Organic LETTERS

Letter

Cite This: Org. Lett. XXXX, XXX, XXX–XXX

pubs.acs.org/OrgLett

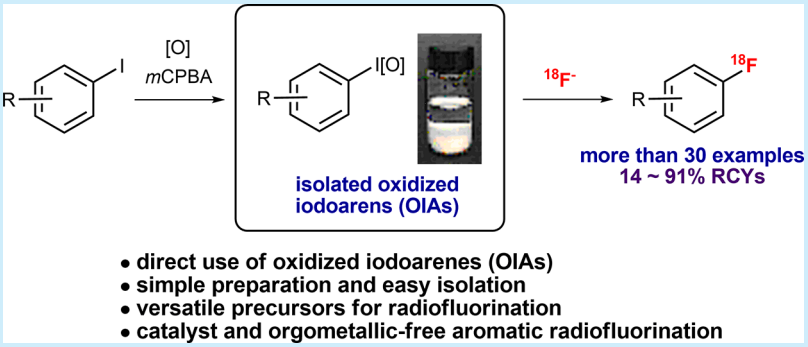
Catalyst-Free Aromatic Radiofluorination via Oxidized Iodoarene Precursors

Young-Do Kwon,[†] Jeongmin Son,[‡] and Joong-Hyun Chun*[,†]

[†]Department of Nuclear Medicine, Yonsei University College of Medicine, Seoul 03722, Republic of Korea

[‡]Department of Nuclear Medicine, Severance Hospital, Yonsei University Health System, Seoul 03722, Republic of Korea

Supporting Information



ABSTRACT: Oxidized iodoarenes (OIAs), prepared via *m*CPBA-mediated oxidation, have been demonstrated as versatile precursors for the synthesis of [^{18}F]fluoroarenes in the absence of catalysts. OIAs have been identified as intermediates in single-pot syntheses of iodonium salts and ylides but have never been recognized as radiofluorination precursors. Here, the isolated OIAs were used without any catalysts to produce functionalized [^{18}F]fluoroarenes, regardless of the electronic nature of the arenes. This method was also applied to the production of radiolabeling synthons for use as aromatic ^{18}F-labeled building blocks.

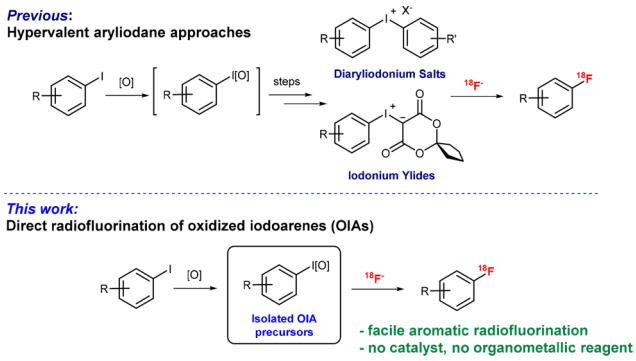
Positron emission tomography (PET) is a noninvasive imaging technique used to trace radioisotope-labeled chemical compounds *in vivo*.[1] Among the many radionuclides used for PET, fluorine-18 is considered ideal due to its half-life ($t_{1/2}$ = 109.8 min) and decay characteristics, which are suitable for chemical modification and PET imaging, respectively.[2] *In vivo* stability is a key criterion for PET radiopharmaceuticals. In most cases, whereas aliphatic radiotracers are relatively easily prepared, they can undergo radiodefluorination in physiological conditions.[3] This issue has been resolved for many aliphatic PET radiotracers,[4] but aromatic fluoro-congeners are still considered more stable against *in vivo* radiodefluorination.[5] Many studies have focused on developing efficient means of introducing fluorine-18 onto aromatic substrates.[6] However, facile radiofluorination protocols that consistently yield aromatic PET radiotracers remain a longstanding challenge. One recent development is the use of hypervalent compounds as labeling precursors for transition-metal-free radiofluorination.[2,5,6c,d] Another strategy is to employ transition-metal-catalyzed radiofluorination to produce [^{18}F]fluoroarenes.[5,7] The former approach showcases the different classes of hypervalent compounds, including diaryliodonium salts, iodonium ylides,[8] diaryl sulfoxides,[9] and sulfonium salts.[10] The latter approaches include the use of transition-metal catalysts in addition to synthetically demanding organometallic precursors.[11] Despite the advantages of the use of these substrates as PET precursors, difficulties associated with the synthesis of labeling precursors continue to limit the broader application of this technology in ^{18}F-radiochemistry.

