

# <sup>18</sup>F-Trifluoromethylation of Unmodified Peptides with 5-<sup>18</sup>F-(Trifluoromethyl)dibenzothiophenium Trifluoromethanesulfonate

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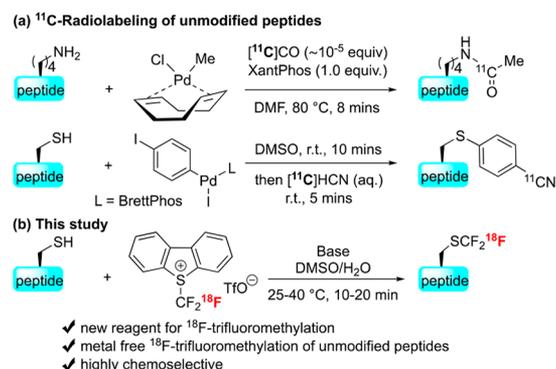
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## Supporting Information

**ABSTRACT:** The <sup>18</sup>F-labeling of 5-(trifluoromethyl)-dibenzothiophenium trifluoromethanesulfonate, commonly referred to as the Umemoto reagent, has been accomplished applying a halogen exchange <sup>18</sup>F-fluorination with <sup>18</sup>F-fluoride, followed by oxidative cyclization with Oxone and trifluoromethanesulfonic anhydride. This new <sup>18</sup>F-reagent allows for the direct chemoselective <sup>18</sup>F-labeling of unmodified peptides at the thiol cysteine residue.

Positron emission tomography (PET) is a molecular imaging technique that can visualize biochemical processes *in vivo*.<sup>1</sup> In practice, these studies require molecules labeled with a positron-emitting radioisotope, for example <sup>11</sup>C or <sup>18</sup>F. Radiolabeled peptides are attractive candidates for PET imaging because of their favorable pharmacokinetics and high specificity targeting characteristics.<sup>2</sup> Such properties have stimulated development of numerous strategies for tagging peptides with a radioactive component.<sup>3</sup> Most methods require prefunctionalization of the peptide with a prosthetic group enabling attachment of the radioisotope itself, or a radiolabeled molecular entity.<sup>4</sup> Alternatively, a radiolabeled prosthetic group is synthesized prior to attachment to the peptides; typically, this approach requires synthetic modification of the peptide prior to radiolabeling.<sup>5</sup> Major structural modifications of the peptide target can result in alteration of their biological function, a concern that has encouraged development of innovative labeling methodologies employing unmodified peptides and minimally sized radioisotope-containing motifs.<sup>3d</sup> Studies have focused on the radioisotope <sup>11</sup>C. For example, Skrydstrup and co-workers reported methyl biphosphine–ligated complexes enable *N*-<sup>11</sup>C-acetylation of lysine residue of native peptides,<sup>6</sup> and the direct <sup>11</sup>CN-labeling of unprotected peptides at a cysteine residue was accomplished by Buchwald, Hooker and co-workers applying a palladium-mediated sequential cross-coupling consisting of *S*-arylation followed by <sup>11</sup>C-cyanation (Figure 1a).<sup>7</sup> Our objective was to demonstrate unmodified peptides are amenable to direct labeling with the longer half-life radioisotope fluorine-18 applying a method that does not require chemical manipulation of the peptide prior to <sup>18</sup>F-incorporation, and employs a “zero-size” <sup>18</sup>F-motif. Herein, we report radiosynthesis of a newly



**Figure 1.** (a) <sup>11</sup>C-Radiolabeling of unmodified peptides. (b) This work, <sup>18</sup>F-labeling of unmodified peptides with the CF<sub>3</sub> group.

designed <sup>18</sup>F-reagent and its application toward a metal-free technology to radiolabel unmodified peptides at the cysteine residue with the smallest symmetrical <sup>18</sup>F-labeled multifluorine group possible: CF<sub>3</sub> (Figure 1b). This approach generates the noncanonical trifluoromethylcysteine residue, a structural re-engineering operation unmatched by alternative <sup>18</sup>F-labeling methods.<sup>8</sup>

