Rapid and Efficient Synthesis of $[^{11}C]$Trifluoromethylarenes from Primary Aromatic Amines and $[^{11}C]$CuCF$_3$

Nicholas J. Young, Victor W. Pike,* and Carlotta Taddei*

ABSTRACT: Prior studies have shown that trifluoromethylarenes can be labeled in high molar activities ($A_m > 200$ GBq/μmol) with positron-emitting carbon-11 ($t_{1/2} = 20.4$ min) by the reaction of the copper(I) derivative of $[^{11}C]$fluoromethane ($[^{11}C]$CuCF$_3$), with several types of precursors, such as aryl iodides, aryloboronic acids, and aryl diazonium salts. Nonetheless, these precursors can be challenging to synthesize, and in the case of diazonium salts, are unstable. Methods that reduce challenges in precursor preparation for the synthesis of $[^{11}C]$trifluoromethylarenes are desirable to enhance possibilities for developing biologically relevant $^{11}$C-labeled compounds as radiotracers for biomedical imaging with positron emission tomography (PET). Here, we explored the production of no-carrier-added $[^{11}C]$trifluoromethylarenes from commercially available primary aromatic amines through reactions of $[^{11}C]$CuCF$_3$ with diazonium salts that were generated in situ. Moderate to high isolated decay-corrected radiochemical yields (RCY) (32−84%) were obtained rapidly (within 2 min) for many para-substituted and meta-substituted primary aromatic amines bearing a halo, methoxy, thiomethyl, hydroxy, nitro, nitrile, carboxyl, ethylcarboxy, or trifluoromethyl substituent. Null to low RCYs (0−13%) were observed only for ortho bromo-, nitro-, or nitrile-substituted precursors. This new radiosynthetic method usefully expands options for producing PET radiotracers bearing a $[^{11}C]$trifluoromethyl group, especially from aryl amine precursors.

INTRODUCTION

Positron emission tomography (PET) is a powerful, quantitative, and highly sensitive imaging technique that is widely used in biomedical and pre-clinical research, clinical diagnosis, and drug development.\textsuperscript{1−5} PET enables the study and quantification of the binding of specifically labeled molecules (radiotracers) to biological targets of interest within living animals and human subjects. These targets are often neurotransmitters, transporter proteins, enzymes, or protein plaques involved in disease processes. The type of information gained from the use of target-selective PET radiotracers can provide insights into many pathological conditions, such as neurodegenerative diseases (e.g., Alzheimer’s disease), neuro-psychiatric disorders (e.g., clinical depression), and cancer (e.g., prostate cancer). In addition, this information can guide the development of new methods for drug therapy and disease diagnosis. Therefore, progress in the development of new PET radiotracers and novel radiosynthetic methods is always sought within the nuclear medicine field. Ideally, new methods should be applicable at a no-carrier-added (NCA) level for producing PET radiotracers with high molar activity ($A_m$)\textsuperscript{4} (i.e., high ratio of radioactivity to mass),\textsuperscript{5} and in high radiochemical purity. Radiochemical purity is the extent to which a radioactive compound is free of other radioactive compounds, such as radioactive byproducts. A PET radiotracer may be radiochemically pure but not completely free of chemical impurities. Typically, for PET radiotracers, the aim is to achieve a radiochemical purity $\geq 98\%$ in the isolated formulated dose ready for intravenous injection with chemical impurities below 2 ppm.

Carbon-11 and fluorine-18 are the two positron emitters that are most widely used for the labeling of PET radiotracers. Carbon-11 has a short half-life ($t_{1/2} = 20.4$ min) and is usually generated with a cyclotron according to the $^{14}$N(p,$\alpha$)$^{11}$C nuclear reaction. The proton bombardment of nitrogen gas in the presence of admixed oxygen (0.5−1%) or hydrogen (5−10%) produces $[^{11}C]$carbon dioxide or $[^{11}C]$methane, respectively. These are the two main precursors for virtually all $^{11}$C-chemistry.

The short half-life of carbon-11 has an advantage over longer-lived fluorine-18 ($t_{1/2} = 109.8$ min) in enabling more than one PET experiment to be performed in the same subject in a single day.\textsuperscript{6,7} Moreover, the replacement of a carbon atom with carbon-11 in a molecule of interest does not perceptibly modify its biological or physicochemical properties.\textsuperscript{6} Nonetheless, because of the short half-life constraint of carbon-11, methodologies for producing $^{11}$C-labeled PET radiotracers must be quick and efficient.\textsuperscript{8−12} Widely applied and established
methodologies include \(^{11}\text{C}\)-methylation, \(^{11}\text{C}\)-carboxylation,\(^{9,11}\) and \(^{11}\text{C}\)-carbonylation.\(^{11,12}\) The trifluoromethyl group is becoming increasingly prevalent in drug candidates for several reasons, such as its ability to resist metabolism and to improve binding affinity and selectivity toward biological targets of interest.\(^{14-18}\) Derivatives of \(^{19}\text{F}\)luoroform (CHF\(_3\)), such as the copper derivative, CuCF\(_3\), have been extensively explored in nonradiochemical studies as reagents to introduce the trifluoromethyl group into organic molecules.\(^{17-23}\) These advances in medicinal and synthetic chemistry have prompted strong interest in discovering methods for labeling the trifluoromethyl group with either fluorine-18 or carbon-11 as tools for new PET radiotracer development.

