How to cite: *Angew. Chem. Int. Ed.* **2024**, e202404957
doi.org/10.1002/anie.202404957

Radiochemistry

The ^{18}F-Difluoromethyl Group: Challenges, Impact and Outlook

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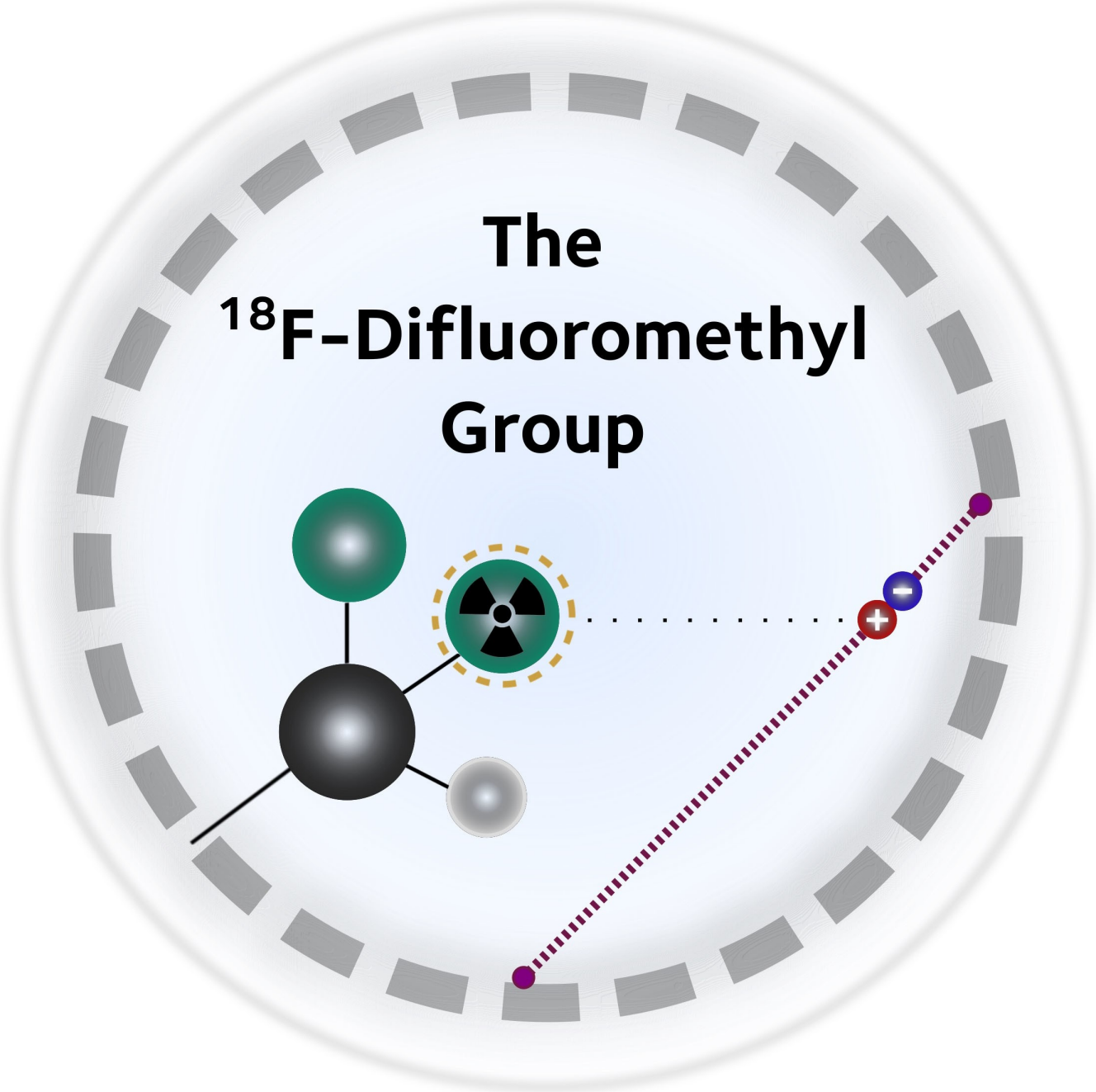

Abstract: The difluoromethyl functionality has proven useful in drug discovery, as it can modulate the properties of bioactive molecules. For PET imaging, this structural motif has been largely underexploited in (pre)clinical radiotracers due to a lack of user-friendly radiosynthetic routes. This Minireview provides an overview of the challenges facing radiochemists and summarises the efforts made to date to access ^{18}F-difluoromethyl-containing radiotracers. Two distinct approaches have prevailed, the first of which relies on ^{18}F-fluorination. A second approach consists of a ^{18}F-difluoromethylation process, which uses ^{18}F-labelled reagents capable of releasing key reactive intermediates such as the [^{18}F]CF_2H radical or [^{18}F]difluorocarbene. Finally, we provide an outlook for future directions in the radiosynthesis of [^{18}F]CF_2H compounds and their application in tracer radiosynthesis.

1. Introduction

Positron emission tomography (PET) is a powerful and highly sensitive medical imaging technique that allows for in vivo tracking of biological processes.[1] As such, this technology has found significant application in clinical medicine, e.g. for diagnosis and staging, as well as in drug discovery, where it facilitates biodistribution, receptor occupancy and dosing studies.[2] PET requires molecules labelled with a positron-emitting radionuclide, most commonly ^{18}F, ^{11}C, ^{68}Ga or ^{89}Zr.[3] Fluorine-18 is a widely used PET radioisotope due to its excellent decay properties ($t_{1/2}$ = 109.8 min, 97 % β^+ decay, 0.63 MeV positron energy). Furthermore, fluorinated molecules have made a significant impact in medicinal chemistry and pharmaceutical discovery.[4] Difluorinated functionalities, such as the difluoromethyl (CF_2H) and difluoromethylene (CF_2) groups, have attracted increased interest from medicinal chemists, prompting synthetic advances to facilitate their inclusion in bioactive molecules (Scheme 1a).[5]

1.1. Properties of the Difluoromethyl Group

The interest in difluoromethyl motifs in pharmaceuticals and agrochemicals results from their unique set of favourable properties (Scheme 1b).[5,6] The CF_2H group can act as a moderate hydrogen bond donor and modulate the lipophilicity of drug-like compounds.[7] In addition, it has been considered as a bioisostere for alcohol, thiol and methyl functionality and can also exert conformational effects.[6a,7d,8] Moreover, the difluoromethyl group can impart stability and was found to be more chemically resistant to defluorination under acidic and basic conditions than monofluorinated groups, likely driven by increasing C–F bond dissociation energy (BDE) with additional fluorine substitution.[6a,9]

As a result, several case studies exist where difluoromethylation has been considered for the optimisation of a drug candidate, resulting in a marked improvement in its pharmacokinetic properties (Scheme 1c). Difluoromethyl or difluoromethylene groups can be introduced during structure-based optimisation of pharmaceutical targets for drug potency and selectivity. This was shown with the fibroblast activation protein inhibitor UAMC-1110 (**1**) and the PI3K inhibitor bimirasilib (**2**).[10,11] Difluoromethylation can also modulate the pK_a of nearby functionalities as observed for structurally related proton pump inhibitors including the OCF_2H compound pantoprazole (**3**).[12] Crucially, difluoromethylated compounds can have improved metabolic profiles; in the development of DDD100097 (**4**) as a *Trypanosoma bruceiN*-myristoyltransferase inhibitor, a sulfonamide bearing an N-CF_2H group had reduced clearance relative to its *N*-methyl analogue.[13]

1.2. The ^{18}F-Difluoromethyl Group

Based on these advantages, difluoromethyl-containing radiotracers are equally valuable for PET ligand discovery. This Minireview distinguishes the radiosynthetic approaches to the ^{18}F-difluoromethyl group mechanistically as either ^{18}F-fluorination, where the key step involves the formation of a C–^{18}F bond, or as ^{18}F-difluoromethylation, where a [^{18}F]CF_2H or [^{18}F]CF_2 unit is transferred to the substrate (Scheme 2a). Both approaches are viable with distinct advantages and challenges for each methodology (Scheme 2b). As with any chemical process, the method must provide sufficient product (expressed by radiochemical yield, RCY, or activity yield, AY) for the desired application, and ideally be broad in scope.[14] To minimise bottlenecks due to complex precursor synthesis, the use of commercially available/prevalent substrates is highly preferred. Furthermore, due to the half-life of fluorine-18, the number of post-labelling steps should be minimised. Especially pertinent to the synthesis of polyfluorinated molecules is molar activity (A_m), which is an expression reflecting the extent of isotopic dilution with non-radioactive product. High A_m is typically preferred to avoid pharmacological effects (e.g. toxicity) from carrier, for image quality or for imaging of diffuse targets, e.g. in the central nervous system.[15] This presents a substantial challenge in the synthesis of [^{18}F]CF_2H radiotracers, due to the unavoidable necessity for ^{19}F-fluorine-containing substrates, which could release ^{19}F-fluoride, thereby lowering A_m.

This Minireview examines the methods that radiochemists have developed to access ^{18}F-difluoromethyl motifs and

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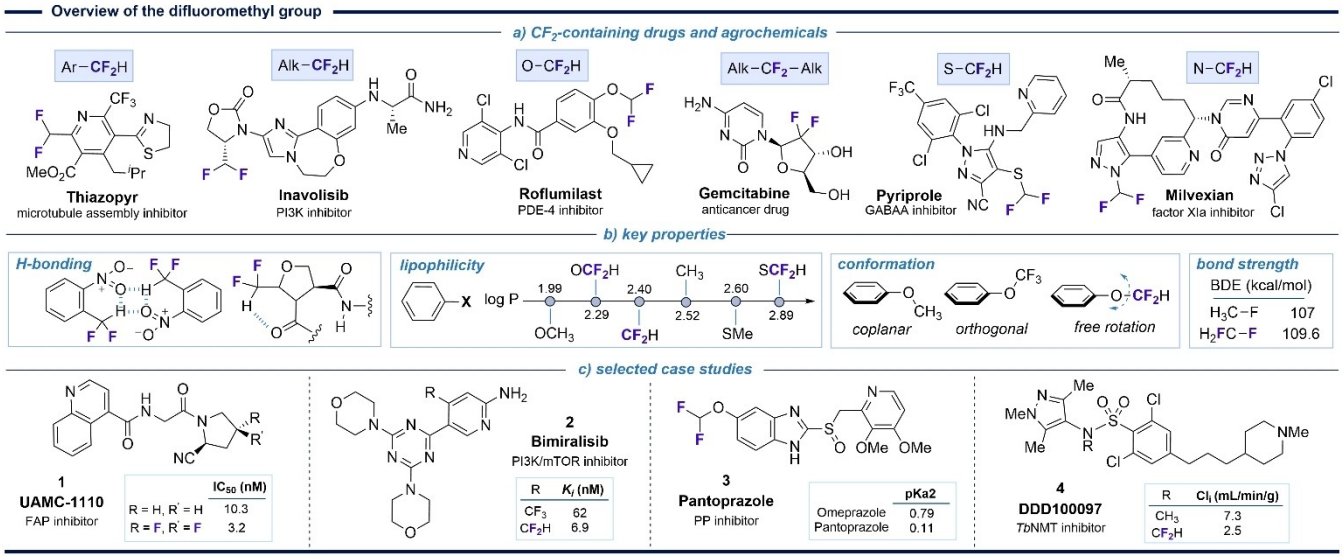


Scheme 1. The difluoromethyl group. (a) Examples of CF_2H/CF_2-containing pharmaceuticals/agrochemicals. (b) Key CF_2H properties. (c) Case-studies of CF_2H/CF_2-containing bioactive molecules.

how they have addressed the challenges associated with their radiosynthesis.

