

Preparation of ^{18}F -labeled aromatic amino acids by copper-mediated radiofluorination



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Objectives:

- ^{18}F -Labeled aromatic amino acids exhibit high potential for diagnostic applications using PET.
- Lack of convenient preparation methods.

- The corresponding ^{18}F -labeled aromatic amino acids were obtained in 40–66 % RCY within 110 to 120 min (cf. Table 1).
- Enantiomeric excess (ee) of 2- ^{18}F FPhe, 6- ^{18}F FDOPA and 6- ^{18}F FMT > 94 %.

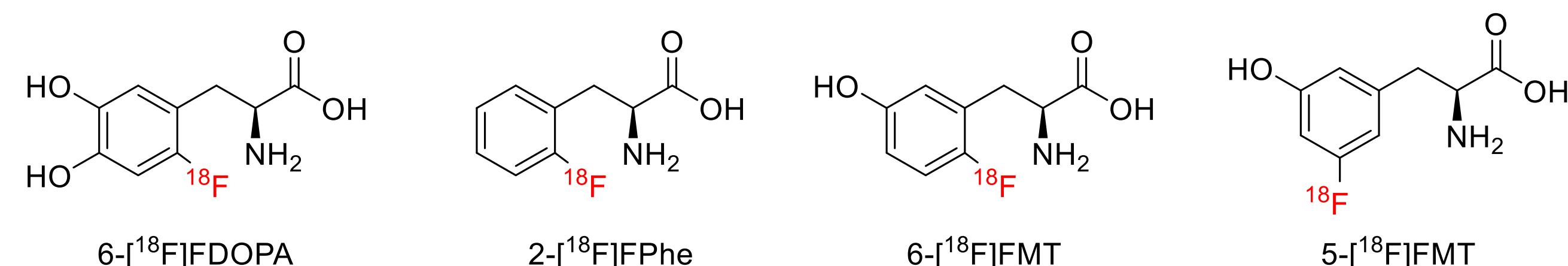


Fig. 1: Structures of studied ^{18}F -labeled aromatic amino acids prepared within this study

Aim: Development of a practical procedure for the preparation of ^{18}F -labeled aromatic amino acids on a preparative scale.

Methods:

- Synthesis of pinacol boronate ester (Bpin) precursors synthesized by Miyaura borylation.

