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Communication

Photoredox-Catalyzed C−F Bond Allylation of Perfluoroalkylarenes at the Benzylic Position

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ABSTRACT: Site-selective and direct C−F bond transformation of perfluoroalkylarenes was achieved with allylic stannanes via an iridium photoredox catalyst system. The present defluoroallylation proceeds exclusively at the benzylic position through perfluoroalkyl radicals generated by a single-electron transfer from an excited photoredox catalyst to perfluoroalkylarenes. A variety of perfluoroalkyl groups are applicable: linear perfluoroalkyl-substituted arenes such as Ar−^{n}C$_4$F$_9$ and Ar−^{n}C$_6$F$_{13}$ and heptafluoroisopropylarenes (Ar−CF(CF$_3$)$_2$) underwent site-selective defluoroallylation. DFT calculation studies revealed that the *in situ* generated Bu$_3$SnF traps F$^-$ to prevent a retroreaction from the unstable perfluoroalkyl radical intermediate, and the radical intermediate favorably reacts with allylic stannanes. The synthesis of a bis(trifluoromethyl)methylene unit containing compound, which is an analog that is useful as a pharmaceutical agent for the prophylaxis or treatment of diabetes and inflammatory diseases, demonstrated the utility of this reaction.

The importance of organic fluorides is well established in the production of pharmaceutical, agrochemical, and organic electronic materials.[1] In particular, polyfluoroalkyl substances have attracted great interest because polyfluoroalkyl moieties dramatically enhance thermal stability and exert a unique surface effect on surfactants and lubricants.[2] The most practical synthetic method is the installation of perfluoroalkyl groups (−C$_n$F$_{2n+1}$) to organic compounds, and fully fluorinated alkyl group-substituted compounds (R−C$_n$F$_{2n+1}$) can be easily prepared by many well-established methods (Figure 1A).[3] Further functionalization of perfluoroalkyl units is rare, however, despite the fact that the C−F bond activation of readily available R−C$_n$F$_{2n+1}$ has shown huge potential for access to functionalized perfluoroalkyl compounds. The transformation of C−F bonds has intrinsic problems with site selectivity due to the harsh conditions and highly reactive reagents that are needed to activate the robust C−F bonds.[4] These factors lead to undesired non-site-selective transformations and multiactivations of C−F bonds.[5]

Many groups have reported single C−F bond transformations of the CF$_3$ group in which the issue of site-selectivity is not included (Figure 1B, n = 1). Hosoya and Yoshida reported the transformation of ArCF$_3$ bearing a hydrosilyl group.[6] Young reported a frustrated Lewis-pair-mediated transformation.[7] Following a report by Mattay that described a photoinduced C−F bond activation,[8] many methodologies involving a single-electron transfer (SET) mechanism have been developed.[9] Recently, photoredox catalysis has become a significant protocol; König[10] and Jui[11] independently reported efficient C−F bond transformations of ArCF$_3$ with alkenes. In contrast to the CF$_3$ group, the single C−F bond activation of longer perfluoroalkyl groups is rare, and only two reports are known to have described a transformation of the CF$_2$CF$_3$ group (Figure 1B, n = 2). The two-electron reduction of ArCF$_2$CF$_3$ via either an electrochemical method or Mg metal generates [ArCFCF$_3$]$^-$ species as key intermediates and accomplishes either a nucleophilic addition to CO$_2$[12] or a nucleophilic substitution with Me$_3$SiCl,[13] respectively. Additionally, as far as double C−F activation of CF$_2$CF$_3$ group, Ichikawa reported Ni-mediated [3 + 2] cycloaddition of 2-pentafluoroethyl-1-alkene with 4-octyne.[14] These methods, however, have never been applied to longer perfluoroalkyl compounds most likely due to steric hindrance and the electron-withdrawing effect of perfluoroalkyl groups that decrease the nucleophilicity of the corresponding carbanions (Figure 1B, $n \geq 3$). Instead of a two-electron reduction, we focused on a mechanism via SET (Figure 1C) wherein the reduction of perfluoroalkylarene **1** by an excited photoredox catalyst (PC*) followed by F$^-$ elimination from radical anion **A** selectively gives benzylic carbon radical **B**.[10,11] Even in this case, the perfluoroalkyl groups cause serious problems such as destabilization of the generated radical **B**[15] and inhibition of a sequential bond-forming reaction via large steric hindrance.[16] As a result, a retroprocess that includes back electron transfer (BET) and F$^-$ addition returns the reaction to its starting point.[17] We speculated that the utilization of organometallic reagents (R−M) would overcome these problems. The efficient reactivity of R−M toward a radical intermediate and the trapping of F$^-$ by M$^+$ kinetically and thermodynamically favored the progress of the reaction. Herein, we report a photoredox-catalyzed, selective C−F bond allylation of perfluoroalkyl-substituted arenes by using

