## Preparation of <sup>18</sup>F-labeled aromatic amino acids by copper-mediated radiofluorination

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**Objectives:** [<sup>18</sup>F]Fluorophenylamino acids exhibit great potential for diagnostic applications using PET. Nevertheless, their clinical application is still strongly restricted owing to cumbersome production methods. Recently novel transition metal-mediated <sup>18</sup>F-fluorination methods have been introduced into radiochemistry enabling to achieve radiofluorination of arenes regardless of their electronic properties [1]. The aim of this work was to develop a method for the efficient production of <sup>18</sup>F-labeled aromatic amino acids in high doses by means of alcohol-enhanced Cu(II)-mediated radiofluorination of arylboronic acid pinacol esters (PBE) [2].

**Methods:** The PBE precursors were synthesized by Miyaura borylation of the corresponding N-BOC protected iodoaromatic amino acid esters. The synthesis of  $6-[^{18}F]FDOPA$ ,  $L-2-[^{18}F]fluorophenylalanine$  ( $2-[^{18}F]FPhe$ ),  $6-[^{18}F]fluoro-L-meta$ -tyrosine ( $6-[^{18}F]FMT$ ) and  $5-[^{18}F]fluoro-L-meta$ -tyrosine ( $5-[^{18}F]FMT$ ) were performed with (py)<sub>4</sub>Cu(II)(OTf)<sub>2</sub> as catalyst. The labeling conditions were optimized with respect to temperature, solvent and amount of (py)<sub>4</sub>Cu(II)(OTf)<sub>2</sub>. The intermediates were purified by SPE and hydrolyzed with HCl affording after HPLC-purification the desired product.

**Results:** The precursors for radiolabeling were synthesized in overall yields of 3 to 17 %. The <sup>18</sup>F-labelling reactions were performed using *n*-butanol as a co-solvent improving the RCYs significantly. In the case of 6-[<sup>18</sup>F]fluoro-L-3,4-dihydroxyphenylalanine (6-[<sup>18</sup>F]FDOPA), RCY increased from 8 % (without the use of n-butanol for alcohol enhancement) to 40 % using alcohol-enhanced Cu(II)-mediated radiofluorination. Furthermore, the radiosynthesis of 2-[<sup>18</sup>F]FPhe, 6-[<sup>18</sup>F]FMT and 5-[<sup>18</sup>F]FMT using boronic acid pinacol esters was transferred to a remote-controlled synthesis device. High RCYs lead to product activities of 2.4–18.8 GBq enabling preclinical studies.

**Conclusions:** The combination of alcohol—enhanced and copper-mediated radiofluorination of BPE as labelling precursors was studied with regard to the automated synthesis of several aromatic amino acids.  $6-[^{18}F]FDOPA$ ,  $2-[^{18}F]FPhe$ ,  $6-[^{18}F]fluoro-L-meta$ -tyrosine ( $6-[^{18}F]FMT$ ) and  $5-[^{18}F]fluoro-L-meta$ -tyrosine ( $5-[^{18}F]FMT$ ) were obtained in high RCY of 40-66% and up to > 99% ee. This enables their synthesis in large amount of radioactivity and high radiochemical and enantiomeric purity, which is necessary for their use in preclinical studies.

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**References:** [1] S. Preshlock, M. Tredwell, V. Gouverneur, *Chem. Rev.* **2016**, *116*, 719-766. [2] J. Zischler, N. Kolks, D. Modemann, B. Neumaier, B. D. Zlatopolskiy, *Chem. - Eur. J.* **2017**, *23*, 3251-3256.

BocO 
$$(P)_4$$
Cu(II)(OTf)<sub>2</sub>  $(P)_4$ Cu(III)(OTf)<sub>2</sub>  $(P)_4$ Cu(III)(OTf)<sub>3</sub>  $(P)_4$ Cu(III)(OTf)<sub>4</sub>Cu(III)(OTf)<sub>4</sub>Cu(III)(OTf)<sub>4</sub>Cu(III)(OTf)<sub>4</sub>Cu(III)(OTf)<sub>4</sub>Cu(III)(OTf)<sub>4</sub>Cu(III)(OTf)<sub>4</sub>Cu(III)(OTf)<sub>4</sub>Cu(III)(OTf)<sub>4</sub>Cu(III)(OTf)<sub>4</sub>Cu(III)(OTf)<sub>4</sub>Cu(III)(OTf)<sub>4</sub>Cu(III)(OTf)<sub>4</sub>Cu(III)(OTf)<sub>4</sub>Cu(III)(OTf)<sub>4</sub>Cu(III)(OTf)<sub>4</sub>Cu(III)(OTf)<sub>4</sub>Cu(III)(OTf)<sub>4</sub>Cu(III)(OTf)<sub>4</sub>Cu(III)(OTf)<sub>4</sub>Cu(III)(OTf)<sub>4</sub>Cu(III)(OTf)<sub>4</sub>Cu(III)(OTf)<sub>4</sub>Cu(III)(OTf)<sub>4</sub>Cu(III)(OTf)<sub>4</sub>Cu(III)(OTf)<sub>4</sub>Cu(III)(OTf)<sub>4</sub>Cu(III)(OTf)<sub>4</sub>Cu(III)(OTf)<sub>4</sub>Cu(III)(OTf)<sub>4</sub>Cu(III)(OTf)<sub>4</sub>Cu(III)(OTf)<sub>4</sub>Cu(III)(OTf)<sub>4</sub>Cu(III)(OTf)<sub>4</sub>Cu(III)(OTf)<sub>4</sub>Cu(III)(OTf)<sub>4</sub>C