Recently, Pike et al.[12] have reported the use of (diacetoxyiodo)arenes, a class of λ^3-hypervalent iodine compounds, as precursors for [^{18}F]fluoroarenes. They reported the syntheses of [^{18}F]fluoroarenes from λ^3-aryliodanes with two acetoxy ligands on the central iodine and pivaloyl or trifluoroacetyl ligands. One particularly interesting aspect of their report is the radiofluorination of isolated oxo-μ-aryliodane acquired from 1-iodo-4-(trifluoromethyl)benzene to provide 1-[^{18}F]fluoro-4-(trifluoromethyl)benzene. Although the use of λ^5-iodoxyarenes as a labeling precursors for [^{18}F]fluoroarenes has been patented, studies employing the patented process are rare.[13] These reports suggest that oxidized, higher valent iodoarenes can be radiofluorinated, regardless of the oxidation state of the iodine atom. This prompted us to investigate the possibility that oxidized iodoarene (OIA) intermediates could be directly employed as potential precursors for radiofluorination, obviating cumbersome synthetic procedures involving diaryliodonium salts or iodonium ylides (Scheme 1). The following are the foreseeable advantages of our approach: (1) OIAs can be

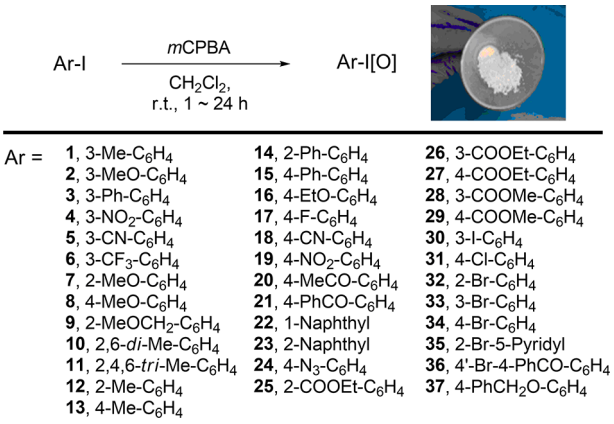
Received: October 29, 2018

DOI: 10.1021/acs.orglett.8b03450
Org. Lett. XXXX, XXX, XXX–XXX

Scheme 1. Radiosyntheses of [^{18}F]Fluoroarenes via Oxidized Iodoarenes and Hypervalent Aryliodane Precursors



Scheme 2. Oxidized Iodoarene Precursors Used in This Study



[a]Oxidized 1-[(4-iodophenyl)methyl]-4-phenyltriazole.

conveniently prepared by the simple oxidation of aryl iodides with *meta*-chloroperbenzoic acid (*m*CPBA). This strategy is also applicable to aromatic systems with an activatable iodine using a simple oxidant. (2) Radiofluorination of OIAs can be performed in the absence of a catalyst. This simplifies downstream purification processes and quality control procedures for the potential production of clinical PET radiotracers.

Higher valent oxidized iodoarenes as precursors of [^{18}F]-fluoroarenes were prepared by reacting iodoarenes with *m*CPBA, a commercially available, widely employed oxidant.[14] We used commercial *m*CPBA (70−77% active peroxy content; stabilized with H_2O and *meta*-chlorobenzoic acid). No iodometric titration was made to determine the exact peroxy content. Although the resulting OIAs have been used as *in situ* intermediates in the syntheses of diaryliodonium salts and iodonium ylides,[8e,15] they have never been isolated and recognized as viable precursors for radiofluorination. To reiterate our method, iodoarenes were oxidized with *m*CPBA in CH_2Cl_2 at room temperature for 1−24 h and without any of the precautionary conditions often required for organic syntheses, such as an anhydrous environment, inert atmosphere, or high reaction temperature. After the reaction, the product mixture was concentrated under reduced pressure, and the precipitation of a white to pale yellow solid was triggered by adding Et_2O to the resulting residue. The oxidation products were filtered to recover OIAs. In order to avoid unexpected explosive behavior of higher valent OIAs, we used a plastic filter funnel and spatula during filtration where appropriate. The removal of excess *m*CPBA and *m*CBA byproduct was easily achieved by washing with Et_2O.

To streamline the synthetic procedure, 1-fluoro-4-iodobenzene was oxidized by three different relative amounts of *m*CPBA: 0.4, 1, and 2.5 equiv. The reaction time, which was determined by the complete consumption of iodoarene, was shorter with higher proportions of *m*CPBA in the reaction mixture. The yield of the resulting oxidized precursor was also higher when higher concentrations of *m*CPBA were employed. The OIAs used in the following labeling experiments and throughout this study were prepared with 2.5 equiv of *m*CPBA (Scheme 2; see preparation details in the Supporting Information (SI)).

