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COMMUNICATION

The synthesis of [^{18}F]SynVesT-1 and [^{18}F]SynVesT-2 from enantioenriched boronic esters

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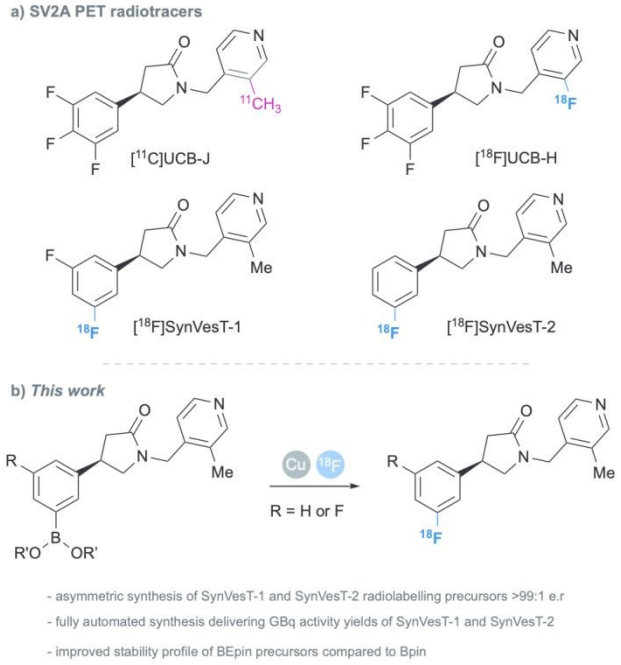
Enantioenrcihed [^{18}F]SynVesT-1 and [^{18}F]SynVesT-2 are prepared from the corresponding enantioenriched arylboronic esters and [^{18}F]fluoride mediated by $(Py)_4Cu(OTf)_2$. The ^{18}F-reaction is optimised on an automated synthesiser to produce multi-GBq quantites of both radiotracers to support (pre)clinical imaging.

Positron emission tomography (PET) imaging is a non-invasive technology that can provide quantitative information on biochemical processes to diagnose and monitor diseases in living subjects.[1] The loss or alteration of synaptic density is closely associated with neurodegenerative disorders including Alzheimer's and Parkinson's disease.[2,3] The synaptic vesicle glycoprotein 2A (SV2A) has been shown to play an essential role in neurotransmission and levels of SV2A been validated as a biomarker for synaptic density.[4] Several small molecule PET radiotracers to target SV2A have been developed allowing for the non-invasive quantification and visualisation of SV2A in-vivo with applications towards the diagnosis and development of treatments for neurological diseases. The PET radiotracer [^{11}C]UCB-J has been shown to be a competent imaging agent of SV2A,[5] but the relatively short half-life of ^{11}C ($t_{1/2}$ = 20.4 minutes) prohibits the broader use of this radiotracer, particularly in sites without an on-site cyclotron, thus the development of PET radiotracer with fluorine-18 ($t_{1/2}$ = 110 minutes) is highly desirable. The presence of three aryl-fluoride bonds in UCB-J theoretically allows for a direct synthesis of the ^{18}F isotopologue, however, to date attempts to radiolabel this compound with ^{18}F have been met with limited success.[6b,7] This led to the development of the structurally related compounds [^{18}F]SynVestT-1 and [^{18}F]SynVesT-2 which can accessed in improved radiochemical yields (RCY) and molar activities (A_m) (Scheme 1a).[6]



Scheme 1: a) PET radiotracers for imaging SV2A; b) this work

PET imaging studies revealed the *R*-enantiomer of both SynVestT-1 and SynVestT-2, have superior imaging characteristics to the *S*-enantiomer,[6e] yet to date most studies access the desired *R*-enantiomer by chiral HPLC separation of the ^{18}F-racemate resulting in decreased RCYs. A single asymmetric synthesis of ^{18}F-SynVest-1 aryl stannane radiolabelling precursor has been reported, while none for a SynVesT-2 radiolabelling precursor.[8] We have recently demonstrated the translation of the copper-mediated ^{18}F-fluorination of aryl boronic esters onto an automated synthesis platform resulting in a good manufacturing practice (GMP)

