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Fluorine

# Introduction of Fluorine and Fluorine-Containing Functional Groups

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*Over the past decade, the most significant, conceptual advances in the field of fluorination were enabled most prominently by organo- and transition-metal catalysis. The most challenging transformation remains the formation of the parent C–F bond, primarily as a consequence of the high hydration energy of fluoride, strong metal–fluorine bonds, and highly polarized bonds to fluorine. Most fluorination reactions still lack generality, predictability, and cost-efficiency. Despite all current limitations, modern fluorination methods have made fluorinated molecules more readily available than ever before and have begun to have an impact on research areas that do not require large amounts of material, such as drug discovery and positron emission tomography. This Review gives a brief summary of conventional fluorination reactions, including those reactions that introduce fluorinated functional groups, and focuses on modern developments in the field.*

**From the Contents**



## Introduction

The development of fluorination chemistry began more than 100 years ago, with the first examples of nucleophilic and electrophilic fluorination reactions being reported in the second half of the 19th century.[1] However, significant challenges in fluorination chemistry still remain. Current interest in fluorination chemistry is largely a consequence of the properties that fluorine substitution can impart on molecules, such as pharmaceuticals,[2] agrochemicals,[3] materials,[4] and radiotracers for positron emission tomography (PET).[5] Despite a longstanding appreciation of fluorine's utility, fluorination methods still lack generality, practicality, and predictability. Carbon–fluorine bond formation is a challenging chemical transformation largely due to the high electronegativity of fluorine and the high hydration energy of the fluoride anion.[6] In nature, haloperoxidase enzymes[7] give rise to thousands of organochlorides and organobromides,[8] but no fluoroperoxidase enzyme has been identified. Despite fluorine being the 13th most abundant element in the Earth's crust,[9] only a handful of natural biosynthesized organofluorides[9] are known.[10]

A few decades ago, the development of several fluorinating reagents such as Selectfluor[11] and DAST (diethylaminosulfur trifluoride)[12] resulted in the rapid 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 the incorporation of fluorine. 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[13] and their relevance to modern developments are discussed briefly to put modern fluorination chemistry[14] 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 nonfluorinated analogues, 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 as 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 because of editorial constraints.

## 1. Fluorination

Fluorine can provide many beneficial properties when incorporated into a molecule. Modulation of the $pK_aH$ value of functional groups proximal to fluorine substitution[2a,15] can result in increased membrane penetration at a physiological pH value.[16] Fluorinated arenes are more lipophilic than their nonfluorinated counterparts,[15,17] which can be used to advantage in drug development.[2a,c–e,g,h] 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 fluorine versus 1.52 Å for oxygen and 1.20 Å for hydrogen).[18] Fluorinated compounds can be strategically used as transition-state inhibitors.[2c]

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The high electronegativity of fluorine contributes to the high strength of the carbon–fluorine bond because of coulombic attraction between the carbon and fluorine atoms through the polarized covalent bond; the large bond polarization[2f,19] results in attractive interactions of the C–F fragment with hydrogen-bond donors,[20] other fluorinated compounds,[4c,d,h,21] polar functional groups such as carbonyl groups,[22] and hydrophobic moieties.[23] Fluorinated molecules can show increased binding affinity to proteins[22–,23c,24] likely because of attractive polar interactions;[25] however, in many cases this phenomenon is observed empirically and rationalized subsequently, and is difficult to predict or design a priori. Most fluorinated compounds, but not all,[26] also exhibit increased metabolic stability by impeding undesired oxidative metabolism pathways.[27]

### 1.1. Electrophilic Fluorination

Most electrophilic fluorinating reagents are ultimately derived from fluorine gas, the strongest elemental oxidant known, which is synthesized by electrolysis of potassium difluoride in hydrogen fluoride.[28] Electrophilic fluorination reactions with highly oxidizing fluorinating reagents[29] such as fluorine gas, hypofluorites, fluoroxysulfates, and perchloryl fluoride are challenging to perform due to the high reactivity of the reagents. Xenon difluoride was developed as a more stable electrophilic fluorination source, but its high oxidation potential still limits the tolerance of this reagent to functional groups.[13e] The development of crystalline, benchtop-stable fluorinating reagents such as *N*-fluorobis(phenyl)sulfonimide (NFSI)[30] and related analogues,[30,31] *N*-fluoropyridinium salts,[32] and 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo-[2.2.2]octane bis(tetrafluoroborate) (Selectfluor, F-TEDA-$BF_4$)[11] was crucial for the development of selective, functional-group-tolerant fluorination methods (Figure 1). Even though *N*-fluoro reagents can formally behave as a source of fluoronium cations ("$F^+$"), the N–F bonds are polarized toward fluorine, with a partial negative charge on fluorine. Reactions may occur through $S_N2$ displacement with nucleophilic attack at the fluorine atom; the $\sigma^*_{N\text{-}F}$ orbitals are sterically inaccessible on the nitrogen atom for nucleophilic attack. Possibly as a consequence of the small orbital coefficient of the $\sigma^*_{N\text{-}F}$ orbital on the fluorine atom and the low energy level of the $\sigma^*_{N\text{-}F}$ orbital, other mechanism pathways, such as single-electron transfer, can compete. Often the process by which an overall two-electron oxidation proceeds is under discussion; two single-electron transfers or concerted two-electron transfer for fluorination have both been proposed.[33]

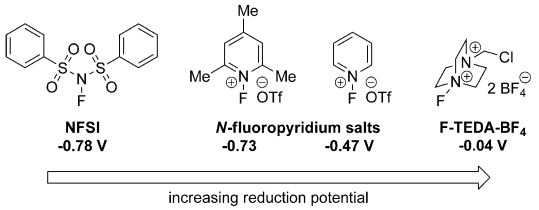


***Figure 1.*** Comparison of the redox potentials of crystalline, bench-top-stable fluorinating reagents (versus SCE).

#### 1.1.1. Electrophilic Fluorination for the Synthesis of Fluorinated Aromatic Carbon Centers

Main group organometallic compounds can be fluorinated electrophilically to afford aryl fluorides. More recently, it was found that transition-metal organometallic compounds could give rise to aryl fluorides with an enhanced substrate scope. Compared to main group organometallic compounds, transition-metal organometallic compounds can afford aryl fluorides through a wider spectrum of mechanisms, which contributes to their successful use for carbon—fluorine bond formation. Currently, the development of functional-group-tolerant, direct conversion of C(aryl)–H bonds to the corresponding C–F bonds with predictable regioselectivity is a frontier in the field.

The fluorination of arenes by electrophilic aromatic substitution (C–H→C–F) is challenging compared to other halogenations, possibly because the electronegativity of fluorine disfavors the rate-limiting formation of the halocyclohexadienyl cation. Aryl metal reagents, including aryl tin,[34] mercury,[34d,35] lead,[34b,36] germanium,[34f] silicon,[37] and boron,[38] can react with fluorine gas, xenon difluoride, hypofluorites, and fluoroxysulfates to afford fluorinated arenes; however, the substrate scope is limited due to the high reactivity of the reagents, and often results in unselective fluorination. On the other hand, aryl nucleophiles with more

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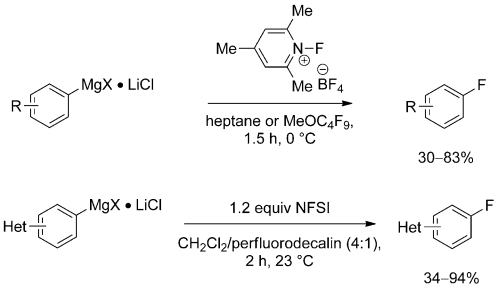
electropositive metals, such as aryl lithium reagents,[39] can react with less-reactive electrophilic fluorinating reagents, such as N-fluorinated reagents. Such basic nucleophiles can undergo single-electron transfer to give rise to protodemetalation by-products. The fluorination of Grignard reagents 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 aryl magnesium reagents (Scheme 1).[39a,40] Undesired protodemetalation

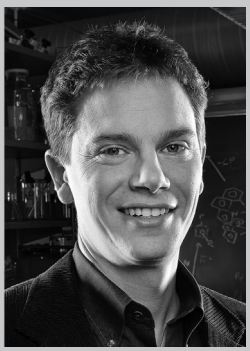



***Scheme 1.*** Synthesis of aryl fluorides from aryl Grignard reagents.

products can be minimized through appropriate choice of the solvent and reagents.[40] More recent studies by Meng, Li, and co-workers demonstrated the regioselective *para* fluorination of anilides with $PhI(OPiv)_2$ and hydrogen fluoride/pyridine.[41]

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 by transmetalation or direct C–H metalation, followed by oxidation of the metal center with an electrophilic fluorinating reagent. Depending on the reaction conditions, oxidation can result in the formation of a monometallic high-valent intermediate[42] or a high-valent multimetallic complex.[43]

The first transition-metal-catalyzed aromatic fluorination reactions were developed by Sanford and Yu through the use of an *ortho*-coordinating group (Scheme 2).[44a,b] 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* fluorinations was addressed with the



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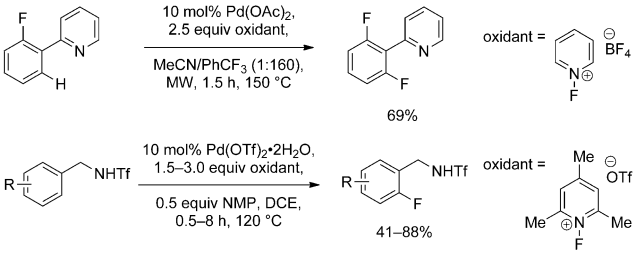
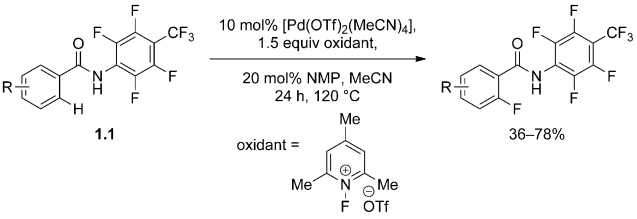
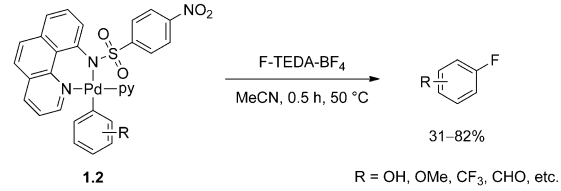



***Scheme 2.*** *N*-Directed Pd-catalyzed fluorination of arenes. MW = microwaves, NMP = *N*-methylpyrrolidine, DCE = dichloroethane, Tf = trifluoromethanesulfonyl.




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

weakly coordinating anionic *ortho*-directing group *N*-perfluorotolylamide, as in the benzoic acid derivative **1.1**, which allows for rapid displacement of the monofluorinated product by the substrate, thus affording high selectivity for monofluorination (Scheme 3).[44c]

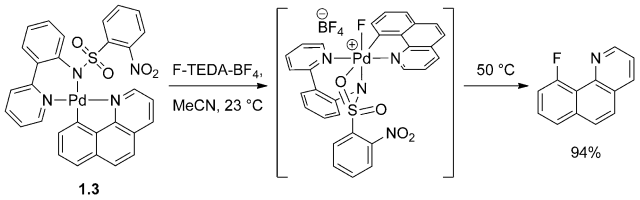



***Scheme 4.*** Fluorination of $Pd^{II}$–benzoquinolylsulfonamide complexes with F-TEDA-$BF_4$.

Aryl boronic acids have been used to synthesize $Pd^{II}$/aryl benzoquinoline/sulfonamide complexes **1.2** that undergo fluorination with F-TEDA-$BF_4$ in the presence of a variety of functional groups (Scheme 4);[44d] however, stoichiometric amounts of the Pd complex are needed. Mechanistic studies on the oxidation of the benzoquinoline phenylpyridinesulfonamide-stabilized palladium(II) complex **1.3** with F-TEDA-$BF_4$ support the presence of a distinct intermediary $\kappa^3$-sulfonamide-$Pd^{IV}$ fluoride species that undergoes reductive elimination to afford C(aryl)–F bonds (Scheme 5).[45]

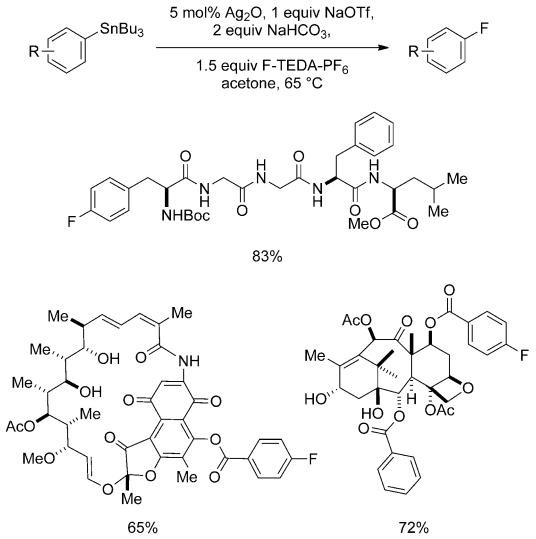
Following initial studies by Tius et al. on silver-mediated fluorination with $XeF_2$,[34i,46] a silver-mediated fluorination of functionalized aryl stannanes,[47] boronic acids,[48] and silanes[49] has been developed. These transformations are assumed to proceed through multimetallic, high-valent silver species, obtained by oxidation of $Ag^I$ complexes with F-TEDA-$PF_6$ followed by reductive elimination. The formation




***Scheme 5.*** Reductive elimination from $Pd^{IV}$–phenylpyridylsulfonamide complexes.

of a C–F bond by reductive eliminations is generally a difficult process with requires high temperature to overcome the often high activation barriers. Redox synergy of the multiple metallic centers may explain why the fluorination of aryl stannanes and boronic acids with silver can occur at 23 °C. Following the discovery of silver-mediated fluorination reactions with a range of aryl nucleophiles, a silver-catalyzed fluorination was developed, which, however, necessitates the use of toxic aryl stannanes. This method displays the broadest substrate scope and functional group tolerance in the field so far, including nitrogenous heteroaryl and mesityl nucleophiles, nucleophiles containing electron-rich, electron-poor, electrophilic, and protic functional groups, as well as complex natural product derived substrates (Scheme 6).[50]




***Scheme 6.*** Ag-catalyzed fluorination of complex aryl stannanes. Boc = *tert*-butyloxycarbonyl.

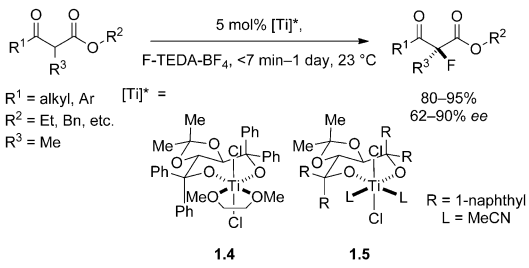
### 1.1.2. *Electrophilic Fluorination for the Synthesis of Fluorinated $sp^3$ Carbon Centers*

Nucleophiles employed in aliphatic electrophilic fluorination reactions are often stabilized carbanions, such as those derived from β-ketocarbonyl compounds. Other methods for the synthesis of aliphatic fluorides can involve fluorination/nucleophile addition cascades across double bonds,[51] which was also reported with alkynes.[52] Enantioselective variants for both the fluorination of C–H acidic substrates[53] 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 occuring via radical intermediates have been disclosed and can provide a substrate scope complementary to reactions involving two-electron-transfer processes.

