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ARTICLE TYPE

Transition-Metal-Free C-H Oxidative Activation: Persulfate-Promoted Selective Benzylic Mono- and Difluorination

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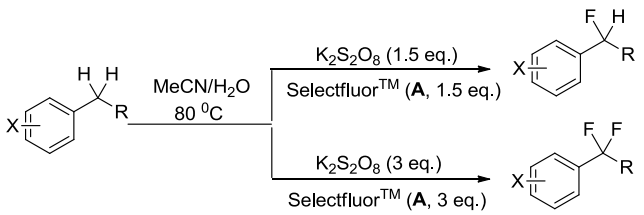
An operationally simple and selective method for the direct conversion of benzylic C-H to C-F to get the mono- and difluoromethylated arenes using Selecfluor™ as a fluorine source was developed. Persulfate can be used to selectively activate benzylic hydrogen atoms toward C-F bond formation without the aid of transition metal catalysts.

Fluorine-containing molecules are of particular interest in the fields of pharmaceuticals, perfumes, flavorings, dyes, agricultural chemicals, monomers, and polymers, as well as many other applications due to fluorine's low surface energy, biocompatibility and extreme hydrophobic properties.[1] For instance, monofluoromethyl (-CFH_2) and difluoromethyl (-CF_2H) arenes have been used as oxygen mimics in molecules such as nucleotides, phosphate esters and sulfate esters.[2-3] Recently, a variety of methods have been successfully developed for the preparation of these fluorine-containing compounds, including functional group transformation, transition-metal-catalyzed C-H insertion/abstraction[4-8] and direct benzylic C-H fluorination.[9-18] Direct benzylic C−H fluorination is an ideal protocol for the synthesis of fluoromethylarenes without prior installation of a functional group at the reaction site. There are two main strategies of direct benzylic C−H fluorination: transition-metal-catalyzed C-H activation[9-15] and radical (induced *via* organocatalysts and visible light) reactions under transition-metal-free conditions.[16-18]

The challenge of direct C-F functionalization of benzylic sp^3 C-H bonds has been overcame using copper(I) or iron(II) catalysts by Lectka's group in recent two years.[9-10] In 2012, a $Pd(OAc)_2$-catalyzed direct fluorination of functionalized 8-methylquinolinyl substrates in the presence of hypervalent iodine and silver fluoride (AgF) *via* redox process was reported by Sanford and co-workers.[11,12]Groves *et al*. developed a late stage method for C-H fluorination with [^{18}F]fluoride for PET imaging by using Mn(Salen)OTsas F-transfer catalyst, enabling the facile labeling a variety ofbioactive molecules and building blocks with monofluorobenzylic group in 2014.[13,14] Tang's group reported the difluorination of benzylic C-H under Ag(I)/$S_2O_8^{2-}$ co-catalytic system, in which the benzylic radical model induced by persulfate oxidative intermediate Ag(Ⅱ) was proposed.[15] Metal-free fluorination of C(sp^3)-H bonds using a catalytic *N*-oxyl radical was reported by Inoue *et. al*. in 2013.[16] Chen and co-workers first demonstrated a visible light promoted metal-free C-H activation in the presence of diarylketone to selectively form mono- and difluoromethylarenes in 2013.[17] Very recently, Kappe found a light-induced fluorination of benzylic compounds bearing different functional groups applying residence times below 30 min.[18]

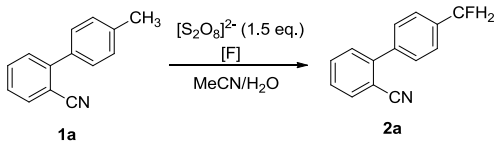
Scheme 1 Persulfate-promoted benzylic C-H fluorination.



With our interest in radical fluorination systems that use simple and relatively cheap reagents, we found recently that this stable, inexpensive,[19] and commercially available potassium persulfate can smoothly promote direct benzylic C-H fluorination to form mono- and difluoromethylated arenes under transition metal free conditions using Selectfluor™(1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octanebis(*tetra*fluoroborate), **A**) as fluorine source. To the best of our knowledge, there is no example using such a simple and easily system for oxidative C-H fluorination (Scheme 1).