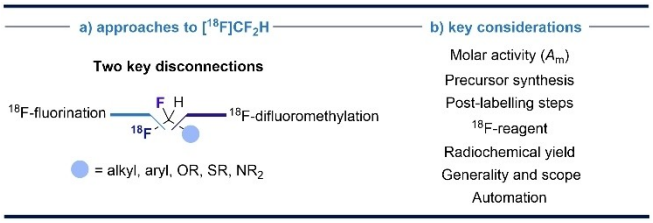
2. The ^{18}F-Fluorination Approach

The availability of cyclotron-produced [^{18}F]fluoride renders direct ^{18}F-fluorination an attractive solution (Scheme 3). Despite its apparent simplicity, this approach to ^{18}F-difluoromethylated compounds presents severe challenges. This disconnection demands the synthesis of a bespoke labelling precursor bearing an α-fluorine atom and a leaving group, a hurdle for complex targets. Furthermore, the effect of α-fluorine substitution has been demonstrated to hinder the rate of nucleophilic substitution at carbon.[16] This has required radiochemists to implement targeted activation strategies.

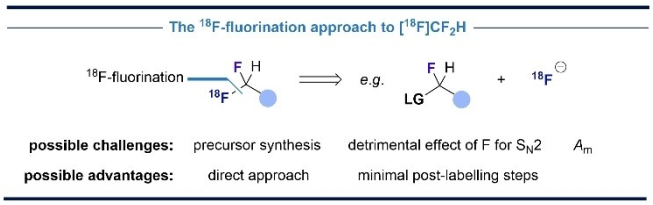
Joseph Ford received his MChem in Chemistry in 2019 from the University of Oxford (UK). During this time, he completed a visiting studentship in the group of Prof. Tobias Ritter (MPI-KoFo, Germany). In 2019, he started a DPhil at the University of Oxford as part of the Centre for Doctoral Training in Synthesis for Biology and Medicine, under the supervision of Prof. Véronique Gouverneur. His doctoral work focuses on ^{18}F-radiochemistry, including ^{18}F-difluoromethylation methodology.

Sebastiano Ortalli received his BSc degree in Pharmaceutical Chemistry from Queen Mary University of London in 2019, after which he conducted a placement at the University of Milan (Italy). In 2020, he started a PhD at the University of Oxford under the supervision of Prof. Véronique Gouverneur in collaboration with Johnson & Johnson Innovative Medicine. His work focuses on the development on novel one-electron (radio)fluorination and (radio)fluoroalkylation reactions.

Véronique Gouverneur FRS received her PhD from Université Catholique de Louvain (Belgium). After holding positions at the Scripps Research Institute (USA) and the Université Louis Pasteur (Strasbourg, France), she started her independent research career in 1998 at the University of Oxford. She was promoted to Professor of Chemistry in 2008 and in 2022, was appointed Waynflete Professor of Chemistry at Magdalen College. Her research focuses on fluorine (radio)chemistry, with the global challenges of sustainability and healthcare in mind.



Scheme 2. (a) Approaches to the ^{18}F-difluoromethyl group. (b) Key radiosynthetic considerations.

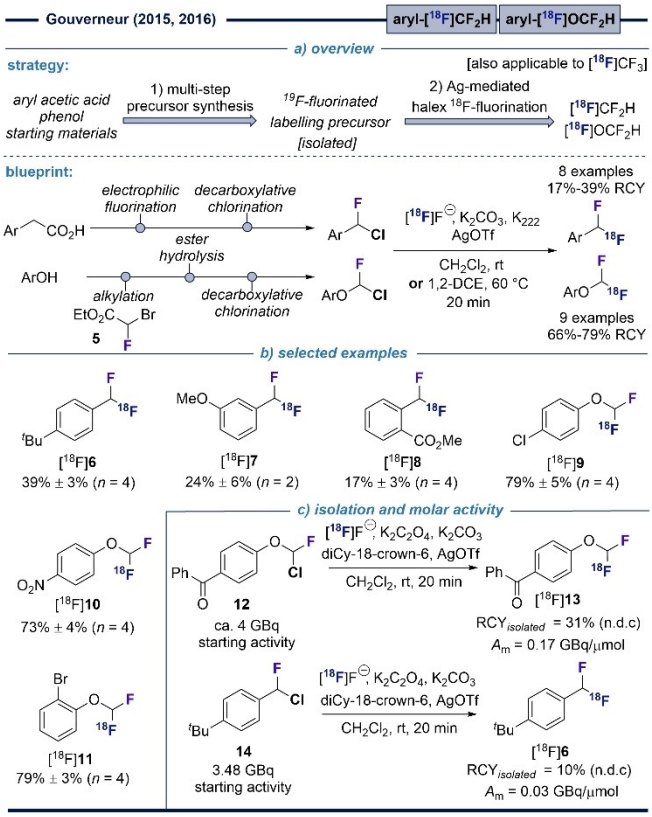


Scheme 3. The ^{18}F-fluorination approach to ^{18}F-difluoromethyl compounds. LG = leaving group.

2.1. 'Halex' (Halogen exchange) ^{18}F-fluorination

The reactivity of alkyl (pseudo)halides towards nucleophilic ^{18}F-fluorination is well documented.[17] However, the extension of this radiosynthetic disconnection to the synthesis of ^{18}F-difluoromethyl compounds has proven challenging. This section documents the body of work made to date to apply halex strategies to access the ^{18}F-difluoromethyl group.

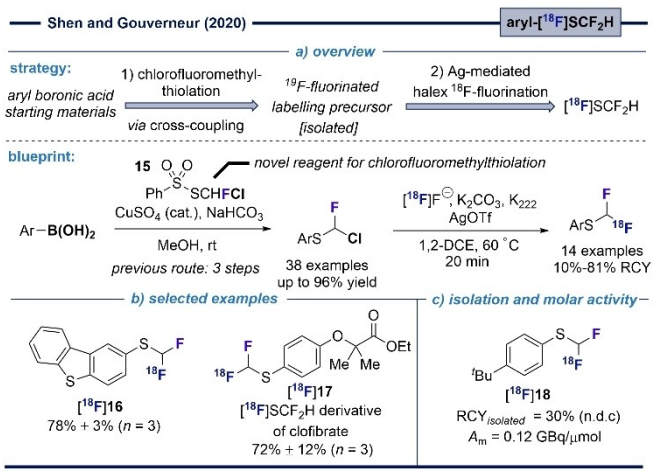
A first example applying a halex approach was disclosed by Gouverneur and co-workers in 2015, which described the synthesis of aryl-[^{18}F]OCF_2H, -[^{18}F]OCF_3, and -[^{18}F]SCF_3, and this was further expanded to the synthesis of aryl-[^{18}F]CF_3 and aryl-[^{18}F]CF_2H in 2016.[18] Both reports hinge on the same core strategy, whereby a fluorohalomethyl precursor is reacted with [^{18}F]fluoride and a AgOTf activator with the halophilic Ag(I) salt promoting the substitution of the halogen with [^{18}F]KF.K_{222}; in the absence of this additive, no desired radiofluorination occurs. The multi-step preparation of the labelling precursor proceeds from aryl acetic acids for aryl-[^{18}F]CF_2H and from phenols and ethyl bromofluoroacetate (**5**) for aryl-[^{18}F]OCF_2H (Scheme 4a). While effective for small molecule examples, extension to complex [^{18}F]CF_2H targets was not demonstrated. Electronically and sterically differentiated aryl-[^{18}F]CF_2H compounds were obtained in 17–39 % RCY (8 examples, e.g. [^{18}F]**6**–[^{18}F]**8**) and aryl-[^{18}F]OCF_2H compounds in 66–79 % RCY (9 examples, e.g. [^{18}F]**9**–[^{18}F]**11**) respectively (Scheme 4b). The methodology was amenable to multi-GBq radiosynthesis; starting from **12**, the isolation of aryl-[^{18}F]OCF_2H compound [^{18}F]**13** (31 % RCY, A_m = 0.17 GBq/μmol) was possible, and from precursor **14**, aryl-[^{18}F]CF_2H compound [^{18}F]**6** (10 % RCY, A_m = 0.03 GBq/μmol) could be prepared (Scheme 4c). While the A_m of the isolated products was low, this method serves as a valuable proof-of-concept for halex strategies.



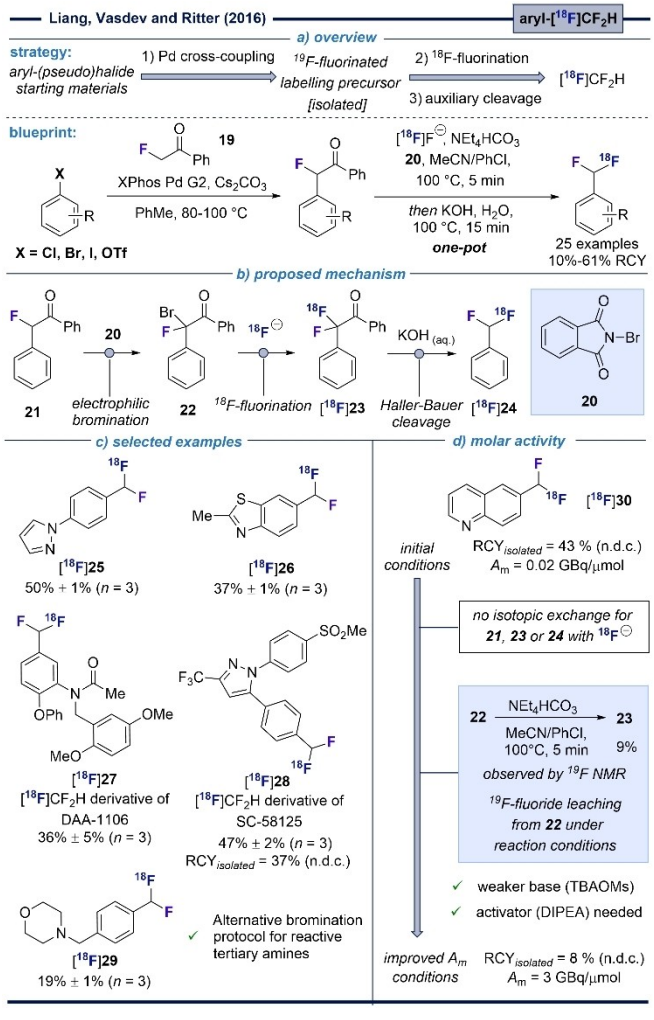
Scheme 4. Ag(I)-mediated halex ^{18}F-fluorination for radiosynthesis of aryl-[^{18}F]CF_2H and aryl-[^{18}F]OCF_2H. a) Summary. b) Representative substrate scope. c) ^{18}F-Product isolation and A_m measurement. n.d.c. = non-decay corrected.

