



Cite this: *Chem. Commun.*, 2025, 61, 19505

Received 19th July 2025,  
Accepted 12th November 2025

DOI: 10.1039/d5cc03503a

rsc.li/chemcomm

**This study introduces a mild method for the direct decarboxylative  $^{18}\text{F}$ -fluorination of (hetero)aromatic carboxylic acids via a photo-induced ligand-to-metal charge transfer (LMCT) process. The method allows for the successful  $^{18}\text{F}$ -labeling of various benzoic acids (16–40% RCC) and the full-batch preparation of 1-fluoro-4- $^{18}\text{F}$ fluorobenzene with an overall RCY of  $27 \pm 2\%$ .**

The aryl halide functional group has found widespread application in organic chemistry. In particular, (hetero)aryl fluorides are of importance in drug discovery because of significant improvements in the biological properties, including membrane permeability, *in vivo* metabolic stability and protein binding affinities.<sup>1</sup> This remarkable role of fluorinated molecules is aptly demonstrated by the FDA approval of thirteen aryl fluoride-containing small molecule drugs in the past three years.<sup>2</sup> The presence of fluorine in clinically successful small molecule drugs is of great interest for positron emission tomography (PET). Upon substitution of the fluorine atom by its positron emitting fluorine-18 isotope ( $t_{1/2} = 110$  minutes), a putative PET tracer is obtained without alteration of the original structure. PET enables the non-invasive visualization of physiochemical and pathological processes *in vivo* at a molecular level and is an essential imaging technology within patient care, clinical research and drug development.

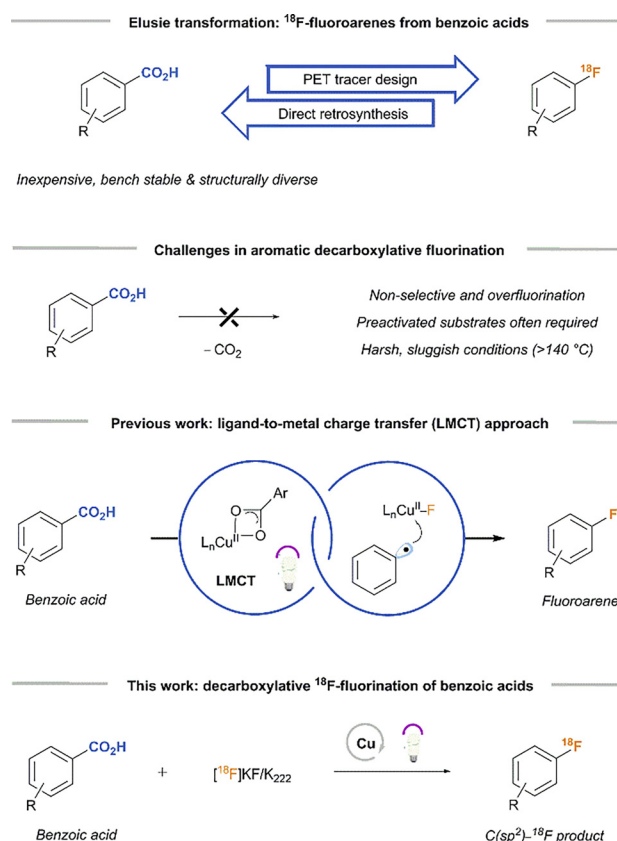
Traditionally, simple aryl [ $^{18}\text{F}$ ]fluorides are mainly accessed via the Balz-Schiemann reaction, the nucleophilic aromatic substitution of a nitro or tri-alkyl ammonium group positioned *ortho* or *para* to an electron-withdrawing group, or the Halex process.<sup>3</sup> However, the harsh reaction conditions generally limit the reaction scope. Structurally diverse aryl [ $^{18}\text{F}$ ]fluorides have been prepared under milder reaction conditions by Cu-mediated  $^{18}\text{F}$ -fluorination of aryl boronates, stannanes, iodides, iodonium ylides and sulfonium salts.<sup>3,4</sup> However, accessing aryl [ $^{18}\text{F}$ ]fluorides from native functional groups is

## Direct decarboxylative $^{18}\text{F}$ -fluorination of benzoic acids using visible light catalysis

Lizeth Y.F. Haveman,<sup>1</sup> \* Cornelis A. J. Broersen,<sup>1</sup> Danielle J. Vugts<sup>1</sup> and Albert D. Windhorst<sup>1</sup>

still a challenge. Along these lines, benzoic acids are attractive precursors because of their abundance, structural diversity and accessibility from commercial sources. Yet, no chemistry is available for the  $^{18}\text{F}$ -fluorination of arenes with benzoic acids as a starting point and, as such, remains an important radio-synthetic challenge (Fig. 1).

