Supporting information for:

Radiofluorination of a NHC-PF_5: Toward new probes for ^{18}F PET imaging

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Experimental

General Procedures.

1-Methylimidazole and methyl iodide were purchased from Alfar Aesar. Sodium acetate was purchased from Mallinckrodt. Dichlorophenylphosphine, and bromine were purchased from Strem Chemicals. Potassium fluoride was purchased from Sigma Aldrich. All chemicals were used without further purification. Potassium fluoride was stored in an oven at 100 °C and dried under vacuum at 100 °C for 2h before use. Solvents were dried by passing through an alumina column (CH_2Cl_2), refluxing under N_2 over Na (Et_2O and THF), refluxing under N_2 over CaH_2 and stored over 3 Å molecular sieves (CH_3CN). Electrospray mass spectra were acquired on a MDS Sciex API QStar Pulsar. NMR spectra were recorded on a Varian Unity Inova 300 NMR and an Inova 500B spectrometer at ambient temperature. Chemical shifts are given in ppm, and are referenced to residual ^1H and ^{13}C solvent signals as well as external BF_3-Et_2O (^{19}F NMR) and H_3PO_4 (^{31}P NMR).

We followed a previously published procedures for compound **1**[1] and dimethylimidazolium iodide[2].

Procedure for KPF_5Ph and $(NHC)PF_4Ph$ (2) synthesis.

KPF_5Ph. Bromine (6.2 mL, 120 mmol) is added to a mixture of potassium fluoride (42 g, 723 mmol) and dichlorophenylphosphine (16.3 mL, 120 mmol) in acetonitrile (250 mL), which caused an instantaneously color change to yellow. The mixture is stirred at room temperature for 18h to give a dark brown a solution with a white precipitate. Volatiles are evaporated under vaccum, the mixture is extracted with acetonitrile (2 × 100 mL), and filtered. Evaporation of the solvent is followed by washing of the solid residue with Et_2O (2 × 50 mL), and drying under vacuum yield the desired product as a white powder (26.7 g, 92%). Xray quality crystals were obtained from a saturated solution in acetonitrile at -18 °C. This compound must be protected from ambient atmosphere, because it appears to be hydrolysed: the white powder becomes an acidic oil (pH<2) after 15 min exposure to air. ^{1}H NMR (500 MHz, CD_3CN): δ 7.23-7.30 (m, 3H, $H^{ortho+para}$), 7.63-7.68 (m, 2H, H^{meta}). ^{31}P {^{1}H} NMR (202 MHz, CD_3CN): δ -137.0 (quintd, J_{PF} = 673 Hz, J_{PF} = 822 Hz). ^{19}F {^{1}H} NMR (470 MHz, CD_3CN): δ -58.4 (dd, 4F, J_{FP} = 822 Hz, J_{FF} = 36 Hz), -61.1 (dquint, 1F, J_{FP} = 673 Hz, J_{FF} = 36 Hz). ^{13}C {^{1}H} NMR (125 MHz, CD_3CN) : δ 127.79 (d, J_{CP} = 19 Hz, CH^{ortho}), 127.90 (m, CH^{meta}), 131.47 (dquint, J_{CF} = 4.2 Hz, J_{CP} = 9.3 Hz, CH^{para}), 150.31 (dquint, J_{CP} = 306 Hz, J_{CF} = 45 Hz, C^{ipso}), HRMS (ESI-) calcd for $[M]^-$: 203.0063, found: 203.0049. Anal. Calcd. for $C_6H_5F_5KP$ (242,17): C, 29.76 ; H, 2.08. Found: C, 29.91; H, 1.98.

$(NHC)PF_4Ph$, (2). A 2.2 M solution of *n*-BuLi in hexane (4.54 mL, 10 mmol) is added dropwise at -78 °C to a heterogeneous mixture of KPF_5Ph (2.42 g, 10 mmol) and dimethylimidazolium iodide (2.24 g, 10 mmol) in THF (50 mL). The solution is slowly reheated to room temperature then heated for 18h at 65 °C. The volatiles are evaporated under vacuum, the solid residu is washed with several portions of water (100 mL), filtered, washed with a small portion of EtOH (10 mL), and dried under vacuum to yield a white powder (1.83 g, 65%). Xray quality crystals were obtained by slow evaporation of a solution of acetonitrile under ambient atmosphere. ^{1}H NMR (300 MHz, CD_3CN): δ 3.97 (s, 6H, CH_3), 7.09 (d, J_{PH} = 3.1 Hz, 2H, CH^{NHC}), 7.24-7.31 (m, 3H, $H^{Ph\text{-}ortho+para}$), 7.65-7.70 (m, 2H, $H^{Ph\text{-}meta}$). ^{31}P {^{1}H} NMR (121 MHz, CD_3CN): δ -141.1 (quint, J_{PF} = 849 Hz). ^{19}F {^{1}H} NMR (282 MHz, CD_3CN): δ -43.9 (d, J_{FP} = 849 Hz). ^{13}C {^{1}H} NMR (75 MHz, CD_3CN) : δ 39.10 (quint, J_{CF} = 4.4 Hz, CH_3), 123.09 (d, J_{CP} = 9.9 Hz, CH^{NHC}), 127.93 (d, J_{CP} = 20.3 Hz, $CH^{Ph\text{-}ortho}$), 128.26 (d, J_{CP} = 4.0 Hz, $CH^{Ph\text{-}meta}$), 131.49 (dquint, J_{CF} = 4.0 Hz, J_{CP} = 11.3 Hz, $CH^{Ph\text{-}para}$), 150.01 (dquint, J_{CF} = 43 Hz, J_{CP} = 297 Hz, $CH^{Ph\text{-}ipso}$), 159.84 (dquint, J_{CF} = 71 Hz, J_{CP} = 334 Hz, C_q^{NHC}). HRMS (ESI+) calcd for $[M\text{-}F]^+$: 261.0768, found: 261.0640. Anal. Calcd. for $C_{11}H_{13}F_4N_2P$ (280,21): C, 47.15 ; H, 4.68. Found: C, 47.05; H, 4.57.

Crystal Structure Determinations. The crystallographic measurement of **KPF_5Ph** and **2** were performed using a Bruker APEX-II CCD area detector diffractometer with graphite-monochromated Mo-Kα 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 the absorption correction. 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. Data reduction and further calculations were performed using the Bruker SAINT+ and SHELXTL NT program packages.

Complete details of the X-ray analyses reported herein have been deposited at *The Cambridge Crystallographic Data Centre* (CCDC 1504580 (**KPF_5Ph**), 1504579 (**2**)). This data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

Kinetic studies of the hydrolysis reactions for 1 and 2

A sample of **1** (5 mg) was dissolved in a mixture of 0.2 mL CD_3CN and 0.8 mL D_2O phosphate buffer solution (pH 7.5, 500 mM) while a sample of **2** (5 mg), was dissolved in a mixture of 0.3 mL DMSO-*d6*, 0.63 mL H_2O phosphate buffer (pH 7.5, 500 mM) and 70 mg of Triton X-100. The ^{19}F NMR spectra of **1** and **2** were collected periodically. The decomposition of **2** was monitored by integration of the decreasing of the signal of **2** in conjunction with the increasing signal corresponding to free F^-. The rate constant, k_{obs} , was calculated using a well-established NMR method reported in the literature.[3] This method is based on the fact that that the concentration of **2** is proportional to the ^{19}F NMR integration of the signal of **2** divided by the sum of the integration of the signal of **2** and the free fluoride signal. For convenience, the value of the integration of **2** is arbitrarily set at 100 and the free fluoride integration determined. The resulting data is provided in Table S3.

