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Selective fluorination of alkyl C-H bond via photocatalysis

Cite this: DOI: 10.1039/x0xx00000x

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Received 00th January 2012,
Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

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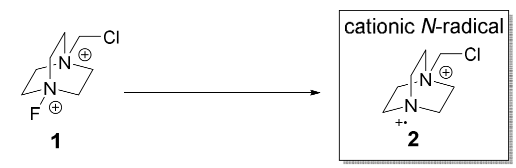
We report the generation of cationic *N*-radical from Selectfluor® via energy transfer with Anthraquinone as photocatalyst for the fluorination of unactivated C-H bond.

Fluorinated compounds are of paramount importance in medicinal chemistry.[1] Access to diverse fluorinated building blocks has the potential to broaden our existing library of fluorinated drugs. Significant progress has been made in the introduction of fluorine to arenes[2] and asymmetric fluorination *via* electrophilic and nucleophilic fluorine source.[2b, 3] Recently, radical-based approach to introduce fluorine into sp^3 carbon centres has received increased attention.[4] C-F bond formation through the generation of *C*-radical *via* functionalized substrates was demonstrated by Li[5] and Sammis.[6] These studies utilized Selectfluor® and *N*-fluorobenzenesulfonimde (NFSI) as radical fluorine source, respectively.

Selective fluorination *via* alkyl C-H functionalization is highly attractive due to the ubiquity of alkyl C-H bonds and avoidance of the need to pre-functionalise substrates.[7] Fluorination of aliphatic, allylic, and benzylic sp^3 C-H bonds has been demonstrated by Britton,[8] Chambers and Sandford,[9] Chen,[10] Dolye,[11] Groves,[12] Lectka,[13] Inuoe[14] and Sanford.[15]

Two strategies for selective functionalization of unactivated C-H bonds have been coined by Baran and co-workers: Innate[16] and guided[17] C-H activation.[18] Pertinent to innate C-H functionalization, the literature of radical chemistry indicates that selective abstraction of unactivated C-H bond could be achieved *via* the use of electrophilic/nucleophilic radicals.[19] In particular, the use of cationic *N*-radicals as electrophilic radicals to selectively chlorinate or brominate electron rich C-H bond has been well documented in literature.[20] However, to the best of our knowledge, analogous fluorination reaction which exploits the selectivity of cationic *N*-radical to achieve selective fluorination *via* C-H functionalization has not been developed. Pertinent to the use of *N*-radical in C-H functionalization, Li and co-workers reported preliminary results on the guided fluorination of C-H bond with amidyl radical recently.[5c]

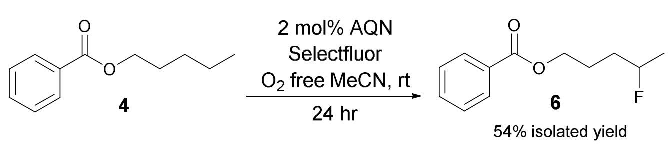
The stable and commercially available Selectfluor® is a well-established electrophilic fluorine source[21] and is amenable to structural modification.[22] Structurally, it possesses a dicationic core and is thus an attractive starting point to generate cationic *N*-radical for C-H functionalization.



Scheme. 1 Generation of cationic *N*-radical from Selectfluor®

Photochemistry is an important tool in organic synthesis,[23] and in particular, photoredox catalysis has experienced tremendous advancement recently.[24] Photochemistry has a long history in C-H functionalization;[25] for example, bromination of alkanes with Br_2 could be performed with visible light[26] and the use of polyoxomelate[27] as photocatalyst in C-H activation.[25a] Given our interest in C-H functionalization *via* photochemistry,[28] we decided to explore the feasibility of photo-chemically generate cationic *N*-radicals to selectively fluorinate alkyl C-H bonds.

We found that site selective fluorination of secondary C-H bond most distal to electron withdrawing group (EWG) can be achieved with Selectfluor® and catalytic amount of anthraquinone (AQN). Benzoyl ester **4** was chosen as the model substrate to study the effects of various factors on the fluorination reaction (Scheme 2).



