Contemporary synthetic strategies in organofluorine chemistry

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Abstract | Fluorinated molecules have a wide range of applications and are used as medicines, agrochemicals and refrigerants and in smartphone liquid crystal displays, photovoltaic solar cells, Teflon tapes and the coatings of textiles and buildings. Fluorination and fluoroalkylation — incorporation of a trifluoromethyl, difluoromethyl or monofluoromethyl group — are the major strategies used for the construction of carbon–fluorine bonds and fluorinated carbon–carbon bonds, respectively. The past two decades have witnessed a rapid growth in fluorination and fluoroalkylation methods thanks to the development of new reagents and catalysts. This Primer aims to provide an overview of state-of-the-art strategies in fluorination, trifluoromethylation, difluoromethylation and monofluoromethylation, with an emphasis on using C–H functionalization, although other strategies for fluorination and fluoroalkylation are also discussed. Further landmark achievements are expected in the fields of fluorination and fluoroalkylation as organofluorine compounds are used increasingly in everyday applications.

Heteroelement
Any element in the periodic table that is not carbon or hydrogen.

Positron emission tomography
(PET). A functional imaging technique that uses radiotracers to visualize and measure changes in metabolic processes, and in other physiological activities.

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Fluorine is the most electronegative element in the periodic table and the second most used heteroelement in life science research after nitrogen[1]. Approximately 20% of marketed drugs and 50% of agrochemicals registered in the past 20 years are estimated to contain one or more fluorine atoms[2–7]. Fluorine atoms can be incorporated through fluorination or fluoroalkylation, which introduces a trifluoromethyl (CF_3), difluoromethyl (CF_2H) or monofluoromethyl (CH_2F) group. The incorporation of fluorine atoms into a drug molecule can modulate several important properties including its metabolism, pharmacokinetics and ability to permeate biological tissues; as a result, the pharmaceutical industry relies on fluorination and fluoroalkylation methods, and pressure is mounting to make these processes more environmentally friendly[2,8–10]. In addition, because the unnatural fluorine-18 isotope possesses many desirable properties for applications in positron emission tomography (PET) imaging, there is great demand for convenient methods enabling late-stage ^{18}F fluorination and ^{18}F fluoroalkylation[11].

Although inorganic fluorides such as CaF_2 are abundant on earth, the organofluorine compounds typically required for the synthesis of pharmaceuticals are extremely rare in nature[12,13]. As a result, almost all of the organofluorine compounds and materials used in industry and academia are synthetic. The source of fluorine for all fluorination and fluoroalkylation reactions is HF, which is prepared from the reaction of CaF_2 mineral (also called fluorite or fluorspar) with sulfuric acid.

FIGURE 1a outlines historical developments in organofluorine chemistry. The first chemically synthesized organofluorine compounds can be dated back to 1835, when fluoromethane was prepared from dimethyl sulfate and KF[14,15]. Over the past 200 years, many fluorination and fluoroalkylation methods have been developed to prepare structurally diverse organofluorine compounds[15–22]. Before the 1960s, fluorination mainly relied on corrosive or explosive reagents such as HF, F_2, SbF_3 and CoF_3 and classical reactions such as the Swarts reaction, the Balz–Schiemann reaction, the halex reaction, the Simons process (electrochemical fluorination) and direct fluorination. Although these classical fluorination methods are inexpensive, they can be unsafe, require special equipment and offer low tolerance of common functional groups; as a result, they are only used in a small number of specialized chemical plants and research facilities. After the 1960s, more mild and selective fluorination reagents emerged, including diethylaminosulfur trifluoride (DAST), Deoxo-Fluor, Selectfluor and *N*-fluorobenzenesulfonimide (NFSI). Nucleophilic, electrophilic and radical fluoroalkylation reagents have also been developed, such as trifluoromethyltrimethylsilane ($TMSCF_3$; also known as Ruppert–Prakash reagent), methyl fluorosulfonyldifluoroacetate ($FSO_2CF_2CO_2Me$; also known as Chen's reagent), sodium trifluoromethanesulfinate (CF_3SO_2Na; also known as Langlois reagent), Umemoto reagent and Togni reagent. Fluorination and fluoroalkylation reactions mediated or catalysed by transition metals

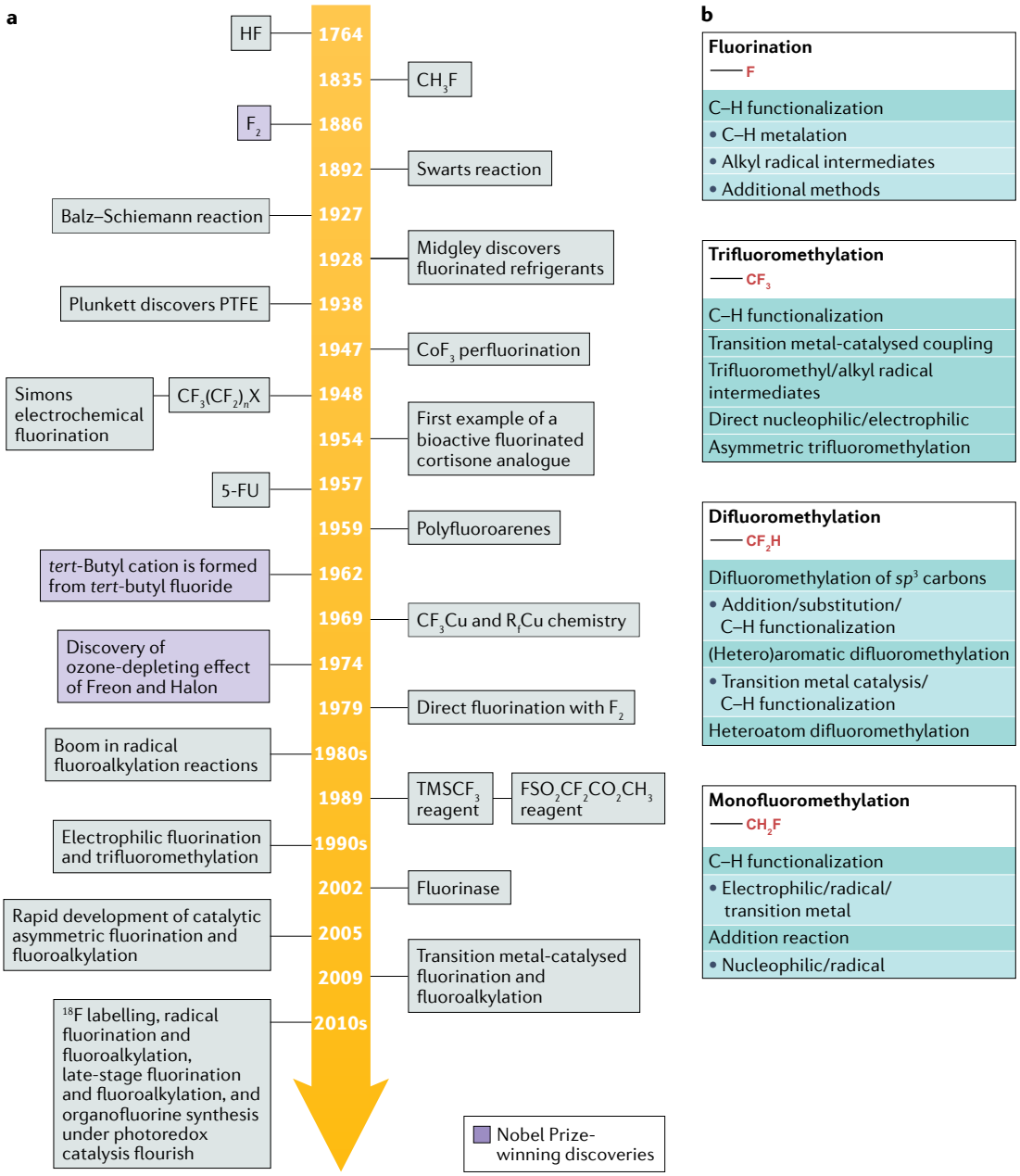


Fig. 1 | **Outline of synthetic organofluorine chemistry. a** | Historical developments in organofluorine chemistry. Brief description of major landmarks in the development of organofluorine chemistry. Purple boxes show Nobel Prize-winning discoveries. **b** | Overview of fluorination, trifluoromethylation, difluoromethylation and monofluoromethylation, as discussed in this Primer. An overview of state-of-the-art strategies that are suitable for late-stage modification of complex organic molecules. Both C–H functionalization and transformations of pre-functionalized substrates are covered. 5-FU, 5-fluorouracil; PTFE, polytetrafluoroethylene; R_fCu, perfluoroalkylcopper; $TMSCF_3$, trifluoromethyltrimethylsilane (also known as Ruppert–Prakash reagent).

Swarts reaction
A fluorination method used to prepare alkyl fluorides from alkyl chlorides or bromides. The typical fluorination reagent is antimony(III) trifluoride in the presence of a catalytic amount of antimony(V) salts.

Balz–Schiemann reaction
A method for the production of aryl fluorides from primary aromatic amine via a diazonium tetrafluoroborate intermediate.

Halex reaction
The nucleophilic substitution reaction between an aryl or alkyl halide and the other halide ions.

have improved the functional group tolerance of these methods and now enable the late-stage fluorination and fluoroalkylation of complex molecules. Synthetic organofluorine chemistry has flourished in the past 20 years with the development of many new fluorination and fluoroalkylation methods including enzymatic fluorination, enantioselective fluorination and fluoroalkylation, transition metal-catalysed fluorination and fluoroalkylation, radical fluorination and fluoroalkylation, and ^{18}F labelling of PET probes, among others[11,15,23–27].

This Primer focuses on C–H fluorination, trifluoromethylation, difluoromethylation and monofluoromethylation, and gives an introductory overview of other strategies for fluorination and fluoroalkylation (FIG. 1b), specifically discussing the substrate scope, plausible mechanisms and applications of these reactions for the synthesis of bioactive molecules and ^{18}F-labelled PET agents. When choosing examples to illustrate fluorination and fluoroalkylation chemistry, we have taken into account the recent guidance from industry that

Phase transfer catalysis
A process in which the rate of a reaction in a heterogeneous two-phase system is enhanced by the addition of a substance that transfers one of the reactants across the interface between the two phases.

fluorination and fluoroalkylation methods should be safe, practical, cost-effective, environmentally responsible and capable of being performed in the presence of heterocycles, with a reasonable functional group tolerance[2]. In the last part of this Primer, we briefly provide our outlook on the future of fluorination and fluoroalkylation chemistry.

Experimentation

There have been great advances in the development of catalytic methods for the incorporation of single fluorine atoms or fluorinated groups into organic molecules over the past few decades. Many of these advances result from strategies aimed at optimizing reactivity and selectivity, for example combining judicious selection of fluorination and fluoroalkylation reagents with innovations in catalyst design[28,29]. This section gives a brief introduction to fluorination with an emphasis on recently developed late-stage C–H fluorination methods, before discussing trifluoromethylation, difluoromethylation and monofluoromethylation strategies.

Fluorination

Several highly efficient reagents have been developed for fluorination at both sp^2 and sp^3 carbons. The most prominent are novel nucleophilic reagents, including HF derivatives such as HF-pyridine, triethylamine trihydrofluoride ($Et_3N{\cdot}3HF$) and HF complexed with 1,3-dimethyl-3,4,5,6-tetrahydro-2-pyrimidinone (DMPU)[30–32]; deoxyfluorinating reagents that gradually release fluoride in solution, such as DAST, Deoxo-Fluor, PhenoFluor and PyFluor[33]; hydrogen-bonded tetrabutylammonium fluoride (TBAF) complexes such as TBAF(^{t}BuOH)$_4$ and TBAF(pin)$_2$ that are tunable in terms of their nucleophilicity[34]; and electrophilic reagents such as Selectfluor and NFSI that can also serve as powerful oxidants[35].

New catalytic manifolds have also played a critical role in augmenting fluorination approaches. Early studies focused on the use of pre-functionalized substrates and transition metal catalysis to overcome the problem of reductive elimination for C–F bond formation; it is now clear that reductive elimination using Pd^0/Pd^{II} catalytic cycles is feasible with a bulky ancillary ligand that forces C–F bond formation from a 14-electron Pd^{II} complex[36]. Additional advances were made with the realization that reductive elimination is energetically more facile using high oxidation metal complexes featuring in Pd^{II}/Pd^{IV} and Cu^{I}/Cu^{III} catalytic cycles, and with the design of novel ligands[37–39]. Photoredox catalysis approaches have also emerged in recent years, for example those using decarboxylative fluorinations[40,41].

Fluorination at sp^3 carbons can give rise to the challenge of controlling stereoselectivity, and most enantioselective methodologies developed to date require electrophilic fluorination reagents and transition metal catalysis, or organocatalytic approaches such as enamine catalysis or cationic/anionic phase transfer catalysis[42–45]. Recently, an alternative strategy inspired by the fluorinase enzyme and based on the merger between hydrogen bonding and phase transfer catalysis has allowed the use of cost-effective and easy-to-handle alkali metal fluorides as fluorine sources in asymmetric catalysis[46–48].