Radiochemistry Experiment

All chemicals were purchased as analytical grade and used without further purification. Analytical reversed-phase high-performance liquid chromatography (HPLC) was performed on a SPD-M30A photodiode array detector (Shimadzu) and model 105S single-channel radiation detector (Carroll & Ramsey Associates) using a Gemini 5µ C18 column (250 x 4.6 mm). The flow was set to 1 mL/min. The mobile phase was programmed to change from 95% solvent A and 5% solvent B (0-2 min) to 5% solvent A and 95% solvent B at 22 min, where solvent A is 0.1% TFA in water and solvent B is 0.1% TFA in acetronitrile.

Radiolabeling

Radiolabeling reactions were performed using the following protocol. Compound **1** (0.9 µmol) was mixed with $SnCl_4$ (5 equiv.) in 30 µL of anhydrous MeCN. The resulting solution was then combined with [^{18}F]-TBAF in MeCN. After incubating at reaction temperature (room temperature, 60 °C, 80 °C, or 100 °C) for 10 min, the reaction was quenched by adding 10 mL of water. The mixture was passed through a Sep-Pak cartridge (Sep-Pak Plus tC18) and washed with another 10 mL of water to remove all Sn-by-products. The radiolabeled derivative [^{18}F]-**1** was eluted off the cartridge using 1 mL of MeCN.

***In vitro* stability test**

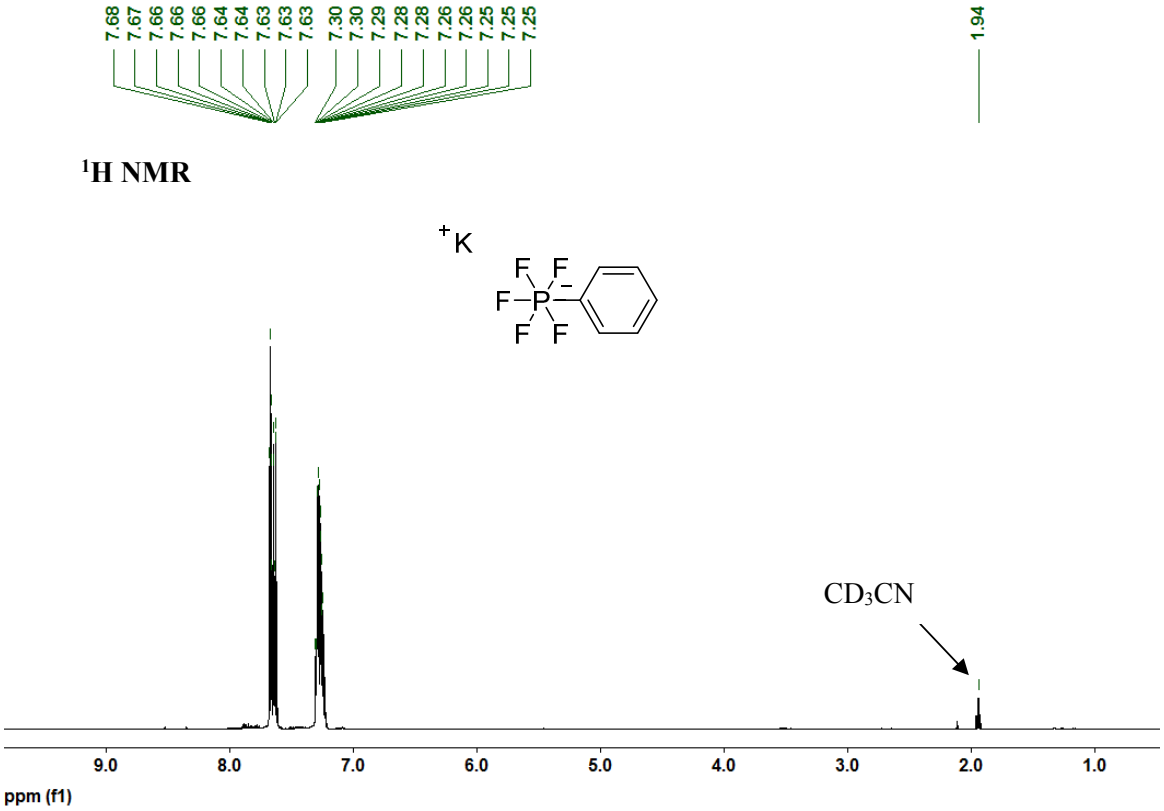
After HPLC purification, [^{18}F]-**1** was re-injected into HPLC as a radio profile standard. Then, the probe was added with 10X PBS to reconstruct the solution to 1X PBS and 0.1 N NaOH to adjust the pH to 7, respectively. After 1 hour and 3 hours incubation periods, a fraction of [^{18}F]-**1** was injected into HPLC. The radio purity was calculated based on the integration of the product peak and other minor peaks.

