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Photoredox Catalysis

Sequential C–F Bond Transformation of the Difluoromethylene Unit in Perfluoroalkyl Groups: A Combination of Fine-Tuned Phenothiazine Photoredox Catalyst and Lewis Acid

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Abstract: A sequential process via photoredox catalysis and Lewis acid mediation for C–F bond transformation of the CF_2 unit in perfluoroalkyl groups has been achieved to transform perfluoroalkylarenes into complex fluoroalkylated compounds. A phenothiazine-based photocatalyst promotes the defluoroaminoxylation of perfluoroalkylarenes with (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) under visible light irradiation, affording the corresponding aminoxylated products. These products undergo a further defluorinative transformation with various organosilicon reagents mediated by $AlCl_3$ to provide highly functionalized perfluoroalkyl alcohols. Our novel phenothiazine catalyst works efficiently in the defluoroaminoxylation. Transient absorption spectroscopy revealed that the catalyst regeneration step is crucial for the photocatalytic aminoxylation.

The carbon–fluorine (C–F) bond transformation in perfluoroalkyl compounds not only is an important synthetic method in organic chemistry,[1] but also is an urgent issue to solve PFAS (polyfluoroalkyl substances) environmental problems.[2] Numerous C–F bond activation protocols have been reported for single C–F bond transformations of perfluoroalkyl group.[3,4] However, a sequential C–F bond transformation of a difluoromethylene unit (–CF_2–) into two different functional groups remains underdeveloped (Figure 1A) despite being an important clue to the solution of PFAS problems. This is because the harsh reaction conditions needed to cleave robust C–F bonds cause the undesired installation of the same functional group. In fact, dialkoxylation,[5] dimethylation[6] and dichlorination[6] of a CF_2 moiety have been reported. To avoid installing the same groups, amino alcohols were used in the aminoalkoxylation of α-perfluoroalkyl ketones in a three-component tandem reaction (Figure 1B, a).[7] Recently, two distinguished reactions were reported: a sequential defluorinative alkylation of trifluoroacetyl compounds by a radical mechanism (Figure 1B, b)[8] and a coupling reaction of 1,1-difluoroalkyl compounds (RCF_2R') with Grignard reagents and chlorosilanes or alkyl tosylates by $CrCl_2$ catalysis via chromium carbenoid species (Figure 1B, c).[9] Neither method is applicable to the transformation of longer perfluoroalkyl compounds ($RCF_2(CF_2)_nR'$). Herein we propose a reaction design based on a sequential process via radical and ionic paths (Figure 1C). The primary substitution of F with RO groups involves C–F bond activation by photocatalysis[4g] and capture of the perfluoroalkyl radical by an oxyl radical.[10] Then the second transformation employs a Lewis acid and nucleophiles. Because the reaction mechanism includes an oxonium intermediate, diverse nucleophiles can be introduced. Based on our proposed design using a dual activation system, in this study we achieved a sequential C–F bond transformation of perfluoroalkylarenes via aminoxylation with a fine-tuned phenothiazine photocatalyst and aminoxyl radical reagent followed by $AlCl_3$-mediated nucleophilic substitution with organosilicon reagents (Figure 1D).

