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Concerted nucleophilic aromatic substitution with $^{19}\text{F}^-$ and $^{18}\text{F}^-$

Constanze N. Neumann¹, Jacob M. Hooker^{2,3}, and Tobias Ritter^{1,2,4,*}

¹Department of Chemistry and Chemical Biology, Harvard University, Cambridge, MA 02138

²Division of Nuclear Medicine and Molecular Imaging, Department of Radiology, Massachusetts General Hospital, Boston, MA 02114

³Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital and Harvard Medical School, Charlestown, MA 02129

⁴Max-Planck-Institut für Kohlenforschung, Kaiser-Wilhelm-Platz 1, D-45470 Mülheim an der Ruhr

Abstract

Nucleophilic aromatic substitution ($\text{S}_{\text{N}}\text{Ar}$) is widely used by organic chemists to functionalize aromatic molecules, and it is the most commonly used method to generate arenes that contain a ^{18}F for use in PET imaging.¹ A wide range of nucleophiles exhibit $\text{S}_{\text{N}}\text{Ar}$ reactivity, and the operational simplicity of the reaction means that the transformation can be conducted reliably and on large scales.² During $\text{S}_{\text{N}}\text{Ar}$, attack of a nucleophile at a carbon atom bearing a ‘leaving group’ leads to a negatively charged intermediate called a Meisenheimer complex. Only arenes with electron-withdrawing substituents can sufficiently stabilize the resulting build-up of negative charge during Meisenheimer complex formation, limiting the scope of $\text{S}_{\text{N}}\text{Ar}$ reactions: the most common $\text{S}_{\text{N}}\text{Ar}$ substrates contain strong π -acceptors in the ortho and/or para position(s).³ In this manuscript, we present an unusual concerted nucleophilic aromatic substitution reaction ($\text{CS}_{\text{N}}\text{Ar}$) that is not limited to electron-poor arenes, because it does not proceed via a Meisenheimer intermediate. We show a phenol deoxyfluorination reaction for which $\text{CS}_{\text{N}}\text{Ar}$ is favored over a stepwise displacement. Mechanistic insights enabled us to develop a functional group-tolerant ^{18}F -deoxyfluorination reaction of phenols, which can be used to synthesize ^{18}F -PET probes. Selective ^{18}F introduction, without the need for the common, but cumbersome, azeotropic drying of ^{18}F , can now be accomplished from phenols as starting materials, and provides access to ^{18}F -labeled compounds not accessible through conventional chemistry.

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Correspondence and requests for materials should be addressed to T.R. (ritter@mpi-muelheim.mpg.de).

Supplementary Information is available in the online version of the paper.

Author Contributions: C.N.N. designed and performed the experiments and analyzed the data. T.R. directed the project. C.N.N. and T.R. prepared the manuscript with input from J.M.H.

Atomic coordinates and structure factors for the reported crystal structures have been deposited in the Cambridge Crystallographic Data Centre under the accession code CCDC-1419728.

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Readers are welcome to comment on the online version of the paper.

