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FULL PAPER

Cu-mediated radiofluorination of aryl pinacolboronate esters: alcohols as solvents with application to 6-L-[^{18}F]FDOPA synthesis.

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Abstract: Cu-mediated radiofluorination of arylboronic acid pinacol esters (ArylBPin) using $Cu(OTf)_2(Py)_4$ complex is a useful approach for the introduction [^{18}F]fluorine into non-activated arenes and heteroarenes. Due to complexity of the mechanism and wide variation in substrate reactivity the choice of reaction conditions must be made individually for every precursor. Careful selection of phase-transfer catalysts also plays a role, as Cu-catalyst and ArylBPin precursors are known to be unstable in basic conditions. Using tetrabuthylammonium triflate alcohol solution for elution of [^{18}F]fluoride from ion-exchange cartridge and employing same alcohol as a co-solvent in the following labelling step, we have developed a general protocol resulting in >80% fluorination efficiency of ArylBPin precursors for 4-[^{18}F]fluoro-D,L-phenylalanine and 6-L-[^{18}F]FDOPA. Radiofuorination in neat alcohol was particularly effective for the synthesis of 6-L-[^{18}F]FDOPA, allowing for substantial increase of yield and decrease of synthesis time compared to current methods (activity yield 14.5 ± 0.5%, 70 min synthesis time).

Introduction

Positron emission tomography (PET) serves as a highly sensitive routine diagnostic tool for the diagnosis of cancer, cardiovascular and neurological disorders. It has also become an important tool in drug discovery and development. Fluorine-18 is currently the predominant PET radionuclide due to its useful nuclear imaging properties and broad availability in multi-GBq quantities from commercial cyclotrons. The relatively long half-life and well-developed chemistry enable access to a great variety of ^{18}F-labelled radiopharmaceuticals. Significant number of them (fluorinated amino acids, drug-like molecules etc.) contain Ar-F group with a metabolically stable C-F bond. While methods for the introduction of fluorine-18 into aromatic functionality via electrophilic radiofluorination using [^{18}F]F_2 are well-established, they suffer from several limitations such as difficulties in handling radionuclide in a gaseous form and unavoidable introduction of unlabeled carrier lowering the molar activity (A_m). Due to this, labelling starting from fluoride-18 in aqueous solution offers multiple benefits, including easier handling and greater availability of no-carrier-added nucleophilic [^{18}F]fluoride from water targets, while also affording significantly higher A_m compared to electrophilic methods. [1]

Nucleophilic S_N2 radiofluorination has been applied for decades in the synthesis of a number of PET radiotracers. As for nucleophilic aromatic substitution (S_NAr), it was generally limited to introducing ^{18}F into aromatic structures containing electron-withdrawing groups in the *para*- or *ortho*-positions to the appropriate leaving group. In the past few years several innovative ^{18}F-labeling approaches have been introduced, allowing for "late-stage radiofluorination" of non-activated (electron-rich) aromatic structures using, for example, iodonium salts, spirocyclic hypervalent iodine (III) complexes, organoborons, and stannanes. [2] Among methods reported, Cu-catalyzed radiofluorination of pinacol esters of arylboronic acids (ArylBPin) (Figure 1) introduced by the Gouverneur's group [3a] following chemistry developed by Sanford's group [3b] is one of the more promising synthetic avenues for the preparation of a range of radiotracers that cannot be readily accessed through conventional approaches. Based on copper-promoted Chan-Lam type C-F cross-coupling reaction [4] adapted to radiofluorinations in the presence of commercially available $Cu(OTf)_2(Py)_4$, this approach was found to be effective for introducing fluorine-18 into electron-rich , -neutral and -poor arenes. [1a, 1d] In the follow-up studies Cu-mediated radiofluorination of organoborons [5a] and (hetero)aryl organostannanes [5b] was developed, employing catalyst generated *in-situ* from copper triflate and pyridine [5a,b] or pre-formed $Cu(OTf)_2(Py)_4$ complex [5c,d]. However, copper-promoted radiofluorination of ArylBPin precursors is, to date, the most versatile method [2d] applied to the preparation of various ^{18}F-fluorinated amino acids [6] as well as a number of other clinically significant tracers. [7] The value of the method was confirmed by the application for radiolabeling of a large variety of drug-like molecules [8] for preclinical and biomedical research.

Nevertheless, despite of the success of Cu-mediated radiofluorination in a small-scale synthesis using small aliquots of aqueous [^{18}F]F^-, attempts to implement this method into full-batch clinical production usually reveals several problems, including modest or fluctuating radiochemical yields, long synthesis times and problematic protocols that not always prove to be adaptable to automation. Also, amounts of ArylBPin precursors employed can pose a number of practical challenges at purification step(s). One of the problems associated with low radiochemical yield (RCY) at the radiofluorination step has been the sensitivity of Cu-mediated process to basic conditions [9] that are realized when using classical [^{18}F]KF/K_{222} approach with K_2CO_3 as base [3a]. The improvement in radiofluorination efficiency was achieved using less basic $K_2C_2O_4/K_2CO_3$ combination [7] or substantially reducing both base and kryptofix amounts [9] ("low-base protocol"). Also, use of less basic phase transfer catalysts (PTC) - tetraethylammonium hydrocarbonate (Et_4NHCO_3), [5c] tetrabutyl ammonium triflate (Bu_4NOTf) [6d,e] and pyridinium sulphonates [10] was found to be effective for this radiolabeling approach. In addition to improving radiofluorination efficiency, using organic solutions of PTCs [5c, 6d, 10b, 10c] to elute [^{18}F]F^- from the anion-

