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A broadly applicable [^{18}F]trifluoromethylation of aryl and heteroaryl iodides for PET imaging

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Molecules labelled with the unnatural isotope fluorine-18 are used for positron emission tomography. Currently, this molecular imaging technology is not exploited at its full potential because many ^{18}F-labelled probes are inaccessible or notoriously difficult to produce. Typical challenges associated with ^{18}F radiochemistry are the short half-life of ^{18}F (<2 h), the use of sub-stoichiometric amounts of ^{18}F, relative to the precursor and other reagents, as well as the limited availability of parent ^{18}F sources of suitable reactivity ([^{18}F]F^- and [^{18}F]F_2). There is a high-priority demand for general methods allowing access to [^{18}F]CF_3-substituted molecules for application in pharmaceutical discovery programmes. We report the development of a process for the late-stage [^{18}F]trifluoromethylation of (hetero)arenes from [^{18}F]fluoride using commercially available reagents and (hetero)aryl iodides. This [^{18}F]$CuCF_3$–based protocol benefits from a large substrate scope and is characterized by its operational simplicity.

Positron emission tomography (PET) is a non-invasive quantitative imaging technology that can detect pre-symptomatic biochemical changes in body tissues where no evidence of abnormality is available using computed tomography (CT) or magnetic resonance imaging (MRI), or before structural changes occur from disease[1,2]. This technology helps researchers in understanding diseases and can assist clinicians in the selection of the best treatment for an individual patient, provided that competent biomarkers are available. The unrivalled sensitivity of PET also makes this technique suitable for addressing questions fundamental to drug development for oncology, cardiology, neurosciences and inflammatory diseases[3,4]. For these studies, ^{18}F is one of the most commonly used positron-emitting radioisotopes[5,6], in part due to the extensive use of 2-deoxy-2-[18F]fluoroglucose ([^{18}F]FDG) in the clinic and the importance of fluorine substitution in the context of drug discovery[7,8].

Despite the success of PET and the consequent upsurge of interest in [^{18}F]radiochemistry[9–11], no general method is available to radiolabel trifluoromethyl arenes and heteroarenes[12–15]. Today, there is a pressing need for such methodology as these compounds are notoriously important pharmacophores present in a large number of prescribed drugs, so their potential for PET imaging as a tool to facilitate drug discovery is unquestionable. Here we report a new strategy for the direct [^{18}F]trifluoromethylation of aryl and heteroaryl iodides using methyl chlorodifluoroacetate and [^{18}F]fluoride through a copper-mediated cross-coupling reaction. We demonstrate the broad utility of this multicomponent transformation with the [^{18}F]labelling of functionalized trifluoromethyl arenes and heteroarenes including pharmaceutical agents.

This radiochemistry based on *in situ* generated [^{18}F]$CuCF_3$ is operationally simple and uses [^{18}F]fluoride and commercially available reagents. This advance enlarges considerably the range of [^{18}F] molecules available for PET studies and can accelerate both drug discovery and development. The short half-life of ^{18}F (110 min) dictates a preference for protocols based on late-stage fluorination. Classically, the CF_3 motif is installed on arenes and heteroarenes

