



A Fluoride-Derived Electrophilic Late-Stage Fluorination Reagent for PET Imaging

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A Fluoride-Derived Electrophilic Late-Stage Fluorination Reagent for PET Imaging

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The unnatural isotope fluorine-18 (¹⁸F) is used as a positron emitter in molecular imaging. Currently, many potentially useful ¹⁸F-labeled probe molecules are inaccessible for imaging because no fluorination chemistry is available to make them. The 110-minute half-life of ¹⁸F requires rapid syntheses for which [¹⁸F]fluoride is the preferred source of fluorine because of its practical access and suitable isotope enrichment. However, conventional [¹⁸F]fluoride chemistry has been limited to nucleophilic fluorination reactions. We report the development of a palladium-based electrophilic fluorination reagent derived from fluoride and its application to the synthesis of aromatic ¹⁸F-labeled molecules via late-stage fluorination. Late-stage fluorination enables the synthesis of conventionally unavailable positron emission tomography (PET) tracers for anticipated applications in pharmaceutical development as well as preclinical and clinical PET imaging.

Positron emission tomography (PET) is a noninvasive imaging technology used to observe and probe biological processes in vivo (1, 2). Although several positron-emitting isotopes can be used for PET imaging, fluorine-18 (¹⁸F) is the most clinically relevant radioisotope (3, 4). For example, the radiotracer [¹⁸F]fluorodeoxyglucose ([¹⁸F]FDG) has revolutionized clinical diagnosis in oncology. Despite the success of PET and decades of research, there remains a major deficiency in the ability to synthesize complex PET tracers; in fact, no general method is available to radiolabel structurally complex molecules with ¹⁸F. In organic molecules, fluorine atoms are typically attached by carbon-fluorine bonds (5), yet carbon-fluorine bond formation is challenging, especially in the presence

of the variety of functional groups commonly found in structurally complex molecules (6). For PET applications, chemical challenges are exacerbated by the short half-life of ¹⁸F (110 min), which dictates that carbon-fluorine bond formation occur at a late stage in the synthesis to avoid unproductive radioactive decay before injection in vivo.

The unnatural isotope ¹⁸F is generated using a cyclotron, either as nucleophilic [¹⁸F]fluoride or as electrophilic [¹⁸F]fluorine gas ([¹⁸F]F₂). [¹⁸F]Fluoride, formed from proton bombardment of oxygen-18-enriched water, is easier to make and handle than [¹⁸F]F₂. Moreover, [¹⁸F]F₂ gas is liberated from the cyclotron with [¹⁹F]F₂; ¹⁹F is the natural, PET-inactive isotope of fluorine. As a result, the ¹⁸F/¹⁹F ratio, quantified as specific activity, is substantially lower when [¹⁸F]F₂ is used than when [¹⁸F]fluoride is used. High specific activity is often critical to PET imaging. If a biological target of a radiotracer is saturated with the non-positron-emitting ¹⁹F-isotopolog of the tracer, a meaningful PET image cannot be obtained. PET tracers of low specific activity cannot be used to visualize biological targets that are of low concentration. For example, imaging neurotransmitter receptors in the brain typically necessitates tracers of high specific activity (3).

Research toward PET tracer development has focused on the use of [¹⁸F]fluoride to make PET tracers with high specific activity. Incorporation of ¹⁸F still usually relies on simple nucleophilic substitution reactions, a class of reactions originally developed more than 100 years ago (7) and often not suitable to address modern challenges in imaging. Recent advances in nucleophilic fluorination (8–11) include a palladium-catalyzed fluorination reaction of aryl triflates with anhydrous cesium fluoride developed by the Buchwald group in which carbon-fluorine bond formation proceeds by reductive elimination from palladium(II) aryl fluoride complexes (12, 13). Challenges associated with the application of fluorination reactions to PET include the requirement of short reaction times, as well as different reaction conditions for ¹⁸F chemistry relative to ¹⁹F chemistry. For example, extensive drying of fluoride is readily achieved for ¹⁹F chemistry but can be impractical for radiochemistry, which is typically executed on a nanomole scale. When transitioning from ¹⁹F chemistry to ¹⁸F chemistry, the smaller ratio of fluorine to water can be problematic because hydrated fluoride has diminished nucleophilicity. As a consequence, even promising modern fluorination reactions developed for ¹⁹F chemistry are often not translated to radiochemistry.

