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Fluorohalogenation of *gem*-Difluoroalkenes: Synthesis and Applications of α-Trifluoromethyl Halides

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Dedication ((optional))

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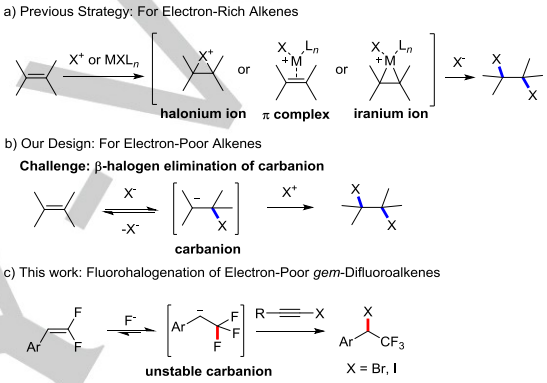
Abstract: A novel strategy for 1,2-dihalogenation of alkenes is reported that occurs *via* sequential nucleophilic halide addition and electrophilic halogenation. By trapping the *in situ* generated unstable α-trifluoromethyl carbanion intermediates derived from the nucleophilic fluoride addition to electron-poor *gem*-difluoroalkenes, this fluorohalogenation of *gem*-difluoroalkenes with electrophilic haloalkynes affords various useful α-trifluoromethyl halides in high yields. A pesticidal active compound and various attractive trifluromethylated molecules could be smoothly synthesized from these obtained α-trifluoromethyl halides.

1,2-Dihalogenation of alkenes is a frontier in organic chemistry,[1] because the synthesized vicinal dihalides not only represent a large component of natural organohalogens but also might serve as progenitors to useful artificially halogenated compounds.[2] The reported strategies for 1,2-dihalogenation of alkenes are mainly focused on activating the electron-rich alkene substrate either by a halenium ion,[3] and / or by an electrophilic transition-metal[4] or main group electrophile,[5] via a halonium or π-complex or -iranium ion, and then followed by an outer sphere attack of a halide ion (Scheme 1, a). On the other hand, 1,2-dihalogenation of the electron-poor alkenes is quite challenging and still underdeveloped, probably related to their intrinsic electrophilic property.[6] Inspired by it, we envisioned that if the nucleophilic addition of electron-poor alkene substrate with a halide ion could happen firstly, and subsequently followed by the process of electrophilic halogenation. This strategy might become a useful protocol for the 1,2-dihalogenation of electron-poor alkenes and construct valuable halogenated compounds (Scheme 1, b). However, owing to the favored β-halogen elimination process of β-halogenated carbanion, this novel strategy is quite challenge and still unreported.

Trifluoromethyl group is a privileged moiety in pharmaceutical and agrochemical research because of its positive influence on the metabolic stability, lipophilicity, and cell-membrane permeability of potential drugs.[7] Consequently, the development of novel and efficient methods for the introduction of trifluoromethyl group into biologically active molecules has particularly gained much attention.[8] Electron-poor *gem*-difluoroalkenes are readily available, useful and versatile synthons. It was found that the regioselective nucleophilic fluoride addition of these substrates could generate the α-trifluoromethyl-alkylsilver intermediates[9] with AgF or unstable α-trifluoromethyl carbanion[10] for the preparation of various

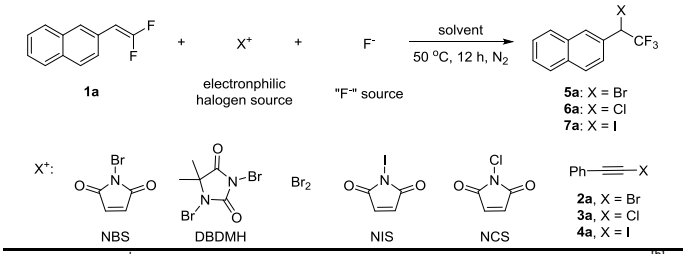


Scheme 1. 1,2-Dihalogenation of Alkenes.

