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Review

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Novel mild fluorination method using light

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ABSTRACT

Fluorine compounds have attracted interest of scientists for immense applications in medicinal chemistry and pharmaceuticals. Recently, photoredox catalysts, both organic-based and metal-based compounds, have been employed in organic synthetic methodology to achieve desirable products due to facile operation and mild reaction condition. Various protocols to prepare fluorination adducts in the presence of photoredox catalysts have been developed from several starting materials with formation of radical scaffolds. In this review, we describe recent advances in the fluorination using light.

Key Word: Fluorination, radiofluorination, photoredox catalysis, light

Fluorine atoms have special capacity to stimulate various applications such as medicinal chemistry, agrochemicals, and specialized materials (1-4). Typically, the substitution of single hydrogen atoms by fluorine atoms significantly enhances properties of drugs, including the prevention of undesired metabolic reactions at a particular site, the increase of binding affinity or lipophilicity, and modification of drug absorption, distribution, or excretion (1). In addition, fluorine atom is widely exploited in positron emission tomography (PET) imaging technique, which is a non-invasive technique. Specifically, invaluable biological information can be obtained by this method under form of ^{18}F-labeled probes in vivo (5). Moreover, about one-third of the most efficient drugs bear fluorine atoms in its structure, which proves the vital role of fluorine in drug discovery. Thus, various preparation procedures of fluorination have been developed (6-12).

Over the past decade, radical chemistry revived in organic synthesis, which initiated the resurgent interest in photochemistry. This happened due to high reactivity of radical intermediate, which is usually difficult to afford that efficient yield by other chemical catalysis. Perhaps photoredox catalysis is one of the most promptly expanding areas of radical chemistry. Several chemists exploited photoredox catalysis to obtain unique chemical structure because of its availability, sustainability, non-toxicity, and simple handling. Besides, reactions using photoredox catalyst have several advantages such as mild condition, and the absence of radical initiators or stoichiometric number of chemical reductants or oxidants. The general mechanism of most photoredox catalytic reaction has been described in (**Figure 1**) (13).

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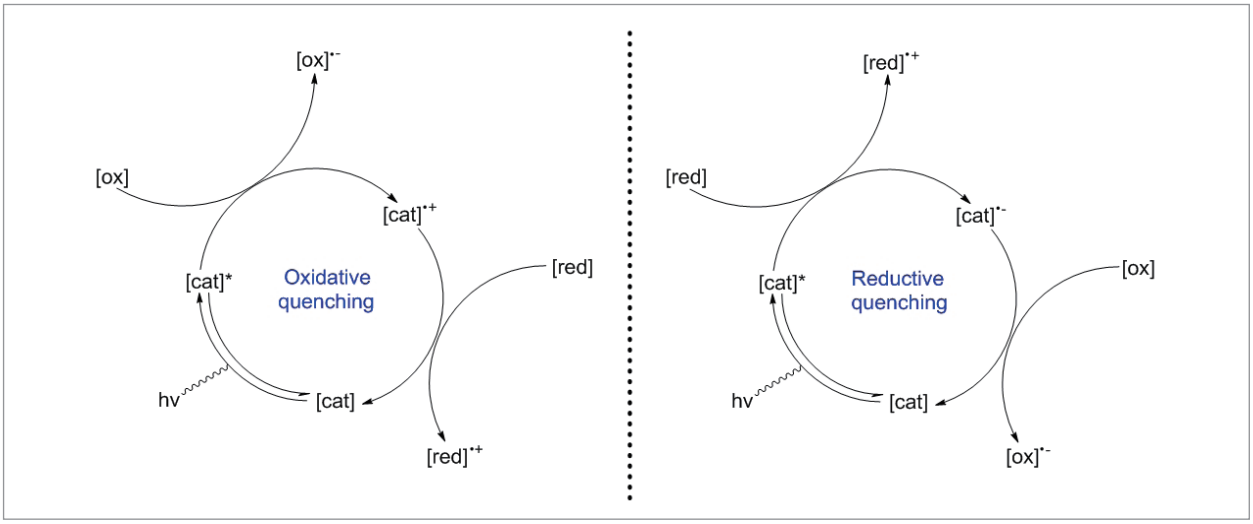


Figure 1. General mechanism of a photoredox-catalyzed reaction.

