Radiofluorination

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Efficient Pathway for the Preparation of Aryl(isoquinoline)iodonium(III) Salts and Synthesis of Radiofluorinated Isoquinolines

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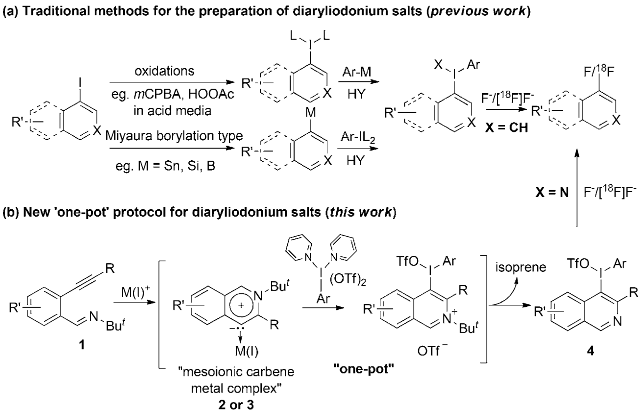
***Abstract:** Iodonium compounds play a pivotal role in ^{18}F-fluorination of radiopharmaceuticals containing non-activated arenes. However, preparation of these species is limited to oxidation conditions or exchange with organometallics that are prepared from aryl halides. Herein we describe a novel "one-pot" process to assemble aryl(isoquinoline)iodonium salts in 40–94 % yields from mesoionic carbene silver complex and Aryl-I-Py$_2$(OTf)$_2$. The method is general, practical, and compatible with well-functionalized molecules as well as useful for the preparation of a wide range of ^{18}F-labeled isoquinolines resulting in up to 92 % radiochemical conversion. As proof of concept, a fluorinated isoquinoline alkaloid, ^{18}F-aspergillitine is prepared in 10 % isolated radiochemical yield from the corresponding phenyl(aspergillitine)iodonium salt.*

Fluorine-18 (^{18}F, $t_{1/2} = 109.7$ min) is the most widely used nuclide for positron emission tomography (PET). New methodologies to incorporate [^{18}F]fluoride into a variety of unprecedented targeted molecular probes has become a major focus of academic and industrial PET research programs.[1] Attributed to the increasing prevalence of fluorine-containing pharmaceuticals and obstacles to the access of low specific activity electrophilic [^{18}F]F$_2$, focused efforts have been made to design novel methods to radiolabel non-activated arenes using nucleophilic [^{18}F]fluoride ion.[2] Among these advances include transition metal-mediated reactions,[3] and metal-free sulfonium[4] & iodonium-based approaches.[5] In particular, radiofluorination based on iodonium ylide precursors has demonstrated a wide range of compatibility in the labeling of well-functionalized molecules and radiopharmaceuticals, for instance, [^{18}F]FPPMP,[5h] [^{18}F]FPPMP,[5h] [^{18}F]-5-fluorouracil,[5i] [^{18}F]-safinamide,[5m] [^{18}F]-*meta*-fluorobenzylguanidine ([^{18}F]mFBG),[5m] [^{18}F]fluoro-*meta*-tyrosine ([^{18}F]FMT)[5m] and [^{18}F]3-fluoro-5-(2-pyridinylethynyl)benzonitrile ([^{18}F]FPEB),[5j] as well as application of ^{18}F-azido arenes in bioconjugation reactions.[5k,l] Diaryliodonium salts have also shown to be useful in the production of PET radiotracers, including [^{18}F]TFB,[5d] [^{18}F]flumazenil,[6] [^{18}F]mFBG,[7] [^{18}F]6-fluorodopamine,[5g,8] [^{18}F]FPhe,[5g] [^{18}F]DAA1106,[5g] and [^{18}F]6-F-DOPA.[5e,9] Despite the significant role of radiofluorination using iodonium methods in the PET tracer development, the preparation of these hypervalent iodine precursors[10] necessitates oxidation of iodoarene in acid media[11] or exchange with organometallic species,[12] for example stannylated/boronated compounds, which are prepared from "Miyaura borylation" type cross-coupling reactions with the corresponding aryl halides (Scheme 1 a). These common procedures have potential risks of contamination, if heavy metal reagents, for example tin, is utilized or show incompatibility with oxidation conditions in the presence of sensitive functionalities, including alkene and nitrogenous compounds. Therefore there is an unmet need for a robust and efficient method to prepare iodonium precursors for radiofluorination to fully realize the translational potential of these methods in the preparation of radiopharmaceuticals for molecular imaging and personalized medicine.

