Oxidation of difluorocarbene and subsequent trifluoromethoxylation

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As a versatile intermediate, difluorocarbene is an electron-deficient transient species, meaning that its oxidation would be challenging. Herein we show that the oxidation of difluorocarbene could occur smoothly to generate carbonyl fluoride. The oxidation process is confirmed by successful trifluoromethoxylation, ¹⁸O-trifluoromethoxylation, the observation of AgOCF₃ species, and DFT calculations.
Due to the unique properties of fluorine element such as strong electronegativity and small atomic radius, the incorporation of fluorine atom(s) into organic molecules could usually lead to profound changes of the latter’s physical, chemical, and biological properties. Therefore, significant efforts have been directed towards the development of efficient methods for introducing fluorine or fluorinated moieties into organic compounds. Difluorocarbene (CF₂) has served as a versatile intermediate and the transformations of difluorocarbene has proved to be quite efficient for fluorine incorporation. Typical difluorocarbene conversions, including insertions into X-H bonds ([X = O, N, Se, etc.]) and [2 + 1] cycloadditions with multi-bonds, and coupling with other carbene, can conveniently construct various fluorinated functionalities, such as difluoromethyl, gem-difluorocyclopropyl and gem-difluoroalkenyl groups. However, these typical reactions are limited to the incorporation of a CF₂ moiety. We have previously found that difluorocarbene is so reactive that it can be readily trapped by a suitable sulfur, selenium, or nitrogen source to generate thiocarbonyl, selenocarbonyl, or carbonyl derivatives.

Herein we describe the oxidation of difluorocarbene by using diphenyl sulfoxide (Ph₃S=O) as the oxidant to provide carbonyl fluoride, a process which is confirmed by successful trifluoromethylation and O-trifluoromethylation reactions, the observation of AgOCF₃ species, and DFT calculations. A late-stage trifluoromethylation for the synthesis of Trioxsalen derivative is shown to further demonstrate the synthetic utility of this trifluoromethylation protocol.

Results
Optimization of the trifluoromethylation conditions. Ph₃P⁺CF₃CO₂⁻, developed by us recently, and AgF were used as a difluorocarbene reagent and the fluorine source, respectively, in our efforts to ascertain the oxidation process via the trifluoromethylation of benzyl bromide 1-1 (Table 1). AgF was used to convert CF₂=O into AgOCF₃, which may be experimentally observed to support the oxidation process. The oxidants were initially screened, but no desired trifluoromethylation product was detected in most cases (Table 1, entries 1–5). To our delight, the use of DMSO (dimethyl sulfoxide) as the oxidant afforded the expected product in 9% yield (Table 1, entry 6), suggesting that sulfoxides may be a suitable class of oxidants. We then examined other sulfoxides (Table 1, entries 7–8) and diphenyl sulfoxide was found to be a superior choice (Table 1, entry 8). Other fluorine sources, including inorganic (Table 1, entries 9–11) and organic (Table 1, entry 12, TBAF=tetra-n-butylammonium fluoride) fluorine salts, were examined, but they were all ineffective. This indicates that the Ag ion may play an important role in the reaction. A brief survey of reaction solvents (Table 1, entries 13–17) showed that THF (tetrahydrofuran) or DCM (dichloromethane) was the suitable solvent for this conversion (Table 1, entries 15 and 16). The use of 2,2'-bipyridine or a crown ether as a ligand (Table 1, entries 18 and 19) significantly increased the product yield. A 67% yield was obtained if both bipyridine and the crown ether were present (Table 1, entry 20). The concentration affected the reaction slightly, and the yield increased with increasing concentration (Table 1, entry 21 vs entry 20). At this concentration, the yield decreased if either the crown ether or 2,2'-bipyridine was not used (Table 1, entries 22–23).