The incorporation of fluorine through C–H activation[24] avoids the need to pre-functionalize the substrate. In principle, it allows for selective functionalization at a late stage in synthesis, which is highly desirable when preparing novel drugs and chemical libraries[49]. To date, the field has been dominated by processes using electrophilic fluorine (F^+) sources as these can act as both a fluorine source and an oxidant; however, approaches have emerged that use a nucleophilic fluorine (F^-) source in combination with a suitable external oxidant. C–H fluorinations can be broadly divided into two classes depending on the activation mode employed: transition metal-catalysed protocols, in which the metal is directly involved in the C–H activation step, and radical-based methodologies, in which a carbon-centred radical is involved (FIG. 2a).

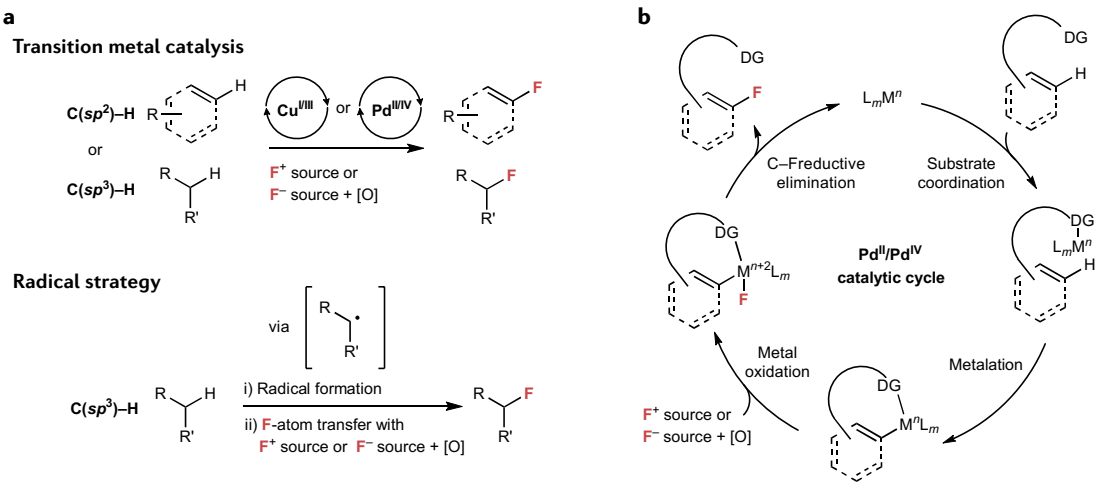


Fig. 2 | **Incorporation of fluorine via C–H activation. a** | Two main modes of activation for C–H fluorination; transition metal-mediated catalysis and a radical-mediated strategy. The carbon-centred radicals are commonly formed via hydrogen abstraction by heteroatom radicals or high-valent metal-oxo intermediates. **b** | Proposed catalytic cycle for Pd^{II}-catalysed C–H fluorination from high-valent metal species. DG, directing group; F^+ source, electrophilic fluorine source; F^- source, nucleophilic fluorine source; L_m, ligand(s); M, metal; [O], oxidant.

Transition metal-catalysed C–H activation protocols. The most commonly used transition metal-catalysed strategy uses a Pd^{II}/Pd^{IV} catalytic cycle, which begins with the metal coordinating a directing group followed by metalation of a specific aromatic or aliphatic C–H bond (FIG. 2b). Oxidation of the metal by a F^+ source or an oxidant used in combination with a F^- source ensures the generation of a high-valent species that undergoes C–F bond formation through reductive elimination and regeneration of the catalyst. The conversion of aromatic C–H bonds into C–F bonds can be performed on substrates bearing a 2-pyridinyl directing group, using *N*-fluoropyridinium tetrafluoroborate as both an oxidant and a fluorinating agent and $Pd(OAc)_2$ as a catalyst[37] (mechanistic studies have reported the involvement of a high-valent metal species for this reaction[50]). Several methodologies using various directing groups in combination with N–F reagents have now been described, expanding the scope of aromatic C–H fluorination[24,51,52] (FIG. 3A). An alternative approach uses a Cu^I/Cu^{III} catalytic cycle[38,39] and has been successfully translated to ^{18}F radiolabelling[53] (FIG. 3A).

Aliphatic functionalization is more challenging than aromatic functionalization owing to the absence of a π-system for pre-coordination of the metal to the substrate and the greater conformational flexibility of aliphatic groups. Initial studies showed the feasibility of C(sp^3)–F reductive elimination from high-valent Pt^{IV} and Pd^{IV} species[54,55]. Subsequent reports proved that both bidentate and monodentate auxiliaries (FIG. 3Ba) are suitable directing groups for the selective catalytic β-fluorination of amino acid derivatives using Selectfluor[56,57]. Various additional carboxylic acid derivatives were successfully fluorinated by applying a similar strategy[24]. Enantioselective C–H fluorination can also be performed; asymmetric C(sp^3)–F bond formation through C–H activation has been achieved up to 96% enantiomeric excess using a chiral α-amino acid derivative to form a transient chiral imine directing group and 2-alkyl benzaldehyde derivatives as substrates[58,59]. A mechanistically distinct C(sp^3)–H fluorination on allylic substrates (FIG. 3Bb) uses $Pd(TFA)_2$ as a catalyst, a bis-sulfoxide ligand and a chromium-salen salt co-catalyst to generate the active Pd^{II} π-allyl intermediate, which reacts with $Et_3N{\cdot}HF$ (REF.[60]).

Radical-based protocols. The main alternative to metal-catalysed protocols for C–H fluorination is protocols using carbon-centred radical intermediates. In these approaches, the absence of directing groups makes regioselectivity less predictable and reactivity follows general trends based on C–H bond dissociation energies; consequently, only aliphatic, allylic and benzylic C–H bonds are reactive. Polar and steric effects can also contribute to regioselectivity, with the least substituted sites generally favoured.

Radical-based methodologies can be broadly categorized into non-photocatalytic and photocatalytic approaches. Non-photocatalytic approaches emerged following the discovery that reagents with low N–F bond dissociation energies such as NFSI or Selectfluor can be employed for fluorine atom transfer through the decarboxylative fluorination of peroxy esters[61]. The first C–H to C–F conversion of aliphatic, allylic and benzylic substrates using carbon-centred radicals used a Cu^I initiator and *N*-hydroxyphthalimide as a co-catalyst[62] (FIG. 4a). Following this breakthrough, many other protocols involving metals such as silver and/or various radical precursors were reported[24]. Heteroaromatic benzylic C–H bonds can be selectively fluorinated using a radical mechanism even in the absence of an external radical initiator when Selectfluor is employed as a fluorine source[63], and a complementary ionic approach to achieve the same transformation using NFSI has been proposed[64]. Recently, a novel method has been reported for generating carbon-centred radicals for C–H fluorination using formal Cu^{III} fluorides[65]. A further advance in the field is a bioinspired manganese-porphyrin catalytic system for aliphatic C–H fluorination using a nucleophilic source of fluoride — AgF and TBAF — in the presence of PhIO as the oxidant (FIG. 4a). High regioselectivity was achieved using the above technique in the fluorination of complex steroids[66] and, later, benzylic C–H bonds[67]. The nucleophilic fluorine source used in the above method can be used for ^{18}F radiolabelling[68]. Alternative non-photocatalytic approaches ensure site selectivity by incorporating a specific functional group in the substrate that, upon activation, enables a 1,5-hydrogen atom transfer process. These approaches generally feature Fe^{II}/Fe^{III} catalytic cycles and are applied to aliphatic and benzylic C–H fluorination reactions[24,69] (FIG. 4b).

Photocatalytic strategies use xanthones and 9-fluorenones as photocatalysts to enable the monofluorination and difluorination of benzylic C–H bonds in the presence of Selectfluor and visible light[70] (FIG. 4c). This methodology sparked the broad use of aryl ketones and decatungstate salts as photocatalysts for radical C–H fluorination[24], including the elegant use of [^{18}F] NFSI for site-selective radiolabelling of amino acids and peptides[71,72].

Additional C–H fluorination methods. Additional mechanistically distinct methods for fluorination include the late-stage C–H fluorination of pyridines and diazines under mild conditions using AgF_2 for nucleophilic heteroaromatic substitutions[73] and non-directed aromatic C–H fluorination using a non-bound Pd^{II} complex oxidized in situ to Pd^{IV} by F^+ reagent[74]. In the latter method, fluoride delivery occurs through a transition state that density functional theory calculations have determined as a Pd^{III} singlet diradical[74]. Both electron-rich and electron-poor arenes are tolerated, which is in stark contrast to uncatalysed electrophilic aromatic fluorinations that require electron-rich arenes. *Ortho*-regioisomeric and *para*-regioisomeric mixtures are obtained using this method[74].

Trifluoromethylation

Numerous trifluoromethylation reagents have been developed, such as $TMSCF_3$, $FSO_2CF_2CO_2Me$, CF_3SO_2Na, Togni reagent, Umemoto reagent and $[Ph_2S^+CF_3]TfO^-$ (also known as Yagupolskii–Umemoto reagent). The

C–H bond dissociation energies
Measures of the strength of C–H bonds, which can be defined as the standard enthalpy change when C–H is cleaved by homolysis to give a carbon radical and a hydrogen atom.

Density functional theory
A computational quantum mechanical modelling method to investigate the electronic structure or nuclear structure of atoms, molecules and the condensed phases.

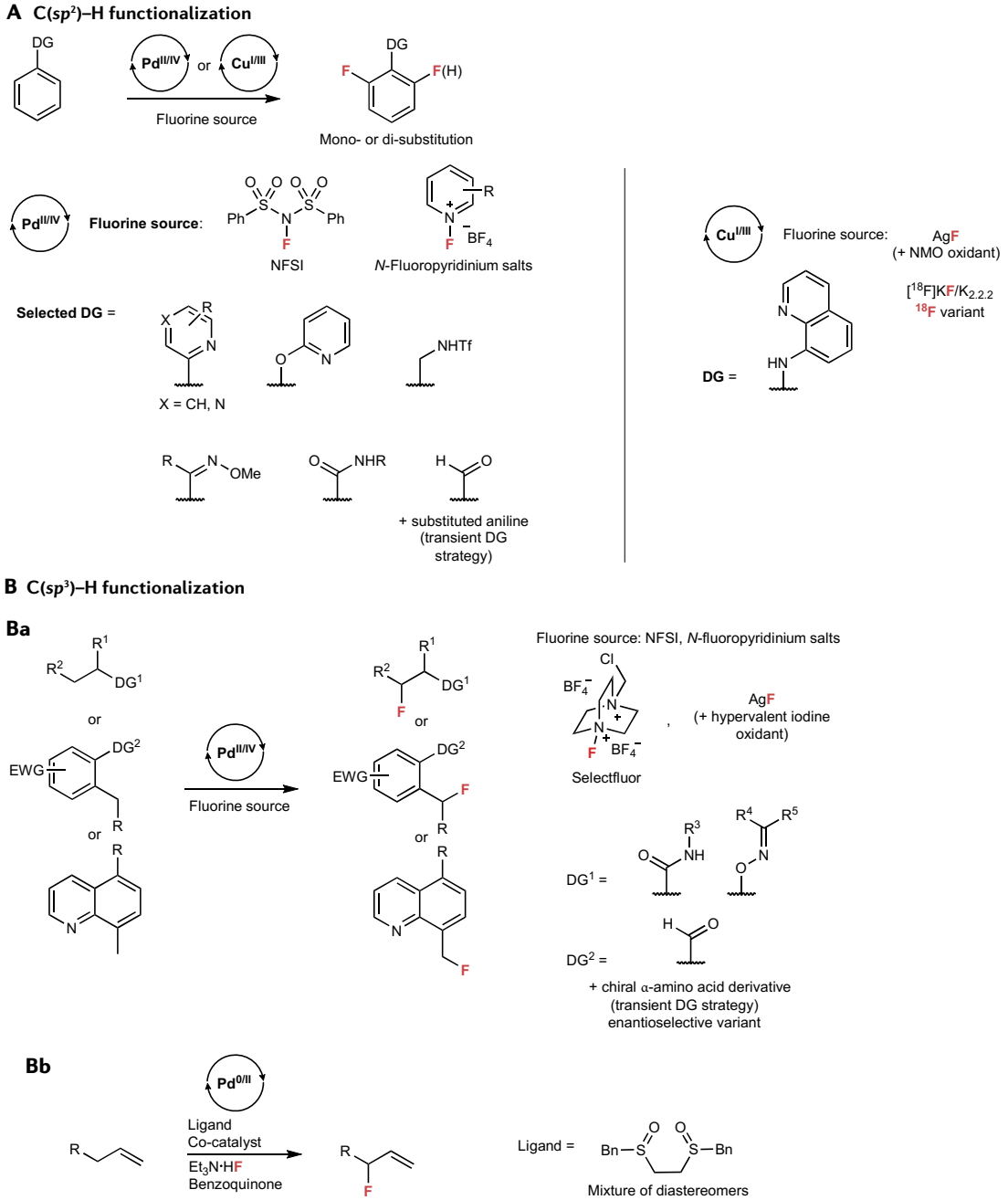


Fig. 3 | **Main palladium-catalysed and copper-catalysed C–H fluorination protocols. A** | Palladium-catalysed or copper-catalysed C(sp^2)–H functionalization. Potential fluorine sources and directing groups (DGs) shown for both palladium-catalysed and copper-catalysed reactions. **B** | Palladium-catalysed C(sp^3)–H functionalization. Reactions achieved through a Pd^{II}/Pd^{IV} catalytic cycle (part **Ba**) and a Pd^0/Pd^{II} catalytic cycle (part **Bb**). Pd^{II}/Pd^{IV} catalytic cycle is applicable for various substrates with a proper DG, and potential fluorine sources and representative DGs are shown. Pd^0/Pd^{II} catalytic cycle is limited to allylic compounds and proceeds under the control of a ligand. EWG, electron-withdrawing group; $K_{2.2.2}$, Kryptofix 222; NFSI, *N*-fluorosulfonamides; NMO, *N*-methylmorpholine *N*-oxide.

emergence of these reagents has stimulated the development of various trifluoromethylation methods, including electrophilic, nucleophilic, radical and transition-metal catalysed or mediated reactions[75] (general reaction schemes shown in FIG. 5).

