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Difluorocarbene-derived rapid late-stage trifluoromethylation of 5-iodotriazoles for the synthesis of ^{18}F-labeled radiotracers

Fang Yuan[a,1], Hongbao Sun[a,1], Cheng Yang[a], Haojie Yang[a], Lili Pan[b], Xiaoyang Zhang[a], Rong Tian[b], Lingjun Li[c], Wei Chen[b], Xiaoai Wu[b,*], Haoxing Wu[a,*]

[a] Huaxi MR Research Center, Department of Radiology, Functional and Molecular Imaging Key Laboratory of Sichuan Province, Frontiers Science Center for Disease-Related Molecular Network, West China Hospital, Sichuan University, Chengdu 610041, China
[b] Department of Nuclear Medicine, Laboratory of Clinical Nuclear Medicine, West China Hospital, Sichuan University, Chengdu 610041, China
[c] School of Chemistry and Chemical Engineering, Collaborative Innovation Center of Henan Province for Green Manufacturing of Fine Chemicals, State Key Laboratory of Cell Differentiation Regulation and Target Drug, Henan Normal University, Xinxiang 453007, China

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ABSTRACT

Difluorocarbene has emerged as a valuable intermediate to synthesize fluorides. However, difluorocarbene-derived synthesis of ^{19}F/^{18}F-trifluoromethyl triazoles has not been explored. Herein, we reported the Cu(I)-promoted difluorocarbene-derived ^{19}F/^{18}F-trifluoromethylation of iodotriazoles using KF/K^{18}F as the fluorine source. This approach rapidly generated a wide range of 5-trifluoromethyl-1,2,3-triazoles in good yields showing high functional group compatibility. The reaction was effective for late-stage functionalization of bioactive molecules and ^{18}F-trifluoromethylation of iodotriazoles. This work provides a practical synthetic methodology for the development of triazole drugs and ^{18}F-radiotracers for positron emission tomography.

Difluorocarbene (:CF_2) is a versatile intermediate widely used in synthetic chemistry to introduce mono-, di-, and tri-fluorine fragments. It plays a vital role in the total synthesis of natural products and drugs, and in the preparation of radiotracers for positron emission tomography (PET) [1–4]. Difluorides are usually prepared *via* difluorocarbene-derived difluoromethylation, *gem*–difluorocyclization and *gem*–difluoroolefination [5,6], while trifluoromethylation has been used to synthesize ^{18}F-radiotracers for PET imaging and to optimize the physicochemical properties of drug leads [7–12]. However, the difluorocarbene-derived synthesis of trifluoromethyl triazoles and ^{18}F-trifluoromethyl triazole radiotracers has not been adequately explored.

Difluorocarbene as a singlet carbene with an empty p-orbital, has been used as an electrophile in difluoromethylation reactions involving diverse nucleophiles to generate multifunctional molecules bearing C-, N-, O-, S-, P- and Sn-CF_2H groups [13–18]. Difluorocarbene is also a useful intermediate in *gem*–difluoroolefination reactions involving carbonyl compounds [19,20], while it has been used as a bipolar unit for [2 + 1], [4 + 1] and [8 + 1] cycloadditions to construct mono- and di-fluorides such as fluoroindoles, *gem*–difluorocyclopropanes, *gem*–difluorocyclopropenes, *gem*–difluorinated azetidines and *gem*–difluorinated 2,3-dihydrobenzofurans [14,21–24]. Very recently, the Gouverneur group developed [^{18}F]difluorocarbene to construct ^{18}F-labeled difluorides for PET [25].

Difluorocarbene can also be trapped by the nucleophilic fluoride ion and converted into the trifluoromethyl anion (CF_3^-), which serves as a nucleophilic intermediate in trifluoromethylation [13,26–33]. For instance, SCF_3^-, OCF_3^- and $SeCF_3^-$ have been used for the trifluoromethylthiolation, trifluoromethoxylation, and trifluoromethylselenolation of halides by the Xiao and the Liang group [26–30], while ^{18}F-labeled trifluorides for PET imaging have been synthesized *via* difluorocarbene-derived ^{18}F-trifluoromethylthiolation ($SCF_2{}^{18}F$) of halides [27,28] and ^{18}F-trifluoromethylation ($CF_2{}^{18}F$) of (hetero)aryl iodides (Scheme 1a) [31–33].

