The fluorination of C–H bonds: developments and perspectives

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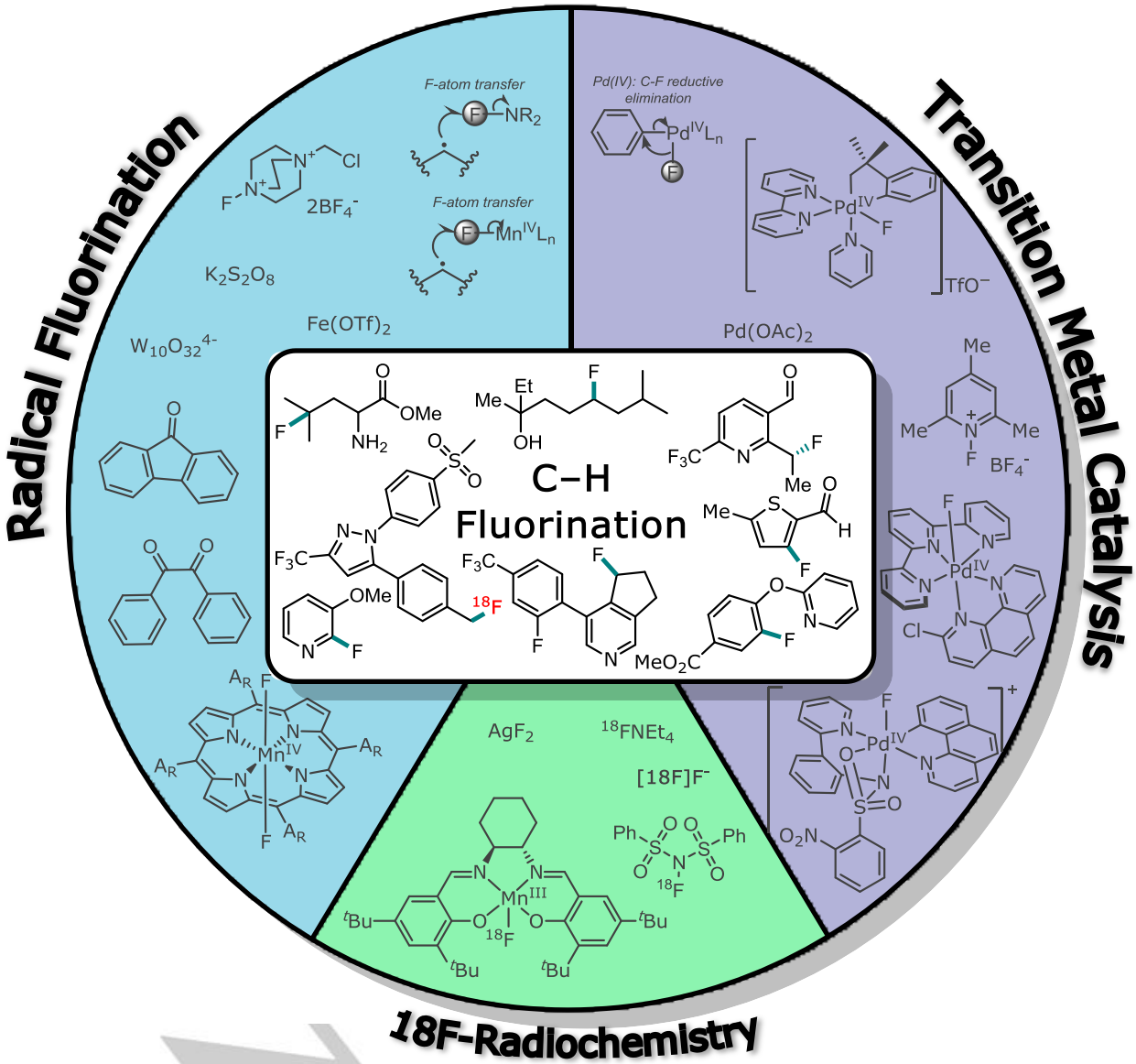
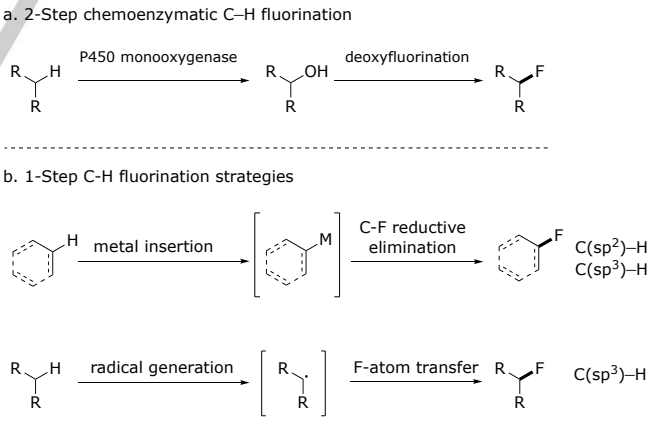


Abstract: This Review summarizes the advances in fluorination via C(sp^2)–H and C(sp^3)–H activation. Transition metal catalyzed approaches championed by palladium have allowed the installation of a fluorine substituent at C(sp^2) and C(sp^3) sites exploiting the reactivity of high oxidation transition metal fluoride complexes combined with the use of directing group (some transient) to control regio- and stereoselectivity. The large majority of known methods employ electrophilic fluorination reagents, but methods combining a nucleophilic fluoride source with an oxidant have appeared. A number of ligands have proven to be effective for C(sp^3)–H fluorination directed by weakly coordinating auxiliaries, thereby enabling control over reactivity and selectivity. Methods relying on the formation of radical intermediates are complementary to transition metal catalyzed processes as they allow for undirected C(sp^3)–H fluorination. To date, radical C–H fluorinations mainly employ electrophilic N–F fluorination reagents but a unique bio-inspired Mn(III)-catalyzed oxidative C–H fluorination has been developed. Overall, the field of late stage nucleophilic C–H fluorination has progressed much more slowly, a state of play explaining why C–H ^{18}F-fluorination is still in its infancy.

1. Introduction

Numerous methods for C–F bond formation have been developed in response to demand from the pharmaceutical and agrochemical sectors.[1] In 2018, around 50% of novel small molecule drugs approved by the Food and Drug Administration contained fluorine. Fluorine substitution in drug or agrochemical discovery often serves the purpose of increasing metabolic stability, modulating properties such as lipophilicity and pKa, and/or exerting conformation control.[2],[3],[4],[5] Methods for ^{18}F-C bond formation are also sought-after as the radioisotope ^{18}F is widely used to label imaging agents for Positron Emission Tomography, due to its convenient half-life ($t_{1/2}$ = 110 minutes), and its low positron energy resulting in images of high resolution.[6],[7] Amongst the myriad strategies for carbon-fluorine bond formation, the fluorination of carbon-hydrogen bonds has been extensively studied over the past decade.[8],[9],[10] The field has now reached the maturity at which a critical review is timely. Compared to classical methods of fluorination, such as the Balz-Schieman reaction, deoxyfluorination or substitutions, these C–H fluorination methods are advantageous because they do not require substrate pre-functionalization. This not only expedites syntheses when judiciously deployed, but also allows fluorination at positions, which might otherwise be challenging to functionalize.

Many highly selective transformations involving unactivated C–H bonds have used or were inspired by enzymes. The only native fluorinase enzyme known to date catalyzes C–F bond formation by nucleophilic displacement at the pre-activated carbon centre of S-adenosylmethionine.[11] The absence of enzyme-catalyzed C–H fluorination process has encouraged the development of detoured strategies. Specifically, one method has combined the ability of cytochrome P450 monooxygenases to selectively insert oxygen into unreactive C–H bonds with a conventional deoxyfluorination of the resulting alcohol with the nucleophilic fluorinating reagent diethylaminosulfur trifluoride (DAST). This chemo-enzymatic approach enabled site-selective incorporation of fluorine at metabolically vulnerable sites in the target molecule, an attractive feature for applications in medicinal chemistry (Scheme 1a).[12] Departing from methods employing enzymes, the direct C–H fluorination methods reported to date can be broadly categorized into one of two classes based on activation mode; those that employ a transition metal capable of activating C(sp^2)–H or C(sp^3)–H bonds, and those that proceed via carbon-centered radical intermediates resulting from C(sp^3)–H bond activation (Scheme 1b). These strategies are more often electrophilic fluorination processes with commercially available and easy to handle N-F reagents such as 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (Selectfluor) or *N*-fluorobenzenesulfonimide (NFSI). To date, only few C–H fluorination methods utilize nucleophilic fluorine sources. This state of play reflects the difficulties associated with fluoride reagents, especially metal alkali fluoride, and explains why the field of C–H ^{18}F-fluorination has progressed more slowly. Indeed, cyclotron-produced [^{18}F]fluoride is by far the reagent of choice for ^{18}F-radiochemistry.



Scheme 1. a) Two-step chemoenzymatic C–H fluorination sequence, comprising of enzymatic C–H oxidation followed by synthetic deoxyfluorination.[12] b) The two most widely adopted synthetic C–H fluorination strategies consisting of transition metal insertion, and carbon centered radical formation.

In this review, we will describe first C–H fluorination processes of organometallic intermediates, a field of research dominated by palladium catalysis. The discussion will then focus on C–H fluorination via carbon-centered radicals, followed by a section describing methods that conform to neither of these categories.

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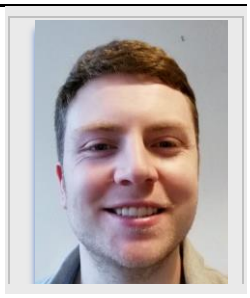
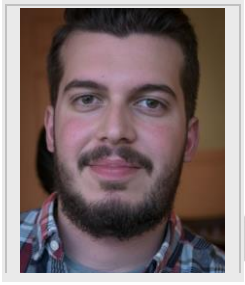
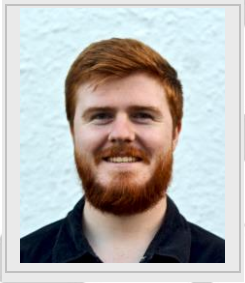
To conclude, we will compare these different strategies, and allude to future challenges in the field. The fluorination of innately activated C–H bond such as those positioned alpha to carbonyl groups are not discussed in this review.



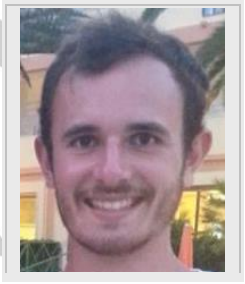
Robert Szpera received his MChem degree from the University of Southampton, after completing research on fluorinated polymers and carbohydrates in the group of Prof. B. Linclau. Robert then moved to the University of Oxford as a DPhil student, briefly working with Prof. Stephen P. Fletcher on asymmetric copper catalysis, before moving to Prof. V. Gouverneur's lab where he now works on transition metal catalysis.



Lewis Smith graduated from the University of Bristol in 2017, and completed his MSci degree in Chemistry under the supervision of Prof. J. Bower. During his studies, he undertook a year internship at GlaxoSmithKline (Stevenage). Following graduation, he completed a short internship at Genentech (San Francisco). He is currently carrying out his PhD at the University of Oxford under the supervision of Professor T. J. Donohoe. His research focuses on developing novel hydrogen borrowing catalysis.



Alistair Sterling received his MChem degree in 2017 from the University of Oxford, under the supervision of Prof E. A. Anderson. He spent a semester in the group of Prof. E. M. Carreira (ETH Zürich), and is now a doctoral student at the University of Oxford in the groups of Prof. F. Duarte and Prof. E. A. Anderson. His research interests include the computational study of the electronic structure of strained organic molecules, and the application of this research to organic synthesis.



Daniel Moseley received his MChem degree from Cardiff University. During this time, he undertook an industrial placement at Merck, Southampton, before carrying out his final year project in the field of organocatalysis under the supervision of Dr L. C. Morrill. He is currently conducting postgraduate research with Prof. M. C. Willis, at Oxford University, where he is looking into the diastereoselective development of saturated heterocycles, through a Rhodium-catalyzed hydroacylation cascade.

Véronique Gouverneur secured a PhD in chemistry at the Université Catholique de Louvain (Belgium). In 1992, she moved to a postdoctoral position at the Scripps Research Institute (California, USA). After four years as Maître de Conférence at the University Louis Pasteur in Strasbourg (France), she started her independent research career at the University of Oxford (UK) in 1998, and was promoted to Professor of Chemistry in 2008. Since her appointment in Oxford, she holds a tutorial fellowship at Merton College Oxford where she teaches organic chemistry. Her research focused on fluorine (radio)chemistry has been disseminated in more than 180 publications, and awarded numerous prizes and distinctions.

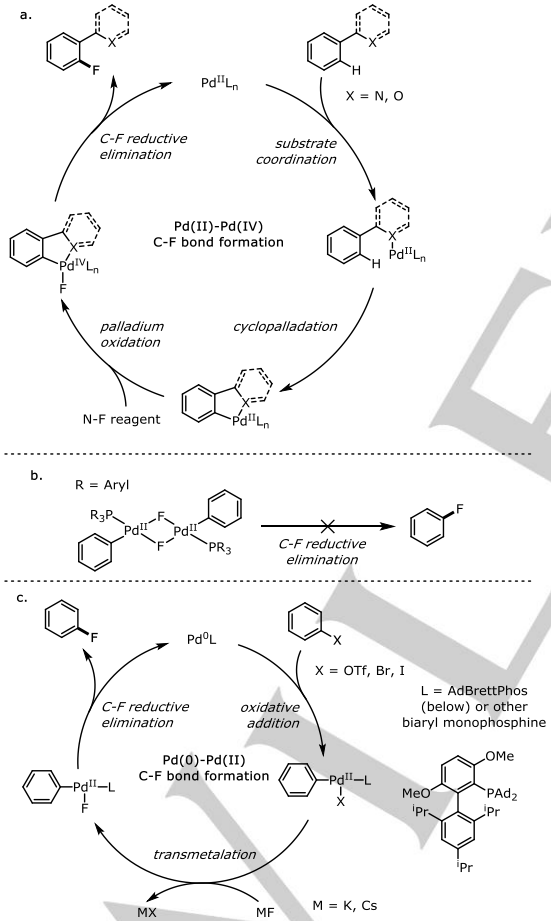
2. C–H Fluorination via transition metal insertion into C–H bonds

Late stage fluorination applying C─H activation under transition metal catalysis is a challenging problem. Although the C–H bond is weaker than the C–F bond, C–F activation with transition metal is well documented and should therefore be considered in reaction design. A thorough discussion on competition between C─H and C─F activation in fluorocarbons has been recently reviewed.[13] To date, palladium stands out as the most studied catalytic metal for C─H fluorination. Specifically, the past decade has witnessed the development of Pd(II) catalyzed fluorination of C─H bonds via high valent Pd(IV) fluoride complexes. Early contributions reported C(sp^2)─H fluorination,[14] and this field has today progressed to enable state of the art enantioselective C(sp^3)─H fluorination.[15] Copper catalyzed C─H fluorination via high valent Cu(III) fluoride complexes has also been studied, although less explored than palladium.