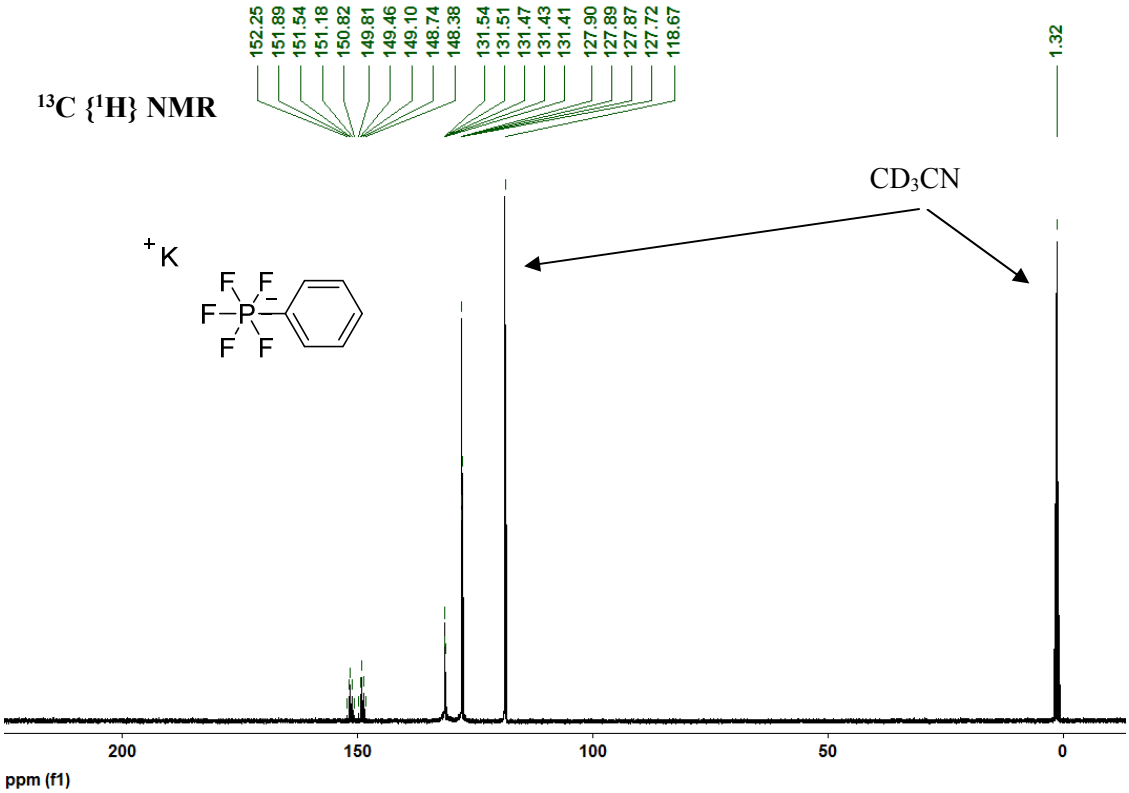
MicroPET imaging

MicroPET images were acquired 3 h post injection. For PET image acquiring, a female nude mouse was injected with 0.1 mCi of [^{18}F]-**1** *via* the tail vein. At 3 hour post injection, the mouse was anesthetized using isoflurane (2% in oxygen), then placed into imaging chambers equipped with a heated coil to maintain body

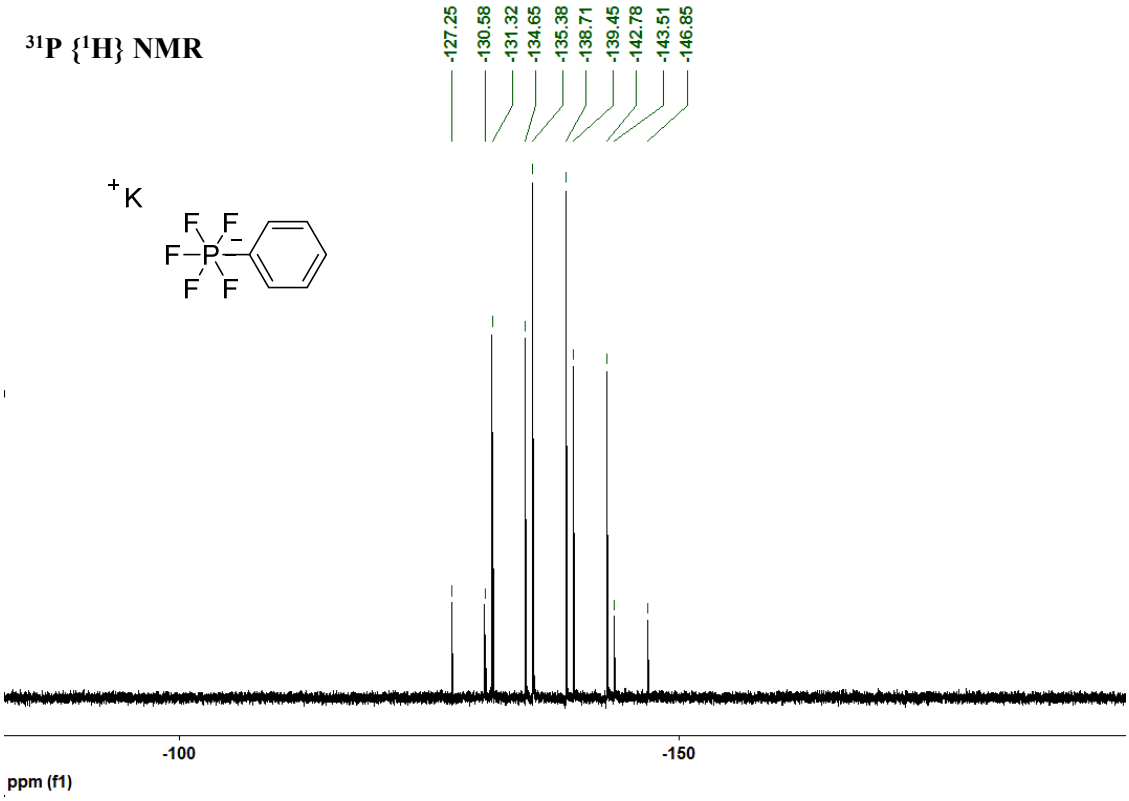
temperature and gas anesthesia. The static microPET acquisitions were then achieved and reconstructed for analysis.

Figure S1. ^{1}H, ^{13}C {^{1}H}, ^{31}P {^{1}H} and ^{19}F {^{1}H} NMR spectra of [K][PF_5Ph].





