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Iron- or Silver-Catalyzed Oxidative Fluorination of Cyclopropanols for the Synthesis of β-Fluoroketones

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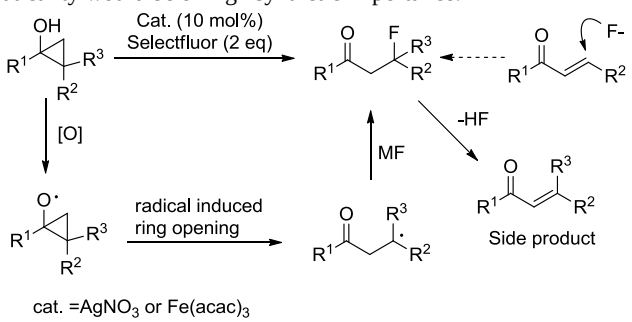
The Fe^{III}- or Ag^{I}-catalyzed oxidative fluorination of cyclopropanols via radical rearrangement is disclosed. This process features a straightforward and highly effective protocol for the site-specific synthesis of β-fluoroketones and represents an expedient method for the synthesis of γ-, δ- and ε-fluoroketones. Notably, this reaction proceeds at room temperature and tolerates a diverse array of cyclopropanols.

Fluorine-containing molecules have become increasingly important in material sciences, agrochemicals, pharmaceuticals and life science because of its intrinsic properties. The introduction of fluorine into pharmaceutical molecules was routinely adopted as an effective strategy for the drug development by increasing their lipophilicity, metabolic stability, membrane permeability and bioavailability,[1] in addition, ^{18}F-labeled organic compounds are also widely used in positron-emission tomography (PET).[2] Despite its importance, there are only 30 natural organofluorides identified till date.[3] Therefore, considerable efforts were thus invested in the development of new methods for the incorporation of fluorine into organic frameworks during the past decade. While significant progress has been achieved in the realm of C(sp^2)-F bond formation,[4,5] the construction of the C(sp^3)-F counterpart has been comparatively less well explored.[6] Breakthrough in this field comes with the identification of radical based protocols, which makes the incorporation of fluorine atom possible using the following strategies: 1) Terminal C(sp^3)-F bond formation through radical addition to alkenes.[7] For example, Boger and Li have demonstrated hydrofluorination and aminofluorination of unactivated alkene respectively. 2) Functional group interconversion.[8] Representative examples of decarboxylative fluorination were developed by Li and Sammis groups. Very recently, an elegent work of silver-catalyzed fluorination of alkylboronates was also reported by Li group.[8a] 3) Aliphatic C-H fluorination.[9] In this respect, Groves and co-workers have developed a Mn/phorphyrin-mediated fluorination of aliphatic molecules. While Lectka and co-workers used Cu/Schiff base complex to accomplish the same procedure. Notwithstanding considerable advances being attained in the arena of C(sp^3)-F bond construction, prominent limitations still remain, such as heavy reliance on electronic biased substrates as those having benzylic or allylic C-H bonds or requirement of substrate prefunctionalization as well as low regioselectivity in the case of radical based fluorination of unactivated alkanes which possess different potential reaction sites and the situation becames more complicated when the generated C-F moieties possessed acidic protons, such as those of β-fluoroketones, which would easily lose the incorporated fluorine atom through facile dehydrofluorination process. Electrophilic fluorination, however, is mainly restricted to the synthesis of α-fluoro carbonyl compounds.[8b] As such, the development of a general protocol which affords β- or even γ-fluoroketone analogues with high efficiency and praticality would be of high synthetic importance.



Scheme 1. Oxidative Fluorination of Cyclopropanols.

