Harvesting [^{18}F]-fluoride ions in water via direct ^{18}F-^{19}F isotopic exchange: Radiofluorination of zwitterionic aryltrifluoroborates and *in vivo* stability studies.

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SUPPORTING INFORMATION

This document includes:

Materials and Methods

General Consideration. *ortho*-(*i*-$Pr_2P)C_6H_4(BMes_2)$[1] and *ortho*-$(Ph_2P)C_6H_4(Bpin)$[2] were prepared according to the published procedure. CH_3I was purchased from Alfa Aesar. HF-

pyridine was purchased from Sigma-Aldrich and 3-iodoproprionic acid was bought from Oakwood Product, Inc. Solvents were dried by passing through an alumina column (CH_2Cl_2) or refluxing under N_2 over Na/K (Et_2O). Air sensitive compounds were handled under a N_2 atmosphere using standard Schlenk and glovebox techniques. Electrospray mass spectra were acquired from a MDS Sciex API QStar Pulsar. The spray voltage was 4.5 kV. Elemental analyses were performed at Atlantic Microlab (Norcross, GA). NMR spectra were recorded on a Varian Unity Inova 300 NMR and an Inova 400 NMR spectrometer at ambient temperature. Chemical shifts are given in ppm, and are referenced to residual ^{1}H and ^{13}C solvent signals as well as external BF_3-Et_2O (^{11}B), $CFCl_3$ (^{19}F) and H_3PO_4 (^{31}P).

Preparation of *ortho*-(*i*Pr_2MeP)C_6H_4(BF_3) (2)