Transition metal-catalysed trifluoromethylation. Many transition metals have proven to be efficient at catalysing trifluoromethylation reactions, including nickel[76,77], palladium[78], copper[79] and silver[80]. Copper is the most commonly used transition metal catalyst for trifluoromethylation, owing to its high efficiency and low cost (FIG. 6A). Copper-promoted couplings always involve a $CuCF_3$ complex, a key intermediate that can be generated in situ using reagent systems including a Cu^I source with $TMSCF_3$ and a F^- source[81–83]; a Cu^I source with $FSO_2CF_2CO_2Me$ (REFS[84–86]); a Cu^I source with $(MeO)_3B^-CF_3K^+$ (REF.[87]); CuCl with HCF_3 and ^{t}BuOK[88,89]; copper

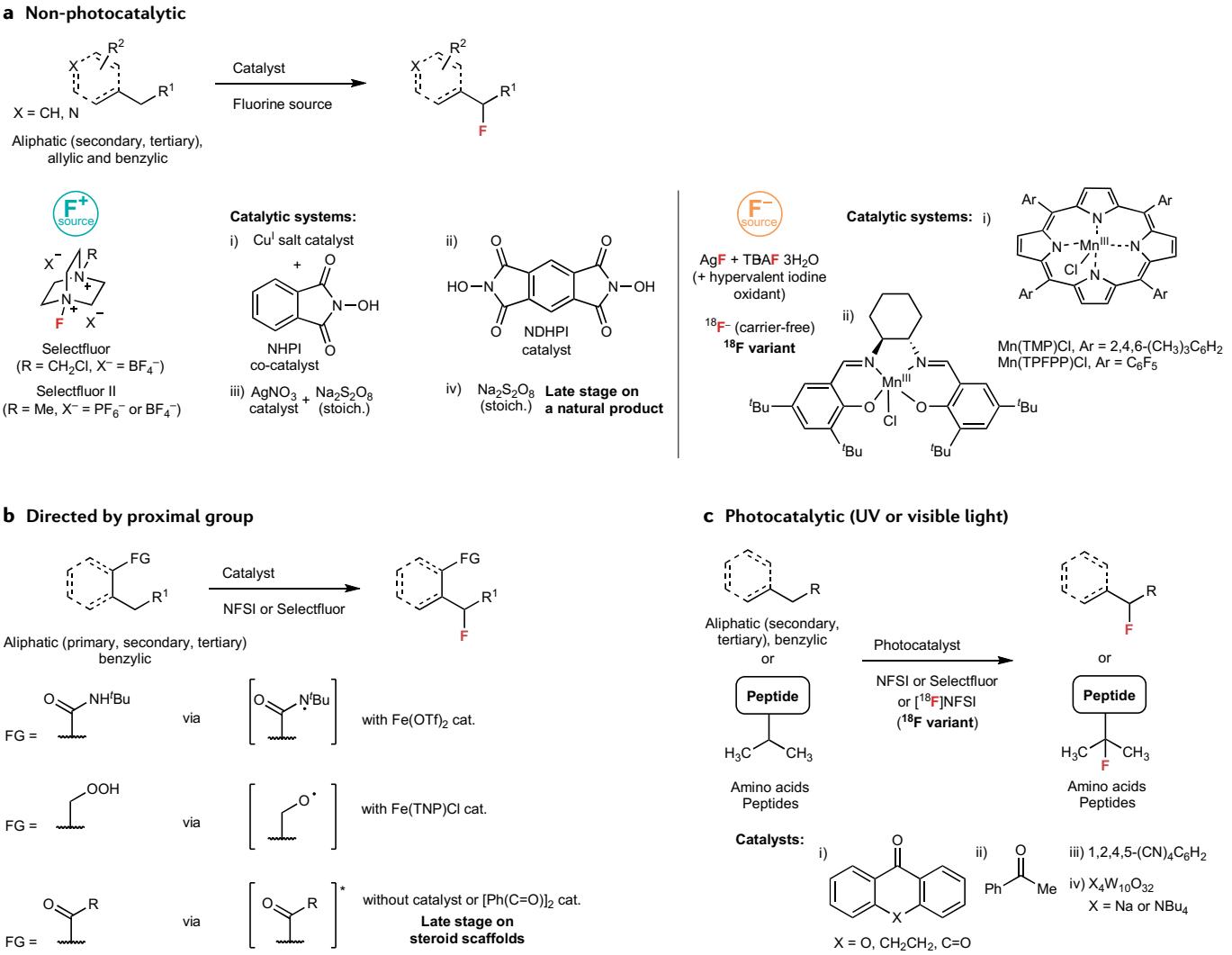


Fig. 4 | **Main C–H fluorination protocols via carbon-centred radical intermediates. a** | C–H fluorination via non-photocatalytic reactions. General scheme, catalytic systems for use with electrophilic fluorine shown on the left and catalytic systems for use with neucleophilic fluorine shown on the right. **b** | C–H fluorination directed by a proximal functional group. Typical directing groups and catalysts shown below. **c** | C–H fluorination via photocatalytic reactions. cat., catalyst; F+ source, electrophilic fluorine source; F− source, nucleophilic fluorine source; FG, proximal functional group; NDHPI, *N*,*N*-dihydroxypyromellitimide; NFSI, *N*-fluorobenzenesulfonimide; NHPI, *N*-hydroxyphthalimide; OTf, trifluoromethanesulfonate; TBAF, *tetra*-*n*-butylammonium fluoride; TMP, tetrakis[2,4,6-(trimethyl)phenyl]porphyrin; TNP, 5,10,15,20-*tetra*-naphthyl-porphyrin; TPFPP, 5,10,15,20-tetrakis(pentafluorophenyl)porphyrin[24].

and $[Ph_2S^+CF_3]TfO^-$ (REF.[90]); and copper and Umemoto reagent[91]. Copper sources may be used in catalytic or stoichiometric quantities, depending on the reaction conditions. Some ligand-coordinated $CuCF_3$ complexes are shelf-stable and can be used directly as reagents, including $(phen)CuCF_3$ (REFS[92,93]) and $(Ph_3P)_3CuCF_3$ (REF.[94]). Copper-promoted coupling could be extended to a wide range of substrates, such as aryl/alkyl halides, aryl diazonium salts and aryl or alkyl boronic acids. It is generally accepted that reductive elimination from a $RCu^{III}CF_3$ complex is a key step in copper-promoted coupling reactions[95–97]; the exact mechanism for this step was elusive until mechanistic investigation of stable isolated $RCu^{III}CF_3$ complexes revealed that reductive elimination proceeds through a concerted C–C bond-forming pathway involving a three-membered ring transition state[95–97]. Electron-withdrawing ligands are favourable for this process as electrons flow from R and trifluoromethyl groups to the metal and ligands during reductive elimination.

Radical trifluoromethylation. Radical trifluoromethylation may occur through the addition of a $CF_3^{\bullet}$ radical into unsaturated functionalities (FIG. 6Ba) or the transfer of a CF_3 group from $Cu^{II}CF_3$ to an alkyl radical (FIG. 6Bb). The $CF_3^{\bullet}$ radical can be generated from various reagents, including CF_3SO_2Na (REF.[98]), $TMSCF_3$ (REF.[99]), Togni reagent[100,101], Umemoto reagent[100], $[Ph_2S^+CF_3]TfO^-$ (REF.[100]) and CF_3I (REF.[102]), under oxidative or reductive conditions. Oxidants or reductants are usually required in stoichiometric quantities, although catalytic conditions can work if the redox reactions of the

Heteroatom
Any atom that is not a carbon atom or a hydrogen atom, similar to heteroelement.

reagents can readily occur. The $CF_3^{\bullet}$ radical can react with alkenes or alkynes to provide various difunctionalized products[103,104]. Trifluoromethylation of alkyl radicals has been much less developed[105]. Alkyl radicals can be produced from alkyl halides, carboxylic acids and C–H bonds, and the $Cu^{II}CF_3$ complex may be generated in situ from $Cu^{III}CF_3$/reductant or $Cu^{I}CF_3$/oxidant. This radical process is limited to primary and secondary radicals; trifluoromethylation of tertiary radicals has not yet been achieved. It is unclear whether trifluoromethylation of the alkyl radical involves the formation of a $RCu^{III}CF_3$ intermediate or the direct transfer of the CF_3 group from $Cu^{II}CF_3$ to the alkyl radical without forming a $RCu^{III}CF_3$ intermediate (FIG. 6Bc).

Nucleophilic and electrophilic trifluoromethylation. The direct nucleophilic attack of a CF_3^- anion on electrophiles is another strategy used for CF_3 incorporation, and $TMSCF_3$ is the most commonly used reagent for this type of nucleophilic trifluoromethylation[106,107] (FIG. 6C). The nucleophilic method can be extended to a wide range of electrophiles, including aldehydes, ketones, esters and imines. Electrophilic trifluoromethylation strategies can be applied to heteroatom-centred nucleophiles and carbon-centred nucleophiles[101] (FIG. 6D). Carbon-centred nucleophiles must be electron-rich species, such as enolates or enamines, which can be generated in situ or prepared in advance. Electrophilic reagents include Umemoto reagent[108], Togni reagent[101] and Shibata reagent[109]. Lewis acids can be used to enhance the electrophilicity of Togni reagent if the nucleophile is not reactive enough.

C–H trifluoromethylation. C–H trifluoromethylation is usually enabled by transition metal-catalysed or transition metal-mediated methods for the metalation of a C–H bond (FIG. 6Ea), or by radical-based approaches using a carbon-centred radical (FIG. 6Eb). Commonly used transition metals include palladium and copper. Reductive elimination involves electron flow from a trifluoromethyl group to a metal; as the trifluoromethyl group is a strong electron-withdrawing group, reductive elimination is more facile when using a high oxidation state metal that can withdraw electrons more easily. Palladium-catalysed C–H trifluoromethylation usually involves a Pd^{II}/Pd^{IV} catalytic cycle. Pioneering work in palladium-catalysed reactions used either pyridinyl[110], amide[111] or amino moieties[112] as directing groups for arene C(sp^2)–H bond trifluoromethylation. For copper-catalysed C–H trifluoromethylation, a Cu^{I}/Cu^{III} catalytic cycle is feasible[113,114]. No directing group is required if the proton from the C–H bond is acidic enough[113].

Radical-based C–H trifluoromethylation methods involve the generation of a radical from a C–H bond through homolysis[115–117]. Homolysis of alkyl C–H bonds is challenging owing to their high bond strength, and radical-based trifluoromethylation of alkyl C–H bonds remains an active area of research. As described in

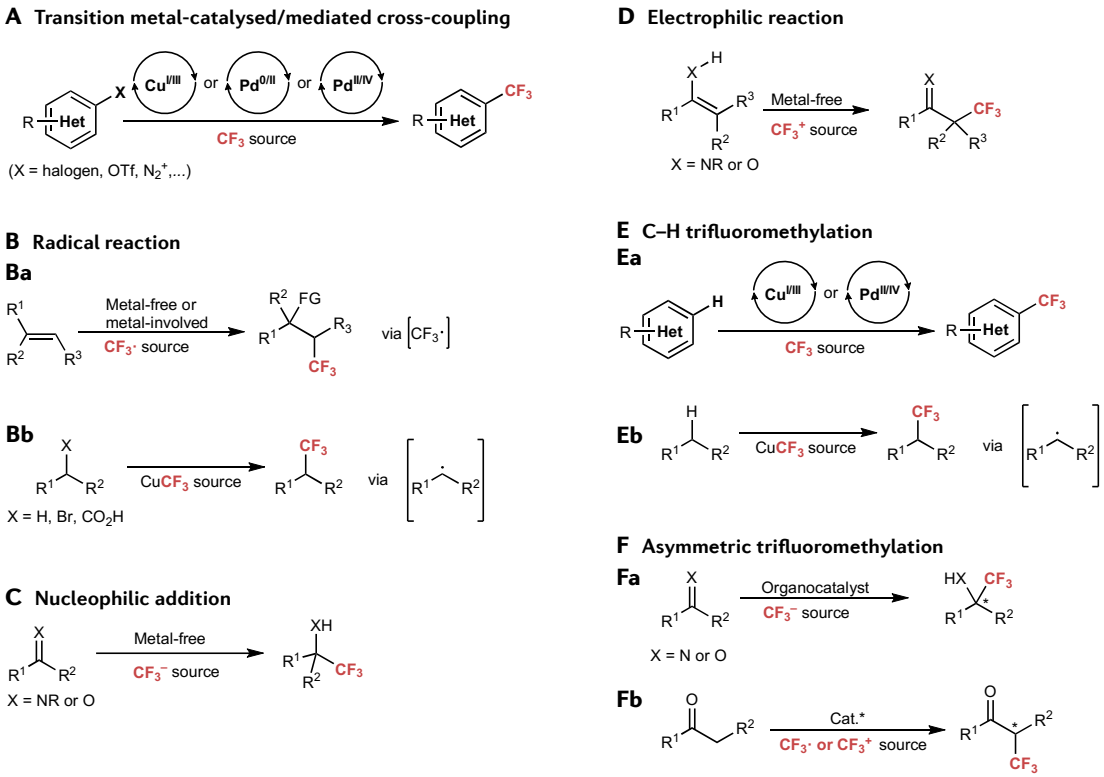


Fig. 5 | **General overview of trifluoromethylation methods. A** | Transition metal-catalysed trifluoromethylation. **B** | Radical trifluoromethylation of alkenes (part **Ba**) and sp^3 carbon atoms (part **Bb**). **C** | Nucleophilic trifluoromethylation of unsaturated systems. **D** | Electrophilic trifluoromethylation. **E** | C–H trifluoromethylation using 'CF_3' sources (part **Ea**) and $CuCF_3$ sources (**Eb**). **F** | Asymmetric trifluoromethylation using 'CF_3^-' synthons (part **Fa**) and '$CF_3^{\bullet}$' or 'CF_3^+' synthons (part **Fb**). Cat.*, catalyst; FG, proximal functional group; OTf, trifluromethanesulfonate.