Electrophilic and nucleophilic fluorination reactions allow access to complementary sets of molecules (6), yet all electrophilic ¹⁸F-fluorination reactions developed to date use electrophilic fluorination reagents that ultimately originate from [¹⁸F]F₂. In 1997, Solin developed a method to generate [¹⁸F]F₂ with higher specific activity than is common for [¹⁸F]F₂, by minimizing the amount of [¹⁹F]F₂ used (14). By using [¹⁸F]F₂ made via the Solin method, Gouverneur succeeded in synthesizing [¹⁸F]N-chloromethyl-N-fluorotriethylenediammonium bis(tetrafluoroborate) ([¹⁸F]F-TEDA), an electrophilic ¹⁸F-fluorination reagent more useful and selective than [¹⁸F]F₂ (15). However, nucleophilic [¹⁸F]fluoride is currently the only practical and generally available source of fluorine to prepare PET tracers with high specific activity (3). If an electrophilic fluorination reagent were to be made from fluoride (16, 17) without the need for F₂, electrophilic fluorination could become a general and widely used method to prepare PET tracers that are currently

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inaccessible via conventional nucleophilic fluorination chemistry.

Previously, we reported the fluorination of palladium aryl complexes with the electrophilic fluorination reagent F-TEDA (Fig. 1) (18). F-TEDA can oxidize palladium(II) aryl complexes, which subsequently afford aryl fluorides by carbon-fluorine reductive elimination from palladium(IV) aryl fluoride complexes (19, 20). Replacement of F-TEDA by a fluorination reagent that mimics the function of F-TEDA but is made from fluoride has the potential for use in the synthesis of ^{18}F radiotracers with high specific activity. Here, we report the design and synthesis of an organometallic complex made from fluoride (**1** $\rightarrow$ **2**, Fig. 1) that behaves as an electrophilic fluorination reagent, and the use of the reagent for the synthesis of ^{18}F -labeled small molecules via late-stage fluorination.

Palladium complex **2** was envisioned to accomplish oxidative fluorine transfer by serving as an electrophile in $\text{S}_{\text{N}}2$ reactions with nucleophilic attack occurring at the fluorine substituent. The complexes **1** and **2** were designed according to the following five considerations (Fig. 2): (i) The palladium center in **1** carries three formal positive charges (countercharges to two triflate anions and one negatively charged borate ligand) and should therefore capture negatively charged fluoride from solution. High fluorophilicity of the palladium complex **1** is required for radiochemistry applications because of the low effective concentration of fluoride in solution (roughly 10^{-4} M). (ii) The palladium centers in **1** and **2** are in the oxidation state +IV [Pd(IV)], a high oxidation state for palladium. Late transition metals such as palladium, when in a high oxidation state, can function as an oxidant and transfer a ligand to a nucleophile while being reduced to a lower oxidation state (21). The palladium in **2** can function as an electron acceptor, which rationalizes the reactivity of **2** as an oxidant. (iii) The supporting benzo[*h*]quinolyl and tetrapyrzole borate (Tp) ligands are multidentate ligands that were selected to impart stability on both **1** and **2** toward undesired reductive processes such as carbon-fluorine reductive elimination. Reductive elimination from **2** would likely require dissociation of one ligand to form a pentacoordinate palladium complex (19, 20), and multidentate ligands such as Tp are less likely to dissociate and hence reduce the rate of potential reductive elimination. (iv) An octahedral Pd(IV) complex was chosen to avoid undesired nucleophilic attack at the transition metal. The palladium-fluorine bond is polarized toward fluorine, with partial negative charge on fluorine and positive charge on palladium. Solely on the basis of coulombic interactions, nucleophilic attack is expected at palladium rather than fluorine. However, the orbitals available for nucleophilic attack on octahedral $(t_{2g})^6(e_g)^0$ Pd(IV) complexes, the $d_{x^2-y^2}$ and d_{z^2} orbitals, are high in energy, and nucleophilic attack on high-energy orbitals is disfavored (22). (v) The multidentate supporting ligands in **2** feature aromatic