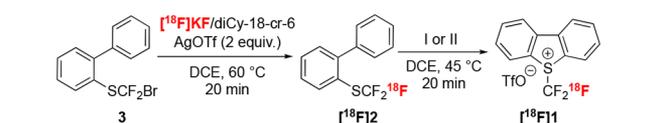
It is well-known reagents based on hypervalent iodine and chalcogenonium salts are well suited to transfer the trifluoromethyl group to *S*-nucleophiles.<sup>9</sup> We opted to <sup>18</sup>F-label 5-(trifluoromethyl)dibenzothiophenium trifluoromethanesulfonate **1**, the so-called Umemoto reagent, due to it being soluble in water and amenable to tunable reactivity through interchange of *S* with *Se* or *Te*, and/or substitution on the aryl groups.<sup>9a,10</sup> We anticipated the soft nature of the nucleophile cysteine thiol and the sulfonium leaving group of this reagent would guide chemoselectivity for the <sup>18</sup>F-labeling of peptides.<sup>11</sup> The most streamlined protocol to prepare **1** consists of treating 1,1'-biphenyl with CF<sub>3</sub>SO<sub>2</sub>K and 2 equiv of Tf<sub>2</sub>O.<sup>12</sup> For radiolabeling, this method would require a route to <sup>18</sup>F-labeled CF<sub>3</sub>SO<sub>2</sub>K. An alternative approach consists of subjecting 2-((trifluoromethyl)sulfinyl)-1,1'-biphenyl to cyclization with Tf<sub>2</sub>O.<sup>9a</sup> This sequence was attractive as our laboratory has demonstrated that [1,1'-

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biphenyl]-2-yl(trifluoromethyl)sulfane [ $^{18}\text{F}$ ]2 is within reach upon treatment of [1,1'-biphenyl]-4-yl(bromodifluoromethyl)sulfane 3 with [ $^{18}\text{F}$ ]KF, diCy-18-cr-6 and AgOTf.<sup>13</sup> This result encouraged development of a process to oxidize [ $^{18}\text{F}$ ]2 into 2-((trifluoromethyl)sulfinyl)-1,1'-biphenyl and induce subsequent cyclization (Table 1).

Table 1. Oxidative Cyclization of [ $^{18}\text{F}$ ]2



entry	[ $^{18}\text{F}$ ]2	additive <sup>a</sup>	purification	RCC [%]
1	~30 MBq <sup>b</sup>	I (3 equiv)	Al <sub>2</sub> O <sub>3</sub> (N) Sep-Pak	98 ± 1 <sup>c</sup>
2	106 MBq <sup>d</sup>	I (3 equiv)	Al <sub>2</sub> O <sub>3</sub> (N) Sep-Pak	13 <sup>e</sup>
3	120 MBq	I (3 equiv)	HPLC	30 <sup>f</sup>
4	224 MBq	II (3 equiv)	HPLC	42 <sup>f</sup>
5	0.2–1.6 GBq	II (3 equiv)	HPLC	49 ± 9 <sup>g</sup>

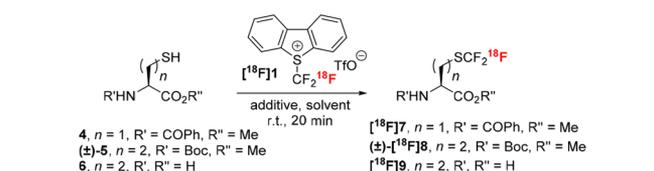
<sup>a</sup>I = *m*CPBA/Tf<sub>2</sub>O; II = Oxone/Tf<sub>2</sub>O. <sup>b</sup>~50 μL aliquot of a solution of [ $^{18}\text{F}$ ]2 in 1 mL of DCE. <sup>c</sup>Radiochemical conversion (RCC) determined by radio-TLC (*n* = 2). <sup>d</sup>~300 μL aliquot of a solution of [ $^{18}\text{F}$ ]2 in 1 mL of DCE. <sup>e</sup>RCC determined by radio-TLC. <sup>f</sup>Radiochemical yield (RCY). <sup>g</sup>*n* = 44

