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Review Article

Radiodifluoromethylation of well-functionalized molecules

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Abstract: The strategic installation of a [^{18}F]fluorine atom at the specific position of the lead molecule is a never-ending challenge for radiochemists in their endeavour to develop novel positron emission tomography (PET) imaging applications. Although the radiosynthesis of [^{18}F]CF_2H-containing molecules has been explored in the past decade, more methods need to be explored for various well-functionalized compounds. Recently, two novel strategies of radiodifluoromethylation were reported, namely the utilization of [^{18}F]difluorocarbene building block and frustrated Lewis pair-mediated C-^{18}F bond formation, respectively. These methods provide an efficient radiofunctionalization of complex CF_2H-containing molecules for drug discovery and PET ligand development.

Keywords: [^{18}F]difluoromethylation, [^{18}F]difluorocarbene, frustrated Lewis pair, positron emission tomography

Introduction

PET has evolved as a functional and noninvasive imaging modality, playing a pivotal role in diagnosing diseases, monitoring disease progression, and aiding drug development. The cornerstone of this technique lies in the development of PET tracers - biologically targeted small or large molecules labeled with positron-emitting radionuclides [1]. Among the PET nuclides, fluorine-18 (^{18}F) stands out as the preferred radioisotope due to its advantageous attributes, including a practical half-life ($t_{1/2}$ = 109.8 min), a favorable positron emission profile (97%), relatively low positron energy (E = 0.635 keV) and high availability. Within the realm of various fluorinated moieties, the difluoromethyl (CF_2H) group, considered a lipophilic bioisostere of conventional hydrogen-bond donor groups such as hydroxy (-OH) and thiol (-SH) groups [2], has garnered significant attention in drug discovery [3]. A plethora of bioactive molecules bearing the CF_2H motif have been discovered, including thiazopyr, pantoprazole, and ZSTK474 etc. (**Figure 1**).

As various methodologies for the synthesis of CF_2H-containing molecules have emerged, there have been continuous efforts in the exploration of radiosynthesis methods involving [^{18}F]CF_2H (**Figure 2**). Gouverneur and coworkers developed a silver(I)-mediated [^{18}F]fluorodecarboxylation method, using electrophilic [^{18}F]fluorinating reagents to convert α-fluorarylacetic acids (**Figure 2A**) [4]. They also introduced an ^{18}F/Cl exchange reaction involving Ar-CHFCl and nucleophilic [^{18}F]fluoride (**Figure 2A**) [5]. Similarly, Shen, Gouverneur and coworkers disclosed the radiosynthesis of [^{18}F]Ar-SCF_2H by an Ag-mediated ^{18}F/Cl exchange strategy [6]. Furthermore, this strategy was implemented for the radiolabeling of ethyl α-bromo-α-fluoro(aryloxy)acetates to generate [^{18}F]α,α-difluoroaryloxy acetic acid, which could be further transformed into [^{18}F]Ar-OCF_2H [7]. In 2019, Gouverneur's work established a Mn-mediated [^{18}F]fluorodecarboxylation process, enabling access to [^{18}F]Ar-CF_2H and [^{18}F]ArO-CF_2H moieties (**Figure 2A**) [8]. Ritter, Vasdev, Liang and coworkers disclosed a cascade method for preparing [^{18}F](het)Ar-CF_2H, which involved the activation of the benzoyl auxiliary, followed by sequential benzylic bromination and ^{18}F/Br exchange (**Figure 2A**) [9]. Subsequently, the Liang group reported a two-step strategy that included the nucleophilic ^{18}F-fluorination of benzyl (pseudo)halides, followed by oxidative benzylic C-H fluorination (**Figure 2B**) [10]. Genicot and coworkers described a photoredox flow approach for direct radical C-H ^{18}F-difluoromethylation of *N*-heteroarenes (**Figure 2C**) [11]. In addition, some multistep syntheses were reported for obtaining [^{18}F]CF_2H-containing compounds. For example, these syntheses involve Ag-mediated desulfurative [^{18}F]fluorination [12] and [^{18}F]fluorination of iodonium salt [13]. In spite of these outstanding results, there is still an unmet need to develop new methods to introduce [^{18}F]CF_2H group on well functionalized drug-like scaffolds. In this highlight, we focus on two recent advances of radiodifluoromethylation using a new type of [^{18}F]difluorocarbene building block and frustrated Lewis pair-activated C-^{18}F bond formation, respectively. These new methodologies may provide a new strategy and 'retro-radiosynthetic' approach to design ^{18}F-labeled difluoromethyl groups beyond conventional methods and enable novel functionalities to be explored in PET pharmaceuticals.

