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Radiochemistry

# Expedient Access to $^{18}$F-Fluoroheteroarenes via Deaminative Radiofluorination of Aniline-Derived Pyridinium Salts

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**Abstract:** Herein, we disclose that pyridinium salts derived from abundant (hetero)anilines represent a novel precursor class for nucleophilic aromatic substitution reactions with [$^{18}$F]fluoride. The value of this new $^{18}$F-fluorodeamination is demonstrated with the synthesis of over 30 structurally diverse and complex heteroaryl $^{18}$F-fluorides, several derived from scaffolds that were yet to be labelled with fluorine-18. The protocol tolerates heteroarenes and functionalities commonly found in drug discovery libraries, and is amenable to scale-up and automation on a commercial radiosynthesiser.

Positron emission tomography (PET) imaging is a powerful modality for the monitoring and quantification of in vivo physiological processes.[1] PET has found applications in clinical settings for disease diagnosis and therapy assessment, and to guide drug discovery programmes.[2] PET requires molecules labelled with a positron-emitting nuclide, often fluorine-18, due to its outstanding decay properties (109.8 min half-life, 97 % $\beta^+$ decay, 0.63 MeV positron energy).[3] The advent of total body PET, combined with the increasing demand for new radioligands, continue to spur innovation in radiochemistry, a common bottleneck in (pre)clinical radiotracer development.[4] In recent years, numerous methods have emerged for the installation of fluorine-18 onto various scaffolds, more specifically $^{18}$F-fluoroarenes that are now accessible from a broad range of precursor types.[5] Although several of these methods have been automated and made GMP-compliant,[6] wide adoption of these technologies has been slow. To maximise translatability of new methodologies to the production of (pre)clinical tracers, ubiquitous substrate classes amenable to rapid library generation are ideal, preferably minimising the need for metals or other additives, thus simplifying subsequent purification and quality control protocols.

For this reason, radiochemistry practitioners often apply easily implementable nucleophilic aromatic substitution ($S_NAr$) reactions with [$^{18}$F]fluoride in the radiofluorination of (hetero)arenes, most commonly pyridines.[3,5a–c,7] While several leaving groups can be utilised including halides and nitro groups, trialkylammonium salts have prevailed as substrates for radiotracer production, including the FDA-approved [$^{18}$F]piflufolastat and [$^{18}$F]flortaucipir (Figure 1A).[8] These precursors display excellent substitution reactivity, and are easily separated from neutral radiolabelled products. However, the commercial availability of these compounds is limited and chemical synthesis can be challenging. Moreover, side-reactivity of trimethylammonium salts has also been reported during $^{18}$F-fluorination, with gaseous [$^{18}$F]fluoromethane produced in competitive $S_N2$ processes.[9]

In response to these constraints, our aim was to develop a protocol to convert readily available (hetero)anilines into structurally diverse and functional $^{18}$F-fluorinated heteroarenes to accelerate PET ligand discovery. In our reaction design, we embraced the reactivity of (hetero)aryl pyridinium salts known as powerful synthetic intermediates for deaminative functionalisation.[10] These salts can either be isolated or prepared in situ, thereby offering the possibility of a one-pot $^{18}$F-fluorodeamination protocol. Moreover, the ionic nature of pyridinium salts could enable elution of [$^{18}$F]fluoride from ion-exchange cartridges in the absence of weak bases and/or phase-transfer catalysts through ion pairing with [$^{18}$F]fluoride.[11] The excess of charged pyridinium salt precursor should therefore be easy to separate from neutral $^{18}$F-products. Finally, the wealth of methods available for the synthesis of pyridinium salts is a key advantage. The late-stage condensation of ubiquitous primary amine precursors with commercial pyrylium reagents

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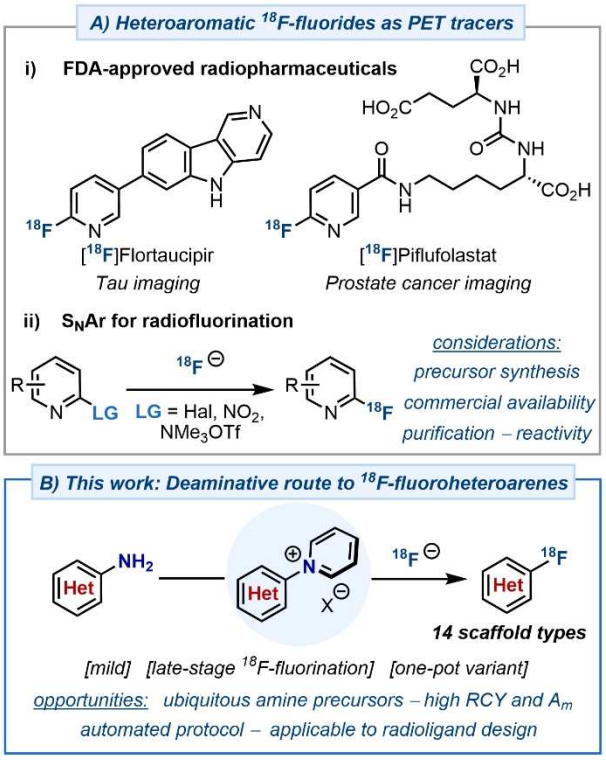



***Figure 1.*** A) i) Heteroaryl $^{18}$F-fluorides as PET radiotracers. ii) $S_NAr$ for $^{18}$F-fluorination (LG = leaving group, Hal = halide). B) This work: $^{18}$F-fluoroheteroarenes via deaminative fluorination (X = $BF_4^-$).

