added. [e] THF (0.10 M) instead of EtOAc. [f] Isolated yield. [g] Yield of **3a**. AIBN = 2,2′-azobis(isobutyronitrile), ADVN = 2,2′-azobis(2,4-dimethylvaleronitrile), AMDVN = 2,2′-azobis(4-methoxy-2,4-dimethylvaleronitrile), BDK = 2,2-dimethoxy-2-phenylacetophenone.

Although increasing the amount of ADVN or elevating the reaction temperature accelerated the reaction, the yield did not reach the optimal condition attributed to the decomposition of **1a** (entries 8–9). Alternation of solvents to acetonitrile, hexane, THF, or 1,2-dichloroethane did not afford satisfactory results (Table S1†), and the formation of a hydrogenated adduct, $PhSF_4CF_2CF_2H$, was predominant in the case of THF (entry 10). Inspired by the result, we examined the selective formation of **3a** *via* a three-component addition reaction with hydrogenating agents.[4f] However, several investigations revealed that the hydrogen sources such as $(Me_3Si)_3SiH$ caused decomposition of **1a** rather than the desired reaction (see the ESI†).

With the optimal reaction conditions in hand, we explored the substrate scope of this radical addition reaction using various $ArSF_4Cl$ compounds. Substrates **1** were synthesized according to the literature method (Scheme 2A).[5c,d] Notably, the electron-rich diaryl disulfide underwent arene chlorination during the oxidative fluorination step, affording **1j** as the major product (Scheme 2B). Bis(pentafluorophenyl) disulfide gave **1n** as a mixture of *cis*- and *trans*-isomers as previously reported, although the oxidative fluorination generally afforded **1** in *trans* conformation (Scheme 2C).[5a,c,d] Initially, the screening of substrates focused on the *para*-substituents on the benzene ring (Scheme 3). Both electron-withdrawing (**2b–e**) and electron-donating groups (**2f–g**) were tolerated, as were protected carboxylic acid and phenol (**2h–i**). *Meta*-substituted (**2j–l**) and



Scheme 2 Synthesis of (A) **1** (except **1j** and **1n**), (B) **1j** and (C) **1n**. Yields were determined by ^{19}F NMR analysis relative to an internal standard (trifluorotoluene). TCICA = trichloroisocyanuric acid, TFA = trifluoroacetic acid.



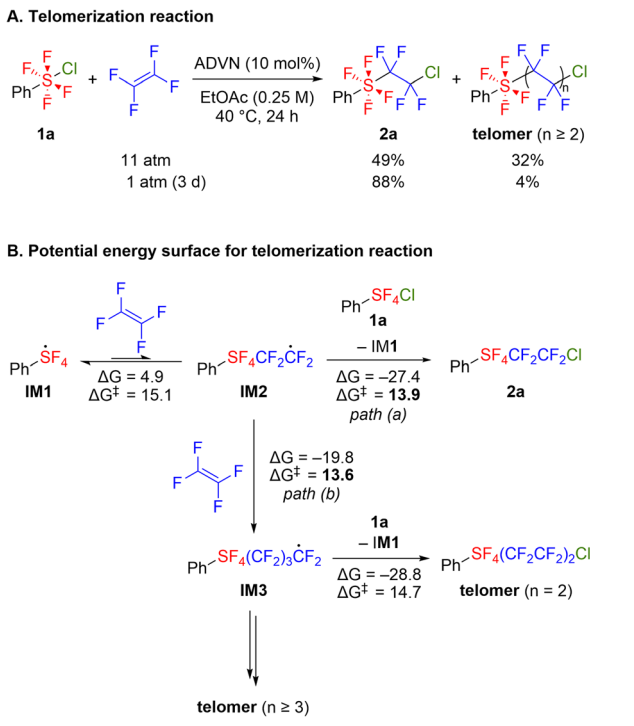
Scheme 3 Substrate scope. **1** (1.0 equiv.) and ADVN (10 mol%) were stirred in anhydrous EtOAc at 40 °C under TFE (1 atm). Yields were determined by ^{19}F NMR analysis relative to an internal standard (1,4-bis(trifluoromethyl)benzene); isolated yields are shown in parentheses. [a] AIBN (10 mol%), 60 °C. [b] ADVN (30 mol%). [c] Substrate was a mixture of *cis*- and *trans*-isomers (39 : 61). [d] EtOAc (0.50 M).

