Radiochemistry

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Metal-Free Oxidative Fluorination of Phenols with [^{18}F]Fluoride**

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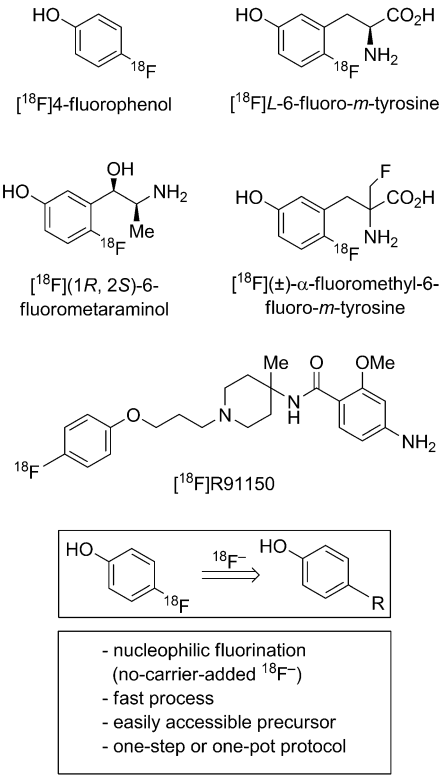
Positron emission tomography (PET) is a molecular imaging technique that captures functional or phenotypic changes associated with pathology.[1] This research field is currently fuelled by the need for conceptually new ^{18}F-radiolabeling methods to satisfy clinical demand.[2] ^{18}F-labeled aryl derivatives are highly sought after in the context of both drug and radiotracer development because of their advantageous metabolic profile for in vivo applications.[3] The most challenging targets are aryl precursors that are not amenable to nucleophilic aromatic substitution reactions with [^{18}F]fluoride. Electrophilic fluorination is a logical strategy to access electron-rich ^{18}F-labeled aryl fluorides, but this approach is not adopted preferentially, as $^{18}F_2$ is difficult to handle and produced in low specific activity in comparison with [^{18}F]fluoride.[2] Electrophilic [^{18}F]N–F-type reagents of tamed reactivity have been developed, but to date they do not address the issue of specific activity.[4,5] The direct coupling of electron-rich aromatic compounds with [^{18}F]fluoride is a conceptually attractive alternative strategy, but notoriously difficult to implement. For reaction discovery, [^{18}F]4-fluorophenol[6] is possibly the most archetypical target, as it is a versatile prosthetic group for the synthesis of complex radiopharmaceuticals,[7] and this structural submotif is thus featured in many tracers that are used clinically. Representative examples include [^{18}F]L-6-fluoro-*m*-tyrosine[8] and [^{18}F]-(1*R*, 2*S*)-6-fluorometaraminol[9] (Scheme 1). Ideally, the radiosynthesis of [^{18}F]fluorophenol from [^{18}F]fluoride should be fast (the half-life of ^{18}F is 109.77 mins), convenient to implement, and include use of a readily accessible or commercially available precursor. A one-step (or one-pot) protocol as simple as the one developed for [^{18}F]fluorodeoxyglucose would be ideal. The methods available to date for accessing [^{18}F]fluorophenol require two steps or more with cartridge purification of intermediates.[6]



Scheme 1. Importance of the [^{18}F]4-fluorophenol motif for positron emission tomography.

Recently, Ritter reported the synthesis of a fluoride-derived electrophilic fluorination reagent for the late stage ^{18}F labeling of electron-neutral and electron-rich aromatic compounds.[10] This chemistry features the coupling of two organometallic species, the ^{18}F-labeled reagent that is prepared by mixing [^{18}F]fluoride with a Pd^{IV} complex, and the substrate, which is activated as a Pd^{II} aryl complex; a protocol that corresponds to a net [^{18}F]fluoride umpolung strategy. Three representative electron-neutral and electron-rich ^{18}F-labeled aryl fluorides were made accessible using this strategy. We reasoned that the coupling of phenol derivatives with [^{18}F]fluoride could arise from a complementary metal-free approach, involving aryl umpolung instead. Such a reactivity switch from a nucleophilic to an electrophilic entity can be imposed on aromatic compounds, such as phenols, using an