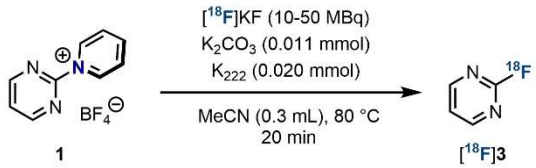
is well explored and offers an expedient approach to pyridinium salts.[10]

We noted only two examples of fluorodeamination applied to $^{18}$F-labelling. Murphy and co-workers reported the $^{18}$F-fluorination of aryl sydnones, prepared from the corresponding aniline in two steps.[12] Also, Riss and co-workers reported a Cu-mediated Sandmeyer-type $^{18}$F-fluorination of diazonium salts, which were formed in situ from anilines with amyl nitrite.[13] These methods were applied to the radiosynthesis of simple $^{18}$F-fluoroarenes, but application to diverse complex heteroaryl $^{18}$F-fluorides has not been demonstrated. Herein, we report that $^{18}$F-fluoroheteroarenes representative of the structural diversity of pharmaceutical drugs are readily accessible upon radiolabelling of pyridinium salts prepared from (hetero)anilines (Figure 1B).

Cornella and co-workers demonstrated in their study on deaminative halogenation that heteroaryl pyridinium tetrafluoroborates were reactive towards rigorously dried KF in excess (2 equiv.).[10f,14] Direct translation of these conditions to $^{18}$F-radiochemistry is complicated by several factors that perturb both reactivity and reaction kinetics.[15] The $^{18}$F-labelled component is used in minute quantities (nano- to picomolar concentrations) compared to vast excesses of labelling precursor, elution bases and/or phase-transfer reagents. The latter are used during the separation of [$^{18}$F]fluoride from target water, and the super-stoichiometric amounts of these reagents have been shown in some instances to complicate reaction scale-up. Preliminary experiments therefore focused on assessing whether pyridinium salts remain suitable electrophiles in $S_NAr$ reactions with [$^{18}$F]fluoride. For initial studies, we selected 1-(pyrimidin-2-yl)pyridin-1-ium tetrafluoroborate (**1**) prepared via a condensation of 2-aminopyrimidine (**2**) with pyrylium tetrafluoroborate. First experiments with **1** using an aliquot (10–50 MBq) of [$^{18}$F]KF/$K_{222}$ in MeCN gave no desired product (Table 1, entry 1). Extensive investigation led us to find that an increase in the concentration of the elution reagents $K_2CO_3$ and $K_{222}$ was crucial to reactivity and thus, reacting **1** with [$^{18}$F]fluoride in the presence of these elution additives at 80 °C in MeCN yielded [$^{18}$F]2-fluoropyrimidine ([$^{18}$F]**3**) in 88 % radiochemical yield as determined by radio-HPLC analysis of the crude reaction ($RCY_{HPLC}$) (Table 1, entry 2). The observation that these common elution additives enabled $^{18}$F-incorporation boded well for scale-up and automation. Polar aprotic solvents such as DMF, DMSO and MeCN provided [$^{18}$F]**3** in excellent $RCY_{HPLC}$ (Table 1, entries 2–4). Polar protic solvents such as EtOH and MeOH were less effective (Table 1, entries 5–6). The reaction proceeded at 50 °C, yielding [$^{18}$F]**3** in 67 % $RCY_{HPLC}$, and even at 30 °C, [$^{18}$F]**3** still formed in 13 % $RCY_{HPLC}$ (Table 1, entries 7–8). For comparison, [$^{18}$F]**3** and other radiofluorinated heteroarenes were not within reach under Cu-mediated Sandmeyer-type conditions (Scheme S6), a result highlighting the radiosynthetic value of this novel pyridinium-based $^{18}$F-fluorodeamination.[13]

The tolerance of the reaction to ubiquitous functional groups was assessed using an additive-based robustness screening approach.[16] Under the optimised reaction conditions using **1**, various additives (1 equiv.) were spiked into the reaction mixture to study their effect on $RCY_{HPLC}$. The reaction tolerates diverse functionalities including oxygen-, nitrogen- and sulfur-based groups, as well as a range of FDA-approved pharmaceuticals (Scheme S2). Nitrogen atoms protected as carbamates, or substituted with an electron-withdrawing group, such as those incorporated in

