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Radiolabelling

[^{18}F]$CuCF_3$: A [^{18}F]Trifluoromethylating Agent for Arylboronic Acids and Aryl Iodides

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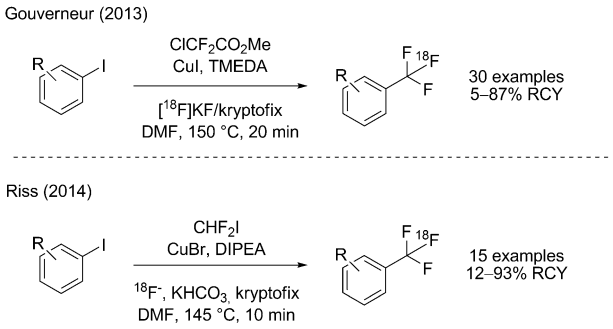
Abstract: Positron emission tomography has emerged as the leading method for medical imaging with fluorine-18 as the most widely used radioactive isotope. Here we report a semi-automated method for the preparation of valuable [^{18}F]trifluoromethylcopper, as well as its use for the radiosynthesis of [^{18}F]trifluoromethylarenes and heteroarenes. Mild conditions of [^{18}F]trifluoromethylation make this method particularly useful for the radiosynthesis of pharmacologically relevant [^{18}F]trifluoromethylarenes and heteroarenes.

Positron emission tomography (PET) is a powerful imaging method widely used in clinic, notably for diagnostics in oncology.[1] Among radioactive isotopes available for PET, fluorine-18 is the most commonly used.[2] Indeed, its half-life ($t_{1/2}$ 110 min) offers a good compromise between high radioactivity and convenience of synthetic manipulations, while the low positron energy associated with fluorine 18 decay leads to high imaging resolution. Typically, the radioactive fluorine atom is introduced into a probe as late as possible in order to minimize the duration of radiosynthesis, thus preserving the maximum amount of initial activity. ^{18}F-Labelled radiotracers are usually produced through the nucleophilic substitution of a suitable leaving group by [^{18}F]fluoride.[2,3]

Trifluoromethylarenes are key moieties for the development of bioactive compounds, especially in medicinal chemistry.[4] A general method for radiolabelling such moieties that complies with the specific constraints inherent to radiochemistry, has great potential for the efficient study of the pharmacological properties of active trifluoromethylated compounds and, more generally, for drug discovery. However, such compounds are severely underrepresented among the ^{18}F-labelled PET probes. This is obviously due to the difficulty of assembling the radiolabelled CF_3 group through either nucleophilic or electrophilic reactions involving fluorine-18. Until recently [^{18}F]CF_3-labelled compounds have been prepared through C—^{18}F bond formation either by oxidative fluorination of dithioesters,[5] a halogen-exchange reaction from a suitable trihalomethylarene precursor,[6] or the decarboxylative electrophilic fluorination of difluorinated aryl carboxylic acids.[7] However, harsh conditions are often required and the scope is mainly limited to electron-deficient substrates. A different approach based on the direct formation of the C–CF_2^{18}F bond was proposed very recently by the research groups of Gouverneur[8] and Riss[9] (Scheme 1).



Scheme 1. Radiolabelled trifluoromethylarenes. DIPEA = *N*,*N*-diisopropylethylamine, TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine.

Aryl iodides were successfully converted into the corresponding radiolabelled trifluoromethylarenes by using a difluoromethylated precursor and [^{18}F]fluoride. The reaction is believed to occur via the in situ formation of a radiolabelled trifluoromethylating agent, presumably [^{18}F]$CuCF_3$. Although harsh conditions are required (150 °C), the subsequent reaction of [^{18}F]$CuCF_3$ with aryl iodides demonstrated moderate to good radiochemical yields and a wide substrate scope.

In the present work, we report an efficient method for preparing well-defined radiolabelled trifluoromethylcopper ([^{18}F]$CuCF_3$), allowing us to then [^{18}F]trifluoromethylate arylboronic acids and aryliodides under mild conditions. Key intermediate [^{18}F]$CuCF_3$ was prepared as a ready-to-use solution in DMF through a semi-automated procedure and the subsequent radiolabelling of arylboronic acids is characterized by conditions that involve a quasineutral solution, room temperature, and air atmosphere.