**Table 1 Optimization of trifluoromethylation conditions.**

| Entry | [O] | [F⁻] | 1:2:3:4 | Solvent | Yield (%) |
|-------|-----|-------|---------|---------|-----------|
| 1     |     |       |         |         |           |
| 2     | a   | 1:2:2:2| CH₃CN  | ND      |           |
| 2     | b   | 1:2:2:2| CH₃CN  | ND      |           |
| 3     | c   | 1:2:2:2| CH₃CN  | ND      |           |
| 4     | d   | 1:2:2:2| CH₃CN  | ND      |           |
| 5     | e   | 1:2:2:2| CH₃CN  | ND      |           |
| 6     | f   | 1:2:2:2| CH₂CN  | 9       |           |
| 7     | g   | 1:2:2:2| CH₂CN  | 9       |           |
| 8     | h   | 1:2:2:2| CH₂CN  | 24      |           |
| 9     | i   | 1:2:2:2| CH₂CN  | ND      |           |
| 10    | j   | 1:2:2:2| CH₂CN  | ND      |           |
| 11    | k   | 1:2:2:2| CH₂CN  | ND      |           |
| 12    | l   | 1:2:2:2| CH₂CN  | ND      |           |
| 13    | m   | 1:2:2:2| DMF    | 15      |           |
| 14    | n   | 1:2:2:2| DMSO   | ND      |           |
| 15    | o   | 1:2:2:2| THF    | 33      |           |
| 16    | p   | 1:2:2:2| DCM    | 32      |           |
| 17    | q   | 1:2:2:2| NMP    | 14      |           |
| 18    | r   | 1:2:2:2| THF    | 55      |           |
| 19    | s   | 1:2:2:2| THF    | 52      |           |
| 20    | t   | 1:2:2:2| THF    | 67      |           |
| 21    | u   | 1:2:2:2| THF    | 74      |           |
| 22    | v   | 1:2:2:2| THF    | 66      |           |
| 23    | w   | 1:2:2:2| THF    | 51      |           |
Mechanistic investigations. Further experimental evidence was collected to support the difluorocarbene oxidation process. The use of other difluorocarbene reagents such as FSO₂CF₂CO₂TMS²³ and TMSCF₂Br⁸ could also give the desired trifluoromethoxylation product, albeit in a low yield, suggesting that difluorocarbene is a key intermediate (Fig. 2a). CF₂=O could not be detected in the reaction mixtures, because it is a highly electrophilic species and would be rapidly attacked by AgF to provide AgOCF₃. Even stirring the mixture of Ph₃P⁺CF₂CO₂⁻ and Ph₂S=O alone could not lead to the observation of CF₂=O, because CF₂=O would easily react with the nucleophile, Ph₃P generated from Ph₃P−AgF to provide AgOCF₃. The AgOCF₃ complex (Fig. 2d). Without the presence of a substrate, a stepwise reaction was performed to confirm the generation of the AgOCF₃ complex (Fig. 2d). However, almost no fluorination byproduct was observed under the optimal conditions (Table 1, entry 21), which suggests that AgOCF₃ was too reactive and decomposed easily.

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**Fig. 2** Mechanistic investigation. a The use of other difluorocarbene reagents for trifluoromethoxylation. b The identification of the oxygen source by ¹⁸O-labeling. c The identification of the oxygen source by isolating Ph₂S. d The confirmation of the AgOCF₃ complex. ² The optimal conditions are shown as Table 1, entry 21: substrate 1 (0.2 mmol), Ph₃P⁺CF₂CO₂⁻ (2.5 equiv), Ph₂S=O (2.5 equiv), AgF (2 equiv), 2,2’-bipyridine (1.5 equiv), and 2,3,11,12-dibenzo-18-crown-6 (0.5 equiv) in THF (1.5 mL) at 60 °C for 0.5 h; ³ Yields were determined by ¹⁹F NMR spectroscopy. ⁴ The ¹⁸O content was determined by EI-MS. ⁵ Isolated yield calculated based on substrate 1-1. ⁶ Isolated yield based on Ph₂S=O consumed.

DFT calculations at the M062X/6-31++G(d,p)/LANL2DZ level provided insights into the mechanism of the oxidation of difluorocarbene and the subsequent trifluoromethoxylation. We have previously demonstrated that Ph₃P⁺CF₂CO₂⁻ is an efficient difluorocarbene precursor, and has proposed that difluorocarbene is generated via a decarboxylation process, i.e., Ph₃P⁺CF₂CO₂⁻ → Ph₃P⁺CF₂⁻ → Ph₃P⁻CF₂⁻ → CF₂O, as shown by the increasing S–O bond length from TS-1 to TS-2. The formation of this bond weakens the S–O bond in Ph₂S=O, as shown by the increasing S–O bond length from TS-1 to TS-2. Back donation of the carbon lone pair strengthens the O–CF₂ bond and further weakens the S–O bond (Fig. 3, TS-2). Complete cleavage of the S–O bond releases Ph₂S and carbonyl fluoride (CF₂=O), a process which is thermodynamically favored. CF₂=O is electrophilic and is therefore trapped by AgF to generate AgOCF₃, which can readily convert the substrates to the final products. The Ag ion can activate the substrates by precipitating the AgBr salt. Identification of transition state TS-2 enabled us to calculate the overall activation energy, i.e., 17.60 kcal mol⁻¹; this value is low and in agreement with the rapid process.