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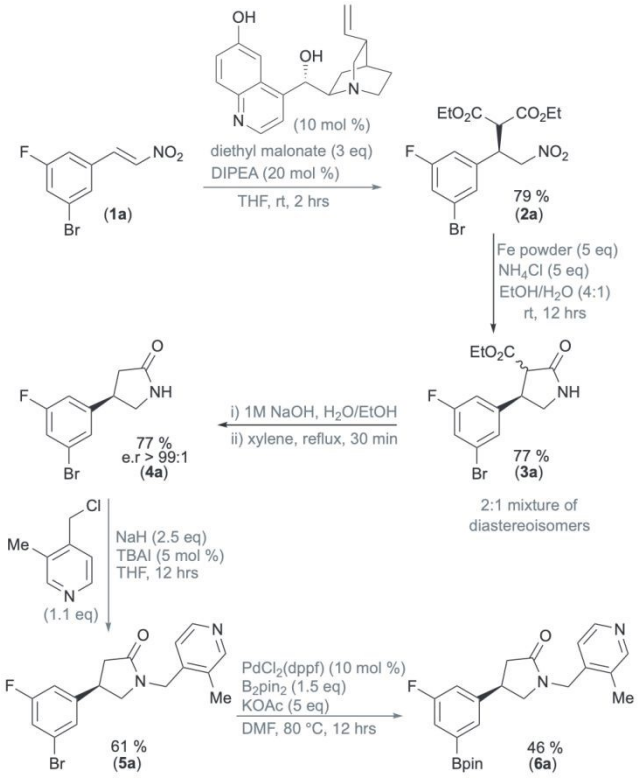
compatible method for [^{18}F]flumazenil, while Scott and Sanford have reported a similar protocol for [^{18}F]FDOPA.[9]

We reasoned the development of an automated protocol for the production of ^{18}F-SynVest radiotracers from aryl Bpin precursors would be beneficial due to the advantageous stability of these precursors and the ability to use tetrabutylammonium carbonate for the preparation of [^{18}F]tetrabutylammonium fluoride (*vide infra*). To this end herein we describe the first asymmetric syntheses of aryl boronic precursors for both SynVesT-1 and SynVesT-2 and their automated syntheses (Scheme 1b).



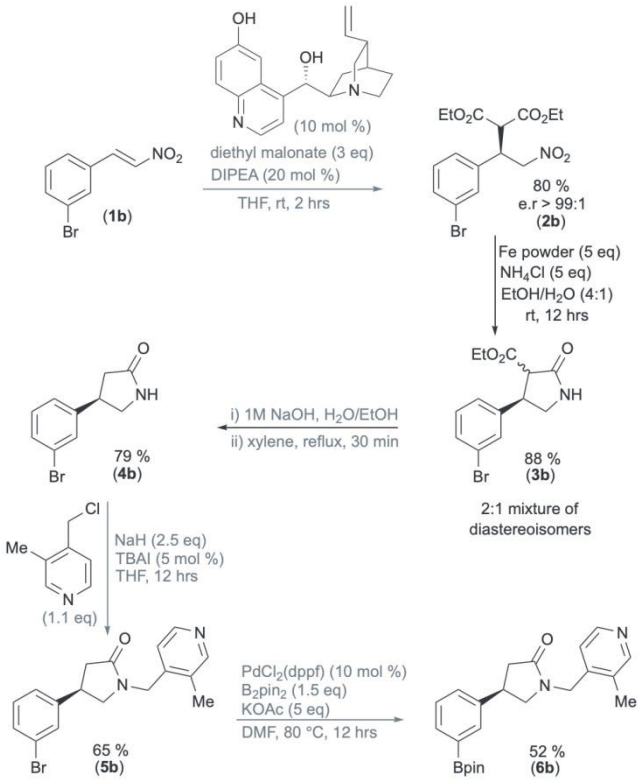
Scheme 2: Asymmetric synthesis of SynVesT-1 Bpin precursor

To access the key aryl Bpin compounds we envisaged an asymmetric synthesis of an aryl bromide (**5**) would allow us to introduce the Bpin functionality as the final step for each of the SynVesT compounds. The start of our synthesis of SynVesT-1 began with the nitroalkene (**1a**), prepared from the commercially available 3-bromo-5-fluorobenzaldehyde. For the asymmetric Michael addition, we followed the protocol by Deng and co-workers that was successfully employed in the asymmetric synthesis of UCB-J.[5,10] Treating **1a** with 10 mol % of (+)-*O*-desmethyl quinidine and 3 equivalents of diethyl malonate in THF at room temperature gave **2a** in 79 % yield. We were unable to determine the enantiomeric ratio (e.r) of **2a** at this stage and so proceeded with a reductive cyclization using Fe/NH_4Cl in EtOH/H_2O which yielded **3a** in 84 % yield as a 2:1 mixture of diastereoisomers (Scheme 2). Hydrolysis of the ester and sequential decarboxylation gave the butyrolactam(**4a**) in 77 % yield. Separation of the two enantiomers of (**4a**) was possible by chiral stationary phase HPLC analysis, giving an e.r of 82:18.