Nucleophilic aromatic substitution reactions generally take place *via* either an addition-elimination or elimination-addition mechanism. Both two-step mechanisms display a high-energy intermediate, either an aryne species (elimination-addition) or a Meisenheimer complex (addition-elimination).^{2,4} A *concerted displacement* of the leaving group by an incoming nucleophile could avoid the formation of high-energy intermediates and thus broaden the scope of suitable electrophiles. Displacements at primary aliphatic centers, where charge build-up in a hypothetical S_N1 mechanism is unfavorable, commonly take place *via* a concerted mechanism involving the σ^* (C_{alkyl}-LG) orbital (S_N2 mechanism). For aromatic substrates a direct substitution pathway involving the σ^* orbital of the arene-leaving group bond (σ^* (C_{aryl}-LG)) is deemed to be impossible: the σ^* orbital is shielded because its large lobe points inwards into the arene ring (Fig. 1a).⁵ Concerted S_NAr substitutions *via* the π orbital framework are considered “*possible but restricted to aromatic structures devoid of the ring activation to generate an intermediate sigma complex of some stability*”.² The intramolecular Newman-Kwart rearrangement has been reported to occur *via* concerted displacement for a wide range of arene substrates, albeit mostly with high activation barriers (35–43 kcal/mol) that reduce synthetic utility.⁶ We show here that the deoxyfluorination reaction of phenols with the reagent PhenoFluor (Fig. 2b) reported by our group^{7,8} proceeds *via* a concerted pathway with electron-rich as well as electron-poor substrates, and how a detailed mechanistic analysis enabled us to design a deoxyfluorination reaction of phenols with ¹⁸F. A concerted reaction with activation energies between 20 and 25 kcal/mol is observed because the concerted pathway is favored rather than because the classic two-step mechanism is disfavored, which sets our reaction apart from previous transformations that proceed with substantially higher activation barriers.^{1,3,6,9} Gas phase nucleophilic aromatic substitutions can take place by concerted nucleophile attack and loss of the leaving group but only isolated cases of intermolecular CS_NAr reactions in solution or ionic melt have been reported.^{10–16}

The orbital interactions involved in a concerted mechanism are similar to those of classical addition-elimination pathways, but the extent of bond-formation and -cleavage in the transition state is crucially different: In the transition state of concerted nucleophilic aromatic substitution (CS_NAr) both the nucleophile and leaving group are attached to the arene by partial rather than full bonds. Loss of the leaving group in the rate-determining step allows the negative charge associated with nucleophilic attack to be located on the incoming nucleophile and the departing leaving group, as opposed to the arene in conventional S_NAr. We propose that selection of leaving groups and reaction conditions tailored to a concerted displacement make it possible to utilize the minimization of charge build-up on the arene to lower the activation barrier (Fig 1b), which expands the scope of electrophiles to include deactivated substrates that feature strong π -donors in the para-position (Fig. 1c). The PhenoFluor-mediated deoxyfluorination reaction allows the interconversion of 4-hydroxyanisole to 4-fluoroanisole at only 110 °C^{7,8} – far below the temperature commonly observed for aromatic substitutions on unactivated arenes.^{3,6,9}

We propose a reaction sequence for the deoxyfluorination reaction in which fluoride attacks the imidazolium core of the reagent to yield tetrahedral intermediate **2** prior to participating in concerted displacement on the arene (Fig. 2a); independently synthesized and

characterized tetrahedral intermediate **2** is converted to aryl fluoride and urea **3** under the reaction condition (Fig. 2b). A single transition state (TS) was localized in a DFT study (B3LYP/6-311++G(d,p)), toluene solvent model) with partial bonds between the nucleophile and arene as well as the leaving group and the arene, the characteristic feature of a concerted transformation.¹⁸ An internal reaction coordinate analysis revealed that the transition state connects tetrahedral intermediate **2** to urea **3** and aryl fluoride, which excludes the existence of additional maxima along the reaction path.

Crucial to the proposal of a concerted substitution mechanism is that loss of the leaving group occurs concurrently with attack of the incoming nucleophile. The rate observed for the fluorination of ¹⁶O-4-phenyl-phenol is 1.08 ± 0.02 times as fast as the rate of fluorination of ¹⁸O-4-phenyl-phenol, corresponding to a large primary kinetic isotope effect (Fig. 2c).¹⁹ A primary ¹⁶O/¹⁸O kinetic isotope effect shows that cleavage of the C–O bond (and therefore loss of the leaving group) occurs during the rate-determining step.^{18,20,21} The rate of deoxyfluorination with PhenoFluor is greater for electron-deficient than for electron-rich substrates, and the continuity in the Hammett plot reveals that no change in mechanism or rate-determining step occurs when the electron density on the phenol is varied (Fig. 2d). An SET mechanism, in which an electron is transferred from the phenol arene to the positively charged imidazolium core, is inconsistent with the observed Hammett plot: For rate-determining electron transfer, reaction rates should be fastest for electron-rich substrates, which is not the case. SET occurring under pre-equilibrium conditions followed by rate-determining fluoride attack, in which case a positive ρ -value would be expected, is unlikely due to the primary ¹⁶O/¹⁸O isotope effect. Fast and reversible fluoride attack followed by rate-limiting expulsion of the leaving group would give rise to a negative ρ -value in the Hammett plot. The regiospecificity of the deoxyfluorination reaction discounts an aryne mechanism (Fig. 2e).