In the organic chemistry fluorodecarboxylation methods rely on poorly selective electrophilic fluorine reagents or metal



**Fig. 1** Direct decarboxylative  $^{18}\text{F}$ -fluorination of (hetero)aryl carboxylic acids via Cu-LMCT catalysis as a strategy for PET tracer synthesis.

Department of Radiology & Nuclear Medicine, Amsterdam UMC, Vrije Universiteit Amsterdam, De Boelelaan, 1117, Amsterdam, The Netherlands.  
E-mail: l.haveman1@amsterdamumc.nl



mediators and often necessitate *ortho*-substituted substrates and high reaction temperatures of  $>140\text{ }^{\circ}\text{C}$  (Fig. 1).<sup>5,6</sup> Hence, the potential transformation of such strategies into  $^{18}\text{F}$ -radiolabeling methods is limited. Moreover, translational difficulties are associated with the slow decarboxylation rate of benzoic acids, conflicting with the short half-life of  $^{18}\text{F}$ -fluoride. Recently, several research groups demonstrated that UV light-induced ligand-to-metal charge transfer (LMCT) activation is a powerful and mild approach to an oxygen-centered aryl carboxylate radical (Fig. 1).<sup>5–9</sup> This *O*-centered radical can release  $\text{CO}_2$  to generate the corresponding aryl radical intermediate, which is then captured by a copper(II) salt to form a high-valent arylcopper(III) fluoride complex. Facile  $\text{C}(\text{sp}^2)\text{-F}$  reductive elimination from this complex affords the desired aryl fluoride at room temperature.

We sought to take advantage of this mild fluorodecarboxylation method to develop a strategy for the direct  $^{18}\text{F}$ -fluorination of benzoic acids *via* the combination of a copper salt, a 365 nm LED light source and a  $^{18}\text{F}$ -fluoride source (Fig. 1). However, transitioning from  $^{19}\text{F}^-$  to  $^{18}\text{F}\text{F}^-$  changes the stoichiometric conditions of the reaction and therefore necessitated a re-examination of the fluoride source and irradiation method. With 4-fluorobenzoic acid (**1**) as the aryl carboxylic acid substrate, we were able to obtain 18% of fluorinated adduct ( $^{19}\text{F}$ **2**) together with the byproducts fluorobenzene (**3**) and 4-fluorophenyl-4-fluorobenzoate (**4**) using  $\text{Cu}(\text{OTf})_2$ ,  $[\text{Cu}(\text{MeCN})_4]\text{BF}_4$  and TBAF ( $t\text{BuOH}$ )<sub>4</sub> (**5**) under inert conditions and a reaction time of 6 hours. We attribute the low yield (compared to 70% as reported by Xu *et al.*) mainly to the absence of a glovebox in the lab, which makes careful handling of the highly air-sensitive copper and fluoride reagents difficult.<sup>5</sup> Although the initial yields were relatively low, potassium fluoride (KF) was an effective fluorinating agent in the synthesis of  $^{19}\text{F}$ **2** ( $31 \pm 4\%$ ). Replacing the 365 nm Kessil lamps with the commercially available “Photo-RedOx Box” photoreactor (365 nm LEDs) resulted in similar conversions ( $34 \pm 1\%$ , see SI for details). Hence, decarboxylative fluorination with KF in a photoreactor was feasible and thus we extended the method to  $^{18}\text{F}$ -radiofluorination.