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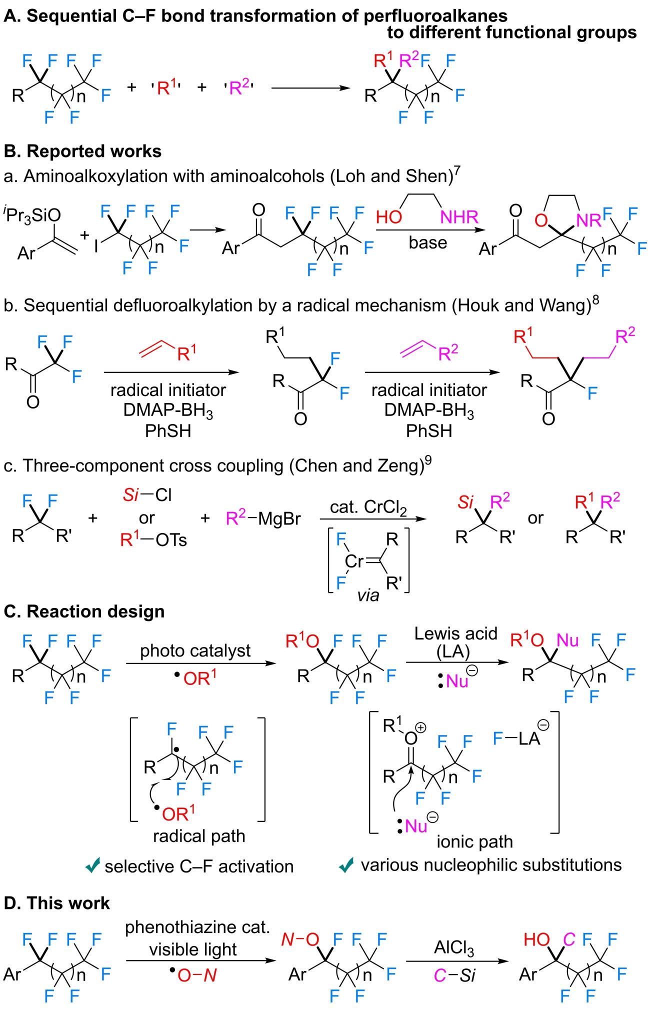
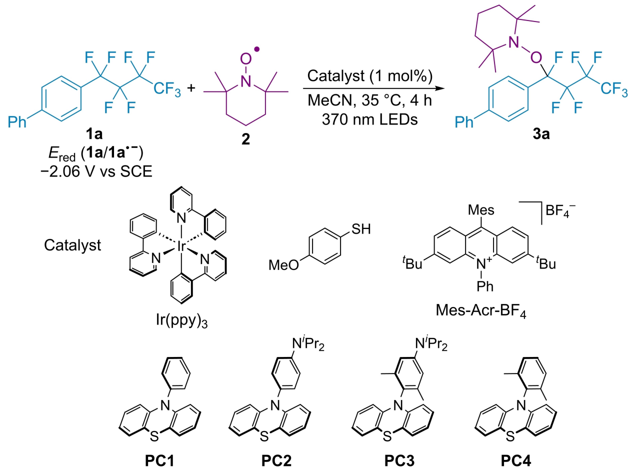


Figure 1. Sequential C–F bond transformation of perfluoroalkyl compounds.

Table 1: Optimization of photo-catalyzed aminoxylation of perfluoroalkylarene **1a** with TEMPO **2**:[a]

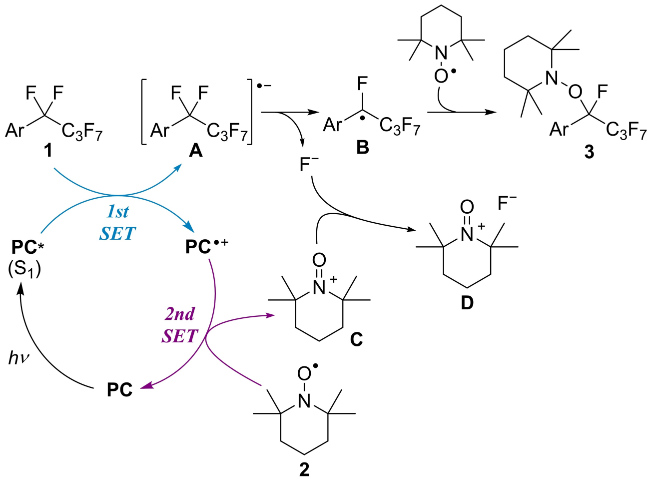


Entry	Catalyst	E_{ox}* (V vs SCE)	Yield
1	Ir(ppy)$_3$	−1.73	0%
2	**PC1**	−2.45	35%
3	**PC2**	−2.68	42%
4	**PC3**	−2.57	60%
5	**PC4**	−2.47	38%
6[b]	4-MeOC$_6$H$_4$SH	−3.31	0%
7[c]	Mes-Acr-BF$_4$	−3.36	trace
8[d]	**PC3**	−2.57	0%
9	none	–	0%
10[e]	**PC3**	−2.57	82% (71%)[f]