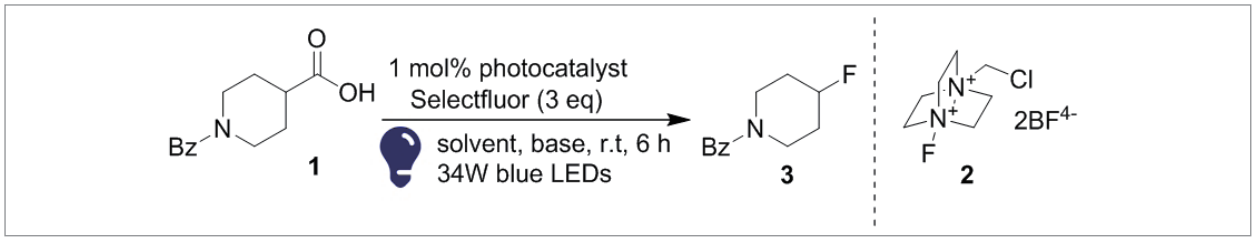
The first organic reaction mediated by photoredox catalysis were reported in 1978 by Kellogg (14). He performed the reduction of phenacyl sulfonium salts under visible light by 1,4-dihydropyridines, which acted as basics for the significant developments in modern photoredox catalysis. In this mini review, we describe the synthetic methodologies of fluorination via photoredox catalysis procedure. Particularly, we would like to focus on recent achievements of two pioneers in Department of Chemistry at Princeton University, USA.

In 2015, the MacMillan group reported a synthetic procedure for decarboxylative fluorination reaction of C(sp^3)-bearing carboxylic acids in the presence of heteroleptic iridium(III) photocatalyst [Ir(dF(CF_3)ppy)$_2$(dtbbpy)]PF_6 4 (**Figure 2**), disodium hydrogenphosphate as a base and Selectfluor reagent as fluorinating source under blue LED light (**Scheme 1**) (15). All reagents employed in this reaction are commercially available. The key point of this reaction is the formation of alkyl radical from the decarboxylation of aliphatic carboxylic acids under photoredox catalytic cycle generated by reduction of N-F bond of 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (Selectfluor). The base acts as a mediating factor to generate alkyl carboxylate prior to carboxyl radical via Single-electron-transfer (SET) oxidation.

With the purpose to find optimal condition of the reaction as mention above, a variety of photocatalysts and bases were investigated by MacMillan group, and [Ir(dF(CF_3)ppy)$_2$(dtbbpy)]PF_6 **4** together with disodium hydrogen phosphate were the most suitable catalyst and base for fluorination reaction. When exploiting other photocatalysts such as Ru(phen)$_3^{2+}$ or Ru(bpz)$_3^{2+}$ **5**, which are more oxidizing than **4**, the reaction occurred slower or no result. Furthermore, there was no products **3** observed while Ru(bpy)$_3^{2+}$ **6** and NaOH were employed (Sammis protocol). The product yield was significantly improved by 2 equiv. of Na_2HPO_4 as a base, perhaps due to the larger deprotonation of carboxylic acid. No fluorinated products were observed when acetonitrile and water was employed independently, which proved the vital role of these two solvents.

With the most suitable reaction condition in hand, various alkyl fluorinated products were successfully achieved through corresponding alkyl carboxylates by MacMillan group. Primary, secondary, and tertiary alkyl carboxylic acids can be used in this reaction without a drop in yield regarding to less substituted acids. Noteworthy, neighbor heteroatom to carboxyl group (α or β) gave CO_2 extrusion/ fluorination reaction in shorter time. Next, in 2019, other

Scheme 1. The direct photoredox-catalyzed transformation of carboxylic acid to fluoroalkane.



