Late-stage difluoromethylation: concepts, developments and perspective

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This review describes the recent advances made in difluoromethylation processes based on X–CF₂H bond formation where X is C(sp), C(sp²), C(sp³), O, N or S, a field of research that has benefited from the invention of multiple difluoromethylation reagents. The last decade has witnessed an upsurge of metal-based methods that can transfer CF₂H to C(sp²) sites both in stoichiometric and catalytic mode. Difluoromethylation of C(sp³)–H bond has also been accomplished through Minisci-type radical chemistry, a strategy best applied to heteroaromatics. Examples of electrophilic, nucleophilic, radical and cross-coupling methods have appeared to construct C(sp³)–CF₂H bonds, but cases of stereoselective difluoromethylation are still limited. In this sub-field, an exciting departure is the precise site-selective installation of CF₂H onto large biomolecules such as proteins. The formation of X–CF₂H bond where X is oxygen, nitrogen or sulfur is conventionally achieved upon reaction with ClCF₂H; more recently, numerous protocols have achieved X–H insertion with novel non-ozone depleting difluorocarbene reagents. All together, these advances have streamlined access to molecules of pharmaceutical relevance, and generated interest for process chemistry.

1. Introduction

It is widely recognised that the introduction of one or more fluorine atoms into molecules can have a significant impact on their physicochemical and biological properties.¹,² A key advantage of fluorinated motifs is their ability to mimic functional groups widespread in biologically active molecules.³ The C–F bond is strong with a bond dissociation energy (BDE) of up to...
130 kcal mol$^{-1}$, and is intermediate in length between C–H and C–O bonds albeit closer to the C–O bond (C–H 1.09 Å, C–F 1.35 Å, C–O 1.43 Å).$^{4,5}$ The C–F bond is also highly polarised with its stability deriving from an electrostatic C$^{+}\text{F}^{-}$ component. As a result, incorporation of fluorine can serve the purpose to improve metabolic robustness as well as modulate cellular membrane permeability.$^6$ Today, the inclusion of one or more fluorine atoms into biologically active compounds has become a common strategy for the design of pharmaceutical drugs and agrochemicals.

Over the past decade, fluorination chemistry has focused on carbon–fluorine (C–F) bond formation,$^{7,8}$ as well as the introduction of perfluoroalkyl (C$_n$F$_m$) group including numerous studies on trifluoromethylation (CF$_3$).$^9$–$^{17}$ In this review, we discuss the recent advances made in the field of difluoromethylation, where we formulate the key challenges, solutions, and future directions related to X–CF$_2$H bond formation where X is C(sp$^3$), C(sp$^3$), C(sp), O, N or S. A brief historical overview of key discoveries and developments is provided followed by a discussion of the unique properties of CF$_2$H. Strategies applied to access difluoromethylene ArCF$_2$H as well as methods leading to C(sp$^3$)–CF$_2$H bond formation are described next. The discussion then focuses on difluorocarbene reagents for the construction of X–CF$_2$H (where X = C, N, O, or S) bonds via X–H insertion, and on strategies to incorporate CF$_2$H onto alkenes and alkynes. Finally, we discuss the application of these technologies in an industrial context.

An early example of a molecule featuring CF$_2$H was disclosed by Swarts in the early 20th century, in the form of chlorodifluoromethane (ClCF$_2$H), also known as Freon-22.$^{18}$ This compound was primarily used as refrigerant, industrial cooling agent,
A motif was the deoxyfluorination of aldehydes (Scheme 1).20–22 Over 20 years, the most widely adopted reaction to construct the CF$_2$H group has provided access to a variety of CF$_2$H containing compounds, including those required for difluoromethylation.19 For many years, the most widely adopted reaction to construct the CF$_2$H motif was the deoxyfluorination of aldehydes (Scheme 1).20–22 Many reagents were developed for this transformation such as N$_2$N-diethylaminosulfur trifluoride (DAST) or bis(2-methoxyethyl)aminosulfur trifluoride (Deoxo-Fluor$^\text{®}$), all derived from gaseous sulfur tetrafluoride (SF$_4$). While these reagents have provided access to a variety of CF$_2$H containing compounds, limitations include scope, scalability, explosivity, and toxicity.23 An important advance was the development of the bench stable crystalline solid XtalFluor-M$^\text{®}$24 Nonetheless, the incompatibility of these reagents with some key functional groups such as unprotected alcohols, carbonyls or carboxylic acids, along with the necessity to pre-install the necessary aldehyde functionality, remains restrictive.25 As a result, new technologies which exploit easy-to-install reactive handles such as halide or boron motifs, or direct C–H difluoromethylation are attractive alternatives, and are discussed in this review. Undoubtedly, these advances have benefited from the invention of a multitude of bespoke difluoromethylation reagents. Approaches towards RCF$_2$H based on carbon–fluorine bond formation or hydrodefluorination are not described in this review.26–30

### 1.1 Properties of the CF$_2$H group

The highly polarised C–H bond of CF$_2$H makes this group a competent hydrogen bond donor, a unique characteristic amongst polyfluorinated motifs.31 The suitability of CF$_2$H as a bioisostere for alcohol, thiol, or amine group, has resulted in its incorporation in numerous bioactive compounds including drugs, herbicides, fungicides, and agrochemicals.2 Recent studies have shown that 1-(difluoromethyl)-2-nitrobenzene can form a dimeric complex similar to the hydrogen bonded dimer of 2-nitrophenol (Fig. 1).32 The conformer enabling intramolecular hydrogen bonding interaction is 4.3 kcal mol$^{-1}$ lower in energy with respect to the conformer lacking such interaction. Comparatively, the stabilisation gained from intramolecular hydrogen bonding of o-nitrophenol is 9.9 kcal mol$^{-1}$.

The ability of the difluoromethyl group to form hydrogen bonds has been quantified as $[\alpha]$, a parameter describing hydrogen bond acidity.33,34 The $[\alpha]$ value is derived from Abraham’s solute $^1$H NMR analysis, whereby the chemical shift of the CF$_2$H-proton is measured in both deuterated DMSO and CDCl$_3$. The difference in chemical shift ($\Delta \delta = \delta_{\text{DMSO}} - \delta_{\text{CDCl}_3}$) correlates with a molecule’s ability to act as a hydrogen-bond donor, where $[\alpha] = 0.0065 + 0.133 \Delta \delta$. These studies revealed that compounds bearing a CF$_2$H group ($A > 0.05$) are better hydrogen-bond donors than their methylated analogues ($A < 0.01$). Interestingly, ArOCF$_2$H and ArSCF$_2$H ($A = 0.10$) have a similar hydrogen bond acidity to thiophenol ($A = 0.12$) and aniline ($A = 0.07$) (Fig. 2A).

CF$_2$H substitution can also modulate lipophilicity with difluoromethylbenzene ($\log P = 2.4$) being more lipophilic than phenol ($\log P = 1.5$). Similarly, difluoromethyl phenyl sulfide ($A = 0.10$; $\log P = 2.9$) is more lipophilic than the weak hydrogen bond donor thiophenol ($A = 0.12$; $\log P = 2.5$) (Fig. 2B).34 Studies on...
because multiple drug candidates feature such structural motif (Fig. 4). The introduction of the CF2H group can lead to increased potency and/or selectivity. For example, Wymann and co-workers demonstrated that the CF2H group in the mTORC1/2 selective inhibitor PQ9620 played a vital role in achieving >1000-fold mTOR selectivity over PI3K. Computational modelling studies suggested that the CF2H group forms a beneficial hydrogen bonding interaction with Glu2190 of mTOR.36

ArCF2H are accessible applying either a stepwise sequence or directly from a CF2H reagent. For the former, different reagents which transfer a CF2Y motif (with Y being a stabilising electron-withdrawing group) can be introduced under transition metal catalysis, more often copper. Reagents featuring the CF2Y motif include BrCF2CO2Et, FSO2CF2CO2H, TMSO2CF2CO2Ph, BrCF2SO2Ph, BrCF2P(O)(OEt)2, ICF2SO2Ph and TMSO2CF2CO2Et. After attachment of CF2Y, the stabilising ester, sulfone or phosphonate “Y” group is cleaved to generate CF2H.37–42 Alternatively, the introduction of a CF2H group can be achieved via direct cross-coupling facilitated by a transition metal or through Minisci-type radical chemistry using a suitable difluormethyla-
tion reagent. In the context of late-stage functionalisation (LSF), direct methods are the most attractive (Scheme 2).

2.1 C(sp2)–CF2H bond formation: cross-coupling

In 1988 and 1990, Burton reported the synthesis of difluormethyl cadmium and its reactivity with allylic halides and propargylic (pseudo)halides to afford allylic difluormethyl products and difluormethyl allenes, respectively.43,44 In 2007, he reported that difluormethyl copper also permits difluoromethylation of allylic halides, propargyl derivatives and 1-idoalkynes.45 A cross-coupling mechanism was proposed whereby oxidative addition into the difluormethyl copper complex affords a CuIII intermediate which underwent reductive elimination to afford the difluormethylated products. Cross-coupling reactions involving a difluormethyl group and an aryl electrophile or nucleophile were not investigated in these seminal reports.

2.1.a Copper-mediated C(sp2)–CF2H bond formation. Copper-catalysed C(sp2)–CF2H bond formation is a demanding process (Fig. 5). Unlike thermally stable CuCF3 complexes, the first isolable CuCF2H complex was not reported until 2017, and required stabilisation from an NHC ligand (IPr) to enable its isolation.46 Mechanistically, the high energy barrier associated with oxidative addition to Cu1 is one of the factors that renders copper cross-coupling reactions involving CF2H challenging. Also, transmetallation with M–CF2H (M = SnR3, SiR3) is less effective than with M–CF3 because CF3 is more electronegative than CF2H. As a result, the formation of the pentacoordinate metallate necessary for transmetallation occurs more easily for M–CF3 than M–CF2H. Despite these challenges, copper has the advantage to undergo facile reductive elimination from high-valent CuIII species. Notably, reductive elimination of Ar–CF2H from CuIII occurs under milder conditions than for Ar–F.

Prior to the development of direct methods for Cu-mediated Ar–CF2H bond formation, Amrii and co-workers conceived a stepwise strategy to access difluormethylated arenes (Scheme 3).37 In this early study, the coupling of aryl iodides with ethyl...
2,2-difluoro-2-(trimethylsilyl)acetate gave access to \( \alpha \)-aryl-\( \alpha,\alpha \)-difluoroacetates. In subsequent steps, the resulting ester was hydrolysed followed by decarboxylation at high temperature to yield the desired difluoromethylenes. The decarboxylation step was successful only for intermediates derived from electron-deficient iodoarenes or iodopyridine. This three-step-one-pot protocol marked the first general route to access ArCF\(_2\)H from aryl halides.