^{31}P {^{1}H} NMR



^{19}F {^{1}H} NMR

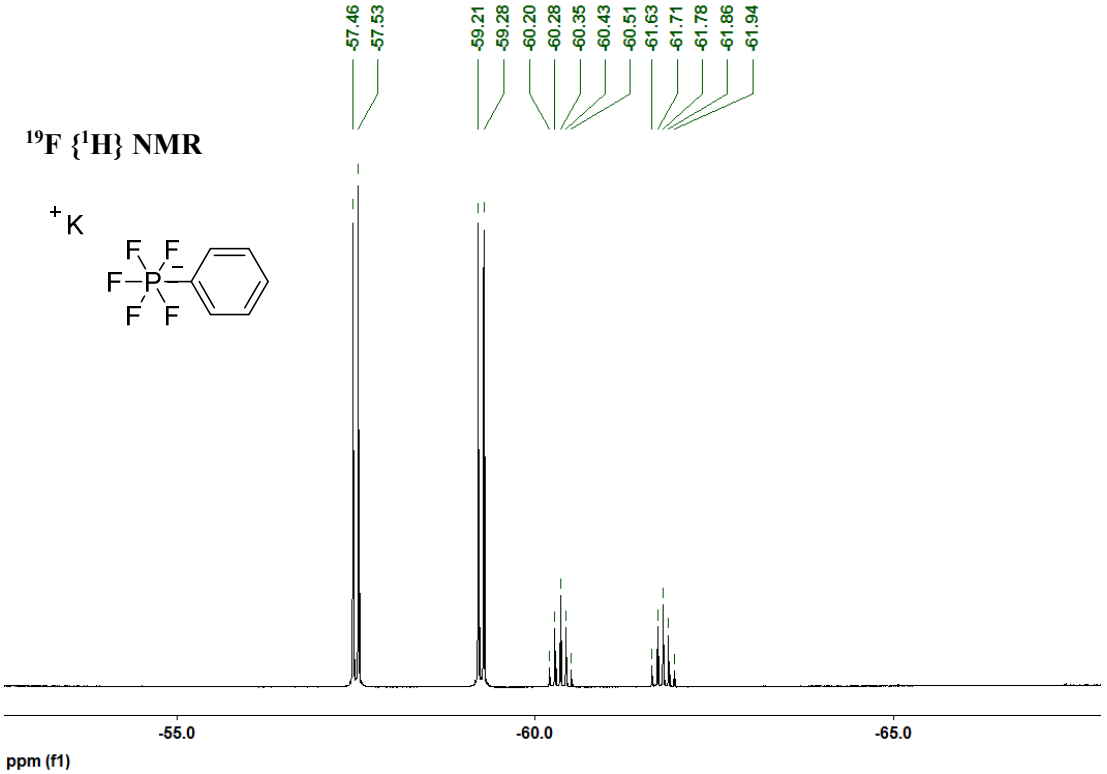
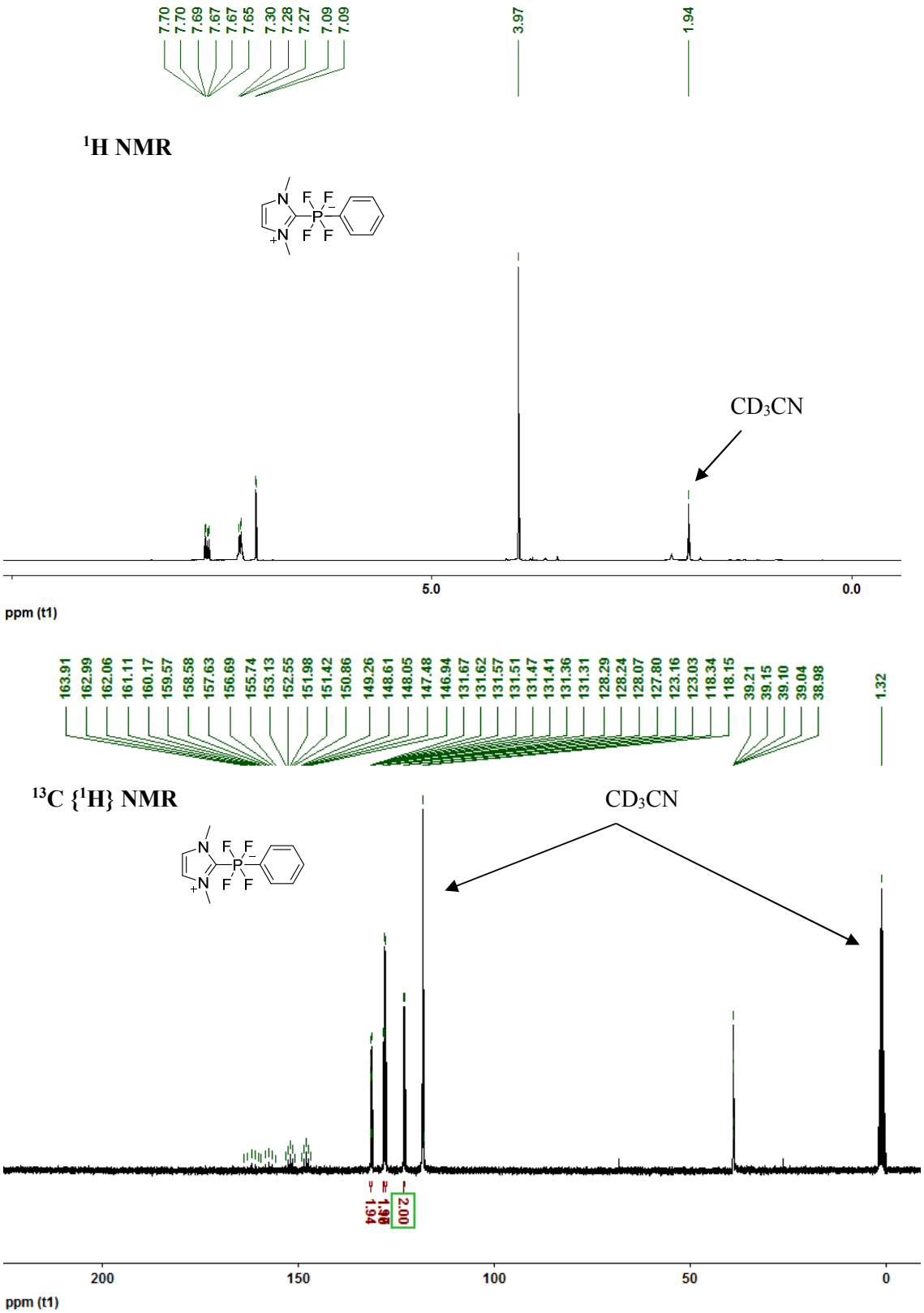
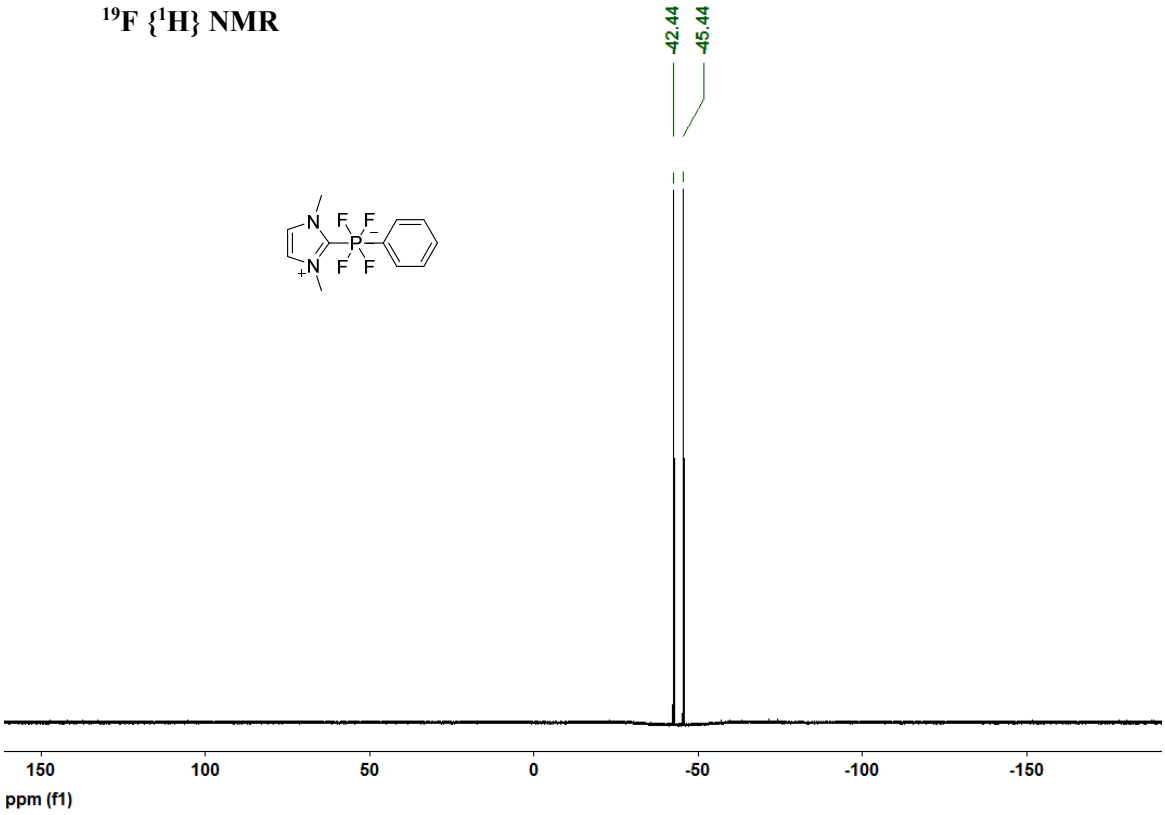


