

# An Investigation of (Diacetoxyiodo)arenes as Precursors for Preparing No-Carrier-Added [ $^{18}\text{F}$ ]Fluoroarenes from Cyclotron-Produced [ $^{18}\text{F}$ ]Fluoride Ion

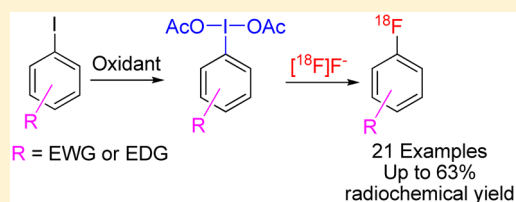
Mohammad B. Haskali,<sup>†</sup> Sanjay Telu,<sup>†</sup> Yong-Sok Lee,<sup>‡</sup> Cheryl L. Morse,<sup>†</sup> Shuiyu Lu,<sup>†</sup> and Victor W. Pike<sup>\*,†</sup>

<sup>†</sup>Molecular Imaging Branch, National Institute of Mental Health, National Institutes of Health, Building 10, Room B3 C346A, 10 Center Drive, Bethesda, Maryland 20892-1003, United States

<sup>‡</sup>Center for Molecular Modeling, Division of Computational Bioscience, Center for Information Technology, National Institutes of Health, Building 12A, Room 2049, 12 South Drive, Bethesda, Maryland 20892-5624, United States

## S Supporting Information

**ABSTRACT:** Treatment of (diacetoxyiodo)arenes (**1a–1u**) with cyclotron-produced [ $^{18}\text{F}$ ]fluoride ion rapidly affords no-carrier-added [ $^{18}\text{F}$ ]fluoroarenes (**2a–2u**) in useful yields and constitutes a new method for converting substituted iodoarenes into substituted [ $^{18}\text{F}$ ]fluoroarenes in just two steps.



Useful methods for the rapid preparation of [ $^{18}\text{F}$ ]fluoroarenes at high specific activity from cyclotron-produced no-carrier-added (NCA) [ $^{18}\text{F}$ ]fluoride ion ( $t_{1/2} = 109.7$  min) are in high demand because of increasing interest in the use of  $^{18}\text{F}$ -labeled tracers in imaging studies with positron emission tomography (PET).<sup>1</sup> In the context of the need for rapidly preparing PET radiotracers for injection into animal or human subjects with minimal separation challenge, metal-free methods are particularly desirable. In this regard, the use of hypervalent diaryliodonium salts<sup>2–4</sup> or iodonium ylides<sup>5,6</sup> as precursors for preparing [ $^{18}\text{F}$ ]fluoroarenes has already come to the fore in expanding substrate scope beyond those of traditional methods, such as classical aromatic nucleophilic substitution or the earlier Balz Schiemann and Wallach reactions.<sup>7,8</sup> Here, we report on the reactivity of a further class of hypervalent precursor that also shows value for preparing [ $^{18}\text{F}$ ]fluoroarenes, namely, the previously unexplored (diacetoxyiodo)arenes.

(Diacetoxyiodo)arenes are often intermediates in the synthesis of diaryliodonium salts<sup>9</sup> and iodonium ylides<sup>6,10</sup> and are useful reagents for oxidation reactions.<sup>11</sup> They may be prepared from iodoarenes,<sup>12–17</sup> do not form extended oligomeric structures, and are readily soluble in many solvents, including DMF. For these encouraging reasons, we were interested to explore whether (diacetoxyiodo)arenes were themselves amenable to radiofluorination to produce NCA [ $^{18}\text{F}$ ]fluoroarenes.

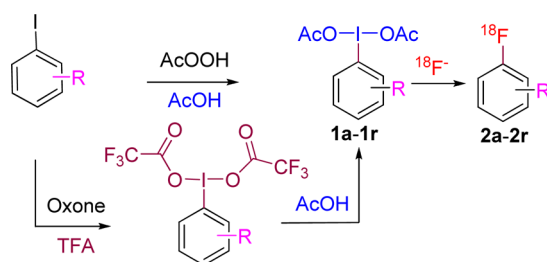
Upon treatment of a  $\lambda^3$ -iodane ( $\text{ArIL}_2$ ), such as a (diacetoxyiodo)arene, with an external nucleophile ( $\text{Nu}$ ), ligand exchange may take place to form an  $\text{ArI}(\text{Nu})\text{L}$  adduct.<sup>17</sup> Thus, it has been postulated that an  $\text{ArI}(\text{F})\text{OAc}$  adduct forms when a (diacetoxyiodo)arene is treated with HF as a source of  $\text{F}^-$  ion.<sup>18</sup> In the presence of excess HF, (diacetoxyiodo)arenes

are also known to give the (difluoroiodo)arenes,<sup>18</sup> presumably via the postulated adducts. Moreover, treatment of (diacetoxyiodo)benzene with  $\text{Bu}_4\text{NF}$  has also been found to constitute a convenient synthesis for the well-known compound, (difluoroiodo)benzene.<sup>19</sup> These prior observations reinforced our interest in testing whether treatment of (diacetoxyiodo)arenes with NCA [ $^{18}\text{F}$ ]fluoride ion would generate  $\text{ArI}(\text{F})\text{OAc}$  adducts and whether they may be converted into NCA [ $^{18}\text{F}$ ]fluoroarenes.

To explore the radiofluorination of (diacetoxyiodo)arenes, several substituted (diacetoxyiodo)arenes (**1a–1r**) were readily prepared in one step and in moderate to high yields from the corresponding iodoarenes, generally by treatment with peracetic acid (see the [Experimental Section](#)).<sup>4,11,13,15,20</sup> Exceptionally, oxidation of 1-iodo-4-(trifluoromethyl)benzene by peracetic acid gave not the (diacetoxyiodo)arene but the bridged compound  $\mu$ -oxa-bis[(acetoxyiodo)-4-trifluoromethylbenzene] (**1s**; structure shown in the [Supporting Information](#)), as characterized by NMR and MS data (see the [Experimental Section](#)). Such bridged compounds may arise from hydrolysis of the corresponding (diacetoxyiodo)arenes when they bear a strong electron-withdrawing group. Iodoarenes containing a strongly electron-withdrawing nitro substituent in position 4 or a cyano substituent in either positions 3 or 4 were best converted into the corresponding (diacetoxyiodo)arenes by initial oxone oxidation in trifluoroacetic acid, followed by ligand exchange in acetic acid ([Figure 1](#)).<sup>21</sup>

