

Synthesis of Aryl Perfluorocyclopropyl Ethers via [2 + 1] Cyclopropanation Using TMSCF_2Br Reagent

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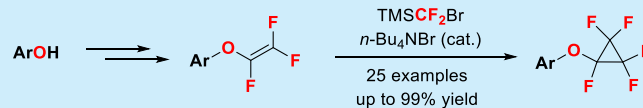


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ABSTRACT: Aryl perfluorocyclopropyl ethers have been synthesized for the first time by [2 + 1] cyclopropanation between aryl trifluorovinyl ethers and a commercially available TMSCF_2Br reagent. This cycloaddition reaction between two fluorine-containing reactants proceeds smoothly in toluene at 120 °C in the presence of a catalytic amount of $n\text{-Bu}_4\text{NBr}$, and the reaction tolerates a variety of functional groups. A wide range of aryl trifluorovinyl ethers, easily accessible from phenols, were successfully transformed to aryl perfluorocyclopropyl ethers.



Because of the unique impact of fluorine substituents on the properties of the target molecules, fluoroorganic compounds have received remarkable attention in the design of pharmaceuticals, agrochemicals, and advanced materials.¹ Thus, extensive research efforts have been devoted to the selective installation of fluorine atoms or fluorinated groups into target molecules.² In this context, molecules containing a fluoroalkoxy group have found wide applications in life-science-related fields. Indeed, many pharmaceutically relevant molecules contain fluoroalkoxy groups, such as trifluoromethoxy (OCF_3) and difluoromethoxy (OCF_2H) functionalities (Figure 1).³ Moreover, other methods have been developed for

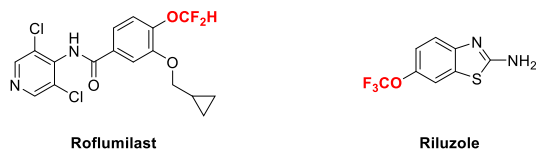


Figure 1. Fluoroalkoxy structural motifs in pharmacological compounds.

the efficient transfer of a perfluoroisopropoxy group [$\text{OCF}(\text{CF}_3)_2$] or a perfluoro-*tert*-butoxy group [$\text{OC}(\text{CF}_3)_3$].⁴ We envisioned that another structurally unique perfluoroalkoxy functionality, the perfluorocyclopropoxy group (OCp_F), may find many applications in life-science- and materials-science-related fields. However, unlike the trifluoromethoxy-, difluoromethoxy-, perfluoroisopropoxy-, and perfluoro-*tert*-butoxy-containing compounds, few methods are available for the synthesis of perfluorocyclopropoxy-containing compounds.⁵

Trifluorovinyl ethers (TFVE) are important monomers that can undergo thermal [2 + 2] cyclodimerization reaction above 150 °C to give perfluorocyclobutyl-containing fluoropolymers.⁶ In particular, aryl trifluorovinyl ethers are stable compounds that are typically synthesized from commercially available phenols.^{6,7} Various highly fluorinated cyclopropanes

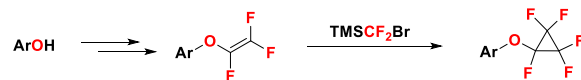
have been prepared from fluorinated olefins and hexafluoropropylene oxide (HFPO) at 180–200 °C by Sargent^{5a} and Yang^{5b} (Scheme 1a). Although the difluorocarbene species

Scheme 1. Strategies for the Synthesis of Perfluorocyclopropyl Ethers

(a) Synthetic protocols for perfluorocyclopropyl ethers



(b) This work: synthetic method for aryl perfluorocyclopropyl ethers

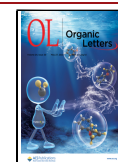


- First report on aryl perfluorocyclopropyl ether
- Readily available reagent
- Good functional group compatibility
- High yields

generated from HFPO is highly reactive toward perfluoroalkyl TFVE, it usually requires a temperature higher than 170 °C, at which aromatic TFVE can undergo thermally induced [2 + 2] cycloaddition reaction. Therefore, HFPO may not be suitable to serve as a difluorocarbene precursor to react with aryl TFVE to synthesize aryl perfluorocyclopropyl ethers. Therefore, a general method for the efficient [2 + 1] cyclopropanation

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between TFVE and a readily available difluorocarbene reagent is still much sought after.