Methyl iodide (0.06 mL, 0.984 mmol) was added to a solution of *ortho*-(*i*-Pr_2P)C_6H_4($BMes_2$) (0.145 g, 0.328 mmol) in dichloromethane (7 mL) at room temperature. After being stirred overnight, the solution was concentrated in *vacuo* to a volume of 1 mL. To the concentrated solution, was added Et_2O (10 mL) which resulted in the precipitation of a pale yellow solid (0.145g, 96% yield).^{1}H NMR (299.9 MHz, $CDCl_3$): δ 1.10 (dd, 6H, isopropyl-C*H*$_3$, $^{3}J_{H\text{-}P}$ = 17.99 Hz, $^{3}J_{H\text{-}H}$ = 7.20 Hz), 1.16 – 1.29 (m, 6H, isopropyl-C*H*$_3$), 1.34 (s, 3H, Mes-C*H*$_3$), 1.84 (d, 3H, P-C*H*$_3$, $^{2}J_{H\text{-}P}$ = 53.98), 1.87 (s, 3H, Mes-C*H*$_3$), 1.98 (s, 3H, Mes-C*H*$_3$), 2.08 (s, 3H, Mes-C*H*$_3$), 2.22 (s, 3H, Mes-C*H*$_3$), 2.26 (s, 3H, Mes-C*H*$_3$), 2.56 – 2.70 (m, 1H, isopropyl-C*H*), 3.38 – 3.52 (m, 1H, isopropyl-C*H*), 6.68 – 6.84 (m, 4H, Mes-C*H*), 7.48 – 7.62 (m, 2H, phenyl-C*H*), 7.78 (t, 1H, phenyl-C*H*, $^{3}J_{H\text{-}H}$ = 7.50 Hz), 8.33 (dd, 1H, phenyl-C*H*, $^{3}J_{H\text{-}P}$ = 11.0 Hz, $^{3}J_{H\text{-}H}$ = 7.50 Hz). ^{13}C NMR (125.6 MHz, $CDCl_3$): δ 2.01, 2.41, 16.59, 17.28, 21.39 (d, $J_{C\text{-}P}$ = 6.28 Hz), 23.21, 23.59, 23.85,24.87, 25.08, 25.56, 25.92, 105.16,121.75, 122.36, 129.20, 129.50,129.77, 129.96, 131.59 (d, $J_{C\text{-}P}$ = 12.43 Hz), 133.58 (d, $J_{C\text{-}P}$ = 3.14 Hz), 136.25, 136.35, 136.66, 136.76, 140.40, 141.26, 141.44, 141.95, 142.12, 142.45. ^{11}B NMR (128.2 MHz, $CDCl_3$): not observed. ^{31}P NMR (121.4 MHz, $CDCl_3$): 40.95. Anal. Calcd for $C_{31}H_{43}PBI$: C, 62.72; H, 7.42. Found: C, 62.22; H, 7.12. Without further purification, the pale yellow solid was treated with excess hydrogen fluoride pyridine in dichloromethane (2 mL) at room temperature. After being stirred for 18 h, the mixture was quenched by water (2 mL). The dichloromethane layer was separated from the mixture, dried with $MgSO_4$, and filtered to remove $MgSO_4$, respectively. The solvent was removed under reduced pressure. The residue was washed with Et_2O (3 × 2 mL) yielding **2** as yellow solid (63.1 mg, 70% yield). ^{1}H NMR (299.9 MHz, $CDCl_3$): δ 1.07 (dd, 6H, isopropyl-C*H*$_3$, $^{3}J_{H\text{-}P}$ = 20.99 Hz, $^{3}J_{H\text{-}H}$ = 7.20 Hz), 1.37 (dd, 6H, isopropyl-C*H*$_3$, $^{3}J_{H\text{-}P}$ = 17.99 Hz, $^{3}J_{H\text{-}H}$ = 7.50 Hz), 1.89 (d, 3H, P-C*H*$_3$, $^{2}J_{H\text{-}P}$ = 11.70 Hz), 3.56 (m, 2H, isopropyl-C*H*), 7.41 – 7.46 (m, 2H, phenyl-C*H*), 7.59 (t, 1H, $^{3}J_{H\text{-}H}$ = 6.30 Hz), 8.13 (dd, 1H, $^{3}J_{H\text{-}P}$ = 6.60 Hz, $^{3}J_{H\text{-}H}$ = 4.80 Hz). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ -1.83 (d, $^{1}J_{C\text{-}P}$ = 54.06 Hz), 17.16 (d, $^{2}J_{C\text{-}P}$ = 2.26 Hz), 17.66 (d, $^{2}J_{C\text{-}P}$ = 2.19 Hz), 23.27 (d, $^{1}J_{C\text{-}P}$ = 4.98 Hz), 23.88 (d, $^{1}J_{C\text{-}P}$ = 4.45 Hz), 126.65 (d, $J_{C\text{-}P}$ = 12.14 Hz), 130.20 (d, $J_{C\text{-}P}$ = 11.00 Hz), 132.83 (d, $J_{C\text{-}P}$ = 3.09 Hz), 136.41 (dd, $^{1}J_{C\text{-}P}$ = 15.98 Hz, $^{3}J_{C\text{-}F}$ = 3.32 Hz). ^{11}B NMR (128.2 MHz, $CDCl_3$): δ 2.37 (q, $^{1}J_{B\text{-}F}$ = 46.28 Hz). ^{31}P NMR (121.4 MHz, $CDCl_3$): δ 41.10. ^{19}F NMR (282.2 MHz; $CDCl_3$): -136.3. Anal. Calcd for $C_{13}H_{21}PBF_3$: C, 54.97; H, 7.67. Found: C, 54.56; H, 7.38.

Preparation of *ortho*-(($HO_2C(CH_2)_2$**)Ph_2P)C_6H_4(BF_3) (3)**

A solution of the *ortho*-(Ph_2P)C_6H_4(Bpin) (0.428 g, 1.102 mmol) and 3-iodoproprionic acid (0.225 g, 1.125 mmol) in toluene (5 mL) was heated to 90 °C for 18 h. After 18 h, the mixture was concentrated in *vacuo* to a volume of 1 mL. Addition of Et_2O (10 mL) to the resulting