trifluoromethylated compounds. Inspired by it, we hypothesized that the in *situ* generated *α*-trifluoromethyl carbanion intermediates derived from nucleophilic fluoride addition to *gem*-difluoroalkenes might be captured by electrophilic halogen sources (Scheme 1, c). Thus, this fluorohalogenation protocol of electron-poor *gem*-difluoroalkenes would lead to the efficient construction of useful *α*-trifluoromethyl halides.[11-12] Especially, this strategy has potential advantages for the preparation of [^{18}F]CF_3 labled *α*-trifluoromethyl halides.[13] However, because of the spontaneous proton abstraction quenching or *β*-fluoride elimination tendency of the *in situ* generated unstable *α*-trifluoromethyl carbanion, its compatibility with the oxidative electrophilic halogen sources is the main challenge in this reaction.

Given the advantages of potassium fluoride (KF) in nucleophilic fluorination such as low-cost, abundant, safe and easy to handle,[14] the initial experiment of this fluorohalogenation of electron-poor *gem*-difluoroalkene **1a** was carried out with *N*-bromosuccinimide (NBS) in the presence of KF in DMF at 50 °C under N_2 (Table 1, entry 1). Although the yield was very poor, the desired fluorobromination product **5a** could be detected by GC-MS analysis. Other oxidative electrophilic halogen sources such as 1,3-dibromo-5,5-dimethylhydantoin (DBDMH), Br_2, *N*-chlorosuccinimide (NCS), and *N*-iodosuccinimide (NIS) have also been tried, however, no corresponding fluorohalogenation products (**5a**, **6a**, and **7a**) were obtained (Table 1, entries 2-5). We thought that the suitable electrophilic halogen source might be the key to the

Table 1. Optimization of the reaction conditions.[a]