2.1. Directed C(sp^2)–H fluorination via high valent palladium fluorides

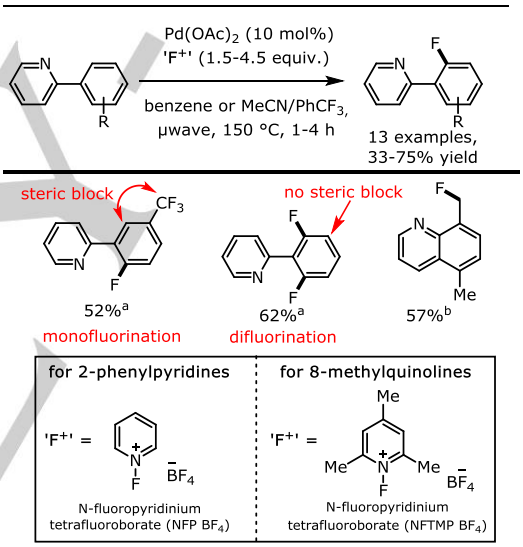
Most Pd(II) catalyzed C–H fluorinations proceed through a Pd(II)–Pd(IV) redox cycle, a catalytic manifold inspired by pioneering work of Catellani and Canty, and implemented for the first time in the context of C–H fluorination by the Sanford group (Scheme 2a).[16],[17],[18],[19],[20],[21] Typically, a directing group is required to promote reactivity and control regioselectivity. Many different motifs can serve as directing groups, all of which feature a heteroatom capable of coordinating to palladium. Hence the directing group brings the palladium into the vicinity of a specific C–H bond, enabling regioselective cyclopalladation. The resulting palladacycle then undergoes oxidation by an electrophilic fluorinating reagent to form a Pd(IV) fluoride complex, which can undergo C–F reductive elimination to afford the product of C–H fluorination.[16],[17],[18],[19]

This approach to forming C–F bonds via a high valent Pd(IV) fluoride complex provided an elegant solution to C–F reductive elimination.[22],[23],[24] Prior to this, C–F reductive elimination was studied from Pd(II). The stability of dimeric Pd(II) fluoride complexes reluctant to dissociate into monomers was found to be the main obstacle to C–F bond formation (Scheme 2b),[22],[23],[24] an observation encouraging the use three-coordinate T-shaped 14 e $Pd^{II}Ar(F)L$ complexes. An effective solution came from Buchwald and co-workers, who reported that such $Pd^{II}Ar(F)L$ complexes, armed with a bulky biaryl monophosphine ligand to prevent unproductive dimerization, undergo thermal C–F reductive elimination (Scheme 2c). Using such ligands, pre-functionalized aryl triflates and aryl bromides are amenable to Pd(0)-catalyzed fluorination affording aryl fluorides.[25],[26],[27] Nonetheless, C–F reductive elimination from Pd(IV) fluorides occurs more readily than from Pd(II) fluorides, and it is the Pd(II)–Pd(IV) redox cycle that is exploited in Pd-catalyzed fluorination of C–H bonds.



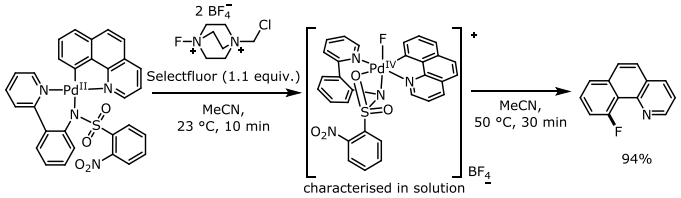
Scheme 2. a) General Pd(II)–Pd(IV) catalytic cycle in C–H fluorination chemistry. b) Inability of Pd(II) fluoride dimers to undergo C–F reductive elimination. c) Pd(0)–Pd(II) catalytic cycle in the fluorination of aryl bromides and triflates.[25],[26],[27]

The first Pd(II)–Pd(IV) aryl and benzyl C–H fluorinations directed by pyridines and quinolones respectively were reported in 2006 by Sanford and co-workers (Scheme 3).[14] These heterocycles were known previously to facilitate cyclopalladation in oxidative C–H functionalization other than fluorination.[28],[29] The use of an electrophilic fluorinating agent was key to the success of this reaction, functioning both as the oxidant to access the high oxidation state Pd(IV), and as the fluorine source. Multiple electrophilic fluorine sources afford the desired fluorinated product, but *N*-fluoropyridinium tetrafluoroborate (NFP BF_4) gave the highest yields for 2-phenylpyridines, while *N*-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate (NFTMP BF_4) was optimal for 8-methylquinolines. The methyl groups of the pyridine, released upon fluorination with NFTMP BF_4, likely prevent competitive binding to palladium. 2-Phenylpyridine underwent two consecutive C–H fluorinations at both *ortho* positions. Double fluorination is not observed with *meta*-substituted substrates, as such substitution hinders the formation of the square planar Pd complex formed upon cyclopalladation, purely on steric grounds. Substrates in which one *ortho*-position was substituted also underwent monofluorination.



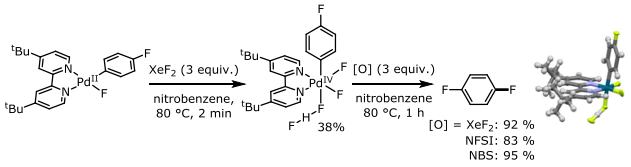
Scheme 3. The seminal Pd(II) catalyzed fluorination of aryl C–H bonds and benzylic C–H bonds with electrophilic fluorinating reagents, reported by Sanford and co-workers.[14] [a] Reaction in MeCN (0.25 ml) and $PhCF_3$ (26 mL), ~0.6 mmol scale. [b] Reaction in benzene (2-6 mL), ~0.6 mmol scale.

Mechanistic work by the Ritter group supported the viability of the proposed Pd(II)–Pd(IV) catalytic cycle.[18],[19] By treating a Pd(II) complex armed with a benzoquinolinyl ligand and a pyridyl sulfonamide ligand with the electrophilic fluorinating agent Selectfluor, a cationic Pd(IV) fluoride complex was observed in solution (Scheme 4). Rigid chelating ligands like benzoquinoline are known to stabalize high-valent metals, and were necessary so that the Pd(IV) fluoride didn't undergo immediate reductive elimination, enabling characterization.[21],[30] Thermolysis was necessary to induce C–F reductive elimination, which experimental data suggested occurred from a cationic pentacoordinate Pd(IV) fluoride intermediate, formed by dissociation of the hemilabile sulfonamide oxygen from the hexacoordinate Pd(IV) complex.



Scheme 4. C–F reductive elimination from a well-defined high valent palladium(IV) fluoride complex, reported by Ritter and co-workers.[18],[19]

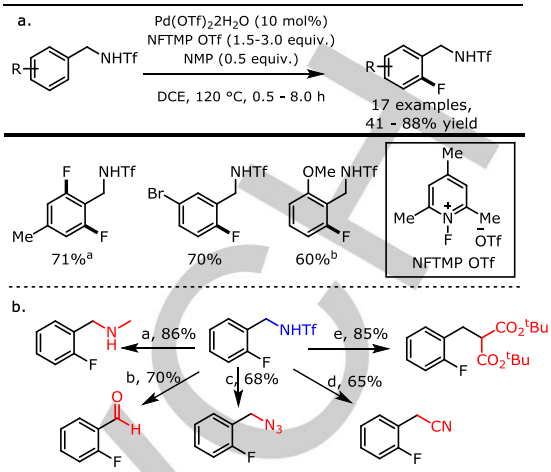
The Sanford group also performed mechanistic work supporting the viability of the Pd(II)–Pd(IV) catalytic cycle.[16] Treatment of an aryl Pd(II) fluoride complex with XeF_2 afforded a neutral Pd(IV) trifluoride species. The use of the rigid 2,2'-bipyridine ligand and the presence of multiple fluorides contributed to the stability of the Pd(IV) complex, allowing its isolation and characterization by X-ray crystallography (Scheme 5). Upon treatment with various oxidizing agents, C–F reductive elimination was induced. The Pd(IV) fluoride complexes reported by Ritter and Sanford support the feasibility of the proposed Pd(II)–Pd(IV) fluoride catalytic cycle, and undoubtably encouraged the development of subsequent palladium catalyzed C–H fluorinations.



Scheme 5. X-ray structure and C–F reductive elimination from a well-defined high valent palladium(IV) fluoride complex, reported by Sanford and co-workers.[31] NFSI = N-fluorobenzenesulfonimide, NBS = N-bromosuccinimide.

The pioneering work of the Sanford group shown in Scheme 3 marked a major breakthrough in the field of C–F bond formation, and the beginning of the field of palladium catalyzed C–H fluorination.[14] However, although the pyridine directing group is widely represented in medicinal chemistry, its inability to be cleaved from the fluorinated products or to undergo functional group manipulation limits the applications of this protocol.[32] In addition, for substrates lacking *ortho* or *meta* substituents, only the difluorinated product could be obtained. Subsequent work sought to address these issues.

The Yu group developed a Pd(II) catalyzed aromatic C–H fluorination directed by the triflamide group (Scheme 6a).[33] In contrast to the pyridine and quinoline auxiliaries used by Sanford and co-workers,[14] the triflamide directing group serves as a versatile handle for subsequent transformations, providing access to a range of synthetically useful functionalities including aldehydes, amines and nitriles (Scheme 6b).

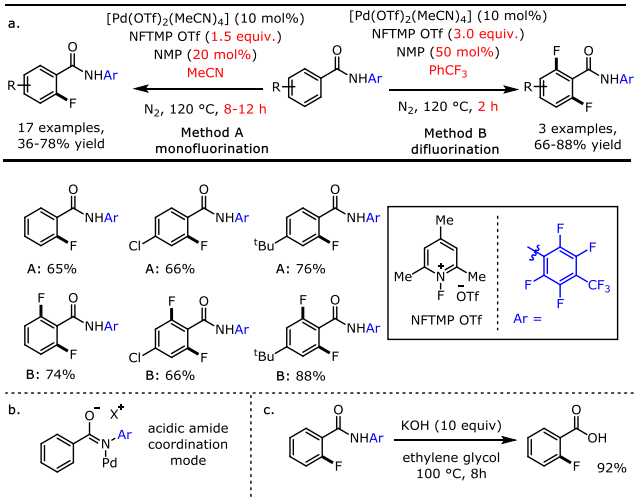


Scheme 6. a) C–H fluorination using the synthetically versatile triflamide directing group reported by Yu and co-workers. [a]$PhCF_3$ used as solvent. [b]$Pd(OAc)_2$ used instead of $Pd(OTf)_2 2H_2O$. Tf = triflyl. b) Derivatization of the product triflamide group.[33] Conditions: (a) (i) MeI (3 equiv.), K_2CO_3 (1.5 equiv.), acetone, reflux, 8 h; (ii) $LiAlH_4$ (2 equiv.), THF, reflux, 10 h; (b) (i) MeI (3 equiv.), K_2CO_3 (1.5 equiv.), acetone, reflux, 8 h; (ii) NaH (3 equiv.), DMF, 100 °C, 10 h; (iii) HCl (2N) : THF (1:2), reflux, 2 h; (c-e) (i) NaH (1.0 equiv.), Tf_2O (1.0 equiv.), CH_2Cl_2, -78-0 °C, 2 h; (ii) NaN_3 (c), NaCN (d) or NaCH(COOt-Bu)$_2$ (e) (1.5 equiv.), HMPT, 24 °C, 8h. HMPT = hexamethylphosphorous triamide.

Through use of $Pd(OTf)_2 \cdot 2H_2O$ instead of $Pd(OAc)_2$, C–H acetoxylation, which presumably occurs via competing C-O reductive elimination from Pd(IV) was avoided. Use of 0.5 equivalents of *N*-methylpyrrolidinone (NMP) was found to be essential for good yields. Its role is uncertain, although the authors suggest that NMP may serve as a ligand to promote C–F reductive elimination from the intermediate high valent Pd(IV) fluoride complex (see Scheme 20). The triflate salt of N-fluoro-2,4,6-trimethylpyridinium (NFTMP OTf) was found to afford higher yields than the BF_4 salt used by Sanford. Both electron rich and electron poor rings are tolerated in this protocol, however as with the work of Sanford, selective monofluorination was not within reach for substrates lacking *ortho* or *meta* substitution.

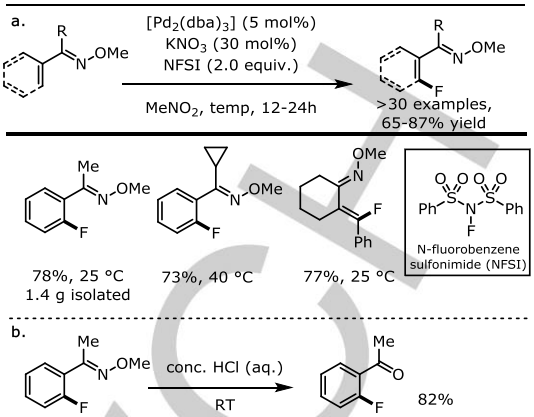
The Yu group subsequently disclosed an alternate protocol for aryl C–H fluorination, in which selectivity for mono- vs difluorination could be controlled for substrates without *ortho* or *meta* substituents (Scheme 7a).[34] Yu proposed that a substrate armed with a weakly coordinating directing group could easily be displaced from the palladium after the first fluorination event, thereby limiting unwanted difluorination. This was achieved by use of an acidic amide auxiliary, which is thought to undergo deprotonation and coordinate to palladium as a neutral ligand through nitrogen (Scheme 7b).[35] MeCN was found to be essential for achieving high monofluorination selectivity, probably as this solvent can ligate Pd thereby displacing the monofluorinated product. In contrast, the non-coordinating solvent $PhCF_3$ in combination with three equivalents of the fluorinating agent was found to be optimal for difluorination. For both mono and difluorination, NMP was found to be beneficial,

consistent with the earlier work from the Yu group.[33] The removal of the amide directing group was achieved with KOH at 100 °C, affording the corresponding benzoic acid in high yield (Scheme 7c).



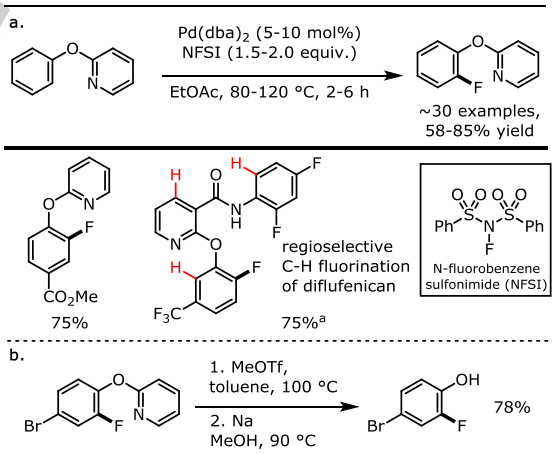
Scheme 7. a) Selective mono and difluorination of benzoic acid derivatives reported by Yu and co-workers.[34] NMP = N-methylpyrrolidinone, NFTMP OTf = N-fluorotrimethylpyridinium triflate. b) Proposed coordination mode of the acidic amide directing group. c) Hydrolysis of the directing group.

While most Pd(II) catalyzed C–H fluorination reactions require significant heating, Xu and co-workers reported an C(sp^2)-H fluorination protocol in which the reaction proceeds at or close to room temperature (Scheme 8a).[36] The authors attribute these mild conditions to a putative cationic palladium nitrate catalyst $[Pd(NO_3)]^+$ generated *in situ* from $Pd_2(dba)_3$ and KNO_3, which could undergo facile C–H insertion due to its high electrophilicity. In support of this hypothesis, similar results were obtained with $Pd(NO_3)_2.2H_2O$. Use of palladium with nitrate additives has been reported for C–H activations other than fluorination.[37] The reaction is directed by O-methyl oxime ethers, which are readily prepared from the corresponding ketones or aldehydes. The protocol allows selective mono- or difluorination of aryl substrates by modifying the reaction temperature and equivalents of N-fluorobenzenesulfonimide (NFSI). The scope of the reaction was broad with respect to ring substituents, and also tolerated alkyl, cycloalkyl and aryl substitution on the oxime carbon. The utility of the chemistry was demonstrated by a gram-scale reaction performed at room temperature, followed by hydrolysis of the directing group in aqueous HCl to afford 2'-fluoroacetophenone (Scheme 8b). The reaction enabled the fluorination of vinyl C–H bonds providing access to a range of α-fluorostyrenes (Scheme 8a).



Scheme 8. a) Selective mono and difluorination of benzoic acid derivatives reported by Yu and co-workers.[34] NMP = N-methylpyrrolidinone, NFTMP OTf = N-fluorotrimethylpyridinium triflate. b) Proposed coordination mode of the acidic amide directing group. c) Hydrolysis of the directing group.

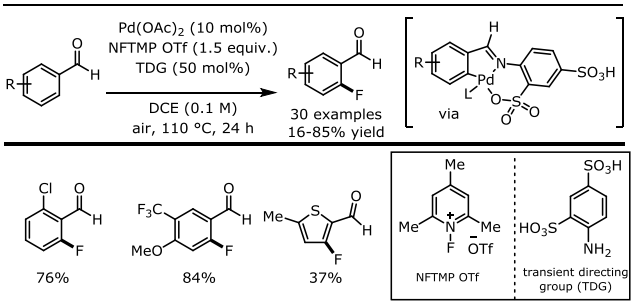
The Xu group subsequently reported a C–H fluorination of masked phenols using the cleavable 2-pyridyloxy directing group (Scheme 9a).[38] While pyridine directing groups are known to afford difluorinated products for substrates without *ortho* or *meta* substitution (Scheme 3), the 2-pyridyloxy group enabled selective monofluorination. The directing group was cleaved by treatment with methyl triflate followed by sodium in methanol, releasing the *ortho*-fluorophenol (Scheme 9b). Notably, 2-phenoxypyridines are common in agrochemicals. The protocol enabled final step C–H fluorination of diflufenican, a herbicide featuring also an amide group; the reaction proceeds exclusively *ortho* to the 2-pyridyloxy group despite the presence of multiple reactive C–H bonds (Scheme 9a).