Radiochemical experiments were performed within a microfluidic apparatus (NanoTek; Advion, Ithaca, NY), which

**Received:** October 9, 2015



**Figure 1.** Syntheses of (diacetoxyiodo)arenes (**1a–1r**) from iodoarenes and their conversion into [ $^{18}\text{F}$ ]fluoroarenes.

allowed us to control reagent stoichiometry, temperature, and residence time in each single experimental run of a consecutive series on any particular (diacetoxyiodo)arene.<sup>20,22</sup>

Initially, we explored the reaction of 4-(diacetoxyiodo)benzonitrile (**1b**) with NCA [ $^{18}\text{F}$ ]fluoride ion, with  $\text{TBA}^+$  as counterion, in DMF. Gratifyingly, [ $^{18}\text{F}$ ]4-fluorobenzonitrile (**2b**) was produced rapidly (90 s) in 11% radiochemical yield at 150 °C (entry 1, Table 1) and also in much higher

**Table 1.** Yields of [ $^{18}\text{F}$ ]4-Fluorobenzonitrile (**2b**) from **1b** under Various Conditions<sup>a</sup>

| entry          | <b>1b</b> conc. (mM) | temp. (°C) | time (s) | yield <sup>b</sup> (%) |
|----------------|----------------------|------------|----------|------------------------|
| 1              | 10                   | 150        | 90       | 11                     |
| 2              | 10                   | 200        | 90       | 31                     |
| 3 <sup>c</sup> | 10                   | 200        | 90       | 31                     |
| 4 <sup>d</sup> | 10                   | 200        | 90       | 19                     |
| 5 <sup>e</sup> | 10                   | 200        | 90       | 7                      |
| 6              | 10                   | 200        | 45       | 21                     |
| 7              | 10                   | 200        | 180      | 25                     |
| 8              | 5                    | 200        | 90       | 54                     |

<sup>a</sup>Reactions were performed by treating **1b** in DMF with [ $^{18}\text{F}$ ] $\text{Bu}_4\text{N}^+\text{F}^-$  under the stated conditions. <sup>b</sup>Based on non-decay-corrected radiochemical conversion of [ $^{18}\text{F}$ ]fluoride ion measured with HPLC. <sup>c</sup>Reaction performed with  $\text{K}^+\text{-K 2.2.2}$  complex. <sup>d</sup>Reaction in DMSO. <sup>e</sup>Reaction in DMA.

radiochemical yield (31%) at 200 °C (entry 2). Replacement of  $\text{TBA}^+$  with  $\text{K}^+\text{-K 2.2.2}$  (entry 3), which is also commonly used as a solubilizing counterion for NCA [ $^{18}\text{F}$ ]fluoride ion,<sup>1</sup> gave the same radiochemical yield. Reactions performed in either DMSO or DMA (entries 4 and 5) gave inferior radiochemical yields to that in DMF. Optimal residence time in the microreactor was found to be 90 s from the use of a 5  $\mu\text{L}/\text{min}$  flow rate for the input of each reagent (compare entry 2 with entries 6 and 7). The radiochemical yield of **2b** increased

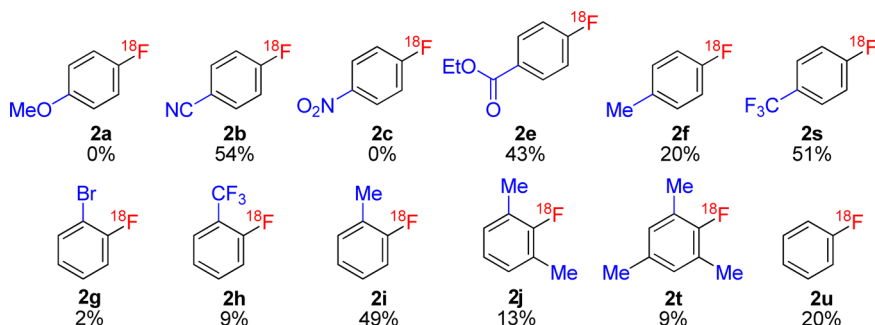
significantly when the precursor concentration was decreased to 5 mM (entry 8). Therefore, the conditions listed in entry 8 were preferred for subsequent radiofluorination experiments on a range of variously substituted (diacetoxyiodo)arenes, and also on (diacetoxyiodo)benzene (**1u**).

(Diacetoxyiodo)benzene (**1u**) gave a modest yield (20%) of [ $^{18}\text{F}$ ]fluorobenzene (**2u**) (Figure 2), whereas 4-(diacetoxyiodo)anisole (**1a**) gave no desired product. 4-(Diacetoxyiodo)toluene (**1f**) also gave a modest yield of [ $^{18}\text{F}$ ]4-fluorotoluene (**2f**; 20%). As already seen for **1b**, radiochemical yield improved appreciably with a weak electron-withdrawing group ( $\text{CO}_2\text{Et}$ , **1e**; 43%) in the para position (Figure 2). However, 4-(diacetoxyiodo)nitrobenzene (**1c**) gave no desired product (Figure 2).

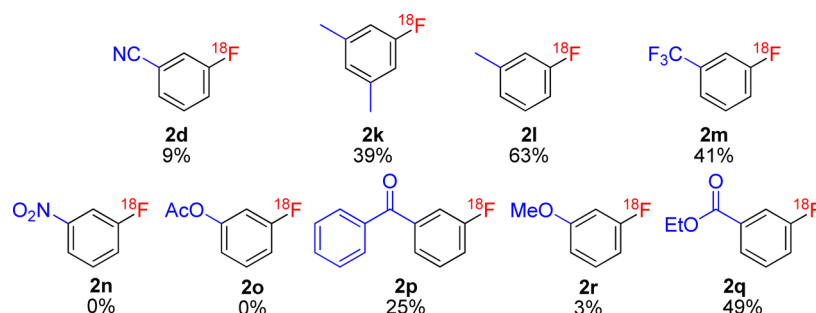
Interestingly, upon subjecting the bridged compound **1s** to the same reaction conditions, [ $^{18}\text{F}$ ]1-fluoro-4-(trifluoromethyl)benzene (**2s**) was obtained in remarkably high radiochemical yield (51%). This indicates that modification of the substituents bonded through oxygen to the hypervalent iodine could be fruitful for future improvement of reaction yields. Preliminary experiments have shown that replacements of the diacetoxy groups with pivaloyl or trifluoroacetyl groups are tolerated (data not shown).