Hartwig and co-workers reported in 2012 the first direct copper-mediated difluoromethylation of aryl iodides using CuI, CsF and commercially available TMSCF\(_2\)H (Scheme 4A).\(^{47}\) The key discovery of this study was the necessity to use an excess of TMSCF\(_2\)H (5.0 equiv.) to convert unstable [CuCF\(_2\)H] into the...
more stable disubstituted \([\text{Cu}(\text{CF}_2\text{H})_2]\) cuprate complex. Electron-neutral, electron-rich, and sterically hindered aryl iodides readily underwent difluoromethylation in good yields. Electron-deficient aryl iodides did not perform well because competing protodeiodination took place. Ketone and aldehyde functional groups were not tolerated due to competing addition of \(\text{CF}_2\text{H}\) to the carbonyl group. This contribution nevertheless sparked the development of alternative Cu-mediated reactions to facilitate C(sp\(^2\))–CF\(_2\text{H}\) bond formation in a direct fashion. In the same year, Prakash and co-workers demonstrated that \(\text{nBu}_3\text{SnCF}_2\text{H}\) can be utilised as a CF\(_2\text{H}\) source to functionalise (hetero)aryl iodides using stoichiometric copper iodide (Scheme 4B). Radial inhibition and trapping experiments suggested that this reaction likely proceeds through a radical pathway involving first transmetallation of the CF\(_2\text{H}\) group at Cu\(^{1+}\) followed by single electron transfer (SET) generating a Cu\(^{2+}\) species and an aryl radical. Outer sphere transfer of CF\(_2\text{H}\) to the aryl radical yielded the desired difluoromethylarene. This scenario is distinct from Hartwig's method, where transmetallation is proposed to occur at Cu\(^{1+}\), followed by oxidative addition of an aryl iodide. Gooßen and co-workers also developed a one-pot sequence from aniline precursors via in situ generation of the corresponding diazonium salts.

In the same year, Gooßen and co-workers illustrated that difluoromethylation of (hetero)aryl diazonium salts was possible using TMSCF\(_2\text{H}\) and CuSCN (Scheme 5).\(^{50}\) Radical inhibition and trapping experiments suggested that this reaction likely proceeds through a radical pathway involving first transmetallation of the CF\(_2\text{H}\) group at Cu\(^{1+}\) followed by single electron transfer (SET) generating a Cu\(^{2+}\) species and an aryl radical. Outer sphere transfer of CF\(_2\text{H}\) to the aryl radical yielded the desired difluoromethylarene. This scenario is distinct from Hartwig's, Prakash's, and Qing's methods, where transmetallation is proposed to occur at Cu\(^{1+}\), followed by oxidative addition of an aryl iodide. Gooßen and co-workers also developed a one-pot sequence from aniline precursors via in situ generation of the corresponding diazonium salts.

Shen and co-workers investigated alternative approaches to generate [CuCF\(_2\text{H}\)] in situ (Scheme 6A).\(^{51}\) Specifically, the N-heterocyclic carbene (NHC) silver complex \([\text{NHC}]\text{Ag}([\text{CF}_2\text{H}])\) (NHC = 1,3-bis(2,6-diisopropylphenyl)imidazolin-2-ylidene) prepared from \([\text{NHC}]\text{AgCl}\) is air and moisture stable, and allowed
in situ generation of $\text{L}_0\text{CuCF}_2\text{H}$ upon treatment with CuI. This strategy led to rapid formation of difluoromethylelenes from diarylodonium triflates at room temperature. Substrates bearing electron-donating and electron-withdrawing substituents were tolerated and afforded the desired products in good yields. Inspired by this work, Sanford and co-workers developed a protocol towards an NHC–copper–CF$_2$H complex which alleviated the need for a bimetallic system (Scheme 6B).$^{46}$ Similarly to [(SIPr)Ag(CF$_2$H)], [(IPr)Cu(CF$_2$H)] was prepared from [(IPr)CuCl] and TMSCF$_2$H, and found sufficiently stable for isolation. Using a stoichiometric amount of [(IPr)Cu(CF$_2$H)], several electron-deficient aryl iodides readily underwent difluomethylation. Electron-rich substrates were also suitable but led to difluomethylated products in lower yields.

2.1.b C(sp$^3$)–CF$_2$H bond formation under copper catalysis. Mikami and co-workers reported the first Cu-catalysed difluoromethylation of aryl iodides using [(DMPU)$_2$Zn(CF$_2$H)$_2$], a reagent developed by Vicic and co-workers (Scheme 7A).$^{52,53}$ This CF$_2$H reagent is prepared from commercially available difluoriodomethane and diethylzinc, in the presence of two equivalents of DMPU. Transmetallation from the zinc reagent to the copper catalyst (CuI) at room temperature generates the [Cu(CF$_2$H)$_2$]$^-$ complex previously proposed by Hartwig.$^{47}$ Under these conditions, a variety of electron-deficient aryl iodides afforded the desired difluomethylated products in moderate to excellent yields.$^{53}$ Similarly, Sanford’s report on the synthesis of [(IPr)Cu(CF$_2$H)], illustrates that the same cuprate complex can be generated in situ using catalytic amounts of [(IPr)CuCl], and TMSCF$_2$H (Scheme 7B).$^{46}$ Under these conditions, electron-rich substrates performed well, whilst electron-deficient substrates performed better under the stoichiometric conditions described in Scheme 6B.

2.1.c C(sp$^3$)–CF$_2$H bond formation under palladium catalysis. The oxidative addition of aryl halides occurs more readily at Pd$^0$ than Cu$^1$. However, a challenge associated with Pd lies in the slower transmetallation to transfer CF$_2$H onto Pd$^{11}$ versus Cu$^1$. These challenges are comparable to those associated with transmetallation of CF$_3$ at Pd$^{11}$. Shen and co-workers reported that reductive elimination of Ar–CF$_2$H at Pd$^{11}$ is more facile than for Ar–CF$_3$ (Fig. 6).$^{54–57}$ To overcome the challenges of transmetallation for CF$_2$H at Pd$^{11}$, Shen and co-workers developed an effective cooperative Pd/Ag catalytic system for the synthesis of difluoromethylelenes from aryl bromides or aryl iodides in the presence of TMSCF$_2$H (Scheme 8A).$^{37}$ The data imply that the in situ generated [(SIPr)Ag(CF$_2$H)] complex acts as a transmetallation shuttle in this system. The use of stoichiometric pre-formed [(SIPr)Ag(CF$_2$H)] in combination with the electron-rich and sterically hindered Buchwald catalyst PdXPhosG3 (10 mol%) in the presence of XPhos (10 mol%), allowed for a broader selection of aryl chlorides and triflates to undergo difluoromethylation in high yields (Scheme 8B).$^{58}$ A selection of functionalised molecules were reacted in high yields, giving medicinal chemists a new tool to access CF$_2$H-containing drug-like molecules in a late-stage fashion. The same authors further illustrated that (hetero)aryl chlorides are amenable to difluoromethylation in the presence of stoichiometric [(SIPr)Ag(CF$_2$H)] and Pd(dba)$_2$ (5 mol%) (Scheme 8C).$^{39}$ This procedure provides a useful alternative to radical methods which are generally promiscuous with respect to regioselectivity (see Section 2.2). In addition to protocols which use Ag$^1$ complexes to readily transfer CF$_2$H to Pd,$^3$ Mikami and co-workers reported a Pd-catalysed Negishi-type cross-coupling of aryl halides with [(TMEDA)Zn(CF$_2$H)$_2$] (Scheme 8D).$^{60}$ This reagent was readily prepared from difluoriodomethane and diethylzinc in presence of $N,N,N',N'$-tetramethylethylenediamine (TMEDA). Electron-deficient and electron-rich (hetero)aryl halides were suitable substrates for this difluoromethylation protocol, affording the desired products in good to excellent yields. In 2019, Sanford and co-workers reported the Pd-catalysed difluoromethylation of aryl chlorides/bromides with TMSCF$_2$H (Scheme 8E).$^{61}$ The authors identified optimal catalysts, either Pd(dba)$_2$/BrettPhos

Scheme 7 Copper-catalysed difluoromethylation of aryl iodides.

Fig. 6 C(sp$^3$)–CF$_2$H bond formation under palladium catalysis.
or Pd(PBu₃)₂, and found that electron-neutral and electron-rich substrates performed well under the optimised reaction conditions. The authors postulated that this reaction operates under a Pd₀/Pd II catalytic cycle.

Difluorocarbene reagents can be used to generate MCF₂H complexes upon protonation of in situ formed (difluorocarbene)-metal ([M = CF₂]) complexes. Several groups have exploited this strategy to convert aryl boron reagents to ArCF₂H compounds under Pd-catalysis. 62–65 Aryl boron reagents are advantageous candidates for difluoromethylation because they are often commercially available or easy to prepare. Furthermore, they are often bench-stable precursors, a desirable feature for cross-coupling reactions. 66–68 Xiao and co-workers developed a Pd-catalysed difluoromethylation of aryl boronic acids using commercially available ethyl bromodifluoroacetate (Scheme 9b). 62 This protocol has a broad substrate scope and functional group compatibility. Bioactive molecules such as flavanone-, ezetimibe- and estrone-derived aryl boronic acids all underwent difluoromethylation without the need to protect carbonyl or hydroxyl groups. Preliminary mechanistic studies demonstrated that a Pd—CF₂ intermediate is generated in this reaction. In 2017, Zhang and co-workers reported the palladium-catalysed difluoromethylation of (hetero)arylboronic acids and esters using chlorodifluoromethane as a difluorocarbene source (Scheme 9c). 64 The reaction proceeded smoothly for electron-rich and electron-deficient (hetero)arylboronic acids, tolerated a variety of functional groups, and allowed access to various bioactive CF₂H-containing analogues. The need for an excess of ozone-depleting chlorodifluoromethane is a limitation of this technology. In 2019, Zhang and Houk developed a controllable Pd-catalysed difluorocarbene transfer reaction which employs aryl boronic acids and BrCF₂P(O)(OEt)₂ as alternative difluorocarbene precursor (Scheme 9d). 65 Alterations of the reaction conditions afforded four distinct types of products, specifically difluoromethylated and tetrafluoroethylated arenes as well as the corresponding fluoroalkylated ketones.

In 2020, Shen and co-workers developed a two-step one-pot C–H borylation–difluoromethylation protocol which allowed site-selective difluoromethylation of a range of (hetero)arenes (Scheme 10). 69 The authors suggest a mechanism which involves concurrent ligand transfer that delivers both the CF₂H group and
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"NHC ligand from [(SIPr)Ag(CF₂H)] to Pd²⁺, generating the [(SIPr)Pd(CF₂H)Cl] complex \textit{in situ}. From a medicinal chemist’s perspective, this novel methodology represents an attractive strategy as it is suitable for the late-stage site-selective introduction of CF₂H onto (hetero)arenes.