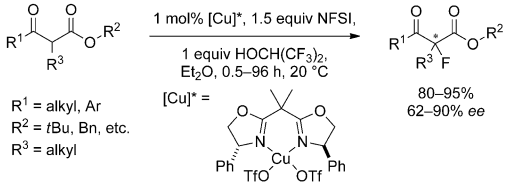
#### 1.1.2.1. *Electrophilic Fluorination of Activated Methylene and Methyne Groups*

The α-fluorination of carbonyl, α′-ketocarbonyl, and related carbonyl derivatives with oxidizing fluorinating reagents including gaseous fluorine,[54] alkyl hypofluorite,[55] perchloryl fluoride,[29b,56] fluoroxysulfate,[57] and $XeF_2$[58] generally gives undesired α,α-difluorinated products in addition to the α-monofluorinated products.[56c,58] Less-reactive, more functional group tolerant electrophilic fluorinating reagents such as *N*-fluoropyridinium salts, NFSI, and F-TEDA-$BF_4$ have been used for the selective α-monofluorination of carbonyl derivatives.[13l,32a,b,f,h,33b,59] The asymmetric α-fluorination of carbonyl substrates was explored first with chiral electrophilic fluorinating reagents[31b,c,60] 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. The asymmetric fluorination of β-keto esters was achieved with titanium-TADDOLate-based catalysts **1.4** and **1.5** by Togni and co-workers (Scheme 7),[61] $Cu^{II}$-box complexes by Ma and Cahard (Scheme 8)[62] and $Ni^{II}$-box complexes by Shibata, Toru, and

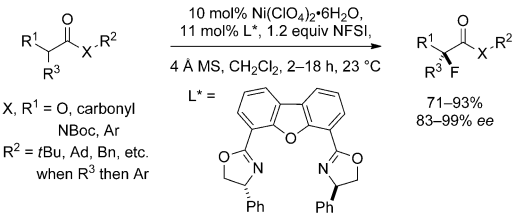



***Scheme 7.*** Ti-catalyzed asymmetric α-fluorination of β-keto esters.

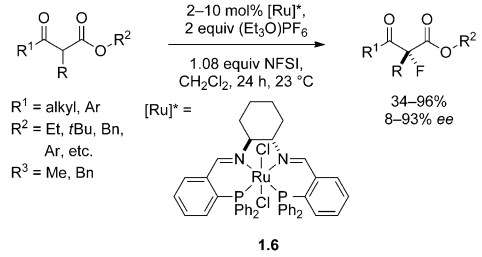



***Scheme 8.*** Cu-catalyzed asymmetric α-fluorination of β-keto esters.

co-workers (Scheme 9),[63] chiral bis(imino)bis(phosphine)-ruthenium(II) complex **1.6** by Togni and co-workers (Scheme 10),[64] and scandium binapthylphosphate complexes by Inanaga and co-workers.[65] The Ni-catalyzed reaction with 10 mol% catalyst has the broadest substrate scope so far, and allows the α-fluorination of a variety of β-keto esters and *N*-



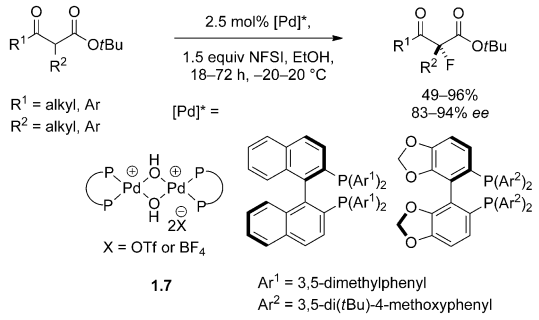

***Scheme 9.*** Ni-catalyzed asymmetric α-fluorination of β-keto esters and *N*-Boc-oxindoles. Ad = adamantyl, Bn = benzyl.




***Scheme 10.*** Ru-catalyzed asymmetric α-fluorination of β-keto esters.

Boc-protected amides[63] in 71–93% yield and 83–99% *ee*, respectively. The catalytic enantioselective α-fluorination of α-substituted methyl *tert*-butyl malonate was accomplished by chiral Lewis acid catalysis with $Zn^{II}$ acetate, the ligand (*R*,*R*)-4,6-dibenzofurandiyl-2,2′-bis(4-phenyloxazoline), and NFSI.[66] This approach was specifically optimized for the malonate substrate en route to the enantioselective synthesis of fluorinated β-lactams.

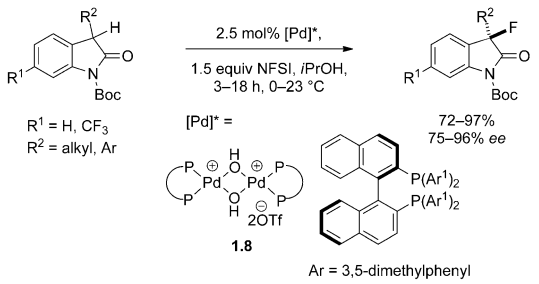
Chiral Pd-BINAP complexes **1.7** and **1.8** developed by Sodeoka and co-workers catalyze the enantioselective fluorination of α-keto esters,[67] β-keto esters (Scheme 11),[68] β-




***Scheme 11.*** Pd-catalyzed asymmetric α-fluorination of β-keto esters.

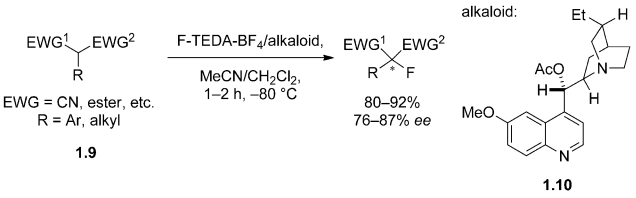
keto phosphonates,[69] oxindoles (Scheme 12),[70] and α-ester lactones/lactams.[71] The use of chiral palladium complexes was particularly successful for the α-fluorination of acyclic α-keto esters, cyclic and acyclic *tert*-butyl β-keto ester as well as oxindoles α-substituted with an electronically diverse range of aryl and alkyl groups.[67–68, 70]

Organocatalysts provide enantioinduction by acting as chiral fluorinating reagents or through reaction with the substrate to generate chiral nucleophiles.



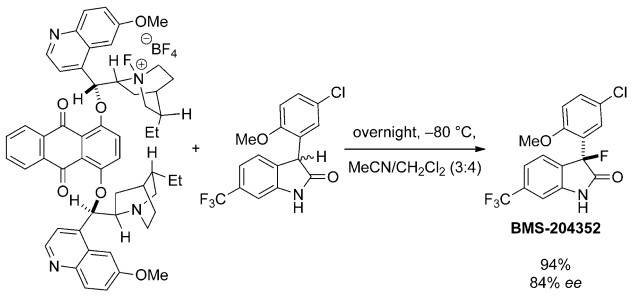

***Scheme 12.*** Pd-catalyzed asymmetric α-fluorination of oxindoles.

Cinchona alkaloids have been used to enantioselectively fluorinate nucleophiles in the presence of an achiral fluorinating reagent. The enantioselective fluorination of the activated methyne groups in **1.9** was accomplished by Takeuchi and co-workers, by using stoichiometric amounts of cinchona alkaloid derivatives such as **1.10** (Scheme 13).[72]




***Scheme 13.*** Enantioselective fluorination of C–H acidic substrates in the presence of a cinchona alkaloid.

Cinchona alkaloids have also been used to mediate the enantioselective α-fluorination of silylenol ethers, α,α-cyanoester C–H acids, β-keto esters, and oxindoles.[73] The method was applied to the synthesis of BMS-204352 (Scheme 14),[74] a potassium channel opener, which has also



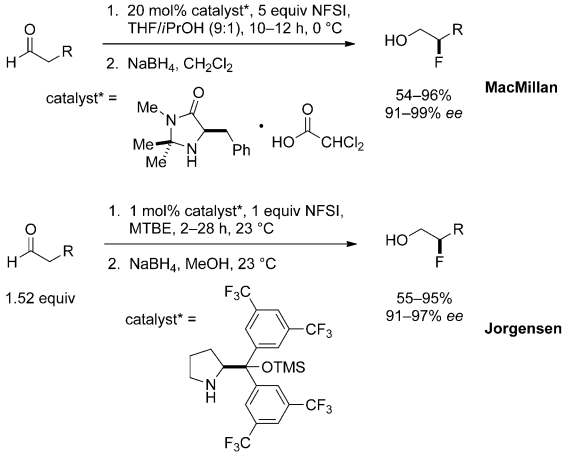

***Scheme 14.*** Enantioselective α-fluorination of oxindoles mediated by *N*-fluoroammonium salts of cinchona alkaloids.

been synthesized by utilizing chiral scandium Lewis acid catalysts.[75] The enantioselective α-fluorination of β-keto esters can be accomplished by using cinchona-alkaloid-derived thiourea catalysts.[76] Despite the reduced substrate scope currently tolerated in enantioselective fluorinations with cinchona alkaloids when compared to the Lewis acid catalyzed fluorinations of β-keto esters and oxindoles, it has

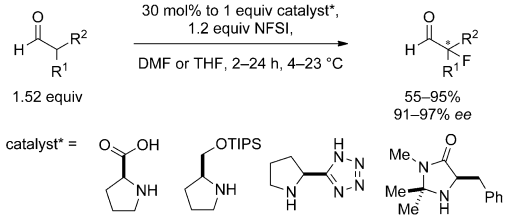
the advantage of not being restricted by the need for a two-point binding site.

The enantioselective organocatalytic α-fluorination of aldehydes was accomplished by the research groups of Enders,[77] MacMillan (Scheme 15),[78] Jørgensen




***Scheme 15.*** Organocatalytic asymmetric α-fluorination of aldehydes.

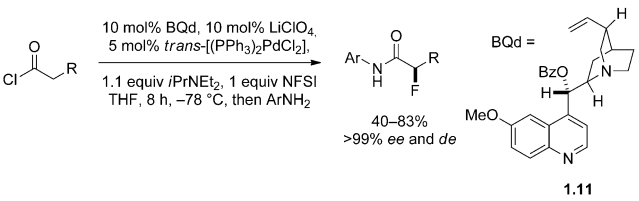
(Scheme 15),[79] and Barbas (Scheme 16);[80] similarly, the enantioselective α-fluorination of ketones is possible by using enamine catalysis.[81] The method for the α-fluorination of aldehydes described by MacMillan and co-workers demonstrates a broader substrate scope, while the method described




***Scheme 16.*** Organocatalytic asymmetric α-fluorination of α-branched aldehydes. TIPS = triisopropylsilyl.

by Jørgensen and co-workers makes use of lower loadings of catalyst and electrophilic fluorinating reagent. Branched aldehydes constitute difficult substrates for enantioselective α-fluorination; nonetheless, Barbas and co-workers 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 sulfinylimine condensation and directed reduction sequence of the enantioenriched fluorinated aldehyde.[82]

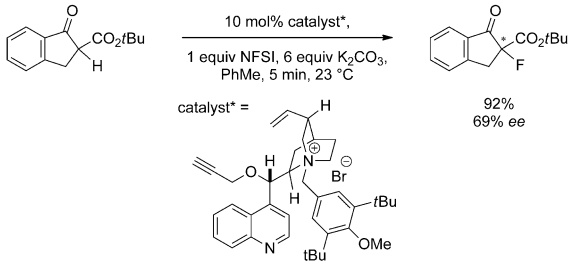
The enantioselective α-fluorination of acid chlorides was accomplished by the Lectka research group by combining a palladium catalyst, a chiral nucleophile **1.11**, and an alkali metal (Scheme 17).[83] The cinchona alkaloid based nucleophile reacts with the acid chloride in the presence of the palladium catalyst to generate a chiral zwitterion amide-




***Scheme 17.*** Organocatalytic asymmetric α-fluorination of acid chlorides. Bz = benzoyl.

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, the 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-keto esters with NFSI.[76] 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 high enantioselectivity.

Phase-transfer catalysis (PTC)[84] can offer benefits for enantioselective fluorination, 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 the enantioselective fluorination of β-keto esters with ion pairing between the enolate and chiral ammonium counterion (Scheme 18).[85] Enantioselectivities of up to 69% have thus




***Scheme 18.*** Enantioselective α-fluorination of β-keto esters with quaternary ammonium salts.

far only been achieved for the α-fluorination of β-keto esters; this is likely due to insufficiently tight ion pairing between the chiral ammonium salt and the enolate or a fast background reaction.