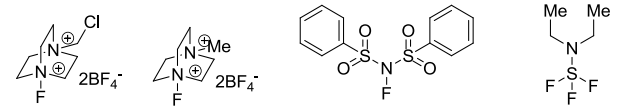
Our initial investigations were focused on the mono-fluorination of benzylic C-H bonds promoted by persulfate, which is a well-known economic and efficient radical initiator.[20] **1a** was selected as a standard substrates to carry out this monofluorination reaction, and a set of conditions were screened (Table1). The best results was achieved by using 1.5 equiv. of Selectfluor™ and 1.5 equiv. of potassium persulfate in MeCN/H_2O (v/v=1:1) at 80 ℃ for 4 h, giving 4'-fluoromethyl-2-cyanobiphenyl (**2a**) in 84% yield (entry 4).There was only trace of product could be detected at 45 ℃ by GC-MS (entry 1) indicating that the fluorination is temperature-dependent. Lower yields were obtained by reducing the content of fluorine source and persulfate (entries 2-3). It was found that difluorination product occurred when the loading of Selectfluor™ was increased (entry 5). $K_2S_2O_8$/$AgNO_3$ system, which is already known for the C-H activation,[21] did not significantly improve this reaction (entry 6). Beside the potassium persulfate, other persulfates were also screened, but there was no obvious difference was found (entries 7-8), which proved that $S_2O_8^{2-}$ plays a crucial role in this reaction. In terms of different fluorination reagents, it was found that Selectfluor™ (II)(1-methyl-4-fluoro-1,4-diazoniabicyclo[2.2.2] octanebis(tetrafluoroborate), **B**) could also give the corresponding product with satisfactory yield (entry 9). Other electrophilic

Table 1 Screenings of the monofluorination



1a 2a

Entry	Promoter	[F](eq.)	T (℃)	Yield (%)
1	$K_2S_2O_8$	A(1.5)	45	Trace
2	$K_2S_2O_8$	A(0.5)	80	37
3	$K_2S_2O_8$	A(1.0)	80	61
4	$K_2S_2O_8$	A(1.5)	80	84
5	$K_2S_2O_8$	A(2.0)	80	71
6	$K_2S_2O_8$	A(1.5)	80	85[b]
7	$Na_2S_2O_8$	A(1.5)	80	81
8	$(NH_4)_2S_2O_8$	A(1.5)	80	82
9	$K_2S_2O_8$	B(1.5)	80	83
10	$K_2S_2O_8$	C(1.5)	80	Trace
11	$K_2S_2O_8$	D(1.5)	RT	N.D.[a]
12	$K_2S_2O_8$	AgF(1.5)	80	N.D.[a]
13	$K_2S_2O_8$	LiF(1.5)	80	N.D.[a]



Selectfluor (A) Selectfluor (II) (B) NFSI (C) DAST (D)

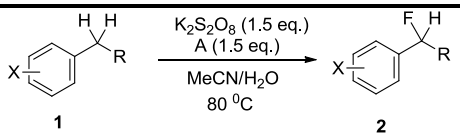
Reaction condition: **1a** (0.2 mmoL) in MeCN/H_2O (1:1, 4 mL), isolated yield; [a] not detected by GC-MS; [b] 0.1 equiv. of $AgNO_3$ was added.

fluorination reagent, such as NSFI (*N*-fluorobenzenesulfonimide, **C**), could not serve as efficient fluorination reagents to produced fluorinated arene **2a** and only trace of fluorinated product could be detected (entry 10). No fluorinated product was observed in the reaction with nucleophilic fluorination reagent DAST (diethyl -aminosulfurtrifluoride, **C**) and metal fluoride AgF and LiF (entries 11-13).