***Table 1:*** $^{18}$F-Fluorination of model pyridinium tetrafluoroborate **1**.[a]

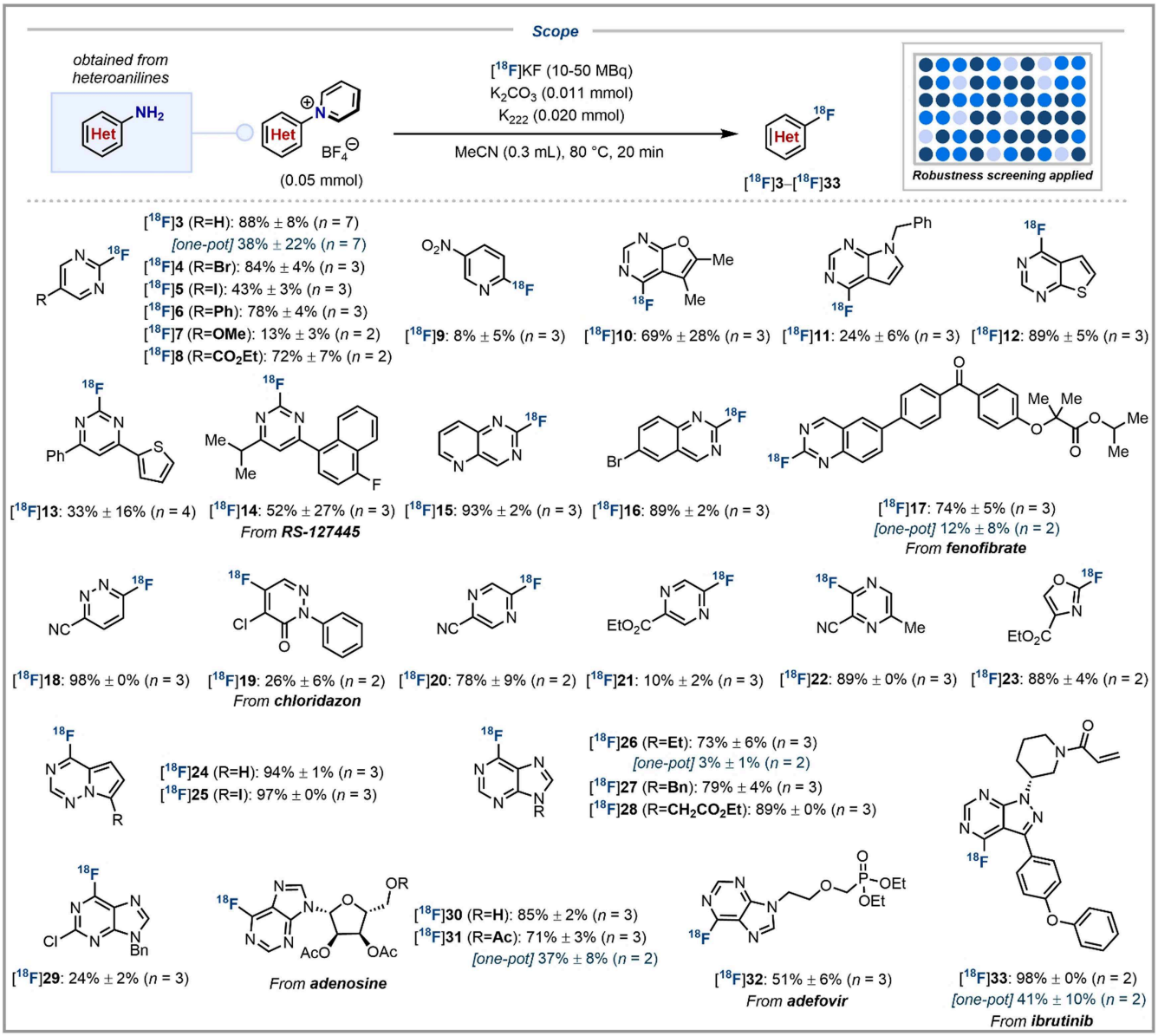



| Entry | Deviation from standard conditions | $RCY_{HPLC}$ [b] |
|---|---|---|
| 1 | No additional $K_2CO_3$ and $K_{222}$ | 0 % ($n=1$) |
| 2 | None | 88 % ± 8 % ($n=7$) |
| 3 | DMF as solvent | 85 % ($n=1$) |
| 4 | DMSO as solvent | 94 % ($n=1$) |
| 5 | EtOH as solvent | 56 % ($n=1$) |
| 6 | MeOH as solvent | 7 % ($n=1$) |
| 7 | Reaction at 50 °C | 67 % ($n=1$) |
| 8 | Reaction at 30 °C | 13 % ($n=1$) |

[a] **1** (0.05 mmol). [$^{18}$F]KF prepared with a $K_2CO_3$ (0.011 mmol)-$K_{222}$ (0.020 mmol) elution protocol and aliquots of this were dispensed as a solution in MeCN. [b] $RCY_{HPLC}$: radiochemical yield as determined by radio-HPLC analysis of crude reaction mixtures.

phthalimide, sulfonamide or amide moieties, were well tolerated. As expected, strongly nucleophilic functional groups such as secondary alkyl amines, thiophenols and phenols were problematic as these likely competed with [$^{18}$F]fluoride to react with the substrate. Free acids were not tolerated, likely consuming the $K_2CO_3$ elution base, which we demonstrate promotes radiofluorination (Table 1, entry 2). With the aim to implement a one-pot radiofluorination of amines, the reagents used to prepare pyridinium salts from amines were also considered in the robustness study. While heteroaniline **2** was well tolerated as a spiking additive, the addition of pyrylium tetrafluoroborate resulted in no formation of [$^{18}$F]**3**; as expected, no desired radiofluorination took place when a one-pot $^{18}$F-fluorodeamination sequence was attempted with 1 equiv. of both 2-aminopyrimidine (**2**) and pyrylium tetrafluoroborate. However, upon increasing the loading of **2** to ensure complete consumption of the pyrylium reagent and further optimisation of the solvents used for the condensation and radiofluorination, reactivity was restored leading to [$^{18}$F]**3** in 38 % $RCY_{HPLC}$ ($n=7$), albeit in lower yield than for the direct $^{18}$F-fluorination of **1** (Table S3).

