Introduction of Fluorine and Fluorine-Containing Functional Groups

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Introduction of Fluorine and Fluorine-Containing Functional Groups

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Keywords:
C–H functionalization fluorine catalysis trifluoromethylation transition metals
Theresa was born in 1985 in San Jose, California and received her undergraduate education at University of California, Berkeley pursuing research under the mentorship of Prof. Richmond Sarpong in total synthesis. After UC Berkeley, she moved from sunny California to Harvard University and obtained her PhD in 2012 working with Prof. Tobias Ritter on the trifluoromethoxylation of aryl nucleophiles and fluorination of complex natural products.

Constanze was born in 1988 in Fürth, Germany and received her MChem at the University of Oxford. She conducted undergraduate research with Prof. Timothy J. Donohoe and then moved to Harvard University where she is pursuing doctoral studies in the group of Prof. Tobias Ritter. Constanze’s PhD work revolves around the development of new methods for the C-H functionalization of arenes.

Tobias was born in 1975 in Lübeck, Germany. He received his undergraduate education in Braunschweig, Germany, Bordeaux, France, Lausanne, Switzerland, and Stanford, US, and received a master of science from Braunschweig University in 1999. He has performed undergraduate research with Prof. Barry M. Trost at Stanford, obtained his PhD working with Prof. Erick M. Carreira at ETH Zürich in 2004, and was a postdoc with Prof. Robert H. Grubbs at Caltech. In 2006, Tobias was appointed as Assistant Professor in the Department of Chemistry and Chemical Biology at Harvard and promoted to Associate Professor in 2010. His research program is based on synthetic organic and organometallic chemistry. The Ritter lab currently focuses on fluorination chemistry for late-stage functionalization of complex natural and unnatural products.

Introduction

Fluorination chemistry has been developed for more than 100 years with the first examples of nucleophilic and electrophilic fluorination reactions reported in the second half of the 19th century,[5] yet still today, significant challenges in fluorination chemistry remain. Current interest in fluorination chemistry is largely a consequence of the properties that fluoride substitution can impart on molecules, such as pharmaceuticals,[6] agrochemicals,[7] materials,[8] and radiotracers for positron emission tomography (PET).[9] Despite longstanding appreciation of fluoride’s utility, fluorination methods still lack generality, practicality, and predictability. Carbon–fluorine bond formation is a challenging chemical transformation largely due to fluoride’s high electronegativity and the high hydration energy of fluoride anion.[10] In Nature, haloperoxidase enzymes[11] give rise to thousands of organochlorides and organobromides[12] but no fluoroperoxidase enzyme has been identified. Despite fluoride being the 13th most abundant element in the Earth crust,[13] only a handful of natural biosynthesized organofluorides[14] are known.[15]

A few decades ago, the development of several fluorinating reagents such as Selectfluor®[16] and DAST (diethylaminosulfur trifluoride)[17] resulted in fast development of new fluorination methods. Within the past ten years, a similar leap in fluorination chemistry has occurred, which we ascribe to increased efforts towards catalytic methods for fluoride incorporation. The merger of fluorination chemistry and synthetic organic chemistry—considered separate fields for a long time—has resulted in the recent advances that constitute the focus of this review. Traditional fluorination reactions[18] and their relevance to modern developments are discussed briefly in order to put modern fluorination chemistry,[19] into perspective. In addition to C–F bond formation chemistry, methods for the introduction of fluorinated functional groups, which exhibit significantly different reactivity than their non-fluorinated analogs, are also presented. For example, while the trifluoromethyl group is formally a fluorine-substituted methyl group, its reactivity is significantly different from that of a methyl group, and it should thus be considered its own functional group. We attempt to cover the existing strategies in the field of fluorination published before 2013 under the aforementioned guidelines, and regret that we were unable to include a more complete view of the field due to editorial constraints.

1. Fluorination

Fluorine can provide many beneficial properties when incorporated into a molecule. Modulation of the pK_a of functional groups proximal to fluoride substitution[20,21] can result in increased membrane penetration at physiological pH.[22] Fluorinated arenes are more lipophilic than their non-fluorinated counterparts,[23] which can be used to advantage in drug development.[24,25] Fluorine is sometimes used as an isostere for hydrogen in medicinal chemistry, but the van der Waals radius of fluorine is more similar to oxygen (1.47 Å for fluoride versus 1.52 Å for oxygen and 1.20 Å for hydrogen).[26] Fluorinated compounds can be strategically used as transition state inhibitors.[27]

The high electronegativity of fluoride contributes to the high carbon–fluorine bond strength due to coulombic attraction between carbon and fluoride due to the polarized covalent bond; the large bond polarization[28,29] results in attractive interactions of the C–F fragment with hydrogen bond donors,[30] other fluorinated compounds,[31] and hydrophobic moieties.[32] Fluorinated molecules can show increased binding affinity to proteins[33,34] likely due to attractive polar interactions,[35] however, in many cases this phenomenon is empirically observed and rationalized ex post facto and is difficult to predict or design a priori. Most fluorinated compounds, but not all,[36] also exhibit increased metabolic stability by impeding undesired oxidative metabolism pathways.[37]

1.1. Electrophilic fluorination

Most electrophilic fluorinating reagents are ultimately derived from fluorine gas, the strongest elemental oxidant known, synthesized by electrolysis of potassium bifluoride in hydrogen fluoride.[38] Electrophilic fluorination reactions with highly oxidizing fluorinating reagents[39] such as fluorine gas, hypofluorites,
fluorinated reagents. Such basic nucleophiles can undergo single high reactivity reagents including aryltin, limiting formation of the halocyclohexadienyl cation. Arylmetal possibly C\(\text{H}\) regioselectivity is a frontier in the field of the development of functional group tolerant, direct conversion of aryl successful use for carbon wider spectrum of mechanisms, which the necessity of coordinating groups for rapid displacement of the aryl–H bonds to the corresponding C–F bonds with predictable regioselectivity is a frontier in the field.

Fluorination of arenes via electrophilic aromatic substitution (C–H \(\rightarrow\) C–F) is challenging when compared to other halogenations, possibly because the electronegativity of fluorine disfavors the rate-limiting formation of the halocyclohexadienyl cation. Arylmetal reagents including aryltin, -mercury, -lead, -germanium, -silicon and -boron can react with fluorine gas, xenon difluoride, hypofluorites, and fluoroxy sulfates to afford fluorinated arenes; however, the substrate scope is limited due to the high reactivity of the reagents, often resulting in unsselective fluorination. On the other hand, aryl nucleophiles with more electropositive metals, such as aryllithium reagents, can react with less reactive electrophilic fluorinating reagents, such as N-fluorinated reagents. Such basic nucleophiles can undergo single electron transfer giving rise to protodemetalation byproducts. Fluorination of Grignard reagents with electrophilic N-fluorinated reagents is the most reliable method with simple aryl nucleophiles but is narrow in scope due to the basicity and nucleophilicity of the aryllithium reagents. Through appropriate choice of solvent and reagents, undesired protodemetalation products can be minimized. More recent work by Meng and Li demonstrated the effective para fluorination of anilides with PhI(OPiv)\(_2\); and hydrogen fluoride/pyridine.

Functional-group tolerant and regioselective fluorination with redox active transition metals can proceed through the intermediacy of high-valent organotransition metal fluorides. The metal–carbon bond can be formed via transmetalation or direct C–H metatation, followed by oxidation of the metal center with an electrophilic fluorinating reagent. Depending on the reaction conditions, oxidation can result in formation of a monometallic high valent intermediate or a high valent multi-metallic complex.

The first transition-metal-catalyzed aromatic fluorination reactions were developed by means of utilizing an ortho-coordinating group by Sanford and Yu (Scheme 2). Direct C–H fluorination is desirable, but the necessity of coordinating groups currently limits the structural diversity of the substrates that can be fluorinated. Double fluorination through two subsequent ortho fluorination events was addressed with a weakly coordinating anionic ortho-directing group N-perfluorotolylamide as in I.1, derived from benzoic acid that allows for rapid displacement of the mono- and multifluorinated product by the substrate, thus affording high selectivity for monofluorination (Scheme 3).

**Scheme 1.** Synthesis of aryl fluorides from aryl Grignard reagents

![Scheme 2. N-directed Pd-catalyzed fluorination of arenes](image-url)
heteroaryl and mesityl nucleophiles. The method displays which, however, necessitates the use of toxic aryl stannanes.

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functional groups

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benzoquinoline -

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poor, electrophilic, and protic functional

groups as well as complex natural product-derived substrates (Scheme 6).

Arylboronic acids have been used to synthesize Pd(II) aryl benzoquinoline-sulfonamide complexes 1.2 that undergo fluorination with \(\text{F-TEDA-BF}_4\) in the presence of a variety of functional groups (Scheme 4), however, stoichiometric amounts of Pd complex are needed. Mechanistic studies on the oxidation of the benzoquinoline phenylpyridinesulfonamide-stabilized palladium(II) complex 1.3 with \(\text{F-TEDA-BF}_4\) support the presence of a distinct intermediary \(\text{Pd(IV)}\) fluoride species that undergoes reductive elimination to afford aryl carbon–fluorine bonds (Scheme 5).

Following initial work by Tius on silver-mediated fluorination with \(\text{XeF}_2\), a silver-mediated fluorination of functionalized aryl stannanes, boronic acids, and silanes has been developed. These transformations are assumed to proceed through multi-metallic, high-valent silver species, obtained by oxidation of Ag(I) complexes with \(\text{F-TEDA-PF}_6\) followed by reductive elimination. The formation of C-F bonds via reductive eliminations is generally a difficult process with requires high temperature to overcome the often high activation barriers. Multi-metallic redox synergy may explain why fluorination of aryl stannanes and boronic acids with silver can occur at 23 °C. Following the discovery of silver-mediated fluorination reactions using a range of aryl-nucleophiles, a silver-catalyzed fluorination of was developed, which, however, necessitates the use of toxic aryl stannanes. This method displays as of yet the broadest substrate scope and functional group tolerance in the field, including nitrogenous heteroaryl and mesityl nucleophiles, nucleophiles containing electron-rich, electron-poor, electrophilic, and protic functional

Scheme 3. N-Perfluorotolylamide–directed Pd-catalyzed fluorination of arenes

Arylboronic acids have been used to synthesize Pd(II) aryl benzoquinoline-sulfonamide complexes 1.2 that undergo fluorination with \(\text{F-TEDA-BF}_4\) in the presence of a variety of functional groups (Scheme 4), however, stoichiometric amounts of Pd complex are needed. Mechanistic studies on the oxidation of the benzoquinoline phenylpyridinesulfonamide-stabilized palladium(II) complex 1.3 with \(\text{F-TEDA-BF}_4\) support the presence of a distinct intermediary \(\text{Pd(IV)}\) fluoride species that undergoes reductive elimination to afford aryl carbon–fluorine bonds (Scheme 5).

Scheme 4. Fluorination of Pd(II) benzoquinolyl sulfoamide complexes with \(\text{F-TEDA-BF}_4\)

Scheme 5. Reductive elimination from \(\text{Pd(IV)}\) phenylpyridyl sulfoamide complexes

Following initial work by Tius on silver-mediated fluorination with \(\text{XeF}_2\), a silver-mediated fluorination of functionalized aryl stannanes, boronic acids, and silanes has been developed. These transformations are assumed to proceed through multi-metallic, high-valent silver species, obtained by oxidation of Ag(I) complexes with \(\text{F-TEDA-PF}_6\) followed by reductive elimination. The formation of C-F bonds via reductive eliminations is generally a difficult process with requires high temperature to overcome the often high activation barriers. Multi-metallic redox synergy may explain why fluorination of aryl stannanes and boronic acids with silver can occur at 23 °C. Following the discovery of silver-mediated fluorination reactions using a range of aryl-nucleophiles, a silver-catalyzed fluorination of was developed, which, however, necessitates the use of toxic aryl stannanes. This method displays as of yet the broadest substrate scope and functional group tolerance in the field, including nitrogenous heteroaryl and mesityl nucleophiles, nucleophiles containing electron-rich, electron-poor, electrophilic, and protic functional

Scheme 6. Ag-catalyzed fluorination of complex aryl stannanes

1.1.2. Electrophilic fluorination for the synthesis of fluorinated \(sp^3\) carbon centers

Nucleophiles employed in aliphatic electrophilic fluorination reactions are often stabilized carbanions, such as those derived from \(\beta\)-ketocarbonyl compounds. Other methods for the synthesis of aliphatic fluorides can involve fluorination-nucleophile addition cascades across double bonds, which was also reported with alkynes. Enantioselective variants for both fluorination of C-H acidic substrates and fluorination-addition cascades have been reported and can be promoted with Lewis acids, organocatalysts, or phase-transfer catalysts. Aliphatic C-F bond forming reactions occurring via radical intermediates have been disclosed and can provide a substrate scope complementary to reactions involving two-electron chemistry.

1.1.2.1. Electrophilic fluorination of activated methylene and methyne groups

\(\alpha\)-Fluorination of carbonyls, \(\alpha\prime\)-ketocarbonyls, and related carbonyl derivatives with oxidizing fluorinating reagents including gaseous fluorine, alkyl hypofluorite, perchloryl fluoride, fluoroxysulfate, and XeF\(_2\) generally give undesired \(\alpha,\alpha\prime\)-difluorinated products in addition to the \(\alpha\)-monofluorinated products. Less reactive, more functional group tolerant electrophilic fluorinating reagents such as N-fluoropyridinium salts, NFSI, and F-TEDA-BF\(_4\) have been used to accomplish selective \(\alpha\)-monofluorination of carbonyl derivatives. The asymmetric \(\alpha\)-fluorination of carbonyl substrates was explored first with chiral electrophilic fluorinating reagents and later with chiral catalysts which generate chiral enolate intermediates.

Several methods have exploited the two-point binding of dicarbonyl compounds to chiral Lewis acid complexes to control enantioselective fluorination. Asymmetric fluorination of \(\beta\)-ketesters was achieved with titanium-TADDOLate-based catalysts and by Togni (Scheme 7) Cu(II)- (Scheme 8) and
Ni(II)-BOX complexes (Scheme 9) by Cahard and Shibata/Toru, respectively, chiral bis(imino)bis(phosphate)ruthenium(II) complex 1.6 by Togni (Scheme 10), and scandium binaphthylphosphate complexes by Inanaga. The Ni-catalyzed reaction, using a 10 mol% catalyst loading, has demonstrated the broadest substrate scope so far, and allows for α-fluorination of a variety of β-ketoesters and N-Boc-protected amides in 71–93% yield and 83–99% ee, respectively. The catalytic enantioselective α-fluorination of α-substituted methyl, tert-butyl malonate was accomplished via chiral Lewis acid catalysis with Zn(II) acetate, (R,R)-4,6-dibenzofurandiyi-2,2′-bis(4-phenoxyazoline) ligand, and NFSI. This approach was specifically optimized for the malonate substrate en route to the enantioselective synthesis of fluorinated β-lactams.

Scheme 7. Ti-catalyzed asymmetric α-fluorination of β-ketoesters

Scheme 8. Cu-catalyzed asymmetric α-fluorination of β-ketoesters

Scheme 9. Ni-catalyzed asymmetric α-fluorination of β-ketoesters and N-Boc oxindoles

Scheme 10. Ru-catalyzed asymmetric α-fluorination of β-ketoesters

Chiral Pd-BINAP complexes 1.7 and 1.8 developed by Sodeoka shown in Scheme 11 and Scheme 12 catalyze the enantioselective fluorination of α-ketoesters, β-ketoesters (Scheme 11), β-ketophosphonates (Scheme 12), and α-ester lactones/lactams. The use of chiral palladium complexes was particularly successful for the α-fluorination of acyclic α-ketoesters, cyclic and acyclic tert-butyl β-ketoester as well as oxindoles α-substituted with an electronically diverse range of aryl and alkyl groups.

Organocatalysts provide enantioinduction in the role of chiral fluorinating reagents or through reaction with the substrate to generate chiral nucleophiles.

Cinchona alkaloids have been used to enantioselectively fluorinate nucleophiles in the presence of an achiral fluorinating reagent. Enantioselective fluorination of the activated methyne groups in 1.9 was accomplished by Takeuchi and co-workers using stoichiometric amounts of cinchona alkaloid derivatives such as 1.10 (Scheme 13). Cinchona alkaloids have also been used to mediate enantioselective α-fluorination of silylenol ethers, α,α-cyanoester C–H acids, β-ketoesters, and oxindoles. The methodology was applied to the synthesis of BMS-204352 (Scheme 14), which has also been synthesized utilizing chiral scandium Lewis acid catalysts. Enantioselectively α-fluorination of β-ketoesters can be accomplished using cinchona-alkaloid-derived thiourea catalysts. Despite the reduced substrate scope currently tolerated in enantioselective fluorinations with cinchona alkaloids when compared to the Lewis acid–catalyzed fluorinations of β-ketoesters and oxindoles, chinoa-alkaloid-based catalysis has the advantage of not being restricted by the need for a two-point binding site.
Enantioselective cinchona-alkaloid–mediated fluorination of C–H acidic substrates

Scheme 13. Enantioselective cinchona-alkaloid–mediated fluorination of C–H acidic substrates

Enantioselective organocatalytic α-fluorination of aldehydes was accomplished by Enders, MacMillan (Scheme 15), Jørgensen (Scheme 15) and Barbas (Scheme 16), similarly, enantioselective α-fluorination of ketones is possible using enamine catalysis. The aldehyde α-fluorination method described by MacMillan demonstrates a broader substrate scope, while the method described by Jørgensen utilizes lower loadings of catalyst and electrophilic fluorinating reagent. Branched aldehydes constitute difficult substrates for enantioselective α-fluorination; nonetheless, Barbas reported a promising 98–99% yield and 45–66% ee for this class of substrates. The fluorinated aldehyde products are especially useful for the synthesis of enantiopure β-fluoroamines, which can be obtained by a chiral sulfonimidoyl condensation, directed reduction sequence of the enantioenriched fluorinated aldehyde.

Scheme 14. Enantioselective α-fluorination of oxindoles mediated by N-fluoroammonium salts of cinchona alkaloids

Phase-transfer catalysis (PTC) for enantioselective fluorination can offer benefits such as simple operational procedures. The formation of chiral tight ion pairs is vital for enantioinduction; thus, nonpolar solvents in which ion pairs remain associated such as dichloromethane and toluene are preferred for PTC. Chiral quaternary ammonium salts have been used as cationic phase-transfer catalysts for enantioselective fluorination of β-ketoesters with ion pairing between the enolate and chiral ammonium counterion (Scheme 18). Only ee’s of up to 69% have thus far been achieved for the α-fluorination of β-ketoesters; this is likely due to insufficiently tight ion pairing between the chiral ammonium salt and the enolate or a fast background reaction.