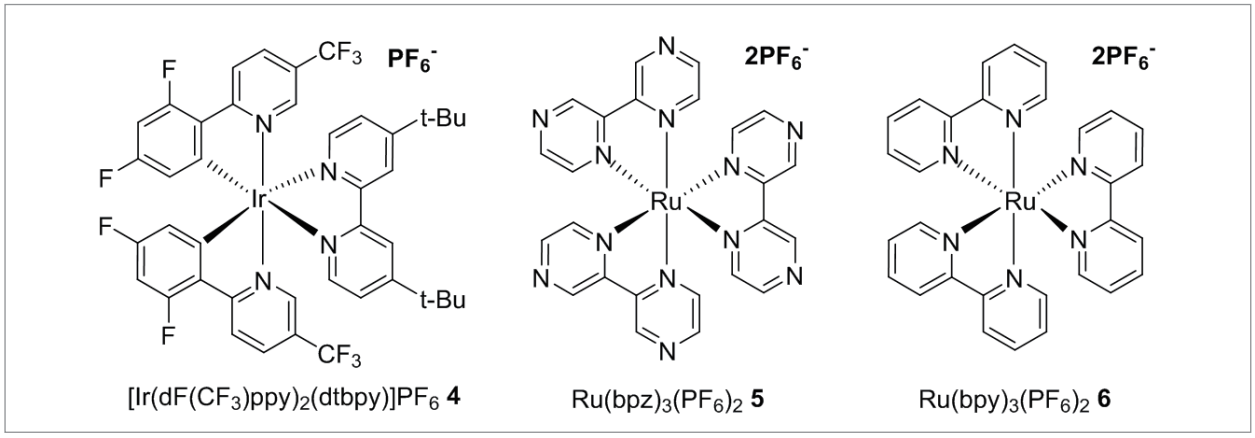


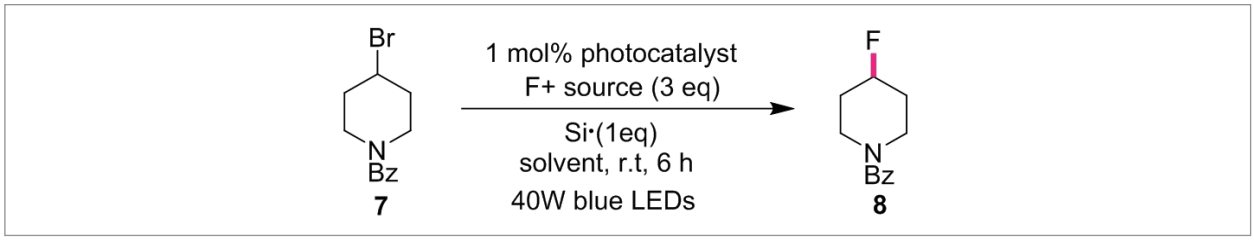
Figure 2. Structure of several photoredox catalysts in the publication of MacMillan group.

$C(sp^3)$–F bond formation protocol has been reported by the MacMillan group, which exploiting alkyl bromides, *N*-Fluorobenzenesulfonimide (NFSI) as mild fluorinating agent, K_3PO_4 as base, and a photocatalyst under visible light irradiation (blue LEDs) in the presence of silyl radical source-supersilanol [$(TMS)_3SiOH$] (**Scheme 2**) (16).

Before finding the most suitable condition for this transformation as above, they performed several investigation reactions. Particularly, they began the screening with 1-benzoyl-4-bromopiperidine **7**, tris(trimethylsilyl)silane [$(TMS)_3SiH$] as the silyl radical source, Selectfluor **2** as the fluorine reagent, together with Na_2HPO_4 in MeCN/H_2O co-solvent under 40W blue LEDs in the presence of [$Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ **4** (**Figure 3**). However, only 1% of fluorinated product **8** was obtained from this reaction. The desirable product (4-fluoro-piperidinyl) **8** were successfully synthesized in 46% yield when the exploitation NFSI as fluorine source and photocatalyst **9**, [$Ir(dF(CF_3)ppy)_2((5,5'\text{-}CF_3)bpy)]PF_6$ were applied. Furthermore, the yield of final fluorinated adduct significantly increased to 87% when supersilanol [$(TMS)_3SiOH$] instead of the $(TMS)_3SiH$, and K_3PO_4 as base were employed for this transformation. No desirable product was observed in the absence of light and supersilanol [$(TMS)_3SiOH$].

With the optimization of reaction in hand, the MacMillan group successfully obtained a wide variety of alkyl fluorinated products from corresponding alkyl bromides. Particularly, the toleration of wide range of 4- to 7-membered rings were achieved in good yield. The sensitive moiety to nucleophilic fluorination protocol, such as benzylic alcohols and phenols, were fully prone to this transformation. Noteworthy, they also delivered fluorinated product of β-fluoroamine, a popular structure in pharmaceutical product, from a corresponding β-bromoamine in 83% yield. Furthermore, several monosaccharides and nucleosides successfully generated α-fluoride-analogs. Other motif could be compatible with this open-shell fluorination reaction to such as: cyclic and acyclic tertiary alcohols, primary alcohols, and several

Scheme 2. Reaction of the direct formation of fluoroalkane from alkyl bromides.