On the other hand, the Cu(I)-catalyzed azide–alkyne cycloaddition (CuAAC) reaction is considered a powerful tool for the preparation of 1,2,3-triazoles, which are widely used in pharmaceutical research, preparation of biocompatible materials, and late-stage modification of biomacromolecules [34–36]. Its size and geometry make the 1,2,3-triazole ring a frequently used bioisostere of native peptide-based trans-amide connectors [37], and it has become one of the most widespread heterocycles in medicinal scaffolds due to

* Corresponding authors.
E-mail addresses: xiaoai.wu@scu.edu.cn (X. Wu), haoxingwu@scu.edu.cn (H. Wu).
[1] These authors contributed equally to this work.

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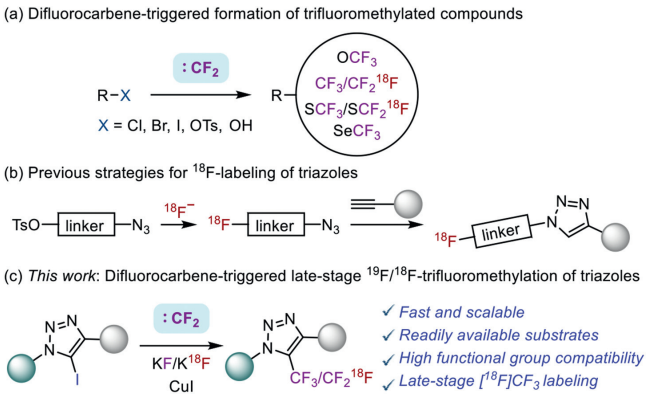


Scheme 1. Difluorocarbene-derived trifluoromethylation and ^{18}F-labeling of triazoles.

its wide range of bioactivities against bacteria, viruses, and cancer [34,37].

In recent years, the synthesis of trifluoromethyl 1,2,3-triazoles has attracted attention due to the metabolic stability, high lipophilicity, and high bioavailability of the trifluoromethyl group [38–42]. ^{18}F-Labeled triazoles have also been developed as PET imaging agents for disease diagnosis and *in vivo* monitoring of the metabolism and distribution of tagged drugs [43–45]. ^{18}F-Labeled triazoles are usually prepared through the click reaction of alkynes with ^{18}F-labeled azides in at least two steps (Scheme 1b) [43–45]. However, the difluorocarbene-derived synthesis of ^{19}F/^{18}F-trifluoromethyl 1,2,3-triazoles has not yet been reported.

Since the half-life of ^{18}F is 109.8 min, it should be preferably introduced into the triazole ring in the last synthesis step. Therefore, in the present study, we developed a novel strategy for difluorocarbene-derived late-stage trifluoromethylation of iodotriazoles with high functional group compatibility (Scheme 1c). A wide range of 5-trifluoromethyl-1,2,3-triazoles were generated in good yields, including rarely reported analogues. The usefulness of this approach for late-stage functionalization was demonstrated by producing trifluoromethylated derivatives of bioactive molecules. Late-stage ^{18}F-trifluoromethylation of iodotriazoles generated triazole radiotracers for PET imaging.

Based on a previous study [31], the trifluoromethylation of 1-benzyl-5-iodo-4-phenyl-1*H*-1,2,3-triazole (**1a**) was first performed in DMF using $ClCF_2CO_2Me$ as difluorocarbene source, KF as fluoride source, CuI as metal source, and *N,N,N′,N′*-tetramethylethylenediamine (TMEDA) as ligand (Table S1 in Supporting information). However, the desired product did not form; the main product was a protonated analogue generated by reductive dehalogenation. Interestingly, the addition of a base can successfully obtain the target product **2a**, while 1,10-phenanthroline (Phen) proved to be the most effective ligand, probably due to the generation of the stable intermediate $PhenCuCF_3$ [46]. Various Cu(I) salts were also well tolerated, with the combination of CuI and Phen giving the highest yield of 61% in 25 min (Tables S1 and S2 in Supporting information).

