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An Organometallic Gold(III) Reagent for ^{18}F-Labeling of Unprotected Peptides and Sugars in Aqueous Media

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Abstract

The ^{18}F-labeling of unprotected peptides and sugars with a Au(III)-[^{18}F]fluoroaryl complex is reported. The chemoselective method generates ^{18}F-labeled *S*-aryl bioconjugates in an aqueous environment in 15 min with high radiochemical yields and displays excellent functional group tolerance. This approach utilizes an air and moisture stable, robust organometallic Au(III) complex and highlights the versatility of designer organometallic reagents as efficient agents for rapid radiolabeling.

Graphical Abstract

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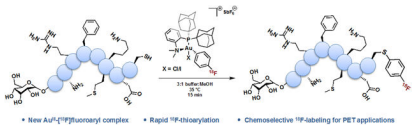
Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. Detailed experimental procedures, optimization data, radiochemical experiments and compound characterization data (PDF).

The authors declare no competing financial interest.



The rapid kinetics and high chemoselectivity of transition-metal-based transformations have resulted in major advances in organic synthesis, in particular for the modification of complex small molecules.[1, 2] In the context of ^{18}F-labeling, significant effort has been devoted to the development of transition-metal mediated radiofluorination methods, often translated from modern fluorine-19 related approaches.[3–5] Importantly, the translation of fluorine-19 to fluorine-18 chemistry presents distinct challenges that are non-trivial and rigorous optimization is required for smooth translation to radiochemistry.[4] Perhaps the most notable obstacle is that ^{18}F is in nanomole or lower quantities amongst an excess of other reagents. Additionally, chemical modifications must be conducted quickly, ideally within minutes, due to the radioactive decay of ^{18}F.

Over the last decade, reports exploiting the redox activity of transition-metals such as Pd, Ni and Cu to lower the barrier for C-^{18}F bond formation have surged.[3, 4, 6–9] In particular, Cu-mediated methods have found wide use in the construction of ^{18}F-labeled small molecules for positron emission tomography (PET) imaging applications.[10, 11] Modern Cu-mediated methods have become a truly powerful advancement in radiochemical synthesis, unlocking access to radiolabeled constructs that were previously inaccessible. However, metal-based modifications employing unprotected peptides for direct radiofluorination processes are scarce.[12–16]

The unique properties of cysteine have stimulated efforts toward the chemoselective bioconjugation of this key residue.[17, 18] Pioneering work by the Buchwald and Pentelute groups demonstrating palladium-mediated cysteine arylation to afford *S*-aryl bioconjugates has encouraged the development of Pd-based strategies for labeling peptides with positron-emitting radioisotopes, such as ^{11}C or ^{18}F.[19–21] In the context of ^{11}C-labeling, Hooker and Buchwald utilized a biarylphosphine supported Pd(II)-complex to prepare ^{11}CN-labeled unprotected peptides (Figure 1a).[22]

The Pd-mediated sequential cross-coupling proceeds with initial *S*-arylation of the cysteine-containing peptides followed by direct ^{11}C-cyanation. In addition, Neumaier recently reported a Pd-mediated cysteine *S*-arylation using the XantPhos Pd-based cyclometallated precatalyst system previously developed by Buchwald[23] with 2-[^{18}F]fluoro-5-iodopyridine (Figure 1a).[16] The radiolabeled aryl iodide was obtained after solid-phase extraction with a molar activity of 29 GBq·μmol^{-1} and could be directly used for bioconjugation. However, nonradioactive impurities formed in the initial radiofluorination were shown to impede the consecutive *S*-arylation step. To sequentially perform the protocol and maintain high conversion during *S*-arylation, minimal precursor was used, triggering a modest RCY of 2-[^{18}F]fluoro-5-iodopyridine.