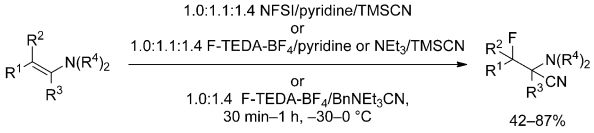
A nontraditional approach for the synthesis of chiral allylic and propargylic fluorides described by the Jørgensen research group utilizes organocatalysis to facilitate the asymmetric fluorination step with a subsequent olefination or the introduction of a propargyl group.[86] The fluorination of α-methylstyrene can occur by oxidative fluorination of the

allylic C–H bond with an *N*-fluoropyridinium salt promoted by catalytic amounts of ytterbium(III) triflate.[87] The electrophilic fluorodesilyation of allenyl and allylsilanes was reported to yield propargylic and allylic fluoride products.[88] Thibaudeau and Gouverneur have demonstrated that acyclic secondary allylic fluorides can be prepared through a cross-metathesis/electrophilic fluorodesilyation sequence,[89] while chiral tertiary allylic fluorides can be prepared by cinchona alkaloid mediated electrophilic fluorodesilyation.[90]

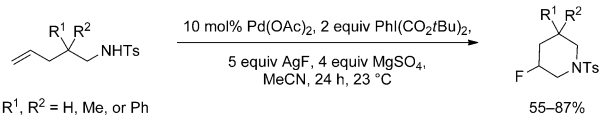
#### 1.1.2.2. *Fluorination/Nucleophile Addition Cascades across Double Bonds*

Activated alkenes such as enamines can be fluorinated without catalysts. For example, the fluorocyanation of enamines is hypothesized to occur by electrophilic fluorination of the enamine with NFSI followed by trapping of the iminium intermediate with cyanide (Scheme 19).[51a]



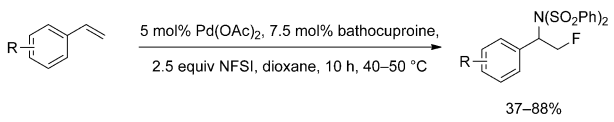

***Scheme 19.*** Fluorocyanation of enamines.

With unactivated alkenes, fluorination/nucleophile addition reactions need to be assisted by a catalyst. Both the intramolecular aminofluorination of unactivated alkenes (Scheme 20)[51b] and the intermolecular aminofluorination of




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

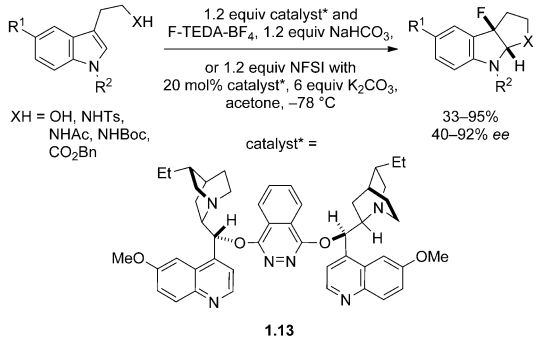
styrenes (Scheme 21)[51c] can be facilitated by the use of palladium catalysts, as described by Liu and co-workers. Although both reactions accomplish the aminofluorination of alkenes, different approaches were employed and different




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

reaction mechanisms proposed for each case. The intramolecular variant with substrate **1.12** makes use of an iodine(III) oxidant coupled with fluoride to accomplish the oxidative fluorination of a complex resulting from an intramolecular aminopalladation with an alkene. Intermolecular aminofluorination, on the other hand, is thought to occur through fluoropalladation involving the substrate, NFSI, and the active palladium complex, followed by oxidation to a putative $Pd^{IV}$ species, and a subsequent reductive elimination to form a carbon–nitrogen bond. The formation of C–F bonds at $sp^3$ carbon centers by reductive elimination from high-valent transition-metal complexes[91] has also been investigated with $Pt^{IV}$ complexes.[91c] The oxidation of stoichiometric alkyl-$Au^{I}$ complexes with $XeF_2$ to yield $Au^{III}$ intermediates followed by reductive elimination affords the corresponding aliphatic fluorides.[91a] 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 alkanes. Additionally, Sanford and co-workers reported the synthesis of alkyl fluorides by reductive elimination from $Pd^{IV}$ complexes.[91c]

The enantioselectivity in the fluorocyclization of indole substrates mediated or catalyzed by cinchona alkaloids is proposed to arise from the chiral fluorinating reagent generated from the achiral fluorinating reagent and the cinchona alkaloid catalyst **1.13** (Scheme 22).[92]



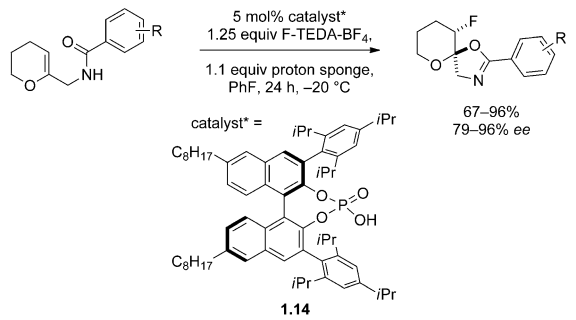

***Scheme 22.*** Enantioselective fluorocyclizations mediated or catalyzed by cinchona alkaloids. Ts = toluene-4-sulfonyl.

An enantioselective fluoro-spirocyclization reaction by chiral anionic phase-transfer catalysis (PTC) has been realized by Toste and co-workers through the pairing of chiral anion **1.14** with cationic F-TEDA to provide a source of the chiral electrophilic fluorinating reagent (Scheme 23).[93] Due to F-TEDA-$BF_4$ being sparingly soluble in the reaction solvent, thus minimizing the background reaction, chiral anion catalysis of the fluorination/spirocyclization reaction results in an enantiomeric excess of up to 96%. Similarly, enamides can be enantioselectively fluorinated through the use of PTC with chiral anions to afford α-fluoroimines[94] or α-fluoroalkyoxylation products.[95]

### 1.2.3. *Transition-Metal-Catalyzed Oxidative Fluorination of Aliphatic C–H Bonds with Fluoride*

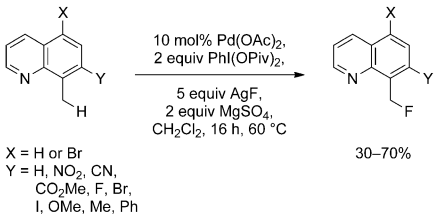
The transition-metal-catalyzed oxidative fluorination of aliphatic C–H bonds using fluoride was reported for the first time in 2012.[96] Sanford and co-workers reported the oxidative fluorination of functionalized 8-methylquinolinyl substrates catalyzed by $Pd(OAc)_2$ by using a hypervalent



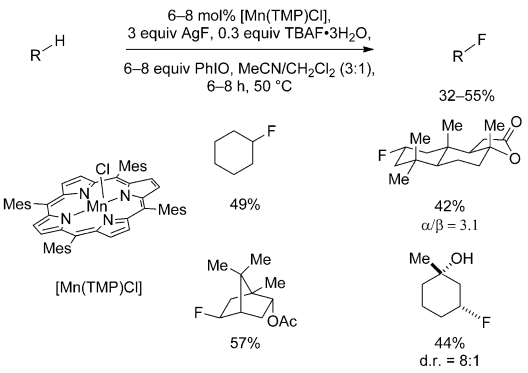

***Scheme 23.*** Enantioselective spirocyclizations by chiral anionic phase-transfer catalysis.

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. The




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

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 and co-workers (Scheme 25).[96a] This transformation

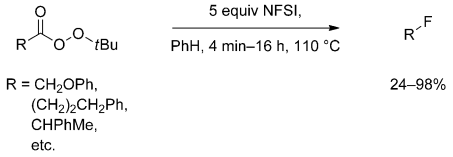



***Scheme 25.*** Mn-catalyzed oxidative aliphatic fluorination with AgF/$TBAF{\cdot}3H_2O$ and iodosylbenzene. Mes = 2,4,6-trimethylphenyl.

is proposed to occur by an 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/hydroxide ligand exchange at the manganese center compared to the reaction between the alkyl radical and the $Mn^{IV}$-hydroxide complex as well as the resulting selectivity achieved for the fluorination over hydroxylation is remarkable.

### *1.2.4. Fluorination by a Radical Mechanism*

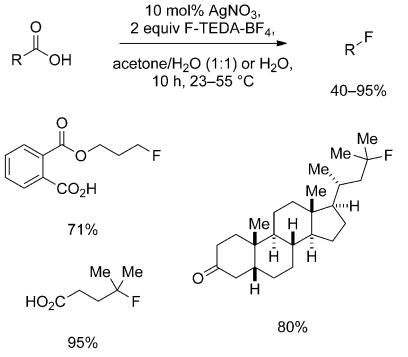
The N–F bonds in electrophilic fluorinating reagents have relatively low bond-dissociation energies (2.84 eV for *N*-fluorosultam).[97] A variety of *tert*-butyl alkylperoxoates afforded the corresponding alkyl fluorides upon treatment with NFSI under either photolysis or thermolysis conditions (Scheme 26).[98] The formation of primary alkyl fluorides was




***Scheme 26.*** Fluorination of *tert*-butyl alkylperoxoates with NFSI.

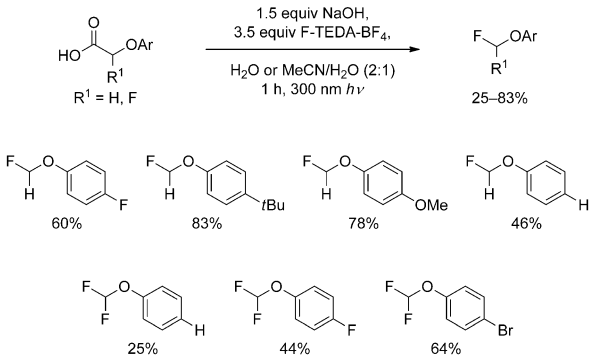
not efficient, which supports the hypothesis of radical intermediates being involved in the mechanism.

Decarboxylative fluorination, first explored by Patrick et al.,[99] was recently reported by Li and co-workers for secondary and tertiary aliphatic carboxylic acids with F-TEDA-$BF_4$ by silver catalysis (Scheme 27).[100] This approach




***Scheme 27.*** Silver-catalyzed decarboxylative fluorination of aliphatic carboxylic acids with F-TEDA.

is complementary to traditional nucleophilic fluorination reactions with DAST-type reagents. The involvement of Ag-mediated decarboxylation to form an alkyl radical during the reaction was demonstrated, but the detailed mechanism for the formation of the key C–F bond still remains undetermined. Photo-fluorodecarboxylation of α-aryloxyacetic acids and α-aryloxy-α-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 (Scheme 28).[101]




***Scheme 28.*** Photodecarboxylative fluorination of α-aryloxycarboxylic acids with F-TEDA and NaOH.

### *1.2. Nucleophilic Fluorination*

The challenges associated with nucleophilic fluorination ultimately derive from the high electronegativity of fluorine, which contributes to the high kinetic barriers in forming carbon–fluorine bonds, despite the thermodynamic driving force of forming the C–F bond, the strongest carbon–heteroatom single-bond known. The propensity of fluoride to form strong hydrogen bonds can attenuate its nucleophilicity when hydrogen-bond donors are present. Rigorous exclusion of potential hydrogen-bond donors renders fluoride a good nucleophile, but it also increases its basicity, which often leads to side reactions.

The use of alkali-metal fluoride salts is desirable due to their low cost, especially compared to electrophilic fluorinating reagents.[102] The strong lattice energy of such salts makes them weak nucleophiles and poorly soluble in organic solvents. Crown ethers such as [18]crown-6 can be used in combination with alkali-metal fluorides to increase the solubility of fluoride salts such as KF, which often leads to an increase in the reactivity.[103] Aprotic solvents especially polar aprotic solvents[103b,104] are preferred for nucleophilic fluorination reactions so that the nucleophilicity of fluoride anions remains unattenuated by hydrogen-bonding interactions; the concomitant increase in the fluoride's basicity can, however, lead to elimination by-products. The addition of tertiary alcohols such as *tert*-butanol[105] has been shown to maintain the nucleophilicity of the fluoride while diminishing its basicity, thereby reducing the formation of undesired by-products. Tetrabutylammonium difluorotriphenylsilicate (TBAT), tetramethylammonium fluoride (TMAF), and tetrabutylammonium fluoride (TBAF, anhydrous TBAF can also be synthesized[106]) are commonly used soluble fluoride sources.

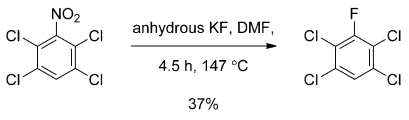
Fluorodeoxygenation of carbon centers commonly requires specialized fluorinating reagents that can accomplish oxygen activation/deoxygenation as well as provide a fluoride source. Various aryl and aminosulfur trifluorides[12a,107] and derivatives thereof as well as 2,2-difluoroimidazoline-type reagents[108] participate in fluorodeoxygenation reactions. Several hydrogen fluoride based reagents[109] have been developed to assist the displacement of sulfur with fluoride in fluorodesulfurization reactions. Electrochemical fluorination with alkali-metal fluorides has been explored as an approach for the synthesis of organofluorides.[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 with electron-rich substrates because the rate-determining step is the addition of the nucleophile to the arene to form a Meisenheimer-type complex.[111] Additionally, chiral transition-metal and organocatalysts can be used for nucleophilic fluorination reactions to afford enantioenriched 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,[112] although one or more electron-withdrawing groups on the arene are typically required. Aromatic substitution, catalyzed and noncatalyzed, is currently one of the most direct methods for nucleophilic fluorination with control over the regioselectivity. Improvement in the substrate scope is desirable because nucleophilic fluorination is preferred over electrophilic fluorination both on an industrial scale, because of the low cost of alkali-metal fluorides, and in radiochemical applications, because of facile access to [$^{18}$F]fluoride.

##### *1.2.1.1. Traditional Nucleophilic Fluorination Methods with Main-Group Elements*

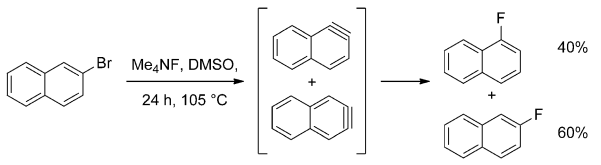
Balz and Schiemann developed the first nucleophilic fluorination of arenes by thermal decomposition of aryl diazonium tetrafluoroborate salts in 1927,[113] a process which was improved subsequently.[114] Displacement of the chloride in 1-chloro-2,4-dinitrobenzene under forcing conditions with anhydrous potassium fluoride (the Halex process) was developed in 1936,[115] followed by the fluorodenitration of arenes by *ipso* attack at the carbon atom bearing the nitro group (Scheme 29).[116] More recent work in this area has




***Scheme 29.*** Nucleophilic aromatic substitution with KF.

allowed for the fluorination of electron-poor, chloro-, nitro-, or trimethylammonium arenes with anhydrous tetrabutylammonium fluoride at room temperature in up to >95% yield.[117] Aryl fluorides can also be accessed from the reaction of aryl bromides with anhydrous tetramethylammonium fluoride; however, the process actually occurs through fluoride trapping of the aryne intermediates generated from the elimination of the bromide with the strongly basic anhydrous fluoride and, therefore, provides a mixture of constitutional isomers (Scheme 30).[118] Other approaches that have been explored involve two-step nucleophilic

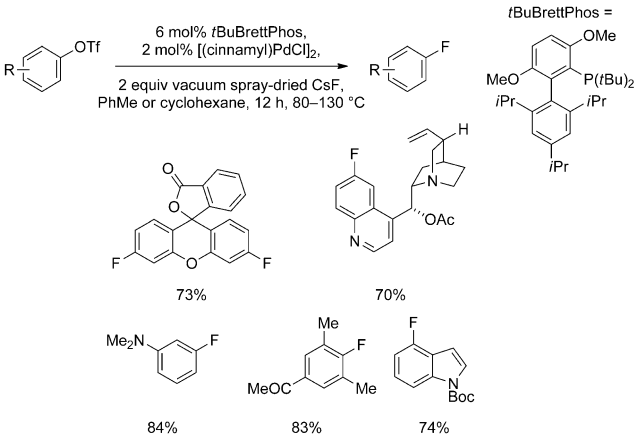



***Scheme 30.*** Fluorination of naphthyl bromide via aryne intermediates.

fluorodemetalation of toxic organothallium(III) substrates[119] as well as diaryl iodonium substrates.[120] Although simple fluorinated arenes can be synthesized with some of the aforementioned reactions, even on an industrial scale,[112] none of these methods are tolerant of many functional groups or exhibit broad substrate scope.