In 2018, the Ritter group reported the catalytic decarbonylative difluoromethylation of aroyl chlorides, a reaction requiring 5 mol% Pd\textsubscript{(dba)}\textsubscript{2}, 6 mol% RuPhos and 1 equivalent of [[DMPU\textsubscript{2}Zn(CF₂H)₂] (Scheme 11).\textsuperscript{70} Electron-deficient, electron-rich and heterocycle-containing benzyl chlorides all underwent difluoromethylation at ambient conditions. A range of bioactive compounds including diacetylrhein, probenecid and ataluren led to the desired products in good to excellent yields. The proposed catalytic cycle involves oxidative addition of the aroyl chloride to Pd\textsuperscript{0} which affords [(aroyl)Pd\textsuperscript{II}(Cl)], followed by CF₂H transmetallation from (DMPU)\textsubscript{2}Zn(CF₂H)₂, an event leading to the Pd\textsuperscript{II} intermediate undergoing decarbonylation. Reductive elimination furnishes the desired difluoromethylarene with regeneration of the Pd\textsuperscript{0} catalyst.

2.1.d C(sp\textsuperscript{2})–CF₂H bond formation under nickel catalysis.

Nickel’s open-shell electronic configurations (i.e. Ni\textsuperscript{I}, Ni\textsuperscript{II}) display higher stability than its second and third period counterparts [Pd, Pt] (Fig. 7).\textsuperscript{71} As a result, the activation of an electrophile by Ni can occur through either a two-electron (oxidative addition) or via a single electron process. In addition, Ni\textsuperscript{0} has the ability to readily undergo oxidative addition to Ni\textsuperscript{II}, Ni\textsuperscript{III} transmetallation is facile, as is radical addition converting Ni\textsuperscript{II} to Ni\textsuperscript{III}. Furthermore, rapid reductive elimination for Ar–CF₂H bond formation from both Ni\textsuperscript{II} and Ni\textsuperscript{III} makes nickel an attractive metal for arene functionalisation including difluoromethylation.

In 2016, Vicic and co-workers reported the nickel-catalysed difluoromethylation of aryl halides and triflates with [[DMPU\textsubscript{2}Zn(CF₂H)₂ (Scheme 12A).\textsuperscript{52} [[DMPU\textsubscript{2}Zn(CF₂H)₂] was found to be stable for long periods under an inert atmosphere and readily reacts with a variety of electron-deficient arenes in the..."
presence of the nickel pre-catalyst [(DPPF)Ni(COD)]. Electron-rich substrates gave lower yields. The authors postulated that this Negishi-type cross-coupling operates under a traditional Ni^{II}/Ni^{III} redox shuttle. Baran and co-workers reported the synthesis of difluoromethylated products using redox active 5-((difluoromethyl)sulfonyl)-1-phenyl-1H-tetrazole combined with Ni(acac)_{2} \cdot H_{2}O and an excess of aryl zinc reagents (Scheme 12B). The authors postulate a mechanism whereby the aryl zinc reagent first undergoes transmetallation with nickel, yielding a nickel aryl species. This species can then reduce 5-((difluoromethyl)sulfonyl)-1-phenyl-1H-tetrazole, oxidizing the nickel aryl complex in the process. Fragmentation of the 5-((difluoromethyl)sulfonyl)-1-phenyl-1H-tetrazole radical anion yields the difluromethyl radical which adds to [L_{2}Ni^{II}Ar]. The resulting [Ar–Ni^{II}–CF_{2}H] complex undergoes reductive elimination to release the difluoromethylarene with regeneration of L_{2}Ni^{III}. 

Zhang and co-workers modified their Pd^{0}-catalysed difluoromethylation of aryl chlorides with the development of a method that utilizes a Ni^{II} catalyst (Scheme 13A). The authors suggest a mechanism which commences with the reduction of the Ni^{II} catalyst to Ni^{0} in the presence of Zn^{0} serving as stoichiometric reductant. Subsequent oxidative addition of the aryl chloride, and reaction with an in situ generated CF_{2}H radical yielded the Ar[Ni^{II}–CF_{2}H] complex which readily underwent reductive elimination to furnish the difluoromethylarene product. The method is scalable (up to 10 g), and the mild reaction conditions are suitable for LSF of biologically relevant compounds. The requirement of an excess of ozone depleting ClCF_{2}H is a disadvantage of this methodology. In 2018, Wang and Zhang simultaneously reported the nickel-catalysed difluoromethylation of arylboronic acids, with bromodifluromethane. Wang and co-workers screened different combinations of phosphine and nitrogen ligands in a high-throughput fashion, with various iterations being necessary to optimise the reaction conditions found to be substrate-dependent (Scheme 13B). Zhang and co-workers reported that commercially available 2,2′-bipyridine in combination with [Ni(PPh_{3})_{2}Br] (5–10 mol%) was sufficient to access various electron-rich and electron-withdrawing difluoromethylarenes in good yields (Scheme 13C). Both reports postulate a Ni^{II}/Ni^{III} catalytic cycle whereby the initial step involves transmetallation of the aryl boronic acid. Subsequent reaction of [([Ar]Ni^{II}L)] with bromodifluromethane via SET, followed by radical recombination, yields the [(Ar)(CF_{2}H)-Ni^{III}L_{2}Br] intermediate which reductively eliminated to furnish the desired difluoromethylarene. In the same year, Mikami and co-workers reported that aryl Grignard reagents underwent successful difluoromethylation in the presence of difluorodioctane, [Ni(COD)]_{2} (2.5 mol%) and TMEDA (2.5 mol%) (Scheme 13D). In the same year, the MacMillan group merged nickel and photoredox catalysis for the difluoromethylation of a broad range of (hetero)aryl halides (Scheme 13E). This nickel/photoredox-catalyzed cross-electrophile coupling reaction proceeds at room temperature. A unique mechanistic feature which allows this reaction to proceed under mild conditions is the implementation of a silyl radical mediated bromine atom abstraction from bromodifluromethane. This mild activation mode allows for the LSF of biologically relevant compounds. Of note is the tolerance of the method to several pharmaceutically-relevant heterocycles such as electron-rich pyrimidines, pyrazoles, and indoles. In particular, the successful difluoromethylation of 1-(3-bromo-1H-pyrazol-1-yl)ethan-1-one is of interest considering that 3-(difluoromethyl)-1-methyl-1H-pyrazole is a motif important to the agrochemical industry.

2.1.e C(sp^{3})–CF_{2}H bond formation under iron catalysis. Using widely abundant earth crust iron, Hu and co-workers reported in 2018 a mild and broadly applicable Fe-catalysed cross-coupling protocol for the difluoromethylation of diaryl zinc reagents. This was achieved, using commercially available difluoromethyl 2-pyridyl sulfone (2-PySO_{2}CF_{2}H), TMEDA and Fe(acac)_{3} (20 mol%) (Scheme 14A). This difluoromethylation proceeds under mild reaction conditions and gives access to electron-rich and electron-deficient difluoromethylarenes. In the same year, Zhang and co-workers reported the iron-catalysed difluoromethylation of aryl Grignard reagents with bromodifluromethane in combination with catalytic FeBr_{2}. The use of the bulky diamine ligand 1-((dimethylamino)methyl)-N,N-dimethylcyclopentan-1-amine (L1) over other commonly used diamine ligands such as N,N,N′,N′-tetramethyl-ethane-1,2-diamine (TMEDA) proved crucial to circumvent the formation of by-products resulting from defluorination (Scheme 14B).
2.1.f C(sp²)–CF₂H bond formation mediated by gold. The demand for stable yet reactive MCF₂H complexes led Shen and co-workers to prepare the first isolable AuCF₂H complex, cis-[Au(PCy₃)(4-FC₆H₄)(CF₂H)(Cl)] through transmetallation from [(SIPr)Ag(CF₂H)] and cis-[Au(PCy₃)(4-FC₆H₄)(Cl)₂] (Scheme 15).80 The reaction of this complex at room temperature with a silver salt such as AgSbF₆ or AgPF₆, allowed for facile reductive elimination to yield 4-(difluoromethyl)fluorobenzene in very short reaction times (<1 min). In the absence of silver, the reductive elimination proceeded at elevated temperatures (115 °C), and required longer reaction times (80 min). The authors suggest that the cationic intermediate [Au(PCy₃)(4-F-C₆H₄)(CF₂H)]⁺ can form from cis-[Au(PCy₃)(4-F-C₆H₄)(CF₂H)(Cl)] in the presence of Ag⁺. This cationic Au complex is required to achieve rapid reductive elimination at room temperature.

From Section 2.1, it is evident that there is currently an abundance of methods to access difluoromethylenes in a single step under catalytic conditions from a wide array of accessible precursors. Scheme 16 provides a guide for practitioners of this chemistry, illustrating some key features with respect to the CF₂H source and activation manifold employed for each class of substrates. This information may aid selection of the methodology best suited to the problem at hand.

2.2 C(sp³)–CF₂H bond formation via C–H difluoromethylation

The field of C–H difluoromethylation mostly relies on the generation and reactivity of the difluoromethyl radical although cross-coupling methodologies have appeared. The radical stability of fluoroalkylated radicals varies with fluorine content (CH₂F > CF₂H > CF₃).81 The geometry of fluoroalkyl radicals is also
affected by the degree of fluorine substitution, becoming progressively more tetrahedral with increased fluorine substitution as evidenced by the respective out of plane (oop) bending angles, oop$_{\text{CF}}$ = 55.1°, oop$_{\text{CF,H}}$ = 49.5°, oop$_{\text{CH,F}}$ = 31.4°. This distortion from planarity results in less effective overlap of fluorine lone pairs with the single occupied molecular orbital (SOMO) (Fig. 8). Combined with the lesser electron-withdrawing effect of CF$_2$H versus CF$_3$, the CF$_2$H radical has a comparatively higher energy SOMO and is more nucleophilic than the CF$_3$ radical. These properties lead to differences in reactivity and selectivity between CF$_2$H and CF$_3$ radicals for example in Minisci-type chemistry.

The difluoromethyl radical is often generated by SET from a suitable difluoromethyl radical precursor. The most common reagents and their redox potentials are listed in Fig. 9. Methods for radical difluoromethylation have proliferated rapidly over the last few years. Several reagents can serve as CF$_2$H radical precursor via a variety of activation processes including single-electron oxidation (e.g. Zn(SO$_2$CF$_2$H)$_2$), single-electron reduction (e.g. ClSO$_2$CF$_2$H), or radical abstraction (e.g. BrCF$_2$H) (Scheme 17).