Figure S2. ^{1}H, ^{13}C {^{1}H}, ^{31}P {^{1}H} and ^{19}F {^{1}H} NMR spectra of **(NHC)PF_4Ph (2).**



^{19}F {^{1}H} NMR



^{31}P {^{1}H} NMR

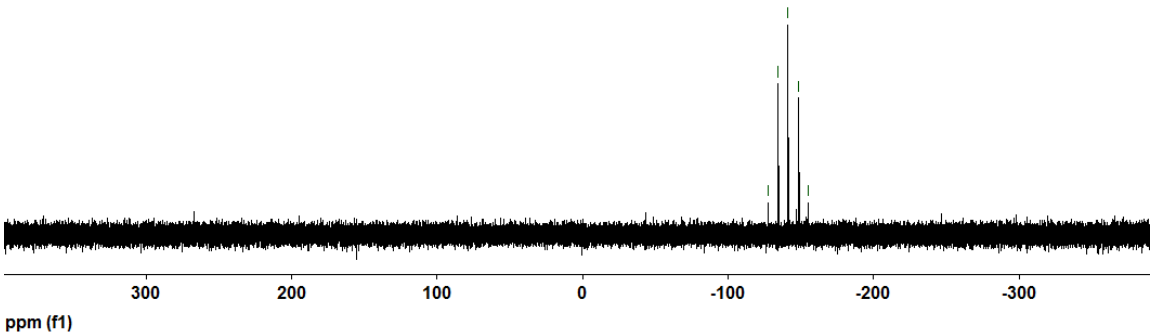


Figure S3. HRMS spectra of **[K][PF$_5$Ph]**.

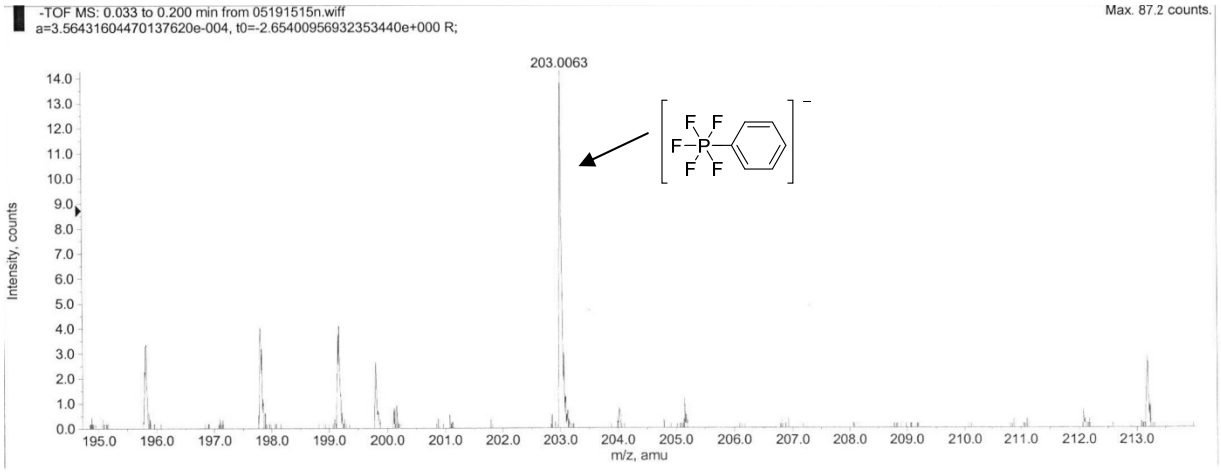


Figure S4. HRMS spectra of **(NHC)PF$_4$Ph (2).**

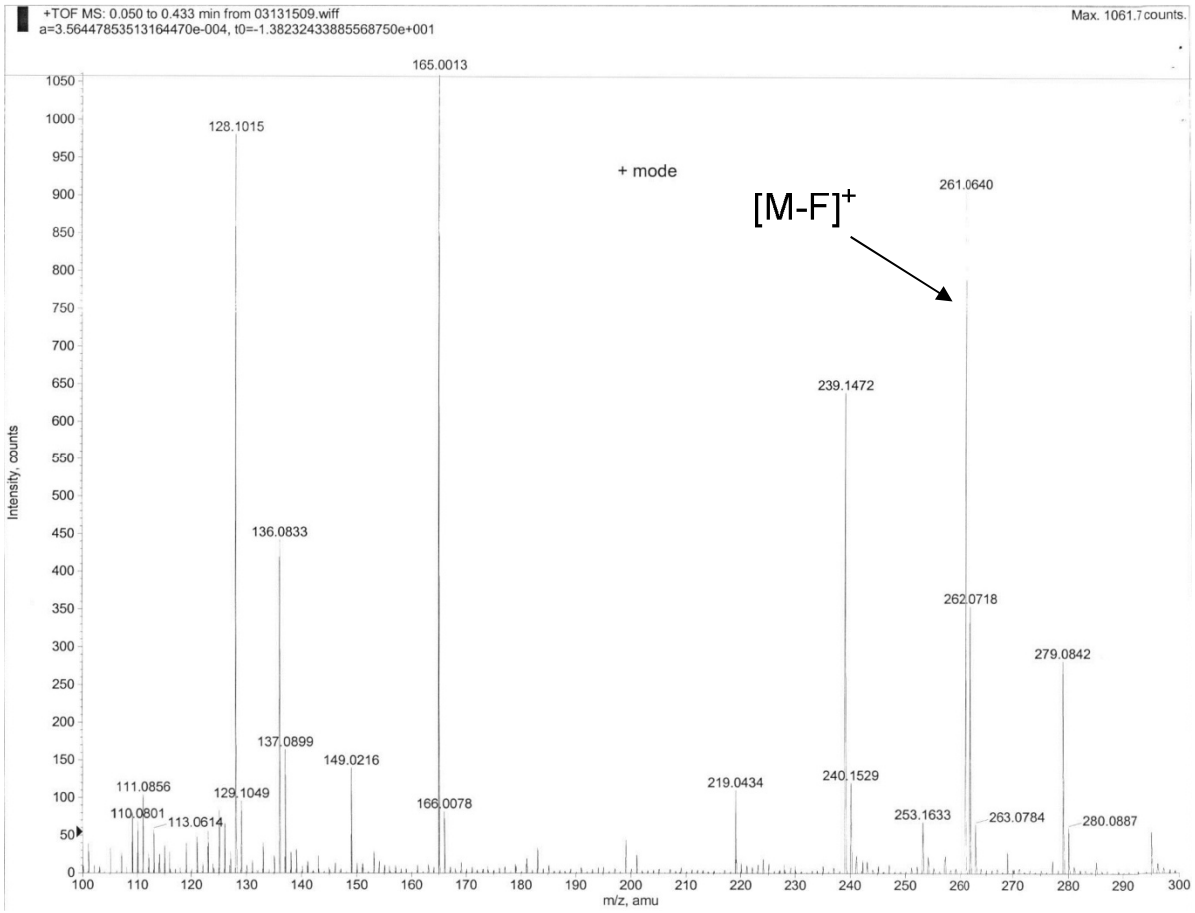


Figure S5 . $^{19}F\{^{1}H\}$ NMR analysis of an aliquot of the crude reaction mixture for the synthesis of **2** after addition of *n*-BuLi. The aliquot of the crude mixture is heated at 66 °C and analyzed over time by $^{19}F\{^{1}H\}$ NMR.

