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Copper-mediated radiofluorination of aryl pinacolboronate esters: a straightforward protocol by using pyridinium sulfonates

Dmitrii Antuganov,[a] Michail Zykov,[a] Vasilii Timofeev,[a] Ksenija Timofeeva,[a] Yulija Antuganova,[a] Victoriya Orlovskaya,[b] Olga Fedorova, [b] Raisa Krasikova*[b,c]

Abstract: Radiofluorination of arylboronic acids pinacol esters (ArylBPin) mediated by copper triflate pyridine complex is one of the more promising synthetic approaches for the direct introduction of nucleophilic [^{18}F]fluoride into non-activated arenes and heteroarenes. However, the application of this method to the production of positron emission tomography (PET) radiotracers in automated synthesizers remains a challenging task. The choice of phase-transfer catalyst (PTC) and corresponding base used for the generation of reactive [^{18}F]fluoride species has a profound impact on the efficiency of the ^{18}F-fluorination process. Here we report the development of a simple procedure involving trapping of the aqueous [^{18}F]fluoride on a weak anion-exchange resin (WAX) and its release by elution with pyridinium sulfonate in dimethyl acetamide. Obtained reactive [^{18}F]fluoride was used as-is in a copper-catalyzed fluorination reaction employing pyridinium salt as both PTC and base. High radiochemical conversion rates (RCCs) achieved for a series of simple ArylBPin substrates and 4-[^{18}F]fluoro-D,L-phenylalanine demonstrate the efficiency of this novel ^{18}F-processing approach. Notably, the proposed method obviates conventional azeotropic drying steps, solvents evaporation and/or changeover and can be implemented on commercial automated synthesizers.

Introduction

Fluorine-18 has proven to be useful in a wide array of clinical and research positron emission tomography (PET) applications due to its advantageous nuclear properties. Emitted positron energy is the lowest of all nuclides commonly used in PET (97% β^+, $E_{\beta max}$ 0.63 MeV) enabling high spatial resolution imaging while its relatively long half-life (109.8 min) allows multi-step radiosyntheses and permits transportation of produced imaging agents for off-site administration. Fluorine-18 is usually produced in the form of [^{18}F]fluoride using ^{18}O(p,n)^{18}F nuclear reaction, by irradiation of oxygen-18 enriched water in dedicated cyclotron targets. Produced aqueous [^{18}F]fluoride is easy to isolate and concentrate using ion-exchange chromatography for further use. Aliphatic nucleophilic S_N2 substitution is currently the most prominent method for ^{18}F-labelling of clinically relevant radiotracers such as [^{18}F]FDG, [^{18}F]FMISO, [^{18}F]FLT and others.

[a] *Dmitrii Antuganov, Dr. Michail Zykov, Vasilii Timofeev, Ksenija Timofeeva, Yulija Antuganova*
National Almazov Medical Research Centre
PET Centre
197341, 2 Akkuratova street, St. Petersburg, Russia
[b] *Victoriya Orlovskaya, Dr. Olga Fedorova, Dr. Raisa Krasikova*
N.P. Bechtereva Institute of Human Brain
Russian Academy of Science
Laboratory of Radiochemisty
197376, 9 Ak. Pavlova st., St. Petersburg, Russia
E-mail: raisa@ihb.spb.ru
[c] *Dr. Raisa Krasikova*
St.-Petersburg State University
Institute of Chemistry
199034, Universitetskaya Emb., 13B, St. Petersburg, Russia
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As for nucleophilic aromatic substitution (S_NAr), this method is generally limited to the introduction of ^{18}F into aromatic structures containing electron-withdrawing groups in the *para*- or *ortho*-position to the appropriate leaving group.