Pioneering work by Chen and co-workers showed that gaseous CF$_2$HI can be used as a source of CF$_2$H radical for the iododi fluoromethylation of alkenes. This report inspired Baran and co-workers to develop [Zn(SO$_2$CF$_2$H)$_2$] (DFMS), an easy-to-handle bench stable solid CF$_2$H radical precursor. With this reagent, N-heterocyclic substrates undergo C–H difluoromethylation in the presence of excess tBuOOH and trifluoroacetic acid (TFA). This report marks the first general C–H difluoromethylation protocol for heteroarenes (Scheme 18A). Their results corroborate the nucleophilic character of /C$_15$/CF$_2$H radical which contrasts with the electrophilic character of /C$_15$/CF$_3$. This was exemplified with the difluoromethylation of dihydroquinine, which was selective for C$_2$ rather than C$_7$, the latter being the preferred site for CF$_3$ radical addition. The solvent system had a profound effect on selectivity. Using 1-(pyridin-4-yl)ethan-1-one as model substrate, a C$_2$ : C$_3$ selectivity superior to 10 : 1 was obtained in DCM/H$_2$O (2.5 : 1). When the same reaction was conducted in DMSO/H$_2$O (2.5 : 1), the C$_3$ regioisomer was formed preferentially (C$_2$ : C$_3$, 1 : 1.5). Christensen, Nielsen and co-workers showed that inexpensive difluoroacetic acid undergoes Minisci-type difluoromethylation with a variety of pyridines and other heteroarenes (Scheme 18B). Mono-difluoromethylation versus bis-difluoromethylation was controlled by tuning the reaction temperature, with mono-difluoromethylated compounds obtained at lower temperatures. Maruoka and co-workers developed a hypervalent iodine(III) reagent adorned with difluoroacetoxy ligands. This reagent enables C–H difluoromethylation of heteroarenes upon photolysis under blue light irradiation (Scheme 18C). In 2019, Stephenson and co-workers illustrated that the CF$_2$H radical can be generated via photocatalytic activation of pyridinium or quinolinium complexes generated from the corresponding N-oxides and difluoroacetic anhydride (Scheme 19A). In 2018, Zhang and Deng developed a visible-light driven metal-free
More recently, Meng, Li, and co-workers found that the use of the same reagent combined with rose bengal as photocatalyst and green LEDs as light source, enabled difluoromethylation of a broad range of heteroarenes relevant to medicinal chemistry, including pyrindines, pyrazines, imidazoles, pyrazoles, indoles and electron-rich arenes (Scheme 19C). In 2019, König and co-workers disclosed an alternative activation of DFMS, using an organic semiconductor photocatalyst with applications to C–H difluoromethylation of heteroarenes (Scheme 19D). This strategy provides a milder alternative to peroxide activation of DFMS reported by Baran but requires irradiation with blue light. Qing, Chu and co-workers recently reported a silver mediated C–H difluoromethylation of a range of heteroarenes employing TMSCF2H as a CF2H source (Scheme 19E). The reaction proceeded in high yields for quinoxalin-2(1H)-ones. Other heteroarenes including a benzoxazole derivative also afforded the difluoromethylated product.

In 2019, Noisier, Gopalakrishnan and co-workers reported a single example of a C–H difluoromethylation of a histidine residue in a pentapeptide (Scheme 20A). In 2021, Davis and co-workers demonstrated the site-selective difluoromethylation of tryptophan (Trp) residues in proteins (Scheme 20B). A range of proteins undergoing difluoromethylation at the C2 position of Trp, include annexin A5, lysozyme, cationic trypsin and lactalbumin. Once installed, the CF2H spontaneously hydrolysed resulting in net C–H formylation. The HC(O)–Trp residue is a privileged handle for further functionalisation.

To overcome the limitations of site-selectivity in C–H difluoromethylation, Qing and co-workers envisioned that a two-electron cross-coupling of heteroarenes with a [CuCF2H] complex could be achieved under oxidative conditions (Scheme 21). The authors found that when [CuCF2H] was generated in situ from [CuCN] and TMSCF2H, a variety of heterocycles activated under basic conditions could coordinate CuI. When this CuI complex was further oxidised with 9,10-phenanthrenequinone, subsequent reductive elimination furnished the difluoromethylated product. This report hallmarked the first transition-metal mediated C–H difluoromethylation protocol under oxidative conditions. C–H bonds of oxazoles, thiazoles, imidazoles, 1,3,4-oxadiazoles, benzo[d]oxazoles, benzo[d]thiazoles, benzo[d]thiophenes, pyridines, thiophenes, and thiazolo[5,4-c]pyridines were readily difluoromethylated in good to excellent yields.
Complementary to the radical C–H difluoromethylation protocol developed by Baran and co-workers, Qing’s copper mediated oxidative C–H difluoromethylation illustrated that substrates bearing multiple reactive sites such as thiazole- [5,4-c]pyridine or 5-(quinoxaline-6-yl)oxazole undergo oxidative difluoromethylation at the more acidic C–H azole bond. In contrast, conditions developed by Baran and co-workers enable difluoromethylation at the most electron-deficient carbons adjacent to the nitrogen of the 6-membered heterocyclic ring (Scheme 22).

Other than direct methods to install CF₂H groups onto heteroaromatics via Minisci-type chemistry, Dolbier and co-workers envisioned that the CF₂H radical could react with 2-isocyano-1,10-biphenyl to generate a series of substituted 6-(difluoromethyl)phenanthridines (Scheme 23A). In this transformation, fac-Ir(ppy)₃ (1 mol%) activates HCF₂SO₂Cl to generate the CF₂H radical which subsequently adds to a series of biphenyl isocyanides, affording the corresponding difluoromethylated phenanthridine products upon oxidation of the intermediate radical species followed by proton loss. Similarly, Fu and co-workers prepared a selection of 3-difluoromethylated coumarins from aryl alkynoates in a process suggested to proceed through a difluoromethylation/cyclisation sequence (Scheme 23B).

In summary, it is evident that there is an abundance of methods to access a range of heteroarenes substituted with CF₂H groups in a single step through C–H difluoromethylation. Scheme 24 provides a selection of heteroarenes that are important to medicinal chemists, and the difluoromethylation reagents that have been used for selective C–H difluoromethylation of functionalised analogues of these heteroarenes.

2.3 C(sp²)-[¹⁸F]CF₂H bond formation for PET radiochemistry

The first radiosynthesis towards [¹⁸F]ArCF₂H was disclosed by Gouverneur and co-workers in 2013 and accomplished using [¹⁸F]F₂-derived [¹⁸F]selectfluor bis(triflate). In 2016, Gouverneur and co-workers disclosed a more broadly applicable method which
involved the AgI-mediated halogen exchange reaction of electron-rich (chlorofluoromethyl)arenes and [18F]fluoride. In the same year, Ritter and co-workers disclosed an alternative radiosynthesis of [18F]ArCF2H from aryl (pseudo)halides and [18F]fluoride. In 2017, Liang and co-workers disclosed a two-step strategy towards [18F]ArCF2H. This was accomplished through nucleophilic radiofluorination of benzyl (pseudo)halides with [18F]fluoride followed by oxidative C–H fluorination with Selectfluor. In 2019, Gouvré and co-workers published a novel approach towards [18F]ArCF2H using aryl (pseudo)halides and [18F]fluoride. The reaction sequence commences with a copper-catalysed cross-coupling with ethyl bromofluoroacetate and an aryl boronic acid. In situ hydrolysis then yielded a wide selection of α-fluoroarylacetic acids. The radioisotope18F was introduced in the final step applying a Mn-mediated fluorodecarboxylation using Mn(tmp)Cl, iodosylbenzene and [18F]fluoride. Pre-complexation of two equivalents of α-fluoroarylacetic acid with iodosylbenzene to generate the hypervalent iodine complex prior to 18F-fluorination led to increased F-18 incorporation. The application of the methodology was demonstrated with the radiosynthesis of a [18F]CF2H analogue of the COX-II inhibitor ZA140 which was obtained in 15% ± 2% radiochemical yield (RCY). In contrast to the aforementioned reports which disclosed radiosyntheses towards [18F]ArCF2H through halogen exchange and fluorodecarboxylation procedures, Genicot and Luxen disclosed the first 18F-difluromethylation (Scheme 25). For this purpose, 2-[18F]((difluoromethyl)sulfonyl)benzo[d]thiazole was prepared in 11.9% ± 1.4% RCY, and a decay corrected molar activity (MA) of up to 75 GBq μmol⁻¹. This reagent was activated photocatalytically to generate the [18F]CF2H radical that was incorporated into a variety of N-heterocycles including pharmaceutical drugs. The authors made a first attempt towards a more user-friendly methodology by fully automating the protocol on the ‘AllinOne’ TRASIS module. This seminal report marks the first application of an F-18 labelled reagent to access the [18F](het)ArCF2H motif.

3. C(sp3)-Difluoromethylation

CF2H groups linked to C(sp3) have attracted great interest in medicinal chemistry as a bioisosteric replacement of aliphatic alcohols and thiols. Several compounds featuring C(sp3)-CF2H are FDA approved drugs or are currently undergoing clinical trials (Fig. 10). Eflornithine, an essential medicine according to the World Health Organization, contains a CF2H group bound to the α-carbon of the non-proteinogenic amino acid ornithine. GDC-0077, a phosphoinositide 3-kinase (PI3K) inhibitor, contains a CF2H bound to an oxazolidinone fragment and is in clinical trials for the treatment of tumours. Glecaprevir and Voxilaprevir both featuring an unnatural β-difluoromethylated α-amino acid are marketed macrocyclic protease inhibitors for the treatment of hepatitis C. In a structure–activity relationship (SAR) study of Voxilaprevir analogues, the CF2H group was predicted to play a beneficial role by improving metabolic stability compared with the ethyl or vinyl groups.

Analogously to traditional routes towards C(sp3)-CF3H, deoxyfluorination of C(sp3)-CHO with sulfur tetrafluoride-derived...
reagents such as DAST®, Deoxo-Fluor® or XtalFluor® has served as a robust strategy towards C(sp³)–CF₂H.¹¹⁶ Both GDC-0077 and Voxilaprevir are prepared by deoxyfluorination of an aldehyde-containing building block. As discussed for the synthesis of difluoromethylarenes, the lack of chemoselectivity for substrates containing reactive functional groups such as alcohols, ketones and carboxylic acids is a limitation of this approach. Therefore, alternative methods to install a CF₂H group through nucleophilic, electrophilic, or radical difluoromethylation pathways are of immense benefit, especially in the context of LSF.