#### 1.2.1.2. *Transition-Metal-Catalyzed and -Mediated Nucleophilic Fluorination*

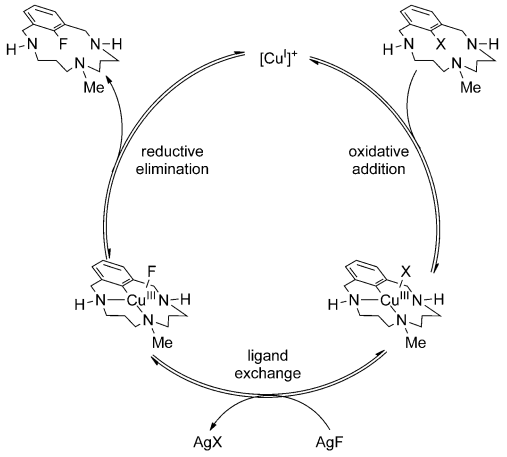
Transition-metal-catalyzed cross-coupling with fluoride as the nucleophile has been investigated with late-transition metals such as nickel, copper, ruthenium, rhodium, palladium, iridium, and platinum.[121] The reductive elimination of C–F bonds by $Pd^{II}$ is challenging; the difficulty of the reductive elimination step rises with the increasing electronegativity of the nucleophilic coupling partner. For $Pd^{II}$ complexes stabilized by monodentate ligands, fluoride-bridged dimer complexes are readily formed, from which reductive elimination has never been observed. The cross-coupling fluorination of aryl triflates with fluoride by palladium catalysis (Scheme 31)[121g,122] was developed by




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

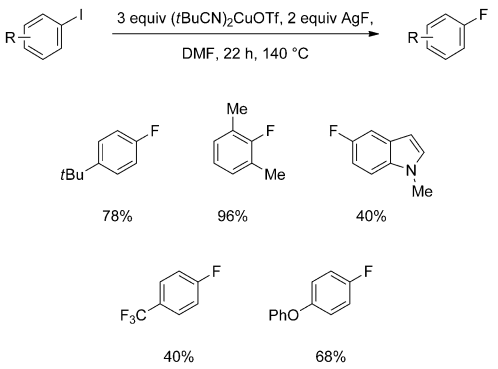
Buchwald and co-workers, who used the bulky monodentate phosphine ligand *t*BuBrettPhos, which was crucial for the successful C–F reductive elimination through a mononuclear, tricoordinate palladium(II) complex. The fluorination of aryl triflates displays a broad substrate scope and tolerates nucleophilic functional groups not often tolerated in electrophilic fluorination methods because of 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.[122] Importantly, the 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.[123]

An oxidative addition/C–F reductive elimination sequence was established by the Ribas research group with a $Cu^{I}$–$Cu^{III}$ cycle by using a designed substrate that allowed for isolation of key intermediates (Scheme 32).[121f] The




***Scheme 32.*** Cu-catalyzed halide exchange on arenes with AgF.

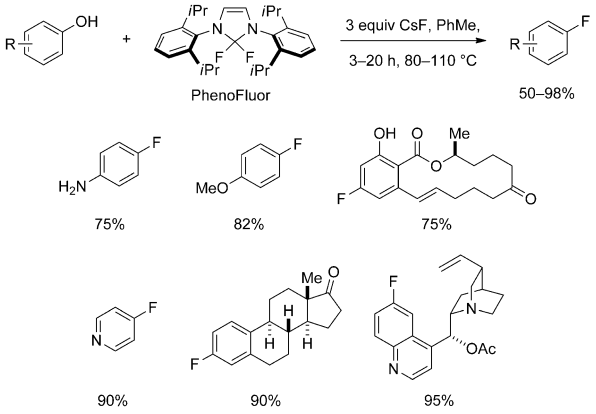
oxidative addition of copper(I) to the aryl halide supported by the tris(amine) ligand generates a copper(III) complex, which upon ligand metathesis with silver fluoride gives a copper(III) fluoride complex that undergoes reductive elimination to liberate the aryl fluoride product. Copper-mediated fluorination of electron-rich, electron-poor, as well as hindered aryl iodide substrates was reported by Hartwig, who used three equivalents of a copper(I) complex and AgF (Scheme 33).[124] The formation of hydrodehalogenated side products renders purification of the aryl fluoride products challenging.




***Scheme 33.*** Cu-mediation fluorination 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 prefunctionalization of the phenol. Catechol can be monodeoxyfluorinated by oxidation of the catechol to the *ortho*-quinone followed by nucleophilic deoxofluorination with Deoxo-Fluor.[125] This oxidation/fluorination method affords a mixture of *ortho*-fluorinated phenol isomers. One of the first examples of the deoxyfluorination of nitro-substituted phenol was accomplished with *N*,*N*′-dimethyl-2,2-difluoroimidazolidine.[108a] A general method, as described by our research group, for the *ipso*-deoxyfluorination of phenols was accomplished with the commercially available difluoroimidazoline reagent PhenoFluor and cesium fluoride (Scheme 34).[108b] Electron-poor, -neutral, and -rich aryl fluorides in addition to heteroaromatic fluorides can be synthesized from the corresponding phenol precursors by using this method.



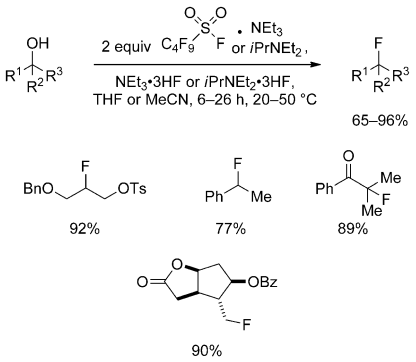

***Scheme 34.*** Deoxyfluorination of phenols with PhenoFluor.

### 1.2.2. Nucleophilic Fluorination for the Synthesis of Fluorinated $sp^3$ Carbon Centers

Nucleophilic fluorination at primary $sp^3$ carbon centers through appropriate selection of the fluoride source, leaving group, and solvent is well-established.[13a,103a,126] Nucleophilic fluorination at a secondary or tertiary $sp^3$ carbon center is inherently more difficult and no general functional group tolerant method has been available. Deoxyfluorination with sulfur tetrafluoride or derivatives thereof can afford fluoride from secondary or tertiary carbinols, but competing elimination[12a] and rearrangement[12a,127] reactions occur frequently. Halofluorination of alkenes was accomplished by treatment of the alkene with *N*-iodosuccinimide and tetraalkylammonium hydrogen fluoride.[128] The nucleophilic opening of epoxides[129] and aziridines[130] with fluoride affords vicinal fluoro alcohols and fluoroamines, respectively, which have been elaborated to multiple vicinal fluoroalkanes.[129d,131]

Carbonyl compounds were first converted into geminal difluoromethylene derivatives with sulfur tetrafluoride.[132] The toxicity and volatility of sulfur tetrafluoride led to the development and use of less-volatile reagents such as aryl and aminosulfur trifluorides.[12a,107] Diethylaminosulfur trifluoride (DAST)[12] has been used most commonly to fluorinate oxygenated (carbonyl, hydroxy) or sulfur-containing (thiocarbonyl, sulfide) substrates.[107c,133] The mechanism of DAST-mediated fluorination is proposed to begin with nucleophilic attack of the alcohol substrate on the sulfur atom of DAST to form an alkoxyaminodifluorosulfane intermediate[134] that is activated for $S_N2$ attack by fluoride. In some cases, however, the fluorination with DAST affords products consistent with an $S_N1$ mechanism.[133h] Additional drawbacks of DAST include moisture sensitivity as well as a propensity to explode upon heating.[107e]

Besides DAST, deoxyfluorination and dethiofluorination can be accomplished with several different reagents: pyridinium poly(hydrogen fluoride) (Olah's reagent),[109a,b,d] nitrosonium tetrafluoroborate/pyridinium poly(hydrogen fluoride),[109c] triethylamine tris(hydrogen fluoride) (TREAT·HF),[109e] perfluoro-1-butanesulfonyl fluoride (PBSF),[135] sulfonyl fluoride/TREAT·HF mixture (Scheme 35),[136] Yarovenko's reagent,[137] Ishikawa's




***Scheme 35.*** Deoxyfluorination of various alcohols with the perfluorobutanesulfonyl fluoride/trialkylamine adduct and TREAT·HF.

reagent,[138] TFEDMA,[139] *N*,*N*′-dimethyl-2,2,-difluroimidazolidine,[108a] 4-morpholinosulfur trifluoride,[107d,140] Deoxo-Fluor,[107f,141] bromine trifluoride,[142] and 4-*tert*-butyl-2,6-dimethylphenylsulfur trifluoride (Fluolead; Figure 2).[143] Deoxo-Fluor is currently the most commonly used reagent for fluorination reactions and is considered a safer, more

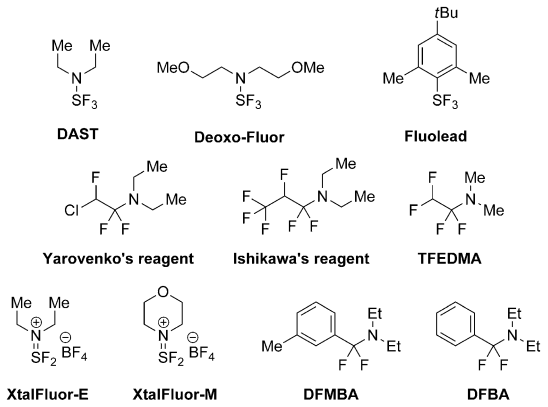
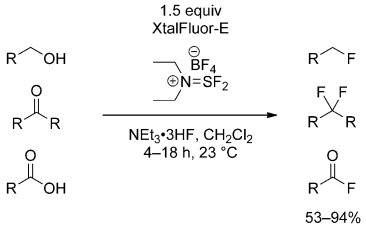



***Figure 2.*** A selection of deoxofluorinating reagents.

thermally stable alternative to DAST, but is similarly moisture sensitive and prone to decomposition to generate toxic HF. Likewise, Olah's reagent is corrosive and toxic due to the presence of HF; TREAT·HF is considered to be a less hazardous alternative and is mild enough to be used in borosilicate glassware.

The development of the non-explosive, crystalline, less-moisture-sensitive deoxyfluorinating reagent XtalFluor-E (diethylaminodifluorosulfinium tetrafluoroborate)[144] and related reagents[145] has resulted in fluorodeoxygenation with fewer by-products (Scheme 36). Unlike DAST or

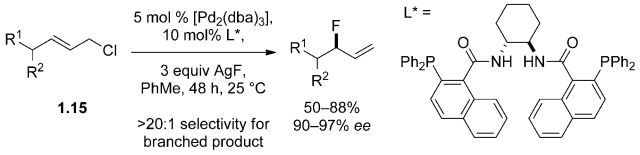



***Scheme 36.*** Deoxyfluorination of alcohols, carbonyl compounds, and carboxylic acids with XtalFluor-E.

Deoxo-Fluor, the fluorination with XtalFluor-type reagents requires the addition of an amine hydrogen fluoride such as triethylamine tris(hydrogen fluorine) as a fluoride source because after the addition of an alcohol to XtalFluor, the diethylamino group is fully protonated and release of the fluoride does not occur. Instead of adding an external fluoride source, the addition of DBU can also promote the release of fluoride by deprotonation.

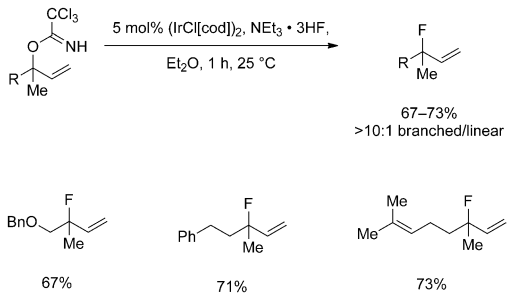
The synthesis of propargylic fluorides can be accomplished by the deoxyfluorination of propargylic alcohols with DAST[146] or fluorination of a variety of activated propargylic substrates[147] such as propargylic mesylates or silyl ethers. Other commonly used deoxofluorinating reagents for the synthesis of propargylic fluorides include $SF_4$,[147a,b,148] dialkylaminosulfur trifluorides,[147c,d,f,g] Yarovenko's reagent (Figure 2),[149] and Ghosez's reagent (*N*,*N*-diisopropyl-1-fluoro-2-methylpropenamine).[150] Grée and co-workers achieved the synthesis of chiral propargylic fluorides through an $S_N2$ reaction between chiral, nonracemic propargylic alcohols and fluoride.[151] This approach is substrate dependent; many chiral propargylic alcohols give products with lower enantiomeric excess or racemized products through a competing $S_N1$ pathway. The majority of syntheses of progarylic fluorides utilize nucleophilic fluorination; the research groups of Hammond[152] and Gouverneur[88a] have investigated electrophilic fluorination routes to propargylic fluorides.

