Isotopic Labeling

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A Universal Procedure for the [^{18}F]Trifluoromethylation of Aryl Iodides and Aryl Boronic Acids with Highly Improved Specific Activity

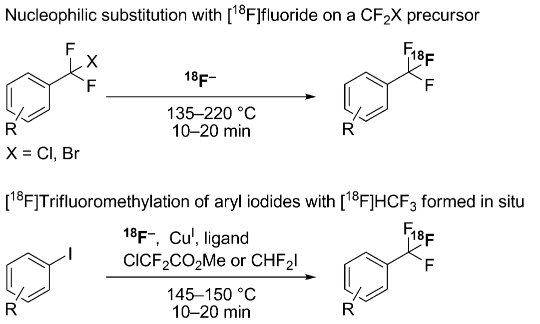
*Dion van der Born, Claudia Sewing, J. (Koos) D. M. Herscheid, Albert D. Windhorst, Romano V. A. Orru, and Danielle J. Vugts**

Abstract: *Herein, we describe a valuable method for the introduction of the [^{18}F]CF$_3$ group into arenes with highly improved specific activity by the reaction of [^{18}F]trifluoromethane with aryl iodides or aryl boronic acids. This [^{18}F]trifluoromethylation reaction is the first to be described in which the [^{18}F]CF$_3$ products are generated in actual trace amounts and can therefore effectively be used as PET tracers. The method shows broad scope with respect to possible aryl iodide and aryl boronic acid substrates, as well as good to excellent conversion. In particular, the [^{18}F]trifluoromethylation of boronic acids was found to outperform [^{18}F]trifluoromethylation reactions of halogenated aryl precursors with regard to conversion, reaction conditions, and kinetics.*

Positron emission tomography (PET) is a noninvasive molecular-imaging technique for the visualization of human physiology by the use of biomarkers labeled with a positron-emitting radionuclide.[1] As only trace amounts of a radiolabeled biomarker are required for the emission of enough positrons for a PET scan, PET is a very valuable technique for the imaging of low-density biological targets without inducing any biological effects. Therefore, PET has proven to be an excellent diagnostic tool in all areas of medicine and is frequently used to detect, characterize, and monitor cancer as well as neurodegenerative and cardiovascular diseases; it can even lead to diagnosis well before structural changes or symptoms occur.[2] Furthermore, PET imaging is of added value in drug-discovery and drug-development programs.[3]

Among the various positron-emitting isotopes available, fluorine-18 is most commonly used. Fluorine-18 has a relatively low positron energy ($E_{\max} = 634$ keV) and is readily produced with a low-energy cyclotron. This characteristic, in combination with a half-life of 110 min, makes fluorine-18 perfectly suited for introduction in small-molecule PET radiopharmaceuticals. Still, short synthesis times are required, and for optimal utilization, the introduction of fluorine-18 and subsequent purification, formulation, and quality control of the ^{18}F-labeled PET radiopharmaceutical has to be completed within 2 h. Consequently, there is an increasing demand for new robust, reliable, and rapid radiochemical synthetic methodology for the late-stage introduction of fluorine-18 into radiopharmaceuticals. Of particular interest are methods that utilize [^{18}F]fluoride, as this reagent is obtained by the ^{18}O(p,n)^{18}F nuclear reaction in high yields and is commercially available.[4]

The CF$_3$ group is a popular functional group in many active pharmaceutical ingredients (APIs) and/or drug candidates, because it improves binding selectivity, lipophilicity, and metabolic stability.[5] Efficient methodology to introduce ^{18}F-labeled CF$_3$ groups into such compounds makes them useful as potential PET tracers. Today, only a few methods are available for the radiolabeling of trifluoromethyl arenes with [^{18}F]fluoride (Scheme 1). These methods can be divided into two categories: the direct treatment of [^{18}F]fluoride with a precursor of the type ArCF$_2$X,[6] and the introduction of a [^{18}F]CF$_3$ group by the treatment of an aryl iodide with [^{18}F]CuCF$_3$ formed in situ.[7,8] Both approaches require harsh reaction conditions and long reaction times. Furthermore, the labeled products are not suitable as PET tracers. Owing to degradation of the RCF$_2$X (ArCF$_2$X, HCF$_2$I, COOMeCF$_2$I) precursors, not only radioactive ^{18}F, but also mass amounts of ^{19}F are incorporated into the products. In radiochemistry, the ratio of ^{18}F over the total mass of the product is expressed as the specific activity (SA) in GBq μmol^{-1}. The reported specific activities of 100–139 MBq μmol^{-1} for methods based on the use of [^{18}F]CuCF$_3$ make these products unsuitable for the imaging of low-density biological targets.[9]