Scheme 9. a) Selective monofluorination of masked phenols and application to late stage functionalization as reported by Xu. dba = dibenzylideneacetone. [38] [a]KNO_3 (30 mol%) was added. b) Removal of the directing group.

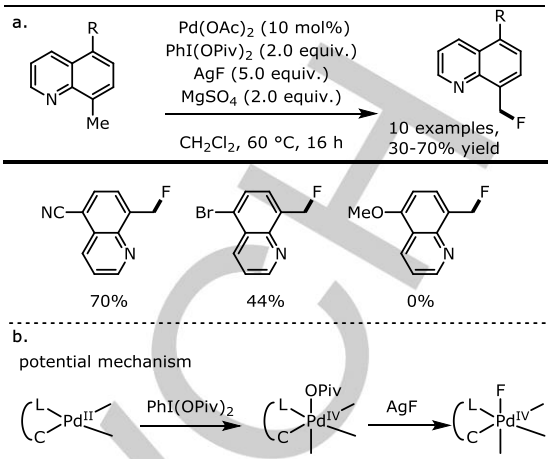
Many Pd(II) catalyzed C–H activation reactions require purpose built directing groups which must be installed and removed. One alternative is to use catalytic transient directing groups (TDGs), which reversibly form covalent links with substrates *in situ* to promote C–H activation.[39] Sorensen and co-workers reported a Pd(II) catalyzed C–H fluorination of benzaldehydes, using an orthanilic acid derived TDG (Scheme 10).[40] The ligand condenses onto the substrate to form an imine, which can bind

to palladium through both the nitrogen and the sulfonate oxygen. Post-functionalization, the imine is hydrolyzed to release the benzaldehyde. No product formation was observed in the absence of TDG. While many C-H activation procedures using TDGs require acidic solvents such as hexafluoroisopropanol (HFIP) to facilitate hydrolytic turnover of the TDG, Sorensen proposes the sulfonic acid moiety of the TDG itself to be sufficient for this purpose. The scope of the procedure demonstrates electron-withdrawing ring substituents to be well tolerated, but not electron donating groups. The study was limited to *ortho* or *meta* substituted substrates, likely to avoid difluorination.



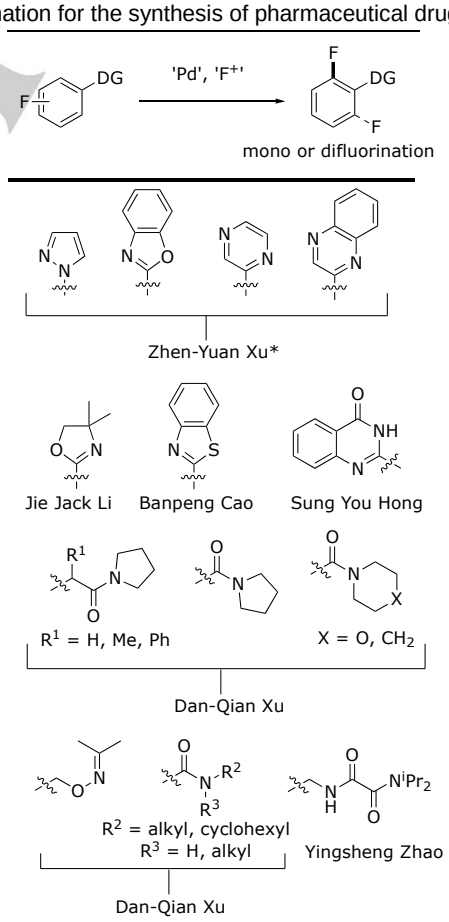
Scheme 10. C–H Fluorination of benzaldehydes enabled by a transient directing group reported by Sorensen and co-workers.[40] DCE = 1,2-dichloroethane.

To this point, all C–H fluorinations employed electrophilic N-F reagents acting both as oxidant and fluorine source. In 2012, the Sanford group reported a Pd(II) catalyzed C–H fluorination of 8-methylquinolines using the nucleophilic fluorine source AgF, a process requiring the stoichiometric hypervalent iodine oxidant (Scheme 11a).[41] The use of nucleophilic fluorine sources can be advantageous especially for applications to C–H ^{18}F-fluorination because cyclotron-produced ^{18}F-fluoride is preferred over electrophilic N-^{18}F reagents that are prepared from [^{18}F]F_2 and made available in lower molar activity. The reaction is proposed to operate by initial oxidation of Pd(II) to Pd(IV) by the hypervalent iodine reagent, followed by ligand exchange with fluoride to furnish the putative Pd(IV) fluoride complex (Scheme 11b). Fluoride sources other than AgF including TBAF, KF and CsF afforded no fluorinated product, however CsF could be used when combined with AgOTf. A range of 8-methylquinolines underwent fluorination, with halogens and electron withdrawing groups well tolerated. Methoxy substitution resulted in no product formation.



Scheme 11. a) C–H Fluorination using a nucleophilic fluorine source reported by Sanford and co-workers. b) Suggested reaction mechanism.[41] OPiv = pivalate.

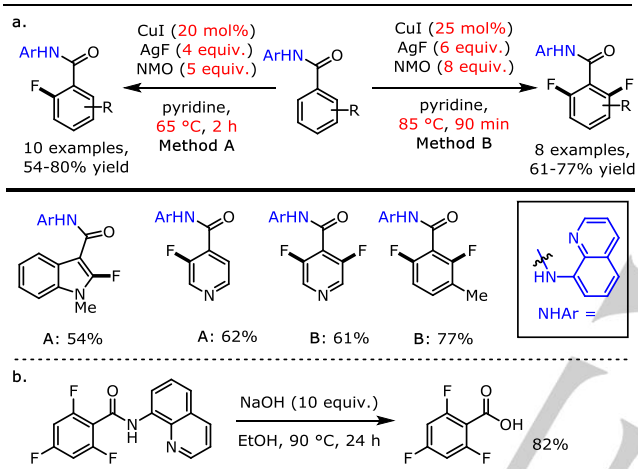
In addition to those discussed, various other directing groups have been reported for aryl C–H fluorination with electrophilic fluorination reagents (Scheme 12).[42],[43],[44],[45],[46],[47][48] These include a diverse range of N-heterocycles and amides, motifs commonly encountered in medicinal chemistry.[49] This suggests that native motifs might be used as handles to direct late stage C–H fluorination for the synthesis of pharmaceutical drugs.



Scheme 12. Diverse directing groups for Pd(II) catalyzed aryl C–H fluorination.[42],[43],[44],[45],[46],[47],[48]

2.2. Directed C(sp^3)-H fluorination via high valent copper fluorides

Copper catalyzed directed C–H functionalization's are reported in the literature, but have received less attention than their palladium counterparts.[50] High valent Cu(III) species share many features in common with high valent Pd(IV) species, both participating in similar carbon-carbon, carbon-heteroatom and carbon-fluorine bond forming reductive eliminations, and both stabilized by rigid chelating ligands.[51],[52]In 2013, Daugulis and co-workers reported the first example of Cu-catalyzed C–H fluorination. The reaction directed by an 8-aminoquinoline amide was performed with CuI, AgF and *N*-methylmorpholine N-oxide (NMO) in pyridine at 65 °C (Scheme 13).[53] This C–H fluorination is proposed to proceed via C–F reductive elimination from a high oxidation state Cu(III) fluoride complex.



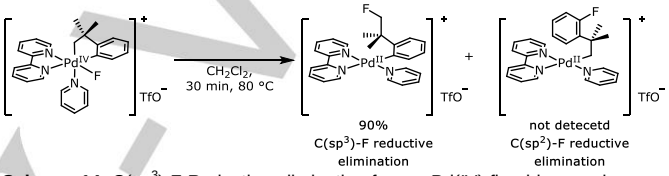
Scheme 13. a) Copper catalyzed C–H fluorination with nucleophilic fluoride reported by Daugulis and co-workers. NMO = N-methylmorpholine-N-oxide. b) Removal of the directing group.[53]

Daugulis and co-workers reported that selective mono or difluorination can be achieved by adjusting the reaction temperature and reagent equivalents (method A vs method B, Scheme 13). In contrast to palladium catalyzed methods, *ortho*-fluorination in the presence of *meta* substituents can be achieved under these conditions, resulting in three contiguous ring substituents. The method tolerates indoles and pyridines, which are uncommon in C–H fluorination under palladium catalysis. The directing group was removed upon heating with sodium hydroxide in ethanol (Scheme 13b).

2.3 Directed C(sp^3)-H fluorination via high valent palladium fluorides

The activation of C(sp^3)-H bonds by Pd(II) catalysis is generally more challenging than for C(sp^2)-H bonds. The greater conformational flexibility of sp^3 scaffolds results in a higher entropic penalty for cyclopalladation. In addition, C(sp^2)-H functionalization is preceded by pre-coordination of palladium to the arene π-system, not possible for alkane C(sp^3)-H functionalization.[54] Benzylic C(sp^3)-H bonds, and C(sp^3)-H bonds adjacent to heteroatoms generally undergo more facile Pd(II) insertion than other C(sp^3)-H bonds, due to the relative weakness of these bonds, and their proximity to an aromatic system or lone pair respectively.[54][55] Bidentate directing groups have proven to be particularly effective in promoting difficult C(sp^3)-H activation.

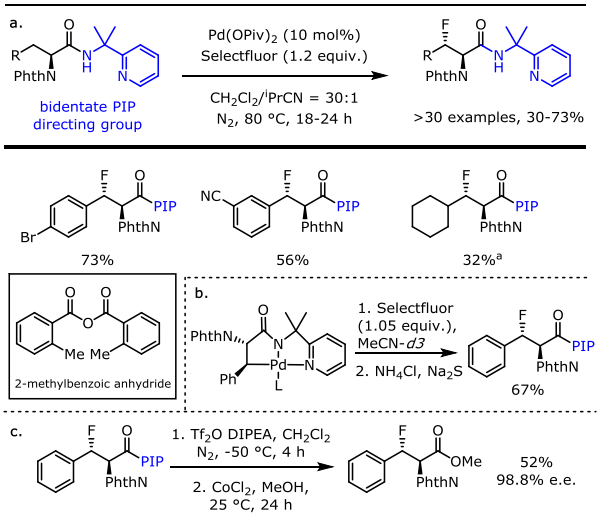
The Sanford group has studied C(sp^3)-F bond formation from alkyl Pd(IV) fluoride complexes (Scheme 14).[17] Their data suggest that C(sp^3)-F bond formation occurs via a mechanism similar to that for C(sp^2)-F bond formation from aryl Pd(IV) fluorides, that is reductive elimination from a cationic pentacoordinate Pd(IV) fluoride complex. While either alkyl C–F or aryl C–F bond formation is conceivable from Sanford's Pd(IV) fluoride complex, the product of alkyl C–F coupling is observed exclusively.



Scheme 14. C(sp^3)-F Reductive elimination from a Pd(IV) fluoride complex as reported by Sanford and co-workers.[17]

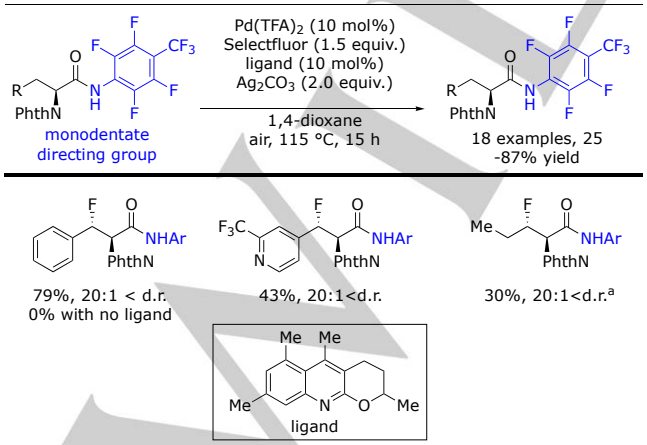
The Shi group[56] reported Pd(II) catalyzed C(sp^3)-H fluorination of N-phthaloyl α-amino acid derivatives, affording the *anti*-fluorinated products with excellent diastereoselectivity (Scheme 15a). Shi uses the strongly binding bidentate 2-(pyridine-2-yl)-isopropylamine (PIP) auxiliary to direct fluorination, proposing the steric congestion caused by the *geminal* dimethyl of the auxiliary promotes C–F reductive elimination from the putative Pd(IV) complex. The reaction is proposed to proceed via the *trans*-substituted 5-membered palladacycle, with subsequent oxidative fluorination and stereoretentive C–F reductive elimination to afford the *anti*-fluorinated products.[57] In a control stoichiometric experiment, an isolated *trans*-substituted palladacycle afforded the *anti*-fluorinated product (Scheme 15b).

A wide range of phenylalanine derivatives with different ring substituents performed well in the reaction. Yields for such substrates, in which a benzylic C–H is present, were higher than those for aliphatic substrates. Yields for aliphatic substrates were slightly improved by the addition of 2-methylbenzoic anhydride. Following fluorination, the PIP directing group was removed without erosion of d.r. and e.e. (Scheme 15c).



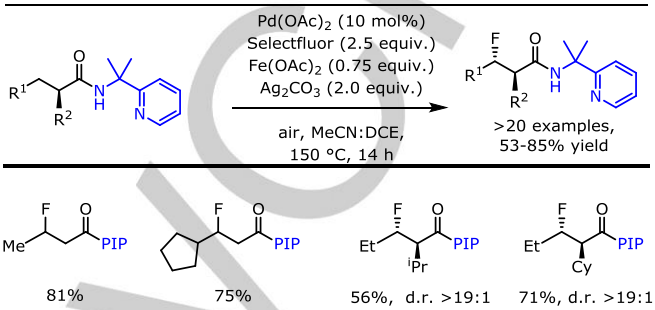
Scheme 15. a) Diastereoselective fluorination of N-phthaloyl-α-amino acids reported by the Shi group.[56] [a]20 mol% 2-methylbenzoic anhydride, and $Pd(OAc)_2$ instead of $Pd(TFA)_2$. b) Stoichiometric fluorination of an isolated palladacycle, showing stereoretentive C–F bond formation. c) Removal of the directing group. DIPEA = diisopropylethylamine.

At the same time as Shi, the Yu group reported C(sp^3)-H fluorination of N-phthaloyl α-amino acid derivatives.[58] Instead of a bidentate auxiliary, Yu's protocol uses a monodentate acidic amide auxiliary in combination with an external quinoline-derived ligand (Scheme 16). In many Pd(II) C–H activations, external ligands are ineffective as the strongly binding directing group of the substrate outcompetes the ligand for binding to palladium. However, in Yu's protocol the acidic amide is only a weak coordinator to palladium. In addition, the monodentate directing group leaves a vacant coordination site on palladium, that can be occupied by external ligands.[59] Indeed, the effect of the ligand is stark, considering the fluorinated phenylalanine derivative is obtained in 83% yield in the presence of 10 mol% of the quinoline ligand, while no product is observed in its absence. A range of N-phthaloyl α-amino acid derivatives underwent fluorination with excellent diastereoselectivity. As with the work of Shi, aliphatic substrates gave lower yields than benzylic substrates.



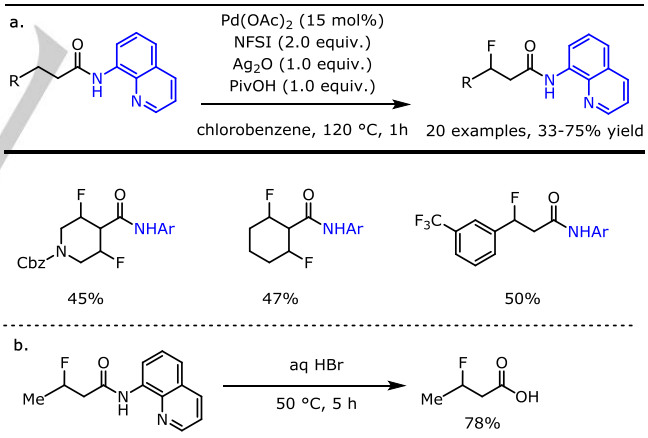
Scheme 16. Diastereoselective fluorination of N-phthaloyl-α-amino acids, promoted by a quinoline derived external ligand, as reported by the Yu group.[58] [a]20 mol% ligands and 1 equiv. of $KHCO_3$ used.