ortho-fluorinated substrates (**2m–n**) afforded the desired products in moderate to high yields. Using a mixture of *cis*- and *trans*-$ArSF_4Cl$, only the *trans* product was obtained (**2n**). Additionally, this reaction could be applied to pyridines and pyrimidines (**2o–q**). The structure of **2e** was unambiguously determined through X-ray diffraction analysis. Expectedly, the sulfur atom of **2e** shows an octahedral geometry characteristic of the hexavalent sulfur species as well as the $ArSF_4CF_3$ compound[9c] (see the ESI†).

In several cases where $ArSF_4Cl$ compounds were added to TFE, the dimerized products ($ArSF_4(CF_2CF_2)_2Cl$) were also obtained (less than 5%).[12] To shed light on the mechanism of the present reactions, a radical addition reaction was performed at higher TFE pressures. Consequently, **2a** and the telomer were obtained in 49% and 32% yields, respectively (Scheme 4A). Compared to the standard conditions under atmospheric pressure of TFE, the telomer ratio showed significant improvement. The telomers ($2 \leq n \leq 7$) were detected using GC-MS after treating with silica-gel column chromatography (Fig. S1†).

DFT calculations

Based on the single addition and telomerization reaction results, our next objective was to elucidate the energy profiles associated with these reactions. In the context of the radical reactions involving hexavalent sulfur fluorides, DFT calculations were performed to study the addition of SF_5Cl to alkynes, demonstrating the high stability of the SF_5 radical resulting from hyperconjugation.[4f] According to the literature, DFT calculations were performed at the M06-2X/Def2TZVPP/SMD(EtOAc) level of theory at 25 °C (Scheme 4B, see the ESI† for more details). Firstly, we computed the energy diagram for the formation of **2a** (Scheme 4B, path (a)). After abstracting chlorine from **1a**, **IM1** adds to TFE with a free energy barrier of 15.1 kcal mol^{-1} to form **IM2**. Notably, the formation of **IM2** from **IM1** and TFE was endergonic owing to the high stability of **IM1**. When the SF_5 radical was added, the formation of the

