Organocatalytic Asymmetric Synthesis of SynVesT-1, a PET Imaging Agent of the SV2A Receptor

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[18F]SynVesT-1 is a potent and selective positron emission tomography imaging agent for synaptic vesicle glycoprotein 2 (SV2A).1 SV2A is an integral transmembrane glycoprotein widely expressed in the brain. Although the exact role of SV2A has not been confirmed, it is known that SV2A participates in key vesicular processes. Furthermore, SV2A is a validated target for epilepsy and a biomarker of synaptic density.2 The established synthetic strategy to obtain [18F]SynVesT-1 involves the multistep synthesis of a racemic intermediate, requiring late-stage separation of the two enantiomers via chiral HPLC.3 Our aim was to develop an asymmetric synthetic route to access [18F]SynVesT-1.

In this work, we optimised a seven-step route to an organotin precursor of [18F]SynVesT-1 starting with a Wittig reaction of 3-bromo-5-fluorobenzaldehyde.4 This was followed by the asymmetric conjugate addition of nitromethane to the resulting cinnamaldehyde utilising the Hayashi-Jørgensen organocatalyst (Figure 1). Subsequently, a number of standard transformations facilitated the synthesis of the organotin precursor which was then subjected to automated copper(II)-mediated fluoro-destannylation for the preparation of [18F]SynVesT-1. This work will be discussed, along with a second-generation route detailing the synthesis of a boronic ester-derived precursor to [18F]SynVesT-1.

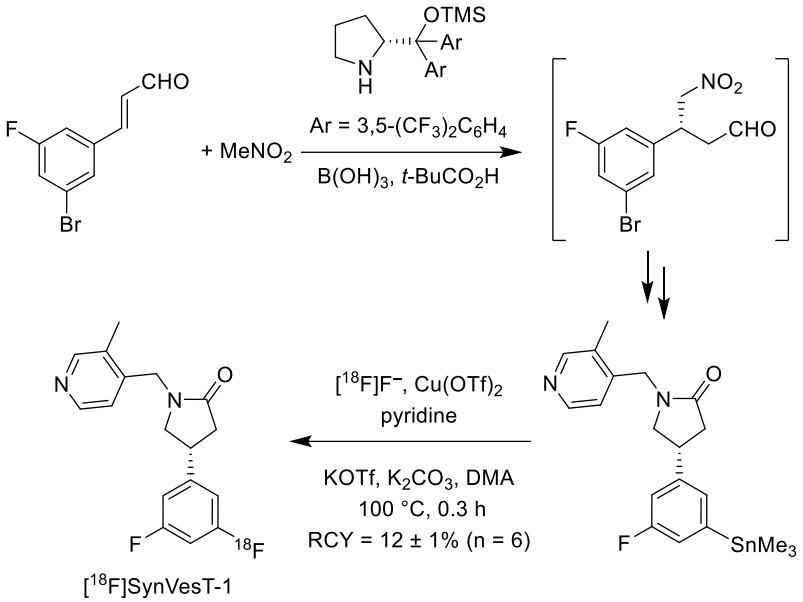

Figure. 1 Asymmetric synthetic route for the synthesis of [18F]SynVesT-1.

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