Isoquinoline is often found in biological natural products and utilized as a pharmacophore in drug discovery.[13] For instance, the natural product berberine shows therapeutic potential in treatment of cancer and diabetes,[14] and aspergillitine, isolated from *Aspergillus versicolor* in marine sponge, exhibited antibacterial activity against *Bacillus subtilis*.[15] Fluorine incorporation into isoquinoline has been proven to reduce in vivo metabolism,[16] particularly as



(a) Traditional methods for the preparation of diaryliodonium salts (*previous work*)

(b) New 'one-pot' protocol for diaryliodonium salts (*this work*)

Scheme 1. a) Traditional preparation of diaryliodonium salts and b) this work.

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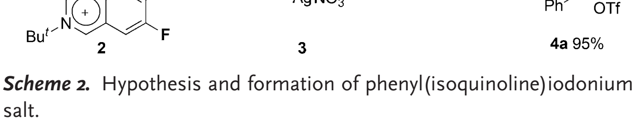
a bioisostere of hydrogen to block oxidation at C-4 (the major metabolism), and thus serves as a valuable fluorine-containing component in pharmaceutical design,[17] for example Glanatec.[17d] For the purpose of molecular imaging by PET, ^{18}F-isotopologues of fluoroisoquinoline would provide a unique and non-invasive way to track in vivo behavior of labeled drug candidates and their interactions with biological targets. However, there are only limited methods for the synthesis of fluoroisoquinolines with common theme focused on the electrophilic fluorinating agents, including Selectfluor[18] and *N*-fluorobenzenesulfonylimide (NFSI).[19] Applying these approaches for radiofluorination would require an electrophilic fluorinating agent, nearly all of which are generated from gaseous [^{18}F]F_2 and only available in a few PET centers worldwide with specialized apparatus, and also associated with serious shortcomings, i.e., unselective fluorination and low specific activities. In order to obviate the need for electrophilic fluorinating reagents during ^{18}F-fluoroisoquinoline preparation, we report a new and efficient process for synthesis of aryl(isoquinoline)iodonium salts by sequential silver-catalyzed amination of alkynes and exchange with hypervalent iodine reagents (Scheme 1 b). This approach represents the first example of diaryliodonium salts prepared from mesoionic carbene-metal [(mic)M] complex (**2** or **3**), which eradicates the use of aryl halides in oxidation or metal halide exchange conditions. Using concomitant isoprene emission as the driving force, the "one-pot" cyclization provides high yields for a wide range of aryl(isoquinoline)iodonium salts and demonstrates their usefulness in the (radio)fluorination of isoquinolines and synthesis of fluorinated natural product ^{18}F-fluoroaspergillitine.