Recent radiochemical studies have generated \(^{11}\text{C}\)-fluoroform and \(^{18}\text{F}\)fluoroform to produce \(^{11}\text{C}\)CuCF\(_3\)\(^{24}\) and \(^{18}\text{F}\)CuCF\(_3\),\(^{25,26}\) respectively. \(^{11}\text{C}\)CuCF\(_3\) and \(^{18}\text{F}\)CuCF\(_3\) have now been shown to be useful for synthesizing a diverse array of substituted \(^{11}\text{C}\)- and \(^{18}\text{F}\)-labeled trifluoromethylarenes.\(^{24-51}\) In the reported syntheses of \(^{11}\text{C}\)trifluoromethylarenes, \(^{11}\text{C}\)fluoroform was generated from cyclotron-produced \(^{11}\text{C}\)methane and treated with copper(I) bromide and potassium tert-butoxide to form a reactive copper(I) derivative of \(^{11}\text{C}\)fluoroform, \(^{11}\text{C}\)CuCF\(_3\). This was then coupled with a reactive aryl precursor, such as an aryl iodide, arylboronic acid, or aryldiazonium salt, to produce the desired \(^{11}\text{C}\)trifluoromethylarene. High radiochemical yields (RCY: 88–99%) and high molar activities \(A_m > 200 \text{ GBq/\mu mol} (>5 \text{ Ci/\mu mol})\) were achieved with these methods.\(^{27}\) \(^{18}\text{F}\)Trifluoromethylarenes have been obtained similarly from \(^{18}\text{F}\)CuCF\(_3\) with \(A_m\) values up to 163 GBq/\mu mol (4.4 Ci/\mu mol), depending on the method of \(^{18}\text{F}\)fluoroform synthesis from cyclotron-produced \(^{18}\text{F}\)fluoride ion.\(^{26,28,29}\) Despite the wide substrate scope of these labeling methods, desired radiotracer precursors may be commercially unavailable, very challenging to synthesize, or, in the case of diazonium salts, unstable over long storage periods. Therefore, these factors can limit the utility of current labeling methodologies with \(^{11}\text{C}\)CuCF\(_3\) and \(^{18}\text{F}\)CuCF\(_3\).

In nonradiochemical studies, Sandmeyer-type reactions have been widely used to convert primary aromatic amines into iodo, bromo, boronic acid, boronate, and trifluoromethyl derivatives through in situ generated diazonium salts.\(^{53-57}\) Two recent studies have utilized Sandmeyer trifluoromethylation reactions with silver and copper fluoroform derivatives to synthesize a diverse range of trifluoromethylarenes in good quantitative yields (30–97%) from aromatic amines through diazonium salts generated in situ.\(^{36,39}\) However, the long reaction times (3–8 h), high reagent amounts, near equal stoichiometries, and other conditions used in these studies are not directly transferable to \(^{11}\text{C}\)- or \(^{18}\text{F}\)-chemistry at the NCA level, where high activities but only trace amounts of the NCA labeling agent are used. Despite such challenges, we aimed to investigate the Sandmeyer trifluoromethylation reaction with the copper(I) \(^{11}\text{C}\)fluoroform derivative, \(^{11}\text{C}\)CuCF\(_3\), because of its potential value for expanding the arsenal of methods available for PET radiotracer development.

Herein, we report the development of a Sandmeyer-type \(^{11}\text{C}\)-trifluoromethylation reaction using \(^{11}\text{C}\)CuCF\(_3\) with commercially available primary aromatic amines to yield a wide range of \(^{11}\text{C}\)trifluoromethylarenes under mild conditions and within a very short labeling time.

### RESULTS AND DISCUSSION

Preliminary nonradiochemical and radiochemical studies were performed with aniline (1a) as primary aromatic amine. Reaction conditions compatible with \(^{11}\text{C}\)-chemistry (e.g., short reaction times) were used to investigate the insertion of the trifluoromethyl group onto an aryl ring via a Sandmeyer-type reaction on the diazonium salt generated in situ with the copper(I) derivative of fluoroform, CuCF\(_3\). CuCF\(_3\) was prepared by bubbling fluoroform gas for a few seconds into a vial containing CuBr (0.7 mg) and t-BuOK (50 \(\mu\text{L}, 0.3 \text{ M}\) in anhydrous DMF. Triethylamine trihydrofluoride (3HF·Et\(_3\)N) in anhydrous DMF was added to stabilize the CuCF\(_3\) (Scheme 1A), as described in the reported procedure for \(^{11}\text{C}\)CuCF\(_3\).\(^{24}\) For all radiochemical experiments in this study, \(^{11}\text{C}\)fluoroform gas was produced using the previously reported apparatus and method developed in our laboratory\(^{24}\) (Figure S1) with yields of 44 ± 3% \((n = 22)\)\(^{40}\) from trapped cyclotron-produced \(^{11}\text{C}\)methane (Figure S2).

A similar procedure to that described by Wang et al.\(^{38}\) was followed for the diazotization of primary aromatic amines. The solution containing the in situ generated diazonium salt was transferred to the vial containing CuCF\(_3\) or \(^{11}\text{C}\)CuCF\(_3\) at \(-42 ^\circ\text{C}\) (dry-ice/acetonitrile bath) over 1 min, and then
warmed to room temperature (RT) and left to react for 10 min (Scheme 1).

Both 3HF·Et₃N and aqueous concentrated hydrochloric acid (HCl(aq.)) were investigated as acidic species for the diazotization of 1a (50 μmol) with tert-butyl nitrite (t-BuONO) (1.1 equiv) in anhydrous DMF at 0 °C in a total reaction time of 20 min (Scheme 1A). When using 3HF·Et₃N (2 equiv) as the acid source, the desired ( trifluoromethyl)benzene (1b) from the reaction with CuCF₃ was not observed. Nor under these same diazotization conditions was [ ¹¹C]-( trifluoromethyl)benzene ([¹¹C]1b) obtained in experiments with [¹¹C]CuCF₃ (Scheme 1B). Nonetheless, by using HCl(aq.) (2 equiv) as the acid source under the same conditions, 1b was readily produced and identified through HPLC co-injection with the reference compound (Figure S3). Furthermore, [¹¹C]( trifluoromethyl)benzene ([¹¹C]1b) was obtained in a reproducible yield of 84% from starting [¹¹C]fluoroform within a total labeling time of 11 min (Figure 1; Table 1, entry 1).