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At the onset of our project, we were inspired by Grushin's pioneering work concerning the cupration of fluoroform and the use of the resulting $CuCF_3$ reagent in various trifluoromethylation reactions.[10] In addition to the high synthetic potential of the $CuCF_3$ reagent, high rate of cupration and unusually rapid trifluoromethylation of boronic acids, even at room temperature, were observed, thus suggesting that this approach could be well-adapted to the radiochemistry constraints.

In that context, efficient generation of $[^{18}F]CHF_3$ under conditions that are compatible with the cupration chemistry is of primary importance. CHF_3 is a usual byproduct in reactions involving a difluorocarbene (CF_2), for example, the industrial production of polytetrafluoroethylene (PTFE), as well as a number of difluoromethylation and cyclopropanation reactions.[11] Therefore, we decided to generate $[^{18}F]CHF_3$ from $[^{18}F]$fluoride and a suitable source of CF_2.[12] Among several CF_2 precursors, difluoromethylsulfonium salt **1**[13] provided the best yield and the highest purity of CHF_3, when it was treated with tetra-*n*-butylammonium fluoride ($TBAF{\cdot}3H_2O$) or KF/18-C-6 in acetonitrile under nonradioactive conditions.[14] Its structure was confirmed by X-ray analysis (Figure 1). Sulfonium salt $\mathbf{1}{\cdot}CH_2Cl_2$ is an easy-to-manipulate and bench-stable crystalline solid, which are essential characteristics for a precursor that would have widespread use for the preparation of PET radiotracers.

In mmol-scale experiments with non-radioactive fluoride, we confirmed that the whole sequence of reactions was feasible:

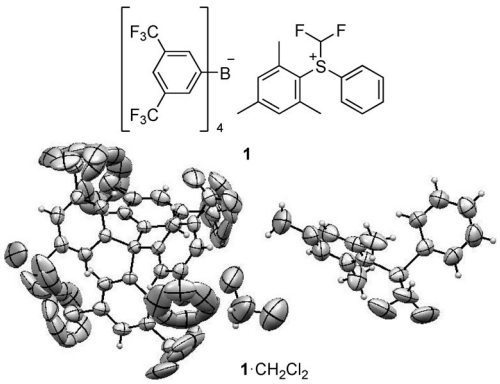
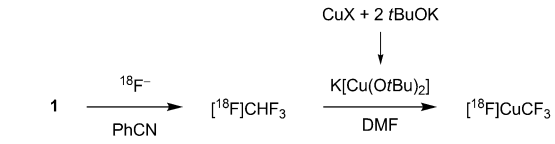


Figure 1. Crystal structure of $\mathbf{1}{\cdot}CH_2Cl_2$.

CHF_3 was instantaneously generated from **1**[14] in CH_3CN, pulled out with a stream of N_2, and trapped in a solution of $K[Cu(OtBu)_2]$.[10a] The resulting $CuCF_3$ solution could be immediately used for the trifluoromethylation of aryl iodides and arylboronic acids.[15] Radiochemical synthesis of $[^{18}F]CuCF_3$ was successfully realized by using a semi-automated module.[16] $[^{18}F]$Fluoride anions previously dried according to the usual procedure were solubilized in PhCN; the solution was then transferred onto neat **1** and the resulting $[^{18}F]CHF_3$ formed was pulled out using a flow of He and trapped in a solution of $K[Cu(OtBu)_2]$ in DMF (prepared form either CuI or CuCl and *t*BuOK) as $[^{18}F]CuCF_3$.

At first, $[^{18}F]KF/K_{222}$ was used as the fluoride source. With 17 μmol of precursor **1** and 3 equivalents of $K[Cu(OtBu)_2]$,

Table 1. Optimization of $[^{18}F]CuCF_3$ preparation from **1**.

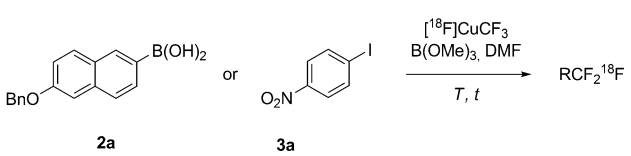


Entry	$^{18}F^-$ Source[a]	**1** [μmol]	Cu/**1**	X	[Cu] [mol L^{-1}]	RCY transfer [%][b]	RCY [%][c]
1	KF/K_{222}	17	1:3	Cl	0.06	62	29
2	KF/K_{222}	50	1:5	Cl	0.25	47	40
3	KF/K_{222}	50	1:3	I	0.18	61	10
4	TBAF	13	1:40	Cl	0.25	ND[d]	10
5	TBAF	79	1:13	Cl	0.25	ND[d]	33
6	TBAF	50	1:3	I	0.18	93	36
7	TBAF	50	1:3	I	0.03	94[e]	36[e]