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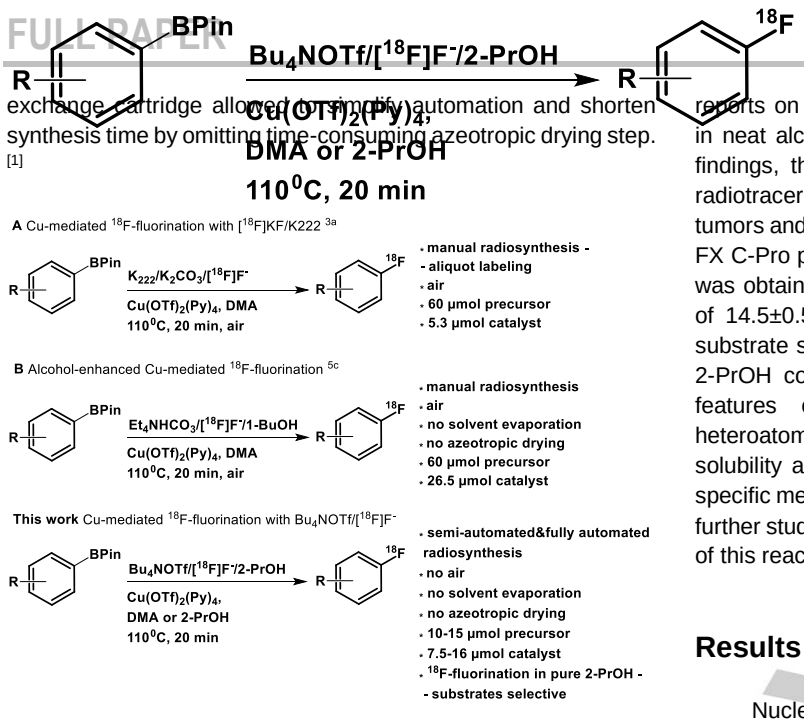

Figure 1. Cu-mediated ^{18}F-fluorination of ArylBPin precursors.

As copper-mediated radiofluorination approach has been taken up for the labeling of ArylBPin precursors, [2a,d] a number of other factors, in addition to the base sensitivity of the Cu-complex and ArylBPin substrates, have been shown to have an impact on the outcome of this complex catalytic process. [11] Reaction solvents, in particular, have a profound effect, [5c, 6a, 8e, 8f] as well as the amount of labelling precursor used and the stoichiometry of the precursor to the copper complex. [5c, 10,12a] Radiolabeling is commonly carried out in DMF or DMA, however, following several studies that have revealed the enhancing effects of alcohols as co-solvents with DMA [5c] successful radiofluorinations of various ArylBPin substrates were performed using DMA/1-BuOH system with Et_4NHCO_3 as the PTC. [6c,6g, 8d,12b]

It should be emphasized that numerous attempts to optimize Cu-catalyzed reaction have been undertaken using simple model compounds; yet the results obtained often cannot be directly translated to ^{18}F-labeling of complex molecules. A recent review on the radiofluorination screening of a large series of heteroaryl boronic acid esters [13] has shed considerable light on the importance the structure of the labeling substrate plays, in particular, the presence of specific functional groups and substituents that can influence or even prevent ^{18}F-fluorination in certain circumstances. In this study we put forward two effective protocols for catalytic radiofluorination of arylBPin substrates using Bu_4NOTf as a neutral PTC and 2-PrOH both as an elution solvent for ^{18}F-fluoride and also the labelling reaction solvent/co-solvent. The methods proposed remove the need for conventional azeotropic drying steps or any process of solvent removal preceding the fluorination reaction. When carrying out the reaction in DMA/2-PrOH, high radiochemical conversions rates (>80%) were obtained for model arylpinacol boronates and ArylBPin precursors for 4-[^{18}F]fluoro-D,L-phenylalanine and 6-L-[^{18}F]FDOPA, demonstrating versatility and efficiency of this procedure. In addition, radiofluorination in neat 2-PrOH was observed as well, but in a substrate-specific manner, being efficient only for the preparation of 6-L-[^{18}F]FDOPA, but not for other substrates under study. To the best of our knowledge, no reports on Cu-catalyzed radiofluorination of ArylBPin substrates in neat alcohols have been published to date. Based on these findings, the synthesis of 6-L-[^{18}F]FDOPA, a widely-used PET radiotracer for diagnosis of Parkinson disease, neuroendocrine tumors and gliomas, was fully automated on a modified TracerLab FX C-Pro platform implementing our new approach. The product was obtained in the activity yield (isolated, not decay-corrected) of 14.5±0.5% (n=3) with 70 min average synthesis time. The substrate selectivity in the Cu-mediated radiofluorination in neat 2-PrOH could be due to many factors related to the specific features of the radiolabeling substrate: coordination of heteroatoms in the molecule with copper complex, specific solubility and solvation in 2-PrOH and so on, however, lack of specific mechanistic evidence leaves this open to speculation and further studies would be required to fully elucidate the mechanism of this reaction.

Results and Discussion

Nucleophilic ^{18}F-fluorination reactions traditionally include the steps of [^{18}F]fluoride adsorbtion/elution on the anion-exchange cartridge followed by an azeotropic drying with acetonitrile. However, the time-consuming azeotropic drying step is associated with radioactivity losses due to decay, absorption on the walls of the reactor and often difficulties in automation. As of late, several adsorbtion/elution protocols have been proposed to shorten ^{18}F-recovery step and, which is more important, to provide less basic and milder ^{18}F-fluorination conditions. For kryptofix-mediated radiofluorinations using K_{222}/K_2CO_3 the standard amount of base required for efficient elution of [^{18}F]F$^-$ retained on the anion-exchange cartridge is too high (2.0-3.5 mg; 14-25 μmol) for base sensitive reactions such as Cu-mediated radiofluorination of ArylBPin precursors to proceed efficiently. To address this problem a reversed loading/elution procedure (the so-called “back-flushing protocol”) has been suggested [9] allowing for a substantial reduction in the amounts of K_{222}/K_2CO_3 or other PTCs, such as Et_4NHCO_3, used. The work-up procedure includes loading of an aqueous [^{18}F]fluoride onto an anion-exchange cartridge from the male side, flushing with MeOH from the same side, followed by elution of [^{18}F]F$^-$ from the female side using solution of the PTC in an appropriate solvent. A further refinement to the Cu-mediated radiofluorination procedure was introduced later [5c], eliminating azeotropic drying and evaporation steps which is advantageous for automation. As has been described, the [^{18}F]F$^-$ is eluted directly with an alcohol (usually 1-BuOH) solution of a suitable salt, like Et_4NHCO_3, into a DMA or DMF solution of an appropriate precursor and $Cu(OTf)_2Py_4$ for the fluorination reaction. The presence of alcohol as co-solvent in Cu-mediated process has a beneficial effect on the radiofluorination efficiency [5c] leading to substantial increases in the radiochemical yield (RCY) for various ArylBPin substrates. [6c,6g; 8d,12b] The main drawback of this approach is the need for high amount of the reactants (up to 60 μmol of precursor and 30 μmol of Cu-catalyst). Therefore, in the follow-up studies possibility of reduction in the amount of Et_4NHCO_3 was investigated using less viscous and more polar MeOH as eluting solvent; correspondingly the quantities of precursor/copper catalyst could be reduced to 10-15 and 5-10 μmol, respectively. [6c,6g] However, the solvent evaporation step preceding ^{18}F-fluorination is still required in this iteration of the method, making this modification of the alcohol-

enhanced radiofluorination less attractive for automation and implementation into routine production.