Recently, Au(III)-aryl oxidative addition complexes supported by the aminophosphine Me-DalPhos ligand[24] (Me-DalPhos = ($Ad_2P(o\text{-}C_6H_4)NMe_2$)) provided rapid access to

S-aryl bioconjugates under mild conditions at ambient temperature.[25–27] The air-stable organometallic Au(III) complexes were prepared in a straightforward one-step synthesis from commercial (Me-DalPhos)AuCl with a 3-fold excess of aryl iodides.[28] The extremely rapid reaction rate of *S*-arylation for this system (approaching 10^4 $M^{-1}s^{-1}$) suggests this chemistry can be potentially amenable to transformations where rapid kinetics is critical. Importantly, competition experiments revealed superior kinetics for the Au-mediated system over the Pd-mediated system, with a ratio of 9:1.[25] We therefore hypothesized that an ^{18}F-labeled Au(III)-aryl oxidative addition complex could be prepared by using a radiolabeled aryl iodide such as 4-[^{18}F]fluoroiodobenzene and subsequently used for rapid radiolabeling of biomolecules.

Despite differences in the stoichiometry by several orders of magnitude when transitioning to fluorine-18, we reasoned that the high efficiency of the oxidative addition and the rapid reaction kinetics of the Au(III) arylation could provide a powerful platform for the chemoselective radiofluorination of thiols. Here, we report the synthesis of a Au(III)-[^{18}F]fluoroaryl complex and its application toward Au-mediated radiofluorination of thiol-containing substrates to afford stable *S*-[^{18}F]fluoroaryl bioconjugates (Figure 1b). This approach is, to our knowledge, the first gold-mediated methodology for chemoselective ^{18}F-labeling of thiol-containing substrates.

We first sought to prepare a radiolabeled aryl iodide that could undergo oxidative addition with the (Me-DalPhos)AuCl complex to generate the radiolabeled Au(III)-aryl complex, [(Me-DalPhos)Au(4-[^{18}F]fluorobenzene)Cl][SbF_6] ([**^{18}F]1**).[25, 28] Synthesis of 4-[^{18}F]fluoroiodobenzene ([**^{18}F]2**) was achieved using a one-step radiofluorination protocol via a spirocyclic hypervalent iodonium ylide (Table 1).[29] Iodonium ylide **3** was prepared and subsequently subjected to radiofluorination.[30, 31] Preparation of [**^{18}F]2** was fully automated on the ELIXYS radiochemical synthesis module and conducted using [^{18}F]Et_4NF in DMF at 120 °C which, after HPLC purification, furnished aryl iodide [**^{18}F]2** in 26 ± 8% isolated radiochemical yield (RCY), decay-corrected (Table 1).

We next focused on the oxidative addition reaction to yield [**^{18}F]1** (Table 1). In contrast to 4-fluoroiodobenzene, which can be employed at 3-fold excess, 4-[^{18}F]fluoroiodobenzene is the limiting reagent that is present in nanomolar or picomolar concentration, severely altering the stoichiometry of the oxidative addition step. Formation of [**^{18}F]1** proceeded in 38% ± 27% radiochemical conversion (RCC) upon the treatment of 4-[^{18}F]fluoroiodobenzene in CH_2Cl_2 with (Me-DalPhos)AuCl (15 μmol) in the presence of $AgSbF_6$ (15 μmol) heated at 55 °C in a sealed vial for 10 min (Table 1, entry 1). Lowering the stoichiometry of Au(I) to 9 μmol afforded [**^{18}F]1** in 95% ± 7% RCC at 55 °C in 10 min (Table 1, entry 3). The reaction was also evaluated in DCE at elevated temperatures and [**^{18}F]1** was obtained in comparable yields albeit at slightly extended reaction times (Table 1, entries 5–7). Of note, these reactions were performed in a sealed reaction vial with no rigorous exclusion of oxygen or water and conducted using commercial, unpurified solvents. Precursor **3** showed excellent stability when stored in the dark at −20 °C for up to 18 months with no detectable degradation or loss in RCC. The Au(I) complex could be stored on the benchtop and the $AgSbF_6$ in the glovebox with exclusion from light for up to 3 months and used with no detectable degradation.