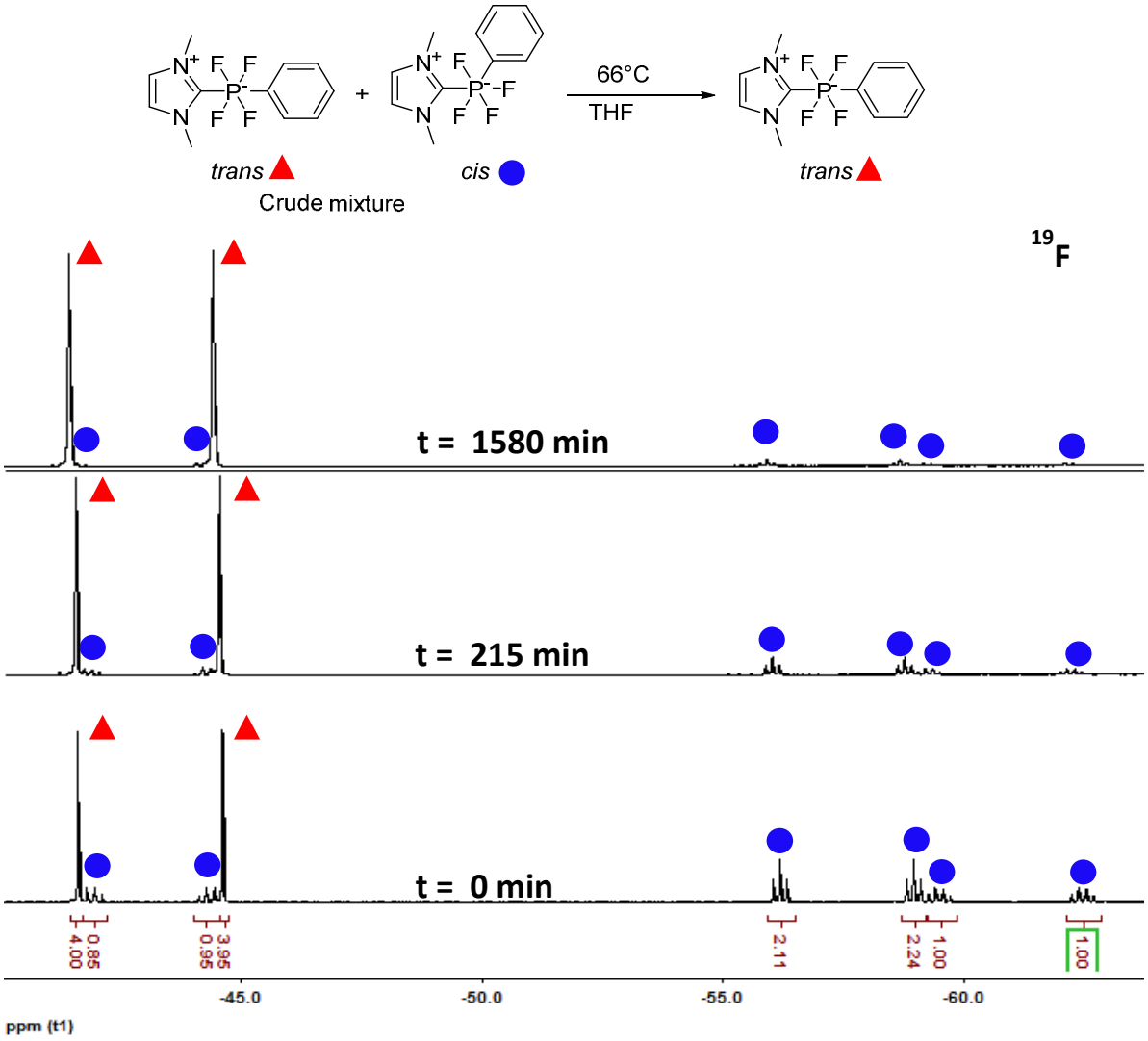


Figure S6. Ratio of NHC-PF_4Ph cis and trans (**2**) isomers over time at 66°C in THF. Ratios are calculated by ^{19}F NMR integration using $BF_3.Et_2O$ as internal standard.

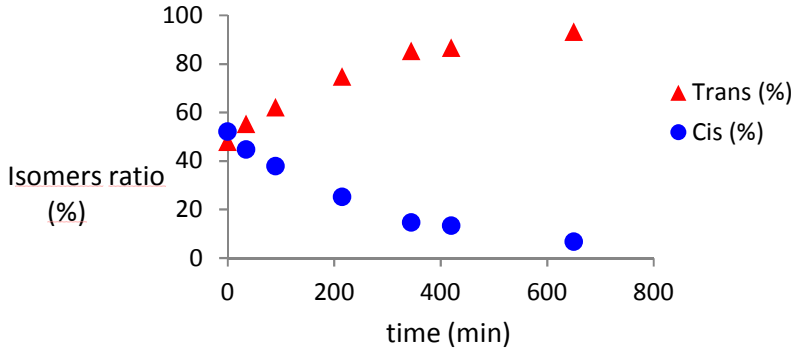


Figure S7. ORTEP diagrams of the asymmetric unit (top) and of the packing (bottom) of **KPF_5Ph.** Thermal ellipsoids are shown at the 50% probability level. Hydrogen atoms and K, CH_3CN labels are omitted for clarity. Blue : nitrogen atoms, green : fluorine atoms, purple : potassium atoms, orange : phosphorus atoms, grey : carbon atoms.

