

Nickel-Mediated Oxidative Fluorination for PET with Aqueous [^{18}F] Fluoride

Eunsung Lee,[†] Jacob M. Hooker,^{‡,§} and Tobias Ritter^{*,†,§}

[†]Department of Chemistry and Chemical Biology, Harvard University, 12 Oxford Street, Cambridge, Massachusetts 02138, United States

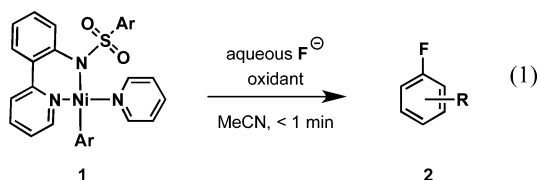
[‡]Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital and Harvard Medical School, Charlestown, Massachusetts 02129, United States

[§]Division of Nuclear Medicine and Molecular Imaging, Department of Radiology, Massachusetts General Hospital, Boston, Massachusetts 02114, United States

S Supporting Information

ABSTRACT: A one-step oxidative fluorination for carbon–fluorine bond formation from well-defined nickel complexes with oxidant and aqueous fluoride is presented, which enables a straightforward and practical ^{18}F late-stage fluorination of complex small molecules with potential for PET imaging.

Positron emission tomography (PET) requires synthesis of molecules that contain positron-emitting isotopes, such as ^{11}C , ^{13}N , ^{15}O , and ^{18}F .¹ The ^{18}F isotope is typically the preferred radionuclide for clinically relevant PET applications due to its longer half-life of 110 min, which permits synthesis and distribution of radiotracer quantities appropriate for imaging.² But C–F bond formation is challenging, especially with ^{18}F .³ Here we report a practical late-stage fluorination reaction with high-specific activity ^{18}F fluoride to make aryl and alkenyl fluorides from organometallic nickel complexes. A direct oxidative fluorination of organotransition metal complexes with an oxidant and fluoride has never been reported and enables practical one-step access to complex ^{18}F -labeled small molecules from [^{18}F]fluoride. When nickel complexes **1** are combined with an oxidant and aqueous fluoride, the organic fluorides **2** are formed at room temperature in less than 1 min (eq 1).



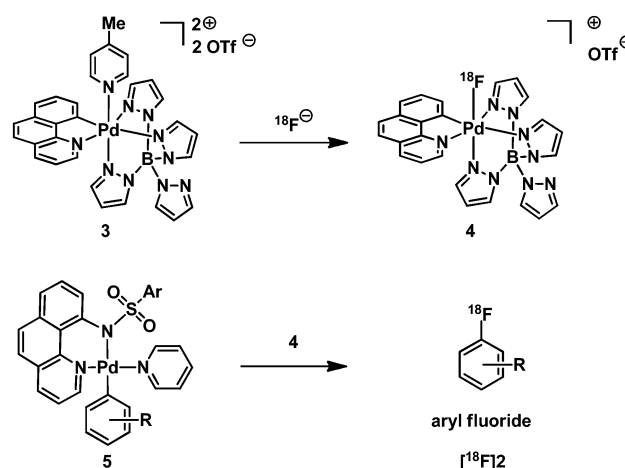
Synthesis of simple ^{18}F PET tracers is typically accomplished with conventional nucleophilic substitution reactions with [^{18}F]fluoride.^{1,4} [^{18}F]Fluoride is the only readily available source of F-18. But conventional nucleophilic substitution reactions commonly only give access to simple molecules and have a small substrate scope. C–F bond formation is more difficult with ^{18}F than with the naturally occurring ^{19}F , and most modern, functional-group-tolerant fluorination reactions are not currently useful for applications in PET.⁵ In addition to

the challenges associated with ^{19}F fluorination,³ chemistry with ^{18}F needs to take into account the small concentration of ^{18}F (roughly 10^{-4} M), the impracticality to work under rigorously anhydrous conditions, and the side product profile. We sought to develop a practical, one-step, functional-group-tolerant, electrophilic fluorination reaction that employs [^{18}F]fluoride.