Middleton first reported the dehydroxyfluorination of allylic alcohols with DAST,[146] which was used subsequently to study the fluorination of allylic alcohol substrates containing different substituents and substitution patterns.[153] Temporary complexation of the π system of allylic alcohols with a stoichiometric amount of rhenium[154] or iron[155] can prevent allylic transposition, a common side reaction, during dehyroxyfluorination reactions. 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,[146,156] Yarovenko's reagent,[157] Ghosez's reagent,[158] and $IF_5$ in $NEt_3·3HF$.[159] The reactivity of other activated allylic substrates has also been explored.[160] An attractive route to allylic fluorides is the Tsuji–Trost-type fluoride displacement of a leaving group catalyzed by a transition-metal complex. As fluoride is a better leaving group than acetate, which is a commonly employed leaving group in Tsuji–Trost reactions,[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[162] in the Tsuji–Trost-type allylic displacement reaction. Doyle and co-workers reported the enantioselective fluorination of cyclic[163] and acyclic (Scheme 37)[164] allylic chlorides in the presence of a chiral




***Scheme 37.*** Pd-catalyzed enantioselective synthesis of branched allylic fluorides.

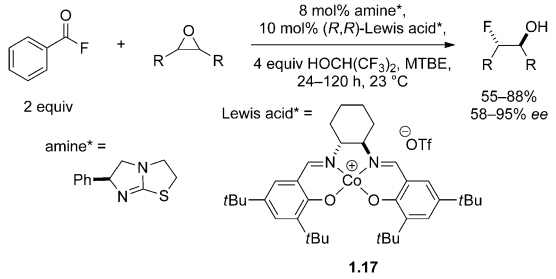
palladium catalyst with branched/linear selectivities of $>20:1$ for most substrates. A variety of functional groups can be tolerated; currently, long reaction times and an excess of silver fluoride is required for optimum yields. Oxabicyclic alkenes can undergo ring opening with fluoride and a rhodium catalyst.[165] Secondary and tertiary allylic fluorides can be synthesized from allylic trichloroacetamidates **1.16** under iridium catalysis (Scheme 38),[166] while terminal allylic fluorides can be synthesized from cinnamyl allylic carbonates, as reported by Gouverneur, Brown, and co-workers,[167] and cinnamyl allylic phosphorothioate esters, as reported by Lauer and Wu, both through palladium catalysis.[168]




***Scheme 38.*** Ir-catalyzed fluorination of allylic trichloroacetamidates. cod = 1,5-cyclooctadiene.

#### 1.2.3. Nucleophilic Fluorination of Olefins and Epoxides

In addition to $S_N2$ reactions, the 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 Bruns and Haufe with stoichiometric amounts of chiral Lewis acid complexes[170] and later with a $Co^{III}$-salen catalyst **1.17** by Kalow and Doyle (Scheme 39)[171] for nonlinear *meso*-




***Scheme 39.*** $Co^{III}$-catalyzed asymmetric opening of *meso*-epoxides with fluoride. MTBE = methyl *tert*-butyl ether.

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 cobalt(salen) units (Scheme 39).

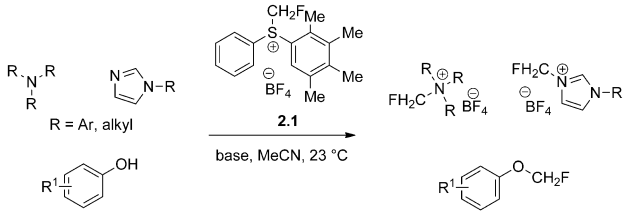
## 2. Fluoromethylation

Fluorinated functional groups such as monofluoromethyl and difluoromethyl groups have been used as oxygen mimics in molecules such as nucleotides, phosphate esters, and sulfate esters.[172]

The introduction of fluoromethyl groups through an $S_N2$ reaction with fluoromethyl halide reagents is more challenging than methylation with methyl halide reagents because the transition state involves the build up of a partial positive charge on the pentacoordinate carbon atom functionalized with the electronegative fluorine. Reactive nucleophiles and fluoromethylating reagents with good leaving groups are thus required for electrophilic fluoromethylation. Difluoromethylation and trifluoromethylation reactions that occur through an $S_N2$ mechanism are increasingly impeded by the compounded destabilizing effect of each additional fluorine atom. The 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 carbenes. Although rare, an example of a radical fluoromethylation has been reported.[173]

#### 2.1. Electrophilic Methods for Fluoromethylation

The 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 through an $S_N2$ mechanism, rather than through single-electron transfer processes.[174] Monofluoromethylated amines, ethers, and sulfides can be unstable due to the hyperconjugation of the lone pairs of electrons with the $\sigma^*_{C-F}$ orbitals, which results in elongation of the C–F bond and can lead to fluoride extrusion. The 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, Olah et al. (Scheme 40).[175] The

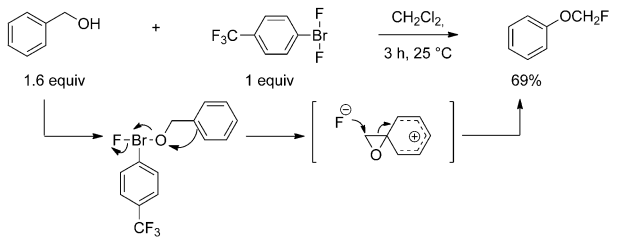



***Scheme 40.*** Monofluoromethylation of various N, O, C nucleophiles.

process by which the electrophilic fluoromethyl transfer occurs is currently unclear; both two-electron and one-electron pathways are conceivable. Given that reagent **2.1** is synthesized through the alkylation of sodium thiophenolate with chlorofluoromethane, the fluoromethylation with chlorofluoromethane is more efficient and can afford comparable yields for reactive substrates such as phenols, thiophenols, and imidazoles.[175] The electrophilic fluoromethylation of carbon nucleophiles is limited to methyne nucleophiles containing mesomeric stabilizing groups: in the case of the corresponding methylene nucleophiles, the reaction products are susceptible to hydrogen fluoride elimination. Another fluoromethylating reagent *N*-dimethyl-*S*-fluoromethyl-*S*-phenylsulfoximinium, developed by Shibata and co-workers, is used for alkylation at the oxygen atom of nucleophiles such as phenols and α-carbonylenols; the reason for the chemoselectivity is currently under investigation.[176] To the best of our knowledge, the electrophilic fluoromethylation of aryl nucleophiles has not yet been reported.

Another approach for the synthesis of fluoromethylated ethers involves the oxidative rearrangement of benzyl alcohols induced by $XeF_2$[177] or aryl difluoro-$\lambda^3$-bromane (Scheme 41)[178] through participation of the phenyl group in the aryl carbon–oxygen bond-forming step in the synthesis of aryl α-fluoromethyl ethers. The electrophilic fluorination of *O*,*S*-acetals[179] and α-carboxymethyl ethers[99,180] can also afford α-fluoromethyl ethers. Similarly, *N*-fluoropyridium triflate can be used to oxidize the C–H bond in the methyl group of methyl sulfide to afford α-fluoromethyl sulfides.[181]

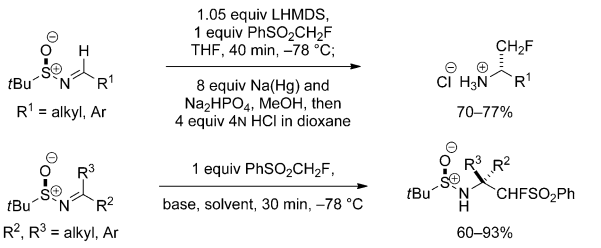



***Scheme 41.*** Oxidative rearrangement of benzyl alcohol to monofluoromethylphenol with aryl difluoro-λ³-bromane.

### 2.2. Nucleophilic Methods for Fluoromethylation

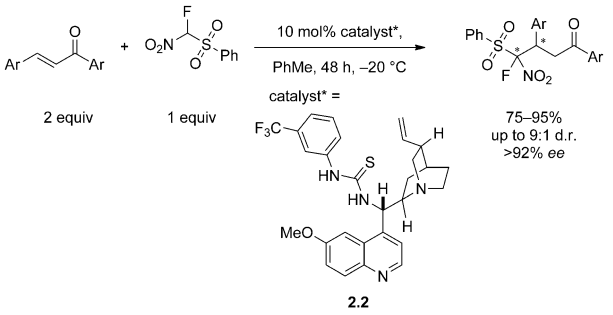
The synthesis of α-fluoromethyl ethers[182] and sulfides[183] can be accomplished from chloromethyl ethers or thioethers through chloride displacement with KF. Nucleophilic displacement requires heating to reflux in acetonitrile, and starting materials often decompose before displacement occurs. Additionally, nucleophilic fluorinating reagents such as DAST,[184] tetrabutylammonium dihydrogentrifluoride,[185] and Deoxo-Fluor[141c] have been used to induce fluoro-Pummerer rearrangements of sulfides and sulfoxides to yield α-fluoromethylsulfides. It should be noted that α-fluoromethyl sulfides are easily oxidized to the α-fluoromethyl sulfoxides in ambient conditions.

The general approach to nucleophilic fluoromethylation involves nucleophilic attack by stabilized fluoromethide equivalents generated by deprotonation of pronucleophiles such as fluorobis(phenylsulfonyl)methane (FBSM) or α-fluoro(phenylsulfonyl)methane (FSM). The diasteroselective fluoromethylation of chiral *N*-(*tert*-butylsulfinyl)aldimines[186] and ketimines (Scheme 42)[187] and chiral α-amino *N*-(*tert*-butylsulfinyl)aldimines[188] have been reported, as well as the fluoromethylation of aldehydes[189] (followed by a Ritter-type reaction to give α-fluoromethylated acetamides[190]) and the 1,4-fluoromethylation of α,β-unsaturated carbonyl compounds.[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. The diastereoselectivity is proposed to originate from a closed six-membered transition state involving a metal cation chelated with the sulfinyl directing group and the α-fluoro-(phenylsulfonyl)methyl anion. Fluorobenzylation has also been reported with fluorobenzylsulfone pronucleophiles.[192]

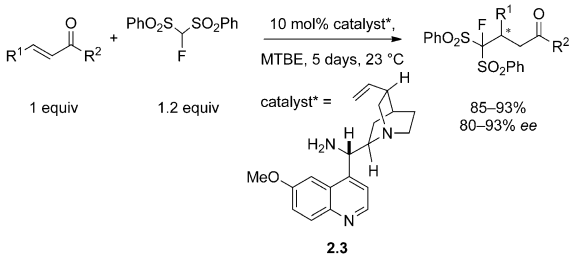



***Scheme 42.*** Addition of monofluoromethyl pronucleophiles to chiral *N*-(*tert*-butylsulfinyl)aldimines and ketimines. LHMDS = lithium hexamethyldisilazide.

The nucleophilic reactivity of resonance-stabilized fluoromethyl anions has been used in the Mitsunobu reaction of alcohols[193] as well as substitution reactions with alkyl halides[194] en route to monofluoroalkenes. The hydrofluoromethylallylation of alkynes with palladium catalysts[195] affords 3-fluoropropene products. The enantioselective fluoromethylation by transition-metal catalysis, PTC, and organocatalysis has been established with fluoromethyl pronucleophiles, most commonly with FBSM. Analogous to asymmetric allylic alkylation reactions with other nucleophiles with $pK_a$ values $\leq 10$, the palladium-catalyzed asymmetric alkylation of allylic acetates with FBSM[196] most likely occurs through external addition of the fluoromethyl nucleophile to the chiral palladium–allyl complex to afford the enantioenriched fluoromethylated product. Cross-coupling of 2-pyridylsulfonyl iodofluoromethane with aryl iodides in the presence of copper(I) salts has also been reported.[197] FBSM was used in the enantioselective Mannich reaction under PTC for the synthesis of enantioenriched 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. Organocatalysts were used as bifunctional catalysts for the enantioselective addition of α-fluoro-α-nitro(phenylsulfonyl)methane (Scheme 43)[199] or FBSM (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




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




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

the electrophile and nucleophile with the quinuclidine moiety as well as the thiourea (Scheme 43) or amine (Scheme 44) is postulated to induce the enantioselectivity.

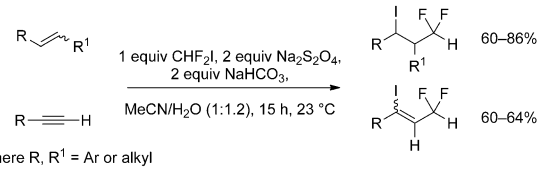
## 3. Difluoromethylation

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 a potential replacement for hydroxy groups etc.[202] Many approaches towards electrophilic difluoromethylation as well as electrophilic trifluoromethylation (Section 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 to difluorocarbene as well as difluoromethyl radicals compared to their nonfluorinated counterparts and leads to moderate, controlled reactivity.[13g] The increased acidity of $XF_2C{-}H$ compared to $XFHC{-}H$ facilitates the formation of $F_2CX^-$ (X is a leaving group), the precursor to difluorocarbenes. The challenge of the difluoromethyl anion being prone to α-elimination and decomposition needs to be overcome when developing nucleophilic difluoromethylation reactions, and this is often addressed through the use of pronucleophiles stabilized with electron-withdrawing groups. 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

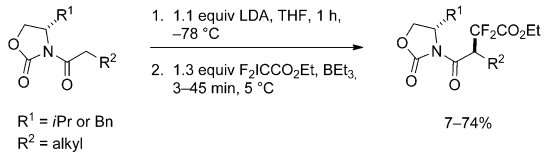
#### 3.1.1. Radical Difluoromethylation

Radical difluoromethylation of alkenes and alkynes has been reported with difluoroiodomethane and is facilitated by sodium dithionite as a radical initiator (Scheme 45).[203]




***Scheme 45.*** Radical addition of iododifluoromethane across alkenes and alkynes.

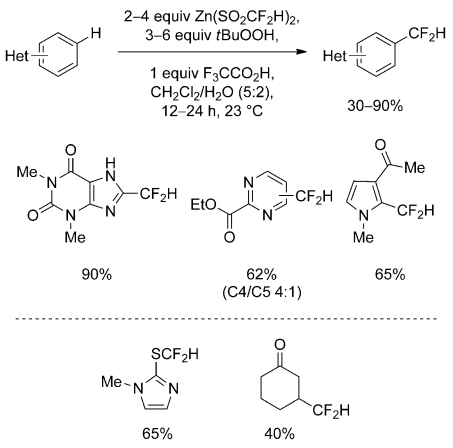
Similarly, difluorodibromomethane or difluorobromochloromethane in combination with the radical initiator CuCl is used for the difluoromethylation of olefins.[204] The radical α-difluoromethylation of enamines and ynamines[205] can be performed with difluorodihalomethane reagents under UV irradiation. Additionally, alkenes can be difluoromethylated with halodifluorosulfides,[206] halodifluorosulfonyl reagents,[207] halodifluorosulfonamide reagents,[208] halodifluorosulfanyl reagents,[209] and halodifluoromethane[203,210] in the presence of appropriate radical initiators. The α-difluoromethylation of enolates with iododifluoroacetate can be mediated by the radical initiator triethylborane (Scheme 46).[211]




***Scheme 46.*** Diastereoselective α-alkylation with a difluoromethylating reagent mediated by a chiral auxiliary. LDA = lithium diisopropylamide.