Scheme 1. Reported methods for the synthesis of [^{18}F]trifluoromethyl arenes.

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[*] D. van der Born, C. Sewing, Dr. J. D. M. Herscheid,
Prof. Dr. A. D. Windhorst, Dr. D. J. Vugts
Department of Radiology and Nuclear Medicine
VU University Medical Center
De Boelelaan 1085c, 1081 HV Amsterdam (The Netherlands)
E-mail: d.vugts@vumc.nl
Prof. Dr. R. V. A. Orru
Department of Chemistry and Pharmaceutical Sciences and
Amsterdam Institute for Molecules, Medicines and Systems
(AIMMS), VU University Amsterdam
De Boelelaan 1083, 1081 HV, Amsterdam (The Netherlands)

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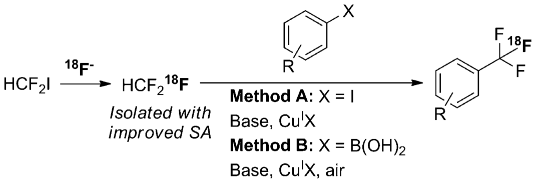
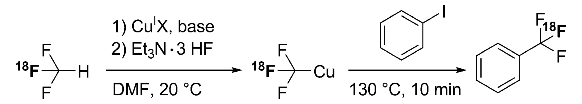
Recently, we reported the synthesis of [^{18}F]HCF$_3$ and its application as a labeling agent for the [^{18}F]trifluoromethylation of aldehydes and ketones.[10] To further extend the application of [^{18}F]HCF$_3$, we focused on broadening the scope of the reaction by exploring the labeling of aryl iodides and aryl boronic acids. To make the products useful for PET imaging, we also investigated the synthesis of [^{18}F]HCF$_3$ with an improved SA. We suspect that all [^{18}F]trifluoromethylation products derived from [^{18}F]HCF$_3$ with an improved SA will also be obtained with an improved SA. Herein we report the broad applicability of [^{18}F]HCF$_3$ as a labeling agent with improved SA for the aromatic [^{18}F]trifluoromethylation of aryl iodides and aryl boronic acids (Scheme 2).



Scheme 2. Our strategy for [^{18}F]trifluoromethylation by the use of [^{18}F]HCF$_3$ with highly improved specific activity as a versatile labeling agent.

First, we focused on the [^{18}F]trifluoromethylation of aryl iodides by using iodobenzene as a model substrate. Initial experiments with various strong bases and Cu$^{\rm I}$ sources did not lead to satisfactory yields of the desired [^{18}F](trifluoromethyl)benzene, and decomposition of [^{18}F]CuCF$_3$ to [^{18}F]fluoride was observed.[11] However, the addition of Et$_3$N·3 HF to the solution was found to stabilize the CuCF$_3$ species owing to precipitation of the K$^+$ cation as KF(s), as was reported by Zanardi et al.[12] With this approach, we obtained [^{18}F]trifluoromethylbenzene in satisfactory yields (Table 1). The formation of [^{18}F]CuCF$_3$ and subsequent stabilization with Et$_3$N·3 HF was completed in just 2 min at room temperature.