Based on those findings and our recent experience in the use of alkylammoinum sulphonates as effective catalysts of the aliphatic radiofluorination [14] we have proposed to replace basic Et_4NHCO_3 with a neutral Bu_4NOTf in conjunction with 2-PrOH as the eluting solvent. Preliminary studies have revealed that Bu_4NOTf/2-PrOH is an effective catalyst for the preparation of 6-[^{18}F]fluoro-L-*m*-tyrosine via Cu-mediated radiofluorination of BPin-substituted Ni-BPB-AA complex. [6d] Also, this PTC has been recently applied for elution of [^{18}F]F^- as an aqueous Bu_4NOTf/Cs_2CO_3 solution to obtain the reactive [^{18}F]fluoride after removal of water via several cycles of azeotropic drying with acetonitrile. [6e] In contrast, our protocol based on organic solution of Bu_4NOTf allows not only to avoid the time-consuming azeotropic drying step but bypasses any solvent removal/replacement process altogether. The reactive [^{18}F]fluoride thus obtained can be used "as is" for the radiofluorination reaction where 2-PrOH serves as co-solvent, enhancing fluorination efficiency.

As a starting point of method development, the elution efficiency (EE) of Bu_4NOTf solution in 2-PrOH was evaluated for a series of commercially available cartridges (Table 1).

Table 1. Dependency of ^{18}F-fluoride elution efficiency (EE) and RCY of the radiofluorination of **1** on the type of anion exchange cartridge. All the experiments except 3 were performed in triplicate.

Entery	Cartridge	Counterion	EE (%)	RCY (%)
1	Sep-Pak QMA light (130 mg)	Cl^-	80	96±2
2	PS-HCO3 (46 mg)	HCO_3^-	53	91±3
3	Oasis WAX 3cc (30 mg)	-	33	84
4	Sep-Pak QMA light carb (46 mg)	CO_3^{2-}	88	76±1
5	Vac QMA 1cc (100 mg)	Cl^-	95	96±2

Prior to use, all the cartridges, except Oasis WAX 3cc, were rinsed with $NaHCO_3$ (0.05 M) solution followed by water. As shown in Table 1, the type of anion exchange cartridge substantially influenced the efficacy of ^{18}F-elution and especially the subsequent radiolabeling step. The highest recovery rate (EE 95%) was obtained with Sep-Pak Vac QMA 1cc (100 mg) followed by Sep-Pak QMA light carb (46 mg) and Sep-Pak QMA light (130 mg) cartridges (88 and 80%, respectively). As a side-note, when using barrel-type Vac QMA cartridge in the automated synthesis module the problem was encountered with complete removal of the residual water drops from the inner surface of the cartridge. The "back-flushing" protocol [5c] was used for loading/elution of the [^{18}F]F^- using 5 mg (12.7 µmol) of Bu_4NOTf in 0.6-0.8 ml of 2-PrOH. The [^{18}F]Bu_4NOF thus obtained was reacted with a model substrate - 2-(3,4-dimethoxyloxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**1,** 15 µmol) - bearing BPin leaving group in a non-activated position (Figure 2) together with 7.5 µmol $Cu(OTf)_2(Py)_4$ dissolved in 0.3 ml of DMA at 110 °C for 20 min under air. In regards to radiofluorination efficiency, the highest RCY (96%) in radiofluorination of **1** (Figure 2) was obtained using Sep-Pak QMA light (130 mg) cartridge (Table 1, entry 1). Therefore, this type of the cartridge, incidentally the most commonly used in automated synthesizers, was selected for all the further experiments in semi-automated and automated applications.

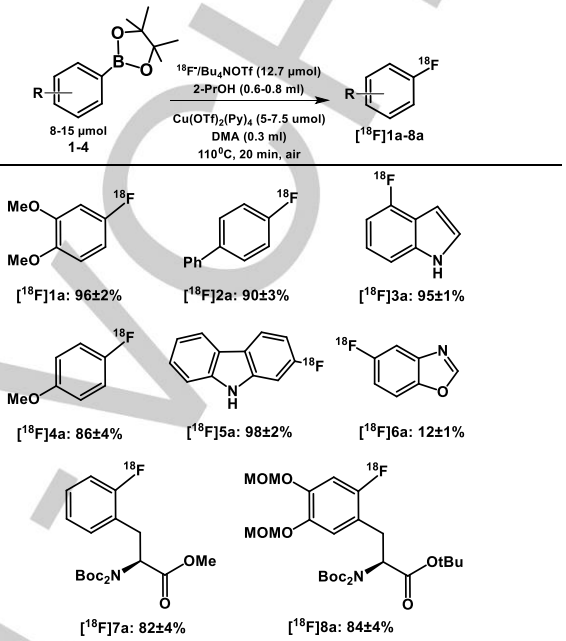

Figure 2. [^{18}F]fluoroarenes prepared from the corresponding arylBPin precursors via Cu-mediated radiofluorination in DMA/2-PrOH using Bu_4NOTf as a neutral PTC; here and elsewhere RCY - radiochemical yield of the radiofluorination step as calculated from radioTLC data.