solution resulted in the precipitation of a pale yellow solid (0.578 g). Without further purification, the precipitate was dissolved in methanol (4 mL) and treated with a solution of KHF_2 (0.307 g, 3.931 mmol) in water (4 mL). The resulting solution was sonicated for 15 minutes and stirred for 1 h. The mixture was extracted by dichloromethane (3 x 15 mL) and the organic layer was dried with $MgSO_4$. After filtration, the solution was concentrated to 1 mL and treated with Et_2O (15 mL), leading to the precipitation of **3** as a pale yellow solid (0.421g, 72 % yield). ^{1}H NMR (399.5 MHz, CD_3CN): δ 2.66 (dt, 2H, -C*H*$_2$COOH, $^3J_{H\text{-}P}$ = 6.79 Hz, $^3J_{H\text{-}H}$ = 8.79 Hz), 3.62 (dt, 2H, -PC*H*$_2$CH$_2$COOH, $^2J_{H\text{-}P}$ = 13.18 Hz, $^3J_{H\text{-}H}$ = 8.79 Hz), 7.13 (dd, 1H, phenyl-C*H*, $^3J_{H\text{-}P}$ = 14.38 Hz, $^3J_{H\text{-}H}$ = 7.19 Hz), 7.32 (tdd, 1H, phenyl-C*H*, *J* = 7.59, 3.16, 1.24 Hz), 7.51 – 7.68 (m, 9H, phenyl-C*H*), 7.75 (td, 2H, phenyl-C*H*, *J* = 7.59, 1.20 Hz), 7.95 (dd, 1H, phenyl-C*H*, *J* = 7.59, 5.19 Hz). ^{13}C NMR (125.6 MHz, CD_3CN): δ 20.38 (d, -P*C*H$_2$CH$_2$COOH, $^1J_{C\text{-}P}$ = 55.26 Hz), 28.62 (d, -PCH$_2$*C*H$_2$COOH, $^2J_{C\text{-}P}$ = 2.39 Hz), 122.96, 123.65, 127.95 (d, $J_{C\text{-}P}$ = 13.82 Hz), 130.45 (d, $J_{C\text{-}P}$ = 11.93 Hz), 131.18 (d, $J_{C\text{-}P}$ = 12.43 Hz), 134.06, 134.09, 134.13, 134.28 (d, $J_{C\text{-}P}$ = 9.17 Hz), 134.73 (d, $J_{C\text{-}P}$ = 3.01 Hz), 136.06 (d, $J_{C\text{-}P}$ = 15.07 Hz), 136.24 (dq, $J_{C\text{-}P}$ = 17.58 Hz, $J_{C\text{-}F}$ = 3.26 Hz), 172.42 (d, $J_{C\text{-}P}$ = 15.07 Hz). ^{11}B NMR (128.2 MHz, CD_3CN): δ 2.83. ^{31}P NMR (161.7 MHz, CD_3CN): δ 30.6. ^{19}F NMR (375.9 MHz; CD_3CN): δ -133.6. MS (ESI$^-$) calcd for **3** $(C_{21}H_{18}BF_3O_2P)^-$: 400.8211, found: 401.1122.

Crystallographic Measurements

Single crystals of **2** were obtained by slow diffusion of Et_2O into a CH_2Cl_2 solution of **2**. Single crystals of **3** were obtained by slow diffusion of pentane into a THF solution of **3**. The crystallographic measurement of **2** and **3** were performed using a Bruker APEX-II CCD area detector diffractometer, with graphite-monochromated Mo-K_α radiation (λ = 0.71069 Å). A specimen of suitable size and quality was selected and mounted onto a nylon loop. The semi-empirical method SADABS was applied for absorption correction.[3] The structure was solved by direct methods, and refined by the full-matrix least-square metahod against F^2 with the anisotropic temperature parameters for all non-hydrogen atoms. All H atoms were geometrically placed and refined using the riding model approximations.[4] Data reduction and further calculations were performed using the Bruker SAINT+ and SHELXTL NT program packages. The crystal data are included in Table S1.