A mixture of **1** (25  $\mu\text{mol}$ ),  $[\text{Cu}(\text{MeCN})_4]\text{BF}_4$  (2.5 eq),  $\text{Cu}(\text{OTf})_2$  (2.5 eq), KF (2.5 eq) and  $^{18}\text{F}\text{KF}/\text{K}_{222}$  in 1.0 mL MeCN was exposed to 365 nm LED irradiation for 2 h and the desired  $\text{C}(\text{sp}^2)\text{-}^{18}\text{F}$  product ( $^{18}\text{F}$ **2**) was obtained in  $24 \pm 6\%$  radiochemical conversion (RCC) (Table 1, entry 1).<sup>10,11</sup> While control experiments revealed that the copper(II) salt and purple-light irradiation were all individually necessary (Table 1, entries 2–4), the absence of an inert atmosphere and 30 minutes pre-stirring of the reaction mixture before adding  $^{18}\text{F}\text{F}^-$  showed no significant effect on the RCC (Table 1, entries 5 and 6). In contrast, drying of the reaction vial equipped with a stir bar,  $\text{Cu}(\text{OTf})_2$  and KF at  $150\text{ }^{\circ}\text{C}$  for 2 hours prior to use was necessary to obtain reliable conversions, since omission resulted in decreased product formation (Table 1, entry 7). As expected water proved to be deleterious to the reaction, as no product was observed when a 9/1 MeCN/ $\text{H}_2\text{O}$  stock solution of  $\text{K}_2\text{CO}_3/\text{K}_{222}$  was used for the trapping (see SI for details). The trapping solution also required a minimum of 2 mM  $\text{K}_2\text{CO}_3$

**Table 1** Optimization of the  $^{18}\text{F}$ -fluorodecarboxylation of 4-fluorobenzoic acid and control reactions<sup>a</sup>

Entry	Deviations	RCC
1	None	$24 \pm 6\%$
2	No $\text{Cu}(\text{OTf})_2$	0%
3	No light	0%
4	455 nm instead of 365 nm	0%
5	No Ar sparge	$25 \pm 3\%$
6	No pre-stirring	$24 \pm 3\%$
7	No drying of chemicals and vial	$18 \pm 2\%$
8	$^{18}\text{F}$ TBAF instead of $^{18}\text{F}\text{KF}/\text{K}_{222}$	$22 \pm 2\%$
9	2.0 eq. $\text{Cu}(\text{OTf})_2$ , 1.5 eq. $[\text{Cu}(\text{MeCN})_4]\text{BF}_4$ and KF	$30 \pm 2\%$
10	Entry 9 without $[\text{Cu}(\text{MeCN})_4]\text{BF}_4$	$24 \pm 1\%$
11	Entry 9 without KF	0%
12	Entry 9 with 4 h irradiation	$46 \pm 0\%$
13	Entry 9 with 12.5 mM MeCN	$34 \pm 3\%$

Formed (by)products		
1,4-difluorobenzene ( <b>2</b> )	Fluorobenzene ( <b>3</b> )	4-fluorophenyl-4-fluorobenzoate ( <b>4</b> )

<sup>a</sup> Conditions: 25  $\mu\text{mol}$  scale with 2 h drying of  $\text{Cu}(\text{OTf})_2$  and  $^{19}\text{F}$ -source at  $150\text{ }^{\circ}\text{C}$ , Ar sparge and 30 minutes pre-stirring. Radiochemical conversions determined by radio-HPLC, mean  $\pm$  standard deviation,  $n = 3$ . See SI for experimental details.

and 4 mM  $\text{K}_{222}$  in order to completely transform the triflyl  $^{18}\text{F}$ -fluoride to  $^{18}\text{F}\text{KF}/\text{K}_{222}$  and prevent diminished conversions (see SI for details). Alternative  $^{18}\text{F}$ -sources, *e.g.*  $^{18}\text{F}$ TBAF also afforded the desired product (Table 1, entry 8), but extensive drying had to be performed in order to completely remove water used in the eluents to ensure good conversions. Surprisingly, more soluble  $^{19}\text{F}$ -carriers such as tetramethylammonium fluoride (TMAF) and tetrabutylammonium difluorotriphenylsilicate (TBAT) were not as efficient as KF, presumably due to the strong hygroscopic character of TMAF and fluorodesilylation performed by the difluorotriphenylsilicate ion in TBAT (see SI for details).

A survey of the amounts of copper catalysts and KF showed that a reduction in  $\text{Cu}(\text{OTf})_2$ ,  $[\text{Cu}(\text{MeCN})_4]\text{BF}_4$  and KF equivalents led to an improved RCC of  $30 \pm 2\%$  (Table 1, entry 9) (see SI for details). Similarly to Xu *et al.*, a slight decrease in RCC was observed when  $[\text{Cu}(\text{MeCN})_4]\text{BF}_4$  was removed from the reaction (Table 1, entry 10), however the effect of  $\text{Cu}(\text{I})$  ability to capture aryl radicals and suppress the formation of the proto-decarboxylated product **3** appeared to be minimal under optimized reaction conditions.<sup>5</sup> Hence, the presence of  $[\text{Cu}(\text{MeCN})_4]\text{BF}_4$  is not necessary for obtaining high conversions and can be excluded for the purpose of operational