Scheme 16. Organocatalytic asymmetric α-fluorination of α-branched aldehydes

The enantioselective α-fluorination of acid chlorides was accomplished by the Lectka group by combining a palladium catalyst, a chiral nucleophile, and an alkali metal (Scheme 17). The cinchona alkaloid-based nucleophile reacts with the acid chloride in the presence of the palladium catalyst to generate a chiral zwitterion amide–enolate intermediate. Both catalysts work cooperatively to generate a chiral enolate for fluorination. It is hypothesized that the lithium cation activates NFSI for nucleophilic attack by the chiral enolate through chelation of the sulfonyl oxygen atoms. After fluorination, addition of an amine nucleophile affords the α-fluorinated amide product in >99% ee and de. Thiourea catalysts derived from cinchona alkaloids can also be used as synergistic bifunctional catalysts for the asymmetric α-fluorination of cyclic and acyclic β-ketoesters with NFSI. The catalyst is able to act as a base (via the quinuclidine moiety) and also as a hydrogen-bond donor (via the thiourea moiety) and is proposed to hydrogen-bond with the substrate and NFSI to afford good enantioselectivity.

Scheme 17. Organocatalytic asymmetric α-fluorination of acid chlorides

Phase-transfer catalysis (PTC) for enantioselective fluorination can offer benefits such as simple operational procedures. The formation of chiral tight ion pairs is vital for enantioinduction; thus, nonpolar solvents in which ion pairs remain associated such as dichloromethane and toluene are preferred for PTC. Chiral quaternary ammonium salts have been used as cationic phase-transfer catalysts for enantioselective fluorination of β-ketoesters with ion pairing between the enolate and chiral ammonium counterion (Scheme 18). Only ee’s of up to 69% have thus far been achieved for the α-fluorination of β-ketoesters; this is likely due to insufficiently tight ion pairing between the chiral ammonium salt and the enolate or a fast background reaction.

Scheme 15. Organocatalytic asymmetric α-fluorination of aldehydes
A non-traditional approach for the synthesis of chiral allylic and propargylic fluorides described by the Jørgensen group utilizes organocatalysis to facilitate the asymmetric fluorination step followed by olefination or the introduction of a propargyl group.\[95\] Fluorination of α-methylstyrene can occur via oxidative fluorination of the allylic C–H bond with a N-fluoropyridinium salt promoted by catalytic amounts of ytterbium(III) triflate.\[96\] Electrophilic fluorodesilylation of allenyl and allylsilanes was reported to yield propargylic and allylic fluoride products.\[97\] Gouvement and co-workers have demonstrated that acyclic secondary allylic fluorides can be prepared via a cross-metathesis–electrophilic fluorodesilylation sequence\[98\] while chiral tertiary allylic fluorides can be prepared via cinchona alkaloid-mediated electrophilic fluorodesilylation.\[99\]

### 1.1.2.2. Fluorination–nucleophile addition cascades across double bonds

For activated alkenes like enamines, fluorination can occur without catalysts. For example, fluorocyanation of enamines is hypothesized to occur via electrophilic fluorination of the enamine with NFSI followed by trapping of the iminium intermediate with cyanide (Scheme 19).\[101\]

**Scheme 19.** Fluorocyanation of enamines

With unactivated alkenes, fluorination-nucleophile addition reactions need to be assisted by a catalyst. Both the intramolecular aminofluorination of unactivated alkenes (Scheme 20)\[102\] and the intermolecular aminofluorination of styrenes (Scheme 21)\[103\] can be facilitated by the use of palladium catalysts as described by Liu. Although both reactions accomplish aminofluorination of alkenes, different approaches were employed and different reaction mechanisms proposed for each case. The intramolecular variant with substrate 1.12 utilizes an iodine(III) oxidant coupled with fluoride to accomplish oxidative fluorination of a complex resulting from intramolecular amino-palladation with an alkene. Intermolecular aminofluorination, on the other hand, is thought to occur via fluoro-palladation involving substrate, NFSI and the active palladium complex, followed by oxidation to a putative Pd(IV) species, and subsequent reductive elimination to form a carbon–nitrogen bond. The formation C-F bonds at sp\(^3\) carbon centers by reductive elimination from high-valent transition-metal complexes.\[104\] Oxidation of stoichiometric alkyl Au(I) complexes with XeF\(_2\) to yield Au(III) intermediates followed by reductive elimination affords the corresponding aliphatic fluorides.\[105\] The propensity for β-hydride elimination from Au(III) complexes and the need for the strong oxidant XeF\(_2\) has limited the substrate scope to mostly β,β-disubstituted alkenes. Additionally, Sanford reported the synthesis of allyl fluorides by reductive elimination from Pd(IV) complexes.

**Scheme 20.** Intramolecular Pd-catalyzed aminofluorocyclization of alkene sulfonamides

**Scheme 21.** Intermolecular aminofluorination of styrenes with NFSI

In the enantioselective fluorocyclization of indole substrates mediated or catalyzed by cinchona alkaloids, the enantioselectivity is proposed to arise from the chiral fluorinating reagent generated from the achiral fluorinating reagent and the cinchona alkaloid catalyst 1.13 (Scheme 22).\[106\]

**Scheme 22.** Enantioselective fluorocyclizations mediated and catalyzed by cinchona alkaloids

An enantioselective fluoro–spiro cyclization reaction via chiral anionic phase-transfer catalysis (PTC) has been realized by Toste through the pairing of chiral anion 1.14 with cationic F-TEDA to provide a source of chiral electrophilic fluorinating reagent (Scheme 23).\[107\] Because F-TEDA-BF\(_4\) is sparingly soluble in the reaction solvent, thus minimizing the background reaction, chiral anion catalysis of the fluorination–spiro cyclization reaction results in enantiomeric excess of up to 96%. Similarly, through the use of PTC with chiral anions, enamides can be enantioselectively fluorinated to afford α-fluoroimines\[108\] or α-fluoroalkoxylation products.\[109\]
1.2.3. Transition metal–catalyzed oxidative fluorination of aliphatic C–H bonds with fluoride

Transition metal–catalyzed oxidative fluorination of aliphatic C–H bonds using fluoride has been reported for the first time in 2012.[96] The oxidative fluorination of functionalized 8-methyl quinolinyl substrates catalysed by $\text{Pd(OAc)}_2$ was reported by Sanford using a hypervalent iodine oxidant in the presence of silver fluoride (Scheme 24).[96b] This transformation is postulated to occur through high valent palladium fluoride intermediates and is enabled by the strategic concurrent use of PhI(OPiv)$_2$ and AgF. Oxidative C–H fluorination of aliphatic substrates with a manganese(III) porphyrin catalyst in the presence of silver fluoride and iodosylbenzene was established by Groves (Scheme 25).[96a] C–H fluorination is proposed to occur via initial radical C–H bond cleavage by the Mn(V) oxo intermediate, which results from oxidation of the Mn(III) catalyst with PhIO. Radical recombination occurs between the substrate and a Mn(IV) difluoride complex generated from AgF and a Mn(IV) hydroxide complex. The faster rate of the fluoride for hydroxide ligand exchange on manganese compared to the reaction between the alkyl radical and the Mn(IV) hydroxide complex and the resulting selectivity achieved for fluorination over hydroxylation is remarkable.

Scheme 23. Enantioselective spiro-cyclizations via chiral anionic PTC

Scheme 24. Pd-catalyzed N-directed oxidative fluorination of $sp^3$ C–H bonds with AgF and Phl(OPiv)$_2$

1.2.4. Fluorination via a radical mechanism

The N–F bonds in electrophilic fluorinating reagents have relatively low bond dissociation energies (2.84 eV for $N$-fluorosultam).[97] Under either photolysis or thermolysis conditions, a variety of tert-butyl alkylperoxoates afforded the corresponding alkyl fluorides upon treatment with NFSI (Scheme 26).[98] Primary alkyl fluoride formation was not efficient, which supports the mechanism hypothesis of radical intermediates.

Scheme 25. Mn-catalyzed oxidative aliphatic fluorination with AgF/TBAF·3H$_2$O and iodosylbenzene

Scheme 26. Fluorination of tert-butyl alkylperoxoates with NSFI

Decarboxylative fluorination, first explored by Patrick,[99] was recently reported for secondary and tertiary aliphatic carboxylic acids with F-TEDA-BF$_4$ by Li via silver catalysis (Scheme 27).[100] This approach is complementary to traditional nucleophilic fluorination reactions with DAST-type reagents. Involvement of Ag-mediated decarboxylation to form an alkyl radical during the reaction was demonstrated, but the detailed mechanism for the key C–F bond formation still remains undetermined. Photo-fluorodecarboxylation of $\alpha$-arylxyacetic acids or $\alpha$-arylxy-$\alpha$-fluoroacetic acids was accomplished by treating the acid with NaOH in the presence of F-TEDA-BF$_4$ to afford aryl fluoromethyl ethers or aryl difluoromethyl ethers, respectively.[101]
fluoride (TBAF, anhydrous TBAF can be synthesized\textsuperscript{106}) are commonly used soluble fluoride sources.

Fluorodeoxygenation of carbon centers commonly requires specialized fluorinating reagents that can accomplish oxygen activation/deoxygenation as well as provide a fluoride source. Various aryl and aminosulfur trifluorides\textsuperscript{12a, 107} and derivatives thereof as well as 2,2-difluoromimidazoline-type reagents\textsuperscript{108} participate in fluorodeoxygenation reactions. Several hydrogen fluoride–based reagents\textsuperscript{109} have been developed to assist sulfur displacement with fluoride in fluorodesulfurization reactions. Electrochemical fluorination with alkali metal–fluorides has been explored as an approach for the synthesis of organofluorides.\textsuperscript{110} Catalysis has enabled many nucleophilic fluorination reactions that are otherwise kinetically difficult to accomplish, such as the fluorination of arenes. Uncatalyzed nucleophilic aromatic substitution with fluoride does not proceed for electron-rich substrates because the rate-determining step is addition of the nucleophile to the arene to form a Meisenheimer–type complex.\textsuperscript{111} Additionally, chiral transition-metal and organocatalysts can be used for nucleophilic fluorination reactions to afford enantoienriched fluorinated compounds.

1.2.1. Nucleophilic fluorination for the synthesis of fluorinated aromatic carbon centers

$S_NAr$ reactions are currently used on an industrial scale in the Halex (halogen exchange) process\textsuperscript{112} although one or more electron-withdrawing groups on the arene are typically required. Aromatic substitution, catalyzed and non-catalyzed, is, at this point, one of the most direct methods for nucleophilic fluorination with control of regioselectivity. Improvement in the substrate scope is desirable because nucleophilic fluorination is preferred over electrophilic fluorination both on an industrial scale owing to the low cost of alkali metal fluorides and in radiochemical applications due to facile access to $^{19}$F-fluoride.

1.2.1.1. Traditional nucleophilic fluorination methods with main group elements

Balz and Schiemann first developed the nucleophilic fluorination of arenes via thermal decomposition of aryl diazonium tetrafluoroborate salts in 1927,\textsuperscript{113} a process which was improved subsequently.\textsuperscript{114} Displacement of chloride in 1-chloro-2,4-dinitrobenzene under forcing conditions with anhydrous potassium fluoride (the Halex process) was developed in 1936\textsuperscript{115} followed by fluorodinitration of arenes, by ipso-attack at the carbon bearing the nitro group (Scheme 29).\textsuperscript{116} More recent work in this area has allowed for the fluorination of electron-poor, chloro-, nitro-, or trimethylammoniumarenes with anhydrous tetrafluoroboric fluoride at room temperature in up to $>$95% yield.\textsuperscript{117} Aryl fluorides can also be accessed from reaction of aryl bromides with anhydrous tetramethylammonium fluoride; however, the process actually occurs through fluoride trapping of arene intermediates generated from the elimination of the bromide with the strongly basic anhydrous fluoride and therefore provides a mixture of constitutional isomers (Scheme 30).\textsuperscript{118} Other approaches that have been explored involve two-step nucleophilic fluoro-demetalation of toxic organothallium(III) substrates\textsuperscript{119} as well as diaryliodonium substrates.\textsuperscript{120} Although simple fluorinated arenes can be synthesized with some of the aforementioned reactions, even on
industrial scale\cite{112} none of these methods are tolerant of many functional groups or exhibit broad substrate scope.

Scheme 29. Nucleophilic aromatic substitution with KF

\[
\begin{align*}
\text{Scheme 30.} & \quad \text{Fluorination of naphthyl bromide via aryne intermediates} \\
\end{align*}
\]

1.2.1.2. Transition-metal–catalyzed and –mediated nucleophilic fluorination

Transition-metal–catalyzed cross-coupling with fluoride as nucleophile has been investigated with late transition-metals such as nickel, copper, ruthenium, rhodium, palladium, iridium, and platinum.\cite{121} Reductive elimination of C–F bonds from Pd(II) is challenging; the difficulty of the reductive elimination step rises with increasing electronegativity of the nucleophilic coupling partner. For Pd(II) complexes stabilized by monodentate ligands, fluoride-bridge dimer complexes are readily formed, from which reductive elimination has never been observed. Cross-coupling fluorination of aryl triflates with fluoride via palladium catalysis (Scheme 31)\cite{121g,122} was developed by Buchwald and co-workers with the bulky monodentate phosphine ligand tBuBrettPhos, which was crucial for successful C–F reductive elimination through a mononuclear, tri-coordinate palladium(II) complex. The fluorination of aryl triflates displays a broad substrate scope and tolerates nucleophilic functional groups not often tolerated in electrophilic fluorination methods due to competing fluorination of these electron rich sites. Protic functional groups are not tolerated under the reaction conditions, and the formation of constitutional isomers, potentially a result of the use of basic fluoride salts, was observed in some cases.\cite{122} Importantly, formation of reduced arenes (C–H bond formation instead of C–F bond formation) could be suppressed to a minimum, which enables practical purification of the fluoroarene products. Applications for positron emission have been evaluated and are currently limited to the synthesis of radiotracers of low specific activity.\cite{123}

Scheme 31. Pd-catalyzed cross-coupling of aryl triflates with CsF

An oxidative addition—C–F reductive elimination sequence was established by the Ribas group via a Cu(I)-Cu(III) cycle using a contrived substrate that allowed for isolation of key intermediates (Scheme 32).\cite{121f} Oxidative addition of copper(I) into the aryl halide supported by the tris(amine) ligand generates a copper(III) complex, which upon ligand metathesis with silver fluoride, gives a copper(III) fluoride complex that undergoes reductive elimination to liberate the aryl fluoride product. Copper-mediated fluorination of electron-rich, electron-poor, as well as hindered aryl iodide substrates was reported by Hartwig, using three equivalents of a copper(I) complex and AgF (Scheme 33).\cite{124} The formation of hydrodehalogenated side products renders purification of the aryl fluoride products challenging.

Scheme 32. Cu-catalyzed halide exchange on arenes with AgF
derivatives thereof can afford fluoride from secondary or tertiary
available. Deoxyfluorination with sulphur tetrafluoride or
and no general, functional
secondary or tertiary sp
is well established.

Scheme 33. Cu-mediation florination of aryl iodides with AgF

1.2.1.3 Nucleophilic deoxyfluorination

The ability to directly substitute the hydroxy group in phenols
with fluoride obviates the need for pre-functionalization of the
phenol. Catechol can be monodeoxyfluorinated by oxidation of the
catechol to the ortho-quinone followed by nucleophilic
deoxygenation with Deoxo-Fluor®.
This oxidation-fluorination method affords a mixture of ortho-fluorinated phenol
isomers. One of the first examples of deoxyfluorination of nitro
fluorination method affords a mixture of
deoxyfluorination with Deoxo
catechol to the
fluorides can be synthesized from the corresponding phenol
-PhenoFluor with the
group, for the
difluoroimidazoline.

Substituted phenol was accomplished with
isomers. One of the first examples of deoxyfluorination of nitro
flourination method affords a mixture of

Additional drawbacks of DAST include moisture sensitivity as well
a propensity to explode upon heating.

Besides DAST, deoxyfluorination and dethiofluorination can be
accomplished with several different reagents: pyridinium poly(hydrogen fluoride) (Olah’s reagent),
nitrosium tetrafluoroborate/pyridinium poly(hydrogen fluoride),
triethylamine tris(hydrogen fluorine) (TREAT•HF),
perfluoro-1-butanesulfonyl fluoride (PBSF),
sulfonyl fluoride/TREAT•HF mixture (Scheme 35),
Yarovenko’s reagent,
Ishikawa’s reagent,
TFEDMA, N,N’-dimethyl-2,2,-
difluoroimidazolidine,
4-morpholinosulfur trifluoride,
bromine trifluoride,
and 4-tert-butyl-2,6-
dimethylphenylsulfur trifluoride (Fluolead®).

Carbonyl compounds were first converted to geminal
difluoromethylene functional groups with sulphur tetrafluoride.
The toxicity and volatility of sulfur tetrafluoride led to the
development and use of less volatile reagents such as aryl and
aminosulfur trifluorides.

The mechanism of DAST-mediated fluorination is proposed to begin with nucleophilic attack of the alcohol substrate on the sulphur atom of DAST to form an
alkoxysaminodifluorosulfane intermediate that is activated for
Sn2 attack by fluoride. In some cases, however, fluorination with
DAST affords products consistent with an Sn1 mechanism.
Additional drawbacks of DAST include moisture sensitivity as well
a propensity to explode upon heating.

Figure 2. A selection of deoxofluorinating reagents

Nucleophilic fluorination at primary sp3 carbon centers through
appropriate selection of fluoride source, leaving group, and solvent,
is well established. Nucleophilic fluorination at a
secondary or tertiary sp3 carbon center is inherently more difficult
and no general, functional-group-tolerant method is currently
available. Deoxofluorination with sulphur tetrafluoride or
derivatives thereof can afford fluoride from secondary or tertiary
carbons, but competing elimination and rearrangement reactions occur frequently. Halo-fluorination of alkenes
were accomplished via treatment of the alkene with N-iodosuccinimide
and tetraalkylammonium hydrogen fluoride.
Nucleophilic opening of epoxides and aziridines with fluoride affords
vicinal fluoroalcohols and fluoroamines respectively which have
been elaborated to multivinical multi-fluoroalkanes.