3.1 C(sp³)–CF₂H bond formation: nucleophilic difluoromethylation

The most common nucleophilic difluoromethylation reagent used for C(sp³)–CF₂H bond formation is TMSCF₂H. Various difluoromethylation reactions with silane reagents have been reported as early as the 1990s but required harsh conditions.⁹ In 2011, Hu and co-workers reported a general and mild protocol to access a broad variety of CF₂H containing alcohols and sulfonamides (Scheme 26A).¹¹⁷ The use of TMSCF₂H as “--CF₂H” synthon was demonstrated with nucleophilic addition reactions to aldehydes, ketones and N-tert-butylsulfinyl imines. In the case of aldehydes, a catalytic amount of CsF in DMF was required for activation. TBAF was also added after completion of the reaction to deprotect the in situ formed silylated difluoromethyl carbinol. These reaction conditions were low yielding for less electrophilic substrates such as ketones that afforded the difluoromethylated products in 30–40% yield; this is because DMF competes as electrophile. This limitation was circumvented by the use of tBuOK to serve as a stoichiometric activator of the silane reagent. However, such basic conditions did not allow the difluoromethylation of enolisable ketones. Base activation was also applied to Ellman’s N-tert-butylsulfinyl imines. These reactions were generally high yielding and showed good diastereoselectivity. In 2015, He and co-workers disclosed the use of the organic Lewis base phosphazene to activate TMSCF₂H.¹¹⁸ The method transformed (hetero)aryl-aldehydes and cinnamaldehyde into the difluoromethyl addition product si nu pt o99% yield. For enolisable aldehydes and diarylketones, the yields did not exceed 46%. In 2016, Hu and co-workers demonstrated that in situ formation of the pentavalent [(CH₃)₃Si(CF₂H)₂]⁻ anionic species enabled difluoromethylation of enolisable ketones (Scheme 26B).¹¹⁹ In this instance, the activation of TMSCF₂H was accomplished by employing catalytic amounts of CsF or tBuOK. A crown ether (10 mol%) was required to stabilise the pentavalent silicate anion and to increase the activator’s nucleophilicity. This methodology gave access to a broad variety of aliphatic difluoromethyl carbinols in good to excellent yields. In 2019, Pace and co-workers reported the synthesis of difluoromethyl ketones and difluoromethyl(thio)amides (Scheme 26C).¹²⁰ Specifically, when TMSCF₂H was activated by potassium tert-pentoxide (tPentOK), Weinreb amides underwent difluoromethylation leading to difluoromethyl ketones. The same authors reported an efficient difluoromethylation of iso(thio)cyanates leading to difluoromethyl(thio)amides (Scheme 26D).¹²¹ For this reaction, TMSCF₂H was also activated by tPentOK as the use of this sterically hindered base prevented undesired addition of the base itself onto the isothiocyanates, a side reaction observed with tBuOK. In 2020, Wu and Xiao reported the dehydroxylative difluoromethylation of alcohols.¹²² Their system involves activation of the alcohol using R₃P and ICH₂CH₂I and requires stoichiometric quantities of preformed [CuCF₂H]. Their reaction proceeds under mild conditions and shows good functional group tolerance (Scheme 26E).

3.2 C(sp³)–CF₂H bond formation: electrophilic difluoromethylation

Net electrophilic difluoromethylation at C(sp³)-centres has been well studied. For example, the key step in the synthesis of the ornithine decarboxylase (ODC) inhibitor Efornithine, a drug developed in the 1970’s and brought to market in 1990 to treat sleeping sickness is prepared by α-difluoromethylation
with ClCF₂H, an ozone-depleting substance (ODS) (Scheme 27). This transformation was proposed to proceed via difluorocarbene mechanism.

With the Montreal protocol urging scientists to develop chemistries not employing ozone-depleting fluorine-containing reagents, fluoroform was considered as a suitable alternative. The activation of HCF₃ for difluoromethylation of C(sp³) centres was achieved by Mikami and co-workers in 2012 with the difluoromethylation of lithium enolates (Scheme 28A). It is well known that the high bond dissociation energy of the C–F bond (117 kcal mol⁻¹) poses a challenge to S_N_2 reactions of organo-fluorides. In this case, the authors propose that the high enthalpy of formation for LiF (147 kcal mol⁻¹) allows for nucleophilic substitution with fluoride displacement on fluoroform. The methodology was applied to a variety of ketones, amides and esters, and later to nitriles (Scheme 28B). In 2018, Kappe and co-workers extended this methodology to continuous flow conditions for the α-difluoromethylation of esters. Several substrates were subjected to difluoromethylation including protected amino acids (Scheme 28C).

Various difluoromethylations were performed with non-gaseous reagents (Scheme 29). In 2011, Shibata and co-workers reported the electrophilic difluoromethylation of β-ketoesters using the sulfoximine reagent developed by Hu and co-workers (Scheme 29A). When comparing the reactivity of this difluoromethyl reagent with the corresponding monofluoromethyl reagent (O-selectivity) and trifluoromethyl reagent (C-selectivity), they noted the formation of a mixture of products resulting from C- and O-difluoromethylation (63 : 37). In 2018, Shen and co-workers developed a highly C-selective process for β-ketoesters (Scheme 29B); up to 100 : 0, C : vs. O-alkylation) using a difluoromethyl sulphonium ylide suggested to serve as difluorocarbene source. This method allowed the direct α-difluoromethylation of ketene silyl acetals. In 2019, Hu and co-workers demonstrated that commercially available TMSCF₂Br was an efficient reagent for the C-difluoromethylation of a range of C(sp³) and C(sp) nucleophiles, such as esters, amides, fluorenes, terminal alkenes, malonates, β-ketoesters and other activated C–H nucleophiles (Scheme 29C). For this protocol, the authors also propose a difluorocarbene mechanism.

### 3.3 C(sp³)–CF₂H bond formation: radical difluoromethylation

In 2012, Baran and co-workers disclosed the hydrodifluoromethylation of enones with DFMS (Scheme 30A). Dolbier and co-workers reported in 2015 a more broadly applicable and higher yielding hydrodifluoromethylation of electron-deficient alkenes by making use of the photocatalyst fac-Ir(ppy)₃ to activate difluoromethanesulfonyl chloride with tris(trimethylsilyl)silane ((TMS)₃SiH) as hydrogen-atom donor (HAD) (Scheme 30B). In the same year, Qing and co-workers expanded the hydrodifluoromethylation to alkenes of different electronic profiles, as well as alkene-containing bioactive molecules (Scheme 30C). This method required a non-commercial difluoromethylation reagent and careful handling under inert atmosphere, limiting its applicability to large-scale synthesis. Inspired by Maruoka’s report for the direct C–H difluoromethylation of heteroarenes,
Gouverneur and co-workers disclosed an operationally simple procedure using difluoroacetic acid, PIDA and THF (Scheme 30D). In contrast to other hydrodifluoromethylation procedures, this methodology does not require an inert atmosphere and was demonstrated on decagram scale, providing access to medicinally relevant building blocks. Recently, Maestro and Aleman developed a photocatalytic hydrodifluoromethylation of (a)cyclic imines upon activation of DFMS with rhodamine 6G (Scheme 30E). In 2020, Davis and Gouverneur reported for the first time a protocol enabling precise incorporation of a CF₂H group on a protein (Scheme 30F). 2-PySO₂CF₂H was employed to release a CF₂H radical capable of reacting at the terminal carbon of a SOMOphilic dehydroalanine (Dha) residue. The reaction is performed at ambient and biocompatible conditions, allowing for the preparation of hydrodifluoromethylated proteins in high yields (up to quantitative) and short reaction times. This seminal work by Davis and Gouverneur sets a benchmark for further developments for the late-stage incorporation of perfluoroalkyl group onto biomolecules.

A more recent report from Qing, Chu and co-workers provided a solution to the important problem of regiocontrolled hydrodifluoromethylation of alkenes (Scheme 31). The authors disclosed a silver mediated difluoromethylation of a broad range of alkenes using TMSCF₂H as the difluoromethyl radical source. The authors reported high regioselectivity towards either the anti-Markovnikov or the Markovnikov product when reacting vinyl benzoate in presence or absence of silver, respectively.

In 2015, Dolbier and co-workers disclosed an atom-economical atom transfer radical addition (ATRA) enabling chlorodifluoromethylation of alkenes with difluoromethyl sulfonyl chloride (Scheme 32A; X = Cl). In 2016, Qing and co-workers disclosed a related photocatalytic bromodifluoromethylation of alkenes with difluoromethylphosphonium bromide (Scheme 32A; X = Br). The method tolerates a broad range of substrates bearing different functional groups. Moreover, a one-pot bromo difluoromethylation–elimination process enabled access to α,β-unsaturated CF₂H motifs (see Section 5.1). In the same year, Qing and co-workers expanded their ATRA protocol to the oxydifluoromethylation of styrenes (Scheme 32A; X = OAlk). Running the reaction in alcoholic solvents rendered etherified products, whilst the use of water-acetone mixture afforded alcohol-containing products (Scheme 32A, X = OH). Shortly after, Akita and co-workers also disclosed an oxydifluoromethylation of styrenes (Scheme 32A; X = OAlk, OH). More recently, Xu and co-workers reported an electrochemical variant to access hydroxydifluoromethylated products from N-arylacrylamides, utilizing CF₂HSO₂NHNBoc as a source of CF₂H radical (Scheme 32A, X = OAc). In 2019, Xiao and co-workers disclosed a photoredox catalysed cyanodifluoromethylation of alkenes (Scheme 32A, X = CN). In 2019, Koike, Akita and co-workers reported that styrenes can undergo photoredox catalysed keto-difluoromethylation in...
flow by using a sulfoximine based difluoromethylating reagent and DMSO as oxidant and oxygen source (Scheme 32B). Compared to electrophilic methods that mainly focus on the synthesis of CF₂H groups bound to quaternary centres, Koike and Akita’s method is amenable to the synthesis of CF₂H groups bound to secondary and tertiary centres.

Intramolecular vicinal functionalisations have also been considered. Tan and co-workers reported that the combination of DFMS and ammonium persulfate with catalytic silver nitrate, allowed for a one-step synthesis of 2,2-difluoroethyl oxindoles (Scheme 33A).¹⁴²,¹⁴³ In 2017, Dolbier, and co-workers demonstrated that allyl malonates also undergo difluoromethylation–cyclisation to give fluoroalkyl tetralins (Scheme 33B).¹⁴⁴ In the same year, Wang and co-workers disclosed the difluoromethylation–cyclisation of N-methacryloyl benzamides affording difluoromethyl-containing isoquinolinediones (Scheme 33C).¹⁴⁵ Dolbier and co-workers reported a photoredox difluoromethylation–cyclisation of N- and O-based nucleophiles to form pyrrolidines and γ-lactones (Scheme 33D).¹⁴⁶ Activation of difluoromethanesulfonyl chloride (CF₂HSO₂Cl) by a copper-based photo catalyst rendered the CF₂H radical which added to the terminal alkene. The resulting C-centred radical intermediate underwent oxidation and cyclisation, or halide abstraction to form a chlorinated intermediate that readily cyclised under the reaction conditions. In 2016, a similar strategy was developed by Akita and co-workers used for the highly diastereoselective synthesis of difluoromethyl spiroroethers from aryl-fused cycloalkenylalkanols (Scheme 33E).¹⁴⁷ In 2019, Xu and co-workers disclosed the electrochemical difluoromethylation-lactonization of alkenes using CF₂HSO₂Na in a Pt/Pt cell immersed in a 7 : 1 MeCN/H₂O mixture (Scheme 33G).¹⁴⁹ Under these mild acidic conditions (HOAc (3 equiv.)), various carboxydifluoromethylated products were obtained in moderate to good yields (up to 76%).