Compared with the original "alcohol-enhanced" radiofluorination protocol using Bu_4NOTf as a neutral PTC, high ^{18}F-fluorination efficiency was achieved while substantially reducing ArylBPin precursor and Cu-catalyst amounts [5c] (15/7.5 µmol vs 60/30 µmol respectively). Further reduction in reactant amounts to 5/3 µmol has resulted in a dramatic decrease in yield (Table 2, entry 1). Attempts to replace DMA with acetonitrile as a more convenient reaction solvent failed in achieving reasonable radiofluorination efficacy (Table 2, entry 3). Poor fluorination rate was accompanied by losses of radioactivity on the inner surfaces of the reaction vessel (up to 30-50% of total radioactivity). Overall, the 15/7.5 µmol ratio of precursor to catalyst was found to be optimal for fluorinations in DMA/2-PrOH. It also afforded high RCY in the preparation of simple [^{18}F]fluoroarenes [^{18}F]**1a**-**5a** as well as protected 4-[^{18}F]-D,L-fluorophenylalanine ([^{18}F]**7a)** (Figure 2). However for poorly fluorinated substrate [^{18}F]**6a** (RCY of radiofluorination of 8±2 % reported by Gouverneur' group [13]) our protocol was also not efficient providing RCY of 12±1 %.

Table 2. Optimization of the Cu-mediated radiofluorination of **1** with Bu_4NOTf; reaction conditions from Figure 2.

Entry	**1**, µmol	$Cu(OTf)_2(Py)_4$, µmol	Radiofluorination Solvent	RCY, %
1	5	3	DMA/2-propanol	59±8
2	5	7.5	DMA/2-propanol	96±2 (n≥10)

3	15	7.5	AcN/2-propanol	18±1

As mentioned above, the outcome of radiofluorination of ArylBpin precursors depends upon several key parameters like PTC/base combination, main reactant amounts and reaction solvent (Table 3). The suggested use of the neutral Bu_4NOTf as phase-transfer catalyst and 2-PrOH as reaction co-solvent (Table 3, entry 4) appears to be optimal, affording high efficacy of the fluorination of **1** while using substantially lower amounts of precursor and catalyst. The ease of generating reactive ^{18}F-species makes this protocol attractive for the implementation into automated production routine.

Table 3. The results of Cu-mediated radiofluorination of **1** using different PTC and reactants amounts (110 ^{0}C, 20 min, under air).

Entry	**1**, μmol	Cu-catalyst, μmol	Eluent		EE, %	Reaction solvent	RCY, %	Refs
			PTC, μmol	Solvent				
1	60	5.3	K_{222}/ K_2CO_3	AcN / H_2O	≥ 95	DMF	54	[3a]
2	20	40	K_{222}/$K_2C_2O_4$/ K_2CO_3	AcN / H_2O	95	DMA	68	[7]
3	60	26.5	Et_4NHCO_3 14.1	1-BuOH	80-95	1-BuOH /DMA	83	[5c]
4	15	7.5	Bu_4NOTf 12.7	2-PrOH	80-94	2-PrOH /DMA	96±2 (n≥1)	This work

1 and 2 - “aliquot labelling”; 3 and 4: no azeotropic drying, no solvent evaporation

Our next step was implementing our new methodology into the automated synthesis of 6-L-[^{18}F]fluoro-3,4-dihydroxyphenylalanine (6-L-[^{18}F]FDOPA), a common radiotracer used for evaluating progression of Parkinson’s disease, as well as detection of gliomas and neuroendocrine tumors. [15] The radiosynthesis of 6-L-[^{18}F]FDOPA using nucleophilic [^{18}F]F$^-$ process has been a long-standing challenge for PET radiochemists. [16] The applicability of Cu-mediated radiofluorination of ArylBPin precursors for 6-L-[^{18}F]FDOPA with different protecting groups on the catechol and amino acid moieties was previously evaluated by several groups in manual (“aliquot labeling”), semi-automated and fully automated procedures, resulting low-to-moderate activity yields. [3a, 5c, 6e, 7a] For our work we have chosen 3,4-OMOM-6-(BPin)DOPA(Boc)$_2$-OtBu (**8,** Figure 3) for the precursor as it was commercially available and MOM- and Boc-protecting groups can be removed easily in acidic conditions. Considering high cost of the precursor and limits on copper for iv administration in pharmaceuticals the amounts of **8** and Cu-catalyst were reduced to 8 и 5 μmol, respectively; even with those amounts the radiofluorination in DMA/2-propanol proceeded without any drop in the ^{18}F-fluorination efficiency (Table 4, entry 1).

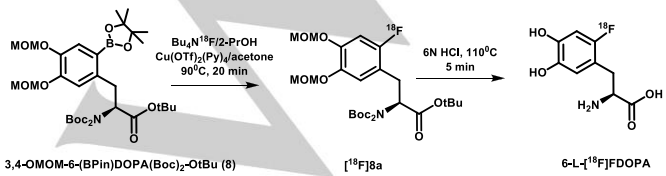

Figure 3. Radiosynthesis of 6-L-[^{18}F]FDOPA via copper-mediated radiofluorination of 3,4-OMOM-6-(BPin)DOPA(Boc)2-OtBu (**8**) using Bu_4NOTf as the PTC.

While the optimal conditions are chosen based on the consideration of results from semi-automated syntheses, it is often impossible to apply those methods directly to fully-automated productions. In regards to the prospects for automation the limitation of our protocol has been the high boiling point of DMA - complete removal of the solvent after radiofluorination was found to be a critical point for ensuring high efficiency of the deprotection step following the radiolabelling (Figure 3). An attempt to replace DMA with acetonitrile led to a substantial reduction in radiolabelling efficiency (Table 4, entry 2) even when using 15/7 μmol ratio of precursor to catalyst. Varying the amounts of the reactants (Table 4, entries 4-6) we were able to slightly increase the RCY, however the values were far below those obtained with DMA/2-PrOH mixture.

Somewhat unexpectedly, the radiofluorination of **8** in neat 2-PrOH proceeded well, resulting in high RCY **(**Table 4, entries 7 and 8). Using same solvent in fluorination reaction as in the ^{18}F-fluoride elution step provides additional benefits cutting the need for any solvent removal steps. The fluorination in 2-PrOH proceeded well only when stoichiometry of reactants was reversed (16 - 20 μmol of $Cu(OTf)_2(Py_4)$ to 10 μmol of **8 (**Table 4, entries 7 and 8). To the best of our knowledge, no reports supporting the use of neat alcohols as the reaction solvents in copper-mediated radiofluorinations ArylBPin precursors have been published previously. In contrast, the replacement of DMA/1-butanol mixture with neat 1-butanol has resulted in a

dramatic decrease of efficiency in the radiofluorination of phenylboronic acid pinacol ester from 99 to 8%. [5c]

Table 4. Optimization of Cu-mediated radiofluorination of **8** under various protocols (semi-automated module, under air).