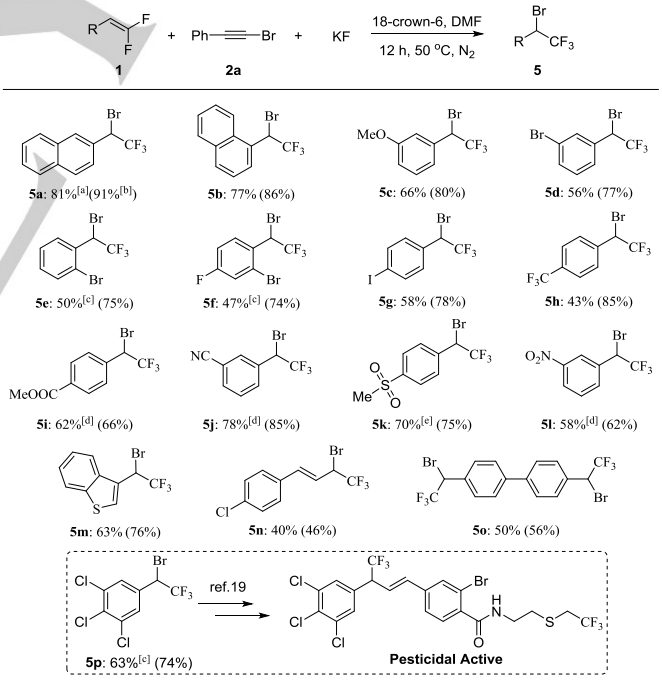


Entry	X^+	F^-	Solvent	Product	Yield (%)[b]
1	NBS	KF	DMF	**5a**	< 2%
2	DBDMH	KF	DMF	**5a**	0
3	Br_2	KF	DMF	**5a**	0
4	NCS	KF	DMF	**6a**	0
5	NIS	KF	DMF	**7a**	0
6	**2a**	KF	DMF	**5a**	63 (50)
7	**2a**	LiF	DMF	**5a**	0
8	**2a**	NaF	DMF	**5a**	0
9	**2a**	CsF	DMF	**5a**	32
10	**2a**	CuF	DMF	**5a**	0
11	**2a**	AgF	DMF	**5a**	0
12	**2a**	$(n\text{-Bu})_4NF$	DMF	**5a**	16
13[c]	**2a**	KF	DMF	**5a**	91 (81)
14[c]	**2a**	KF	DMSO	**5a**	90
15[c]	**2a**	KF	MeCN	**5a**	53
16[c]	**2a**	KF	1.4-dioxane	**5a**	0
17[c]	**2a**	KF	THF	**5a**	0
18[c]	**2a**	KF	DCE	**5a**	0
19[c]	**2a**	KF	cyclohexane	**5a**	0
20[c]	**2a**	KF	toluene	**5a**	0
21[d]	**2a**	KF	DMF	**5a**	89
22[c]	**3a**	KF	DMF	**6a**	<5
23[c]	**4a**	KF	DMF	**7a**	78 (61)

[a] Unless otherwise noted, all reactions were carried out with **1a** (0.2 mmol), 'X^+' (2 equiv), 'F^-' (2 equiv), and solvent (4 mL) in a 25 mL Schlenk tube at 50 °C for 12 h under N_2. [b] The yields were determined by ^{19}F NMR spectroscopy of the crude product with $PhCF_3$ as an internal standard. The numbers in the parentheses were isolated yields. [c] With 18-crown-6 (2.5 equiv) as additives. [d] Under open air and undried DMF.

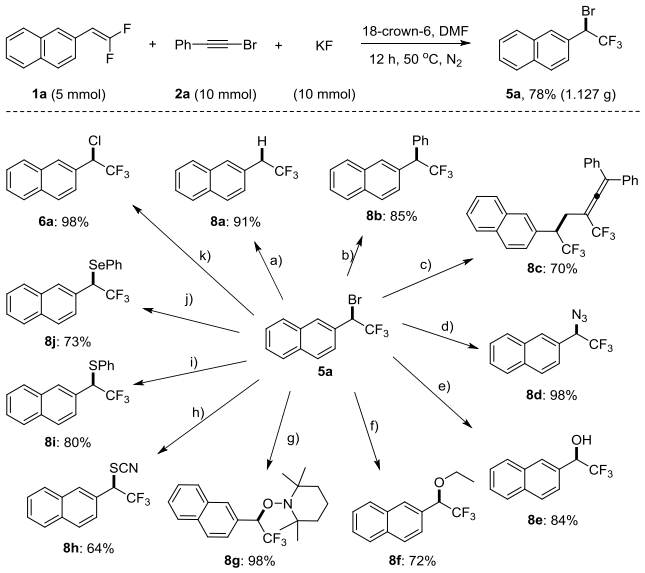
success of this transformation. Owing to the sp hybridization of the triple bond and the adjacent halogen atom, haloalkynes exhibit rich and tunable reactivity in synthetic chemistry,[15] and which were used to capture the *in situ* generated aryl carbanion.[16] Inspired by it, bromoalkyne **2a** was then examined to capture the *in situ* generated unstable *α*-trifluoromethyl carbanion (Table 1, entry 6). To our delight, the desired fluorobromination product **5a** was isolated in 50% yield, while the product of fluoride nucleophilic addition to bromoalkyne **2a** was completely undetectable.[17] Next, different nucleophilic fluoride sources, such as LiF, NaF, CsF, CuF, AgF, and $(n\text{-Bu})_4NF$ were investigated, and no superior results were obtained (Table 1, entries 7-12). Furthermore, an additive of 18-crown-6 improved the yield of **5a** to 91% (Table 1, entry 13).[18] Different solvents such as DMSO, MeCN, 1,4-dioxane, THF, 1,2-dichloroethane (DCE), cyclohexane, and toluene were then screened (Table 1, entries 14-20), however, the yields of **5a** was not further improved. We believed that the strong polar aprotic solvent might help to stabilize the *α*-trifluoromethyl carbanion intermediates. This reaction is not air sensitive, because **5a** was obtained in 89% yield under open air and undried DMF (Table 1, entry 21).[10a, 12] Additionally, chloroalkyne **3a** and iodoalkyne **3b** were also used to capture the *in situ* generated unstable *α*-trifluoromethyl carbanion. The fluorochlorination product **6a** was not obtained in isolatable yield (Table 1, entry 22), however, the fluoroiodonation product **7a** was isolated in 61% yield (Table 1, entry 23).