Table 1: Optimization of the [^{18}F]trifluoromethylation of iodobenzene.[a]



Entry	Base	Cu$^{\rm I}$ source	Cu$^{\rm I}$ [mM]	Ratio[b]	*t* [min]	Conversion [%] (*n* = 3)
1	KO*t*Bu	Cu$^{\rm I}$Cl	20	1:3:1	10	48 ± 3
2	KO*t*Bu	Cu$^{\rm I}$Br	20	1:3:1	10	56 ± 3
3	KO*t*Bu	Cu$^{\rm I}$I	20	1:3:1	10	57 ± 3
4	NaO*t*Bu	Cu$^{\rm I}$Br	20	1:3:1	10	3 ± 3
5	KHMDS	Cu$^{\rm I}$Br	20	1:3:1	10	12 ± 5
6	KO*t*Bu	Cu$^{\rm I}$Br	20	1:3:0.5	10	4 ± 2
7	KO*t*Bu	Cu$^{\rm I}$Br	20	1:3:1.5	10	46 ± 3
8	KO*t*Bu	Cu$^{\rm I}$Br	40	1:3:1	10	34 ± 2
9	KO*t*Bu	Cu$^{\rm I}$Br	10	1:3:1	10	61 ± 2
10	KO*t*Bu	Cu$^{\rm I}$Br	10	1:3:1	5	32 ± 5

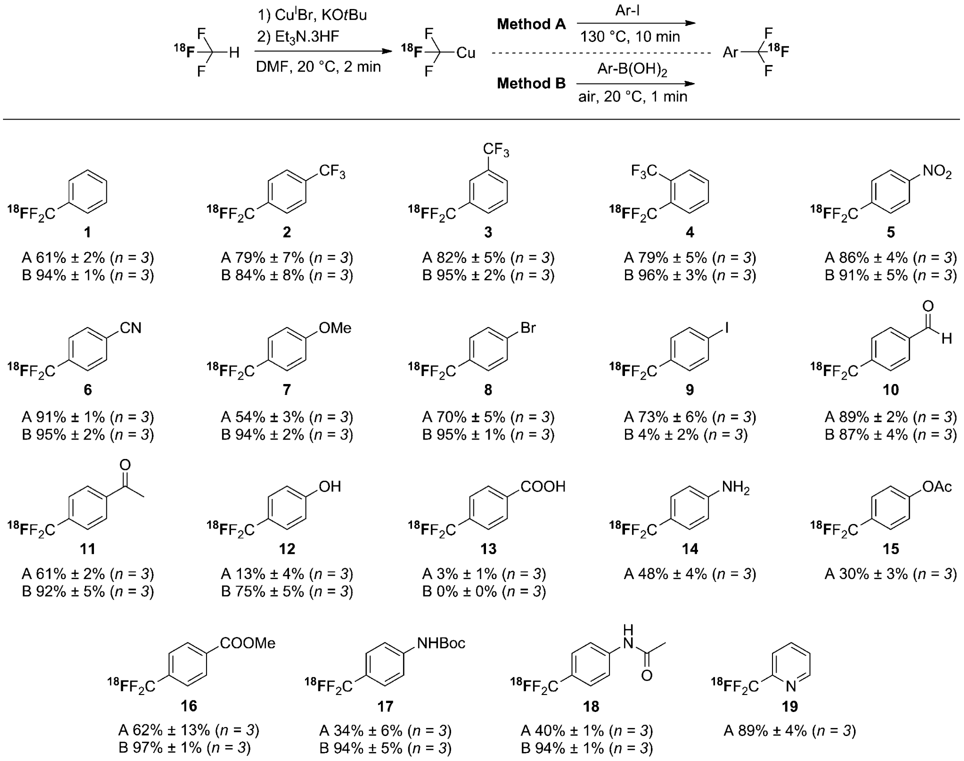
[a] Standard reaction conditions: [^{18}F]CuCF$_3$ formation at 20 °C for 1 min; Et$_3$N·3HF stabilization at 20 °C for 5 min; [^{18}F]trifluoromethylation at 130 °C; DMF (0.5 mL). [b] Cu$^{\rm I}$X/base/Et$_3$N·3 HF ratio. DMF = *N*,*N*-dimethylformamide, HMDS = hexamethyldisilazide.