TMSCF₂Br, a difluorocarbene reagent developed by us, is now commercially available and frequently applied in organic synthesis.⁸ It has been used in the cyclopropanation or cyclopropenation of alkenes and alkynes^{8a,j} as well as the difluoromethylation of C-,^{8b} O-,^{8c,h,i} S-, N-,⁸ⁱ and P-nucleophiles,^{8a} among other applications.^{8d–g} As part of our ongoing effort to develop TMSCF₂Br as a general difluorocarbene reagent, we describe herein our recent success in the difluoromethylation of TFVE with TMSCF₂Br, providing easy access to various aryl perfluorocyclopropyl ethers in high yields (Scheme 1b).

Initially, we chose 4-[(1,2,2-trifluorovinyl)oxy]-1,1'-biphenyl (1a) as a model substrate, and the reaction was carried out using toluene as solvent (Table 1). In our previous report,^{8a} we

precursor provided the desired product 2a in 17% yield (entry 9). In 2011, it was reported that the difluorocarbene generation system (the combination of TMSCF₃ and NaI) could convert the nonactivated alkenes into the gem-difluorocyclopropanes.⁹ When heating a solution of 1a, TMSCF₃, and NaI (0.2 equiv.) in THF at 70 °C for 3 h, no 2a was observed; however, when the reaction employing 2.0 equiv. of TMSCF₃ and 2.2 equiv. of NaI was performed in THF at 110 °C for 3 h, 2a was obtained in 71% yield (entry 11). These results showcase the unique reactivity and advantage of TMSCF₂Br as a privileged difluorocarbene reagent.

By using the optimized conditions as standard (Table 1, entry 12), we explored the substrate scope of the reaction (Scheme 2). The [2 + 1] cycloaddition of aromatic TFVE with difluorocarbene proceeded smoothly, and the corresponding aryl perfluorocyclopropyl ethers were obtained in good to excellent yields (71–99%). It was found that the reaction was compatible with both electron-poor (1m–1r, 1t) and electron-rich (1f–1l) aryl trifluorovinyl ethers, and it also worked with aryl trifluorovinyl ethers bearing a range of functional groups. Generally, a range of aryl trifluorovinyl ethers with electron-withdrawing groups, such as halo (1d, 1e), cyano (1m, 1p), ester (1q, 1r), ketone (1n, 1o), sulfone (1t), and amide (1v), reacted with TMSCF₂Br reagent to give the corresponding products in good to excellent yields (72–99%). In contrast, the substrates bearing electron-donating groups (1f–1l) also gave high product yields (71–98%). In the case of substrate bearing an OH, only difluoromethylation of the C=C bond was observed (2u). This result suggests that the OH group is compatible with the present reaction conditions. Heterocycle substrate, such as benzotriazole, was also compatible with the reaction condition, and 86% yield of product was observed (2w). Notably, the electron-deficient alkenes such as phenyl acrylate, which could undergo [2 + 1] cycloaddition with difluorocarbene species, were found to be compatible with the present difluoromethylation reaction conditions, providing perfluorocyclopropyl ethers with high yields (90% for 2x, and 92% for 2y, respectively).

