

Cite this: *Chem. Sci.*, 2018, **9**, 7115 All publication charges for this article have been paid for by the Royal Society of ChemistryReceived 10th June 2018  
Accepted 20th July 2018DOI: 10.1039/c8sc02547a  
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## Metal-free alkene oxy- and amino-perfluoroalkylations *via* carbocation formation by using perfluoro acid anhydrides: unique reactivity between styrenes and perfluoro diacyl peroxides†

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We present a strategy for metal-free, alkene difunctionalization-type, oxy- and amino-perfluoroalkylations, using perfluoro acid anhydrides as practical and user-friendly perfluoroalkyl sources. This method provides efficient access to oxy-perfluoroalkylation products *via* carbocation formation due to the unique reactivity between styrenes and bis(perfluoroacyl) peroxides generated *in situ* from perfluoro acid anhydrides. This reaction is also applicable to metal-free intramolecular amino-perfluoroalkylation of styrenes bearing a pendant amino group. Synthetic utility of the oxy-trifluoromethylation products was confirmed by demonstrating derivatization *via* hydrolysis, elimination, and acid-catalyzed substitution with carbon nucleophiles. The mechanism of the carbocation formation was investigated experimentally and theoretically.

## Introduction

Introduction of perfluoroalkyl groups is an important strategy for modifying the properties of bioactive compounds, agrochemicals and functional materials.<sup>1</sup> Various methods are available for C-CF<sub>3</sub> bond formation to construct functionalized CF<sub>3</sub>-containing compounds, and alkene difunctionalization-type trifluoromethylation has recently attracted particular interest.<sup>2-10</sup> Styrene derivatives are often used as substrates in these reactions because of their unique reactivity and the utility of the products as CF<sub>3</sub>-containing synthetic building blocks.<sup>2-5</sup> For example, transition-metal-catalyzed intermolecular oxy-trifluoromethylation to form C-O bonds has been well studied (Scheme 1a).<sup>3</sup> As pioneering works, Szabó<sup>3a</sup> and we<sup>3b</sup> independently reported Cu-catalyzed intermolecular oxy-trifluoromethylation of styrenes with Togni reagent in 2012. In this reaction, the trifluoromethyl group is introduced into the  $\beta$ -position, and then 2-iodobenzoate group derived from the Togni reagent is introduced at the benzylic position *via* carbocation intermediate formation with the aid of copper-catalyst. In contrast to transition-metal-catalyzed reactions, metal-free oxy-trifluoromethylations generally proceed *via* the following steps: (1) formation of a CF<sub>3</sub> radical, (2) formation of an alkyl