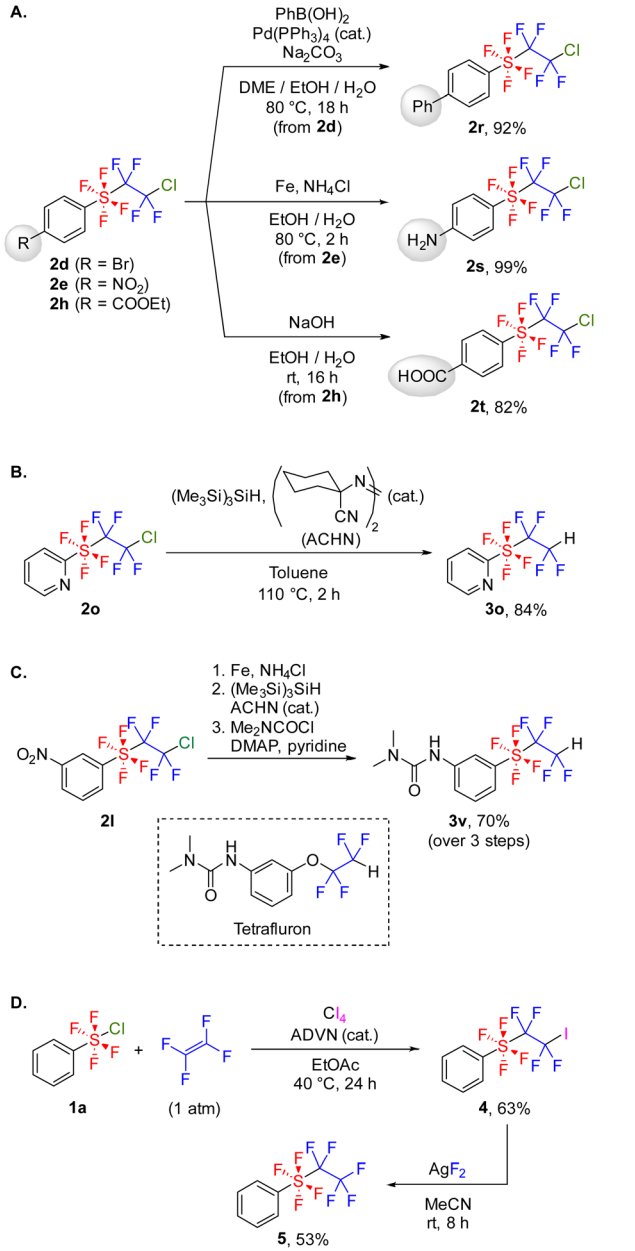


Scheme 4 (A) Telomerization reaction. Yields were determined by ^{19}F NMR analysis relative to an internal standard (1,4-bis(trifluoromethyl) benzene). (B) Free energy change and free energy of activation at 25 °C (in kcal mol^{-1}).

$SF_5CF_2CF_2$ radical was slightly exergonic, indicating apparent resonance stabilization by the benzene ring of **IM1** (Scheme S4†). After **IM2** is formed, chlorine abstraction from **1a** proceeds with a 13.9 kcal mol^{-1} free energy barrier, regenerating **IM1** and yielding **2a**. The chlorine transfer is significantly exergonic and is the driving force of a series of reactions. Next, we investigated the propagation reaction (Scheme 4B, path (b)). A dimerized product was obtained from **IM2** through a second addition to TFE, followed by chlorine abstraction from **1a**. Notably, the formation of **2a** through chlorine abstraction was irreversible, and further elongation from **2a** could no longer occur. The stability of **2a** was also supported by the unsuccessful telomerization from **2a** (Scheme S2†). Therefore, the telomer/**2a** ratio is influenced by the selectivity of chlorine abstraction and propagation from **IM2**. The calculations showed that these two reactions proceed with comparable activation energies. Considering that the reaction rate depends on the activation energy and the concentrations of reactants, the concentration ratio of TFE and **1a** should affect the selectivity. This is consistent with the experimental results (Scheme 4A).

Synthetic applications

Compound **2** exhibited stability against silica gel column chromatography and could be stored in air at room temperature for several months. Next, we carried out the transformation of **2** to investigate its stability and reactivity. Several transformations retaining the $SF_4CF_2CF_2Cl$ group were tested initially (Scheme 5A). Bromoarene **2d** was converted to **2r** *via* a Suzuki–Miyaura cross-coupling reaction, facilitating the synthesis of various $ArSF_4CF_2CF_2Cl$ compounds. $SF_4CF_2CF_2Cl$-substituted aniline **2s** and benzoic acid **2t** were successfully synthesized from **2e** and **2h**, respectively. These methods overcome the difficulty in synthesizing **2s** and **2t** through radical addition because of the low stability of $ArSF_4Cl$ with amino and carboxyl groups. In contrast, the $SF_4CF_2CF_2Cl$ group can be reduced to the $SF_4CF_2CF_2H$ group using tris(trimethylsilyl)silane (Scheme 5B). The set of transformation reactions mentioned in Schemes 5A–B enables the synthesis of functional molecules; for instance, an analog of the bioactive molecule Tetrafluron[13] was synthesized from **2l** in 70% yield over three steps (Scheme 5C). Furthermore, the iodosulfanylation of tetrafluoroethylene followed by fluorination was investigated to prepare a perfluorinated $SF_4CF_2CF_3$ group (Scheme 5D). After evaluating several external iodine sources, carbon tetraiodide was identified as the most effective iodinating agent in yield and selectivity (Table S4†). Under the optimized reaction conditions, tetrafluoro(tetrafluoroiodoethyl)(phenyl)-λ^6-sulfane **4** was synthesized from **1a** and TFE in 63% yield. Subsequently, **4** underwent fluorination using AgF_2 to form **5**. When AgF as a fluorinating agent or **2a** ($PhSF_4CF_2CF_2Cl$) as a substrate was employed, the fluorination did not proceed (Table S5†). We then compared the stability of **5** and $PhCF_2CF_2CF_3$ to clarify the difference between the SF_4 and CF_2 linkers (Table 2). Under high temperature conditions, **5** was decomposed by nearly 30%, but $PhCF_2CF_2CF_3$ was not decomposed at all (entries 1–2). In addition, heating under the basic conditions[14] or exposure to large excess of $TfOH/C_6H_6$ (ref. 15)