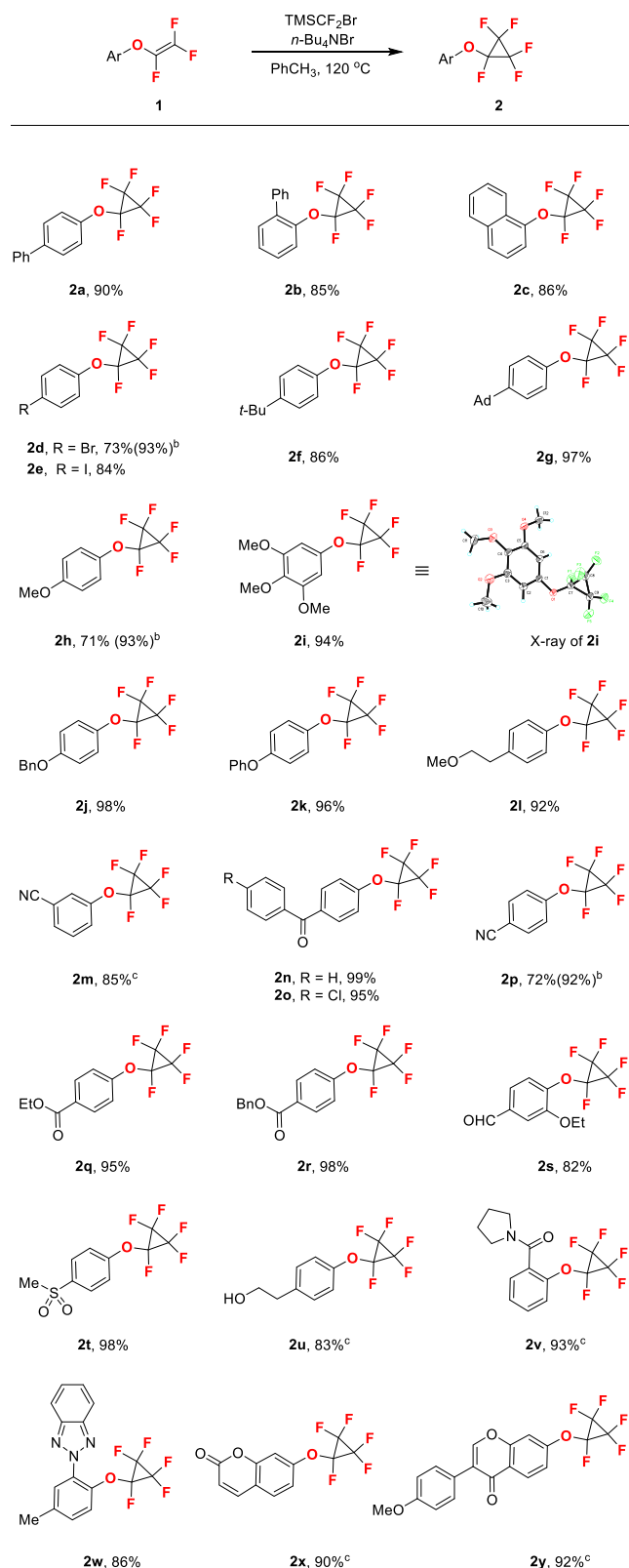
To further showcase the practicability of this method, we carried out gram-scale synthesis as well as other synthetic applications of aryl perfluorocyclopropyl ether (Scheme 3). The synthesis of 2o was easily scaled up to 4.0 mmol with only a slight decrease in yield (1.36 g, 94%). The *para*-bromophenylperfluorocyclopropyl ether 2d was explored in aromatic functionalization reactions to assess the compatibility of the perfluorinated ring with mainstream reaction conditions. For example, amination of 2d using 4-phenylpiperidine, with Pd₂(dba)₃ and DavePhos, furnished the cross-coupling product 3 in 73% yield. A Suzuki coupling of 2d with (4-methoxyphenyl)boronic acid, under the catalysis of Pd₂(dba)₃ and SPhos, provided 4,4'-substituted biphenylether 4 in 76% yield. Furthermore, we also successfully expanded this [2 + 1] cycloaddition reaction from aryl trifluorovinyl ether to aryl trifluorovinyl thioether. Accordingly, phenyl trifluorovinyl thioether 5, easily accessible from phenylthiol, can be readily converted into aryl perfluorocyclopropyl sulfone 6 via [2 + 1] cycloaddition and the subsequent oxidation reaction. Because fluoroalkyl sulfones have been recognized as robust fluoroalkylation reagents,¹⁰ the present perfluorocyclopropyl sulfone may open a door for selective perfluorocyclopropylation reactions.

