Expanding the ^{18}F-Radiochemical Space: Synthesis and Applications of 1,1-^{18}F-Difluorinated Alkenes.

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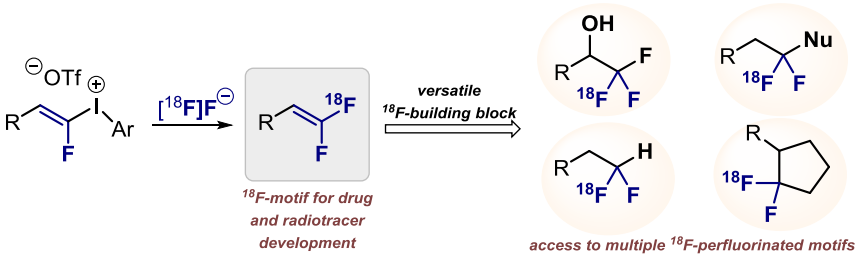

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Abstract The synthesis of ^{18}F-perfluorinated motifs from [^{18}F]fluoride is a non-trivial undertaking as highlighted by the few methods and range of motifs that are known. In this Synpacts article we highlight our recent work on the synthesis and derivatization of 1,1-^{18}F-difluoroalkenes to expand the accessible radiochemical space with fluorine-18.

Key words fluorine-18, radiochemistry, fluorination, *gem*-difluoroalkenes, perfluorination

1. Introduction

Alkyl ^{18}F-fluorides are arguably the most widely synthesized fluorinated motif with the radionuclide fluorine-18. This is in stark contrast to the abundance of alkyl ^{19}F-fluorides in FDA approved active pharmaceutical ingredients, which stands at 14 %, with the predominant motif being aryl fluorides.[1] The discrepancy in the incidence of fluorinated motifs in the fields of radiochemistry and medicinal chemistry may simply be a result of the differing requirements of these molecules in their respective fields. However, we believe it more likely reflects the relative difficulty in introducing fluorine-18 into organic molecules, under radiochemical conditions, for the majority of fluorinated functional groups.

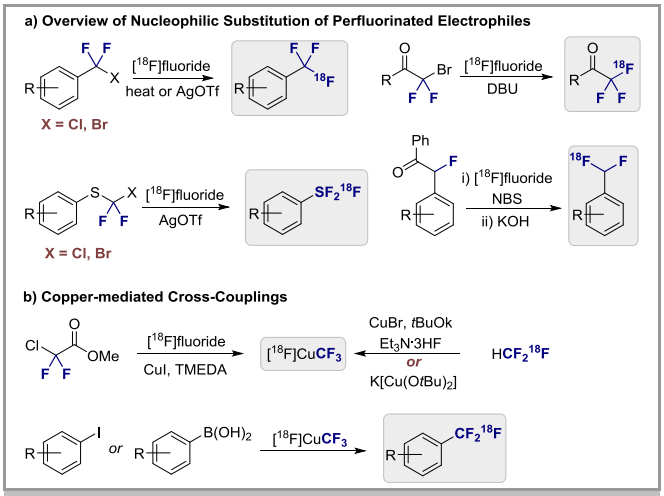
It is well recognized that nucleophilic substitution of primary alkyl electrophiles with [^{18}F]fluoride will normally yield the desired alkyl ^{18}F-fluorides, and in sufficient quantities and high molar activities (A_m), to allow for subsequent biological studies. Additionally, incorporation of a relatively small [^{18}F]fluoroethyl group, for example, would be assumed to minimally perturb the biological properties of the compound of interest.[2] However, in order for a radiolabeled molecule to be widely adopted for clinical use, its production should be compliant with the stringent requirements of current Good Manufacturing Practice (cGMP).[3] The extra levels of complexity in many of the new synthetic methods to form ^{18}F-(per)fluorinated motifs make cGMP compliance a non-trivial undertaking. As a consequence the tried and tested method of incorporating an ^{18}F-alkyl fluoride is often preferred. While the majority of the recent ^{18}F-fluorination reactions for the synthesis of aryl fluorides, for example, have yet to be translated clinically, with continued development it is perhaps only a matter of time before this situation changes.