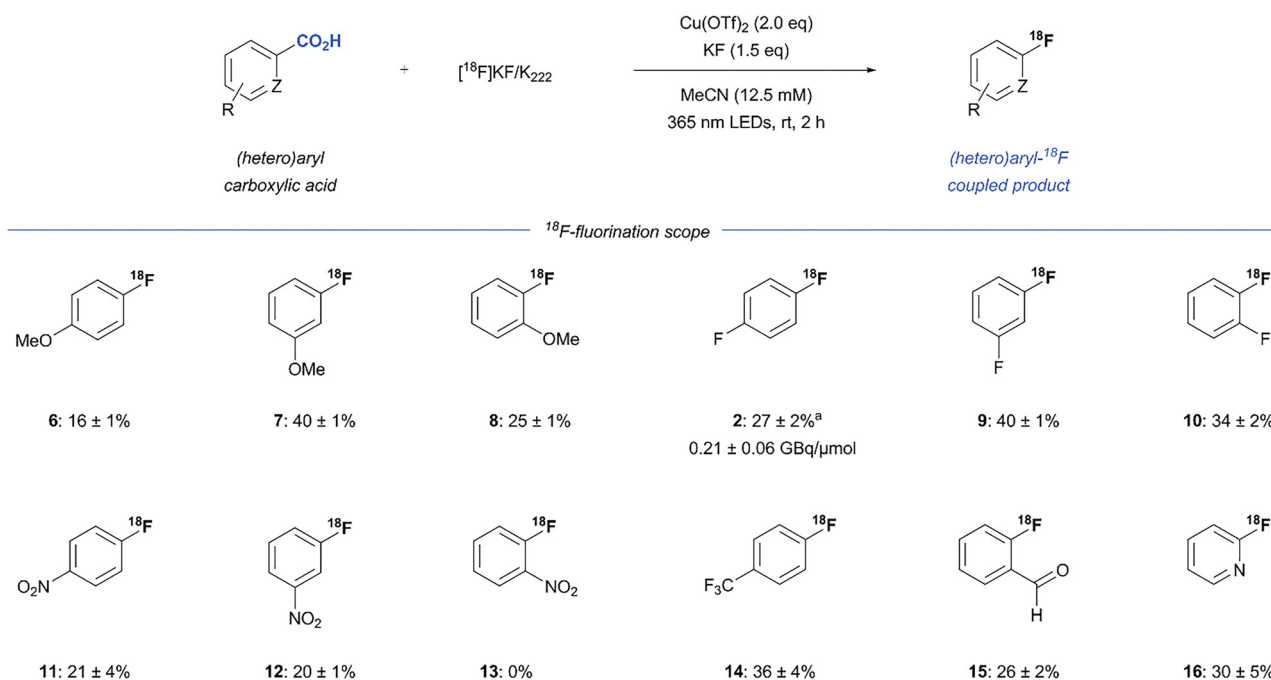
simplicity. We observed that the presence of exogenous fluoride anion ( $F^-$ ) proved critical to the overall success of the reaction (Table 1, entry 11). Since in our hypothesized mechanism KF also acts as the base to generate the carboxylate, which then coordinates to copper(II) and readily forms photoactive copper(II) carboxylates, several stoichiometric bases were investigated in order to make the transformation carrier-free. Unfortunately, neither  $Me_4NHCO_3$  nor  $K_2CO_3$ , DBU or BTMG in the absence of KF were able to provide the desired  $^{18}F$ -adduct (see SI for details).

Although the  $^{18}F$ -fluorodecarboxylation protocol requires rather long reaction times, already after 30 minutes  $16 \pm 3\%$  product could be observed (see SI for details). Whilst not interesting from a PET imaging perspective, elongating the reaction time to 4 hours resulted in a further increase of the RCC to  $46 \pm 0\%$  (Table 1, entry 12). Since the yield significantly increases over time, longer reaction times in the presence of low amounts of KF can be considered in case the molar activity is an important goal, however at the expense of loss of  $[^{18}F]F^-$  due to the decay.