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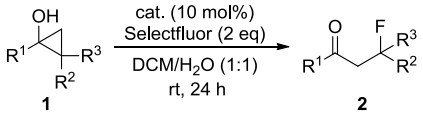
Cyclopropanols are versatile compounds which can be easily prepared by the Kulinkovich[10,11] reaction or by treatment of sily enol ether with diiodomethane in the presence of Et_2Zn.[12] Because of its unique structure, cyclopropanol can be treated as the equivalent of homoenolate in the case of transition metal catalysis[13,14] on one hand and as *β*-keto radical, provided that suitable oxidants such as manganese salts,[12a] CAN,[15b] persulfate[15c] were employed. Based on our continuing interest in fluorine chemistry, we envisage that oxidative fluorination of cyclopropanol would be an efficient and straightforward protocol for the ready access to *β*-fluoroketones by taking advantage of such radical rearrangement (Scheme 1).[16] Herein we would like to report a silver- or iron-catalyzed ring opening fluorination of cyclopropanol with Selectfluor® reagent in aqueous solution under mild reaction conditions, which provides a convenient and efficient method for the access to *β*-fluoroketones. It also needs to be pointed out that this strategy could be further extended to cyclobutanol or even cyclopentanol thus providing site-specific formation of *γ*- or *δ*-fluoroketones.[17]

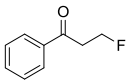
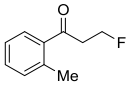
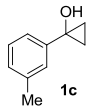
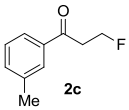
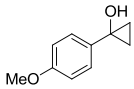
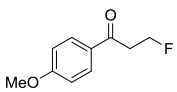
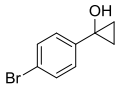
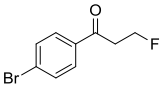
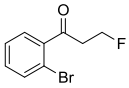
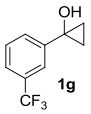
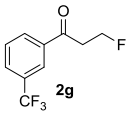
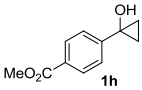
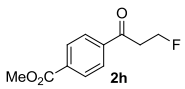
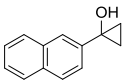
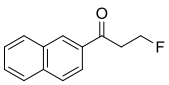
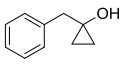
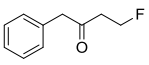
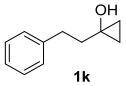
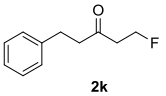
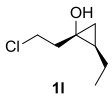
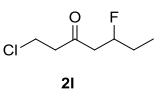
To test our hypothesis, 1-phenylcyclopropan-1-ol (**1a**) and Selectfluor® were employed as model substrates and the reaction parameters were systematically investigated. We were rather pleased to find that the desired fluorination product **2a** was produced in 13% yield with $AgNO_3$ as catalyst, MeOH/H_2O (1:1) as solvent (refer to supporting information for details of reaction condition optimization). Upon screening diverse solvents, DCM/H_2O (1:1) mixed solvent was proved to be the optimal choice, which delivered **2a** in 92% yield. It was found that $K_2S_2O_8$, which is widely used in silver-catalyzed fluorination reaction as a co-oxidant, was not required in this reaction.[18] Although $Fe(acac)_3$ stood out as a more effective catalyst in the model reaction, which gave **2a** in 96% yield, limited substrate scope was observed in the following investigations (vide infra). When NFSI was employed in place of Selectfluor® as the fluorine donor, no desired fluorination product **2a** was detected. Finally, the control experiment clearly demonstrated the pivotal role of silver or iron as catalysts in this transformation as only 8% yield of product was obtained in their absence.