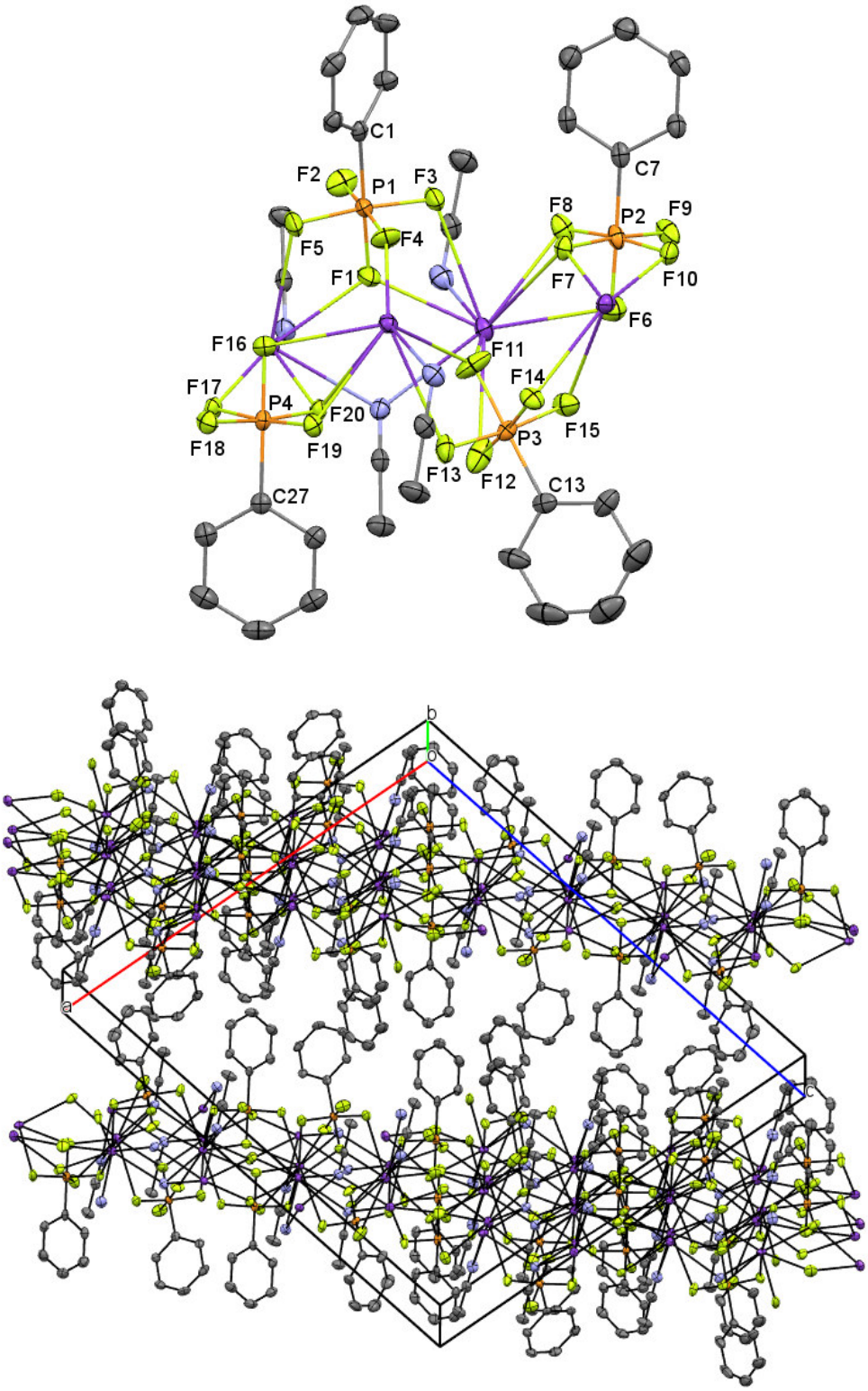


Table S1. Crystal data collection and refinement parameters for compounds **2** and **KPF_5Ph**.

	2	KPF_5Ph
chemical formula	$C_{11}H_{13}F_4N_2P$	$C_{32}H_{32}F_{20}K_4N_4P_4$
Fw	280.20	1132.90
***T* (K)**	110(2)	110(2)
wavelength (Å)	0.71073	0.71073
space group	P21/n	P21/n
***a* (Å)**	7.5298(13)	21.180(3)
***b* (Å)**	11.1769(19)	8.8602(13)
***c* (Å)**	14.477(3)	24.220(4)
α (deg)	90.00	90.00
β (deg)	104.313(2)	102.725(2)
γ (deg)	90.00	90.00
Z	4	4
***V* (Å^3)**	1180.6(4)	4433.4(11)
ρ_{calcd} (g cm^{-3})	1.577	1.697
μ (mm^{-1})	0.268	0.662
θ range (deg)	2.33 – 28.29	1.97 – 27.25
R1 [I > 2σ(I)]	0.0352	0.0418
wR2 [I > 2σ(I)]	0.0954	0.0952
R1 [all data]	0.0425	0.0594
wR2 [all data]	0.1004	0.1036
GOF	1.069	1.036

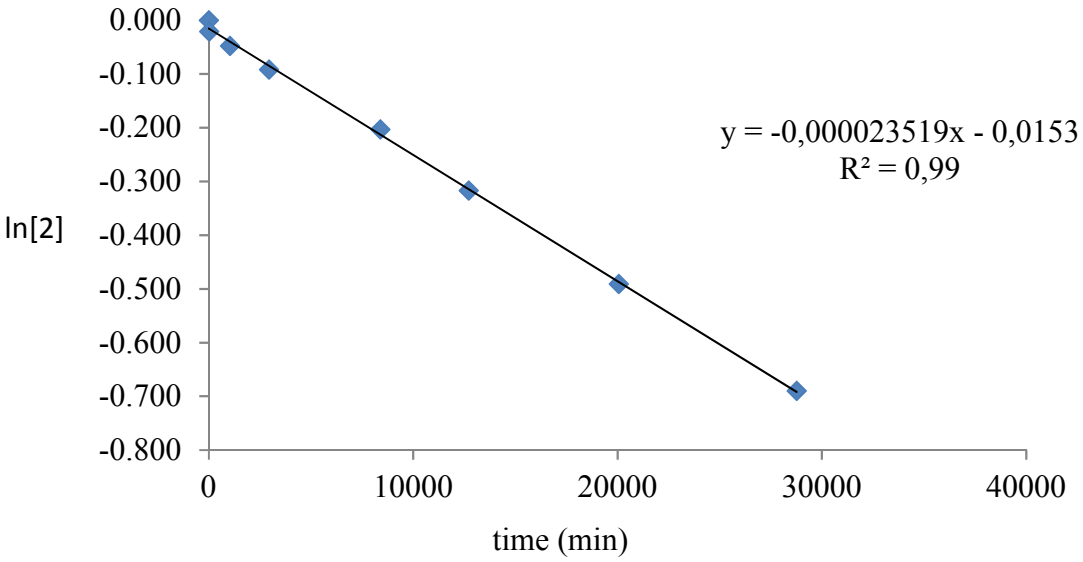
Table S2. Selected distances (Å) and angles (°) for **KPF_5Ph**.

	Molecule 1	**Molecule 2**	**Molecule 3**	**Molecule 4**
P-C	P_1-C_1 =1.837(3)	P_2-C_7 =1.829(3)	P_3-C_{13} =1.831(3)	P_4-C_{27} =1.833(3)
P-F*trans*	P_1-F_1 =1.6391(16)	P_2-F_6 =1.5857(19)	P_3-F_{11} =1.6512(17)	P_4-F_{16} =1.6323(16)
P-F*cis*	P_1-F_2 =1.6187(17)	P_2-F_7 =1.6460(15)	P_3-F_{12} =1.6064(17)	P_4-F_{17} =1.6394(15)
	P_1-F_3 =1.6121(16)	P_2-F_8 =1.6287(16)	P_3-F_{13} =1.6132(16)	P_4-F_{18} =1.6203(15)
	P_1-F_4 =1.6288(17)	P_2-F_9 =1.6318(16)	P_3-F_{14} =1.6292(16)	P_4-F_{19} =1.6281(15)
	P_1-F_5 =1.6263(16)	P_2-F_{10} =1.6367(17)	P_3-F_{15} =1.6236(17)	P_4-F_{20} =1.6321(15)
C-P-F*trans*	C_1-P_1-F_1 =178.84(11)	C_7-P_2-F_6 =178.68(12)	C_{13}-P_3-F_{11} =179.15(12)	C_{27}-P_4-F_{16} =179.70(11)
C-P-F*cis*	C_1-P_1-F_2 =92.63(10)	C_7-P_2-F_7 =92.60(10)	C_{13}-P_3-F_{12} =93.57(11)	C_{27}-P_4-F_{17} =92.45(10)
	C_1-P_1-F_3 =93.02(10)	C_7-P_2-F_8 =92.86(10)	C_{13}-P_3-F_{13} =93.50(11)	C_{27}-P_4-F_{18} =92.92(10)
	C_1-P_1-F_4 =91.83(10)	C_7-P_2-F_9 =92.32(10)	C_{13}-P_3-F_{14} =92.11(10)	C_{27}-P_4-F_{19} =92.78(10)
	C_1-P_1-F_5 =93.10(10)	C_7-P_2-F_{10} =92.72(10)	C_{13}-P_3-F_{15} =92.80(10)	C_{27}-P_4-F_{20} =93.03(10)