In an attempt to increase the e.r we took inspiration from the patent literature,[11] and repeated the asymmetric Michael addition using 10 mol % of (+)-*O*-desmethyl quinidine, 3 equivalents of diethyl malonate in addition to 20 mol % of *N*,*N*-diisopropylethylamine (DIPEA) which ultimately gave (**4a**) in improved e.r =>99:1.

The absolute stereochemistry of the major enantiomer was assigned as the desired *R*-enantiomer based comparison of the optical rotation with literature values.[8,12] *N*-Alkylation of the butyrolactam with 4-(chloromethyl)-3-methylpyridine gave (**5a**) in 61 %. The target SynVesT-1 Bpin precursor (**6a**) was synthesised from B_2pin_2 (1.5 eq.), KOAc (5 eq.) and 10 mol % $PdCl_2$(dppf) in DMF at 80°C in 46 % yield. The same synthetic strategy was applied to the synthesis of SynVesT-2 Bpin precursor (**6b**) (Scheme 3). The addition of 20 mol % of DIPEA was found again to be necessary in the asymmetric Michael addition to achieve high levels of asymmetric induction (e.r =>99:1 with DIPEA vs. 90:10 in absence). In contrast to the previous route, here we were able to measure the e.r of (**2b**) directly, the assignment of the absolute stereochemistry was done based on analogy with SynVesT-1.

Having established synthetic routes to the two enantioenriched Bpin radiolabelling precursors for SynVesT-1 (**6a**) and SynVesT-2 (**6b**), our next consideration was optimisation of the ^{18}F-fluorination on an automated radiochemical synthesizer.



Scheme 3: Asymmetric synthesis of SynVesT-2 Bpin precursor

From a safety, and good manufacturing practice (GMP) perspective, the synthesis ^{18}F-radiotracers on an automated synthesis unit is a key challenge to address in method development.[13] Due to the higher dead-volumes, restrictions on

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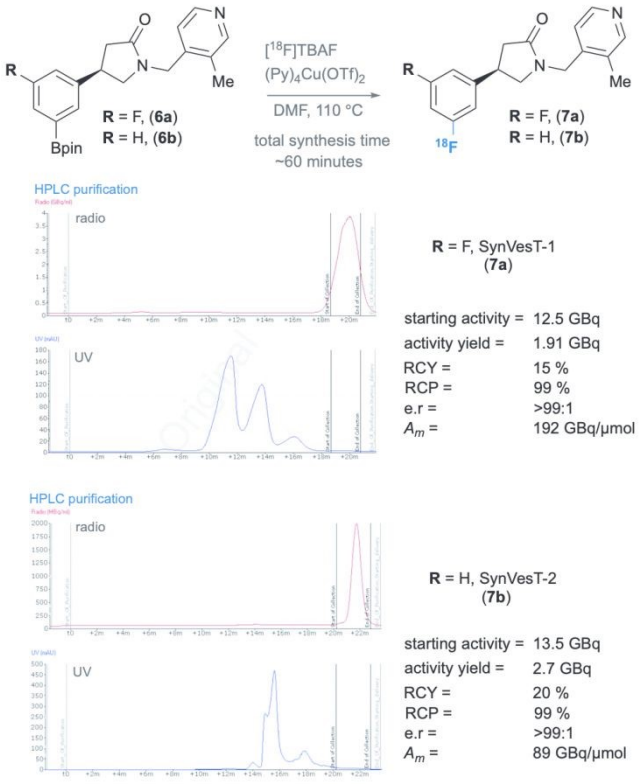
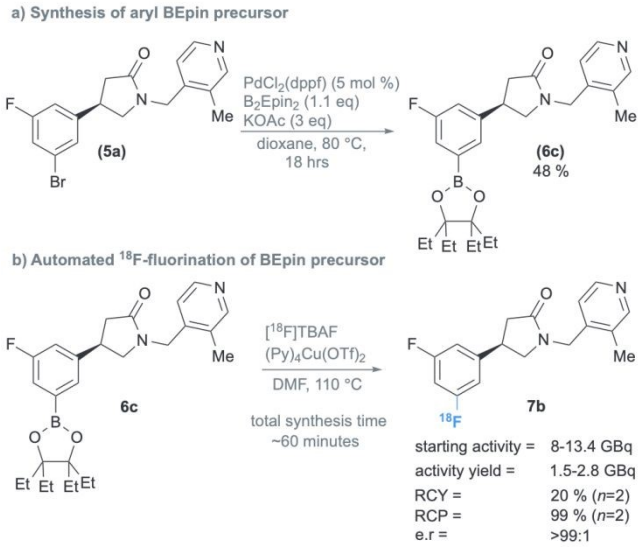
reagents/solvents and the inability to work typical inert chemistry conditions this process can often be non-trivial and can require significant optimization.