Simple oxidations of 4-iodoanisole, 4-iodotoluene, and 1-fluoro-4-iodobenzene with *m*CPBA (2.5 equiv) gave the corresponding OIAs (compounds **8**, **13**, and **17**) as white precipitates. However, the difficulties encountered in identifying and characterizing the resulting products are worthy of discussion (see the SI for details). Initial ^{1}H and ^{19}F NMR analyses indicated that the resulting precipitate was a mixture of iodoarene species of different oxidation states, such as λ^3- and λ^5-hypervalent species, or presumably, a mixture of other oxidized species. Elemental analyses revealed that the carbon, hydrogen, and oxygen content do not exactly match any single component among the higher valent iodine intermediates, indicating a mixture. Further assessments with high-resolution mass spectrometry (HRMS) confirmed the simultaneous presence of multiple oxidation species. Similar mixtures of the oxidation products of iodoarene were reported when dimethyldioxirane (DMDO) was used as the oxidant for iodobenzene.[16] Note that disproportionation is a well-known process between iodoso- and iodoxyarenes and seems to have occurred during oxidation with commercial *m*CPBA with a relatively high H_2O content.[17] This made the exact identification of individual oxidation products more challenging. In addition, the observed broad melting point ranges were also indicative of a variety of oxidation products.

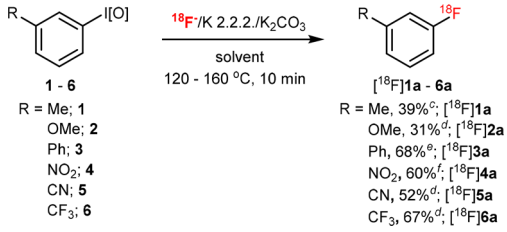
Notwithstanding the difficulties associated with exact characterization of isolated OIAs, we explored the feasibility of radiofluorination with the acquired precursors to give [^{18}F]fluoroarenes under catalyst-free conditions. A preliminary investigation was made with **8**, which was labeled with a cyclotron-produced [^{18}F]fluoride ion. Radiofluorination performed with 4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8]-hexacosane (K 2.2.2.)/K_2CO_3 as a phase-transfer agent (PTA) gave a 6% radiochemical yield (RCY) of 4-[^{18}F]fluoroanisole ([^{18}F]**8a**). Interestingly, changing from K 2.2.2./K_2CO_3 to tetrabutylammonium hydrogen carbonate ($TBAHCO_3$) increased the RCY from 6% to 27%. Additional screening of solvents helped identify an ideal radiofluorination medium for oxidized precursors. The most common solvents for nucleophilic radiofluorination were evaluated, including dimethyl sulfoxide (DMSO), *N*,*N*-dimethylformamide (DMF), and *N*,*N*-dimethylacetamide (DMA). Although many studies have used acetonitrile (MeCN) in PET radiotracer syntheses, we found MeCN to be limiting in terms of the solubility of OIAs and unattainable reaction temperatures above 100 °C. DMSO has been deemed nonideal in the radiofluorination of diaryliodonium salts,[18] whereas some OIA precursors yielded high RCYs in DMSO. Among

DOI: 10.1021/acs.orglett.8b03450
Org. Lett. XXXX, XXX, XXX−XXX

the radiofluorination reactions conducted with different PTAs, $TBAHCO_3$ yielded the highest RCY when **8** was radiofluorinated in DMSO. However, the suitability of a particular PTA and solvent is not universal when considering different substrates. The reproducibility of this methodology was demonstrated using oxidized 4-iodotoluene (see the SI for details).

Taking this into account, OIAs were radiolabeled with a [^{18}F]fluoride ion. This was initially performed with *meta*-substituted iodoarenes (Scheme 3), as the unactivated *meta*-

Scheme 3. Radiosyntheses of *Meta*-Substituted [^{18}F]Fluoroarenes from OIAs[a,b]

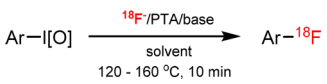


[a]Reaction conditions: Precursor (2 mg), K 2.2.2. (3.7 mg, 9.7 μmol), K_2CO_3 (0.7 mg, 4.8 μmol), solvent (2 mL). [b]RCY was determined on the basis of radio-HPLC (n = 2). [c]DMA, 120 °C. [d]DMA, 160 °C. [e]DMF, 140 °C. [f]DMA, 140 °C.