Building on this study, Shen and Gouverneur reported in 2020 the radiosynthesis of aryl-[^{18}F]SCF_2H compounds with a Ag(I)-halex strategy.[19] Challenges associated with the synthesis of a highly-prefunctionalised labelling precursor were mitigated with a novel chlorofluoromethylthiolation using reagent **15**, allowing access to a wider scope of substrates in a single step from aryl boronic acids (Scheme 5a). 14 examples of aryl-[^{18}F]SCF_2H compounds were prepared in 10–81 % RCY, including those derived from heterocycles ([^{18}F]**16**, 78 % RCY) and complex molecules, such as the pharmaceutical clofibrate ([^{18}F]**17**, 72 % RCY) (Scheme 5b). Isolation of [^{18}F]**18** was also achieved (30 % RCY, A_m = 0.12 GBq/μmol) (Scheme 5c).

An alternative halex ^{18}F-fluorination strategy successfully applied to the radiosynthesis of ^{18}F-difluoromethylarenes was reported by Ritter, Vasdev, Liang and co-workers in 2016.[20] Rather than a direct ^{18}F-fluorination, this approach relied on the application of a benzoyl auxiliary group, conveniently installed via a Pd-catalysed arylation of commercial α-fluoroacetophenone (**19**) and readily available aryl halide/triflate starting materials (Scheme 6a).[21] The benzoyl group served to direct a C–H bromination with *N*-bromophthalimide (**20**) of α-aryl-α-fluoroacetophenone (**21**) to yield an α-bromo intermediate (**22**) that was reactive towards [^{18}F]fluoride. As a carbonyl functionality, the benzoyl group could also assist nucleophilic substitution at



Scheme 5. Ag(I)-mediated halex ^{18}F-fluorination for radiosynthesis of aryl-[^{18}F]SCF_2H. a) Summary. b) Representative substrate scope. c) ^{18}F-Product isolation and A_m measurement. n.d.c. = non-decay corrected.

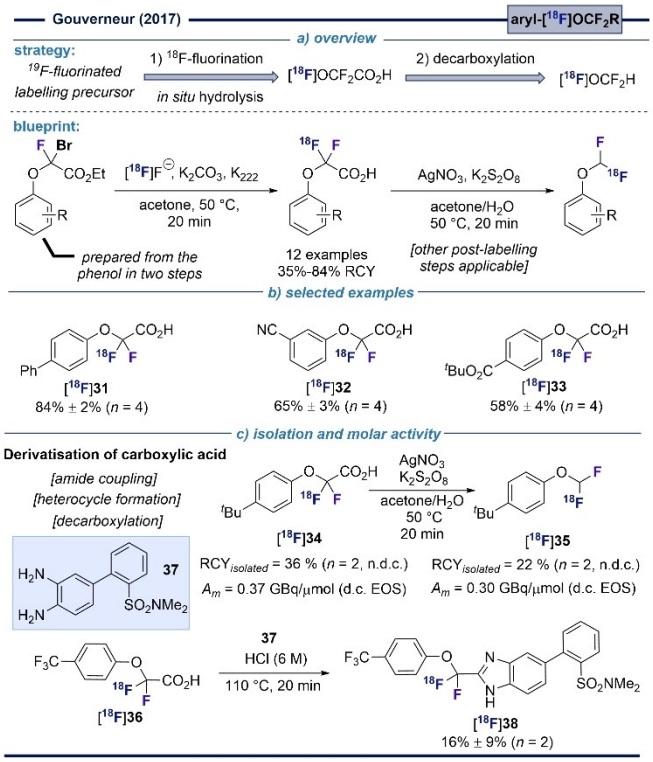


Scheme 6. Radiosynthesis of aryl-[^{18}F]CF_2H via a benzoyl auxiliary group. a) Summary. b) Proposed mechanism. c) Representative substrate scope. d) ^{18}F-Product isolation, A_m measurement and optimisation. n.d.c. = non-decay corrected.

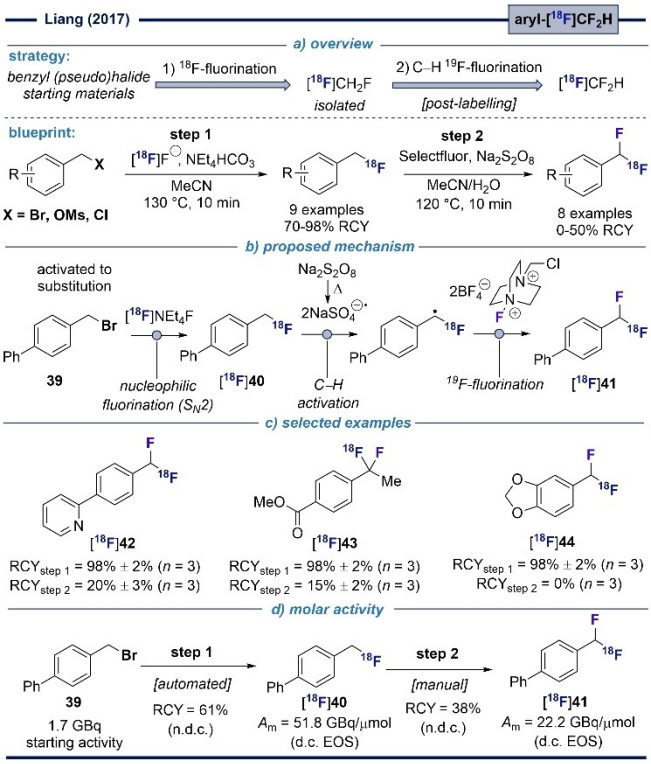
the α-carbon, in contrast to the detrimental effects of α-fluorine substitution.[22] Cleavage of the auxiliary from [^{18}F]**23** with aqueous KOH, gave the desired ^{18}F-difluoromethylarene ([^{18}F]**24**) in a one-pot protocol (Scheme 6b). 25 examples of aryl-[^{18}F]CF_2H compounds were prepared, in up to 61 % RCY, including several heterocycles (e.g. [^{18}F]**25**, [^{18}F]**26**), radiotracers and bioactive molecules (e.g. [^{18}F]**27**, [^{18}F]**28**) (Scheme 6c). As tertiary amines could engage in side reactivity with **20** by reacting at nitrogen instead of the α-carbonyl position, the Li-enolate formed by deprotonation with LiHMDS could be brominated separately and the crude material subjected to ^{18}F-fluorination, e.g. [^{18}F]**29** (19 % RCY). Ritter and co-workers studied A_m in detail, after [^{18}F]**30** was initially isolated in 43 % RCY and in low A_m (0.02 GBq/μmol) (Scheme 6d). In their study of isotopic dilution, no isotopic exchange with [^{18}F]fluoride was observed for **21**, **23** and **24**, suggesting these intermediates were unlikely to release ^{19}F-fluoride under the reaction conditions. In a separate experiment, the α-bromo-α-fluoro intermediate **22** was found to form the ^{19}F-fluorination product **23** in 9 % yield in the presence of tetraethylammonium hydrogencarbonate, likely via ^{19}F-fluoride release. Employing tetrabutylammonium mesylate as an alternative [^{18}F]fluoride elution base with a diisopropylethylamine activator, [^{18}F]**30** was obtained in 8 % RCY and improved A_m (3 GBq/μmol).

Gouverneur and co-workers disclosed an approach to ^{18}F-difluoromethoxy derivatives exploiting the halex reactivity of α-bromo-carbonyl compounds in 2017 (Scheme 7a).[23] Ethyl α-bromo-α-fluoro(aryloxy)acetates were prepared from the relevant phenol in two steps, and these materials were radiofluorinated with [^{18}F]KF.K_{222} at 50 °C, in 12 examples (e.g. [^{18}F]**31**-[^{18}F]**33**, 35–84 % RCY) (Scheme 7b). The [^{18}F]α,α-difluoroaryloxy acetic acid [^{18}F]**34** was isolated in 36 % RCY and A_m of 0.37 GBq/μmol (Scheme 7c). The carboxy fragment could be cleaved using $AgNO_3$ and $K_2S_2O_8$ to give [^{18}F]OCF_2H compound [^{18}F]**35** (22 % RCY, A_m = 0.30 GBq/μmol). Alternative post-labelling transformations were also applicable, such as cyclisation of [^{18}F]**36** with diamine **37** to yield [^{18}F]**38** (Scheme 7c).

A third halex strategy was disclosed by Liang and co-workers in 2017 (Scheme 8a).[24] Their method relies on the favourable substitution reactivity of [^{18}F]fluoride with benzylic (pseudo)halide substrates (e.g. **39**) to yield intermediate ^{18}F-monofluoro-methylarenes (e.g. [^{18}F]**40**, 9 examples, up to 98 % RCY). This approach avoids isotopic dilution considering that the substrate is not fluorinated. This product was then HPLC-purified in advance of a post-labelling C–H ^{19}F-fluorination with $Na_2S_2O_8$ and Selectfluor, proposed to proceed via a radical mechanism to yield the ^{18}F-difluoromethylarene (e.g. [^{18}F]**41**) (Scheme 8b). The desired products were obtained in 0–50 % RCY (8 examples, e.g. [^{18}F]**42**-[^{18}F]**44**) (Scheme 8c). Starting from 1.7 GBq [^{18}F]fluoride, an automated ^{18}F-fluorination of **39** gave [^{18}F]**40**, isolated in 61 % RCY in high A_m of 51.8 GBq/μmol (Scheme 8d). The C–H fluorination was carried out manually and furnished [^{18}F]**41** in 38 % isolated RCY and in a promising A_m of 22.2 GBq/μmol. The authors suggest that



Scheme 7. Radiosynthesis of aryl-[^{18}F]OCF_2- compounds from ethyl aryl(oxy) acetates. a) Summary. b) Representative substrate scope. c) ^{18}F-Product isolation, derivatisation and measurement of A_m. n.d.c. = non-decay corrected, d.c. EOS = decay-corrected to end-of-synthesis.