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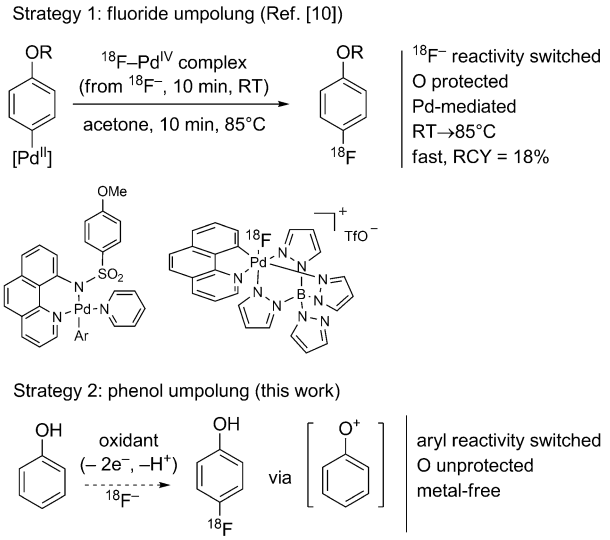
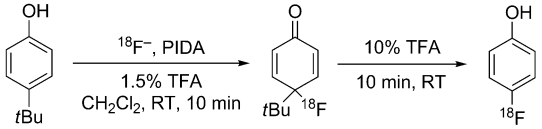
external oxidant.[11,12] Based on these principles, [^{18}F]fluorophenol could be accessed directly from phenol in the presence of a [^{18}F]fluoride source upon oxidative fluorination/dearomatization, followed by rearomatization (Scheme 2). The oxidative nucleophilic fluorination of phenols is known from the majority of studies targeting mono- or difluorocyclohexadienones.[13] Mechanistically, a hypovalent phenyloxenium ion is more often proposed as the key intermediate captured with fluoride.[14] In 2002, Langlois and co-workers established that 4-*tert*-butylphenol can be converted to 4-fluorophenol upon treatment with bis(trifluoroacetoxy)iodobenzene (PIFA) and $Et_3N{\cdot}3HF$.[15] This study built on the previously reported oxidative fluorination of aromatic compounds, including phenol derivatives.[16] Based on these precedents, we were poised to examine the potential of metal-free oxidative fluorination in the context of ^{18}F radiochemistry.[17] Herein, we report the successful validation of the proposed aryl umpolung radiolabelling strategy with a new method to access no-carrier-added (NCA) [^{18}F]4-fluorophenol from [^{18}F]fluoride and 4-*tert*-butylphenol, a commercially available precursor. The strategy, which is easy to implement, is extended to variously substituted phenol derivatives.



Scheme 2. Fluorination of phenol and derivatives with [^{18}F]fluoride.

Our optimum protocol for the oxidative fluorination of 4-*tert*-butylphenol **1a** consists of its treatment with one equivalent of phenyliodine diacetate (PIDA; 0.05 M) and four equivalents of HF·pyridine in CH_2Cl_2 at room temperature for 15 minutes followed by treatment with neat trifluoroacetic acid (TFA; until 10% *v*/*v* in CH_2Cl_2 is reached) at room temperature for 10 minutes. Under these conditions, 4-fluorophenol is isolated analytically pure in 35% yield (50% yield determined by ^{19}F NMR spectroscopy of the crude material).[18] For transferring the method to ^{18}F labeling, use of [^{18}F]poly(hydrogen fluoride)pyridinium is disfavored (carrier-added synthesis), because this known ^{18}F-labeled reagent leads to a labeled product of low specific activity.[19] It was therefore critical to identify an alternative NCA fluoride source that is competent for the planned oxidative fluorination. The use of CsF or TBAF·3 H_2O was not successful for the conversion of 4-*tert*-butylphenol into 4-fluoro-4-*tert*-butyl-2,5-cyclohexadien-1-one. However, when combined with TFA, both CsF and TBAF·3 H_2O led to the formation of 4-fluoro-4-*tert*-butyl-2,5-cyclohexadien-1-one (47% and 29% conversion, respectively). This lead result prompted us to explore the direct ^{18}F fluorination of 4-*tert*-butylphenol from [^{18}F]fluoride as a route to [^{18}F]4-fluorophenol. Several possible complications intrinsic to ^{18}F labeling had to be considered. The [^{18}F]fluoride source is the limiting reagent, thus implying that the starting material and the oxidant are present in large excess. This reverse stoichiometry with respect to cold experimentation can facilitate undesired processes, such as overoxidation of any in situ formed [^{18}F]4-fluorophenol.[20] The excess starting material could also act as a competing nucleophile in preference to [^{18}F]fluoride. The validation of the oxidative fluorination from [^{18}F]fluoride, leading to [^{18}F]4-fluorophenol, is presented in Table 1. Three [^{18}F]fluoride sources were reacted with 4-*tert*-butylphenol and PIDA/TFA in CH_2Cl_2, [^{18}F]KF/Kryptofix 222,[^{18}F]CsF, and [^{18}F]TBAF. All reagents used in combination with PIDA and TFA led to the formation of [^{18}F]-**2a**, but were not equally efficient (entries 1–3). Only trace amount of [^{18}F]-**2a** was observed with [^{18}F]CsF. Both [^{18}F]KF/Kryptofix 222 and [^{18}F]TBAF led to [^{18}F]-**2a** with a decay-corrected radiochemical yield (RCY) of around 8%, but since [^{18}F]TBAF typically led to a cleaner reaction mixture, this reagent was used for further experimentation. Because the concentration did not seem to have a significant impact on the RCY, all reactions were subsequently performed at a concentration of 0.2 M (entries 4–7). This validation study established a suitable operating protocol for ^{18}F radiolabeling. Cyclotron-produced NCA aqueous [^{18}F]fluoride (1–3 GBq) was adsorbed onto an anion-

