Nucleophilic synthesis of 6-[^{18}F]fluoro-L-DOPA via copper mediated radiofluorination

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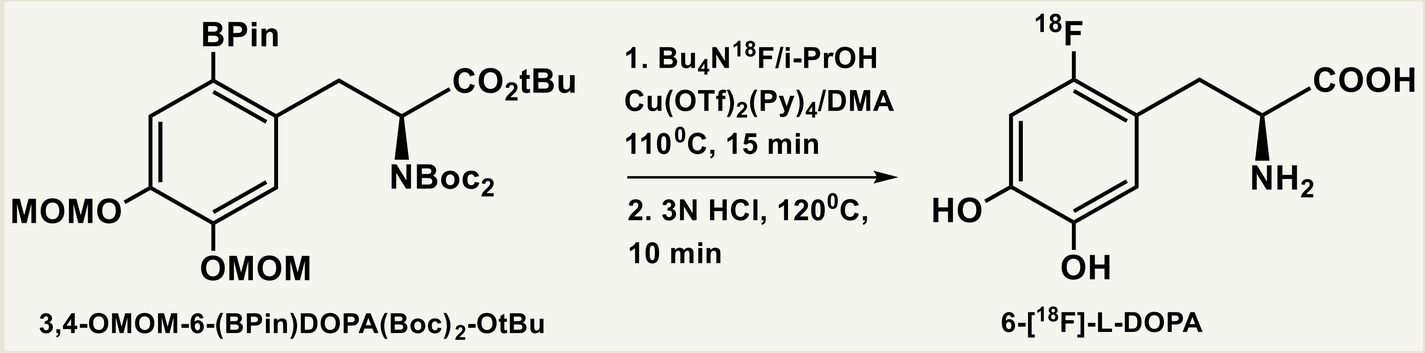
Background and objectives Radiopharmaceuticals for positron emission tomography (PET) bearing electron rich [^{18}F]fluorinated arenes are still in limited use as the direct introduction of [^{18}F]fluoride via commonly used S_NAr is not suitable. Recently, several transition metal-mediated labeling strategies have been introduced, to address this problem. Among them radiofluorination of pinacol esters of arylboronic acids (ArylBPin) mediated by copper triflate complex with pyridine [1] is one of the more promising synthetic avenues under development. This new methodology allows facilitate access to clinically relevant radiotracers, ^{18}F-ring fluorinated aromatic amino acids, drug-like molecules and others. However, implementation of the copper-mediated fluorination in automated synthesizers remains a challenging task. Several studies indicated that 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 ^{18}F-fluorination fluorination of base-sensitive ArylBPin precursors.

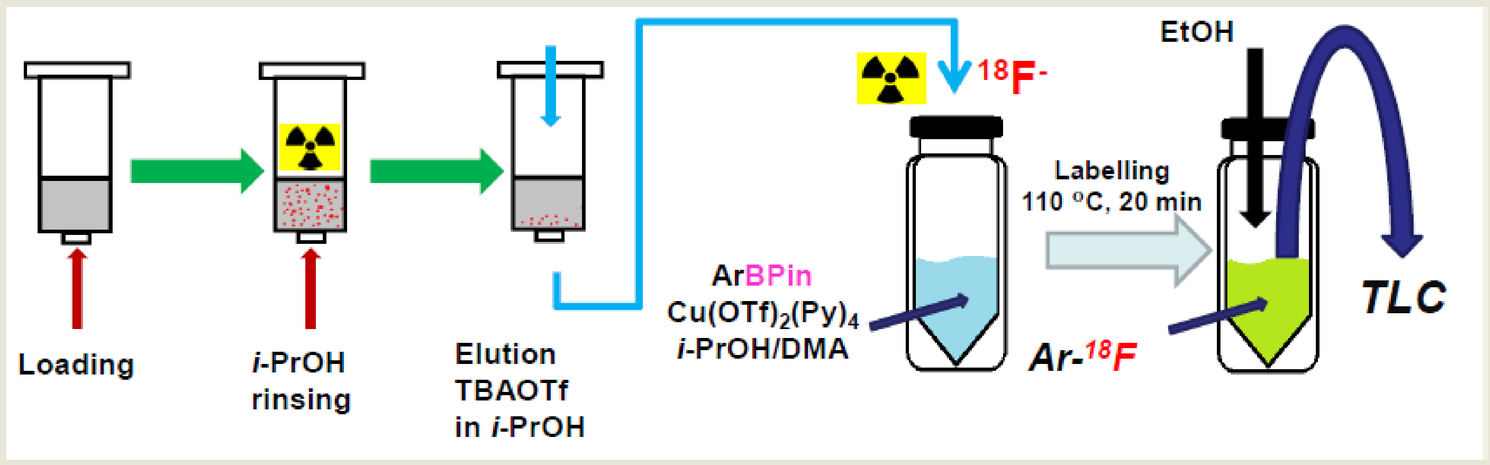
Here we introduce a new ^{18}F-processing protocol using tetrabutylammonium triflate (TBAOTf) as a neutral PTC and its application in the preparation of 6-[^{18}F]fluoro-L-DOPA *via* copper-mediated fluorination of commercially available ArylBPin precursor.