Product identity and purity of [**^{18}F]1** were determined by analytical HPLC analysis via coinjection with the reference standard. Clean conversion of 4-[^{18}F]fluoroiodobenzene to [**^{18}F]1** enabled its direct use without the need for HPLC purification. The crude reaction mixture was simply filtered and concentrated under mild heating to afford cartridge-isolated [**^{18}F]1** in 25 mins (relative to [**^{18}F]2**), which was directly used in subsequent thioarylation reactions (Figure S9).

The reactivity of the novel Au(III)-complex, [**^{18}F]1**, was examined and optimized with L-glutathione as a model peptide substrate (Table 2). Initial thioarylation was observed in 16% ± 13% RCC upon treatment of L-glutathione 4 (16 μmol) with [**^{18}F]1** in PBS buffer (pH 7.4) at 23 °C in 30 min (Table 2, entry 1). A buffer screen revealed that Tris buffer (pH 8.0) increased the conversion to 54 ± 16% but the reaction remained sluggish at ambient temperature (Table 2, entry 3). Upon slight heating to 35–45 °C, the [^{18}F]fluoroaryl product [**^{18}F]7** was generated in 93–95% RCC (Table 2, entries 4–5). Attempts to shorten the reaction time led to a reduction in yield with a significant drop for reactions under 15 min (Table 2, entries 6–8).

From our previous results with peptide conjugation chemistry,[32] we predicted that a co-solvent could further boost the Au(III)-[^{18}F]fluoroaryl solubility and facilitate complete reaction conversion. Employing a Tris buffer/methanol (3/1) solvent system improved the conversion and provided the [^{18}F]fluoroaryl conjugate [**^{18}F]7** in 97% ± 3% RCC in 15 min (Table 2, entry 9). Similarly, peptides **5** and **6** also revealed a significant improvement in RCC with the new solvent system (Table 2, entries 10–11). High radiolabeling efficiency while using low mass amounts of peptide precursor is advantageous in the context of radiolabeling expensive peptides with limited availability, and allows for a simplified purification process of the ^{18}F-labeled product. With sub-micromolar peptide loading, ^{18}F-thioarylation was achieved in 70% RCC using 0.71 μmol **4** and in 52% RCC using 0.39 μmol **4** (Table 2, entries 12–13).

The optimized *S*-arylation conditions were applied to a series of thiol-containing substrates to establish the versatility and scope of our methodology (Figure 2). High chemoselectivity for *S*-arylation of thiol-containing substrates in the presence of a variety of additional functional groups was observed in Tris buffer (pH 8.0)/methanol (3/1) within 15 min in 72–97% RCY. Substrates containing a free carboxylic acid, primary or secondary amine, guanidine residue, and thioether functional groups were well tolerated as well as sugar-based substrates containing free alcohols. Additionally, *S*-arylation of peptides in which the cysteine residue is positioned at the N-terminus ([**^{18}F]9**) or within an intrachain position ([**^{18}F]10**) still maintained high efficiency. Performing the ^{18}F-thioarylation with 3 μmol L-glutathione **4**, afforded the ^{18}F-labeled conjugate [**^{18}F]7** in 97% ± 1% RCY (Figure 2). A hexapeptide containing a nucleophilic lysine residue cleanly delivered the *S*-aryl conjugate [**^{18}F]8** in 97% ± 4% RCY with 7 μmol precursor loading. Notably, [**^{18}F]8** was furnished in 49% ± 6% RCY when using only 0.62 μmol precursor.

A critical motif utilized for noninvasive PET imaging of angiogenesis is the RGD sequence and numerous peptide-based analogues have demonstrated value, including clinical benefit.[33] The Au(III)-mediated ^{18}F-thioarylation of peptides containing the RGD

sequence was successfully executed to provide peptide conjugates [**^{18}F]9** and [**^{18}F]10** in 72% ± 11% and 94% ± 5% RCY, respectively. In addition, synthesis of an ^{18}F-labeled β-amyloid peptide fragment[34] was successfully accomplished, using 4 μmol peptide precursor, to afford [^{18}F]fluoroaryl conjugate [**^{18}F]11** in 77% ± 10% RCY. Finally, the protocol was applied to sugar-based substrates to assess compatibility with alternative thiol-containing constructs containing free alcohols. Thio-β-D-glucose and thio-β-D-galactose underwent efficient [^{18}F]fluoroarylation in MeCN/H_2O (1/1) in 93% ± 8% and 88% ± 11% RCY, respectively.