Table 1. Time Optimization for Labeling Method (Time A Set at 1 min)

| entry | time B (min) | RICY* of [¹¹C]1b (%) |
|-------|-------------|---------------------|
| 1     | 10          | 84                  |
| 2     | 15          | 86                  |
| 3     | 5           | 85                  |
| 4     | 3           | 86                  |
| 5ᵇ    | 1           | 83 ± 3              |

*RCYs as average of two experiments unless otherwise noted. ᵇn = 3.

Five different time settings were explored to optimize the labeling step with the aim of developing a very quick radiosynthesis (Scheme 2; Table 1). [¹¹C]1b was obtained in a yield of 86% by the reaction for 1 min at −42 °C (Scheme 2; time A) and then 15 min at RT (Scheme 2; time B) (Table 1, entry 2). Yields of 84 and 85% were obtained with shorter time Bs of 10 and 5 min, respectively (Table 1, entries 1 and 3). By further reducing time B to 3 and 1 min, [¹¹C]1b was obtained in yields of 86% (Table 1, entry 4) and 83 ± 3% (Table 1, entry 5), respectively. Yields obtained in an overall 2 min labeling time (Table 1, entry 5) were very similar to those observed with longer labeling times (Table 1, entries 1−4) and minimized radioactive decay to give a higher practical radioactivity yield. Therefore, the 2 min labeling time was selected as optimal for investigating the substrate scope of the methodology.

Twenty-three monosubstituted primary aromatic amines were explored to investigate the substrate scope of the new labeling methodology (Scheme 3B). For all substrates investigated the total radiosynthesis time from the end of receipt of cyclotron-produced [¹¹C]methane to the end of radiosynthesis was 12−15 min. This time is composed of 9−12 min to transform cyclotron-produced [¹¹C]methane into [¹¹C]fluoroform, 1 min to distribute the [¹¹C]fluoroform to reaction vials, and 2 min for the labeling of the primary amines after the in situ diazotization.

[¹¹C]1b was obtained from 1a in a reproducible isolated yield of up to 83% in a 2 min labeling time (Scheme 3A; Table 2, entry 1). Under these same conditions, monosubstituted primary aromatic amines with a halogen in the para-position, 2a−5a, produced the desired [¹¹C]trifluoromethylarenes, [¹¹C]2b−[¹¹C]5b, in yields ranging from 64 to 81% (Table 2, entries 2−5). These yields approach that observed for [¹¹C]1b from the unsubstituted precursor 1a. This indicates that the inductive electron-withdrawing and mesomeric electron-donating effects of halo substituents do not greatly affect the formation of the diazonium salt in situ nor the labeling step.

For amines bearing a weak para-electron-donating group (EDGs), such as 6a (p-Me) and 7a (p-SMe), the corresponding [¹¹C]trifluoromethylarenes, [¹¹C]6b and...
Scheme 3. Optimized Labeling Methodology (A); Substrate Scope for the Labeling Methodology (B)

Table 2. $^{11}$C-Trifluoromethylation of a Diverse Range of Primary Aromatic Amines

| entry | $[^{11}\text{C}]$trifluoromethylarene substituent (R) | RCY (±)% |
|-------|--------------------------------------------------|---------|
| 1     | $[^{11}\text{C}]$1b H                               | 83 ± 3  |
| 2     | $[^{11}\text{C}]$2b F                               | 81 ± 5  |
| 3     | $[^{11}\text{C}]$3b Cl                              | 64 ± 8  |
| 4     | $[^{11}\text{C}]$4b Br                              | 68 ± 6  |
| 5     | $[^{11}\text{C}]$5b I                               | 77 ± 9  |
| 6     | $[^{11}\text{C}]$6b Me                              | 84 ± 1  |
| 7     | $[^{11}\text{C}]$7b SMe                             | 72 ± 2  |
| 8     | $[^{11}\text{C}]$8b OMe                             | 61 ± 17 |
| 9     | $[^{11}\text{C}]$9b OH                              | 32 ± 17b|
| 10    | $[^{11}\text{C}]$10b COOH                           | 65 ± 10 |
| 11    | $[^{11}\text{C}]$11b COOEt                           | 71 ± 1  |
| 12    | $[^{11}\text{C}]$12b COPh                           | 69 ± 4  |
| 13    | $[^{11}\text{C}]$13b CN                              | 36 ± 16b|
| 14    | $[^{11}\text{C}]$14b NO$_2$                         | 48 ± 8  |
| 15    | $[^{11}\text{C}]$15b CF$_3$                         | 54 ± 18 |
| 16    | $[^{11}\text{C}]$16b Br                             | 68 ± 6  |
| 17    | $[^{11}\text{C}]$17b Me                             | 67 ± 18c|
| 18    | $[^{11}\text{C}]$18b NO$_2$                         | 41 ± 7  |
| 19    | $[^{11}\text{C}]$19b CN                              | 50 ± 1  |
| 20    | $[^{11}\text{C}]$20b Br                             | 1 ± 1   |
| 21    | $[^{11}\text{C}]$21b OMe                            | 73 ± 8d |
| 22    | $[^{11}\text{C}]$22b NO$_2$                         | 13 ± 8  |
| 23    | $[^{11}\text{C}]$23b CN                              | 0       |