The radiosynthesis of [ $^{18}\text{F}$ ]1 began with the  $^{18}\text{F}$ -fluorination by halogen exchange of 3 with [ $^{18}\text{F}$ ]KF/diCy-18-cr-6 in the presence of AgOTf,<sup>14,15</sup> a reaction performed in DCE at 60 °C for 20 min. Purification using an Alumina (N) Sep-Pak provided a solution of [ $^{18}\text{F}$ ]2 in DCE (approximately 1 mL). The oxidative ring closure was investigated adding an aliquot of [ $^{18}\text{F}$ ]2 (50 μL, approximately 30 MBq) to a vial containing the oxidant, followed by addition of Tf<sub>2</sub>O in DCE. After 20 min, the radiochemical conversion (RCC) was determined by analysis of the crude reaction mixture by radio-TLC. The  $^{18}\text{F}$ -Umemoto reagent [ $^{18}\text{F}$ ]1 was obtained using an excess of *m*-chloroperbenzoic acid (*m*CPBA) and Tf<sub>2</sub>O in DCE at 45 °C (Table 1, entry 1). Having validated the two steps converting 3 into [ $^{18}\text{F}$ ]1, we focused on establishing a protocol to prepare, purify and isolate this novel  $^{18}\text{F}$ -trifluoromethylation reagent for subsequent use. The use of a larger aliquot of [ $^{18}\text{F}$ ]2 in DCE (300 μL, 106 MBq) resulted in a lower RCC of 13% (Table 1, entry 2), and informed that the presence of unreacted 3, which cannot be removed from [ $^{18}\text{F}$ ]2 through Alumina (N) Sep-Pak purification, was detrimental for oxidative cyclization. Purification by HPLC resulted in removal of 3, and provided a solution of [ $^{18}\text{F}$ ]2 in a CH<sub>3</sub>CN/H<sub>2</sub>O mixture. Reformulation by C18 Sep-Pak was necessary prior to oxidative cyclization. The final purification of [ $^{18}\text{F}$ ]1 was achieved using a Silica Sep-Pak. Elution with CHCl<sub>3</sub> removed all nonpolar impurities, after which [ $^{18}\text{F}$ ]1 was eluted with CH<sub>3</sub>CN. Following this procedure, [ $^{18}\text{F}$ ]1 was isolated in 30% RCY but *m*CPBA was present as an impurity (Table 1, entry 3). This was circumvented using Oxone with Tf<sub>2</sub>O, a modification that provided [ $^{18}\text{F}$ ]1 in 42% RCY (Table 1, entry 4). The optimized protocol for the radiosynthesis of [ $^{18}\text{F}$ ]1 began with the  $^{18}\text{F}$ -fluorination of 3 applying the original elution conditions (K<sub>2</sub>C<sub>2</sub>O<sub>4</sub>/diCy-18-cr-6). This step afforded [ $^{18}\text{F}$ ]2 in 11% ± 4% RCY (*n* = 47), and a molar activity (MA) of 0.24 GBq/μmol. Oxidative cyclization with Oxone afforded [ $^{18}\text{F}$ ]1 in 49% ± 9% RCY (*n* = 44) from [ $^{18}\text{F}$ ]2 (MA of 0.08 GBq/μmol) (Table 1, entry 5). The overall nondecay corrected activity yield of isolated [ $^{18}\text{F}$ ]1 calculated from  $^{18}\text{F}$ -fluoride is 5% ± 2% (*n* = 41). Using this protocol, up to 840 MBq of [ $^{18}\text{F}$ ]1 was isolated from ~6–10

GBq of  $^{18}\text{F}$ -fluoride. The identity of [ $^{18}\text{F}$ ]1 was established by HPLC and electrospray ionization (ESI) mass spectrometry ([ $^{19}\text{F}$ ]1, C<sub>14</sub>H<sub>8</sub>F<sub>4</sub>O<sub>3</sub>S<sub>2</sub> *m/z* 253.1, calcd 253.0).<sup>15</sup>

The reactivity of the novel  $^{18}\text{F}$ -trifluoromethylation reagent [ $^{18}\text{F}$ ]1 was examined with ethyl benzoyl-L-cysteinate 4 and (*tert*-butoxycarbonyl)-DL-homocysteinate 5 (Table 2).