Fluorination of unactivated aliphatic C–H bonds has been reported by the Ge group, using the PIP auxiliary developed by Shi (Scheme 17).[60] Both a silver and iron additive are required to achieve good yields of the products, although their roles are unclear. Excellent diastereoselectivity was observed for substrates with α-substitution, consistent with the work of Yu and Shi on of N-phthaloyl α-amino acids. [56],[58]



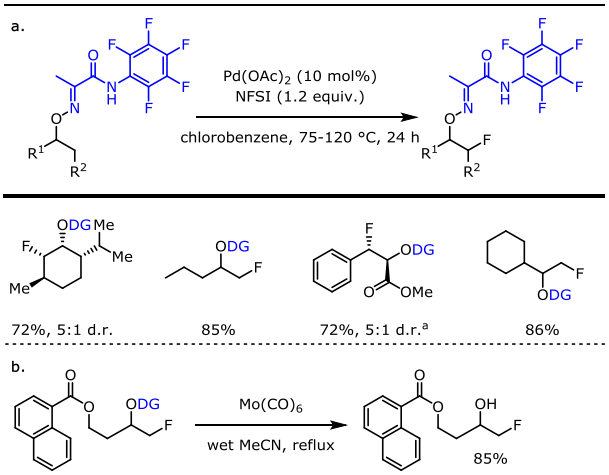
Scheme 17. Fluorination of unactivated C(sp^3)-H bonds directed by the bidentate 2-(pyridine-2-yl)-isopropylamide (PIP) auxiliary reported by Ge and co-workers.[60]

The Xu group used the bidentate 8-aminoquinoline auxiliary for both benzylic and aliphatic C–H fluorination (Scheme 18).[61] Similarly to various other C(sp^3)-H fluorinations, addition of a silver(I) salt was found to be essential for good yields. Notable examples in the scope of this reaction include the fluorination of a cyclohexyl and a Cbz-protected piperidine. The amide can by hydrolyzed to afford the corresponding acid in good yield without loss of the β-positioned fluorine.



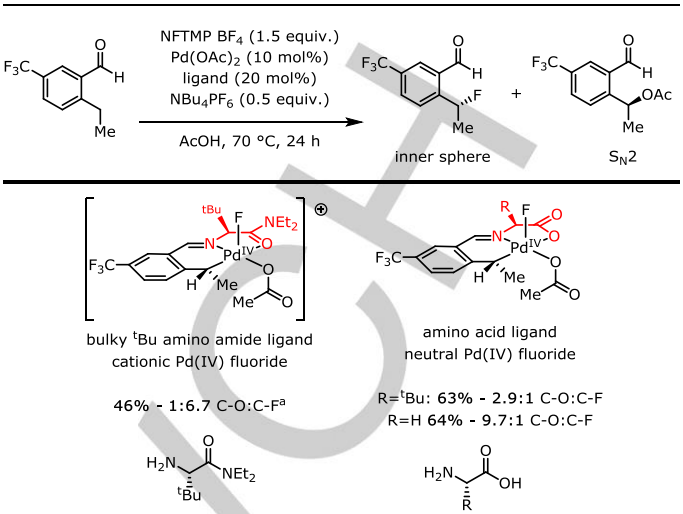
Scheme 18. a) Fluorination of alkyl and benzylic C–H bonds directed by bidentate 8-aminoquinoline amides, reported by Xu.[61] b) Hydrolysis of the directing group. Cbz = carboxybenzyl, NFSI = N-fluorobenzenesulfonimide.

The Xu group also reported fluorination of aliphatic and benzylic C–H bonds directed by masked alcohols (Scheme 19).[48] The *N*,*N*-bidentate oxime directing group promotes fluorination at primary methyl and methylene positions. Removal of the directing group with $Mo(CO)_6$ affords β-fluoroalcohols.



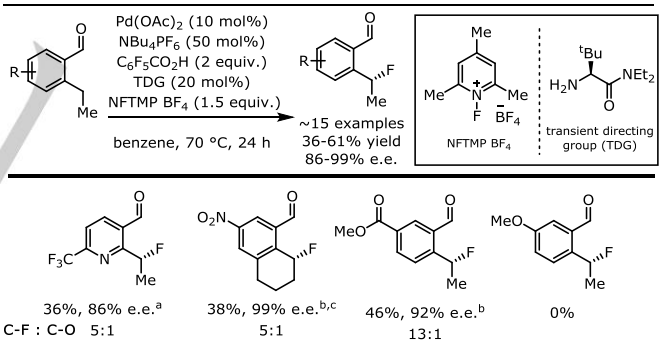
Scheme 19. a) Directed fluorination alkyl and benzylic C–H bonds of masked alcohols reported by Xu.[48] b) Directing group removal. [a]Ag_2CO_3 (2.0 equiv) and L-leucine (10 mol%) also added. NFSI = N-fluorobenzenesulfonimide,

In 2018, Yu and co-workers reported the first general enantioselective electrophilic C(sp^3)-H fluorination, through use of a chiral α-amino amide transient directing group with benzaldehyde substrates, affording enantioenriched benzyl fluorides (Scheme 20). The bulky amino amide condenses on the aldehyde, controlling the stereochemistry of the irreversible enantiodetermining cyclopalladation, and favoring C–F reductive elimination from the Pd(IV) fluoride over a competing C-O bond forming pathway. In contrast, when α-amino acid ligands were used, C-O bond formation with the carboxylic acid co-solvent dominated. As discussed previously, literature precedence supports C–F reductive elimination occurring from pentacoordinate cationic Pd(IV) fluorides. Using an α-amino amide ligand such a complex could form, favoring C–F bond formation. However, the complex ligated by the α-amino acid is neutral, slowing down C–F reductive elimination and giving way to C-O bond formation. The C-O product has the opposite stereochemistry to the C–F product, and so is thought to form through an S_N2 outer sphere attack on the Pd(IV) complex, while C–F bond formation proceeds through a stereoretentive reductive elimination. The bulky ^{t}Bu group of the ligand is essential for promoting the C–F over C-O bond formation, in agreement with previous work on C(sp^3)-F reductive elimination from high valent Pt and Pd.[57]



Scheme 20. The effect of different ligands on C-O vs C–F product distribution in the Yu's enantioselective benzylic C–H fluorination, and mechanistic rational as to the origin of the effect showing proposed cationic and neutral Pd(IV) fluoride intermediates.[15] [a]10% AcOH in benzene used as solvent.

Under these conditions a range of substrates underwent benzylic fluorination with high enantioselectivity and moderate yields (Scheme 21). Electron withdrawing ring substituents are well tolerated as is a pyridine ring, while an electron donating *meta* methoxy resulted in no product formation. An unsubstituted phenyl ring gave rise to *ortho* aryl C–O bond formation, and hence it appears a blocking group is required to prevent aryl C–H activation.

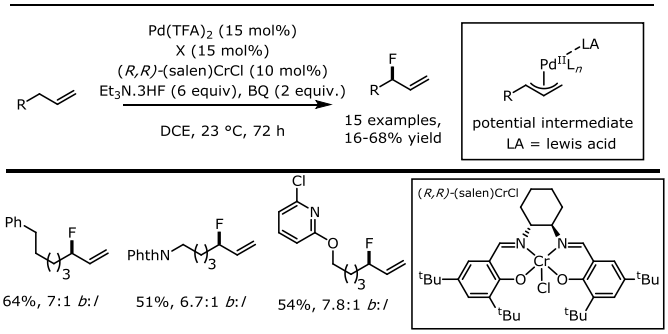


Scheme 21. Enantioselective benzylic C–H fluorination with a chiral transient directing group, reported by Yu and co-workers.[15] [a] Yield determined by ^{1}H NMR due to volatility. [b] CH_2Cl_2 used as solvent. [c]25 mol% ligand used.

2.4. C(sp^3)-H fluorination via Pd(II) π-allyl complexes

In 2013, the Doyle group reported a palladium catalyzed allylic C–H fluorination of terminal alkenes.[62] Distinct from the work discussed hitherto, there is no evidence that reaction proceeds via reductive elimination from a high valent palladium fluoride complex. Instead, coordination of the palladium to the alkene, and subsequent oxidation generates a Pd(II) π-allyl species, which can engage fluoride to furnish the allylic fluorides. The *bis*-sulfoxide ligand, a derivative of the ligand found in White's catalyst,[63] is believed to facilitate allylic C–H cleavage, while the chromium salen co-catalyst might act as a Lewis acid to

increase the electrophilicity of the intermediate palladium π-allyl complex.[64],[65],[66]

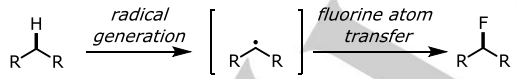


Scheme 22. Allylic C–H fluorination of terminal alkenes reported by Doyle and co-workers.[62] BQ = benzoquinone, DCE = dichloroethane, TFA = trifluoroacetate.

In Doyle's protocol, the fluorinated products are obtained with good regioselectivity, with branched:linear ratios generally exceeding 6:1. The method displays good functional group compatibility, tolerating amides, esters, heterocycles and an alkyl bromide. In addition, the use of fluoride rather than electrophilic fluorine reagents is advantageous due to reasons previously discussed. Although White and co-workers have developed enantioselective allylic C–H functionalization protocols with enantioenduction from chiral salen complexes, Doyle and co-workers report formation of racemic allyl fluorides.

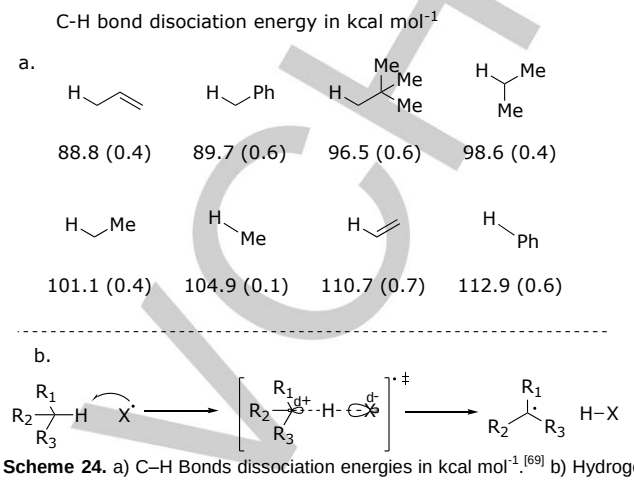
3. C–H Fluorination via the intermediacy of carbon-centered radicals

In addition to transition metal insertion, the most studied alternative strategy for C–H fluorination is via the intermediacy of carbon-centered radicals. These reactions proceed via a common mechanism, consisting of radical generation by either hydrogen atom transfer (HAT), stepwise electron transfer-proton transfer (ET-PT) or proton coupled electron transfer (PCET), followed by fluorine atom transfer to the nucleophilic carbon radical from an N-F reagent (section 3.1) or a metal fluoride complex (section 3.2) (Scheme 23).



Scheme 23. General mechanism for radical C–H fluorination.

Regioselectivity in radical C–H fluorination is less predictable than in directed Pd(II) catalysis and varies between protocols, however some key factors are known to contribute.[67] Consistent with bond dissociation energies (BDEs), alkyl, benzylic and allylic C–H bonds are reactive while aryl and vinyl C–H bonds are inert (Scheme 24a). In addition to BDEs, the polar effect is commonly invoked to rationalize regioselectivity, and manifests in the kinetic preference for hydrogen abstraction at more hydridic C–H bonds by electrophilic hydrogen atom abstracting species. This is due to stabilization of the positive charge building up on the substrate in the HAT transition state (Scheme 24b).[68] Steric effects also contribute, with large hydrogen abstracting species favoring less hindered C–H bonds.[68]



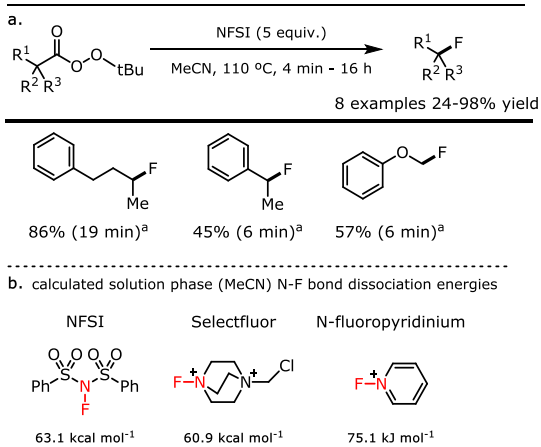
Scheme 24. a) C–H Bonds dissociation energies in kcal mol^{-1}.[69] b) Hydrogen atom transfer transition state showing the origin of the polar effect.

Methods using either electrophilic or nucleophilic fluorine sources have been developed, although electrophilic fluorination is more prevalent. Methods using electrophilic fluorine sources are split into non-photocatalytic, photocatalytic, and directed methodologies.

3.1. Radical C–H fluorination with electrophilic fluorine sources

3.1.1 Non-photocatalytic methods

A discovery that preceded the rapid development of radical C–H fluorination and the renaissance of the wider field of radical fluorination was made by the Sammis group, who reported that carbon radicals, generated via decarboxylation of peresters, react with electrophilic N–F reagents to afford the corresponding fluorinated products (Scheme 25a).[70] Sammis exploited the calculated low N-F bond dissociation energies of 63.1 and 60.9 kcal mol^{-1} (in MeCN) for NFSI and Selectfluor respectively, that suggest potential as fluorine atom transfer reagents (Scheme 25b). *N*-Fluoropyridinium, commonly used in Pd(II) catalyzed C–H fluorination, was calculated to have a higher BDE of 75.1 kcal mol^{-1}. Experimentally, *N*-fluoropyridinium salts failed to react,[70] and therefore have been less frequently considered as fluorine atom source.[71] Fluorine atom transfer to radicals was known long before Sammis work, but these transformations were carried out with reagents such as fluorine gas,[72],[73] hypofluorites,[74] and XeF_2,[75] all requiring expert handling procedures.

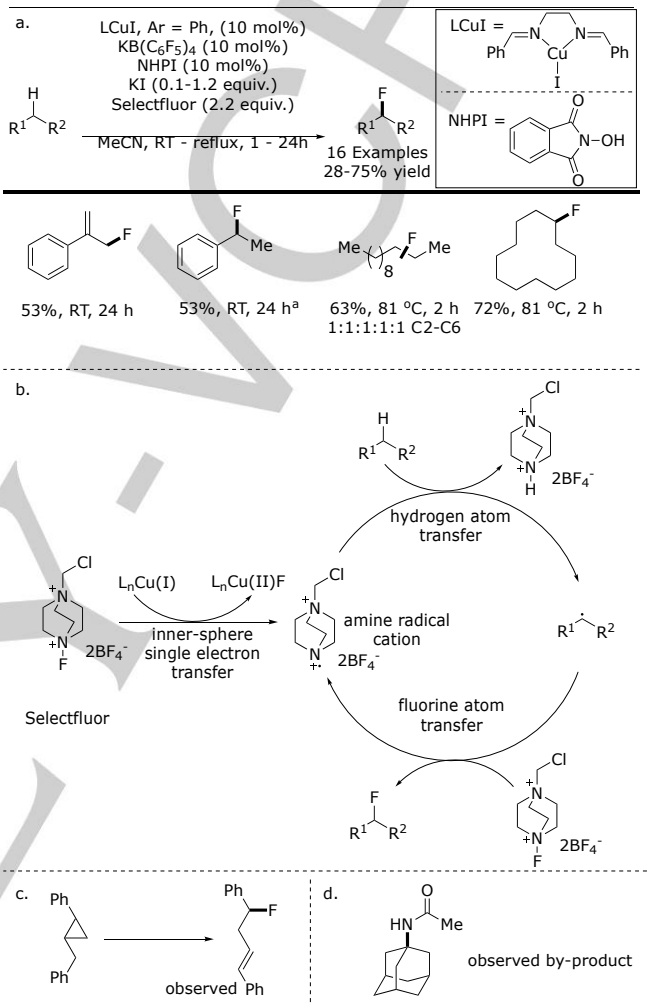


Scheme 25. a) Decarboxylative fluorination of peresters reported by Sammis and co-workers.[70] [a] ^{1}H NMR yield. b) Calculated N-F bond dissociation energies of various electrophilic fluorinating agents in MeCN.