“All RCYs (n = 3, unless otherwise indicated) were calculated from the radioactivity of the isolated $[^{11}\text{C}]$trifluoromethylarene as a percentage of the total radioactivity collected from the HPLC column (excluding $[^{11}\text{C}]$labeled byproducts from the synthesis of $[^{11}\text{C}]$-fluorofrom). They are decay-corrected $^{[^{11}\text{C}]$_7}b, were obtained in yields of 84 and 72%, respectively (Table 2, entries 6 and 7). By contrast, amines with a stronger para-EDG, such as 8a (p-OMe) and 9a (p-OH), gave $[^{11}\text{C}]$8b and $[^{11}\text{C}]$9b in lower yields of 61 and 32%, respectively (Table 2, entries 8 and 9). These lower yields may be due to the higher stabilization of the generated diazonium species by stronger EDGs. This stabilization may in turn have hindered the labeling step. In fact, a strong retarding effect of p-Ome and p-OH substituents on the decomposition of aromatic diazonium salts has been noted previously. Amines having a bromo, methyl, nitro, or nitrile substituent in ortho- or meta-positions (16a–23a) were tested to investigate the effect of the substituent position on the labeling outcome. The amine 16a bearing a meta-bromo substituent, gave $[^{11}\text{C}]$16b in a 68% yield (Table 2, entry 16). By contrast, 20a with an ortho-bromo substituent gave $[^{11}\text{C}]$20b in a very low yield of 1% (Table 2, entry 20).

Amines having a methyl group in meta- (17a) or ortho-positions (21a) produced $[^{11}\text{C}]$17b and $[^{11}\text{C}]$21b in yields of up to 67 and 73%, respectively (Table 2, entries 17 and 21). These yields are slightly lower than those obtained with the methyl group in the para-position (Table 2, entry 6). However, this decrease in yield (c.f., Table 2, entry 6 with entries 17 and 21) was smaller than that observed with substrates bearing bromine in para-, meta- and ortho-positions (c.f., Table 2, entry 4 with entries 16 and 20).

Yields of up to 41% ($[^{11}\text{C}]$18b) were obtained with a nitro substituent in the meta-position (Table 2, entry 18). However, the yield dropped to 13% ($[^{11}\text{C}]$22b) with the nitro group in the ortho-position (Table 2, entry 22; see Figures S4 and S5 for HPLC of trifluoromethyl-nitrobenzene isomers). With the meta-substituted nitrite precursor (19a), $[^{11}\text{C}]$19b was obtained in 50% yield (Table 2, entry 19). By contrast, no $[^{11}\text{C}]$-labeled product was observed with the nitrite group in the ortho-position ($[^{11}\text{C}]$23b, Table 2, entry 23).

For the three amines having an ortho-substituted EWG (e.g., bromo, nitro, or nitrile), yields of the corresponding $[^{11}\text{C}]$-trifluoromethylbenzenes (Table 2, entries 20, 22, and 23) were
appreciably lower than from the corresponding para- (Table 2, entries 4, 13, and 14) and meta-substituted amines (Table 2, entries 16, 18, and 19). EWGs therefore seem more detrimental to labeling outcome when in the ortho-position than when in meta- or para-positions. By contrast, the ring position of an EDG, such as methyl, did not have a major effect on the labeling yield (c.f. Table 2, entries 6, 17, and 21).

The synthesized $[^{11}C]$trifluoromethylenes were obtained with isolated decay-corrected yields in the 32−84% range from starting $[^{11}C]$fluoromethane, and in the $2−12\%$ range from initial activity of cyclotron-produced $[^{11}C]$methane (representative yield calculations can be found in the Supporting Information).

More studies are needed to further elucidate and confirm the yield trend according to substituent identity and ring position. In addition, steric effects may also influence the reaction mechanism and therefore the labeling outcome.

Our yields from $[^{11}C]$fluoromethane, where comparable, are in line with those obtained by Danoun et al. for the macroscale Sandmeyer-type trifluoromethylation of aryl diazonium tetrafluoroborates with trifluoromethyltrime-thylsilane in the presence of copper(I) thiocyanate (nine examples), and similarly with those observed by Bayarmagnai et al. (six examples). Based on radical trapping experiments, it is generally presumed that this type of Sandmeyer reaction proceeds through a radical pathway. In this study, the diazotization of the primary aromatic amine, followed by the dissociation of the diazonium species (I), may yield a radical intermediate (II). This intermediate may undergo oxidative addition with $[^{11}C]$CuCF$_3$ to produce an unstable $[^{11}C]$- CuCF$_3$-aryl adduct (III), which is then subject to reductive elimination yielding the desired $[^{11}C]$trifluoromethylenes (Scheme 4). However, in-depth mechanistic studies and additional substrates screening are necessary to affirm this suggested mechanism.

The developed Sandmeyer-type reaction between diazonium salts and $[^{11}C]$CuCF$_3$ is effective for the efficient and rapid synthesis of $[^{11}C]$trifluoromethylenes. Several mono-substituted $[^{11}C]$trifluoromethylenes were synthesized from substituted amines within 2 min labeling time under mild reaction conditions in moderate to high isolated decay-corrected yields (32−84%) from starting $[^{11}C]$fluoromethane.

For the tested para-substituted substrates, overall yields decreased as the strength of the EDG or EWG substituents increased. For the investigated meta-substituted substrates, similar yields were obtained. Null to low yields (0−13%) were observed only for three substrates, which each had an ortho-EWG substituent.

CONCLUSION

In summary, the described Sandmeyer reaction with $[^{11}C]$CuCF$_3$ enables a variety of $[^{11}C]$trifluoromethylenes to be produced without the need for pre-synthesis, isolation, and purification of unstable diazonium salts. This methodology has potential for labeling biologically relevant compounds from aryl amine precursors to create new PET radiotracers. Moreover, this method could be applied to the synthesis of $[^{18}F]$trifluoromethylenes through the likewise use of $[^{18}F]$CuCF$_3$ because of the identical chemical reactivities of $[^{18}F]$fluoromethane and $[^{11}C]$fluoromethane. This novel radio-synthetic approach therefore constitutes a useful addition to the arsenal of methods for producing $^{11}$C- and $^{18}$F-labeled tracers.