[a] **1a** (0.4 mmol), **2** (0.8 mmol), catalyst (0.004 mmol), MeCN (2 mL), irradiation with 370 nm LEDs at 35 °C for 4 h. Yields were determined by ^{1}H NMR spectroscopy using an internal standard. [b] 4-MeOC$_6$H$_4$SH (0.08 mmol), HCO$_2$Cs (0.8 mmol), DMSO (2 mL) irradiation with 427 nm LEDs at 35 °C for 24 h. [c] Mes-Acr-BF$_4$ (0.04 mmol), N^{i}Pr$_2$Et (1.2 mmol), MeCN (1.3 mL), irradiation with 390 nm LEDs at 35 °C for 24 h. [d] No irradiation. [e] **PC3** (0.02 mmol), 24 h. [f] Isolated yield.

Firstly, we investigated reaction conditions for the photo-catalyzed aminoxylation using 4-phenyl(perfluorobutyl)benzene **1a** (E_{red} = −2.06 V vs SCE) and (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) (**2**) under visible light irradiation (370 nm) (Table 1). The use of Ir(ppy)$_3$ resulted in no reaction due to the low reducing ability of excited Ir(ppy)$_3$ (Entry 1).[4g] We focused on phenothiazines exhibiting higher reducing abilities than Ir(ppy)$_3$. Their photocatalytic activities can be tuned by a substituent effect.[11] *N*-Phenylphenothiazine **PC1** exhibited a catalytic activity to mediate the aminoxylation, giving product **3a** (Entry 2). To access more negative redox potentials, phenothiazine **PC2** was used, leading to an improved yield (Entry 3). It should be noted that newly developed phenothiazine **PC3** bearing diisopropylamino and two methyl groups showed the best catalytic activity (Entry 4), suggesting the effect of the two Me groups is crucial to the aminoxylation. *N*-Dimethylphenylphenothiazine **PC4** was less effective, which indicates the increase of reducing ability by an amino group is significant (Entry 5). Next, to utilize much lower reduction potential of photocatalysts, we applied thiolate catalysis[12] and consecutive photo-induced electron transfer (conPET) system[13] to this reaction. Thiolate catalysis resulted in no reaction, and **1a** was hardly converted (Entry 6). In the conPET system, **1a** was completely consumed, but only a trace amount of **3a** was obtained according to complicated products (Entry 7). In this case, the high reducing ability of the active catalytic species generated by conPET would cause the undesired overreduction or side-reactions. Both photocatalyst and photo-irradiation were essential for the reaction progress (Entries 8 and 9). Finally, under the optimized conditions using the 5 mol % amount of **PC3**, **3a** was obtained in 82 % yield (Entry 10). Further optimization for addition amount of TEMPO **2** and solvent screening is described in the Supporting Information.[14]

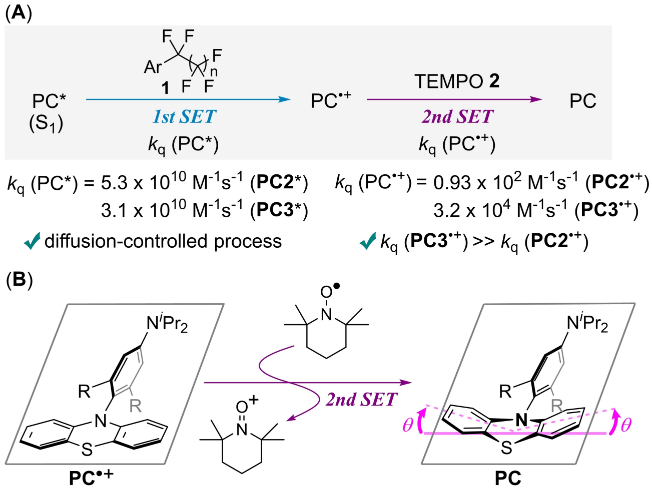
Scheme 1 depicts a plausible mechanism for the aminoxylation of **1** with TEMPO **2** catalyzed by phenothiazine **PC**. The photoexcited **PC*** reduces **1** via single electron transfer (SET), affording radical anion **A** and radical cation **PC**$^{•+}$. Mesolysis of a C–F bond affords benzyl radical **B**.[4g] Then, **B** associates with **2** to give product **3**. **PC** (E(**PC3**$^{•+}$/**PC3**) =



Scheme 1. Proposed mechanism for photo-catalyzed aminoxylation of perfluoroalkylarenes.