position on an aryl ring is known to be difficult to radiofluorinate using the conventional S_NAr approach. Although recent advances with diaryliodonium salts and iodonium ylides have overcome some of the major limitations associated with *meta*-[^{18}F]fluoroarenes, the ability to radiofluorinate *meta*-substituted, weakly activated aryl rings is a good criterion for evaluating the efficacy of this new method. Radiofluorination of **1** in DMA at 120 °C yielded a 39% RCY. Likewise, radiofluorination proceeded smoothly, yielding RCYs of 31% ([^{18}F]**2a**) and 68% ([^{18}F]**3a**), respectively, when electron-donating methoxy (**2**) or phenyl (**3**) substituents were placed at the *meta*-position. Radiofluorination was also relatively well tolerated with *meta*-electron-withdrawing substituents, such as nitro- (**4**), cyano- (**5**), or trifluoromethyl (**6**) groups. In general, *meta*-[^{18}F]fluoroarenes were obtained in RCYs of 31−68%, as determined by reversed-phase radio-HPLC chromatography. Compared with fully identified and isolated λ^3-(diacetoxyiodo)arenes[12] and λ^5-iodoxyarenes,[13] RCYs were significantly higher with OIAs bearing NO_2-, CN-, and CF_3-groups at the *meta*-position.

Radiofluorination with OIAs bearing *ortho*- and *para*-substitutions proceeded smoothly to provide the corresponding [^{18}F]fluoroarenes in moderate to excellent RCYs, regardless of the electronic nature of the substituents (Table 1). Notably, 2-[^{18}F]fluoroanisole ([^{18}F]**7a**) was acquired in 22% RCY, which had been previously accessible only with low RCY using unsymmetrical diaryliodonium salts (entry 1, Table 1).[19] Labeling precursors with other *ortho*-substituents, such as 2-methoxymethyl (**9**) and 2,6-dimethyl (**10**) groups, were radiofluorinated with 68% and 25% RCY, respectively (entries 3 and 4, Table 1). Unlike the "*ortho*-effect" that is observed in the radiofluorination of diaryliodonium salts, RCYs of these OIA precursors via radiofluorination were not dramatically influenced by bulky substituents or substituents at the *ortho*-position in aromatic systems. For example, 2-[^{18}F]-fluorotoluene ([^{18}F]**12a**) was obtained with an RCY

Table 1. *Ortho*- or *Para*-Substituted [^{18}F]Fluoroarenes from OIA Precursors



entry	substrate[a], Ar, no.	conditions[b,c]	[^{18}F]fluoroarene RCY (%)[d]
1	2-$MeOC_6H_4$, **7**	A	[^{18}F]**7a**, 22
2	4-$MeOC_6H_4$, **8**	A	[^{18}F]**8a**, 27
3	2-$MeOCH_2$-C_6H_4, **9**	B	[^{18}F]**9a**, 68
4	2,6-*di*-MeC_6H_3, **10**	C	[^{18}F]**10a**, 25
5	2,4,6-*tri*-MeC_6H_2, **11**	C	[^{18}F]**11a**, 14
6	2-MeC_6H_4, **12**	B	[^{18}F]**12a**, 37
7	4-MeC_6H_4, **13**	B	[^{18}F]**13a**, 24[e]
8	2-PhC_6H_4, **14**	B	[^{18}F]**14a**, 81
9	4-PhC_6H_4, **15**	C	[^{18}F]**15a**, 31
10	4-$EtOC_6H_4$, **16**	D	[^{18}F]**16a**, 29
11	4-FC_6H_4, **17**	D	[^{18}F]**17a**, 26
12	4-NCC_6H_4, **18**	B	[^{18}F]**18a**, 64
13	4-$O_2NC_6H_4$, **19**	D	[^{18}F]**19a**, 17
14	4-$MeCOC_6H_4$, **20**	E	[^{18}F]**20a**, 59
15	4-$PhCOC_6H_4$, **21**	C	[^{18}F]**21a**, 14
16	1-naphthyl, **22**	F	[^{18}F]**22a**, 53
17	2-naphthyl, **23**	F	[^{18}F]**23a**, 59

[a]Substrate (2 mg). [b]PTA/Base (K 2.2.2. (3.7 mg, 9.7 μmol) and K_2CO_3 (0.7 mg, 4.8 μmol); or $TBAHCO_3$ (10 μL, 13.2 μmol; 40% aq. solution)), solvent (2 mL). [c]Conditions: (A) $TBAHCO_3$/DMSO, 160 °C; (B) K 2.2.2./K_2CO_3/DMA, 120 °C; (C) $TBAHCO_3$/DMA, 160 °C; (D) K 2.2.2./K_2CO_3/DMA, 160 °C; (E) K 2.2.2./K_2CO_3/DMA, 140 °C; (F) K 2.2.2./K_2CO_3/DMF, 140 °C. [d]RCY was determined based on radio-HPLC (n = 2). [e]RCY = 24 ± 6% (n = 12).