Cyclodextrin-based polymers have been used as carrier systems for chemotherapeutics or small molecule drugs and their unique properties, such as enhanced solubility, improved pharmacokinetics and increased efficacy compared to the small molecules, have garnered interest towards utility in biomedical imaging applications.[35] For example, a cyclodextrin polymer-based nanoparticle containing the chemotherapeutic camptothecin was labeled with ^{64}Cu and imaged in tumor-bearing mice to noninvasively determine multi-organ pharmacokinetics, whole-body biodistribution and tumor localization.[36] Limited examples of ^{18}F-labeled β-cyclodextrins in the literature prompted us to investigate our protocol for radiofluorination of the cyclic oligosaccharides. The Au(III)-mediated ^{18}F-thioarylation was performed with 4 μmol of a thiolated β-cyclodextrin precursor to furnish construct [**^{18}F]14** in 90% ± 5% RCY.

To evaluate the practicality of our approach, *S*-aryl glutathione conjugate [**^{18}F]7** was synthesized using 6–8 mCi of [**^{18}F]1** and subjected to HPLC purification which afforded isolated [**^{18}F]7** in 23% ± 5% activity yield in 46 min (relative to [**^{18}F]1**, non-decay-corrected, n=3), with >99% radiochemical purity (RCP). The molar activity of [**^{18}F]7** was 2.9 ± 1.8 Ci·μmol^{-1} (108 ± 68 GBq·μmol^{-1}, n=4). ICP-OES analysis revealed that the purified product contained less than 50 ppb of Au (n=3), which is well below the acceptable limit for in-human injection.[37] The focus of this work is the design, optimization and construction of a novel Au^{III}-[^{18}F]fluoroaryl complex for the ^{18}F-labeling of unprotected peptides and sugars. Future work is directly aimed at automating the full protocol and conducting PET imaging studies in preclinical mouse models.

In summary, we report a robust Au(III)-[^{18}F]fluoroaryl reagent [**^{18}F]1** for the ^{18}F-labeling of thiol-containing substrates via *S*-arylation in aqueous media. To our knowledge, this is the first Au-mediated ^{18}F-labeling methodology of unprotected peptides and thiosugars. The practical advantages of our method are highlighted by the mild reaction conditions, broad substrate scope and rapid reaction kinetics. The oxidative addition complex [**^{18}F]1** was generated in 10 min and directly used to furnish ^{18}F-labeled conjugates in excellent chemoselectivity, up to 97% RCY and high molar activity in 15 min. The protocol was applied to a diverse range of thiol-containing substrates including unprotected peptides and, when using nanomolar peptide loading, good RCYs were achieved. This work expands on the growing space of organometallic reagents that are applied towards radiochemical modifications which demand rapid reaction rates.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENT

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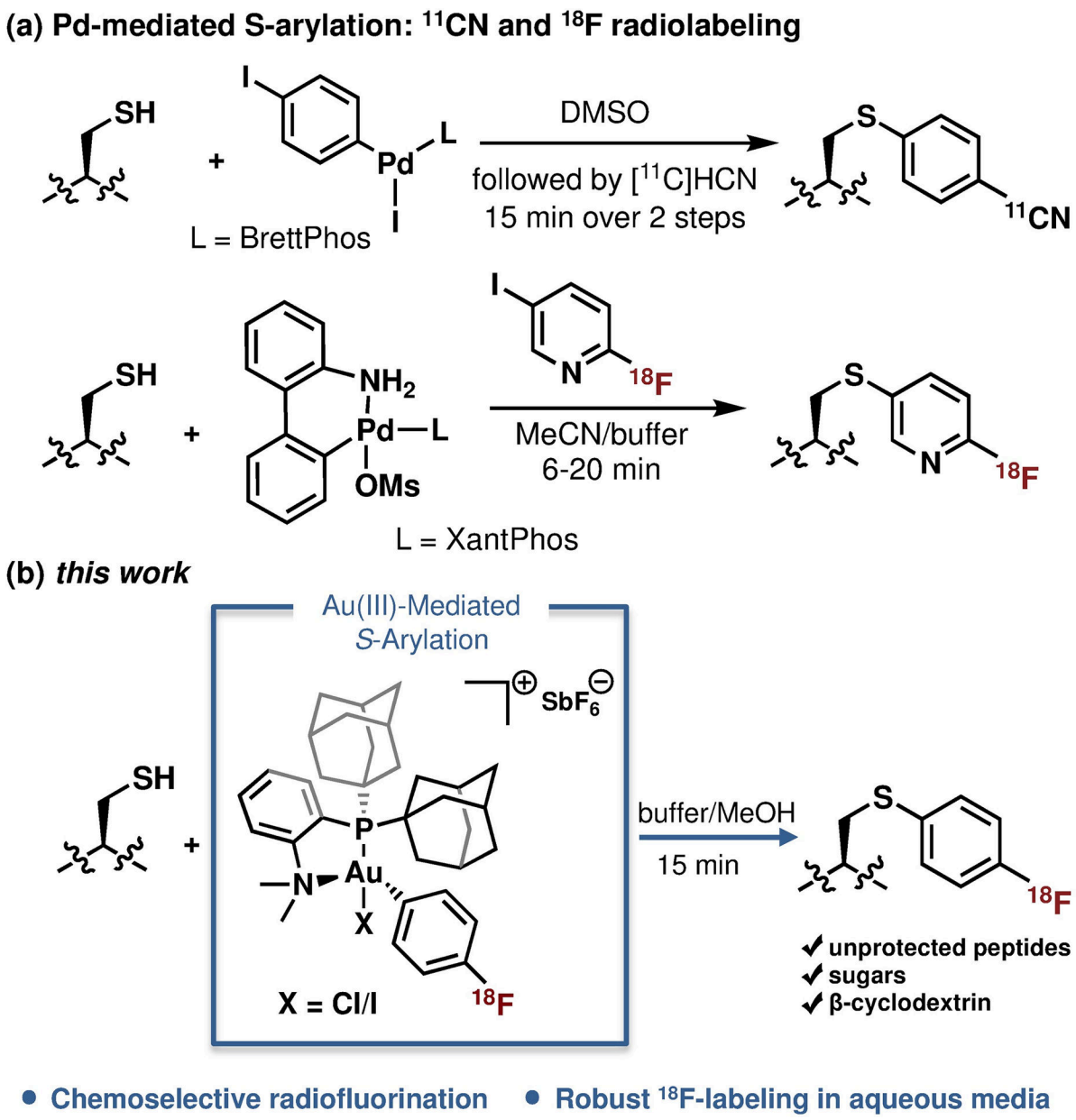


Figure 1.

(a) ^{11}C- and ^{18}F-labeling of unprotected peptides via Pd-mediated *S*-arylation.[16, 22] (b) This work, ^{18}F-labeling of unprotected peptides, sugars and β-cyclodextrin via Au-mediated *S*-arylation.