The continued expansion in the variety of transformations with fluorine-18 available to radiochemists to include a wide range of perfluorinated motifs, will help to maintain the development and increase the potential of ^{18}F-PET for molecular imaging applications.[4] This Synpacts article highlights our recent work detailing the synthesis and derivatization of 1,1-^{18}F-difluorinated alkenes,[5] in the context of current methods to synthesize ^{18}F-perfluorinated compounds.

2. Overview of the Main Strategies to Access ^{18}F-Perfluorinated Motifs with [^{18}F]Fluoride

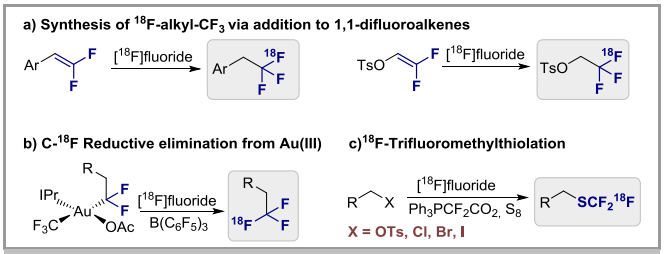
The first reported methods to access ^{18}F-perfluorinated functional groups examined the nucleophilic displacement of α,α-difluorinated electrophiles that were activated by the presence of an aromatic ring, or carbonyl group.[6] While successful, these methods gave ^{18}F-labelled products with molar activities much lower than that observed for non-fluorinated electrophiles. This decrease in A_m was found to be due to the ability of the fluorinated precursors to act as sources of [^{19}F]fluoride. These reactions have been re-visited by a number of research groups, describing milder reaction conditions and expanded substrate scopes, inclusive of sulfur and oxygen activated alkyl halides (Scheme 1a).[7] An alternative route to ^{18}F-labelled aryl-CF_3 compounds has been the development of

copper-mediated couplings between arylboronic acids or aryl iodides with [^{18}F]CuCF$_3$. The key difference between these new routes is the means of producing the key [^{18}F]CuCF$_3$ species (Scheme 1b).[7]



Scheme 1 Main strategies to access ^{18}F-perfluorinated motifs by nucleophilic substitution of perfluorinated electrophiles[7]

While radiochemists can now readily access ^{18}F-labelled aryl-CF$_2$H and aryl-CF$_3$ substrates, albeit in low A_m, general methods to access simple aliphatic systems are scarcer.[8] The addition of [^{18}F]fluoride to 1,1-difluorinated alkenes has been shown to be regioselective to give the corresponding aliphatic ^{18}F-trifluoromethyl compounds, although it appears to require systems whereby the intermediate anion is stabilized by the neighbouring functional group (Scheme 2a).[9] Toste and co-workers have reported arguably the only method that can produce aliphatic [^{18}F]trifluoromethyl groups in positions that are neither structurally or electronically biased.[10] Treatment of isolable Au(III) precursors with [^{18}F]fluoride underwent reductive elimination to yield the desired aliphatic ^{18}F-trifluoromethylated compounds (Scheme 2b). To complement the synthesis of ^{18}F-aryl-SCF$_3$ compounds the related ^{18}F-alkyl-SCF$_3$ substrates have also been reported. Key to this work was the synthesis of the [^{18}F]SCF$_3$ anion from difluorocarbene and sulfur, followed by subsequent reaction with an alkyl halide (Scheme 2c).[11] This brief overview shows how major advances have been made recently in ^{18}F-radiochemistry to increase the range of accessible labelled compounds for PET imaging. However, numerous perfluorinated functional groups, readily accessible to medicinal chemists, are not yet in reach for radiochemists.