Table 2.  $^{18}\text{F}$ -Trifluoromethylation of 4–6

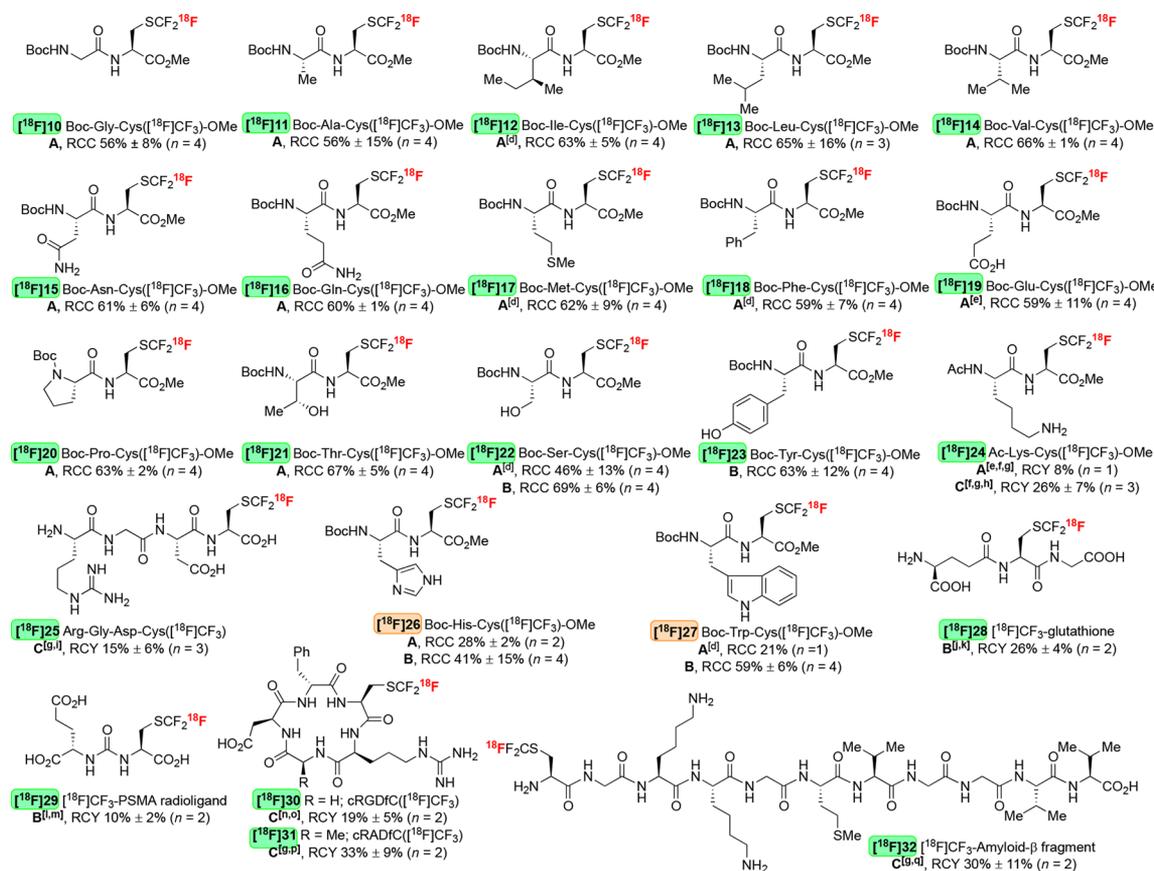


entry <sup>a</sup>	4–6 <sup>b</sup>	additive <sup>c</sup>	solvent <sup>d</sup>	RCC 7–9 [%] <sup>e</sup>
1	4 (40)	DMAP	CH <sub>3</sub> CN <sup>f</sup>	0
2	4 (40)	DMAP	CH <sub>3</sub> CN <sup>g</sup>	6 ± 1
3	4 (40)	DMAP	CH <sub>3</sub> CN	60 ± 7
4	4 (40)	DMAP	DMF	65 ± 2
5	4 (40)	DMAP	DMSO	59 ± 2
6	4 (40)	–	DMSO	2 ± 1
7	4 (20)	DMAP	DMSO	72 ± 4 <sup>h</sup>
8 <sup>i</sup>	4 (20)	DMAP	DMSO	69 ± 1
9 <sup>j</sup>	4 (20)	DMAP	DMSO/H <sub>2</sub> O, 4/1	66 ± 4
10	4 (20)	KHCO <sub>3</sub>	DMSO/H <sub>2</sub> O, 1/1	71 ± 6 <sup>h</sup>
11	(±)-5 (20)	DMAP	DMSO/H <sub>2</sub> O, 4/1	75 ± 8
12 <sup>j</sup>	6 (20)	KHCO <sub>3</sub> <sup>k</sup>	DMSO/H <sub>2</sub> O, 1/9	26 ± 6 <sup>l</sup>

<sup>a</sup>~20–25 MBq of [ $^{18}\text{F}$ ]1 per reaction. <sup>b</sup>μmol. <sup>c</sup>1 equiv. <sup>d</sup>100 μL. <sup>e</sup>RCC = radiochemical conversion based on [ $^{18}\text{F}$ ]1, determined by radio-TLC and radio-HPLC (*n* = 2). <sup>f</sup>400 μL. <sup>g</sup>200 μL. <sup>h</sup>*n* = 4. <sup>i</sup>Reaction time = 10 min. <sup>j</sup>Reaction temp. = 40 °C. <sup>k</sup>2 equiv. <sup>l</sup>RCY of 6 isolated after Oasis MCX cartridge purification.

