Chemical Science



EDGE ARTICLE

View Article Online
View Journal | View Issue



Cite this: Chem. Sci., 2018, 9, 7115

All publication charges for this article have been paid for by the Royal Society of Chemistry Metal-free alkene oxy- and aminoperfluoroalkylations 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.

Received 10th June 2018 Accepted 20th July 2018

DOI: 10.1039/c8sc02547a

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Introduction

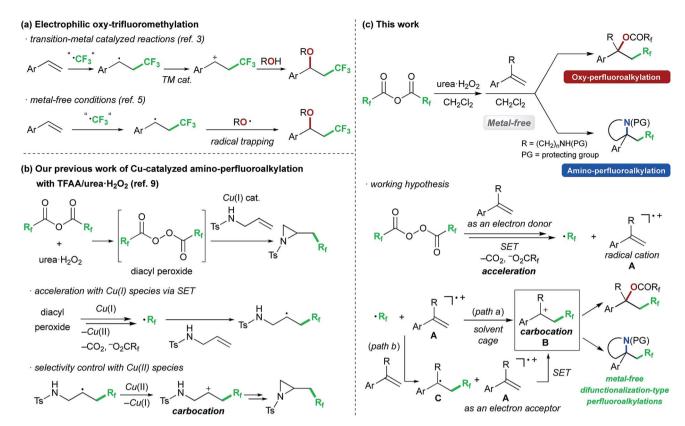
Introduction of perfluoroalkyl groups is an important strategy for modifying the properties of bioactive compounds, agrochemicals and functional materials.1 Various methods are available for C-CF3 bond formation to construct functionalized CF₃-containing compounds, and alkene difunctionalizationtype trifluoromethylation has recently attracted particular interest.2-10 Styrene derivatives are often used as substrates in these reactions because of their unique reactivity and the utility of the products as CF₃-containing synthetic building blocks.²⁻⁵ For example, transition-metal-catalyzed intermolecular oxytrifluoromethylation to form C-O bonds has been well studied (Scheme 1a).3 As pioneering works, Szabó3a and we3b indepen-Cu-catalyzed intermolecular reported trifluoromethylation of styrenes with Togni reagent in 2012. In this reaction, the trifluoromethyl group is introduced into the β-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 CF₃ radical, (2) formation of an alkyl

radical intermediate by reaction of the CF₃ radical and alkene, (3) trapping with an O-radical species.⁵ In 1993, Uneyama reported an electrochemical reaction of butyl acrylate with trifluoroacetic acid (TFA) and O₂ as the trapping agent, affording CF₃-containing alcohol products.^{5b} In 2011, Xiao found that S-(trifluoromethyl)diphenylsulfonium salt could react with styrenes under aerobic conditions to afford ketone products.5c A similar transformation was also achieved by using CF₃SO₂Na in the presence of O₂, obtaining a mixture of ketone and alcohol products.5e Lei developed the reaction with CF3SO2Na in the presence of O₂ with the aid of K₂S₂O₈ or the combination of NMP/PPh3, to obtain the ketone or alcohol product selectively.5f,h Fu reported oxazoline forming-trifluoromethylation of allylamide with CF₃SO₂Na by using oxidant.^{5g} In 2012, Studer reported efficient TEMPONa-promoted trifluoromethylation with Togni reagent,5dj in which Togni reagent was decomposed via single electron transfer with TEMPONa as an electron donor, affording CF3 and TEMPO radicals and eventually providing the CF3-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 aminoxyl group.51 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.5a 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·H₂O₂, 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 dihydrofuran products.5k,6

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.9-12 We found that perfluoro diacyl peroxides prepared in situ from perfluoro acid anhydrides and urea · H2O2 showed excellent reactivity and selectivity in allylic perfluoroalkylation9a and in intramolecular amino-perfluoroalkylation^{9b} of alkenes in the presence of Cu(1) salt as a catalyst. Our mechanistic studies of the aminoperfluoroalkylation indicated that it proceeds via (1) formation of a perfluoroalkyl radical ($\cdot R_f$) and Cu(II) species from the peroxide and Cu(1) catalyst, (2) addition of the Rf 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(1) 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·H₂O₂ 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; 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 · H2O2 in DCM at 0 °C for 1 h, reaction with 1a at 40 °C for 1 h afforded the desired oxytrifluoromethylation product 2a. Careful tuning of the ratio of the reagents and the reaction temperature improved the yield.¹³

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Finally, the reaction with TFAA (10 equiv.) and urea H₂O₂ (2.5 equiv.) provided the corresponding oxy-trifluoromethylated product 2a in 80% isolated yield (85% NMR yield) (Scheme 2).14 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).15 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 10 afforded the target compound 20 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.9b,16 In contrast to metal-free oxyperfluoroalkylation, metal-free amino-perfluoroalkylation has rarely been reported, 50,8 probably because of the lack of appropriate N-radical trapping agents. Thus, we examined the reaction of styryl group-containing aminoalkene 3a with in situgenerated BTFAP under the optimal conditions for the oxytrifluoromethylation (Scheme 4).17 As we had hoped, the amino-trifluoromethylation proceeded well to afford the corresponding CF₃-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.18 In this reaction, the oxytrifluoromethylation product was obtained as a by-product in 40% yield, and it was not converted to the aminotrifluoromethylation product 4b even upon prolonged

Scheme 2 Metal-free oxy-trifluoromethylation of styrene 1a with TFAA/urea \cdot H_2O_2 under optimized conditions.