Shortly after Sammis's report, Lectka and co-workers disclosed the radical fluorination of C(sp^3)–H bonds with Selectfluor, initiated by a sub-stoichiometric Cu(I) complex (Scheme 26a).[76] Mechanistic work supported a mechanism whereby Cu(I) reduces Selectfluor by an inner sphere single electron transfer (SET) to form an amine radical cation (Scheme 26b).[77] This species abstracts hydrogen from the substrate to form a carbon radical, which abstracts fluorine from Selectfluor to afford the product and reform the amine radical cation, propagating the radical chain reaction. The intermediacy of a carbon-centered radical was supported by the opening of a radical clock substrate (Scheme 26c). A primary kinetic isotope effect of 2.0 for cyclohexane vs cyclohexane-d_{12} was observed, suggesting that HAT occurs via an early or bent transition state if it is indeed the rate-limiting step.

A range of substrates underwent C–H fluorination under these conditions, at either alkyl, allylic or benzylic positions. Cycloalkanes gave a single monofluorinated product, while regioisomeric mixtures were obtained for alkanes with multiple inequivalent C(sp^3)–H bonds. Product yields were found to be highly time dependent, with increased reaction duration resulting in product depletion. This was proposed to arise from acidification of the reaction mixture over time, promoting a Ritter-type reaction with the fluorinated product (Scheme 26d). Radical oxidation and cation capture with MeCN can't however be ruled out. Later work reported optimized conditions using potassium carbonate base, which reduced the dependence of yield on reaction duration.[77]

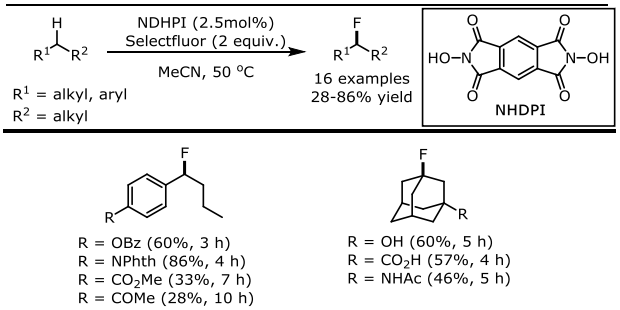
Lectka and co-workers also describe the selectivity for mono- fluorination over polyfluorination as a manifestation of the polar effect. Due to the electrophilicity of the amine radical cation (Scheme 26b), hydrogen abstraction by this species is kinetically favored at more hydridic C–H bonds. Abstraction is therefore favored from the substrate rather than from the fluorinated product, likely due to the electronegativity of fluorine. It is striking how this polar effect appears to operate over multiple bonds, with even large cycloalkanes undergoing selective monofluorination (Scheme 26a). The polar effect also accounts for preferential fluorination distal to electron withdrawing groups. Similar selectivity for hydrogen abstraction distal from electron withdrawing groups by amine radical cations has been reported by Minisci in free radical chlorination reactions.[68]



Scheme 26. a) Letcka's Cu(I) initiated radical benzylic and aliphatic C–H fluorination.[76] Yields determined by ^{19}F NMR. NHPI = N-hydroxyphthalimide. [a]No KI. b) Proposed catalytic cycle showing the initiator to be Cu(I), and the amine radical cation as the radical chain carrier. c) Opening of a radical clock under Lectka's reaction conditions. d) Ritter-type by-product, potentially resulting from reaction of the fluorinated product with MeCN.[76]

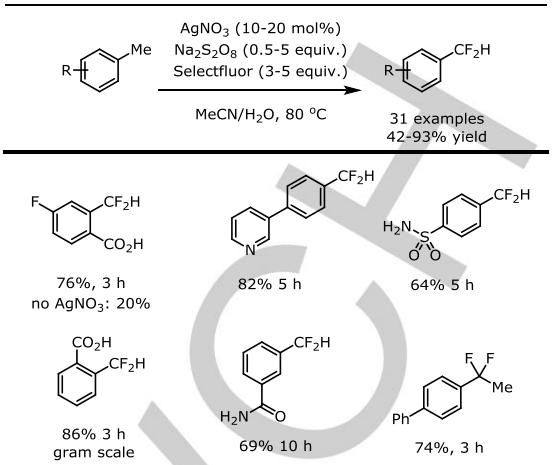
Subsequent to Lectka's report, many similar protocols for radical C–H fluorination were disclosed, featuring an N–F reagent, an initiator or HAT catalyst, and MeCN as solvent. Due to these similarities, some of the points discussed for Lectka's Cu(I) initiated system are relevant to these other protocols. This includes a strong time dependence on product distribution due to formation of Ritter-type by-products, and selectivity for mono- over polyfluorination.

The Inoue group reported that the combination of the *N*-oxy radical precursor *N*,*N*-dihydroxypyromellitimide (NDHPI) with Selectfluor in MeCN enables benzylic and aliphatic C–H fluorination (Scheme 27).[78] The authors propose that the *N*-oxy radical abstracts a hydrogen from the substrate to generate the carbon-centered radical. The H-atom abstracting capacity of related *N*-oxy radicals is well documented in radical C–H oxidations.[79] A stark difference in yield was observed with different electrophilic fluorinating agents, Selectfluor performing well while NFSI and *N*-fluoropyridinium triflate resulted in no product formation. Inoue's protocol[78] displayed good functional group tolerance, including carboxylic acids, tertiary alcohols, protected amines, alkyl bromides and cyanides.



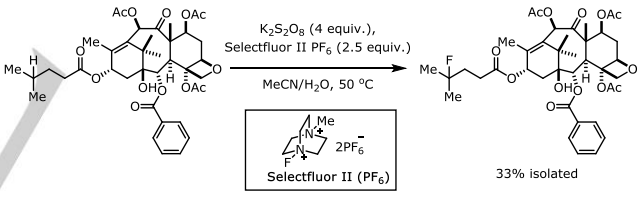
Scheme 27. Inoue's N-oxy radical catalyzed method for aliphatic and benzylic C–H fluorination.[78]

Tang and co-workers developed a process enabling double benzylic C–H fluorination to convert toluene derivatives into difluoromethyl arenes; the method used catalytic silver(I) nitrate, sodium persulfate, and Selectfluor (Scheme 28).[80] The authors propose that Ag(I) is oxidized to Ag(II) by $Na_2S_2O_8$, then Ag(II) oxidizes a benzylic C–H bond, ultimately forming the benzyl radical which is trapped by Selectfluor. This process can occur a second time to afford the difluorinated product. The difluorinated product was formed in the absence of silver, however in lower yield (20% vs 76% for 4-fluoro-2-methyl-benzoic acid (Scheme 28)). Reagent equivalents and reaction duration were adjusted for different substrates to minimize the formation of mono- and trifluorinated products, but under individually optimized conditions selectivity for the difluorinated product was good. A solvent mixture of water/MeCN was found to be essential, with no fluorinated products yielded from anhydrous MeCN. The protocol tolerates amides, carboxylic acids, halides and selected heterocycles, and was demonstrated on gram-scale. Secondary benzylic positions also underwent difluorination. Substrates with carbonyl groups at the *ortho* position reacted faster, which the authors attribute to coordination to the silver(II) catalyst. This approach is distinct from most contemporary methods for difluoromethyl arene preparation which rely on cross coupling of pre-functionalized aryl precursors.[81]



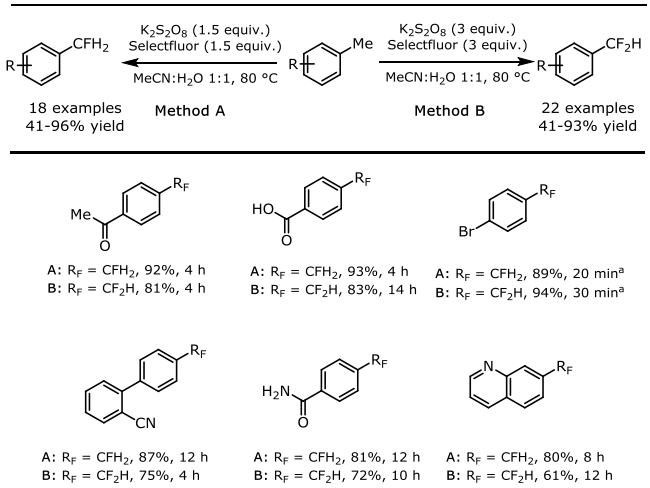
Scheme 28. Tang's silver catalyzed production of difluoromethylated arenes via oxidative active of benzylic C–H bonds.[80]

Tang later reported a similar system for aliphatic C–H fluorination, persulfate and Selectfluor II in the absence of silver salt. The authors proposed homolysis of the persulfate ion to the sulfate radical anion ($S_2O_8^{2-} \rightarrow 2SO_4^{\cdot}$) as the initiation process. The method enabled C–H fluorination of taxol, a densely functionalized molecule containing a double bond and free hydroxyl group. Regioselective fluorination occurred in 33% yield along with recovery of the starting material (50%), a result demonstrating the value of late stage radical C–H fluorination (Scheme 29).[82]



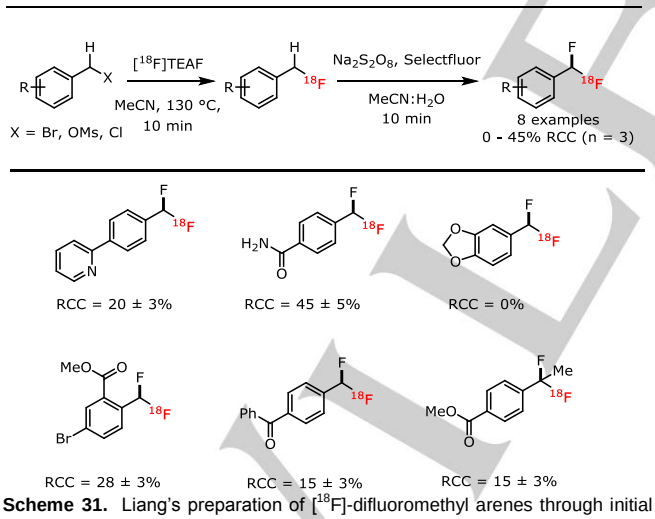
Scheme 29. Late stage aliphatic C–H fluorination of taxol, reported by Tang and co-workers.[82]

Very similar chemistry was reported by Cai and co-workers, who provided reaction conditions based on different reagent stoichiometries towards either mono- and di- benzylic C–H fluorination using potassium persulfate and Selectfluor (Scheme 30).[83] A large temperature dependence was observed, with lower temperature favoring oxidation to the benzaldehyde, while the fluorinated product was obtained almost exclusively at 80 °C. As with the work of Tang, a mixture of water and MeCN was found to be essential for high yields. The scope for both mono and difluorination includes carboxylic acids, sulfonamides, and amides. Electron donating ring substituents are not well tolerated.



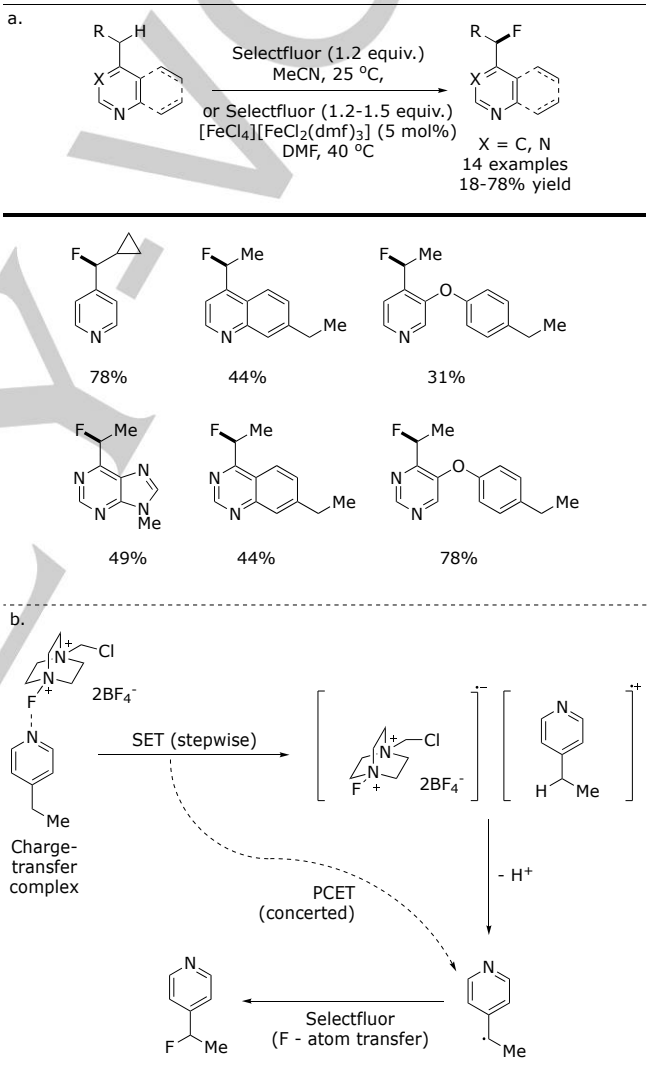
Scheme 30. Cai's selective benzylic mono- and difluorination using persulfate.[83] [a]GC yield.

Inspired by these advances, the Liang group used C–H fluorination for the ^{18}F-radiolabeling of ^{18}F-difluoromethylarenes (Scheme 31).[84] Following initial formation of [^{18}F]fluoromethylarenes by nucleophilic substitution with [^{18}F]fluoride, C–H fluorination with Selectfluor and sodium persulfate affords the desired ^{18}F-labeled products. Although ^{18}F could be introduced in either the first or second fluorination step, the use of [^{18}F]fluoride instead of [^{18}F]Selectfluor (or any other ^{18}F-labeled electrophilic fluorinating reagent) is by and large preferred due to availability and higher molar activity. Consistent with the observations of Cai, methoxylated phenyl rings were not tolerated.



Scheme 31. Liang's preparation of [^{18}F]-difluoromethyl arenes through initial nucleophilic radiofluorination of a *(pseudo)*halide followed by radical C–H fluorination.[84] RCC = radiochemical conversion.

While multiple methods exist for benzylic C–H fluorination, heterobenzylic fluorination has received less attention. A notable exception is the study of Van Humbeck and co-workers who reported that heterobenzylic C–H fluorination of azaheterocycles is possible at RT in the presence of Selectfluor (Scheme 32a).[85] The reaction is proposed to proceed via a charge transfer complex of Selectfluor and the substrate, a mechanism supported by UV/Vis spectrophotometry studies. Subsequent stepwise electron transfer/proton transfer or concerted proton coupled electron transfer then ensues to generate the heterobenzylic radical, which undergoes fluorination. Formation of the charge transfer complex also accounts for heterobenzylic over benzylic C–H selectivity. A range of heteroarenes underwent heterobenzylic fluorination under these conditions, including pyridines, pyrimidines and a purine derivative. The authors reported that the addition of Fe(III) complex [$FeCl_4$][$FeCl_2$(dmf)$_3$] increases yields in some cases, but did not propose a mechanistic rational for this observation.



Scheme 32. a) Selective heterobenzylic C–H fluorination with Selectfluor reported by Van Humbeck.[85] b) Proposed mechanism proceeding via a substrate-Selectfluor charge transfer complex.