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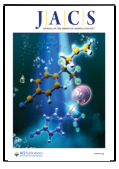

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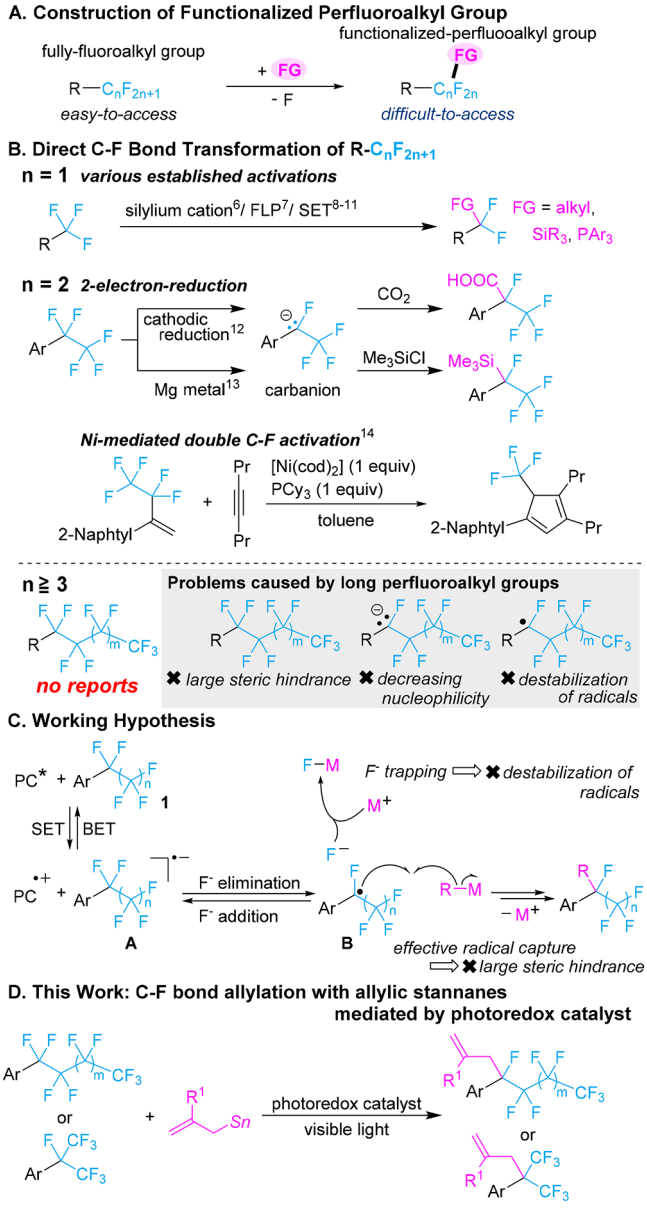
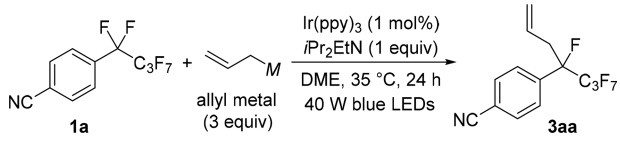


Figure 1. Site-selective C−F bond transformation of perfluoroalkyl compounds.

allylic stannanes (Figure 1D). This is the first achievement of a selective C−F bond transformation in long perfluoroalkyl groups ($n \geq 3$).