With the optimised reaction conditions and the data from the robustness screening in hand, we next applied our protocol to the radiosynthesis of structurally diverse heteroaromatic $^{18}$F-fluorides, including complex bioactive molecules (Scheme 1). Pyridinium tetrafluoroborate salts were prepared by condensation of heteroanilines with pyrylium tetrafluoroborate in variable yields (31–85 %) in line with literature precedents.[10] Substrates derived from pyrimidines

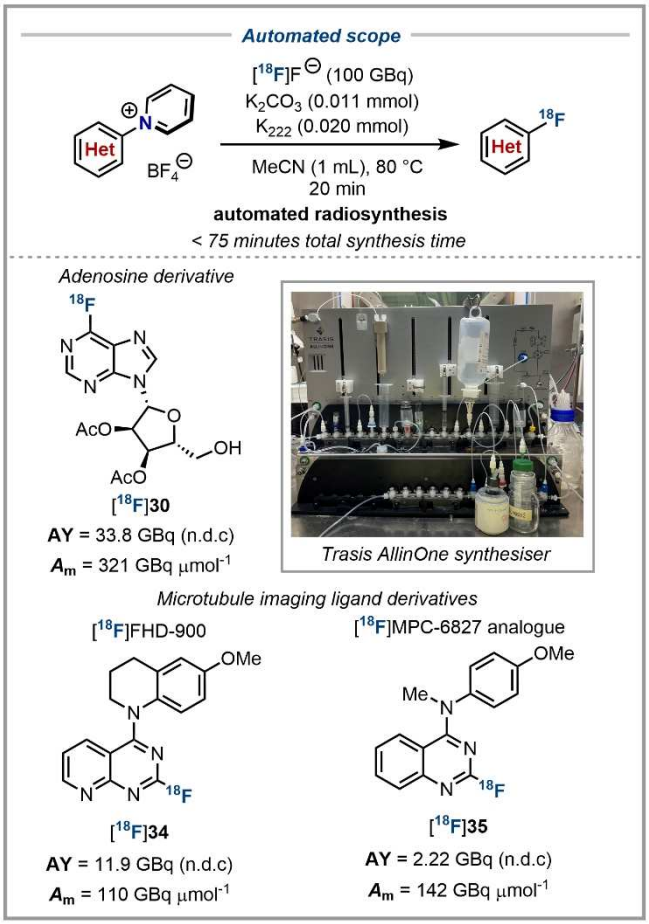



***Scheme 1.*** Scope of the radiofluorination of heteroaryl pyridinium salts. Radiochemical yields were determined by radio-HPLC analysis of the crude reaction mixture ($RCY_{HPLC}$). One-pot $RCY_{HPLC}$ data are indicated, where the reaction gave the desired product (Scheme S4) (see SI for details).