Significant progress in the field has been recently made with the development of transition metal-mediated radiofluorination reactions, enabling the direct introduction of nucleophilic [^{18}F]fluoride into non-activated arenes and heteroarenes.[1] Some of these new methods remain at an experimental stage as they are difficult to implement into routine productions.[2] Radiofluorination of pinacol esters of arylboronic acids (ArylBPin) mediated by copper triflate complex with pyridine introduced by the Gouverneur group[3a] following cold chemistry developed by Sanford's group[3b] is one of the more promising synthetic avenues currently under development.[3] It provides high radiochemical conversion (RCC) for the range of simple aromatic substrates on small-scale[2b] and has been adapted for the automated synthesis of several clinically relevant radiotracers with low-to-moderate radiochemical yields.[4] This approach was later expanded by other groups to facilitate access to ^{18}F-fluorinated aromatic amino acids and other complex molecules.[5, 6]

ArylBPin precursors for the radiosynthesis of some clinically relevant PET radiotracers, such as 6-[^{18}F]fluoro-L-DOPA, are already commercially available. However, implementation of the copper-mediated ArylBPin ^{18}F-fluorination for large scale production of the radiotracers in automated synthesizers still remains a challenging task. First, the [^{18}F]fluoride must be separated from target water to be made suitable for a nucleophilic substitution reaction. This is usually achieved by adsorption/elution of [^{18}F]fluoride on an anion-exchange resin followed by removal of residual water using azeotropic drying. The latter procedure is associated with radioactivity losses due to decay, adsorption on the walls of reaction vessels and difficulties in automation of the whole process. Furthermore, elution of the [^{18}F]fluoride requires basic conditions which are not always compatible with the labeling of ArylBPin substrates. For example, use of the common phase-transfer catalyst (PTC)/base combination potassium carbonate/Kryptofix$_{2.2.2}$ results in low efficiency of ^{18}F-fluorination of aryl pinacol boronic esters due to the high carbonate content (20-25 μmol).[7]

Due to the difficulties outlined above, steps aimed at improving the methodology of ArylBPin substrates fluorination, in particular the ^{18}F-recovery steps, are the focus of considerable efforts. For instance, reducing the amounts of carbonate and Kryptofix with a reversed loading/elution procedure,[7] as well as the use of less basic potassium oxalate have been reported.[4] Alternatively, alcoholic solutions of tetraethyl ammonium bicarbonate have been used as an eluting agent for ^{18}F-fluoride which allows for elimination of conventional azeotropic drying steps and simplifies automation.[5a,5b] Those techniques allowed «late-stage» introduction of ^{18}F-label into indoles, phenols and anilines starting from unprotected precursors with radiochemical yields (RCY) in the range of 80-99%. However, this methodology requires large amounts of precursors (up to 60 μmol) which

significantly complicates purification procedure employed at a later step. Furthermore, RCYs are significantly lower in case of the *ortho*-substituted precursors, possibly due to unfavorable steric interactions with the leaving groups, impeding the trans-metallation step.

Previously we have shown that addition of small amounts of pyridine to the reaction medium resulted in a significant boost to the copper-catalyzed ^{18}F-fluorination efficiency for various [^{18}F]fluoroanisoles, including *ortho*-substituted ones.[8] The recent publication of the Scott group on the customized [^{18}F]fluoride elution technique reports the enhancement of the ^{18}F-fluorination efficiency of ArylBPin substrates.[9] One of the outcomes of that study was that ^{18}F-fluoride can be eluted from the anion-exchange resin (QMA cartridge) using an aqueous solution of weak non-ionic base, such as 4-dimethylaminopyridine, with high elution efficiency (EE). However, using aqueous solution necessitates inclusion of water removal and conventional azeotropic drying steps, making this procedure inconvenient and less attractive for automation. The summary of all the above-mentioned ^{18}F-fluoride recovery techniques and relevant subsequent steps is presented in Table 1.