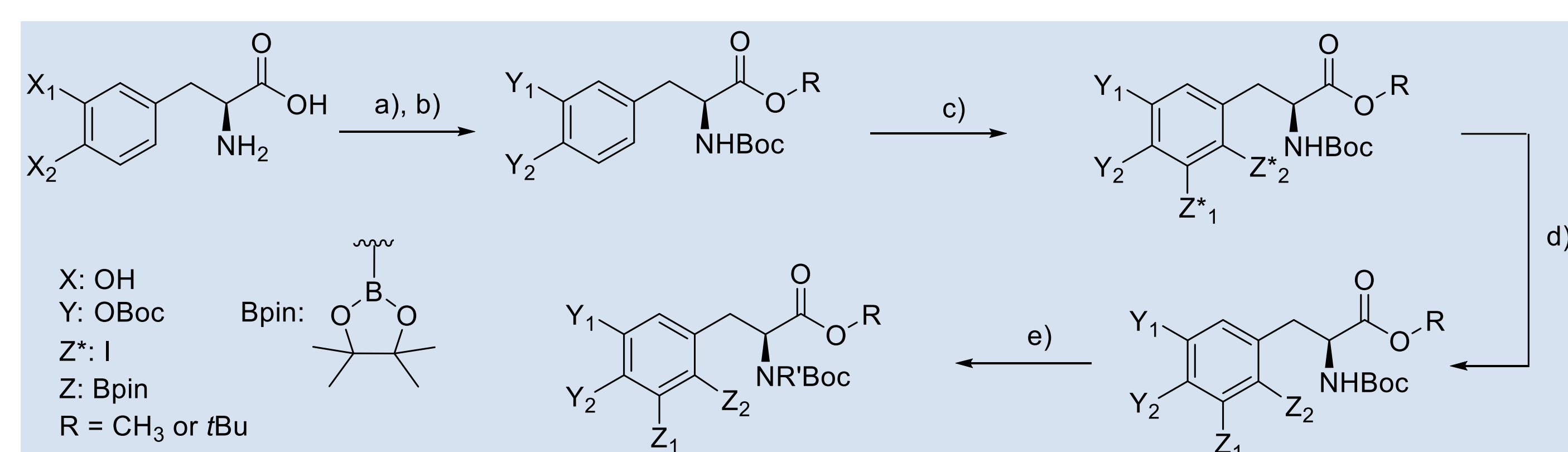


Fig. 2: Synthesis of Bpin precursors for 6- ^{18}F FDOPA 1, 2- ^{18}F FPhe, 5- and 6- ^{18}F FMT; conditions: a) (for R= tBu) AcOtBu, HClO_4 . b) Boc_2O , c) BTI, I_2 in DCM d) B_2pin_2 , $\text{Pd}(\text{dppf})\text{Cl}_2$, KOAc in DMF, e) 4-DMAP, Boc_2O in MeCN.

Bpin precursor for 6- ^{18}F FDOPA: $\text{X}_{1,2} = \text{OH}$, $\text{Y}_{1,2} = \text{OBoc}$, $\text{Z}_1 = \text{H}$, $\text{Z}_2 = \text{Bpin}$, $\text{R} = \text{tBu}$, $\text{R}' = \text{Boc}$;
Bpin precursor for 2- ^{18}F FPhe: $\text{X}_{1,2} = \text{H}$, $\text{Y}_{1,2} = \text{H}$, $\text{Z}_1 = \text{H}$, $\text{Z}_2 = \text{Bpin}$, $\text{R} = \text{tBu}$, $\text{R}' = \text{Boc}$;
Bpin precursor for 6- ^{18}F FMT: $\text{X}_1 = \text{OH}$, $\text{X}_2 = \text{H}$, $\text{Y}_1 = \text{OBoc}$, $\text{Y}_2 = \text{H}$, $\text{Z}_1 = \text{H}$, $\text{Z}_2 = \text{Bpin}$, $\text{R} = \text{tBu}$, $\text{R}' = \text{Boc}$;

Bpin precursor for 5- ^{18}F FMT: $\text{X}_1 = \text{OH}$, $\text{X}_2 = \text{H}$, $\text{Y}_1 = \text{OBoc}$, $\text{Y}_2 = \text{H}$, $\text{Z}_1 = \text{Bpin}$, $\text{Z}_2 = \text{H}$, $\text{R} = \text{CH}_3$, $\text{R}' = \text{H}$.

- Alcohol-enhanced Cu-mediated radiofluorination with $\text{Cu}(\text{Py})_4(\text{OTf})_2$:^{1,2}
 - $^{18}\text{F}\text{F}^-$ fixed on a QMA-cartridge and eluted with Et_4NHCO_3 (1 mg) in MeOH with subsequent MeOH evaporation.
 - Addition of precursor (10 μmol) and $\text{Cu}(\text{Py})_4(\text{OTf})_2$ (20 μmol) in a mixture of DMA (500 μL) and *n*-BuOH (250 μL).
 - Heating to 110 °C for 20 min.
 - Hydrolysis with HCl (10.8 mol, 0.8 mL) 80 °C for 10 min.
 - HPLC-separation: Phenomenex Hydro-RP 4 μm 80 Å (4.6x250mm) column with 2 % EtOH 2- ^{18}F FPhe and 5- ^{18}F FMT) or 1 % EtOH: 6- ^{18}F FMT (1 mL/min); Hamilton PRP-C18 (10x250 mm); 6- ^{18}F FDOPA: 0.05 M $\text{HCl}_{(\text{aq})}$ (3 mL/min).