An elegant asymmetric difluoromethylation–cyclisation reaction was reported by Liu and co-workers in 2017 (Scheme 34).¹⁵⁰ Urea-containing styrenes underwent difluoromethylation–cyclisation under Cu⁺ catalysis in the presence of catalytic amount of chiral phosphoric acid (S)-A1. The products were formed in enantiomeric excesses up to 97%. The Cu⁺ catalyst is involved both in the activation of difluoromethanesulfonyl chloride and the enantiodetermining cyclisation of the urea to form enantioenriched pyrrolidines.

### 3.4 C(sp³)–CF₂H bond formation: cross-coupling

As eluded to in the introduction of Section 2.1, the first reports disclosing the use of transition metal–CF₂H compounds for C(sp³)–CF₂H bond formation date back to 1988 when Burton demonstrated that a difluoromethyl cadmium reagent was prepared by metal insertion into difluorodimethane (Scheme 35).²³,²⁴ This cadmium reagent was used for the difluoromethylation of allylic halides and propargylic (pseudo)halides to afford allylic difluoromethyl products and difluoromethyl allenes, respectively. In 2007,

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**Scheme 33** Difluoromethylation–cyclisation reactions.

**Scheme 34** Catalytic asymmetric difluoromethylation–cyclisation.

**Scheme 35** Pioneering studies on the synthesis and reactivity of [CdCF₂H] and [CuCF₂H] complexes for C(sp³)–CF₂H bond formation.
the same authors demonstrated the transmetallation of CdCF₂H species to Cu¹, as well as the use of both CdCF₂H and CuCF₂H for the difluoromethylation of allylic halides, propargylic derivatives and 1-iodoalkynes. The authors found that CuCF₂H is less stable than CdCF₂H, and decomposes readily at room temperature. Moreover, the copper species allows for higher level of regiocontrol in allylic difluoromethylation.

These findings inspired Mikami and co-workers to re-investigate allylic difluoromethylation. They reported that regioselective difluoromethylation of allylic carbonates was feasible using nucleophilic [(DMPU)₂Zn(CF₂H)₂] in the presence of catalytic CuI (Scheme 36A). In 2019, the same authors disclosed an asymmetric variant employing CuI and the chiral phosphoramidite ligand L₂ in substoichiometric amount (Scheme 36B).

In 2019, Liu and co-workers applied a Cu-catalysed C(sp³)–CF₂H metal mediated or catalysed bond formation. a Enantiomeric excess measured on a derivative of the product shown.

Scheme 36

C(sp³)–CF₂H metal mediated or catalysed bond formation. a Enantiomeric excess measured on a derivative of the product shown.

In 2019, Liu and co-workers applied a Cu-catalysed C(sp³)–CF₂H metal mediated or catalysed bond formation. a Enantiomeric excess measured on a derivative of the product shown.

This species participates into a single-electron reduction of the redox-active esters. After decarboxylation, the alkyl radical recombines with L₅Cu¹(CF₂H)₂ to afford L₅Cu[H(CF₂H)]- (alkyl) that undergoes reductive elimination to afford the difluoromethyl alkane with concomitant regeneration of the Cu¹ catalyst. The applicability of this methodology was demonstrated on primary, secondary and tertiary carboxylic acids, as well as biologically relevant molecules. In the same year, the same authors disclosed a benzyl C–H difluoromethylation via H-atom abstraction by amidyl radicals formed from N-chlorocarboxamides (Scheme 37B). The method was demonstrated on several examples (up to 91% yield), and allowed for the difluoromethylation of primary and secondary C(sp³)–H bonds; however, only substrates bearing a benzyl C–H bond were sufficiently activated to furnish the desired product. More recently, Liu and co-workers reported a two-step deaminative difluoromethylation (Scheme 37C). Various pyridinium salts derived from amines underwent difluoromethylation under Cu-catalysis ( > 50 examples, up to 93% yield).

In 2021, Shen and co-workers described the direct difluoromethylation of unactivated alkyl bromides, iodides, tosylates and mesylates (Scheme 38). The authors illustrated that alkyl...
iodides, tosylates, and mesylates readily reacted with TMSCF₂H and CsF as activator under copper catalysis. Alkyl bromides required a combination of stoichiometric CuI and catalytic amounts of Pd(dba)₂. This method is complementary to existing hydrodifluoromethylation technologies applied to access similar products from unactivated alkenes.

4. (O/S/N)–Difluoromethylation

Apart from their different conformational preference (Fig. 3), (per)fluoroalkoxy (RfO) groups vary in a number of additional parameters such as Hammett constants $\sigma_m$ and $\sigma_p$. While the OCF₃ group has $\sigma_m$ and $\sigma_p$ values of 0.38 and 0.35 respectively, the OCF₂H group exhibits weaker electron-withdrawing effects ($\sigma_m = 0.31$ and $\sigma_p = 0.18$). A further decrease is observed for OCH₂F ($\sigma_m = 0.20$ and $\sigma_p = 0.02$). These trends have direct implications on physicochemical properties. For example, lipophilicity and metabolic stability tend to increase with fluorine substitution. Due to its intermediary status within the RfO family, the OCF₂H group has become a prevalent motif amongst pharmaceuticals and agrochemicals, with several FDA approved drugs bearing this motif (Fig. 11). Among these, a prominent example is the blockbuster drug Pantoprazole, a marketed proton-pump inhibitor used in the treatment of gastroesophageal reflux disease (GERD).

In the past decade, with the growing number of RfO containing bioactive molecules in drug discovery pipelines, the demand for novel methods to construct X–CF₂H (X = O, S, N) both on aromatic and aliphatic backbones increased. The most common strategy for their synthesis is difluorocarbene insertion into the X–H bond. Alternative methods include decarboxylative fluorination, electrophilic difluorination, and more recently difluoromethoxylation and difluoromethylthiolation. This review focuses on X–CF₂H bond disconnection, which relies on the availability of difluorocarbene reagents. Various modes of activation of these reagents are known including the use of base, nucleophile, as well as thermal activation (Scheme 39).

4.1 O–/S–difluoromethylation

4.1.a Difluoromethylation of (thio)phenols applying difluorocarbene chemistry. As early as 1960, Haszeldine reported sodium chlorodifluoroacetate (ClCF₂CO₂Na) as a difluorocarbene reagent. Scheme 38
Since then, various difluorocarbene reagents have been developed. Many of these hazardous gaseous reagents are limited in scope and require harsh reaction conditions for their activation. These characteristics hamper wider application in modern organofluorine chemistry. As a result, many research groups have developed a new generation of non-ozone depleting difluorocarbene reagents which can be activated under mild conditions and exhibit broader functional group tolerance. In 2006, Hu and co-workers invented the new difluorocarbene reagent 2-chloro-2,2-difluoroacetophenone, which was prepared without the need to use ozone-depleting chemicals (Scheme 40A). This reagent was successfully employed for the difluoromethylation of phenol derivatives, offering moderate yields of up to 76%. One year later, the same authors reported the synthesis of chlorodifluoromethyl phenyl sulfone, another non-ODS-based difluorocarbene reagent, which provided access to N–CF2H (further detail in section 4.2) as well as O-difluoro-methylated phenols with different ring electronics (Scheme 40B). As an extension of their work, Hu and co-workers published an additional report in 2011 on the effect of aromatic ring substituents on the reactivity of these difluorocarbene reagents (Scheme 40C). Substituent effects were more pronounced for the sulfone-based reagents. Extensive screening revealed that p-chlorophenyl chlorodifluoromethyl sulfone and p-nitrophenyl chlorodifluoromethyl sulfone were the most efficient for transferring difluorocarbene to phenols.

In 2009, Zafrani and Segall, described the difluorocarbene reactivity of BrCF2P(O)(OEt)2 on both phenols (9 examples, up to 96% yield) and thiophenols (6 examples, up to 98% yield) (Scheme 41A). The difluoromethylated products were obtained in the presence of 20 equivalents of KOH in a solvent mixture of MeCN/H2O within 30 minutes. Wu and Zou further extended this methodology to the preparation of ArOCF2D (Scheme 41B). The authors found that their protocol was broad in scope, tolerating electron-rich and electron-deficient arenes, as well as heterocyclic substrates (22 examples, up to 93% yield) with excellent deuterium incorporation (>98%D). The protocol was scaled up to 30 g, with no compromise on yield (90%) or deuterium incorporation (99%D). A general method to access ArOCF2D presents a valuable addition to the medicinal chemist toolbox for application in drug discovery programs. It is indeed well established that substitution of hydrogen for deuterium can lead to improvement of the pharmacokinetics, pharmacodynamics and overall metabolic stability of a drug molecule.

In 2013, the Hartwig group described the synthesis difluoromethyl triflate and its application as a difluorocarbene reagent for the difluoromethylation of phenols and thiophenols (Scheme 42A). This commercially available non-gaseous and non-ODS reagent allows difluoromethyl ethers and sulfides to be prepared within a few minutes at ambient conditions under aqueous basic conditions. The broad substrate scope and short reaction times make this method amenable to one-pot sequences involving in situ generation of phenols from either aryl boronic acids or simple arenes. For electron-rich phenols that led to side-products, difluoromethyl triflate was replaced by difluoromethyl nonaflate, a modification increasing conversions towards the desired difluoromethyl ether products. Leroux and co-workers expanded the original substrate scope reported by Hartwig to N-containing heteroaromatics. They also prepared a series of OCF2H analogues of imidacloprid and thiacloprid, two blockbuster insecticides. Dolbier and co-workers reported that fluoroform is suitable for the difluoromethylation of phenols (15 examples, up to 88% yield) and thiophenols.
Building on the studies of Zhang,62,64,65 and Xiao,6,3 who had investigated the reactivity of [L\textsubscript{m}Pd = CF\textsubscript{2}] complexes, Weng designed [Cu(phen)\textsubscript{2}]\textsubscript{O\textsubscript{2}CCF\textsubscript{2}Cl], a stable copper complex readily prepared from CuCl and CICF\textsubscript{2}CO\textsubscript{2}H (Scheme 44). Under aqueous basic conditions and heat, [Cu(phen)\textsubscript{2}]\textsubscript{O\textsubscript{2}CCF\textsubscript{2}Cl] readily releases difluorocarbene and converts phenols to the corresponding difluoromethoxyarenes.