Carbonyl compounds were first converted to geminal
difluoromethylene functional groups with sulphur tetrafluoride.
The toxicity and volatility of sulfur tetrafluoride led to the
development and use of less volatile reagents such as aryl and
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alkoxysaminodifluorosulfane intermediate that is activated for
Sn2 attack by fluoride. In some cases, however, fluorination with
DAST affords products consistent with an Sn1 mechanism.

Additional drawbacks of DAST include moisture sensitivity as well
a propensity to explode upon heating.
Development of the non-explosive, crystalline, less moisture-sensitive deoxyfluorinating reagent XtalFluor-E\textsuperscript{®} (diethylaminodifluorosulfinium tetrafluoroborate\textsuperscript{144}) and related reagents\textsuperscript{145} has resulted in fluorodeoxygenation with fewer byproducts (Scheme 36). Unlike DAST or Deoxo-Flour\textsuperscript{®}, fluorination with XtalFluor-type reagents requires the addition of amine hydrogen fluoride such as triethylamine tris(hydrogen fluoride) as a fluoride source because after addition of amine hydrogen fluoride such as triethylamine tris(hydrogen fluoride) the sensitive deoxyfluorinating reagent XtalFluor does not occur. Instead of adding an external fluoride source, addition of DBU can also promote release of fluoride by deprotonation.

The synthesis of propargylic fluorides can be accomplished via deoxyfluorination of propargylic alcohols with DAST\textsuperscript{146} or fluorination of a variety of activated propargylic substrates such as propargylic mesylates or silyl ethers. Other commonly used deoxyfluorinating reagents for the synthesis of propargylic fluorides include SF\textsubscript{5}Cl\textsuperscript{147a, b, 148} dialkylaminodifluorosulfinium trifluoroborate\textsuperscript{149, d, 147f, g} Yarovenko’s reagent (Figure 2),\textsuperscript{149b} and Ghosez’s reagent (N,N-disopropyl-1-fluoro-2-methylpropenamine).\textsuperscript{150} Grée achieved the synthesis of chiral propargylic fluorides through an S\textsubscript{N}2 reaction between chiral, non-racemic propargylic alcohols and fluoride.\textsuperscript{151} This approach is substrate dependent; many chiral propargylic alcohols give enantiomeric excess–eroded or racemized products through a competing S\textsubscript{N}1 pathway. The majority of syntheses of propargylic fluorides utilize nucleophilic fluorination; Hammond\textsuperscript{152} and Gouverneur\textsuperscript{153} have investigated electrophilic fluorination routes to propargylic fluorides.

Middleton first reported the dehydroxyfluorination of allylic alcohols with DAST\textsuperscript{146} which was used subsequently to study the fluorination of allylic alcohol substrates containing different substituents and substitution patterns.\textsuperscript{153} Temporary complexation of the π-system of allylic alcohols using a stoichiometric amount of rhenium or iridium can prevent allylic transposition during dehydroxyfluorination reactions, a common side reaction. Complexation of chiral racemic allylic alcohols leads to two diastereomeric transition metal complexes, which can be separated and fluorinated stereospecifically. The need for stoichiometric amounts of transition metals, as well as additional protection–deprotection steps has limited the utility of this approach. Besides DAST, other reagents display reactivity in dehydroxyfluorinations, such as bis(dialkylamino)sulfur difluorides\textsuperscript{146, 156} Yarovenko’s reagent,\textsuperscript{157} Ghosez’s reagent,\textsuperscript{158} and IF\textsubscript{3} in NEt\textsubscript{3}•3HF\textsuperscript{159} The reactivity of other activated allylic substrates has also been explored.\textsuperscript{160} An attractive route to allylic fluorides is the Tsuji-Trost–type fluoride displacement of a leaving group catalyzed by a transition-metal complex. Because fluoride is a better leaving group than acetate, which is a commonly employed leaving group in Tsuji-Trost reactions,\textsuperscript{161} the selection of an appropriate leaving group proved crucial in the development of this transformation. The selective synthesis of either linear or branched allylic fluorides constitutes an additional challenge in the Tsuji-Trost-type allylic displacement reaction. Doyle reported an enantioselective fluorination of cyclic\textsuperscript{163} and acyclic (Scheme 37)\textsuperscript{164} allylic chlorides in the presence of a chiral palladium catalyst with branched : linear selectivities of >20:1 for most substrates. A variety of functional groups can be tolerated; currently, long reaction times and an excess of silver fluoride is required for optimum yields. Oxabicyclic alkenes can undergo ring-opening with fluoride and a rhodium catalyst\textsuperscript{165} Secondary and tertiary allylic fluorides can be synthesized from allylic trichloroacetimidates under iridium catalysis (Scheme 38)\textsuperscript{166} while terminal allylic fluorides can be synthesized from cinnamyl allylic carbonates as reported by Gouverneur and Brown\textsuperscript{167} and cinnamyl allylic phosphorothioate esters as reported by Wu, both via palladium catalysis.\textsuperscript{168}
In addition to S$_n$2 reactions, nucleophilic fluorination of olefins through bromofluorination of olefins$^{[169]}$ and epoxide opening with fluoride can provide access to fluorinated secondary or tertiary carbon centers. Asymmetric opening of meso-epoxides with fluoride was first reported by Haufe with stoichiometric amounts of chiral Lewis acid complexes$^{[170]}$ and later with a Co(III)-salen catalyst$^{[171]}$ by Doyle and co-workers (Scheme 39)$^{[172]}$ for non-linear meso-epoxides and terminal epoxides. In situ fluoride release from benzoyl fluoride was employed to suppress background reactions and catalyst inhibition. Mechanistic studies suggest that the rate-determining epoxide opening step proceeds via a bimetallic complex, which led to the design of a more efficient dimeric catalyst containing two linked molecules of the cobalt-salen complex (Scheme 39).

![Scheme 39. Co(III)-catalyzed asymmetric opening of meso-epoxides with fluoride](image)

### 2. Fluoromethylation

Fluorinated functional groups such as monofluoromethyl and difluoromethyl groups have been used as oxygen mimics in molecules such as nucleotides, phosphate esters, and sulphate esters.$^{[172]}$

Introduction of fluoromethyl groups via a S$_n$2 reaction with fluoromethyl halide reagents is more challenging than methylation with methyl halide reagents because the transition state involves build-up of partial positive charge on the pentacoordinate carbon functionalized with electronegative fluorine. Reactive nucleophiles and fluoromethylating reagents with good leaving groups are thus required for electrophilic fluoromethylation. Difluoromethylation and trifluoromethylation reactions via a S$_n$2 mechanism are increasingly impeded by the compounded destabilizing effect of each additional fluoride atom. Nucleophilic fluoromethylation of electrophiles relies on the use of fluoromethide equivalents, typically containing mesomeric stabilizing groups such as sulfones. Many α-fluorinated carbanions are kinetically unstable due to 1,1-elimination to form carbones. Although rare, an example of radical fluoromethylation has been reported.$^{[173]}$

#### 2.1. Electrophilic methods for fluoromethylation

Fluoromethylation of phenols, thiophenols, as well as of imidazole and indole can be accomplished with chlorofluoromethane as the alkylating reagent as described by Hu and co-workers.$^{[174]}$ The reaction is postulated to occur via an S$_n$2 mechanism, rather than through single electron transfer processes.$^{[174]}$ Monofluoromethylated amines, ethers, and sulfides can be unstable due to the hyperconjugation of the lone pair electrons with the $\sigma^*_{C-F}$ orbitals, which results in the elongation of the C–F bond and can lead to fluoride extrusion. Fluoromethylsulfonium reagent 2.1, which undergoes fluoromethylation reactions with tertiary amines, imidazoles, phosphines, carbon-based nucleophiles, and even carboxylic and sulfonic acids was developed by Prakash and Olah (Scheme 40)$^{[175]}$. The process by which electrophilic fluoromethyl transfer occurs is currently unclear; both two-electron and one-electron pathways are conceivable. Because reagent 2.1 is synthesized through chlorofluoromethane alkylation of sodium thiophenolate, fluoromethylation with chlorofluoromethane is more efficient and can afford comparable yields for reactive substrates such as phenols, thiophenols, and imidazoles.$^{[175]}$ Electrophilic fluoromethylation of carbon nucleophiles is limited to methyne nucleophiles containing mesomeric stabilizing groups because for the corresponding methylene nucleophiles, the reaction products are susceptible to hydrogen fluoride elimination. Another fluoromethylating reagent N-dimethyl-3-fluoromethyl-3-phenylsulfoximinium, developed by Shibata and co-workers, is used for alkylation at oxygen of nucleophiles such as phenols and α-carbonyl-enols; the reason for the chemoselectivity is currently under investigation.$^{[176]}$ To the best of our knowledge, electrophilic fluoromethylation of aryl nucleophiles have not yet been reported in the literature.

![Scheme 40. Monofluoromethylation of various N-, O-, C-nucleophiles](image)

Another approach for the synthesis of fluoromethylated ethers involves the oxidative rearrangement of benzyl alcohols induced by XeF$_2$$^{[177]}$ or aryl difluoro-2,2-bromane (Scheme 41)$^{[178]}$ through phenyl group participation in the aryl carbon–oxygen bond forming step of aryl α-fluoromethyl ether synthesis. Electrophilic fluorination of O,S-acetals$^{[179]}$ and α-carboxymethyl ethers$^{[99, 180]}$ can also afford α-fluoromethyl ethers. Relatedly, N-fluropyridinium triflate can be used to oxidize the C–H bond on the methyl group of methyl sulfide to afford α-fluoromethyl sulfides.$^{[181]}$

![Scheme 41. Oxidative rearrangement of benzyl alcohol to monofluoromethyl phenol with aryl difluoro-2,2-bromane](image)

#### 2.2. Nucleophilic methods for fluoromethylation

The synthesis of α-fluoromethyl ethers$^{[182]}$ and sulfides$^{[183]}$ can be accomplished from chloromethyl ethers or thioethers through...
chloride displacement with KF. Nucleophilic displacement requires heating in refluxing acetoni trile and starting materials often decompose before displacement occurs. Additionally, nucleophilic fluorinating reagents such as DAST,[184] tetrabutylammonium dihydrogen trifluoride,[185] and Deoxo-Fluor[141] have been used to induce fluoropPummerer rearrangements of sulfides and sulfoxides to yield α-fluoromethyl sulfides. It should be noted that α-fluoromethyl sulfides are easily oxidized to the α-fluoromethyl sulfoxide in ambient atmosphere.

The general approach to nucleophilic fluoromethylation involves electrophiles bearing electron-withdrawing group-stabilized fluoromethide equivalents generated by deprotonation of pronucleophiles such as fluorobenzylsulfone or α-fluoro(phenylsulfonyl)methane (FSM). Diastereoselective fluoromethylation of chiral N-(tert-butylsulfinyl)aldimines (Scheme 42)[186] and ketimines (Scheme 42),[187] chiral α-amino N-(tert-butylsulfinyl)aldimines[188] have been reported as well as fluoromethylation of aldehydes[189] (followed by a Ritter-type reaction to give a fluoromethylated acetamide[190]) and the 1,4-fluoromethylation of α,β-unsaturated carboxylic acids.[191] The use of a chiral auxiliary implies the need for stoichiometric amounts of chiral material, but >99:1 facial selectivity can be obtained in the transformation. Diastereoselectivity is proposed to originate from a closed six-membered metal cation–chelation transition state with the sulfinyl directing group and the α-fluoro(phenylsulfonyl)methyl anion. Fluorobenzylazine has also been reported with fluorobenzylsulfone pronucleophiles.[192]

Organocatalysts were used as bifunctional catalysts for the enantioselective addition of α-fluoro-α-nitrophenylfluoromethane (Scheme 43)[199] or FSM (Scheme 44)[200] to α,β-unsaturated ketones with cinchona alkaloid-derived catalysts 2.2 and 2.3 to afford β-fluoromethylated ketones. Hydrogen-bonding between both the electrophile and nucleophile with the quinuclidine moiety as well as the thiourea (Scheme 43) or amine (Scheme 44) is postulated to induce enantioselectivity.

**Scheme 42.** Monofluoromethyl pronucleophiles addition to chiral N-(tert-butylsulfinyl)aldimines and ketimines

The nucleophilic reactivity of resonance-stabilized fluoromethyl anions have been used in the Mitsunobu reaction of alcohols[193] as well as substitution reactions with alkyl halides[194] en route to monofluoroalkanes. Fluorohydromethylallylation of alkynes with palladium catalysts[195] affords 3-fluoropropene products. Enantioselective fluoromethylation via transition-metal catalysis, PTC, and organocatalysis have been established with fluoromethyl pronucleophiles, most commonly with FSM. Analogous to asymmetric allylic alkylation reaction with other nucleophiles with pKa values ≤10, the palladium-catalyzed asymmetric alkylation of allylic acetates with FSM[196] most likely occurs via external addition of the fluoromethyl nucleophile to the chiral palladium-allyl complex to afford the enantioenriched fluoromethylated product. Cross-coupling of 2-pyridylsulfonyl iodosfluoromethane with aryl iodides via copper(I) salts has been also been reported.[197] FSM was used in the enantioselective Mannich reaction under PTC for the synthesis of enantoienriched α-monofluoromethylated amines.[198] Ion-pairing between the chiral ammonium salt and the α,α-substituted fluoromethyl anion in a polar aprotic solvent gives rise to enantioselective addition to the imine intermediate.

**Scheme 43.** Organocatalytic enantioselective 1,4-conjugate addition of fluoromethyl pronucleophile to α,β-unsaturated aryl ketones

**Scheme 44.** Organocatalytic enantioselective 1,4-conjugate addition of fluoromethyl pronucleophile to α,β-unsaturated aryl ketones

### 3. Difluoromethylation

Molecules containing α-fluoro and α,α-difluoro groups are important components of pesticides and pharmaceuticals.[201] The α,α-difluoromethyl group has been examined for its propensity to serve as a hydrogen bond donor as potential replacement for hydroxyl groups inter alia.[202] Many approaches towards electrophilic difluoromethylation as well as electrophilic trifluoromethylation (chapter 4), are based on radical reactivity. This is likely due to the stability imparted by multiple fluorine substitution on radical intermediates and explains the scarcity of radical reactions that achieve electrophilic monofluoromethylation. Additionally, a significant number of electrophilic difluoromethylation methods involve difluorocarbene intermediates. The π-donating ability of fluorine imparts stability difluorocarbene as well as difluoromethyl radicals compared to their nonfluorinated counterparts and leads to moderate, controlled reactivity.[18] The increased acidity of XF₂–H compared to XFH–H facilitates the formation of F₂CX, where X is a leaving group, the precursor to difluorocarbenes. In developing nucleophilic difluoromethylation reactions, the challenge of difluoromethyl anion being prone to α-elimination and decomposition, needs to be overcome and this is often addressed through the use of electron-withdrawing group-stabilized pronucleophiles. Difluoromethyl pronucleophiles such as...
difluoromethyl phenyl sulfone typically contain one substituent that can provide mesomeric stabilization to the anion and often another substituent (usually a halide or silyl group), which is used to generate the anion.

3.1. Electrophilic methods for difluoromethylation

3.1.1. Radical difluoromethylation

Radical difluoromethylation of alkenes and alkynes has been reported with difluorodiiodomethane facilitated by sodium dithionite as a radical initiator (Scheme 45). Similarly, difluoroiodobromomethane or difluoroiodochloromethane in combination with the radical initiator CuCl is used for the difluoromethylation of olefins. Radical α-difluoromethylation of enamines and ynamines can be performed with difluoroiodohalomethanes and halodifluorosulfanyl reagents in the presence of appropriate radical initiators. 

Radical addition of iododifluoromethane across alkenes and alkynes

\[
R=\text{Ar or alkyl}
\]

\[
R=\text{Ar or alkyl}
\]

\[
R=\text{Ar or alkyl}
\]

\[
R=\text{Ar or alkyl}
\]

Scheme 45. Radical addition of iododifluoromethane across alkenes and alkynes

Diastereoselective chiral auxiliary–mediated α-alkylation with difluoromethylating reagent

 radial difluoromethylation of C–H bonds in heteroarenes with tert-butylhydrogen peroxide and crystalline, bench-top stable 

\[ \text{Zn(SO}_2\text{CF}_2\text{H})_2 \]

at ambient temperature and atmosphere was established by the Baran group (Scheme 47). Stable fluoroalkyl metal sulfinate complexes for the generation of trifluoromethyl radicals were previously used for the radical trifluoromethylation of heteroarenes, but \[ \text{Zn(SO}_2\text{CF}_2\text{H})_2 \] as a source of difluoromethyl radicals gives access to a larger variety and higher yield of functionalized heteroarenes. In the reaction, difluoromethyl radicals are generated and observed to preferentially react with the electron-poor sites of arenes and electron-deficient π-systems such as enones at the β-position, likely due to the electrophilic character of difluoromethyl radicals.

3.1.2. Electrophilic difluoromethylation through carbene intermediates

Aryl difluoromethyl ethers and thioethers can be synthesized from phenoxides\textit{[214]} and thiophenolates\textit{[214c-e, 214g]} with sources of difluorocarbene such as difluoroiodomethane,\textit{[214a, 214c, 214d]} difluoroiodohalomethane,\textit{[214b, 214c, 214d]} diethylbromodifluoromethyl phosphonate (Scheme 48),\textit{[214e]} and fluorosulfonyl difluoroacetic acid reagents.\textit{[214e]} Difluoromethylation with diethylbromodifluoromethyl phosphonate, as described by Zafrani and Segall, has proven most successful, allowing for difluoromethylation of simple electron-rich or -poor phenols and thiophenols in 60–96% yield (Scheme 48). In addition, enolizable functional groups such as acetyl groups do not undergo side reactions with the reagent. The proposed mechanism for the generation of difluorocarbene from diethylbromodifluoromethyl phosphonate consists in saponification of diethyl phosphonate with release of difluorobromomethyl anion followed by α-elimination of bromide from difluorobromomethyl anion to give difluorocarbene.

15
sulphonamides,\textsuperscript{[221]} sulfanyltetrazoles,\textsuperscript{[222]} benzo triazoles and tetrazoles,\textsuperscript{[223]} 2-acetaminopyridine,\textsuperscript{[224]} and indazoles\textsuperscript{[225]} can be converted into N-difluoromethylated products. Historically, other reagents used in N-difluoromethylation include Zn(CF\textsubscript{3})\textsubscript{2}\textsuperscript{[226]} Cd(CF\textsubscript{3})\textsubscript{2}\textsuperscript{[226a, 226b, 226d]} and Bi(CF\textsubscript{3})\textsubscript{3}/AlCl\textsubscript{3}\textsuperscript{[226d]} all of which react through difluorocarbene intermediates. More recently, non-ozone-depleting reagents 2-chloro-2,2-difluoroacetophenone\textsuperscript{[228]} and chlorodifluoromethyl phenyl sulfone (Scheme 49)\textsuperscript{[229]} have been used to generate difluorocarbene in the presence of nucleophiles to afford O- and N-difluoromethylated products.