METHODS

General Information. All reagents, reference compounds, and anhydrous solvents were obtained commercially. Radio-HPLC analyses were performed with a system comprising a HPLC pump (DGU-20AR; Shimadzu), a UV absorbance detector (CBM-20A; Shimadzu), and a radioactivity detector (flow-count #0605-31;3 Bioscan). All radiochemistry was performed in lead-shielded hot-cells for radiation protection to personnel.

Preliminary Nonradiochemical Experiments. Reagent Preparation for In Situ Diazotization of Aniline. Three screw-cap V-vials (1 mL) were loaded with reaction components, as follows: vial 1: HCl (conc., aqueous, 24.7 μL); vial 2: t-BuONO (19.7 μL); vial 3: aniline (1a, 50 μmol, 1.0 equiv). The three screw-cap vials were then transferred to a glovebox (N$_2$ atmosphere) and further additions were made to each vial, as follows:

- Vial 1: Anhydrous DMF (125.3 μL) to make a stock HCl solution (150 μL, 2 M in DMF).
- Vial 2: Anhydrous DMF (130.3 μL) to make a t-BuONO stock solution (150 μL, 1.1 M in DMF).
- Vial 3: Anhydrous DMF (100 μL).

A syringe (1 mL) fitted with a needle (0.5 mm × 40 mm; Becton Dickinson) was then loaded with a HCl stock solution (50 μL, 100 μmol, 2.0 equiv) and another syringe (1 mL), fitted with the same type of needle, was loaded with the t-BuONO stock solution (50 μL, 55 μmol, 1.1 equiv). These reagents were kept in the glovebox until used on the same day of their preparation.

Reagent Preparation for the Synthesis of CuCF$_3$. CuBr (0.7 mg, 5 μmol) was placed in an empty crimp-cap V-vial (1 mL). This vial was sealed with parafilm and transferred to the glovebox. In the glovebox, t-BuOK (33 mg) was dissolved in DMF (1.0 mL) within a screw-cap vial (3 mL) to make a stock solution (0.3 M in DMF) under an inert atmosphere. An aliquot (50 μL) of this stock t-BuOK solution was added to the

**Scheme 4. Possible Sandmeyer-Type Mechanism for the Synthesis of $[^{11}C]$Trifluoromethylenes from Mono-Substituted Aryldiazonium Salts and $[^{11}C]$CuCF$_3$**

\[ \text{Amine} \xrightarrow{a} \text{I} \xrightarrow{b} \text{II} \xrightarrow{c} \text{III} \]

\[ ^{11}\text{C}]\text{CF}_3 \]

\[ a = \text{diazotization}; b = \text{diazonium dissociation}; c = \text{oxidative addition}; d = \text{reductive elimination} \]
crimp-cap V-vial of CuBr (0.7 mg, 5 μmol) and sealed. These reagents were also kept in the glovebox until used on the same day of their preparation.

**Coupling with CuCF3 Complex and (Trifluoromethyl)benzene Synthesis.** A similar procedure to that in the literature was followed for the diazotization of primary aromatic amines. The vial containing aniline (1a, 50 μmol, 1.0 equiv) in DMF was cooled in an ice bath (0 °C). The HCl solution (50 μL, 2 M in DMF, 100 μmol, 2.0 equiv) was added to the primary aromatic amine. After 5 min, the t-BuONO solution (50 μL, 1.1 M in DMF, 55 μmol, 1.1 equiv) was added and left for 15 min to form the diazonium salt in *situ*. Fluoroform gas was bubbled from a balloon through the CuBr/t-BuOK for a few seconds to yield the CuCF3 complex. The diazonium salt solution was transferred with a syringe to the CuCF3 complex at −42 °C (dry-ice/acetonitrile bath) and left to react for 1 min. The vial was then removed from the cooling bath and allowed to warm to RT over 10 min. The reaction was quenched with acetonitrile/water (50:50, 50 μL) and analyzed with HPLC on a Luna 10 μm C18(2) column (100 Å; 250 × 4.6 mm) eluted with 30−80% acetonitrile/water at 2 mL/min, with absorbance detection at 254 nm (this is later referred to as the Standard HPLC Method). The desired product (trifluoromethyl)benzene (1b) was identified and then co-injected with the reference compound (Figure S3).

**Radiochemical Experiments. Reagent Preparation for In Situ Diazotization of Primary Aromatic Amines.** Reagents for the diazotization of primary aromatic amines were prepared as described for the diazotization of 1a in the preliminary nonradiochemical experiments.

**Reagent Preparation for the Synthesis of [11C]CuCF3.** CuBr (0.7 mg, 5 μmol) was placed in an empty crimp-cap V-vial (1 mL), and this was sealed with parafilm. A second empty crimp-cap V-vial (1 mL) was sealed with parafilm. These V-vials were then transferred to a glovebox. In the glovebox, t-BuOK (33 mg) was dissolved in DMF (1.0 mL) within a screw-cap vial (3 mL) to make a stock t-BuOK solution (0.3 M in DMF) under an inert atmosphere. An aliquot of this stock solution (50 μL) was added to the crimp-cap V-vial prepared with CuBr (0.7 mg, 5 μmol) and sealed. The second empty crimp-cap V-vial was sealed under the glovebox under an inert atmosphere.

These reagents (e.g., syringes with stock solutions and vials containing precursors) were kept in the glovebox until used on the same day of their preparation (generally for only 30–60 min).

