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Oxidative trifluoromethylation and fluoroolefination of unactivated olefins

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The fluorine-containing organic compounds are becoming privileged in medicinal chemistry. Described herein is a mild and efficient method for the radical addition of olefins with $TMSCF_3$ and $TMSCF_2R$ (R=COOEt or CF_3) to deliver various α-trifluoromethylated ketones and α-fuoroolefinated ketones.

Fluorine, emerged as a magic element in pharmaceuticals, agrochemicals and functional materials, has become more and more significant for a large range of applications.[1] Unique physical and chemical advantages conferred by the C-F bond usually result in enhanced membrane permeability, elevated electronegativity and oxidation resistance.[2] Among them, the CF_3 unit is of extensive interest owing to its strong electron-withdrawing power and high lipophilicity. Hence, the development of new synthetic methods for the direct installation of CF_3 containing small molecules has already become one of the hottest fields in modern organic chemistry.

α-trifluoromethylated carbonyl compounds as versatile building blocks have been well-developed in construction of diverse fluorinated compounds.[3] The traditional synthetic methods for preparing α-trifluoromethylated ketones rely on electrophilic or radical trifluoromethylation of enolates prepared from the corresponding aldehydes, ketones, esters, and amides.[4] In 2012, Grushin and co-workers developed a nucleophilic trifluoromethylation of α-haloketones with the fluoroform-derived $CuCF_3$ reagent.[5] Despite this significant progress to deliver α-trifluoromethylated ketones, methods for the direct oxidative trifluoromethlation of widely available alkenes remain sluggish. In 2011, Xiao and co-workers reported the oxidative trifluoromethylation of styrenes with an *S*-(trifluoromethyl)diphenylsulfonium salt in the presence of an excess amount of $Na_2S_2O_4$ or $HOCH_2SO_2Na$, but the yields of α-trifluoromethylated ketones are only 20-40%.[6] In 2013, some progress has been made by Maiti's group, accomplishing the reaction with inexpensive CF_3SO_2Na as the CF_3 source in excellent yields.[7] Akita et al. developed photoredox-catalyzed trifluoromethylation and oxidation mediated by an alkoxysulfonium ion.[8] These radical processes implied that the outcome of the reaction is significantly affected by the means for the generation of the trifluoromethyl radical. $AgCF_3$ has been utilized effectively as the source of the trifluoromethyl radical, starting from commercially available $TMSCF_3$ and AgF.[9] Besides, $TMSCF_3$ has been used extensively in organic synthesis due to the advantages such as low cost, easy handling and storage. Inspired by these results, we wonder if $AgCF_3$, generated *in situ* from $TMSCF_3$ and AgF, could react with olefins and O_2 to offer a direct entry towards the α-trifluoromethylated carbonyl compounds.

On the other hand, fluoroalkenes as building blocks and targets are important in organic synthesis.[11] The fluoroalkene group is considered isopolar and isosteric with amide and possesses distinct biophysical properties, including decreasing H-bond donating and accepting abilities.[12] Synthetic methods for constructing fluoroalkenes have not been thoroughly investigated to date and only few strategies were published. In 2012, Jiang et. al reported a new route to bromofluoroalkenes via the silver-assisteded difunctionalization of terminal alkynes with NBS and AgF.[13] More recently, Poisson and co-workers developed a copper salt-controlled divergent reactivity toward α-diazocarbonyl compounds. The reported method allowed an easy access to α-fluorovinylphosphonate in good yields.[14] Base on our initial investigations, here we also described a new method to access α-fluoroolefinated carbonyl compounds.

Initially, we commenced our investigation by treating styrene (**1a**) with $TMSCF_3$ (**2a**) in the presence of AgF. To our delight, the reaction provided a 75% yield of the desired product **3a**. When other silver (I) salts and CsF were used in placing of AgF, less product was obtained (Table 1, entries 2-4). After screening different solvents, DMF gave the best result

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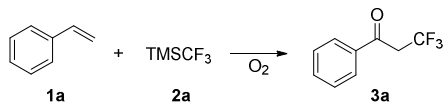
(entries 5-7). Further screening of the reaction conditions revealed that the adding method of **2a** is crucial to obtaining higher yields of **3a**. With the optimized reaction conditions established, the substrate scope of the protocol was surveyed (Table 2).