4.1.b Difluoromethylation of aliphatic alcohols/thiols. The syntheses of aryldifluoromethyl ethers have focused on difluorocarbene chemistry under basic conditions. Applying similar conditions to the difluoromethylation of alkyl alcohols was found less effective, an observation consistent with the higher pK\textsubscript{a} of alkyl alcohols (pK\textsubscript{a} B 16) compared to phenols (pK\textsubscript{a} B 10). Notably, alkyl alcohols can react with difluorocarbene without prior deprotonation.174 These insertion reactions required mild reaction conditions to avoid competing pathways triggered by additives such as bases. Nonetheless, Hine and Tanabe,175 and later Mizukado176 reported that the difluoromethylation of aliphatic alcohols was possible with CICF\textsubscript{2}H under basic conditions (Scheme 45). Similarly, Burton177 and Hu178 showed that the difluoromethylation of aliphatic alcohols was possible with BrCF\textsubscript{2}P(O)OEt\textsubscript{2} and TMSCF\textsubscript{2}Br under basic conditions, albeit in low conversions. A variety of early reports which operate under neutral conditions, have proven more effective. As early as 1965, Mitsch and Robertson179 showed that the photolysis of difluorodiazirine could generate difluorocarbene and permit the difluoromethylation of a limited selection of alcohols. In 1995, Miethchen and co-workers reported the O-difluoromethylation of monosaccharides mediated by trifluoromethylzinc bromide,180 and in 2005, Mizukado and co-workers described the use of hexafluoropropene oxide as a difluorocarbene reagent capable of reacting with aliphatic alcohols.181 However, all of these methods either exhibit poor reactivity or lack generality in scope.

More recently, several developments within this area have addressed the above-mentioned limitations which has led to more general protocols for the difluoromethylation of aliphatic alcohols. In 2016, the Shen group discovered that difluoromethyl-(4-nitrophenyl)-bis-(carbomethoxy)-methylide sulfonium ylide is ideal for the difluoromethylation of alkyl alcohols (Scheme 46A).182 This reagent in conjunction with a Lewis acid...
activator (LiBF₄) resulted in the synthesis of a series of alkyl difluoromethylethers in good yields. Mechanistically, this reaction is different from classical difluorocarbene based reactions, as shown to proceed via nucleophilic substitution. Inspired by Weng’s work, Mykhailiuk and co-workers reported the activation of FSO₂CF₂CO₂H with CuI for the synthesis of structurally diverse difluoromethyl ethers from polyfunctional alcohols (Scheme 46B). This methodology astutely exploits copper catalysis to mediate the transfer of difluorocarbene. The conditions are mild and produce the desired products in moderate to high yields. The method was scalable and tolerated various functional groups such as carbamates and esters. However, only primary and secondary alcohols displayed useful reactivity. Significantly lower yields were indeed obtained for tertiary alcohols.

In 2017, Hu showed that activation of TMSCF₂Br with NaOH, KOAc or KHF₂ allowed for the difluoromethylation of a variety of aliphatic alcohols (primary, secondary and tertiary) (Scheme 47). For tertiary alkyl difluoromethylethers, excess TMSCF₂Br was required to obtain high yields. The authors noted that the higher nucleophilicity of aliphatic alcohols compared to phenols, permitted difluoromethylation under mild acidic conditions. In contrast, phenols required basic conditions with difluoromethylation proceeding via phenolate anions. Furthermore, chemoselective difluoromethylation was elegantly achieved by tuning the reaction conditions. Under weakly acidic conditions, employing KHF₂ as an activator, difluorocarbene selectively inserted into the aliphatic O–H bond of 4-(4-hydroxypentyl)phenol in good yield (80%). Conversely, when KOH was used, difluoromethylation occurred at the phenol oxygen in good yield (71%). Similarly, in the case of (4-mercaptophenyl)methanol, difluorocarbene inserted into the O–H bond when the reaction was performed under mild acidic conditions. When aqueous NaOH was used, difluoromethylation occurred at the thiol. With (E)-5-(naphthalen-2-yl)pent-4-en-1-ol, a two-phase system consisting of DCM and water facilitated the insertion of difluorocarbene into the O–H bond at 0 °C under mild acidic conditions. In contrast, under homogeneous conditions (toluene at high temperature), the difluorocyclopronated product was formed exclusively in the presence of nBu₄NBr as activator.

In 2019, Zhang and co-workers reported that S-(difluoromethyl)sulfonium salt is suitable for the facile difluoromethylation of aliphatic alcohols (Scheme 48). The optimised reaction conditions involved the use of NaOAc (5.0 equivalents) and nBu₄NBF₄ (20 mol%) as initiator, in a solvent mixture of CH₂Br₂ and H₂O at room temperature. Similar to the seminal reports from Hu and Shen, a wide array of functional groups including ester, nitro, methoxy and boronic ester were tolerated in the alcohol substrate. The method showed high selectivity for the difluoromethylation at the aliphatic OH site in the presence of functional groups such as phenol, carbamate, alkyne, alkene, or N-heterocycles. Furthermore, difluoromethylation of aliphatic thiols was possible by omitting the initiator (nBu₄NBF₄), changing the counter-ion of their difluorocarbene reagent from PF₆⁻ to BF₄⁻, the base from NaOAc to KOH (2.4 equiv.), and the solvent to MeCN.

### 4.1.c Difluoromethylation of thiols under radical conditions
One-electron chemistry has been shown to proceed with selectivity complementary to two-electron pathways. Baran and co-workers were the first to successfully difluoromethylate with DFMS, a series of heteroaromatic thiols including 2-mercaptobenzothiazole, 2-mercaptobenzoxazole and 2-mercapto-1-methylbenzimidazole in moderate yields (Scheme 49A). In 2017, Yi and co-workers...

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**Scheme 46** Difluoromethylation of aliphatic alcohols under difluorocarbene conditions.

**Scheme 47** TMSCF₂Br as a multi-purpose difluorocarbene reagent for the chemoselective difluoromethylation of aliphatic alcohols.

**Scheme 48** S-(Difluoromethyl)sulfonium salts as effective difluoromethylating reagents of aliphatic alcohols and thiols.
developed an alternative silver-catalysed difluoromethylation process (Scheme 49B). The reaction employs NaSO$_2$CF$_2$H as source of CF$_2$H radical, K$_2$S$_2$O$_8$ as oxidant and AgNO$_3$ (10 mol%). Products were formed in good yields, showing good functional group tolerance including groups that would be reactive towards difluorocarbene. The Studer group recently presented a facile difluoromethylation of various thiols using (difluoromethyl)-triphenylphosphonium bromide (Scheme 49C). Mechanistic studies revealed that an S$_{RN1}$-type mechanism is at play. The authors illustrate the power of this radical process with the selective difluoromethylation of thiol with no competing reaction taking place at phenol or aniline. Aliphatic thiols were not reactive.

4.2 N-Difluoromethylation

N-Heteroaromatic scaffolds such as imidazoles and benzimidazoles, are prevalent structural motifs in medicinal chemistry. Methods for the selective insertion of a CF$_2$H group into a N-H bond have therefore a myriad of applications ranging from medicinal to agricultural chemistry. In this context, N-difluoromethylated pyrazoles were investigated in SAR studies of calpain inhibitors and in herbicide research (Fig. 12). Recently, André and co-workers were able to modulate receptor residence times in a family of pyridone-containing CRTh2 antagonists by varying the substituent at the pyridine nitrogen. Their study showed that N-difluoromethyl 2-pyridones had a significantly higher dissociation half-life than the corresponding non-substituted or N-methylated pyridones.

Sundermeyer was amongst the first to report the difluoromethylation of an N-nucleophile as early as 1985, by reaction of CF$_2$HSO$_2$Cl with trimethylammonium chloride (Scheme 50). In the years that followed, more general strategies were reported for N-difluoromethylation, but mostly employed gaseous ODS such as ClCF$_2$H. In 1998, Lyga et al. described the difluoromethylation of five-membered NH-heterocycles using sodium hydride as a base followed by treatment with excess ClCF$_2$H (Scheme 51A). In 2002, Petko et al. expanded the difluoromethylation of nitrogen nucleophiles to various sulfonamides using ClCF$_2$H under strong alkaline conditions (Scheme 51B). Since then, further difluoromethylation protocols for additional classes of N-nucleophiles have emerged.

In 2006 Ando et al. reported the difluoromethylation of 2-acetamidopyridines (Scheme 52). The use of catalytic amounts of 18-crown-6 in combination with sodium chlorodifluoroacetate (SCDA) allowed for chemoselective difluoromethylation at the pyridine nitrogen. Treatment with KHSO$_4$ under reflux gave the corresponding N-difluoromethyl-2-pyridones in good yields.

In 2007, Hu and co-workers developed chlorodifluoromethyl phenyl sulfone as a novel non-ODS difluorocarbene source.
The reagent was activated under aqueous basic conditions for the N-difluoromethylation of NH-heterocycles including imidazoles, benzimidazoles and benzotriazoles (Scheme 53A). The same group reported the difluoromethylation of similar substrates in non-aqueous conditions using instead N-tosyl-S-difluoromethyl-S-phenylsulfoximine (Scheme 53B). This sulfoximine-based reagent is a crystalline solid prepared via a carbene reagent. 178 (Benz)imidazoles, benzotriazole and tetrazoles reported the Freon-free synthesis of TMSCF$_2$ Br, a powerful difluoromethylating agent under mild conditions. Simultaneously, Hu and co-workers disclosed alternative conditions for the difluoromethylation of tertiary amines employing BrCF$_2$PO(O)(OEt)$_2$ activated by CsF (Scheme 53B). The authors proposed that BrCF$_2$PO(O)(OEt)$_2$ reacts with fluoride liberating the difluorocarbene intermediate. Nucleophilic attack by the amine followed by protonation affords α-difluoromethylated quaternary ammonium salts. Notably, hydroxyl, alkenyl, alkynyl and ester groups were all tolerated under these mild conditions. In 2018, Jana and co-workers disclosed alternative conditions for the difluoromethylation of N-tosyl protected anilines (Scheme 54C). Using an aqueous solution of LiOH in DMF to generate difluorocarbene from BrCF$_2$CO$_2$Et at room temperature, a broad range of N-difluoromethylated products were accessible. Neither electronic or steric perturbation compromised reactivity. In 2015, Shen et al. extended the use of [NHC]Ag(CF$_2$H) complex to successfully difluoromethylate various aryldiazonium salts at nitrogen (Scheme 54D). The reaction afforded difluoromethyl diazene compounds in good to excellent yields. Good functional group tolerance was observed and reactions with aryldiazonium salts bearing electron-donating or electron-withdrawing groups all resulted in high yields. This N-difluoromethylation is unique because it does not proceed through a difluorocarbene mechanism.

The Tang group reported a unique transformation leading to N-difluoromethylated thioureas from azoles (Scheme 55A). To successfully prepare these products, the authors reacted...

Scheme 53  Difluoromethylation of N-heterocycles.