Entry	**8**, µmol	$Cu(OTf)_2(Py)_4$, µmol	Radiofluorination Solvent	RCY [^{18}F]**8a**, % radioTLC
1	8	5	DMA/2-propanol	84±4 (n=3)
2	15	7	AcN / 2-propanol	30
3	15	30	AcN / 2-propanol	49±1 (n=2)
4	10	10	AcN / 2-propanol	37
5	10	20	AcN / 2-propanol	64
6	10	50	AcN / 2-propanol	65
7	10	16	2-propanol	79±2 (n=2)
8	10	20	2-propanol	87±2 (n=3)
9	10	16	acetone/ 2-propanol	82±5 (n=3)
10	10	20	acetone/ 2-propanol	85±3 (n=2)

In addition to 2-PrOH, we have screened a series of alcohols by using the alcohol as the elution solvent for [^{18}F]F^- and allowing reactive species thus generated to react with 10 µmol of **8** and 16 µmol of $Cu(OTf)_2(Py)_4$ in 0.3 ml of the alcohol (100 - 105 ^{o} C, 20 min) using a semi-automated module. As expected, ^{18}F-recovery was highest for methanol (96%) while poor radiofluorination efficiency (< 30%) was associated with its use as reaction solvent. Ethanol was moderately effective in terms of both elution (75%) and fluorination yield (60%). 1-propanol and 2-propanol produced similar results within margin of error in terms of elution efficiency (c.a. 80-90%) and labelling yield (c.a. 85%).

Encouraging results obtained for fluorination of **8** in neat 2-PrOH prompted further studies investigating the applicability of this "pure alcohol radiofluorination" for a series of other substrates. However, use of neat 2-PrOH as a radiofluorination reaction solvent was found to be beneficial only for the synthesis of [^{18}F]**8a.** Under similar conditions [^{18}F]**1a,** [^{18}F]**2a, [^{18}F]3a, [^{18}F]4a, [^{18}F]5a, [^{18}F]6a** and [^{18}F]***7a,*** were obtained in 8±1, 12±2, 41±1, 10±1, 34±2, 7±2 and 31±13% RCY, respectively (n=3). This result was not entirely unexpected considering the recent study demonstrating dependence of the Cu-catalyzed process outcome on the structure of substrate molecule, with presence of functional groups often impairing labelling efficiency. [13] In our limited series of substrates the key structural difference between **8** and the simple model substrates **1** - **6** is the presence of the amino acid moiety. Precursor **8** for 6-L-[^{18}F]FDOPA contains catechol motif with MOM-protection; the protection of carboxyl group in **7** and **8** are also different (OMe and OtBu). Possibly, high reactivity of **8** in the copper-mediated radiofluorination in 2-PrOH is a result of many factors related to the specific features of this substrate: coordination of heteroatoms in the molecule with copper complex, specific solubility and solvation in 2-PrOH, for the proof of which more extensive studies are required.

With optimized conditions for the fluorination of **8** developed, we have applied them to the automated synthesis of 6-L-[^{18}F]FDOPA using TRACERlab FX C Pro (GE Healthcare) synthesis module. This two-reactor automated module was originally designed for the preparation of ^{11}C-labelled compounds and was later adapted to ^{18}F-fluorination use as well. Despite efficient radiofluorination of **8** in 2-PrOH, the poor solubility of $Cu(OTf)_2(Py)_4$ in this solvent at room temperature was associated with difficulties in the automated mode. The catalyst had to be placed directly into the reaction vessel necessitating its disconnection from the holder before performing each run, if neat 2-propanol was used as reaction solvent. Given greater solubility of Cu-catalyst in acetone (which was a good solvent for **8** as well) the reagents were dissolved in acetone, which was then used as co-solvent together with 2-PrOH in radiofluorination. Introduction of acetone into the reaction had not had any negative impacts on the RCYs (Table 3, entries 9, 10) resulting in values similar to those obtained with neat alcohol. Additionally, acetone was used for flushing QMA cartridge to remove any residual water before elution of the [^{18}F]fluoride. An additional benefits of our novel protocol was that there was no need to provide the access to the atmospheric oxygen usually required for Cham-Lam coupling-like oxidation cycle. [3a] This is an important issue as the standard automated modules for PET radiochemistry are flushed and operated with the inert gas and the introduction of the atmospheric oxygen can be difficult.

Briefly, the automated synthesis of 6-L-[^{18}F]FDOPA started from the preparation of reactive [^{18}F]fluoride using Bu_4NOTf (12.5 µmol in 0.9 ml of 2-PrOH) using back-flushing protocol approach. Executing this step in the automated mode improved ^{18}F-recovery rate from 80% obtained in semi-automated regime (Table 1, Entry 1) to 91-96%. Reactive [^{18}F]F^- was collected into the round-bottom reaction vessel (2 ml volume) pre-filled with solution of 10 µmol of **8** and 16 µmol of $Cu(OTf)_2(Py)_4$ in 0.3 ml of acetone and the reaction mixture was heated to 90°C for 20 min under N_2 while stirred. At the deprotection step, in the original approach the removal of the catechol protective groups has been always associated with difficulties - the common methodology for removal of 4,5-methylenedioxy or 4,5-*bis*-methoxy groups employs 57% aq. HI and high temperatures (180-200 ^{o} C), which is not compatible with most synthesis modules. However, the precursor **8** was designed with methoxymethyl ether (MOM) and OtBu protective groups that can be removed using aqueous HCl solution. 6 N HCl was inefficient in removal of the protecting groups, however, using a combination of 6 N HCl (0.4 ml), MeOH (0.3 ml) and 0.25 M ascorbic acid (0.2 ml in water) with heating to 110 °C for 5 min resulted in near-100% deprotection reaction efficiency. The ascorbic acid was added as it was known to prevent decomposition of 6-L-[^{18}F]FDOPA, [6e] while methanol increased solubility of the liphophilic intermediate [^{18}F]**8a.** Notably, for performing this step successfully removal of the fluorination solvent was essential and easily achieved in case of acetone/2-PrOH. 6-L-[^{18}F]FDOPA was isolated from the reaction mixture by semi preparative reverse phase HPLC using an aqueous 0.1% CH_3COOH (pH 4) as a mobile phase at 4 ml/min flow rate on a Ascentis RP-AMIDE (5 µm, 250×10 mm) column. The product fraction (R_t 12-13 min, 4-5 ml volume, Figure **S6**) corresponding to pure 6-L-[^{18}F]FDOPA was collected into a vented sterile vial

pre-filled with 5 ml of normal saline following on-line sterilization through the 0.22 µm filter.