performed well and substitution at the 5-position with a range of electronically differentiated functionalities was tolerated, in 13 %–88 % $RCY_{HPLC}$ ([$^{18}$F]**3**-[$^{18}$F]**8**). Substrates derived from pyridines proved more challenging (e.g. [$^{18}$F]**9**), however given that previous studies focused their attention on the radiofluorination of pyridines and quinolines,[7j–m] we instead directed our efforts towards the radiosynthesis of other classes of $^{18}$F-fluoroheteroarenes. Thieno-, furo- and pyrrolo-fused pyrimidines reacted in up to 89 % $RCY_{HPLC}$ ([$^{18}$F]**10**-[$^{18}$F]**12**). Such structures are of interest for microtubule imaging and these scaffolds have not been previously radiolabelled at the 6-position.[17] More elaborate pyrimidine scaffolds derived from amines with biological activity were radiofluorinated in good yield (e.g. [$^{18}$F]**13**, 33 % $RCY_{HPLC}$). An $^{18}$F-fluorinated derivative of the bioactive compound RS-127445 ([$^{18}$F]**14**), a 5-HT receptor antagonist used in the treatment of gastrointestinal disorders, was prepared in 52 % $RCY_{HPLC}$.[18] Various quinazoline-derived pyridinium salts were found to be amenable to $^{18}$F-labelling under our conditions ([$^{18}$F]**15**-[$^{18}$F]**16**, up to 93 % $RCY_{HPLC}$). In addition to this, the antilipidemic agent fenofibrate was functionalised with a 2-aminoquinazoline fragment and the resulting pyridinium salt was radiofluorinated in good yield ([$^{18}$F]**17**, 74 % $RCY_{HPLC}$). Other diazine scaffolds, including pyridazines ([$^{18}$F]**18**-[$^{18}$F]**19**, up to 98 % $RCY_{HPLC}$) and pyrazines ([$^{18}$F]**20**-[$^{18}$F]**22**, 10–89 % $RCY_{HPLC}$) underwent radiofluorination in moderate to excellent yield. The transformation was applicable to 5-membered heterocycles including [$^{18}$F]ethyl-2-fluoro-oxazole-4-carboxylate ([$^{18}$F]**23**), which was obtained in 88 % $RCY_{HPLC}$. A pyridinium tetrafluoroborate derived from pyrrolo[2,1-*f*]-[1,2,4]triazine was $^{18}$F-fluorinated at the 4-position in 94 % $RCY_{HPLC}$ ([$^{18}$F]**24**), as well as an iodinated derivative of the same scaffold ([$^{18}$F]**25**) in 97 % $RCY_{HPLC}$. This scaffold present in the antiviral drug remdesivir has not previously been radiofluorinated. Adenine and purine-derived scaffolds were radiofluorinated in excellent yields and could be substituted at the 9-position with various groups, without a detrimental impact on radiochemical yield ([$^{18}$F]**26**-[$^{18}$F]**28**, up to 89 % $RCY_{HPLC}$). When the 2-position was substituted with chlorine, which may be reactive towards [$^{18}$F]fluoride under $S_NAr$, chemoselective conversion to the 6-$^{18}$F-product was observed, with no side reactivity due to substitution of chloride ([$^{18}$F]**29**). Di- and tri-acetylated adenosines were subjected to our $^{18}$F-fluorodeamination protocol and the desired product ([$^{18}$F]**30**-[$^{18}$F]**31**) was formed in 85 % and 71 % $RCY_{HPLC}$, respectively. A pyridinium tetrafluoroborate salt derived from an antiviral agent used in the treatment of hepatitis B, adefovir diethyl ester, was radiofluorinated in 51 % $RCY_{HPLC}$ ([$^{18}$F]**32**). The tyrosine kinase inhibitor ibrutinib, which is used in the treatment of leukemia and lymphoma, was successfully transformed into an $^{18}$F-labelled analogue in 98 % $RCY_{HPLC}$ ([$^{18}$F]**33**).

Pyridinium salts being ionic species, we next investigated their ability to act as [$^{18}$F]fluoride elution bases, in place of conventional elution and drying protocols with inorganic bases, such as $K_2CO_3$; this latter process can indeed be time consuming, resulting in activity losses to decay. Building on the work of the groups of Ritter, Neumeier and Zlatopolskiy with other ionic substrates,[19] we found that the pyridinium salt **1** in methanol can elute [$^{18}$F]fluoride from a Waters Sep-Pak QMA Carbonate cartridge, with good elution efficiency (88 %) (Table S4). Furthermore, a solvent exchange to MeCN allowed for direct radiofluorination of **1** in up to 40 % $RCY_{HPLC}$, and in up to 81 % $RCY_{HPLC}$ in the presence of additional **1**, $K_2CO_3$ and $K_{222}$ additives (Table S8).

For the production of (pre)clinically relevant tracers, it is important that this methodology is amenable to multi-GBq production and automation. We therefore next turned our attention to the automated radiosynthesis of heteroaromatic $^{18}$F-fluorides using a Trasis AllinOne radiosynthesiser. After testing the automated program for the radiosynthesis of [$^{18}$F]**3**, this was then applied to the preparation of three bioactive heteroaromatic $^{18}$F-fluorides (Scheme 2). Starting from 100 GBq of [$^{18}$F]fluoride, [$^{18}$F]**30** was prepared from the requisite pyridinium salt in an activity yield (AY) of 33.8 GBq (non-decay corrected) and in high radiochemical purity (>98 %). The molar activity of the obtained product was high ($A_m$ = 321 GBq μmol$^{-1}$), corroborating an earlier experiment, where subjecting **1** to the reaction conditions in the absence of [$^{18}$F]fluoride showed no formation of **3** by $^{19}$F




***Scheme 2.*** Automated radiofluorination of heteroaryl pyridinium salts and application to radiotracer synthesis. AY (n.d.c.) = activity yield, non-decay corrected; $A_m$ = molar activity. Automated radiosynthesis was achieved using a Trasis AllinOne radiosynthesiser.

NMR (Figure S11). This suggests that isotope exchange with the tetrafluoroborate counterion is not competitive with the desired $^{18}$F-fluorination, a result consistent with a previous report on the radiofluorination of aryliodonium tetrafluoroborate salts.[20] Furthermore, two molecules with potential application in microtubule imaging were prepared using the same automated program; [$^{18}$F]FHD-900 ([$^{18}$F]**34**, AY = 11.9 GBq, $A_m$ = 110 GBq μmol$^{-1}$) and an $^{18}$F-analogue of [$^{11}$C]MPC-6827 ([$^{18}$F]**35**, AY = 2.22 GBq, $A_m$ = 142 GBq μmol$^{-1}$).[17,21]

Nucleophilic aromatic substitution is a high value disconnection for the synthesis of radiofluorinated compounds and PET radiotracers that can be readily implemented in PET centres. This work introduces (hetero)aniline-derived pyridinium salts as a new class of reactive and versatile precursors for $S_NAr$ with [$^{18}$F]fluoride. The technology enables efficient $^{18}$F-labelling under mild conditions of diverse and structurally complex heteroarenes, commonly found in drug discovery. The reaction is easy to scale up and automate on a commercial radiosynthesiser, and can therefore be immediately adopted to advance PET ligand discovery. Considering that pyridinium salts are readily prepared from a diverse pool of precursors other than primary amines, we anticipate this technology to advance $^{18}$F-radiochemistry far beyond fluorodeamination.[22]

## Supporting Information

The authors have cited additional references within the Supporting Information.[23–32]

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## Conflict of Interest

The authors declare no conflict of interest.

## Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

**Keywords:** Fluorine · Radiochemistry · Heterocycles · Nucleophilic substitution · Radiopharmaceuticals

[1] S. M. Ametamey, M. Honer, P. A. Schubiger, *Chem. Rev.* **2008**, *108*, 1501.
[2] a) J. K. Willmann, N. van Bruggen, L. M. Dinkelborg, S. S. Gambhir, *Nat. Rev. Drug Discovery* **2008**, *7*, 591; b) P. M. Matthews, E. A. Rabiner, J. Passchier, R. N. Gunn, *Br. J. Clin. Pharmacol.* **2012**, *73*, 175; c) L. Zhang, A. Villalobos, *EJNMMI Radiopharm. Chem.* **2017**, *1*, 13; d) S. G. Nerella, P. Singh, T. Sanam, C. S. Digwal, *Front. Med.* **2022**, *9*, 812270.
[3] a) X. Deng, J. Rong, L. Wang, N. Vasdev, L. Zhang, L. Josephson, S. H. Liang, *Angew. Chem. Int. Ed.* **2019**, *58*, 2580; b) J. Rong, A. Haider, T. E. Jeppesen, L. Josephson, S. H. Liang, *Nat. Commun.* **2023**, *14*, 3257.
[4] a) S. Reardon, *Nature* **2019**, *570*, 285; b) M. G. Campbell, J. Mercier, C. Genicot, V. Gouverneur, J. M. Hooker, T. Ritter, *Nat. Chem.* **2017**, *9*, 1.
[5] a) M. Tredwell, V. Gouverneur, *Angew. Chem. Int. Ed.* **2012**, *51*, 11426; b) A. F. Brooks, J. J. Topczewski, N. Ichiishi, M. S. Sanford, P. J. H. Scott, *Chem. Sci.* **2014**, *5*, 4545; c) S. Preshlock, M. Tredwell, V. Gouverneur, *Chem. Rev.* **2016**, *116*, 719; d) J. S. Wright, T. Kaur, S. Preshlock, S. S. Tanzey, W. P. Winton, L. S. Sharninghausen, N. Wiesner, A. F. Brooks, M. S. Sanford, P. J. H. Scott, *Clin. Transl. Imaging* **2020**, *8*, 167; e) R. Halder, T. Ritter, *J. Org. Chem.* **2021**, *86*, 13873; f) J. Ajenjo, G. Destro, B. Cornelissen, V. Gouverneur, *EJNMMI Radiopharm. Chem.* **2021**, *6*, 33.
[6] T. Gendron, G. Destro, N. J. W. Straathof, J. B. I. Sap, F. Guibbal, C. Vriamont, C. Caygill, J. R. Atack, A. J. Watkins, C. Marshall, R. Hueting, C. Warnier, V. Gouverneur, M. Tredwell, *EJNMMI Radiopharm. Chem.* **2022**, *7*, 5.
[7] a) G. C. Finger, C. W. Kruse, *J. Am. Chem. Soc.* **1956**, *78*, 6034; b) M. S. Berridge, C. Crouzel, D. Comar, *J. Label. Compd. Radiopharm.* **1985**, *22*, 687; c) G. Angelini, M. Speranza, A. P. Wolf, C.-Y. Shiue, *J. Fluorine Chem.* **1985**, *27*, 177; d) M. S. Haka, M. R. Kilbourn, G. L. Watkins, S. A. Toorongian, *J. Label. Compd. Radiopharm.* **1989**, *27*, 823; e) D. J. Adams, J. H. Clark, *Chem. Soc. Rev.* **1999**, *28*, 225; f) L. Dolci, F. Dollé, S. Jubeau, F. Vaufrey, C. Crouzel, *J. Label. Compd. Radiopharm.* **1999**, *42*, 975; g) S. D. Kuduk, R. M. DiPardo, M. G. Bock, *Org. Lett.* **2005**, *7*, 577; h) H. Sun, S. G. DiMagno, *Angew. Chem. Int. Ed.* **2006**, *45*, 2720; i) S. D. Schimler, S. J. Ryan, D. C. Bland, J. E. Anderson, M. S. Sanford, *J. Org. Chem.* **2015**, *80*, 12137; j) P. Brugarolas, R. Freifelder, S.-H. Cheng, O. DeJesus, *Chem. Commun.* **2016**, *52*, 7150; k) G. R. Naumiec, L. Cai, S. Lu, V. W. Pike, *Eur. J. Org. Chem.* **2017**, *2017*, 6593; l) S. J. Lee, M. T. Morales-Colón, A. F. Brooks, J. S. Wright, K. J. Makaravage, P. J. H. Scott, M. S. Sanford, *J. Org. Chem.* **2021**, *86*, 14121; m) M. T. Morales-Colón, Y. Y. See, S. J. Lee, P. J. H. Scott, D. C. Bland, M. S. Sanford, *Org. Lett.* **2021**, *23*, 4493; n) C. M Hong, A. M. Whittaker, D. M. Schultz, *J. Org. Chem.* **2021**, *86*, 3999.
[8] Selected radiosynthetic examples using nitro, halide and trimethylammonium precursors. a) F. Dollé, L. Dolci, H. Valette, F. Hinnen, F. Vaufrey, I. Guenther, C. Fuseau, C. Coulon, M. Bottlaender, C. Crouzel, *J. Med. Chem.* **1999**, *42*, 2251; b) R. Smits, S. Fischer, A. Hiller, W. Deuther-Conrad, B. Wenzel, M. Patt, P. Cumming, J. Steinbach, O. Sabri, P. Brust, A. Hoepping, *Bioorg. Med. Chem.* **2014**, *22*, 804; c) A. V. Mossine, A. F. Brooks, B. D. Henderson, B. G. Hockley, K. A. Frey, P. J. H. Scott, *EJNMMI Radiopharm. Chem.* **2017**, *2*, 7; d) Y.-Y. Huang, M.-J. Chiu, R.-F. Yen, C.-L. Tsai, H.-Y. Hsieh, C.-H. Chiu, C.-H. Wu, L.-W. Hsin, K.-Y. Tzen, C.-Y. Cheng, K.-H. Ma, C.-Y. Shiue, *PLoS ONE* **2019**, *14*, e0217384; e) D. E. Olberg, J. M. Arukwe, D. Grace, O. K. Hjelstuen, M.