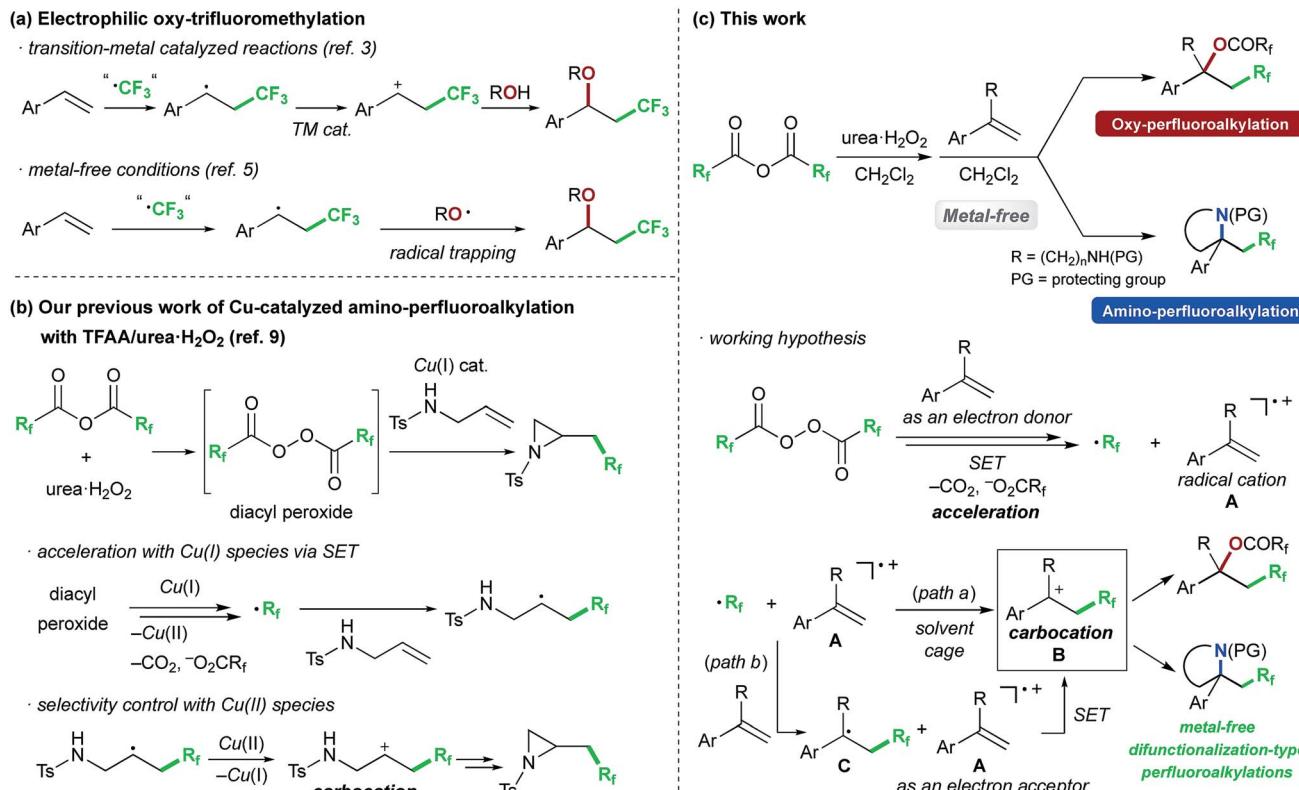
radical intermediate by reaction of the CF<sub>3</sub> radical and alkene, (3) trapping with an O-radical species.<sup>5</sup> In 1993, Uneyama reported an electrochemical reaction of butyl acrylate with trifluoroacetic acid (TFA) and O<sub>2</sub> as the trapping agent, affording CF<sub>3</sub>-containing alcohol products.<sup>5b</sup> In 2011, Xiao found that *S*-(trifluoromethyl)diphenylsulfonium salt could react with styrenes under aerobic conditions to afford ketone products.<sup>5c</sup> A similar transformation was also achieved by using CF<sub>3</sub>SO<sub>2</sub>Na in the presence of O<sub>2</sub>, obtaining a mixture of ketone and alcohol products.<sup>5e</sup> Lei developed the reaction with CF<sub>3</sub>SO<sub>2</sub>Na in the presence of O<sub>2</sub> with the aid of K<sub>2</sub>S<sub>2</sub>O<sub>8</sub> or the combination of NMP/PPH<sub>3</sub>, to obtain the ketone or alcohol product selectively.<sup>5f,h</sup> Fu reported oxazoline forming-trifluoromethylation of allylamide with CF<sub>3</sub>SO<sub>2</sub>Na by using oxidant.<sup>5g</sup> In 2012, Studer reported an efficient TEMPONa-promoted oxy-trifluoromethylation with Togni reagent,<sup>5d,j</sup> in which Togni reagent was decomposed *via* single electron transfer with TEMPONa as an electron donor, affording CF<sub>3</sub> and TEMPO radicals and eventually providing the CF<sub>3</sub>-containing TEMPO adduct by addition to the alkene. In 2015, Tan and Liu reported the metal-free oxy-trifluoromethylation using hydroxamic acids, affording products containing an aminoxy group.<sup>5i</sup> As regards metal-free reaction *via* a carbocation intermediate, Uneyama developed an electrochemical oxy-trifluoromethylation of butyl methacrylate with TFA and water as the oxygen nucleophile and solvent by careful tuning the current density to oxidize the radical intermediate, obtaining the alcohol product in up to 35% yield.<sup>5a</sup> Further, in 2016, Liu reported an amine-catalyzed intramolecular oxy-trifluoromethylation of alkenes bearing