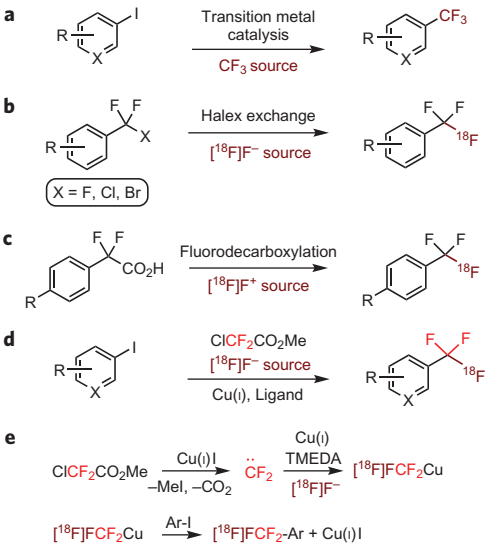

Figure 1 | Direct trifluoromethylation of aryl and heteroaryl iodides. **a**, Modern methodology to prepare non-labelled trifluoromethylated (hetero)arenes using transition metal-catalysed cross-coupling chemistry and commercially available pre-made CF_3 reagents. **b**, Halex exchange with [^{18}F]fluoride is a known protocol to access [^{18}F]CF_3 arenes; this strategy is severely limited in scope and uses starting materials that require multistep synthesis. **c**, This [^{18}F]fluorodecarboxylation process uses the electrophilic reagent [^{18}F]Selectfluor, which is prepared from [^{18}F]F_2. **d**, Our strategy offers a direct route to [^{18}F]CF_3 (hetero)arenes from [^{18}F]fluoride and (hetero)aryl iodides. The broad scope of this reaction and its logistical simplicity allows access to [^{18}F]CF_3 (hetero)arenes not within reach using known methodologies. **e**, The multicomponent assembling of [^{18}F]fluoride, methyl chlorodifluoroacetate and CuI towards [^{18}F]$CuCF_3$ is the breakthrough advance paving the road to [^{18}F]CF_3-based cross-coupling radiochemistry.

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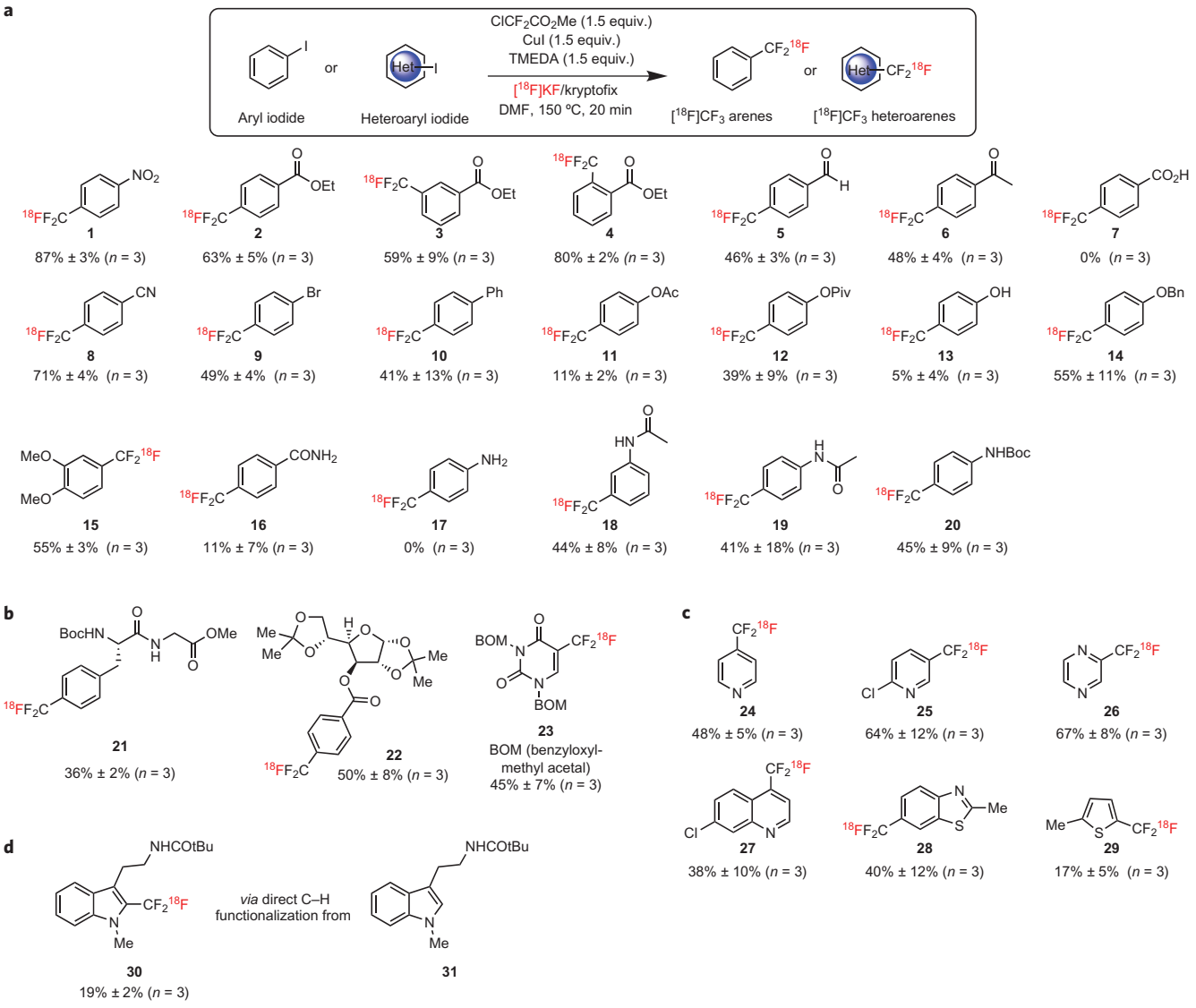