Eyring plots were constructed for a selection of substrates, which revealed $G^\ddagger = 20.3 \pm 0.1$ kcal·mol⁻¹ for 4-nitrophenol, $G^\ddagger = 21.0 \pm 0.2$ kcal·mol⁻¹ for 4-cyanophenol, $G^\ddagger = 21.2 \pm 0.5$ kcal·mol⁻¹ for 4-trifluoromethylphenol and, $G^\ddagger = 23.4 \pm 0.2$ kcal·mol⁻¹ for phenol, respectively. Computational activation barriers $G^\ddagger = 20.8$ kcal·mol⁻¹ for 4-nitrophenol and $G^\ddagger = 25.0$ kcal·mol⁻¹ for phenol are in good agreement with the experimental values. Compared to classical S_NAr reactions, the increase in activation energies as the aromatic system becomes more electron-rich is far less pronounced for concerted S_NAr reactions, which is also apparent from the smaller Hammett ρ -values; conventional S_NAr reactions have ρ -values ranging from 3 to 8, compared to 1.8 for the CS_NAr reaction reported here (Fig. 3c).¹⁰ Limited delocalization of negative charge onto the aromatic substrate in the transition state can thus extend the scope of nucleophilic aromatic substitution to electron-rich substrates.

Why is the barrier for CS_NAr in the presented deoxyfluorination low relative to hypothetical S_NAr reactions on electron-rich arenes? Firstly, facile loss of the leaving group is crucial for a concerted nucleophilic aromatic substitution reaction.²² Unlike in a two-step sequence, where a second smaller activation barrier is associated with loss of the leaving group, a concerted transformation has a single barrier to which both nucleophilic attack, disruption of aromaticity, and loss of the leaving group contribute. A neutral leaving group (urea **3**) will

aid in stabilizing the partial negative charge which resides on both the nucleophile and the leaving group in the transition state.²² An earlier transition state with a lower reaction barrier will occur for $\text{CS}_\text{N}\text{Ar}$ reactions if loss of the leaving group is energetically favorable.¹ Formation of urea **3** is highly exergonic, and because partial C–O cleavage occurs in the transition state, the exergonicity of the overall transformation is expected to lower the activation barrier for deoxyfluorination, an effect also apparent in the ^{18}F displacement of arenes from triarylsulfonium salts.²³ Compared to the Newman-Kwart rearrangement, which can take place on substrates deactivated by electron-donating substituents, the PhenoFluor mediated deoxyfluorination proceeds with considerably lower reaction barriers, likely due to the higher enthalpic gain associated with leaving group loss. Secondly, rearrangement of solvent molecules is commonly a large contributor to the activation barriers of nucleophilic aromatic substitutions, particularly when anionic nucleophiles are employed.²⁴ Association of the (bi)fluoride nucleophile with the cationic uronium **1** solubilizes the nucleophile in the non-polar solvent toluene, and can subsequently form neutral tetrahedral adduct **2**. We propose that the contribution of solvation to the activation barrier is small because neither the associated reaction partners nor the transition state carry an overall charge and little nuclear motion is required to proceed from **2** to **TS**. Computational data suggests that the use of a non-polar solvent favors the occurrence of a concerted deoxyfluorination reaction (supplementary information, Fig. S46).