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† Electronic supplementary information (ESI) available: General experimental procedures, experimental method, compound characterization, and NMR spectroscopic data. See DOI: 10.1039/c8sc02547a





**Scheme 1** (a) Proposed mechanisms of previous oxy-trifluoromethylations, (b) our previous work on Cu-catalyzed amino-perfluoroalkylation with TFAA/urea·H<sub>2</sub>O<sub>2</sub>, and (c) metal-free difunctionalization-type perfluoroalkylation of styrenes by using perfluoro acid anhydrides (this work).

a 1,3-diaryl diketone group with Togni reagent, affording dihydronaphthalene products.<sup>5,6</sup>

Recently, we have been interested in alkene perfluoroalkylation by using perfluoro acid anhydrides, which are convenient and practical perfluoroalkyl sources because of their low cost, ready availability and reasonable stability compared to conventional perfluoroalkylating reagents.<sup>9–12</sup> We found that perfluoro diacyl peroxides prepared *in situ* from perfluoro acid anhydrides and urea·H<sub>2</sub>O<sub>2</sub> showed excellent reactivity and selectivity in allylic perfluoroalkylation<sup>9a</sup> and in intramolecular amino-perfluoroalkylation<sup>9b</sup> of alkenes in the presence of Cu(I) salt as a catalyst. Our mechanistic studies of the amino-perfluoroalkylation indicated that it proceeds *via* (1) formation of a perfluoroalkyl radical ( $\cdot\text{R}_f$ ) and Cu(II) species from the peroxide and Cu(I) catalyst, (2) addition of the  $\cdot\text{R}_f$  radical to the double bond of the alkene, (3) oxidation of the resulting alkyl radical with Cu(II) species to afford a carbocation intermediate with recovery of the Cu(I) species, and (4) nucleophilic cyclization (Scheme 1b). In the absence of copper catalyst, the reaction of alkenes gave complex mixtures. Exceptionally, reaction of alkenes bearing an aromatic ring at an appropriate position selectively generated perfluoroalkyl group-containing carbocycles, because the aromatic ring acted as a scavenger of the alkyl radical. We were interested in the unique reactivity of styrenes and radical cation species in perfluoroalkylation with the perfluoro acid anhydride/urea·H<sub>2</sub>O<sub>2</sub> system (Scheme 1c), and postulated that the styrene substrate serves to control the

reactivity and selectivity in the formation of the carbocation intermediate without transition-metal-catalyst,<sup>9b</sup> *i.e.*, styrene serves as an electron donor to accelerate generation of the perfluoroalkyl radical *via* decomposition of the diacyl peroxide by SET. Then, addition of the perfluoroalkyl radical to the resulting radical cation A affords the carbocation B (path a). Another possibility is that the perfluoroalkyl radical reacts with another styrene molecule (having higher electron density compared to the radical cation A), and the resulting benzyl radical intermediate C is oxidized by the radical cation A as an electron acceptor to afford the same benzyl cation intermediate B (path b). In this work, we focused on this carbocation formation, as a key process in difunctionalization-type perfluoroalkylation, and aimed to develop metal-free oxy- and amino-perfluoroalkylations of styrene derivatives by using perfluoro acid anhydrides. We also carried out various derivatizations to confirm the synthetic potential of the products.