Table S1. Crystal data for **2**

Empirical formula	$C_{13}H_{21}BF_3P$	
Formula weight	276.08	
Crystal size/mm	0.25 x 0.2 x 0.2	
Temperature	110(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	Pna2(1)	
Unit cell dimensions	a = 11.372(4) Å	α = 90°
	b = 11.428(5) Å	β = 90°
	c = 11.129(4) Å	γ = 90°
Volume	1446.3(10) $Å^3$	
Z	4	
Density (calculated)	1.268 g cm^{-3}	
μ	0.203 mm^{-1}	
F(000)	584.0	
Scan mode	ω, φ	
hkl ranges	-14 → +14	
	-14 → +15	
	-14 → +14	
Reflections collected	16834	
Unique reflections [Rint]	3484 [0.0393]	
Reflection used for refinement	3484	
Refined parameters	163	
GooF	0.776	
R1,[a] *w*R2[b] (all data)	0.0317, 0.0991	
Largest diff. peak and hole	0.293, -0.183 e.$Å^{-3}$	

[a] $R1 = \Sigma||F_o| - |F_c||/ \Sigma|F_o|$. [b] $wR2\ ([w(F_o^2 - F_c^2)^2]/[\Sigma w(F_o^2)^2])^{1/2}$; $w = 1/[\sigma^2(F_o^2) + (ap)^2 + bp]$; $p = (F_o^2 + 2F_c^2)/3$ with $a = 0.1000$ and $b = 0$.

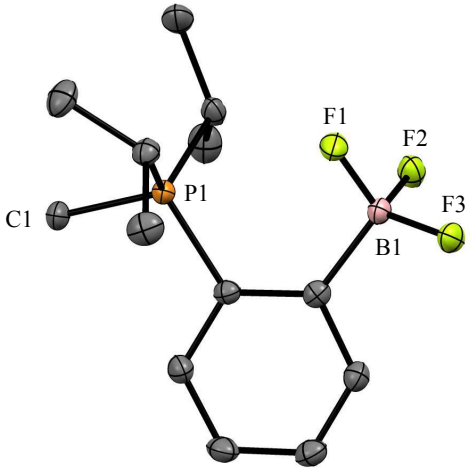

Figure S1. Crystal structure of the **2**. Ellipsoids are scaled to the 50% probability level and hydrogen atoms have been omitted for clarity.

Table S2. Crystal data for **3**

Empirical formula	$C_{21}H_{19}BF_3O_2P$	
Formula weight	382.99	
Crystal size/mm	0.33 x 0.07 x 0.02	
Temperature	110(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P21/c	
Unit cell dimensions	a = 9.163(1) Å	α = 90°
	b = 12.426(14) Å	β = 100.483(2)°
	c = 17.335(2) Å	γ = 90°
Volume	1941(4) $Å^3$	
Z	4	
Density (calculated)	1.376 g cm^{-3}	
μ	0.181 mm^{-1}	
F(000)	756.0	
Scan mode	ω, φ	
hkl ranges	-9 → +10	
	-14 → +14	
	-20 → +19	
Reflections collected	11319	
Unique reflections [Rint]	3212 [0.0675]	
Reflection used for refinement	3212	
Refined parameters	253	
GooF	1.032	
R1,[a] *w*R2[b] (all data)	0.0895, 0.2884	
Largest diff. peak and hole	1.001, -0.405 e.$Å^{-3}$	

[a] $R1 = \Sigma||F_o| - |F_c||/ \Sigma|F_o|$. [b] $wR2\ ([w(F_o^2 - F_c^2)^2]/[\Sigma w(F_o^2)^2])^{1/2}$; $w = 1/[\sigma^2(F_o^2) + (ap)^2 + bp]$; $p = (F_o^2 + 2F_c^2)/3$ with $a = 0.1533$ and $b = 2.95$.

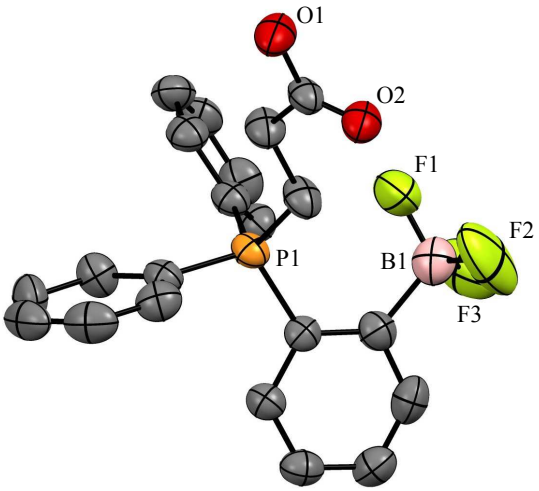

Figure S2. Crystal structure of the **3**.
Ellipsoids are scaled to the 50% probabil
and hydrogen atoms have been omitted f