Figure 2 | Cu(I)-mediated [^{18}F]trifluoromethylation of arenes, heteroarenes and pyrimidine-2,4(1H,3H)-dione with [^{18}F]fluoride. a, Arenes bearing a variety of functional groups are efficiently labelled with [^{18}F]CF_3. **b**, Substrate scope includes a dipeptide, carbohydrate and a uracil derivative. **c**, A variety of heteroarenes are within reach using this new radiochemistry. **d**, Direct C–H functionalization of an indole derivative. The RCYs are indicated below each product.

by means of cross-coupling technologies catalysed by transition metals (Fig. 1a)[16–18]. These reactions, which employ either a nucleophilic or electrophilic source of CF_3, have not been considered for radiochemistry as [^{18}F]labelling of the CF_3 sources is required before the cross-coupling event. To date, access to [^{18}F]CF_3 arenes relies on arylCF_2–^{18}F bond formation, typically via halex exchange processes[12–15]. This radiochemistry is low yielding, limited in scope and requires harsh reaction conditions due to the low reactivity of aryl difluoromethylene precursors armed with a halide-based leaving group (Fig. 1b). More recently, the Ag(I)-mediated [^{18}F]fluorodecarboxylation[19] of arylCF_2COOH was successfully implemented using [^{18}F]Selectfluor bis(triflate)[20], an electrophilic fluorinating reagent prepared from high specific activity [^{18}F]F_2 (Fig. 1c)[21]. These strategies suffer from either a lack of operational simplicity or broad applicability, hampering translational studies and rapid progress of PET imaging.

To address this challenge, we reasoned that a more direct installation of a [^{18}F]CF_3 group to a biomarker candidate would obviate the need to prepare an 'arylCF_2' precursor armed with a leaving group amenable to [^{18}F]fluoride displacement. This [^{18}F]trifluoromethylation would, in a single operation, build the (hetero)aryl–CF_2^{18}F linkage directly from (hetero)aryl iodide precursors through consecutive (hetero)aryl–CF_2–^{18}F two bond construction using [^{18}F]fluoride and a reagent acting as a difluorocarbene source (Fig. 1d). Specifically, we sought to take advantage of the reactivity of methyl chlorodifluoroacetate known to undergo, in the presence of fluoride, halide-promoted decarboxylation to give trifluoromethide, an intermediate that can be captured with copper iodide[22–25]. In our design plan, if the reaction is performed with [^{18}F]fluoride, the resulting *in situ* generated [^{18}F]$CuCF_3$ species could undergo cross-coupling with the aryl or heteroaryl iodide with release of [^{18}F]labelled trifluoromethyl (hetero)arene (Fig. 1e). We were poised to test the proposed 'difluorocarbene–fluoride–CuI' multicomponent strategy towards [^{18}F]$CuCF_3$ because the value of unligated and ligated trifluoromethylcopper complex for trifluoromethylation of (hetero)aryl iodides is amply demonstrated in the literature[26–28]. We recognized that the proposed transient formation of CF_2-carbene may lead to side reactions, but considered that the short reaction time imposed by [^{18}F]radiochemistry could bypass these complications.

Overcoming these challenges unveils a new reactivity space unexplored for [^{18}F]trifluoromethylation.