substituents to prevent nucleophilic attack on the carbon and nitrogen atoms coordinated to palladium. Complex **2** was devised to act as an electrophilic fluorination reagent through nucleophilic attack at the antibonding palladium-fluorine-based orbital ($\sigma^*_{\text{Pd-F}}$) at fluorine in an $\text{S}_{\text{N}}2$ reaction. In such a putative $\text{S}_{\text{N}}2$ reaction, palladium would function as a leaving group, with concomitant reduction to the oxidation state +II [Pd(II)]. Nucleophilic attack would occur at the lowest unoccupied molecular orbital (LUMO) of **2**. The calculated LUMO of **2** (Fig. 2B) shows that only the lobe on fluorine points into unoccupied space; no other LUMO lobe is available for nucleophilic attack because the aromatic ligands block the trajectories.

Treatment of the palladium complex **1** with nucleophilic fluoride (KF) afforded the palladium fluoride complex **2** within 5 min at 90% yield (Fig. 2A). The ability of **2** to function as an electrophilic fluorination reagent was confirmed by fluorination of Pd(II) aryl complex **3** (Fig. 2C). Fluorine transfer from **2** to **3** results in oxidation of **3** to form Pd(IV) aryl fluoride intermediate **5**, assigned by ^1H and ^{19}F nuclear magnetic resonance (NMR). Carbon-fluorine reductive elimination from reactive intermediate **5** occurs at a rate comparable to oxidation of **3** with **2**. Oxidation of **3** with the electrophilic fluorination reagent F-TEDA afforded **5** at a faster rate than oxidation with **2**, which allowed independent synthesis and identification of **5** (fig. S2). Reduction of palladium from Pd(IV) in oxidant **2** to Pd(II) was established by isolation of Pd(II) complex **4**.

Oxidative fluorine transfer from **2** to **3** could proceed by $\text{S}_{\text{N}}2$ reaction as designed, with nucle-

ophilic attack of the d_{z^2} -based orbital on palladium of **3** (fig. S17) on the $\sigma^*_{\text{Pd-F}}$ -based orbital of the LUMO of **2**, or via electron transfer (23, 24) from **3** to **2** with interposed or subsequent fluorine transfer. Currently available data cannot distinguish between these mechanisms. In addition, other pathways that intercept intermediates such as **5** could potentially be used for carbon-fluorine bond formation. Palladium complex **2** is both an oxidant and a fluoride donor. The oxidation equivalents are inherent in the transition metal oxidation state, and the fluorine substituent is negatively polarized, because fluorine is the most electronegative element. But oxidation of **3** with an external oxidant followed by a reaction with an independent fluoride source could also provide **5**. In such a stepwise approach, potential side reactions of putative intermediates, such as undesired reductive elimination reactions, must be prevented. Conceptually, several combinations of an oxidant and a fluoride source are conceivable for successful oxidative fluorination.

The fluorination reagent **2** was subsequently evaluated for late-stage fluorination. Fluorination of the Pd(II) aryl complexes **8** to **11** with **2** afforded aryl fluorides **12** to **15** at 67 to 93% yield (Fig. 3). We propose that Pd(IV) fluoride complex **2** oxidizes the Pd(II) aryl complexes by fluorine transfer to form high-valent Pd(IV) aryl fluoride complexes, analogous to **5**, from which carbon-fluorine reductive elimination can occur to form aryl fluoride products **12** to **15**. The aryl fluoride molecules shown in Fig. 3 were selected on the basis of their structure and exhibition of a variety of functional groups, akin to potential small-molecule PET tracers (25, 26). The molecules