Literature highlight

Direct [^{18}F]difluoromethylation from [^{18}F]difluorocarbene

The Gouverneur group introduced a novel method for [^{18}F]difluoromethylation using [^{18}F]difluorocarbene ([^{18}F]DFC) to generate a variety of (hetero)arenes bearing [^{18}F]CF_2H

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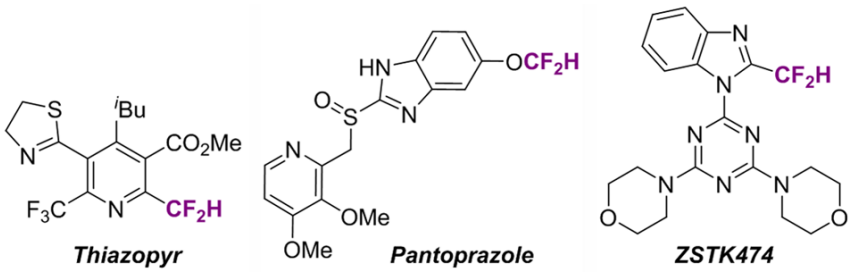

Figure 1. Representative CF_2H-containing bioactive molecules.

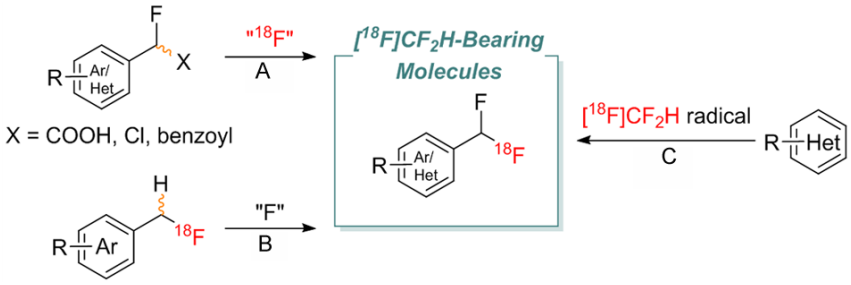

Figure 2. Previous approaches to access [^{18}F]CF_2H-containing molecules.

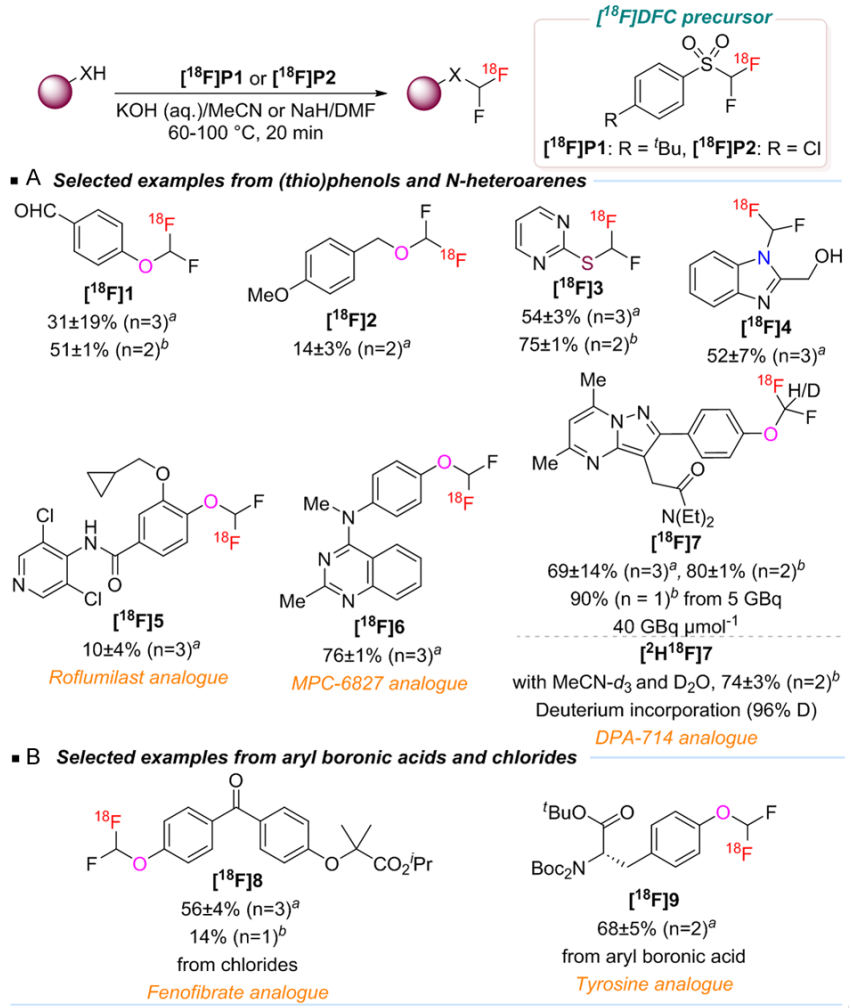

Figure 3. [^{18}F]DFC insertion to form [^{18}F]CF_2H-X-Arene motifs (X = O, S and N). [a][^{18}F]P1 was used. [b][^{18}F]P2 was used.

motif [14]. The work entailed [^{18}F]DFC insertion into X-H (X = O, S, and N) bonds, and cross-coupling reactions with palladium-DFC complexes.