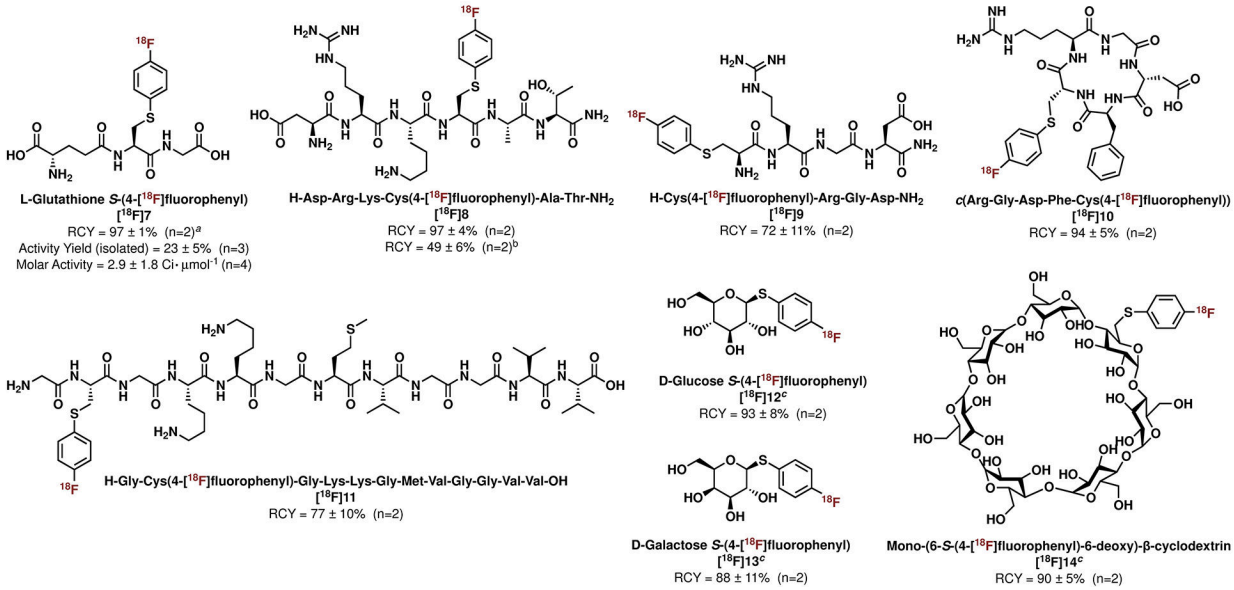
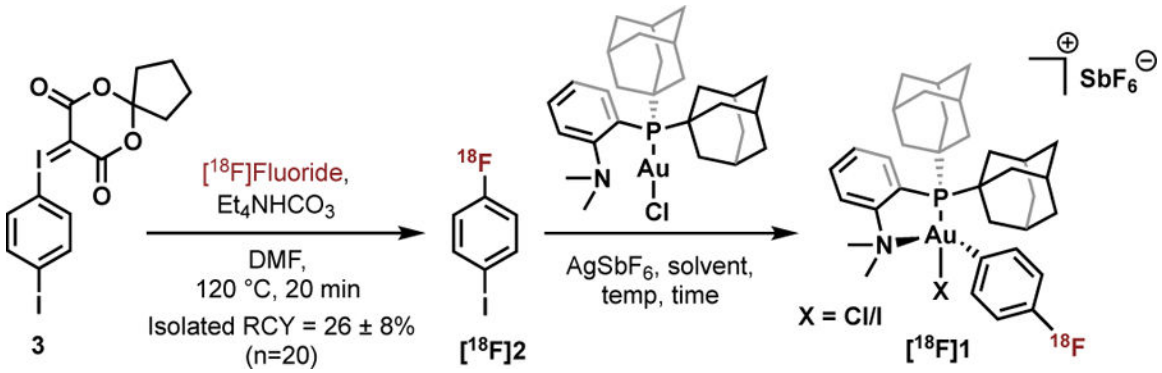


Figure 2.

^{18}F-Labeling of peptides via Au^{III}-mediated *S*-arylation. Reaction conditions: substrate (5 mg), [**^{18}F]1** (0.5 – 2.0 mCi), Tris buffer pH 8.0 (750 μL), MeOH (250 μL), 35 °C, 15 min. RCP was calculated by dividing the integrated area of the ^{18}F-labeled product peak by the total integrated area of all ^{18}F-labeled peaks, as determined by radio-HPLC. The decay-corrected radiochemical yield (RCY) was calculated by dividing final activity of the labeled product by starting [**^{18}F]1** activity, multiplied by the RCP. Identity of each labeled product was confirmed by co-injection with the ^{19}F-reference standard. [a]Substrate (3 μmol). [b]Substrate (0.62 μmol), Tris buffer pH 8.0 (562 μL), MeOH (188 μL). [c]MeCN (500 μL), H_2O (500 μL).