Based on our previous report, we hypothesized that pyridinium sulfonates may serve as viable alternative catalysts for use in transition metal catalyzed fluorination reactions. These salts can serve both as a source of pyridine to increase efficiency of the copper catalyst, [8] and as a PTC. Elution of [^{18}F]fluoride with an aqueous solution of pyridinium *p*-toluenesulfonate was earlier examined by Scott' group.[10] Despite of high ^{18}F-recovery (73%), the notable loss of radioactivity (50−60%) was detected during azeotropic drying. An important advantage of pyridinium sulfonates is that they can be used in conjunction with organic solvents. Here we present a detailed study of the Cu-mediated radiofluorination reaction of a model substrate 4-biphenylboronic acid pinacol ester (**1**) in the presence of pyridinium sulfonates (Figure 1). We demonstrated that by using pyridinium sulfonates we were able to achieve high yields of ^{18}F-fluorination without having to resort to solvent evaporation or azeotropic drying steps. This approach has proven effective for labeling of several simple aromatic substrates and a previously described amino acid radiotracer 4-[^{18}F]fluoro-D,L-phenylalanine.

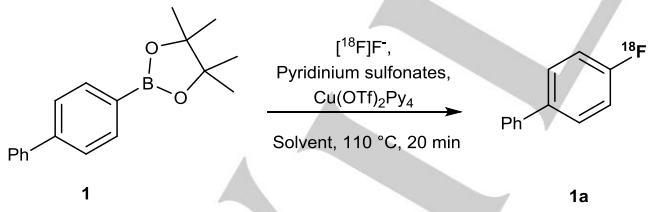

Figure 1. Radiofluorination of 4-biphenylboronic acid pinacol ester (**1**) with pyridinium sulfonates as PTC (this work).

Table 1. Processing of [^{18}F]fluoride for copper-mediated radiofluorination of various aryl pinacol boronates.

Elution Agent	Elution Solvent	Azeotropic Drying or Solvent evaporation step	Refefence
K_2CO_3/K_{222} * (20-25 µmol/ 25-50 µmol)	AcN/Water	**Yes**	[7]
K_2CO_3/K_{222} (0.43 µmol/ 0.72 µmol)	AcN/Water	**Yes**	[7]
$K_2CO_3/K_2C_2O_4/K_{222}$ (0.72 µmol/ 6 µmol/ 16.7 µmol)	AcN/Water	**Yes**	[4]
4-Dimethylaminopyridine (25 µmol)	Water	**Yes**	[9]
Et_4HCO_3 (0.7-1 µmol)	MeOH	**Yes**	[5a]
	*n*BuOH	**No**	[5b]
Pyridinium sulfonates (25 µmol)	MeOH	**Yes**	*This work*
	DMF	**No**	
	DMA	**No**	

[*]Almost no fluorination observed.

Results and Discussion

Several pyridinium sulfonates **2-5** (Fig. 2) were synthesized and used as eluting agents for ^{18}F-fluoride from anion exchange resin and as PTC in subsequent Cu-mediated radiofluorination reaction. The synthesis of the sulfonates was performed simply by the mixing of the corresponding pyridines with the sulfonic acids.[11] The precipitates were filtered and dried in vacuum, providing title compounds.

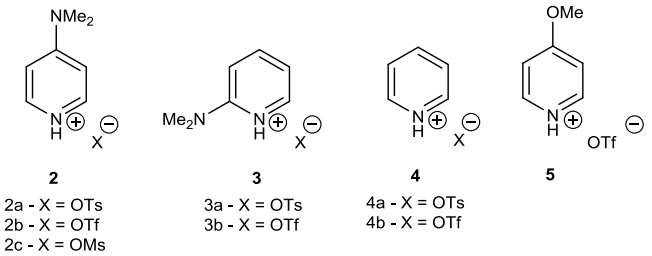

Figure 2. Structures of pyridinium sulfonates **2-5** used in this study.