^{18}F -Fluoride is a desirable nucleophile for the development of $\text{CS}_\text{N}\text{Ar}$ reactions, particularly concerted deoxyfluorination: Phenols are easily accessible and their high polarity facilitates purification of aryl fluoride product from phenol starting material.²⁵ However, in addition to the two equivalents of fluorine inherent to PhenoFluor itself, additional fluoride must be added for efficient deoxyfluorination (Fig. 3a), which, a priori, renders PhenoFluor-mediated deoxyfluorination effectively useless for ^{18}F chemistry. Even attempts towards a low-specific activity radiodeoxyfluorination initially proved fruitless: Both isolated reaction intermediate **1** (and derivatives featuring different counteranions) and tetrahedral intermediate **2** did not react with external ^{18}F -fluoride to yield ^{18}F -aryl fluoride products (Fig. 3 b, c). Mechanistic work (supplementary information) revealed that fluoride was not incorporated into tetrahedral intermediate **2** *via* attack by external fluoride on uronium **1** or anion metathesis; instead the fluoride on the aryl fluoride originated from PhenoFluor. We thus devised a strategy to alter the mechanism of fluoride incorporation into **2** to access ^{18}F -**2** in high specific activity: While anion exchange of **1** with ^{18}F does not occur in solution, productive anion exchange occurs on an anion exchange cartridge (Fig. 3d).

^{18}F -Fluoride is typically prepared by proton bombardment of $^{18}\text{O}\text{-H}_2\text{O}$, and ^{18}F -fluoride is subsequently trapped on an ion exchange cartridge. Elution of the radioisotope is commonly achieved with an aqueous solution of a base.²⁰ Here we can use uronium **5** directly for elution of ^{18}F -fluoride from the anion exchange cartridge. Uronium **5** can readily be prepared from chloroimidazolium chloride **4** and a suitable phenol and used after simple filtration. The elution procedure obviates the need for azeotropic drying of ^{18}F -fluoride, and subsequent heating of the resulting solution of ^{18}F -**2** directly provides aryl fluoride.

No special care is required to exclude air or moisture from the ^{18}F -deoxyfluorination reaction, and the radiolabeled product can be conveniently separated from the reaction

precursor. A wide variety of functional groups including amines and phenols as well as thioethers and amides are tolerated, and arenes as well as heteroarenes undergo radio-deoxyfluorination with high radiochemical conversion (Fig. 4a). Substrates containing carboxylic acids did not undergo ^{18}F -deoxyfluorination because carboxylic acids inhibit the formation of uronium **5**. Competing nucleophilic aromatic substitution of activated chloride does not occur under the reaction conditions. Classical $\text{S}_{\text{N}}\text{Ar}$ chemistry is the most widely applied method for the synthesis of PET probes but suffers from a very limited reaction scope, and protic functional groups are commonly not tolerated. Modern methods,^{26–30} while capable of introducing ^{18}F -fluoride into a more diverse range of structures, often suffer from the need for complex starting materials, operating- or purification procedures. Heterocycles are present in many bioactive compounds but are often problematic substrates for metal-mediated fluorination protocols with ^{18}F ; several heterocycles undergo PhenoFluor deoxyfluorination with high radiochemical conversion. To highlight the operational simplicity of ^{18}F -deoxyfluorination, ^{18}F -5-fluorobenzofurazan was synthesized from 34 mCi aqueous ^{18}F -fluoride and subjected to HPLC purification. Within 34 minutes from the end of bombardment, 9.3 mCi of isolated and purified ^{18}F -5-fluorobenzofurazan could be obtained in 27% non-decay-corrected radiochemical yield (RCY) with a specific activity of $3.03 \text{ Ci} \times \mu\text{mol}^{-1}$.

We have established that tetrahedral intermediate **2** is in equilibrium with uronium fluoride **6** (Fig. 4b, supplementary information Fig. S36). Clean first order decay of **2** was observed in the presence of added fluoride, but a marked deviation from first order kinetics was observed for the deoxyfluorination of silylated phenols in the absence of added fluoride. Hence, the fluoride anion in **6** likely engages in unproductive processes, such as precipitation or other fluoride sequestrations. In ^{19}F deoxyfluorination, excess CsF negates such potential side reactions, but for radiofluorination, fluoride is present in small quantities (nmol). For most compounds shown in Figure 4, potential decomposition of **2** does not disrupt productive fluorination, but when more electron-rich phenols are employed, the equilibrium constant K between **6** and tetrahedral intermediate **2** decreases. We have already shown that more electron-rich substrates can afford acceptable radiochemical conversions, when the conversion is based on soluble fluoride (Fig. 4b). While fluoride sequestration from **6** currently precludes the isolation of electron-rich ^{18}F aryl fluorides in high radiochemical yields, efficient $\text{C}-^{18}\text{F}$ bond formation bodes well for mechanism-based strategies to increase K , that would render electron-rich arenes accessible.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