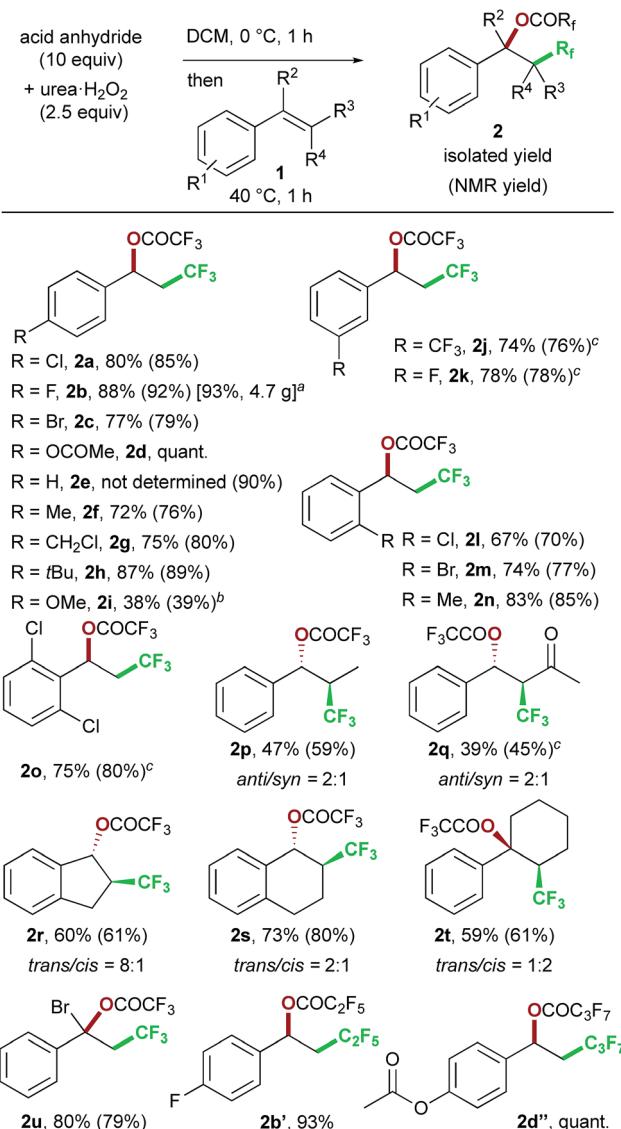
## Results and discussion

We chose commercially available 4-chlorostyrene **1a** as a model substrate to explore the reaction. To our delight, after *in situ* generation of bis(trifluoroacetyl)peroxide (BTFAP) from trifluoroacetic anhydride (TFAA) with urea·H<sub>2</sub>O<sub>2</sub> in DCM at 0 °C for 1 h, reaction with **1a** at 40 °C for 1 h afforded the desired oxy-trifluoromethylation product **2a**. Careful tuning of the ratio of the reagents and the reaction temperature improved the yield.<sup>13</sup>

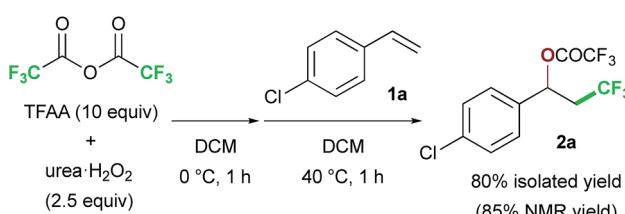


Finally, the reaction with TFAA (10 equiv.) and urea·H<sub>2</sub>O<sub>2</sub> (2.5 equiv.) provided the corresponding oxy-trifluoromethylated product **2a** in 80% isolated yield (85% NMR yield) (Scheme 2).<sup>14</sup> The scope of the optimized reaction conditions was then explored using a range of styrene-based substrates (Scheme 3). Various functional groups at the *para* position were tolerated and the corresponding oxy-trifluoromethylated products were formed efficiently (**2a–i**).<sup>15</sup> The usefulness of the reaction was demonstrated in a gram-scale experiment with 4-fluorostyrene **1b**, which was transformed into the desired compound **2b** in 93% yield (4.7 g). *meta*- and *ortho*-substituted styrene substrates performed well in the oxy-trifluoromethylation reaction (**2j–n**), although higher temperatures were needed for *meta*-substituted substrate because of slow conversion compared to *para*- and *ortho*-substituted styrenes. A disubstituted styrene **1o** afforded the target compound **2o** in good yield. The generality of the reaction was also assessed with several internal alkenes, which afforded the corresponding difunctionalized products in moderate to good yields (**2p–s**). Quaternary carbon centres could be constructed successfully, and more complex compounds **2t** and **2u** were isolated in 59% and 80% yield, respectively. Finally, this metal-free procedure was applied to the oxy-perfluoroalkylation of styrene-based substrates with other perfluoro acid anhydrides, and the desired products **2b'** and **2d''** were isolated in excellent yields.