Table 1: ^{18}F Fluorination of 4-*tert*-butylphenol **1a**.



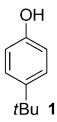
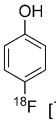
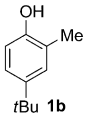
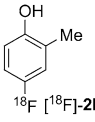
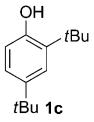
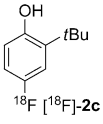
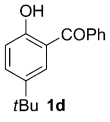
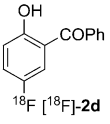
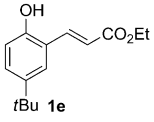
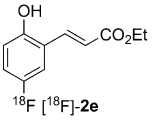
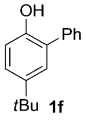
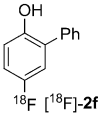
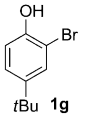
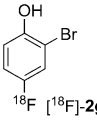
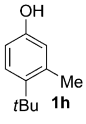
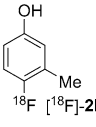
Entry	^{18}F$^-$ source[a]	*c*(**1a**)	RCY [%][c]	*n*
1	**A**	0.2 M	8[d,e]	3
2	**B**[b]	0.2 M	trace[d]	1
3	**C**	0.2 M	8[d,f]	3
4	**C**	0.05 M	26[g]	3
5	**C**	0.1 M	21[g]	3
6	**C**	0.2 M	21[g]	3
7	**C**	0.4 M	21[g]	3

[a] **A** = [^{18}F]KF/Kryptofix 222, **B** = [^{18}F]CsF, **C** = [^{18}F]TBAF. [b] [^{18}F]CsF is not soluble in CH_2Cl_2. [c] Decay-corrected RCY. [d] Experiments performed with same batch of [^{18}F]fluoride (i.e., same day). [e] 38% Purity determined by radio-HPLC analysis excluding [^{18}F]fluoride. [f] 47% Purity determined by radio-HPLC analysis excluding [^{18}F]fluoride. [g] Experiments performed with same batch of [^{18}F]fluoride (i.e., same day). *n* = number of experiments, TBAF = tetra-*n*-butylammonium fluoride.

exchange cartridge and released with a solution of Bu_4NHCO_3 in acetonitrile/water (*v*/*v* 4:1). The solution was azeotropically dried with MeCN, the remaining MeCN was evaporated, and the residue was solubilized in CH_2Cl_2. The substrate 4-*tert*-butylphenol (40 μmol) was added at room temperature to an aliquot of [^{18}F]TBAF solution (≈5–50 MBq), followed by a freshly prepared solution of PIDA (1 equiv) and TFA (4 equiv) in CH_2Cl_2. The reaction mixture was stirred for 15 minutes, after which a supplement of TFA was added. Radio-TLC and radio-HPLC analysis was performed after 10 minutes. This protocol gave [^{18}F]4-fluorophenol in 21% decay-corrected RCY ($n = 3$).