comparable to that of 4-[^{18}F]fluorotoluene ([^{18}F]**13a**) (entries 6 and 7, Table 1). When producing [^{18}F]fluorobiphenyls, 2-[^{18}F]fluorobiphenyl ([^{18}F]**14a**) was acquired in high RCY (81%) compared to 3- and 4-[^{18}F]fluorobiphenyl (([^{18}F]**3a**) and ([^{18}F]**15a**), respectively), which yielded good RCYs (compound [^{18}F]**3a**, Scheme 3; entries 8 and 9, Table 1). Electron-rich 4-[^{18}F]fluorophenetole ([^{18}F]**16a**) was also obtained in a single step from the corresponding OIA precursor. Useful RCYs were obtained with *para*-substituted 4-[^{18}F]fluorobenzonitrile {([^{18}F]**18a**); 64% RCY} and 4-[^{18}F]fluoronitrobenzene {([^{18}F]**19a**); 17% RCY}. Radiosyntheses of [^{18}F]fluoroaryl ketones yielded 4-[^{18}F]-fluoroacetophenone {([^{18}F]**20a**); 59% RCY} and 4-[^{18}F]-fluorobenzophenone {([^{18}F]**21a**); 14% RCY}.

Regioselective radiofluorination with aromatic systems is also an important issue in the production of [^{18}F]fluoroarenes. Grushin and Marshall[20] demonstrated the formation of an aryne intermediate in the nucleophilic halex-exchange fluorination of 2-bromonaphthalene with a Pd(II) catalyst. Analogous radiofluorination of oxidized iodonaphthalene in the absence of catalyst provided a single [^{18}F]-fluoronaphthalene isomer in a regioselective manner, thereby excluding the possible formation of an aryne intermediate with an oxidized iodonaphthalene (entries 16 and 17, Table 1).

Potential radiolabeling synthons were also evaluated to determine the efficacy of this method for producing ^{18}F-labeled aromatic building blocks. We hypothesize that the operational simplicity of the method described herein for preparing labeling precursors would be equally applicable to the production of radiolabeling synthons for use in subsequent labeling reactions. To test this hypothesis, oxidized iodoaryl precursors for [^{18}F]fluoroaryl azide, alkyl [^{18}F]fluorobenzoate,

DOI: 10.1021/acs.orglett.8b03450
Org. Lett. XXXX, XXX, XXX−XXX

[^{18}F]fluorohaloaryl compounds, and [^{18}F]fluoroaryl ether were prepared (Figure 1). Radiofluorinated "click" labeling synthon

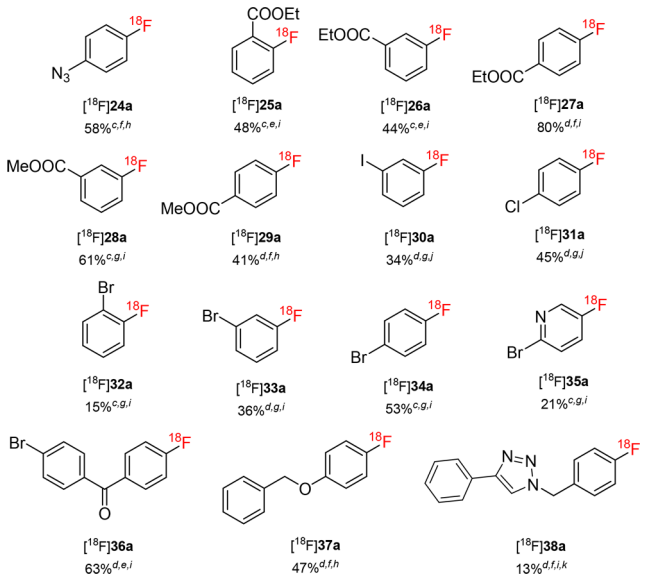


Figure 1. Radiosyntheses of ^{18}F-labeled synthons obtained from oxidized iodoaryl precursors.[a,b] [a]Reaction conditions: precursor (2 mg), solvent (2 mL), 10 min. [b]RCY was determined based on radio-HPLC (n = 2). [c]K 2.2.2. (3.7 mg, 9.7 μmol), K_2CO_3 (0.7 mg, 4.8 μmol). [d]$TBAHCO_3$ (10 μL, 13.2 μmol; 40% aq solution). [e]120 °C. [f]140 °C. [g]160 °C. [h]DMF. [i]DMA. [j]DMSO. [k]20 min.