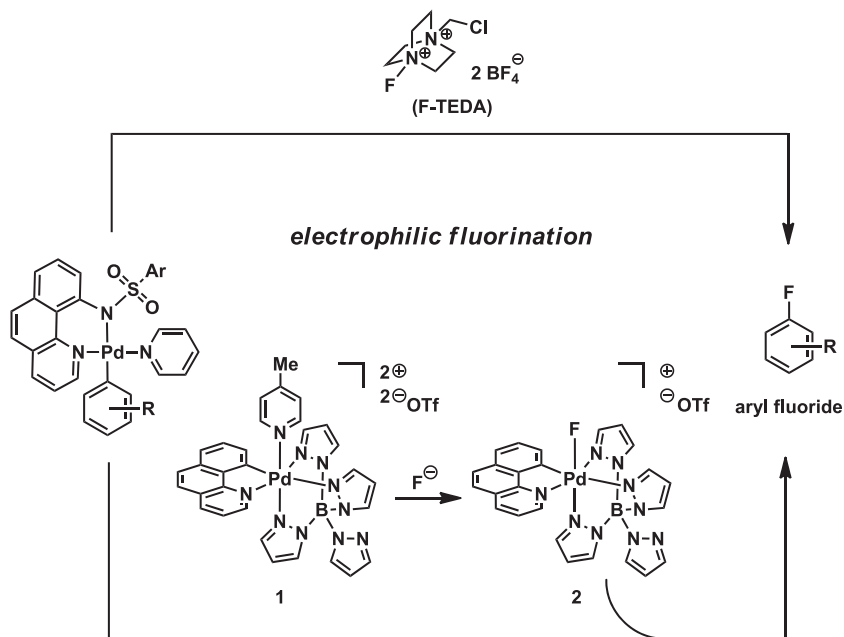


Fig. 1. Electrophilic fluorination of palladium aryl complexes to afford aryl fluorides. **Top:** With the electrophilic fluorination reagent F-TEDA. **Bottom:** With the Pd(IV) fluoride complex **2**, made from fluoride (F^-). Ar, aryl; Me, methyl; Tf, trifluoromethanesulfonyl.

are electron-rich arenes, which would be difficult to prepare by conventional fluorination reactions with [^{18}F]fluoride.

The transition from ^{19}F chemistry to ^{18}F chemistry is challenging because the concentration of the limiting reagent (fluoride) changes from millimolar to micromolar, and because syntheses must be performed in the presence of ionizing radiation and under a time constraint due to the 110-min half-life of ^{18}F . Therefore, reaction chemistry applicable to ^{18}F chemistry must be robust and as simple as possible for broad applications

in medical imaging. Organometallic synthesis in a hospital setting would be impractical. However, the palladium complexes discussed here can be prepared conveniently on scale, stored, and subsequently transported to imaging sites when needed. The palladium(II) aryl complexes such as **8** to **11** can be purified by chromatography or recrystallization and can be stored and transported in air at ambient temperature. Palladium complex **1** is stable at room temperature and can be manipulated briefly in air. Palladium complex **2** is stable toward heat (no observed decomposition

for 24 hours at 100°C), and water (no observed decomposition in 10% aqueous acetonitrile solution after 3 hours at 23°C). Thermal stability and tolerance toward water are beneficial for practical PET applications, because reaction mixtures are often heated to increase reaction rates and [^{18}F]fluoride is made from oxygen-18-enriched water.