To further explore the ability of the styryl functionality to provide the carbocation intermediate, we next investigated whether pyrrolidines could be obtained by intramolecular amino-perfluoroalkylation of styrene derivatives bearing a pendant amino group *via* nucleophilic cyclization, based on our previous work.<sup>9b,16</sup> In contrast to metal-free oxy-perfluoroalkylation, metal-free amino-perfluoroalkylation has rarely been reported,<sup>5a,8</sup> probably because of the lack of appropriate N-radical trapping agents. Thus, we examined the reaction of styryl group-containing aminoalkene **3a** with *in situ*-generated BTFAP under the optimal conditions for the oxy-trifluoromethylation (Scheme 4).<sup>17</sup> As we had hoped, the amino-trifluoromethylation proceeded well to afford the corresponding CF<sub>3</sub>-containing pyrrolidine **4a** in 76% yield. This styrene-driven amino-trifluoromethylation was also applicable to internal alkene **3b**, which provided disubstituted pyrrolidine **4b** as a *syn*-diastereomer.<sup>18</sup> In this reaction, the oxy-trifluoromethylation product was obtained as a by-product in 40% yield, and it was not converted to the amino-trifluoromethylation product **4b** even upon prolonged



Scheme 3 Substrate scope of the metal-free oxy-perfluoroalkylation reaction. <sup>a</sup>Gram-scale synthesis using 2.0 g (16 mmol) of **1b**. <sup>b</sup>Run at 0 °C for 10 min with Cs<sub>2</sub>CO<sub>3</sub> (5 equiv.) as an additive. <sup>c</sup>Run at 60 °C in 1,2-dichloroethane.

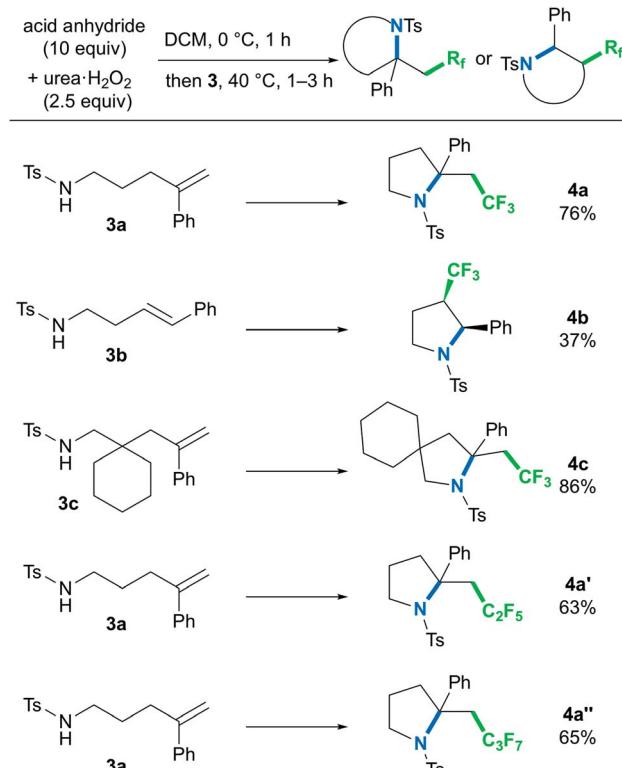


Scheme 2 Metal-free oxy-trifluoromethylation of styrene **1a** with TFAA/urea·H<sub>2</sub>O<sub>2</sub> under optimized conditions.

reaction. This observation suggested that this amino-trifluoromethylation does not proceed *via* nucleophilic substitution of the oxy-trifluoromethylation product under the conditions. Alkenyl amine **3c** featuring a 6-membered ring as a tethering group in the carbon chain was tolerated, and the spirocyclic product **4c** was formed in high yield. The use of acid anhydrides bearing longer perfluoroalkyl chains furnished C<sub>2</sub>F<sub>5</sub>- and C<sub>3</sub>F<sub>7</sub>-substituted pyrrolidines **4a'** and **4a''** in good yields.