Results and Discussion:

- Labeling precursors prepared in total yields of 5–17 % in 3–5 steps.
- N,N*-Boc precursors of 6- ^{18}F FDOPA, 2- ^{18}F FPhe and 6- ^{18}F FMT enabled more efficient radiosynthesis of the corresponding ^{18}F -labeled tracers in contrast to mono-Boc protected ones.
- During the copper-mediated ^{18}F -for-Bpin radiofluorination partial deprotection (loss of one Boc-group) (see Fig. 3).

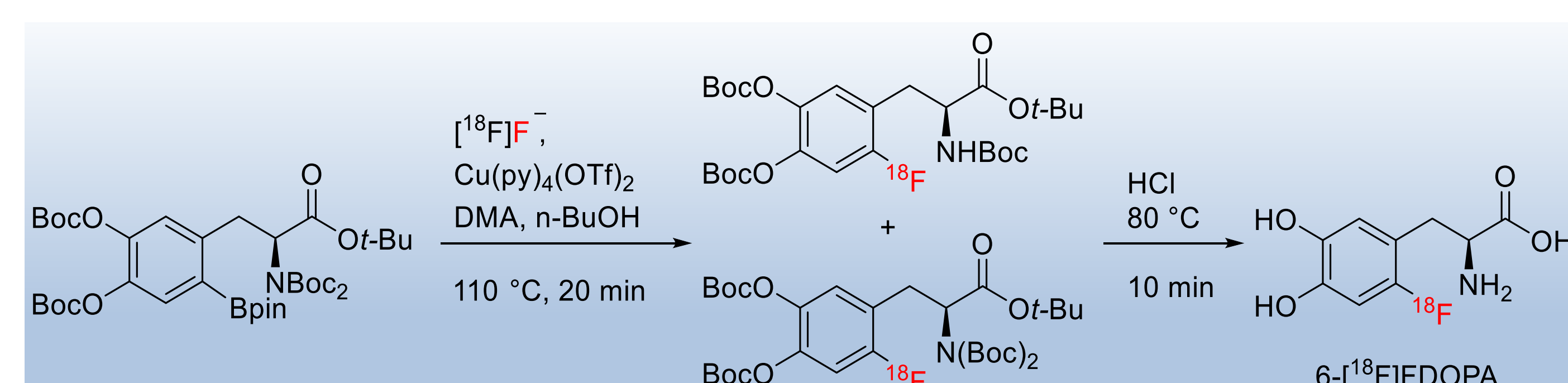


Fig. 3: Preparation of 6- ^{18}F FDOPA.