0.61 V vs SCE) is regenerated by single electron reduction with **2** ($E(\mathbf{2}^{+}/\mathbf{2})=0.62$ V vs SCE).[15] A by-product, *N*-oxoammonium cation **C** captures F^{-}, suppressing the retro-reaction from **B** to **A**.[16] HRMS and ^{19}F NMR confirmed *N*-oxoammonium fluoride **D** was generated.[17] The appropriate reduction potential of **PC3*** achieves selective reduction of starting material **1** and not product **3**, realizing a single C–F bond transformation without overreduction and side-reactions.[18]

We focused on the fact that our developed **PC3** exhibited a more efficient catalytic activity than **PC2** despite the lower reducing ability of **PC3*** than **PC2*** (Table 1).[19] We conducted mechanistic studies to understand the origin of the high activity of **PC3**. First, the fluorescence quenching experiments of PC* with 4-trifluoromethyl(perfluorohexyl)benzene **1e** were performed. Stern–Volmer plots determined that the rate constants of the dynamic quenching of excited singlet species **PC2*** and **PC3*** were 5.3×10^{10} $M^{-1}s^{-1}$ and 3.1×10^{10} $M^{-1}s^{-1}$, respectively (Figures S2 and S4).[20,21] The 1st SET between **1e** and PC* is a diffusion-controlled process,[22] which indicates that the catalytic turnover is independent of the reducing ability of PC*.[23] We then considered the 2nd SET between $PC^{\bullet+}$ and TEMPO for the catalyst regeneration. The sub-microsecond transient absorption spectroscopy using laser flash photolysis method at 355 nm (4 mJ/pulse, 4 ns pulse-width) was conducted for a mixture of PC, 4-phenyl(perfluoroethyl)benzene **1n**, and TEMPO to monitor the generation and quenching of $PC^{\bullet+}$.[24] The quenching rate constant of $\mathbf{PC3}^{\bullet+}$ (3.2×10^{4} $M^{-1}s^{-1}$) was found to be much larger than that of $\mathbf{PC2}^{\bullet+}$ (0.93×10^{2} $M^{-1}s^{-1}$) (Figures S19 and S20).[25] Thus, the fast regeneration of **PC3** dominates the catalytic turnover (Figure 2A). Next, Gibbs free energy changes (ΔG_r) and reorganization energies (λ) in the 2nd SET were obtained by DFT calculation to estimate activation energies ($\Delta G^{\neq}$) according to Marcus-Hush theory (Figure 2B).[26,27] While two ΔG_r values are almost identical (3.8 and 3.7 kcal/mol), λ value for **PC3** (38.8 kcal/mol) is lower than that for **PC2** (42.3 kcal/mol). Finally, $\Delta G^{\neq}$ for