[a] TBAF and KF/K_{222} were released from the anion exchange cartridge with $TBAHCO_3$ and K_2CO_3/K_{222}, respectively. [b] RCY of fluoride transfer from the drying reactor onto **1**. Calculated from activity remaining in $[^{18}F]F^-$ drying reactor. [c] Calculated from activity of $[^{18}F]CuCF_3$ solution and initial activity eluted from the anion exchange cartridge. [d] No relevant quantity of activity was detected in the drying reactor. [e] Average of two experiments.

$[^{18}F]CuCF_3$ was obtained with 29% radiochemical yield (RCY; Table 1, entry 1). Increasing the amount of reactants to 50 μmol of **1** and 5 equivalents of copper salt resulted in 40% RCY (Table 1, entry 2). However, in our next trials to optimize the stoichiometry of the reaction and the copper source, some reproducibility issues emerged (Table 1, entry 3). In particular, using $[^{18}F]KF/K_{222}$, we had difficulties in controlling the efficiency of activity transfer (that is, $^{18}F^-$ anions) from the drying reactor to the reactor containing precursor **1**.[16]

Table 2. Optimization of coupling reactions.[a]



2a **3a**

Entry	Substrate	*n*	CuX[b]	*T* [°C]	*t* [min]	RCY [%][c]
1	**2a**	2	CuCl	RT	27	75
2[d]	**2a**	2	CuCl	RT	23	78
3	**2a**	0.14	CuCl	RT	38	22
4	**2a**	1.4	CuCl	RT	16	22
5	**2a**	1.4	CuCl	60	16	29
6	**2a**	2	CuI	RT	25	80[e]
7	**3a**	1	CuCl	100	25	30
8	**3a**	3	CuCl	100	50	24
9	**3a**	1	CuI	100	15	63
					40	79
					120	79
10	**3a**	2	CuI	100	25	78[e]

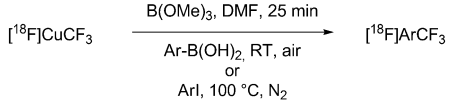
[a] Performed by adding $[^{18}F]CuCF_3$ solution in DMF to the corresponding substrate under air for **2a** and under N_2 for **3a**. [b] Copper source used to generate CuO*t*Bu. [c] Calculated from activities of organic and aqueous layers. Radiochemical purity confirmed by radio-HPLC analysis. [d] AgOTf was used as an additive (1 equiv). [e] Average of two experiments.

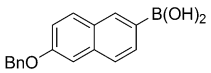
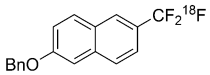
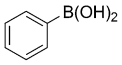
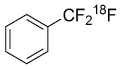
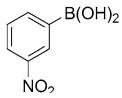
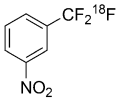
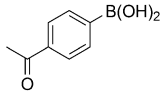
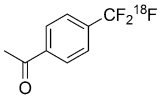
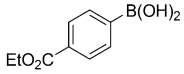
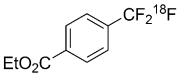
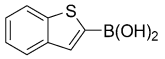
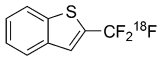
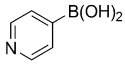
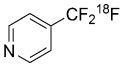
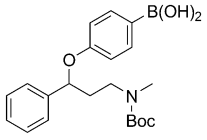
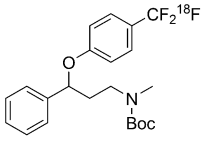
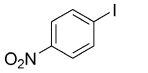
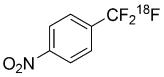
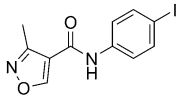
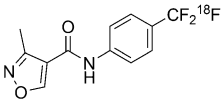
Consequently, we turned our attention to [^{18}F]TBAF as the fluoride source (Table 1, entries 4–7). The better solubility of [^{18}F]TBAF in PhCN ensured the efficient transfer of $^{18}F^-$ anions from the drying reactor into precursor **1**. Indeed, by using 13 μmol of **1** and 40 equivalents of CuCl, [^{18}F]$CuCF_3$ was produced with only 10% RCY but no relevant remaining quantity of activity was detected in the drying reactor (Table 1, entry 4). By increasing the loading of **1**, we were pleased to get [^{18}F]$CuCF_3$ with 33% RCY (Table 1, entry 5). The amount of precursor **1** was adjusted to 50 μmol along with 3 equivalents of copper salt without loss in yield (Table 1, entry 6). Finally, the sequence was reproduced under more dilute conditions to facilitate further use of the [^{18}F]$CuCF_3$ solution (Table 1, entry 7). At the end of [^{18}F]CHF_3 distillation, trimethylborate was added to the DMF solution to neutralize the excess of *t*BuOK. Although the present approach requires distillation of [^{18}F]CHF_3, it compares favorably to the recently reported one-pot procedures, because it allows the fast and room-temperature preparation (2 min) of a neutral solution of [^{18}F]$CuCF_3$.