The overall RCY of the radiofluorination strongly depends on both ^{18}F-elution efficiency (EE) from the anion-exchange resin and the radiochemical conversion (RCC) in fluorination of the aromatic substrate. Therefore, our first priority was to determine efficiency of the different sulfonate salts for elution of [^{18}F]fluoride trapped on the anion exchange cartridge (Chromafix® PS-HCO_3) from the cyclotron-irradiated target water. This type of cartridge is commonly used in the automated production of [^{18}F]FDG and other PET radiotracers. Prior to the use, the cartridge was rinsed with $NaHCO_3$ (0.5 M) followed by water. Ideally, the PTC should be dissolved in the reaction

solvent, to eliminate the subsequent solvent exchange step. Therefore, dimethylformamide (DMF), commonly used for copper-mediated fluorinations of ArylBpin substrates,[3b, 5b] was initially selected as an eluting solvent. In our procedure the aqueous [^{18}F]fluoride was loaded onto the cartridge, which was then rinsed with 1 mL of methanol or other organic solvent in the same direction and dried using compressed air. Next, the [^{18}F]fluoride was eluted from the cartridge in the direction opposite to loading[7] using different sulfonate salts **2-5** (12.5 - 100 µmol dissolved in 0.5 mL of DMF) which were tested for their elution efficiency. The eluate was collected into a 5 ml Wheaton V-vial pre-filled with **1** (Fig. 1), copper catalyst and 0.1 ml of DMF. Radiofluorinations were carried out under previously established conditions[8] (Table 2). Unfortunately, the EE of [^{18}F]fluoride was relatively poor for all the investigated sulfonate salts dissolved in DMF. However the results of radiofluorination of **1** in DMF in the presence of 4-dimethylaminopyridinium trifluoromethanesulfonate **(2b)** appeared to be promising (Table 2, entry 2), indicating that this sulfonate salt may be useful as a PTC.

Table 2. [^{18}F]Fluoride elution from Chromafix PS-HCO_3 cartridge using different sulfonates solutions in DMF and the RCC in the radiofluorination of **1** (no azeotropic drying, 17.9 µmol of **1**, 5.3 µmol of $Cu(OTf)_2Py_4$, 0.6 mL of DMF, 110°C, 20 min).

Entry	Sulfonate salt	υ, µmol	EE, % (n=3)	RCC, % (n=3) (radioTLC)
1	2a	12.5	16±4	82±2
		25	41±4	58±7
		50	51±4	33±8
		100	60±5	0
2	2b	25	33±2	70±4
		50	37±7	33±8
3	**2c**	25	32±3	36±5
4	**3a**	25	40±3	0
5	**3b**	25	33±2	52±1
		50	50±7	0
6	**4a**	25	48±1	0
7	**4b**	25	44±2	0
8	**5**	25	30±5	10±3

Considering these results, our next aim was to develop a more effective adsorption/elution process for use in conjunction with **2b** as a PTC. Next, we evaluated different solvent systems for their efficiency in elution of [^{18}F]fluoride trapped on Chromafix® PS-HCO_3. Rinsing the cartridge with organic solvent to remove residual water was an important consideration, and the use of alcohols was found to be an effective solution as previously reported[5b] (Table 3, entries 1-11). Methanol appeared to be the best rinsing/elution solvent with the EE reaching 84 % (entry 11, Table 3). However no fluorination occurred in the presence of MeOH (Table S1, entry 1). Therefore, MeOH had to be replaced with another solvent suitable for copper-mediated fluorination such as DMF, DMA, *n*-BuOH/DMA etc.[4, 5a-b] Solvent exchange procedure (evaporation of MeOH followed by addition of another solvent) resulted in the RCCs under 50% (Table S1, entry 2-6), while RCC in the 70% range was achieved with direct ^{18}F-elution/fluorination protocol using solution of **2b** in DMF (Table 2, entry 2).