Scheme 5 Derivatizations of aryltetrafluoro(polyfluoroethyl)-λ^6-sulfanes. Isolated yields are provided. (A) Transformation reactions retaining the $SF_4CF_2CF_2Cl$ group. (B) Reduction of the $SF_4CF_2CF_2Cl$ group. (C) Synthesis of an analog of Tetrafluron. (D) Synthesis of tetrafluoro(perfluoroethyl)(phenyl)-λ^6-sulfane **5**.

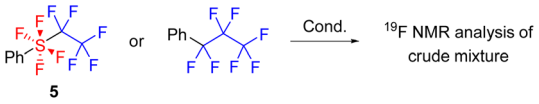
resulted in complete degradation of **5**, whereas $PhCF_2CF_2CF_3$ was partially degraded (entries 3–6). These results indicate the higher degradability of the SF_4 linker than that of the CF_2 linker.

Substituent effects

Since aromatic compounds with the $SF_4CF_2CF_2Cl$ and $SF_4CF_2CF_3$ groups were synthesized for the first time, we investigated their substituent effects such as hydrophobic parameters (π_{Ph})[16] and Hammett substituent parameters (σ_m and σ_p).[17]

The log *P* (*P* being the partition coefficient in an *n*-octanol/water system) values for **2a** and **5** were measured using

Table 2 Comparison of degradability of **5** and $PhCF_2CF_2CF_3$



Entry	Substrate	Cond.	Result[a]
1	**5**	8 : 1 DMSO : H_2O, 120 °C, 24 h	Decomposition 32%
2	$PhCF_2CF_2CF_3$	8 : 1 DMSO : H_2O, 120 °C, 24 h	Decomposition 0%[b]
3	**5**	NaOH, 8 : 1 DMSO : H_2O, 120 °C, 24 h	Decomposition 100%
4	$PhCF_2CF_2CF_3$	NaOH, 8 : 1 DMSO : H_2O, 120 °C, 24 h	Decomposition 49%
5	**5**	1 : 1 TfOH : C_6H_6, rt, 4 h	Decomposition 100%
6	$PhCF_2CF_2CF_3$	1 : 1 TfOH : C_6H_6, rt, 4 h	Decomposition 77%

[a] Conversion of **5** or $PhCF_2CF_2CF_3$ was determined by ^{19}F NMR analysis of the crude mixture relative to an internal standard (trifluorotoluene or 4,4′-difluorobiphenyl). [b] 100% recovery of substrate.

HPLC.[18] The log *P*(**2a**) and log *P*(**5**) were measured to be 4.62 and 4.44, respectively. Based on these values, $\pi_{Ph}(SF_4CF_2CF_2Cl)$ and $\pi_{Ph}(SF_4CF_2CF_3)$ were estimated to be 2.49 and 2.31, respectively, indicating a slight hydrophobic effect of the terminal chlorine. Subsequently, the hydrophobicity of other fluorinated groups was compared with that of the $SF_4CF_2CF_2Cl$ and $SF_4CF_2CF_3$ groups (Fig. 1). $\pi_{Ph}(SF_4CF_2CF_2Cl)$ and $\pi_{Ph}(SF_4CF_2CF_3)$ exhibited higher values than $\pi_{Ph}(SF_5)$ (1.23) and $\pi_{Ph}(SF_4CF_3)$ (2.13) owing to their longer carbon chains.[2,9c] Comparing the $SF_4CF_2CF_3$ group with the perfluoroalkyl groups, $\pi_{Ph}(SF_4CF_2CF_3)$ was higher than $\pi_{Ph}(C_3F_7)$ and lower than $\pi_{Ph}(C_4F_9)$, suggesting that the hydrophobic effect of the SF_4 group falls between those of one and two difluoromethylene (CF_2) groups.