Next, we investigated the influence of different functional groups of 5-iodotriazoles on the efficiency of difluorocarbene-derived trifluoromethylation reaction (Scheme 2). Under the optimized conditions, all iodotriazoles were completely transformed in 25 min, confirmed by thin-layer chromatography (TLC), and iodotriazoles bearing electron-neutral/rich and electron-deficient aryl groups rapidly gave the corresponding 5-trifluoromethyl triazoles (**2a–2l**) in moderate to good yields up to 85%. Compared with para-substituted aryl iodotriazoles, the reaction was slightly less efficient for *meta*- and *ortho*-substituted aryl iodotriazoles (**2m–2q**). Nevertheless, various aryl substituents, including ether (**2e**, **2f**), nitro (**2g**), bromine (**2i**, **2p**), aldehyde (**2j**, **2q**), amide (**2k**), ester (**2l**, **2o**), and fluorine (**2f**, **2 h**, **2m**, **2n**) groups, were well tolerated, providing opportunities for further conversion. Iodotriazoles bearing fused (**2r**) and heterocyclic (**2s–2u**) ring systems also reacted smoothly under these conditions, and acetyl- and benzoyl-substituted iodotriazoles were successfully trifluoromethylated, affording analogues not yet reported in previous trifluoromethylation (**2v–2x**). Moreover, alkyl-substituted iodotriazoles bearing protected amino and alcohol groups were well tolerated, giving analogues **2y** and **2z**, which are suitable for further modifications (Scheme 2).

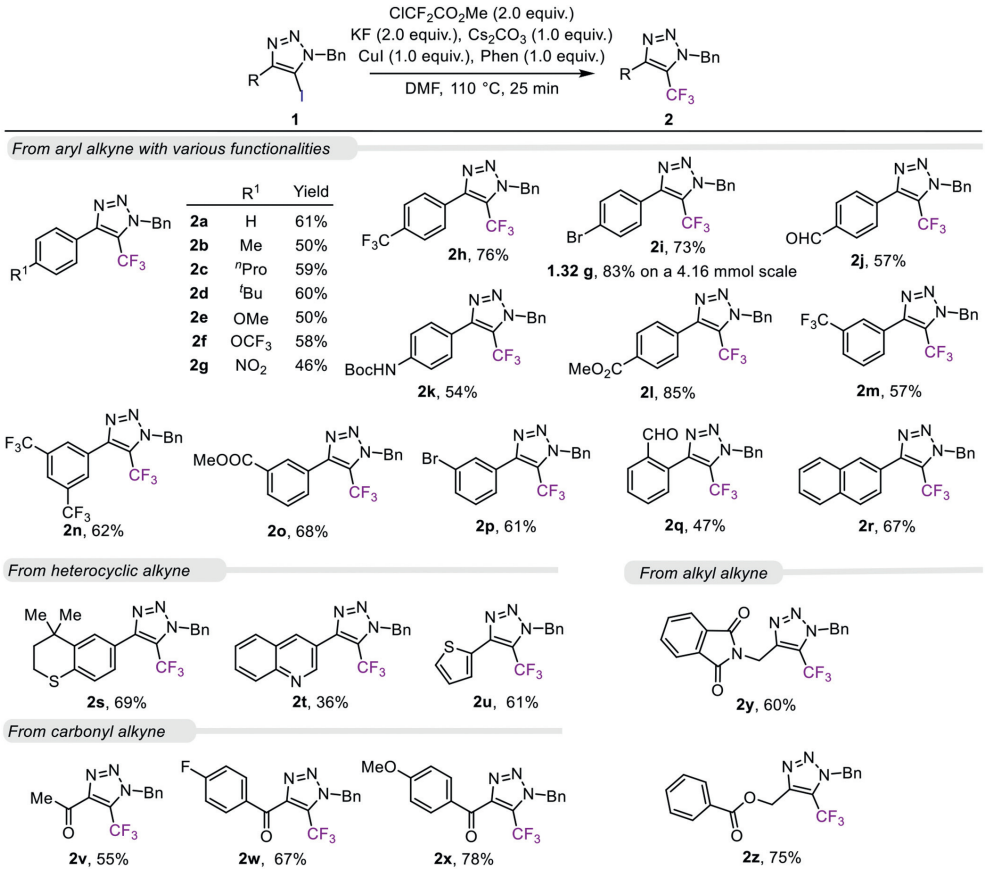
The developed reaction proceeded well on a gram scale with bromoaryl iodotriazole **1i** (4.16 mmol), giving analogue **2i** in 83% isolated yield (1.31 g) (Scheme 2). This product could be used as an intermediate for additional transformations.