A range of heterobenzylic C–H bonds were fluorinated under these conditions, including those of pyridine, pyrimidine and a purine derivative. Heterobenzylic C–H bonds were fluorinated selectively in the presence of benzylic C–H bonds. Addition of Fe(III) complex [$FeCl_4$][$FeCl_2$(dmf)$_3$] was found to increase yields

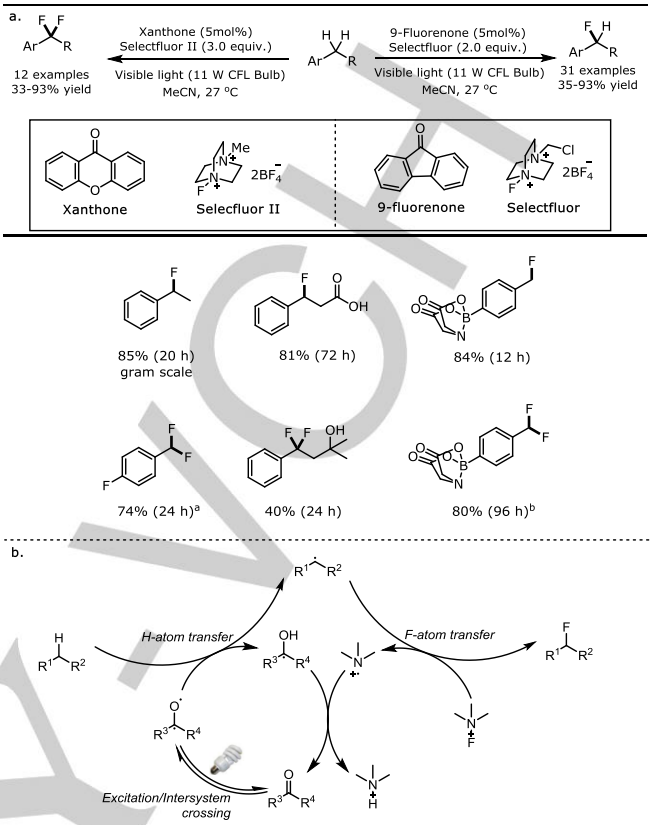
in some cases, however further analysis is required to unveil its specific function.

Various other non-photocatalytic methods for radical C–H fluorination have been reported, each using Selectfluor as a fluorine source, and MeCN (or a mix of MeCN with water) as solvent, but differing in the catalyst or initiator used. Lectka reported that C–H fluorination with Selectfluor can be achieved using BEt_3/O_2 for initiation of a radical chain reaction.[86] Lectka also showed that $Fe(acac)_2$ catalyzes benzylic monofluorination.[87] Baxter reported a Ag(I)-catalyzed, glycine mediated benzylic fluorination,[88] and Chen demonstrated that V_2O_3 is a suitable catalyst for benzylic and aliphatic C–H fluorination.[89]

3.1.2 Photocatalytic methods

Photocatalysts xanthone and 9-fluorenone, activated by visible light, were used by Chen and co-workers for selective benzylic C–H mono and difluorination (Scheme 33a). Chen proposes that the photoexcited aryl ketone abstracts a benzylic hydrogen from the substrate. The benzyl radical is then trapped by Selectfluor to form the fluorinated product and an amine radical cation. The latter abstracts a hydrogen from the photosensitizer by-product to reform the aryl ketone thereby closing the catalytic cycle. The absence of reaction with $Ir(ppy)_3$ (tris[2-phenylpyridinato-C^2,*N*]iridium(III)), which has a similar triplet energy to 9-fluorenone (ET = 55.3 kcal mol^{-1} for fluorenone vs 55.6 kcal mol^{-1} for $Ir(ppy_3)$), indicates that 9-fluorenone acts as a HAT agent, and not as an energy transferring photosensitizer (Scheme 33b).[90],[91],[92]

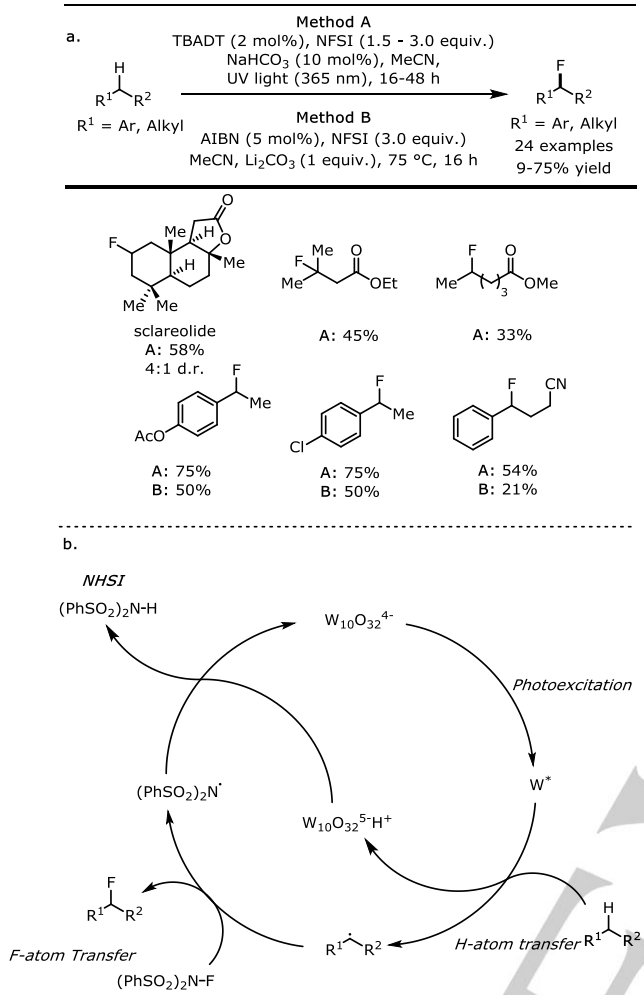
With this protocol, either the monofluorinated or *gem*-difluorinated products could be obtained selectively, depending on which photosensitizer and which fluorine source is used. Using 9-fluoreneone and Selectfluor, exclusive monofluorination was observed. Increasing reaction duration and Selectfluor equivalents resulted in an insignificant increase in yield of the difluorinated product, however by using the more electron rich photosensitizer xanthone in combination with Selectfluor II, *gem*-fluorination could be readily achieved.[93] Chen's protocol tolerates tertiary alcohols, carboxylic acids, aryl halides, and MIDA-boronates (Scheme 33a). The scalability of the protocol was demonstrated by the gram-scale monofluorination of ethyl benzene afforded the isolated product in 85% yield.



Scheme 33. a) Chen's photocatalyzed benzylic C–H mono and difluorination, CFL = compact fluorescent lamp.[93] [a] ^{19}F NMR yield. [b] 5mol% 9-fluorenone, 4 equiv. Selectfluor. b) Proposed catalytic cycle.

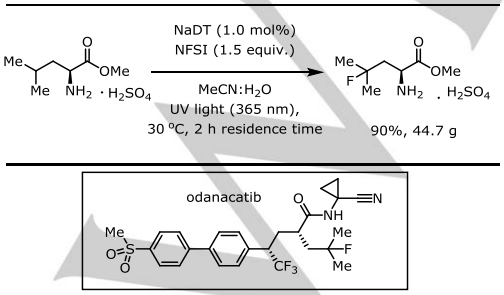
The Britton group reported a UV light promoted C–H fluorination of both aliphatic and benzylic substrates using the well-established HAT photocatalyst tetrabutyl ammonium decatungstate (TBADT), and NFSI as the fluorine atom transfer reagent (Scheme 34a).[94],[95] The photoexcited TBADT abstracts a hydrogen from the substrate to generate the intermediate carbon radical, which is trapped by NFSI (Scheme 34b). Addition of the base $NaHCO_3$ was required to avoid formation of Ritter-type acetamide by-products. Notable examples include the fluorination of amino acid derivatives, which are selectively fluorinated at the branched positions, aldehydic C–H activation to yield acyl fluorides and aliphatic fluorination of the natural products sclareolide.

Use of NFSI here is distinct from most other radical C–H fluorination protocols which employ Selectfluor. Lectka has previously shown that NFSI is ineffective as a chain carrier in BEt_3/O_2 initiated radical chain fluorination of alkyl C–H bonds.[86] However Britton shows that radical chain reactions with NFSI and AIBN initiator are possible for benzylic C–H fluorination, however with reduced yields relative to the protocol using the decatungstate catalyst (Scheme 34a).



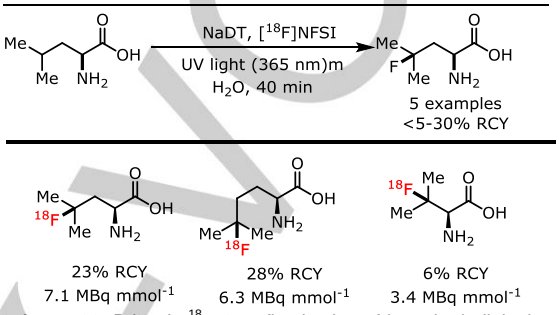
Scheme 34. a) Britton's decatungstate photocatalyzed system C–H fluorination with NFSI.[94][95]. TBADT = tetrabutylammonium decatungstate, AIBN = azobisisobutyronitrile. NFSI = N-fluorobenzenesulfonimide. b) Proposed mechanism. $W_{10}O_{32}^{4-}$ = decatungsdate anion.

A collaboration between the Britton group and Merck applied this decatungstate catalyzed process for a decagram-scale C–H fluorination of leucine methyl ester affording a precursor of Odanacatib, an investigational drug for the treatment of osteoporosis (Scheme 35).[96] The reaction was performed in a 365nm flow reactor to afford 44.7 g of product (90% yield). This single step route compares favorably to other multistep procedures towards fluoro-Leucine esters, and demonstrates how C–H fluorination can expedite synthesis.



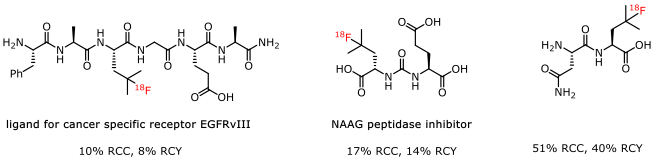
Scheme 35. Britton's in-flow, decagram-scale synthesis of an odanacatib precursor.[96] DT=decatungstate.

Britton and co-workers applied their methodology to C–H ^{18}F-fluorination of amino acids for PET applications (oncology).[97] Using [^{18}F]NFSI, a reagent developed by Gouverneur and co-workers,[98] sodium decatungstate, and 365 nm irradiation, unprotected aliphatic amino acids underwent site selective C–H [^{18}F]fluorination at branched positions. This allowed the rapid evaluation of a range of ^{18}F labelled leucine analogues without the requirement of multiple syntheses. The work culminated in the identification of [^{18}F]-5-fluorohomoleucine as a metabolic PET radiotracer for imaging human glioma and prostate cancer xenografts in mice (Scheme 36).



Scheme 36. Britton's ^{18}F C–H fluorination of branched aliphatic amino acids using NaDT as photocatalyst.[97] RCY = radiochemical yield. Specific activity in MBq mmol^{-1} also quoted. NaDT = sodium decatungstate.

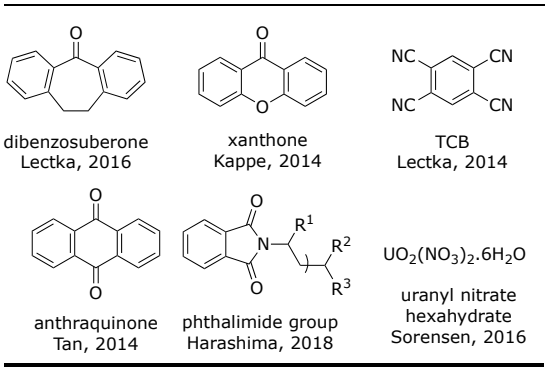
Britton and co-workers subsequently applied this [^{18}F]NFSI dependent radiofluorination to site selective C–H fluorination of leucine residues in polypeptides (Scheme 37).[99] A range of unprotected di- and tetrapeptides were ^{18}F-labeled selectively at the branched position of the leucine residue. The procedure tolerates phenylalanine residues with no sign of competing benzylic C–H ^{18}F-fluorination. The protocol compares favorably with other methods for ^{18}F labeling of peptides, which generally rely on the use of prosthetic groups, which can laborious to install and require protecting groups on the peptide. Hence this method provides a means for converting native peptides into PET imaging agent candidate, and thereby serves as an excellent demonstration of how late stage C–H fluorination can be used to accelerate advances in medicinal chemistry.



Scheme 37. Further expansion of Britton's methodology towards site-selective ^{18}F-radiolabeling of leucine residues within peptides, with toleration of benzylic C–H sites. Conditions: peptide-TFA, NaDT (2 mol%), [^{18}F]NFSI, MeCN/H_2O, hυ (365 nm), 40 min. RCC = radiochemical conversion, RCY = radiochemical yield.

Various other photocatalysts are competent for light-promoted fluorination of C–H bonds. Lectka reported the use of dibenzosuberone for selective benzylic C–H fluorination of phenylalanine residues in protected peptides.[100] This catalytic system displays interesting complementarity to the protocol of Britton.[99] Letcka's also used the photocatalyst tetracyanobenzene (TCB) with UV light for alkyl C-H fluorination, thought to operate via a photoredox mechanism.[101],[102] Kappe

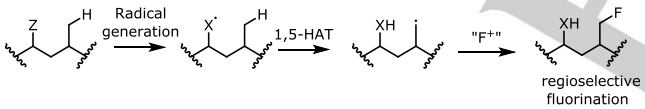
has reported benzylic C–H fluorination in flow with Xanthone (previously used by Chen).[103] A recent account by Hamashima described the C–H fluorination of various alkyl phthalimides without an external photocatalyst. Instead, the phthalimide motif acts as an internal photosensitizer.[104] Other competent photocatalysts include anthraquinone,[105] acetophenone[106] and the particularly unusual uranyl nitrate hexahydrate.[107],[108]



Scheme 38. Various other photocatalysts reported for alkyl and benzylic C–H fluorination. [99],[100],[101],[102],[103],[104],[105]

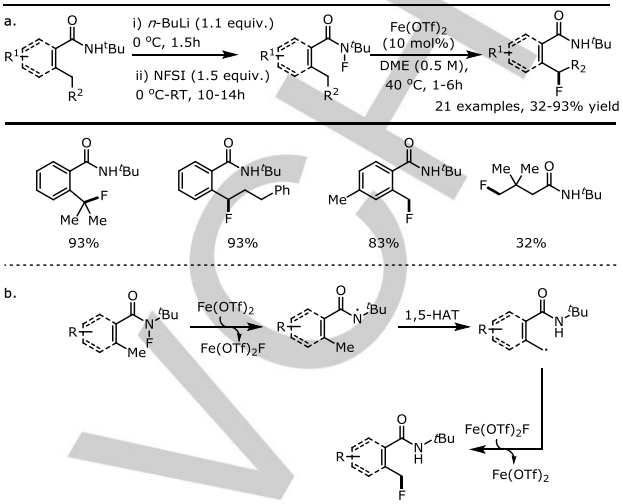
3.1.3 Directed methods

While most radical C–H fluorinations afford regioselectivity based on the relative reactivity of the different C–H bonds, directed methods have been investigated where selectivity is determined by proximity to a directing group. Generally, a heteroatom-centered radical is formed at a directing group, and a subsequent 1,5-HAT controls precise regioselectivity for the carbon-centered radical, which is trapped by a fluorinating agent (Scheme 39).



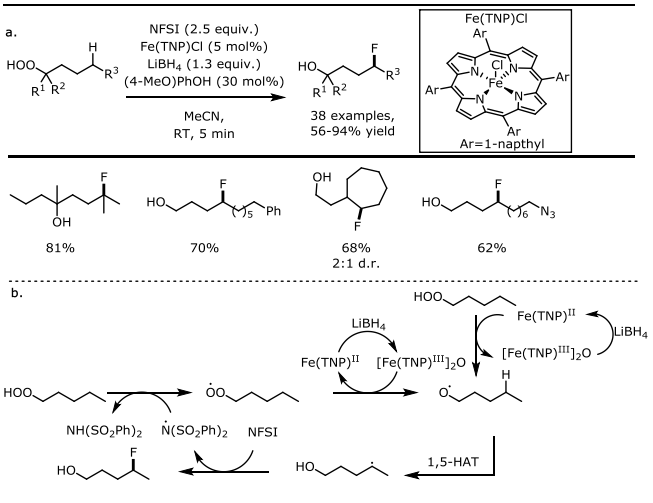
Scheme 39. General reaction mechanism for the directed radical fluorination of C–H bonds

Cook and co-workers pioneered this approach in 2016, utilizing an *N*-butyl fluoroamide, as both the directing group and fluorine source, in the presence of catalytic $Fe(OTf)_2$ in DME (Scheme 40a).[109] Mechanistically, the authors proposed that an *N*-centered radical is generated by fluorine atom abstraction with $Fe(OTf)_2$ to form an Fe(III)F salt (Scheme 40b). Analogous to Hofmann-Löffler-Freytag reaction, the carbon-centered radical is formed *via* 1,5 HAT.[110] Fluorine atom transfer from the Fe(III) fluoride to the carbon radical affords the fluorinated product and release the Fe(II) catalyst. High yields were obtained for primary, secondary and tertiary C–H bonds (Scheme 40a). The reaction remains site-selective in the presence of benzylic C–H bonds of similar bond dissociation energies, which supports the mechanistic hypothesis of radical generation via 1,5-HAT. Such selectivity would be highly challenging to achieve using non-directed radical fluorination methods. Cook demonstrates that a non-benzylic C–H bond can be fluorinated by this method, albeit in a lower yield of 32%.