([^{18}F]**24a**) was prepared in good RCY. Various alkyl [^{18}F]fluorobenzoates ([^{18}F]**25a**–**29a**) were prepared for potentially labeling proteins/peptides via *N*-succinimidyl [^{18}F]fluorobenzoate ([^{18}F]SFB). Particularly noteworthy are the good RCYs that were attained even from *meta*-substituted substrates. Ethyl 3-[^{18}F]fluorobenzoate ([^{18}F]**26a**) and methyl 3-[^{18}F]fluorobenzoate ([^{18}F]**28a**) were acquired in 44% and 61% RCY, respectively. Other methyl and ethyl [^{18}F]-fluorobenzoic acid esters were obtained in RCYs up to 80%, regardless of the substituent position. Considering the ensuing chemical steps that are required to obtain [^{18}F]SFB,[21] high RCYs attained at the initial fluorine-18 labeling stage facilitate the building of more complex molecules in subsequent reactions. ^{18}F-Fluorinated coupling agents with chloro-, bromo-, or iodo-substituents at the *ortho*-, *meta*-, and *para*-positions unequivocally produced ^{18}F-labeled haloaromatic coupling synthons ([^{18}F]**30a**–**36a**) in 15–63% RCYs. Halogen-functionalized 4-bromo-4′-[^{18}F]fluorobenzophenone ([^{18}F]**36a**) was radiosynthesized in a useful RCY, thereby extending the use of bromo-substituents to more complex systems. The operational simplicity of preparing labeling precursors from haloiodoarenes makes this approach much easier and more attractive to implement than approaches involving diaryliodonium salts and iodonium ylides. This is especially true when the relative difficulties of concomitant labeling with ^{18}F-fluorinated synthons are weighed against the difficulties in preparing [^{18}F]fluoro-building blocks. In the same manner, [^{18}F]fluorohalopyridine ([^{18}F]**35a**) yielded a useful RCY (21%) for heteroaryl coupling agents, despite the presumably uncontrollable formation of aryl *N*-oxide during the oxidative activation of iodine at the pyridinyl ring. The high-yielding radiosynthesis of [^{18}F]**37a** provides ready access to 4-[^{18}F]fluorophenol as a versatile radiolabeling building block. Extending this process to labeling synthons for potential coupling reactions was also successful. Following radiofluorination, 4-(benzyloxy)[^{18}F]fluorobenzene ([^{18}F]**37a**) was acquired in 47% RCY, which is a noticeable improvement over the previously reported thienyl(aryl)iodonium salt approach.[22] ^{18}F-labeled triazole derivative ([^{18}F]**38a**) was also accomplished using this methodology.

In conclusion, OIAs were prepared as radiofluorination precursors through the oxidation of iodoarenes with commercially available *m*CPBA. Although not yet fully characterized, the catalyst-free radiofluorination of higher valent OIAs gave comparable or better RCYs than those obtained with other hypervalent aryliodine approaches and proved to be an expeditious method to provide various [^{18}F]fluoroarenes. In depth characterization to identify the isolated oxidized intermediates is ongoing, and future work will describe the application of this method to the synthesis of relevant clinical PET radiotracers and nonradioactive fluoroarenes.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03450.

Experimental procedures, characterization, radiofluorination procedures, and radio-HPLC and radio-TLC chromatograms (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: jchun@yuhs.ac.

ORCID

Young-Do Kwon: 0000-0002-7515-6021

Joong-Hyun Chun: 0000-0002-9665-7829

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support for this research was provided by the National Research Foundation of Korea (NRF-2015R1D1A1A02061420) and a faculty research grant of Yonsei University College of Medicine (6-2018-0100). We thank Professor Eunsung Lee (POSTECH, Republic of Korea) for helpful discussions.

■ REFERENCES

(1) Ametamey, S. M.; Honer, M.; Schubiger, P. A. Molecular imaging with PET. *Chem. Rev.* **2008**, *108*, 1501–1516.

(2) Tredwell, M.; Gouverneur, V. ^{18}F Labeling of arenes. *Angew. Chem., Int. Ed.* **2012**, *51*, 11426–11437.

(3) (a) Pike, V. W. PET radiotracers: crossing the blood–brain barrier and surviving metabolism. *Trends Pharmacol. Sci.* **2009**, *30*, 431–440. (b) Pike, V. W. Considerations in the development of reversibly binding PET radioligands for brain imaging. *Curr. Med. Chem.* **2016**, *23*, 1818–1869.

(4) Kuchar, M.; Mamat, C. Methods to increase the metabolic stability of ^{18}F-radiotracers. *Molecules* **2015**, *20*, 16186–16220.

(5) Preshlock, S.; Tredwell, M.; Gouverneur, V. ^{18}F-Labeling of arenes and heteroarenes for applications in positron emission tomography. *Chem. Rev.* **2016**, *116*, 719–766.