To further expand the chemical space of the perfluoroalkylated compounds, we focused on the reactivity of the perfluoroacetoxy group, as a labile functional group, in the oxy-trifluoromethylation products (Scheme 5). First, we examined the reaction of **2b**, as a representative substrate, with bases. When DBU was reacted with **2b** in DME, the alcohol **5b** was

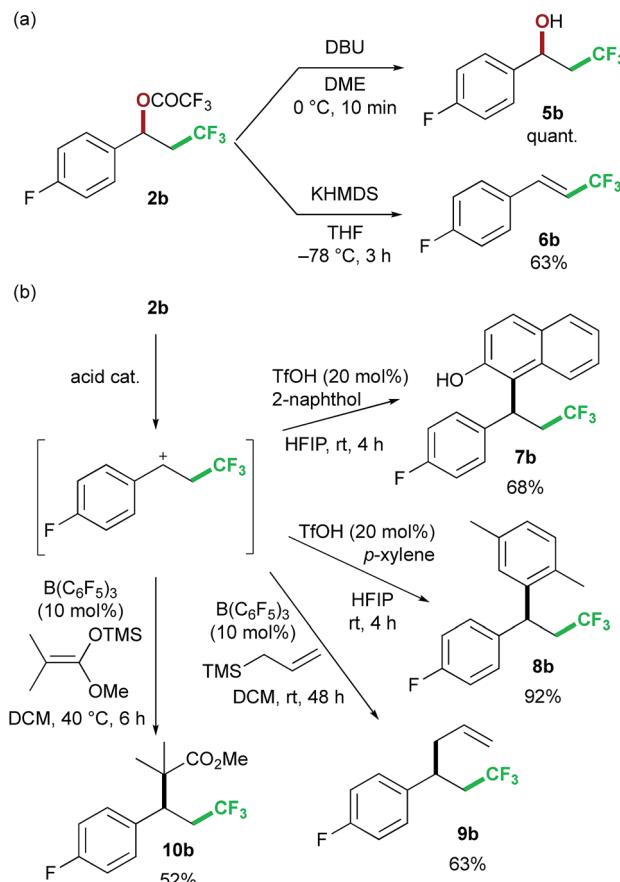




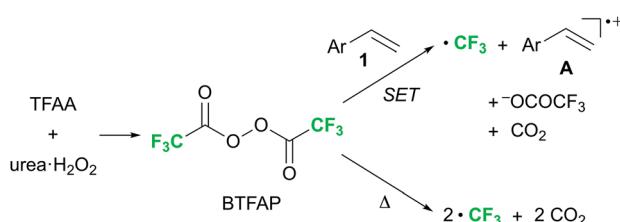
Scheme 4 Metal-free amino-perfluoroalkylation reaction of alkenes.

obtained in quantitative yield. On the other hand, KHMDS as the base was found to give the vinyl product **6b** *via* elimination reaction. Next, we attempted to construct attractive carbon skeletons and examined *S<sub>N</sub>1*-type nucleophilic substitution reactions with various carbon nucleophiles in the presence of acid catalysts. The trifluoroacetoxy group was readily dissociated with triflic acid, and trapping of the resulting carbocation with arenes resulted in C–C bond formation to give **7b** and **8b**.<sup>19</sup> In the presence of a catalytic amount of  $B(C_6F_5)_3$  to promote formation of the carbocation, allylation with allylsilane proceeded to afford **9b** in good yield.<sup>20</sup> This approach was also applicable to the reaction with a ketene silyl acetal as a nucleophilic partner, providing **10b**. The presented procedures for the substitution reactions of the benzylic trifluoroacetoxy group provide rapid access to various perfluoroalkyl-group-containing molecules, which should be useful building blocks in organic synthesis.