![Scheme 49. Difluoromethylation of phenols with chlorodifluoromethyl phenyl sulfone](image)

Various nucleophiles including tertiary amines, imidazoles, phosphines, and sulfoxides can be treated with difluoromethylsulfoximium reagent 3.1 developed by Prakash to afford N-, P-, and O-difluoromethylated products (Scheme 50); however, the reagent did not give the corresponding difluoromethylated products with either phenols, carbon-based nucleophiles or primary/secondary amines. Decomposition of the reagent via deprotonation of the acidic proton on the difluoromethyl group in the presence of the nucleophile may provide a rationale for why some more basic nucleophiles prove incompatible with the reagent.\textsuperscript{[230]} Similarly, N,N-dimethyl-S-difluoromethyl-S-phenylsulfoximium tetrafluoroborate can be used to alkylate N-, P-, and N-nucleophiles.\textsuperscript{[238]}

![Scheme 50. Difluoroalkylation of tertiary amines and phosphines, imidazoles, and sulfonic acids](image)

Difluoromethylation of C-nucleophiles with pK\textsubscript{a} values (in DMSO) in the range of 16.3 to 19.1 can be accomplished with chlorodifluoromethane (Freon R-22) and affords products in 7–64% yield.\textsuperscript{[231]} Treatment of enolates with chlorodifluoromethane gives rise to α-difluoromethylated carbonyl products,\textsuperscript{[232]} while diastereoselective α-difluoromethylation of N-acyloxazolidinones utilizes bromodifluoromethane.\textsuperscript{[233]} Trimethylsilyl fluoro sulfonyldifluoroacetate (TFFA), which also acts as a source of difluorocarbene, reacts with alkynes,\textsuperscript{[234]} alkynes,\textsuperscript{[234a]} and ketones\textsuperscript{[235]} to form gem-difluorocyclopropanes, gem-difluorcycloprenes, and gem-difluoropropane ethers respectively. Less commonly, this reagent is used for difluoromethylation reactions at heteroatoms.\textsuperscript{[234b, 236]}

3.1.3. Electrophilic difluoromethylation by other mechanisms

The development of alkylating reagent N-tosyl-S-difluoromethyl-S-phenylsulfoximine led to the successful difluoromethylation of S-, N-, and C-nucleophiles (Scheme 51).\textsuperscript{[237]} The results of deuterium-exchange studies have rendered the formation of difluorocarbene intermediates unlikely since deprotonation/protonation steps would likely occur in the mechanism, leading to deuterium incorporation, which was not observed. This observation may provide a rationale for why the sulfoximine reagent is not competent for the difluoromethylation of phenols, which have been shown to react with difluorocarbene. Aryl α,α-difluoroethers can be synthesized, however, via oxidative rearrangement of aldehydes with difluoroarylbromane.\textsuperscript{[238]}

![Scheme 51. Difluoromethylation S-, C-, N-nucleophiles with N-tosyl-S-difluoromethyl-S-phenylsulfoximine](image)

When iodosdifluoromethane is treated with lithium enolates, alkylation occurs selectively with fluoride displacement instead of iodide displacement.\textsuperscript{[239]} The selective fluoride displacement is attributed to activation of fluoride with lithium, driven by the formation of lithium fluoride, which has the highest alkali metal–halide lattice energy.\textsuperscript{[240]} Copper-catalyzed decarboxyative difluoromethylation of α,β-unsaturated carboxylic acids was accomplished with electrophilic iodonium-based difluoromethyl reagent 3.2 in 60–91% yield with stereocontrol of double-bond geometry (Scheme 52).\textsuperscript{[241]} Difluoromethylation of boronic acids can be accomplished with copper, ethyl difluoroiodoacetate and N,N-diethyl-difluorooxycarbamid.\textsuperscript{[242]}

![Scheme 52. Cu-catalyzed decarboxyative difluoromethylation of α,β-unsaturated carboxylic acids](image)

3.2. Nucleophilic methods for difluoromethylation

Nucleophilic approaches to the synthesis of α,α-difluoromethylenes are still in use, but their importance declined with the development of milder, high-yielding electrophilic difluoromethylation methods. Nucleophilic fluorodesulfurization of thioesters\textsuperscript{[141a, 141i]} and xanthates\textsuperscript{[240, 241b, 243]} in addition to nucleophilic fluoride oxidation of aryl formyl esters\textsuperscript{[244]} have been used to synthesize α,α-difluorinated ethers. Similarly the α,α-difluorination of thioacetal-protected esters can be accomplished with TREAT + HF and bromine.\textsuperscript{[245]} Fluorination of carbonates with SF\textsubscript{6} results in bis(alkoxy)difluoromethane products.\textsuperscript{[246]} An extensive review was published on the synthesis of α-fluorinated ethers, sulfides, amines, and phosphines.\textsuperscript{[20b]}

16
3.2.1. **Nucleophilic difluorination to form C$_{sp^2}$–CF$_2$X bonds**

C–H acidic difluoromethyl pronucleophiles containing sulfone, sulfoxide, or phosphonate electron-withdrawing groups are deprotonated prior to reaction with alkyl halides,[247] carboxyl substrates,[190, 248] chiral sulfinylimines[249] amino sulfinylimines[188] and cyclic sulfates (Scheme 53) and sulfimidates[250]. Difluoromethyl phenyl sulfoxides[251] and phosphonates[252] reagents have also been used. The electron-withdrawing group in the pronucleophile used for nucleophilic difluoromethylation such as a sulfone is cleaved to give the difluoromethyl group after the pronucleophile is introduced into the substrate. The aforementioned difluoromethyl pronucleophiles are readily prepared,[214c, 214d, 253] thermally stable after deprotonation,[254] and the electron-withdrawing group can be removed after difluoromethylation.[255] Phase-transfer catalysis with 3,3 for the enantioselective addition of difluoromethyl phenyl sulfone to aldehydes was explored, with enantioselectivity ranging from 4–64% ee (Scheme 54).[255]

\[
\begin{align*}
\text{Scheme 53. Ring opening of cyclic sulfates with difluoromethyl} \\
\text{phenyl sulfone}
\end{align*}
\]

\[
\begin{align*}
\text{Scheme 54. Enantioselective addition of fluoromethyl pronucleophile} \\
\text{to aryl aldehydes using a chiral ammonium cinchona alkaloid catalyst}
\end{align*}
\]

The electron-rich organic reductant tetrakis(dimethylamino)ethylene (TDAE) has an oxidation potential similar to zinc metal[256] and can transfer two-electrons via sequential single-electron transfer (SET). TDAE is used to reduce the carbon–halogen bond in difluoromethyl pronucleophiles to generate difluoromethyl anion equivalents which can react with aldehydes.[257] Reaction of trimethylsilyldifluoromethyl pronucleophiles with carbonyl substrates are mediated by fluoride or Lewis acids.[258] Advantages of utilizing silyl-based difluoromethyl pronucleophiles include easy preparation of the reagents[259] and compatibility with enolizable carbonyl compounds. More recently, reagent (R)-N-tert-butyldimethylsilyl-S-difluoromethyl-S-phenylsulfoximine has been developed for the diastereoselective nucleophilic difluoromethylation of aryl ketones.[260]

3.2.2. **Nucleophilic difluorination to form C$_{sp^2}$–CF$_2$X bonds**

In the presence of copper chloride, cadmium difluoromethylphosphonate reagents can be cross-coupled with iodosoarenes to afford aryl difluoromethylphosphonates (Scheme 55).[261] Similarly, copper-based difluoromethylating reagents derived from halodifluoroacetate undergo cross-coupling with aryl or alkynyl iodides.[262] The copper-catalyzed cross-coupling of aryl halides and ethyl trimethylsilyldifluoracetate to yield substituted difluoromethyl benzoates, which, after saponification and decarboxylation, afford difluoromethylenes, was reported by Amii.[263] Ethyl ortho-iodobenzoate derivatives can undergo copper-catalyzed cross-coupling with zinc diethylidifluoromethylphosphonate as reported by Zhang.[264] Direct difluoromethylation of aryl and alkynyl iodides using five equivalents of TMSCF$_3$H as the difluoromethyl pronucleophile with copper salts was established by Hartwig and co-workers (Scheme 56).[265] The latter method tolerates electron-rich as well as electron-poor functional groups and directly affords the desired difluoromethylated products in 30–91% isolated yield. Prakash and co-workers recently developed a method for the difluoromethylation of aryl and alkynyl halides as well as heteroaryl halides with Bu$_3$SnCF$_3$H and copper salts (Scheme 57).[266] Difluoromethyl aryls can also be synthesized by nucleophilic deoxyfluorination of aromatic aldehydes with Deoxo-Fluor[267]

![Scheme 55. Cu-mediated cross-coupling of cadmium-based difluoromethyl pronucleophile with aryl iodides](image)

![Scheme 56. Direct difluoromethylation of aryl and alkynyl iodides with copper iodide and TMSCF$_3$H](image)

![Scheme 57. Direct difluoromethylation of aryl, heteroaryl, and alkynyl iodides with copper iodide and Bu$_3$SnCF$_3$H](image)

4. **Trifluoromethylation**

Trifluoromethyl groups are electron-withdrawing substituents that increase the lipophilicity of molecules.[173] Functionalization of
anti-cancer agent epothilone with a trifluoromethyl group (later named fludelone) serves as an example of how trifluoromethylation can increase the metabolic stability of the molecule while retaining comparable cytotoxic potency.\textsuperscript{268} Hence, there is considerable interest in developing methods for controlled introduction of trifluoromethyl groups into small molecules. Compared to mono- and difluoromethylation, fewer synthesis strategies are available for the introduction of trifluoromethyl groups; because three of the four substituents on the carbon atom are pre-determined, only one other substituent can be varied, which limits potential synthetic handles. Transition-metal-mediated trifluoromethylation is complicated by the strong metal–CF\textsubscript{3} bond originating from both the polar contribution of the bond as well as backbonding from filled metal d orbitals into the σ\textsuperscript{C.F\textsubscript{3}} bonds, which therefore results in a high barrier to C–CF\textsubscript{3} bond formation.

4.1. Electrophilic trifluoromethylation

A range of substrates can be trifluoromethylated employing functional group tolerant reagents and conditions. In laboratory settings, crystalline and easily workable electrophilic trifluoromethylating reagents are preferable due to ease of handling, while for industrial processes lower cost reagents such as CF\textsubscript{3}I, or even better CF\textsubscript{3}H, are favored.

The development of widely used crystalline electrophilic trifluoromethylating reagents (Figure 3)\textsuperscript{260} such as the Togni reagents,\textsuperscript{270} S-(trifluoromethyl)dibenzothiophenium salts,\textsuperscript{271} and S-trifluoromethylidarylsulfonium salts\textsuperscript{272} has enabled the development of functional group tolerant methods that encompass a broad substrate scope. These trifluoromethylating reagents are two-electron oxidants but the exact mechanisms for trifluoromethylation have not been firmly established in many cases; the mechanism could occur via two SET or one two-electron transfer concurrent with or followed by trifluoromethyl group transfer.\textsuperscript{273}

![Figure 3. A selection of widely used electrophilic trifluoromethylating reagents](image)

An alternative to using electrophilic trifluoromethylating reagents is the use of nucleophilic trifluoromethylating reagents in conjunction with oxidants to accomplish oxidative trifluoromethylation. Transition-metals have facilitated the aryl carbon–trifluoromethyl group formation in trifluoromethyl arenes from aryl nucleophiles by exploiting redox chemistry at the metal center. Organocatalysts, on the other hand, have allowed for the development of enantioselective α-trifluoromethylation reactions\textsuperscript{274} of carbonyl substrates via radical and non-radical mechanisms.

4.1.1. Electrophilic methods for the synthesis of trifluoromethylated sp\textsuperscript{3} carbon centers via radicals

Initial forays into radical trifluoromethylation of arenes utilized photochemically-induced radical addition of trifluorooiodomethane to substituted benzenes\textsuperscript{275} and imidazoles\textsuperscript{276} as well as flash thermolysis of aryl trifluoroacetates\textsuperscript{277} to afford a mixture of trifluoromethylated products in circa 15\% yield. Copper(II)-catalyzed electrophilic radical trifluoromethylation was later established using sodium trifluoroethylsulfinate for trifluoromethylation of electron-rich arenes.\textsuperscript{278} Ensuing endeavors have focused on developing trifluoromethylation methods that afford trifluoromethylated product in high yield and selectivity, which was recently accomplished via radical trifluoromethylation.\textsuperscript{279}

Direct trifluoromethylation of C–H bonds would obviate the need for pre-functionalization, but is rendered difficult by the inertness of arene C–H bonds. In the case of N-heteroarenes and electron-rich arenes, reaction with Togni’s reagent affords multiple trifluoromethylated products for most substrates.\textsuperscript{280} The use of solid and bench-top stable reagent NaSO\textsubscript{3}CF\textsubscript{3} in radical trifluoromethylations was first described by Langlois for the trifluoromethylation of electron-rich arenes.\textsuperscript{278} Baran and coworkers used the Langlois reagent in conjunction with excess tert-butyl hydrogen peroxide for the trifluoromethylation of heteroarenes (Scheme 58).\textsuperscript{281} The method is operationally simple, takes place at ambient temperature and atmosphere through in situ generation of electrophilic CF\textsubscript{3} radicals without additional catalysts. The selectivity for this reaction ranges from a 1:1 isomeric product mixture to the formation of a single isomer. The Baran group has since improved radical trifluoromethylation with Zn(SO\textsubscript{3}CF\textsubscript{3})\textsubscript{2} and extended the use of other fluorinated zinc sulfinate salts to include a variety of fluorinated derivatives.\textsuperscript{213b} Photooxidation catalysis with a reox-active ruthenium(II) catalyst and CF\textsubscript{3}SO\textsubscript{2}Cl, as described by MacMillan and co-workers, has been used to generate the electrophilic CF\textsubscript{3} radical and leads to the formation of mononitrifluoromethylated products for heteroarenes and trifluoromethylated arenes (Scheme 59).\textsuperscript{282} The trifluoromethylation methods described by Baran and MacMillan allow for the efficient direct synthesis of complex trifluoromethyl arenes, which had not previously been possible. Iron-catalyzed radical trifluoromethylation of arenes and heteroarenes yields less than 50\% for most substrates,\textsuperscript{283} while Fe(II)-catalyzed trifluoromethylation of potassium alkenyltrifluoroborates with Tognis reagent II affords the desired trifluoromethylated alkenes in 49–79\% yield in up to >93.5 E/Z selectivity (Scheme 60).\textsuperscript{284} Silver-mediated trifluoromethylation of unactivated arenes and heteroarenes with TMS(CF\textsubscript{3})\textsubscript{2} is likewise postulated to occur via a radical mechanism to afford trifluoromethylated products (Scheme 61).\textsuperscript{285}
4.1.2. Electrophilic methods for the synthesis of trifluoromethylated sp and sp² carbon centers with copper

The trifluoromethylation of boronic acids has been successfully accomplished with copper catalysts via two approaches: 1) oxidation with an electrophilic trifluoromethylating reagent or 2) using an oxidant in conjunction with trifluoromethyl anion equivalent. Trifluoromethylation of aryl and alkenylboronic acids with electrophilic trifluoromethylating reagents was reported with Togni reagent as described by Shen (Scheme 62)²⁸⁶ and diaryltrifluoromethylsulfonium salts as described by Liu²⁸⁷ and Xiao²⁸⁸. Shen’s method encompasses a broad range of boronic acid substrates and affords trifluoromethylated products in 50–95% yield while utilizing a lower copper catalyst loading. The use of the combination between a nucleophilic trifluoromethyl source and an oxidant is illustrated by the oxidative copper-mediated trifluoromethylation of arylboronic acids and alkenylboronic acids with silver carbonate and trimethylsilyltrifluoromethane (TMSCF₃) developed by the Qing group (Scheme 63)²⁸⁹. Similarly, oxygen can be used as the terminal oxidant instead of less-desirable metal-based oxidants²⁹⁰ as shown by Buchwald and provides a complementary method to the one described by Shen. In lieu of TMSCF₃, the crystalline and shelf-stable potassium trifluoromethyltrimethoxyborate was used by Gooßen with oxygen as a terminal oxidant.²⁹¹ The Grushin group developed a method that utilizes low-cost fluoroform as the CF₃ source in conjunction with copper complexes to trifluoromethylate arylboronic acids (Scheme 64)²⁹². Sanford and co-workers demonstrated radical trifluoromethylation of arylboronic acids with CF₃I and Cu/Ru co-catalysts (Scheme 65)²⁹³ which subsequently was made more practical with the use of NaSO₂CF₃ as the trifluoromethyl radical source.²⁹⁴

Scheme 62. Cu-catalyzed electrophilic trifluoromethylation of aryl and alkenyl boronic acids with Togni reagent

Scheme 63. Cu-mediated electrophilic trifluoromethylation of aryl and alkenyl boronic acids
more practical and economical for large creation of large amounts of waste and renders the transformations using Ag\((\text{bpy})_2\text{CF}_3\) mediated trifluoromethylation of aryl boronic acids. This transformation reported by Hu allows for facile conversion of \(\alpha,\beta\)-unsaturated esters and other carboxylic acid derivatives to the trifluoromethylalkenes after saponification.