An unusual reactivity pattern was observed for ortho-substituted (diacetoxyiodo)arenes (Figure 2). Those with electron-withdrawing groups, such as 2-(diacetoxyiodo)-bromobenzene (**1g**) and 2-(diacetoxyiodo)trifluoromethylbenzene (**1h**), gave the desired [ $^{18}\text{F}$ ]fluoroarenes, **2g** and **2h**, in low radiochemical yields. By contrast, 2-(diacetoxyiodo)-toluene (**1i**) gave a moderately high yield of [ $^{18}\text{F}$ ]2-fluorotoluene (**2i**; 49%). This suggested that an “ortho effect” may be operating in a manner similar to that which is well-known for the radiofluorination of diaryliodonium salts.<sup>20</sup> However, addition of a methyl group to the other ortho position, or to both the other ortho and para positions, decreased yields (**2j** and **2t**, respectively). Nonetheless, the tolerance of these reactions for weakly electron-donating methyl groups is quite striking.

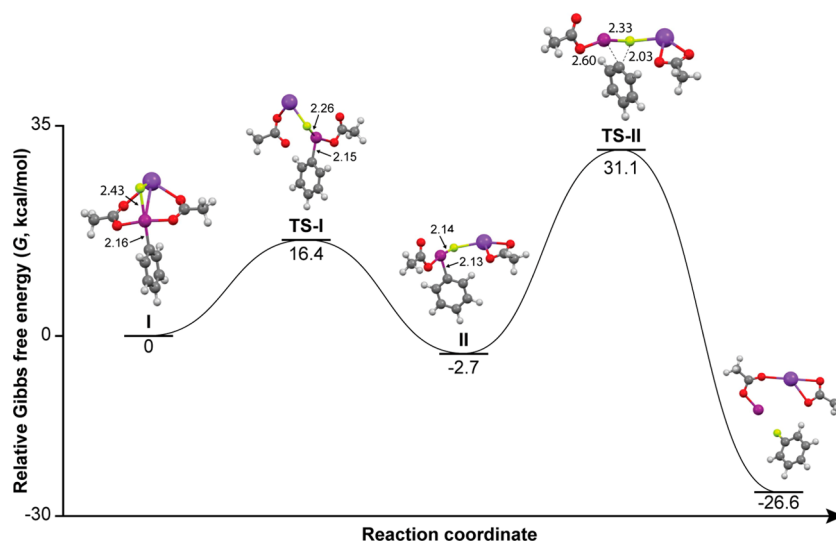
With regard to meta-substituted (diacetoxyiodo)arenes, some compounds with electron-withdrawing substituents, such as  $\text{CF}_3$  (**1m**),  $\text{PhCO}$  (**1p**), and  $\text{CO}_2\text{Et}$  (**1q**), gave appreciable yields of the respective substituted [ $^{18}\text{F}$ ]fluoroarenes (**2m**, **2p**, and **2q**), whereas the compound with a CN substituent (**1d**) gave a low yield and the compounds with a nitro (**1n**) or acetyl (**1o**) substituent gave no desired product (Figure 3). Generally, the introduction of [ $^{18}\text{F}$ ]fluoride ion into an aryl meta position with respect to an electron-donating group is especially challenging. Remarkably, the



**Figure 2.** Para- and ortho-substituted [ $^{18}\text{F}$ ]fluoroarenes prepared from the corresponding (diacetoxyiodo)arenes (except **2s** was prepared from bridged compound **1s**). Yields represent radiochemical conversion of [ $^{18}\text{F}$ ]fluoride ion, measured with HPLC.



**Figure 3.** Meta-substituted [ $^{18}\text{F}$ ]fluoroarenes prepared from the corresponding (diacetoxyiodo)arenes. Yields represent radiochemical conversion of [ $^{18}\text{F}$ ]fluoride ion, measured with HPLC.



**Figure 4.** Reaction coordinate for the interaction of fluoride ion with **1u** (see the [Experimental Section](#) for quantum chemical calculation). TS-I and TS-II represent transition states I and II, respectively. Atoms are colored as follows: white, hydrogen; gray, carbon; yellow, fluorine; purple, iodine; red, oxygen; blue, potassium. Distances are in Å.

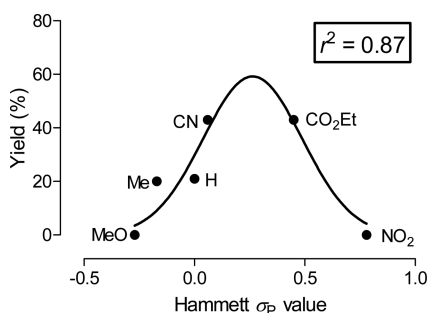
compound with a 3-methyl group (**1l**) gave 3-[ $^{18}\text{F}$ ]fluorotoluene (**2l**) with the highest radiochemical yield (63%) of all tested compounds, and the 3,5-dimethyl compound (**1k**) gave a moderately useful yield of compound (**2k**) (39%) (Figure 3). The 3-methoxy compound (**1r**) gave very low yield (3%).

In order to gain some mechanistic insight on the reactions observed between [ $^{18}\text{F}$ ]fluoride ion and (diacetoxyiodo)arenes, we performed experiments to examine whether 3-(diacetoxyiodo)toluene (**1l**) undergoes ligand exchange with  $\text{Bu}_4\text{NF}\cdot\text{hydrate}$ . The latter (0.83 equiv) was added to **1l** (1 equiv) in chloroform. Upon exposing this solution to slow ingress of diethyl ether, crystals formed overnight.  $^1\text{H}$  NMR spectroscopy revealed that these crystals were  $\text{Bu}_4\text{NOAc}$  unaccompanied by fluoride ion, as determined by the absence of an  $^{19}\text{F}$  NMR signal. Furthermore, the  $^{19}\text{F}$  NMR spectrum of the remaining filtrate presented a single signal ( $-131$  ppm relative to the signal from  $\text{CFCl}_3$ ) that was significantly different from that of  $\text{Bu}_4\text{NF}\cdot\text{hydrate}$  ( $-122$  ppm). This experiment affirmed the ability of fluoride ion to undergo ligand exchange at the iodine center of a (diacetoxyiodo)arene.