Results

Our initial studies began with the validation of the difluorocarbene–[^{18}F]fluoride–CuI strategy to access [^{18}F]CuCF$_3$ and the identification of a robust protocol for aryl [^{18}F]trifluoromethylation (Supplementary page S12). *p*-Iodonitrobenzene served as model substrate for optimization studies. All reactions were conducted without deliberate addition of [^{19}F]fluoride (no carrier added). The [^{18}F]trifluoromethylation requires the presence of CuI and a ligand to proceed. CuBr or CuCl were less efficient than CuI and the reaction was best performed in the presence of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA). Notably, 1,10-phenanthroline was not suitable as a replacement for TMEDA, a result contrasting with the well-established reactivity of (phen)CuCF$_3$ (refs 26,27), a complex allowing for the conversion of aryl iodides into trifluoromethylated arenes. The [^{18}F]trifluoromethylation proceeded at 150 °C using [^{18}F]KF/K$_{222}$ in dimethylformamide (DMF) or in *N*-methylpyrrolidone, but higher radiochemical yields (RCYs) were obtained in DMF. [^{18}F]Tetraethylammonium fluoride was also a competent [^{18}F]fluoride source. Stoichiometric amounts of aryl iodide, methyl chlorodifluoroacetate, CuI and TMEDA (ratio 1:1.5:1.5:1.5) were used for the reaction. When the quantity of aryl iodide was increased with respect to the other reagents, the RCY decreased significantly. The optimized protocol started with the preparation of a vial containing CuI (11 mg), to which was added [^{18}F]KF/K$_{222}$ in MeCN. The solvent was evaporated under N_2 at 100 °C (2 min). The vial was removed from heat, and a solution of methyl chlorodifluoroacetate (6 μl), TMEDA (9 μl) and aryl (or heteroaryl) iodide (0.037 mmol) in DMF (300 μl) was added via syringe. The sealed vial was heated at 150 °C for 20 min. The reaction was quenched by addition of water (100 μl) and analysed by radioactive thin-layer chromatography (radioTLC) and radioactive high-performance liquid chromatography (HPLC) to identify the RCY and derive the product identity, respectively. Applying these conditions, [^{18}F]trifluoromethyl nitrobenzene was obtained in 87% RCY within 30 min.

As illustrated in Fig. 2, we found that this new [^{18}F]CF$_3$Cu-mediated protocol allows for the direct incorporation of [^{18}F]CF$_3$ into a broad range of arenes and heteroarene rings. A wide range of arenes and functional groups are tolerated, including esters, nitro and cyano groups, and aryl halides other than iodide, ethers and amides. The [^{18}F]trifluoromethylation occurred with good to excellent RCY and regioselectivity, the attachment of the [^{18}F]CF$_3$ group occurring through cross-coupling at the iodo-substituted carbon. Unprotected alcohols, amines and carboxylic acids are not compatible with this protocol, probably due to competing alkylation with methyl chlorodifluoroacetate or *in situ* generated methyl halide (Fig. 2a). A dipeptide, DNA base analogue (*N*-benzyloxyl-methyl acetal (BOM) protected uracil derivative)[29] and carbohydrate all responded to [^{18}F]trifluoromethylation with RCYs exceeding 30% (Fig. 2b). We next turned our attention to heteroarenes with the knowledge that there is an unmet pressing need for CF$_3$ [^{18}F]labelling technologies for these valuable pharmacophores. As shown in Fig. 2c, we found that pyrazine, quinoline, pyridine, indoles, thiophene and benzothiazole are compatible with this new [^{18}F]labelling approach. For these heterocyclic motifs, the RCY ranged from 17% to 67%. Notably, 2-chloropyridine underwent selective [^{18}F]trifluoromethylation with no side reaction, resulting from direct substitution of the chloro substituent with [^{18}F]fluoride. For these reactions, radio-HPLC analysis of the crude reaction mixtures typically showed the [^{18}F]trifluoromethylated arene or heteroarene as a single product together with unreacted [^{18}F]fluoride. An additional development is the demonstration that C3-substituted *N*-methyl indole

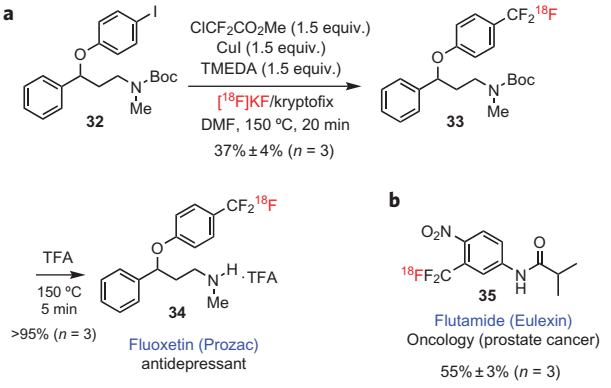

Figure 3 | [^{18}F]Labelling of fluoxetine and flutamide. Biologically active molecules were subjected to the standard reaction conditions. **a**, The antidepressant fluoxetine was [^{18}F]labelled in a two-step protocol within 25 min. **b**, [^{18}F]Flutamide could be accessed in a single step in 55% RCY.

underwent direct C–H oxidative [^{18}F]trifluoromethylation under our standard [^{18}F]labelling conditions[30,31]. The indole with the [^{18}F]CF$_3$-substituent installed at the C2 position was formed as the predominant regioisomer. This transformation is a unique example of direct CH functionalization in the context of ^{18}F-radiochemistry. This transformation may be mediated by oxygen or CuI present in the system (Fig 2d).