$^{18}\text{F}$ -Trifluoromethylation of 4 took place upon treatment with [ $^{18}\text{F}$ ]1 and DMAP<sup>16</sup> (1 equiv) in CH<sub>3</sub>CN (0.2 M), with the RCC of [ $^{18}\text{F}$ ]7 increasing to 60% at higher concentration (0.4 M) (Table 2, entries 2–3). DMF and DMSO are suitable solvents for this reaction, and a control experiment verified the base is essential (Table 2, entries 5–6). Water as a cosolvent is compatible with the reaction, but it is preferable to replace DMAP with KHCO<sub>3</sub> (Table 2, entries 10). Methyl (*tert*-butoxycarbonyl)homocysteinate (±)-5 also underwent thiol  $^{18}\text{F}$ -trifluoromethylation affording [ $^{18}\text{F}$ ]8 in 75% ± 8% RCC (*n* = 4) (Table 2, entry 11). Increasing the H<sub>2</sub>O ratio to 90% allowed for the  $^{18}\text{F}$ -labeling of unprotected amino acids. Under these conditions, L-homocysteine 6 led to [ $^{18}\text{F}$ ]9 isolated in 26% ± 6% RCY (*n* = 2) (Table 2, entry 12).

The method exhibits high chemoselectivity for the radio-labeling of the cysteine residue in the presence of other nucleophilic functional groups (Figure 2).<sup>17</sup> Model dipeptides and tetrapeptides containing asparagine, glutamine, methionine, glutamic acid, proline, threonine, serine, tyrosine, lysine or arginine all underwent  $^{18}\text{F}$ -trifluoromethylation at room temperature in the presence of DMAP in DMSO/H<sub>2</sub>O 4/1 with RCCs superior to 55%. Exclusive chemoselectivity for the cysteine residue was verified by comparison with authentic references based on UV- and radio-HPLC.<sup>15</sup> For the model dipeptides [ $^{18}\text{F}$ ]22 and [ $^{18}\text{F}$ ]24 containing a serine or lysine residue, the RCCs were improved by replacing DMAP with KHCO<sub>3</sub> or Et<sub>4</sub>NHCO<sub>3</sub>. Dipeptides featuring tryptophan and histidine resulted in the formation of more than one  $^{18}\text{F}$ -radiolabeled product. The  $^{18}\text{F}$ -trifluoromethylation of methyl (*tert*-butox-



**Figure 2.** [a] Conditions A: 20 μmol peptide, 20 μmol DMAP, DMSO/H<sub>2</sub>O 4:1 (100 μL), RT, 10 min. [b] Conditions B: 20 μmol peptide, 20 μmol KHCO<sub>3</sub>, DMSO/H<sub>2</sub>O 1:1 (100 μL), RT, 10 min. [c] Conditions C: 20 μmol peptide, 20 μmol Et<sub>4</sub>NHCO<sub>3</sub>, DMSO/H<sub>2</sub>O 4:1 (100 μL), 40 °C, 20 min. [d] DMSO (100 μL) was used. [e] 40 μmol DMAP was used. [f] Substrate is Ac-Lys-Cys-OMe.TFA. [g] Isolated yield after cartridge purification (Oasis HLB). [h] 40 μmol Et<sub>4</sub>NHCO<sub>3</sub> was used. [i] 3.5 μmol H-Arg-Asp-Gly-Cys.TFA, 10 μmol Et<sub>4</sub>NHCO<sub>3</sub>, DMSO/H<sub>2</sub>O 4:1 (40 μL), 40 °C, 20 min. [j] 20 μmol substrate, 60 μmol NaHCO<sub>3</sub>, DMSO/H<sub>2</sub>O 1:1 (140 μL), 30 °C, 10 min. [k] Isolated yield after cartridge purification (Oasis MCX). [l] 20 μmol substrate, 50 μmol K<sub>2</sub>CO<sub>3</sub>, DMSO/H<sub>2</sub>O 1:1 (100 μL), 40 °C, 20 min. [m] Isolated yield after cartridge purification (Oasis MAX). [n] 3.1 μmol peptide AcOH salt, 10 μmol Et<sub>4</sub>NHCO<sub>3</sub>, DMSO/H<sub>2</sub>O 4:1 (40 μL). [o] Isolated yield after HPLC purification. [p] 2.8 μmol peptide TFA salt, 10 μmol Et<sub>4</sub>NHCO<sub>3</sub>, DMSO/H<sub>2</sub>O 4:1 (40 μL). [q] 1.0 μmol peptide TFA salt, 5.2 μmol Et<sub>4</sub>NHCO<sub>3</sub>, DMSO/H<sub>2</sub>O 4:1 (40 μL). Color coding: green = single <sup>18</sup>F-radiolabeled product; orange = more than one <sup>18</sup>F-radiolabeled product.