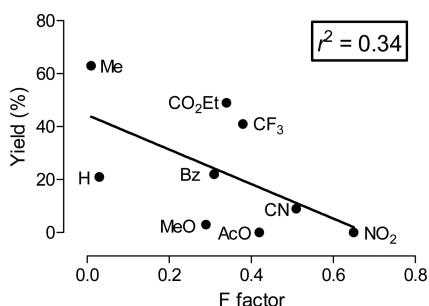
Encouraged by these observations, we also performed quantum chemical calculations to assess the energetics for ligand exchange of fluoride ion with (diacetoxyiodo)benzene (**1u**) and for subsequent conversion of the postulated intermediate adduct into fluorobenzene. These calculations

predict that the formation of (acetoxyfluoriodo)benzene is thermodynamically favored with a low energy barrier of  $16.4$  kcal  $\text{mol}^{-1}$  (Figure 4). Moreover, the conversion of **1u** into fluorobenzene was calculated to have a free energy of activation ( $\Delta G^\ddagger$ ) of  $33.8$  kcal  $\text{mol}^{-1}$  with respect to the intermediate state (**II**), with energetically favored formation of fluorobenzene (relative free energy  $-26.6$  kcal  $\text{mol}^{-1}$ ). In terms of bond distances, the covalent Ar–I distance shortens slightly from  $2.16$  Å in the first stage (**I**) to  $2.13$  Å in **II**, while the ionic I–F bond ( $2.43$  Å) in **I** becomes covalent ( $2.14$  Å) in **II**. At transition state **II** (TS-II), this covalent Ar–I bond is lengthened to  $2.60$  Å, and the fluorine forms a partial bond ( $2.03$  Å) with the *ipso* aryl carbon atom.

We further noted that radiochemical yields of para-substituted [ $^{18}\text{F}$ ]fluoroarenes were not linear with substituent Hammett  $\sigma_p$  constants<sup>23</sup> but showed a bell-shaped relationship (Figure 5). This may indicate that the rate-determining step of the reaction (and/or the mechanism itself) changes with increasing  $\sigma_p$  value. For meta-substituted [ $^{18}\text{F}$ ]fluoroarenes, no such clear relationship was seen between radiochemical yields and Hammett  $\sigma_m$  values. However, a weak inverse relationship between radiochemical yield and the  $F$  (field) factors<sup>23</sup> was observed (Figure 6). This indicates that inductive effects are somewhat important for the radiofluorination of (diacetoxyiodo)arenes with meta substituents. Overall, the mechanisms of



**Figure 5.** Radiochemical yields of *p*-[<sup>18</sup>F]fluoroarenes show a strong bell-shaped relationship to Hammett  $\sigma_p$  values. The line represents a Gaussian fit of the data and  $r$  the correlation coefficient.



**Figure 6.** Radiochemical yields of *m*-[<sup>18</sup>F]fluoroarenes show a weak linear relationship with  $F$  values. The line represents a linear fit of the data and  $r$  the correlation coefficient.

these reactions appear complex and heterogeneous and require deeper investigation for full understanding.

Finally, we explored whether radiofluorinations of (diacetoxyiodo)arenes could also be achieved on a conventional automated batch-reactor platform, such as the TRACERlab FX<sub>FN</sub> module, which is more widely used for PET radiotracer productions than microfluidic platforms. The treatment of **1d** (5 mM) with [<sup>18</sup>F]fluoride ion-TBA<sup>+</sup> in DMF for 5 min at 170 °C gave **2d** in 20% radiochemical yield on this module. When the bridged compound **1s** was subjected to these conditions, **2s** was obtained in 63% radiochemical yield. [<sup>18</sup>F]N-Succinimidyl 4-fluorobenzoate is a useful labeling synthon for biomolecules, which is usually prepared from [<sup>18</sup>F]ethyl 4-fluorobenzoate (**2e**) as intermediate.<sup>24,25</sup> We found that the treatment of **1e** readily gave **2e** in a useful 32% radiochemical yield. Recoveries of radioactivity from the TRACERlab FX<sub>FN</sub> module in these reactions ranged from 60% to 79%, which are typical for other radiofluorination procedures. Thus, reactions in the more conventional FX<sub>FN</sub> module also rapidly gave useful practical yields, even at lower temperature than in the microfluidic apparatus.

In conclusion, the treatment of (diacetoxyiodo)arenes with NCA [<sup>18</sup>F]fluoride ion proved viable for preparing several substituted [<sup>18</sup>F]fluoroarenes in moderate to good radiochemical yields, especially [<sup>18</sup>F]fluoroarenes having a range of strong para electron-withdrawing substituents and [<sup>18</sup>F]fluoroarenes that have methyl groups in the meta position. This method is a useful supplement to others for preparing NCA [<sup>18</sup>F]fluoroarenes to serve as labeling synthons or radiotracers from hypervalent precursors. Especially, this method constitutes a novel two-step procedure for converting a substituted iodoarene into a substituted [<sup>18</sup>F]fluoroarene.

## EXPERIMENTAL SECTION

**Materials and Methods.** Fluoroarenes, 3-iodobenzophenone, (diacetoxyiodo)benzene (**1u**), (diacetoxyiodo)2,4,6-trimethylbenzene (**1t**), and other chemicals and solvents were purchased commercially. <sup>1</sup>H (400 MHz), <sup>13</sup>C (100 MHz), and <sup>19</sup>F (376.5 MHz) NMR spectra were recorded on an Avance 400 instrument at rt in deuterated solvents, as later indicated. <sup>1</sup>H and <sup>13</sup>C NMR signals are reported as  $\delta$  (ppm) downfield from the signal for tetramethylsilane. <sup>19</sup>F NMR signals are reported as  $\delta$  (ppm) downfield from the signal for trichlorofluoromethane. ESI-MS spectra could not be obtained for (diacetoxyiodo)arenes in keeping with the absence of such spectra for all such compounds in this study that had been reported previously. However, ESI-MS data for the bridged compound **1s** were successfully obtained. An aqueous Bu<sub>4</sub>NHCO<sub>3</sub> solution of approximately 1 M concentration was prepared for radiochemical experiments by passing carbon dioxide gas through an aqueous solution of Bu<sub>4</sub>NOH (0.5 mL, 1 M). The pH of the reaction mixture was monitored. As the pH dropped to about 8 and remained stable, the flow of carbon dioxide through the solution mixture was ended and the volume was brought back to 0.5 mL. Bu<sub>4</sub>NHCO<sub>3</sub> was stored at 4 °C and discarded after 1 week of use.