Scheme. 2 For more details and control experiments please refer to ESI.

Control experiments established that both AQN and light are essential to the reaction. Triplet dioxygen was found to be detrimental to the reaction (refer to ESI for more detail).

A diverse variety of functional groups can be tolerated with the photo-fluorination (Figure 1). For aliphatic linear substrates, secondary C-H bond most distal to the EWG was fluorinated with the highest selectivity. Benzoyl esters of aliphatic alcohols are fluorinated predominantly at the secondary C-H bond most distal to the OBz group (Figure 1, **5**-**8**). For **8**, the tertiary C-H bond is disfavoured due to its proximity to the OBz group; hence selective fluorination of secondary C-H over the thermodynamically weaker tertiary C-H bond could be achieved. Sulfonate compound **9** gave similar result to Bz protected compounds.

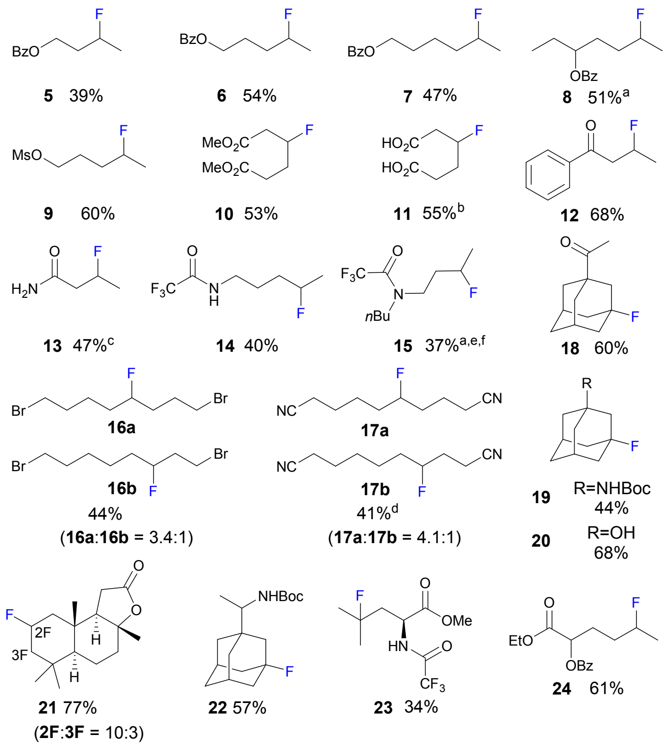


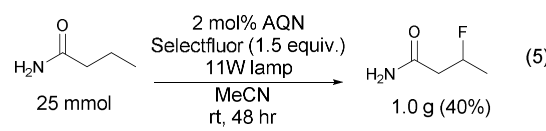
Fig. 1 Scope of the reaction; Protocol: 2 mol% of AQN, Substrate: Selectfluor = 1.5:1 (2 mmol), 8 mL of anhydrous and O_2 free MeCN, under Ar and irradiation from an 11W fluorescent bulb, unless otherwise stated; Isolated yield. [a] Inseparable diastereomers/isomers. [b] Converted to ester to facilitate separation. [c] 5 mmol of substrate [d] 1.5 equiv. of Selectfluor. [e] 2 equiv. of substrate [f] 2-Cl-AQN (2-chloroanthracene-9,10-dione) was used as photocatalyst, R_f of AQN and product is the same on TLC. Only the major product is depicted. For detailed information on experimental procedure and ratio of other minor isomeric fluorinated products please refer to ESI.