ycarbonyl)-L-histidyl-L-cysteinate led to the <sup>18</sup>F-labeled peptide [<sup>18</sup>F]26 in 41% ± 15% RCC (n = 4) as the major product (68% RCP) (RCP = radiochemical purity), along with radiolabeled products resulting from <sup>18</sup>F-trifluoromethylation at the imidazole ring along with some disulfide formation resulting from oxidative dimerization.<sup>15</sup> In addition to predominant <sup>18</sup>F-trifluoromethylation at the cysteine residue (64% RCP), similar competitive pathways were observed for the tryptophan-containing dipeptide precursor of [<sup>18</sup>F]27. For these challenging peptides, the ratio of <sup>18</sup>F-radiolabeled products can be modified to maximize thiol <sup>18</sup>F-trifluoromethylation by using 1 equiv of KHCO<sub>3</sub> as base instead of DMAP, but side reactions could not be entirely suppressed (41% vs 21% for [<sup>18</sup>F]26, 59% vs 28% for [<sup>18</sup>F]27). Glutathione and ((1-carboxy-2-mercaptoethyl)-carbamoyl)-glutamic acid, a core structure found in PET radioligands targeting prostate specific membrane antigen (PSMA),<sup>18</sup> were selected to test the robustness of this methodology toward multiple carboxylic acids. Glutathione underwent successful thiol <sup>18</sup>F-trifluoromethylation in 26% ± 4% RCY (n = 2) when the reaction was carried out with an excess of KHCO<sub>3</sub> (3 equiv) in DMSO/H<sub>2</sub>O (1/1). These conditions gave PSMA radioligand [<sup>18</sup>F]29 in 10% ± 2% RCY (n = 2).

Radiolabeled Arg-Gly-Asp (RGD) peptides have been a focus for noninvasive assessment of angiogenesis because of their high affinity and selectivity for integrin α<sub>v</sub>β<sub>3</sub>.<sup>19</sup> It was thus of interest to study the <sup>18</sup>F-labeling of cyclic peptide containing the RGD sequence. The <sup>18</sup>F-trifluoromethylation was performed with 3 μmol of peptide and 10 μmol of Et<sub>4</sub>NHCO<sub>3</sub> at 40 °C in 40 μL of solvent (DMSO/H<sub>2</sub>O 1/1). After 20 min of reaction, cRGDFC([<sup>18</sup>F]CF<sub>3</sub>) [<sup>18</sup>F]30 was purified and isolated by prep-HPLC in 19% ± 5% RCY as a single <sup>18</sup>F-radiolabeled product. The cyclic peptide cRADfC([<sup>18</sup>F]CF<sub>3</sub>) [<sup>18</sup>F]31 was obtained in 33% ± 9% after cartridge purification. Finally, a beta-amyloid peptide fragment<sup>20</sup> (1 μmol, MW = 1034) also underwent successful <sup>18</sup>F-trifluoromethylation in 40 μL of solvent (DMSO/H<sub>2</sub>O 1/1). The reaction proceeded exclusively at the cysteine residue affording the single product [<sup>18</sup>F]32 isolated in 30% ± 11% RCY (n = 2). This assignment was confirmed by mass spectrometry (ESI) and comparison of the authentic reference by UV- and radio-HPLC.<sup>15</sup>

To investigate the *in vivo* stability of peptides functionalized with an [<sup>18</sup>F]SCF<sub>3</sub> moiety, a biodistribution profile was obtained by injecting naïve CBA mice (n = 3) with cRGDFC([<sup>18</sup>F]CF<sub>3</sub>) [<sup>18</sup>F]30, followed by dynamic whole-body PET imaging.<sup>15</sup> Biodistribution studies by imaging and dissection show [<sup>18</sup>F]30

is predominantly excreted by the hepatobiliary route and to a lesser extent by the kidneys. Although these excretion organs contain a considerable amount of radioactivity at 1 h post-injection, most radioactivity in nontargeted tissues and blood was cleared. This biodistribution profile is consistent with RGD peptides labeled applying alternative methods.<sup>21</sup> The absence of uptake in the bones indicated [<sup>18</sup>F]30 is metabolically stable toward [<sup>18</sup>F]SCF<sub>3</sub> elimination and that no [<sup>18</sup>F]F<sup>-</sup> was released.<sup>8b</sup>