For radiochemical experiments with K<sup>+</sup>-kryptofix 2.2.2 (K 2.2.2) as counterion, a solution composed of K 2.2.2 (101 mg in 1.8 mL MeCN) and K<sub>2</sub>CO<sub>3</sub> (10.5 mg in 0.2 mL H<sub>2</sub>O) solution was prepared.

**Quantum Chemical Calculations.** The X-ray structure of **1u**<sup>26</sup> was used to build **1u** complexed with potassium fluoride. The geometry and energetics of this complex were then obtained by resorting to quantum chemical calculations at the level of B3LYP/DGDZVP. The reaction path in the gaseous phase was constructed by moving a fluoride ion to the *ipso* aryl carbon atom in increments of 0.1 Å while relaxing the rest of the geometry. At each stationary point, the geometry was then further refined in the reaction field of MeCN with the polarizable continuum model together with the UAQS parameters set as implemented in the Gaussian 09 software.<sup>27</sup> A single imaginary frequency was obtained for each TS in Figure 4.

**Syntheses of (Diacetoxyiodo)arenes.** All (diacetoxyiodo)arenes were obtained in  $\geq 95\%$  purity, before or after recrystallization from hot ethyl acetate and hexane, as required.

**4-(Diacetoxyiodo)anisole (1a).** Sodium perborate monohydrate (30 mmol) was added portionwise to a solution of 4-iodoanisole (3 mmol) in AcOH:Ac<sub>2</sub>O (1:1 v/v, 60 mL) over 5 min at rt. The mixture was then heated to 40 °C and left stirring overnight. Reaction progress was monitored with tlc, and when complete, the reaction mixture was filtered. The filtrate was extracted with DCM (50 mL) and washed with water (50 mL  $\times$  3). The organic solvent was then evaporated off under vacuum. The residual oil was triturated with ether (10 mL). The generated solid was rinsed with diethyl ether (10 mL  $\times$  3) and dried under vacuum to provide **1a** as a fluffy white solid (0.475 g, 45%). <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  8.01 (d, 2H,  $J$  = 9.0 Hz), 6.97 (d, 2H,  $J$  = 9.0 Hz), 3.86 (s, 3H), 2.00 (s, 6H). These data match literature data.<sup>16</sup>

**General Method A.** Oxone monopersulfate (0.92 g, 3 mmol) was added to a solution of the iodoarene in TFA:DCM (70:30 v/v; 20 mL), and the resultant mixture was stirred at rt. The reaction was monitored with tlc and was over in less than 1 h. Solvents were then removed under vacuum. The residual oil was extracted with DCM and washed with water (50 mL  $\times$  3). The organic solvent was then evaporated off under vacuum. The residual oil was resuspended in AcOH (10 mL) for 1 h. Water (100 mL) was then added, giving a precipitate that was washed successively with water (15 mL  $\times$  3), diethyl ether (10 mL  $\times$  3), and hexanes (10 mL  $\times$  3), and then dried under vacuum for 2 h.

Thus, were prepared:

**4-(Diacetoxyiodo)benzonitrile (1b).** 4-Iodobenzonitrile (0.69 g, 3 mmol) gave **1b** as white crystals (0.781 g, 75%). <sup>1</sup>H NMR (*d*<sub>6</sub>-DMSO):  $\delta$  8.43 (d, 2H,  $J$  = 8.7 Hz), 8.04 (d, 2H,  $J$  = 8.7 Hz), 1.93 (s, 6H). <sup>13</sup>C NMR (*d*<sub>6</sub>-DMSO):  $\delta$  175.8, 136.3, 134.9, 118.1, 114.9, 20.6. These data match literature data.<sup>28</sup>

**4-(Diacetoxyiodo)nitrobenzene (1c).** 4-Iodonitrobenzene (0.75 g, 3 mmol) gave **1c** as pale yellow crystals (0.80 g, 73%). <sup>1</sup>H NMR (*d*<sub>6</sub>-

DMSO):  $\delta$  8.52 (d, 2H,  $J$  = 8.9 Hz), 8.34 (d, 2H,  $J$  = 9.0 Hz), 1.94 (s, 6H).  $^{13}\text{C}$  NMR ( $d_6$ -DMSO):  $\delta$  175.2, 149.1, 136.4, 128.3, 125.7, 20.1. These data match literature data.<sup>11</sup>

**3-(Diacetoxyiodo)benzonitrile (1d).** 3-Iodobenzonitrile (0.69 g, 3 mmol) gave **1d** as white crystals (0.822 g, 76%).  $^1\text{H}$  NMR ( $d_6$ -DMSO):  $\delta$  8.36 (t, 1H,  $J$  = 1.3 Hz), 8.31 (dq, 1H,  $J$  = 5.4, 1.1 Hz), 7.88 (dt, 1H,  $J$  = 1.1, 5.4 Hz), 7.64 (t, 1H,  $J$  = 8.0 Hz), 2.04 (s, 6H).  $^{13}\text{C}$  NMR ( $d_6$ -DMSO):  $\delta$  176.8, 138.9, 138.1, 134.9, 131.4, 120.9, 116.7, 115.1, 20.3. These data match literature data.<sup>22</sup>

**General Method B.** Peracetic acid (32 wt %; 10 mL) was added dropwise to a solution of the appropriate iodoarene (3 mmol) in  $\text{AcOH}:\text{Ac}_2\text{O}$  (1:1 v/v; 5 mL) at  $-10^\circ\text{C}$ . This mixture was slowly warmed to rt and left stirring. Reaction progress was monitored with tlc, and when complete, water (100 mL) was added to the mixture. If a precipitate was generated, this was then washed successively with water (15 mL  $\times$  3), ether (10 mL  $\times$  3), and hexanes (10 mL  $\times$  3), and then dried under vacuum for 2 h to give the product (diacetoxyiodo)-arene. In cases of no precipitation, the aqueous mixture was extracted with DCM (50 mL  $\times$  3), and the combined organic extracts were evaporated under vacuum. The resultant oil was then triturated with ether (10 mL). Any solid was then rinsed with ether (10 mL  $\times$  3) and dried under vacuum to give the product (diacetoxyiodo)arene. In cases where trituration gave no solid, hexane (10 mL) was added and the mixture was cooled in a fridge until the product (diacetoxyiodo)arene precipitated out. This precipitate was then washed with hexanes (10 mL  $\times$  3) and dried in vacuo for 2 h.