The introduction of CF₃O installation. The above results revealed that difluorocarbene could indeed be oxidized to give carbonyl fluoride. The oxidation of difluorocarbene and the subsequent trifluoromethoxylation provides an efficient protocol for CF₃O incorporation. CF₃O incorporation has received increasing attention because the CF₃O group is a common structural motif in pharmaceuticals²⁵,²⁶, agrochemicals²⁷,²⁸, and functional materials²⁹,³⁰. A number of effective trifluoromethoxylation methods have been developed, including nucleophilic₃¹–₃₇.
radicals\textsuperscript{38–40}, and transition-metal-promoted\textsuperscript{41–44} reactions. As the use of a CF\textsubscript{3}O-containing reagent is required, these approaches cannot be directly applied to \textsuperscript{18}O-labeling trifluoromethylation. Furthermore, the CF\textsubscript{3}O-containing reagents used are usually volatile, expensive, or difficult to prepare. In contrast, in the above protocol, CF\textsubscript{3}O moieties were formed from a reagent system consisting of Ph\textsubscript{2}p\textsuperscript{+}CF\textsubscript{3}CO\textsuperscript{2−}, which could be easily prepared and easy-to-handle, an oxygen source and fluoride anion. Apparently, this reaction provides a strategy for \textsuperscript{18}O-labeling trifluoromethylation, which may be achieved by replacing the oxygen source with \textsuperscript{18}O-source. \textsuperscript{18}O-trifluoromethylation may show great value as \textsuperscript{18}O-labeling has found widespread application in various research areas such as proteomics\textsuperscript{45–47} and synthetic chemistry\textsuperscript{48–50}.

The substrate scope of trifluoromethylation. Since difluorocarbene could be oxidized and the subsequent trifluoromethylation proceeded smoothly (Table 1, entry 21), we then investigated the substrate scope of trifluoromethylation. Figure 4 shows that electron-deficient, neutral, and -rich benzyl bromides were all converted to the desired products in moderate to good yields (5–1 ~ 5–17). Various functional groups were tolerated, e.g., halide, ketone, ester, alkene, cyano, nitro, ether, and various heterocycles. Heterocycles usually have interesting physicochemical properties, and therefore the easy access to CF\textsubscript{3}O-containing heterocycles could be useful in the life sciences (5–15 ~ 5–17). Transformation of secondary benzyl bromides gave moderate yields (5–18 ~ 5–22). The diphenyl substituted product (5–22) was unstable, and a heterolytic cleavage of the C–OCF\textsubscript{3} bond readily occurred to form a diphenyl-stabilized methyl cation, hydrolysis of which led to an alcohol by product (Ph\textsubscript{2}CH–OH) in 35% isolated yield. In addition to benzyl bromides, allyl bromides were also converted under these conditions (5–23 ~ 5–28). The reactivity of alkyl bromide (5–29) was much lower than that of benzyl bromides. Alkyl iodides (5–30 ~ 5–33) underwent the desired reaction smoothly to give the expected products in moderate yields. A method for achieving direct access to a flavone derivative was developed (5–34) and a moderate yield was obtained for a large-scale reaction (5–34), demonstrating the synthetic utility of this trifluoromethylation protocol.

\textbf{18}O-Trifluoromethylation. \textsuperscript{18}O-Labeling trifluoromethylation is challenging, because all reported trifluoromethylation methods have to use a CF\textsubscript{3}O-containing reagent and the corresponding CF\textsubscript{3}\textsuperscript{18}O-reagents are difficult to prepare. Recently, Tang used an \textsuperscript{18}O-labeled reagent, ArSO\textsubscript{2}–18OCF\textsubscript{3}, to explore and elucidate the mechanism of the trifluoromethylation reaction; only a 33\% \textsuperscript{18}O content was obtained in the desired product\textsuperscript{37}. They proposed that the low \textsuperscript{18}O-content was because of the \textsuperscript{16}O–18O exchange in the SO\textsubscript{2}–18OCF\textsubscript{3} moiety from the reagent. We employed \textsuperscript{18}O-labeled diphenyl sulfoxide (Ph\textsubscript{2}S–18O, \textsuperscript{18}O content: 89\%) as the oxygen source in this difluorocarbene-oxidation-based trifluoromethylation reaction. Since the reagent, Ph\textsubscript{2}S–18O, did not contain any \textsuperscript{16}O atom, no \textsuperscript{16}O–18O exchange would occur and therefore the expected products were obtained with high \textsuperscript{18}O contents (Fig. 6).