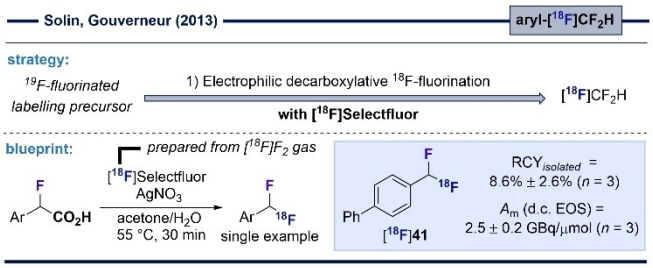


Scheme 8. Radiosynthesis of aryl-[^{18}F]CF_2H via aryl-[^{18}F]CFH_2 intermediates. a) Summary. b) Proposed mechanism. c) Representative substrate scope, RCY given for each step (step 1 = ^{18}F-fluorination, step 2 = ^{19}F-fluorination). d) ^{18}F-Product isolation and measurement of A_m. n.d.c. = non-decay corrected, d.c. EOS = decay-corrected to end-of-synthesis.

the good A_m indicates limited isotopic exchange processes of [^{18}F]**40** with BF_4-containing Selectfluor.

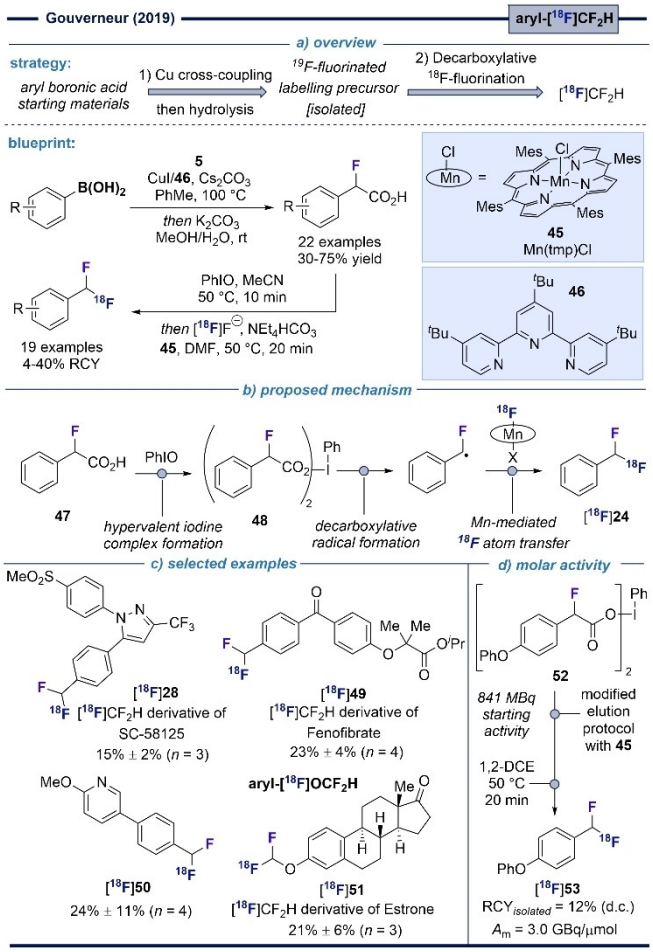
2.2. Decarboxylative ^{18}F-fluorination

Decarboxylative functionalisation is attractive to synthetic chemists,[25] and as described in the previous section, carboxyl fragments are versatile synthetic handles, rendering them well suited for ^{18}F-radiochemistry.[23] A seminal radiosynthesis of aryl-[^{18}F]CF_2H compounds was disclosed in 2013 by Gouverneur, Solin and co-workers. Employing a previous radiosynthesis of [^{18}F]Selectfluor bistriflate,[26] a Ag-mediated electrophilic decarboxylative fluorination of α-fluoro aryl acetic acids could be applied to the radiosynthesis of [^{18}F]**41**, isolated in 8.6 % RCY and in moderate A_m of 2.5 GBq/μmol (Scheme 9).[27] The use of [^{18}F]F_2-derived [^{18}F]Selectfluor could however limit this method's applicability.



Scheme 9. Radiosynthesis of aryl-[^{18}F]CF_2H with [^{18}F]Selectfluor bistriflate. d.c. EOS = decay-corrected to end-of-synthesis.

In order to allow for the use of [^{18}F]fluoride instead of [^{18}F]Selectfluor, Groves and co-workers developed a decarboxylative (radio)fluorination platform, which proceeded via a radical mechanism with a manganese(III) tetramesitylporphyrin catalyst (**45**) and an iodosylbenzene oxidant.[28] With this mode of reactivity in mind, Gouverneur and co-workers devised a radiosynthesis of aryl-[^{18}F]CF_2H compounds in 2019 (Scheme 10a).[29] A cross-coupling of aryl boronic acids and ethyl bromofluoroacetate (**5**) using a Cu(I) and terpyridine (**46**) catalyst system was developed to prepare the α-fluoro carboxylic acid labelling precursors in a single step. The radiofluorination of such substrates (**47**) then proceeded with prior formation of the iodine(III) carboxylate intermediate (**48**) in MeCN, followed by a solvent exchange to DMF, where [^{18}F]fluoride and **45** were added. A key ^{18}F–Mn complex is proposed to form, capable of an ^{18}F-atom transfer to alkyl radicals generated by decarboxylation (Scheme 10b). This method yielded the desired ^{18}F-difluoromethylarenes (19 examples, up to 40 % RCY) (Scheme 10c). Complex molecules, including those derived from pharmaceuticals, such as [^{18}F]**28** and [^{18}F]**49**,

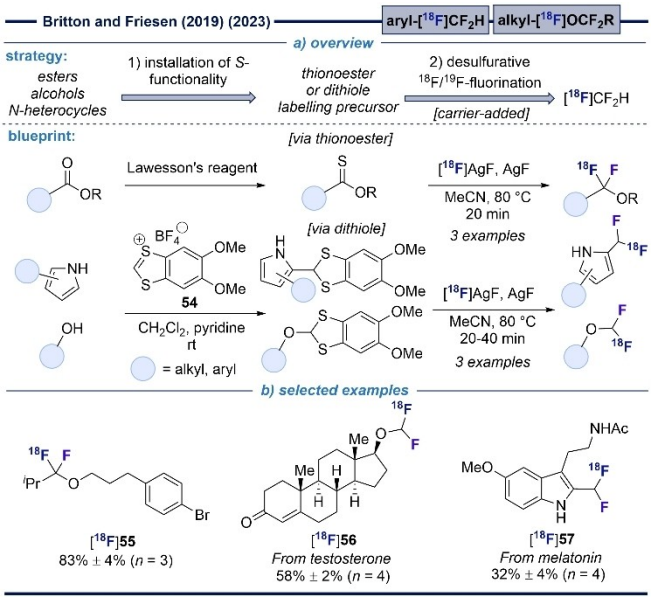


Scheme 10. Radiosynthesis of aryl-[^{18}F]CF_2H via a Mn-mediated decarboxylative ^{18}F-fluorination. a) Summary. b) Proposed mechanism. c) Representative substrate scope. d) ^{18}F-Product isolation and A_m measurement. d.c. = decay-corrected.

could be prepared. The technology was also adapted to the radiosynthesis of an aryl-[^{18}F]OCF_2H compound [^{18}F]**51**, prepared in 21 % RCY. Applying a modified elution protocol with the catalyst **45** and using the pre-formed iodine(III) carboxylate **52**, the ^{18}F-difluoromethylarene [^{18}F]**53** was isolated in 12 % RCY, with A_m of 3 GBq/μmol (Scheme 10d).

2.3. Desulfurisation-^{18}F-fluorination

Desulfurisation has proven to be a viable strategy for the synthesis of *N*-difluoromethyl compounds and this can also be used for the carrier-added synthesis of [^{18}F]CF_2 compounds.[30] In an early report by Haufe and co-workers in 2010, an α-fluorinated alkyl aryl thioether was transformed to the ^{18}F-difluorinated compound in an oxidative desulfurisation. However, despite the use of a pre-fluorinated substrate, the reaction only proceeded successfully under carrier-added conditions in up to 9 % RCY.[31] Britton, Friesen and co-workers reported that sulfur-based functionalities, such as thionoesters and dithioles (obtained using a reagent, **54**), were amenable to silver-mediated desulfurisation-fluorination (Scheme 11a).[32] The reaction successfully



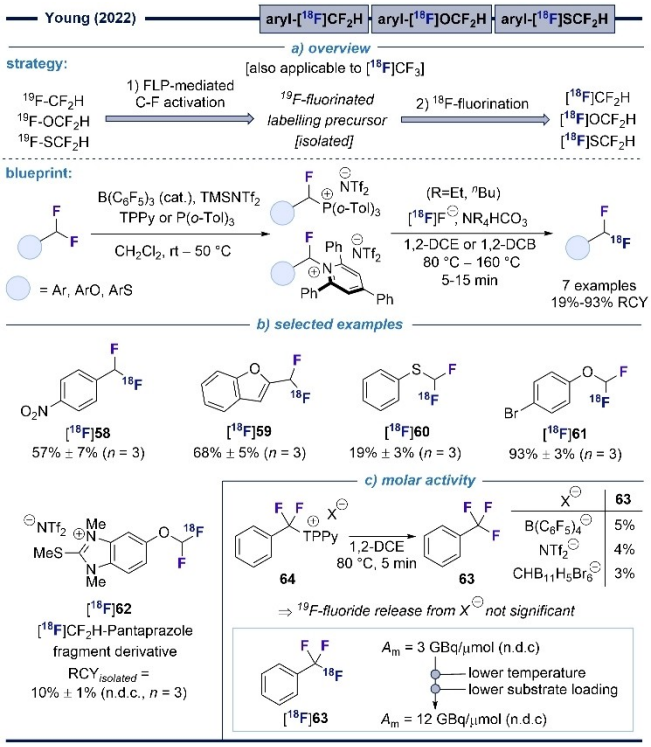
Scheme 11. Carrier-added radiosynthesis of [^{18}F]CF_2-compounds via desulfurisation. a) Summary. b) Representative scope molecule examples.

furnishes ^{18}F-difluorinated compounds (alkyl-[^{18}F]OCF_2R, [^{18}F]**55**; alkyl-[^{18}F]OCF_2H, [^{18}F]**56**; and heteroaryl-[^{18}F]CF_2H, [^{18}F]**57**) with the addition of excess Ag^{19}F, required as the substrates are not fluorinated (Scheme 11b).