A wide range of electronically and/or sterically diverse (hetero)aryl phenols, thiophenols, and *N*-heteroarenes were investigated, yielding the desired products featuring [^{18}F]OCF_2H, [^{18}F]SCF_2H, and [^{18}F]NCF_2H moieties (**Figure 3**).

Notably, [^{18}F]DFC selectively inserted into the phenolic O-H bond of 4-hydroxybenzaldehyde ([^{18}F]1, 51% radiochemical yield, RCY). Selective ^{18}F-difluoromethylation at the nitrogen atom was achieved in the case of (1H-benzo[d]imidazol-2-yl) methanol, yielding [^{18}F]4 with 52% RCY. Subsequently, late-stage ^{18}F-difluoromethylation of complex biologically active molecules was successfully demonstrated, including analogues of roflumilast ([^{18}F]5), MPC-6827 ([^{18}F]6) and DPA-714 ([^{18}F]7). Additionally, [^{2}H^{18}F]7 was obtained using deuterated solvents, such as CD_3CN and D_2O, which is significant because deuterium (D) incorporation is a common strategy to enhance the metabolic stability of drug molecules and radiotracers. An in vivo study was conducted with [^{18}F]7 in the application of imaging microglial activation of Huntington's disease. The authors also reported a one-pot tandem procedure, involving borylation, oxidation, and sequential ^{18}F-difluoromethylation, for producing labeled analogues of drugs and bioactive molecules (for example [^{18}F]8 and [^{18}F]9). One plausible reaction mechanism involves a series of cascade steps, namely the deprotonation of DFC precursor, DFC expulsion and addition, and protonation. The free DFC is favored as the predominant pathway for this DFC insertion transformation (**Figure 4A**). By contrast, the concerted SN2-like pathway is of higher energy barrier (**Figure 4B**).

Pd-catalyzed [^{18}F]difluoromethylation of aryl boronic acids was also successfully achieved through the capture and transfer of [^{18}F]DFC (**Figure 5**). This method was applied to a diverse array of aryl boronic acids, including those featuring heterocycles and vinyl groups. Importantly, [^{18}F]CF_2H analogues of various drugs and bioactive molecules, such as Fenofibrate and protected phenylalanine,

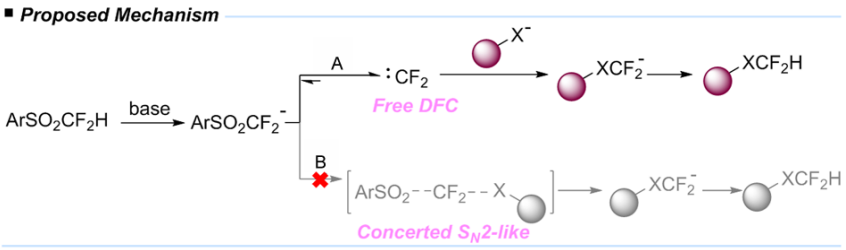

Figure 4. [^{18}F]DFC insertion transformation (X = O, S and N).