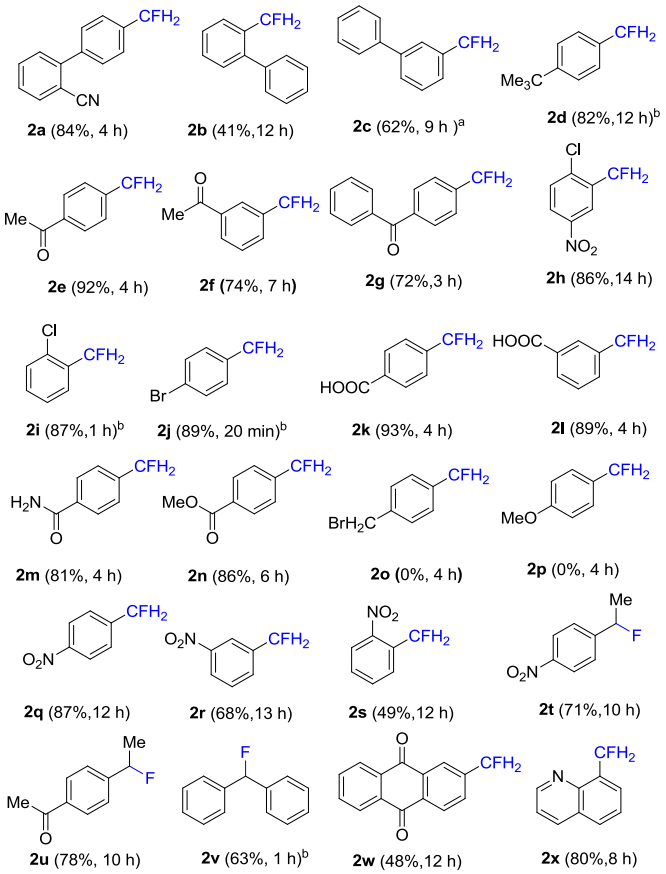
The scope of reactions promoted by the $K_2S_2O_8$ system under the optimize conditions described above were explored. As the results displayed in Table 2, a wide variety of functional groups, including cyanide (**2a**), phenyl (**2b-2c**), *tert*-butyl (**2d**), ketones (**2e-2g**), halos (**2h-2j**), derivatives of carboxylic acid (**2k-2m**) were tolerated in the reaction, and the monofluorinated products were obtained in moderate to good yields. However, benzyl bromide and anisole failed to give the desired outcome (**2o-2p**). Steric hindrance was shown to significantly affect the efficacy of the fluorinations and demonstrated by the reactions of the three nitrotoluene isomers (**2q-2s**) (*o*: *m*: *p* = 49% : 68% : 87%). α-branched benzylic substrates, afforded the corresponding mono-fluorinated products (**2t-2v**) smoothly. However, the present method did not work for α,α-disubstituted benzylic arenes, such as isopropyl benzene. Fused cyclic compounds 2-methyl -anthracene-9,10-dione and 8-methylquinoline were also investigated, providing the desired fluorinated products **2w** and **2x** in 48% and 80% respectively.

We suspected that the difluorinated product could be obtained by increasing of the amount of Selectfluor™ and $K_2S_2O_8$ and difluorination could be easily achieved in 75% yield in the presence of 3 equiv. of fluorination regent and $K_2S_2O_8$ with no

Table 2 Scope of $K_2S_2O_8$-promoted the monofluorination

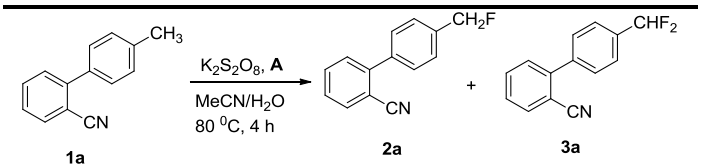


1 2



Reaction condition: **1** (0.2 mmoL), A (1.5 equiv.) and $K_2S_2O_8$ (1.5 equiv.) in MeCN/H_2O (v/v = 1:1, 4 mL), isolated yield; [a] ^{1}H-NMR yield based on **1c**; [b] GC yield (challenging to get purification due to high volatility and the reported yields are the average GC yields of three trials and determined by ^{19}F-NMR).

Table 3 Screenings of the difluorination



1a 2a 3a

Entry	$K_2S_2O_8$ (eq.)	A (eq.)	Yield (**2a**/**3a**, %)
1	1.5	2	71/13
2	2.5	2	41/26
3	3	2	15/50
4	3	3	0/75
5	4	4	0/63

Reaction condition: **1a** (0.2mmoL), MeCN/H_2O (v/v = 1:1, 4 mL), isolated yield.