We had previously developed the electrophilic fluorination reagent **4** made from high-specific activity [^{18}F]fluoride via reductive elimination from high-valent palladium fluoride complexes (Scheme 1).⁶ Palladium complex **4** can be used

Scheme 1. Two-Step Late-Stage Fluorination via Pd(IV) Fluoride Complex **4**

Previous work: 2-step sequence



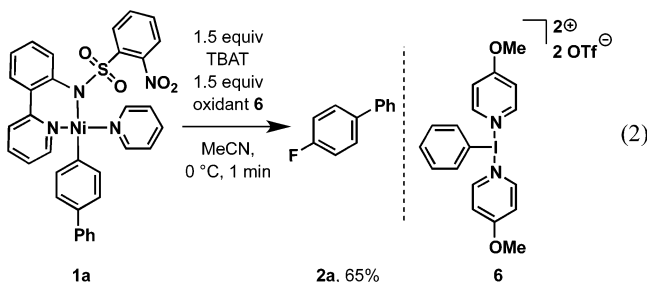
for late-stage ^{18}F fluorination of complex arenes and was the first reagent to capture fluoride and subsequently function as an electrophilic fluorination reagent. Yet, use of **4** requires a two-step sequence: fluoride capture (**3** → **4**), followed by fluoride transfer via electrophilic fluorination (**5** → [^{18}F]2). The two-step sequence increases reaction time and the possibility for error and makes the method less suitable for adoption by

Received: August 27, 2012

Published: October 12, 2012

nonchemists. Moreover, the fluoride must be dried azeotropically, as is common for most reactions that use [^{18}F]fluoride.¹

This manuscript reports on fluorination of arylnickel complexes that avoid some of the limitations inherent to the palladium chemistry shown in Scheme 1, most notably the two-step procedure. We established the relevance of nickel aryl complexes **1** to the direct oxidative fluorination with fluoride through reaction of **1a** with hypervalent iodine oxidant **6** and tetrabutylammonium difluorotriphenylsilicate (TBAT) as the fluoride source, which afforded a 65% isolated yield of aryl fluoride **2a** after chromatographic purification on silica gel (eq 2).



For radiofluorination, a solution of aqueous [^{18}F]fluoride (2–5 μL , 100–500 μCi) containing 2 mg of 18-cr-6 in MeCN (200–500 μL) was added to a mixture of 1.0 mg of nickel complex **1** and 1.0 equiv (relative to **1**) of oxidant **6** at room temperature under ambient atmosphere in a vial. After less than 1 min after addition, the fluorination reactions were analyzed by radioTLC and HPLC for radiochemical yield and product identity, respectively (Table 1). All reactions proceeded without deliberate addition of [^{19}F]fluoride (no-carrier-added). No carrier-added ^{18}F fluorination allows for the synthesis of ^{18}F -labeled molecules of high specific activity.¹ For example, compound **2g** was prepared in 1.1 Ci/ μmol . The transformation is successful for the synthesis of electron-rich, electron-poor, ortho-, meta-, and para-substituted, and densely functionalized aryl fluorides, as well as for alkenyl fluorides. Tertiary amines are currently not tolerated, presumably due to the unproductive reaction of oxidant **6** with nucleophiles such as amines.

The ability to use aqueous fluoride solutions makes extensive drying procedures, which are typical for radiochemistry with [^{18}F]fluoride,¹ superfluous. Drying procedures increase the time from [^{18}F] production to tracer purification; for example, drying fluoride for the reaction shown in Scheme 1 takes longer than the 20-min reaction time. The direct use of aqueous fluoride solution presented here avoids unproductive radioactive decay and also increases the yield based on fluoride because drying commonly results in significant fluorine content being absorbed onto walls of glass reaction vessels. The aqueous fluoride solution can be used without ion exchange that is normally required for radiochemistry with [^{18}F]fluoride, which further increases practicality and reduces reaction time. To facilitate purification subsequent to fluorination, it is desirable to employ as little starting material (e.g., **1**) as possible for radiofluorination, and 1 mg of nickel complex (ca. 1 μmol) is a low amount compared to other [^{18}F] radiofluorination reactions. For example, the method presented here requires an order of magnitude less starting material than the palladium-mediated method described in Scheme 1 and yet affords generally higher radiochemical yields.^{6d}