Having developed an efficient and reproducible method for the preparation of [^{18}F]$CuCF_3$, we moved on to the coupling reaction. In the case of boronic acids, our preliminary studies under nonradiochemical conditions showed that the addition of an Ag^I salt dramatically improved the rate of the reaction.[15] Surprisingly, under radiochemical conditions, AgOTf seemed to have no effect at all (Table 2, entries 1 and 2). Indeed, by using 2 equivalents of boronic acid **2a** (with respect to initial copper loading), we observed rapid formation of the desired coupling product in the presence or absence of AgOTf (75% versus 78%). Using a substoichiometric amount of **2a** resulted in poor yield (Table 2, entry 3); we assumed that the excess of copper salt used for the preparation of [^{18}F]$CuCF_3$ reacts with the substrate. With 1.4 equivalent of **2a**, only 22% of the desired product was detected (Table 2, entry 4). Raising the temperature to 60 °C had no effect (Table 2, entry 5). Finally, the replacement of CuCl for CuI[17] for the generation of K[$Cu(OtBu)_2$] had a very positive effect on the rate and the reproducibility of the coupling reaction of **2a** and the corresponding trifluoromethylated product was obtained in 80% yield (Table 2, entry 6).

The same enhancing effect of the use of CuI on the coupling reaction rate was observed for the trifluoromethylation of aryl iodide **3a**. Indeed, using CuCl as copper source along with 1 equivalent of **3a**, the coupling reaction gave the desired product with only 30% yield after 25 min at 100 °C (Table 2, entry 7). No improvement was observed when 3 equivalents of **3a** were used (Table 2, entry 8). However, using CuI as a copper source, the rate of the trifluoromethylation reaction of **3a** was notably increased. Indeed, with 1 equivalent of aryl iodide, 63% of the coupling product was obtained after 15 min, reaching a maximum of 79% after 40 min (Table 2, entry 9). Finally, the best compromise between rate and stoichiometry was found with 2 equivalents of **3a** and 25 min reaction time (Table 2, entry 10).

Table 3. Scope the [^{18}F]trifluoromethylation.[a]



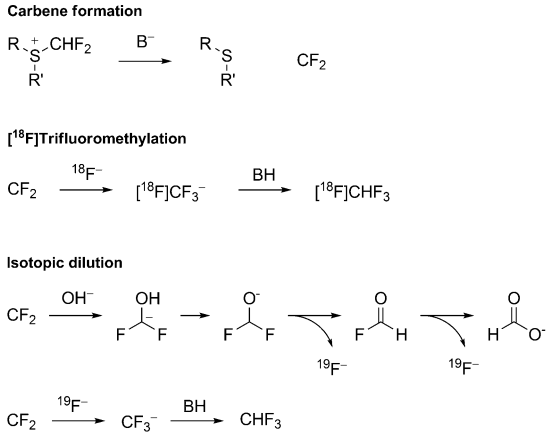
Entry	Substrate		Product		RCY [%][b]	Radio-HPLC [%][c]
1		**2a**		**4a**	80	99.8
2		**2b**		**4b**	82	100
3		**2c**		**4c**	88	100
4		**2d**		**4d**	86	99.9
5		**2e**		**4e**	86	99.9
6		**2f**		**4f**	87	100
7		**2g**		**4g**	78	100
8		**2h**		**4h**	85	100
9		**3a**		**4i**	78	100
10		**3b**		**4j**	18	98.9

[a] Reactions performed on 0.05 mmol scale of substrate (**1**:CuX = 2:1). [b] Calculated from activities of organic and aqueous layers after extraction with EtOAc:H_2O. Average of two experiments. [c] Radiochemical purity determined by radio-HPLC analysis of the crude organic phase.