Kinetic studies of the hydrolysis reactions

As previously reported for **1**,[5] a sample of **2** and **3** (5 mg) was dissolved in 0.2 mL CD_3CN and 1.0 mL D_2O phosphate buffer (pH 7.5, 500 mM). The ^{19}F NMR spectra of **2** and **3** were collected periodically. The decomposition of aryltrifluoroborate species were monitored by integration of the decreasing aryltrifluoroborate signal in conjunction with the increasing signal corresponding to free F^-. All spectra were processed using the VNMRJ Version 2.2 NMR software. The rate constant, k_{obs}, was calculated using a well-established NMR method reported in the literature.[6] This method is based on the fact that that the concentration in $ArBF_3$ species is proportional to the ^{19}F NMR integration of $ArBF_3$ signal divided by the sum of the integration of $ArBF_3$ signal and the free fluoride signal. For convenience, the value of the $ArBF_3$ integration is arbitrarily set at 100 and the free fluoride integration determined. The resulting data is provided in Table S3 and S4.

Table S3: Kinetic data for the hydrolysis of **2**. The values provided for F^- and $ArBF_3$ correspond to the integration of the corresponding NMR signal.

		Data for **2**		
				k_{obs} = 3.90E-05
			exp. ratio	calc. ratio
Time (min)	F^-	$ArBF_3$	$ArBF_3/(ArBF_3+F^-)$	$ArBF_3/(ArBF_3+F^-)$
0	0	100	1.000	1.000
520	3.8	100	0.96	0.98
1280	7.7	100	0.93	0.95
2210	11.6	100	0.90	0.92
3160	15.1	100	0.87	0.88
4280	18.8	100	0.84	0.85
10100	48.3	100	0.67	0.67
14420	76.2	100	0.57	0.57
20110	126.2	100	0.44	0.46
25000				0.38
30000				0.31
35000				0.25
40000				0.21
45000				0.17
50000				0.14

Table S4: Kinetic data for the hydrolysis of **3**. The values provided for F^- and $ArBF_3$ correspond to the integration of the corresponding NMR signal.

		Data for **3**		
				k = 1.50E-05
			exp. ratio	calc. ratio
Time (min)	F^-	$ArBF_3$	$ArBF_3/(ArBF_3+F^-)$	$ArBF_3/(ArBF_3+F^-)$
0	0	100	1.000	1.000
1440	3.9	100	0.96	0.98
2940	5.3	100	0.95	0.96
8610	12.4	100	0.89	0.88
12990	20.7	100	0.83	0.82
28800	53.1	100	0.65	0.65
35000				0.59
40000				0.55
45000				0.51
50000				0.47

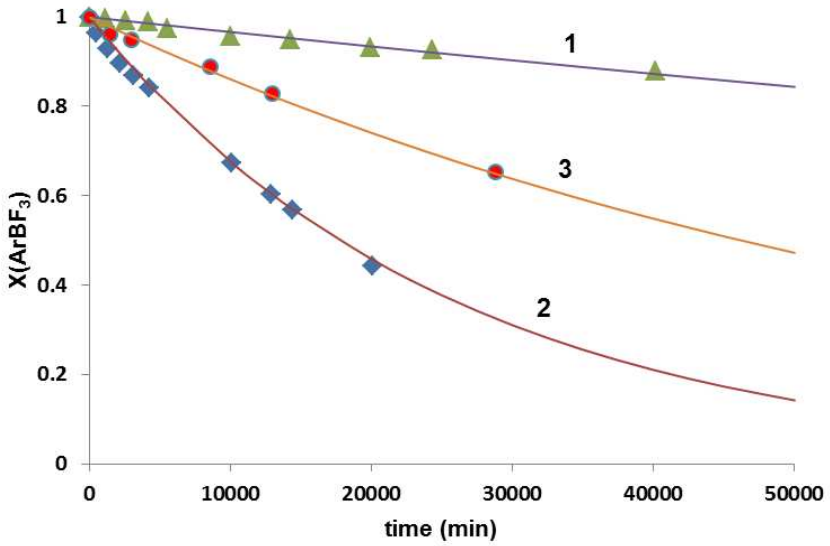

Figure S3. Kinetic plots for the hydrolysis of **1**, **2**, and **3**.The data were obtained at room temperature in D_2O/CD_3CN (8/2 vol.) at pH 7.5. The data shown for **1** has been previously reported[5] and is provided for the sake of comparison.