Optimal [^{18}F]trifluoromethylation of iodobenzene proceeded at 130 °C in DMF in 10 min in the presence of Cu$^{\rm I}$Br, KO*t*Bu, and Et$_3$N·3 HF in a molar ratio of 1:3:1 and with a total Cu$^{\rm I}$Br concentration of 10 mM. Various other Cu$^{\rm I}$ sources can also be used (Table 1, entries 1–3). Of the various bases, however, only KO*t*Bu led to good conversion (Table 1, entries 4 and 5), when used in 3 molar excess relative to the amount of Cu$^{\rm I}$Br. For the stabilization of the formed [^{18}F]CuCF$_3$, all K$^+$ ions had to react with Et$_3$N·3 HF; thus, relative to KO*t*Bu, 1 equivalent of HF, which corresponds to 0.33 equivalents of Et$_3$N·3 HF, had to be present in the reaction mixture. A decrease in the amount of Et$_3$N·3 HF led to a drastic reduction in conversion into the product (Table 1, entry 6). We also found that the total concentration of the Cu$^{\rm I}$Br, KO*t*Bu, and HF reagents is quite important. Higher concentrations of these reagents led to lower conversion (Table 1, entry 8).

Having optimized the reaction conditions for the [^{18}F]trifluoromethylation of aryl iodides, we turned our attention to the scope of this reaction (Scheme 3). A broad range of aryl iodides could be converted successfully into the desired [^{18}F]trifluoromethyl arenes. From Scheme 3, it becomes clear that electronic effects do not have a large impact, and a wide array of functional groups in the precursor structure are compatible with the reaction. Even more interesting is that both 4-iodobenzaldehyde and 4-iodoacetophenone are exclusively converted into the [^{18}F]ArCF$_3$ products **10** and **11**, with no [^{18}F]trifluorocarbinol formation observed. Trifluorocarbinols are known to be formed by the reaction of the trifluoromethyl anion with aldehydes and ketones.[10,13] However, as we did not observe any [^{18}F]trifluorocarbinol side products, we can conclude that no sources of the [^{18}F]CF$_3$ anion were present in the reaction mixture. Unprotected alcohols and carboxylic acids were found to be incompatible with our method. The use of unprotected aniline, however, did lead to product formation with good conversion.

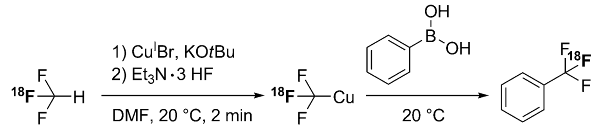
To further extend the application of [^{18}F]HCF$_3$ as a labeling agent, we investigated the oxidative [^{18}F]trifluoromethylation of boronic acids (Table 2).[14] The required [^{18}F]Cu$^{\rm I}$CF$_3$ reagent was prepared as described for the [^{18}F]trifluoromethylation of aryl iodides. Next, [^{18}F]Cu$^{\rm I}$CF$_3$ was oxidized to [^{18}F]Cu$^{\rm II}$CF$_3$ in the presence of the boronic acid precursor by purging the reaction mixture with air during the first minute of the reaction. Oxidation with air is required, as only a low conversion was found when the reaction mixture was not purged with air (Table 2, entry 1). The preparation of [^{18}F]trifluoromethyl arenes by using boronic acid substrates led to some major improvements over the [^{18}F]trifluoromethylation of aryl iodides, thus making this method more appropriate for the synthesis of PET radiopharmaceuticals.

Significant advantages over the [^{18}F]trifluoromethylation of aryl iodides are the reduction in the amount of the precursor required from 100 to 50 µmol (Table 2, entries 3–6), the completion of the synthesis in just 1 min instead of 10 min (Table 2, entries 7 and 8), and a reaction temperature of 20 °C instead of 130 °C. All in all, these conditions result in less



Scheme 3. Scope of the [^{18}F]trifluoromethylation of aryl iodides and aryl boronic acids. Standard reaction conditions: [^{18}F]CuCF$_3$ formation: 1) Cu^{I}Br (5 μmol), KO*t*Bu (15 μmol), DMF, 20 °C, 1 min; 2) Et$_3$N·3 HF (5 μmol), 20 °C, 1 min; method A: aryl iodide (100 μmol), 130 °C, 10 min; method B: aryl boronic acid (50 μmol), air (10 mL), 20 °C, 10 min. Boc = *tert*-butoxycarbonyl.