**Cyclotron Production of NCA [11C]Methane.** A PETtrace cyclotron (GE Healthcare) was used to produce NCA [11C]methane (~4 GBq (~110 mCi)] by bombarding nitrogen (initial pressure, 225 psi) containing hydrogen (10% v/v) with a proton beam (16.5 MeV; 5 μA) for 5 min.

**Preparation of [11C]Fluoroform.** [11C]Fluoroform was prepared from NCA [11C]methane by fluorination over heated CoF3, essentially as described previously24 and from the same reported apparatus (Figure S1). Pin diode detectors were used to monitor radioactivity flow through the apparatus at key positions, namely, the CoF3 column, and the [11C]fluoroform trap. At 70 min before each [11C]methane delivery from the cyclotron, helium was passed through the apparatus at 20 mL/min. The PTFE tube to be used for [11C]fluoroform delivery was pre-cleaned with CH2Cl2 (10 mL). At 60 min before [11C]methane delivery, the apparatus was opened to a clean oven-dried V-vial (5 mL) through the [11C]fluoroform delivery line. This V-vial, which was to be used to trap the generated [11C]fluoroform, was flushed with helium for about 15 min. At 10–15 min before [11C]methane delivery to the apparatus, this vial was cooled with dry-ice/acetonitrile (−42 °C) and loaded with anhydrous DMF (500 μL). The [11C]methane that was initially trapped on cold Porapak Q was measured in a calibrated ionization chamber.

**Preparation of [11C]CuCF3.** During [11C]fluoroform synthesis, 3HF-Et3N (8.2 μL) was placed in an Eppendorf tube (1 mL) with anhydrous DMF (500 μL) to make a stock 3HF-Et3N solution (0.3 mM in DMF). A syringe (1 mL) with a needle (0.5 mm × 40 mm; Becton Dickinson) was loaded with the stock 3HF-Et3N solution (50 μL). The V-vial containing the collected crude [11C]fluoroform was disconnected from the apparatus, and a lead-shielded syringe (1 mL) with a female adaptor (1/4-28 Fem to Fem Luer Tefzel) was connected to withdraw the trapped [11C]fluoroform in DMF. A small aliquot (~10–30 μL) of [11C]CHF3 in DMF was placed in a sealed empty crimp-cap V-vial. This was used to determine the yield of [11C]fluoroform by the HPLC analysis (Figure S2). The remaining [11C]fluoroform in DMF was distributed into the reaction crimp-cap V-vials containing CuBr/t-BuOK to produce the [11C]CuCF3 complex. The 3HF-Et3N solution (50 μL) was immediately added to the reaction V-vials and the radioactivity in the V-vials was measured.

**Syntheses of [11C]Trifluoromethylarenes.** The reagents were removed from the glovebox about 5–15 min before [11C]methane production. The vial with the primary aromatic amine solution (50 μmol, 1.0 equiv) was placed in an ice bath (0 °C). The HCl solution (50 μL, 2 M in DMF, 100 μmol, 2.0 equiv) was added to the amine solution 5 min before [11C]methane delivery. After 5 min, the t-BuONO solution (50 μL, 1.1 M in DMF, 55 μmol, 1.1 equiv) was added to the acidified amine solution and allowed to react for 15 min at 0 °C to form the diazonium salt in *situ*. After the radioactivity in the V-vial containing [11C]CuCF3 was recorded, the V-vial was placed in the dry-ice/acetonitrile bath (−42 °C) and the diazonium salt solution was added to this using an argon-flushed syringe. This was left for 1 min at −42 °C. Then, the V-vial was transferred to a lead-shielded container and left for 1 min at RT. The reaction was quenched with acetonitrile/water (50:50, 50 μL). The radioactivity in the V-vial was measured at the end of synthesis and the crude reaction mixture was analyzed with radio-HPLC with the Standard HPLC Method. Each [11C]trifluoromethylarene was identified with analytical radio-HPLC by comparing its elution time with the nonradioactive reference compound and by confirmation of mobility when co-injected with reference compound. The [11C]trifluoromethylarene was collected. The isolated radiochemical yield was determined as the collected activity of the [11C]trifluoromethylarene as a percentage of the total radioactivity collected from the HPLC column after correction for decay. ([11C]Difluoromethane and [11C]Fluoromethane were excluded from this calculation as they represent noninterfering [11C]-labeled byproducts from the [11C]fluoroform synthesis). See Figures S5–S28 for representative radiochromatograms for crude products [11C]2b–[11C]23b obtained with the Standard HPLC Method.

**ASSOCIATED CONTENT**

**Supporting Information**

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.0c02027.
Apparatus scheme for the synthesis of $[^{11} \text{C}]$ fluoroform; representative calculations for synthesis time and yields; representative UV absorbance chromatograms for non-radiochemical studies; and representative radiochromatograms for $[^{11} \text{C}]$ fluoroform and the produced $[^{11} \text{C}]$ trifluoromethylenes (PDF)

## Author Information

### Corresponding Authors

**Victor W. Pike** — Molecular Imaging Branch, National Institute of Mental Health, National Institutes of Health, Bethesda, Maryland 20892-1003, United States; orcid.org/0000-0001-9032-2553; Email: pikev@mail.nih.gov

**Carlotta Taddei** — Molecular Imaging Branch, National Institute of Mental Health, National Institutes of Health, Bethesda, Maryland 20892-1003, United States; orcid.org/0000-0002-2271-2127; Email: dr.taddei.carlotta@gmail.com

Complete contact information is available at: https://pubs.acs.org/10.1021/acsomega.0c02027

### Notes

The authors declare no competing financial interest.

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## References

(1) Pike, V. W. The status of PET radiochemistry for drug development and evaluation. Drug Inf. J. 1997, 31, 997–1013.

(2) Phelps, M. E. Positron emission tomography provides molecular imaging of biological processes. Proc. Natl. Acad. Sci. U.S.A. 2000, 97, 9226–9233.

