Radical Fragmentation

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Radical Desulfur-Fragmentation and Reconstruction of Enol Triflates: Facile Access to α-Trifluoromethyl Ketones

Xiaolong Su, Honggui Huang, Yaofeng Yuan, and Yi Li**

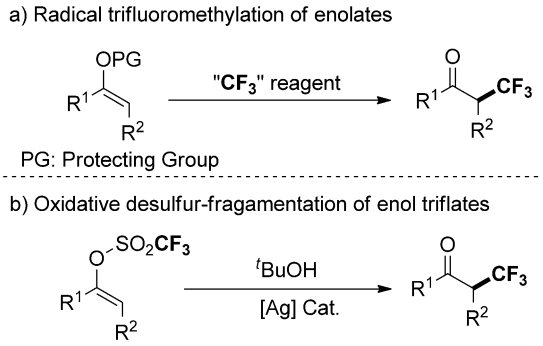
Abstract: *We report an efficient oxidative radical desulfur-fragmentation and reconstruction of enol triflates for the synthesis of α-CF_3 ketones. Preliminary mechanistic studies disclosed that oxidative fragmentation to release a CF_3 radical from the triflyl group of enol triflate and subsequent addition of the CF_3 radical to another enol triflate form the desired α-CF_3 ketones. This method provides a new approach to α-CF_3 ketones, featuring the utilization of catalytic amount of oxidants, broad substrate scope, and potential to control the regioselectivity.*

The introduction of trifluoromethyl group into organic molecules may have a dramatic effect on their lipophilicity, electronegativity, metabolic stability, and bioavailability.[1] Hence, intense interest has been paid to develop efficient methods for the synthesis of CF_3-containing compounds.[2] α-CF_3 carbonyl compounds have drawn special attention as they serve as valuable building blocks for various CF_3-containing complex moieties.[3] Significant efforts have been made to develop novel and diverse synthetic tools for the generation of α-CF_3 carbonyl compounds.[4]

General strategies to radical trifluoromethylation include using enolates in reactions with trifluoromethylation reagents, such as CF_3SO_2Na(Cl),[5] CF_3I,[6] or Togni reagent[7] (Scheme 1 a). While impressive progress has been made in this area, many of the reported examples generally required the addition of a large excess of the trifluoromethylation reagents or expensive reagents. Therefore, there is still a demand to develop methods to generate α-CF_3 carbonyl compounds with broad scope under mild conditions.

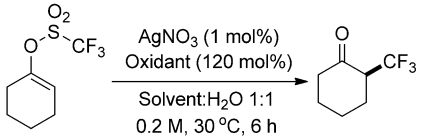
Enol triflates have become indispensable substrates and engaged in a broad array of transition-metal-catalyzed cross-coupling processes to give an access to C–C bond formations.[8] Recent progress in the synthesis of well-defined enol triflate derivatives may allow the scope to be broadened.[9] In addition, this trifluormethylation starting from enol tiflates has the advantage of controlling the regioselectivity with the use of different regioisomers of the enol triflates. Herein, we envisioned a radical desulfur-fragmentation and reconstruction of enol triflates which could efficiently generate α-CF_3 ketones (Scheme 1 b). Through the fragmentation of the enol triflate, a CF_3 radical was released from the triflyl group and subsequent addition to another enolate eventually formed the desired product.

As initially reported by Minisic, the combination of Ag^I with persulfate yields Ag^{II} and the sulfate radical anion which turns out to be an efficient electron-transfer oxidant.[10] Notably, Maiti group reported an elegant work of radical trifluoromethylation of alkenes.[11] With a catalytic amount of $AgNO_3/K_2S_2O_8$ and air as the oxidant, the CF_3 radical was generated from CF_3SO_2Na. Thereby, our investigation com-



Scheme 1. Pathways of trifluoromethylation.

Table 1: Optimizations of the reaction conditions.[a,b]



1a **2a**

Entry	Oxidant	Solvent	Yield of **2a**
1	$(NH_4)_2S_2O_8$	^{t}BuOH	95%
2[c]	$(NH_4)_2S_2O_8$	^{t}BuOH	no reaction
3[d]	$(NH_4)_2S_2O_8$	^{t}BuOH	no reaction
4	-	^{t}BuOH	no reaction
5	$K_2S_2O_8$	^{t}BuOH	55%
6	$Na_2S_2O_8$	^{t}BuOH	66%
7[e]	Other oxidants	^{t}BuOH	no reaction
8	20 mol% of $(NH_4)_2S_2O_8$, 12 h	^{t}BuOH	95%
9	$(NH_4)_2S_2O_8$	CH_3CN	21%
10[e]	$(NH_4)_2S_2O_8$	Acetone	41%

[a] Reaction conditions: **1a** (0.8 mmol), $AgNO_3$ (0.008 mmol), $(NH_4)_2S_2O_8$ (0.96 mmol) in mixed solvents (2 mL of solvent and 2 mL of water) at 30 °C. [b] Yield was determined by crude ^{19}F NMR using trifluoromethoxy benzene as the internal standard. [c] Without $AgNO_3$. [d] ^{t}BuOH was used as the sole solvent. [e] See the Supporting Information for more details of optimizations.