Table 1. Optimization of reaction conditions [a]



1a 2a 3a

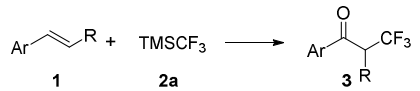
Entry	catalyst	Solvent	Yield [b](%)
1[c]	AgF	DMF	75
2[c,d]	$AgNO_3$	DMF	trace
3[c,d]	AgOAc	DMF	17
4[c,d]	Ag_2CO_3	DMF	trace
5	AgF	DMF	85
6	AgF	MeCN	30
7	AgF	THF	trace
8	AgF	DMSO	60
9	None	DMF	nr
10[e]	AgF	DMF	93 (89)[f]

[a] Reaction conditions: **1a** (0. 25 mmol), **2a** (2 equiv.), Ag(I) salt (1.5 equiv.), solvent (1 mL), vigorous stirring under O_2 atmosphere at room temperterature, 2 h. [b] Yield based on ^{19}F NMR spectroscopy using trifluoroacetophenone as an internal standard. [c] **2a** (1.5 equiv.). [d] CsF (1.5 equiv.) was added. [e] **2a** was added in two portions, one at the beginning and another one after 1h. [f] Value in parentheses refers to the isolated yield.

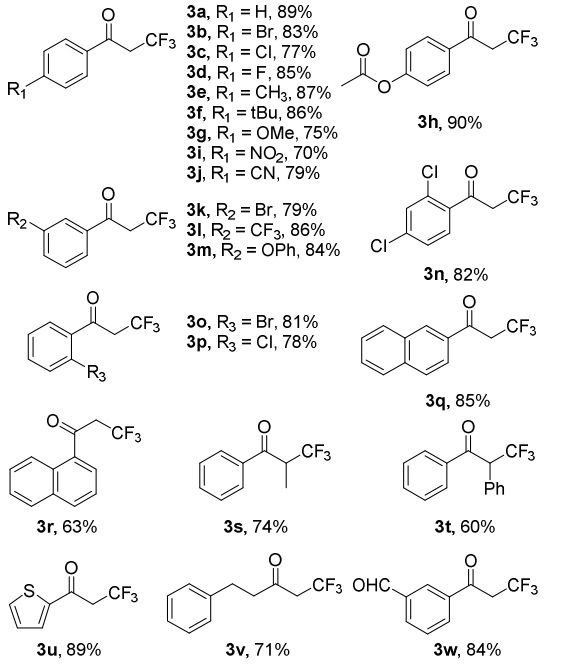
The reaction condition has shown excellent tolerance to both electron-withdrawing and electron-donating substituents, including many common functional groups such as ester, ether, aldehyde, cyano, nitro, trifluoromethyl, methoxy, and halogen, owing to the mild reaction conditions. Also, 2-substituted and 3-substituted styrenes reacted efficiently to generate α-trifluoromethylated ketones (**3k-3p**, **3w**). Note that olefins bearing carbonyl groups were selectively trifluoromethylated at the double bond without nucleophilic addition to the carbonyl group. Heteroaromatic olefin including 2-vinylthiophene also underwent the oxidative trifluoromethylation successfully (**3u**). Fortunately, aliphatic olefin reacted as efficiently as aromatic olefins (**3v**). Besides, this oxidative trifluoromethylation method was suitable for styrenes with a methyl group or aryl group at the β position (**3s**, **3t**).

Because of the easy setup of "$AgCF_2R$" species, we investigated whether it was possible to expand this transformation to other fluorinated substrates. Meanwhile, difluoroalkylation compared with perfluoroalkylation can not only introduce fluorine atoms into a molecule, but also install a nonfluorinated moiety simultaneously which can be further modified into various CF_2 containing functional groups.[10] Hence, we explore the difluoroalkylation using $TMSCF_2COOEt$ instead of $TMSCF_3$. This regent could be obtained from commercially available $BrCF_2COOEt$. Surprisingly, the undesired fluoroolefinated product **4a** was generated in a 85% yield under the previously optimized reaction conditions. Exploring other substrates, the results were consistent with **4a** (table 3). Generally, a range of substrates which bear electron-donating and neutral groups could react with **2b** to give the corresponding adducts in moderate to good yields (**4a-4g**). However, styrene bearing electron-withdrawing substituent demonstrated lower yield (**4i**).

Table 2. Synthesis of α-CF_3 substituted ketones from styrenes [a, b]



1 2a 3



[a] Reaction conditions: **1a** (0. 25 mmol), **2a** (2 equiv.), AgF (1.5 equiv.), DMF (1 mL), vigorous stirring under O_2 atmosphere at room temperterature, 2 h. [b] isolated yield.