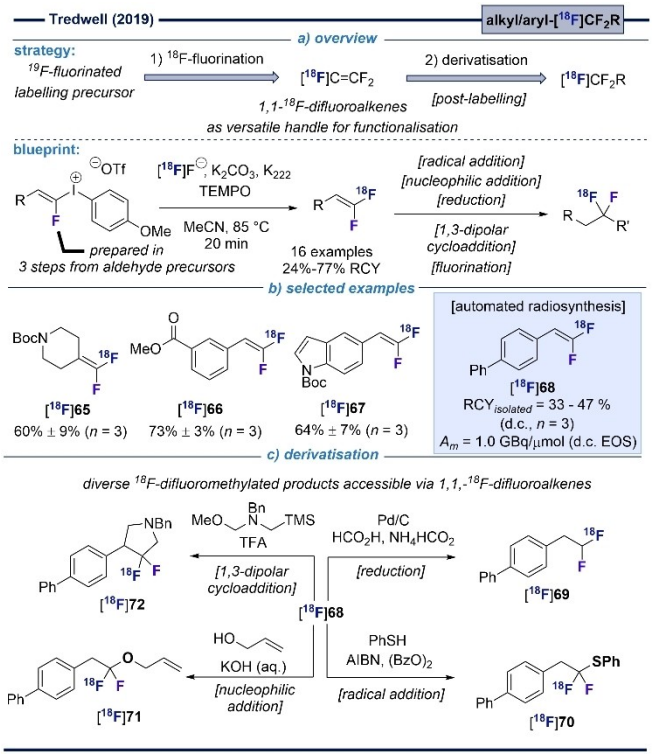
2.4. ^{18}F-Fluorination of onium salts

Onium (e.g. ammonium, phosphonium, sulfonium and halonium) salts have attracted significant attention from radiochemists, due to their favourable properties, including their excellent reactivity in radiofluorination.[33] As such, they can also be used to install ^{18}F-difluoromethyl functionalities.

Young and co-workers have recently developed a solution to the synthesis of ^{18}F-polyfluorinated motifs, including several [^{18}F]CF_2H moieties.[34] Overall, the process represents a formal isotopic exchange, achieved via an intermediate onium salt synthesised directly from the ^{19}F-compound. By applying their Frustrated Lewis Pair (FLP)-mediated C–F activation technology, a single C–F bond trifluoromethyl- or difluoromethylarene could be selectively activated and subsequently trapped with either tri(*o*-tolyl)phosphine (P(*o*-Tol)$_3$) or 2,4,6-triphenylpyridine (TPPy) to deliver an onium salt intermediate.[35] Previously, Young and co-workers had demonstrated the reactivity of these intermediates with various nucleophiles, and in 2022, this was extended to [^{18}F]fluoride (Scheme 12a). Various classes of [^{18}F]CF_2H compounds are accessible, including



Scheme 12. Radiosynthesis of [^{18}F]CF_2H compounds via C–F activation-derived onium salts. a) Summary. b) Representative substrate scope. c) A_m optimisation and measurement. n.d.c. = non-decay corrected.



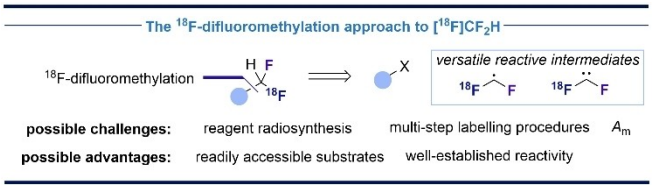
Scheme 13. Radiosynthesis of 1,1-^{18}F-difluoroalkenes. a) Summary. b) Representative substrate scope. c) Derivatisation. d.c. EOS = decay-corrected to end-of-synthesis.

(hetero)aryl-[^{18}F]CF_2H ([^{18}F]**58**, [^{18}F]**59**), aryl-[^{18}F]SCF_2H ([^{18}F]**60**) and (hetero)aryl-[^{18}F]OCF_2H ([^{18}F]**61**, [^{18}F]**62**), in RCY up to 93 % (Scheme 12b). While A_m for an [^{18}F]CF_2H compound was not measured, isolated [^{18}F]trifluorotoluene ([^{18}F]**63**) had a promising A_m of 12 GBq/μmol, after optimisation of both temperature and substrate (**64**) loading (Scheme 12c). Despite the use of a triflimide counterion, ^{19}F NMR experiments suggested that the amount of ^{19}F-fluorinated product formed in the presence of alternative counterions was similar, implying this was not responsible for ^{19}F-isotopic contamination.

In 2019, Tredwell and co-workers reported a radiosynthesis of 1,1-^{18}F-difluoroalkenes from iodonium triflate precursors and [^{18}F]fluoride (Scheme 13a).[36] A series of 16 molecules were prepared in up to 77 % RCY (e.g. [^{18}F]**65**-[^{18}F]**68**). The radiosynthesis of [^{18}F]**68** was automated and this was isolated in 33–47 % RCY and in modest A_m of 1.0 GBq/μmol (Scheme 13b). These compounds, while themselves of interest as a difluorinated motif, can also act as versatile synthetic intermediates to access [^{18}F]CF_2-compounds (Scheme 13c). 1,1-^{18}F-difluoroalkene [^{18}F]**68** could be hydrogenated to the alkyl-[^{18}F]CF_2H compound [^{18}F]**69**, as well as reacted with radicals and nucleophiles to yield [^{18}F]SCF_2-compound [^{18}F]**70** and [^{18}F]OCF_2-compound [^{18}F]**71**, respectively. Reacting [^{18}F]**68** in a 1,3-dipolar cycloaddition yielded [^{18}F]CF_2-containing pyrrolidine [^{18}F]**72**.

3. The ^{18}F-Difluoromethylation Approach

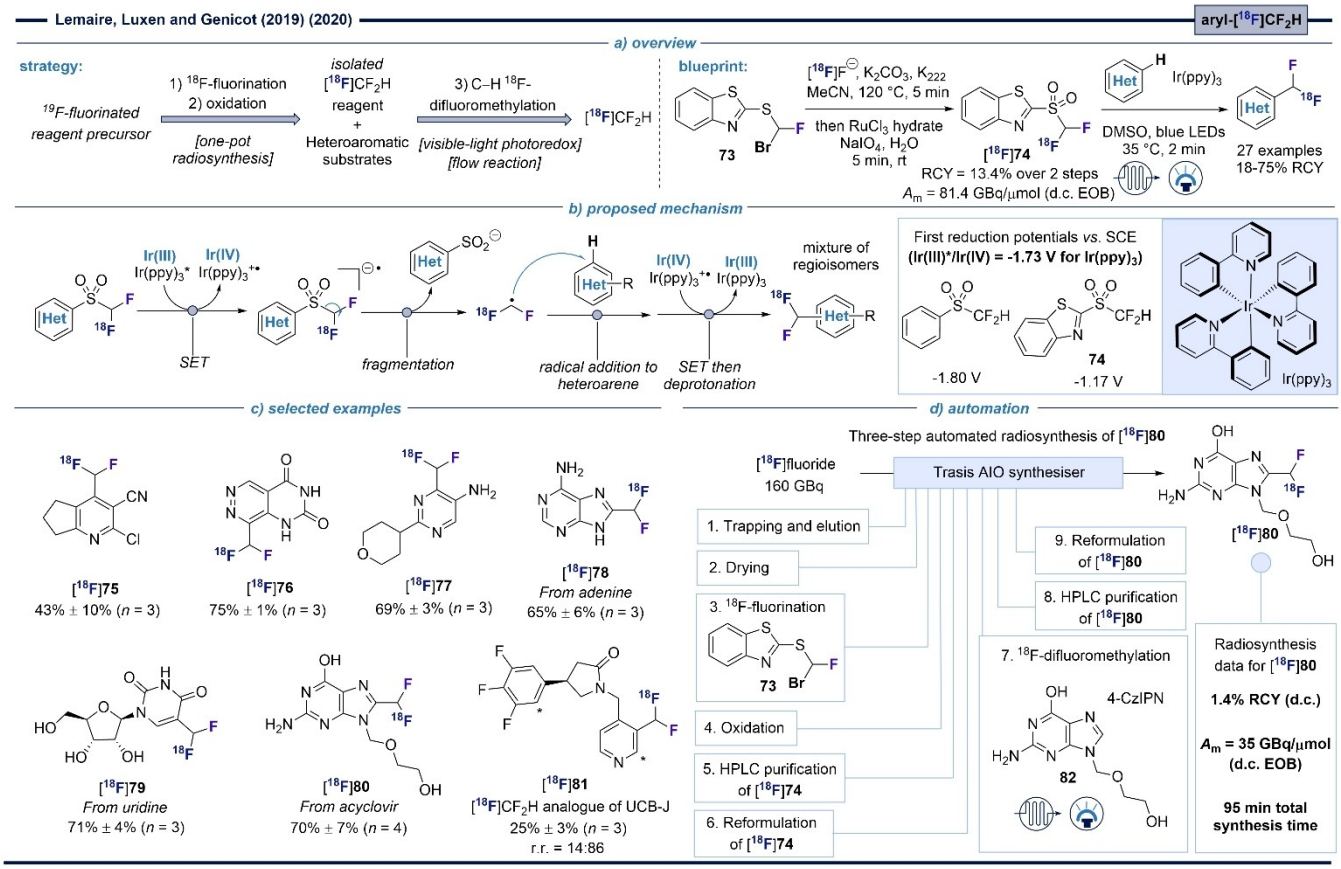
A second approach to [^{18}F]CF_2H compounds is ^{18}F-difluoromethylation (Scheme 14). Radiochemists have



Scheme 14. The ^{18}F-difluoromethylation approach to ^{18}F-difluoromethyl compounds.

drawn inspiration from the wealth of methods for difluoromethylation, the preferred disconnection in ^{19}F chemistry.[5] This approach requires a difluoromethylating reagent, which releases a reactive [^{18}F]CF_2-intermediate (or equivalent), e.g. difluoromethyl radical, cation, anion, or difluorocarbene. The reagent must be easily accessible in radiolabelled form in sufficient RCY and high A_m.