The synthesis of ^{18}F -radiolabeled molecules using such a fluoride-derived reagent is operationally simple. Pd(IV) complex **1** reacts with conventionally prepared solutions of [^{18}F]fluoride

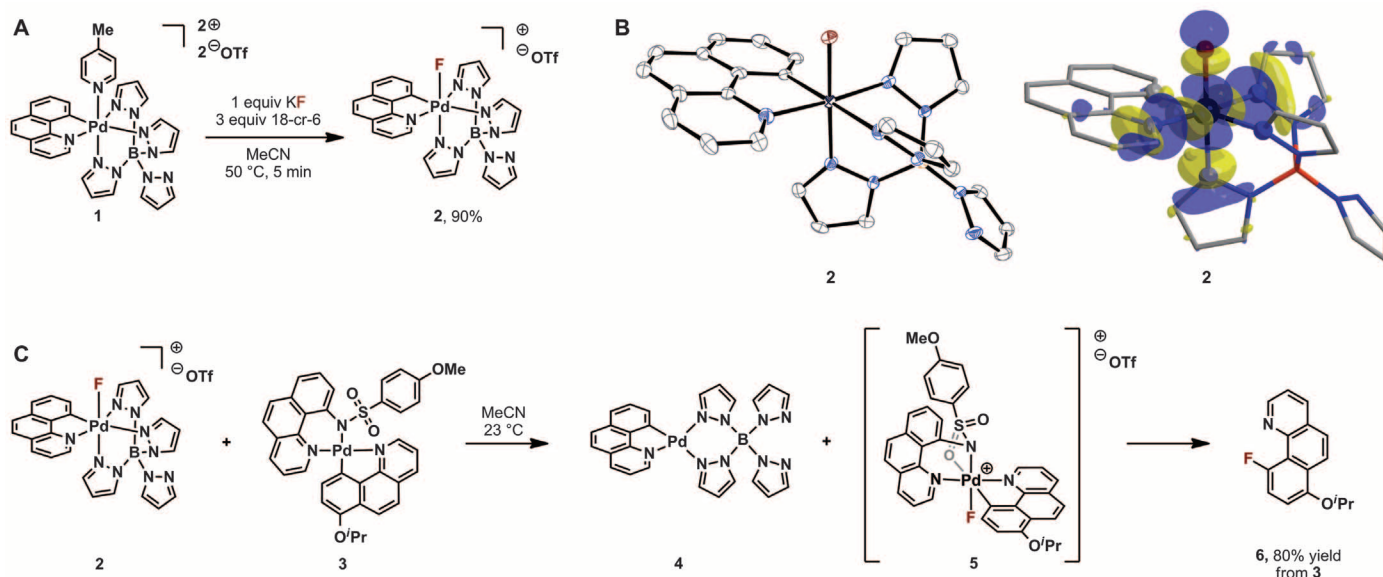


Fig. 2. Reactivity and structure of **1** and **2**. (A) Nucleophilic fluoride capture by Pd(IV) complex **1** to form electrophilic fluorination reagent **2**. (B) X-ray structure of **2** (ORTEP drawing at 50% probability; hydrogen atoms and counteranion omitted for clarity) and calculated lowest unoccupied molecular orbital (LUMO) of **2**. (C)

Fluorination of Pd(II) aryl complex **3** by reagent **2** to form Pd(IV) aryl fluoride complex **5**, followed by C–F reductive elimination from **5**. Reductive elimination from reactive intermediate **5** to **6** proceeds at 23°C; the highest yield of **6** (80%) was obtained upon heating **2** and **3** at 85°C. 18-cr-6, 18-crown-6; ^iPr , isopropyl.