Inspired by these results, we tried to expand this kind of reaction to other fluorinated TMS-sources, such as $TMSCF_2CF_3$. To our delight, the oxidative fluoroolefinated products were generated in good yield (**5a-5c**). Lately, $TMSCF_2H$ was also tested. This difluoromethylation reagent is easily prepared by reducing $TMSCF_3$ with $NaBH_4$.[15] However, only trace of the desired product could be observed via GC-MS analysis, owing to the substantially less reactive of $TMSCF_2H$. Either an increase of the temperature or an extansion of the reaction time did not lead to higher conversion.

A preliminary investigation of the reaction mechanism suggested that the reaction is likely to involve CF_3 or CF_2R (R=COOEt or CF_3) radical.[16] Under the optimized reaction conditions, styrene did not produce α-CF_3-substituted or α-fuoroolefinated ketone in the presence of TEMPO. Consistent with this observation, TEMPO-CF_3 and TEMPO-CF_2R was

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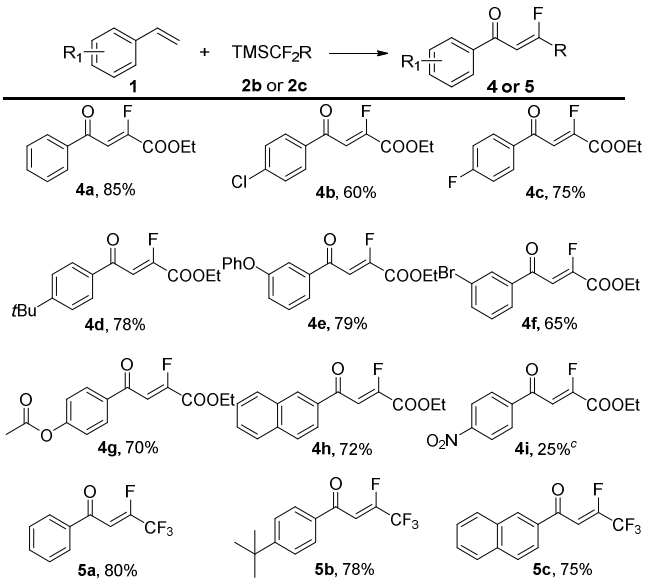
detected in the reaction mixture by GC-MS. Then to gain insight

Table 3. Synthesis of fluoroolefinated carbonyl compounds from styrenes [a, b]



[a] Reaction conditions: **1a** (0. 25 mmol), **2b** or **2c** (2 equiv.), AgF (1.5 equiv.), DMF (1 mL), vigorous stirring under O_2 atmosphere at room temperterature, 4 h. [b] isolated yield.[c] yield based on GC-MS.

formation process of α-fluoroolefinated carbonyl compounds, further control experiments (Scheme S1, ESI) were performed. When R is CF_3, **5c** is afforded from compound **4** (Fig. 1) via elimination of HF, which is thermodynamically stable because of its conjugated structure. Based on these studies, a proposed mechanism is illustrated in Fig. 1. When R is -COOEt or -CF_3, intermediate **4** would generate E-isomer product via antiperplnar elimination of HF, but E-isomer is expected to be less stable than Z-isomer due to a large repulsion between the benzoyl and the ethoxycarbonyl groups. The isomerization from E-isomer to Z-isomer might occur due to low isomerization barrier at the double bond.[17]

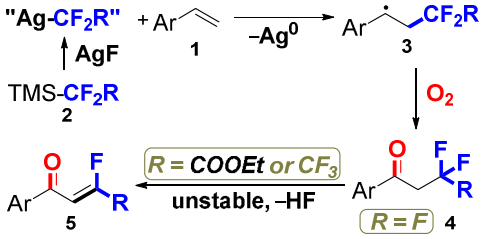


Figure 1. A proposed mechanism for the difluoro-methlylation of diazonium salts

Conclusions

In conclusion, we have discovered a direct, efficient, and general method to access α-trifluoromethylated and α-fluoroolefinated carbonyl compounds. The key advantages of the process are its wide functional-group tolerance, mild reaction conditions. $TMSCF_2COOEt$ and $TMSCF_2CF_3$ were also successfully applied in the reaction to deliver fluoroolefinated products. Its simple settings underline the great potential for the application in synthetic, medicinal, and agrochemical research.

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