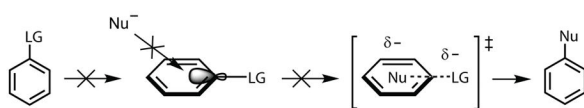
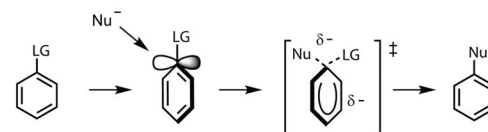
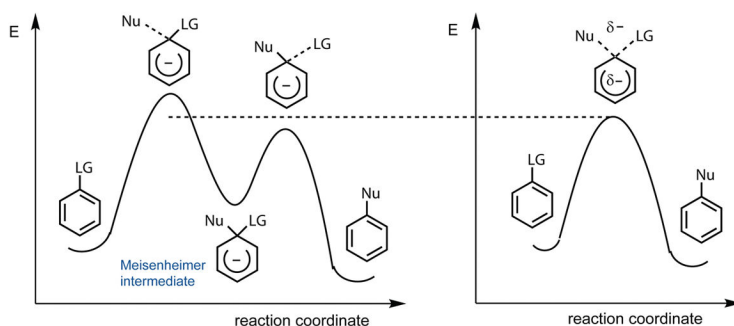
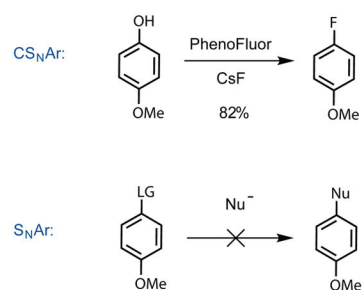
Acknowledgments

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a Potential Concerted Nucleophilic Aromatic Substitution Pathways σ^* pathway π^* pathway**b** S_NAr CS_NAr **c****Figure 1. Comparison of orbital interactions and energy profiles in S_NAr and CS_NAr**

a: The aromatic ring blocks the approach of the nucleophile to the σ^*_{C-LG} orbital; attack on the π -framework is feasible. **b:** The energy profiles of S_NAr and CS_NAr differ in the number of transition states and in the magnitude of the activation energies. **c:** Minimization of charge build-up in the transition state renders nucleophilic displacement feasible even on electron-rich arenes in CS_NAr reactions.