To further expand the scope of the reaction, we successfully synthesized 5-iodotriazoles from benzyl azide (**2aa**, **2ak**, **2am**), azidobenzene (**2ab**, **2aj**), ethyl azidoacetate (**2ac–2ai**), and (1-azidoethyl)benzene (**2al**) moieties, and obtained the corresponding 5-trifluoromethylated triazoles in a short time with moderate yields (Scheme 3). These 5-trifluoromethyl triazoles are rarely available through previously reported strategies.

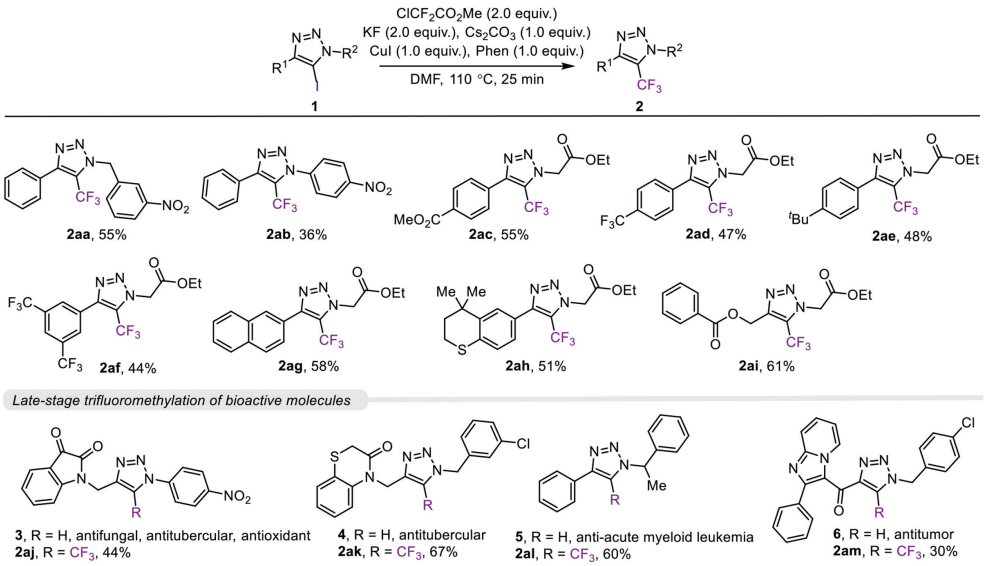
The usefulness of the proposed method was demonstrated by the successful late-stage trifluoromethylation of bioactive triazoles (Scheme 3). For example, analogue **2ak** was obtained in 67% yield from the benzothiazinone derivative **4**, which is effective against the H37Ra strain of *Mycobacterium tuberculosis* [47]. Similarly, **2aj** was synthesized in moderate yield from the isatin derivative **3**, which is known for its activity against fungal, oxidative damage, and *M. tuberculosis* [48]. Analogue **2al** was obtained in 60% yield from compound **5**, which acts against acute myeloid leukemia [37]. Moreover, analogue **2am** was obtained from the imidazopyridine-linked triazole **6**, which shows antitumor activity [49].