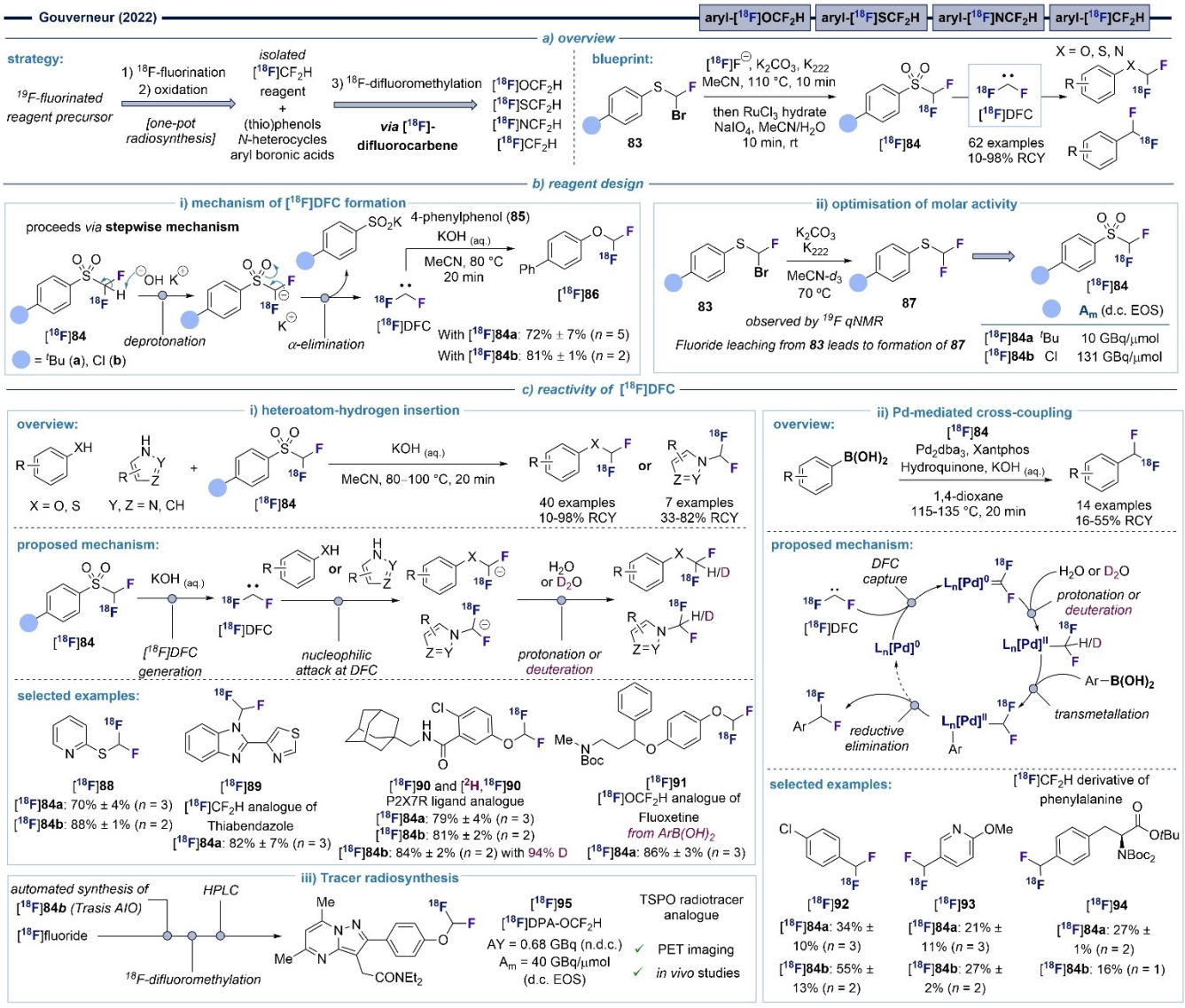
The preparation of a labelled reagent necessitates multi-step radiosynthesis, but this can be offset by removing the need for lengthy precursor synthesis. At least one step with this labelled reagent is then necessary to obtain the desired radiotracer.



Scheme 15. ^{18}F-Difluoromethylation of heteroarenes via [^{18}F]CF_2H radical. a) Summary. b) Proposed mechanism. c) Representative substrate scope. r.r. = regioisomeric ratio of desired:undesired product(s), other reactive positions indicated (*). d) Automation. d.c. EOB = decay-corrected to end-of-bombardment.

3.1. ^{18}F-Difluoromethylation via ^{18}F-difluoromethyl radical

The CF_2H radical is a powerful intermediate for difluoromethylation; it can be engaged in addition to alkenes and heteroarenes, transition metal catalysed cross-coupling and for bioconjugation. Harnessing this radical in ^{18}F-difluoromethylation therefore presents an attractive prospect for radiochemists.[5,37] In 2019, Lemaire, Luxen, Genicot and co-workers disclosed the radiosynthesis and application of a reagent that could be activated in a photoredox flow process to generate a [^{18}F]CF_2H radical (Scheme 15a).[38] A ^{18}F-difluoromethyl heteroaryl sulfone was chosen, as such reagents are effective in radical difluoromethylation,[39] and could be prepared applying a two-step, one-pot radiosynthesis. Starting from a benzothiazole-derived bromofluoromethyl heteroaryl sulfide (**73**), the ^{18}F-difluoromethyl heteroaryl sulfone ([^{18}F]**74**) was synthesised in 13.4 % RCY over 2 steps and in a high A_m of 81.4 GBq/μmol. The design of the sulfone reagent was further investigated, and structural optimisation resulted in similarly reactive reagents that were accessible in up to 8 % RCY and A_m up to 139 GBq/μmol.[40] The photocatalytic generation of [^{18}F]CF_2H radicals under blue light irradiation is suggested to proceed via reduction of the ^{18}F-difluoromethyl heteroaryl sulfone by photoexcited $Ir(ppy)_3$, which triggers a mesolytic cleavage of the radical anion to yield a sulfinate anion and a [^{18}F]CF_2H radical (Scheme 15b). In a photochemical Minisci-type reaction, 27 [^{18}F]CF_2H-functionalised heteroarenes were obtained in RCYs up to 75 % (e.g. [^{18}F]**75**–**81**) (Scheme 15c). Diverse heteroarenes were amenable to this transformation, including those derived from biorelevant compounds, (e.g. [^{18}F]**78**, [^{18}F]**79**). An ^{18}F-difluoromethylated analogue of the SV2A tracer [^{11}C]UCB–J ([^{18}F]**81**) was also accessible. As this substrate possessed multiple reactive sites, this led to a mixture of regioisomeric products. [^{18}F]**81** was obtained in an isolated RCY of 1.5 % and found to have similar target binding affinity to [^{11}C]UCB–J. In 2020, this method was fully automated using a Trasis AllInOne (AIO) radiosynthesiser (Scheme 15d).[41] The protocol included the radiosynthesis and purification of the sulfone reagent ([^{18}F]**74**), and the photoredox flow C–H ^{18}F-difluoromethylation of the antiherpetic drug acyclovir (**82**). ^{18}F-Difluoromethylated acyclovir ([^{18}F]**80**) was obtained in 1.4 % RCY and in A_m of 35 GBq/μmol, decay-corrected to the end of bombardment (EOB). The procedure took 95 minutes. The development of readily implementable, automated protocols for the synthesis of heteroaryl-[^{18}F]CF_2H compounds is important to enable PET imaging studies with novel ^{18}F-difluoromethylated radiotracers.



Scheme 16. ^{18}F-Difluoromethylation of *O*,*S*,*N*-nucleophiles and aryl boronic acids via [^{18}F]DFC. a) Summary. b) Reagent design i) Proposed mechanism of [^{18}F]DFC release. ii) A_m optimisation. c) Reactivity of [^{18}F]DFC in i) heteroatom-hydrogen insertion, ii) Pd-mediated cross-coupling and iii) tracer synthesis. n.d.c. = non-decay corrected, d.c. EOS = decay-corrected to end-of-synthesis.

3.2. ^{18}F-Difluoromethylation via [^{18}F]difluorocarbene

Difluorocarbene (DFC) is another powerful synthetic intermediate for the preparation of difluoromethylated compounds.[5,42] It possesses a singlet ground state and as an electrophile, reacts efficiently with nucleophiles.[43] In addition, this reactive intermediate can be engaged in metal-catalysed cross-coupling processes.[44] Tens of reagents have been reported for its application in organic synthesis.[42]

In 2022, Gouverneur and co-workers disclosed a [^{18}F]DFC-releasing reagent for radiosynthesis (Scheme 16a).[45] ^{18}F-Difluoromethyl aryl sulfones were selected as they could be readily prepared from [^{18}F]fluoride via a ^{18}F-fluorination-oxidation route from **83**, purified readily by HPLC and are non-volatile.[38] A proof-of-concept radiosynthesis and ^{18}F-difluoromethylation was demonstrated with [^{18}F]difluoromethyl 4-*tert*-butylphenyl sulfone ([^{18}F]**84a**), which successfully reacted with 4-phenylphenol (**85**) under basic conditions to give [^{18}F]**86** in 72 % RCY (Scheme 16bi). Computational studies suggested that this O–H insertion takes place via a stepwise mechanism of [^{18}F]DFC release, with deprotonation followed by α-elimination of aryl sulfinate. Several analogues of **84** were prepared, and their A_m and reactivity were compared. [^{18}F]Difluoromethyl 4-chlorophenyl sulfone ([^{18}F]**84b**) was a superior [^{18}F]DFC reagent to [^{18}F]**84a**, as it was accessible in higher A_m (131 GBq/μmol) and displayed higher reactivity towards model substrate **85**, ([^{18}F]**86**, RCY = 81 %). Optimisation of A_m was guided by ^{19}F NMR experiments, which suggested that ^{19}F-fluoride leaching from **83** caused the formation of ^{19}F-difluoromethyl compound **87**, inherently leading to lower A_m. The amount of ^{19}F-fluoride leaching

from **83** varied with the substituent at the 4-position, which facilitated the discovery of [^{18}F]**84b** that was accessible in higher A_m and less susceptible to isotopic dilution via this pathway (Scheme 16bii).