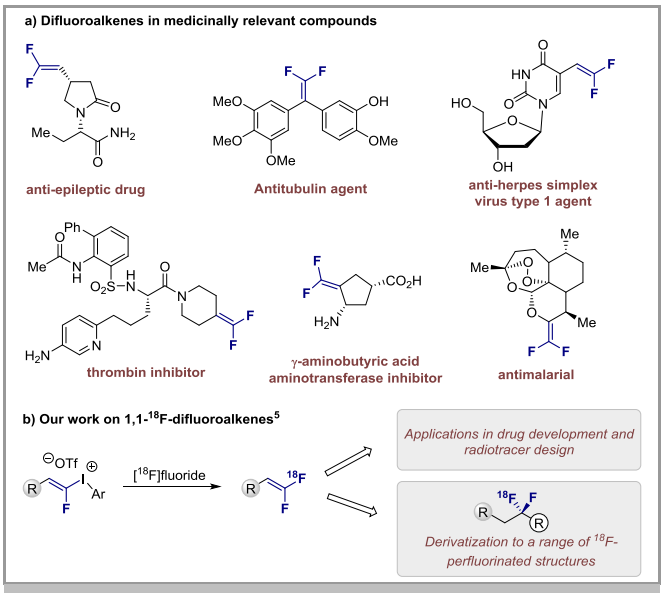


Scheme 2 General methods for the synthesis of alkyl-^{18}F-CF$_3$ motifs

3. 1,1-^{18}F-Difluoroalkenes

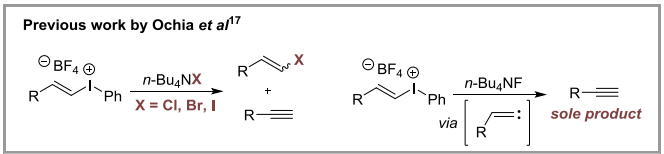
One of the research themes within our group is to address the lack in diversity of ^{18}F-perfluorinated motifs, and we were drawn to the synthesis of *gem*-^{18}F-difluoroalkenes (Scheme 3a).[12] This functional group was attractive for two main reasons: firstly it is present in a range of pharmaceuticals,[13] particular interesting was its presence in compounds to treat neurological disorders;[14] secondly it displays a unique reactivity profile,[15] which we envisaged taking advantage of to gain access to additional ^{18}F-perfluorinated motifs.

The use of diaryliodonium salts for the synthesis ^{18}F-aryl fluorides is a well-developed method,[7] although to the best of our knowledge this methodology has never been adapted to the synthesis of ^{18}F-alkenyl fluorides (Scheme 3b).



Scheme 3 a) Prevalence of the 1,1-difluoroalkene functional group. b) Overview of our work on 1,1-^{18}F-difluoroalkenes

Based on the work of Ochiai *et al* on the reactivity alkenyl(aryl)iodonium salts with a variety of nucleophiles,[16] we reasoned that ^{18}F-fluorination of a fluoroalkenyl(aryl)iodonium salt should be regioselective to yield the desired 1,1-^{18}F-difluoroalkene. It is noteworthy that Ochiai had previously examined the nucleophilic substitution of alkenyl(phenyl)iodonium tetrafluoroborates with halides.[17] Iodide, bromide and chloride all gave the expected alkenyl halides, but the use of fluoride resulted in solely α-elimination and formation of the alkylidenecarbene (Scheme 4).