Table 3. ^{18}F-Elution using **2b** (25 µmol) in various solvents (EE - Elution Efficiency)

Entry	Rinsing Solvent	Elution Solvent	EE, %	Cartridge
1	MeOH	DMF	33	PS-HCO_3^-
2	MeOH	DMA	30	PS-HCO_3^-
3	MeOH	DMF/*n*BuOH = 4:1	25	PS-HCO_3^-
4	MeOH	DMA/*n*BuOH = 4:1	30	PS-HCO_3^-
5	-	*n*BuOH	0 (insoluble)	PS-HCO_3^-
6	MeOH	DMF/MeOH = 4:1	50	PS-HCO_3^-
7	MeOH	DMF/MeOH = 4:1	42	PS-HCO_3^-
8	MeOH	*n*BuOH/MeOH = 4:1	48	PS-HCO_3^-
9	*i*PrOH	*i*PrOH	20	PS-HCO_3^-
10	EtOH	EtOH	48	PS-HCO_3^-
11	MeOH	MeOH	84	PS-HCO_3^-
12	MeOH	MeOH	39	SB (45 mg)
13	*i*PrOH	DMF	70	Oasis WAX 1 cc
14	*i*PrOH	DMA	78	Oasis WAX 1 cc
15	*i*PrOH	*i*PrOH	25	Oasis WAX 1 cc

Next, we considered use of solution of **2b** in DMF (Table 3, entry 13) for elution of [^{18}F]fluoride trapped on Oasis WAX cartridge (30 mg), a weak lipophilic anion-exchange resin with a mixed mode retention mechanism. The elution efficiency from this resin was 70%; while using DMA as an eluting solvent increased EE value even further (entry 14, Table 3). Both DMF and DMA allow for elimination of conventional azeotropic drying and solvent exchange steps, thus simplifying the synthesis work-up (See Suppl. **VIII**). Briefly, prior to the use, the Oasis WAX was rinsed with $NaHCO_3$ (0.5 M) followed by water. The [^{18}F]fluoride was quantitatively (98±1%) retained on the cartridge (Table **S2**) and water discarded. The cartridge was rinsed with *i*PrOH in the load direction. Next, [^{18}F]fluoride was eluted from the cartridge in the opposite direction using 25 µmol of **2b** in DMA into the reaction vial containing **1** (17.9 µmol) and copper catalyst (5.3 µmol) dissolved in DMA (0.5 mL). The final concentration of water in the eluate determined by Karl Fischer method was 0.15±0.01 % (n=3). ^{18}F-fluorination was carried out at 110 °C for 20 min under air atmosphere. Using this straightforward procedure, we achieved RCC values of **1a** in excess of 95%. In some experiments, other solvents than *i*-PrOH were used to rinse the WAX cartridge, providing similar RCC values for **1a** (**Table S3**). The reduced amount of precursor resulted in slightly lower RCCs (93% and 85% for 10 and 5 µmol of **1,** respectively) (Table **S4**, entries 4 and 5).

Generally, this approach relies on formation of the 4-dimethylaminopyridinium [^{18}F]fluoride ($DMAP^+$ $^{18}F^-$), which was earlier applied by the Scott group in an aqueous solution.[9] An advantageous feature of our method is that by using an organic solution of this PTC neither azeotropic drying step nor any solvent evaporation is required. The elimination of these steps to simplify the automation was the focus of multiple studies.[5b,12]