Thus, were prepared:

**Ethyl 4-(Diacetoxyiodo)benzoate (1e).** White solid (0.576 g, 56%). m.p.:  $110\text{--}113^\circ\text{C}$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  8.17–8.12 (m, 4H), 4.42 (q, 2H,  $J$  = 7.1 Hz), 2.02 (s, 6H), 1.41 (t, 3H,  $J$  = 7.1 Hz).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  176.5, 165.0, 134.9, 133.5, 131.8, 125.7, 61.7, 20.3, 14.3.

**4-(Diacetoxyiodo)toluene (1f).** Fluffy white solid (0.323 g, 32%).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.98 (d, 2H,  $J$  = 7.3 Hz), 7.29 (d, 2H,  $J$  = 8.0 Hz), 2.44 (s, 3H), 2.00 (s, 6H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  176.0, 142.9, 134.9, 131.4, 117.0, 20.2, 19.1. These data match literature data.<sup>11</sup>

**2-(Diacetoxyiodo)bromobenzene (1g).** White solid (0.806 g, 67%).  $^1\text{H}$  NMR ( $d_6$ -DMSO):  $\delta$  8.48 (d, 1H, 8.0), 8.03 (d, 1H,  $J$  = 8.0 Hz), 7.62 (t, 1H,  $J$  = 7.3 Hz), 7.53 (t, 1H,  $J$  = 7.2 Hz), 1.92 (s, 6H).  $^{13}\text{C}$  NMR ( $d_6$ -DMSO):  $\delta$  176.2, 139.5, 134.8, 133.4, 131.0, 129.0, 127.1, 20.6. These data match literature data.<sup>20</sup>

**2-(Diacetoxyiodo)trifluoromethylbenzene (1h).** White solid (0.644 g, 55%). m.p.:  $148\text{--}150^\circ\text{C}$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  8.48 (d, 1H,  $J$  = 7.8 Hz), 7.95 (dd, 1H,  $J$  = 6.7, 1.1 Hz), 7.79 (t, 1H,  $J$  = 7.6 Hz), 7.67 (dt, 1H,  $J$  = 7.6, 1.0 Hz), 1.97 (s, 6H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  176.9, 140.1, 134.3, 132.4, 131.4 (q,  $J$  = 32.3 Hz), 128.0 (q,  $J$  = 5.1 Hz), 122.6 (q,  $J$  = 274.4 Hz), 117.8, 20.2.  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ ):  $\delta$   $-60.22$ .

**2-(Diacetoxyiodo)toluene (1i).** White solid (0.655 g, 65%).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  8.17 (d, 1H,  $J$  = 7.6 Hz), 7.53–7.51 (m, 2H), 7.28–7.25 (m, 1H), 2.72 (s, 3H), 1.99 (s, 6H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  176.4, 140.6, 137.2, 132.7, 130.9, 128.4, 127.2, 25.6, 20.3. These data match literature data.<sup>20</sup>

**2,6-Dimethyl(diacetoxyiodo)benzene (1j).** White solid (0.725 g, 69%).  $^1\text{H}$  NMR ( $d_6$ -DMSO):  $\delta$  7.39 (dd, 1H,  $J$  = 6.4, 1.6 Hz), 7.31–7.27 (m, 2H), 2.75 (s, 6H), 1.98 (s, 6H) ppm.  $^{13}\text{C}$  NMR ( $d_6$ -DMSO):  $\delta$  176.5, 141.4, 132.9, 132.5, 128.1, 27.0, 20.3. These data match literature data.<sup>20</sup>

**3,5-Dimethyl(diacetoxyiodo)benzene (1k).** White crystals (0.798 g, 76%).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.74 (s, 2H), 7.22 (s, 1H), 2.39 (s, 6H), 2.02 (s, 6H).  $^{13}\text{C}$  NMR (DMSO):  $\delta$  176.4, 141.1, 133.7, 132.5, 121.3, 21.3, 20.4. These data match literature data.<sup>15</sup>

**3-(Diacetoxyiodo)toluene (1l).** White needles (0.837 g, 83%).  $^1\text{H}$  NMR (DMSO):  $\delta$  8.10 (s, 1H), 8.03 (d, 1H,  $J$  = 7.6 Hz), 7.50–7.43 (m, 2H), 2.37 (s, 3H), 1.91 (s, 3H).  $^{13}\text{C}$  NMR (DMSO):  $\delta$  175.8, 141.5, 135.9, 133.1, 132.8, 131.2, 122.3, 21.2, 20.7. These data match literature data.<sup>22</sup>

**3-(Diacetoxyiodo)trifluoromethylbenzene (1m).** White crystals (0.807 g, 69%).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  8.33 (s, 1H), 8.28 (d, 1H,  $J$  = 8.2 Hz), 7.85 (d, 1H,  $J$  = 7.8 Hz), 7.65 (t, 1H,  $J$  = 8.0 Hz), 2.03 (s, 6H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  176.7, 138.2, 133.1 (q,  $J$  = 33.6 Hz), 131.8

(q,  $J$  = 3.9 Hz), 131.3, 128.5 (q,  $J$  = 3.5 Hz), 122.8 (q,  $J$  = 273.1 Hz), 20.3 ppm.  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ ):  $\delta$   $-62.74$  ppm. These data match literature data.<sup>22</sup>