Under the optimized reaction conditions, the scope of *gem*-difluoroalkenes in this fluorobromination reaction was examined. Owing to their highly volatile property, selected α-trifluoromethyl bromides were isolated and illustrated in Scheme 2. Electron neutral naphthyl *gem*-difluoroalkenes promisingly gave products **5a**-**b** in high yields. *α*-Trifluoromethyl bromides **5c**-**l** with electron-withdrawing substituents such as 3-methoxyl, fluoro, bromo, iodo, trifluoromethyl, formic ester, cyano, sulfonyl, and nitro groups on the phenyl ring were all isolated in good to high yields. Furthermore, 3-benzo[*b*]thiophenyl bearing *gem*-difluoroalkene delivered product **5m** in 63% yield. *gem*-Difluoro-1,3-diene was also found to be a suitable substrate, providing 1,2-fluorobrominated product **5n** in reasonable yield. Double fluorobromination of *gem*-difluoroalkene afforded symmetric α-trifluoromethyl bromide **5o** in 50% isolated yield, which has ample potential for polymer synthesis. Significantly, trichloro substituted *α*-trifluoromethyl bromide **5q** was isolated in 63% yield, which is a key intermediate for the synthesis of pesticidal active compound.[19]



Scheme 2. Isolated α-trifluoromethyl bromides. Reaction conditions: **1** (0.2 mmol), **2a** (0.4 mmol), KF (0.4 mmol), DMF (4 mL). [a] Average isolated yield of two parallel runs. [b] ^{19}F-NMR yields. [c] **2a** (2 equiv) and 1-(bromoethynyl)-4-nitrobenzene (2 equiv) at room temperature. [d] **2a** (4 equiv). [e] 4-(bromoethynyl)benzonitrile (2 equiv) at room temperature.

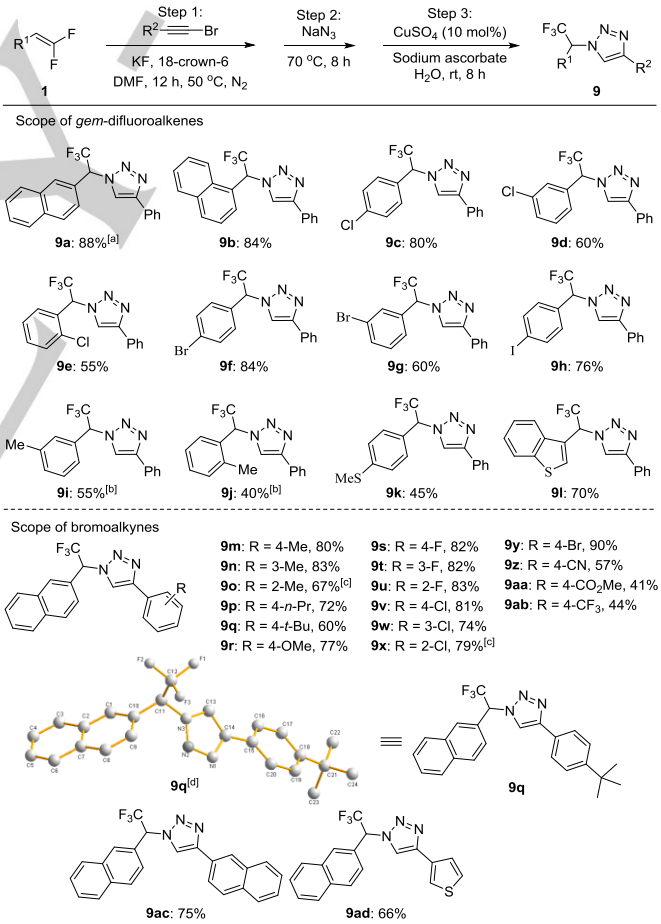
Intrigued by this unique protocol, a 5 mmol scale reaction of fluorobromination of *gem*-difluoroalkene **1a** was carried