These optimized conditions were successfully applied to a variety of arylboronic acids and aryl iodides (Table 3). Electron-rich arene **2a** gave the corresponding product in a very good 80% yield along with excellent radiochemical purity (99.8%; Table 3, entry 1). We were pleased to observe that all other boronic acids tested gave similar results regarding yields (78–88%) and radiochemical purities (>99.8%). Phenylboronic acid **2b** (Table 3, entry 2) and electron poor arenes **2c**–**e** were suitable substrates in this process (Table 3, entries 3–5). It is noteworthy that ketone and ester functions are compatible with this reaction, as well as benzothiophene and pyridine heterocycles **2f** and **2g** (Table 3, entries 6 and 7). Fluoxetine precursor **2h** furnished valuable radiolabelled *N*-Boc-fluoxetine **4h** with a very good yield (85%).[18] Aryl iodide **3a** bearing an electron-withdrawing group was efficiently engaged in this process leading to the expected trifluoromethylated compound in 78% yield and excellent radiochemical purity. Finally, this process allowed us to prepare [^{18}F]leflunomide **4j** with 18% yield and excellent radiochemical purity. We assume that this moderate result, which was already observed under nonradiochemical conditions, is due to the incompatibility between the amide function and the harsher conditions (100 °C) used to convert aryl iodides.

The specific activity of the [^{18}F]trifluoromethylarenes prepared with our process (100 MBq μmol^{-1} for **4i**) is of the same level as that reported by Gouverneur et al.[9] by using in situ generated [^{18}F]$CuCF_3$. This range of specific activity is adequate for numerous applications in PET, but it is still 10^3 times lower than the typical values obtained in S_N2 [^{18}F]fluorination reactions of the nonfluorinated substrates. As illustrated on Scheme 2, and based on control experiments,[15] we suppose that the observed isotopic dilution originates from the partial hydrolysis of CF_2 by traces of water and the excess of carrier base (such as $TBAHCO_3$). That can in principle be improved through development of a better [^{18}F]fluoride drying technique.

In conclusion, we report here the first method for preparing well-defined [^{18}F]$CuCF_3$ as a radiolabelling agent and demonstrate its utility through the preparation of radiolabelled trifluoromethylarenes and heteroarenes, such as [^{18}F]leflunomide or [^{18}F]fluoxetine precursor. We have developed a rapid (2 min) and semi-automated preparation of [^{18}F]$CuCF_3$ from dried [^{18}F]TBAF and the precursor **1**, thus making [^{18}F]$CuCF_3$ almost as accessible as [^{18}F]fluoride itself. The resulting [^{18}F]$CuCF_3$ is suitable for the efficient and clean trifluoromethylation of both arylboronic acids and aryl iodides. This two-step procedure allows the coupling reaction to proceed at much lower temperature and neutral conditions than methods previously described and can therefore potentially be applied to larger classes of substrates possessing various functions.



Scheme 2. Proposed origin of isotopic dilution.

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Keywords: arylboronic acid · copper · fluorine · radiochemistry · trifluoromethylation

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[16] See the Supporting Information for detailed semi-automated process.
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Radiolabelling

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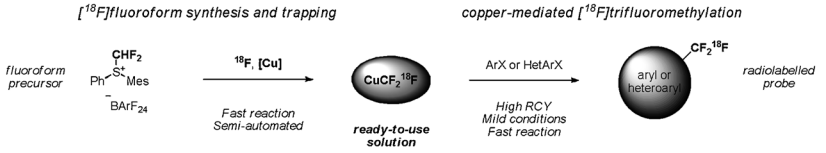
■■ – ■■

[^{18}F]$CuCF_3$: A [^{18}F]Trifluoromethylating Agent for Arylboronic Acids and Aryl Iodides



^{18}F Radiochemistry: A semi-automated method for the fast preparation of radiolabelled (trifluoromethyl)copper is reported (see scheme), thus making [^{18}F]$CuCF_3$ almost as accessible as [^{18}F]fluoride itself for the preparation of radiolabelled trifluoromethylated probes. It can be used for the preparation of radiolabelled trifluoromethylarenes from arylboronic acids and aryliodides. This methodology is clean, efficient and consistent with the specific requirements of radiochemistry.