Table 1. Fluorination of Ni(II)–Aryl Complexes with [^{18}F]Fluoride^a

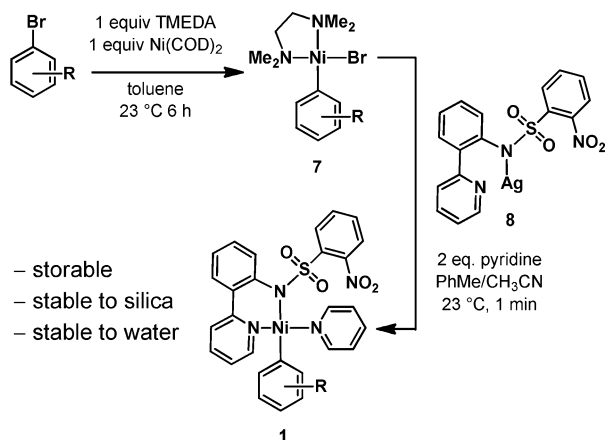
 [^{18}F]2a 42% \pm 8% RCY (n = 6)	 [^{18}F]2b 51% \pm 9% RCY (n = 6)	 [^{18}F]2c 53% \pm 7% RCY (n = 6)
 [^{18}F]2d 17% \pm 3% RCY (n = 6)	 [^{18}F]2e 21% \pm 5% RCY (n = 6)	 [^{18}F]2f 54% \pm 9% RCY (n = 6)
 [^{18}F]2g 58% \pm 6% RCY (n = 6)	 [^{18}F]2h 43% \pm 9% RCY (n = 6)	 [^{18}F]2i 15% \pm 7% RCY (n = 6)
 [^{18}F]2j 38% \pm 7% RCY (n = 6)	 [^{18}F]SFB, [^{18}F]2k 21% \pm 4% RCY (n = 6)	 [^{18}F]2l 13% \pm 3% RCY (n = 6)

^aReaction conditions: 1.0 mg of nickel complex **1**, 1.0 equiv of **6** (with respect to **1**), aqueous solution of [^{18}F]fluoride (2–5 μL , 100–500 μCi ; 500 μCi in 5 μL of water corresponds to a concentration of 42 nM in [^{18}F]), and 2.0 mg of 18-cr-6 in MeCN (200–500 μL) at 23 °C. Radiochemical yields (RCYs) were measured by radio-TLC, are based on original aqueous [^{18}F] content, and are averaged over *n* experiments. Boc, *tert*-butoxycarbonyl; Bz, benzoyl; SFB, *N*-succinimidyl 4-fluorobenzoate.

The synthesis of the nickel organometallics (**1**) is accomplished by oxidative addition of aryl or alkenyl bromides to commercially available Ni(COD)₂ in the presence of tetramethylethylenediamine (TMEDA), followed by addition of silver salt **8** (Scheme 2). All reported nickel organometallics used for fluorination in this manuscript are moisture- and air-stable solids that can be purified by column chromatography on silica gel or recrystallization. The nickel complexes were prepared from the corresponding bromides in 30–92% yield and can be stored under ambient atmosphere.

The one-step oxidative fluorination of well-defined nickel complexes with oxidant and aqueous fluoride enables a straightforward and practical ^{18}F late-stage fluorination of complex small molecules.⁷ Operational simplicity of the fluorination, most notably the ability to use aqueous solutions of [^{18}F]fluoride, will also empower nonexperts to obtain previously unavailable ^{18}F -labeled molecules and showcases the potential of modern organometallic chemistry for applications

Scheme 2. Synthesis of Ni(II) Aryl Complexes



in PET.⁷ The transformation represents the first example of fluorination with a first row transition metal organometallic and the first example of a reaction that affords aryl fluoride by ^{18}F –C bond formation at room temperature within seconds using an aqueous solution of ^{18}F fluoride. Going forward, we will evaluate the possibility of translating the transformation to automated radiosyntheses as well as PET imaging applications.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures, spectroscopic data for all new compounds, crystallographic data for 1c (CIF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

■ AUTHOR INFORMATION

Corresponding Author

ritter@chemistry.harvard.edu

Notes

The authors declare the following competing financial interest(s): A patent application has been filed through Harvard on methods and reagents presented in this manuscript.

■ ACKNOWLEDGMENTS

Funding was provided by NIH-NIGMS (GM088237) and NIH-NIBIB (EB013042), as well as for a shared instrument grant (S10RR017208). We thank Dr. A. Kamlet for the synthesis of material used to prepare ^{18}F 2h. We thank S.-L. Zheng (Harvard) for X-ray crystallographic analysis. We thank S. Carlin (Massachusetts General Hospital) for technical assistance with ^{18}F fluoride. TR is a Sloan fellow, a Lilly Grantee, an Amgen Young Investigator, a Camille Dreyfus Teacher-Scholar, and an AstraZeneca Awardee.