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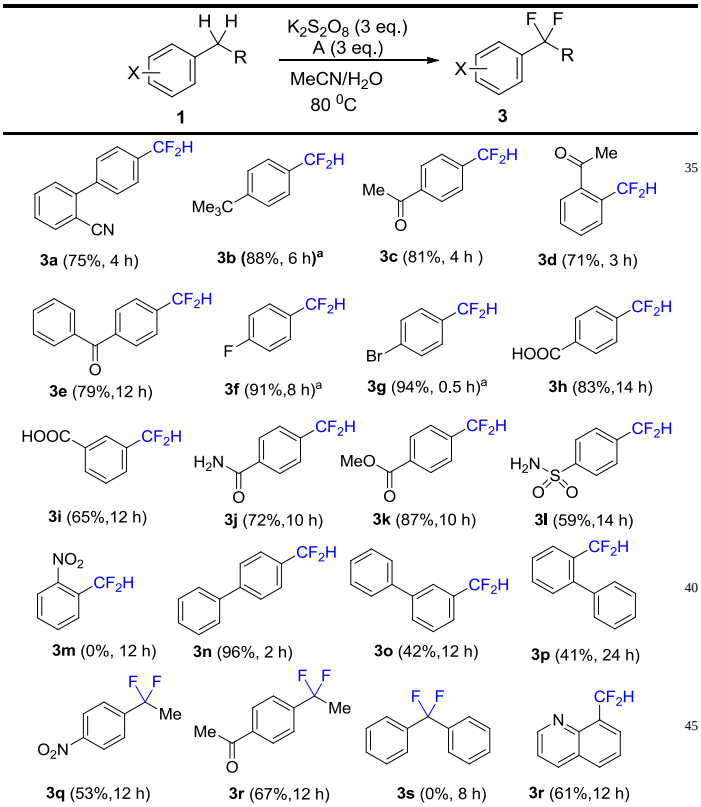
monofluorinated product being detected (entry 4). Further increasing the content of fluorination reagent and persulfate led to oxidation byproducts (entry 5).

Table 4 Scope of $K_2S_2O_8$-promoted the difluorination

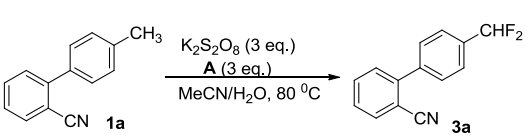


Reaction condition: **1** (0.2 mmoL), A (3.0 equiv.) and $K_2S_2O_8$ (3.0 equiv.) in MeCN/H_2O (v/v =1:1, 6 mL), isolated yield; [a] GC yield based (challenging to get purification due to high volatility and the reported yields are the average GC yields of three trials and determined by ^{19}F-NMR)

Under the new conditions, a broad range of substrates can be difluorinated cleanly (Table 4). A variety of substituent groups (cyanide, **3a**; *tert*-butyl, **3b**; ketones, **3c-3e**; halos, **3f-3g**; carboxylic acid derivatives, **3h-3k**; phenyls, **3n-3p**) on the aromatic ring can be tolerated. Similar to the monofluorination reaction, steric factors have a significant effect on the outcome shown by *o*-nitrotoluene (**3m**, 0%) and biphenyl cases (**3n-3p**)(*o* : *m* : *p* = 41% : 42% : 96%). Ethyl-4-nitrobenzoate and 1-(4-ethylphenyl)ethanone, as α-branched benzylic substrates, were also difluorinated to the desired products (**3p-3q**). However, diphenylmethane failed to deliver difluorinated product (**3s**). 8-methylquinine provided the difluoromethyl product in 61% yield (**3r**).