Lastly, investigating the influence of the precursor concentration identified substrate **1** ( $12.5 \mu\text{mol}$ ) with a combination of  $[^{18}F]KF/K_{222}$  derived from triflyl  $[^{18}F]$ fluoride,  $Cu(OTf)_2$  (2.0 eq), KF (1.5 eq) and 365 nm LED light in 1.0 mL MeCN as optimal. After 2 h, the  $^{18}F$ -fluorinated product  $[^{18}F]\mathbf{2}$  was obtained in  $34 \pm 3\%$  RCC (Table 1, entry 13). Notably, an increase in the concentration of precursor to  $25 \mu\text{mol}$  resulted in a significant drop in RCC ( $24 \pm 1\%$ ) (see SI for details). This observation suggests the importance of maintaining a balanced amount of substrate for a successful  $^{18}F$ -fluorodecarboxylation. We

postulate that in the presence of higher concentrations of precursor, oxidecarboxylation *via* C–O reductive elimination of the aryl-copper(III) intermediate with **1** is favored over the formation of the desired  $^{18}F$ -adduct, resulting in the formation of **4**.

After investigation of the reaction conditions, we explored the substrate scope of aryl decarboxylative  $^{18}F$ -fluorination (Scheme 1). This approach proved generally competent for benzoic acids with electron-donating (**6–8**, 16–40%), electron-neutral (**2**, **9** and **10**, 34–40%) and electron-withdrawing (**11–15**, 20–36% RCC) substituents on the aryl ring. Notably, electron-deficient rings with a high oxidative potential are generally known to be problematic for photoinduced radical decarboxylation, but the oxidation-sensitive aldehyde **15** was successfully  $^{18}F$ -fluorinated ( $26 \pm 2\%$ ) with this approach. As shown in Scheme 1, *para*- and *meta*-substituted aryl carboxylic acids generated  $^{18}F$ -adducts in good yields (**2**, **6**, **7**, **9**, **11**, **12** and **14**, 16–40%). Moreover, the efficiency of the reaction was not hindered by *ortho* substitution on the aryl ring (**8**, **10** and **15**, 25–34%), except in case of the relatively large and strongly electron-withdrawing nitro-group (**13**, 0%). Lastly, this copper-mediated protocol was effective for the heterocyclic substrate picolinic acid, furnishing the  $^{18}F$ -fluorinated derivative **16**, a widely used scaffold in drug discovery, in  $30 \pm 5\%$  RCC. Due to solubility issues, the pyridine-derived substrates nicotinic and isonicotinic acid were not successfully functionalized. Although we believe that the selected examples show a representative range of electronic and steric demands relevant to bioactive molecules, this method will show limitations inherent to copper-catalysis. We do notice that functionalities strongly



**Scheme 1** Scope of the direct decarboxylative  $^{18}F$ -fluorination of (hetero)aryl carboxylic acids *via* photoredox catalysis. Radiochemical conversions were determined by radio-HPLC of the crude mixtures. Reactions were performed at least three times ( $n = 3$ ) and are given in the form mean  $\pm$  standard deviation.<sup>a</sup> Radiochemical yield, mean  $\pm$  SD,  $n = 3$ . See SI for experimental details.



coordinating to copper or undergoing rapid redox reactions, *e.g.* free amines and hydroxyl groups, will generally not be tolerated by this method and do need to be protected. In addition, polar groups like amides and esters and electrophilic groups of synthetic value, *e.g.* succinimidyl esters, are expected to be tolerated, but with extended reaction times and as a consequence the risk of forming more of the byproducts **3** and **4**.

Finally, all optimization reactions up to this point were carried out by transferring aliquots of a [ $^{18}\text{F}$ ]KF/K<sub>222</sub> stock solution to a 4 mL vial containing the reagents. To validate the utility of this transformation on a preparative scale and to determine the overall RCY and molar activity, triflyl [ $^{18}\text{F}$ ]fluoride was synthesized from 3 GBq [ $^{18}\text{F}$ ]fluoride and trapped in a 4 mL vial containing MeCN with K<sub>2</sub>CO<sub>3</sub>/K<sub>222</sub> and KF. After addition of Cu(OTf)<sub>2</sub> and **1**, the vial was irradiated for 2 hours at rt. To our delight, **1** was  $^{18}\text{F}$ -fluorinated with an overall radiochemical yield of  $27 \pm 2\%$  and a molar activity of  $0.21 \pm 0.06$  GBq/ $\mu\text{mol}$  (Scheme 1,  $n = 3$ ). The low  $A_m$  is mainly due to the presence of 1.5 eq. of KF as well as the long reaction time and is an important challenge of our method. However, the full batch application of this new  $^{18}\text{F}$ -fluorodecarboxylation protocol emphasizes the potential utility of this copper-mediated protocol for late-stage  $^{18}\text{F}$ -applications.