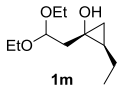
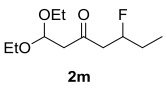
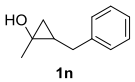
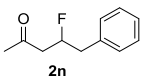
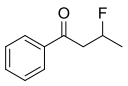
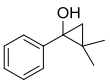
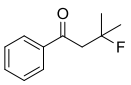
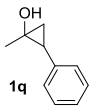
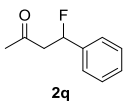
With the optimal reaction conditions in hand, the reaction generality with respect to cyclopropanol was examined, and the results were summarized in Table 1. It was found that $Fe(acac)_3$ was the proper catalyst in the case of aryl substituted cyclopropanols, with **1a**, **1c, 1o** smoothly transformed into **2a**, **2c**, **2o** in 96%, 95%, 94% yields, respectively. However, with respect to alkyl and electron-deficient or stericallly encumbered aryl derived cyclopropanols, $Fe(acac)_3$ proved to be unsuitable.[19] In contrast, $AgNO_3$ based protocol accommodated a wide variety of cyclopropanols ranging from monosubstituted to trisubstituted ones, thus affording the desired fluorination products in high to excellent yield. Alkyl substituted cyclopropanols, which exhibited low reactivity with $Fe(acac)_3$, were soomthly transformed into the desired products in the yields ranging from 74% to 94% (**1j** – **1n**). A variety of synthetically useful functional group, such as methoxyl, acetal, ester, and trifluoromethyl, as well as halogen, which would provide the opportunity for further elaboration *via* traditional coupling strategies, were all well tolerated. It is worth mentioning that when 1,2-disubstituted or 1,2,2-trisubstituted cyclopropanols were employed, the fluorine atom was introduced onto the more substituents containing carbon atom *via* selective cleavage of C-C bonds (**1l-1q**). To prove the scalability of this method, a gram scale reaction of **1m** was attempted and provided product **2m** in 78% yield.

Table 1 Substrate scope of oxidative fluorination.[a]



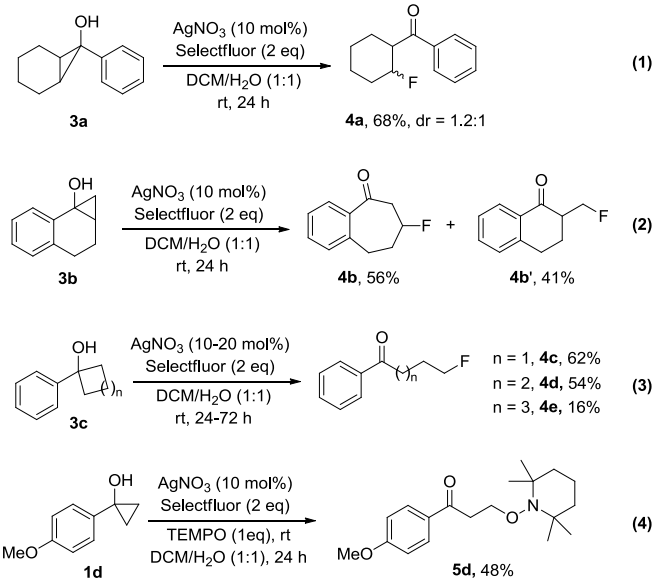
1 2

Entry	Substrate	Product	Yield[a] (%)
1	 1a	 2a	96[b]
2	 1b	 2b	89
3	 1c	 2c	95[b]
4	 1d	 2d	99
5	 1e	 2e	92
6	 1f	 2f	97
7	 1g	 2g	83
8	 1h	 2h	74[c]
9	 1i	 2i	93
10	 1j	 2j	91
11	 1k	 2k	94
12	 1l	 2l	74

13	 1m	 2m	88
14	 1n	 2n	79
15	 1o	 2o	94[b]
16	 1p	 2p	90[b]
17	 1q	 2q	99

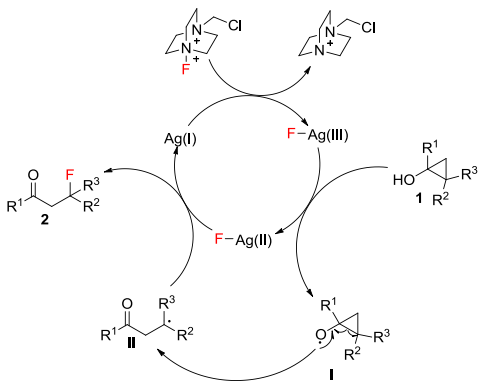
[a] Unless otherwise noted, the reactions were carried out at rt using 1a (0.1 mmol), Selectfluor® (0.2 mmol), $AgNO_3$ (0.01 mmol) in DCM/H_2O (1:1,1 mL) for 24 h. Yield of isolated products are given. [b] Using $Fe(acac)_3$ as catalyst. [c] Reaction was run at 50 °C.