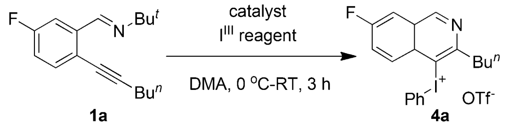
Our mechanistic investigations[19d] (see Section 11 for plausible mechanism in the Supporting Information, SI) on the Ag-catalyzed amination of alkynes delineated an unusual mesoionic carbene silver [(mic)$_2$Ag] complex **3**, which makes the isoquinoline C-4 position accessible after the alkyne cyclization. We found that when silver complex **3** was treated with hypervalent iodine reagent $\mathrm{PhIPy'_2(OTf)_2}$ (Py′ = *p*-methoxypyridine), an unprecedented $\mathrm{I^{III}}$ adduct appeared in nearly quantitative yield, which was subsequently characterized as **4a** by X-ray crystallography (Scheme 2 and Section 14, SI). This serendipitous discovery inspired us to speculate that an apparent "umpolung" would occur at C-4 if nucleophiles, for example fluoride ion, can be introduced to the newly formed aryl(isoquinoline)iodonium(III) species to furnish the synthesis of fluorinated isoquinoline instead of "^{18}F" electrophiles. Therefore, we adopted this one-pot tandem protocol involving Ag-catalyzed amination of alkynes and exchange with I(III) reagent to create a new and efficient approach to prepare diaryliodonium precursors for the synthesis of [^{18}F]fluoroisoquinolines.



Scheme 2. Hypothesis and formation of phenyl(isoquinoline)iodonium salt.

Initial efforts were focused on the exploration of a concise and general protocol to assemble diaryliodonium products (Table 1). The imine **1a** was readily synthesized in 90 % yield via condensation reactions between the corresponding aldehyde and *tert*-butyl amine. Treatment of substrate **1a** by catalytic amount of $AgNO_3$ (20 mol %) at 0 °C for 20 minutes, followed by addition of $\mathrm{PhIPy'_2(OTf)_2}$, provided product **4a** in 80 % yield (entry 1). Efforts towards optimization of this one-pot method indicated that addition of Pyox ligand or base did not effectively increase the reaction yields (entries 2 and 3). Silver salts screening showed that $AgNO_3$ is most effective (entries 4–6). Increase of $AgNO_3$ loading (to 1 equiv) improved the yield to 95 % (entries 7 and 8). When other hypervalent iodine reagents, such as $\mathrm{PhI(OAc)_2}$ and $\mathrm{PhI(OCOCF_3)_2}$, were employed, the desired product **4a** was also provided, yet in 30 % yield using $\mathrm{PhI(OAc)_2}$, and 78 % yield using $\mathrm{PhI(OCOCF_3)_2}$ (enties 9 and 10). When we switched $\mathrm{PhIPy'_2(OTf)_2}$ to $\mathrm{PhIPy_2(OTf)_2}$, the reaction could avoid contamination with an unknown impurity from AgPy′ complex, and improve the yield to 98 % by ^{19}F-NMR spectroscopy. As a result, the final product **4a** was obtained in 88 % isolated yield (entry 11). Finally, other transition metal catalysts, such as $\mathrm{Cu(CH_3CN)_4OTf}$, $\mathrm{Pd(O_2CCF_3)_2}$, $\mathrm{PtCl_2}$ and $\mathrm{AuCl_3}$ which are used in the cyclization of alkyl-imine **1a** in the literatures,[20] were also investigated. However, none of desired products **4a** was detected. These observations reveal the unique reactivity of [(mic)Ag] complex to hypervalent iodine reagent.

Table 1: Preparative conditions for aryl(isoquinoline)iodonium salts.[a]