\(\alpha,\beta\)-Unsaturated carboxylic acids undergo copper-catalyzed decarboxylative trifluoromethylation with Togni reagent II to afford the trifluoromethylated alkene products in 42–74% yield with ≥92:8 selectivity for the \(E\)-isomer (Scheme 66). This transformation reported by Hu allows for facile conversion of \(\alpha,\beta\)-unsaturated esters and other carboxylic acid derivatives to the trifluoromethylalkenes after saponification.

\[\text{Ar-COOH} + 20 \text{mof CuOAc, CF}_3\text{I, 1 eq KHCO}_3, 20 \text{Wt H}_2\text{O, DMSO, 12 h, 60°C} \rightarrow \text{Ar-CF}_3\]  

\(\text{Scheme 65. Cu-catalyzed trifluoromethylation of arylic acids with Ru(bpy)_3Cl_2*6H}_2\text{O and CF}_3\text{I} \)

An illustrative example of how transition metals can be employed to control reactivity is the one-pot arene C–H borylation/trifluoromethylation sequence. Direct trifluoromethylation of heteroarenes can be accomplished by copper-catalyzed oxidative trifluoromethylation with TMSCF\(_3\) and bis(tert-butyl)peroxide as well as with oxygen as the oxidant (Scheme 67). Oxidative trifluoromethylation of terminal alkynes using Ag–CO\(_2\text{H}\) and air has also been investigated. The use of oxygen as the stoichiometric (terminal) oxidant avoids the creation of large amounts of waste and renders the transformations more practical and economical for large-scale trifluoromethylation reactions. Regioselective indole trifluoromethylation had been a long-standing challenge; selectivity for the C2 position could be accomplished via copper catalysis\(^{300}\) utilizing an electrophilic trifluoromethylating reagent and in a palladium-catalyzed\(^{301}\) transformation using Ph(OAc)\(_2\) and trifluoromethyl anion.

\[\text{PhI(OAc)}_2 + 4 \text{equiv CF}_3\text{I} \rightarrow \text{PhCF}_3\text{I} + 2 \text{equiv Ph(OAc)}_2 + 2 \text{equiv I}_2\]  

\(\text{Scheme 67. Cu-catalyzed trifluoromethylation of 1,3,4-oxadiazoles} \)

\[\text{HCO}_2\text{H} + 20 \text{mof CuOAc, CF}_3\text{I, 1 eq KHCO}_3, 1 \text{equiv oxidant, 14 h, 80°C} \rightarrow \text{Ar-CF}_3\]  

\(\text{Scheme 66. Cu-catalyzed trifluoromethylation of } \alpha,\beta\text{-unsaturated carboxylic acids with Togni reagent II} \)

\[\text{MoO}_3\text{CO}_2\text{H} + 20 \text{mof CuOAC, CF}_3\text{I, 1 equiv oxidant, 14 h, 80°C} \rightarrow \text{Ar-CF}_3\]  

\(\text{Scheme 66. Cu-catalyzed trifluoromethylation of } \alpha,\beta\text{-unsaturated carboxylic acids with Togni reagent II} \)

\[\text{MoO}_3\text{CO}_2\text{H} + 20 \text{mof CuOAC, CF}_3\text{I, 1 equiv oxidant, 14 h, 80°C} \rightarrow \text{Ar-CF}_3\]  

\(\text{Scheme 66. Cu-catalyzed trifluoromethylation of } \alpha,\beta\text{-unsaturated carboxylic acids with Togni reagent II} \)

\[\text{MoO}_3\text{CO}_2\text{H} + 20 \text{mof CuOAC, CF}_3\text{I, 1 equiv oxidant, 14 h, 80°C} \rightarrow \text{Ar-CF}_3\]  

\(\text{Scheme 66. Cu-catalyzed trifluoromethylation of } \alpha,\beta\text{-unsaturated carboxylic acids with Togni reagent II} \)
4.1.4. Electrophilic methods for the synthesis of trifluoromethylated sp^3 carbon centers

In 1949, Haszeldine reported the photochemical and thermal addition of trifluoromethyl radical to alkenes. The use of ruthenium(II) complexes afforded the addition products of trifluoromethylsulfonyl chloride across alkenes with extrusion of SO_2 in a controlled fashion. Continued interest in controlled addition of fluorinated reagents across double bonds led to the development of lauryl peroxide-initiated radical addition of aminotrifluoroethyl dichloroacarbonyl across alkenes to afford α-trifluoromethylamines. Incorporation of trifluoromethyl groups vicinal to amine functional groups has been accomplished with other approaches besides radical addition of α-trifluoromethylated amino derivatives. These methods include benzoyl peroxide–promoted oxidative coupling between the α-carbon of the amine and TMS CF_3 and the synthesis of anti-α-trifluoromethyl-β-amino alcohols via three-component condensation reaction. Controlled radical trifluoromethyl-aminoalkylation across unactivated alkenes with Togni reagent II, TEMPO, and sodium metal has recently been reported by Studer.

Chiral auxiliary–functionalized lithium imide enolates can undergo trifluoromethylation with trifluoroiodomethane in the presence of radical initiator triethylborane. This transformation was later applied more broadly to the lithium and titanium-based enolates of ketones. Similarly, chiral auxiliary–functionalized zirconium enolates can be trifluoromethylated and perfluoroalkylated in the presence of a ruthenium catalyst in up to 99% yield and ≥9:1 diastereoselectivity. Diastereoselective α-trifluoromethylation of chiral imides was developed with Togni reagent, circumventing the need to condense iodotrifluoromethane gas for use in reactions. Cyclic ketones and carboxylic acid derivatives have also been α-trifluoromethylated through photochemical radical processes. Trifluoroacetaldehyde methyl hemiacetal has been established as a source of trifluoromethyl groups through acid-mediated Friedel-Crafts reaction with arenes.
The initial approach used for the synthesis for 3,3,3-trifluoropropene groups involved trifluoromethylation of pre-functionalized allyl nucleophiles such as allylic silanes and allylic stannanes in addition to trifluorothylation of alkene/stannanes. The combination of allyl halides with TMSCF₃ and stoichiometric Cu for allylic trifluoromethylation has been reported as well. Subsequently, in an effort to obviate the need for toxic stannyl precursors, unactivated alkenes were examined as substrates for trifluoromethylation. As reported by Buchwald, terminal alkenes can undergo C–H activation at the allylic position and oxidation with Togni reagent I in the presence of catalytic amounts of Cu(I) salts to afford >9:1 E/Z selectivity of terminal trifluoromethyl allyl products (Scheme 74, top). Subsequently, this transformation was extended to the intramolecular oxytrifluoromethylation of terminal alkenes. Copper-catalyzed allylic C–H trifluoromethylation of terminal alkenes was reported by Qin, Fu and Liu as well as Wang (Scheme 74, bottom). The latter transformation is hypothesized by Wang and co-workers to occur via SET; Buchwald and co-workers have found through the use of radical scavengers and radical clock substrates that a mechanism involving a free allylic radical is unlikely. Additional reactivity of alkenes with electrophilic trifluoromethylation reagents include the oxidative trifluoromethylation of styrenes to give α-trifluoromethyl ketones and an arene cyclization-trifluoromethylation cascade with activated alkenes. More recently, oxidative trifluoromethylation of primary and secondary Scheme 75) alkylboronic acids has been accomplished with a substoichiometric amount of copper salts in the presence of silver salts and TMSCF₃ to afford the corresponding products in 36–78% yield and 35–54% yield respectively.

Various electrophilic trifluoromethylating reagents such as trifluoro-methylazosulfonylarenes, perfluroiodonium salts, (trifluoromethyl)dibenzothiophenium, selenophenium, and tellurophenium salts, N-trifluoromethyl-N-nitrosobenzenesulfonamide and N-trifluoromethyl-N-nitroso-type reagents have been synthesized for the trifluoromethylation of sulfur and carbon nucleophiles. More commonly used hypervalent iodine reagents developed by Togni have been applied to the trifluoromethylation of carbon and sulfur-based nucleophiles as well as sulfonates. Additionally, fluorinated Johnson reagent [(o-iodophenyl)(trifluoromethyl)-1,2- sulfanylidene]dimethylammonium tetrafluoroborate has been developed as a reagent for the trifluoromethylation of C–H acidic substrates.

4.2. Nucleophilic trifluoromethylation

The synthesis of trifluoromethylated products was initially accomplished via nucleophilic fluoride displacement of trifluoromethyl substrates or fluorodeoxygenation of carboxylic acid derivatives under harsh conditions. Subsequent approaches for nucleophilic trifluoromethylation utilized stabilized trifluoromethyl anion equivalents for cross-coupling, substitution, or addition reactions with electrophiles. Nucleophilic trifluoromethylation with trifluoromethyl anion is challenging due to a competing fluoride elimination pathway that gives rise to difluorocarbene. The relative rates of the productive and the decomposition pathway as well as the rate at which trifluoromethyl anion is generated from the pronucleophile is of great importance, which renders the selection of the correct pronucleophile crucial to the success of nucleophilic trifluoromethylation methods. The trifluoromethyl anion can be generated by reduction of trifluoromethyl iodide or bromide with transition metal or organic reductants or by transmetallations of the pronucleophile to yield a metal-bound CF₃ group.

TMSCF₃, a commonly employed pronucleophile of trifluoromethyl anion, is a hydrolyzable, moisture sensitive liquid which, when compared to weighable, crystalline reagents, is more difficult to handle. Crystalline, weighable reagents have been developed as trifluoromethyl pronucleophiles but can be rather expensive. Trifluoroacetate salts are cheap and easy to handle, but so far no mild, functional group tolerant trifluoromethylation method has been reported using this pronucleophile. Inexpensive, gaseous trifluoromethane can be used for trifluoromethylation reactions.

4.2.1. Nucleophilic methods for the synthesis of trifluoromethylated sp² carbon centers
Swarts first reported the synthesis of trifluoromethylbenzene in 1898 via nucleophilic fluoride substitution of the corresponding trichloride. Benzoic substrates were likewise exhaustively fluorinated at the carbonyl carbon to afford the trifluoromethylated arenes. The yield for nucleophilic trifluoromethylation could be improved when copper powder and CF$_3$I were used to synthesize trifluoromethylbenzene from iodobenzene and subsequent optimization with different sources of copper and metal mixtures allow for lower reaction temperatures. Studies by Burton revealed that the trifluoromethyl-copper complex generated upon reduction of dihalodifluoromethane with zinc metal and metathesis with a copper(I) salt was the active species responsible for trifluoromethylation. This discovery led to the development of different methods using copper-trifluoromethyl complexes to trifluoromethylate aryl bromides, aly chloride, aliphatic halides, and heteroaromatic halides.

Copper has been used stoichiometrically and also as a catalyst with various reagents: dibromodifluoromethane, sodium trifluoroacetate, fluorosulphonyldifluoromethyl iodide, bis(trifluoromethyl)mercury, and trifluoroacetate. The use of trifluoromethyl diphenyl sulfonium triflate has been established in efforts to replace the use of volatile and moisture-sensitive trifluoromethyltrialkylsilanes. Trifluoromethylborate salts are crystalline, air-stable, storage-stable reagents that can act as a donor of trifluoromethyl anion in the presence of copper salts. Similarly, fluoral hemiaminal has been shown to be a stable and inexpensive source of trifluoromethyl anion; however, two equivalents of the reagent relative to the substrate are required.

Trifluoromethylorganosilanes, reported first by Ruppert, are the most commonly used nucleophilic trifluoromethylation reagent in cross-coupling reactions and addition reactions. Trifluoromethylorganosilanes such as trimethylsilyl trifluoromethane (TMSCF$_3$) and triethylsilyltrifluoromethane (TESCF$_3$) can be desilylated with fluoride to give trifluoromethyl anion. The first report of copper-mediated trifluoromethylation of aryl iodides with TMSCF$_3$/K$_2$ [363] by Fuchikami laid the foundation for trifluoromethylation cross-coupling using trifluoromethyltrialkylsilanes. Aryl halides in conjunction with trifluoromethylorganosilanes can react with copper carbene complexes described by Vicic (Scheme 77) and copper/silver co-catalysts by Weng, Feng, and Huang. Copper-nitrogenous ligand catalysts by Amii isolated stoichiometric copper-phenanthroline complexes by Hartwig (Scheme 78) and stoichiometric copper phosphine complexes by Grushin (Scheme 79) to afford trifluoromethylated arenes. The method by Hartwig and co-workers is the most functional group tolerant and allows for trifluoromethylation of electron-poor to electron-rich arenes and even ortho, ortho-disubstituted arenes while the catalytic system by Amii utilizes only 10 mol% copper catalyst loading to afford trifluoromethylated arenes in 44–99% yield.

![Scheme 77. Cu-mediated trifluoromethylation of organic halides with TMSCF$_3$](image)

![Scheme 78. Trifluoromethylation of aryl halides with Trifluoromethylator](image)

![Scheme 79. Trifluoromethylation of aryl halides with Cu-phosphone trifluoromethyl complex](image)

Copper-catalyzed trifluoromethylation of aryl iodides with trifluoromethylborate salts (Scheme 80) and with α-trifluoromethylmorpholinotrialkylsilylether (fluoral hemiaminal) (Scheme 81) have been established in efforts to replace the use of volatile and moisture-sensitive trifluoromethyltrialkylsilanes. Trifluoromethylborate salts are crystalline, air-stable, storage-stable reagents that can act as a donor of trifluoromethyl anion in the presence of copper salts. Similarly, fluoral hemiaminal has been shown to be a stable and inexpensive source of trifluoromethyl anion; however, two equivalents of the reagent relative to the substrate are required. This necessity is postulated to arise from dimerization of the reagent to a silicate species that then acts as the reactive trifluoromethyl anion donor.
A Reformazky-elimination reaction sequence between methyl α-trifluoromethyl-α,α-dichloroacetate with aldehydes mediated by zinc and copper(I) in acetic or trifluoroacetic anhydride afforded trifluoromethyl olefins (Scheme 82).\[371]\] Additionally, alkenyl bromides treated with nuclophilic trifluoromethyl copper complexes generated from fluorosulfonyldifluoroacetate (Scheme 83).\[372]\] mercury bis(trifluoromethyl) and TMSCF$_3$ can afford the desired trifluoromethyl alkenes.

Cross-coupling with TMSCF$_3$ and alkenyl sulfonates has been developed with palladium catalysts to afford trisubstituted trifluoromethyl alkenes (Scheme 86).\[376]\] An unconventional approach to installing trifluoromethylalkenyl groups on alkenes uses palladium-catalyzed cross-coupling and β-hydride elimination to selectively afford disubstituted E-trifluoromethyl alkenes (Scheme 87).\[379]\] Electrophilic trifluoromethylation of alkenes with Togni reagent II mediated by copper iodide can afford trisubstituted trifluoromethyl alkyl carbonates.\[380]\] For the synthesis of β-trifluoromethyl styrenes, alkyl iodides underwent cross-coupling with E-trimethylsilyl-3,3,3-trifluoropropene with retention of double-bond geometry.\[381]\]

**Scheme 81.** Cu-catalyzed trifluoromethylation of aryl halides with fluorinal hemiaminal

**Scheme 82.** Cu-mediated Reformazky-elimination reaction sequence to afford trifluoromethylated alkenes

**Scheme 83.** Cu-mediated trifluoromethylation of alkenyl bromides

The strong Pd-CF$_3$ bond in trifluoromethyl palladium complexes renders reductive elimination of trifluoromethylarenes difficult compared to reductive elimination from aryl methyl palladium complexes, which readily undergo reductive elimination to afford toluene.\[375]\] The viability of reductive elimination from Pd(II) aryl complexes to form aryl-CF$_3$ bonds was established by Grushin with chelating ligand XantPhos at 80 °C (Scheme 84, complex 4.3).\[376]\] Palladium-catalyzed cross-coupling of aryl chlorides with TESCF$_3$ was achieved by Buchwald and co-workers using BrettPhos, a bulky monodentate phosphine, which allows reductive elimination to occur from the T-shaped trifluoromethyl aryl palladium phosphine complex (Scheme 85).\[377]\] While protonic functional groups are not tolerated, possibly due protonation of trifluoromethyl anion to generate fluoroform, electron-rich and poor aryl chlorides as well as heteroaromatic halides can be trifluoromethylated.

**Scheme 84.** Reductive elimination of trifluoromethyl arenes from Pd(II) complex

**Scheme 85.** Pd-catalyzed cross-coupling of aryl halides with TMSCF$_3$

Cross-coupling with TMSCF$_3$ and alkenyl sulfonates has been developed with palladium catalysts to afford trisubstituted trifluoromethyl alkenes (Scheme 86).\[376]\] An unconventional approach to installing trifluoromethylalkenyl groups on alkenes uses palladium-catalyzed cross-coupling and β-hydride elimination to selectively afford disubstituted E-trifluoromethyl alkenes (Scheme 87).\[379]\] Electrophilic trifluoromethylation of alkenes with Togni reagent II mediated by copper iodide can afford trisubstituted trifluoromethyl alkyl carbonates.\[380]\] For the synthesis of β-trifluoromethyl styrenes, alkyl iodides underwent cross-coupling with E-trimethylsilyl-3,3,3-trifluoropropene with retention of double-bond geometry.\[381]\]

**Scheme 86.** Pd-catalyzed trifluoromethylation of alkyl triflates

**Scheme 87.** Pd-catalyzed cross-coupling of aryl iodides and 1,1,1-trifluoro-3-iodopropane with sequential β-hydride elimination

### 4.2.2. Nucleophilic methods for the synthesis of trifluoromethylated sp$^3$ carbon centers

Trifluoromethylating reagents of mercury,\[382]\] zinc,\[226a, 226c, 383]\] and cadmium,\[226a, 384]\] were explored but difficulties and inefficient processes for reagent generation have made their use impractical. Currently, trifluoromethylorganosilanes are the most commonly used nucleophilic trifluoromethyl reagents in the laboratory setting.