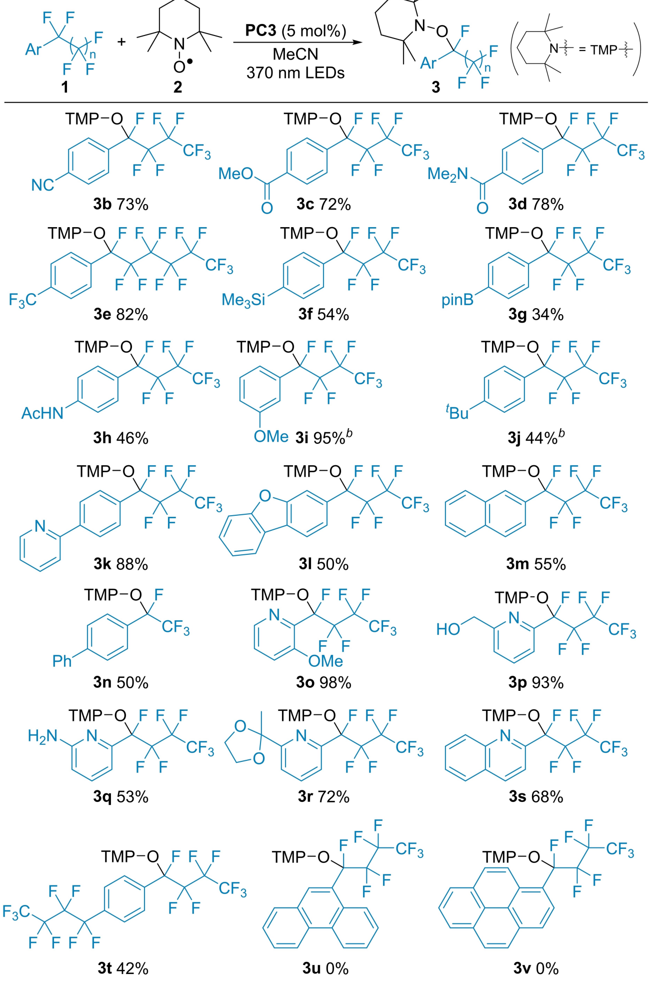


	PC2 (R = H)	PC3 (R = Me)
$\Delta G^{\ddagger}$ (kcal/mol)	12.6	11.6
ΔG_r (kcal/mol)	3.8	3.7
λ (kcal/mol)	42.3	38.8
θ (°)	18.0	14.5

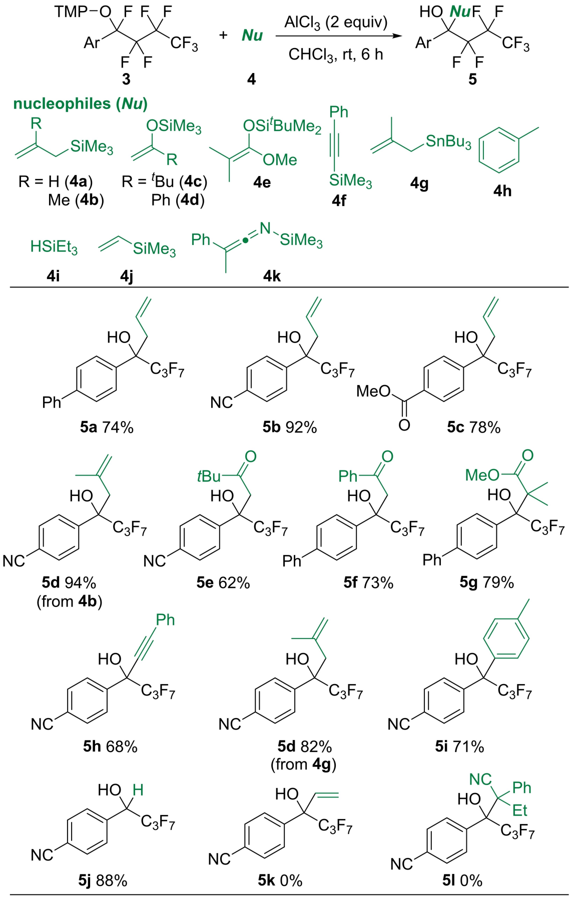
Figure 2. (A) Quenching rate constants of PC* and $PC^{\bullet+}$. (B) Activation energies ($\Delta G^{\neq}$), Gibbs free energy changes (ΔG_r), reorganization energies (λ), and bent angles (θ) in the 2nd SET by DFT calculation studies ((U)ωB97XD/6-31+G(d,p)/SMD(acetonitrile)).

PC3 (11.6 kcal/mol) is lower than that for **PC2** (12.6 kcal/mol). This trend in $\Delta G^{\neq}$ is consistent with that in the catalyst regeneration rate. Thus, we focused on the geometry change of PC because a smaller λ value leads to the decrease of $\Delta G^{\neq}$ for SET. The planar structure of phenothiazine backbone in $PC^{\bullet+}$ changes to the bent one upon reduction (Figure 2B). This bending is the dominant geometry change and would be deeply related to λ values. We adopted the bent angle (θ) in Figure 2B right to represent the extent of a bent structure of PC. The smaller value of θ in **PC3** ($\theta=14.5°$) shows the smaller geometry change in the reduction of $\mathbf{PC3}^{\bullet+}$ compared to **PC2** ($\theta=18.0°$). The steric repulsion of Me groups of **PC3** suppresses bending of a phenothiazine backbone, eventually decreasing $\Delta G^{\neq}$. A catalyst design including both fast catalyst regeneration and effective photo-excited reduction potential is achieved by the rigidity of molecular structure and the introduction of an electron-donating group.