To expand the applicability of this strategy, we investigated the late-stage ^{18}F-trifluoromethylation of 5-iodotriazoles for the preparation of PET imaging agents (Scheme 4). PET is a non-invasive molecular imaging technique that relies on radiolabeled probes and has become an invaluable tool for drug discovery and clinical diagnosis [50–52]. Among the positron-emission radionuclides used in PET, ^{18}F is the most frequently applied due to its relatively short half-life of 109.8 min, low positron energy (635 keV), and clean decay profile with 97% positron emission [52–57]. The $[^{18}F]KF/K_{222}$ complex is a commonly available fluorine source for ^{18}F-labeling. Our late-stage trifluoromethylation approach can also be applied for ^{18}F-labeling molecules of interesting by replacing KF with $[^{18}F]KF/K_{222}$ without excessive condition screening as 25 min is suitable reaction time for ^{18}F radiolabeling (Scheme 4, Tables S3–S12, Figs. S1–S10 in Supporting information). The reaction tolerated benzyl azide (**3a–3e**, **3j**), ethyl azidoacetate (**3f–3h**), azidobenzene (**3i**), aryl groups (**3a**, **3f**, **3g**), alkyl groups (**3b**, **3h**, **3i**), and carbonyl groups (**3c–3e**, **3j**) as substituents. The reaction also tolerated a broad range of functional groups, including esters (**3a**, **3f–3h**) amides (**3b**), ketones (**3c–3e**, **3j**), halides (**3c**, **3j**), ethers (**3d**), nitro groups (**3i**), and fluorine groups (**3c**, **3g**). In all cases, ^{18}F labeling proceeded with moderate to good radiochemical conversion (RCC).

The same protocol also supported efficient late-stage ^{18}F-trifluoromethylation of bioactive triazoles. For instance, the triazole-incorporated isatin derivative was labeled with $[^{18}F]CF_3$ in 56% RCC (**3i**, Scheme 4). Analogue **3j** was synthesized in 24% RCC from the iodide derivative of imidazopyridine-linked triazole **6** (Scheme 3). Analogue **6** is a known tubulin inhibitor that can effectively trigger apoptosis, making it quite toxic against A549 human lung cancer cells ($IC_{50} = 0.63$ μmol/L) [49]. Thus, the ^{18}F-labeled tracer **3j** can be used in PET imaging to study the distri-



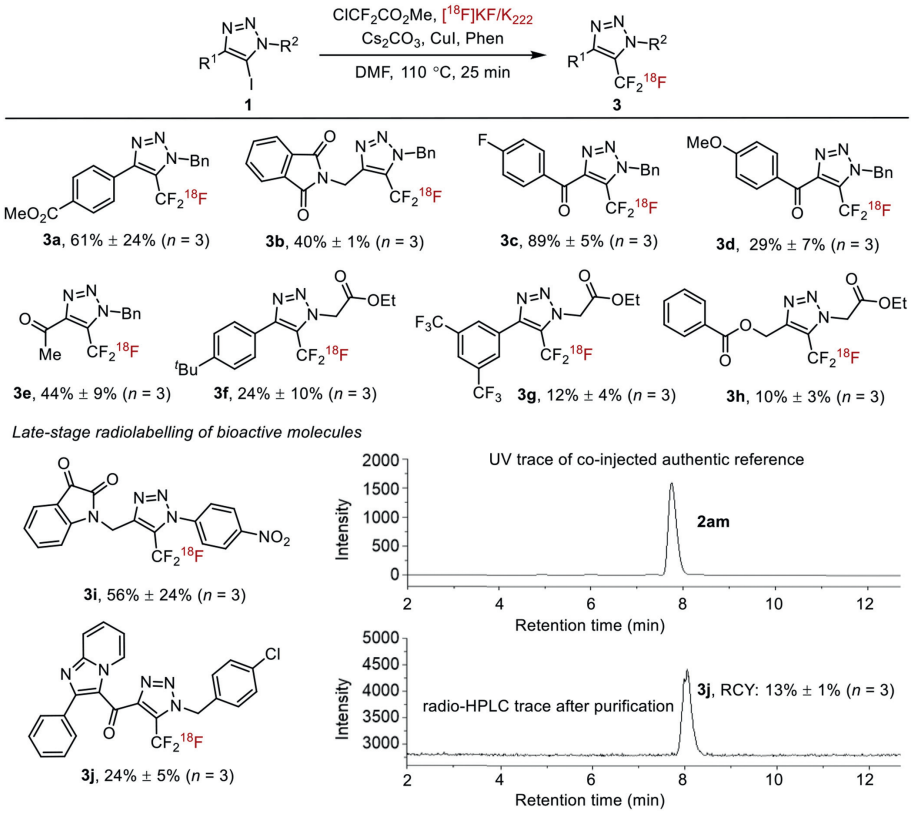
Scheme 2. Difluorocarbene-derived trifluoromethylation of 5-iodotriazoles transformed from benzyl azide and various alkynes. Reactions conditions: **1** (0.1 mmol, 1.0 equiv.), $ClCF_2CO_2Me$ (0.2 mmol, 2.0 equiv.), KF (0.2 mmol, 2.0 equiv.), Cs_2CO_3 (0.1 mmol, 1.0 equiv.), CuI (0.1 mmol, 1.0 equiv.), Phen (0.1 mmol, 1.0 equiv.), DMF (1.6 mL), 110 °C, 25 min. Yield of isolated product.