Finally, we focused on the reaction mechanism of the perfluoroalkylation (Scheme 1c). The reaction starts with the generation of an electrophilic  $CF_3$  radical *via* decomposition of the diacyl peroxide, *i.e.* BTFAP which is formed *in situ* from TFAA and urea·H<sub>2</sub>O<sub>2</sub>. Decomposition of BTFAP would be triggered by SET with styrene as the electron donor and/or by heating (Scheme 6). To trace the decomposition, TEMPO instead of styrene was reacted with *in situ*-generated BTFAP (Scheme 7a). TEMPO- $CF_3$  adduct **11** was obtained in only 2% yield, which suggested that thermal decomposition would be very slow under these reaction conditions.<sup>21</sup> Furthermore, the decomposition could not be observed by <sup>19</sup>F NMR monitoring of

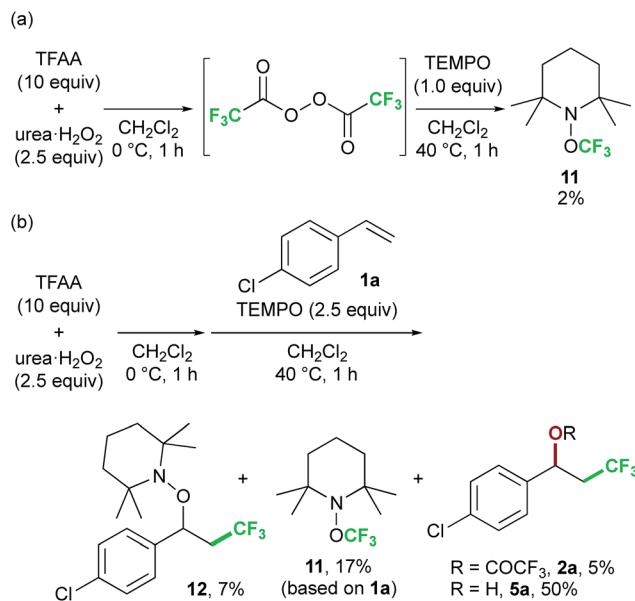
Scheme 5 Examples of derivatization of benzyl trifluoroacetate **2b**: (a) hydrolysis and elimination reaction (b) intermolecular C–C bond formation reactions.

the peroxide in  $CD_2Cl_2$  at 40 °C without any substrate.<sup>13</sup> Yoshida similarly found that aromatic compounds such as benzene accelerate the decomposition of BTFAP by SET.<sup>11b</sup> The HOMO level of 4-chlorostyrene **1a** (−6.41 eV), used as the model substrate in this work, is higher than that of benzene (−7.09 eV).<sup>13</sup> Accordingly, decomposition of BTFAP was concluded to be induced by SET with styrene under the present conditions at 40 °C, affording  $CF_3$  radical and radical cation **A**. Radical trapping with TEMPO under the optimized conditions afforded the  $CF_3$ -containing TEMPO-benzyl adduct **12**, generated *via* the benzyl radical intermediate **C**, in 7% yield (Scheme 7b). In addition to **12**, TEMPO- $CF_3$  **11** was formed, together with a mixture of oxy-trifluoromethylation products **2a** and its



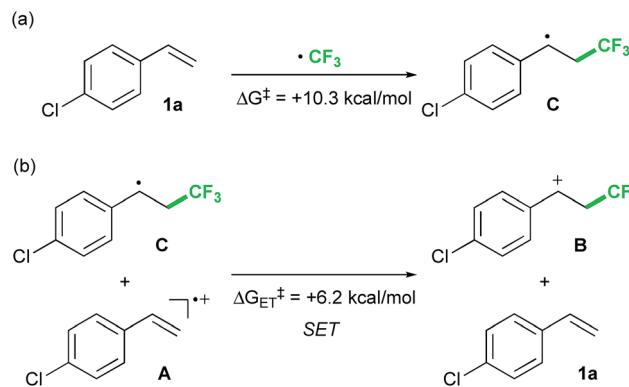
Scheme 6 Possible pathway of decomposition of BTFAP.





