Electronic Supplementary Material (ESI) for Reaction Chemistry & Engineering.

Supplemental Information:
Green and efficient synthesis of the radiopharmaceutical [^{18}F]FDOPA using a microdroplet reactor

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1 Optimization of fluorination step

Optimization of the fluorination step using the manual setup is summarized in **Fig. 4** of the main paper, in which overall fluorination yield is plotted as a function of several reaction variables. In **Fig. S1**, we plot the corresponding fluorination efficiency and radioactivity recovery values.

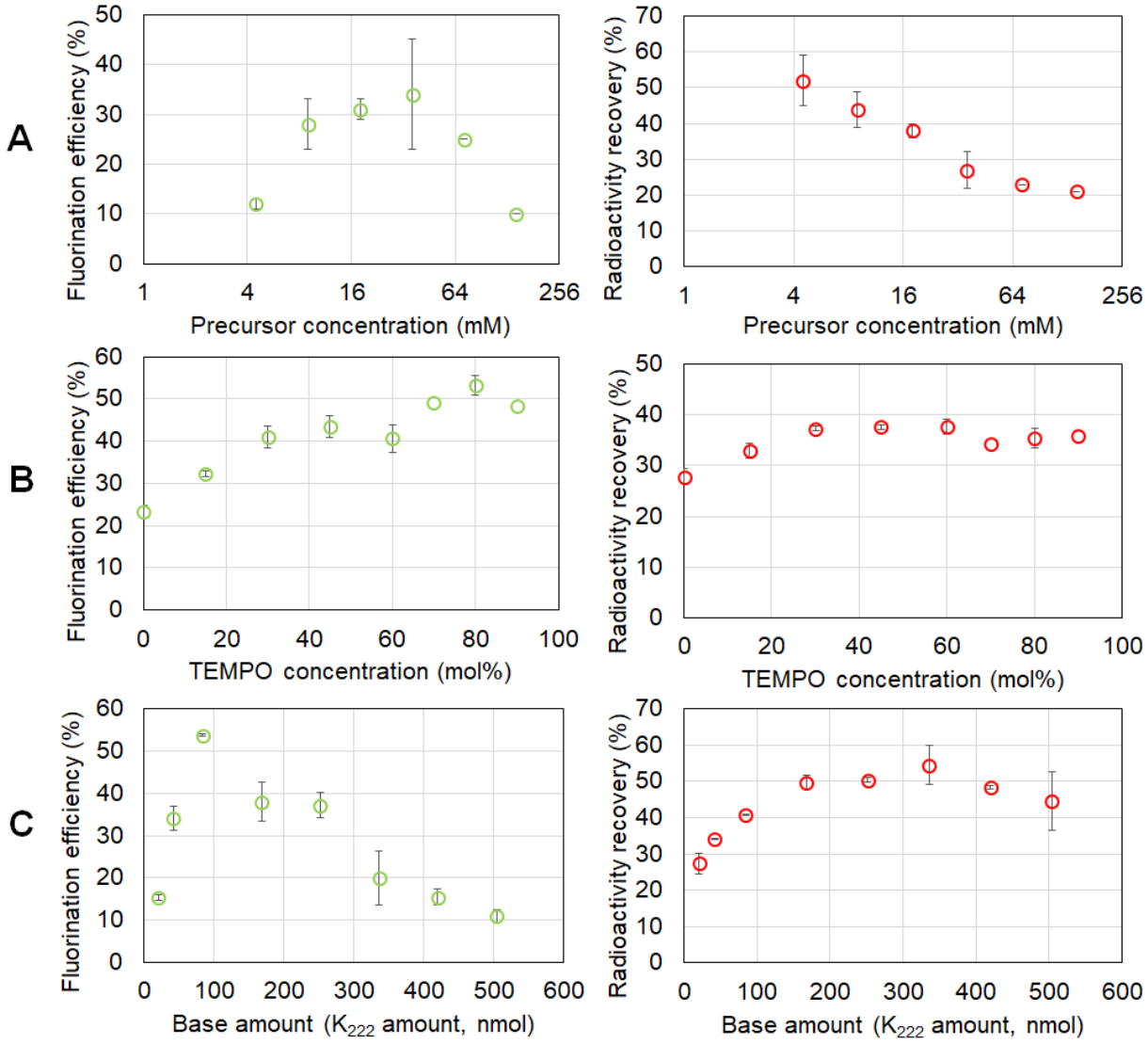

Figure S1. Optimization of microdroplet synthesis of [^{18}F]FDOPA using the manual setup. (A) Effect of precursor concentration on fluorination efficiency and radioactivity recovery. Number of repeats (n) for data points are 2, 3, 3, 2, 1, 1, in order of increasing precursor amount. (B) Effect of TEMPO concentration on fluorination efficiency and radioactivity recovery. n=2 for all points except 70 and 90% mol% (where n=1). (C) Effect of base amount on fluorination efficiency and radioactivity recovery, represented by K_{222} amount (K_2CO_3 amount is 2.05x lower). n=2 for all points. In all plots, data points represent averages and error bars represent standard deviations.

2 Optimization of deprotection step

Using single-reaction microfluidic chips, the influence of several deprotection reaction parameters was investigated, including type of acid (HCl and H_2SO_4), acid concentration, reaction time, and reaction temperature. These experiments were performed prior to complete optimization of the fluorination step, and used 84 nmol K_{222}, 41 nmol K_2CO_3, 36 mM precursor, and 20 mol% TEMPO. Results are tabulated in **Table S1**.

Table S1. Effect of various deprotection conditions (without cover plate). Radioactivity loss indicates the combined activity losses (due to formation of volatile species) during evaporation, fluorination and deprotection steps. Percentages are corrected for decay. For most conditions, only n=1 experiment was performed. * indicates n=2 replicates were performed, and values indicate average ± standard deviation.