After saponification of the imide, decarboxylative bromination of the resulting carboxylic acid to afford the difluorobromomethyl group followed by reduction of the carbon–bromine bond yields the difluoromethylated product. An example of enantioselective α-difluoromethylation of octanal was reported by using ethyl difluoroiodoacetate and photoredox catalysis.[212]

The radical difluoromethylation of C–H bonds in heteroarenes with *tert*-butylhydrogen peroxide and crystalline, bench-top-stable $Zn(SO_2CF_2H)_2$ at room temperature and an ambient atmosphere was established by the Baran research group (Scheme 47).[213] Stable fluoroalkyl metal sulfinate




***Scheme 47.*** Radical difluoromethylation of heteroarenes with $Zn(SO_2CF_2H)_2$ and *tert*-butylhydrogen peroxide.

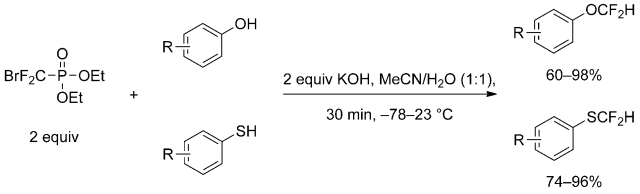
complexes for the generation of trifluoromethyl radicals were previously used for the radical trifluoromethylation of heteroarenes, but the use of $Zn(SO_2CF_2H)_2$ as a source of the difluoromethyl radicals gives access to a larger variety and higher yield of the functionalized heteroarenes. In the reaction, the difluoromethyl radicals generated preferentially react with the electron-poor sites of arenes and electron-deficient π systems, such as enones at the β position, likely

because of the electrophilic character of difluoromethyl radicals.

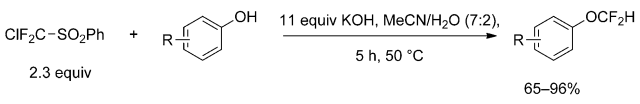
### 3.1.2. Electrophilic Difluoromethylation through Carbene Intermediates

Aryl difluoromethyl ethers and thioethers can be synthesized from phenoxides[214] and thiophenolates[214c–e,g] with difluorocarbene sources such as difluorohalomethane,[214a,c,d] difluorohalomethane,[214b,e] diethylbromodifluoromethyl phosphonate (Scheme 48),[214g] and fluorosulfonyl difluoroacetic acid reagents.[214f] Difluoromethylation with diethylbromodifluoromethyl phosphonate, as described by Zafrani et al., has proven most successful, and allows the difluoromethylation of simple electron-rich or -poor phenols and thiophenols in 60–96% yield (Scheme 48).[214g] 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 of saponification of diethyl phosphonate with release of the difluorobromomethyl anion followed by α-elimination of bromide from the difluorobromomethyl anion to give the difluorocarbene.



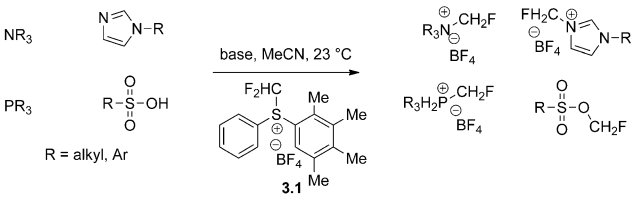

**Scheme 48.** Difluoromethylation of phenols and thiophenols with ethyl bromodifluoromethylphosphanate.

Fluorinated alcohols,[214f,215] quinoxalinones,[216] as well as amides and oximes[217] can undergo *O*-difluoromethylation with various difluoromethylating reagents. Nonfluorinated aliphatic alcohols remain problematic substrates for difluoromethylation and often give rise to low yields.[218] Likewise, nitrogenous nucleophiles such as azoles,[219] 2-mercaptoazoles,[220] sulfonamides,[221] sulfanyltetrazoles,[222] benzotriazoles and tetrazoles,[223] 2-acetaminopyridine,[224] and indazoles[225] can be converted into *N*-difluoromethylated products. Historically, other reagents used in *N*-difluoromethylations include $Zn(CF_3)Br$,[226] $Cd(CF_3)_2$,[226a,b,d,227] and $Bi(CF_3)_3/AlCl_3$,[226d] all of which react through difluorocarbene intermediates. More recently, the non-ozone-depleting reagents 2-chloro-2,2-difluoroacetophenone[228] and chlorodifluoromethyl phenyl sulfone (Scheme 49)[229] have been used to generate difluorocarbenes in the presence of nucleophiles to afford *O*- and *N*-difluoromethylated products.




**Scheme 49.** Difluoromethylation of phenols with chlorodifluoromethyl phenyl sulfone.

Various nucleophiles including tertiary amines, imidazoles, phosphines, and sulfonates can be treated with difluoromethylsulfonium reagent **3.1** developed by Prakash et al. 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 through 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.[230] Similarly, *N*,*N*-dimethyl-*S*-difluoromethyl-*S*-phenylsulfoximinium tetrafluoroborate can be used to alkylate N, P, and S nucleophiles.[218]

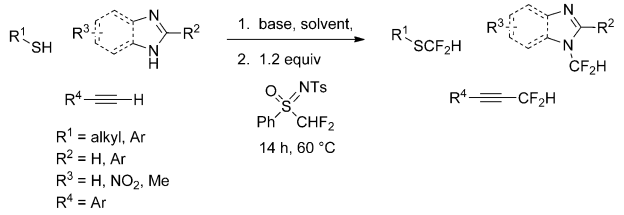



**Scheme 50.** Difluoroalkylation of tertiary amines and phosphines, imidazoles, and sulfonic acids.

The difluoromethylation of C nucleophiles with $pK_a$ 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.[231] Treatment of enolates with chlorodifluoromethane gives rise to α-difluoromethylated carbonyl products,[232] while diasteroselective α-difluoromethylation of *N*-acyloxazolidinones is achieved with bromodifluoromethane.[233] Trimethylsilyl fluorosulfonyldifluoroacetate (TFDA), which also acts as a source of difluorocarbene, reacts with alkenes,[234] alkynes,[234d] and ketones[235] to form geminal difluorocyclopropanes, difluorocyclopropenes, and difluoropropane ethers, respectively. Less commonly, this reagent is used for difluoromethylation reactions at heteroatoms.[234a,236]

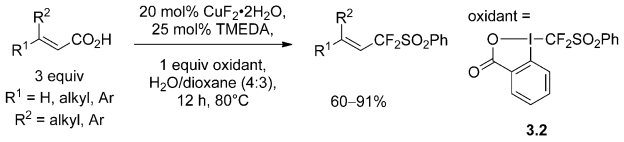
### 3.1.3. Electrophilic Difluoromethylation by Other Mechanisms

The development of the alkylating reagent *N*-tosyl-*S*-difluoromethyl-*S*-phenylsulfoximine led to the successful difluoromethylation of S, N, and C nucleophiles (Scheme 51).[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, thereby leading to deuterium incorporation, which was not observed. This observation may provide a rationale for why the sulfoximinium 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, by the oxidative rearrangement of aldehydes with difluoroarylbromane.[238]




***Scheme 51.*** Difluoromethylation of S, C, and N nucleophiles with *N*-tosyl-*S*-difluoromethyl-*S*-phenylsulfoximine.

Treatment of iodotrifluoromethane with lithium enolates results in alkylation occurring selectively with fluoride displacement instead of iodide displacement.[239] The selective displacement of fluoride is attributed to the activation of fluoride with lithium, driven by the formation of lithium fluoride, which has the highest alkali-metal halide lattice energy.[240] A copper-catalyzed decarboxylative difluoromethylation of α,β-unsaturated carboxylic acids was accomplished with electrophilic iodonium-based difluoromethyl reagent **3.2** in 60–91% yield with stereocontrol of the double-bond geometry (Scheme 52).[241] The difluoromethylation of boronic acids can be accomplished with copper, ethyl difluoroiodoacetate, and *N*,*N*-diethyldifluoroiodoacetamide.[242]



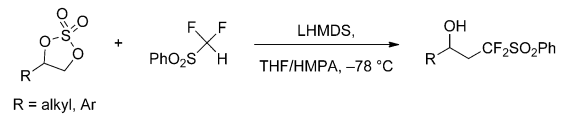

***Scheme 52.*** Cu-catalyzed decarboxylative difluoromethylation of α,β-unsaturated carboxylic acids. TMEDA = tetramethylethylenediamine.

### 3.2. Nucleophilic Methods for Difluoromethylation

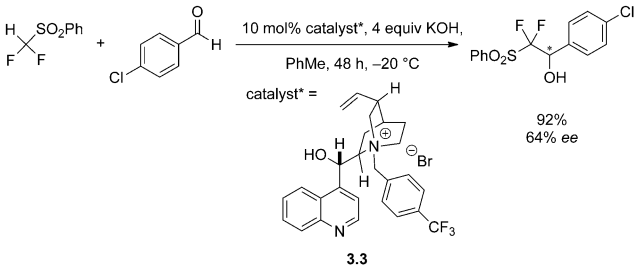
Nucleophilic approaches for the synthesis of α,α-difluoromethylene ethers are still in use, but their importance declined with the development of milder, high-yielding electrophilic difluoromethylation methods. The nucleophilic fluorodesulfurization of thionoesters[141a,i] and xanthates[205,214b,243] in addition to the nucleophilic fluorodeoxygenation of aryl formyl esters[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.[245] The fluorination of carbonates with $SF_4$ results in bis(alkoxy)difluoromethane products.[246] An extensive review was published on the synthesis of α-fluorinated ethers, sulfides, amines, and phosphines.[201b]

#### 3.2.1. Nucleophilic Difluorination To Form $C_{sp3}$–$CF_2X$ Bonds

C–H-acidic difluoromethyl pronucleophiles containing sulfone, sulfoxide, or phosphonate electron-withdrawing groups are deprotonated prior to their reaction with alkyl halides,[247] carbonyl substrates,[190,248] chiral sulfinylimines,[249] amino sulfinylimines,[188] and cyclic sulfates (Scheme 53) and sulfimidates.[250] Difluoromethylphenylsulfoxide[251] and phosphonate[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,[214e,g,253] thermally stable after deprotonation,[254] and the electron-withdrawing group can be removed after difluoromethylation.[254] Phase-transfer catalysis with **3.3** for the enantioselective addition of the difluoromethyl phenyl sulfone to aldehydes was explored, with enantioselectivity ranging from 4 to 64% *ee* (Scheme 54).[255]




***Scheme 53.*** Ring opening of cyclic sulfates with difluoromethyl phenyl sulfone. HMPA = hexamethyl phosphoramide.



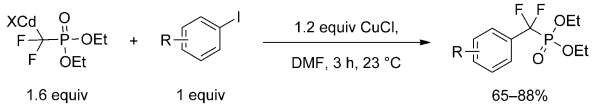

***Scheme 54.*** Enantioselective addition of a fluoromethyl pronucleophile to an aryl aldehyde in the presence of a chiral ammonium salt of a cinchona alkaloid as the catalyst.

The electron-rich organic reductant tetrakis(dimethylamino)ethylene (TDAE) has an oxidation potential similar to zinc metal[256] and can transfer two-electrons through 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] The reaction of trimethylsilyldifluoromethyl pronucleophiles with carbonyl substrates are mediated by fluoride or Lewis acids.[258] The advantages of utilizing silyl-based difluoromethyl pronucleophiles include easy preparation of the reagents[259] and compatibility with enolizable carbonyl compounds. More recently, the 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 $C_{sp2}$–$CF_2X$ Bonds

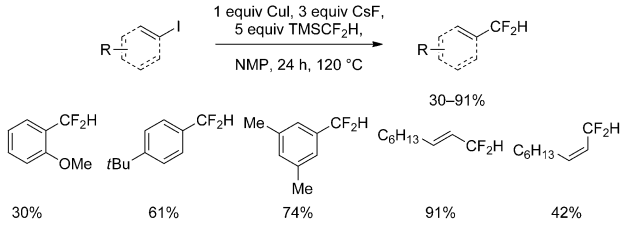
Cadmium difluoromethylphosphonate reagents can be cross-coupled with iodoarenes in the presence of copper chloride to afford aryl difluoromethyl phosphonates (Scheme 55).[261] Similarly, copper-based difluoromethylating reagents derived from halodifluoroacetate undergo cross-



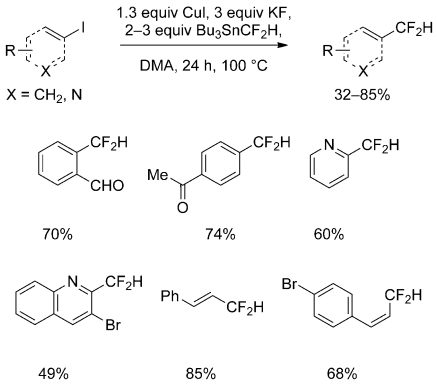

***Scheme 55.*** Cu-mediated cross-coupling of a cadmium-based difluoromethyl pronucleophile with aryl iodides.

coupling with aryl or alkenyl iodides.[262] The copper-catalyzed cross-coupling of aryl halides and ethyl trimethylsilyldifluoroacetate to yield substituted difluoromethyl benzoates, which, after saponification and decarboxylation, afford difluoromethyl arenes, was reported by Amii and co-workers.[263] Ethyl *ortho*-iodobenzoate derivatives can undergo copper-catalyzed cross-coupling with zinc diethyldifluoromethyl phosphonate, as reported by Zhang and co-workers.[264] Direct difluoromethylation of aryl and alkenyl iodides using five equivalents of $TMSCF_2H$ as the difluoromethyl pronucleophile with copper salts was established by Hartwig (Scheme 56).[265] This method tolerates electron-rich as well




***Scheme 56.*** Direct difluoromethylation of aryl and alkenyl iodides with copper iodide and $TMSCF_2H$.

as electron-poor functional groups and directly affords the desired difluoromethylated products in 30–91% yield. Prakash et al. recently developed a method for the difluoromethylation of aryl and alkenyl halides as well as heteroaryl halides with $Bu_3SnCF_2H$ and copper salts (Scheme 57).[266] Difluoromethyl arenes can also be synthesized by nucleophilic deoxyfluorination of aromatic aldehydes with Deoxo-Fluor.[267]




***Scheme 57.*** Direct difluoromethylation of aryl, heteroaryl, and alkenyl iodides with copper iodide and $Bu_3SnCF_2H$. DMA = *N*,*N*-dimethylacetamide.

## 4. Trifluoromethylation

Trifluoromethyl groups are electron-withdrawing substituents that increase the lipophilicity of molecules.[15] Functionalization of the anticancer 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.[268] Hence, there is considerable interest in developing methods for the controlled introduction of trifluoromethyl groups into small molecules. Compared to mono- and difluoromethylation, fewer synthetic strategies are available for the introduction of trifluoromethyl groups: since three of the four substituents on the carbon atom are predetermined, only one other substituent can be varied, which limits potential synthetic handles. Transition-metal-mediated trifluoromethylation is complicated by the strong metal–$CF_3$ bond originating from both the polar contribution of the bond as well as backbonding from filled metal d orbitals into the $\sigma^*_{C-F}$ bonds, which therefore results in a high barrier to formation of the C–$CF_3$ bond.