[*] X. Su, H. Huang, Prof. Dr. Y. Yuan, Prof. Dr. Y. Li
Department of Chemistry
Fuzhou University
Fuzhou 350116 (China)
E-mail: yaofeng_yuan@fzu.edu.cn
liyi-chem@fzu.edu.cn

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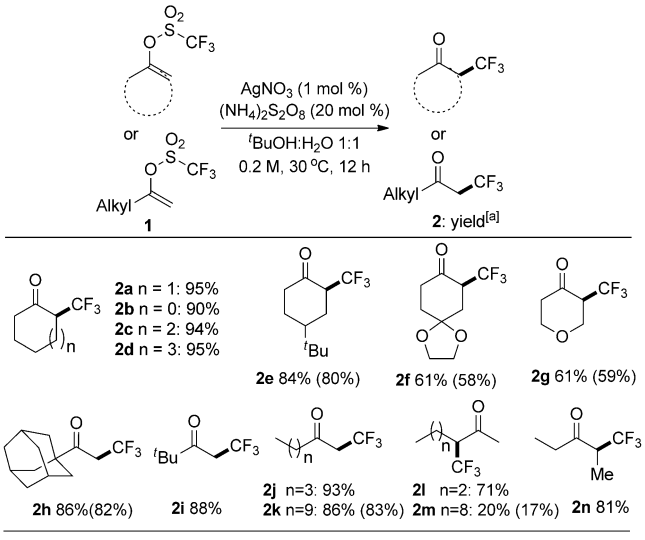
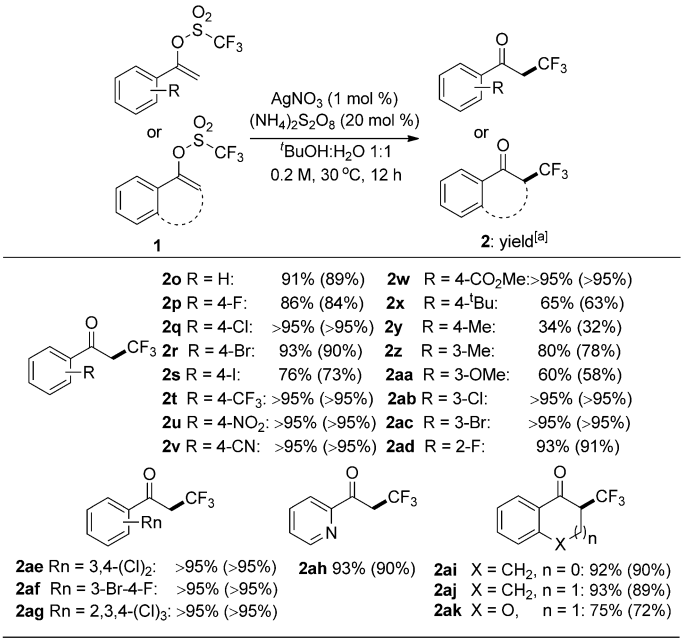
menced by subjecting enol triflate **1a** to catalytic amounts of silver along with $(NH_4)_2S_2O_8$ in a co-solvent system of ^{t}BuOH and water at 30 °C (Table 1, entry 1).

The desired α-CF_3 ketone **2a** was produced in a 95 % NMR yield. We found that in the absence of silver salt or $(NH_4)_2S_2O_8$, product **2a** was not formed (Table 1, entry 2 and 4). It is worth noting that using ^{t}BuOH as the sole solvent did not promote the reaction (Table 1, entry 3). The use of $K_2S_2O_8$ or $Na_2S_2O_8$ instead of $(NH_4)_2S_2O_8$ resulted in dramatically diminished yield of **2a** (Table 1, entries 5 and 6), while other commonly used oxidants afforded no product (Table 1, entry 7, see the Supporting Information for details). Although $(NH_4)_2S_2O_8$ is inexpensive, we sought to render the reaction catalytic which will endow this methodology with low cost and high efficiency. Gratifyingly, the amount of oxidant could be further decreased to 0.2 equivalent with the same efficiency as the use of 1.2 equivalents of oxidant (Table 1, entry 8). Only a few organic solvents, such as acetonitrile and acetone, could provide the desired product albeit in moderate yields (Table 1, entries 9 and 10, see the Supporting Information for more details).