DOI: 10.1021/acs.orglett.8b03450
Org. Lett. XXXX, XXX, XXX–XXX

(6) (a) Cole, E. L.; Stewart, M. N.; Littich, R.; Hoareau, R.; Scott, P. J. H. Radiosyntheses using fluorine-18: the art and science of late stage fluorination. *Curr. Top. Med. Chem.* **2014**, *14*, 875−900. (b) Neumann, C. N.; Hooker, J. M.; Ritter, T. Concerted nucleophilic aromatic substitution with $^{19}F^-$ and $^{18}F^-$. *Nature* **2016**, *534*, 369−373. (c) Telu, S.; Siméon, F. G.; Lu, S.; Pike, V. W. Hypervalent iodine compounds as precursors for biomedical radiotracers. In *The Chemistry of Hypervalent Halogen Compounds*; Patai's Chemistry of Functional Groups; John Wiley & Sons, Ltd: New York, DOI: 10.1002/9780470682531.pat0955. Published online: June 13, 2018. https://onlinelibrary.wiley.com/doi/full/10.1002/9780470682531.pat0955 (accessed November 12, 2018). (d) Pike, V. W. Hypervalent aryliodine compounds as precursors for radiofluorination. *J. Labelled Compd. Radiopharm.* **2018**, *61*, 196−227.

(7) Campbell, M. G.; Ritter, T. Modern carbon−fluorine bond forming reactions for aryl fluoride synthesis. *Chem. Rev.* **2015**, *115*, 612−633.

(8) (a) Yusubov, M. S.; Svitich, D. Yu.; Larkina, M. S.; Zhdankin, V. V. Applications of iodonium salts and iodonium ylides as precursors for nucleophilic fluorination in positron emission tomography. *ARKIVOC* **2013**, 364−395. (b) Cai, L.; Lu, S.; Pike, V. W. Chemistry with [^{18}F]fluoride ion. *Eur. J. Org. Chem.* **2008**, *2008*, 2853−2873. (c) Cardinale, J.; Ermert, J.; Humpert, S.; Coenen, H. H. Iodonium ylides for one-step, no-carrier-added radiofluorination of electron rich arenes, exemplified with 4-(([^{18}F]fluorophenoxy)-phenylmethyl)-piperidine NET and SERT ligands. *RSC Adv.* **2014**, *4*, 17293−17299. (e) Rotstein, B. H.; Stephenson, N. A.; Vasdev, N.; Liang, S. H. Spirocyclic hypervalent iodine(III)-mediated radiofluorination of non-activated and hindered aromatics. *Nat. Commun.* **2014**, *5*, 4365.

(9) Chun, J.-H.; Morse, C. L.; Chin, F. T.; Pike, V. W. No-carrier-added [^{18}F]fluoroarenes from the radiofluorination of diaryl sulfoxides. *Chem. Commun.* **2013**, *49*, 2151−2153.

(10) (a) Sander, K.; Gendron, T.; Yiannaki, E.; Cybulska, K.; Kalber, T. L.; Lythgoe, M. F.; Årstad, E. Sulfonium salts as leaving groups for aromatic labelling of drug-like small molecules with fluorine-18. *Sci. Rep.* **2015**, *5*, 9941. (b) Mu, L.; Fischer, C. R.; Holland, J. P.; Becaud, J.; Schubiger, P. A.; Schibli, R.; Ametamey, S. M.; Graham, K.; Stellfeld, T.; Dinkelborg, L. M.; Lehmann, L. ^{18}F-Radiolabeling of aromatic compounds using triarylsulfonium Salts. *Eur. J. Org. Chem.* **2012**, *2012*, 889−892.

(11) (a) Wilson, T. C.; Cailly, T.; Gouverneur, V. Boron reagents for divergent radiochemistry. *Chem. Soc. Rev.* **2018**, *47*, 6990−7005. (b) Tredwell, M.; Preshlock, S. M.; Taylor, N. J.; Gruber, S.; Huiban, M.; Passchier, J.; Mercier, J.; Génicot, C.; Gouverneur, V. A general copper-mediated nucleophilic ^{18}F fluorination of arenes. *Angew. Chem., Int. Ed.* **2014**, *53*, 7751−7755. (c) Makaravage, K. J.; Brooks, A. F.; Mossine, A. V.; Sanford, M. S.; Scott, P. J. H. Copper-mediated radiofluorination of arylstannanes with [^{18}F]KF. *Org. Lett.* **2016**, *18*, 5440−5443. (d) Mossine, A. V.; Brooks, A. F.; Makaravage, K. J.; Miller, J. M.; Ichiishi, N.; Sanford, M. S.; Scott, P. J. H. Synthesis of [^{18}F]arenes via the copper-mediated [^{18}F]fluorination of boronic acids. *Org. Lett.* **2015**, *17*, 5780−5783. (e) Beyzavi, M. H.; Mandal, D.; Strebl, M. G.; Neumann, C. N.; D'Amato, E. M.; Chen, J.; Hooker, J. M.; Ritter, T. ^{18}F-Deoxyfluorination of phenols via Ru π-complexes. *ACS Cent. Sci.* **2017**, *3*, 944−948. (f) Hoover, A. J.; Lazari, M.; Ren, H.; Narayanam, M. K.; Murphy, J. M.; van Dam, R. M.; Hooker, J. M.; Ritter, T. A transmetalation reaction enables the synthesis of [^{18}F]5-fluorouracil from [^{18}F]fluoride for human PET imaging. *Organometallics* **2016**, *35*, 1008−1014. (g) Lee, E.; Hooker, J. M.; Ritter, T. Nickel-mediated oxidative fluorination for PET with aqueous [^{18}F]fluoride. *J. Am. Chem. Soc.* **2012**, *134*, 17456−17458.