\textbf{Discussion}

In summary, we have shown that difluorocarbene could be oxidized to afford carbonyl fluoride. This process was confirmed by the successful trifluoromethylation, \textsuperscript{18}O-trifluoromethylation, the observation of AgOCF\textsubscript{3} species, and DFT calculations. It is worth noting that the \textsuperscript{18}O-products were obtained with high \textsuperscript{18}O-contents. A CF\textsubscript{3}O-containing Trioxsalen derivative was synthesized by this trifluoromethylation protocol. The oxidation of difluorocarbene may provide more possibilities for difluorocarbene chemistry.
Methods

Typical procedure for trifluoromethoxylation. Into a 20 mL sealed tube were added benzyl bromide 1 (0.8 mmol, 197.7 mg, 1.0 equiv), Ph₃P⁺CF₂CO₂⁻ (2.0 mmol, 712.0 mg, 2.5 equiv), Ph₂S=O (2.0 mmol, 404.6 mg, 2.5 equiv), AgF (1.6 mmol, 203.2 mg, 2.0 equiv), 2,2’-bipyridine (1.2 mmol, 187.4 mg, 1.5 equiv), 2,3,11,12-dibenzo-18-crown-6 (0.4 mmol, 144.2 mg, 0.5 equiv), and THF (6 mL) under a N₂ atmosphere. The tube was sealed and the reaction mixture was stirred at 60 °C for 30 min. After the mixture was cooled to room temperature, the pure product was isolated by flash column chromatography.

Typical procedure for ¹⁸O-trifluoromethoxylation. Into a 10-mL sealed tube were added benzyl bromide 1 (0.2 mmol, 49.4 mg, 1.0 equiv), Ph₃P⁺CF₂CO₂⁻ (0.5 mmol, 178.0 mg, 2.5 equiv), Ph₂S=¹⁸O (0.5 mmol, 102.1 mg, 2.0 equiv), AgF (0.4 mmol, 51.0 mg, 2.0 equiv), 2,2’-bipyridine (0.3 mmol, 47.0 mg, 1.5 equiv), 2,3,11,12-dibenzo-18-crown-6 (0.1 mmol, 36.0 mg, 0.5 equiv), and THF (1.5 mL) under a N₂ atmosphere. The tube was sealed and the reaction mixture was stirred at 60 °C for 30 min, and the mixture was cooled to room temperature. The pure product was isolated by flash column chromatography, and the ¹⁸O contents were determined by GC-MS (EI) spectroscopy.

For the preparation of starting materials and the characterization data of the products, see Supplementary Methods. For the NMR spectra of the compounds, see Supplementary Figs. 5–184. For EI spectra of the ¹⁸O-products, see Supplementary Figs. 185–214. For DFT calculations, see Supplementary Figs. 3 and 4 and Supplementary Data 1 and 2.
**Fig. 5** The synthesis of CF₃O-containing Trioxsalen derivative. The derivative was synthesized by a late-stage trifluoromethoxylation reaction.

**Fig. 6** Difluorocarbene-oxidation-based ¹⁸O-trifluoromethoxylation. Isolated yields. Reaction conditions: substrate 1 (0.2 mmol), Ph₃P⁺CF₂CO₂⁻ (2.5 equiv), Ph₂S=¹⁸O (2.5 equiv), AgF (2 equiv), 2,2'-bipyridine (1.5 equiv), and 2,3,11,12-dibenzo-18-crown-6 (0.5 equiv) in THF (1.5 mL) at 60 °C for 0.5 h. The ¹⁸O contents were determined by EI-MS.
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**Author contributions**

J.Y. performed the experiments. D.Y. performed the DFT calculations. R.D. analyzed the data. J.-H.L. analyzed the data and wrote the manuscript. J.-C.X. designed the experiments and wrote the manuscript.

**Competing interests**

The authors declare no competing interests.

**Additional information**

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