To further probe the reaction profile with respect to fluorine atom incorporation step, 7-phenylbicyclo[4.1.0]heptan-7-ol **3a** was synthesized and subjected to the optimized reaction condition, which produced product **4a** as a mixture of 1.2:1 diastereoisomers in 68% yield, implying a non-stereoselective C-F bond formation step in this case (Equation 1). In stark contrast to the selective C-C bond scission in the cases of **1l**-**1q**, the bicyclic substrate **3b** underwent unselective C-C bond cleavage to provide a mixture of **4b** and **4b'** in 56% and 41% yields, which could be ascribed to the torsion effect encountered during the ring enlargement process (Equation 2). With the success obtained for the expedient synthesis of *β*-fluoroketone *via* oxidative ring opening fluorination of cyclopropanol, we wondered if the fluorination could also be implemented with four-membered or even higher-membered substrates to synthesize *γ*- or *δ*-fluoroketones. To our delight, when expanded cyclic substrate **3c**-**3e**



were examined with slight modification of reaction condition, corresponding *γ*-, *δ*- and *ε*-fluoroketone products **4c**-**4e** were readily obtained, albeit with decreased reactivity with the enlargement of the ring size (Equation 3). It is well known that cyclopropanols could deliver reactive *β*-keto radicals under suitable oxidative conditions.[15] The selective cleavage of C-C bonds with respect to 1,2-disubstituted cyclopropanols also indicated the radical pathway of this protocol. Furthermore, with the addition of 1 equivalent of 2,2,6,6-tetramethylpiperidinooxy (TEMPO) as a radical scavenger, the desired reaction between **1d** and selectfluor was totally inhibited while product **5d**, a putative *β*-keto radical trapped by TEMPO, was instead obtained in 48% isolated yield (Equation 4).

Based on these experiment results and precedents, the reaction pathways were tentatively proposed as shown in Scheme 2.[20] The reaction starts with the oxidation of Ag(I) by Selectfluor® reagent to generate Ag(III)-F intermediate, presumably via oxidative addition.[7a, 7b, 8a, 8b] Single electron transfer between **1** and Ag(III)-F intermediate happens to generate oxygen centered radical **I**, which undergoes fast and selective rearrangement to deliver a carbon centered *β*-keto radical **II**. The subsequent abstraction of the fluorine atom from the adjacent Ag(II)-F occurs to produce the *β*-fluoroketone **2** and regenates the Ag(I) species. At this stage, the reaction pathway that proceeded through the formation of dinuclear Ag(II) intermediate but not Ag(III)-F congener could not be precluded.[5g]



Scheme 2. Proposed reaction mechanism.

In conclusion, we have reported an efficient and general method for the synthesis of *β*-fluoroketone under very mild conditions using Selectfluor® as the fluorine source. This reaction works efficiently and delivers the desired *β*-fluoroketones in high to excellent yields. In addition, because of the mild reaction conditions, this reaction exhibits tolerance of a variety of synthetically useful functional groups. Furthermore, by simply employing cyclobutanol, cyclopentanol and cyclohexanol as substrates, *γ*-, *δ*- and even *ε*-fluoroketone could be readily obtained with this protocol.

Acknowledgements

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19 The mechanism of Fe-catalysed reaction was assumed to be similar with the Ag system, wherein the in situ generated Fe(IV)-F may act as both oxidant and fluorine transfer intermediate.

20 Another possible mechanistic pathway which proceed through Selectfluor induced radical chain process was also took into account, however, experiment using $Mn(OAc)_3$, which is an effective single electron oxidant of cyclopropanol, as catalyst affords the desired product in less than 10% yield.