(3) McCluskey, S. P.; Plisson, C.; Rabiner, E. A.; Howes, O. Advances in CNS PET: the state-of-the-art for new imaging targets for pathophysiology and drug development. Eur. J. Nucl. Med. Mol. Imaging 2019, 47, 451.

(4) Coenen, H. H.; Gee, A. D.; Adam, M.; Antoni, G.; Cutler, C. S.; Fujibayashi, Y.; Jeong, J. M.; Mach, R. H.; Mindt, T. L.; Pike, V. W.; Windhorst, A. D. Consensus nomenclature rules for radiopharmaceutical chemistry — Setting the record straight. Nucl. Med. Biol. 2017, 55, ν–xi.

(5) Pike, V. W. Considerations in the development of reversibly binding PET radiogandis for brain imaging. Curr. Med. Chem. 2016, 23, 1818–1869.

(6) Scott, P. J. H. Methods for the incorporation of carbon-11 to generate radiopharmaceuticals for PET imaging. Angew. Chem., Int. Ed. 2009, 48, 6001–6004.

(7) Antoni, G. Development of carbon-11labelled PET tracers—radiochemical and technological challenges in a historic perspective. J. Label. Compd. Radiopharm. 2015, 58, 65–72.

(8) Miller, P. W.; Long, N. J.; Vilar, R.; Gee, A. D. Synthesis of $^{13}$C, $^{14}$F, $^{15}$O, and $^{18}$F radiolabels for positron emission tomography. Angew. Chem., Int. Ed. 2008, 47, 8998–9033.

(9) Rotstein, B. H.; Liang, S. H.; Holland, J. P.; Collier, T. L.; Hooker, J. M.; Wilson, A. A.; Vasdev, N. $^{11}$CO$_3$-Fixation: a renaissance in PET radiochemistry. Chem. Commun. 2013, 49, 5621–5629.

(10) Rotstein, B. H.; Liang, S. H.; Placek, M. S.; Hooker, J. M.; Gee, A. D.; Dollé, F.; Wilson, A. A.; Vasdev, N. 11C=O Bonds made easily for positron emission tomography radiopharmaceuticals. Chem. Soc. Rev. 2016, 45, 4708–4726.

(11) Taddei, C.; Gee, A. D. Recent progress in $[^{11} \text{C}]$ carbon dioxide ($[^{11} \text{C}]$CO$_2$) and $[^{11} \text{C}]$ carbon monoxide ($[^{11} \text{C}]$CO) chemistry. J. Label. Compd. Radiopharm. 2018, 61, 237–251.

(12) Taddei, C.; Pike, V. W. $[^{11} \text{C}]$ Carbon monoxide: advances in production and application to PET radiotracer development over the past 15 years. ENMMA Radiopharm. Chem. 2019, 4, 55.

(13) Wuest, F.; Berndt, M.; Kniess, T. Carbon-11 labeling chemistry based upon $[^{11} \text{C}]$methyl iodide. PET Chemistry—The Driving Force in Molecular Imaging, 2007 ed.; Springer-Verlag: Berlin, 2007; pp 183–213.

(14) Kirk, K. L. Fluorination in medicinal chemistry: methods, strategies, and recent developments. Org. Process Res. Dev. 2008, 12, 305–321.

(15) Zhu, W.; Wang, J.; Wang, S.; Gu, Z.; Aceña, J. L.; Izawa, K.; Liu, H.; Soloshonok, V. A. Recent advances in the trifluoromethylation methodology and new CF$_3$-containing drugs. J. Fluorine Chem. 2014, 167, 37–54.

(16) Alonso, C.; Martínez de Mariorga, E.; Rubiales, G.; Palacios, F. Carbon trifluoromethylation reactions of hydrocarbon derivatives and heteroarenes. Chem. Rev. 2015, 115, 1847–1935.

(17) Zanardi, A.; Novikov, M. A.; Martin, E.; Benet-Buchholz, J.; Grushin, V. V. Direct cupration of fluoroform. J. Am. Chem. Soc. 2011, 133, 20901–20913.

(18) Novák, P.; Lischchynskyi, A.; Grushin, V. V. Fluoroform-derived CuCF$_3$ for low-cost, simple, efficient, and safe trifluoromethylation of aryl boronic acids in air. Angew. Chem., Int. Ed. 2012, 51, 7767–7770.

(19) Lischchynskyi, A.; Novikov, M. A.; Martin, E.; Escudero-Adán, E. C.; Novák, P.; Grushin, V. V. Trifluoromethylation of aryl and heteroaryl halides with fluoriform-derived CuCF$_3$: scope, limitations, and mechanistic features. J. Org. Chem. 2013, 78, 11126–11146.

(20) Lischchynskyi, A.; Berthon, G.; Grushin, V. V. Trifluoromethylation of arenediazonium salts with fluoriform-derived CuCF$_3$ in aqueous media. Chem. Commun. 2014, 50, 10237–10240.

(21) Mazloomi, Z.; Bansode, A.; Benavente, P.; Lischchynskyi, A.; Urakawa, A.; Grushin, V. V. Continuous process for production of CuCF$_3$ via direct cupration of fluoriform. Org. Process Res. Dev. 2014, 18, 1020–1026.

(22) Li, G.-B.; Zhang, C.; Song, C.; Ma, Y.-D. Progress in copper-catalyzed trifluoromethylation. Belstein J. Org. Chem. 2018, 14, 155–181.

(23) Yang, X.; Tsui, G. C. Copper-mediated trifluoromethylation—allylation of arynes. Org. Lett. 2018, 20, 1179–1182.

(24) Haskali, M. B.; Pike, V. W. $[^{11} \text{C}]$ Fluoroform, a Breakthrough for versatile scalable PET radiotracer trifluoromethyl groups in high molar activity. Chem.—Eur. J. 2017, 23, 8156–8160.