Table 2: Optimization of the [^{18}F]trifluoromethylation of phenylboronic acid.[a]

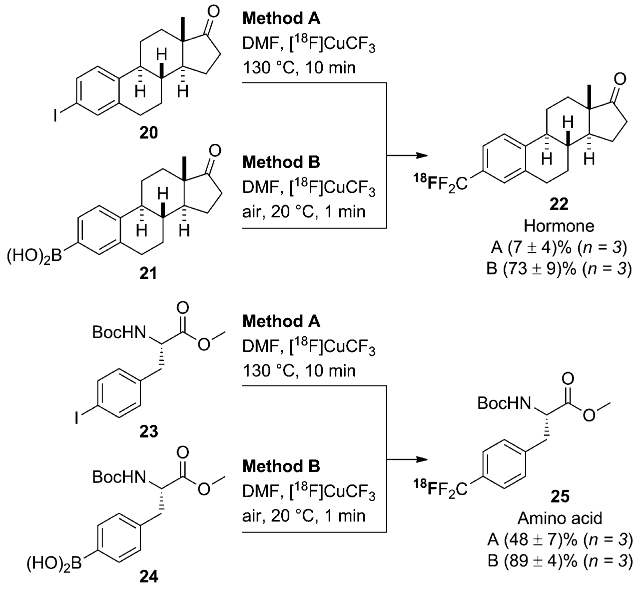


Entry	Phenylboronic acid [μmol]	Air [mL]	*t* [min]	Conversion [%] (*n* = 3)
1	100	0	10	19 ± 22
2	100	0.5	10	62 ± 19
3	100	5	10	87 ± 8
4	50	5	10	94 ± 1
5	20	5	10	55 ± 17
6	10	5	10	4 ± 5
7	50	5	1	85 ± 10
8	50	10	1	94 ± 1

[a] Standard reaction conditions: Cu^{I}Br (5 μmol), KO*t*Bu (15 μmol), Et$_3$N·3 HF (5 μmol), DMF (0.5 mL); [^{18}F]CuCF$_3$ formation at 20 °C for 1 min; Et$_3$N·3 HF stabilization at 20 °C for 1 min; [^{18}F]trifluoromethylation at 20 °C.

degradation of the precursor. In general, improved generality of the reaction and higher conversion were observed when boronic acids were used instead of aryl iodide precursors (Scheme 3). Again, electronic effects did not have a large impact on conversion into the product, and the reaction of boronic acids with an aldehyde or ketone functionality only led to the [^{18}F]ArCF$_3$ products **10** and **11**. From the boronic acid precursor, even the unprotected [^{18}F]trifluoromethylated phenol **12** could be formed; thus, acetyl protection of phenol groups is not required. The reaction to form aniline **14** could unfortunately not be investigated owing to the unsuccessful synthesis of the boronic acid precursor; however, the N-Boc-protected aniline **17** and phenylamide **18** were formed with excellent conversion. Carboxylic acid **13** could not be formed: Protection of the acid group was required. The low conversion in the formation of iodide **9** was attributed to the poor solubility of 4-iodophenylboronic acid in DMF.