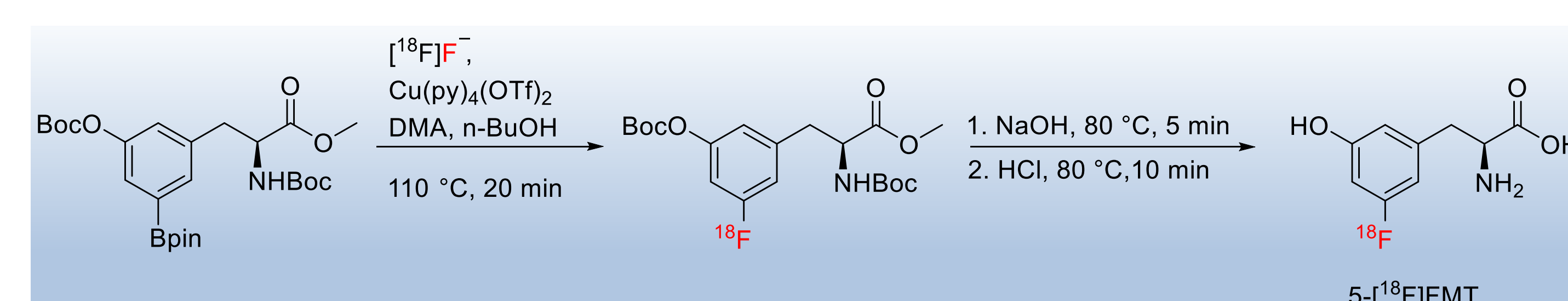
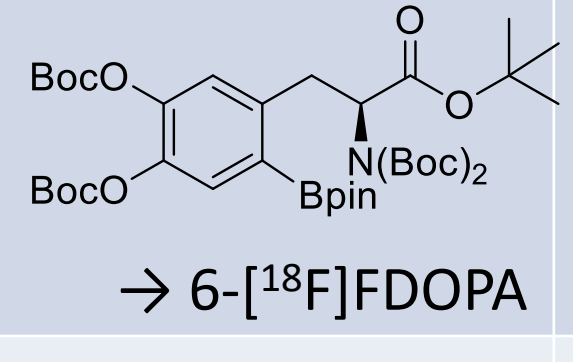
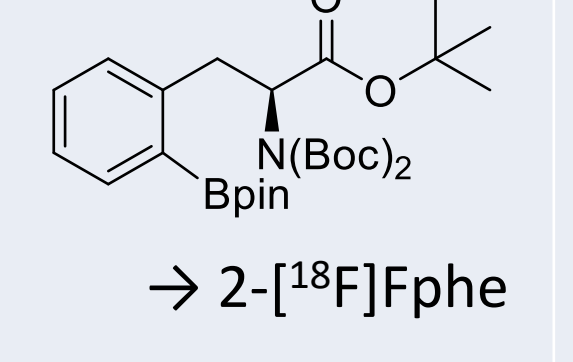
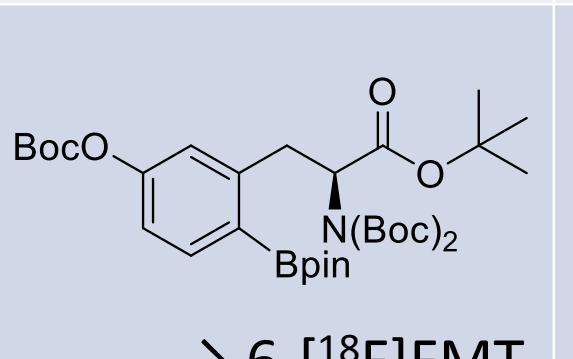
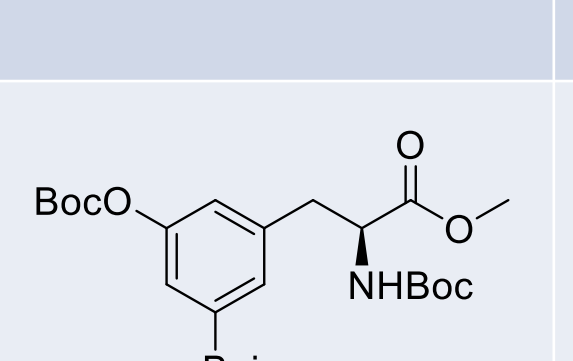


Fig. 4: Preparation of 5- ^{18}F FMT.

- Successful transfer of the novel method into an automated synthesis module for the production of 2- ^{18}F FPhe, 5- and 6- ^{18}F FMT in 31–50 % RCY (see Tab. 1).

Tab. 1: Summary of results

Precursor →Tracer	RCY (manually)	RCY (automated)	Molar activity	ee
 → 6- ^{18}F FDOPA	40 ± 4 % 110 min (n = 3)	n. d.	37 GBq/ μmol	> 99 %
 → 2- ^{18}F FPhe	57 ± 6 % 110 min (n = 3)	31 ± 6 % 110 min (n = 3)	185 GBq/ μmol	> 99 %
 → 6- ^{18}F FMT	48 ± 5 % 110 min (n = 3)	41 ± 8 % 110 min (n = 4)	251 GBq/ μmol	> 99 %
 → 5- ^{18}F FMT	66 ± 1 % 120 min (n = 3)	50 ± 2 % 120 min (n = 3)	121 GBq/ μmol	94 %

Summary:

Convenient production of ^{18}F -labeled aromatic amino acids using alcohol enhanced Cu-mediated radiofluorination enabling the production of 6- ^{18}F FDOPA, 2- ^{18}F FPhe, 6- ^{18}F FMT and 5- ^{18}F FMT, in high amounts, sufficient for preclinical and clinical applications.

References:

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

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