In summary, we have developed the first protocol enabling direct <sup>18</sup>F-labeling of unmodified peptides at the cysteine residue with the minimally sized CF<sub>3</sub> group. The strategy required the novel designed <sup>18</sup>F-reagent [<sup>18</sup>F]1 for thiol <sup>18</sup>F-trifluoromethylation. Biodistribution studies demonstrated the [<sup>18</sup>F]SCF<sub>3</sub> moiety is viable for imaging. Considering the number of reactions that use the Umemoto's reagent 1, we anticipate the availability of [<sup>18</sup>F]1 will expand the radiochemical space available for radioligand production well beyond the peptides described in this study.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b10227.

Experimental and characterization data (PDF)

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### Notes

The authors declare no competing financial interest.

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## ■ REFERENCES

- (1) (a) Miller, P. W.; Long, N. J.; Vilar, R.; Gee, A. D. *Angew. Chem., Int. Ed.* **2008**, *47*, 8998–9033. (b) Placzek, M. S.; Zhao, W.; Wey, H. Y.; Morin, T. M.; Hooker, J. M. *Semin. Nucl. Med.* **2016**, *46*, 20–27.
- (2) (a) Richter, S.; Wuest, F. *Molecules* **2014**, *19*, 20536–20556. (b) Charron, C. L.; Hickey, J. L.; Nsima, J. K.; Cruickshank, D. R.; Turnbull, W. L.; Luyt, L. G. *Nat. Prod. Rep.* **2016**, *33*, 761–800.
- (3) (a) Fani, M.; Maecke, H. R. *Eur. J. Nucl. Med. Mol. Imaging* **2012**, *39*, 11–30. (b) Cutler, C. S.; Hennkens, H. M.; Sisay, N.; Huclier-Markai, S.; Jurisson, S. S. *Chem. Rev.* **2013**, *113*, 858–883. (c) Jackson, I.

M.; Scott, P. J. H.; Thompson, S. *Semin. Nucl. Med.* **2017**, *47*, 493–523. (d) Krishnan, H.; Ma, L.; Vasdev, N.; Liang, S. *Chem. - Eur. J.* **2017**, *23*, 15553–15577.

(4) (a) Li, Y.; Liu, Z.; Lozada, J.; Wong, M. Q.; Lin, K. S.; Yapp, D.; Perrin, D. M. *Nucl. Med. Biol.* **2013**, *40*, 959–966. (b) Bernard-Gauthier, V.; Wängler, C.; Schirmacher, E.; Kostikov, A.; Jurkschat, K.; Wängler, B.; Schirmacher, R. *BioMed Res. Int.* **2014**, *2014*, 454503. (c) Laverman, P.; McBride, W. J.; Sharkey, R. M.; Goldenberg, D. M.; Boerman, O. C. *J. Labelled Compd. Radiopharm.* **2014**, *57*, 219–223. (d) Cornilleau, T.; Audrain, H.; Guillemet, A.; Hermange, P.; Fouquet, E. *Org. Lett.* **2015**, *17*, 354–357. (e) Perrin, D. M. *Acc. Chem. Res.* **2016**, *49*, 1333–1343.

(5) (a) Marik, J.; Sutcliffe, J. L. *Tetrahedron Lett.* **2006**, *47*, 6681–6684. (b) Gao, M.; Gouverneur, V.; Davis, B. G. *J. Am. Chem. Soc.* **2013**, *135*, 13612–13615. (c) Jacobson, O.; Yan, X.; Ma, Y.; Niu, G.; Kiesewetter, D. O.; Chen, X. *Bioconjugate Chem.* **2015**, *26*, 2016–2020. (d) Way, J. D.; Bergman, C.; Wuest, F. *Chem. Commun.* **2015**, *51*, 3838–3841. (e) Chiotellis, A.; Sladojevich, F.; Mu, L.; Herde, A. M.; Valverde, I. E.; Tolmachev, V.; Schibli, R.; Ametamey, S. M.; Mindt, T. L. *Chem. Commun.* **2016**, *52*, 6083–6086.