Electronic Supplementary Material (ESI) for Medicinal Chemistry Communications

Radiochemistry Experiments: All chemicals obtained commercially were of analytic grade and used without further purification. The syringe filter and polyethersulfone membranes (pore size, 0.22 μm; diameter, 13 mm) were obtained from Nalge Nunc International (Rochester, NY). Analytical reversed-phase high-performance liquid chromatography (HPLC) was accomplished on a Waters 515 chromatography system with a Waters 2487 dual λ absorbance detector (218 and 254 nm) and model 2200 scaler ratemeter radiation detector from Ludlum Measurements, Inc. (Sweetwater, TX). Empower 2 software from Waters Corporation (Milford, MA) was used to record chromatograms. HPLC was performed on a phenomenex Luna 5μ C18 column (250 × 4.6 mm). The flow was 1 mL/min, with the mobile phase starting from 95% solvent A (0.1% TFA in water) and 5% solvent B (0.1% TFA in acetonitrile) (0–2 min) to 5% solvent A and 95% solvent B at 22 min.

Radiochemistry: Unless otherwise noted, the reactions were performed using the following protocol. ^{18}F-Fluoride was produced with an in-house cyclotron. Zwitterions **1**, **2**, or **3** (dissolved in MeCN, 15 ± 5μL) was added to 30 ± 3 mCi ^{18}F-fluoride in 100 ± 10 μL [^{18}O]water (The activity/volume ratio was adjusted by dilution when necessary). The reaction mixture stayed at room temperature for 20 min. The final % conversion of each reaction was measured by loading approximately 30 μCi reaction mixture onto a reverse phase analytical HPLC equipped with radio detector. The retention time of [$^{18/19}$F]**1**, [$^{18/19}$F]**2** and [$^{18/19}$F]**3** is 18.1, 11.6, and 17.4 min, respectively. The identities of the compounds were confirmed by comparison of the retention times with those of the starting (non-radioactive) compounds as well as by co-injection of the starting and radiofluorinated derivatives.

Specific activity: In order to determine the specific activity of the product after labeling, a standard solution was made at a concentration 0.1 mg/mL. This solution was used to establish a UV-HPLC calibration curve, which could be easily done by correlating the volume of the injection with the resulting UV peak area. To determine the specific activity of the product at the time of analysis, a portion of crude reaction mixture (4μL) was taken out. The total amount of radio-activity of the portion was measured using a dosimeter. The % of activity incorporated in the captor compound was then determined by radio-HPLC, which was then converted to the absolute amount of activity by multiplying the % of activity conversion with the total amount of activity (mCi). The specific activity of the product was calculated by dividing the total amount of product activity by the amount of product (μmol, based on the integration of the UV-HPLC-UV and determined with the calibration curve (Figure S4). For entry 1, 7 and 8, the experiments were repeated four times and the average values reported. The radio traces obtained for the four independent syntheses in entry 7 are shown in Figure S5 for illustrative purposes.

MicroPET Imaging: Animal procedures were performed according to a protocol approved by the University of Southern California Institutional Animal Care and Use Committee. The animal care and use program at USC meets the requirements of the Federal Law (89-544 and 91-570). The USC program is also accredited by the American Association for Accreditation of Laboratory Animals. MicroPET scans were performed on a microPET R4 rodent model scanner (Siemens Medical Solutions USA, Inc., Knoxville, TN). The scanner has a computer-controlled bed and 10.8-cm transaxial and 8-cm axial fields of view (FOVs). It has no septa and operates exclusively in the 3-dimensional (3D) list mode. Animals were placed near the center of the FOV of the scanner. For static microPET scans, normal nu/nu mice were injected with about 3.7 MBq