Table S3. Hydrolytic kinetics of **2**. The values provided for int [F^-] and int [**2**] correspond to the integration of the corresponding ^{19}F NMR signal.

Time (min)	int[F^-]	int[**2**]	[**2**]/([**2**]+[F^-]) exp	[**2**]/([**2**]+[F^-]) calc	ln[**2**]
0	0	100	1,000	1,000	0,000
5	2	100	0,979	1,000	-0,021
1035	5	100	0,954	0,976	-0,048
2940	10	100	0,912	0,933	-0,092
8380	22	100	0,816	0,821	-0,203
12715	37	100	0,729	0,742	-0,317
20050	63	100	0,612	0,624	-0,491
28759	99	100	0,502	0,509	-0,690

Figure S8. Kinetic plots for the hydrolysis of **2**.



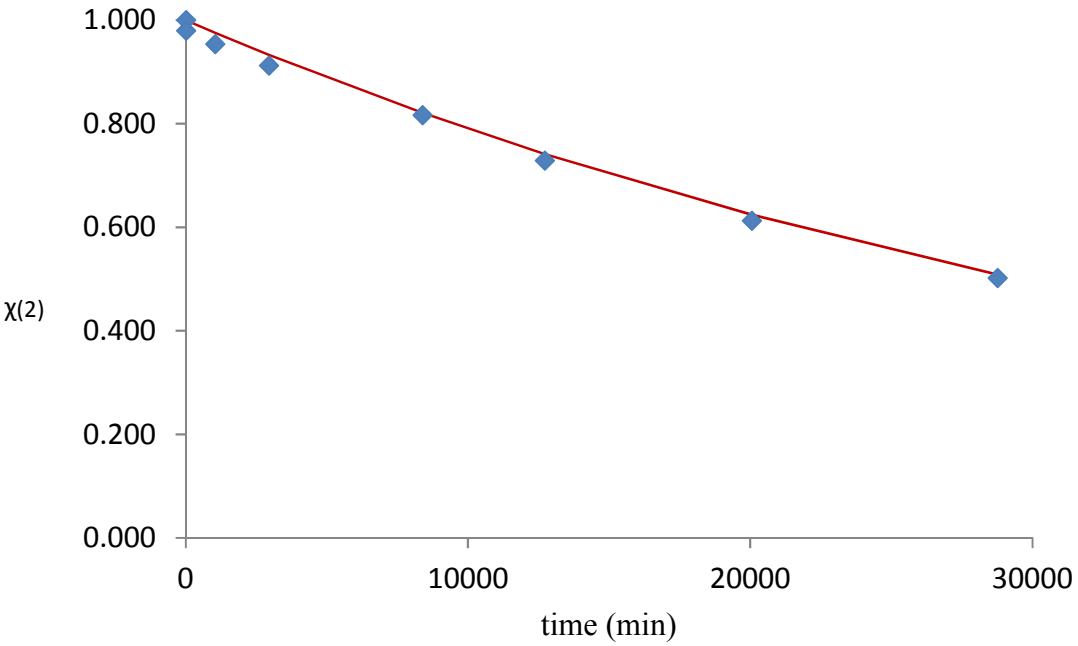
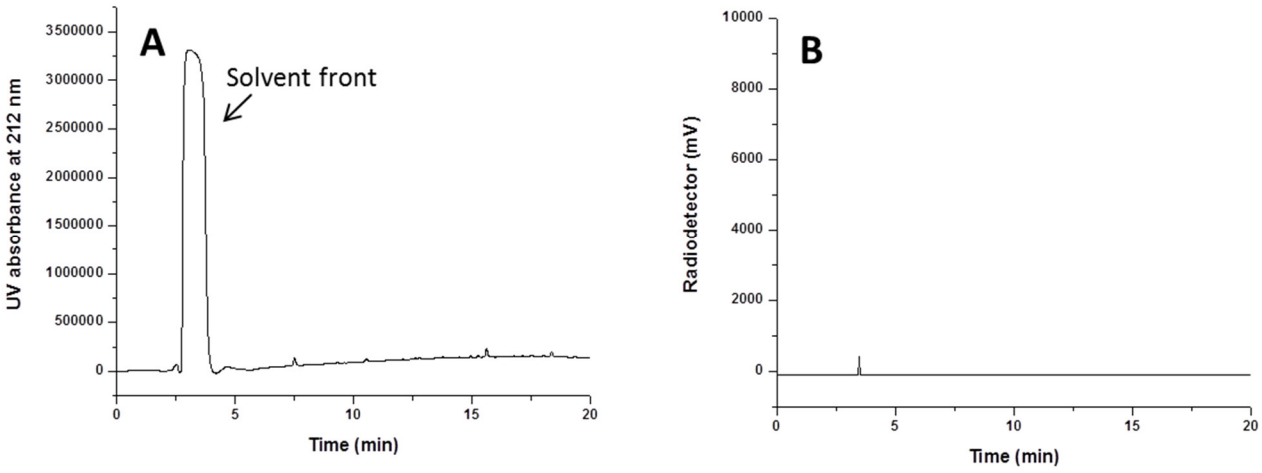


Table S4. Radiosynthetic results for [^{18}F]-**1** (n=3)

Pre Sep-Pak purification							Post Sep-Pak purification		Post HPLC	
Entry	Starting activity (mCi)	Amount of [**1**] (µmol)	MeCN Volume (µL)	$SnCl_4$ (eq)	Temp (°C)	Time (min)	Activity (mCi)	solution volume (mL)	Amount of [**1**] (µmol)	Activity (mCi)
1	98.8-108.2	0.9	30	5	25	10	No [^{18}F]- **1** observed			
2	368.2-410.5	0.9	30	5	60	10	17.4-18.0	1	0.72-0.75	16.4-16.8
3	370.0-415.6	0.9	30	5	80	10	27.7-30.2	1	0.75-0.78	24.4-27.7
4	102.5-110.8	0.9	30	5	100	10	No [^{18}F]- **1** observed			

Figure S9. **A**: UV-HPLC chromatogram of the MeCN portion obtained after radiolabeling of **1** at 100 °C. **B**: Radio-HPLC chromatogram of the MeCN portion obtained after radiolabeling of **1** at 100 °C



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