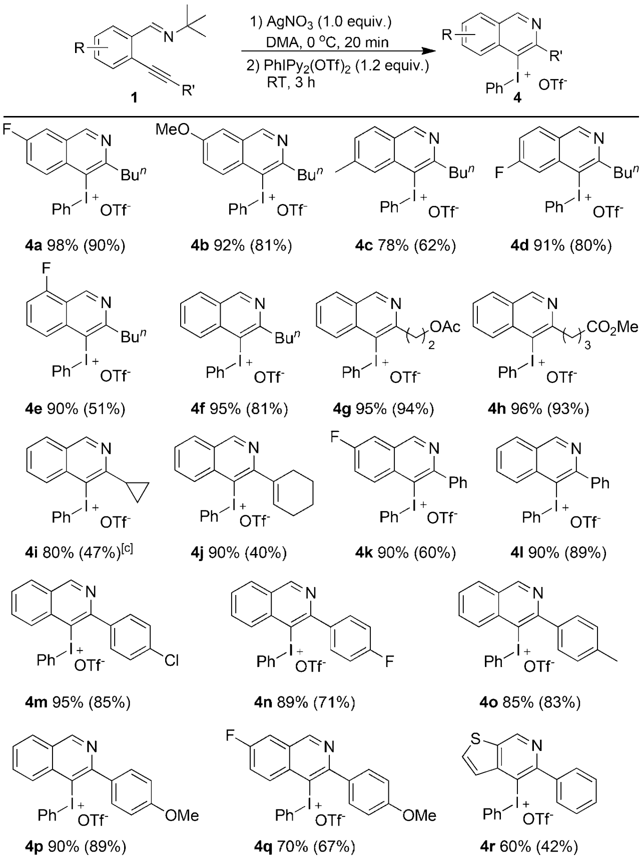
1a **4a**

Entry	Catalyst (mol %)	$\mathrm{I^{III}}$ reagent	Yield [%][b]
1	$AgNO_3$ (20)	$\mathrm{PhIPy'_2(OTf)_2}$	80
2[c]	$AgNO_3$ (20)	$\mathrm{PhIPy'_2(OTf)_2}$	78
3[d]	$AgNO_3$ (20)	$\mathrm{PhIPy'_2(OTf)_2}$	27
4	$AgNO_2$ (20)	$\mathrm{PhIPy'_2(OTf)_2}$	74
5	AgOTf (20)	$\mathrm{PhIPy'_2(OTf)_2}$	79
6	Ag_2CO_3 (10)	$\mathrm{PhIPy'_2(OTf)_2}$	79
7	$AgNO_3$ (50)	$\mathrm{PhIPy'_2(OTf)_2}$	86
8	$AgNO_3$ (100)	$\mathrm{PhIPy'_2(OTf)_2}$	95
9[e]	$AgNO_3$ (100)	$\mathrm{PhI(OAc)_2}$	30
10[f]	$AgNO_3$ (100)	$\mathrm{PhI(O_2CCF_3)_2}$	78
11	$AgNO_3$ (100)	$\mathrm{PhIPy_2(OTf)_2}$	98 (88)

[a] Reaction conditions: **1a** (0.1 mmol), $\mathrm{I^{III}}$ reagent (0.12 mmol), reaction was initiated at 0 °C then RT for 3 h. [b] ^{19}F-NMR yields with CF_3-DMA (2,2,2-trifluoro-*N*,*N*-dimethylacetamide) as internal standard. [c] 20 mol % Pyox. [d] 1 equiv of Li_2CO_3. [e] OAc as counter anion. [f] O_2CCF_3 as counter anion; $\mathrm{PhIPy'(OTf)_2}$: Py′ = 4-methoxypyridine, Pyox = (*S*)-4-isopropyl-2-(6-methylpyridin-2-yl)-4,5-dihydrooxazole.

The scope and practicality of this tandem alkynyl-imine cyclization and hypervalent iodine exchange was investigated and the results are summarized in Table 2. Alkynyl-imines with a series of substituents (R) on the (hetero)aromatic ring,

Table 2: Substrate scope for aryl(isoquinoline)iodonium salts.[a,b]

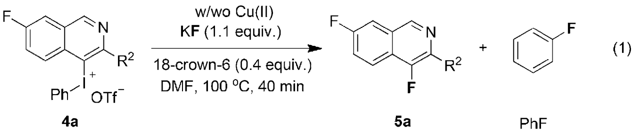


4a 98% (90%)
4b 92% (81%)
4c 78% (62%)
4d 91% (80%)
4e 90% (51%)
4f 95% (81%)
4g 95% (94%)
4h 96% (93%)
4i 80% (47%)[c]
4j 90% (40%)
4k 90% (60%)
4l 90% (89%)
4m 95% (85%)
4n 89% (71%)
4o 85% (83%)
4p 90% (89%)
4q 70% (67%)
4r 60% (42%)