(6) Andersen, T. L.; Nordeman, P.; Christoffersen, H. F.; Audrain, H.; Antoni, G.; Skrydstrup, T. *Angew. Chem., Int. Ed.* **2017**, *56*, 4549–4553.

(7) Zhao, W.; Lee, H. G.; Buchwald, S. L.; Hooker, J. M. *J. Am. Chem. Soc.* **2017**, *139*, 7152–7155.

(8) (a) Marsh, E. N. *Acc. Chem. Res.* **2014**, *47*, 2878–2886. (b) Gadais, C.; Saraiva-Rosa, N.; Chelain, E.; Pytkowicz, J.; Brigaud, T. *Eur. J. Org. Chem.* **2017**, *2017*, 246–251. (c) Zeng, J.-L.; Chachignon, H.; Ma, J.-A.; Cahard, D. *Org. Lett.* **2017**, *19*, 1974–1977.

(9) (a) Umemoto, T.; Ishihara, S. *J. Am. Chem. Soc.* **1993**, *115*, 2156–2164. (b) Kieltisch, L.; Eisenberger, P.; Togni, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 754–757. (c) Capone, S.; Kieltisch, I.; Flögel, O.; Lelais, G.; Togni, A.; Seebach, D. *Helv. Chim. Acta* **2008**, *91*, 2035–2056. (d) Shibata, N.; Matsnev, A.; Cahard, D. *Beilstein J. Org. Chem.* **2010**, *6*, 65–73. (e) Santschi, N.; Togni, A. *J. Org. Chem.* **2011**, *76*, 4189–4193.

(10) (a) Li, M.; Wang, Y.; Xue, X.-S.; Cheng, J.-P. *Asian J. Org. Chem.* **2017**, *6*, 235–240. (b) Umemoto, T.; Zhang, B.; Zhu, T.; Zhou, X.; Zhang, P.; Hu, S.; Li, Y. *J. Org. Chem.* **2017**, *82*, 7708–7719.

(11) Chalker, J. M.; Bernardes, G. J. L.; Lin, Y. A.; Davis, B. G. *Chem. - Asian J.* **2009**, *4*, 630–640.

(12) Mace, Y.; Raymondeau, B.; Pradet, C.; Blazejewski, J.-C.; Magnier, E. *Eur. J. Org. Chem.* **2009**, *2009*, 1390–1397.

(13) Khotavivattana, T.; Verhoog, S.; Tredwell, M.; Pfeifer, L.; Calderwood, S.; Wheelhouse, K.; Collier, T. L.; Gouverneur, V. *Angew. Chem., Int. Ed.* **2015**, *54*, 9991–9995.

(14) The quality of AgOTf is important for reproducibility.

(15) See the Supporting Information.

(16) Cheng, Y.; Yuan, X.; Ma, J.; Yu, S. *Chem. - Eur. J.* **2015**, *21*, 8355–8359.

(17) A control experiment demonstrated that the cysteine disulfide dimethyl 3,3'-disulfanediy(2R,2'R)-bis(2-benzamidopropanoate) did not undergo trifluoromethylation.<sup>15</sup>

(18) Schwarzenboeck, S. M.; Rauscher, I.; Bluemel, C.; Fendler, W. P.; Rowe, S. P.; Pomper, M. G.; Asfhar-Oromieh, A.; Herrmann, K.; Eiber, M. *J. Nucl. Med.* **2017**, *58*, 1545–1552.

(19) Hatley, R.; Macdonald, S.; Slack, R.; Le, J.; Ludbrook, S.; Lukey, P. *Angew. Chem., Int. Ed.* **2017**, *10.1002/anie.201707948*.

(20) Vandenbergh, R.; Adamczuk, K.; Dupont, P.; Laere, K. V.; Chételat, G. *Neuroimage Clin* **2013**, *2*, 497–511.

(21) (a) Chen, X.; Park, R.; Shahinian, A. H.; Tohme, M.; Khankaldyann, V.; Bozorgzadeh, M. H.; Bading, J. R.; Moats, R.; Laug, W. E.; Conti, P. S. *Nucl. Med. Biol.* **2004**, *31*, 179–189. (b) Cai, W.; Zhang, X.; Wu, Y.; Chen, Z. *J. Nucl. Med.* **2006**, *47*, 1172–1180. (c) Liu, S.; Hassink, M.; Selvaraj, M.; Yap, L.-P.; Park, R.; Wang, H.; Chen, X.; Fox, J. M.; Li, Z.; Conti, P. S. *Mol. Imaging* **2013**, *12*, 121–128.