(100 μCi) of radio products ([$^{18/19}$F]**1**, [$^{18/19}$F]**2**) via the tail vein. At 0.5 h, and 2 h post injection (p.i.), the mice were anesthetized with isoflurane (5% for induction and 2% for maintenance in 100% O_2) using a knock-down box. With the help of a laser beam attached to the scanner, the mice were placed in the prone position and near the center of the field of view of the scanner. The 3-min static scans were then obtained. Images were reconstructed by use of a 2-dimensional ordered-subsets expectation maximization (OSEM) algorithm. No background correction was performed. Regions of interest (ROIs; 5 pixels for coronal and transaxial slices) were drawn over the tumor on decay-corrected whole-body coronal images. The maximum counts per pixel per minute were obtained from the ROI and converted to counts per milliliter per minute by using a calibration constant. With the assumption of a tissue density of 1 g/ml, the ROIs were converted to counts per gram per min. Image ROI-derived %ID/g values were determined by dividing counts per gram per minute by injected dose. No attenuation correction was performed. Finally, the animals are awake between the scans, which can accelerate the rate of excretion.

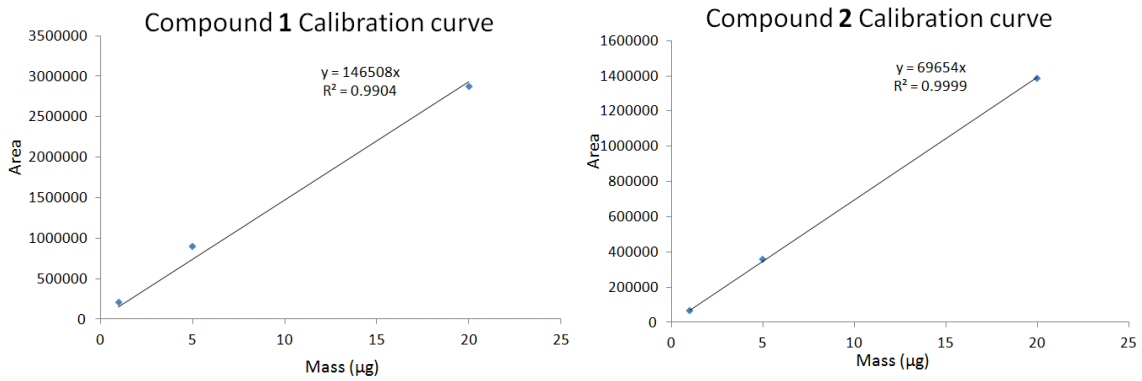

Figure. S4. Calibration curves of compound **1** and **2** used for specific activity measurements. The standard injection volume is 200 μL. The first data point is obtained by diluting 10 μL of the standard solution to a total volume of 200 μL. The second data point is obtained by diluting 20 μL of the standard solution to a total volume of 200 μL. The third data point is obtained by injecting 200 μL of the stock solution.