[a] Reactions in 0.5-1 mmol scale; [b] ^{1}H NMR yields with 2,2,2-trifluoro-*N*,*N*-dimethylacetamide as internal standard (isolated yield in parenthesis). [c] Upon completion, the mixture was heated at 50 °C for 4 h to remove *tert*-butyl group.

including electron-withdrawing fluorine, electron-donating methoxy and methyl groups, were compatible with current transformation to afford products **4a–f** in good to excellent yields of 51–90 %. For the substituents (R′) in the terminal alkynes, various functional groups like ester, cyclopropyl and alkenyl, were tolerated to give desired products **4g–j** in 40–94 % yields. Furthermore, substrates with various aryl groups in terminal alkyne showed excellent compatibility in the reaction and provided **4k–q** with 60–89 % yields, along with one thienopyridine salt **4r** of 42 % yield. It is worth noting that the reaction of **1a** can be readily scaled up to gram-scale to obtain the desired phenyl(isoquinoline)iodonium salt **4a** in 90 % yield.

We next studied the regioselectivity of fluorination reactions on phenyl(isoquinoline) iodonium salts **4** under nonradioactive conditions. The fluorination was carried out with KF (1.1 equiv) and 18-crown-6 (0.4 equiv) in DMF at 100 °C for 40 min with or without $Cu(OTf)_2$ catalyst. In the presence of copper(II) catalyst, fluorination of iodonium salt **4a** predominately occurred in the phenyl group to provide fluorobenzene in 73 % yield determined by ^{19}F-NMR spectroscopy. The desired positional selectivity, i.e., fluorination at the C-4 of isoquinoline was achieved in the absence of metal catalyst and delivered the favorable fluorinated product **5a** in 70 % NMR yield [Eq. (1)]. These observations were consistent with prior reports,[5d,21] and indicated the translation to radiofluorination and control of ^{18}F-regioselectivity could be achieved from nucleophilic [^{18}F]fluoride ion under transition metal free conditions. In addition, this method can be used to prepare non-radioactive standard compound in line with radiolabeling, and requires no ad hoc route for ^{19}F-standard preparation.



	5a	PhF
with $Cu(OTf)_2$:	trace	73%
without $Cu(OTf)_2$:	70%	trace

A variety of phenyl(isoquinoline)iodonium salts were fluorinated with nucleophilic ^{19}F or [^{18}F]fluoride ion under transition metal free protocols (see conditions B in Table 3 and Section 7.3 in the SI for optimal radiolabeling conditions). Fluorinated and radiofluorinated isoquinolines were obtained in 54–88 % isolated chemical yields and 11–92 % radiochemical conversions, respectively, which demonstrated the compatibility with diverse functionalities with alkyl, aryl, alkenyl, halide, cyclopropyl, and ester groups. The scope of this method was further extended to other fused pyridines. The results of fluorination (82 %) and radiofluorination (77 %) showed that this protocol was equally applicable to the synthesis of thienopyridine (Table 3, **5r** and **6r**). In particular, to verify the efficiency and practical use of this method, two radiochemical purification methods, i.e., solid phase extraction and semi-preparative HPLC, were utilized to isolate and purify [^{18}F]fluoroisoquinolines. Compounds **6j**, **6m**, **6p**, **6r** and **6a**, **6l** were isolated in 51–65 % yields by SPE and 40–48 % yields by HPLC, respectively. The specific activity of 3-*n*-butyl-4-[^{18}F]fluoro-7-fluoroisoquinoline (**6a**) was determined to be 1.53 Ci μmol^{-1} and is suitable for the majority of in vivo PET imaging studies, including most low density biological targets.[23] We then studied the regioselectivity of (radio)fluorination by measuring the ratio of desired fluoroisoquinoline **5a**/**6a** and byproduct 4-fluorobiphenyl (**8a**/**9a**) under both non-radioactive and ^{18}F-labeling conditions. As shown in Equation (2), labeling precursor **7** was prepared from a new hypervalent reagent Ph-PhIPy$_2$(OTf)$_2$ in 77 % yield. Both fluorination and radiofluorination demonstrated excellent and desired regioselectivity (> 20:1) based on the results on iodonium salt **7**.[22] In addtion to fluoride, other nucleophiles, such as acetate and azide, are also compatible to the nucleophilic substition of phenyl(isoquino-