Attempts were made to obtain insights into this reaction. Tetramethylpiperidine *N*-oxide (TEMPO) and 1,1-diphenylethylene (diyldibenzene), two typical radical scavengers, were employed in the reaction (Scheme 2). Although no trapped products could be isolated, the incorporation of scavengers at any point during the reaction was found to inhibit the reaction (Table 3). These

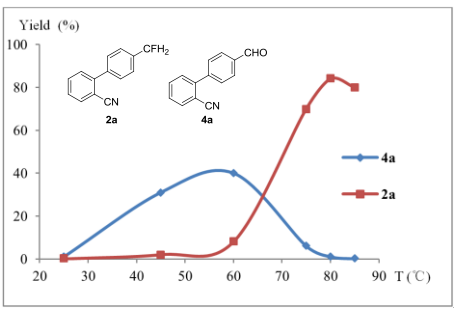
Scheme 2 Radical trapping experiment



No Scavenger	75%
TEMPO (3 eq.)	0
diyldibeneze (3 eq.)	0

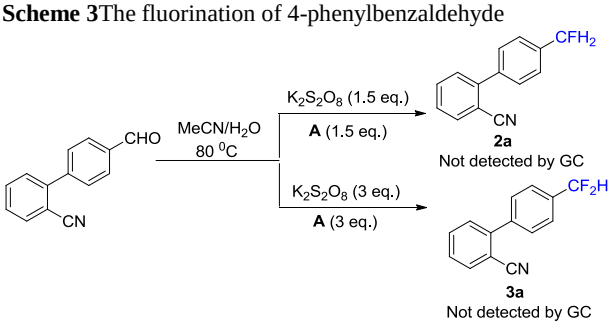
results demonstrate that such a fluorination process may involve a radical reaction mechanism.

Figure 1 Persulfate-promoted competitive benzylic oxidation and fluorination.

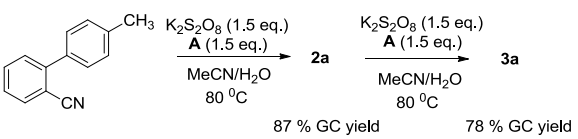


To better understand this temperature-dependent fluorination, which was shown by Figure **1**, competitive mechanism between the oxidation and fluorination was systematically studied using the model reaction of Scheme 2 monitored by GC-MS. The compound distribution in the reaction mixture at different temperature shown in Figure 1 indicates the oxidation product **4a** dominates the reaction below 60 ℃ and then slowly decreased to <1% yield at 80℃, while the GC yield of fluorination product **2a** dramatically increases to 87% at 80℃from 8% at 60 ℃.

Scheme 3 The fluorination of 4-phenylbenzaldehyde



Scheme 4 The one-pot two step fluorination



The reaction of 4'-formyl-[1,1'-biphenyl]-2-carbonitrile failed to give the corresponding fluorinated products (Scheme 3), proving experimentally that aldehyde is not an intermediate for the fluorination[22]. The sequence of this persulfate-promoted

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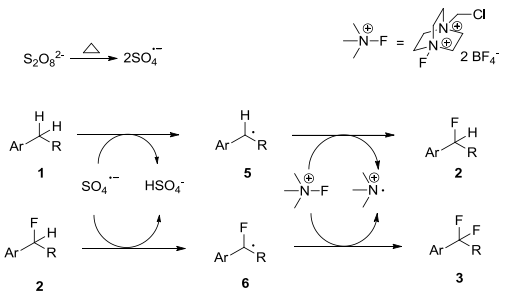
fluorination was further conformed by a one-pot two step protocol (Scheme 4).

Figure 2 The plausible mechanism for persulfate-promoted benzylic C-H fluorination



Although the precise reaction mechanism remains to be clarified, we prefer a plausible radical mechanism is shown in Figure 2. Firstly, a benzylic hydrogen is abstracted by a $SO_4^{\cdot-}$ radical, which is generated from the homolytic cleavage of persulfate[23], gives rise to a benzylic radical **5.** Next, a fluorine atom is transfered to the benzylic radical **5** to provide the monofluoride product **2**. Difluorinated arenes were formed according ananalogous protocol *via* a fluorinated benzylic radical **6**.

In conclusion, we have disclosed a direct benzylic C-H fluorination under transition-metal-free conditions in the presence of cheaper and readily available potassium persulfate. By modulating the amounts of Selectfluor™ and persulfate, mono- and difluoromethylarenes could be selectively obtained in moderate to good yields. Further studies on the application to other fluorinations are currently undergoing in our laboratory.

Notes and references

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