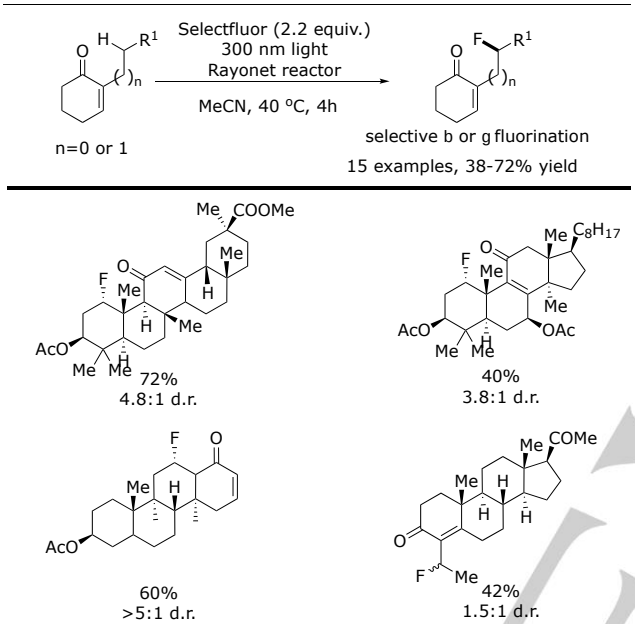
Scheme 40. Iron-Catalyzed fluoroamide directed C–H fluorination. a) Reaction conditions for the synthesis of N-F reagent and iron-catalyzed fluorination.[109] b) Proposed reaction mechanism. HAT = H atom transfer, DME = 1,2-dimethoxyethane.

Liu and co-workers published an alternative approach to regioselective sp^3 C–H fluorination utilizing the hydroperoxide functional group as a precursor of an alkoxy radical to control site selective carbon-centered radical formation (Scheme 41a).[111] High yields for δ-fluorination were obtained for secondary and tertiary alkyl C–H bonds, tolerating a range of sterically and electronically diverse hydroperoxides. The reaction proceeded regioselectively in the presence of possibly reactive benzylic and propargylic C–H bonds. Initiation by reaction of Fe^{II}(TNP) (TNP = 5,10,15,20-tetranaphthylporphyrin) catalyst with the hydroperoxide group forms the alkoxyl radical. 1,5 HAT from the alkoxyl radical provides the carbon-centered radical, which reacts with NFSI to give the product.



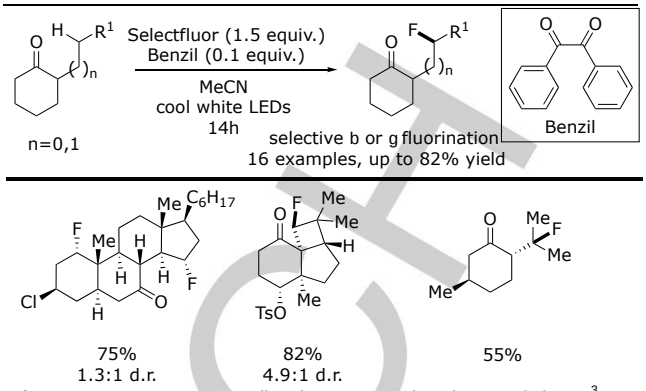
Scheme 41. a) Fe(II)-catalyzed site selective fluorination of sp^3 C–H bonds directed by alkoxyl radical reported by Liu and co-workers.[111] b) Proposed reaction mechanism. TNP = 5,10,15,20-tetranaphthylporphyrin.

Lectka and co-workers utilize photoexcitable enones to direct C–H fluorination of bioactive polycycles and terpenoid derivatives (Scheme 42).[112] In the presence of UV-light and Selectfluor, polycyclic enones underwent site selective β- and γ- fluorination. To rationalize selectivity, the authors suggest that photoexcitation generates a singlet state excited enone, which undergoes rapid intersystem crossing to the triplet state diradical enone. Regioselective intramolecular HAT then follows, generating a radical positioned β- or γ- to the enone. Site selective fluorination was achieved on steroids and bioactive polycycles with up to 65 different sp^3 C–H bonds.



Scheme 42. Photoexcitable enone-directed C–H fluorination of polycyclic terpenoid derivatives reported by Lectka and co-workers.[112]

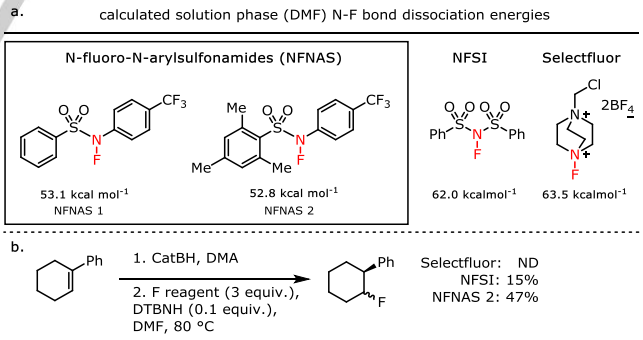
Lectka and co-workers also showed that cyclic ketones can direct β- and γ- C–H fluorination (Scheme 43).[113] This was realized with the triplet sensitizer benzil in the presence of Selectfluor under visible light activation. The authors reported that higher energy UV light with ketone directing groups resulted in no regiocontrol. In addition to enabling the fluorination of polycyclic structures, a simple cyclohexanone derivative underwent regioselective monofluorination. In contrast, the fluorination of linear substrates was not regioselective. This reaction isn't thought to proceed via photoexcitation of the ketone. Instead, the ketone is proposed to act as an intramolecular base in generation of the intermediate radical via either ET-PT or PCET. Lectka later showed that this sensitized approach was also applicable to enone directing groups, also demonstrating the protocol in continuous flow.[114]



Scheme 43. Ketones as directing groups in photocatalytic sp^3 C–H fluorination as reported by Lectka and co-workers.[113]

3.1.4 New radical fluorinating reagents

The discovery that N-F reagents such as Selectfluor and NFSI could react with alkyl radicals transformed the field of radical C–H fluorination. Future advances will depend in part on the development of new reagents. To this end, the Renaud group has recently disclosed *N*-fluoro-*N*-arylsulfonamides as a new class of radical fluorinating agents, with N-F bond dissociation energies between 7 and 10 kcal mol^{-1} lower than Selectfluor and NFSI (Scheme 44a), and reduced electrophilicity of the fluorine.[115] Such reagents should therefore favor fluorine atom transfer to radicals, minimizing competing electrophilic and single electron transfer pathways. This might increase tolerance to nucleophilic functional groups and minimize over-oxidation of intermediate radicals. Renauld demonstrated the utility of these reagents in hydroborylation-deborylative fluorination reactions (Scheme 44b), but their application in radical C–H fluorination remains to be explored.

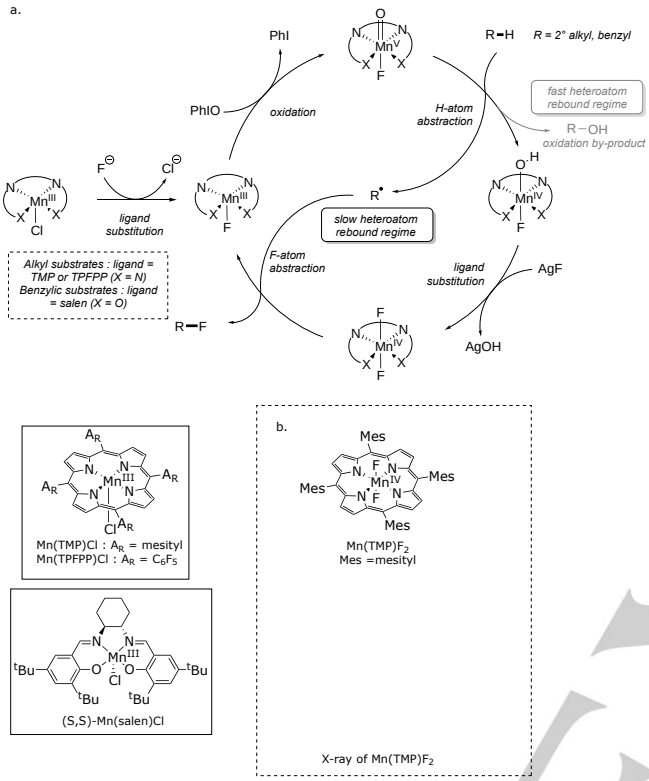


Scheme 44. a) New generation of radical fluorinating reagents with low N-F BDEs developed in the Renaud group.[115] b) Performance of different fluorinating agents in a hydroboration-deborofluorination sequence. DTBNH = di-*tert*-butylhyponitrite. DMA = dimethylacetamide. ND = not detected. GC yields reported.

3.2. C–H Fluorination with nucleophilic fluorine sources

Nucleophilic alkyl radicals readily react with electrophilic but not nucleophilic fluorine sources. However, C–H fluorination methods using fluoride reagents are highly desirable due to their lower cost, and for applications in ^{18}F-radiochemistry. Pioneering studies from Groves and co-workers demonstrated that a

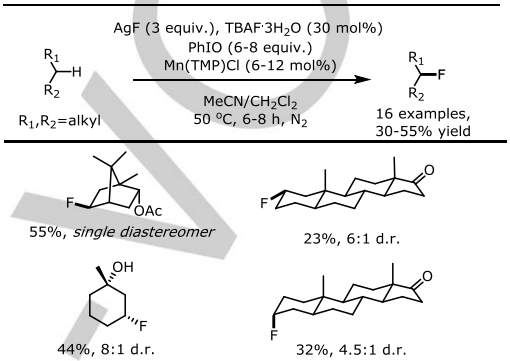
manganese porphyrin catalyst is capable to induce C–H fluorination with fluoride in the presence of PhIO, the stoichiometric oxo-transfer reagent.[116] This method inspired by halogenating metalloenzymes was applied to alkyl and benzylic C–H fluorinations and ^{18}F-radiofluorinations.[117][118]



Scheme 45. a) Catalytic cycle for the fluorination of aliphatic C–H bonds with porphyrin-derived catalysts Mn(TMP)Cl (A_R = 2,4,6-trimethylphenyl) and Mn(TPFPP)Cl (A_R = C_6H_5). A_R = mesityl, C_6F_5; R = alkyl, benzyl. b) Crystal structure of Mn(TMP)F_2, the active fluorinating agent.

Utilizing a chloromanganese(III) precatalyst with a tetradentate ligand (TMP, TPFPP or salen), a fluoride source (TBAF.3H_2O, Et_3N.3HF or AgF) and the oxidant iodosobenzene, the active oxoMn^V–F catalyst is formed (Scheme 45a).[119] This species abstracts a hydrogen atom from the substrate to form a carbon-centred radical and a Mn(IV)OH complex. Following OH to F ligand exchange at the manganese, the Mn(IV) difluoride transfers fluorine to the carbon radical, affording the product. The regioselectivity for C–H cleavage is governed by the polar effect, so the most hydridic C–H bond reacts preferentially. The steric bulk of the catalyst also influences regioselectivity. Formation of difluorinated products was negligible, also due to the polar effect. A kinetic isotope effect (KIE) of 6.1 for cyclohexane vs cyclohexane-d_{12} supports that hydrogen abstraction is the rate-determining step. The role of the Mn(IV) difluoride as the fluorinating agent was supported by DFT calculations, isolation and x-ray analysis of Mn^{IV}(TMP)F_2, and its successful use as a stoichiometric fluorinating reagent (Scheme 45b). Formation of alcohol and ketone by-products, which occur due to fast radical recombination of the hydroxymanganese species with the carbon-centered radical, is suppressed due to the fluoride ligand *trans* to hydroxide reducing the rate of C–O bond formation. However the by-products are still observed in typically 15-20% yield (Scheme 45a).[120]

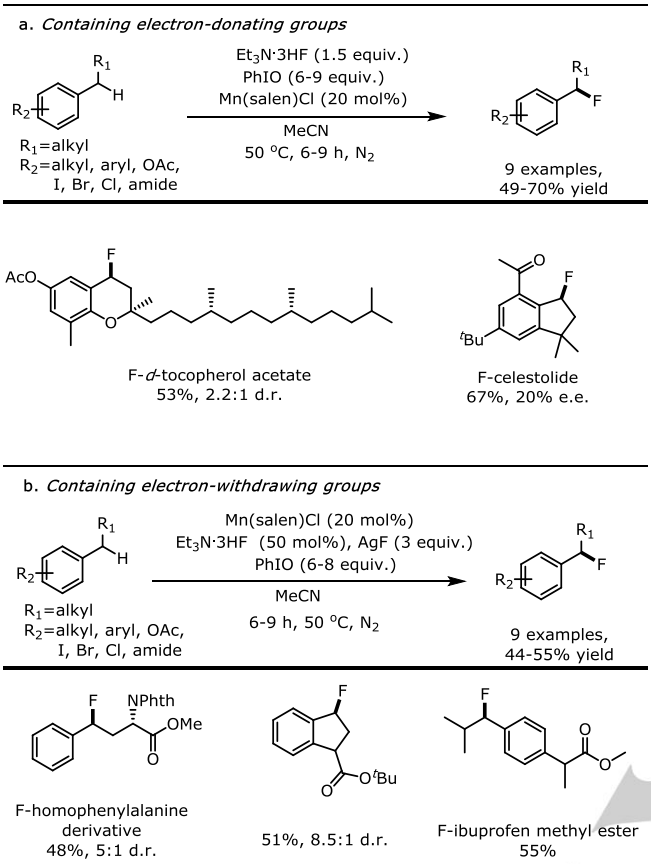
Initially, Groves reported this method for the C–H fluorination of aliphatic substrates using the porphyrin-derived Mn(TMP)Cl precatalyst (Scheme 46).[121] Steroidal natural products were fluorinated with impressive regioselectivity, distal from electron withdrawing groups. The reaction tolerates various functional groups such as 3° alcohols and ketones. Good diastereoselectivity is observed for rigid carbocycles.[119]



Scheme 46. Groves fluorination of aliphatic substrates using fluoride and Mn(TMP)Cl catalyst.[121] TMP = tetramesitylporphyrin.

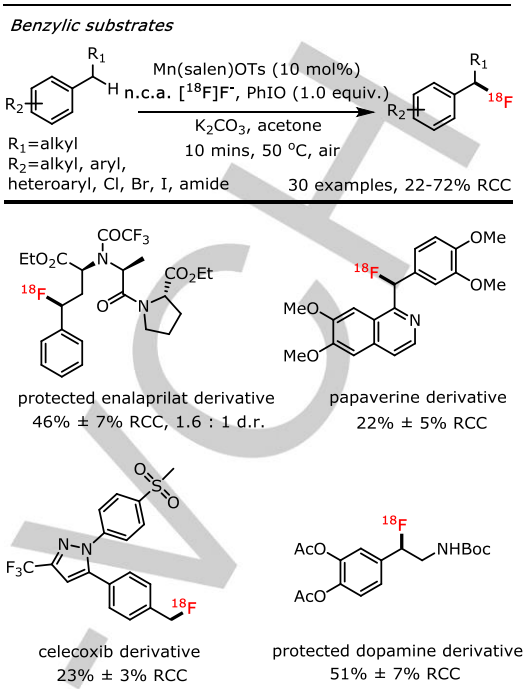
The translation of this methodology onto benzylic systems yielded roughly 1:1 mixtures of fluorination and oxidation products (benzylic alcohol and ketone), due to fast carbon radical rebound with the HOMn^{IV}(salen)F.[117] However, use of Jacobsen's Mn(salen)Cl catalyst successfully suppressed oxidation products, with F/O selectivity reaching 12:1.[122,123] Electron-rich benzylic precursors underwent efficient fluorination with Et_3N.3HF (Scheme 47a), while a combination of Et_3N.3HF and AgF was required to achieve high conversion for substrates containing electron-withdrawing groups, at the expense of the F/O ratio (Scheme 47b).