(12) Haskali, M. B.; Telu, S.; Lee, Y.-S.; Morse, C. L.; Lu, S.; Pike, V. W. An investigation of (diacetoxyiodo)arenes as precursors for preparing no-carrier-added [^{18}F]fluoroarenes from cyclotron-produced [^{18}F]fluoride ion. *J. Org. Chem.* **2016**, *81*, 297−302.

(13) Satyamurthy, N.; Barrio, J. R. Nucleophilic fluorination of aromatic compounds. WO2010/008522A2, 2010.

(14) Hussain, H.; Al-Harrasi, A.; Green, I. R.; Ahmed, I.; Abbas, G.; Ur Rehman, N. *meta*-Chloroperbenzoic acid (*m*CPBA): a versatile reagent in organic synthesis. *RSC Adv.* **2014**, *4*, 12882−12917.

(15) (a) Stephenson, N. A.; Holland, J. P.; Kassenbrock, A.; Yokell, D. L.; Livni, E.; Liang, S. H.; Vasdev, N. Iodonium ylide−mediated radiofluorination of ^{18}F-FPEB and validation for human use. *J. Nucl. Med.* **2015**, *56*, 489−492. (b) Seidl, T. L.; Sundalam, S. K.; McCullough, B.; Stuart, D. R. Unsymmetrical aryl(2,4,6-trimethoxyphenyl)iodonium salts: one-pot synthesis, scope, stability, and synthetic studies. *J. Org. Chem.* **2016**, *81*, 1998−2009. (c) Lindstedt, E.; Reitti, M.; Olofsson, B. One-pot synthesis of unsymmetric diaryliodonium salts from iodine and arenes. *J. Org. Chem.* **2017**, *82*, 11909−11914.

(16) Bravo, A.; Fontana, F.; Fronza, G.; Minisci, F.; Serri, A. Oxidation of alkyl and aryl iodides, phenylacetaldehyde and alkenes by dimethyldioxirane. Reaction products and mechanism. *Tetrahedron Lett.* **1995**, *36*, 6945−6948.

(17) (a) Kazmierczak, P.; Skulski, L.; Kraszkiewicz, L. Syntheses of (diacetoxyiodo)arenes or iodylarenes from iodoarenes, with sodium periodate as the oxidant. *Molecules* **2001**, *6*, 881−891. (b) Kraszkiewicz, L.; Skulski, L. Optimized syntheses of iodylarenes from iodoarenes, with sodium periodate as the oxidant. Part II. *ARKIVOC* **2003**, 120−125.

(18) Ross, T. L.; Ermert, J.; Hocke, C.; Coenen, H. H. Nucleophilic ^{18}F-fluorination of heteroaromatic iodonium salts with no-carrier-added [^{18}F]fluoride. *J. Am. Chem. Soc.* **2007**, *129*, 8018−8025.

(19) Chun, J.-H.; Lu, S.; Lee, Y.-S.; Pike, V. W. Fast and high-yield microreactor syntheses of *ortho*-substituted [^{18}F]fluoroarenes from reactions of [^{18}F]fluoride ion with diaryliodonium salts. *J. Org. Chem.* **2010**, *75*, 3332−3338.

(20) Grushin, V. V.; Marshall, W. J. Fluorination of nonactivated haloarenes via arynes under mild conditions, resulting from further studies toward Ar-F reductive elimination from palladium(II). *Organometallics* **2008**, *27*, 4825−4828.

(21) Vaidyanathan, G.; Zalutsky, M. R. Synthesis of *N*-succinimidyl 4-[^{18}F]fluorobenzoate, an agent for labeling proteins and peptides with ^{18}F. *Nat. Protoc.* **2006**, *1*, 1655−1661.

(22) Ross, T. L.; Ermert, J.; Coenen, H. H. Synthesis of no-carrier-added 4-[^{18}F]Fluorophenol from 4-benzyloxyphenyl-(2-thienyl)-iodonium bromide. *Molecules* **2011**, *16*, 7621−7626.

DOI: 10.1021/acs.orglett.8b03450
Org. Lett. XXXX, XXX, XXX−XXX