Using the determined optimal reaction conditions, we explored the substrate scope of this aminoxylation (Scheme 2). Electron withdrawing groups such as CN, CO_2Me, and $CONMe_2$ were available for the transformation (**3b**, **3c**, **3d**). The CF_3-substituted perfluoroalkylarene selectively underwent the aminoxylation in the perfluoroalkyl group (**3e**).[28] Silyl and boryl substituents were also tolerated (**3f** and **3g**). It is noted that perfluoroalkylarenes with electron-donating groups smoothly underwent aminoxylation (**3h**, **3i**, and **3j**). The development of **PC3** with high reducing ability overcame the limitation of the substrate scope in our previous report for defluoroallylation.[4g] Substrates including pyridine, benzofuran, or naphthalene



Scheme 2. Substrate scope of perfluoroalkylarenes in the aminoxylation with TEMPO.[a] [a] **1a** (0.4 mmol), **2** (0.8 mmol), **PC3** (0.02 mmol), MeCN (2 mL), irradiation with 370 nm LEDs at 35 °C for 24 h. Isolated yields are shown. [b] **2a** (1.2 mmol) and **PC3** (0.04 mmol).



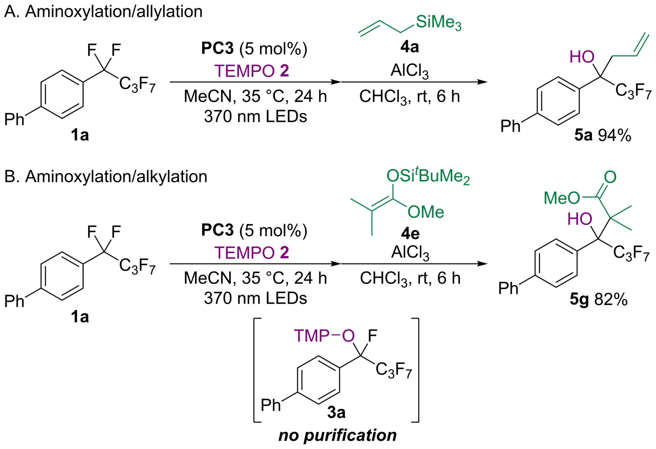
Scheme 3. Second defluorinative transformation mediated by a Lewis acid.[a] [a] **3** (0.2 mmol), **4** (1.0 mmol), and $AlCl_3$ (0.4 mmol) in $CHCl_3$ (2 mL) at room temperature for 6 h. Isolated yields are shown. [b] **4h** (1 mL).

moieties efficiently gave the corresponding products (**3k**, **3l**, and **3m**). The reaction of perfluoroethylarene also gave **3n** in a moderate yield. Perfluoroalkyl-substituted pyridines were feasible substrates, and various functional groups such as OMe, OH, NH_2, and acetal groups were compatible with the present reaction (**3o**, **3p**, **3q**, and **3r**). A quinoline-based substrate afforded desired product **3s** in 68 % yield. The substrate with two C_4F_9 groups underwent single aminoxylation to give product **3t**. Reactions of perfluoroalkylphenanthrene and -pyrene gave no products (**3u** and **3v**).[29]