In conclusion, for the first time the direct decarboxylative  $^{18}\text{F}$ -fluorination of benzoic acids under mild conditions *via* photoinduced LMCT has been described. By leveraging a high-valent arylcopper(III) [ $^{18}\text{F}$ ]fluoride intermediate and subsequent C(sp<sup>2</sup>)-[ $^{18}\text{F}$ ]F reductive elimination, this strategy overcomes the harsh reaction conditions and limited substrate scope that have historically hampered aromatic decarboxylative  $^{18}\text{F}$ -fluorination reactions. The method demonstrates broad applicability, efficiently transforming a range of (hetero)aromatic substrates, including electron-deficient, -neutral and -rich aryl rings with *para*-, *meta*- and *ortho*-substituents. Its efficiency and operational simplicity were proven by the successful preparation of 1-fluoro-4-[ $^{18}\text{F}$ ]fluorobenzene on preparative scale in good isolated yield, despite a low  $A_m$ . Having laid the foundation for a practical and versatile aromatic decarboxylative  $^{18}\text{F}$ -fluorination reaction for PET tracer synthesis, future work should focus on improving the molar activity and

extending the substrate scope to bioactive compounds. Given the great diversity of benzoic acid precursors and the mildness of the reaction conditions, we expect that this transformation can become a valuable tool in the late-stage  $^{18}\text{F}$ -functionalization of drug-like molecules.

## Conflicts of interest

There are no conflicts to declare.

## Data availability

All experimental procedures and data are given in the supplementary information (SI). Supplementary information is available. See DOI: <https://doi.org/10.1039/d5cc03503a>.

## Notes and references

- 1 N. A. Meanwell, *J. Med. Chem.*, 2018, **61**, 5822–5880.
- 2 Food and Drug Administration, New Drugs at FDA: CDER's New Molecular Entities and New Therapeutic Biological Products, <https://www.fda.gov/drugs/development-approval-process-drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products>, (accessed 18 June 2025).
- 3 S. Preshlock, M. Tredwell and V. Gouverneur, *Chem. Rev.*, 2016, **116**, 719–766.
- 4 T. E. Spiller, K. Donabauer, A. F. Brooks, J. A. Witek, G. D. Bowden, P. J. H. Scott and M. S. Sanford, *Org. Lett.*, 2024, **26**, 6433–6437.
- 5 P. Xu, P. López-Rojas and T. Ritter, *J. Am. Chem. Soc.*, 2021, **143**, 5349–5354.
- 6 T. Q. Chen, P. S. Pedersen, N. W. Dow, R. Fayad, C. E. Hauke, M. C. Rosko, E. O. Danilov, D. C. Blakemore, A. M. Dechert-Schmitt, T. Knauber, F. N. Castellano and D. W. C. Macmillan, *J. Am. Chem. Soc.*, 2022, **144**, 8296–8305.
- 7 Z. He and P. Dydio, *Angew. Chem., Int. Ed.*, 2024, **63**, e202410616.
- 8 N. W. Dow, P. S. Pedersen, T. Q. Chen, D. C. Blakemore, A. M. Dechert-Schmitt, T. Knauber and D. W. C. Macmillan, *J. Am. Chem. Soc.*, 2022, **144**, 6163–6172.
- 9 P. S. Pedersen, D. C. Blakemore, G. M. Chinigo, T. Knauber and D. W. C. Macmillan, *J. Am. Chem. Soc.*, 2023, **145**, 21189–21196.
- 10 H. H. Coenen, A. D. Gee, M. Adam, G. Antoni, C. S. Cutler, Y. Fujibayashi, J. M. Jeong, R. H. Mach, T. L. Mindt, V. W. Pike and A. D. Windhorst, *Nucl. Med. Biol.*, 2017, **55**, v–xi.
- 11 M. M. Herth, S. Ametamey, D. Antuganov, A. Bauman, M. Berndt, A. F. Brooks, G. Bormans, Y. S. Choe, N. Gillings, U. O. Häfeli, M. L. James, K. Kopka, V. Kramer, R. Krasikova, J. Madsen, L. Mu, B. Neumaier, M. Piel, F. Rösch, T. Ross, R. Schibli, P. J. H. Scott, V. Shalgunov, N. Vasdev, W. Wadsak and B. M. Zeglis, *Nucl. Med. Biol.*, 2021, **93**, 19–21.