We chose allylmetal reagents that possess an efficient level of reactivity to carbon radical species[18] in the reaction of nonafluorobutyl arene **1a** with $Ir(ppy)_3$ (1 mol %) and $^{i}Pr_2EtN$ (1 equiv) under irradiation from 40 W blue LEDs (Table 1). The use of allyltrimethylsilane (entry 1), allylboronic ester (entry 2), or allyltrifluoroborate salt (entry 3) resulted in no reaction. On the other hand, allyltributylstannane **2a** gave the desired allylated compound **3aa** in 52% yield (entry 4). In this reaction, allylation occurred exclusively at the benzylic position without the formation of multiallylated products because the reduction of defluoroallylated product **3aa** would be more difficult than that of starting material **1a** due to its high reduction potential.[19] Both $Ir(ppy)_3$ and photoirradiation were essential to the reaction progress (entries 5 and 6). Under the conditions without $^{i}Pr_2EtN$, the yield of **3aa** was decreased and a large consumption of **2a** was observed (entry 7).[20] As described above, we discovered that allylstannane **2a** showed outstanding efficiency toward

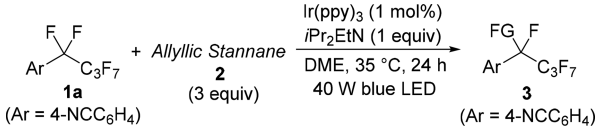
Table 1. Optimization of Photoredox-Catalyzed Defluoroallylation of Nonafluorobutyl Arene 1a with Allyl Metal Reagents[a]

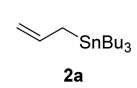
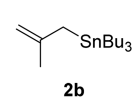
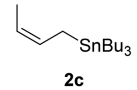
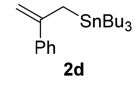
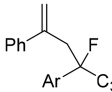
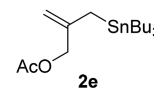
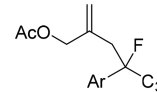
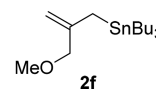
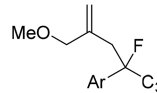


Entry	Allyl Metal	Yield of **3aa**
1	$SiMe_3$	0%
2	Bpin	0%
3	BF_3K	0%
4	$SnBu_3$ (**2a**)	52%
5[b]	**2a**	0%
6[c]	**2a**	0%
7[d]	**2a**	38%

[a]Conditions: **1a** (0.4 mmol), allyl metal (1.2 mmol), $Ir(ppy)_3$ (0.004 mmol), $^{i}Pr_2EtN$ (0.4 mmol), DME (2 mL), irradiation with 40 W blue LEDs at 35 °C. Yields were determined by ^{1}H NMR spectroscopy using 1,1,1,2-tetrachloroethane as an internal standard. [b]No irradiation with 40 W blue LEDs. [c]Without $Ir(ppy)_3$. [d]Without $^{i}Pr_2EtN$.

Table 2. Scope of Allylic Stannanes in Defluoroallylation of 1a[a]



Entry	*Allyllic Stannane* **2**	Product **3**	Yield
1	 **2a**	 **3aa**	52%
2	 **2b**	 **3ab**	85%
3	 **2c**	 **3ac**	0%
4	 **2d**	 **3ad**	51%
5	 **2e**	 **3ae**	47%
6	 **2f**	 **3af**	69%

[a]Conditions: **1a** (0.4 mmol), **2** (1.2 mmol), $^{i}Pr_2EtN$ (0.4 mmol), and $Ir(ppy)_3$ (0.004 mmol), DME (2 mL), irradiation with blue LEDs at 35 °C for 24 h. Isolated yields are shown.