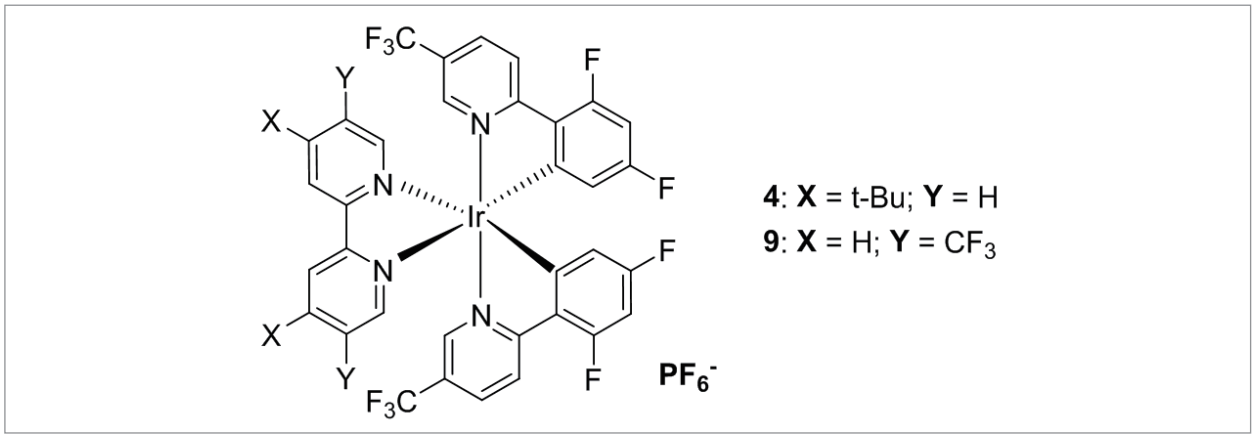


Figure 3. Structure of photoredox catalysts for fluorination reaction derived from alkyl bromides.

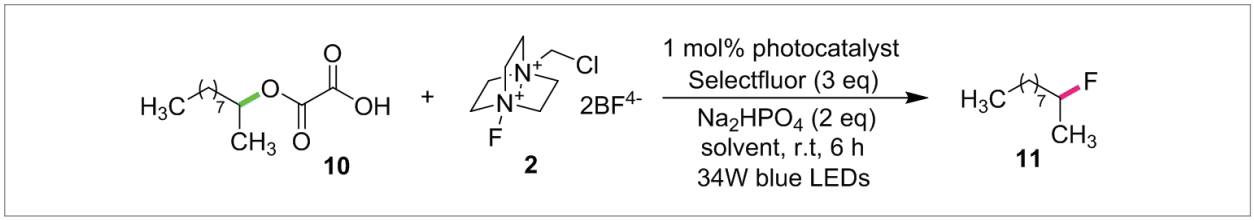
substrate containing carbonyl motif.

Another example of C(sp^3)-fluorination under photoredox catalysis was reported by the MacMillan group within same year (17). In this study, the deoxyfluorination reaction was achieved from irradiation under blue LED light of half oxalate esters (derived from alcohols) with **12** as photocatalyst (**Figure 4**), Na_2HPO_4 as base, and SelectFluor **2** as efficient fluorine source.

They also carried out the screening of different conditions as well as solvents for finding the most suitable reaction condition. Specifically, oxalate of 2-decanol **10** was chosen in optimized reactions together with employment of **2**, Na_2HPO_4 (base), and **4** as photocatalyst under 34W blue LED lamp (**Scheme 3**). As a result, the corresponding deoxyfluorinated product **11** was obtained in 54% yield. When the combination of acetone and water was exploited as solvent, the product was achieved in higher yield (72%). Moreover, photocatalyst **12** provided the best yield for the deoxyfluorination reaction with 87% yield. Water was proven as the critical role for this transformation, the reaction yield decreased to 42% when using only acetone as solvent. This is due to the role of water in maintaining homogeneity for Na_2HPO_4 and **2** in the mixture. Another photocatalyst **13** did not provide desirable product **11** in satisfactory yield as **12**.