FIG. 6Bc, the radical reaction proceeds through the transfer of a CF_3 group — generated in situ from $Cu^{II}CF_3$ — to the alkyl radical, although it is not very clear how the CF_3 group is transferred.

Asymmetric catalytic trifluoromethylation remains largely unexplored[118–120]. Reported asymmetric catalytic methods include nucleophilic, electrophilic and radical trifluoromethylation using organocatalysts or transition metal catalysis (FIG. 6F). Asymmetric nucleophilic reactions are limited to active electrophiles such as ketones and imines, and asymmetric electrophilic and radical reactions require the generation of enolates or enamines from substrates. Mild and general asymmetric catalytic trifluoromethylation approaches need to be further developed because current asymmetric catalytic trifluoromethylation methods have limited substrate scope. Additional examples of trifluoromethylations are shown in Supplementary Fig. 1.

Difluoromethylation

Difluoromethyl compounds — organic compounds containing a CF_2H group — are generally synthesized through difluorination[121] or difluoromethylation[122] reactions, hydrogenation of *gem*-difluoroalkenes[123] or hydrodefluorination of trifluoromethyl compounds[124]. Difluoromethylation is the most straightforward of the above approaches owing to its good step economy and high functional group tolerance in introducing CF_2H groups, and has progressed rapidly over the past decade[29,125–128]. Here, we introduce state-of-the-art methods for the formation of C(sp^3)–CF_2H, (hetero)aryl–CF_2H and heteroatom–CF_2H bonds, all of which are of

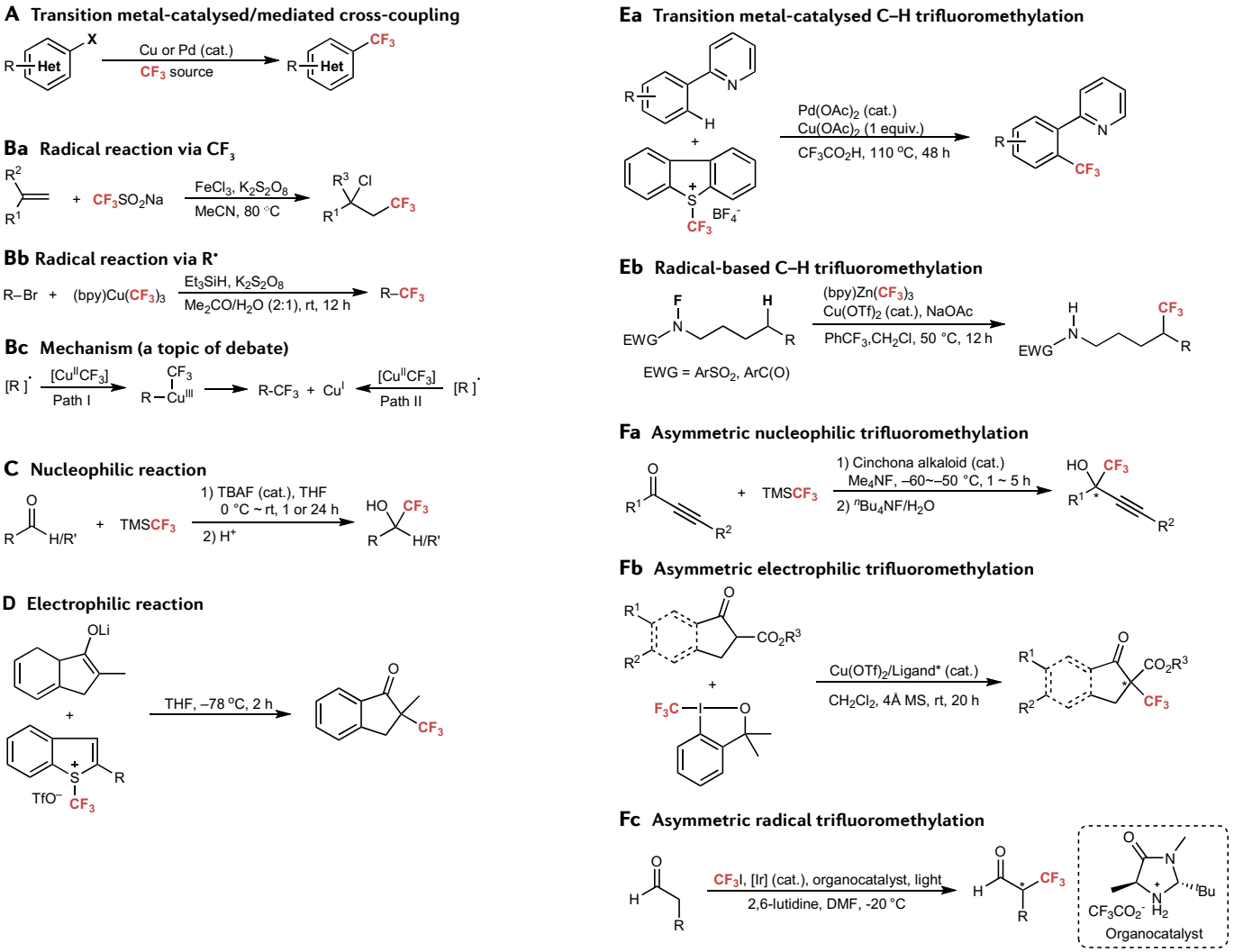


Fig. 6 | **Example trifluoromethylation protocols. A** | Transition metal-catalysed or transition metal-mediated cross-coupling. Both aryl and alkyl substrates can act as the coupling partners. **B** | Radical trifluoromethylation can occur via the attack of a $CF_3^{\bullet}$ radical on an unsaturated bond (part **Ba**) or via the transfer of a CF_3 group to a radical (part **Bb**). Proposed mechanisms shown in part **Bc**. **C** | Nucleophilic trifluoromethylation. Trifluoromethyltrimethylsilane ($TMSCF_3$) is one of the most commonly used reagents. **D** | Electrophilic trifluoromethylation. This protocol may have limited application because use of active substrates is usually required. **E** | C–H trifluoromethylation. The activation of a C–H bond is usually achieved by C–H metalation (part **Ea**) or by radical-mediated homolysis of the C–H bond (part **Eb**). **F** | Asymmetric catalytic trifluoromethylation. Method includes nucleophilic (part **Fa**), electrophilic (part **Fb**) and radical (part **Fc**) reactions. bpy, 2,2′-bipyridine; cat., catalyst; DMF, dimethylformamide; EWG, electron-withdrawing group; MS, molecular sieve; rt, room temperature; TBAF, *tetra-n*-butylammonium fluoride; TfO^-, trifluoromethanesulfonate; THF, tetrahydrofuran.

strong interest in pharmaceutical chemistry and have benefited from either reagent or catalyst design.

Difluoromethylation of* sp³ *carbons. Difluoromethylated sp^3 carbon centres can be constructed via addition or substitution reactions of pre-functionalized substrates with a proper difluoromethylation reagent (FIG. 7). The nucleophilic addition of a difluoromethanide anion (HCF_2^-) or its equivalent (FG-CF_2^-) to electrophiles such as aldehydes, ketones and imines has been developed for the synthesis of difluoromethylated functional molecules such as alcohols and amines (FIG. 7a) and is normally achieved using either $PhSO_2CF_2H$ or $TMSCF_2H$ as the reagent in the presence of a base[22,127–130]. However, non-catalysed nucleophilic substitution at sp^3 carbons is limited to the difluoromethylation of primary alkyl halides, such as RCH_2I, and pseudohalides, such as triflates. The use of metal catalysts allows for the difluoromethylation of a wide range of alkyl electrophiles[131–134]. Recently, copper-catalysed difluoromethylation of alkyl radicals has been developed, inspired by the trifluoromethylation of alkyl radicals (FIG. 7b). This method proceeds through a $Cu^I/Cu^{II}/Cu^{III}$ catalytic cycle that involves single-electron transfer between $CuCF_2H$ species and redox-active alkyl electrophiles such as *N*-hydroxytetrachlorophthalimide (TCNHPI) esters and pyridinium salts[131,132]. In the above case, the structurally well-defined zinc complex $(DMPU)_2Zn(CF_2H)_2$ is the most suitable nucleophilic difluoromethyl source. This strategy allows the installation of a CF_2H group at unactivated primary, secondary and even tertiary carbon centres. Addition of the difluoromethyl radical to alkenes represents a reliable method for the construction of C(sp^3)–CF_2H bonds under mild conditions[127,128,135] (FIG. 7c), which has recently stimulated the exploitation of structurally diverse, novel and practical difluoromethyl radical sources that can be readily activated under either chemical oxidation conditions or photoredox catalysis conditions[136–139]. C–H difluoromethylation at sp^3 carbon centres mainly focuses on the reaction of activated carbon acids with a difluorocarbene intermediate under the activation of a base[140] (FIG. 7d). The development of new difluorocarbene sources, including $TMSCF_2Br$ and several *S*-(difluoromethyl)sulfonium salts, has significantly improved reaction efficiency and greatly expanded the substrate scope[127,128,141–143]. The difluoromethylation of unactivated C–H bonds is still rare (FIG. 7e); however, copper-catalysed benzylic C–H difluoromethylation can proceed through the formation of benzylic radicals after intramolecular C–H activation, followed by the copper-catalysed transfer of difluoromethyl groups to the benzylic radicals[144].

(Hetero)aromatic difluoromethylation. (Hetero)aromatic difluoromethylation is a rapidly developing and practical method of synthesizing difluoromethyl (hetero)arenes[29,125,126] (FIG. 8). These reactions can be categorized as cross-couplings of organohalides or pseudohalides with $TMSCF_2H$ (REFS[145,146]), structurally well-defined difluoromethyl metal complexes[147–151] or difluoromethyl radical sources[152,153] (FIG. 8Aa–c); cross-couplings of organoboron or other organometallic reagents with difluoromethyl radical sources[154–157] or difluorocarbene sources[158–161] (FIG. 8Ba–c); and C–H difluoromethylation with $TMSCF_2H$ (REFS[162,163]) or difluoromethyl radical sources[164–169] (FIG. 8Ca,b). Difluoromethylation is more compatible with palladium, nickel and iron catalysis than trifluoromethylation, owing to the relative ease of the reductive elimination of heteroaryl–CF_2H from the corresponding metal complexes[147,152,154]. Difluoromethylation of aryl borons using palladium difluorocarbene represents a novel method in this field that efficiently incorporates a CF_2H group into an aromatic ring by using various difluorocarbene sources (FIG. 8Bc), including the inexpensive industrial chemical HCF_2Cl (also known as Freon-22, an ozone-depleting substance)[158–161]. As for fluorination and trifluoromethylation, the introduction of CF_2H through C–H bond activation is highly attractive for the late-stage modification of drug molecules and natural products. Available methods mainly rely on the innate nucleophilic reactivity of the CF_2H radical towards heteroarenes[164–169]. Strategies that offer different site selectivities to direct radical difluoromethylation include the reaction of masked difluoromethyl radicals[170,171] such as $\cdot CF_2SO_2Ph$ with CF_2Cl, or the use of copper-mediated oxidative C–H difluoromethylation with $TMSCF_2H$ (REF.[162]) (FIG. 8Cc). In addition, metal-catalysed C–H functionalization of arenes followed by difluoromethylation offers a complementary approach for late-stage C–H difluoromethylation[160,172,173]. Vinylic difluoromethylation can be achieved[29,125–128], although this method has attracted less attention than (hetero)aromatic difluoromethylation. Addition protocols are shown in Supplementary Fig. 2.

Heteroatom difluoromethylation. Difluoromethylation of heteroatom nucleophiles with difluorocarbene is the most convenient method for obtaining functional molecules containing HCF_2O, HCF_2S and HCF_2N (REF.[174]) (FIG. 8D). The ozone-depleting substance HCF_2Cl had been the most commonly used reagent for difluoromethylation of heteroatoms, although the environmentally benign alternatives $ClCF_2CO_2Na$, $BrCF_2P(O)(OEt)_2$, $FSO_2CF_2CO_2H$ and $TMSCF_2Br$ are commercially available and frequently used[127,128,175]. Unlike phenols, alcohols can react with difluorocarbene without deprotonation owing to the increased electron density of oxygen; $FSO_2CF_2CO_2H$ and $TMSCF_2Br$ are therefore suitable reagents for difluoromethylation of alcohols as they can release difluorocarbene under non-basic conditions[175,176]. Recently, numerous methods for incorporation of the HCF_2S moiety have been developed to synthesize difluoromethyl thioethers[177].