Solbakken, G. M. Kindberg, A. Cuthbertson, *J. Med. Chem.* **2010**, *53*, 1732; f) Z. Szabo, E. Mena, S. P. Rowe, D. Plyku, R. Nidal, M. A. Eisenberger, E. S. Antonarakis, H. Fan, R. F. Dannals, Y. Chen, R. C. Mease, M. Vranesic, A. Bhatnagar, G. Sgouros, S. Y. Cho, M. G. Pomper, *Mol. Imaging Biol.* **2015**, *17*, 565; g) V. Bouvet, M. Wuest, H.-S. Jans, N. Janzen, A. R. Genady, J. F. Valliant, F. Benard, F. Wuest, *EJNMMI Res.* **2016**, *6*, 40; h) M. H. Dornan, J.-M. Simard, A. Leblond, D. Juneau, G. Delouya, F. Saad, C. Ménard, J. N. DaSilva, *J. Label. Compd. Radiopharm.* **2018**, *61*, 757.

[9] H. Sun, S. G. DiMagno, *J. Fluorine Chem.* **2007**, *128*, 806.

[10] a) A. R. Katritzky, *Tetrahedron* **1980**, *36*, 679; b) A. R. Katritzky, C. M. Marson, *Angew. Chem. Int. Ed.* **1984**, *23*, 420; c) F.-S. He, S. Ye, J. Wu, *ACS Catal.* **2019**, *9*, 8943; d) S. L. Rössler, B. J. Jelier, E. Magnier, G. Dagousset, E. M. Carreira, A. Togni, *Angew. Chem. Int. Ed.* **2020**, *59*, 9264; e) D. Moser, Y. Duan, F. Wang, Y. Ma, M. J. O'Neill, J. Cornella, *Angew. Chem. Int. Ed.* **2018**, *57*, 11035; f) C. Ghiazza, T. Faber, A. Gómez-Palomino, J. Cornella, *Nat. Chem.* **2022**, *14*, 78; g) A. Gómez-Palomino, C. Ghiazza, J. Busch, L. Wagner, J. Cornella, *Org. Synth.* **2023**, *100*, 361.

[11] H. H. Coenen, J. Ermert, *Clin. Transl. Imaging* **2018**, *6*, 169.

[12] M. K. Narayanam, G. Ma, P. A. Champagne, K. N. Houk, J. M. Murphy, *Angew. Chem. Int. Ed.* **2017**, *56*, 13006.

[13] R. M. Pérez-García, G. Grønnevik, P. J. Riss, *Org. Lett.* **2021**, *23*, 1011.

[14] D. Cressy, M. Akula, A. Frederick, K. Shipley, D. Osborne, *Results Chem.* **2023**, *5*, 100706.

[15] a) J. P. Holland, *Chem. Eur. J.* **2018**, *24*, 16472; b) L. Y. F. Haveman, D. J. Vugts, A. D. Windhorst, *EJNMMI Radiopharm. Chem.* **2023**, *8*, 28.

[16] a) K. D. Collins, F. Glorius, *Nat. Chem.* **2013**, *5*, 597; b) N. J. Taylor, E. Emer, S. Preshlock, M. Schedler, M. Tredwell, S. Verhoog, J. Mercier, C. Genicot, V. Gouverneur, *J. Am. Chem. Soc.* **2017**, *139*, 8267.

[17] D. Kumar, J. J. Mann (Columbia University) WO2019089575 A1, **2019**.