The Hammett parameters of the $SF_4CF_2CF_2Cl$ group were estimated through the ^{19}F NMR approach developed by Taft (Table 3).[19] As a result, the *meta*- and *para*-σ values (σ_m and σ_p) of the $SF_4CF_2CF_2Cl$ group were estimated to be 0.61 and 0.66, respectively. Among electron-withdrawing functional groups, the values were higher than those of the CF_3 group (σ_m: 0.43, σ_p: 0.54), comparable to those of the CN (σ_m: 0.56, σ_p: 0.66), SF_5 (σ_m: 0.61, σ_p: 0.68), and SF_4CF_3 (σ_p: 0.68) groups, and lower than those of the NO_2 group (σ_m: 0.71, σ_p: 0.78).[9c,17b] Although the $SF_4CF_2CF_2Cl$ group has a longer carbon chain than the SF_4CF_3 group, the electron-withdrawing ability decreases; a similar trend has been reported for linear perfluoroalkyl groups ($\sigma_p(CF_3)$: 0.54, $\sigma_p(CF_2CF_3)$: 0.52, $\sigma_p(CF_2CF_2CF_3)$: 0.48).[17b]

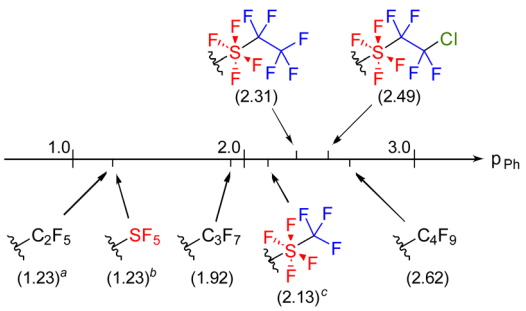


Fig. 1 Hydrophobicity of fluorinated substituents. [a] From ref. 16c. [b] From ref. 2. [c] From ref. 9c.

Table 3 Hammett substituent parameters for the $SF_4CF_2CF_2Cl$ group

$\delta_H^{m\text{-}X}$	$\delta_H^{p\text{-}X}$	σ_I	σ_R^0	σ_m^0	σ_p^0
−3.41[a]	−6.29[a]	0.56	0.10	0.61	0.66

[a] Negative values of $\delta_H^{m\text{-}X}$ and $\delta_H^{p\text{-}X}$ represent downfield ^{19}F NMR shifts of the fluorobenzene derivatives relative to fluorobenzene.

Conclusions

In summary, we unveiled an unexplored synthetic route for $ArSF_4R_F$ compounds based on the addition reaction of $ArSF_4Cl$ compounds to TFE. It was demonstrated that the inexpensive and scalable radical addition reactions can be applied to the synthesis of an analog of the bioactive molecule and perfluoroalkyl compounds. Additionally, we have estimated the π_{Ph} constant for the $SF_4CF_2CF_2Cl$ and $SF_4CF_2CF_3$ groups, providing preliminary evidence of the significantly higher hydrophobicity of the SF_4 group compared to the CF_2 group. We believe that the development of the SF_4R_F groups and the elucidation of their fundamental properties achieved in this study provide promising options for the application of fluorinated functional groups.

The $ArSF_4R_F$ compounds are related to per- and polyfluoroalkyl substances (PFAS), and therefore potential accumulation cannot be ruled out at present.[20] Close attention should be paid to this issue for further application.

Data availability

All experimental data and detailed procedures are available in the ESI.†

Author contributions

E. Y. conducted the experiments, analysed the data, and wrote the original draft. K. A. and T. O. directed the project. K. N. provided advice and discussed the data. All the authors

discussed the results and contributed to the review and editing of the manuscript.

Conflicts of interest

An application for a patent (application number: WO2022JP035414) related to this work has been submitted by K. A., E. Y., K. N., and T. O. as co-inventors.

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