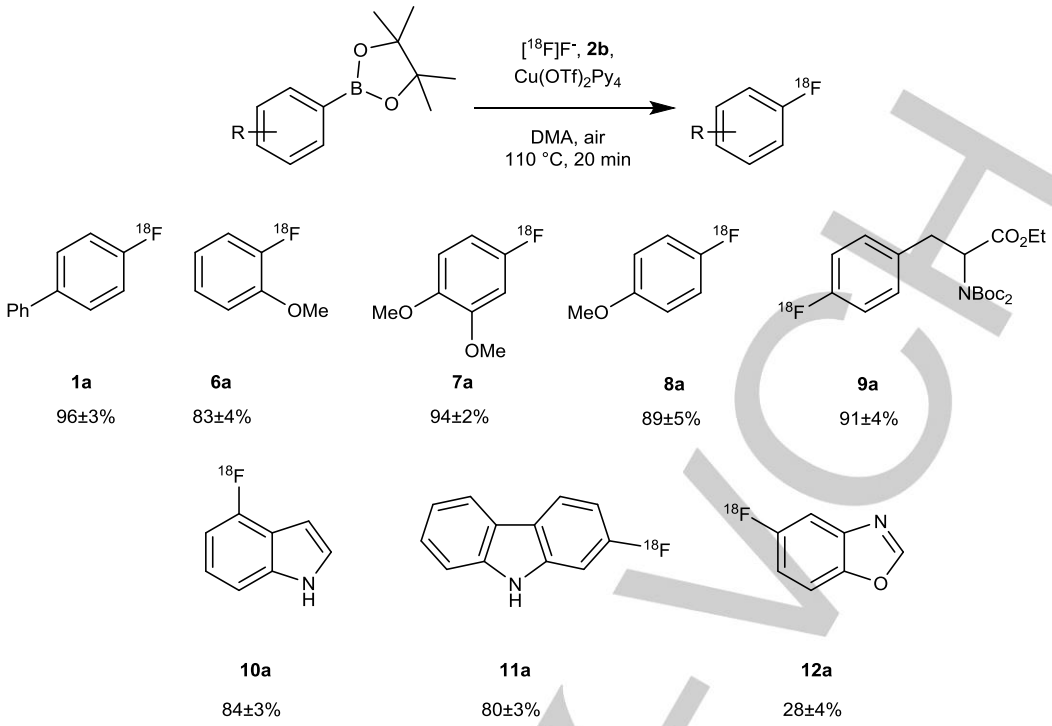

Figure 3. [^{18}F]Fluoroarenes prepared from the corresponding ArylBPin precursors. Conditions: 17.9 μmol of precursor, 5.3 μmol of $Cu(OTf)_2(Py)_4$, 25 μmol of **2b**, 1 mL of DMA, 110 °C, 20 min. RCC was determined by radioTLC.

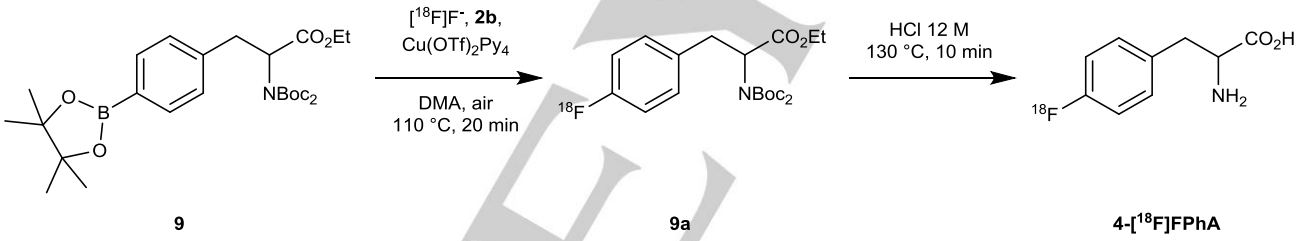

Figure 4. Synthesis of 4-[^{18}F]fluoro-D,L-phenylalanine. Conditions: 17.9 μmol of **9**, 5.3 μmol of $Cu(OTf)_2(Py)_4$, 25 μmol of **2b**, 1 mL of DMA, 110 °C, 20 min.

This novel approach was applied to the preparation of several model [^{18}F]fluoroarenes (Fig. 3). All the substrates underwent fluorination with high RCC values. Even for electron-rich *O*-substituted in the *ortho*-position substrate **6a** the fluorination efficiency was in excess of 80% - something hard to achieve by other means.[3b, 5b] Labeling of indole **10a** and carbazole **11a** can be performed using small amount of precursors and with RCC's up to 80% without employing *N*-protection.[5b,13] For benzoxazole derivative **12a** that has been difficult to synthesize under other labeling conditions,[13] the RCC value reached 30%.