With the optimal conditions at hand, the substrate scope of the oxidative fluorination was investigated. Various 4-*tert*-butyl substituted phenols **1a–h** were subjected to labeling with [^{18}F]fluoride using the optimized protocols (Table 2). All precursors **1a–h** (except **1f**) were successfully ^{18}F-labeled with decay-corrected RCYs, which were evaluated by radio-HPLC and radio-TLC analyses, ranging from 11% to 32%. The radio-HPLC traces of crude material indicated that the radiochemical purity was variable. This observation prompted us to provide isolated decay-corrected RCYs of analytically pure ^{18}F-labeled phenols for all transformations. The isolated yields (calculated from the starting [^{18}F]TBAF activity) ranged from 7% to 21%. The reaction tolerates various *ortho*-positioned substituents, including methyl and *tert*-butyl, as well as ketone and vinylogous ester functionalities. [^{18}F]2-Bromo-4-fluorophenol is within reach, a pleasing result as this compound can be cross-coupled after fluorination. The ^{18}F fluorination of 2,5-di-*tert*-butylphenol is *para* selective, the *tert*-butyl group in *ortho* position remained intact under the reaction conditions. The reaction tolerates *meta* substitution on the phenol, as shown with the preparation of 3-methyl-4-fluorophenol [^{18}F]-**2h**. The only substrate that is not responsive to ^{18}F labeling is 4-*tert*-butyl-2-phenyl-phenol **1f**, an unexpected result since this compound was successfully fluorinated in 37% yield under our optimized nonradiochemical conditions.[18] Only trace amounts of [^{18}F]-**2f** and ^{18}F-labeled impurities in addition to unreacted [^{18}F]fluoride could be detected by radio-HPLC of the crude reaction mixture. Pleasingly, compound [^{18}F]-**2g** was obtained with a specific activity of 420 GBq μmol^{-1}.[18]

Table 2: Oxidative ^{18}F fluorination of **1a–h** with [^{18}F]TBAF.

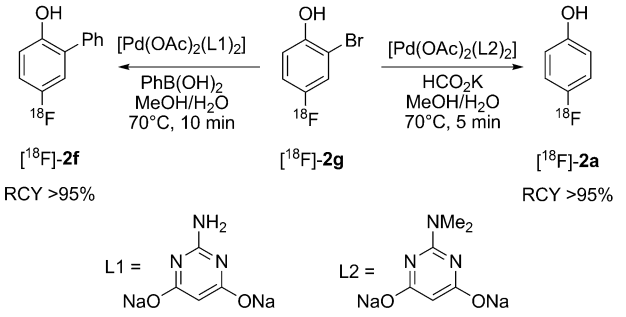
Entry	Substrate	Product	RCY of [^{18}F]-**2a–h** [%][a] (*n*)	RCY of [^{18}F]-**2a–h** [%][b]
1	 *t*Bu **1a**	 ^{18}F [^{18}F]-**2a**	15 (5)	13 (20)
2	 *t*Bu **1b**	 ^{18}F [^{18}F]-**2b**	15 (8)	16 (15)
3	 *t*Bu **1c**	 ^{18}F [^{18}F]-**2c**	32 (5)	21 (22)
4	 *t*Bu **1d**	 ^{18}F [^{18}F]-**2d**	11 (6)	7 (12)
5	 *t*Bu **1e**	 ^{18}F [^{18}F]-**2e**	13 (8)	20 (33)
6	 *t*Bu **1f**	 ^{18}F [^{18}F]-**2f**	trace (4)	–
7	 *t*Bu **1g**	 ^{18}F [^{18}F]-**2g**	16 (11)	18 (22)
8	 *t*Bu **1h**	 ^{18}F [^{18}F]-**2h**	13 (7)	16 (23)

[a] Average decay-corrected RCY based on *n* experiments. [b] Decay-corrected RCY of isolated products; numbers in brackets refer to the yield of this experiment determined by radio-TLC analysis.