^{18}F-Difluoromethylation reactivity extended to a range of phenols, thiophenols and *N*-heterocycles (Scheme 16ci). 47 examples of this reactivity were established in RCY up to 98 % (e.g. [^{18}F]**88**-[^{18}F]**91**). The reaction tolerated various heterocycles and functional groups, as well as complex molecules, and [^{18}F]CF_2H analogues of drugs and radiotracers were also accessible. Notably, this method marks the first non-carrier-added synthesis of [^{18}F]NCF_2H compounds. It is suggested reactions with *O*,*S*,*N*- nucleophiles proceeded via nucleophilic attack at [^{18}F]DFC, followed by protonation from the H_2O co-solvent. In D_2O, the [^{2}H,^{18}F]CF_2H product was obtained, e.g. [^{2}H,^{18}F]**90** was prepared with 94 % D incorporation. The ^{18}F-difluoromethylation of phenols was also applied in tandem with the oxidation of aryl boronic acids, which serve as useful handles for derivatisation in synthesis. For example, an [^{18}F]OCF_2H analogue of fluoxetine ([^{18}F]**91**) was prepared in 86 % RCY.

A Pd-mediated ^{18}F-difluoromethylation of aryl boronic acids was also developed, enabling access to aryl-[^{18}F]CF_2H products from aryl boron precursors in a direct and regioselective fashion (Scheme 16cii).[46] The reaction is suggested to proceed as described by Zhang and co-workers via [^{18}F]DFC capture at Pd(0). This was demonstrated in 14 examples in up to 55 % RCY (e.g. [^{18}F]**92**-[^{18}F]**94**).

Finally, in a semi-automated radiosynthesis, 680 MBq of [^{18}F]**95**, a [^{18}F]CF_2H analogue of the TSPO radiotracer [^{18}F]DPA–714, was prepared in A_m of 40 GBq/μmol (Scheme 16ciii).[47] This was sufficient for proof-of-concept PET imaging and in vivo studies, demonstrating the ability of this method to provide radiotracers for preclinical work.

4. Summary and Outlook

This Minireview summarises the state-of-the-art methods to access ^{18}F-difluoromethylated compounds. ^{18}F-Fluorination is an appealing strategy, as it allows for the direct use of [^{18}F]fluoride, but it can be limited by reactivity and synthetic challenges. For example, many of the ^{18}F-fluorination conditions described in this Minireview have not been applied beyond activated benzylic or α-heteroatom positions. The advent of new solutions, either using new classes of substrates or novel activation strategies will continue to impact the field and emerging technologies, such as photochemistry and electrochemistry, may also play a role in future.[48] As ^{18}F-fluorination plays an instrumental role in the radiosynthesis of reagents for ^{18}F-difluoromethylation, further advances in this area have benefits across the field. Meanwhile, ^{18}F-difluoromethylation offers radiochemists the opportunity to exploit the large number of ^{19}F-difluoromethylation conditions reported in the literature. Based on the two examples considered, we can expect this approach will play a role in advancing the field, possibly with expansion of [^{18}F]CF_2H reagents beyond ^{18}F-difluoromethyl sulfones. To date, as the radiosynthesis of ^{18}F-difluoromethylarenes has been well explored, further expansion of the ^{18}F-difluoromethyl radiochemical space would be of interest. For example, the general radiosynthesis of ^{18}F-difluoromethylated alkyl scaffolds (e.g. alkyl-[^{18}F]CF_2H, alkyl-[^{18}F]CF_2R, alkyl-[^{18}F]OCF_2H) and geminal-^{18}F-difluorides/^{18}F-difluoromethylene groups remains unsolved. A_m remains a significant challenge in the radiosynthesis of [^{18}F]CF_2H compounds. While several groups have been able to isolate ^{18}F-difluoromethylated products in high A_m, this will remain central in the development of new methodologies. As highlighted by several examples in this Minireview, experiments that interrogate detrimental isotopic exchange and dilution processes can be valuable in optimising A_m. A complementary carbon-11 based radiolabelling strategy could also provide a new solution to the A_m challenge. Pike and co-workers have demonstrated the value of this concept in ^{11}C-trifluoromethylation with [^{11}C]fluoroform, which is available in high A_m starting from [^{11}C]methane.[49] Given the favourable properties of difluoromethyl functionality and the role these moieties play in drug discovery, we anticipate that the interest in [^{18}F]CF_2H motifs will continue with the discovery of a new generation of ^{18}F-difluoromethyl-containing preclinical radiotracers.

Acknowledgements

J.F. is grateful to the Centre for Doctoral Training in Synthesis for Biology and Medicine for a studentship, generously supported by GlaxoSmithKline, MSD, Syngenta and Vertex. S.O. acknowledges financial support from Global Discovery Chemistry, Therapeutics Discovery, Johnson & Johnson Innovative Medicine, Janssen-Cilag S.A., Toledo, Spain.

Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Keywords: Fluorine · Radiochemistry · Positron Emission Tomography · Difluoromethylation · Radiopharmaceuticals

[1] S. M. Ametamey, M. Honer, P. A. Schubiger, *Chem. Rev.* **2008**, *108*, 1501.
[2] a) J. K. Willmann, N. van Bruggen, L. M. Dinkelborg, S. S. Gambhir, *Nat. Rev. Drug Discov.* **2008**, *7*, 591; b) S. G. Nerella, P. Singh, T. Sanam, C. S. Digwal, *Front. Med.* **2022**, *9*, 812270.
[3] J. Rong, A. Haider, T. E. Jeppesen, L. Josephson, S. H. Liang, *Nat. Commun.* **2023**, *14*, 3257.
[4] a) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, *37*, 320; b) E. P. Gillis, K. J. Eastman, M. D. Hill, D. J. Donnelly, N. A. Meanwell, *J. Med. Chem.* **2015**, *58*,