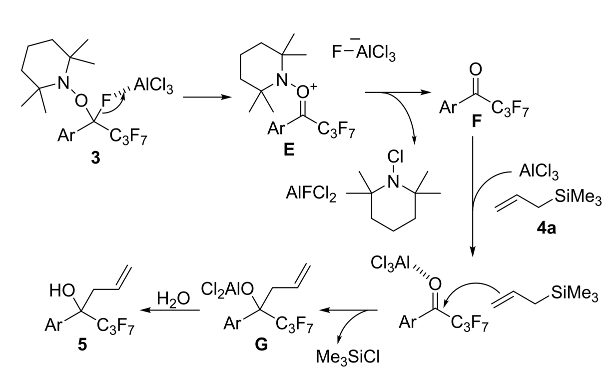
Next, Lewis acid mediators and nucleophilic coupling partners were surveyed for the selective C–F bond transformation of aminoxylated compounds **3** via an ionic path[30] (Tables S3 and S4). The combination of $AlCl_3$ and organosilicon reagents was found to be appropriate in the transformation (Scheme 3). After isolation of **3a**, which was provided by aminoxylation between **1a** and **2** (Table 1, Entry 10), **3a** was treated with allyltrimethylsilane (**4a**) in the presence of $AlCl_3$. The reaction gave allylated alcohol **5a** in 74 % yield, in which the amino group was removed on the O atom (see below). The CN and CO_2Me groups were tolerated in this allylation (**5b** and **5c**). Various organosilicon nucleophiles were applicable to this C–F bond transformation. Methallylsilane **4b**, silyl enol ethers **4c** and **4d**, silyl ketene acetal **4e**, and alkynylsilane **4f** provided functionalized perfluoroalkyl alcohols **5d**, **5e**, **5f**, **5g**, and **5h**, respectively. An organotin reagent, methallyltributyltin (**4g**) also acted well as a nucleophile. Toluene (**4h**) was a suitable nucleophile for the Friedel–Crafts reaction to give product **5i**. The reduction with $HSiEt_3$ smoothly proceeded to yield defluorinated product **5j**. On the other hand, vinylsilane **4j** and silyl ketene imine **4k** were not applicable.

Using the radical and ionic methods to realize two types of C–F bond activation, we demonstrated a one-pot transformation of a CF_2 unit via aminoxylation and allylation reactions (Scheme 4A). After aminoxylation of perfluoroalkylarene **1a** with **2** using **PC3** and 370 nm LED light, the crude product was treated with **4a** and $AlCl_3$ to give product **5a** in high yield. The one-pot aminoxylation/alkylation was also successful using silyl ketene acetal **4e** (Scheme 4B).

Scheme 5 illustrates a proposed mechanism for $AlCl_3$-mediated C–F bond allylation of **3** with allylsilane **4a**. $AlCl_3$



Scheme 4. One-pot sequential C–F bond transformation of CF_2 unit.[a] [a] **1a** (0.4 mmol), **2** (0.8 mmol), **PC3** (0.02 mmol), MeCN (2 mL). Then, **4** (2.0 mmol), $AlCl_3$ (1.2 mmol), $CHCl_3$ (4 mL). Yields were determined by ^1H NMR spectroscopy using an internal standard.



Scheme 5. Proposed mechanism for C–F bond transformation mediated by $AlCl_3$.

abstracts F^- to give oxonium intermediate **E**. Then *N*-chloroamine and $AlFCl_2$ are eliminated to give ketone **F**. $AlCl_3$ activates **F**, and **4a** adds to a carbonyl group, affording **G**.[31] Finally, hydrolysis of **G** yields product **5**. The generation of **F** was confirmed when **3** was treated with $AlCl_3$ in the absence of nucleophiles (Scheme S4). Other typical Lewis acids[30] were not effective (Table S3). $AlCl_3$ can mediate abstraction of fluoride ion of **3** and activation of a less basic carbonyl group of **F** due to high Lewis acidity. In terms of the intermediacy of ketone **F**, our procedure has an impact on the synthesis of perfluoroalkyl ketones from PFAS via defluorination. Traditional methods such as defluorination of fully-perfluorinated alkylbenzenes,[32] perfluoroalkyl-substituted anilines[33] and -enamines,[34] and *α*-hydroperfluoroalkanoic acid esters[5,35] have problems such as narrow substrate scopes. Especially for the synthesis of aryl ketones **F**, available substrates were extremely limited. In this report, compounds **3** can be synthesized and used as synthetic equivalents for **F** with the wide substrate scope and the high compatibility of functional groups. Our process is an efficient synthetic method of functionalized perfluoroalkyl alcohols like **5** from PFAS.