### 4.1. Electrophilic Trifluoromethylation

A range of substrates can be trifluoromethylated by employing functional group tolerant reagents and conditions. In laboratory settings, crystalline and easily weighable electrophilic trifluoromethylating reagents are preferable because of ease of handling, while lower cost reagents such as $CF_3I$, or even better $CF_3H$, are favored for industrial processes.

The development of widely used crystalline electrophilic trifluoromethylating reagents (Figure 3)[269] such as the Togni reagents,[270] *S*-(trifluoromethyl)dibenzothiophenium salts,[271] and *S*-trifluoromethyldiarylsulfonium salts[272] has enabled the

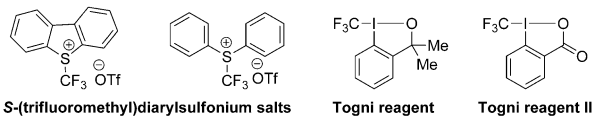



***Figure 3.*** A selection of widely used electrophilic trifluoromethylating reagents.

development of functional group tolerant methods that encompass a broad substrate scope. These trifluoromethylating reagents are two-electron oxidants, but the exact mechanisms for the trifluoromethylation have not been firmly established in many cases; the mechanism could occur by two SET or one two-electron transfer concurrent with or followed by trifluoromethyl group transfer.[273]

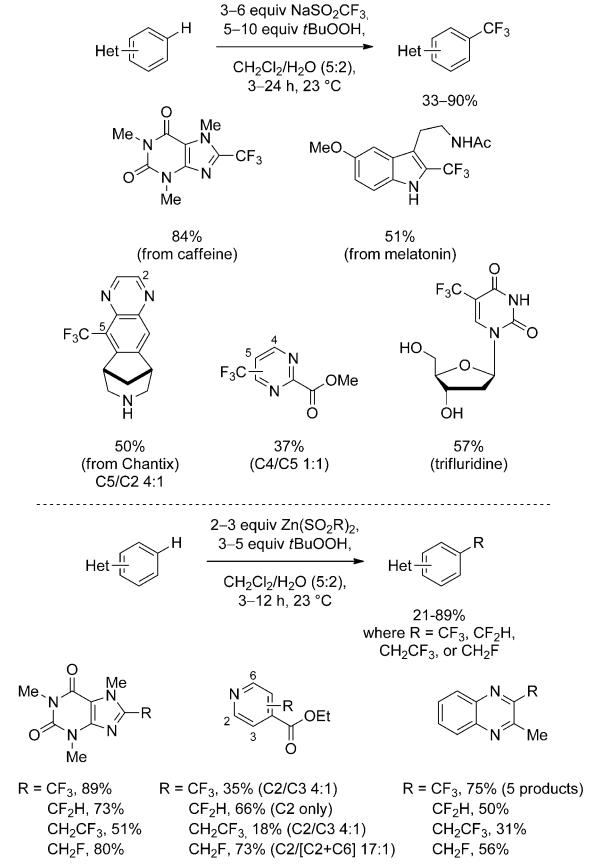
An alternative to using electrophilic trifluoromethylating reagents is the use of nucleophilic trifluoromethylating reagents in conjunction with oxidants to accomplish an oxidative trifluoromethylation. Transition metals have facilitated the formation of a bond between the aryl carbon atom

and the trifluoromethyl group in trifluoromethyl arenes from aryl nucleophiles by exploiting redox chemistry at the metal center. Organocatalysts, on the other hand, have allowed the development of enantioselective α-trifluoromethylation reactions[274] of carbonyl substrates by radical and nonradical mechanisms.

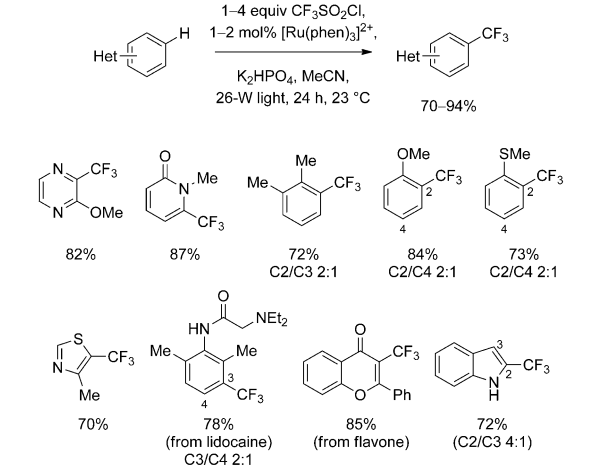
#### 4.1.1. *Electrophilic Methods for the Synthesis of Trifluoromethylated $sp^2$ Carbon Centers with Radicals*

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

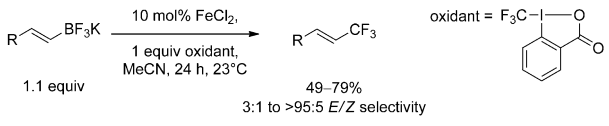
Direct trifluoromethylation of C–H bonds would obviate the need for prefunctionalization, but is rendered difficult by the inertness of C(aryl)–H bonds. In the case of N-heteroarenes and electron-rich arenes, the reaction with Togni's reagent affords multiple trifluoromethylated products for most substrates.[280] The use of the solid and bench-top-stable reagent $NaSO_2CF_3$ in radical trifluoromethylations was first described by Langlois et al. for the trifluoromethylation of electron-rich arenes.[278] Baran and co-workers used the Langlois reagent in conjunction with excess *tert*-butyl hydrogen peroxide for the trifluoromethylation of heteroarenes (Scheme 58).[281] The method is operationally simple, takes place at room temperature and in an ambient atmosphere through in situ generation of electrophilic $CF_3$ radicals without additional catalysts. The selectivity of this reaction ranges from a 1:1 isomeric product mixture to the formation of a single isomer. The Baran research group has since improved the radical trifluoromethylation with $Zn(SO_2CF_3)_2$ and extended the use of other fluorinated zinc sulfinate salts to include a variety of fluorinated derivatives.[213b] Photoredox catalysis with a redox-active ruthenium(II) catalyst and $CF_3SO_2Cl$, as described by MacMillan, has been used to generate the electrophilic $CF_3$ radical and leads to the formation of monotrifluoromethylated products for heteroarenes and trifluoromethylated arenes (Scheme 59).[282] The trifluoromethylation methods decribed by the research groups of Baran and MacMillan allow the efficient direct synthesis of complex trifluoromethyl arenes, which had not previously been possible. Iron-catalyzed radical trifluoromethylation of arenes and heteroarenes give yields of less than 50% for most substrates,[283] while $Fe^{II}$-catalyzed trifluoromethylation of potassium alkenyltrifluoroborates with Togni reagent II affords the desired trifluoromethylated alkenes in 49–79% yield in up to > 95:5 *E*/*Z* selectivity (Scheme 60).[284] Silver-mediated trifluoromethylation of unactivated arenes and heteroarenes with $TMSCF_3$ is likewise postulated to



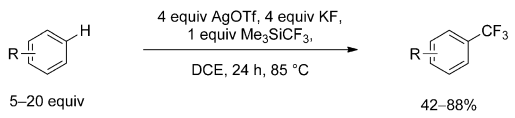

***Scheme 58.*** Radical trifluoromethylation of heteroarenes.




***Scheme 59.*** Ru-photoredox-catalyzed trifluoromethylation of arenes and heteroarenes.




***Scheme 60.*** $Fe^{II}$-catalyzed trifluoromethylation of potassium alkenyltrifluoroborates with Togni reagent II.

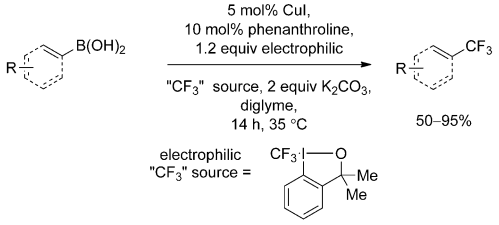



***Scheme 61.*** Ag-mediated trifluoromethylation of unactivated arenes.

occur through a radical mechanism to afford trifluoromethylated products (Scheme 61).[285]

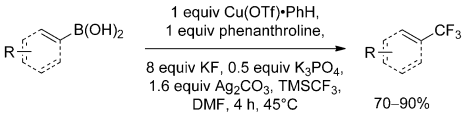
#### *4.1.2. Electrophilic Methods for the Synthesis of Trifluoromethylated sp and sp² Carbon Centers with Copper*

The trifluoromethylation of boronic acids has been successfully accomplished with copper catalysts by two approaches: 1) oxidation with an electrophilic trifluoromethylating reagent and 2) by using an oxidant in conjunction with a trifluoromethyl anion equivalent. The trifluoromethylation of aryl and alkenylboronic acids with electrophilic trifluoromethylating reagents was reported with Togni reagent, as described by Liu and Shen (Scheme 62),[286] and



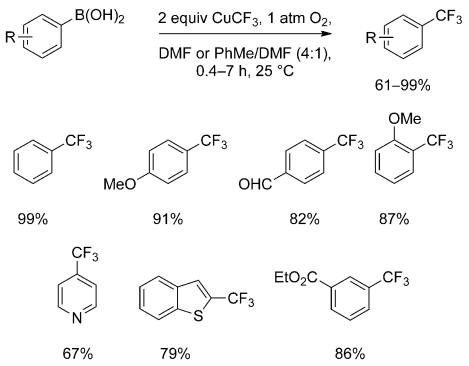

***Scheme 62.*** Cu-catalyzed electrophilic trifluoromethylation of aryl and alkenyl boronic acids with Togni reagent.

diaryltrifluoromethylsulfonium salts, as described by Liu and co-workers[287] and Xiao and co-workers.[288] The method described by Liu and Shen encompasses a broad range of boronic acid substrates and affords trifluoromethylated products in 50–95% yield while utilizing a low loading of the copper catalyst. The combined use of a nucleophilic trifluormethyl source and an oxidant is illustrated by the oxidative copper-mediated trifluoromethylation of aryl boronic acids and alkenylboronic acids with silver carbonate and trimethylsilyltrifluoromethane ($TMSCF_3$) developed by the Qing research group (Scheme 63).[289,290] Similarly, oxygen can



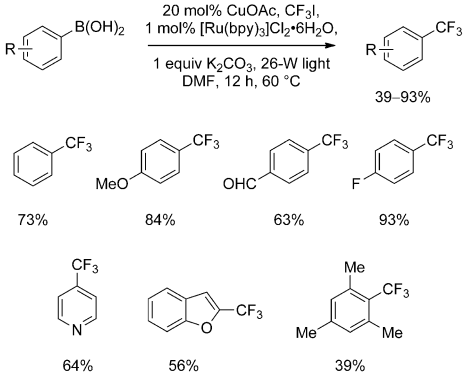

***Scheme 63.*** Cu-mediated electrophilic trifluoromethylation of aryl and alkenyl boronic acids. TMS = trimethylsilyl.

be used as the terminal oxidant instead of the less-desirable metal-based oxidants,[291] as shown by Buchwald and co-workers, and provides a complementary method to the one described by Liu and Shen. Instead of $TMSCF_3$, the crystalline and shelf-stable potassium trifluoromethyltrimethoxy borate was used by Gooßen and co-workers with oxygen as a terminal oxidant.[292] The Grushin research group developed a method that utilizes low-cost fluoroform as the $CF_3$ source in conjunction with copper complexes to trifluoromethylate aryl boronic acids (Scheme 64).[293] Sanford and co-workers



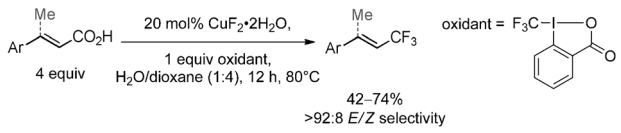

***Scheme 64.*** Cu-mediated trifluoromethylation of aryl boronic acids with $CuCF_3$ generated from $CHF_3$.

demonstrated the radical trifluoromethylation of aryl boronic acids with $CF_3I$ and Cu/Ru co-catalysts (Scheme 65),[294] which subsequently was made more practical with the use of $NaSO_2CF_3$ as the trifluoromethyl radical source.[295]




***Scheme 65.*** Cu-catalyzed trifluoromethylation of aryl boronic acids with $[Ru(bpy)_3]Cl_2 \cdot 6H_2O$ and $CF_3I$. bpy = bipyridine.

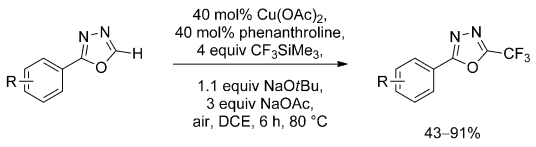
α,β-Unsaturated carboxylic acids[241] undergo copper-catalyzed decarboxylative trifluoromethylation with Togni reagent II to afford the trifluorofluoromethylated alkene products in 42–74% yield with ≥92:8 selectivity for the *E* isomer (Scheme 66). This transformation reported by Hu




***Scheme 66.*** Cu-catalyzed trifluoromethylation of α,β-unsaturated carboxylic acids with Togni reagent II.

and co-workers allows for the facile conversion of α,β-unsaturated esters and other carboxylic acid derivatives into the trifluoromethylalkenes after saponification.

An illustrative example of how transition metals can be employed to control reactivity is the one-pot C(aryl)–H borylation/trifluoromethylation sequence.[296] Direct trifluoromethylation of heteroarenes can be accomplished by a copper-catalyzed oxidative trifluoromethylation with $TMSCF_3$ and bis(*tert*-butyl)peroxide[297] as well as with oxygen as the oxidant (Scheme 67).[297] The oxidative

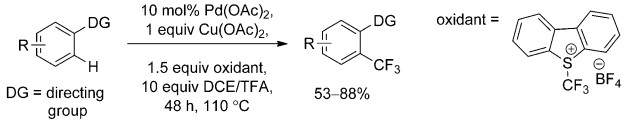



***Scheme 67.*** Cu-catalyzed trifluoromethylation of 1,3,4-oxadiazoles.

trifluoromethylation of terminal alkynes using $Ag_2CO_3$,[298] and air[290,299] 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 with copper catalysis[300] by utilizing an electrophilic trifluoromethylating reagent, and in a palladium-catalyzed[301] transformation using $PhI(OAc)_2$ and the trifluoromethyl anion.

