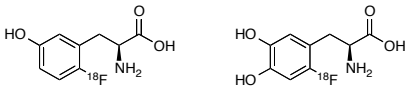
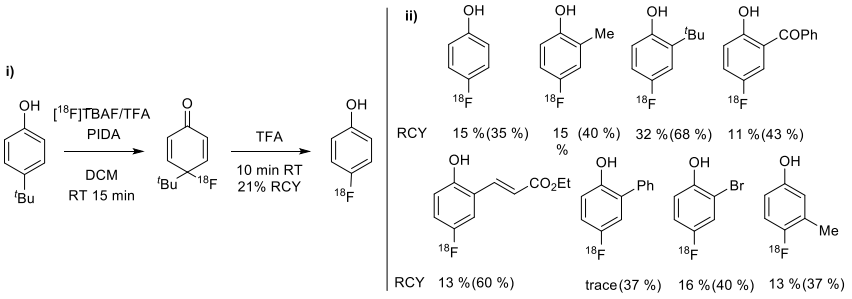
Oxidative Fluorination with [^{18}F]Fluoride: New Radiochemistry for PET Imaging

Positron Emission Tomography (PET) imaging is a highly interdisciplinary area of research, which necessitates the input of physicists (cyclotron, nuclear reaction), chemists (radiochemistry, radiotracer design), clinicians (imaging diagnosis), biologists (imaging pre-clinical work, radiotracer design), mathematicians (image analysis) and engineers (image analysis, technological development). Ultimately, the usefulness of PET for diagnosis, personalised medicine or drug development relies on the availability of robust synthetic routes to access complex labelled molecules or drug candidates. PET relies on the availability of radiotracers labelled with a positron-emitting radioisotope. ^{18}F-Labelled molecules are frequently used because of the advantageous properties of ^{18}F in comparison with other non-metallic radioisotopes (^{11}C, ^{15}O, ^{13}N). The objective of this proposal was to provide with a solution to a well-recognised problem in ^{18}F-radiochemistry: the direct fluorination of electron rich aromatics with a nucleophilic source of ^{18}F-Fluoride. The value of this new radiochemistry could be challenged with the synthesis of 6-[^{18}F]Fluoro-*L*-3,4-dihydroxyphenylalanine (**[^{18}F]FDOPA**) and 6-[^{18}F]Fluoro-*L*-meta-tyrosine (**[^{18}F]FMT**), two high value tracers to image the presynaptic sites of the dopaminergic system; yet these two radiotracers are notoriously difficult to produce using currently available radiochemistry.



[^{18}F]FMT [^{18}F]FDOPA

Conceptually, the nucleophilic fluorination of electron rich aromatics with fluoride may be possible using a so-called "substrate umpolung" approach. Under oxidative conditions, the reactivity profile of the substrate can be reverted from a nucleophilic to an electrophilic entity (umpolung), thereby allowing for nucleophilic ^{18}F-labelling. Langlois et al. reported a metal-free *in situ* oxidation as a phenolic umpolung towards fluoride ions.[i] Inspired by this work Gouverneur *et al.* reported the synthesis of [^{18}F]4-fluorophenol.[ii] This reaction was particularly important due to the possibility of using phenolic compounds as prosthetic groups to introduce ^{18}F fluorine into larger molecules. The reaction conditions were initially screened using non-radiochemical ("cold") fluorinating reagents and different oxidants. The optimised "cold" fluorination protocols (treatment with $PhI(OAc)_2$ (1 eq) and HF.pyridine 70% (4 eq) in dichloromethane at room temperature for 15 min, followed by treatment with trifluoroacetic acid for 10 min) were applied to the synthesis of [^{18}F]4-fluorophenol, and the use of [^{18}F]TBAF as the fluoride source gave the highest radiochemical yield and purity. In addition, the use of a microfluidic reactor (Advion Nano-Tek) allowed the reactions to be performed on a smaller scale and also ensured good control of the stoichiometry and a constant flow.



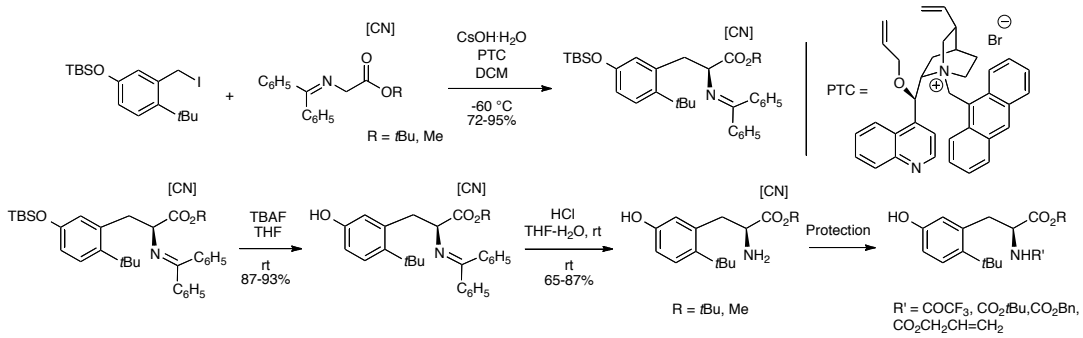
Direct Radiosynthesis of 6-[^{18}F]-Fluoro-*L*-meta-tyrosine

