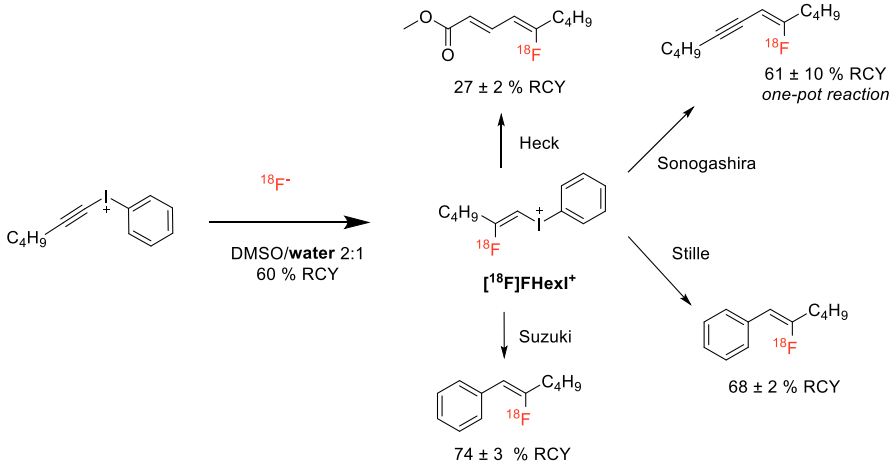
Preparation of [^{18}F]fluoroalkenyliodonium salts and their application for radiolabeling by cross coupling reactions

Objective: Fluoroalkenyliodonium salts can be obtained by nucleophilic addition of fluoride to the triple bond of alkynyliodonium salts [1]. They are valuable building blocks in palladium catalyzed cross coupling reactions [2]. Herein we demonstrate the radiofluorination of alkynyl(aryl)iodonium salts, their application in various cross coupling reactions and their suitability for radiolabelling of biologically relevant molecules.



Methods: Alkynyl(aryl)iodonium salts were radiolabeled with [^{18}F]fluoride in aqueous organic media in the presence of different bases and K[2.2.2]. The reaction parameters were optimized and differently structured iodonium salts were compared. After isolation [^{18}F]fluorohexenyl(phenyl)iodonium ([^{18}F]FHexI$^+$) was used in various cross coupling reactions. To further evaluate this promising novel prosthetic group, alkyne-functionalized model compounds and biomolecules were synthesized and radiolabelled by Sonogashira coupling.

Results: The nucleophilic addition of [^{18}F]fluoride to the triple bond furnished [^{18}F]FHexI$^+$ with 60 % RCY using K[2.2.2]/$KHCO_3$ in DMSO/water (2:1) at 75 °C within 10 min. Remarkably, the reaction afforded highest RCYs in aqueous media without time consuming azeotropic drying. Radiolabeling of phenylethynyl-derived iodonium salts generally resulted in lower RCYs of 20–30 %. Different counter ions (OTs^-, OMs^-, BF_4^-) did not have a significant influence on the RCY.
After the labeling step, [^{18}F]FHexI$^+$ can be isolated from its precursor by HPLC and SPE within 10 minutes and can be directly used for subsequent cross coupling reactions by elution with an appropriate solvent. A common feature of the Sonogashira-, Stille- and Suzuki couplings are a high reaction speed, stereoselectivity and mild reaction condition. The coupling is finished in 3-10 min at room temperature yielding pure *Z*-isomers in good RCY between 61 to 74 %. Although the Heck reaction is very similar in most regards, unfortunately it suffers from a low stereoselectivity which not only reduces the RCY but leads to difficult separable product mixtures.
Sonogashira coupling can be performed as a very fast, mild and robust one-pot procedure. Therefore this reaction was selected to demonstrate the applicability of [^{18}F]FHexI$^+$ for the labeling of biomolecules. Nine amino acid based model compounds containing different alkyne-linkers were conjugated with [^{18}F]FHexI$^+$ in RCYs of 38 – 88 %. As a useful lead structure a Glu-urea-Lys derivative was prepared within 35 min synthesis time giving an overall RCY of 45 %. Conjugation of [^{18}F]FHexI$^+$ to a dipeptide was accomplished as a two pot synthesis with 61 % RCY with as little as 50 nmol precursor.

Conclusion: [^{18}F]FHexI$^+$ is a very versatile novel building block for radiolabeling. It is prepared in high RCY avoiding any drying steps and can be coupled by various cross coupling reactions. The straightforward labeling of several biomolecules by Sonogashira coupling demonstrates its usefulness in indirect radiolabeling.