Scheme 4: Automated synthesis of [18F]SynVesT-1 & [18F]SynVesT-2

Based on this protocol we employed the following conditions for the ^{18}F-fluorination step; 12 mg Bpin precursor, 32 mg $(Py)_4Cu(OTf)_2$ in 0.5 ml dimethylformamide at 110 °C for 20 minutes. Following the fluorination step the crude mixture was purified by C18 HPLC purification and reformulation from a C18 cartridge. Chiral stationary phase HPLC analysis demonstrated that no racemisation of either precursor or ^{18}F-product occurring during the reaction, giving both [^{18}F]SynVesT-1, with an activity yield of 1.91 GBq (n=1) and [^{18}F]SynVesT-2 with an activity yield of 2.7 GBq (n=1), with e.r >99:1 (Scheme 4).

Test strips confirmed that the purification protocol was successful in removing residual copper to levels below the ICH(Q3) limit of 340 μg/V for patient use.[12] During these studies we found that the purification of both Bpin precursors **6a** and **6b** was non-trivial and could often result in decomposition of the material. To address this limitation, we investigated the ^{18}F-fluorination of a boronic ester derived from 3,4-diethylhexane-3,4-diol (Epin) which have been shown to be more stable towards purification but reactive in ^{18}F-fluorination mediated by Cu.[14] Precursor **6c** was synthesised from **5c** using $PdCl_2$(dppf) (5 mol %), B_2Epin_2 (1.1 equiv)and KOAc (3 equiv) in dioxane at 80 °C for 18 hours (Scheme 5a). Pleasingly compound **6c** was easily purified by silica gel column chromatography and isolated in 48 % yield. Subjecting **6c** to our automated ^{18}F-conditions described above we were able to isolate **7c** in 20 % RCY (n=2) and in activity yields of 2.8 GBq and 1.5 GBq, starting from [^{18}F]fluoride activities of 13.4 GBq and 8 GBq, respectively (Scheme 5b). As we observed for the Bpin precursors there was no loss in stereochemical integrity during the fluorination procedure, with **7a** being isolated with an e.r > 99:1. This result further highlights that BEpin esters serve as practical precursors in Cu/^{18}F radiochemistry for unstable and difficult to purify aryl boronic esters.



Scheme 5: Automated synthesis of [18F]SynVesT-1 from BEpin

Herein, we have reported the asymmetric synthesis of Bpin precursors of both SynVesT-1 and SynVesT-2 in e.rs >99:1. Automated copper-mediated ^{18}F-fluorination gave the corresponding enantiopure radiotracers with activity yields sufficient to support (pre)clinical imaging. The purification of the aryl Bpin precursors was found to be challenging but this could be overcome by use of aryl BEpin precursors that gave essentially identical yields under our optimised automated ^{18}F-conditions. We believe this work demonstrates that these compounds are a useful alternative to the commonly used stannyl precursors.

Conflicts of interest

MT is an inventor on a patent (WO201510572A1) relating to a copper-mediated ^{18}F-fluorination method.

Acknowledgements

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Data availability

The data underlying this study are available in the published article, in its Supporting Information, and openly available in the Cardiff

University data catalogue at https://doi.org/10.17035/cardiff.30196870.

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