**3-(Diacetoxyiodo)nitrobenzene (1n).** White solid (0.793 g, 72%).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  8.95 (t, 1H,  $J$  = 1.9 Hz), 8.44 (dd, 1H,  $J$  = 6.2, 1.0 Hz), 8.40 (dd, 1H,  $J$  = 6.4, 1.0 Hz), 7.73 (t, 1H,  $J$  = 8.2, Hz), 2.04 (s, 6H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  176.8, 148.7, 140.4, 131.6, 130.1, 126.4, 120.6, 20.3. These data match literature data.<sup>22</sup>

**3-(Diacetoxyiodo)acetoxybenzene (1o).** Pale yellow solid (0.90 g, 79%).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.95–7.92 (m, 1H), 7.89 (t, 1H,  $J$  = 1.9 Hz), 7.52 (t, 1H,  $J$  = 8 Hz), 7.36–7.33 (m, 1H), 2.34 (s, 3H), 2.02 (s, 6H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  176.6, 168.6, 151.3, 132.1, 131.4, 128.3, 125.3, 120.5, 21.1, 20.4. These data match literature data.<sup>22</sup>

**3-(Diacetoxyiodo)benzophenone (1p).** White crystals (0.511 g, 40%). m.p.:  $175\text{--}178^\circ\text{C}$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  8.49 (t, 1H,  $J$  = 1.6 Hz), 8.28 (dq, 1H,  $J$  = 1.1, 5.1 Hz), 8.02 (dt, 1H,  $J$  = 1.2, 5.2 Hz), 7.84–7.82 (m, 2H), 7.67–7.62 (m, 2H), 7.55–7.51 (m, 2H), 2.03 (s, 6H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  194.1, 176.5, 139.8, 138.1, 136.4, 136.2, 133.3, 132.8, 130.8, 130.1, 128.6, 121.1, 20.4.

**Ethyl 3-(Diacetoxyiodo)benzoate (1q).** White crystals (0.792 g, 67%).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  8.74 (t, 1H,  $J$  = 1.7 Hz), 8.26 (dd, 2H,  $J$  = 1.7, 7.9 Hz), 7.59 (t, 1H,  $J$  = 7.9 Hz), 4.43 (q, 2H,  $J$  = 7.2), 2.02 (s, 6H), 1.43 (t, 3H,  $J$  = 7.1 Hz).  $^{13}\text{C}$  NMR (DMSO):  $\delta$  176.6, 164.5, 138.9, 136.0, 133.1, 132.6, 130.8, 121.1, 61.9, 20.4, 14.3. These data match literature data.<sup>16</sup>

**3-(Diacetoxyiodo)anisole (1r).** Yellow crystals (0.24 g, 23%).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.67–7.64 (m, 2H), 7.41 (t, 1H,  $J$  = 8.4 Hz), 7.10 (dd, 1H,  $J$  = 8.4, 2.4 Hz), 3.87 (s, 3H), 2.02 (s, 6H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  176.4, 160.6, 131.5, 127.1, 121.5, 120.5, 118.0, 55.8, 20.4. These data match literature data.<sup>22</sup>

**$\mu$ -Oxa-bis([acetoxyiodo]-4-trifluoromethylbenzene) (1s).** Application of General Method B to 1-iodo-4-trifluoromethylbenzene gave **1s** as a white fluffy solid (0.427 g, 21%). m.p.:  $176\text{--}178^\circ\text{C}$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.93 (d, 2H,  $J$  = 8.3 Hz), 7.54 (d, 2H,  $J$  = 8.7 Hz), 1.94 (s, 3H).  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ ):  $\delta$   $-63.24$  ppm. ESI-MS: calculated for  $\text{C}_{18}\text{H}_{14}\text{F}_6\text{I}_2\text{O}_5$   $m/z$  677.88, found  $m/z$  677.6. A satisfactory  $^{13}\text{C}$  NMR spectrum in  $\text{CDCl}_3$  was not obtained due to decomposition over the course of the scan time.

**Radiochemistry.** Radiochemistry was performed in a lead-shielded hot-cell to minimize the radiation exposure to personnel. All radioactivity measurements were performed using a calibrated ionization chamber and were corrected for background.

**Production of [ $^{18}\text{F}$ ]fluoride Ion Reagents.** No-carrier-added (NCA) [ $^{18}\text{F}$ ]fluoride ion was obtained through the  $^{18}\text{O}(\text{p},\text{n})^{18}\text{F}$  nuclear reaction by irradiating [ $^{18}\text{O}$ ]water (95 atom %) for 90–120 min with a proton beam (17 MeV; 20  $\mu\text{A}$ ) generated from a biomedical cyclotron.

aq.  $\text{Bu}_4\text{NHCO}_3$  solution (50  $\mu\text{L}$ ; 1 M) or  $\text{K}^+\text{-K}$  2.2.2 solution (50  $\mu\text{L}$ ) was added to the cyclotron-produced no-carrier-added [ $^{18}\text{F}$ ]fluoride ion (50–200 mCi) in [ $^{18}\text{O}$ ]water (200–500  $\mu\text{L}$ ), and four cycles of azeotropic addition and evaporation of acetonitrile (0.65 mL for each addition) were performed, three times at  $110^\circ\text{C}$  for 4 min and once more at  $90^\circ\text{C}$  for 4 min in an oven cavity housed within a modified Synthia<sup>29</sup> module.

**Configuration and Operation of Microfluidic Reactor Apparatus.** The microfluidic reactor apparatus was maintained and operated as previously described.<sup>20</sup>

**Radiofluorination Reactions. In a Microfluidic Apparatus.** Dry [ $^{18}\text{F}$ ]Bu<sub>4</sub>NF complex (20–50 mCi) was dissolved in reaction solvent (0.5 mL, typically DMF). A solution of (diacetoxyiodo)arene was prepared in a matching solvent. Each of the two solutions (255  $\mu\text{L}$ ) was loaded into separate storage loops of the microfluidic apparatus. For reactions, each solution (10–15  $\mu\text{L}$ ) was infused simultaneously into the 4 m length coiled silica glass tube microreactor of the apparatus at a set flow rate in the range of 4–100  $\mu\text{L}/\text{min}$  and at a preset temperature. The microreactor output was quenched with MeCN–H<sub>2</sub>O (0.5 mL, 1:1 v/v) at rt. Non-decay-corrected radiochemical yields (RCYs) of the [ $^{18}\text{F}$ ]fluoroarenes were measured by reverse phase radio-HPLC on a Luna C18 column (10  $\mu\text{m}$ , 100  $\text{\AA}$ , 250  $\times$  4.60 mm) eluted at 2 mL/min with a gradient of MeCN: 0.1% (w/

v)  $\text{HCOONH}_4$ , starting at 35% MeCN for 1 min, increased to 90% B over 5 min and maintained at 90% MeCN for 10 min.