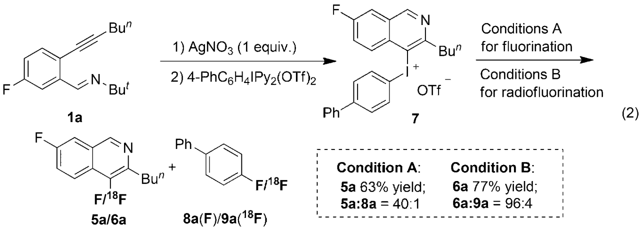
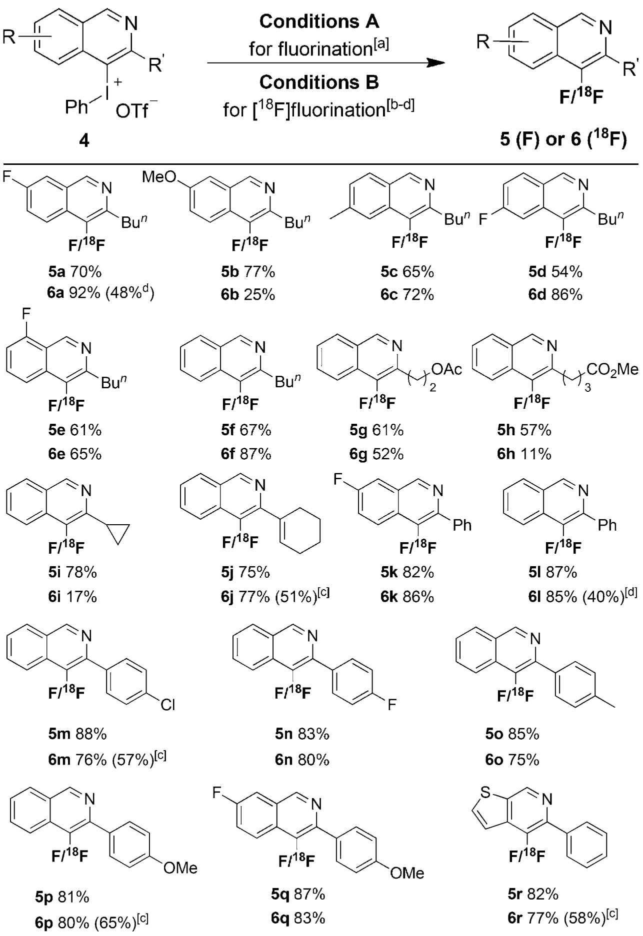


Table 3: Fluorination and radiofluorination of aryl(isoquinoline)iodonium salts.

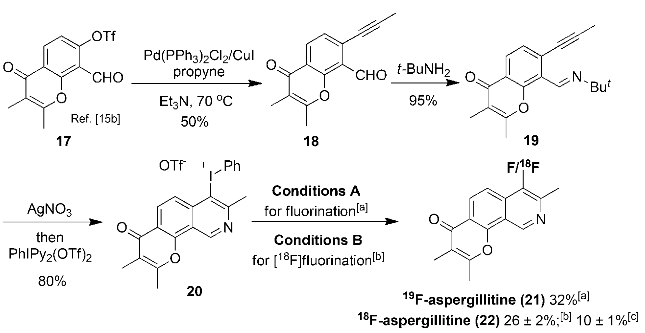


5a 70%, **6a** 92% (48%[d])
5b 77%, **6b** 25%
5c 65%, **6c** 72%
5d 54%, **6d** 86%
5e 61%, **6e** 65%
5f 67%, **6f** 87%
5g 61%, **6g** 52%
5h 57%, **6h** 11%
5i 78%, **6i** 17%
5j 75%, **6j** 77% (51%)[c]
5k 82%, **6k** 86%
5l 87%, **6l** 85% (40%)[d]
5m 88%, **6m** 76% (57%)[c]
5n 83%, **6n** 80%
5o 85%, **6o** 75%
5p 81%, **6p** 80% (65%)[c]
5q 87%, **6q** 83%
5r 82%, **6r** 77% (58%)[c]