With a general method in hand, the broad applicability of this new approach for a library of enol triflates was demonstrated (Scheme 2). The substrate scope with aliphatic enol triflates was explored. The reactions of cyclic enol triflates including those of 5-, 6-, 7-, or 8-membered rings were evaluated under these conditions, and the desired cyclic α-CF_3 ketones were formed efficiently (Scheme 2, **2a**–**2d**). Substituted cyclic enol triflates are accommodated as well (Scheme 2, **2e** and **2f**). Applications of linear enol triflates to the optimized conditions would afford the products successfully, even with sterically demanding substituents such as the adamantly or *tert*-butyl group (Scheme 2, **2h** and **2i**). Linear aliphatic enol triflates with long chains showed equal reactivity to give the corresponding α-CF_3 ketones in good yields (Scheme 2, **2j** and **2k**). We also tried to control the regioselectivity by applying these regioisomers derived from unsymmetrical alphatic ketones. Gratefully, the corresponding products were generated with moderate to good yields in a regioselective manner (Scheme 2, **2l** and **2m**).



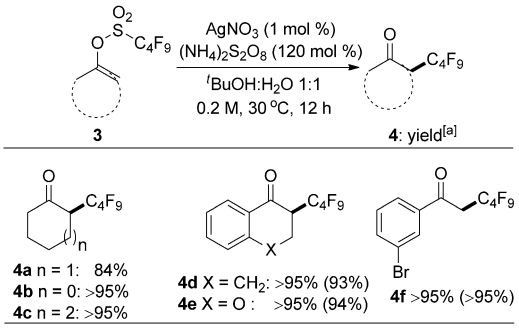
Scheme 2. Reactions with aliphatic enol triflates. Reaction conditions: **1** (0.8 mmol), $AgNO_3$ (0.008 mmol), $(NH_4)_2S_2O_8$ (0.16 mmol) in ^{t}BuOH (2 mL) and H_2O (2 mL) at 30 °C. [a] Yield was determined by crude ^{19}F NMR and isolated yield was given in parentheses.



Scheme 3. Reactions with aromatic enol triflates. Reaction conditions: **1** (0.8 mmol), $AgNO_3$ (0.008 mmol), $(NH_4)_2S_2O_8$ (0.16 mmol) in ^{t}BuOH (2 mL) and H_2O (2 mL) at 30 °C. [a] Yield was determined by crude ^{19}F NMR and isolated yield was given in parentheses.

The results in Scheme 3 reveal that a broad range of aromatic enol triflates with diverse electronic and steric properties could readily participate in this new reaction. Functional groups, such as NO_2, CN, and CO_2Me were well tolerated and the corresponding products were generated in excellent yields (Scheme 3, **2p**–**2w**). Substrates with methyl or methoxyl groups on aromatic rings produced the ketones with lower yields (Scheme 3, **2y**–**2aa**). Hydrogen abstraction on the methoxyl or benzylic C–H position was probably the main reason for these low yields. We also tested enol triflates with di- or tri-substituted aromatic rings and those substrates reacted efficiently with full conversation into the desired products (Scheme 3, **2ae**–**2ag**). To our delight, pyridine-motif was well compatible under these reaction conditions and **2ah** was generated in an isolated yield of 90 %. α-Branched products could also be formed efficiently under these reaction conditions with good to excellent isolated yields (Scheme 3, **2ai**–**2ak**).

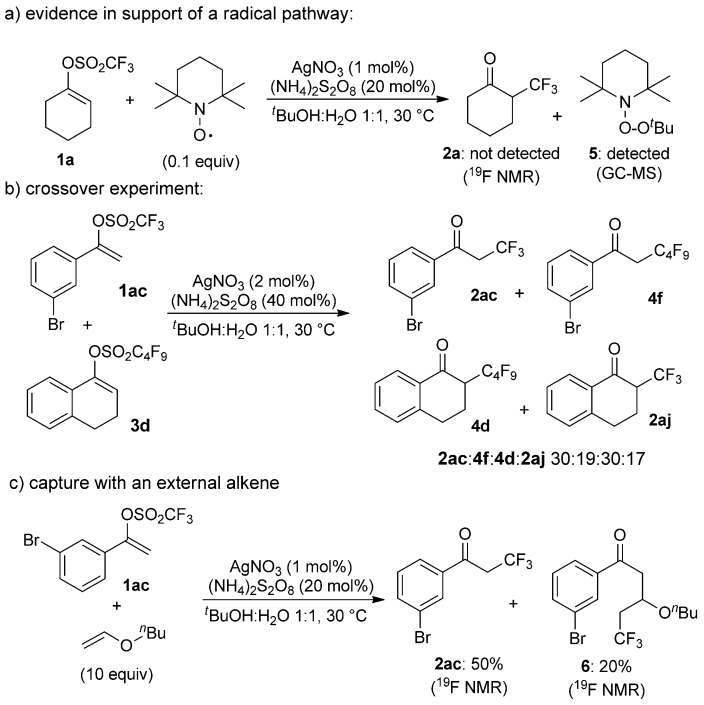
This route also demonstrates applicability to a range of α-perfluoroalkylation (Scheme 4). We found that cyclic enol nonaflates, aromatic enol nonaflates and α-branched substrate were all well tolerated under these reaction conditions and the corresponding α-perfluoroalkyl ketones were generated in excellent yields.