Trifluoromethyltrimethylsilane (TMSCF$_3$) after desilylation with tetrabutylammonium fluoride (TBAF) or tri(dimethylamino)sulfonium difluorotrimethylsilicate (TASF) can react with aldehydes,\[385]\] esters,\[386]\] N-(tertbutylsulfinyl)amines,\[387]\] amino N-(tertbutylsulfinyl)amines (Scheme 88),\[388]\] N-tosyl amines,\[389]\] diketo compounds,\[390]\] α,β-unsaturated carbonyls,\[391]\] imines/iminiums,\[392]\] and isoxazoles. (Scheme 89)\[393]\] The fluoride
source is integral to constructive trifluoromethylation reactivity especially for enolizable substrates. Basic metal fluorides can α-deprotonate enolizable substrates so tetraalkylammonium fluorides have been used because they exhibit the right amount of nucleophilicity and basicity. Other nucleophilic trifluoromethylation methods of carbonyls and carbonyl derivatives have been accomplished with Lewis acids and bases\(^{258e,394}\) as well as tri-tert-butylphosphine as the desilylating reagent.\(^ {395}\)

\[\text{Other nucleophilic trifluoromethylation methods of carbonyls and carbonyl derivatives have been accomplished with Lewis acids and bases, as well as tri-tert-butylphosphine as the desilylating reagent.}\]

\[\text{Scheme 88. Diastereoselective addition of TMSCF}_3\text{ to N-} (\text{tert-butyldisulfanyl})\text{amines}\]

\[\text{Scheme 89. Diastereoselective addition of TMSCF}_3\text{ to isoxazoles}\]

Preliminary efforts toward enantioselective trifluoromethyl group addition reactions involved chiral amine auxiliaries such as 4.4 (Scheme 90)\(^{396}\) or asymmetric induction chiral sulfinyl directing groups.\(^ {397}\) The enantioselective addition of trifluoromethyl anion to carbonyl electrophiles has been challenging to accomplish because tight ion pairing between the chiral catalyst and the substrate has been hard to achieve. The use of chiral ammonium cinchona alkaloid-based catalysts such as 4.5 has enabled the asymmetric trifluoromethylation of aromatic aldehydes and ketones,\(^ {399}\) cyclic electron-neutral aromatic ketones (Scheme 91),\(^ {400}\) and alkynyl ketones.\(^ {401}\) In place of the hydroscopic chiral ammonium fluoride salts, chiral ammonium bromides with exogenous potassium fluoride can be employed;\(^ {402}\) however, because potassium fluoride is sparingly soluble in polar aprotic solvents, phenoxide was investigated as the desilylating agent for TMSCF\(_3\).\(^ {403}\) Beyond carbonyl substrates, activated azomethine imines have similarly been reported as viable substrates for enantioselective trifluoromethylation with a chiral ammonium bromide catalyst 4.6 (Scheme 92).\(^ {404}\)

\[\text{Scheme 90. Synthesis of enantioenriched trifluoromethylated alcohols with chiral amine auxiliary}\]

\[\text{Scheme 91. Enantioselective addition of TMSCF}_3\text{ to aryl ketones using PTC}\]

\[\text{Scheme 92. Enantioselective addition of TMSCF}_3\text{ to azomethine imines using PTC}\]

Other nucleophilic trifluoromethylation reagents such as α-trifluoromethylmorpholinotrimethylsilylether,\(^ {370b}\) α-trifluoromethylpiperazinotrimethylsilylether,\(^ {404a}\) and potassium trifluoromethyborates\(^ {405}\) have been utilized for trifluoromethylation reactions. Trifluoroiodomethane reduced with TDAE\(^ {406}\) as well as copper in conjunction with methyl fluorosulfonyldifluoroacetate,\(^ {407}\) chlorodifluoroacetate,\(^ {408}\) methyl chlorodifluoroacetate,\(^ {409}\) bromotrifluoromethane,\(^ {410}\) and sodium trifluoroacetate\(^ {411}\) have been used to generate nucleophilic trifluoromethylation reagents. While many copper-based methods exist, further development with these copper reagents for substitution and addition reactions would need to be developed for practical and efficient reaction chemistry. More recently, (Ph\(_3\)P)\(_3\)CuCF\(_3\) complexes have been reacted with propargyl halides to afford halide displaced trifluoromethylation products\(^ {412}\) and additionally copper salts in conjunction with TMSCF\(_3\) and CsF has been used for the trifluoromethylation of α-diazo esters.\(^ {413}\)

Enantioenriched trifluoromethyl allyl compounds can be synthesized via enantioselective trifluoromethylation of Baylis-Hilman adducts of allylic acetates (Scheme 93)\(^ {414}\) and carbonates.\(^ {415}\) The substrate scope is limited to compounds containing an ester group beta to the allylic acetate or carbonate moiety.
5. **Trifluoroethylation and perfluoroalkylation**

Direct introduction of trifluoroethyl groups for the synthesis of compounds, many of which find applications as pharmaceuticals, can be accomplished with trifluoromethylmethane using either nucleophilic (i.e. aryl iodide cross-coupling with trifluoromethyl iodomethane) or electrophilic methods (i.e. arylboronic acids cross-coupling with trifluoromethylidomethane). Different iodine-based electrophilic trifluoroethylating reagents have been developed for the trifluoroethylation of N-, O-, and S-nucleophiles. Similarly, perfluoroalkylation reactions can occur with electrophilic perfluoroalkylating reagents such as trifluoroalkylation using aryl iodide as the reductant.

### 5.1. Trifluoroethylation

Trifluoroethylated arenes were first synthesized via nucleophilic substitution of the corresponding benzyl bromide with trifluoromethyl copper or bis(trifluoromethyl) mercury reagents (Scheme 94). A new operationally facile approach for the generation of trifluoromethyl copper complex has been reported by reduction of S-(trifluoromethyl)diphenylsulfonium triflate with copper metal at 60 °C to afford 36–83% yield of trifluoroethylated arene products.

**Scheme 94. Synthesis of trifluoroethylated arenes with nucleophilic trifluoromethylating reagents**

![Scheme 94](image)

Direct trifluoroethylation of iodobenzene was first reported by McLoughlin and Thrower through copper-mediated nucleophilic trifluoroethylation with 1-ido-2,2,2-trifluoroethane (Scheme 95). Drawbacks include the need for excess aryl iodide and low yields of the trifluoroethylated arenes. Subsequently, Hartwig reported the reductive elimination of para-trifluoroethyltoluene from an aryl trifluoroethyl Pd(II) complex, demonstrating the aryl C–CH₂CF₃ bond could be formed by reductive elimination. Palladium-catalyzed cross-coupling of trifluoromethylidomethane with aryl and alkenylboronic acids and esters (Scheme 96) or alkyl stannanes affords trifluoroethylated arenes or alkenes. This cross-coupling method displays broad substrate scope and functional group tolerance, and allows for trifluoroethylation of meta-aminophenylboronic acid with no N-trifluoroethylated byproducts. Additionally, cross-coupling of boronic acids and esters with trifluoromethylidomethane is complimentary to trifluoroethylations using aryl halides.

**Scheme 95. Cu-mediated cross-coupling of aryl iodides with trifluoromethylidomethane**

![Scheme 95](image)

**Scheme 96. Pd-catalyzed trifluoroethylation of arylboronic acids**

Trifluorodihaloethylzinc nucleophiles generated from one-electron reduction with zinc powder of 1,1,1-trihalo-2,2,2-trifluoroethane reagents were used in alkylation addition reactions. Electrophilic trifluoroethylation can occur via radical pathways with alkyl, and alkynes using halogenated trifluoroethane reagents and radical initiators such as copper salts or sodium dithionite (Scheme 97).

**Scheme 97. Radical addition of trifluoromethylhalomethane across alkenes and alkynes**

Nitrogenous nucleophiles such as aniline, amines, and phenols, and carboxylic acids, and thioles can be trifluoroethylated using trifluoromethylidonium salts, which act as sources of electrophilic trifluoroethyl groups. Carbon-based nucleophiles afford trifluoroethylated products in 25–36% yield, although α-trifluoroethylation of silylenol ethers is possible in 49–92% yield. A broader range of non-aromatic N-, O-, and S-nucleophiles than reported in prior works can react with reagent 5.1 by trifluoroethylation of the heteroatom.

**Scheme 98. Trifluoroethylation of amines with electrophilic trifluoroethylation hypervalent iodine reagents**

![Scheme 98](image)
5.2. Perfluoroalkylation

Nucleophilic perfluoroalkyl copper reagents were first used to afford perfluoroalkyl arenes from aryl halides \(^\text{[417a]}\) and perfluoroalkyl-substituted alkenes from alkenyl halides. \(^\text{[426]}\) When ionic liquids were used as solvent for perfluoroalkylation of aryl halides, reaction temperature could be lowered from 150 °C to 75 °C. \(^\text{[427]}\) Perfluoroalkylation of aryl and aryl halides has been investigated with discrete phenanthroline-ligated perfluoroalkyl copper complexes by Hartwig (Scheme 99). \(^\text{[356]}\) and with palladium catalysts and zinc metal under ultrasonic irradiation by Ishikawa. \(^\text{[428]}\) Chambers used sodium perfluoroalkylcarboxylates \(^\text{[429]}\) and Daugulis 1H-perfluoroalkanes \(^\text{[343]}\) in lieu of perfluoroalkyl halides as sources of perfluoroalkyl groups to accomplish perfluoroalkylation. The method reported by Hartwig affords electron-rich and -poor perfluoroalkyl arenes and heteroarenes in 88–99% yield at 50 °C while the method developed by Daugulis can afford perfluoroalkylated products from 1H-perfluoroalkanes ranging from trifluoromethane to 1H-perfluorodecane (Scheme 100). \(^\text{[343]}\) Arylboronic acids undergo electrophilic perfluoroalkylation with perfluoroalkyl halide and copper under ambient atmosphere. \(^\text{[422]}\) This room temperature perfluoroalkylation method by Shen and co-workers yields perfluoroalkylated arenes in 29–65% yield.

**Scheme 99.** Perfluoroalkylation of aryl iodides with Cu-phenanthroline perfluoroalkyl complex

A general strategy for the perfluoroalkylation of arenes has been reported by Hartwig and co-workers via a one-pot borylation/perfluoroalkylation sequence. \(^\text{[298b]}\) Perfluoroalkylation of arenes can be accomplished with a palladium-BINAP catalyst and perfluoroalkyl halide as described by Sanford; solvent quantities of the arene are needed (Scheme 101). \(^\text{[431]}\)

![Diagram of perfluoroalkylation](attachment:image1)

**Scheme 100.** Cu-catalyzed perfluoroalkylation of aryl iodides

A general strategy for the perfluoroalkylation of arenes has been reported by Hartwig and co-workers via a one-pot borylation/perfluoroalkylation sequence. \(^\text{[298b]}\) Perfluoroalkylation of arenes can be accomplished with a palladium-BINAP catalyst and perfluoroalkyl halide as described by Sanford; solvent quantities of the arene are needed (Scheme 101). \(^\text{[431]}\)

**Scheme 101.** Pd-catalyzed perfluoroalkylation of unactivated arenes with perfluoroalkyl iodide

Radical addition of haloperfluoroalkylsulfonyl halides across alkenes can be accomplished with benzoyl peroxide \(^\text{[431]}\) and ruthenium(II) catalysts. \(^\text{[412]}\) Perfluoroalkyl transition metal complexes can react with alkenes, \(^\text{[431]}\) dienes, and aliphatic halides, \(^\text{[413]}\) as well as propargyl halides \(^\text{[415]}\) to afford the corresponding perfluoroalkylated alkenes and allenes. Nucleophilic reagents, such as perfluoroalkyl lithium, \(^\text{[436]}\) magnesium bromide, \(^\text{[437]}\) calcium, \(^\text{[438]}\) tin, \(^\text{[439]}\) trimethylisilane \(^\text{[440]}\) and zinc (with a palladium or nickel catalyst), \(^\text{[434, 441]}\) were used prior to the development of the TDAE/perfluoroalkyl halide combination by Dolbier, which is a straightforward and practical method for the perfluoroalkylation of aldehydes, ketones, imines, disulfides, and diselenides (Scheme 102). \(^\text{[431]}\) affording nonafluorobutylation products in 20–98% yield. Similarly, Prakash reported the alkoxide-induced release of perfluoroalkyl anion from perfluoroethylthiophenylsulfonyl reagents which reacts with carbonyls and imines in 50–99% yield (Scheme 102). \(^\text{[441]}\)

**Scheme 102.** Two methods for the addition of perfluoroalkyl groups to carbonyl and carbonyl derivatives

Aryl perfluoroalkylidonium chloride reagents were developed for perfluoroalkylation of thio- and seleno-nucleophiles by Yagupolskii. \(^\text{[444]}\) The chloride was subsequently exchanged for the less coordinating triflate counterion resulting in the more electrophilic FITS (perfluoroalkylphenyldonium trifluoromethanesulfonate) reagent for perfluoroalkylation (Scheme 102).
103) of carbanion nucleophiles,\textsuperscript{445} arenes,\textsuperscript{446} thiophenols and thiols at sulfur,\textsuperscript{435} substituted phenols at oxygen,\textsuperscript{447} alkynes,\textsuperscript{448} and alkenol ethers at carbon\textsuperscript{449} as described by Umemoto. Additionally, alkenes can be perfluoroalkylated with the FITS reagent to afford perfluoroalkyl olefins\textsuperscript{450} \( \alpha \)-Perfluoroalkylation of silylenol ethers with perfluoroalkyl halides can be initiated with radical promoter triethylborane.\textsuperscript{451} Another approach for the \( O \)- and \( S \)-perfluoroalkylation of phenolates and thiophenolates involves the use of tetrafluorodihaloethane and perfluorodihaloalkanes.\textsuperscript{432} This process is proposed to occur via in situ conversion of the perfluoroalkylating reagent to a perfluorinated alkene intermediate which is supported by separate reports of \( O \)-perfluoroalkylation at phenol with perfluoropropylene\textsuperscript{453} and \( N \)-perfluoroalkylation with tetrafluoroethylene.\textsuperscript{454}

In addition to perfluoroalkyl substituents, the pentafluorosulfanyl substituent has received increased attention over the recent past. Pentafluorosulfanyl substituents are chemically inert, increase lipophilicity, and could develop as useful groups for pharmaceuticals and agrochemicals.\textsuperscript{455} Simple pentafluorosulfanyl-substituted compounds are commercially available, but the difficulty of synthesis and requirement for toxic reagents is currently a drawback for the development of new methods for incorporation of the \( SF_5 \) group into more complex substrates.

\begin{center}
\begin{align*}
\text{Scheme 103. Perfluoroalkylation of arenes, sulfides, terminal alkynes, and 3,5-difert-butylphenol with electrophilic perfluoroalkyl hypervalent iodine reagents}
\end{align*}
\end{center}

\textbf{6. Trifluoromethyl ethers, sulfides, and amines}

Trifluoromethoxylated and trifluoromethylthiolated molecules have been used as agrochemicals, pharmaceuticals, and electro-optical materials.\textsuperscript{456} The increase in lipophilicity\textsuperscript{457} resulting from trifluoromethoxy and trifluoromethylthiol group incorporation has made both functional groups attractive substituents for use in medicinal chemistry. Additionally, the ability to induce conformational changes through the trifluoromethoxy substituent, which adopts an orthogonal orientation with respect to the arene plane,\textsuperscript{458} in contrast to a methoxy group, which normally rests in plane of the arene, can be beneficial to obtain additional binding affinity. Trifluoromethyamines have applications as fluorinating reagents,\textsuperscript{459} these compounds are prone to fluoride ionization followed by hydrolysis of the resulting iminium or imine, which renders many trifluoromethyamines difficult to isolate and store.

The difficulty of trifluoromethylation at heteroatoms is dependent on the nucleophilicity of the heteroatom; trifluoromethylation at nitrogen and oxygen is more difficult to accomplish than at sulfur.\textsuperscript{459} Consequently, the synthesis of trifluoromethyl ethers and amines has classically involved pre-functionalization at oxygen or nitrogen with carbonyl or thiocarbonyl functional groups followed by fluoride introduction. Many approaches for the synthesis of trifluoromethyl ethers and amines have low functional group tolerance due to the use of hydrogen fluoride, Lewis acids, or thermally unstable, reactive trifluoromethylating reagents. Trifluoromethylysulfides can be more easily synthesized using a variety of electrophilic trifluoromethylating reagents. Additionally, the enhanced stability and nucleophilicity of free trifluoromethylthiolate as compared to trifluoromethoxide, which eliminates fluoride at elevated temperature, has facilitated the development cross-coupling methods for the synthesis of trifluoromethylysulfides.

\textbf{6.1. Preparation of trifluoromethyl ethers}

The formation of the oxygen–\( CF_3 \) bond as well as the carbon–\( OCF_3 \) bond has been difficult to accomplish for two main reasons: reactivity of the trifluoromethylating reagents with carbon sites of the oxygenated nucleophile leading to formation of byproducts and the thermal instability of many trifluoromethoxide salts. Many nucleophilic fluorodesulfitization and fluoroxygenation of functionalized alcohols and phenols have been established for the synthesis of trifluoromethyl ethers whereas fewer methods for the formation of oxygen–\( CF_3 \) and carbon–\( OCF_3 \) bonds have been successfully accomplished. Synthesis of aryl trifluoromethyl ethers via O-trifluoromethylation of phenols is currently of limited synthetic use due to carbon trifluoromethylation or the need for impractical reaction conditions with thermally unstable \( O \)-(trifluoromethyl) dibenzofuranium reagents. In contrast, \( O \)-trifluoromethylation of primary and secondary alcohols with thermally stable Togni reagent affords the desired trifluoromethyl ethers.\textsuperscript{460}

\textbf{6.1.1. Preparation of aryl trifluoromethyl ethers}

Nucleophilic fluorination of aryl trichloromethyl ethers,\textsuperscript{461a} aryl chlorothionoformates,\textsuperscript{461b, 462} phenyl fluorooformates,\textsuperscript{463} and aryl xanthates\textsuperscript{464} constitute most of the methods developed for the synthesis of trifluoromethoxyarenes. A general, practical, functional-group-tolerant trifluoromethylation of phenols is not yet available. Aryl trichloromethyl ethers\textsuperscript{461a, 461b, 461d} synthesized in situ\textsuperscript{461c} or prior to the reaction by chlorination of the aryl methyl ether\textsuperscript{461a, 461c, 461f} or aryl chlorothionoformates\textsuperscript{461b, 462} can be nucleophilically fluorinated with hydrogen fluoride,\textsuperscript{461e, 465} \( SF_2 \), \( SF_2 \) in the presence of \( SF_2 \), \( SF_4 \), \( SF_6 \) or molybdenum hexafluoride.\textsuperscript{462, 467} Likewise, phenol fluorooformates can be treated with \( SF_2 \) or \( SF_4 \) to afford trifluoromethoxyarenes (Scheme 104).\textsuperscript{463} Aryl xanthates were used as substrates for fluorodesulfurization with HF/pyridine and dibrominated hydantoin (Scheme 105).\textsuperscript{464a}
cannot currently be tolerated

products of functionalized aryl stannanes and boronic esters with ethers (trifluoromethoxide to afford functionalized aryl trifluoromethyl cross Aryl to benzynes to

OCF$_3$fluoride

S

O

Ar reaction with trifluoromethoxide was attempted, but products from S$_3$Ar with fluoride is observed instead, likely due to trifluoromethoxide degradation into volatile carbonyl difluoride and fluoride. Kolomeitev reported that phenyl and naphthyl carbon–OCF$_3$ formation occurred when trifluoromethoxide anion was added to benzenes to afford ary1 trifluoromethyl ethers (Scheme 108). Aryl stannanes and aryl boronic acids can undergo silver-mediated cross-coupling with tris(dimethylamino)sulfonium trifluoromethoxide to afford functionalized ary1 trifluoromethyl ethers (Scheme 109). This method affords the cross-coupling products of functionalized aryl stannanes and boronic esters with trifluoromethoxide; heteroaryl nucleophiles and nucleophilic amines cannot currently be tolerated. More recently, copper and gold oxygen-bound trifluoromethoxide complexes have been prepared and characterized in efforts to provide better understanding of transition metal interactions with trifluoromethoxide anion. Preliminary efforts toward the direct C–H functionalization of arenes with trifluoromethylhypofluorite has been reported but mixtures consisting mainly of fluorinated arenes in addition to trifluoromethoxylated arenes.