Monofluoromethylation

Few C–H monofluoromethylation reactions had been reported to date, despite the ability of monofluoromethyl groups to serve as bioisosteres for various pharmaceutically relevant functional groups (for example, CH_3, CH_2OH and CH_2NH_2)[22,26,122,178]. A conventional two-step approach to monofluoromethylation involves an initial chloromethylation step known as the Blanc reaction, which uses formaldehyde and hydrogen chloride or zinc chloride to install a monochloromethyl functional group onto arenes and heteroarenes[179].

Bioisosteres
Chemical substituents or groups with similar physical or chemical properties.

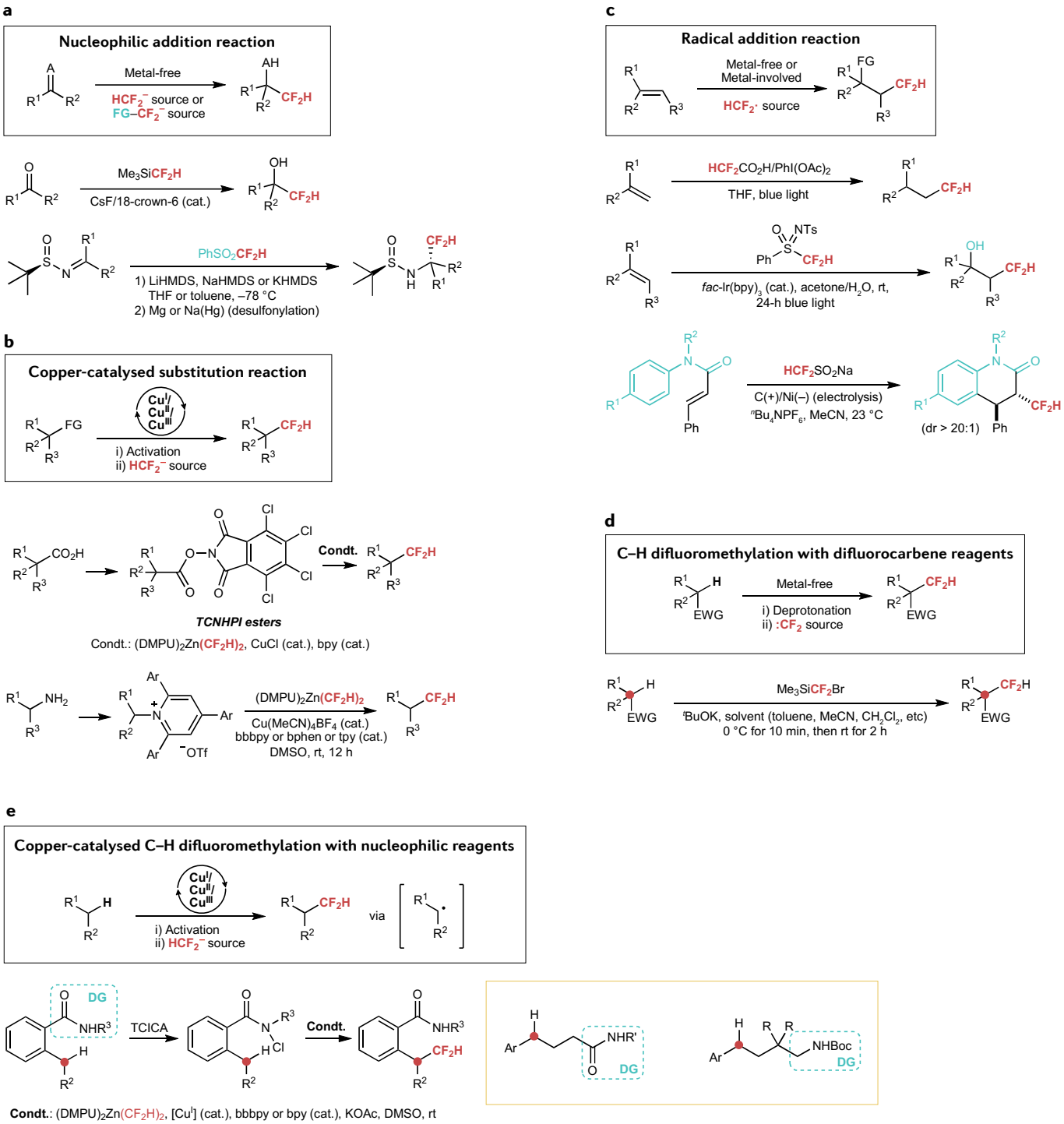


Fig. 7 | **Main protocols of introducing CF_2H at sp^3 carbon centres.** General scheme for each protocol given in each box, specific examples shown below. **a** | Nucleophilic addition of difluoromethyl anion or its equivalent ($FG–CF_2^-$) to unsaturated systems. In the first example, $TMSCF_2H$ is normally activated by a fluoride salt; in the second example, $PhSO_2CF_2H$ is activated by a base such as lithium bis(trimethylsilyl)amide (LiHMDS). Electron-deficient alkenes are also suitable substrates. **b** | Nucleophilic substitution of alkyl electrophiles with a difluoromethyl anion, mainly catalysed by copper through a $Cu^I/Cu^{II}/Cu^{III}$ catalytic cycle. **c** | Addition of difluoromethyl radical to alkenes. After addition to alkenes, hydrogen abstraction, further functionalization and further cyclization can occur as the subsequent reaction. **d** | Difluoromethylation of the C–H bonds of carbon acids with difluorocarbene. **e** | Difluoromethylation of non-activated C–H bonds with nucleophilic difluoromethylation reagents catalysed by copper through a $Cu^I/Cu^{II}/Cu^{III}$ catalytic cycle. The carbon-centred radical is formed through hydrogen abstraction of the C–H bond by a heteroatom radical such as a N radical, which is generated through cleavage of a N–Cl bond. bbbpy, 4,4′-di-*tert*-butyl-2,2′-bipyridine; bphen, bathophenanthroline; bpy, 2,2′-bipyridine; cat., catalyst; $:CF_2$, difluorocarbene; DG, directing group; DMPU, *N*,*N*′-dimethylpropyleneurea; DMSO, dimethylsulfoxide; EWG, electron-withdrawing group; FG, functional group; OTf, trifluoromethanesulfonate; rt, room temperature; TCICA, trichloroisocyanuric acid; TCNHPI, *N*-hydroxytetrachlorophthalimide; THF, tetrahydrofuran; tpy, 2,2′:6′,2″-terpyridine.

Well-established halide-exchange reactions using fluoride salts such as KF or AgF support conversion to the monofluoromethyl derivative[180]. An increased interest in CH_2F has inspired the development of several nucleophilic[181–184], electrophilic[185] and radical[186–188] monofluoromethylating reagents (FIG. 9a). The first example of electrophilic C–H monofluoromethylation was reported in 1953 and involved the reaction

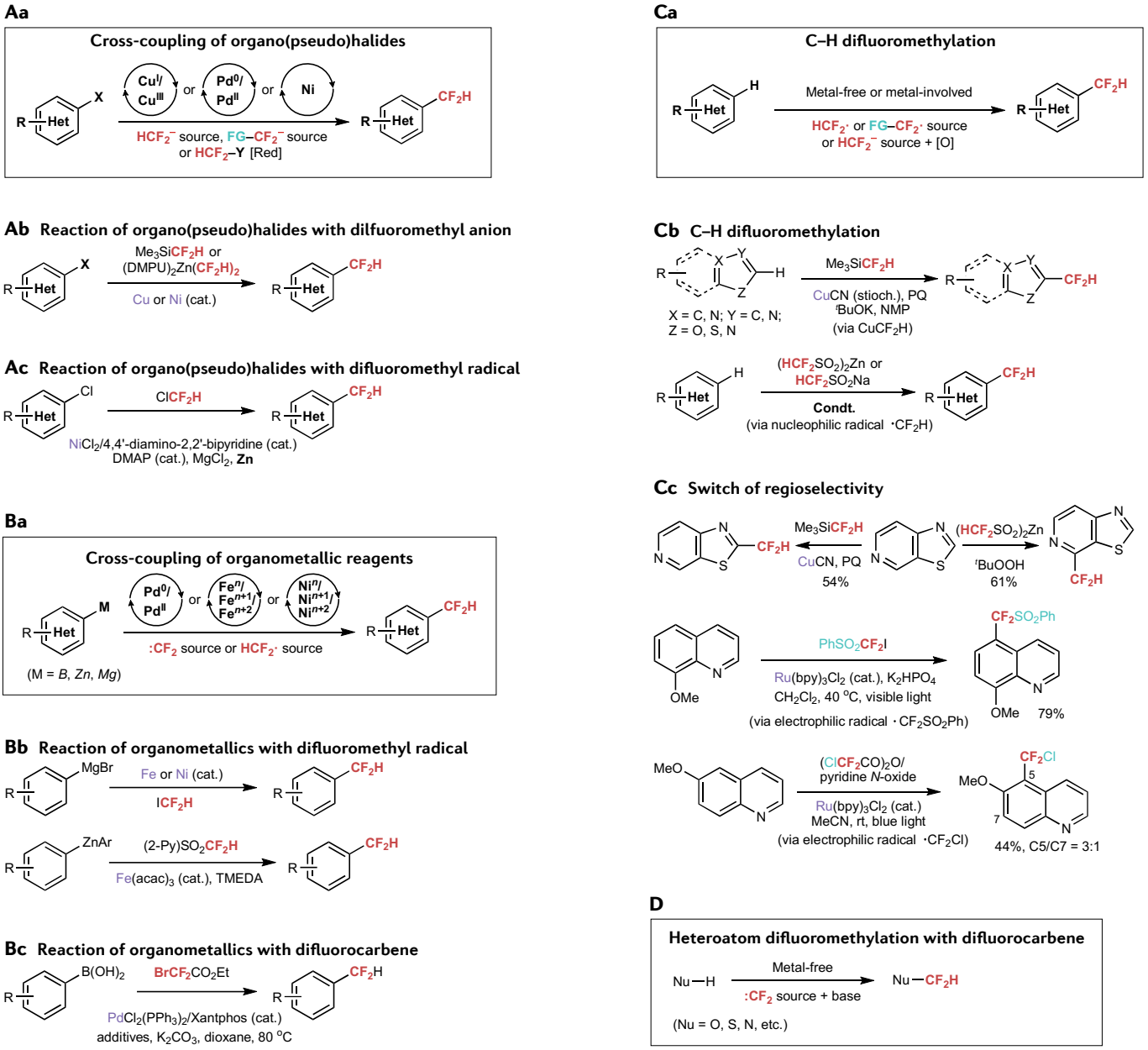


Fig. 8 | **Main protocols of introducing CF_2H at (hetero)aromatic carbons and heteroatoms.** General scheme for each protocol given in the box, examples shown below. **A** | General scheme for difluoromethylation of organohalides or organopseudohalides (such as aryl triflate and aryl diazonium salt) (part **Aa**) and typical examples (parts **Ab**,**Ac**). In part **Ab**, (SIPr)$AgCF_2H$, $TMSCF_2CO_2Et$ and $PhCOCF_2H$ are also suitable difluoromethylation reagents (under palladium catalysis or copper catalysis). In part **Ac**, HCF_2Br/$(TMS)_3SiH$ is also a suitable combination; however, the use of Ar–Br rather than Ar–Cl is required (under photocatalysis). **B** | General scheme for difluoromethylation of organometallic reagents (part **Ba**) and typical examples (parts **Bb** and **Bc**). In part **Bb**, HCF_2Br is also a suitable difluoromethylation reagent (react with arylboronic acids under nickel catalysis). In part **Bc**, $BrCF_2P(O)(OEt)_2$, $Ph_3P^+CF_2CO_2^-$ and HCF_2Cl are also suitable difluorocarbene sources. **C** | General scheme for C–H difluoromethylation of aromatic and heteroaromatic compounds (part **Ca**) and typical examples (parts **Cb**,**Cc**). In part **Cb**, two pathways for C–H difluoromethylation are described; in the radical pathway, both the difluoromethyl radical (HCF_2•) and its equivalents ($FG–CF_2$•) can undergo the reaction. The following are also suitable reagents: HCF_2CO_2H/[O], HCF_2SO_2Cl, $[Ph_3P(CF_2H)]^+Br^-$, $PhSO_2CF_2I$, $(ClCF_2CO)_2O$/[O], $BrCF_2CO_2Et$. In part **Cc**, two methods to alter regioselectivity are described; one to change reaction conditions (the first example), the other to change the electronic nature of the difluoromethyl group (with $PhSO_2CF_2$• or $ClCF_2$•) (the second and third example). In the last two examples, direct reaction with HCF_2• is selective for the 2-position of the quinolone core. **D** | General scheme for difluoromethylation of heteroatoms. For a summary of suitable difluorocarbene sources, refer to REF.[174]. Transition metal catalysts depicted in purple. bpy, 2,2′-bipyridine; cat., catalyst; $:CF_2$, difluorocarbene; DMAP, 4-dimethylaminopyridine; DMPU, *N*,*N*′-dimethylpropyleneurea; FG, functional group; NMP, *N*-methyl-2-pyrrolidone; [O], oxidant; PQ, 9,10-phenanthrenequinone; 2-Py, 2-pyridyl; [Red], reductant; rt, room temperature; SIPr, 1,3-bis(2,6-diisopropylphenyl)imidazolidene; TMEDA, tetramethylethylenediamine.