Deprotection reagent	HCl				H_2SO_4			
Concentration (M)	6				3	6		
Deprotection time (min)	5	10	15	15	5	5		
Deprotection temperature (°C)	90	90	90	100	100	120*	130	140
Radioactivity loss (%)	86	88	86	88	78	84 ± 3	90	87
Residual activity on chip (%)	3	1	2	1	3	3 ± 1	2	2
Radioactivity recovery (%)	8	8	10	8	15	9 ± 1	6	7
[^{18}F]FDOPA conversion (%)	24	37	53	72	42	87 ± 1	83	92
Crude RCY (%)	2.0	3.1	5.2	5.5	6.3	7.2 ± 0.5	4.9	6.8
Isolated RCY (%)	1.4	2.7	4.0	4.5	4.5	4.8 ± 0.6	3.2	3.7

For some experiments, a cover chip consisting of a Teflon-coated glass slide (25 mm x 25 mm) was positioned 150 µm above the reaction mixture (resting on spacers along the chip edges) to reduce evaporation (**Figure S2**). In these experiments, extra dilution and collection processes were performed to recover the crude product from the cover chip as well as the (bottom) chip. A detailed comparison of the reaction performance with and without the cover chip is summarized in **Table S2**.

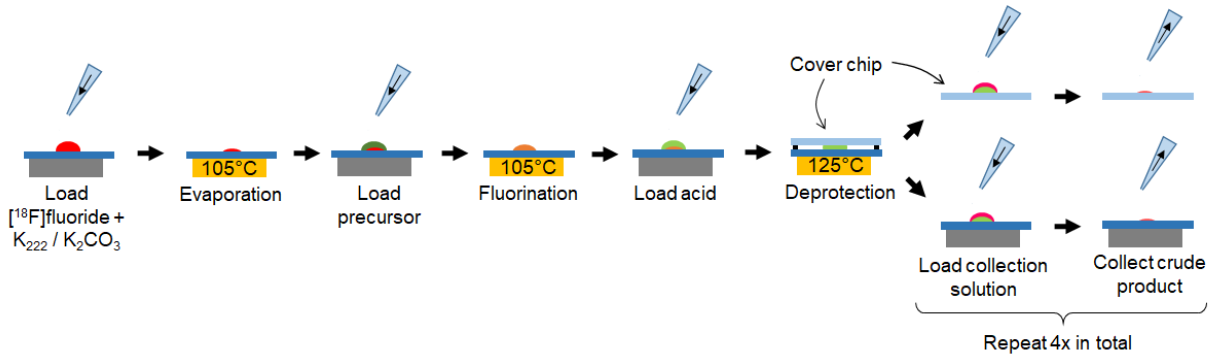

Figure S2. Schematic of [^{18}F]FDOPA synthesis process when a cover chip is used during the deprotection step.

Table S2. Effect of cover plate on the synthesis performance. Radioactivity loss indicates the combined activity losses (due to formation of volatile species) during evaporation, fluorination and deprotection steps. Percentages are corrected for decay. Values of the group "with cover chip" indicate average ± standard deviation computed from the indicated number of replicates.

	No cover chip (n=1)	**With cover chip (n=2)**
Radioactivity loss (%)	84	53.7 ± 0.4
Residual activity on cover chip (%)	NA	26 ± 2
Residual activity on bottom chip (%)	3	1.5 ± 0.2
Radioactivity recovery (%)	12	17 ± 2
[^{18}F]FDOPA conversion (%)	91	84 ± 5
Crude RCY (%)	11.0	14.3 ± 0.5
Isolated RCY (%)	7.2	10.0 ± 0.7

3 Molar activity determination

A calibration curve was generated for molar activity determination. FDOPA reference standard was dissolved in the HPLC mobile phase to make a solution with final concentration 20 µM. Different volumes of this solution (10, 20, 25, 30, 40 µL) were injected into the HPLC, and area under the FDOPA peak in the chromatogram was determined for each. Areas was plotted as a function of amount of FDOPA injected and a linear least-squares fit was calculated (shown in **Figure S3**, R^2=0.9933).

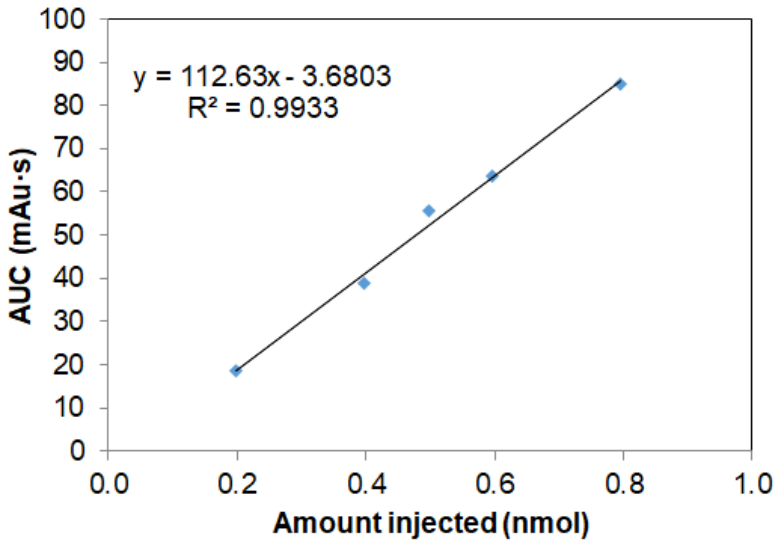

Figure S3. Calibration curve for determining molar activity of FDOPA. AUC= area under the curve.