Currently, few methods allow the direct β-functionalization of carbonyl compounds.[29] The direct β-fluorination of carbonyl groups such as ester, carboxylic acid, ketone and amide is unknown and can be achieved with this methodology. Methyl ester of adipic acid **10**, adipic acid **11** and 1-phenylbutan-1-one **12** were fluorinated at the β-position and were obtained in good yield. For **12**, slight dehydrofluorination occurred during flash chromatography, leading to lower than expected yields. Primary, secondary and tertiary amides functional groups are tolerated, although their yields are generally lower. Butyramide could be fluorinated at the β-position on 5.0 mmol scale; recrystallization yielded 3-fluorobutanamide **13** of high purity. Free amine groups are not tolerated by the photo-fluorination; however, fluorination became viable when the amine is protected with the trifluoroacetyl group. Selectivity of protected amines is similar to that of protected alcohols. Secondary amide of 1-pentylamine was fluorinated at the C-H most distal leading to the amide group. Similar result was observed for tertiary amide of dibutylamine **15**. Aldehyde group is not tolerated; an acid fluoride was formed through the fluorination of aldehydes' C-H bond. Alkyl bromides are generally less reactive. The electron withdrawing effect exerted by bromo group is weaker and thus also resulted in lower selectivity. For example, when 1,8-dibromooctane was used mixture of 4- and 3-fluorinated compounds were obtained in a ratio of 3.4:1(**16a: 16b**) respectively. Nitriles exhibit similar reactivity and selectivity as the alkyl bromides. Decanedinitrile could be fluorinated to give 5-fluoronitrile **17a** and 4-fluoronitrile **17b** in a ratio of 4.1:1.

The adamantane core is present in several biologically active molecules such as antiviral drugs and saxagliptin (Type II diabetes therapeutic). Fluorinated methyl ketone adamantane **18**, -*N*Boc amantadine **19**, tertiary alcohol adamantane **20**, and -*N*Boc rimantadine **22** are obtained through fluorination at the tertiary position on the admantyl group. Due to the high reactivity of the tertiary C-H bond on the adamantane core,[30] some difluorination was observed.

(+)-Sclareolide, a terpenoid from plant with antifungal and cytotoxic properties,[31] was subjected to the photo-fluorination. Amongst its 26 sets of C-H bonds, C2 and C3 was selectively fluorinated to give combined high yield of 77% and a selectivity of 10:3 (**21**). *N*Boc-derivative of Derivative of *L*-Leucine **25** was fluorinated selectively at the tertiary C-H bond furthest from its electron-withdrawing groups (**23**). Fluorination of amino acid via C-H functionalization has also been reported by Britton[8] and Inoue[14]. Analogous hydroxylation has been achieved by White and co-worker with a Fe catalyst.[32] Hydroxyl carboxylic acids (AHAs) are widely used in the cosmetic industrial to treat dermatological disorders.[33] Ester derivative of 2-hydroxyhexanoic acid, an alpha hydroxyl carboxylic acid, could be fluorinated predictably at the secondary C-H bond most distal from its electron-withdrawing groups (**24**).

The scalability of the photo-fluorination was tested by fluorinating butyramide on a 25 mmol scale (Scheme 3).

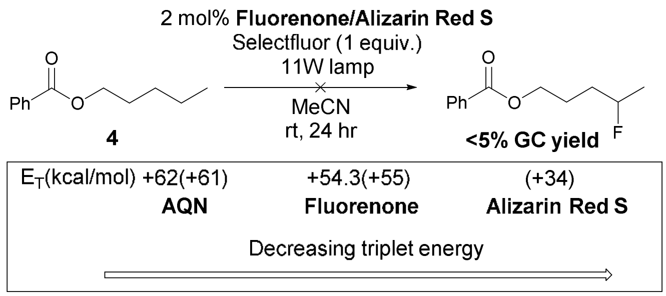


Scheme. 3 Scaling up.

There are two possible species that can play the role of hydrogen abstractor: cationic *N*-radical and triplet AQN. Triplet benzophenone and derivatives are well known as hydrogen abstractor,[25b] while there are less reports for AQN.[34] However, triplet benzophenone[35] and AQN[34a] are reported to be nucleophilic radical. Therefore, they exhibit opposite reactivity observed for the photo-fluorination. Sammis and co-workers had demonstrated that NFSI can be an effective radical fluorine source.[6] The insignificant amount of fluorinated products and most importantly, difference in selectivity when Selectfluor® was replaced with NFSI suggest that Selectfluor® is more than a fluorine source.