In summary, a combination of photoredox catalysis and Lewis acid activation realizes sequential C–F bond transformation of a CF_2 unit in perfluoroalkylarenes. Functionalized perfluoroalkyl alcohols were synthesized by phenothiazine-catalyzed photo-induced defluoroaminoxylation with TEMPO and subsequent $AlCl_3$ mediated substitution of a F atom with various carbon nucleophiles. Mechanistic studies revealed that the rigidity of molecular structure and the introduction of an electron-donating group is important in catalyst design to achieve fast catalyst regeneration and effective photo-excited reduction potential.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Fluorine · Phenothiazine · Photochemistry · Radical reactions · Radical ions

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[18] Excited **PC3*** selectively reduces starting material **1** in prior to product **3** in terms of reduction potential. For example, $E(\mathbf{1a}/\mathbf{1a}^{\bullet-}) = -2.06$ V vs SCE, $E(\mathbf{3a}/\mathbf{3a}^{\bullet-}) = -2.31$ V vs SCE.

[19] In contarast to **PC2** and **PC3**, **PC1** and **PC4** did not work in the aminoxylation of **1j**, which exhibited lower reduction potential than **1a**, due to the lower reducing abilities of **PC1*** and **PC4*** (Tables S6 and S7). This is because that the 1st SET is slower due to lower reducing abilities of **PC1*** and **PC4*** caused by the lack of N^iPr_2 group. Thus, the catalytic activities of **PC1** and **PC4** are lower than those of **PC2** and **PC3**. The Marcus analysis of **PC1** and **PC4** as well as **PC2** and **PC3** is shown in the Supporting Information.

[20] Figures S2 and S4 show the Stern–Volmer fluorescence quenching studies of **PC2** and **PC3** with **1e** (see Supporting Information).

[21] Sub-nano second laser flash photolysis was conducted to determine the lifetimes of singlet states of **PC2** and **PC3**. The singlet lifetime of **PC2** was $^1\tau_0 = 2.4$ ns $(1/^1\tau = k_d = 4.1\times10^8\ s^{-1})$ and that of **PC3** was $^1\tau_0 = 2.5$ ns $(1/^1\tau_0 = k_0 = 4.0\times10^8\ s^{-1})$ (see Supporting Information Figures S22 and S24).

[22] The diffusion-controlled rate constant of acetonitrile is $k_{diff} = 1.9\times10^{10}\ L\,mol^{-1}s^{-1}$. M. Montalti, A. Credi, L. Prodi, M. T. Gandolfi, *Handbook of Photochemistry, 3rd ed.*; CRC Press, **2006**.

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[24] The absorption of radical anion **A** was not observed due to being out of the monitoring range.

[25] Figures S19 and S20 show the Stern–Volmer plots for $1/\tau$ of $PC^{\bullet+}$ versus [TEMPO **2**].

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[27] See Supporting Information for the derivation of ΔG_r, λ, and $\Delta G^{\neq}$.

[28] DFT calculation study revealed that the alkyl radical intermediate generated via C–F bond mesolysis at perfluoroalkyl group was more stable than one generated via the mesolysis at

CF_3 group and that the activation energy for perfluoroalkyl group is lower than that for CF_3 group (Scheme S6).
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Communications

Photoredox Catalysis

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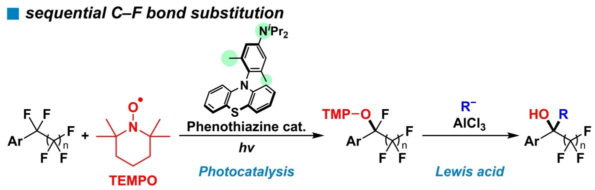
Sequential C–F Bond Transformation of the Difluoromethylene Unit in Perfluoroalkyl Groups: A Combination of Fine-Tuned Phenothiazine Photoredox Catalyst and Lewis Acid



The sequential defluorinative transformation of a difluoromethylene (CF_2) unit in perfluoroalkyl compounds has been achieved by a combination of photoredox catalysis and Lewis acid activation. A newly developed phenothiazine-based catalyst served as an efficient catalyst for defluoroaminoxylation. Spectroscopic measurements revealed the reaction mechanism. $AlCl_3$ facilitated further defluorinative transformation of the aminoxylated compounds.