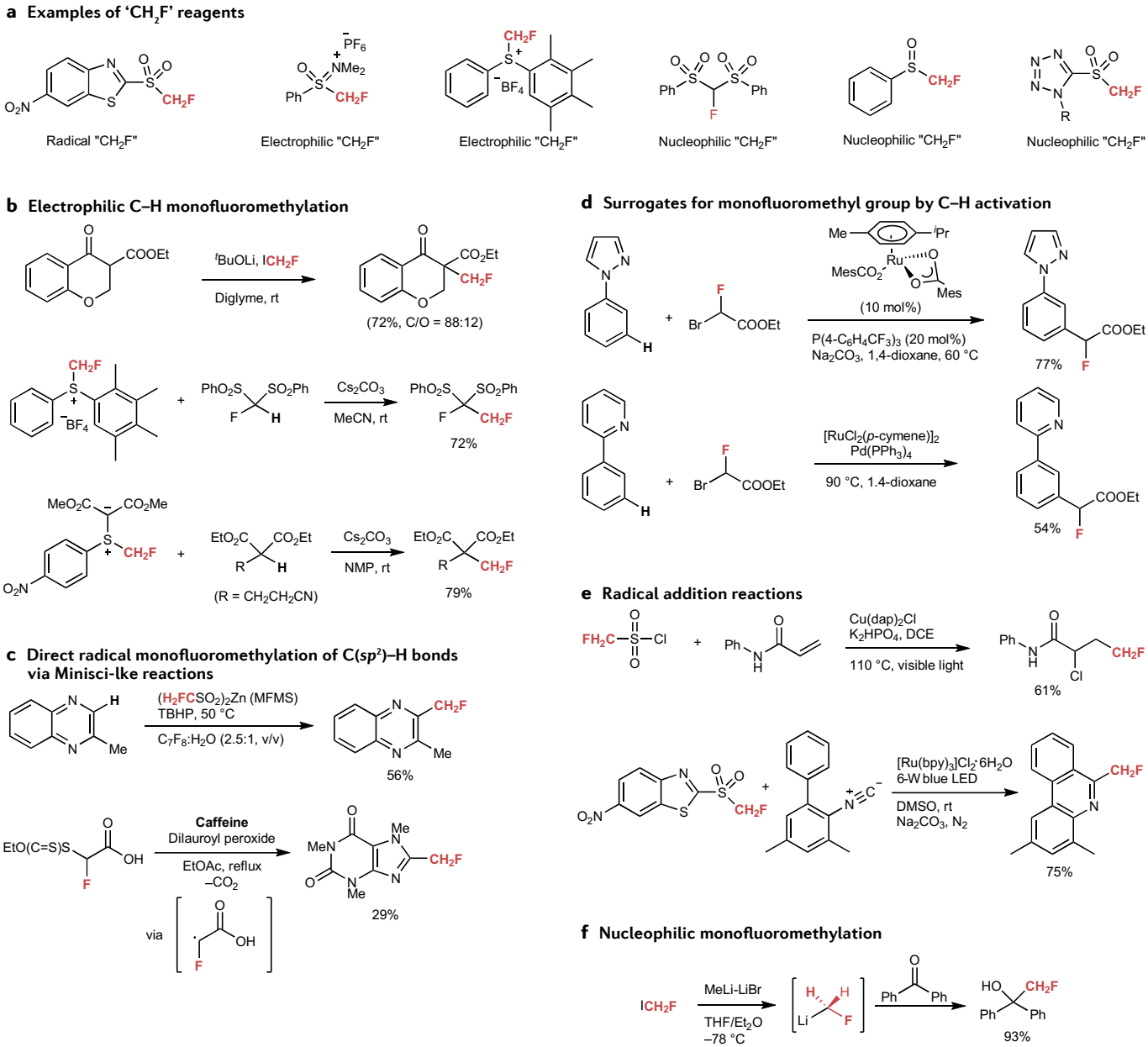


Fig. 9 | **Monofluoromethylating reagents and their use in C–H monofluoromethylation reactions. a** | Examples of radical, electrophilic and nucleophilic monofluoromethylating reagents. **b** | Protocols for electrophilic C–H monofluoromethylation of C(sp^3)–H bonds. **c** | Protocols for addition of monofluoromethyl groups to heterocycles via radical processes. **d** | Addition of monofluoromethyl surrogates to aromatics. **e** | Addition reactions with monofluoromethyl radical. **f** | Protocol for nucleophilic monofluoromethylation of ketones. bpy, 2,2′-bipyridine; DCE, 1,2-dichloroethane; DMSO, dimethylsulfoxide; MFMS, monofluoromethanesulfinate; NMP, *N*-methyl-2-pyrrolidone; TBHP, *tert*-butyl hydroperoxide; THF, tetrahydrofuran; rt, room temperature.

of arenes with fluoromethanol in the presence of zinc(II) chloride, which afforded fluoromethylarenes[189,190]. C–H monofluoromethylation reactions now primarily involve deprotonation of 1,3-dicarbonyls, followed by reaction of the resultant carbanion with an electrophilic monofluoromethylation reagent[191–194] (FIG. 9b). For example, β-ketoesters can react with fluoroiodomethane and lithium *tert*-butoxide to produce α-monofluoromethyl adducts[192]. Commonly, competitive O monofluoromethylation is a complicating factor, and in a few cases is a predominant reaction pathway[195] that is proposed to occur via a radical process[196,197]. Reagents that support C monofluoromethylation while avoiding the use of the ozone-depleting reagents chlorofluoromethane (CFC-31) and bromofluoromethane (CFC-31B1) are needed[178]. *S*-(Monofluoromethyl)diarylsulfonium tetrafluoroborate has been developed as an electrophilic source of CH_2F and supports the α-monofluoromethylation of bis(phenylsulfonyl)methane and diethylmalonate derivatives[193] (FIG. 9b). Subsequent work has also described the use of sulfonium ylides for the monofluoromethylation of 2-aryl-substituted and 2-alkyl-substituted malonates[194].

Minisci reaction
A nucleophilic radical substitution to an electron-deficient aromatic compound, most commonly involving the introduction of an alkyl group to a nitrogen-containing aromatic heterocycle.

Although the CH_2F radical was first observed and characterized in 1971 (REF.[198]), its use for radical C–H monofluoromethylation was not demonstrated until 2012, when a series of zinc sulfinate salts were reported to be capable of transferring fluoroalkyl radicals to nitrogen-containing heteroarenes through a Minisci reaction-like process[199] (FIG. 9c). Among these zinc sulfinate reagents was zinc monofluoromethylsulfinate (MFMS), which reacts with a small collection of heteroarenes with excellent regioselectivity. MFMS can be synthesized in four simple steps from 4-chlorobenzyl mercaptan on the gram-scale; however, unlike other zinc and sodium fluoroalkylsulfinates, it is not commercially available. The fluoroacetate radical, generated from a xanthate precursor, can also engage in a Minisci-like reaction with caffeine[200] (FIG. 9c). Subsequent in situ decarboxylation of the carboxyfluoromethylated caffeine reveals a monofluoromethyl derivative. Further development of fluoroacetates as synthetic surrogates for the monofluoromethyl group has been independently reported[201,202] (FIG. 9d); for example, ruthenium-catalysed, *meta*-selective C–H monofluoromethylations of arenes have been accomplished using bromofluoroacetate. These reactions proceed via *ortho* C–H insertion directed by a nitrogen-containing heteroaryl group and subsequent nucleophilic addition of the fluoroacetate radical into the arene. Under photoredox copper catalysis conditions, fluoromethylsulfonyl chloride can be used as a source of monofluoromethyl radicals for additions into electron-deficient alkenes[187] (FIG. 9e). Similarly, a ruthenium photoredox catalyst can be used for generating monofluoromethyl radicals from monofluoromethyl sulfones for radical additions into isocyanides[186]. As a complementary approach for addition of the monofluoromethyl group, nucleophilic reagents such as the lithium anion (FIG. 9f) have been used for the synthesis of terminal fluoroalkenes[184,203] and 2,2-disubstituted fluorovinyl sulfones[182,183], addition into ketones and imines[181], and cross-coupling reactions[204].

Safety

Safety is an important issue in synthetic organofluorine chemistry. In general, classical fluorination reagents such as anhydrous hydrogen fluoride (HF), elemental fluorine (F_2) and sulfur tetrafluoride (SF_4) are highly corrosive, toxic and, sometimes, even explosive chemicals. When handling these dangerous reagents, protective equipment such as safety goggles, an acid-resistant apron and gloves should be used and experiments should be performed under good ventilation conditions. Glassware should be avoided as these corrosive fluorination reagents readily etch glass. A fume hood fitted with a scrubbing system should be used when handling large quantities of anhydrous HF, as anhydrous and even dilute aqueous HF solutions are corrosive and rapidly damage tissues, owing to resorptive binding of fluoride to calcium and magnesium ions. Antidotes such as calcium gluconate gel should be kept on hand for primary treatment of HF burns of the skin[205].

Modern fluorination and fluoroalkylation reagents are much milder and less dangerous than their classical counterparts. For most of the synthetic methods described in this Primer, experiments can be carried out in a standard organic chemistry laboratory and the reaction set-up is generally no different from other organic reactions. However, some fluorination reagents such as HF–pyridine, HF–$3Et_3N$ and DAST are corrosive and precautions should be taken when handling these chemicals. For ^{18}F-labelled synthesis, a standard radiochemistry laboratory for handling radioactive chemicals is required.

Applications

In this section, we provide an introductory overview of how the above fluorination and fluoroalkylation methods are currently used in life science-related areas (FIG. 10). We initially focus on the application of these methods to drug discovery and development, including the late-stage modification of approved drugs or bioactive molecules and the synthesis of novel drug candidates. We then discuss the recent field of ^{18}F radiolabelling, the products of which are used for disease diagnosis, treatment monitoring and mechanism research. Finally, we introduce the application of these methods to bioorganic chemistry research and the pharmaceutical and agrochemical industries.

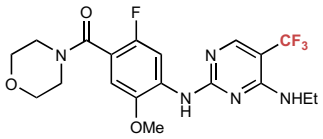
Drug discovery

More than 300 fluorinated drugs have been developed and used worldwide following the introduction of fludrocortisone as the first fluorine-containing pharmaceutical drug in 1954 (REF.[206]). Fluorination of drug molecules can enhance their efficacy by modulating their absorption, distribution, metabolism and excretion profile, and fluorination and fluoroalkylation have therefore become a routine and powerful tool in drug discovery[3–6,8–10,13,25].

Fluorination. C–H fluorination and ^{18}F radiofluorination are at an early stage of research and their use in the late-stage functionalization of drug molecules in the context of drug discovery is still in its infancy, owing to numerous challenges such as difficulties in separating fluorinated derivatives from precursor molecules and achieving high chemoselectivity, regioselectivity and stereoselectivity[49]. Despite these challenges, these techniques have been successfully used to synthesize fluorinated analogues of a handful of natural products and US Food and Drug Administration (FDA)-approved pharmaceuticals. In 2012, oxidative aliphatic C–H fluorination using nucleophilic fluoride was applied to the selective fluorination of terpenoids such as sclareolide and steroids such as 5α-androstan-17-one (REF.[66]). Fluorinated analogues of these natural products have also been accessed through a complementary radical-based approach using a decatungstate photocatalyst[207]. The selective benzylic fluorination of dihydrocoumarin — a scaffold commonly found in bioactive natural products and drugs — was reported using a radical-based strategy[62], and C–H fluorination of sugar derivatives was demonstrated using a site-selective and diastereoselective Pd^{II}-catalysed process[56] (FIG. 10Ba). Further, fluorinated variants of the antidiabetic pioglitazone and of roflumilast — a drug used to treat chronic

A

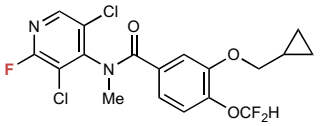
Aa DNL201 (formerly GNE-7915)



Parkinson disease drug (phase Ib)

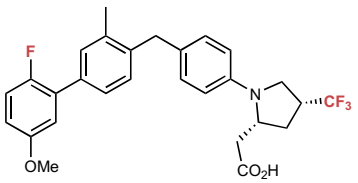
Ab Fluoro-roflumilast

Fluorination modulates the basicity and binding properties of pyridine



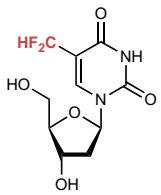
Roflumilast, anti-pulmonary disease (approved)

Ac A GPR40 agonist



Antidiabetic (preclinical)

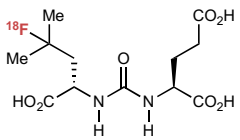
Ad F_2TDR



Anticancer (in vitro)

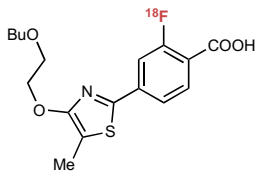
Af [^{18}F]Glu-U-FLeu

Potent receptor binding retained after C–H fluorination



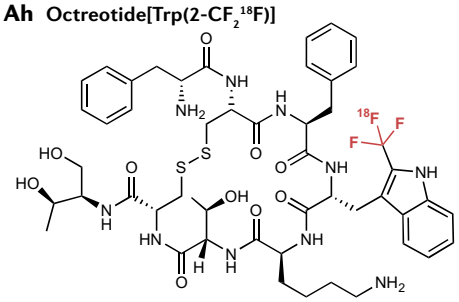
PET imaging of prostate cancer (PSMA-binding ligand)