Scheme 104. Synthesis of aryl trifluoromethyl ethers via fluoroformate intermediates

Scheme 105. Synthesis of aryl trifluoromethyl ethers by fluorodesulfurization of aryl xanthates

Umemoto reported that phenol derivatives can undergo trifluoromethylation with O-(trifluoromethyl)dibenzofuranium reagents in the presence of alkyl amine bases to afford trifluoromethoxynitropentanes (Scheme 106). The reagent needs to be generated prior to use by photochemical decomposition of the trifluoromethoxybaryl diazonium salt at –100 to –90 °C to yield the active O-(trifluoromethyl)dibenzofuranium reagent 6.1. Trifluoromethylation of phenols with Togni reagent II was investigated by Togni and co-workers, and O-trifluoromethylation occurred with 2,4,6-trimethylphenol in 15% yield along with carbon trifluoromethylation products (Scheme 107).[273]

Scheme 106. O-Trifluoromethylation of phenols to afford aryl trifluoromethyl ethers

Scheme 107. O-Trifluoromethylation of phenols with Togni reagent II

The use of trifluoromethoxide anion to form the aryl carbon–oxygen bond has not been as widely explored as other approaches. S$_3$Ar reaction with trifluoromethoxide was attempted, but products from S$_3$Ar with fluoride are observed instead, likely due to trifluoromethoxide degradation into volatile carbonyl difluoride and fluoride. Kolomeitev reported that phenyl and naphthyl carbon–O CF$_3$ formation occurred when trifluoromethoxide anion was added to benzenes to afford ary1 trifluoromethyl ethers (Scheme 108). Aryl stannanes and aryl boronic acids can undergo silver-mediated cross-coupling with tris(dimethylamino)sulfonium trifluoromethoxide to afford functionalized ary1 trifluoromethyl ethers (Scheme 109). This method affords the cross-coupling products of functionalized aryl stannanes and boronic esters with trifluoromethoxide; heteroaryl nucleophiles and nucleophilic amines cannot currently be tolerated. More recently, copper and gold oxygen-bound trifluoromethoxide complexes have been prepared and characterized in efforts to provide better understanding of transition metal interactions with trifluoromethoxide anion. Preliminary efforts toward the direct C–H functionalization of arenes with trifluoromethylhypofluorite has been reported but mixtures consisting mainly of fluorinated arenes in addition to trifluoromethoxylated arenes.

Scheme 108. Trifluoromethoxide anion addition to ortho-trimethylsilylnaphthyl triflate via aryne intermediate

Scheme 109. Ag-mediated cross-coupling of aryl stannanes with trifluoromethoxide salt

6.1.2. Preparation of alkyl trifluoromethyl ethers

Alkyl trifluoromethyl ethers can be synthesized via the trifluoromethylation of alcohols or displacement of a leaving group on alkyl electrophiles by trifluoromethoxide anion. Primary and secondary alcohols can be trifluoromethylated with Togni reagent in the presence of Zn(N(Tf)$_2$)$_2$. The soluble zinc catalyst with non-nucleophilic triflimide anions is proposed by Togni and co-workers to activate the reagent for attack through coordination to the carboxy group of the reagent. Togni reagent II reacts with tetrahydrofuran in the presence of Lewis or Brønsted acids to afford polymeric ring-opened trifluoromethyl ethers and reacts with sulfonic acids to afford O-trifluoromethylated sulfonic acids. 2-Phenylethanol, n-decanol, and (2-naphthyl)methanol were reported by Umemoto to react with O-(trifluoromethyl)dibenzofuranium reagents (shown in Scheme 106 with phenols) to afford the corresponding alkyl trifluoromethyl ethers. Analogous to the fluorination of aryl xanthates, alkyl
xanthates were treated with BrF$_3$ to afford alkyl trifluoromethyl ethers\cite{460} while alkyl triflates were substituted with trifluoromethoxide anion (Scheme 111).\cite{460}

\[
\begin{align*}
R-OH + \text{BrF}_3 & \xrightarrow{0.25-1 \text{ equiv } \text{Zn(TfO)}_2} 24 \sim 3 \text{ d, } 23 \text{ °C} \rightarrow R-\text{OCF}_3 \\
5 \text{ eq as solvent} & \rightarrow 12-99\%
\end{align*}
\]

Scheme 110. $O$-Trifluoromethylation of alcohols with Togni reagent II

\[
\begin{align*}
\text{MeO}_2\text{C} & \xrightarrow{2 \text{ equiv } \text{SCF}_3} \xrightarrow{1-2 \text{ h, } 0-20 \text{ °C}} \text{MeCN} \rightarrow \text{MeO}_2\text{C} \\
75 & \rightarrow 91\%
\end{align*}
\]

Scheme 111. Synthesis of trifluoromethyl ethers via displacement of alkyl triflates with trifluoromethoxide salts

6.2. Preparation of trifluoromethyl sulfides

Alkylation of thiols with various electrophilic trifluoromethylating reagents has been a fruitful approach toward the synthesis of trifluoromethylsulfides. The $S$-trifluoromethylation of a broad range of aliphatic thiols and thiophenols (Scheme 112)\cite{273a} and $S$-hydrogen phosphorothiate\cite{273a} was reported by Togni and co-workers using Togni reagent II and later applied to the trifluoromethylation of cysteine residues in peptide substrates.\cite{473} $Se$-(trifluoromethyl)dibenzoselenophenium reagent 6.2 can likewise afford $S$-trifluoromethylated thiols as demonstrated by Umemoto (Scheme 113).\cite{271b}

\[
\begin{align*}
\text{R} & \xrightarrow{\text{F}_{3}\text{C}-\text{I}} \xrightarrow{-78 \text{ °C}} \xrightarrow{1.1 \text{ equiv } \text{CH}_2\text{Cl}_2} \text{R}\text{SCF}_3 \\
\text{R} & = \text{Ar, alkyl} \rightarrow 51-99\%
\end{align*}
\]

Scheme 112. $S$-Trifluoromethylation of thiols with Togni reagent II

\[
\begin{align*}
\text{R} & \xrightarrow{\text{THF, 0.5 h, } 0-23 \text{ °C}} \xrightarrow{\text{6.2}} \text{R}\text{SCF}_3 \\
\text{R} & = \text{alkyl} \rightarrow 87-99\%
\end{align*}
\]

Scheme 113. $S$-Trifluoromethylation of sodium thiolates with $S$-(trifluoromethyl)dibenzoselenophenium triflate

Trifluoromethylsulfides can be synthesized by photolysis of aryl and alkyl trifluoromethylthiosulfonates\cite{474} to promote desulfonylation and radical recombination or trifluoromethylation of disulfides\cite{475} with TMSCF$_3$ as reported by Langlois. Similarly, disulfides can be trifluoromethylated with a mixture of TDAE and iodos trifluoromethane (Scheme 114).\cite{470} The CF$_3$/TDAE method developed by Dolbier can trifluoromethylate both sulfur atoms of simple disulfides in 65–99% yield. Cysteine derivatives have been trifluoromethylated with sodium trifluoromethylsulfinate and tert-butyl hydrogen peroxide (Scheme 115).\cite{477}

\[
\begin{align*}
\text{R}-\text{S} & \xrightarrow{4.2-5 \text{ equiv } \text{CF}_{3}\text{I}} \text{DMF, } 2-12 \text{ h, } 0-25 \text{ °C} \rightarrow 2 \text{ F}_{3}\text{C}\text{S}\text{R} \\
\text{R} & = \text{Ar, alkyl} \rightarrow 22 \text{ equiv} \rightarrow 65-99\%
\end{align*}
\]

Scheme 114. $S$-Trifluoromethylation of disulfides

\[
\begin{align*}
\text{MeO} & \xrightarrow{3 \text{ eq } \text{NaSO}_2\text{CF}_{3}} \xrightarrow{4.5 \text{ equiv } \text{BuOOH} \text{ in } \text{H}_2\text{O}} \xrightarrow{2.5 \text{ h, } 20 \text{ °C}} \text{MeO} \rightarrow \text{MeO} \\
\text{Scheme 115. $S$-Trifluoromethylation of cysteine derivatives}
\end{align*}
\]

\[
\begin{align*}
\text{Me} & \xrightarrow{\text{Pr} \text{ R} \text{SCF}_3} \xrightarrow{2 \text{ equiv } \text{R} \text{MgCl}} \xrightarrow{\text{THF, 6 h, } 0 \text{ °C}} \text{Me} \text{SCF}_3 \\
\text{Pr} & \xrightarrow{10\%} \text{Me} \rightarrow 81\%
\end{align*}
\]

Scheme 116. Grignard reaction with trifluoromethanesulfanamide reagent to afford trifluoromethylsulfides

Displacement of chloride in $S\text{A}r$ reactions of electron-poor chloroarenes with silver trifluoromethylthiolate is limited in substrate scope but affords the desired aryl trifluoromethylsulfide (Scheme 117).\cite{479} Analogous to the synthesis of aryl trifluoromethyl ethers, ortho-trimethylsilylphenyl trifluoromethanesulfonate can be used to generate a benzyne intermediate that reacts with TDAE-bis(trifluoromethylthiolate) to give phenyl trifluoromethylsulfide (Scheme 118).\cite{468} Although both approaches give rise to trifluoromethylsulfides in high yield, the reported methods are biased toward electron-poor arenes or unfunctionalized ortho-trimethylsilylaryl triflates.

\[
\begin{align*}
\text{ Scheme 117. Nucleophilic aromatic substitution with silver trifluoromethylthiolate}
\end{align*}
\]
Scheme 118. Trifluoromethylation anion addition to ortho-trimethylsilylphenyl triflate via aryne intermediate

Aryl trifluromethyl sulfides were synthesized from aryl diazonium salts (Scheme 119)[480] and electron-poor aryl iodides (Scheme 120)[481] by Clark via reaction with pre-generated copper trifluoromethylthiolate. Chen has reported the in situ generation of copper trifluoromethylthiolate at 100 °C from copper, octathiocane (sulphur, S₈), and fluoro sulfonylfluorooester for trifluoromethylthiolation of aryl iodides.[482]

Scheme 119. Synthesis of aryl trifluoromethyl thioethers from aryl diazonium salts with copper trifluoromethylthiolate

Palladium catalysis for the synthesis of aryl trifluoromethyl thioethers was developed by Buchwald with silver trifluoromethylthiolate activated with tetramethylammonium trifluoromethylthiolate.[483] A combination of a nickel catalyst with tetramethylammonium trifluoromethylthiolate was described by the Vicic group to convert aryl iodides to aryl trifluoromethyl sulfide (Scheme 122).[484] This method was later extended to boronic acid substrates using a copper catalyst.[485] While nickel-catalyzed trifluoromethylthiolation of simple aryl iodides occurs at room temperature and does not necessitate silver trifluoromethylthiolate, the substrate scope is more limited than that displayed by the palladium-catalyzed reaction developed by the Buchwald group. Qing and co-workers established the cross-coupling of aryboronic acids with octathiocane (sulphur, S₈) in the presence of TMSCF₃, and two equivalents of silver carbonate catalyzed by copper(I) at room temperature to afford the desired products in 58–91% yield.[486] Terminal alkynes were also shown to be viable substrates for this transformation.[487] Amidodirected C–H functionalization of arenes with trifluorosulfonyl groups was recently accomplished by Daugulis via copper catalysis with trifluoromethylidisulfide (Scheme 123).[488]

Scheme 120. Synthesis of aryl trifluoromethyl thioethers from aryl iodides and copper trifluoromethylthiolate

Scheme 121. Pd-catalyzed cross-coupling of aryl bromides with silver trifluoromethylthiolate activated with tetrasubstituted ammonium iodide

Scheme 122. Ni-catalyzed cross-coupling of aryl iodides with tetramethylammonium trifluoromethylthiolate

Scheme 123. Cu-catalyzed N-directed C–H functionalization of arenes with trifluoromethylsulfonyl groups

6.3. Preparation of trifluoromethylamines

Primary and secondary alkyl trifluoromethyl amines have been difficult to synthesize due to facile decomposition, mostly via elimination of fluoride, while tertiary alkyl trifluoromethyl amines can be synthesized but are difficult to isolate.[489] Nitrogenous nucleophiles with less nucleophilic nitrogen lone pairs such as anilines, pyridine, and azoles can be successfully trifluoromethylated and isolated.[489, 490]

The main approaches for the synthesis of trifluoromethylamines involve nucleophilic fluorination of thiocarbonyl-functionalized amines and N-trifluoromethylation of amines. Amines are first derivatized to thiuramide sulfides (Scheme 124)[491, 492] N-alkyl dithiocarbamates (Scheme 125)[491] or formamides[495, 496] followed by fluorination with nucleophilic fluoride sources. The formamide approach typically affords trifluoromethylamine products in high yield but involves the use of gaseous and toxic SF₅F. This functionalization–fluorination reaction sequence was also reported with N-perfluoroalkyl dithiocarbamates[497] and N-heteroaryl dithiocarbamates (Scheme 126)[498].
Scheme 124. Fluorodesulfurization of thiuramide sulfides

\[
\begin{align*}
\text{MeS-N=SS-NEt}_2 & \quad + \quad 1.5 \text{ equiv } \text{Et}(\text{NSF}_2) \quad 0 ^\circ \text{C} \\
& \quad \text{then warm to } 20 ^\circ \text{C} \\
\rightarrow & \quad \text{F}_2\text{C-NEt}_2 \\
\text{Yield: } & \quad 70\%
\end{align*}
\]

Scheme 125. Fluorodesulfurization of dithiocarbamates

\[
\begin{align*}
\text{MeS-N=SN=S} & \quad + \quad 3 \text{ equiv } \text{NBu}_4\text{H}_2\text{F}_3 \quad \text{CH}_2\text{Cl}_2 \quad 1 \text{ h}, 0 ^\circ \text{C} \\
\rightarrow & \quad \text{F}_2\text{C-N=S} \\
\text{Yield: } & \quad 62-99\%
\end{align*}
\]

Scheme 126. Fluorodesulfurization of N-heteroaryl dithiocarbamates

Although S-(trifluoromethyl)dibenzothiophenium salts react with nitrogenous nucleophiles to afford C-trifluoromethylated products, O-(trifluoromethyl)dibenzoazanium reagent 6.1 reacts with nitrogenous nucleophiles to afford N-trifluoromethylated anilines, primary, secondary and tertiary alkyl amines, and nitrogenous heteroarenes (Scheme 127). The O-(trifluoromethyl)dibenzoazanium reagent 6.1 by Umemoto is the same, thermally unstable, reagent used for the O-trifluoromethylation of phenols.

Scheme 127. Electrophilic N-trifluoromethylation of amines

\[
\begin{align*}
\text{R}^1 & \quad = \quad \text{Ar}, \text{ alkyl} \\
\text{R}^2 & \quad = \quad \text{alkyl, Ar} \\
\text{Y} & \quad = \quad \text{C or N} \\
\end{align*}
\]

\[
\begin{align*}
\text{R}^1 & \quad \text{N=C} \quad + \quad \text{F}_2\text{C} \quad + \quad \text{H} \quad \text{BF}_3 \\
& \quad \text{BF}_3 \\
& \quad \text{CF}_3 \\
& \quad \text{CF}_3 \\
\text{Yield: } & \quad 38-63\%
\end{align*}
\]

Scheme 128. N-Trifluoromethylation of Ritter-type reaction products

\[
\begin{align*}
\text{X} & \quad = \quad \text{C or N} \\
Y & \quad = \quad \text{C or N} \\
\text{R} & \quad = \quad \text{alkyl, Ar}
\end{align*}
\]

\[
\begin{align*}
\text{MeS} & \quad \text{N=S} \quad + \quad \text{F}_2\text{C} \quad + \quad \text{H} \quad \text{BF}_3 \\
& \quad \text{BF}_3 \\
& \quad \text{CF}_3 \\
& \quad \text{CF}_3 \\
\text{Yield: } & \quad 47-68\%
\end{align*}
\]

Scheme 129. Synthesis of monofluoroalkenes via Wittig olefination of carbonyls

\[
\begin{align*}
\text{R}^1 & \quad = \quad \text{H, Ar} \\
\text{R}^2 & \quad = \quad \text{H, alkyl} \\
\text{THF} & \quad 0.5 \text{ h}, -78 ^\circ \text{C} \\
\rightarrow & \quad \text{R}^1 & \quad \text{R}^2 \\
\text{Yield: } & \quad 16-65\%
\end{align*}
\]

Scheme 130. Synthesis of monofluoroalkenes via Julia-Kocienski reaction with carbonyls

An addition-elimination sequence of fluorobis(phenylsulfonyl)methane with alkyl halides was used to afford monofluoroalkenes (Scheme 131). The selectivity for the E-isomer is proposed to arise from neighboring group participation by the aryl group during the elimination step. The stereoselective synthesis of Z-fluoroalkenes was achieved by addition of fluorosulfoximine 7.1 to nitrones followed by elimination of nitrosobenzene (Scheme 132). In the proposed transition-state, the two aryl groups are positioned gauche for the formation of the disfavored E-isomer; therefore, a preference for the Z-isomers would be predicted.

Scheme 131. Synthesis of monofluoroalkenes via Julia-Kocienski-type reaction with benzyl halides

Fluorinated alkenes

Fluorinated alkenes have applications as peptide mimics and as monomers in polymerization reactions, e.g. for the synthesis of Teflon. Because the fluoroalkene moiety has a size and dipole moment similar to an amide bond while being difficult to hydrolyze, molecules containing the fluoroalkene motif have been used as inhibitors of peptidases.
Monofluoroalkene synthesis via alkyne hydrofluorination was first accomplished with polymer-supported dihydrogen trifluoride \[^{[507]}\] and tetrabutylammonium dihydrogen trifluoride. \[^{[508]}\] Transition-metal–mediated hydrofluorination was demonstrated by Sadighi via reversible gold-mediated hydrofluorination of substituted alkenes with triethylamine-hydrogen fluoride (Scheme 133). \[^{[509]}\] Subsequently, gold-catalyzed N-directed synthesis of fluoroalkenes from disubstituted alkenes and triethylamine trifluoride was shown to yield >50:1 regioselectivity by Miller and co-workers (Scheme 134). \[^{[510]}\] The reaction can also be ester-directed but regioselectivity is lower; 1:1.5 in favor of isomer B in some cases (see Scheme 134).