The 6-L-[^{18}F]FDOPA was obtained with the radiochemical purity above 99%, enantiomeric purity above 95% and molar activity of 34-61 GBq/µmol (0.9-1.7 Ci/µmol). Activity yield (isolated radiochemical yield, not decay corrected) was 14.5±0.5 % (n=3) with synthesis time of ca. 70 min. The residual copper content, measured by ICP/MS, amounted to 0.4±0.2 ppm and was below any level of concern according to the ICH Guideline of Elemental Impurities (Q3D). [17] The amount of tetrabutylammonium hydroxide was negligibly small - below analytical HPLC method limit of detection; no peak with R_t of 5.6 min was detected on the HPLC chromatogram (HPLC system 1, Figure **S8**).

Despite the fact that small-scale synthesis of 6-L-[^{18}F]FDOPA via Cu-mediated radiofluorination of the respective ArylBPin precursor was already considered in the first publication of Gouveneur's group, [3a] the automated production of this radiotracer still remained a challenging task. In the follow-up study by the same group [7] the procedure using Synthra automated synthesis platform has been developed. In a full-batch preparation the originally used K_{222}/K_2CO_3 [3a] was replaced with a less basic $K_{222}/K_2C_2O_4/K_2CO_3$ allowing for efficient recovery of [^{18}F]fluoride retained on the anion-exchange cartridge and better radiofluorination yield. However, due to long synthesis time (146 min) and the presence of unlabelled impurities co-eluting with the product the method required further optimization. One of the most difficult steps in that work [7] was the hydrolysis/deprotection reaction requiring very aggressive conditions (57% HI, 180 °C) leading to a lengthy purification process. While our work was in progress, the Scott's group [6e] has published a fully automated synthesis of 6-L-[^{18}F]FDOPA using the same commercially available BPin precursor as employed by us. This precursor has easy-to-cleave MOM protecting groups on the catechol moiety and tert-butyl ester group protecting the amino acid fragment allowing for hydrolysis/deprotection step using HCl solution. Even so, the automated synthesis procedure reported by Scott et al. [6e] resulted in average synthesis time of 110 min and is relatively complex. The preparation of the reactive [^{18}F]fluoride using QMA eluent being an aqueous solution of Bu_4NOTf and Cs_2CO_3 necessitated azeotropic drying step resulting in longer synthesis time. Radiofluorination of **8** in DMF proceeded in moderate RCY of 55%; the unavoidable transfer of this solvent to hydrolysis step required high concentration of HCl (12 N vs 6N in our protocol) for efficient deptotection reaction. Our efforts were focused on shortening synthesis and simplifying automation through implementation of non-aqueous solution of Bu_4NOTf for elution of the [^{18}F]fluoride removing the need for additional drying steps. The use of 2-propanol both in the elution stage and in radiofluorination reaction allowed us to minimize the number of the intermediate steps and substantially reduce synthesis time (to 70 min) while doubling the yield (14.5±0.5 vs 6±1% [6e]).

Conclusion

In the present work we have developed two practically applicable synthetic protocols for Cu-mediated radiofluorination of arylboronic acid pinacol esters (ArylBPin) employing Bu_4NOTf as a neutral phase-transfer catalyst for the preparation of reactive [^{18}F]fluoride species. Following elution with Bu_4NOTf/2-PrOH solution the radiofluorination reaction can be performed directly with alcohol as the reaction solvent (or co-solvent with DMA), offering significant practical benefits through elimination of the azeotropic drying or solvent removal steps precceding radiofluorination. Radiofluorination in DMA/2-PrOH was fully compatible with simple model substrates and ArylBPin precursors for two aromatic amino acids providing a broadly applicable and efficient route for ^{18}F-labelling of arenes and heteroarenes with different functional groups. Radiofuorination in neat alcohol was substrate-dependent, being particularly effective for the preparation of 6-L-[^{18}F]FDOPA with activity yield of 14.5 ± 0.5% (isolated) in a fully automated mode with average synthesis time of 70 min, which is a significant improvement over currently employed methods in terms of increased yield and decreased synthesis time. To the best of our knowledge no reports have been published previously regarding Cu-mediated fluorination in neat alcohols, and while our findings are confined to production of a single, if a very important, radiotracer - 6-L-[^{18}F]FDOPA, it is also possible that this method could be applied to labeling of other ArylBPin precursors.

Experimental Section

General: Unless otherwise stated, reagents and solvents were commercially available and used without further purification. 2-(3,4-Dimethoxyloxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**1**), 2-(4-biphenylyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**2**), indole-4-boronic acid pinacol ester (**3**), 4-methoxyphenylboronic acid pinacol ester (**4**), 9H-carbazole-2-boronic acid pinacol ester (**5**), benzooxazole-5-boronic acid pinacol ester (**6**), 4-fluorobipheny. Anhydrous ethanol was prepared in-house using common techniques. Methyl-(S)-2-((di-tert-butoxycarbonyl)amino)-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-phenyl)propanoate (**7**) and methyl-(S)-2-(2-((di-tert-butoxycarbonyl)amino)-3-(4-fluorophenyl)propanoate (precursor and reference for protected 4-[^{18}F]fluoro-D,L-phenylalanine) were provided by Dr. Chuan-Lin Chen, National Yang-Ming University, Taiwan. The precursor for 6-L-[^{18}F]FDOPA, tert-butyl-(*S*)2-((di-tert-butoxycarbonyl)amino)-3-(2-4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl-4,5-dimethoxymethylphenyl)propanoate (**8**) was obtained from WuXi AppTec Co (China). An authentic reference standard of 6-D,L-FDOPA was obtained from ABX GmBH (Radeberg, Germany). Sep-Pak Accell Plus QMA Plus Light Cartridge (130 mg), Sep-Pak Accell Plus QMA Carbonate Plus Light Cartridge (46 mg), Sep-Pak Accell Plus QMA 1 cc Vac (100 mg), Oasis Wax 3cc cartridge were acquired from Waters Corporation, USA. Chromafix PS-HCO_3 cartridge (45 mg) (Product No. 731876) was purchased from ABX GmBH (Radeberg, Germany). All the cartridges except Oasis Wax 3 cc were conditioned with 10 mL of 0.05M $NaHCO_3$ followed by 10 mL of water. Oasis Wax 3cc cartridge was applied as received.