Scheme 3. Synthetic application of **5a**. a) $(TMS)_3SiH$, AIBN, anhydrous toluene, 80 °C, 12 h. b) $AgSbF_6$, benzene, 80 °C, 1 h. c) Phenylboronic acid, (3-(trifluoromethyl)but-3-en-1-yn-1-yl)benzene, $Ni(NO_3)_2{\cdot}6H_2O$, 4,4-di-*tert*-butyl bipyridine, K_2CO_3, 1,4-dioxane, 80 °C, 72 h. d) NaN_3, 70 °C, 8 h. e) $(TMS)_3SiH$, H_2O, 30 °C, 12 h. f) $AgNO_3$, EtOH, 80 °C, 12 h. g) $(TMS)_3SiH$, TEMPO, H_2O, 80 °C, 12 h. h) KSCN, 18-crown-6, CH_3CN, 100 °C, 24 h. i) $(PhS)_2$, In, DCE, reflux, 12 h. j) $(PhSe)_2$, In, DCE, reflux, 12 h. k) PPh_3, DCM, 130 °C, 4 d.

out under the standard reaction conditions, delivering α-trifluoromethyl bromide **5a** in 78% yield (1.127 g) (Scheme 3, above). Furthermore, the synthetic applications of these α-trifluoromethyl bromides were explored with **5a** as a model substrate (Scheme 3, below). The C(sp^3)-Br bond of *α*-trifluoromethyl bromide **5a** has ample potential for further transformations, which could be smoothly converted to C-H (**8a**), C-C (**8b** and **8c**), C-N (**8d**), C-O (**8e**, **8f**, and **8g**), C-S (**8h** and **8i**), C-Se (**8j**), and C-Cl (**6a**) bonds.[20] Especially, the obtained substituted trifluoroethane derivatives (**8a**-**c**), *α*-trifluoromethyl azide (**8d**), alcohol (**8e**), ether (**8f**), thiocyanate (**8h**), sulfane (**8i**), selane (**8j**), and chloride (**6a**) are very attractive trifluoromethylated intermediates or building blocks in medicinal chemistry.

In this fluorohalogenation reaction of *gem*-difluoroalkenes with haloalkynes, stoichiometric amount of alkyne byproducts would be generated just like previous literatures.[16b-d] However, inspired by the highly efficient nucleophilic azidation of **5a**, we then explored a one pot, three steps transformation for the construction of *α*-trifluoromethyl *N*-1-triazoles **9** *via* the processes of fluorobromination of *gem*-difluoroalkenes, nucleophilic azidation of the generated α-trifluoromethyl bromides, and the regioselective Click reaction[21] between the newly *in situ* formed *α*-trifluoromethyl azides and the alkyne byproducts. Gratifyingly, a broad spectrum of *gem*-difluoroalkenes **1** and bromoalkynes **2** with different substitution patterns could be tolerated in this one pot, three steps transformation, delivering the corresponding *α*-trifluoromethyl *N*-1-triazoles in moderate to high yields (Scheme 3). Firstly, the scope of *gem*-difluoroalkenes **1** was examined with bromoalkyne **2a** as the reaction partner. 2-Naphthyl or 1-naphthyl substituted *gem*-difluoroalkenes afforded the desired products **9a** and **9b** in high yields. Both electron-withdrawing groups such as chloro, bromo, and iodo groups, and electron-donating groups such as methyl, and methylthio groups on the phenyl ring all could undergo this one pot, three steps transformation smoothly, providing the corresponding α-trifluoromethyl *N*-1-triazoles in moderate to high yields (**9c**-**k**). 3-Benzo[*b*]thiophene substituted *gem*-difluoroalkene also gave the desired product **9l** in 70% yield. Next, the scope of bromoalkynes **2** was investigated with *gem*-difluoroalkene **1a** as the reaction partner. In general, bromoalkynes with electron-donating and electron-withdrawing groups on the *para*-, *meta*-, and *ortho*-position of the phenyl ring all could give the desired *α*-trifluoromethyl *N*-1-triazoles in moderate to high yields (**9m**-**9ab)**. Significantly, product **9q** was proved to be crystalline, thus its structure was determined by means of X-ray crystallographic analysis.[22] Bromoalkynes derived from 2-ethynylnaphthalene and 3-ethynylthiophene were also found to be good substrates, delivering the corresponding products in good yields (**9ac** and **9ad**). It is also worth mentioning that this one pot, three steps transformation is not sensitive to the steric hindrance effect, because these *α*-trifluoromethyl *N*-1-triazoles *ortho*-substitution groups were obtained in reasonable yields (**9b**, **9e**, **9j**, **9o**, **9u**, and **9x**).