An additional major benefit of our [^{18}F]trifluoromethylation procedure is its amenability to labelling biologically active molecules and widely prescribed drugs (Fig. 3). For instance, *N*-Boc protected [^{18}F]fluoxetine[32] was readily prepared in 37% RCY by applying this direct [^{18}F]trifluoromethylation. The subsequent *N*-Boc deprotection delivered [^{18}F]fluoxetine (trifluoroacetic salt) within 5 min at 150 °C (>95% conversion) (Fig. 3a). [^{18}F]Flutamide[33] was obtained with an RCY of 55% (Fig. 3b). Easy access to non-steroidal ^{18}F-labelled radiopharmaceutical such as [^{18}F]flutamide can encourage the development of a wide spectrum of specific prostate cancer PET imaging agents and facilitate image-guided treatment.

Discussion

Specific activity is an important consideration when reviewing new radiochemistry. The mass dose of the tool compound defines the extent of applications and dictates the level of toxicology required to support human use. The specific activity of [^{18}F]4-trifluoromethyl nitrobenzene was found to be 0.1 GBq μmol^{-1} (ref. 34). The method reported here is therefore of particular value to support drug development activities. For translational preclinical and clinical studies, the potential toxicity of CuI was considered, although such concerns are very different for PET imaging because of the small amount of radiotracer that is required. In fact, various radiotracers containing a Cu(I)-based chelate[35] or employing a copper(I)-mediated reaction for their preparation, for example the azide-alkyne 1,3-dipolar cycloaddition (CuAAC), are used for clinical studies on a regular basis[36]. For completeness, inductively coupled plasma mass spectrometry (ICP-MS) analysis was performed on [^{18}F]4-trifluoromethyl nitrobenzene purified by a conventional HPLC technique. This analysis indicated that the labelled material contained 217 ppb Cu-63 residue, a clear demonstration that CuI can be removed effectively.

In this work, we have introduced an efficient no-carrier-added multicomponent protocol that allows for facile [^{18}F]trifluoromethylation of aromatic and heteroaromatic systems using (hetero)aryl iodide, and [^{18}F]CF$_3$Cu generated *in situ* from methyl chlorodifluoroacetate, CuI, TMEDA and [^{18}F]fluoride. This technology may find ample applications in [^{18}F]trifluoromethylation of pharmaceutical candidates to facilitate drug

development, especially for CNS diseases. Previously unavailable ^{18}F-PET tracers for clinical studies may also come within reach. This radiochemistry does not necessitate the preparation of complex organometallic precursors and can be performed with commercially available reagents in a reaction vessel exposed to air. Therefore, this [^{18}F]trifluoromethylation process should be suitable for automated synthesizers and microfluidic development. Its operational simplicity allows for immediate use by most establishments, provided they have access to basic PET chemistry infrastructure.

Methods

General radiochemical procedure for [^{18}F]trifluoromethylation. [^{18}F]KF/K_{222} in MeCN was added to a V-vial containing CuI (11 mg) and a magnetic stirrer bar. The solvent was evaporated under N_2 at 100 °C (2 min). The vial was removed from heat, and a solution of methyl chlorodifluoroacetate (6 μl), TMEDA (9 μl) and aryl (or heteroaryl) iodide (0.037 mmol) in DMF (300 μl) was added via syringe. The sealed vial was heated at 150 °C for 20 min. The reaction was quenched by the addition of water (100 μl). An aliquot was removed for analysis by radioTLC and HPLC to obtain the RCY and product identity, respectively.

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Author contributions

M.H., M.T. and S.M. performed and analysed experiments. All authors contributed to the design of experiments to develop this reaction and probe its utility. V.G. and J.P. prepared the manuscript.

Additional information

Supplementary information and chemical compound information are available in the online version of the paper. Reprints and permissions information is available online at www.nature.com/reprints. Correspondence and requests for materials should be addressed to V.G. and J.P.

Competing financial interests

The authors declare no competing financial interests.