3,4-OMOM-6-(BPin)DOPA(Boc)$_2$-OtBu — 6-[^{18}F]-L-DOPA

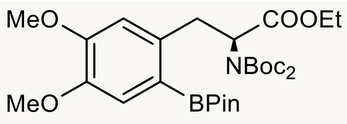
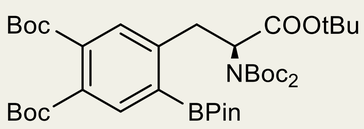
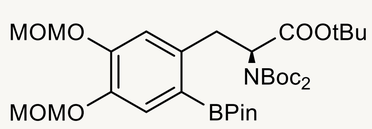
Methodology Radiolabeling precursor, 3,4-OMOM-6-(BPin)DOPA(Boc2)-OtBu (see labeling scheme), was kindly provided by ABX, Germany. Aqueous [^{18}F]fluoride was loaded onto QMA carb SepPak cartidge (46 mg) from the male side, the cartridge was rinsed by 1.5 mL of *i*-PrOH and dried with helium. $^{18}F^-$ was eluted in the opposite direction using a solution of 12.5 μmol of TBAOTf in 0.6 mL *i*-PrOH directly to a solution of 5 μmol of $Cu(OTf)_2Py_4$, 8 μmol of labeling precursor in 0.3 mL DMA. The mixture was heated in a sealed vial at 110°C for 15 min under air. After intermediate purification (two C18 SepPak cartridges in a series) and acid hydrolysis the crude 6-[^{18}F]fluoro-L-DOPA was purified by HPLC: RP-Amide, Supelco, 250 x 10 mm, NaOAc 10 mM + AcOH 50 mM + 0,1 g/l ascorbic acid; flow 4 ml/min; R_t 9 min.

- **no azeotropic drying or solvent evaporation steps**
- **direct fluorination in the *i*-PrOH/DMA**
- **easy to automate**



Results and discussion First, developed ^{18}F-processing protocol allowed eliminate conventional azeotropic drying step and facilitate automation. The use of TBAOTf as a PTC provides a high ^{18}F-elution efficiency (up to 90%) and radiochemical conversion (RCC) of 83±6 (n=7) as determined by radioTLC. The desired tracer was obtained in a RCY of 20% (non-optimized, corrected for decay), radiochemical purity > 97% and enantiomeric purity > 98% within 80 min synthesis time. Notably, the suggested procedure employed reduced amounts of expensive precursor (8 μmol) and Cu-catalyst (8 μmol). Work is now in progress to optimize hydrolysis and purification conditions to increase isolated radiochemical yield.

Table 1. Cu-mediated synthesis of 6-[^{18}F]fluoro-L-DOPA using different PTC/bases

Precursor	PTC, solvent	Azeotropic drying	Precursor, μmol	$Cu(OTf)_2(Py)_4$ μmol	RCC, %	Ref.
	K2.2.2/ $K_2C_2O_4/K_2CO_3$, CH_3CN, H_2O	Yes	22	20	-	[2]
	Et_4NHCO_3, *n*-BuOH	No	60	53	68	[3]
 (ABX, Germany)	Bu_4NOTf/ Cs_2CO_3, H_2O	Yes	4	20 + pyridine	55	[4]
	Bu_4NOTf, *i*-PrOH	**No**	**8**	**8**	**83±6 (n=7)**	**This work**

- **the use of TBAOTf provides high RCC value using lower amounts of expensive precursor and copper catalyst**
- **no residual copper in the final preparations**

References
1. Tredwell M., Preshlock S. M., Taylor N. J. et al., *Angew. Chem., Int. Ed.* ***2014***, 53: 7751
2. Preshlock S., Calderwood S., Verhoog S. et al., *Chem. Commun.*. ***2016,*** 52(54): 8361-4
3. Zischler J., Kolks D., Modemann B. et al., *Chem. Eur. J.*, ***2017***, 23(14): 3251-3256
4. Mossine A.V., Tanzey S.S., Brooks A.F. et al, *Org Biomol Chem*., ***2019***, 17(38): 8701-5

Conclusion The suggested novel ^{18}F-processing protocol enables the simple and efficient production of 6-[^{18}F]fluoro-LDOPA from commercially available ArylBPin precursor avoiding time consuming solvent evaporation steps. This method can be further extended for the preparation of other ^{18}F-ring fluorinated amino acids.