Scheme 4. Synthesis of *α*-trifluoromethyl *N*-1-triazoles. Reaction conditions: step 1): **1** (0.2 mmol), **2** (0.4 mmol), KF (0.4 mmol), DMF (4 mL); step 2): NaN_3 (0.4 mmol); step 3): $CuSO_4$ (10 mol%), H_2O (2 mL), sodium ascorbate (0.1 mmol). [a] Average isolated yield of two parallel runs. [b] At 110 °C for step 1. [c] At 45 °C for step 3. [d] The Oak Ridge Thermal Ellipsoid Plot of a crystal structure **9q** with thermal ellipsoids set at 50% probability. H atoms were omitted for clarity.

In summary, we have reported a novel strategy for 1,2-dihalogenation of alkenes *via* sequential nucleophilic halide addition and electrophilic halogenation. By trapping the *in situ* generated unstable α-trifluoromethyl carbanion intermediates derived from the nucleophilic fluorination of electron-poor *gem*-difluoroalkenes, this fluorohalogenation of *gem*-difluoroalkenes with electrophilic haloalkynes affords various useful α-trifluoromethyl halides in high yields. A pesticidal active compound and various attractive trifluromethylated molecules could be smoothly synthesized from these obtained α-trifluoromethyl halides. Furthermore, a one pot, three steps transformation was developed *via* the processes of fluorobromination of *gem*-difluoroalkenes with haloalkynes, nucleophilic azidation of the generated α-trifluoromethyl bromides, and the regioselective Click reaction between the newly *in situ* formed α-trifluoromethyl azides and the alkyne byproducts, delivering various α-trifluoromethyl *N*-1-triazoles in high yields. Investigation of the asymmetric variants and exploration of this novel strategy in other 1,2-dihalogenation of alkenes are currently underway in our laboratory.

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Keywords: dihalogenation • alkenes • fluorination • α-trifluoromethyl carbanion • potassium fluoride

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[22] CCDC 1936756 (**9q**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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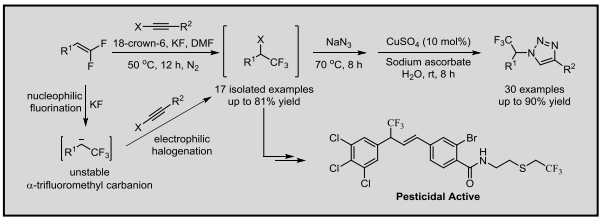
Entry for the Table of Contents



The fluorohalogenation of gem-difluoroalkene is reported that is initiated by nucleophilic fluorination, and followed by electrophilic halogenation of the *in situ* generated unstable α-trifluoromethyl carbanion. The obtained α-trifluoromethyl halides were further transformed into various useful trifluoromethylated compounds.

Institute and/or researcher Twitter usernames: ((optional))