Scheme 7 TEMPO trapping test: (a) reaction of TEMPO with BTFAP and (b) oxy-trifluoromethylation in the presence of TEMPO.

hydrolysis product **5a**. Furthermore, a known radical probe alkene **13**, 1-phenyl-1-(*trans*-2-phenylcyclopropyl)ethane,<sup>8b</sup> was subjected to the reaction (Scheme 8). The corresponding ring-opening product **14** was formed *via* the radical intermediate as the major product, along with a complex mixture of other products.<sup>13</sup> These results proved that the  $\text{CF}_3$  radical reacts with styrene **1a** (path b, Scheme 1c), although both path a and path b may be operated. Indeed, DFT calculation indicated that the activation energy of the reaction of the  $\text{CF}_3$  radical with **1a** is low ( $\Delta G^\ddagger = +10.3 \text{ kcal mol}^{-1}$ , Scheme 9a). Next, we considered the oxidation step of the benzyl radical to the carbocation **B**. Comparison of the calculated LUMO levels of potential oxidants, BTFAP and radical cation **A**, indicated that radical cation **A** ( $-6.26 \text{ eV}$ ) has a lower LUMO level than that of BTFAP ( $-2.35 \text{ eV}$ ). In addition, the LUMO level of **A** was closer to that of  $\text{Cu}(\text{II})(\text{O}_2\text{CCF}_3)_2$  ( $-5.09 \text{ eV}$ ) which was reported to oxidize the radical intermediate in the amino-perfluoroalkylation reaction (Scheme 1b).<sup>9b</sup> Thus, radical cation **A** was considered to act as the oxidant, affording carbocation **B**, which leads to the desired products. The DFT calculated activation energy of oxidation of benzyl radical **C** with **A** was  $\Delta G_{\text{ET}}^\ddagger = +6.2 \text{ kcal mol}^{-1}$  (Scheme 9b), which is much lower than that of the addition of  $\text{CF}_3$  radical to **1a** suggesting rapid conversion of the highly reactive benzyl radical **C** to the metastable benzyl cation intermediate **B**. These



Scheme 9 Activation energies of (a) addition of  $\text{CF}_3$  radical to **1a** and (b) SET between benzyl radical **C** and radical cation **A**.

mechanistic studies supported our original hypothesis shown in Scheme 1c, in which substrate styrene itself acts as SET donor to trigger the perfluoroalkyl radical formation from the diacyl peroxide. The resulting perfluoroalkyl radical could react with styrene affording benzyl radical intermediate **C**, which is rapidly oxidized to the benzyl cation **B** by the radical cation **A**. The generated benzyl cation intermediate **B** is trapped by the perfluoro carboxylate anion or amine yielding the desired oxy- and amino-perfluoroalkylation products, **2** and **4**.

## Conclusions

We have developed a mild and efficient method for the metal-free oxy- and amino-perfluoroalkylation of styrenes *via* carbocation intermediates, using perfluoro acid anhydrides as inexpensive and practical perfluoroalkyl sources. The oxy-trifluoromethylation products were derivatized to a variety of  $\text{CF}_3$ -containing unique molecules. We believe this method will prove useful in medicinal and agro-chemistry discovery programs. In addition, the unique reactivity between styrene and perfluoro diacyl peroxide may provide clues to design new reactions and catalysts in the future.

## Conflicts of interest

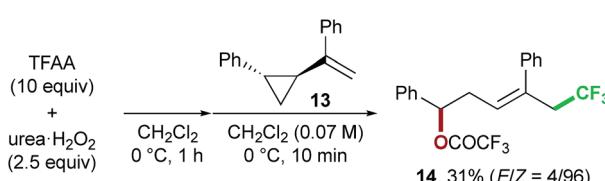
There are no conflicts to declare.

## Acknowledgements

This work was supported by JSPS KAKENHI (No. 15K17860) and Project Funding from RIKEN. E. V. is grateful for a JSPS Post-doctoral Fellowship (15F15340). The computational study was conducted on the HOKUSAI-GW (RIKEN).

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Scheme 8 Radical probe test using **13**.



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