In a TracerLab  $\text{FX}_{\text{FN}}$  Module. The aqueous  $[\text{F}^{18}]\text{Bu}_4\text{NF}$  reagent was dried within the apparatus by two cycles of addition and evaporation of acetonitrile (2.0 mL) under a nitrogen stream and reduced pressure, first at 65 °C, and then at 88 °C. To the dried  $[\text{F}^{18}]\text{fluoride}$  ion complex was added a solution of the (diacetoxyiodo)arene in anhydrous DMF (5 mM; 1.0 mL). The reaction mixture was heated to 170 °C for 5 min, and then transferred into water (10 mL) at rt. The mixture was then analyzed by HPLC, as described above.

## ■ ASSOCIATED CONTENT

### ● Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02332.

$^1\text{H}$ ,  $^{13}\text{C}$ , and  $^{19}\text{F}$  NMR spectra of (diacetoxyiodo)arenes, selected radio-chromatograms, and Cartesian coordinates of the geometry optimized structures in Figure 4 (PDF)

## ■ AUTHOR INFORMATION

### Corresponding Author

\*E-mail: [pikew@mail.nih.gov](mailto:pikew@mail.nih.gov). Fax: +1 301 480 5112. Tel: +1 301 594 5986.

### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

This research was supported by the Intramural Research Program of the National Institutes of Health (NIMH, ZIA-MH002793; CIT, ZIA-CT000265-19). The quantum chemical study utilized PC/linux clusters at the Center for Molecular Modeling of the National Institutes of Health (<http://cit.nih.gov>).

## ■ REFERENCES

- (1) Cai, L.; Lu, S.; Pike, V. W. *Eur. J. Org. Chem.* **2008**, 2843–2873.
- (2) Pike, V. W.; Aigbirhio, F. I. *J. Chem. Soc., Chem. Commun.* **1995**, 2215–2216.
- (3) Ross, T. L.; Ermert, J.; Hocke, C.; Coenen, H. H. *J. Am. Chem. Soc.* **2007**, 129, 8018–8028.
- (4) Chun, J. H.; Pike, V. W. *Org. Biomol. Chem.* **2013**, 11, 6300–6306.
- (5) Satyamurthy, N.; Barrio, J. R. Patent WO 2010117495A2, 2010.
- (6) Rotstein, B. H.; Stephenson, N. A.; Vasdev, N.; Liang, S. H. *Nat. Commun.* **2014**, 5, 4365.
- (7) Tredwell, M.; Gouverneur, V. *Angew. Chem., Int. Ed.* **2012**, 51, 11426–11437.
- (8) Yusubov, M. S.; Svitich, D. Y.; Larkina, M. S.; Zhdankin, V. V. *ARKIVOC* **2013**, No. i, 364–395.
- (9) Merritt, E. A.; Olofsson, B. *Angew. Chem., Int. Ed.* **2009**, 48, 9052–9070.
- (10) Goudreau, S. R.; Marcoux, D.; Charette, A. B. *J. Org. Chem.* **2009**, 74, 470–473.
- (11) Iinuma, M.; Moriyama, K.; Togo, H. *Synlett* **2012**, 23, 2663–2666.
- (12) Zielinska, A.; Skulski, L. *Molecules* **2002**, 7, 806–809.
- (13) Kazmierczak, P.; Skulski, L.; Kraszkiewicz, L. *Molecules* **2001**, 6, 881–891.
- (14) Hossain, M. D.; Kitamura, T. *Synthesis* **2005**, 2005, 1932–1934.
- (15) Yu, P.; Zhang, G.; Chen, F.; Cheng, J. *Tetrahedron Lett.* **2012**, 53, 4588–4590.
- (16) Chun, J.-H.; Pike, V. W. *J. Org. Chem.* **2012**, 77, 1931–1938.
- (17) Zhdankin, V. V. *Hypervalent Iodine Chemistry*; John Wiley & Sons: West Sussex, U.K., 2014.
- (18) Abo-Amer, A. Ph.D. Thesis, University of Duisburg-Essen, Essen, Germany, 2005; p 35.
- (19) Sun, H.; Wang, B.; DiMaggio, S. G. *Org. Lett.* **2008**, 10, 4413–4416.
- (20) Chun, J.-H.; Lu, S.; Lee, Y.-S.; Pike, V. W. *J. Org. Chem.* **2010**, 75, 3332–3338.
- (21) Kasumov, T. M.; Brel, V. K.; Grishin, Y. K.; Zefirov, N. S.; Stang, P. J. *Tetrahedron* **1997**, 53, 1145–1150.
- (22) Chun, J.-H.; Lu, S.; Pike, V. W. *Eur. J. Org. Chem.* **2011**, 4439–4447.
- (23) Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, 91, 165–195.
- (24) Vaidyanathan, G.; Zalutsky, M. R. *Nucl. Med. Biol.* **1992**, 19, 275–281.
- (25) Marik, J.; Sutcliffe, J. L. *Appl. Radiat. Isot.* **2007**, 65, 199–203.
- (26) Lee, C.-K.; Mak, T. C. W.; Li, W.-K.; Kirner, J. F. *Acta Crystallogr., Sect. B: Struct. Crystallogr. Cryst. Chem.* **1977**, 33, 1620.
- (27) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, O.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. *Gaussian 09*, Revision A.02; Gaussian Inc.: Wallingford, CT, 2009.
- (28) Chun, J.-H.; Telu, S.; Lu, S.; Pike, V. W. *Org. Biomol. Chem.* **2013**, 11, 5094–5099.
- (29) Bjurling, P.; Reineck, R.; Westerburg, G.; Gee, A. D.; Sutcliffe, J.; Långström, B. In *Proceedings of the Sixth Workshop on Targetry and Target Chemistry*; Link, J. M., Ruth, T. J., Eds.; TRIUMF: Vancouver, 1995; pp 282–284.