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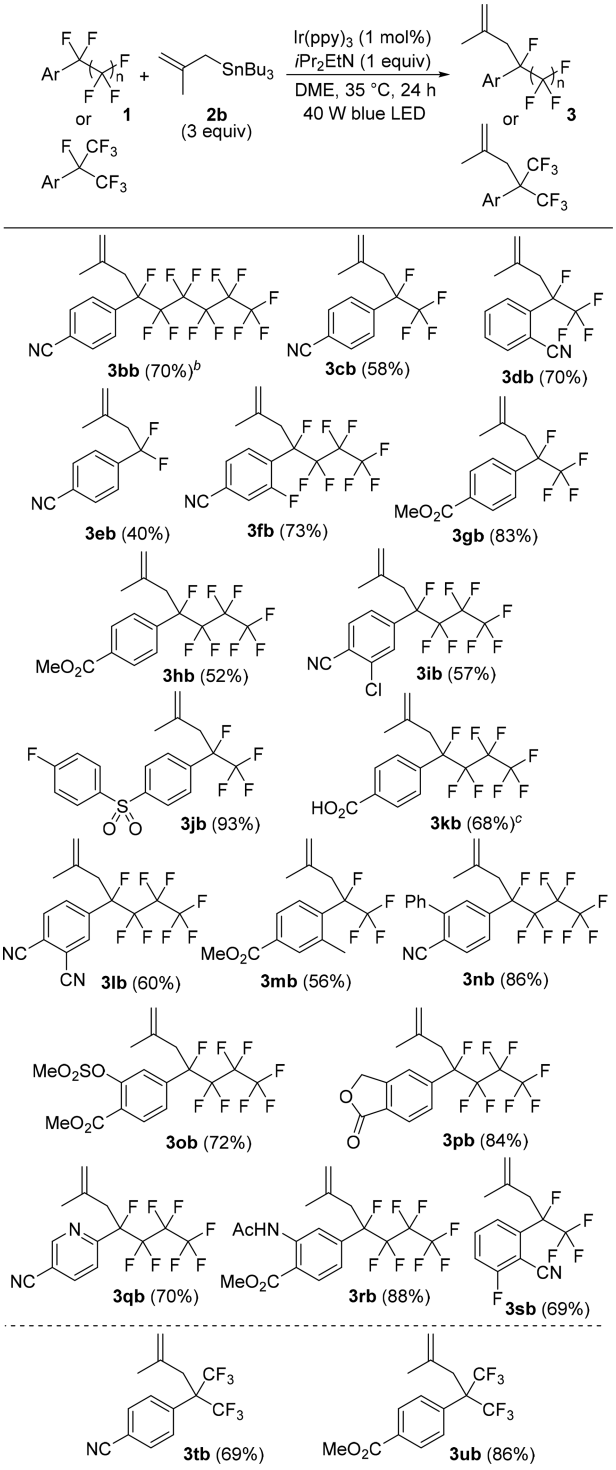
Table 3. Defluoroallylation of Various Perfluoroalkylarenes 1 Using Methallylstannane 2b[a]



[a]Conditions: **1** (0.4 mmol), **2b** (1.2 mmol), $^{i}Pr_2EtN$ (0.4 mmol), and $Ir(ppy)_3$ (0.004 mmol), DME (2 mL), irradiation with blue LEDs at 35 °C for 24 h. Isolated yields are shown. [b]48 h. [c]The yield of **3kb** was determined by ^1H NMR spectroscopy using 1,1,1,2-tetrachloroethane as an internal standard.

defluoroalkylation of perfluoroalkylarene because control experiments in our hands based on either the König[10] or the Jui[11] systems were not applicable to perfluoroalkylarene **1a** (Schemes S1 and S2).

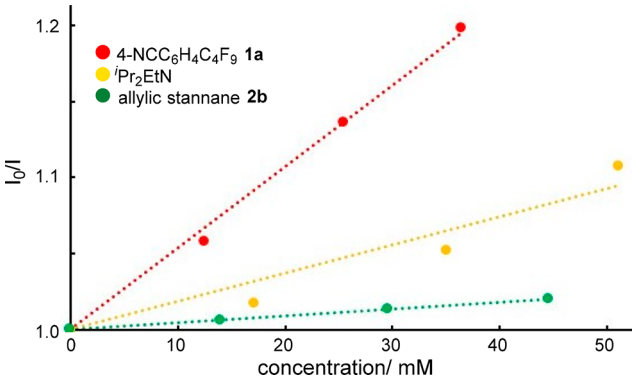


Figure 2. Stern–Volmer luminescence quenching studies of photocatalyst $Ir(ppy)_3$ (excitation 380 nm, emission 514 nm).

Table 2 shows the scope of the allylic stannanes **2** in the reaction of **1a** with the optimized reaction conditions (Table 1, entry 4). Methallylstannane **2b** afforded the defluoroallylated product **3ab** in a higher yield than **2a** (entries 1 and 2). Crotylstannane **2c** was not suitable due to steric hindrance (entry 3). Allylic stannanes bearing substituents at the *β*-position of the Sn atom were applicable substrates. Ph-, $AcOCH_2$-, and $MeOCH_2$-substituted substrates (**2d**, **2e**, and **2f**) afforded the corresponding products (entries 4–6).