Scheme 3 Substrate scope of the metal-free oxy-perfluoroalkylation reaction. $^a\text{Gram}\text{-scale}$ synthesis using 2.0 g (16 mmol) of 1b. ^bRun at 0 °C for 10 min with Cs_2CO_3 (5 equiv.) as an additive. ^cRun at 60 °C in 1,2-dichloroethane.

reaction. This observation suggested that this aminotrifluoromethylation 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_2F_5 - and C_3F_7 -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 oxytrifluoromethylation 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

acid anhydride (10 equiv) + urea·
$$H_2O_2$$
 (2.5 equiv) $\frac{DCM, 0 °C, 1 h}{then 3, 40 °C, 1-3 h}$ $\frac{Ph}{R_f}$ or $\frac{Ph}{R_f}$ $\frac{Ph}{R_$

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_N1-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.19 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.20 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 CF₃ radical *via* decomposition of the diacyl peroxide, *i.e.* BTFAP which is formed *in situ* from TFAA and urea·H₂O₂. 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-CF₃ adduct 11 was obtained in only 2% yield, which suggested that thermal decomposition would be very slow under these reaction conditions.²¹ Furthermore, the decomposition could not be observed by ¹⁹F 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 CD₂Cl₂ at 40 °C without any substrate.¹³ Yoshida similarly found that aromatic compounds such as benzene accelerate the decomposition of BTFAP by SET.^{11b} 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).¹³ Accordingly, decomposition of BTFAP was concluded to be induced by SET with styrene under the present conditions at 40 °C, affording CF₃ radical and radical cation **A**. Radical trapping with TEMPO under the optimized conditions afforded the CF₃-containing TEMPO-benzyl adduct **12**, generated *via* the benzyl radical intermediate C, in 7% yield (Scheme 7b). In addition to **12**, TEMPO-CF₃ **11** was formed, together with a mixture of oxy-trifluoromethylation products **2a** and its

TFAA

$$+$$
 $CF_3 + Ar$
 A
 $+$
 $CF_3 + Ar$
 A
 $+$
 $CF_3 + Ar$
 $+$
 CO_2
 $CF_3 + CO_2$
 $+$
 $CF_3 + CO_2$

Scheme 6 Possible pathway of decomposition of BTFAP.

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(a) TFAA **TEMPO** (10 equiv) (1.0 equiv) CH₂Cl₂ CH₂Cl₂ urea·H₂O₂ (2.5 equiv) 0 °C, 1 h OCF₂ 40 °C, 1 h 11 2% (b) **TFAA** (10 equiv) TEMPO (2.5 equiv) CH₂Cl₂ CH₂Cl₂ urea·H₂O₂ 0 °C, 1 h 40 °C, 1 h (2.5 equiv) OR

11, 17%

(based on 1a)

R = COCF₃, 2a, 5%

R = H, **5a**, 50%

hydrolysis product 5a. Furthermore, a known radical probe alkene 13, 1-phenyl-1-(trans-2-phenylcyclopropyl)ethane, 8b was subjected to the reaction (Scheme 8). The corresponding ringopening product 14 was formed via the radical intermediate as the major product, along with a complex mixture of other products.13 These results proved that the CF3 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 CF₃ radical with 1a is low $(\Delta G^{\ddagger} = +10.3 \text{ kcal mol}^{-1}, \text{ Scheme 9a})$. 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 eV) has a lower LUMO level than that of BTFAP (-2.35 eV). In addition, the LUMO level of A was closer to that of $Cu(\pi)(O_2CCF_3)_2$ (-5.09 eV) which was reported to oxidize the radical intermediate in the amino-perfluoroalkylation reaction (Scheme 1b).96 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 $\Delta G_{\rm ET}^{\ddagger} = +6.2 \text{ kcal mol}^{-1}$ (Scheme 9b), which is much lower than that of the addition of CF₃ radical to 1a suggesting rapid conversion of the highly reactive benzyl radical C to the metastable benzyl cation intermediate B. These

TFAA (10 equiv) + Ph.,... Ph Ph Ph CF₃ + Urea·H₂O₂ (2.5 equiv) 0 °C, 1 h 0 °C, 10 min Ph CF₃ + 14, 31% (
$$E/Z = 4/96$$
)

Scheme 8 Radical probe test using 13.

(a)
$$\begin{array}{c} \cdot \text{CF}_3 \\ \hline \\ \text{CI} \end{array}$$

Scheme 9 Activation energies of (a) addition of 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 metalfree oxy- and amino-perfluoroalkylation of styrenes *via* carbocation intermediates, using perfluoro acid anhydrides as inexpensive and practical perfluoroalkyl sources. The oxytrifluoromethylation products were derivatized to a variety of CF₃-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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- 13 See ESI† for details.

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14 Isolated yields were slightly lower than NMR yields because of hydrolysis of 2 during isolation by means of silica-gel column chromatography.

- 15 Methoxy group-containing substrate showed very high reactivity, and only the moderate yield of the desired product was obtained due to undesired side reactions, even if the reaction was carried out at 0 °C.
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