Silver-mediated electrophilic fluorodestannylation of alkynyl stannanes reported by Tius demonstrated that the synthesis of fluoroalkenes could be accomplished via electrophilic fluorination. \[^{[33]}\] \[^{[46]}\] Gouverneur reported the gold-catalyzed cyclization–fluorination of propargyl ketones with F-TEDA-BF\(_4\) to afford cyclic α-fluoro vinylogous esters (Scheme 135) \[^{[511]}\] with the protodeaaurated product accounting for most of the byproduct. Intermediates of gold-carbene–catalyzed rearranged propargyl acetates can also be fluorinated electrophilically to afford α-fluoroenones as describe by Nevado (Scheme 136). \[^{[512]}\] Only alkyl- or phenyl- functionalized propargyl acetates were reported to undergo this rearrangement.

Nucleophilic S\(_2\)\(^2\) additions of 3,3-difluoropropenes with cuprates \[^{[513]}\] organolithium reagents \[^{[514]}\] and amines \[^{[515]}\] by Paquin and co-workers have been used to synthesize double-bond transposed fluorinated allylic products (Scheme 137). In contrast to highly nucleophilic organolithiums, neutral amine nucleophiles required the use of palladium complexes to first activate 3,3-difluoropropenes as an allyl fragment. With organolithium reagents monomodiiodoalkenes are lithiated and fluorinated with N-fluoro-N-tert-butylphenylsulfonamide affording the same double bond geometry \[^{[516]}\] trifluoromethyl tosylhydrazones, on the other hand, rearrange to monofluoroalkenes with an excess of alkyl lithium reagents. \[^{[517]}\] Palladium-catalyzed cross-coupling of terminal alkenes with iodo-fluoroalkenes affords fluorinated enyne products, \[^{[518]}\] while fluoroaryl tosylate undergoes cross-coupling with boronic acids to yield terminal fluoroalkene. \[^{[519]}\] Copper-catalyzed reaction of Freon-113 (1,1,1-difluoro1chloro-2,2,2-dichlorofluoromethane) with aryl hydrazones produces fluorinated alkenes derivatives with release of N\(_2\). \[^{[520]}\]

### 7.2. Preparation of α,α-difluoroalkenes and 1,2-difluoroalkenes

#### 7.2.1. Preparation of α,α-difluoroalkenes
Approaches used to synthesize difluoroalkenes are similar to those of monofluoroalkenes which include Wittig and (Scheme 138)\(^{501b, 501c, 521}\) Horner-Wadsworth-Emmons olefination \(^{522}\) as well as difluoromethylation with bis(trifluoromethyl) mercury, \(^{523}\) copper and difluorodibromomethane, \(^{524}\) and difluorophenylsulfonylmethylfluorosilane. \(^{525}\) Generally, carbonyl difluoromethylation reactions with difluoromethylenating reagents give rise to yields below 70%. The addition-elimination sequence used to synthesize monofluoroalkenes from alkyl halides and fluoroalkenyl phenyl sulfone \(^{526}\) has adapted to the synthesis of difluoroalkenes through the use of difluoromethyl phenyl sulfone and alkyl halides (Scheme 139). \(^{526b}\) Although the method by Prakash shown in Scheme 139 utilizes a slight excess of starting material to base, it provides access to aliphatic and aryl difluoroolefins in a synthetically practical manner.

Scheme 138. Synthesis of difluoroalkenes via Wittig-type olefination of aldehydes

\[
\text{R} = \text{Ph}, \text{SO}_{2} \text{Ph} \\
\text{R} = 1.5 \text{ eq} \text{ NaOCl, CH}_{2} \text{Cl}_{2} \\
\text{1.5 eq} \text{ PPh}_{3}, \text{ 1.5 eq} \text{ NaOCl, CH}_{2} \text{Cl}_{2} \\
\text{diglyme, 1 h 4 °C, 60–80 °C} \\
\text{R} = \text{Ph}, \text{SO}_{2} \text{Ph} \\
\text{R} = \text{Ph}, \text{SO}_{2} \text{Ph} \\
\text{55–68\%} \\
\text{Scheme 139. Elimination of fluoromethyl alkylated products to afford difluoroalkenes}
\]

Geminally-substituted trifluoromethyl dimethylphenylsilyl alkene can be transformed to the 1,1-difluoroalkenes via \(\text{S}_{\text{N}}2\)’ addition of various nucleophiles like LAH, organolithium reagents, and lithium enolates (Scheme 140). \(^{527}\) Similarly, trifluoromethyl styrenes can rearrange to geminal difluoroalkenyl amines \(^{528}\) after addition of lithium amide or allylic alkyl difluoroalkanes \(^{529\*}\) or organolithium reagents (Scheme 140). More recently, the addition of substituted hydrazine nucleophiles to trifluoromethyl styrene followed by intramolecular cyclization was shown to yield various 3-fluoropirazolone products. \(^{530}\) Trifluoromethyl tosylhydrazones rearrange to difluoroalkenes with 2.5 equivalents of nBuLi or methyl lithium through extrusion of N\(_2\) gas and tolylsulfinate (Scheme 141). \(^{531}\) Similarly, nBuLi induces opening of chlorodifluoromethyl epoxides to afford 1,1-difluoroallylic alcohols. \(^{532}\)

Scheme 140. \(\text{S}_{\text{N}}2\)’ addition of various nucleophiles to 3,3,3-trifluoropropene

\[
\text{Scheme 141. Alkyl lithium-induced rearrangement of aryl trifluoromethyl tosylhydrazones to terminal 1,1-difluorostyrenes}
\]

Cross-coupling methods provide an expedient route for the installation of difluoroalkenyl groups from commercially available arene precursors. Trifluoromethyl groups of \(\alpha\)-trifluoromethylstyrenes undergo \(\beta\)-fluoride elimination in the presence of rhodium catalysts and then participate in a cross-coupling reaction with arylboronic acids to give 1,1-difluoroallylic aryl products (Scheme 142). \(^{532}\) Cross-coupling of difluoroalkenylzinc reagents with aryl iodides under palladium catalysis yields difluorostyrenyl products, \(^{533}\) while difluoroenol derivatives such as \(\alpha\)-difluoroketoneidoacets can be cross-coupled with stannanes or boronic acids to afford aryl difluoroenol products. \(^{534}\)

Scheme 142. Rh-catalyzed coupling of 3,3,3-trifluoropropene with aryloboronic ester with \(\beta\)-fluoride elimination

7.2.2. Preparation of 1,2-difluoroalkenes

1,2-Difluoroalkenes can be synthesized in up to 97% yield by elimination of hydrogen bromide from 1,1,1-dibromofluoro-2-fluorosubstituted substrates with up to 99:1 E/Z selectivity as well as by protodesilylation of 1,2-difluoro-1-silylalkene. \(^{536}\) 1,2-Difluoroolefins can additionally be synthesized via cross-coupling of the fluorinated alkynyl zinc reagent with aryl iodides (Scheme 143) \(^{537}\) allowing for the late-stage introduction of vicinal difluoroalkynyl groups into arenes. Treatment of \(\alpha\)-keto carboxyls with Deoxo-Fluor\(^{\text{R}}\) yields \(\alpha\)-\(\beta\)-difluoroenone (Scheme 144). \(^{538}\)

Scheme 143. Pd-catalyzed cross-coupling of aryl iodides with 1,2-difluoroalkenyl zinc reagent

Scheme 144. Synthesis of \(\alpha\),\(\beta\)-difluoroenones via nucleophilic fluorination of Deoxo-Fluor\(^{\text{R}}\)
8. Fluorination with fluorine-18 for positron emission tomography (PET)

Positron emission tomography (PET) is widely recognized as a clinical tool for cancer diagnosis, with other applications emerging in medical research and patient care.\textsuperscript{[5c–d]} PET relies on the use of radiotracers that bear a radionuclide which decays via positron emission, such as fluorine-18. Simple radiotracers containing fluorine-18 can be synthesized via conventional fluorinations methods. But conventional fluorination methods typically have low functional group tolerance and cannot afford complex, biomedically relevant molecules as PET tracers. Due to the short half-life of 110 minutes of fluorine-18, synthesis of radiotracers requires that fluorine-18 introduction occur at a late-stage of the synthesis to avoid unproductive decay. The time used to synthesize, purify, and formulate radiotracers for injection should be less than two half-lives of the radionuclide. The ideal method for fluorine-18 introduction is functional group tolerant, fast, shows low water-sensitivity, affords a single fluorinated product, and requires only straightforward purification. We will only cover recent, conceptually novel approaches for C–F bond formation; comprehensive reviews are available.\textsuperscript{[Miller, 2008 #855;Cai, 2008 #1032;Ametamey, 2008 #748;Phelps, 2000 #858;Bolton, 2002 #752;Tredwell, 2012 #2848]}

### 8.1. Nucleophilic methods for the incorporation of \(^{18}\)F

Fluorine-18 is synthesized through bombardment of oxygen-18–enriched water with protons to afford aqueous \(^{18}\)F-fluoride in high specific activity. Desolvation of aqueous \(^{18}\)F-fluoride to afford anhydrous \(^{18}\)F-fluoride is difficult due to the strong hydrogen bonding interaction of fluoride anions with water.\textsuperscript{[Emsley, 1980 #2226]} \(^{18}\)F-enriched fluorine gas is generally of lower specific activity than \(^{18}\)F-fluoride, but recent advances have increased the specific activity obtainable for \([^{18}\text{F}]_{2}\).\textsuperscript{[539]} \(^{18}\)F-Fluoride is the most practical and most widely available source of \(^{18}\)F.

Radiofluorination reactions with \(^{18}\)F-fluoride most commonly consist in substitution reactions that occur on alkyl or aryl electrophiles, functionalized with appropriate leaving groups. Alkali salts are typically used along with cryptands to increase fluoride nucleophilicity.\textsuperscript{[150]} Reactions solvents are chosen such that S$_n$-type and S$_n$Ar-type reactions are facilitated, with the most commonly used solvents being polar aprotic solvents such as DMF, DMSO, and acetonitrile. \(t\)-Butyl alcohol may be used to temper the basicity of \(^{18}\)F-fluoride for aliphatic substitution reactions.\textsuperscript{[109]} The most commonly used radiotracer for imaging, 2-deoxy-2-[\(^{18}\)F]fluoro-D-glucose (\([^{18}\text{F}]\text{FDG}\)), is made via nucleophilic substitution of a triflate leaving group on a mannose triflate derivative with \(^{18}\)F-fluoride (Scheme 145).\textsuperscript{[540]} For the synthesis of \(^{18}\)F-functionalized aliphatic fluorides, Gouverneur and co-workers reported the first palladium-catalyzed fluorination reaction with \(^{18}\)F-fluoride.\textsuperscript{[167]}

\[\text{Scheme 145. Nucleophilic radiochemical fluorination with \(^{18}\)F-fluoride to afford \([^{18}\text{F}]\text{FDG}\)}\]

Nucleophilic aromatic substitution with \(^{18}\)F-fluoride can be used to synthesize \(^{18}\)F-labelled arenes.\textsuperscript{[541]} For substrates to undergo S$_n$Ar-type substitution reactions, they generally require at least one electron-withdrawing group on the arene ortho or para to the leaving group, which can be a nitro, triarylammonium, halide, or sulfonate groups. Nicotinic acetylcholine receptor radioligands have been synthesized via nucleophilic aromatic substitution (Scheme 147).\textsuperscript{[542]}

\[\text{Scheme 146. Pd-catalyzed allylic fluorination with \(^{18}\)F-fluoride}\]

Nucleophilic aromatic substitution with \(^{18}\)F-fluoride can be used to synthesize \(^{18}\)F-labelled arenes.\textsuperscript{[541]} For substrates to undergo S$_n$Ar-type substitution reactions, they generally require at least one electron-withdrawing group on the arene ortho or para to the leaving group, which can be a nitro, triarylammonium, halide, or sulfonate groups. Nicotinic acetylcholine receptor radioligands have been synthesized via nucleophilic aromatic substitution (Scheme 147).\textsuperscript{[542]}

\[\text{Scheme 147. Nucleophilic aromatic substitution with \(^{18}\)F-fluoride}\]

Diaryliodonium salts 8.1 can be fluorinated with \(^{18}\)F-fluoride to yield radiolabelled aryl fluorides.\textsuperscript{[543]} The selectivity for fluorination between the arenes attached to iodine is based on the electronic structure of the arenes (the more electron-poor arene is fluorinated) and the steric bulk near iodine (ortho-substituted arenes are more susceptible to fluorination due the ortho-effect\textsuperscript{[544]}) (Scheme 148). Electron rich 2-thiophene can be used to advantage as a dummy ligand on iodine.\textsuperscript{[543]} The countering of the iodonium salts also have a large effect on the yield of fluorination, with the more dissociative and non-nucleophilic counterions promoting higher radiochemical yields. With ortho-substituted substrates, the radiochemical yields can be as high as ~60%. The availability of more straightforward syntheses of complex diaryliodonium salts would increase the utility of the method and its use for PET tracer synthesis. Current syntheses of aryl iodonium salts often employ strong Lewis or Bronsted acids.\textsuperscript{[545]}

\[\text{Scheme 148. Nucleophilic radiochemical fluorination of aryl(2-thienyl)iodonium bromides}\]

### 8.2. Electrophilic methods for the incorporation of \(^{18}\)F

Several \(^{18}\)F-electrophilic fluorinating reagents have been synthesized from \(^{18}\)F-fluoride gas such as \(^{18}\)F-acetyl hypofluorite,\textsuperscript{[546]} \(^{18}\)F-xenon difluoride,\textsuperscript{[544a, 547]} \(^{18}\)F-N-fluorosulfonamide or imide reagents,\textsuperscript{[548]} \(^{18}\)F-N-fluoropyridinium salts,\textsuperscript{[549]} and \(^{18}\)F-TEDA salts.\textsuperscript{[510b]} Electrophilic radiofluorination via direct, non-specific fluorination of substrates such as alkenes\textsuperscript{[550]} for the synthesis of \([^{18}\text{F}]\text{FDG}\) and related sugars as well as arenes\textsuperscript{[551]} for the synthesis of \([^{18}\text{F}]\text{fluoro-3,4-dihydroxy phenylalanine (\([^{18}\text{F}]\text{F-DOPA})}\) can lead to multiple fluorinated
products and typically are not functional group tolerant. Radiochemical fluorodemetallation has been used for aryl organometallic reagents,\[548a\] aryl silanes,\[17c, d\] and aryl stannanes\[34a, 546b\] and can afford selective fluorination.

Gouverneur developed the oxidative fluorination of para-tert-butylphenols with replacement of the para-tert-butyl group with 18\(^{\text{F}}\)-fluoride in the presence of iodobenzene diacetate and trifluoroacetic acid in dichloromethane (Scheme 149).\[552\] The reaction is proposed to occur via oxidative fluorination/dearomatization followed by rearomatization. The radiochemical yields for various para-tert-butylphenol derivatives range from 7–21% and the reaction tolerates a wide range of electronically-diverse ortho-substituents including halides, other tert-butyl groups, carbonyls, and olefins.

**Scheme 149.** Oxidative radiochemical fluorination of para-tert-butylphenols with 18\(^{\text{F}}\)-fluoride and iodobenzene diacetate

An electrophilic radiofluorination for the synthesis of aryl fluorides in high specific activity utilizes Pd(IV) complex 8.2 to incorporate 18\(^{\text{F}}\)-fluoride into complex arenes (Scheme 150).\[553\] The Pd(IV) complex captures fluoride and then functions as electrophilic [18\(^{\text{F}}\)]fluorination reagent. Direct S\(2\) transfer and an electron-coupled fluoride transfer have both been proposed as possible reaction pathways. An advantage of using this method is that 18\(^{\text{F}}\)-fluoride can be incorporated into functionalized arenes at a late stage. Additionally, the Pd(IV)-[18\(^{\text{F}}\)] complex is thermally stable and insensitive to water.

**Scheme 150.** Synthesis of an electrophilic 18\(^{\text{F}}\)-Pd(IV) fluorinating reagent from 18\(^{\text{F}}\)-fluoride to afford e for the synthesis of 18\(^{\text{F}}\)-labelled aryl fluorides

Ni(II) aryl pyridylsulfonamide complexes can be oxidized with oxidant 8.3 in the presence of aqueous 18\(^{\text{F}}\)-fluoride to afford complex 18\(^{\text{F}}\)-labelled arenes in 13-58% RCY (Scheme 151).\[554\] The use of aqueous fluoride-18 solution obviates the need for time consuming anion exchange and azeotropic drying steps during PET tracer synthesis. Radiofluorination takes place at room temperature and is complete within less than one minute.

**Scheme 151.** Synthesis of 18\(^{\text{F}}\)-labelled aryl fluorides from Ni(II) complexes, oxidant, and aqueous 18\(^{\text{F}}\)-fluoride

**Outlook**

The most significant, conceptual advances in the past decade of fluorination chemistry, broadly defined, were made in the areas of carbon–fluorine and carbon–CF\(_3\) bond formation reactions, most prominently via organo- and transition-metal catalysis. The most challenging transformation remains the parent C–F bond formation, primarily due to the high hydration energy of fluoride, strong metal-fluorine bonds, and the highly polarized nature of bonds to fluoride.

Fluorination chemistry still lacks general predictability and practicality. For example, commonly employed electrophilic fluorinating and trifluoromethylating reagents are often not cost efficient on manufacturing scale. Even nucleophilic methods often require expensive reagents or catalysts, which reduce the practicality of modern fluorination reactions for large-scale synthesis. Despite these limitations, modern methods for fluorination chemistry have made fluorinated molecules more readily available than ever before. In particular, the modern methods start to impact research areas that
do not require large amounts of material, such as drug discovery and PET. Future research in the field should focus on the development of practical and selective fluorination reactions, with readily available starting materials and cost-efficient reagents. The ideal fluorination reaction would be predictable, general, and functional group tolerant, use fluoride, and be catalyzed by a readily available, inexpensive catalyst.

The authors thank Dr. Jean Raynaud, Anthony R. Mazzotti, Dr. Jochen R. Brandt, Dr. Ming-Yu Ngi, and Dr. Takeru Furuya for helpful discussions.

Received: {will be filled in by the editorial staff}  
Published online on {will be filled in by the editorial staff}


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[++] ((General Annotations))
Fluorination chemistry is more than 100 years old, yet, it still remains a challenge today. Recent advances, to a large extend enabled by catalysis, have resulted in more efficient methods to introduce fluorine and fluorine-containing functional groups into functionalized molecules. This review focuses on new strategies for fluorination, with a brief introduction to conventional fluorination, so that the modern methods can be put into perspective.

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