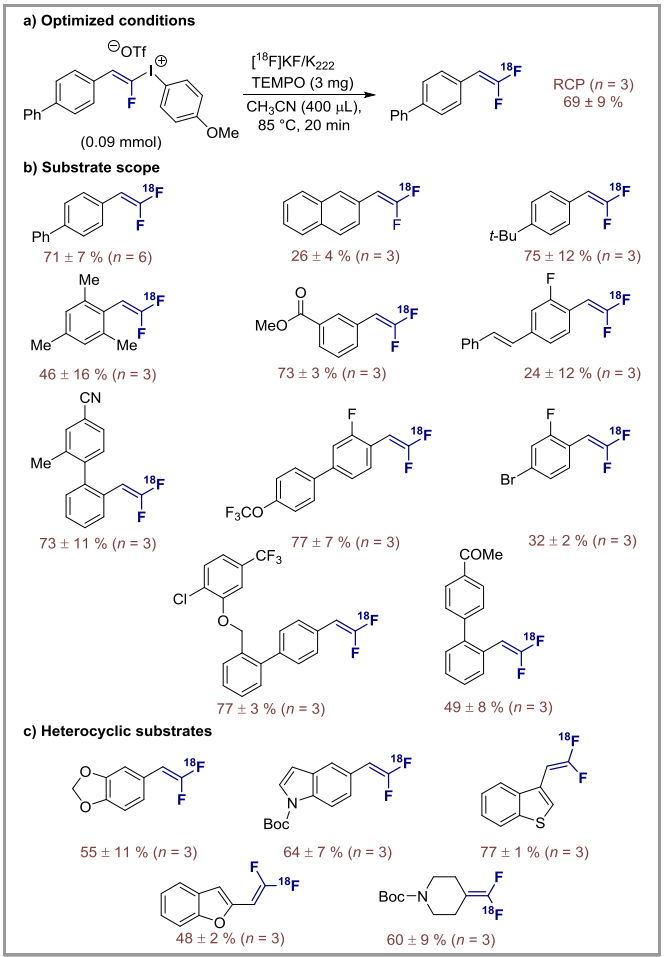


Scheme 4 Nucleophilic substitution of (*E*)-β-alkyl(alkenyl)iodonium tetrafluoroborates with halides[17]

While we were unconcerned by this pathway in our system due to the presence of the fluorine atom in the α-position, it does highlight a potential limitation in the use iodonium salts for the synthesis of fluoroalkenes.

We began our studies by examining the fluorination of a range of fluoroalkenyl(aryl)iodonium triflates, where we varied the

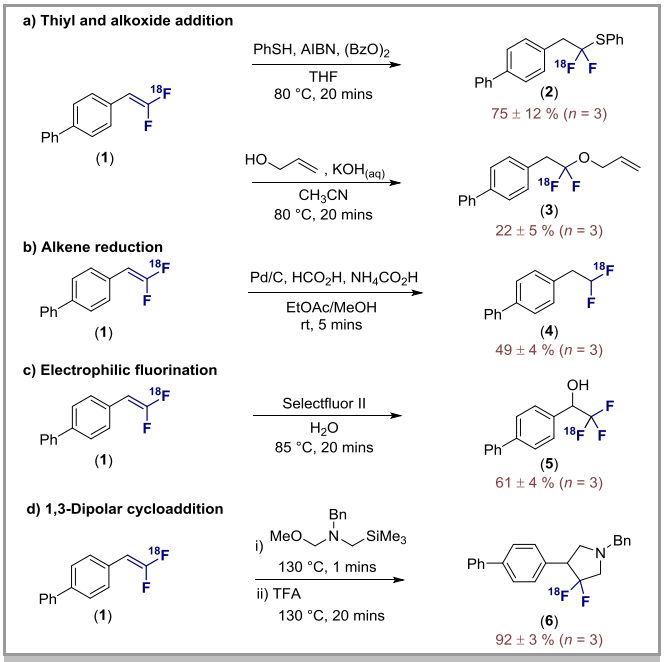
identity of the aryl group.[5] Of the groups tested 4-methoxyphenyl was found to give the desired 1,1-^{18}F-difluoroalkene selectively with no formation of 4-[^{18}F]fluoroanisole. Addition of (2,2,6,6-tetramethylpiperodone-1yl)oxidanyl (TEMPO) was found to significantly improve the reaction (Scheme 5a). With optimized conditions in hand ([^{18}F]KF/K_{222}, TEMPO, CH_3CN, 85 °C, 20 minutes), we proceeded to test the substrate scope and compatibility of the transformation. Pleasingly the reaction tolerated a wide variety of functional groups, inclusive of motifs present in medicinal compounds (Scheme 5b). In all cases the desired 1,1-^{18}F-difluoroalkene was formed selectively, and in good radiochemical purities (RCP), without any deviation from the optimized conditions. A range of heterocyclic compounds were also successfully fluorinated demonstrating the utility of this method for drug and radiotracer development (Scheme 5c).