Scheme 3. Difluorocarbene-derived trifluoromethylation of 5-iodotriazoles and late-stage trifluoromethylation of bioactive molecules. Reactions conditions: **1** (0.1 mmol, 1.0 equiv.), $ClCF_2CO_2Me$ (0.2 mmol, 2.0 equiv.), KF (0.2 mmol, 2.0 equiv.), Cs_2CO_3 (0.1 mmol, 1.0 equiv.), CuI (0.1 mmol, 1.0 equiv.), Phen (0.1 mmol, 1.0 equiv.), DMF (1.6 mL), 110 °C, 25 min. Yield of isolated product.

bution and metabolism of imidazopyridine-linked triazole hybrids *in vivo*, promote drug discovery, and develop lung cancer detection reagents. To further evaluate the applicability of this protocol, we attempted to prepare ^{18}F-labelled triazole **3j**. The radiotracer **3j** was successfully obtained with moderate isolated decay-corrected radiochemical yield (RCY) of 13%, as confirmed by spectroscopic analysis (Scheme 4, Fig. S11 and Table S13 in Supporting information).

In summary, we have developed a rapid difluorocarbene-derived strategy for late-stage $^{19}F/^{18}F$-trifluoromethylation of 5-



Scheme 4. Difluorocarbene-derived ^{18}F-trifluoromethylation of iodotriazoles and late-stage ^{18}F-radiolabelling of bioactive molecules. Reactions conditions: **1** (2.0 mg, 3.7–6.1 μmol), $ClCF_2CO_2Me$ (2.3 μL, 22 μmol), [^{18}F]KF/K_{222} (5–20 mCi), Cs_2CO_3 (1.8 mg, 5.5 μmol), CuI (1.1 mg, 5.5 μmol), Phen (1.0 mg, 5.5 μmol), DMF (0.4 mL), 110 °C, 20 min. Radiochemical conversion (RCC) and product identity were determined by radio-HPLC.

iodotriazoles. This reaction tolerates a wide variety of functional groups, enabling the synthesis of rarely reported derivatives as well as the direct radiolabeling triazoles, demonstrating its potential as an effective tool for the development of novel triazole drugs and radiotracers. Further efforts are underway to explore the scope of substrates, including those with sterically hindered groups in *meta*- or *ortho*-positions, and to improve the method to make it compatible with more functional groups of medicinal molecules. In addition, studies on the production and use of ^{18}F-labeled bioactive molecules in PET imaging are in progress.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2022.107960.

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