Hammett analysis[36] of the photo-fluorination with AQN gave ρ of −3.1 which correlate with σ^+. The ρ of neutral electrophilic hydrogen abstracting radicals are typically from -0.4 to -1.4,[37] thus ρ of −3.1 is consistent with the involvement of cationic *N*-radical.

Chen and co-workers used fluorenone as the photocatalyst for benzylic fluorination, they proposed that triplet fluorenone is the hydrogen abstractor.[10] However, when fluorenone was used to fluorinate **4**, insignificant amount of product was observed. This suggests that a different mechanism is in operation. The reactivity of the photo-fluorination of **4** correlates with the triplet energy (E_T) of the photocatalysts, the singlet-triplet gap of **1** (Scheme 4) is 61.4 kcal/mol, thus triplet-triplet energy transfer[39] is feasible between AQN and **1** but not between **1** and fluorenone or alizarin red S salt.



Scheme. 4 Experiments with relevant photocatalysts. E_T of AQN and fluorenone are taken from Zalesskaya.[38] Numbers in parentheses are calculated E_T.

The selectivity observed for this photo-fluorination resembles that of other reactions using cationic *N*-radicals.[20] Density functional theory was used to predict the selectivity of hydrogen abstraction for triplet AQN and cationic *N*-radical derived from Selectfluor II® **30**. Experimentally, similar selectivity was observed for Selectfluor® and Selectfluor II®. The calculated result shows that **30** has selectivity that is consistent with the experimental results, but not triplet AQN (refer to ESI for more detail).

A preliminary proposal of the mechanism is depicted in Figure 2. Triplet-triplet energy transfer from ^{3}AQN to $\mathbf{1}_{singlet}$ generates $\mathbf{1}_{triplet}$. Significant lengthening of the N-F bond was observed when $\mathbf{1}_{singlet}$ is excited to $\mathbf{1}_{triplet}$. The energy transfer results in the formation of **2** which performs the H abstraction from RH to generate R radical.

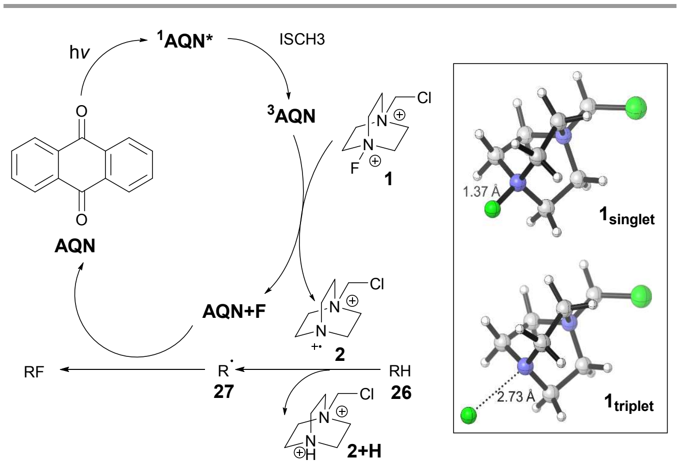


Fig. 2 Proposed mechanism. The singlet ($1_{singlet}$) and triplet state ($1_{triplet}$) geometries of cations of Selectfluor® are in the box. AQN+F implies a possible complex of fluorine and AQN, as fluorine radical is not likely to be formed.

In conclusion, we have developed a photo-fluorination reaction. The reaction can be performed with common low power household lamps. The reaction is selective for electron rich sp^3 C-H bonds due to the involvement of cationic *N*-radical in hydrogen abstraction. This work presents a novel method to generate cationic *N*-radical via triplet-triplet energy transfer catalysed by a photocatalyst AQN and extend the scope of innate C-H functionalization of cationic *N*-radicals to include fluorination. A diverse variety of functional groups can be tolerated by the reaction and it is scalable.

Notes and references

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Electronic Supplementary Information (ESI) available: See DOI: 10.1039/c000000x/

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