We next examined the reactivity of [^{18}F]4-fluoro-2-bromophenol [^{18}F]-**2g** for cross-coupling with phenylboronic acid, because the direct oxidative ^{18}F fluorination of **1f** was unsuccessful as a route to [^{18}F]-**2f**. We optimized the Suzuki–Miyaura cross-coupling of **2g** in MeOH/H_2O (*v*/*v* 1:1), because [^{18}F]-**2g** available in this solvent mixture after semipreparative HPLC purification.[18] The phosphine-free ligands 2-amino-4,6-dihydroxypyrimidine (L1) and 2-dimethylamino-4,6-dihydroxypyrimidine (L2) have been successfully used for various Suzuki–Miyaura[21] and Sonogashira[22] couplings in aqueous medium for functionalization of proteins, however these ligands have not been explored in the context of ^{18}F radiochemistry.[23] We were pleased to find that the $Pd(OAc)_2$/2L1 complex led to the desired cross-coupled product [^{18}F]-**2f** in more than 95% yield after ten minutes at 70 °C. Reducing the time to five minutes was less satisfactory and led to decreased RCY or recovered starting material.[18] $[Pd(OAc)_2(L2)_2]$ was superior for the reductive debromination of [^{18}F]-**2g**, which was completed within five minutes at 70 °C in the presence of potassium formate. Compound [^{18}F]-**2a** was obtained in more than 95% decay-corrected RCY and more than 95% radiochemical purity (Scheme 3).

The oxidative fluorination of **1a** was investigated in a commercially available microfluidic device (Advion NanoTek), which provides well-controlled stoichiometry between the precursor, the oxidant, and [^{18}F]fluoride at set flow rates.[24] The technology[24] is advantageous, because only small quantities of reagents are necessary, thereby allowing multiple reactions to be performed from a single production of radioisotope. In a typical protocol, NCA [^{18}F]fluoride ion in [^{18}O]water was first adsorbed onto a small MP-1 cartridge (ORTG, TN), then released with a solution of Bu_4NHCO_3 (600 μL, 10 mg mL^{-1} in acetonitrile/water, *v*/*v* 4:1) into a 5 mL V-vial. The solution was dried by six cycles of azeotropic evaporation with acetonitrile at 105 °C, and solubilized in

a solution of 4-*tert*-butylphenol in $CH_2Cl_2/(CH_2Cl)_2$ (*v*/*v* 7:3; 0.2 M, 500 μL). Solutions of [^{18}F]TBAF/precursor and freshly prepared PIDA/TFA (0.2 M, 500 μL) in anhydrous $CH_2Cl_2/(CH_2Cl)_2$ (*v*/*v* 7:3) were loaded into separate storage loops of the microreactor apparatus. For optimization of reaction conditions, 10–20 μL of solution from each loop was infused into the coiled microreactor (length: 2 m; i.d., 100 μm) at different flow rates and temperatures.[18] After fluorination, TFA (20–25 μL) was added to the reactor output at room temperature. Analysis was performed in the usual manner by radio-TLC. Under optimized conditions (RT, flow rate 15 μL min^{-1}), [^{18}F]4-fluorophenol was obtained in 18% RCY ($n = 2$).



Scheme 3. Suzuki–Miyaura coupling and reductive debromination of [^{18}F]-**2g**.

In summary, we have prepared various [^{18}F]4-fluorophenols by oxidative fluorination of 4-*tert*-butylphenols using no-carrier-added [^{18}F]fluoride. The reaction is completed in less than 30 minutes by applying a one-pot protocol at room temperature, and can be successfully performed in a commercially available microfluidic device. This novel radiochemical transformation stands out as it is applicable to O-unprotected phenols and does not require the synthesis of complex precursors or the use of organometallic species or reagents.[25] On a more fundamental level, the oxidative fluorination of phenols presented herein demonstrates that the concept of aryl umpolung or more generally substrate umpolung may provide a valuable strategy for the direct nucleophilic ^{18}F fluorination of the most challenging electron-rich substrates.[26]

Experimental Section

General procedure for batch mode ^{18}F labeling. The azeotropically dried fluoride was resolubilized in anhydrous CH_2Cl_2 (500–1000 μL) to give a stock [^{18}F]TBAF solution. A solution of [^{18}F]TBAF in CH_2Cl_2 (50 μL, typically 5–50 MBq) was added to the phenol precursor (40 μmol). A stock solution of PIDA/TFA in CH_2Cl_2 (150 μL, made up from PIDA (429 mg, 1.33 mmol) and TFA (405 μL, 5.33 mmol) in CH_2Cl_2 (4.2 mL)) was added to the precursor solution. The reaction mixture was stirred at room temperature for 15 minutes before additional TFA was added (22 μL), and allowed to react for a further 10 minutes prior to radio-HPLC and radio-TLC analysis.

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