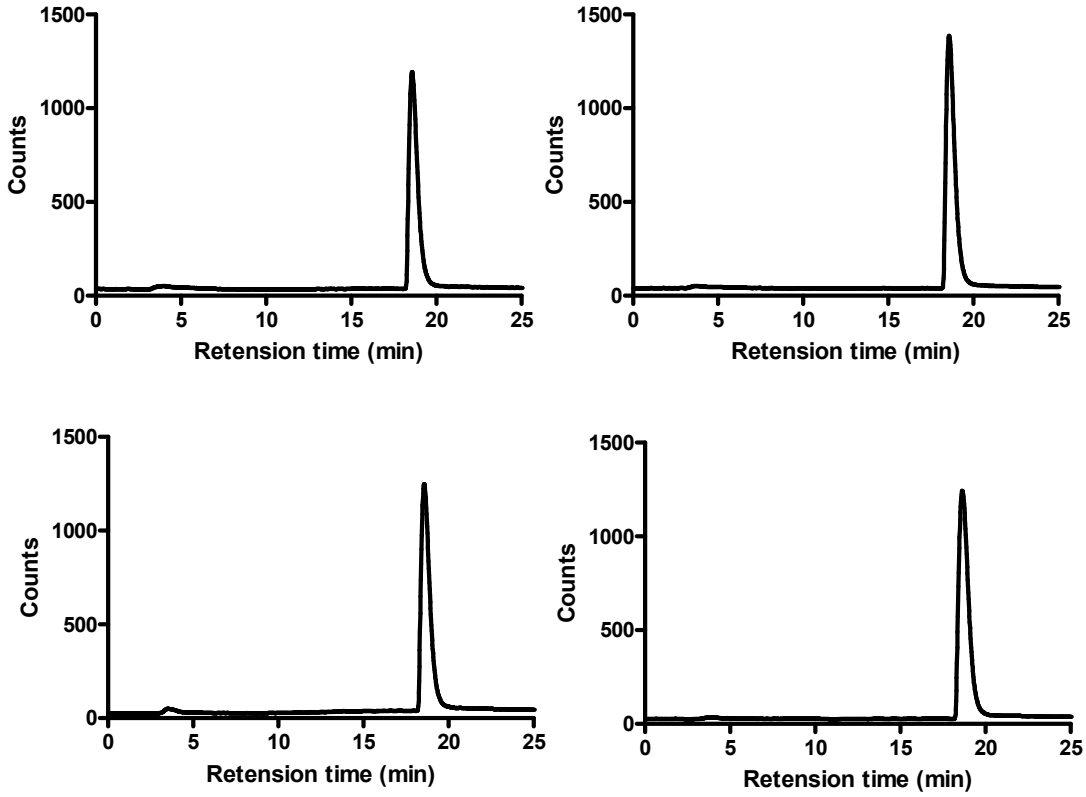

Figure S5. Four representative independent ^{18}F-fluorination of compound **1** using condition mentioned at Table 1, entry 7. HPLC was performed on a phenomenex Luna 5µ C18 column (250 × 4.6 mm). The flow was 1 mL/min, with the mobile phase starting from 95% solvent A (0.1% TFA in water) and 5% solvent B (0.1% TFA in MeCN) (0–2 min) to 5% solvent A and 95% solvent B at 22 min.

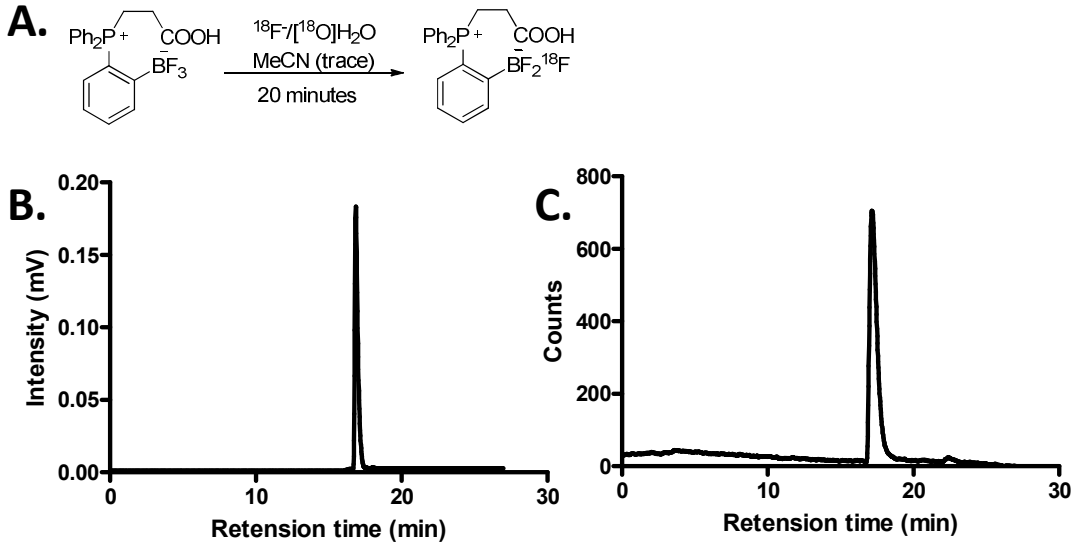

Figure. S6. ^{18}F-fluorination of **3**. B. The standard HPLC profile of **3**. C. The crude radio-HPLC profile for this radiolabeling reaction.

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