Radio-TLC analyses were carried out on silica gel plates (60 F254, Merck or Sorbfil, Lenchrom, Russia); radioactivity distribution was determined by radioTLC scanner miniGita (Raytest, Germany). An aliquot of 2-3 µl of the crude reaction mixture after radiofluorination reaction and cooling was applied to a TLC plate. For 3,4-dimethoxy-[^{18}F]fluorobenzene (**[^{18}F]1a**), 4-[^{18}F]fluorobiphenyl ([^{18}F]2a) and protected 4-[^{18}F]fluoro-D,L-

phenylalanine (**[^{18}F]7a**) the plates were eluted with CH_2Cl_2; the R_f values for [^{18}F]fluoride, **[^{18}F]1a**, **[^{18}F]2a** and **[^{18}F]7a** were 0.05, 0.55, 0.60, 0.47, respectively. For 4-[^{18}F]fluoroindole (**[^{18}F]3a**), 4-methoxy-[^{18}F]fluorobenzene (**[^{18}F]4a**), 2-[^{18}F]fluoro-9H-carbazole (**[^{18}F]5a**) 5-[^{18}F]fluorobenzooxazole (**[^{18}F]6a**) the plates were eluted with ethyl acetate:hexane=1:1; the R_f values for [^{18}F]fluoride, **[^{18}F]3a**, **[^{18}F]4a**, **[^{18}F]5a** and **[^{18}F]6a** were 0.05, 0.60, 0.55, 0.50 and 0.56, respectively. In case of radiofluorination of **8** TLC eluent ethyl acetate was used; the R_f values for [^{18}F]fluoride and **[^{18}F]8a** were 0.05 and 0.83, correspondingly. The radiochemical yield (RCY) of the radiofluorination step was calculated from radioTLC data as the ratio of the product peak area to total peaks area on the TLC plate; it was not corrected for decay.

Analytical HPLC system used, Dionex ISC-5000, consisted of a gradient pump, Rheodyne-type injector with a 20 µl loop, and variable wavelength UV absorbance detector (set to 254 nm) connected in series with a radiodetector model 105-S (Carrol and Ramsey Associates, USA). HPLC analysis of model compounds [^{18}F]1a- [^{18}F]7a was conducted on a XBridge® C18 5 µm, 150×4.6 mm reverse phase HPLC column (Waters, USA) using the following conditions: 5 to 90% gradient (H_2O/CH_3CN, HPLC System 1), flow rate 2.0 mL/min:

0 - 2 min: 5% CH_3CN isocratic;

2 - 13 min: 5 - 90% CH_3CN linear increase;

13 - 13.5 min: 90 - 5% CH_3CN linear decrease;

13.5 - 20 min: 5% CH_3CN isocratic

The UV- and radiodetector were connected in series giving delay of 0.1 min. The R_t values of **[^{18}F]1a**, **[^{18}F]2a**, **[^{18}F]3a**, **[^{18}F]4a**, **[^{18}F]5a** and **[^{18}F]6a** were 9.0, 9.2, 10.6 and 7.3 min, respectively. R_t of radiofluorinated **[^{18}F]7a** was 12.2 min; for partly hydrolyzed **[^{18}F]7a** the R_t value was 10.2 min

The same gradient profile were applied for radioHPLC analysis of 6-L-[^{18}F]FDOPA using trifluoroacetic acid (0,1%) instead of water under flow rate of 2.0 mL/min (TFA 0.1%/CH_3CN, 5 to 90% gradient, same gradient profile, HPLC System 2). The R_t value for 6-L-[^{18}F]FDOPA was 4.0 min, R_t of radiofluorinated intermediate [^{18}F]8a was 12.9 min.; for partly hydrolyzed **[^{18}F]8a** the R_t value was 11.4 min. Residual tetrabutylammonium (TBA) level in the final product was analyzed using the same system; the R_t for TBAOH was 5.6 min Enantiomeric purity of 6-L-[^{18}F]FDOPA was evaluated using Chirobiotic T (Astec) column eluted at 1.0 mL/min with water/ethanol (60/40) (HPLC System 3). R_t values for L- and D-isomers of 6-[^{18}F]FDOPA were 4.3 and 5.6 min, correspondingly. The content of copper in the final formulation was determined using ICP Optical Emission Spectrometer Varian 725-ES.

Anion exchange cartridges screening: A series of commercially available anion exchange cartridges (Table S1) were evaluated for trapping/elution of [^{18}F]fluoride and the efficiency of the following radiofluorination of **1**. Aqueous [^{18}F]fluoride was loaded onto the anion exchange cartridge from the male side. Residual water was removed by rinsing the cartridge with 2 mL of 2-PrOH in the same direction followed by flushing with compressed air. [^{18}F]Fluoride was eluted backwards relative to the loading direction (Fig. S1) using solution of Bu_4NOTf (5 mg) in 0.6 mL of 2-PrOH. The eluate (5 mg of Bu_4NOTf, 0.6 mL of 2-PrOH) was collected into a reaction vessel pre-filled with 15 µmol of ArylBPin precursor **1**, 7.5 µmol $Cu(OTf)_2(Py_4)$, 300 µL DMA. Radiofluorinations were performed in a sealed vial at 110 ^{0}C for 20 min without stirring under atmosphere air. Radiochemical yield (RCY) of the radiofluorination step was calculated based on the radioTLC analysis of reaction mixture.