[18] G. S. Baxter, R. A. Borman (Pharmagene Laboratories Ltd.), WO2001008668 A2, **2001**.

[19] a) R. Richarz, P. Krapf, F. Zarrad, E. A. Urusova, B. Neumaier, B. D. Zlatopolskiy, *Org. Biomol. Chem.* **2014**, *12*, 8094; b) C. Neumann, J. Hooker, T. Ritter, *Nature* **2016**, *534*, 369.

[20] N. Ichiishi, A. F. Brooks, J. J. Topczewski, M. E. Rodnick, M. S. Sanford, P. J. H. Scott, *Org. Lett.* **2014**, *16*, 3224.

[21] J. S. D. Kumar, K. K. S. Sai, J. Prabhakaran, H. R. Oufkir, G. Ramanathan, C. T. Whitlow, H. Dileep, A. Mintz, J. J. Mann, *J. Med. Chem.* **2018**, *61*, 2118.

[22] a) H. Xiong, A. T. Hoye, K.-H. Fan, X. Li, J. Clemens, C. L. Horchler, N. C. Lim, G. Attardo, *Org. Lett.* **2015**, *17*, 3726; b) M. A. Mantell, M. R. Lasky, M. Lee, M. Remy, M. S. Sanford, *Org. Lett.* **2021**, *23*, 5213.

[23] N. Sirisoma, S. Kasibhatla, A. Pervin, H. Zhang, S. Jiang, J. A. Willardsen, M. B. Anderson, V. Baichwal, G. G. Mather, K. Jessing, R. Hussain, K. Hoang, C. M. Pleiman, B. Tseng, J. Drewe, S. X. Cai, *J. Med. Chem.* **2008**, *51*, 4771.

[24] S. Banerjee, K. E. Arnst, Y. Wang, G. Kumar, S. Deng, L. Yang, G. Li, J. Yang, S. W. White, W. Li, D. D. Miller, *J. Med. Chem.* **2018**, *61*, 1704.

[25] E. V. Filho, J. W. S. Pina, M. K. Antoniazi, L. B. Loureiro, M. A. Ribeiro, C. B. Pinheiro, C. J. Guimarães, F. C. E de Oliveira, C. Pessoa, A. G. Taranto, S. J. Greco, *Bioorg. Med. Chem. Lett.* **2021**, *48*, 128240.

[26] C. Liu, N. Han, X. Song, J. Qiu, *Eur. J. Org. Chem.* **2010**, *2010*, 5548.

[27] A. Tikad, S. Routier, M. Akssira, J.-M. Léger, C. Jarry, G. Guillaumet, *Synthesis* **2009**, *14*, 2379.

[28] B. Akinbobuyi, M. R. Byrd, C. A. Chang, M. Nguyen, Z. J. Seifert, A.-L. Flamar, G. Zurawski, K. C. Upchurch, S. Oh, S. H. Dempsey, T. J. Enke, J. Le, H. J. Winstead, J. R. Boquín, R. R. Kane, *Tetrahedron Lett.* **2015**, *56*, 458.

[29] K. L. Billingsley, T. E. Barder, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2007**, *46*, 5359.

[30] X. Huang, S. L. Buchwald, *Org. Lett.* **2001**, *3*, 3417.

[31] J. Ruch, A. Aubin, G. Erbland, A. Fortunato, J.-P. Goddard, *Chem. Commun.* **2016**, *52*, 2326.

[32] A. Casimiro-Garcia, C. Allais, A. Brennan, C. Choi, G. Dower, K. A. Farley, M. Fleming, A. Flick, R. K. Frisbie, J. Hall, D. Hepworth, H. Jones, J. D. Knafels, S. Kortum, F. E. Lovering, J. P. Mathias, S. Mohan, P. M. Morgan, C. Parng, K. Parris, N. Pullen, F. Schlerman, J. Stansfield, J. W. Strohbach, F. F. Vajdos, F. Vincent, H. Wang, X. Wang, R. Webster, S. W. Wright, *J. Med. Chem.* **2022**, *65*, 757.

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# Zuschriften

**Radiochemistry**

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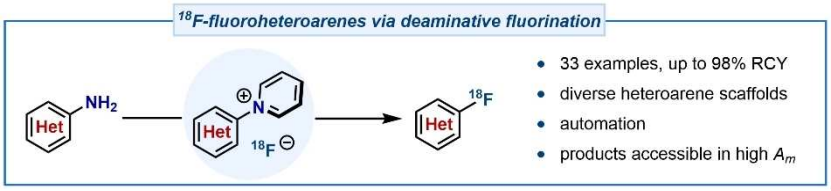
Expedient Access to $^{18}$F-Fluoroheteroarenes via Deaminative Radiofluorination of Aniline-Derived Pyridinium Salts




$^{18}$F-Fluoroheteroarenes find wide application as radiotracers for PET (positron emission tomography) imaging. Here, we present a deaminative radiosynthetic approach via pyridinium tetrafluoroborates that facilitates radiofluorination of 33 structurally diverse heteroarenes in up to 98% RCY (radiochemical yield). This method was also amenable to automation and was successfully translated to an automated synthesiser.