Ae [^{18}F]AC261066



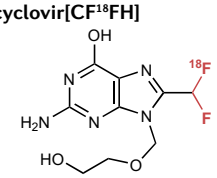
AC261066, RARβ2 receptor agonist (lead compound)

Ah Octreotide[Trp(2-$CF_2{}^{18}F$)]

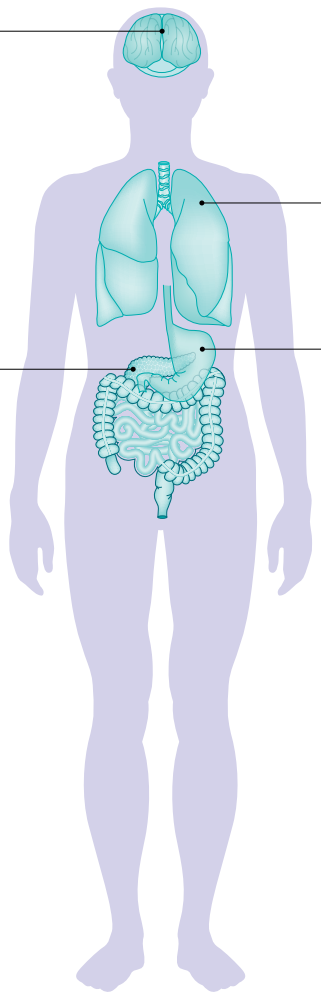


Octreotide, treatment of acromegaly and gigantism (approved)

Ag Acyclovir[$CF^{18}FH$]



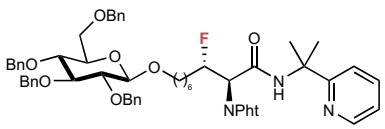
Acyclovir, anti-herpetic (approved)



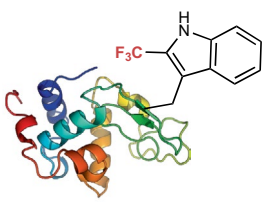
Drug
Imaging agent

B

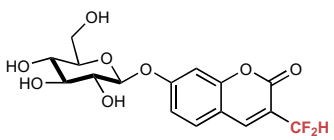
Ba Fluorinated glyco-amino acid derivative



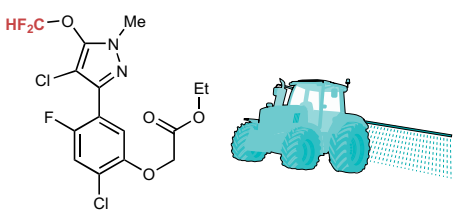
Bb Trifluoromethylated lysozyme



Bc Fluorinated fluorogenic probe



Bd Pyraflufen-ethyl (herbicide)



Be Pyriprole (insecticide)

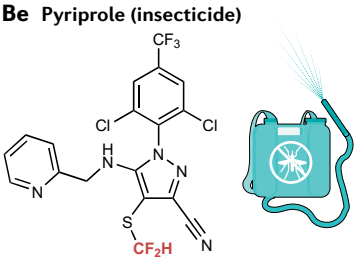


Fig. 10 | **Applications of synthetic organofluorine chemistry in life sciences.** **A** | Applications of organofluorine chemistry in synthesis and modification of drugs, drug candidates, lead compounds and positron emission tomography (PET) imaging agents. Parts **Aa**–**Ad**, organofluorine compounds in different stages of drug development. For a full list of approved fluorinated drugs, refer to REF.[206]. Parts **Ae**–**Ah**, imaging agents synthesized using different methods. **B** | Example applications of organofluorine chemistry in the modification of natural products (part **Ba**), biomacromolecules (part **Bb**), bioactive small molecules (part **Bc**) and the production of agrochemicals (parts **Bd** and **Be**). For a full list of approved agrochemicals, see REF.[7]. F_2TDR, 2-deoxy-5-difluoromethyluridine; GPR40, G-protein-coupled receptor 40; PSMA, prostate-specific membrane antigen.

obstructive pulmonary disease — were synthesized through selective *ortho* fluorination of pyridines with AgF_2 (REF.[73]) (FIG. 10Ab).

Trifluoromethylation. As a bioisostere of a chloride or methyl group, the trifluoromethyl group is often used to adjust the steric and electronic properties of a biologically active molecule or to protect a reactive methyl group from metabolic oxidation[208,209]. Various trifluoromethylation methods have been widely used for the synthesis of CF_3-containing biologically active molecules in the development of drugs and agrochemicals. The copper-promoted coupling reaction of aryl or alkenyl halides is one of the preferred strategies for the construction of a C(sp^2)–CF_3 bond owing to its low cost and high site-selectivity and the convenience of upscaling. The compound GNE-7915 — a potent, selective, metabolically stable and brain-penetrant small-molecule inhibitor of leucine-rich repeat kinase 2 (LRRK2)[210] — contains a CF_3–pyrimidine motif that can be constructed through a copper-promoted coupling reaction on a molar scale (FIG. 10Aa). Alkyl-CF_3 moieties may also be installed using other trifluoromethylation methods; for example, nucleophilic trifluoromethylation was used to synthesize a G-protein-coupled receptor 40 (GPR40) agonist, in which the CF_3 group increases the inhibition constant of the drug with respect to its binding to human GPR40 and improves agonist efficacy[211] (FIG. 10Ac).

Difluoromethylation. CF_2H is a lipophilic bioisostere of hydroxyl and methyl groups and can serve as a weak hydrogen bond donor; it can therefore be used to improve the binding ability or metabolic stability of biologically active molecules[209]. Many recently developed carbon difluoromethylation methods have shown potential for the late-stage modification of pharmaceuticals and complex molecules, both through C–H difluoromethylation[132,139,161,164,166,173,176,212–215] and the substitution of pre-functionalized groups such as halogen[146,148,152], carboxyl[131,150], hydroxyl[161] and amino[144,149] groups with CF_2H. Direct C–H radical difluoromethylation of heterocycles with difluoromethanesulfinate salts is arguably the most significant achievement in this field; together with alkanesulfinate chemistry, this technique has found immediate application in drug discovery owing to its simplicity, the high tolerance towards functional groups and the predictability of site selectivity[216]. The introduction of a CF_2H group into deoxyuridine with HCF_2SO_2Na has led to the discovery of 2-deoxy-5-difluoromethyluridine (F_2TDR) (FIG. 10Ad), a difluorinated analogue of the FDA-approved cancer drug trifluridine with an enhanced capacity to inhibit tumour cell proliferation[166].

Monofluoromethylation. Existing examples of CH_2F-containing molecules are typically made through classical nucleophilic substitution chemistry. To date, contemporary C–H monofluoromethylation reactions have not been reported in drug development programmes, aside from a single demonstration of the use of fluoroiodomethane and a base for the electrophilic C–H monofluoromethylation of androstane derivatives[191].

Radiolabelling

The translation of fluorination to radiofluorination and the use of ^{18}F-containing molecules in PET represents a major application for fluorination techniques[217]. PET is a powerful imaging technique that uses positron-emitting radiotracers to gather quantitative information on metabolic processes, allowing for the early diagnosis of diseases such as cancer. PET requires the development of suitable radiopharmaceuticals that can accumulate in the human body and be detected by the PET scan. The radioisotope ^{18}F ($t_{1/2}$ = 109 min) is ideal for use in PET radiopharmaceuticals as it has a clean positron emission profile and its maximal positron energy is well suited for high-resolution imaging. For these reasons, radiochemists are invested in developing new methodologies to efficiently produce ^{18}F-containing radiopharmaceuticals.

^{18}F fluorination. C–H ^{18}F radiofluorination is an emerging field with only a few existing examples. ^{18}F variants of natural products and some top-selling drug derivatives were elegantly accessed using a variant of the method used for Mn^{III}-catalysed nucleophilic ^{19}F fluorination[68]. Some reports have also accessed ^{18}F radiotracers through late-stage C–H fluorinations, including in the automated synthesis of the retinoic acid receptor β-agonist [^{18}F]AC261066 — which employed a Cu^{I} promoter[53] (FIG. 10Ae) — and radical-based ^{18}F labelling of leucine derivatives[218] (FIG. 10Af).

^{18}F trifluoromethylation. Most radiofluorination efforts have focused on the development of ^{18}F trifluoromethylation methods to support PET imaging experiments in animal models. The coupling of a [$CuCF_2{}^{18}F$] complex is the most commonly used strategy for $CF_2{}^{18}F$ installation. The [$CuCF_2{}^{18}F$] complex could be generated in situ from the combination of a Cu^{I} salt, a difluorocarbene (:CF_2) source and [^{18}F]fluoride[219] or the combination of a Cu^{I} salt, preformed [^{18}F]fluoroform ($HCF_2{}^{18}F$) and a base[220–222]. Recently, a :CF_2/$^{18}F^-$ system was used to develop a Langlois-type ^{18}F labelling reagent ($CF_2{}^{18}FSO_2NH_4$) that enables radical C–H ^{18}F trifluoromethylation of aromatic residues in peptides[223]. Interestingly, the same research group also developed a fully automated radiosynthesis of octreotide[Trp(2-$CF_2{}^{18}F$)] using the Advion NanoTek microfluidic synthesis system[223] (FIG. 10Ah). A preliminary in vivo PET imaging experiment using this labelling peptide on naive rats suggested that this complex is cleared from the body by urinary excretion and through the gastrointestinal tract, facilitating the

measurement of the distribution and pharmacokinetics of octreotide in vivo.

^{18}F difluoromethylation. Direct ^{18}F difluoromethylation is more challenging than direct ^{18}F trifluoromethylation, owing to the difficulty in constructing the ^{18}F difluoromethylation reagent. Inspired by the radical difluoromethylation reagent difluoromethyl 2-benzo-[*d*] thiazolyl sulfone (2-BTSO$_2$CF$_2$H) (REF.[186]), a new reagent, 2-BTSO$_2$CF^{18}FH, was prepared in two steps and successfully applied for C–H ^{18}F difluoromethylation of a broad range of *N*-heteroaromatics, including drug molecules such as the antiviral medication acyclovir[212] (FIG. 10Ag).

^{18}F monofluoromethylation. No examples of C–H ^{18}F monofluoromethylation have been reported thus far, although [^{18}F]fluoromethyl halides have been prepared and used in the electrophilic ^{18}F fluoromethylation of N nucleophiles, O nucleophiles and S nucleophiles for their potential application in PET imaging[224–226]. Additionally, [^{18}F]FCH$_2$X reagents (where X = Br or I) have been used in palladium-catalysed cross-couplings with boronic acids to generate ^{18}F-radiolabelled (hetero)arenes[227]. [^{18}F]Fluoromethyl halides are readily synthesized from CH$_2$X$_2$ (X = I or Br) through halide-exchange reactions with a [^{18}F]fluoride salt[224–226]; for example, in acetonitrile at reflux, the halide exchange[225] of dibromofluoromethane with [^{18}F]KF and Kryptofix 222 — a cryptand that complexes potassium — affords [^{18}F]FCH$_2$Br in excellent radiochemical yield (47 ± 8%, n = 20)[225]. Furthermore, a second halide-exchange reaction of [^{18}F]FCH$_2$Br with silver triflate delivers the corresponding ^{18}F-radiolabelled triflate. These established procedures should inspire the use of C–H ^{18}F monofluoromethylation approaches and the development of new ^{18}F monofluoromethylation reagents. Notably, ≈60% of all FDA-approved drugs contain at least one heterocycle, with pyridine being among the most common[228]; thus, the preparation of [^{18}F]MFMS would be of particular use for radiochemistry owing to its demonstrated regioselectivity when derivatizing medicinally relevant heterocycles, including pyridine and purine ring systems. Such an approach will require a marked reduction in the time required for the synthesis of MFMS (~4 days) for it to be compatible with the half-life of ^{18}F (~110 min).

Bioorganic chemistry research

Radical C–H fluoroalkylation of native aromatic and heteroaromatic residues in peptides or proteins can facilitate their study using ^{19}F nuclear magnetic resonance (NMR) analysis and potentially modulate their functions. Fluoroalkanesulfinate salts are the reagents of choice owing to their biocompatibility and the mildness of their reaction conditions[216]. Selective trifluoromethylation of tyrosine (Tyr) residues in recombinant human insulin[229] and tryptophan (Trp) residues in the enzyme lysozyme[230] (FIG. 10Bb) have been achieved with CF$_3$SO$_2$Na. Trifluoromethylation modification of peptides and proteins provides a sensitive ^{19}F NMR spectroscopic probe of the local environment in the biomacromolecules, while minimally perturbing their overall structure and enzymatic function.

The application of difluoromethylation reactions in biological research has been showcased by the development of a novel quinone methide-based, self-immobilizing fluorogenic probe that allows the measurement of β-galactosidase activity in living cells[215] (FIG. 10Bc). Nucleophilic attack of a CF$_2$H group on the coumarin group of the probe by β-galactosidase activates fluorescence in the molecule and allows measurement of enzyme activity. The 3-difluoromethylated analogue of the probe, obtained through the one-step reaction of coumarin with HCF$_2$SO$_2$Na, was shown to have a higher fluorogenic response and improved fluorescence labelling efficiency over a previously developed 8-difluoromethylated analogue[215].