The synthesis of 6-[^{18}F]-Fluoro-*L*-meta-tyrosine should deliver the radiotracer enantiopure with a method ideally avoiding chiral stationary phase HPLC separation of racemic [^{18}F]FMT. A library of several enantiopure precursors for the oxidative fluorination was prepared using an asymmetric phase transfer catalysed alkylation as the key step. Standard and commercially available Phase

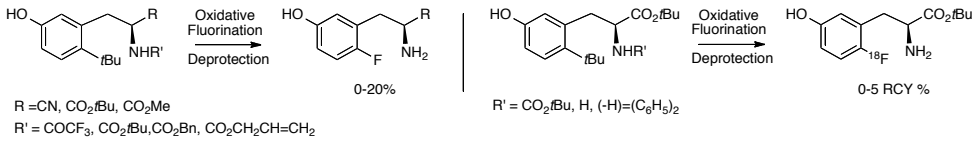
[i] A. Bienvenu, A. Barthelemy, S. Boichut, B. Marquet, T. Billard, B. R. Langlois, *Collect. Czech. Chem. Commun.* **2002,** *67,* 1467.

[ii] Z. Gao, Y. H. Lim, M. Tredwell, L. Li, S. Verhoog, W. Kaluza, T. L. Collier, J. Passchier, M. Huiban, V. Gouverneur, *Angew. Chem. Int. Ed.* **2012**, *51*, 6733-6737.

Transfer catalyst (PTC) was selected for this transformation.[iii] Following deprotection of the required free phenol, protection of the amino group with different protecting groups was evaluated.



The key difference between the FMT precursor and phenol substrates is the presence of the amino acid chain. The yield obtained for the cold oxidative fluorination reaction with the FMT precursor was lower (0-20% yield) than the yield of substituted phenols (35-60% yield). Various attempts to produce the [^{18}F]-FMT employing the optimized 'hot protocol' for the oxidative fluorination employing [^{18}F]TBAF as the fluoride source in a microfluidic reactor (Advion Nano-Tek) produced the ^{18}F-fluorinated compound in low radiochemical yield (up to 5%).

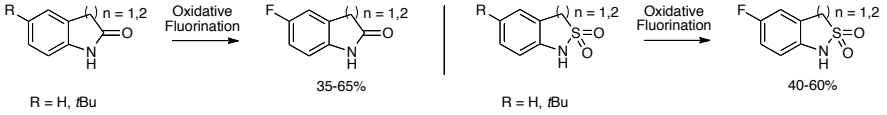


Direct Radiosynthesis of 6-[^{18}F]-Fluoro-3,4-dihydroxy-*L*-phenylalanine

Based on the same principles, we subsequently studied the access to [^{18}F]-*L*-FDOPA from fluoride; this is a more complex system for ^{18}F-radiolabelling compared to [^{18}F]-FMT as the catechol motif requires differential protection to induce control over product distribution and regioselectivity. Different protecting groups (ester, ether) were evaluated; the desired fluorinated product was obtained in 3% yield (^{19}FNMR). In addition, the major product upon fluorination was a compound with the F atom in a different position in the aromatic ring. As a conclusion, this approach will require more extensive studies for future radiolabelling work.

Oxidative Fluorination of Aromatic and Heterocyclic Motifs

In the second part of the OXIFLU project the oxidative fluorination protocols were extended to cyclic amides and sulfonamides. The 4-fluoroaniline motif appears in many biologically active molecules and can be used as a prosthetic group to introduce fluorine into larger molecules.[iv] In general, the reaction conditions for the oxidative fluorination were optimised for each substrate, identifying which hypervalent iodine reagent and how many equivalents of HF.Pyridine give the highest yields. With the optimal non-radiochemical fluorination protocol in hand the labelling of indolin-2-one was attempted using [^{18}F]Et_3N/TFA as the source of [^{18}F]fluoride. First attempts showed an encouraging radiochemical yield reaching up to 6%.



[iii] V. Gouverneur, L. Li, Y.-H. Lim, M. Huiban, WO 2012/004567 A2

[iv] M.C. Lasne, L. Barre, C. Huard, B. Le Secq, M. Collins *App. Radiat. Isot.* **1994**, *45,* 11, 1085.