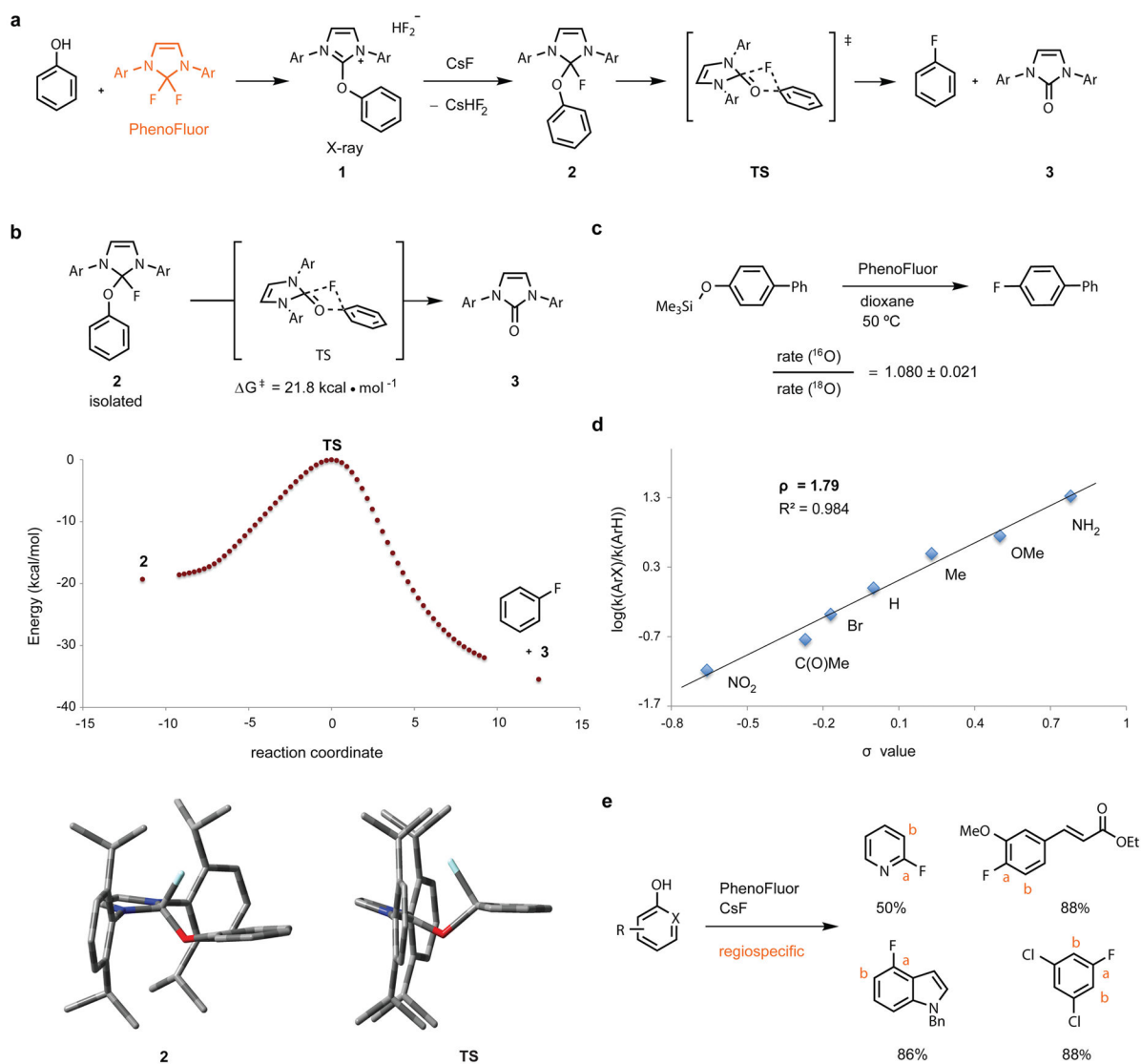


Figure 2. Proposed mechanism of PhenoFluor-mediated deoxyfluorination

a Following formation of uronium intermediate **1**, external CsF abstracts HF to form tetrahedral adduct **2**, which undergoes concerted nucleophilic substitution *via* fluoride shift (Ar = 2,6-diisopropylphenyl). **b** The intrinsic reaction coordinate obtained from DFT calculations (B3LYP/6-31G(d), toluene solvent model) shows a single barrier between tetrahedral adduct **2** and reaction products (Ar = 2,6-diisopropylphenyl). Structures obtained from DFT calculations are shown for **2** and TS. $G^\ddagger = 21.8 \pm 0.2 \text{ kcal} \cdot \text{mol}^{-1}$ was measured for the transformation of **2** to aryl fluoride and urea **3**. **c** The primary $^{16}\text{O}/^{18}\text{O}$ kinetic isotope effect is consistent with cleavage of the C–O bond during the rate-limiting step (supplementary information, Fig. S15). Silylated phenols react with PhenoFluor to form tetrahedral intermediate without CsF. **d** Hammett plot for the deoxyfluorination of *para*-substituted phenols at 110 °C. **e** Regioselective product formation occurs for substrates prone to nucleophilic attack at position **b** if arynes were formed.^{4,17}