Pharmaceuticals and agrochemicals

In the production of pharmaceuticals and agrochemicals, fluorine and fluoroalkyl groups are usually introduced to intermediates at the early stage of the synthesis through the fluorination of pre-functionalized precursors or transformation of fluoroalkyl-containing building blocks, respectively[7,206]. An exception is electrophilic difluoromethylation with difluorocarbene, which has been widely applied in early-stage and late-stage difluoromethylation[4,8,231–235]. This is possible owing to the high reactivity of difluorocarbene towards heteroatom nucleophiles and soft carbon nucleophiles and the low cost of difluorocarbene sources such as HCF$_2$Cl. Pharmaceuticals and agrochemicals synthesized using this electrophilic difluoromethylation method include the aforementioned anti-pulmonary disease drug roflumilast[4] (FIG. 10Ab), pantoprazole — a drug employed for the treatment of gastroesophageal reflux disease[8] — the herbicide pyraflufen-ethyl[233] (FIG. 10Bd) and the insecticide pyriprole[235] (FIG. 10Be), among others.

Reproducibility and data deposition

Reproducibility

All of the fluorination and fluoroalkylation methods highlighted in this Primer should be reproducible by virtue of the fact that they have been published in peer-reviewed journals with detailed experimental procedures and adequate analytical and characterization data. However, most methods have emerged in the past 10–15 years and have only been demonstrated on small (millimolar) scales. More studies will be needed to fully evaluate reproducibility issues and assess the potential of these synthetic methods following process scale-up. For any given transition-metal catalysed fluorination or fluoroalkylation reaction, the commercially available starting materials are used as received from the laboratory chemical suppliers and organic solvents are pre-dried to remove trace water, unless otherwise noted in the original literature. The reaction is usually conducted using standard laboratory equipment under the protection of an inert atmosphere, such as argon or nitrogen.

For nucleophilic fluoroalkylations using fluoroalkyl metal reagents that are generated in situ by deprotonation or halogen–lithium exchange, low temperatures (such as −78 °C) are required to avoid thermal decomposition[22]. The radical C–H fluoroalkylation of (hetero)aromatics with fluoroalkanesulfinate salts can be

Cryptand
A family of synthetic bicyclic and polycyclic multidentate ligands for a range of cations.

Atom economy
The conversion efficiency of a chemical process in terms of all atoms involved and the desired products produced.

performed under open air without an organic co-solvent and in the presence of extensive impurities in the reaction medium; however, portion-wise addition of large excess amounts of the reagents are usually needed to achieve a high yield[216].

The synthesis of PET tracers requires high levels of reproducibility and applicability to biological studies and clinical applications[236]. These syntheses should be efficient (non-decay corrected radiochemical yield of 5–40%) and timeframes should be compatible with the short half-life of ^{18}F (~110 min). Products should be manufactured using automated synthesis, obtained in high radiochemical purity, have sufficient specific radioactivity for imaging (≥8 Mbq kg^{-1}) and must be produced in a form acceptable to regulatory bodies[237]. The latter requirement is valid for all pharmaceuticals and involves using good manufacturing practices so that clinical products are produced consistently and controlled according to quality standards. Good manufacturing practices cover all aspects of production including raw materials, equipment and personnel training. Different countries and authorities have their own good manufacturing practice guidelines aiming to ensure high reproducibility, quality and safety of the finished product[238].

Following the general standard for reporting organic synthesis, all new small-molecule chemical products should be characterized using ^{1}H NMR and ^{13}C NMR spectroscopy, and high-resolution mass spectroscopy analysis, with results reported in publications, either in the main text or in the electronic supporting information. ^{19}F NMR data should also be provided to support the incorporation of the desired fluorinated moieties. Inexperienced chemists can refer to an elegant book on fluorine NMR to interpret the ^{1}H, ^{13}C and ^{19}F NMR data of organofluorine compounds[239]. In the case of ^{18}F labelling, the ^{19}F-substituted analogue should be synthesized as a standard sample for characterization and high-performance liquid chromatography analysis. For the modification of biomacromolecules, the ^{19}F NMR yield is used to assess the efficiency of fluorine incorporation.

Limitations and optimizations

Fluorination

The direct fluorination of C–H bonds represents an ideal solution for late-stage fluorinations; however, it also presents unique challenges[49]. The similar steric parameters and chromatographic behaviour of the precursor and the fluorinated product can cause purification issues if the reaction does not reach full conversion. In many cases, the product has a reactivity profile similar to the starting material; preventing polyfluorination is therefore difficult and overfluorinated products are common. However, some reports have shown the ability to favour monofluorination over difluorination by carefully modifying the reaction conditions[39,51]. A further issue is that C–H oxygenation side products can be formed when carboxylic acid additives are required in the catalytic system or when nucleophilic sources are combined with hypervalent iodine reagents bearing oxygenated substituents.

As elegant as the C–H fluorination approach can be, it strongly relies on state-of-the-art methodologies that require the full consumption of starting material, easy purification of the product and simple scale-up. Yields of isolated products rather than yields determined by ^{19}F NMR should be used to assess the synthetic utility of a protocol. C–H fluorination scale-up processes have emerged[240] and future advances should consider safety issues, particularly when HF and its derivatives are employed. Cost and atom economy represent important parameters as the field is dominated by reagents that suffer from low atom economy and/or relatively high costs, such as Selectfluor, NFSI and silver fluorides. In the case of ^{18}F radiolabelling, ^{18}F-radiolabelled compounds have a very short half-life and should ideally be prepared and used on site; therefore, operational simplicity and automation are paramount and the ultimate aim is to change clinical practice with the availability of readily automated protocols.

Trifluoromethylation

Each trifluoromethylation method has its own limitations in terms of substrate scope, side reactions and potential for scaling up. The coupling reaction with a $CuCF_3$ complex can incorporate a CF_3 group into various molecules and may be easily scaled up; however, reaction selectivity can decrease as the electronic nature of the substrate is altered. For example, although aryl chlorides are usually inert and remain intact in coupling reactions, electron-deficient aryl chlorides can be trifluoromethylated. Therefore, attention must be paid to selectivity when substrates contain an active C–I or C–Br bond and a supposedly inert C–Cl bond. Small-scale radical trifluoromethylation reactions have found widespread use in drug and agrochemical development, although when scaling up radical reactions, issues of safety and reaction selectivity should be carefully considered as radicals are highly reactive and radical reactions are often exothermic processes. Lowering concentrations or adding reagents slowly can help reduce risk for large-scale radical reactions. Nucleophilic trifluoromethylation is usually limited to the synthesis of α-CF_3 amines, alcohols and ketones; further, reaction temperatures should be kept low in the synthesis of α-CF_3 ketones to avoid double trifluoromethylation and the formation of tertiary alcohols. Finally, electrophilic trifluoromethylation is limited to electron-rich molecules such as enolates and enamines, which can be generated in situ or prepared in advance. If substrates or trifluoromethylation reagents are not reactive enough, the use of Lewis acids may be necessary.

Difluoromethylation

Carbon difluoromethylation can introduce a CF_2H group at an early stage or a late stage and has undoubtedly facilitated the design and discovery of difluoromethylated functional molecules with novel or improved properties. However, some problems must be addressed in terms of both chemistry and practical applications. The control of stereoselectivity at the difluoromethylated sp^3 carbon mainly depends on diastereoselective nucleophilic difluoromethylation reactions with either chiral

substrates or chiral reagents[22], whereas enantioselective difluoromethylation remains a challenging synthetic task[45]. Further, $\cdot CF_2H$ prefers reacting with relatively electron-deficient π-systems including heteroarenes owing to its nucleophilic profile; therefore, direct radical C–H difluoromethylation of electron-rich arenes is usually problematic, although reports have shown that the use of electrophilic surrogates such as CF_2SO_2Ph and $\cdot CF_2Cl$ can overcome this limitation[170,171].

The practical application of difluoromethylation methods by the medicinal chemistry community is highly dependent on the commercial availability and cost of difluoromethylation reagents and catalysts, and the simplicity of the experimental procedures. At present, popular carbon difluoromethylation reagents include the commercially available $TMSCF_2H$ (REF.[129]), $PhSO_2CF_2H$ (REF.[22]), $(HCF_2SO_2)_2Zn$ (REF.[164]), $(HCF_2SO_2)_2Na$ (REF.[136]) and 2-$BTSO_2CF_2H$ (REF.[224]), and the corresponding difluoromethylation protocols have been proved to be reproducible in many studies[29,125–128]. However, most newly developed difluoromethylation methods are not practical for industrial application, owing to the high cost of reagents and metal catalysts[2]. To reduce costs, recent research has begun to focus on the use of difluoromethylation reagents closely related to the fluorine industry[144,152,160,167,168] and inexpensive base-metal catalysts such as nickel and iron[151–156].

Monofluoromethylation

Although electrophilic C–H monofluoromethylation provides a means for the α-monofluoromethylation of 1,3-dicarbonyl systems, there is limited evidence to suggest that these processes will translate to broader collections of carbon nucleophiles. Challenges of translating this approach to other systems include competitive O monofluoromethylation, which can represent the predominant product, and an intolerance to even mildly nucleophilic functional groups. Efforts are required to improve functional group compatibility and scope. The demonstration of radical C–H monofluoromethylation of heterocycles represents a critically important advance, although the adoption of this process for medicinal chemistry purposes or further expansion of substrate scope has yet to be described. The development of reactions involving the monofluoromethyl radical and, in particular, the use of this process for late-stage functionalization of heterocycles through Minisci-like processes requires further exploration to establish this strategy as a dependable tool for lead drug modification.

Outlook

The number of fluorine-containing drug candidates is steadily increasing[2–6] and the selective fluorination and fluoroalkylation of organic molecules will continue to play an important role in the drug discovery and large-scale production of pharmaceuticals. Remarkable advances have been made in synthetic organofluorine chemistry during the past two decades, among which C–H fluorination and fluoroalkylation represent frontiers in the field[241,242]. Ideal fluorination and fluoroalkylation methods should enable precise C–H fluorination and fluoroalkylation in a safe, practical, cost-effective and environmentally benign manner[2]. However, owing to cost considerations, the industry still favours classical fluorination methods in large-scale productions, such as the use of anhydrous HF, F_2, Freons or Halons, and innovative new methods are often only used in small-scale synthesis, for example in drug discovery. As a result, it seems paradoxical that although synthetic fluorine chemistry has been flourishing in academia during the past decade, the pharmaceutical industry still calls for action to develop practical fluorination and fluoroalkylation methods for large-scale synthesis[2]. The synthesis of ^{18}F-labelled radiotracers is in small-scale production, although ^{18}F radiochemistry faces other challenges such as dealing with the short half-life of ^{18}F and the necessity for translation to automated platforms for clinical applications. To address the above call for action[2], new fluorination and fluoroalkylation methods and manufacturing technologies need to be developed for practical synthesis by choosing cost-effective reagents and/or catalysts in an environmentally responsible way. Readily available fluorine sources, such as simple inorganic fluorides and organic fluorides, and non-noble metal catalysts or organocatalysts should be preferentially used in synthesis. These new methods need to tolerate heterocycles and other common functional groups and give the desired fluorinated products in high yields for ease of purification. Asymmetric synthesis of organofluorine compounds is also of high importance and should receive special attention.

In the next decade, we expect that the number of transition metal-catalysed fluorination and fluoroalkylation reactions will continue to grow, owing to their diverse reactivity and tunable selectivity. Fluorination and fluoroalkylation reactions involving radical intermediates, especially visible light-promoted catalytic reactions, are expected to further flourish, and these radical reactions should find industrial applications with the development of new reaction engineering techniques. The design and development of new fluorination and fluoroalkylation reagents will add new tools to the synthetic toolbox and enable the construction and introduction of other useful fluorinated functionalities such as SF_5, OCF_3 and $^tC_4F_9$. The incorporation of synthetic biology techniques into synthetic fluorine chemistry, such as the use of enzymatic fluorination and fluoroalkylation strategies, could pave the way for environmentally friendly fluorinations and fluoroalkylations. We also anticipate that electrochemistry will play a major role in facilitating the late-stage installation of a fluorine substituent. ^{18}F labelling technologies are also expected to reach new heights with the development of novel PET imaging agents. More generally, it is likely that the field will expand with further development of site-selective functionalization of biological molecules, such as the functionalization of proteins with fluorine or fluoroalkyl motifs[243]. The combination of synthetic fluorine chemistry with artificial intelligence might lead to exciting opportunities for the smart synthesis of organofluorine compounds. Artificial intelligence could be used to design reaction schemes, optimize reaction conditions and control organic synthesis robots to develop novel fluorinated materials.

In addition to their use in the pharmaceutical industry, selective fluorination and fluoroalkylation reactions find important applications in the agrochemical industry. The production scale of agrochemicals for crop protection is usually larger than that of pharmaceuticals; however, agrochemicals are much more cost-sensitive. As a result, cost-effective fluorination and fluoroalkylation methods are more likely to be used in the large-scale production of crop protection agents. Further, fluorination and fluoroalkylation reactions promise to find wide applications in the development of new fluorinated functional materials, such as fluorinated liquid crystals, fluorinated anti-fingerprint coatings and fluorinated plastics and rubbers, among others. The development of new fluorination and fluoroalkylation methods will also likely stimulate innovations in fluorinated refrigerants and fluorinated polymers, which have great importance in our everyday lives.

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