The scope of perfluoroalkyl arenes was investigated using methallylstannane **2b** (Table 3). Selective allylation of the benzylic C–F bonds of C_6F_{13} and C_2F_5 groups other than the C_4F_9 group proceeded smoothly (**3bb**, **3cb**, **3db**, and **3gb**). The CF_3 group was also applicable to this allylation (**3eb**). $C(sp^2)$–F and $C(sp^2)$–Cl bonds were tolerated and a benzylic F group was selectively substituted (**3fb**, **3jb**, **3sb**, and **3ib**). An electron-withdrawing group on the benzene ring decreases the reduction potential of substrate **1** to accelerate SET from excited $Ir(ppy)_3$ to **1**, and CN, CO_2Me, CO_2H, and SO_2Ar groups were suitable substituents (e.g., **3bb**, **3gb**, **3kb**, **3jb**). On the other hand, perfluoroalkylarenes **1** without electron-withdrawing groups were not available due to their higher reduction potential.[21] Functional groups such as methanesulfonyloxy, methyl, phenyl, and acetylamino groups were compatible with this reaction system (**3ob**, **3mb**, **3nb**, **3rb**). The structure of **3ob** was determined by X-ray diffraction analysis (Figure S8). Perfluoroalkyl-substituted pyridine smoothly gave the desired allylated product **3qb**. The present reaction system was applicable to a heptafluoroisopropyl ($CF(CF_3)_2$) group regardless of the large steric hindrance, and the benzylic C–F bond selectively underwent allylation (**3tb** and **3ub**).

The Stern–Volmer luminescence quenching experiments provided the information for electron transfer involving the Ir catalyst and reagents (Figure 2). The experiments using perfluoroalkylarene **1a**, $^{i}Pr_2EtN$, and allylic stannane **2b** revealed that the principal interaction with the excited state of $Ir(ppy)_3$ was performed by **1a**, and by comparison, $^{i}Pr_2EtN$ and **2b** exhibited a much less efficient quenching effect.

Based on the above results, a plausible mechanism for the reaction of **1c** with **2a** is illustrated in Figure 3A. The blue-light-excited $Ir(ppy)_3$ (E_{red} = −1.73 V vs SCE)[22] reduces **1c** (E_{red} = −1.84 V vs SCE)[23] via SET, affording the Ir(IV) species and radical anion **A**, although this step is an uphill reaction with respect to the redox potential. The elimination of F^- from the benzylic position of **A** affords radical **B**. Bu_3SnF,