8315; c) M. Inoue, Y. Sumii, N. Shibata, *ACS Omega* **2020**, *5*, 10633.
[5] J. B. I. Sap, C. F. Meyer, N. J. W. Straathof, N. Iwumene, C. W. am Ende, A. A. Trabanco, V. Gouverneur, *Chem. Soc. Rev.* **2021**, *50*, 8214.
[6] a) L. Xing, D. C. Blakemore, A. Narayanan, R. Unwalla, F. Lovering, R. A. Denny, H. Zhou, M. E. Bunnage, *ChemMedChem* **2015**, *10*, 715; b) N. A. Meanwell, *J. Med. Chem.* **2018**, *61*, 5822.
[7] a) J. A. Erickson, J. I. McLoughlin, *J. Org. Chem.* **1995**, *60*, 1626; b) Q. A. Huchet, B. Kuhn, B. Wagner, N. A. Kratochwil, H. Fischer, M. Kansy, D. Zimmerli, E. M. Carreira, K. Müller, *J. Med. Chem.* **2015**, *58*, 9041; c) C. D. Sessler, M. Rahm, S. Becker, J. M. Goldberg, F. Wang, S. J. Lippard, *J. Am. Chem. Soc.* **2017**, *139*, 9325; d) Y. Zafrani, G. Sod-Moriah, D. Yeffet, A. Berliner, D. Amir, D. Marciano, S. Elias, S. Katalan, N. Ashkenazi, M. Madmon, E. Gershonov, S. Saphier, *J. Med. Chem.* **2019**, *62*, 5628; e) N. Malquin, K. Rahgoshay, N. Lensen, G. Chaume, E. Miclet, T. Brigaud, *Chem. Commun.* **2019**, *55*, 12487; f) B. Jeffries, Z. Wang, H. R. Felstead, J.-Y. Le Questel, J. S. Scott, E. Chiarparin, J. Graton, B. Linclau, *J. Med. Chem.* **2020**, *63*, 1002; g) Y. Zafrani, S. Saphier, E. Gershonov, *Future Med. Chem.* **2020**, *12*, 361.
[8] N. A. Meanwell, *J. Agric. Food Chem.* **2023**, *71*, 18087.
[9] a) K. B. Wiberg, P. R. Rablen, *J. Am. Chem. Soc.* **1993**, *115*, 614; b) L. Wang, J. Wei, R. Wu, G. Cheng, X. Li, J. Hu, Y. Hu, R. Sheng, *Org. Chem. Front.* **2017**, *4*, 214; c) D. O'Hagan, *Chem. Soc. Rev.* **2008**, *37*, 308.
[10] K. Jansen, L. Heirbaut, R. Verkerk, J. D. Cheng, J. Joossens, P. Cos, L. Maes, A.-M. Lambeir, I. De Meester, K. Augustyns, P. Van der Veken, *J. Med. Chem.* **2014**, *57*, 3053.
[11] C. Borsari, D. Rageot, F. Beaufils, T. Bohnacker, E. Keles, I. Buslov, A. Melone, A. M. Sele, P. Hebeisen, D. Fabbro, P. Hillmann, M. P. Wymann, *ACS Med. Chem. Lett.* **2019**, *10*, 1473.
[12] J. M. Shin, Y. M. Cho, G. Sachs, *J. Am. Chem. Soc.* **2004**, *126*, 7800.
[13] S. Brand, N. R. Norcross, S. Thompson, J. R. Harrison, V. C. Smith, D. A. Robinson, L. S. Torrie, S. P. McElroy, I. Hallyburton, S. Norval, P. Scullion, L. Stojanovski, F. R. C. Simeons, D. van Aalten, J. A. Frearson, R. Brenk, A. H. Fairlamb, M. A. J. Ferguson, P. G. Wyatt, I. H. Gilbert, K. D. Read, *J. Med. Chem.* **2014**, *57*, 9855.
[14] R. Halder, T. Ritter, *J. Org. Chem.* **2021**, *86*, 13873.
[15] a) S. P. McCluskey, C. Plisson, E. A. Rabiner, O. Howes, *Eur. J. Nucl. Med. Mol. Imaging* **2020**, *47*, 451; b) G. Luurtsema, V. Pichler, S. Bongarzone, Y. Seimbille, P. Elsinga, A. Gee, J. Vercouillie, *EJNMMI Radiopharm. Chem.* **2021**, *6*, 34.
[16] H. Martinez, A. Rebeyrol, T. B. Nelms, W. R. Dolbier Jr, *J. Fluorine Chem.* **2012**, *135*, 167.
[17] J. Rong, S. H. Liang, in *Fluorination. Synthetic Organofluorine Chemistry.* (Eds.: J, Hu, T. Umemoto), Springer, Singapore, **2020**, pp. 1–14.
[18] a) T. Khotavivattana, S. Verhoog, M. Tredwell, L. Pfeifer, S. Calderwood, K. Wheelhouse, T. L. Collier, V. Gouverneur, *Angew. Chem. Int. Ed.* **2015**, *54*, 9991; b) S. Verhoog, L. Pfeifer, T. Khotavivattana, S. Calderwood, T. L. Collier, K. Wheelhouse, M. Tredwell, V. Gouverneur, *Synlett* **2016**, *27*, 25.
[19] Q. Zhao, P. G. Isenegger, T. C. Wilson, J. B. I. Sap, F. Guibbal, L. Lu, V. Gouverneur, Q. Shen, *CCS Chem.* **2020**, *2*, 1921.
[20] H. Shi, A. Braun, L. Wang, S. H. Liang, N. Vasdev, T. Ritter, *Angew. Chem. Int. Ed.* **2016**, *55*, 10786.
[21] S. Ge, W. Chaładaj, J. F. Hartwig, *J. Am. Chem. Soc.* **2014**, *136*, 4149.
[22] D. Kost, K. Aviram, *Isr. J. Chem.* **1985**, *26*, 349.
[23] T. Khotavivattana, S. Calderwood, S. Verhoog, L. Pfeifer, S. Preshlock, N. Vasdev, T. L. Collier, V. Gouverneur, *Org. Lett.* **2017**, *19*, 568.
[24] G. Yuan, F. Wang, N. A. Stephenson, L. Wang, B. H. Rotstein, N. Vasdev, P. Tang, S. H. Liang, *Chem. Commun.* **2017**, *53*, 126.
[25] a) A. Varenikov, E. Shapiro, M. Gandelman, *Chem. Rev.* **2021**, *121*, 412; b) Z. Zeng, A. Feceu, N. Sivendran, L. J. Gooßen, *Adv. Synth. Catal.* **2021**, *363*, 2678; c) P. Xiao, X. Pannecoucke, J.-P. Bouillon, S. Couve-Bonnaire, *Chem. Soc. Rev.* **2021**, *50*, 6094.
[26] H. Teare, E. G. Robins, A. Kirjavainen, S. Forsback, G. Sandford, O. Solin, S. K. Luthra, V. Gouverneur, *Angew. Chem. Int. Ed.* **2010**, *49*, 6821.
[27] S. Mizuta, I. S. R. Stenhagen, M. O'Duill, J. Wolstenhulme, A. K. Kirjavainen, S. J. Forsback, M. Tredwell, G. Sandford, P. R. Moore, M. Huiban, S. K. Luthra, J. Passchier, O. Solin, V. Gouverneur, *Org. Lett.* **2013**, *15*, 2648.
[28] X. Huang, W. Liu, J. M. Hooker, J. T. Groves, *Angew. Chem. Int. Ed.* **2015**, *54*, 5241.
[29] J. B. I. Sap, T. C. Wilson, C. W. Kee, N. J. W. Straathof, C. W. am Ende, P. Mukherjee, L. Zhang, C. Genicot, V. Gouverneur, *Chem. Sci.* **2019**, *10*, 3237.
[30] F. G. Zivkovic, G. Wycich, L. Liu, F. Schoenebeck, *J. Am. Chem. Soc.* **2024**, *146*, 1276.
[31] V. Hugenberg, S. Wagner, K. Kopka, O. Schober, M. Schäfers, G. Haufe, *J. Org. Chem.* **2010**, *75*, 6086.
[32] a) J. Newton, D. Driedger, M. B. Nodwell, P. Schaffer, R. E. Martin, R. Britton, C. M. Friesen, *Chem. Eur. J.* **2019**, *25*, 15993; b) J. J. Newton, A. J. Brooke, B. Duhamel, J. M. Pulfer, R. Britton, C. M. Friesen, *J. Org. Chem.* **2020**, *85*, 13298; c) J. J. Newton, G. Engüdar, A. J. Brooke, M. B. Nodwell, H. Horngren-Rhodes, R. E. Martin, P. Schaffer, R. Britton, C. M. Friesen, *Chem. Eur. J.* **2023**, *29*, e202202862.
[33] H. H. Coenen, J. Ermert, *Clin. Transl. Imaging* **2018**, *6*, 169.
[34] S. Khanapur, K. Lye, D. Mandal, X. J. Wee, E. G. Robins, R. D. Young, *Angew. Chem. Int. Ed.* **2022**, *61*, e202210917.
[35] D. Mandal, R. Gupta, A. K. Jaiswal, R. D. Young, *J. Am. Chem. Soc.* **2020**, *142*, 2572.
[36] A. B. Frost, M. Brambilla, R. M. Exner, M. Tredwell, *Angew. Chem. Int. Ed.* **2019**, *58*, 472.
[37] Selected representative examples of difluoromethyl radical reactivity. a) Q.-Y. Lin, X.-H. Xu, K. Zhang, F.-L. Qing, *Angew. Chem. Int. Ed.* **2016**, *55*, 1479; b) C. F. Meyer, S. M. Hell, A. Misale, A. A. Trabanco, V. Gouverneur, *Angew. Chem. Int. Ed.* **2019**, *58*, 8829; c) Y. Fujiwara, J. A. Dixon, R. A. Rodriguez, R. D. Baxter, D. D. Dixon, M. R. Collins, D. G. Blackmond, P. S. Baran, *J. Am. Chem. Soc.* **2012**, *134*, 1494; d) R. R. Merchant, J. T. Edwards, T. Qin, M. M. Kruszyk, C. Bi, G. Che, D.-H. Bao, W. Qiao, L. Sun, M. R. Collins, O. O. Fadeyi, G. M. Gallego, J. J. Mousseau, P. Nuhant, P. S. Baran, *Science* **2018**, *360*, 75; e) V. Bacauanu, S. Cardinal, M. Yamauchi, M. Kondo, D. F. Fernández, R. Remy, D. W. C. MacMillan, *Angew. Chem. Int. Ed.* **2018**, *57*, 12543; f) B. Josephson, C. Fehl, P. G. Isenegger, S. Nadal, T. H. Wright, A. W. J. Poh, B. J. Bower, A. M. Giltrap, L. Chen, C. Batchelor-McAuley, G. Roper, O. Arisa, J. B. I. Sap, A. Kawamura, A. J. Baldwin, S. Mohammed, R. G. Compton, V. Gouverneur, B. G. Davis, *Nature* **2020**, *585*, 530; g) A. F. M. Noisier, M. J. Johansson, L. Knerr, M. A. Hayes, W. J. Drury III, E. Valeur, L. R. Malins, R. Gopalakrishnan, *Angew. Chem. Int. Ed.* **2019**, *58*, 19096.
[38] L. Trump, A. Lemos, B. Lallemand, P. Pasau, J. Mercier, C. Lemaire, A. Luxen, C. Genicot, *Angew. Chem. Int. Ed.* **2019**, *58*, 13149.
[39] a) J. Rong, L. Deng, P. Tan, C. Ni, Y. Gu, J. Hu, *Angew. Chem. Int. Ed.* **2016**, *55*, 2743; b) W. Fu, X. Han, M. Zhu, C.

Xu, Z. Wang, B. Ji, X.-Q. Hao, M.-P. Song, *Chem. Commun.* **2016**, *52*, 13413.
[40] A. L. P. Lemos, L. Trump, B. Lallemand, P. Pasau, J. Mercier, C. Lemaire, J.-C. Monbaliu, C. Genicot, A. Luxen, *Catalysts* **2020**, *10*, 275.
[41] L. Trump, A. Lemos, J. Jacq, P. Pasau, B. Lallemand, J. Mercier, C. Genicot, A. Luxen, C. Lemaire, *Org. Process Res. Dev.* **2020**, *24*, 734.
[42] C. Ni, J. Hu, *Synthesis* **2014**, *46*, 842.
[43] D. L. S. Brahms, W. P. Dailey, *Chem. Rev.* **1996**, *96*, 1585.
[44] W. Zhou, W.-J. Pan, J. Chen, M. Zhang, J.-H. Lin, W. Cao, J.-C. Xiao, *Chem. Commun.* **2021**, *57*, 9316.
[45] J. B. I. Sap, C. F. Meyer, J. Ford, N. J. W. Straathof, A. B. Dürr, M. J. Lelos, S. J. Paisey, T. A. Mollner, S. M. Hell, A. A. Trabanco, C. Genicot, C. W. am Ende, R. S. Paton, M. Tredwell, V. Gouverneur, *Nature* **2022**, *606*, 102.
[46] a) Z. Feng, Q. Q. Min, X. Zhang, *Org. Lett.* **2016**, *18*, 44; b) X.-Y. Deng, J.-H. Lin, J.-C. Xiao, *Org. Lett.* **2016**, *18*, 4384; c) Z. Feng, Q.-Q. Min, X.-P. Fu, L. An, X. Zhang, *Nat. Chem.* **2017**, *9*, 918; d) X.-P. Fu, X.-S. Xue, X.-Y. Zhang, Y.-L. Xiao, S. Zhang, Y.-L. Guo, X. Leng, K. N. Houk, X. Zhang, *Nat. Chem.* **2019**, *11*, 948.
[47] a) M. L. James, R. R. Fulton, J. Vercoullie, D. J. Henderson, L. Garreau, S. Chalon, F. Dollé, S. Selleri, D. Guilloteau, M. Kassiou, *J. Nucl. Med.* **2008**, *49*, 814; b) J. Zheng, A. Winkeler, M.-A. Peyronneau, F. Dollé, R. Boisgard, *Mol. Imaging Biol.* **2016**, *18*, 127.
[48] a) D. Hernández-Valdés, S. Sadeghi, *Chem. Rec.* **2021**, *21*, 2397; b) D. Lin, L. M. Lechermann, M. P. Huestis, J. Marik, J. B. I. Sap, *Angew. Chem. Int. Ed.* **2024**, *63*, e202317136.
[49] a) M. B. Haskali, V. W. Pike, *Chem. Eur. J.* **2017**, *23*, 8156; b) N. J. Young, V. W. Pike, C. Taddei, *ACS Omega* **2020**, *5*, 19557; c) S. Telu, S. Jana, M. B. Haskali, B. Y. Yang, J. E. Jakobsson, Q. Zhao, K. M. Ramos-Torres, P. Brugarolas, V. W. Pike, *Chem. Eur. J.* **2023**, *29*, e202204004.

Manuscript received: March 12, 2024
Accepted manuscript online: April 19, 2024
Version of record online: ■■, ■■

Minireviews

Radiochemistry

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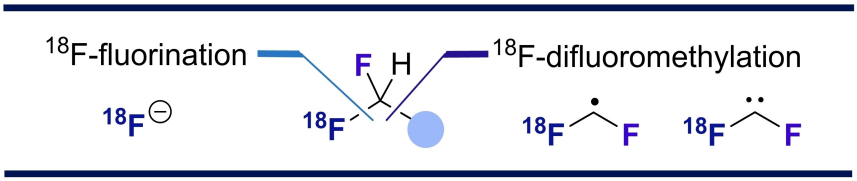
The ^{18}F-Difluoromethyl Group: Challenges, Impact and Outlook



This Minireview summarises the progress radiochemists have made to access the difluoromethyl group in radiolabelled form. Particular attention is given to challenges they have faced, as well as the strategies employed to access this new radiochemical space.