After performing optimized reaction condition, MacMillan group successfully carried out deoxyfluorination reaction of a wide variety of substituted secondary alcohols such as: secondary acyclic-, benzyl-, homobenzyl-, β-benzyl-substituted and tertiary alcohols to corresponding alkyl fluorinated products in moderate to excellent yield (62-96% yield). Besides, oxalates containing rings with five-, six-, seven-, or twelve-carbon were effectively introduced to this deoxyfluorination reaction in good yield (71-84% yield). Also, heterocyclic systems could also be applied this protocol for fluorination. Although the primary alkyl radicals are unstable, primary fluorinated products still can be obtained with this transformation in moderate yield (36-39% yield). Noteworthy, this methodology can tolerate several hindrance structures, such as cedrol or sclareolide, to give good selectivity and yield.

Scheme 3. Transformation of oxalate to generate fluoroalkane.



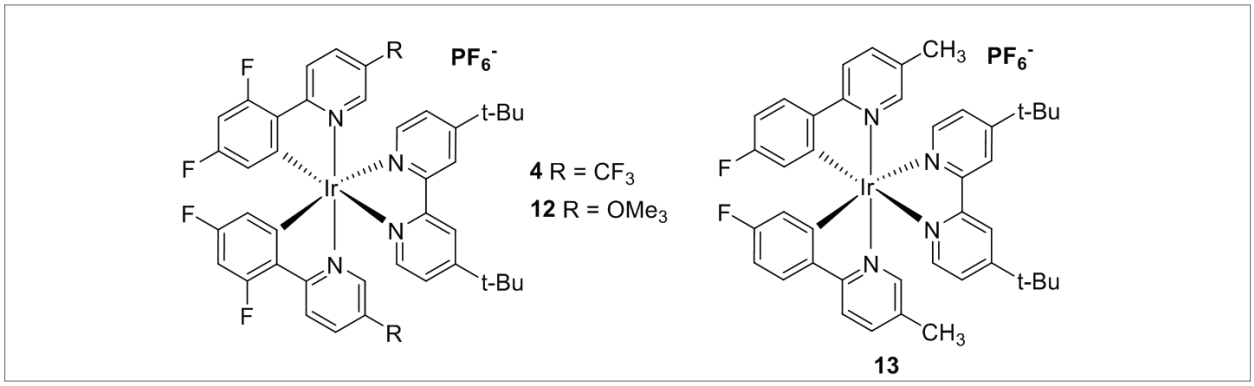


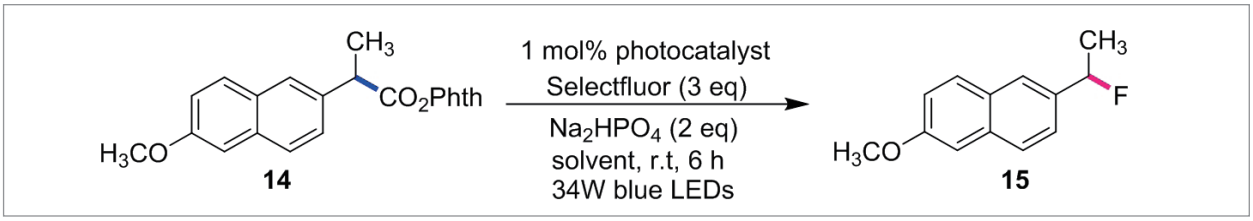
Figure 4. Structure of three photoredox catalysts in optimization procedure.

In March 2020, the Doyle group reported neutral photoredox protocol for the formation of fluorinated products from decarboxylative of *N*-hydroxyphthalimide esters (18). In particular, the fluorination of C(sp^3)-containing *N*-hydroxyphthalimide moiety was achieved in the presence of Ir(dF-ppy)$_3$ **16** photocatalyst (**Figure 5**) and $Et_3N{\cdot}3HF$ as fluorinating source under blue LED light. This procedure happens via the oxidation of radical generated from single-electron reduction of *N*-hydroxyphthalimide esters with **16**. As a result, corresponding carbocation was formed and then reacted with fluoride to generate fluorinated product.