To prove the applicability of this method for the synthesis of PET radiopharmaceuticals, we synthesized the [^{18}F]trifluoromethyl-substituted estrone derivative **22** as well as the Boc- and OMe-protected [^{18}F]4-trifluoromethylphenylalanine **25** (Scheme 4). Both products are radiopharmaceuticals of interest for PET. Estrone has a high binding affinity for the estrogen receptor, and this [^{18}F]trifluoromethylestrone derivative is therefore a potentially useful tracer for the imaging of overexpression of the estrogen receptor in breast cancer. This type of cancer relies on estrogen hormones for growth. If overexpression is found by the use of PET, a hormone-suppression treatment could be started.[15] Radiolabeled amino acids, including [^{18}F]4-fluorophenylalanine, have found their application in the imaging of upregulated amino acid incorporation by various types of cancer cells. Methods for the synthesis of [^{18}F]fluoro-substituted phenylalanine, however, are impractical, as they require multistep synthetic routes and/or electrophilic labeling methods. For both estrone and phenylalanine, direct installment of the fluorine-18 isotope at the aromatic ring by nucleophilic substitution with [^{18}F]fluoride is not possible owing to the high electron density of the aromatic systems. However, as [^{18}F]trifluoromethylation is barely affected by electronic effects, we reasoned that it should be possible to install the [^{18}F]CF$_3$ group at the aromatic ring in these compounds. As anticipated, both the [^{18}F]trifluoromethylation of aryl iodides **20** and **23** and the oxidative [^{18}F]trifluoromethylation of boronic acids **21** and **24** led to the desired products. In particular when the boronic acids were used as the starting material, we observed excellent conversion in just 1 min at 20 °C.



Scheme 4. Synthesis of the [^{18}F]trifluoromethyl-substituted estrone derivative **22** and Boc/OMe-protected [^{18}F]4-trifluoromethylphenylalanine **25**.

Next, we investigated the specific activity (SA) of the products obtained by the method described herein. The initial measured SA of [^{18}F]1-trifluoromethyl-4-nitrobenzene, obtained by the [^{18}F]trifluoromethylation of 1-iodo-4-nitrobenzene, was approximately 1 GBq μmol^{-1}. As CHF_2I in the first step towards [^{18}F]HCF_3 is probably the major source of ^{19}F, we investigated the reduction of the amount of CHF_2I used. Indeed, a decrease in the CHF_2I amount from 40 to 1 μmol and an increase in the reaction temperature to 130 °C led to the formation of [^{18}F]1-trifluoromethyl-4-nitrobenzene with specific activities ranging from 22 to 32 GBq μmol^{-1}. This method did lead to the formation of less [^{18}F]HCF_3, but it was still obtained in an acceptable yield of 36 ± 7 %.

The presence of $Et_3N{\cdot}3HF$ in the next reaction could theoretically reduce the SA of the obtained reaction product through ^{19}F/^{18}F isotopic exchange. We showed by the application of a single batch of [^{18}F]HCF_3 for three reactions with 1-iodo-4-nitrobenzene, 4-nitrophenylboronic acid, and benzophenone that the SA of all three obtained products was the same (see the Supporting Information for details). Since in the reaction of benzophenone with [^{18}F]HCF_3 no addition of $Et_3N{\cdot}3HF$ is required, we thus proved indirectly that no ^{19}F/^{18}F isotopic exchange occurs during the reaction of [^{18}F]HCF_3 with 1-iodo-4-nitrobenzene and 4-nitrophenylboronic acid. We can safely assume that the SA of the reaction products is determined by the SA of [^{18}F]HCF_3, and this reagent could be applied broadly to obtain [^{18}F]CF_3-labeled compounds with improved SA. From all combined experiments we found a SA of 27 ± 8 GBq μmol^{-1} for [^{18}F]HCF_3 and thus a SA of 25 ± 7 GBq μmol^{-1} for the reaction products after a reaction time of 15 min. We did observe a decrease in the yield of the reactions of [^{18}F]HCF_3 of improved SA with 1-iodo-4-nitrobenzene (60 ± 12 % ($n = 6$)) and 4-nitrophenylboronic acid (65 ± 4 % ($n = 2$)). This yield decrease might be caused by unfavorable reaction kinetics due to the lower amounts of HCF_3 present in the reaction mixture; however, more evidence is required to support this finding.

In summary, [^{18}F]HCF_3 was found to be an excellent labeling agent for the [^{18}F]trifluoromethylation of aryl iodides and aryl boronic acids with strongly improved specific activities under mild reaction conditions. As the CF_3 group is a common moiety in drug candidates and active pharmaceutical ingredient, we expect that this methodology will be widely applied in the synthesis of fluorine-18-labeled PET tracers.

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