Scheme 54  Difluoromethylation of other nitrogen-based substrates.
elemental sulfur ($S_8$), HOCH$_2$SO$_2$Na, and BrCF$_2$CO$_2$Et in DMA at 100°C. The reaction was successful on a range of triazoles, imidazoles and benzimidazoles with the products obtained in satisfactory yields. Efforts from the Weng group led to a novel method for the synthesis of 3-difluoromethylbenzoxazole-2-thiones from 2-aminophenols (Scheme 55B). This alternative one-pot sequence employed $S_8$ and ClCF$_2$CO$_2$Na under basic conditions ($t$BuONa) in DMF at 70°C. The use of molecular sieves improved reaction yields.

5. Difluoromethylation of alkenes and alkynes

The difluoromethylation of alkenes has only recently been reported. Various difluoromethylation protocols developed for the conversion of aryl halides to difluoromethylarenes are also suitable for the difluoromethylation of vinyl halides. Furthermore, difluoromethylated alkenes can be accessed through a variety of radical-based methodologies featuring either photochemical or electrochemical activation. In contrast, difluoromethylated alkynes are prepared using difluorocarbene chemistry.

5.1 Difluoromethylation of alkenes

Qing and co-workers described the bromodifluoromethylation of alkenes, with the ATRA products undergoing in situ elimination upon addition of DBU (Scheme 56). This two-step one-pot indirect protocol yielded a small selection of difluoromethylated alkenes (4 examples, up to 83%) with good E/Z selectivity (up to 97:3).

In 2019, Zhao and Loh reported the photoredox catalysed difluoromethylation of enamides using difluoromethyltriphenylphosphonium bromide under Ir-photocatalysis (Scheme 57). A wide selection of enamides were readily difluoromethylated in good yields under the optimised reaction conditions, and in most cases, with complete E/Z stereoselectivity.

With electrochemistry re-emerging as a green strategy for organic synthesis, an electrochemical difluoromethylation approach has recently been considered by Xu and co-workers. Electrochemical C–H difluoromethylation of acrylamides was accomplished with CF$_2$HSO$_2$NHNHBoc as precursor of CF$_2$H radical and Et$_4$NOTs as electrolyte (Scheme 58A). The use of a reticulated vitreous carbon (RVC)/Pt electrode and applying 10 mA of current at 70°C in a TFE/H$_2$O mixture (5:1) afforded β-difluoromethylated acrylamides in good yields (5 examples, up to 97%) and good Z/E selectivity (≥10:1). In 2018, Xu and co-workers reported that ferrocene (Cp$_2$Fe) is a highly efficient mediator for the electrochemical activation of CF$_2$HSO$_2$NHNHBoc for the release of CF$_2$H radical (Scheme 58B). This protocol provided access to difluoromethylated dibenzazepines upon CF$_2$H radical addition to an alkyne followed by 7-membered ring-forming homolytic aromatic substitution.
A recent report from Qing, Chu and co-workers demonstrated that styrenes, cinnamic acids and vinyl trifluoroborate salts efficiently underwent Ag-promoted radical difluoromethylation with TMSCF₂H (Scheme 59).⁹⁷ This method affords difluoromethyl alkenes in high yields with no requirement for light irradiation or electrochemical activation.

### 5.2 Difluoromethylation of alkynes

A seminal report by Hu and co-workers in 2009 illustrated the use of N-tosyl-S-difluoromethyl-S-phenylsulfoximine for the difluoromethylation of alkynes (Scheme 60).ⁱ⁹² While the methodology is limited to electron-rich alkynes, the protocol represents a valuable alternative to previously known Freon-based approaches. The authors proposed a difluorocarbene mechanism with the first equivalent of lithium acetylide acting as a base to deprotonate N-tosyl-S-difluoromethyl-S-phenylsulfoximine, thereby generating a difluorocarbene species which can react with a second lithium acetylide equivalent. The resulting anion is then quenched resulting in the difluoromethylated product.

In 2015 and 2016, Shibata and Mikami reported the difluoromethylation of aryl and heteroaryl-acetylenes under a fluoroform atmosphere in the presence of tBuOK or LHMDS (Scheme 61).²⁰⁴,²⁰⁵ In Shibata’s report, further derivatisation of the difluoromethylated alkyne products to difluoromethylated isoxazoles and triazoles through 1,3-cycloaddition and click reactions was demonstrated (Scheme 61A).

In 2019, Hu and co-workers reported the use of commercially available TMSCF₂Br as a difluoromethylation reagent for a selection of electron-rich and electron-neutral alkynes under ambient conditions (Scheme 62).¹²⁹ Heterocycles such as dibenzothiophene and benzofuran are compatible under the optimised reaction conditions. The authors suggested that a difluorocarbene mechanism is operating.

In 2020, Zhang and co-workers extended the palladium difluorocarbene ([Pd = CF₂]) chemistry (described in Section 2.1.c) to the difluoromethylation of alkynes (Scheme 63).²⁰⁶ The protocol employed chlorodifluoromethane as the difluorocarbene precursor, and featured good functional group tolerance, broad substrate scope, and was applied to the synthesis of complex drug molecules. One limitation of this method is the use of chlorodifluoromethane, an ODS.

### 6. Industrial state of play

The toolbox of reactions that facilitate access to difluormethylated compounds is expanding at a rapid pace.
scientists are continuously considering these reactions to adapt them to large-scale synthesis. For many years, the large scale difluoromethylation of phenols relied on the use of chlorodifluormethane. The ozone-depleting properties of this reagent have prompted scientists to utilise more environmentally friendly reagents. In 2019, Greszler illustrated that diethyl bromodifluoromethyl-phosphonate is a suitable difluorocarbene reagent to access ABBV-2222, a CFTR corrector for the treatment of cystic fibrosis (Scheme 64).207 Despite the exothermic nature of the difluoromethylation process, ABBV-2222 was prepared on 130 g scale.

Scientists from Innocrin Pharmaceuticals recently disclosed that bis-difluoromethylation of a relevant intermediate towards the synthesis of seviteronel is feasible on multikilogram scale using a modified literature procedure (Scheme 65).208 The authors demonstrated that a slight excess of SCDA in combination with a flow mixture of DMF/H2O afforded the desired building block in 57% yield on a multikilogram scale.

In 2018, Kappe and co-workers optimised their continuous flow α-difluoromethylation for a telescoped continuous synthesis of Efornithine (Scheme 66).209 Efornithine hydrochloride monohydrate was produced in more than 17 grams with a throughput of 24 mmol h⁻¹.

While the above examples illustrate that progress has been made to scale up difluoromethylation protocols, many large-scale syntheses of (sp²)–CF₂H compounds still rely on either deoxy-fluorination or a building block approach. The reason may be the limited number of studies focused on the large-scale production of difluoromethylation reagents. Notably, Pfizer recently developed a scalable synthesis of [(DMPU)2Zn(CF₂H)₂] (Scheme 67).210 One of the key challenges to overcome was the high price of the starting material (CF₂HI). To combat this problem, the synthesis of CF₂HI from BrF₂CCO₂H was optimised. With CF₂HI in hand, [(DMPU)2Zn(CF₂H)₂] was prepared from ZnEt₂ in quantities superior to 100 g.

During the review of this manuscript, a metal-free C–H difluoromethylation process for azines involving phosphonium salt formation followed by sp²–sp³ phosphorus ligand-coupling was reported by Paton, McNally and co-workers. Various pyridines, drug-like fragments, and pharmaceuticals were readily converted into difluoromethyl analogues. No pre-installed functional groups or directing groups are required, and for a range of sterically and electronically distinct pyridines, difluoromethylation occurs selectively at the 4-position.211

7. Conclusion and future outlook

Polyfluoroalkylation is an ever-expanding field of research within organic chemistry. This is also the case for difluoromethylation, where a community of chemists have developed numerous synthetic strategies for the successful incorporation of CF₂H onto diverse classes of molecules. Efforts to facilitate the construction of C(sp³)–CF₂H bonds have largely focused on cross-coupling and free radical methods. The state of play in cross-coupling has advanced tremendously over the last decade, and to date, nucleophilic, electrophilic, and radical difluoromethylation reagents as well as difluorocarbene precursors are viable cross-coupling partners for a wide range of arenes. While the development of cross-coupling methodologies has primarily focused on the functionalisation of arenes, technologies which harness the innate selectivity of the nucleophilic CF₂H radical have been applied to electrophilic heteroarenes. Further developments within the area of radical C–H difluoromethylation that go beyond functionalisation at innately reactive sites would be highly desirable. Progress towards this end has been made by Baran and co-workers who illustrated the effect of solvents on reversing regioselectivity of pyridines.83 Furthermore, Qing and co-workers have shown that under oxidative conditions, C–H difluoromethylation of heteroaromatics can occur at the most acidic C–H bond instead of the most electron-deficient carbon.100 C(sp³)–CF₂H bond formation through cross-coupling has also matured to a point where more earth-abundant metals are
employed. This is a welcome development, and so is the use of renewable non-ODS CF₂H source. Future research directions should focus on difluoromethylation that make use of inexpensive reagents, feedstock chemicals and operationally simple procedures. Furthermore, there are still gaps in the area of C(sp³)-CF₂H bond formation such as meta-selective C–H difluoromethylation of (hetero)arenes or decarboxylative difluoromethylation of aryl carboxylic acids. Furthermore, a versatile 18F-difluoromethylation of (hetero)arenes or decarboxylative difluoromethylation of aryl carboxylic acids. The field of C(sp³)-CF₂H bond formation has been addressed from various angles. Nucleophilic difluoromethylation is generally achieved with TMSCF₂H, whilst electrophilic difluoromethylation often proceeds via a difluorocarbene mechanism. Recently, various radical methods have allowed for the construction of C(sp³)-CF₂H bonds in presence of unprotected functional groups, thus allowing for late-stage difluoromethylation. Future developments should aim at filling gaps such as a general method for Markovnikov difluoromethylation of alkenes or undirected C(sp³)-H difluoromethylation. In comparison to asymmetric trifluoromethylation, the field of stereoselective difluoromethylation remains underdeveloped. Specifically, general enantioselective difluoromethylation methodologies which furnish quaternary centres substituted with a CF₂H group would be of value to the pharmaceutical industry. Evidently, the use of difluorocarbene reagents has had a tremendous impact in the construction of X-CF₂H bonds. Current challenges are accessibility to X-CF₂H fragments with high selectivity in presence of multiple reactive functional groups. Finally, the focus of all existing methods has been on small molecules. Today, it is not unthinkable that new methods which allow for incorporation of the CF₂H group on biologically relevant systems, such as peptides, proteins and oligonucleotides, are within reach. A small fluoride-containing motif like the CF₂H group could be useful for probing biological activity or mechanistic studies by 19F NMR. Seminal work in this direction has recently been reported by Davis, Gouverneur and co-workers, who have developed site-selective photocatalytic hydrodifluoromethylation and difluoromethylation of dehydroalanine and tryptophan residues in proteins, respectively.99,134

Conflicts of interest

There are no conflicts to declare.

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