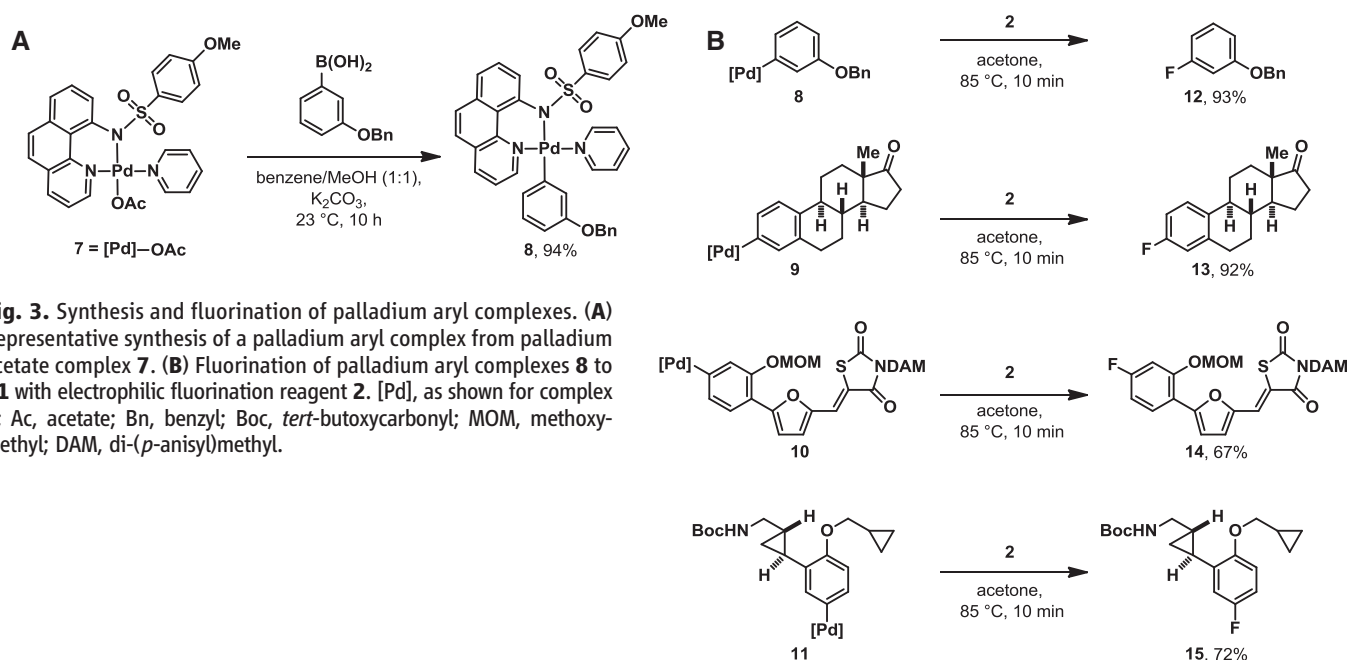


Fig. 3. Synthesis and fluorination of palladium aryl complexes. (A) Representative synthesis of a palladium aryl complex from palladium acetate complex **7**. (B) Fluorination of palladium aryl complexes **8** to **11** with electrophilic fluorination reagent **2**. [Pd], as shown for complex **7**; Ac, acetate; Bn, benzyl; Boc, *tert*-butoxycarbonyl; MOM, methoxymethyl; DAM, di-(*p*-anisyl)methyl.