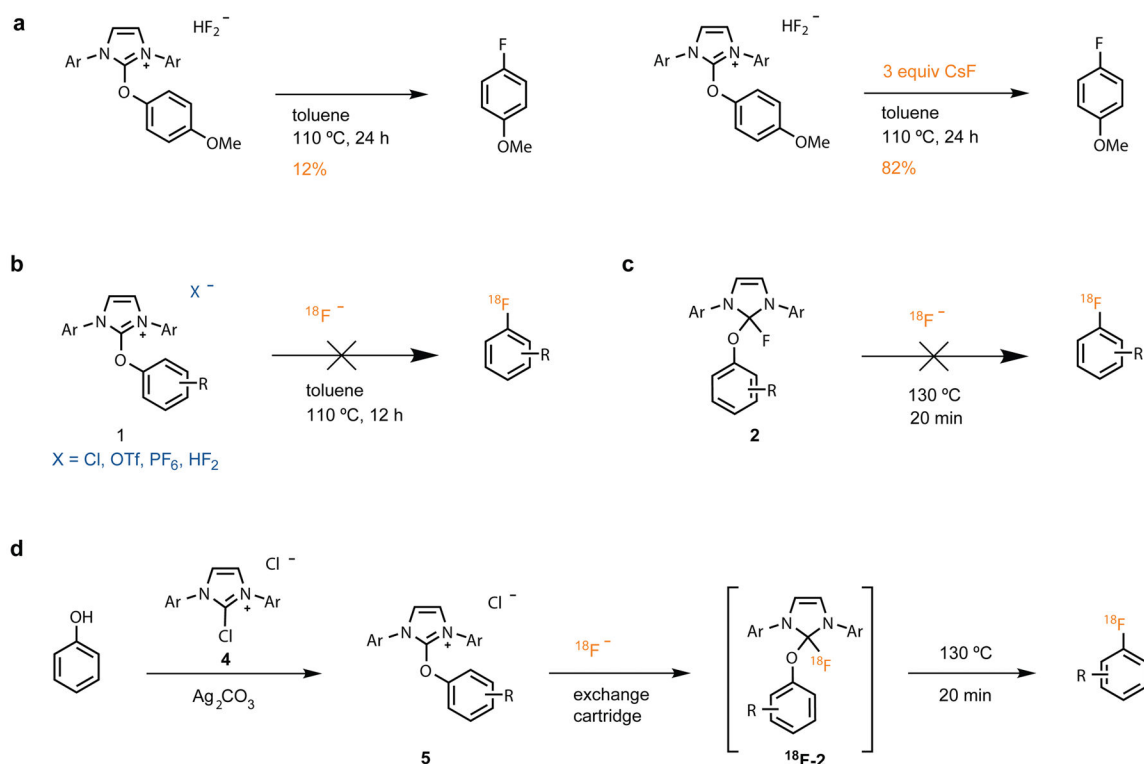


Figure 3. ^{18}F isotopologue 2

a CsF abstracts HF from the HF_2 counteranion: without CsF , deoxyfluorination occurs *via* a different mechanism in which HF_2 attacks the arene. DFT studies reveal that the barrier for C–F bond formation is 6.0 kcal/mol lower with a fluoride instead of a bifluoride nucleophile (see supplementary information Fig. S29). **b** Treatment of uronium **1** with ^{18}F does not give aryl fluoride due to the lack of anion exchange between X and ^{18}F -fluoride in solution. **c** No ^{18}F incorporation is observed. **d** Anion exchange with extraneous fluoride takes place on an anion exchange cartridge ($\text{Ar} = 2,6$ -diisopropylphenyl).