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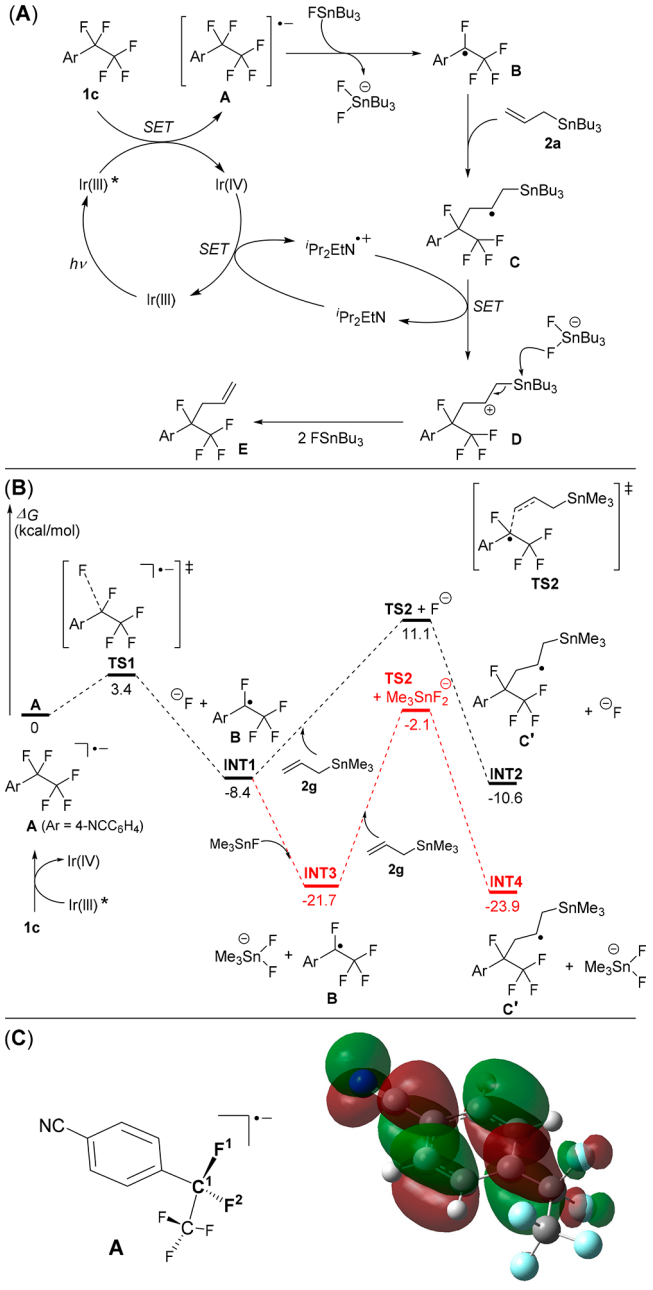
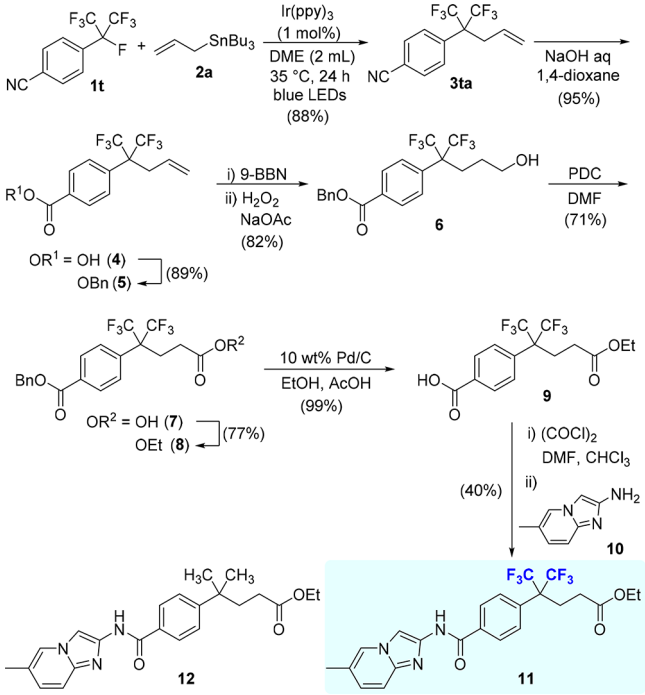


Figure 3. (A) Plausible mechanism for photoredox-catalyzed defluoroallylation of **1c** with **2a**. (B) Free energy profile for tin fluoride-accelerated defluoroallylation. (C) SOMO of radical anion **A**.

which is generated as a byproduct, complexes with F^- to give $Bu_3SnF_2^-$ and avoid the retroreaction step.[24] Then, **B** adds to **2a** to give radical **C**. Reduction of the Ir(IV) species by $^iPr_2EtN$ regenerates Ir(III) with radical cation $^iPr_2EtN^{\bullet+}$.[25] $^iPr_2EtN^{\bullet+}$ oxidizes **C**, which generates $^iPr_2EtN$ and cation **D**. $Bu_3SnF_2^-$ assists in the elimination of the stannyl cation, which leads to product **E** and Bu_3SnF. Light ON/OFF experiments suggested that the contribution of the radical chain mechanism to this reaction was small.[26] Density functional theory by means of the (U)ω97XD/6-31+G(d) method (Figure 3B) revealed the details of the key process from **A** to **C**, in which Bu_3SnF participated (Me groups on a Sn atom instead of Bu groups were adopted for DFT calculation).[27] Elimination of the F^- from radical anion **A** exergonically proceeds, and the