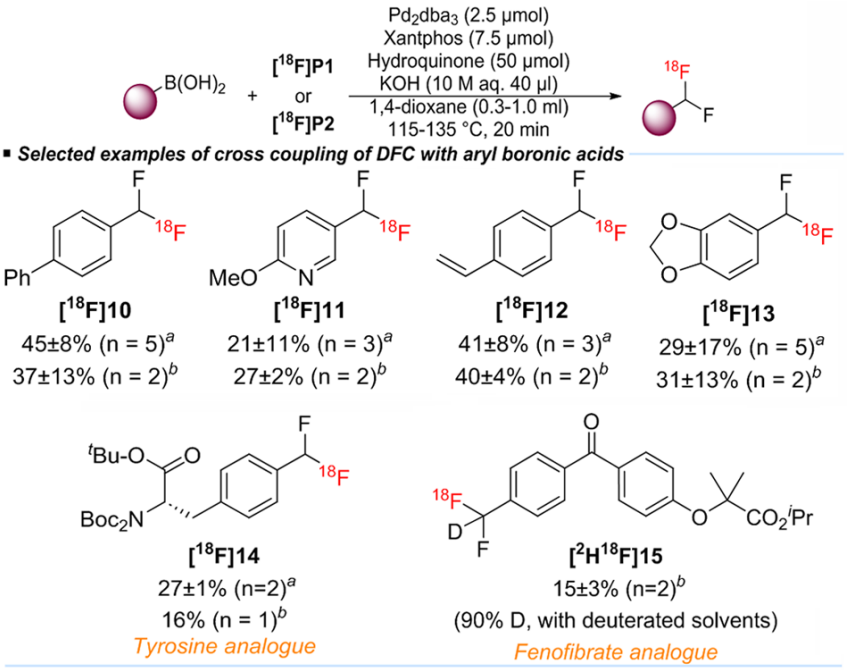

Figure 5. [^{18}F]DFC-mediated cross coupling reactions to form [^{18}F]CF_2H-Arene motifs. [a][^{18}F]P1 was used. [b][^{18}F]P2 was used.

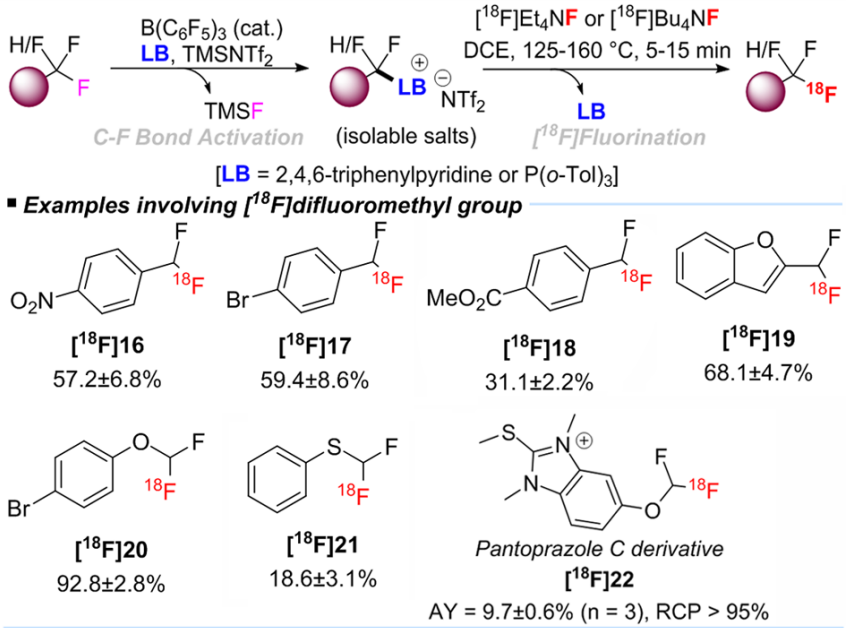

Figure 6. [^{18}F]Difluoromethylation using frustrated Lewis pair method.

were successfully obtained under these conditions.

Frustrated Lewis pair-mediated C-^{18}F bond formation

Young and coworkers have previously reported that the frustrated Lewis pair (FLP) can selectively activate C-F bonds within CF_3- and CF_2H-containing compounds [15]. This activation leads to the formation of pyridinium and phosphonium salts in high yield. These resulting salts can be employed in a diverse range of transformations, involving Wittig coupling [15a], nucleophilic substitution, photoredox alkylation, nucleophilic transfer, and hydrogenation reactions [15b], to incorporate a wide array of functional groups into parent molecules. Building upon their pioneering work, Young and his team have now successfully applied this two-step approach to ^{18}F labeling of difluoromethyl and trifluoromethyl groups [16].

This FLP-mediated transformation process tolerates a variety of well functionalized groups (**Figure 6**). Difluoromethylarenes with electron-withdrawing nitro, bromo, and ester groups can be isotopically labeled, to generate the corresponding products in 31-59% radiochemical conversions. Furthermore, difluoromethylated heteroarenes, difluoromethoxide and difluoromethylsulfide substrates ([^{18}F]19-[^{18}F]21) were also obtained in 19-93% conversions. As a proof-of-concept, a biologically relevant molecule [^{18}F]22, as a derivative of pantoprazole C, was successfully isolated with non-decay corrected yields of ca. 10%. Control experiments indicated that the cationic fragment of the salts likely served as a source of ^{19}F fluoride, which is unfortunately detrimental to obtain higher molar activity in the [^{18}F]fluorination process.

Conclusion

Undoubtably, these recent advances present novel opportunities and stimulate innovative ideas for the development of potential [^{18}F]CF_2H-containing PET imaging probes. It is firmly anticipated that an expanding array of strategies for synthesizing compounds featuring the [^{18}F]CF_2H group will be unveiled, thus contributing to the ongoing advancement

of drug discovery and PET applications across diverse scientific disciplines.

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Disclosure of conflict of interest

None.

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