Scheme 5 Optimized conditions for synthesis of 1,1-^{18}F-difluoroalkenes and substrate scope. RCP is reported for each compound as determined by radio-HPLC and TLC.

The ability to perform fluorine-18 radiochemical transformations on an automated synthesizer, in a shielded hotcell, is of critical importance. If this criterion is not met the protocol in question is likely to have limited applications due to safety considerations. Conscience of this requirement we tested our transformation on an automated synthesis unit (ELIXYS FLEC/CHEM coupled with ELIXYS PURE/FORM), gratifyingly we obtained radiochemical yields of 33-47 % (n = 3), with a A_m of 1 GBqµmol^{-1}. These results are suggestive that this methodology would be easily adopted by other radiochemical facilities for pre-clinical imaging. The origin of the isotopic dilution is not currently clear, although we believe decomposition of the starting material during the transformation and subsequent release of [^{19}F]fluoride is likely responsible. The current A_m of radiolabeled compound by this method is on par with that observed for ^{18}F-perfluorinated systems, and efforts are currently underway to improve the A_m of this transformation.

With a practical method to readily produce the desired 1,1-^{18}F-difluoroalkenes we sought to investigate the use of these compounds to access other ^{18}F-perfluorinated functional groups (Scheme 6). Using (**1**) as a model substrate we found that a thiyl radical and an alkoxide nucleophile both added regioselectively to give (**2**) and (**3**) respectively (Scheme 6a). The reduction of the 1,1-^{18}F-difluorinated alkene was also possible within 5 minutes at room temperature, to yield (**4**) in 49 ± 4 % (n = 3) RCP. Treatment of (**1**) with Selectfluor in water/CH_3CN gave (**5**) in 61 ± 4 % (n = 3) RCP. The 1,3-dipolar cycloaddition of (**1**) with an *in-situ* generated azomethine, gave the 3,3-[^{18}F]difluoropyrrolidine (**6**) in 92 ± 3 % (n = 3) RCP. These results highlighting the potential of 1,1-^{18}F-difluorinated alkenes as useful building blocks to access more complex radiolabeled molecules.



Scheme 6 Diversification of 1,1-^{18}F-difluoroalkenes to other ^{18}F-motifs

4. Conclusion

A radiochemical synthesis of a range of 1,1-^{18}F-difluoroalkenes has been reported from [^{18}F]fluoride and fluoroalkenyl(aryl)iodonium triflates. The method is robust and readily adapted on to a commercially available automated synthesis unit. The *gem*-^{18}F-difluoroalkene motif is of interest due to its presence in numerous pharmaceuticals, but also as a ^{18}F-building block. Five further ^{18}F-perfluorinated motifs were ready accessed by post-labelling transformations that would be challenging to synthesize via currently available ^{18}F-radiochemical methods. Further work is underway on expanding the applications of this method.

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Biosketches

Matthew Tredwell read Chemistry at the University of Oxford and remained there to complete his DPhil under the supervision of Prof. Veronique Gouverneur. After postdoctoral studies with Prof Matthew Gaunt at the University of Cambridge, Matthew returned to the Gouverneur group in Oxford for his second postdoctoral position. In August 2015 he started his independent research career at the Max-Planck-Institut für Kohlenforschung (Germany), where his group's interests are in fluorine chemistry and molecular imaging. In early 2019 his research group will move to the Wales Research and Diagnostic PET Imaging Centre at Cardiff University. (photograph by Frank Vinken)