■ REFERENCES

- (1) Miller, P. W.; Long, N. J.; Vilar, R.; Gee, A. D. *Angew. Chem., Int. Ed.* **2008**, *47*, 8998–9033.
- (2) (a) Fowler, J. S.; Wolf, A. P. *Acc. Chem. Res.* **1997**, *30*, 181–188. (b) Phelps, M. E. *Proc. Natl. Acad. Sci. U.S.A.* **2000**, *97*, 9226–9233. (c) Rohren, E. M.; Turkington, T. G.; Coleman, R. E. *Radiology* **2004**, *231*, 305–332. (d) Ametamey, S. M.; Honer, M.; Schubiger, P. A. *Chem. Rev.* **2008**, *108*, 1501–1516.
- (3) (a) O'Hagan, D. *Chem. Soc. Rev.* **2008**, *37*, 308–319. (b) Furuya, T.; Kamlet, A. S.; Ritter, T. *Nature* **2011**, *473*, 470–477.

(4) (a) Pike, V. W.; Aigbirhio, F. I. *J. Chem. Soc., Chem. Commun.* **1995**, 2215–2216. (b) Chun, J. H.; Lu, S. Y.; Lee, Y. S.; Pike, V. W. *J. Org. Chem.* **2010**, *75*, 3332–3338.

(5) For the first transition metal-catalyzed C– ^{18}F bond formation, see: (a) Teare, H.; Robins, E. G.; Kirjavainen, A.; Forsback, S.; Sandford, G.; Solin, O.; Luthra, S. K.; Gouverneur, V. *Angew. Chem., Int. Ed.* **2010**, *49*, 6821–6824. For other successful recent C– ^{18}F bond formations, see: (b) Hollingworth, C.; Hazari, A.; Hopkinson, M. N.; Tredwell, M.; Benedetto, E.; Huiban, M.; Gee, A. D.; Brown, J. M.; Gouverneur, V. *Angew. Chem., Int. Ed.* **2011**, *50*, 2613–2617. (c) Topczewski, J. J.; Tewson, T. J.; Nguyen, H. M. *J. Am. Chem. Soc.* **2011**, *133*, 19318–19321. (d) Gao, Z. H.; Lim, Y. H.; Tredwell, M.; Li, L.; Verhoog, S.; Hopkinson, M.; Kaluza, W.; Collier, T. L.; Passchier, J.; Huiban, M.; Gouverneur, V. *Angew. Chem., Int. Ed.* **2012**, *51*, 6733–6737.

(6) (a) Furuya, T.; Kaiser, H. M.; Ritter, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 5993–5996. (b) Furuya, T.; Ritter, T. *J. Am. Chem. Soc.* **2008**, *130*, 10060–10061. (c) Furuya, T.; Benitez, D.; Tkatchouk, E.; Strom, A. E.; Tang, P.; Goddard, W. A., III; Ritter, T. *J. Am. Chem. Soc.* **2010**, *132*, 3793–3807. (d) Lee, E.; Kamlet, A. S.; Powers, D. C.; Neumann, C. N.; Boursalian, G. B.; Furuya, T.; Choi, D. C.; Hooker, J. M.; Ritter, T. *Science* **2011**, *334*, 639–642.

(7) For metal-catalyzed C–H to C– ^{19}F bond formation with fluoride and oxidant, see: (a) McMurtrey, K. B.; Racowski, J. M.; Sanford, M. S. *Org. Lett.* **2012**, *14*, 4094–4097. (b) Liu, W.; Huang, X.; Cheng, M.-J.; Nielsen, R. J.; Goddard, W. A., III; Groves, J. T. *Science* **2012**, *337*, 1322–1325. For other modern transition-metal-catalyzed and -mediated C–F bond forming reactions with potential for applications in PET, see: (c) Watson, D. A.; Su, M. J.; Teverovskiy, G.; Zhang, Y.; Garcia-Fortanet, J.; Kinzel, T.; Buchwald, S. L. *Science* **2009**, *325*, 1661–1664. (d) Katcher, M. H.; Doyle, A. G. *J. Am. Chem. Soc.* **2010**, *132*, 17402–17404. (e) Noel, T.; Maimone, T. J.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2011**, *50*, 8900–8903. (f) Fier, P. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **2012**, *134*, 10795–10798.