To find the most suitable reaction condition, the Doyle group investigated an array of photocatalysts and fluorinating sources (**Scheme 4**). The optimal condition was achieved when presenting **14** with 1 mol % of **16** and **3** equiv of $Et_3N{\cdot}3HF$ in dichloromethane under irradiation of 34W blue LEDs after 4 to 6 hours, and benzylic fluoride **15** was delivered in excellent yield (99%). When there was the deficiency of light or photocatalyst, fluorination reaction does not happen, and full recovery of start material **14** was collected afterward. Another photocatalysts, more reducing or oxidizing metal photocatalysts (**4** and **17**), as well as organic photocatalyst such as 4CzIPN **18**, gave product **15** in reduced yield compared to catalyst **16**. While employing the combination of KF and 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) instead of $Et_3N{\cdot}3HF$, merely trace of 15 was observed, and only exploitation of KF in this reaction gave no product. Besides, performing the reaction in another solvent, such as THF and acetonitrile, yielded **15** in moderate to good yield.

The Doyle group exploited various primary benzylic alcohols to generate corresponding fluorinated product in high conversion. Substrates with electron-rich moiety such as: thioether, dioxole, and benzyl-protected phenols were tolerated under reaction condition. Fluorination of medicinal compounds containing amides and trifluoromethoxy groups were carried out in good yields. On the other hand, fluorinated product of substrate bearing electron-withdrawing group such as trifluoromethyl saw a deficiency in yield. This is due to the insufficiency of electron-withdrawing moiety with formation of carbocation from radical. Besides, secondary esters also delivered corresponding fluorinated product in excellent yield.

Scheme 4. Fluorination reaction from *N*-hydroxyphthalimide esters.



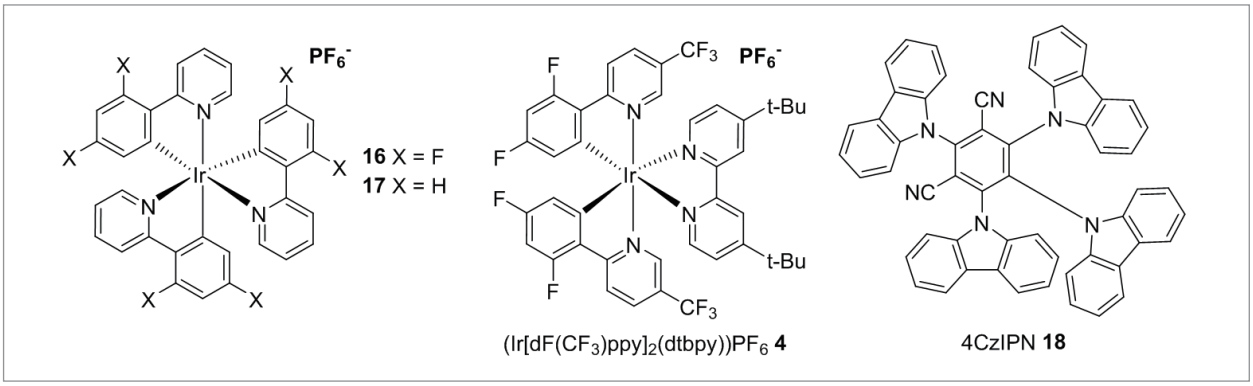


Figure 5. Structure of photoredox catalysts in Doyle's publication.

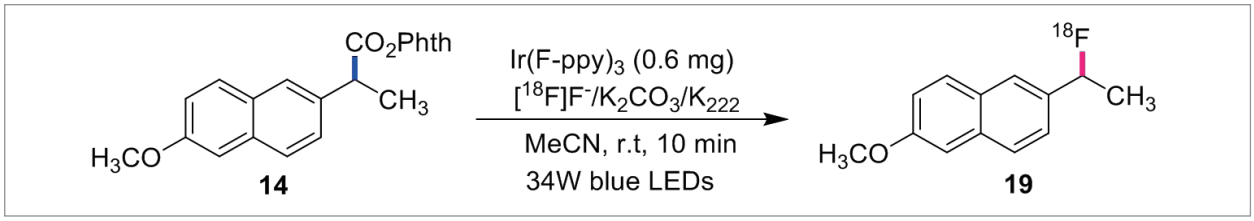
Traditionally, nucleophilic substitution occurred by [^{18}F]/KF to alkyl sulfonates in the presence of Kryptofix 2.2.2 (4,7,13,16,21,24-Hexaoxa-1,10-diazabicyclo[8.8.8] hexacosane, K_{222}), a phase transfer substrate, can be used for the preparation of ^{18}F-aliphatic PET probes. However, this method has significant drawbacks such as high temperature and harsh basic condition, which results in olefin as non-desirable products. The Doyle group were successfully carried out the transformation of *N*-hydroxyphthalimide esters into C(sp^3)-bearing-[^{18}F]-fluoride products via photocatalytic decarboxylative mechanism as mentioned above (**Scheme 5**) (18). This method will overcome drawbacks of conventional protocol to prepare radiotracers.