(25) van der Born, D.; Herscheid, J. D. M.; Orru, R. V. A.; Vugts, D. J. Efficient synthesis of $[^{18} \text{F}]$ trifluoromethane and its application in the synthesis of PET tracers. Chem. Commun. 2013, 49, 4018–4020.

(26) Yang, B. Y.; Telu, S.; Haskali, M. B.; Morse, C. L.; Pike, V. W. A gas phase route to $[^{18} \text{F}]$ fluorofrom with limited molar activity dilution. Sci. Rep. 2019, 9, 14835.

(27) Carbonell, E.; Besset, T.; Poisson, T.; Labar, D.; Pannecoque, X.; Jubault, P. $[^{18} \text{F}]$-Fluorofrom: a $^{18}$F-trifluoromethyllating agent for the synthesis of SCF$_3$-aromatic derivatives. Chem. Commun. 2017, 53, 5706–5709.

(28) Yang, B. Y.; Telu, S.; Haskali, M. B.; Morse, C. L.; Pike, V. W. Mild syntheses of $[^{18} \text{F}]$ trifluoromethylenes from $[^{11} \text{C}]$/$[^{18} \text{F}]$ trifluoromethyl derivatives of nucleobases and L-phenylalanine from $[^{18} \text{F}]$ fluorofrom produced in gas phase. J. Nucl. Med. 2018, 59, 1060.

(29) Ramos-Torres, K.; Zhou, Y.-P.; Yang, B. Y.; Guehl, N. J.; Telu, S.; Normandin, M. D.; Pike, V. W.; Brugarolas, P. Syntheses of $[^{11} \text{C}]$2- and $[^{11} \text{C}]$3-trifluoromethyl-4-aminopyridine: potential PET
radioligands for imaging demyelinating diseases. J. Nucl. Med. 2020, 61, 619.
(31) Jana, S.; Telu, S.; Yang, B. Y.; Haskali, M. B.; Jakobsson, J. E.; Pike, V. W. Rapid syntheses of [11C]arylvinyl trifluoromethanes through treatment of (E)-arylvinyl(phenyl)iodonium tosylates with [11C]trifluoromethylcopper(I). Org. Lett. 2020, 22, 4574–4578.
(32) Zollinger, H. Reactivity and stability of arenediazonium ions. Acc. Chem. Res. 1973, 6, 335–341.
(33) Hanson, P.; Rowell, S. C.; Taylor, A. B.; Walton, P. H.; Timms, A. W. Sandmeyer reactions. Part 6. A mechanistic investigation into the reduction and ligand transfer steps of Sandmeyer cyanation. J. Chem. Soc., Perkin Trans. 2 2002, 1126–1134.
(34) Xue, D.; Zhao, C.-J.; Jia, Z.-H.; Wang, C.; Xiao, J. Methanol-promoted borylation of arylamines: a simple and green synthetic method to arylboronic acids and arylboronates. Synlett 2014, 25, 1577–1584.
(35) He, L.; Qiu, G.; Gao, Y.; Wu, J. Removal of amino groups from anilines through diazonium salt-based reactions. Org. Biomol. Chem. 2014, 12, 6965–6971.
(36) Leas, D. A.; Dong, Y.; Vennerstrom, J. L.; Stack, D. E. One-pot, metal-free conversion of anilines to aryl bromides and iodides. Org. Lett. 2017, 19, 2518–2521.
(37) Mo, F.; Qiu, D.; Zhang, Y.; Wang, J. Renaissance of Sandmeyer-type reactions: conversion of aromatic C–N bonds into C–X bonds (X = B, Sn, P, or CF3). Acc. Chem. Res. 2018, 51, 496–506.
(38) Wang, X.; Xu, Y.; Mo, F.; Ji, G.; Qiu, D.; Feng, J.; Ye, Y.; Zhang, S.; Zhang, Y.; Wang, J. Silver-mediated trifluoromethylation of aryldiazonium salts: conversion of amino group into trifluoromethyl group. J. Am. Chem. Soc. 2013, 135, 10330–10333.
(39) Dai, J.-J.; Fang, C.; Xiao, B.; Yi, J.; Xu, J.; Liu, Z.-J.; Lu, X.; Liu, L.; Fu, Y. Copper-promoted Sandmeyer trifluoromethylation reaction. J. Am. Chem. Soc. 2013, 135, 8436–8439.
(40) All experiments of this study were performed using a five-year old CoF3 column for the [11C]methane to [11C]fluoroform conversion. [11C]Fluoroform was obtained in reproducible yields > 60% after CoF3 column replacement. This is consistent with the [11C]fluoroform yield described in our past publication.
(41) Gould, E. S. Mechanism and Structure in Organic Chemistry; Holt Rinehart & Winston, 1969; pp 457–458.
(42) Canning, P. S. J.; McCrudden, K.; Maskill, H.; Sexton, B. Rates and mechanisms of the thermal solvolytic decomposition of arenediazonium ions. J. Chem. Soc., Perkin Trans. 2 1999, 2735–2740.
(43) Danoun, G.; Bayarmagnai, B.; Grünberg, M. F.; Goossen, L. J. Sandmeyer trifluoromethylation of arenediazonium tetrafluoroborates. Angew. Chem., Int. Ed. 2013, 52, 7972–7975.
(44) Bayarmagnai, B.; Matheis, C.; Risto, E.; Goossen, L. J. One-pot Sandmeyer trifluoromethylation and trifluoromethylthiolation. Adv. Synth. Catal. 2014, 356, 2343–2348.
(45) Browne, D. L. The trifluoromethylating Sandmeyer reaction: a method for transforming C—N into C—CF3. Angew. Chem., Int. Ed. 2014, 53, 1482–1484.