[a] Nonradioactive fluorination conditions (A): KF (1.1 equiv), 18-crown-6 (0.4 equiv), DMF, 100 °C, 40 min; Isolated yield. [b] Radiofluorination conditions (B): precursor **4a** (7.2 mmol), [^{18}F]tetraethylammonium fluoride ([^{18}F]TEAF), DMSO, 100 °C, 10 min. Radiochemical conversions and product identify were determined by radioTLC and radioHPLC, respectively. For a detailed step-by-step radiofluorination procedure, see the SI. [c] Isolated yield by solid phase extraction. [d] Isolated yield by HPLC.

line)iodonium salts. The related isoquinoline derivates **10–16** were obtained in good to excellent yields (58–84%, see Section 5 in the SI).

To demonstrate the utility of this method, we synthesized both fluorinated and radiofluorinated marine natural product aspergillitine by the corresponding phenyl(isoquinoline)iodonium salt derived from the tandem cyclization and iodine(III) exchange. The synthesis commenced with triflate **17**,[15b] followed by Sonogashira coupling with propyne and condensation with *t*-butyl amine to generate alkyne **19** in two steps around 50% yield (Scheme 3). An efficient silver-mediated amination of alkyne **19** followed by rapid exchange with PhIPy$_2$(OTf)$_2$ furnished phenyl(aspergillitine)iodonium salt **20** in 80% yield. Fluorination using KF and 18-crown-6 gave fluoroaspergillitine (**21**) in 32% yield and the radiosynthesis of [^{18}F]fluoroaspergillitine (**22**) was achieved in 26 ± 2% radiochemical conversions with 10 ± 1% isolated radiochemical yields ($n = 3$) by HPLC.



Scheme 3. Synthesis of non-radioactive and ^{18}F-labeled fluoroaspergillitine. [a,b] Same procedures as in Table 3. [c] Isolated yields by semi-preparative HPLC.

In summary, a novel method for the convenient access to [^{18}F]isoquinolines has been developed, which is enabled by a sequential process involving a silver-mediated amination of alkynes and fluorination of phenyl(isoquinoline)-iodonium salts. The methodology has proven to apply to a broad scope of substrates and afford the desired isoquinolines and [^{18}F]isoquinolines in satisfactory to excellent yields. As proof of concept, fluorinated natural product ^{18}F-fluoroaspergillitine was prepared in 10% isolated radiochemical yield. The conceptual advantages of diaryliodonium salts preparation from mesoionic carbene silver intermediate, followed by iodonium exchange showcased in the simple setup and easy handling procedure, and excellent compatibility with a variety of functional groups, all of which warrant this method useful for further applications in [^{18}F]fluoroisoquinoline and other related fluorinated heterocyclic aromatic syntheses.

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[22] It is possible that an alternative fluorination of aryne pathway, initiated from the elimination of phenyl(isoquinoline)iodonium **4**, could occur; however, such intermediate and related fluorinated isomer was not observed. We also compared the results of (radio)fluorination between iodonium salts **4a** and traditional precursors for nucleophilic aromatic substitution, including brominated (see Section 5 in the Supporting Information, **12**)/iodinated (**13**)/nitro (**14**) isoquinolines. While iodonium salt **4a** gave 90% yield in fluorination (**5a**) and 92% yield in radiofluorination (**6a**), respectively, no desired products **5a** and **6a** were observed from traditional precursors (see Sections 12 and 13 in the SI), indicating the unique fluorination reactivity of iodonium precursor **4**.

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