Scheme 4. Reactions with enol nonaflates. Reaction conditions: **3** (0.8 mmol), $AgNO_3$ (0.008 mmol), $(NH_4)_2S_2O_8$ (0.96 mmol) in ^{t}BuOH (2 mL) and H_2O (2 mL) at 30 °C. [a] Yield was determined by crude ^{19}F NMR and isolated yield was given in parentheses.

To shed light on the mechanism of this transformation, several control experiments were conducted (Scheme 5). Firstly, we performed a radical-trapping experiment (Scheme 5a). The standard reaction of **1a** was thus repeated in the presence of 2,2,6,6-tetramethyl-1-piperidinyl oxyl (TEMPO, 0.1 equiv), and the formation of the compound **2a** was completely inhibited, suggesting the involvement of a radical mechanism. The TEMPOO^{t}Bu adduct[12] was detected, as indicated by GC-MS. Insight into the reaction mechanism was subsequently derived from investigation of the fragmentation of the enolates (Scheme 5b). The crossover experiment was carried out by subjecting an equimolar amount of **1ac** and **3d** to the standard conditions. As determined by ^{19}F NMR, all four possible products **2ac**, **4f**, **4d**, and **2aj** were generated in a ratio of 30:19:30:17. Further investigation was conducted by introducing an external electron-rich olefin (10 equiv) into the model reaction system (Scheme 5c). 20% of compound **6** were observed indicating the involvement of free CF_3 radical during the reaction process.

On the basis of the above experiments and literature survey, a putative set of reaction cycles is depicted in Figure 1.



Scheme 5. Mechanistic study. See text for details.

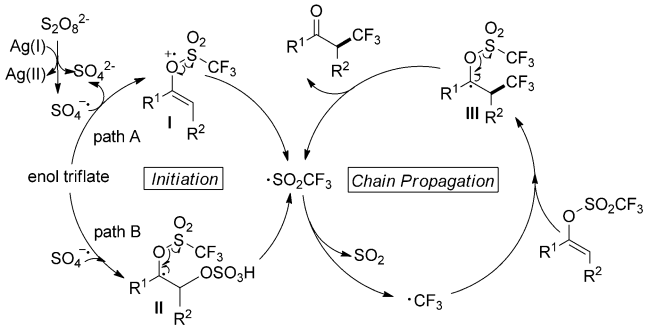


Figure 1. Putative mechanism.

Firstly, sulfate radical ion was produced by the action of Ag^I on persulfate. Initial radical reactions occurred between enol triflate and sulfate radical anion to yield either the intermediate **I** (path A) or intermediate **II** (path B). These radical intermediates (**I** or **II**) underwent fragmentations to form $^{\cdot}SO_2CF_3$ (initiation cycle). The CF_3 radical was generated subsequently after expelling SO_2. The addition of the CF_3 radical to another enol triflate affords the intermediate **III**. Radical reconstruction of **III** would eventually form the desired product and another $^{\cdot}SO_2CF_3$ radical for next reaction cycle (chain propagation).

In summary, we have developed a new strategy for the formation of α-CF_3 ketones through oxidative radical fragmentation and reconstruction of enol triflates. A CF_3 group present in the triflyl group performed as a radical CF_3 source to react efficiently with the enolate. This method utilizes readily available starting materials, is easy to handle, and features a wide substrate scope for both aromatic and aliphatic compounds. Further studies to expand the applicability of the present reaction system and efforts to develop other multi-component reactions through the radical crossover mechanism are currently underway.

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

Keywords: enol triflates · ketones · radical fragmentation · synthetic methods · trifluoromethylation

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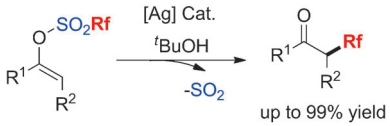
Communications

Radical Fragmentation

X. Su, H. Huang, Y. Yuan,*
Y. Li* _____ ■■■■–■■■■

Radical Desulfur-Fragmentation and Reconstruction of Enol Triflates: Facile Access to α-Trifluoromethyl Ketones



Reconstruction business: Oxidative fragmentation and reconstruction of enol triflates is a new strategy for the synthesis of α-CF_3 ketones. Preliminary mechanistic studies indicated oxidative fragmentation to release a CF_3 radical from the triflyl group of the enol triflate and subsequent addition of the CF_3 radical to another enol triflate forms the desired α-CF_3 ketone.