Table 1.

Preparation of Au^{III}-[^{18}F]Fluoroaryl Complex [^{18}F]1



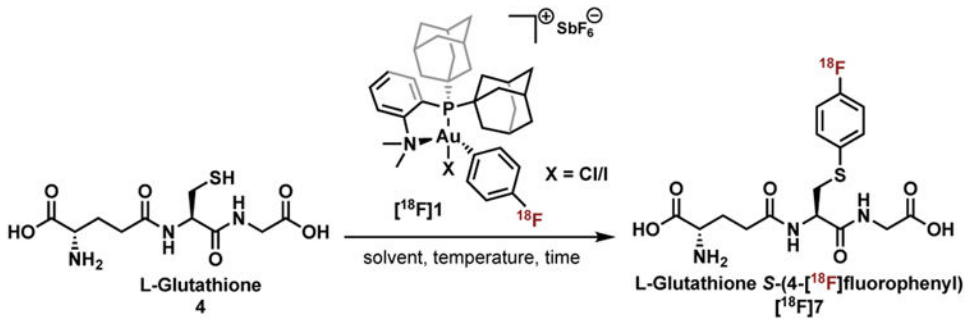
entry[a]	Au(I)/$AgSbF_6$ (μmol)	solvent	time (min)	temp. (°C)	RCC (%)[b]
1	15	DCM	10	55	38 ± 27
2	12	DCM	10	55	49 ± 15
3	**9**	**DCM**	**10**	**55**	**95 ± 7**
4	9	DCM	20	55	87 ± 16
5	9	DCE	10	60	87 ± 8
6	9	DCE	10	80	83 ± 15
7	9	DCE	20	80	94 ± 6

[a]Conditions: [**^{18}F]2** (~500 μCi) per reaction, solvent (1.5 mL).

[b]RCC was determined by radio-TLC analysis of complex [**^{18}F]1**, n > 3 for all entries.

Table 2.

Thio Arylation of L-Glutathione with Au^{III}-[^{18}F]Fluoroaryl Complex [^{18}F]1



entry[a]	solvent system	time (min)	temp. (°C)	RCC (%)[b]
1	PBS pH 7.4	30	23	16 ± 13
2	HEPES pH 7.3	30	23	43 ± 18
3	Tris pH 8.0	30	23	54 ± 16
4	Tris pH 8.0	30	35	93 ± 1
5	Tris pH 8.0	30	45	95 ± 1
6	Tris pH 8.0	20	35	72 ± 14
7	Tris pH 8.0	15	35	78 ± 12
8	Tris pH 8.0	10	35	44 ± 1
9	**Tris pH 8.0/MeOH, 3/1**	**15**	**35**	**97 ± 3**
10 [c]	**Tris pH 8.0/MeOH, 3/1**	**15**	**35**	**97 ± 4**
11 [d]	**Tris pH 8.0/MeOH, 3/1**	**15**	**35**	**91 ± 5**
12[e]	Tris pH 8.0/MeOH, 3/1	15	35	70
13[f]	Tris pH 8.0/MeOH, 3/1	15	35	52

[a] Conditions: Au^{III} complex [**^{18}F]1** (~1 mCi) per reaction, L-glutathione **4** (16 μmol), solvent (1 mL).

[b] RCC is estimated by radio-HPLC analysis of crude peptide [**^{18}F]7**, n = 2–6.

[c] Peptide = H-Asp-Arg-Lys-Cys-Ala-Thr-NH_2 **5** (7 μmol).

[d] Peptide = H-Cys-Arg-Gly-Asp-NH_2 **6** (11 μmol).

[e] L-glutathione **4** (0.71 μmol), n = 1.

[f] L-glutathione **4** (0.39 μmol), n = 1.