Scheme 1. Synthesis of Bis(trifluoromethyl)methylene Unit Containing Compound 11, an Analog Useful as a Pharmaceutical Agent[30]



activation energy for this step is 4.4 kcal/mol. The addition of **B** to allyl stannane **2g** occurs via **TS2** with a much higher activation barrier (19.6 kcal/mol) than the retroreaction from **INT1** to **A** (11.8 kcal/mol). Therefore, the retroprocess including a back electron transfer from **A** to the Ir(IV) species easily occurs in the absence of Me_3SnF. In the presence of Me_3SnF, however, F^- coordinates to Me_3SnF to generate $Me_3SnF_2^-$, and this complexation creates thermodynamical stabilization (ΔG = 13.3 kcal/mol) in the system (**INT3**). Thus, Bu_3SnF suppresses the retroreaction and allows the desired reaction to proceed effectively.[28] In the use of simple alkenes like König's[10] and Jui's[11] systems (Schemes S1 and S2), the addition of perfluoroalkyl radicals to alkenes is slow due to their larger steric hindrance than that of difluoromethyl radicals derived from CF_3 groups so the retroreaction preferentially occurs. On the other hand, the high reactivity of allylic stannanes accelerates the capture of perfluoroalkyl radicals, and Bu_3SnF traps F^- to disturb the retroreaction. Thus, the use of allylic stannanes is the most important key to accomplish the C−F bond activation of perfluoroalkyl groups. The SOMO of radical anion **A** is displayed in Figure 3C. Compound **1c** receives an electron from the excited Ir(III) that delocalizes in a π orbital on the benzene ring and also in the σ^* orbitals of two benzylic C−F bonds (C^1−F^1 and C^1−F^2), and these C−F bonds of **A** are lengthened by comparison with those of neutral **1c** (from 1.365 to 1.402 Å). Therefore, the separation of a benzylic F atom exclusively occurs to give benzylic radical **B**, which accomplishes the site-selective defluoroallylation.

In pharmaceutical compounds, the replacement of alkyl groups by perfluoroalkyl groups is an important issue because significant changes are often found in the biological properties. Therefore, we targeted compound **11**, which is the bis(trifluoromethyl) analogue of compound **12** with ASK1

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inhibitory action that is useful for the prophylaxis or treatment of diabetes and inflammatory diseases (Scheme 1).[29] Substrate **1t** was employed in the defluoroallylation system using **2a** under standard conditions to give bis(trifluoromethyl) compound **3ta** in 88% yield. Hydrolysis of the CN group followed by esterification of the carboxyl group of **4** afforded benzyl ester **5**. The vinyl group in **5** was transformed to a terminal hydroxyl moiety via hydroboration−oxidation, giving **6**. The subsequent oxidation of **6** with pyridinium dichromate (PDC) in DMF was followed by esterification to provide diester **8**. After deprotection of the benzyl ester moiety, the amidation of carboxylic acid **9** with amine **10** gave the targeted compound **11**.

In conclusion, a direct and site-selective C(sp^3)−F bond allylation in perfluoroalkylarenes with allylic stannanes was accomplished via the use of $Ir(ppy)_3$. This defluoroallylation proceeds exclusively at the benzylic position through perfluoroalkyl radicals generated by SET between excited $Ir(ppy)_3$ and perfluoroalkylarenes. The mild conditions promoted compatibility among various functional groups. DFT calculation studies showed that when Bu_3SnF is generated as a byproduct, it traps F^- and prevents the retroreaction from an unstable perfluoroalkyl-substituted carbon radical, which allows the reaction of the radical intermediate with allylic stannanes to proceed. The synthesis of a bis(trifluoromethyl)methylene unit containing compound **11** demonstrated the significance of this reaction to medicinal chemistry.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c03760.

Experimental details, characterization data, NMR spectra, and DFT calculation details (PDF)

Accession Codes

CCDC 2070966 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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(19) An electron transferred from an excited Ir catalyst to **1a** is localized on the arene ring. Therefore, the electron-withdrawing effect of the C_4F_9 group decreases the reduction potential of **1a** to accelerate the single electron transfer. The electron-withdrawing effect of a monoallylated-perfluoroalkyl group is lower than that of a perfluoroalkyl group, so defluoroallylated product **3aa** has a higher reduction potential than **1a**.

(20) The extensive screening of photoredox catalysts, solvents, reaction time, temperature, and equivalents of components was conducted and is presented in Supporting Information (Tables S1, S2, and S3).

(21) Scheme S3 in Supporting Information shows perfluoroalkylarenes **1** that were not available in this reaction system.

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(26) The results of light ON/OFF experiments are shown in Figure S2.

(27) The complete description of energy profiles for the defluoroallylation without or with Me_3SnF are shown in Figures S6 and S7.

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(30) Details of experimental procedures for each step are described in the Supporting Information.

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