Particularly, they utilized acetonitrile as solvent instead of dichloromethane for the decarboxylative radiofluorination reaction. This is to prevent any potential clinical problems can happen with dichloromethane. They presented that the previous optimal photocatalyst **16** was not the most suitable for radiofluorination reaction, instead that Ir(F-ppy)$_3$ delivering the highest yield for this radiochemical fluorinated reaction. When there was no light or photocatalyst, they did not detect any trace of products by radio-TLC or radio-HPLC. With the optimal reaction condition in hand, they achieved **19** after only 2 min of irradiation in 62% of radiochemical conversion (RCC).

Other ^{18}F-radiolabeled products which are struggled to synthesize with traditional protocol, have also been reported under optimal condition. Specifically, the delivery of tertiary fluorinated product from gemfibrozil, **20**, was successfully achieved in 9% RCC. Moreover, they also synthesized ribose derivatives **21** with 42% RCC at room temperature, which overcame the limit of substitution reactions (high temperature) (**Figure 6**).

In conclusion, we reviewed the photoredox-catalyzed formation of fluorinated products, which are profoundly vital in medicinal chemistry. These preparation methods have several advantages such as facile operation and mild reaction condition. Overall, we presented several methods from the MacMillan group to deliver C(sp^3)-F adducts from a variety of start materials with photoredox catalyst under visible light radiation, such as: aliphatic carboxylic acids, alkyl bromides, and activated alcohols. Besides,

Scheme 5. Direct formation of radiofluorination products.



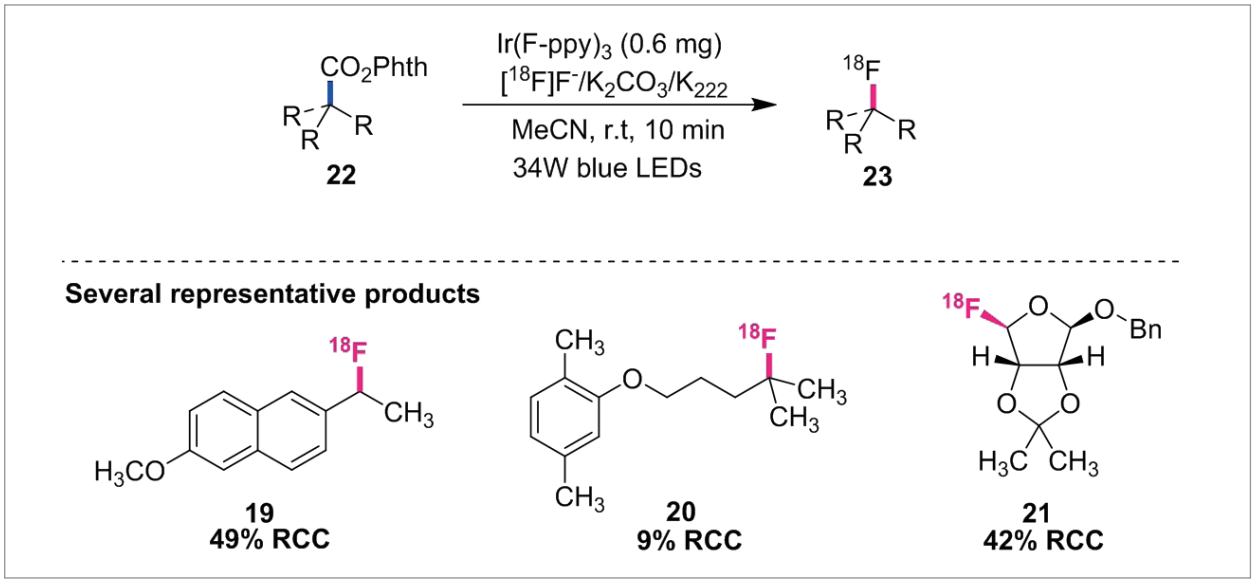


Figure 6. Scope of the photoredox-catalyzed radiofluorination reaction.

the protocols developed by the Doyle group exploiting *N*-hydroxyphthalimide ester could also obtain C(sp^3)-F products under photoredox cycle. This method can be extended for radiofluorination reaction, which shown great potential in synthesis of PET tracers.

Acknowledgments

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