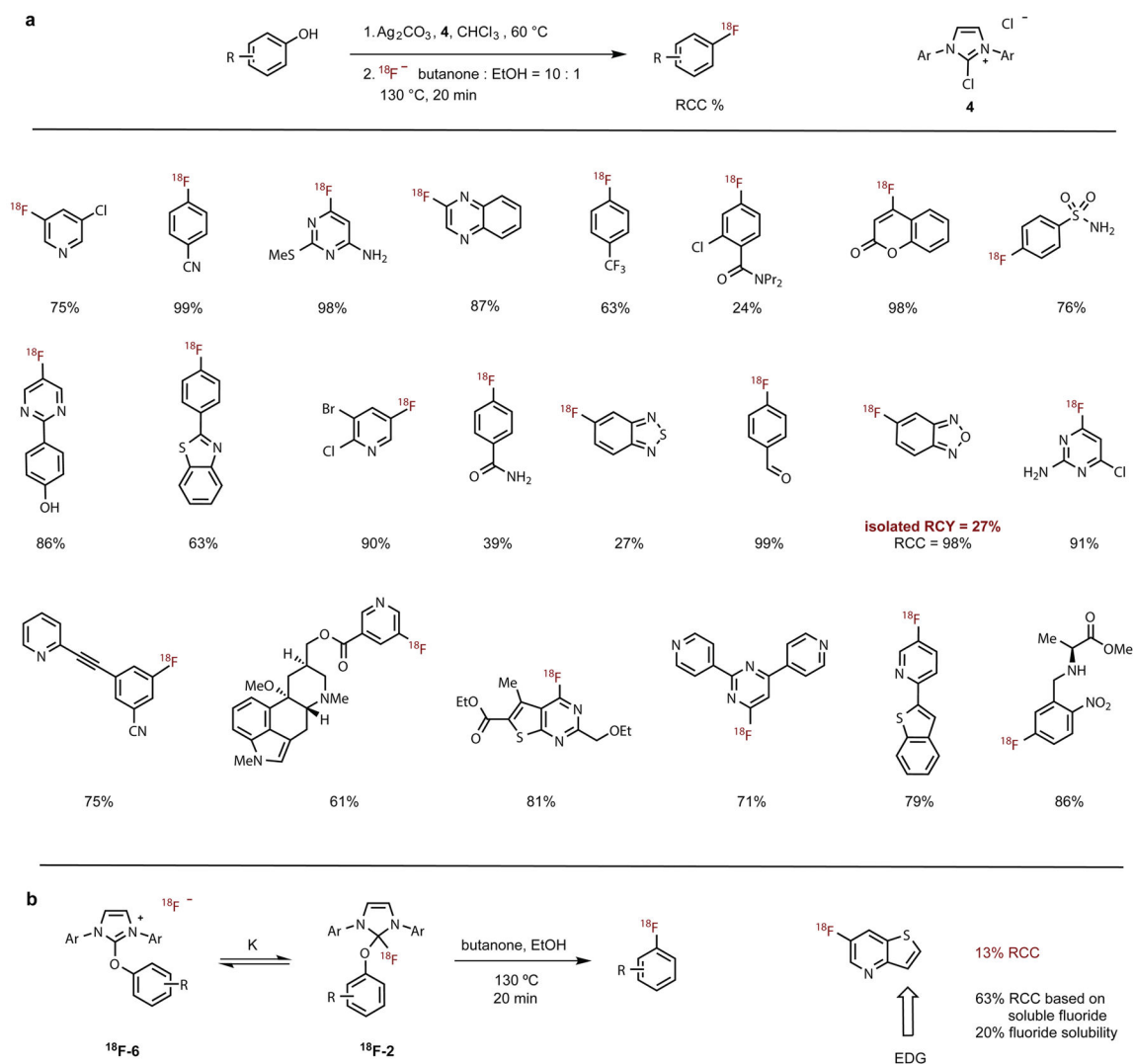


Figure 4. Deoxyfluorination of phenols and heterophenols with ^{18}F

a Decay-corrected radiochemical conversions were determined by comparing the amount of ^{18}F incorporated into the product to the amount of ^{18}F not incorporated. **b** Electron-rich phenols will result in a smaller equilibrium constant K , resulting in fluoride expulsion and decomposition before productive deoxyfluorination from tetrahedral intermediate $^{18}\text{F-2}$ can occur. (Ar = 2,6-diisopropylphenyl).