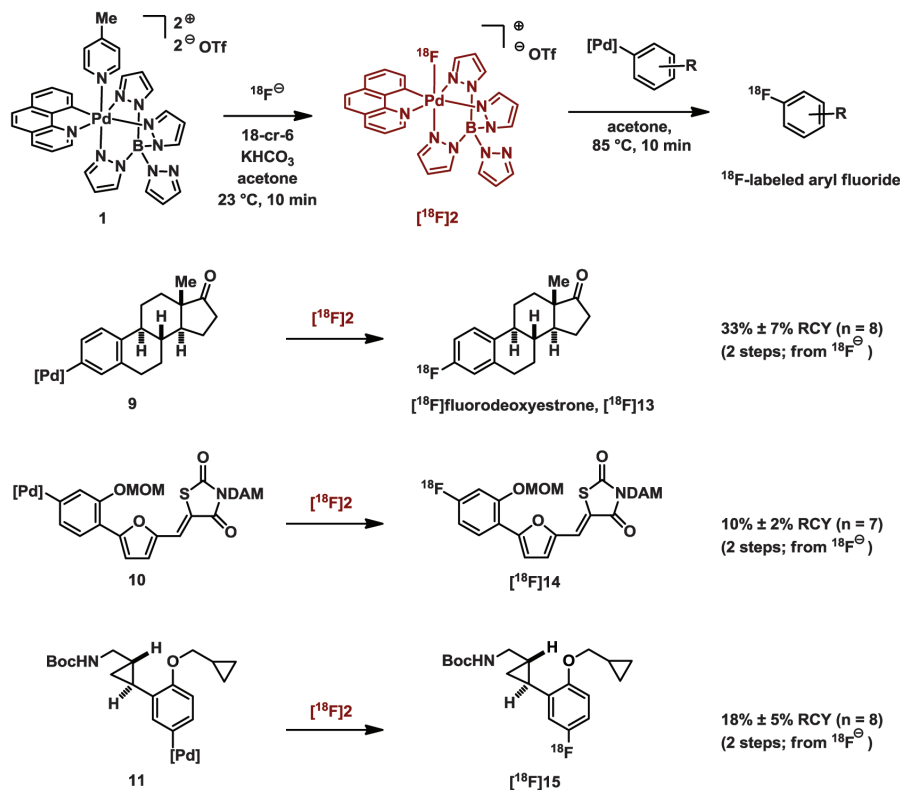


Fig. 4. Late-stage fluorination to form ^{18}F -labeled aryl fluorides. ^{18}F Fluoride capture by Pd(IV) complex **1** to form electrophilic fluorination reagent ^{18}F **2** and subsequent fluorination of palladium aryl complexes **9** to **11**. Reported radiochemical yields (RCYs) are averaged over n experiments at a 500- μCi scale.

in acetone and forms the ^{18}F reagent ^{18}F **2** within 10 min (Fig. 4). Subsequent filtration over a polymer-supported resin and addition of the Pd(II) aryl complexes **9** to **11** yielded, upon heating for 10 min, the ^{18}F -labeled aryl fluorides ^{18}F **13** to ^{18}F **15**, respectively. Azeotropic drying of aqueous ^{18}F fluoride, the two-step reaction sequence (fluoride capture (**1** $\rightarrow$ ^{18}F **2**) followed by fluorine transfer (e.g., **9** $\rightarrow$ ^{18}F **13**), and subsequent purification of the ^{18}F -labeled molecules by high-performance liquid chromatography (HPLC) results in an overall synthesis time of less than 60 min. Automated syntheses with up to 1 Ci of radioactivity have been accomplished. The efficiency of radiochemical synthesis is given in radiochemical yield, which is based on decay-corrected radioactivity rather than on mass of isolated material (4). Radiochemical yields (RCYs) as high as possible are desired, but RCYs as low as 5% can provide meaningful PET imaging (27). The ^{18}F -fluorination method described here has afforded RCYs higher than 30%.

Stoichiometric amounts of precious transition metals such as palladium are typically avoided in syntheses of health care products because of toxicity and cost considerations. However, such considerations are different for the synthesis of PET tracers because of the small amount that is required (28). PET tracers with high specific activity are administered at a dose at least 2 orders of magnitude smaller than is common

for pharmaceuticals because pharmacological effects are not sought (29), and purification is often straightforward because of the small amount of tracer to be purified. For example, inductively coupled plasma mass spectrometry (ICP-MS) analysis of ^{18}F **13** (Fig. 4), purified by conventional HPLC technique (20 min), afforded material with 5 parts per billion (ppb) palladium residue, commensurate with international recommendations on the palladium impurity profile for samples injected into humans, which demand less than 1000 ppb palladium (30). Similarly, the synthesis cost for the palladium complexes is small relative to the cost of ^{18}F -isotope infrastructure and the cost associated with clinical imaging (31).

We have shown that a late-stage fluorination reaction can access ^{18}F -labeled functionalized molecules, which would be particularly difficult to prepare with conventional fluorination reactions. The availability of a fluorination reagent with high specific activity that functions as an electrophile may find applications in ^{18}F fluorination of pharmaceutical candidates for evaluation of their biodistribution to accelerate drug development, as well as in the development of previously unavailable ^{18}F -PET tracers for clinical care.

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Supporting Online Material

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