Our method is also effective for the radiosynthesis of complex molecules, such as aromatic ^{18}F-fluorinated amino acids, exemplified by 4-[^{18}F]fluoro-D,L-phenylalanine (4-[^{18}F]FPhA). Phenylalanine-derived radiotracers accumulate in tumors that overexpress aromatic amino acid transporters and were considered to be promising PET radiotracers in the '80's. However, those early PET imaging studies have not been expanded, perhaps due to the low availability of the radiotracers. Synthesis of 2- or 4-[^{18}F]FPhA was often executed to demonstrate the feasibility of Cu-mediated fluorinations approaches.[3b, 8, 14] Using ArylBPin precursor **9** (Fig. 4) and our labeling protocol, the RCC for **9a** was over 90%. Following acid hydrolysis with 12 M HCl (130°C, 10 min) and HPLC purification in the ethanol-based mobile phase, 4-[^{18}F]FPhA was obtained in RCY of 35-38% (non-optimized, corrected for radioactive decay) within 90 min. The amount of copper in the final preparation was determined by earlier developed method of capillary electrophoresis.[15]. The residual amount was less than 10 ppm which is below the copper limit of 25 ppm recommended in the ICH Guideline of Elemental Impurities (Q3D).

Conclusions

In this study we demonstrate the utility of the pyridinium sulfonates salts in organic solutions as efficient [^{18}F]fluoride elution agents and phase transfer catalysts for copper-mediated radiofluorinations of pinacol esters of arylboronic acids (arylBPin). Following screening, the solution of 4-dimethylaminopyridinium trifluoromethanesulfonate (**2b**) in DMA in combination with an appropriate anion exchange resin (WAX 1cc) was found to be the most efficient agent for ^{18}F-elution and

radiofluorination. The novel ^{18}F-processing protocol was proven to be suitable for fluorinating a range of different arylBPin esters with the RCC values ranging from 80 to 95% using relatively low amounts of precursors (10-18 μmol). Based on the results of this study, a straightforward and fast radiolabeling procedure eliminating conventional azeotropic drying steps, solvents evaporation or changeover was developed. Preparation of 4-[^{18}F]fluoro-D,L-phenylalanine demonstrates high practical value of the approach developed.

Supporting Information

Supporting information for this article is available on the **LINK**.

Acknowledgements

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Keywords: radiopharmaceuticals • arenes • phase-transfer catalysis • copper mediated radiofluorination • [^{18}F]fluoride • pinacol esters of arylboronic acids • positron emission tomography • pyridinium sulfonates

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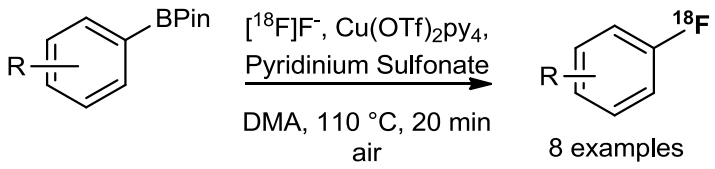

In this work we demonstrated for the first time the application of pyridinium sulfonates (organic solutions) for generation of reactive [^{18}F]fluoride and efficient use in copper-mediated radiofluorination of aryl pinacoloboronate esters. The feasibility of this approach was demonstrated for 8 aromatic substrates.

Aromatic radiofluorinations

*Dmitrii Antuganov, Dr. Michail Zykov, Vasilii Timofeev, Ksenija Timofeeva, Yulija Antuganova, Victoriya Orlovskaya, Dr. Olga Fedorova, Dr. Raisa Krasikova**

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Copper-mediated radiofluorination of aryl pinacolboronate esters: a straightforward protocol by using pyridinium sulfonates