Highlighted examples of highly selective fluorination include δ-tocopherol acetate, an analogue of vitamin E (Scheme 47a), and the unnatural amino acid homophenylalanine (Scheme 47b). Moderate enantioselectivity (11–40%) was observed with F-celestolide, representing a unique case of enantioselective radical C–H fluorination. Groves commented that these results may well represent the upper limit of asymmetry in this reaction due to the early transition state and linear approach angle of the substrate with the catalyst, as determined by DFT calculations.[117]



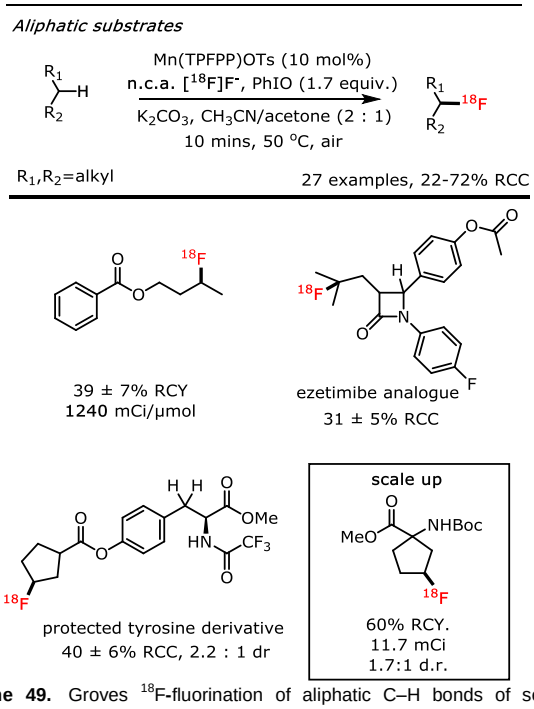
Scheme 47. Groves benzylic fluorination using fluoride and Mn(salen)Cl catalyst.[117] a) Substrates with electron donating groups. b) Substrates with electron withdrawing groups.

Nucleophilic fluorine sources are advantageous for application to ^{18}F-radiolabeling, as cyclotron-produced [^{18}F]fluoride is readily available directly, and obtained in higher specific activity than electrophilic ^{18}F-reagents, which are synthesized from [^{18}F]F_2.[6] High specific activity of radiotracers is required in some applications of PET imaging, such as measuring ligand-receptor interactions. Groves and co-workers have adapted their method for the ^{18}-radiofluorination of benzylic and aliphatic C–H bonds, with high specific activity and good radiochemical conversions. While the salen ligand still proved successful for benzylic ^{18}F-fluorination, a switch from TMP to the more oxidizing fluorinated porphyrin TPFPP was necessary to effect the transformation on aliphatic substrates.[124,125] In the radiochemical procedure, the active fluorine transfer reagent is believed to be the ^{18}F−MnIV−OH because [^{18}F]fluoride is by far the limiting reagent. Benzylic substrates with both electron-donating and electron-withdrawing groups were fluorinated with radiochemical conversions (RCCs) ranging from 20–72%, including analogues of the pharmaceuticals enalaprilat and papaverine (Scheme 48).[118] The pyrazole in the celecoxib derivative is tolerated, which is encouraging given the ubiquity of similar N-heterocycles in many pharmaceutical drugs.[32]



Scheme 48. Groves ^{18}F-fluorination of benzylic C–H bonds with [^{18}F]fluoride.[118] RCC = radiochemical conversion.

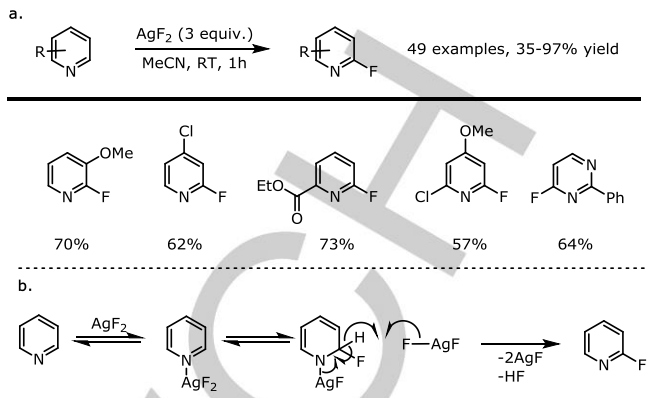
A range of biologically active substrates were radiolabeled at aliphatic positions, including amino acid derivatives and a derivative of the cholesterol lowering drug ezetimibe, with RCCs ranging from 12–67% (Scheme 49).[124] The specific activity of [^{18}F]-3-fluorobutyl benzoate was determined as 1.24 mCi mol^{-1}, which is significantly higher than obtained for C–H fluorination using [^{18}F]NFSI.[97] In addition, ^{18}F-fluorination of a protected oncological PET tracer was performed on a scale sufficient for studies on animal models, providing 11.7 mCi of labeled product.



Scheme 49. Groves ^{18}F-fluorination of aliphatic C–H bonds of selected biologically active compounds with a nucleophilic fluorine source, including the determination of specific activity, and a scale up experiment.[124] RCC = radiochemical conversion. RCY = radiochemical yield.

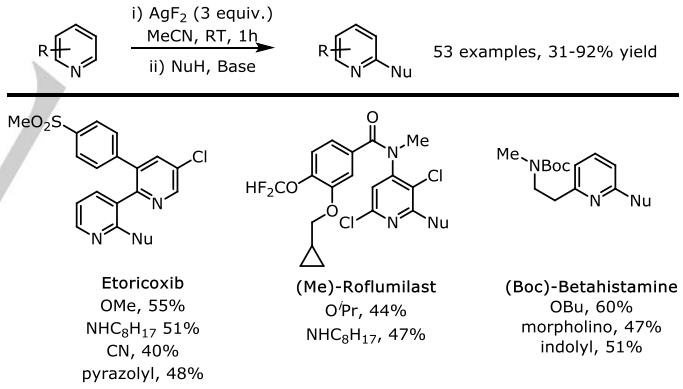
4. Miscellaneous C–H fluorination methods

Some C–H fluorinations are mechanistically distinct from those that proceed through radical intermediates or *via* metal insertion. One such method is the late-stage C–H fluorination of pyridines and diazines, published by Hartwig and co-workers (Scheme 50a).[126] This reaction utilizes AgF_2 in MeCN at room temperature, to install a fluorine substituent on pyridines and diazines exclusively at the 2-position. This process provides a remarkably mild alternative to use of fluorine gas, S_NAr or Balz-Schiemann chemistry to access these motifs. The authors proposed that the reaction proceeds with coordination of AgF_2 to the Lewis-basic nitrogen of the heterocycle, followed by a reversible addition of the [Ag]-F bond across the π system. Subsequent hydrogen atom abstraction of the silver amido-complex yields the 2-fluoropyridine derivative, 2 equivalents of silver (I) fluoride, and HF (Scheme 50b). Substitution is tolerated at the 2-, 3- and 4- position of the ring, and in all cases, the monofluorinated product is obtained selectively. When 3-substituted pyridines were used, the 2-fluoro 3-functionalized pyridine formed preferentially. The authors observed high site selectivity in the fluorination of substrates containing more than one heteroarene, with fluorination occurring on the ring with the most Lewis-basic nitrogen.



Scheme 50. a) C–H fluorination of pyridines and diazines selectively at the 2-position, reported by Hartwig.[126] b) Proposed reaction mechanism. All yields determined by ^{19}F NMR with $PhCF_3$ as an internal standard.

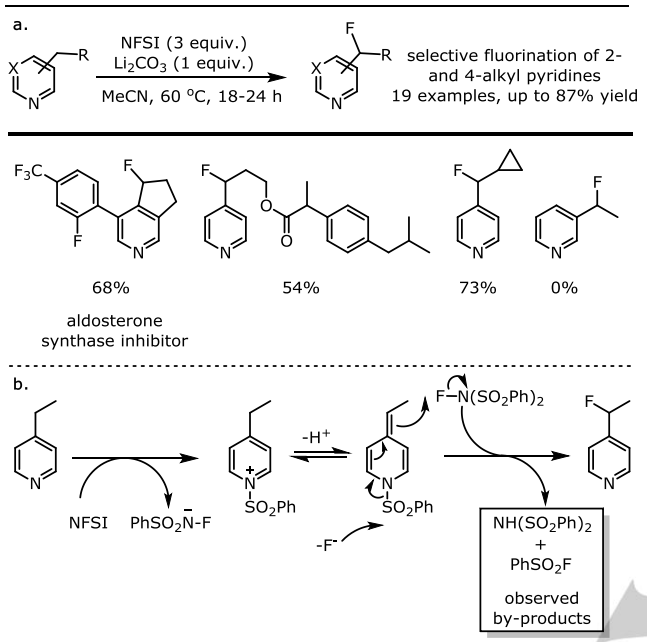
In addition to their value as motifs in biologically active molecules, 2-fluoropyridines/diazines are valuable substrates for S_NAr chemistry. The authors extended the fluorination methodology to a tandem sequence comprising the addition of AgF_2 followed by nucleophile addition (Scheme 51).[127] Compatible nulceophiles include 1^0, 2^0 and 3^0 alcohols, phenols, 1^o and 2^o amines, amides, N-heterocycles, KCN and sodium thiolate salts. The synthesis of several biologically active molecules demonstrates the utility of this method, and its value for the late stage diversification of drug molecules.



Scheme 51. Tandem C–H fluorination and S_NAr reactions of pyridines reported by Hartwig and co-workers.[127]

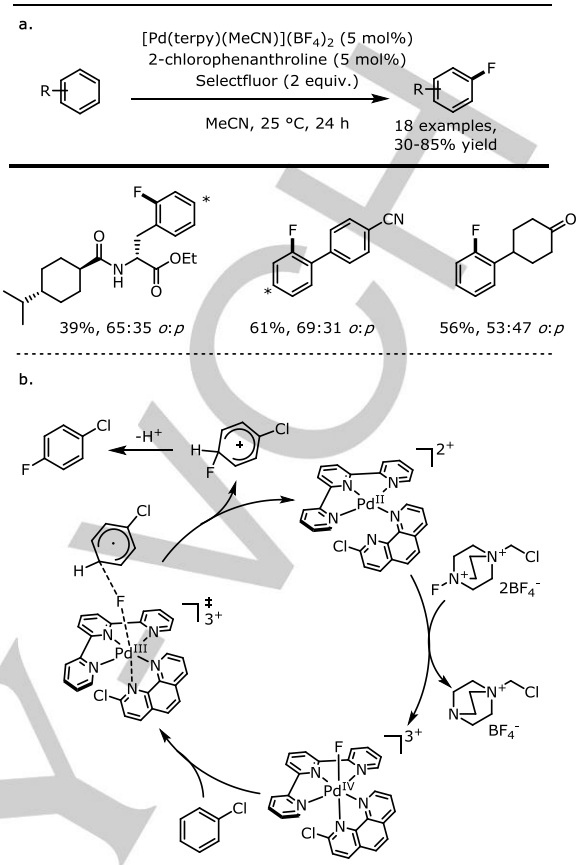
Britton and co-workers reported an elegant method for selective heterobenzylic C–H fluorination (Scheme 52a).[128] They discovered that NFSI used in combination with Li_2CO_3 promoted selective heterobenzylic fluorination of 2- and 4-alkyl pyridines. The authors observed that the reaction was unaffected by the addition of galvinoxyl free-radical trap, and noted that fluorination occurred without ring opening for a cyclopropyl containing substrate. The authors attribute these observations to a polar mechanism initiated by formation of an *N*-sulfonylpyridinium salt (Scheme 52b).[85] *N*-sulfonylation acidifies heterobenzylic C–H bonds adjacent to and in conjugation with the pyridinium intermediate. The positions are deprotonated and undergo electrophilic fluorination with NFSI to afford the product.

The authors observed selectivity for heterobenzylic C–H bonds over benzylic and aliphatic C–H bonds. Pyrimidines required an increased temperature of 150 °C. Heterobenzylic C–H bonds at the 3-position of the pyridine ring didn't undergo fluorination, presumably as not sufficiently activated upon *N*-sulfonylation.



Scheme 52. a) Fluorination of heterobenzylic C–H bonds with NFSI as reported by Britton.[128] b) Proposed reaction mechanism.

Recently, the Ritter group has reported a non-directed Pd(II) catalyzed aromatic C**–**H fluorination (Scheme 53a).[129] The reaction is distinct from other Pd(II) catalyzed methods in that it does not proceed via cyclopalladation leading to an organometallic intermediate. Instead, a non-substrate bound Pd(II) complex is oxidized directly by either NFSI or Selectfluor to form a Pd(IV) fluoride. DFT calculations suggest this Pd(IV) fluoride complex has a higher single electron reduction potential than Selectfluor. The calculated transition state for the fluorination is best described as a singlet diradical; two subsequent fluoride-coupled electron transfers occur asynchronously, as the reaction is proposed to proceed through a single transition state (Scheme 53b). For most substrates, regioisomeric product mixtures are obtained, with product distribution dictated by the innate directing effects of the ring substituents. In contrast to non-catalyzed electrophilic aromatic substitution reactions with NFSI and Selectfluor, which are only compatible with electron rich aromatics, this Pd(II)-catalyzed reaction tolerates arenes deprived of electron donating substituents.[130] For example, the ethyl ester of type 2 diabetes drug Nateglinide afforded 39% yield of a mixture of *ortho* and *para* isomers, while the uncatalyzed reaction gave less than 1% of products.



Scheme 53. a) Non-directed electrophilic aryl C–H fluorination reported by Ritter and co-workers.[129] b) Proposed mechanism.

5. Conclusion and outlook

The field C–H activation and functionalization is becoming a classic in synthetic chemistry that one should not ignore when planning retrosynthetic routes to complex organic molecules. This state of play also applies to C–H fluorination. As demonstrated in this review, the majority of C–H fluorination methods proceed via either directed Pd(II) insertion or via radical intermediates. The former approach offers complete regiocontrol dictated by proximity to a directing group, while the latter affords regioselectivity based on the relative reactivity of C–H bonds. Protocols relying on Pd(II) catalysts lend themselves to enantioselective fluorination though the use of chiral ligands, while achieving enantiocontrol in radical methods is very much in its infancy. Unactivated C(sp^3)–H bonds are more readily fluorinated under radical conditions, but activation of C(sp^2)–H bonds has only be achieved under Pd and Cu catalysis. Radical methods are also distinct from transition metal mediated processes because they do not require the installation and removal of directing groups. Evidently, the activation methods studied to date are complementary and together cover a large chemical space for the discovery of functional fluorinated molecules such as pharmaceutical drugs or PET radiotracers. The field has matured to a point that we could now consider

applying different activation modes as a platform to access multiple fluorinated products via C–H fluorination from a same precursor; this is an exciting prospect saving time and resources. It is likely that further advances in C–H fluorination will require the development of new fluorination reagents. Progress in this direction has most recently led to a superior N-F reagent for radical fluorination. Remaining challenges include the use of inexpensive metal fluoride sources, control of enantioselectivity, and the use of organocatalysts as well as abundant first row transition metal-based catalysts. To this end, recent work demonstrating C–F reductive elimination from high valent Ni(III) fluoride complexes holds promise, as does C–H activation under Cu catalysis that, to date, remains underexplored.[53][131] In addition to C–H fluorination, the introduction of alternative fluorinated motifs applying C–H activation requires development; for example, a transformation enabling direct regio- and enantioselective trifluoromethylation or difluoromethylation of unactivated C(sp^3)–H would be particularly well received.

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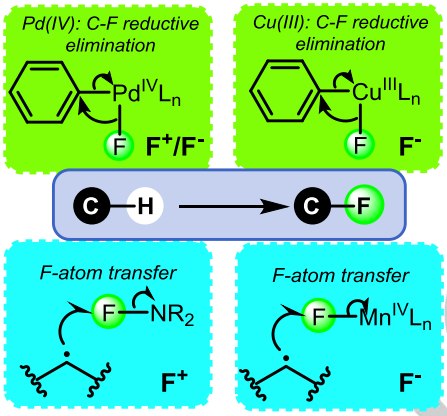
REVIEW

The direct fluorination of C–H bonds has emerged as a powerful method for accessing functional molecules such as pharmaceuticals or PET radiotracers. This Review provides an overview of the state of play of this field with an emphasis on the advantages and limitations of the main activation modes exploited to date. The discussion brings to light the importance of the fluorination reagent, and the challenges associated with nucleophilic C–H fluorination methodologies.



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Page No. – Page No.

The fluorination of C–H bonds: developments and perspectives