Table 1. Survey of the Reaction Conditions^a

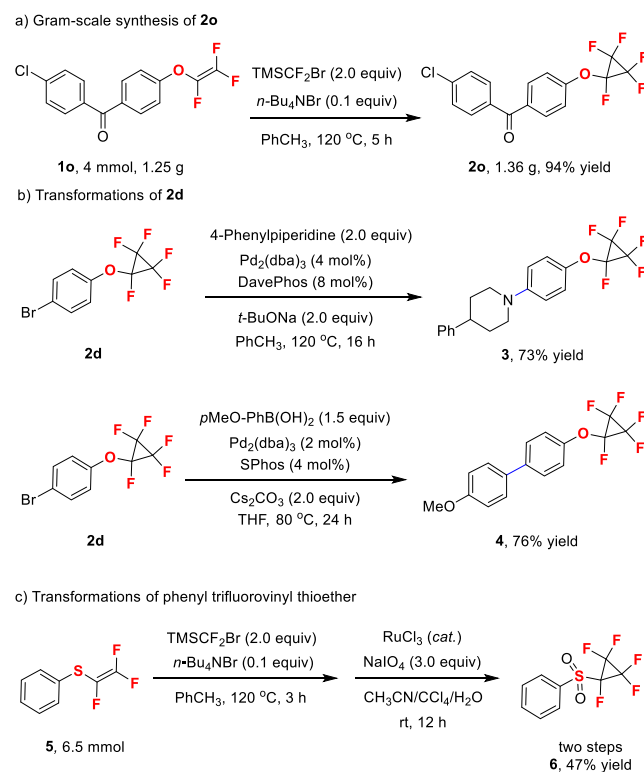
entry	:CF ₂ sources (x)	additive (y)	T	solvent	yield (%) ^b
1	TMSCF ₂ Br (1.5)	<i>n</i> -Bu ₄ NBr (0.2)	120	toluene	95
2	TMSCF ₂ Br (1.5)	<i>n</i> -Bu ₄ NBr (0.2)	100	toluene	75
3	TMSCF ₂ Br (1.5)	<i>n</i> -Bu ₄ NBr (0.2)	80	toluene	39
4	TMSCF ₂ Br (2.0)	<i>n</i> -Bu ₄ NBr (0.1)	120	toluene	97 ^c
5	ClCF ₂ CO ₂ Na (2.0)		120	DMF	0
6	ClCF ₂ CO ₂ Na (2.0)		120	diglyme	0
7	BrCF ₂ CO ₂ Na (2.0)		120	DMF	trace
8	BrCF ₂ CO ₂ Na (2.0)		120	diglyme	trace
9	Ph ₃ P ⁺ CF ₂ CO ₂ [−] (2.0)		120	toluene	17
10	TMSCF ₃ (2.0)	NaI (0.2)	70	THF	0
11	TMSCF ₃ (2.0)	NaI (2.2)	110	THF	71
12	TMSCF ₂ Br (2.0)	<i>n</i> -Bu ₄ NBr (0.1)	120	toluene	>99 ^{cd}

^aReactions were conducted on a 0.05 mmol scale in 1.0 mL of solvent. ^bYields were determined by ¹⁹F NMR with PhCF₃ as an internal standard. ^c5 h. ^d0.1 M.

found that *n*-Bu₄NBr (TBAB) was a better catalyst for the cyclopropanation or cyclopropenation of alkenes and alkynes. So we chose TBAB for desilylation of TMSCF₂Br to generate difluorocarbene. To our delight, when the reaction employing 1.5 equiv. of TMSCF₂Br and 0.2 equiv. of TBAB was carried out in a sealed tube at 120 °C for 3 h, 2a was produced in 95% yield (entry 1). The yields dropped when the temperature was reduced to 100 and 80 °C (entries 2–3, 75% for 100 °C and 39% for 80 °C). To ensure complete conversion of 1a, increasing the amount of TMSCF₂Br to 2.0 equiv. and prolonging the reaction time to 5 h resulted in a higher yield while employing 0.1 equiv. of TBAB (entry 4, 97%). Encouraged by these exciting results, we turned our attention to compare the reactivity of TMSCF₂Br with those of other difluorocarbene sources. Both ClCF₂COONa and BrCF₂COONa showed very low reactivity toward 1a at 120 °C (entries 5–8). Using Ph₃P⁺CF₂COO[−] as a difluorocarbene

Scheme 2. Scope of Aromatic TFVE^a

^aReaction conditions: **1** (0.30 mmol, 1.0 equiv.), TMSCF₂Br (0.60 mmol, 2.0 equiv.), *n*-Bu₄NBr (0.03 mmol, 0.1 equiv.) and PhCH₃ (3.0 mL) at 120 °C for 5 h. Ad = 1-adamantyl. Isolated yields. ^bYields in parentheses were determined by ¹⁹F NMR with PhCF₃ as an internal standard. ^c6 h.

Scheme 3. Gram-Scale Synthesis of **2o** and Synthetic Applications of **2d** and **5**

In summary, we have described a protocol for the synthesis of perfluorocyclopropyl ethers by [2 + 1] cyclopropanation between trifluorovinyl ethers (TFVE) and TMSCF₂Br. Our work represents the first synthetic access to aryl perfluorocyclopropyl ethers from various easily accessible aryl trifluorovinyl ethers (from phenols). This synthetic method promises to serve as a useful synthetic tool for the late-stage modification of bioactive compounds and other functional molecules.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.orglett.2c00958>.

Detailed experimental procedures and spectra data for all new compounds (PDF)

Accession Codes

CCDC 2143781 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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