Preparation of reactive [^{18}F]fluoride for semi-automated synthesis of [^{18}F]1a - [^{18}F]7a: [^{18}F]Fluoride was produced *via* the ^{18}O(p,n)^{18}F nuclear reaction by irradiating [^{18}O]H_2O in a silver target (1.4 mL volume) using 16.4 MeV proton beam on PETtrace 4 cyclotron (GE Healthcare, Sweden). The radionuclide was transferred from the target by means of helium flow and collected in the receiving vial. Aqueous [^{18}F]fluoride was loaded onto the anion exchange cartridge from the male side. Residual water was removed by rinsing the cartridge with 2 mL of 2-PrOH in the same direction followed by flushing with compressed air. [^{18}F]Fluoride was eluted backwards relative to the loading direction using solution of Bu_4NOTf (5 mg) in 0.6-0.8 mL of 2-PrOH; the eluate was collected into the reaction vessel. Model radiolabeling of the precursors **1-7** was conducted on the remotely controlled synthesis module (in-house development [1]) with manual interventions). The module was equipped with a heating block suitable for 5 mL reaction vessel with a screw cup (Wheaton vial). Different protocols were applied for the following radiofluorinations. The RCY was assessed by radioTLC on the aliquot of the crude mixture. The radioactivity loss on the inner surface of reaction vessel was evaluated by measuring of the activity of reaction vessel with reaction mixture and after empting reaction vessel (the content was sucked out with a syringe).

Radiofluorination conditions (optimization study): [^{18}F]fluoride trapped on the Sep-Pak Accell Plus QMA Plus Light Cartridge (130 mg) cartridge was eluted with a solution of Bu_4NOTf (5 mg) in 0.6 mL of 2-PrOH. The eluate was collected into 5 mL vial pre-filled:

For 1: 5-15 µmol of **1**, 3-7.5 µmol $Cu(OTf)_2(Py_4)$, 300 µL of the solvent (DMA, CH_3CN, 2-PrOH);

For 2-7: 15 µmol of **2**-**7**, 7.5 µmol $Cu(OTf)_2(Py_4)$, 300 µL of DMA;

For 8: 8-15 µmol of **8**, 5-50 µmol $Cu(OTf)_2(Py_4)$, 300 µL of the solvent (DMA, CH_3CN, 2-PrOH, acetone).

[^{18}F]fluorination was performed in a sealed vial at 100-110 ^{0}C for 20 min without stirring under access to the atmospheric air.

Automated radiosynthesis of 6-L-[^{18}F]FDOPA: Radiosynthesis was performed on the automated synthesis module TRACERlab FX C Pro (GE Healthcare) equipped with semi-preparative HPLC (SYCAM S1122 solvent delivery system, UV detector and radioactivity detector connected in row). The module was originally designed for the preparation of ^{11}C-labelled compounds and was adapted to ^{18}F-fluorinations. [^{18}F]Fluoride (2-9 GBq) was transferred from the target in a water bolus by means of helium flow and trapped onto the Sep-Pak Accell Plus QMA Plus Light Cartridge (130 mg) from the male side. Residual water was removed by rinsing the cartridge with 7 mL of acetone in the same direction followed by flushing with N_2. The radionuclide was eluted from the cartridge backwards relative to the loading direction with solution of 12.5 µmol (5.0 mg) of Bu_4NOTf in 0.9 mL of 2-PrOH into the round-bottom reaction vessel (2 mL volume) prefilled with solution of 10 µmol of **8** and 16 µmol of $Cu(OTf)_2(Py)_4$ in 0.3 mL of acetone. The fluorination was performed at 90°C for 20 min

with stirring under inert atmosphere (N_2 gas). The solvent was evaporated by heating to 50 °C with stirring and the reaction vessel was cooled down to 40 °C. To the dried residue the mixture of 6 N HCl (0.4 mL), MeOH (0.3 mL) and 0.25 M ascorbic acid (0.2 mL) was added and hydrolysis was carried out for 5 min at 110 °C without stirring. The completeness of hydrolysis was monitored by analysis of the hydrolysate aliquot using radioHPLC, System 2. The liquids were evaporated by heating to 120 °C under nitrogen flow with stirring. After cooling the reaction vessel to 50 °C, 1.8 mL of HPLC mobile phase (0.1% acetic acid) was added. The resulting solution (total volume about 1.8-1.9 mL) was loaded onto the HPLC loop (2 mL) and injected into semi preparative HPLC column Ascentis RP-AMIDE, 5 µm, 250×10 mm (Supelco). The semi preparative column was equipped with a guard column to remove residual copper: Security Guard Cartridge AJO-8327-S in Guard Cartridge Holder KJO-4282 (Phenomenex). The column outlet was connected to an UV absorbance detector (λ=254 nm) in series with a radioactivity detector (module TRACERlab FX C Pro (GE Healthcare). After running HPLC with pure water (0-6 min) the mobile phase was changed to 0.1% CH_3COOH at a flow rate of 4 mL/min giving a radioactive fraction (4-5 mL volume) corresponding to pure 6-L-[^{18}F]FDOPA (R_t from 12 to 13 min). The product fraction with pH 4 was collected into a vented sterile vial pre-filled with 5 mL of sterile normal saline through the 0.22 µm Millipore filter.

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Keywords: Radiopharmaceuticals • Arenes • Copper mediated radiofluorination • Pinacol esters • 6-L-[^{18}F]FDOPA

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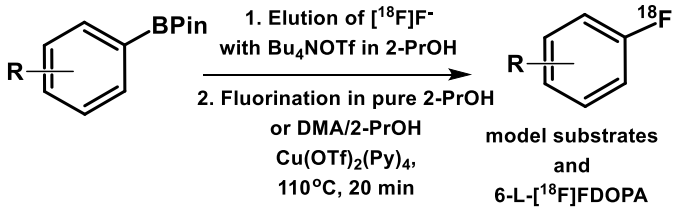
Entry for the Table of Contents



In this work we demonstrated for the first time the possibility of effective copper-mediated radiofluorination of aryl pinacoloboronate esters on the example of precursor for 6-L-[^{18}F]FDOPA in a neat alcohol using a neutral phase-transfer catalyst tetrabutyl ammonium triflate.