#### 4.1.3. Electrophilic Methods for the Synthesis of Trifluoromethylated $sp^2$ Carbon Centers with Other Transition Metals

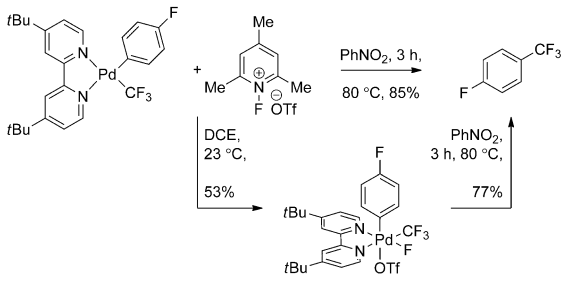
The trifluoromethylation of arenes under rhenium catalysis is possible, but affords multiple isomeric products in a total yield of 11–77%.[302] Progress towards the regioselective trifluoromethylation of arenes has been made with nitrogen directing groups such as the *N*-directed electrophilic trifluoromethylation of arenes with a palladium catalyst (Scheme 68).[303] Unlike with *N*-directed arene fluorination




***Scheme 68.*** Pd-catalyzed *N*-directed trifluoromethylation of arenes. TFA = trifluoroacetic acid.

catalyzed by palladium, the *N*-directed electrophilic trifluoromethylation of arenes does not result in *ortho*,*ortho*-ditrifluoromethylated products, most likely because of steric constraints preventing a second cyclometalation event. Similarly, the *ortho*-trifluoromethylation of aryl triazenes with $TMSCF_3$ can be accomplished with four equivalents of silver fluoride by means of a triazene directing group.[304]

Reductive elimination from $Pd^{IV}$ complexes to form trifluoromethyl arenes was investigated,[305] and these studies established the viability of C(aryl)–$CF_3$ reductive elimination from high-valent organometallic complexes (Scheme 69).[306]




***Scheme 69.*** Reductive elimination of $Pd^{IV}$ complexes to afford trifluoromethyl arenes.

Additionally, it was found that the oxidation of benzoquinoline-cyclometalated $Pd^{II}$ acetate dimers afforded $Pd^{III}$-$Pd^{III}$ dimers,[307] which, in the presence of acetic acid/water, disproportionated to $Pd^{IV}$ complexes.[308] These reports established that aryl trifluoromethylation could be accomplished through high-valent palladium intermediates.

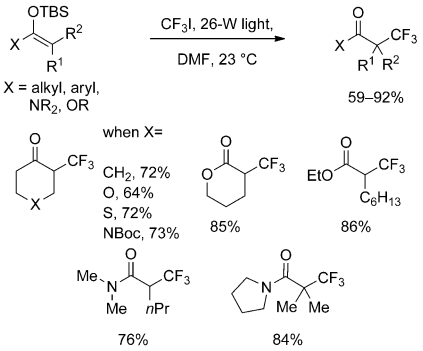
#### 4.1.4. Electrophilic Methods for the Synthesis of Trifluoromethylated $sp^3$ Carbon Centers

In 1949, Haszeldine reported the photochemical and thermal addition of trifluoromethyl radicals to alkenes.[309] The use of ruthenium(II) complexes afforded the products resulting from the controlled addition of trifluoromethylsulfonyl chloride to alkenes with extrusion of $SO_2$.[310] Continued interest in the controlled addition of fluorinated reagents across double bonds led to the development of lauroyl peroxide initiated radical addition of aminotrifluoroethyl dithiocarbamate across alkenes to afford α-trifluoromethylamines.[311] Incorporation of trifluoromethyl groups vicinal to amine functional groups has been accomplished with other approaches besides the radical addition of α-trifluoromethylated amino derivatives. These methods include benzoyl peroxide promoted oxidative coupling between the α-carbon atom of the amine and $TMSCF_3$[312] as well as the synthesis of *anti*-α-trifluoromethyl-β-amino alcohols through a three-component condensation reaction.[313] The controlled radical trifluoromethylaminoalkoxylation across unactivated alkenes with Togni reagent II, TEMPO, and sodium metal has recently been reported by Li and Studer.[314]

Lithium imide enolates functionalized with chiral auxiliaries can undergo trifluoromethylation with trifluoroiodomethane in the presence of the radical initiator triethylborane.[315] This transformation was later applied more broadly to the lithium and titanium enolates of ketones.[316] Similarly, zirconium enolates functionalized with chiral auxiliaries can be trifluoromethylated and perfluoroalkylated in the presence of a ruthenium catalyst in up to 99% yield and ≥9:1 diastereoselectivity.[317] The use of Togni reagent for the diastereoselective α-trifluoromethylation of chiral imides

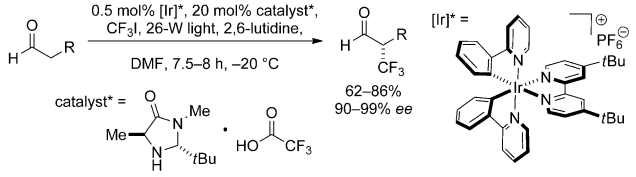
circumvented the need to condense iodotrifluoromethane gas for use in the reactions.[318] Cyclic ketones and carboxylic acid derivatives have also been α-trifluoromethylated through photochemical radical processes (Scheme 70).[319] Trifluoro-




***Scheme 70.*** Photochemical α-trifluoromethylation of silyl enol ethers.

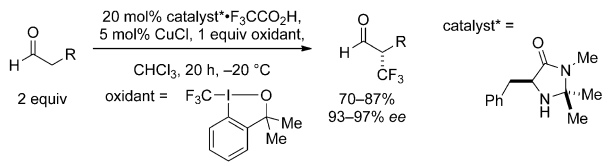
acetadehyde methyl hemiacetal has been established as a source of trifluoromethyl groups through an acid-mediated Friedel–Crafts reaction with arenes.[320]

A preliminary study on the enantioselective α-trifluoromethylation of enolates by Umemoto and Adachi made use of chiral borane Lewis acid/enolate adducts and trifluoromethylsulfonium reagents to afford α-trifluoromethylcarbonyl products.[271c] The enantioselective trifluoromethylation of β-keto esters has been investigated with chiral guanidine bases and are postulated to occur via chiral enolate/guanidinium complexes.[321] Subsequent approaches for the enantioselective α-trifluoromethylation of carbonyl substrates made use of organocatalysis to generate chiral enamines. MacMillan and co-workers described the enantioselective α-trifluoromethylation of aldehydes by iridium photoredox co-catalysis (Scheme 71).[212] The photoredox transformation occurs

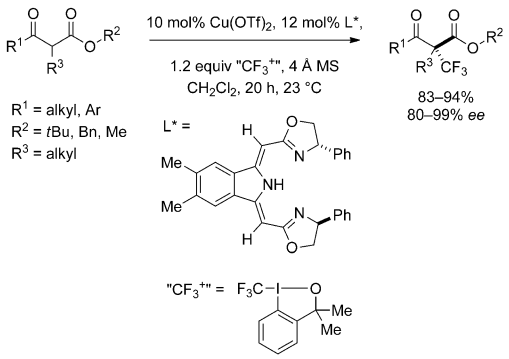



***Scheme 71.*** Ir-photoredox-catalyzed α-trifluoromethylation of aldehydes.

through a radical mechanism, which is likely not the case for the organocatalytic α-trifluoromethylation of aldehydes with trifluoromethyliodonium salts reported in the following year by the same research group (Scheme 72).[322a] The latter method requires two equivalents of aldehyde, is operationally practical in a laboratory setting, and affords products in similar yields and enantiomeric excess as the photochemical method with $CF_3I$. A mild transition-metal-catalyzed method for the α-trifluoromethylation of α-acidic β-keto esters with copper catalysis and 80–99% *ee* has been reported by Gade (Scheme 73).[322b]

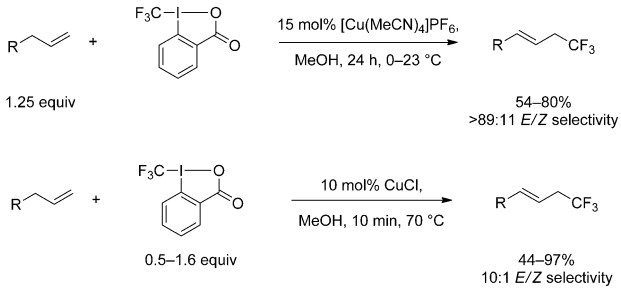



***Scheme 72.*** Organocatalytic α-trifluoromethylation of aldehydes with Togni reagent.



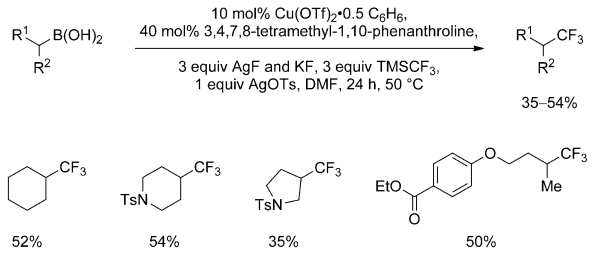

***Scheme 73.*** Electrophilic α-trifluoromethylation of β-keto esters catalyzed by $Cu^{II}$ with Togni reagent I.

The initial approach used for the synthesis of 3,3,3-trifluoropropene groups involved trifluoromethylation of prefunctionalized allyl nucleophiles, such as allylic silanes[323] and allylic stannanes,[324] as well as the trifluoroethylation of alkenylstannanes[324] and trifluoroethylation of alkenylstannanes.[324] The combination of allyl halides[325] with $TMSCF_3$ and stoichiometric amounts of copper for allylic trifluoromethylation has also been reported. Subsequently, in an effort to obviate the need for toxic stannyl precursors, unactivated alkenes were examined as substrates for trifluoromethylation. As reported by Parsons and Buchwald, terminal alkenes can undergo C–H activation at the allylic position and oxidation with Togni reagent II in the presence of catalytic amounts of $Cu^{I}$ salts to afford >9:1 *E*/*Z* selectivity for allyl products with terminal trifluoromethyl groups (Scheme 74, top).[326] Subsequently, this transformation was extended to the intramolecular oxytrifluoromethylation of terminal alkenes.[327] The copper-catalyzed allylic C–H trifluoromethylation of terminal alkenes was reported by Chu and Qing,[328] Fu, Liu, and co-workers,[329] as well as Wang et al. (Scheme 74, bottom).[330] The transformation is hypothesized by Wang et al. to occur by




***Scheme 74.*** Cu-catalyzed allylic C–H trifluoromethylation.

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. Other reactions of alkenes with electrophilic trifluoromethylating reagents include the oxidative trifluoromethylation of styrenes to give α-trifluoromethyl ketones[331] and an arene cyclization/trifluoromethylation cascade with activated alkenes.[332] More recently, the oxidative trifluoromethylation of primary and secondary (Scheme 75) alkyl boronic acids has been accom-




***Scheme 75.*** Cu-promoted oxidative trifluoromethylation of secondary alkyl boronic acids.

plished with a substoichiometic amount of copper salts in the presence of silver salts and $TMSCF_3$ to afford the corresponding products in yields of 36–78% and 35–54%, respectively.[333]

Various electrophilic trifluoromethylating reagents such as trifluoromethylazosulfonyl arenes,[334] perfluoroiodonium salts,[335] (trifluoromethyl)dibenzothiophenium, -selenophenium, and -tellurophenium salts,[271a,b,336] *N*-trifluoromethyl-*N*-nitrosobenzenesulfonamide,[337] and *N*-trifluoromethyl-*N*-nitroso-type reagents[338] have been synthesized for the trifluoromethylation of sulfur and carbon nucleophiles. The more commonly used hypervalent iodine reagents developed by Togni and co-workers have been applied to the trifluoromethylation of carbon- and sulfur-based nucleophiles[270,273a,339] as well as sulfonates.[340] Additionally, the fluorinated Johnson reagent [(oxido)phenyl(trifluoromethyl)-$\lambda^4$-sulfanylidene]dimethylammonium tetrafluoroborate has been developed as a reagent for the trifluormethylation of C–H-acidic substrates.[341]

### 4.2. Nucleophilic Trifluoromethylation

The synthesis of trifluoromethylated products was initially accomplished by nucleophilic fluoride displacement of trihalomethyl substrates or fluorodeoxygenation of carboxylic acid derivatives under harsh conditions.[1c,342] Subsequent approaches for nucleophilic trifluoromethylation utilized stabilized trifluoromethyl anion equivalents for cross-coupling, substitution, or addition reactions with electrophiles. Nucleophilic trifluoromethylation with the 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 the trifluormethyl anion is generated from the pronucleophile is of great importance, and 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 transmetalation of the pronucleophile to yield a metal-bound $CF_3$ group.

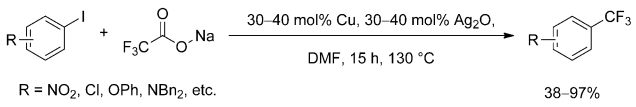
$TMSCF_3$, a commonly employed pronucleophile of the trifluoromethyl anion, is a hydrolyzable, moisture-sensitive liquid which is more difficult to handle than weighable, crystalline reagents that have been developed as trifluoromethyl pronucleophiles, but can be rather expensive. Trifluoroacetate salts are cheap and easy to handle, but so far no mild, functional group tolerant trifluoromethylation method has been reported with this pronucleophile. Inexpensive, gaseous trifluoromethane can be used for trifluoromethylation reactions.[293,343]

#### 4.2.1. Nucleophilic Methods for the Synthesis of Trifluoromethylated $sp^2$ Carbon Centers

Swarts first reported the synthesis of trifluoromethylbenzene in 1898 through nucleophilic fluoride substitution of the corresponding trichloride.[1c,344] Benzoic acid substrates were likewise exhaustively fluorinated with $SF_4$ at the carbonyl carbon atom to afford the trifluoromethylated arenes.[342] The yield of the nucleophilic trifluoromethylation can be improved when copper powder and $CF_3I$ are used to synthesize trifluoromethylbenzene from iodobenzene,[345] and subsequent optimization with different sources of copper and metal mixtures allow for lower reaction temperatures.[346] Studies by Wiemers and Burton revealed that the copper–trifluoromethyl complex generated upon reduction of dihalodifluoromethane with zinc metal and metathesis with a copper(I) salt was the active species responsible for the trifluoromethylation.[347] This discovery led to the development of different methods that made use of copper–trifluoromethyl complexes to trifluoromethylate aryl bromides,[348] aryl chlorides,[349] aliphatic halides,[350] and heteroaromatic halides.[351]

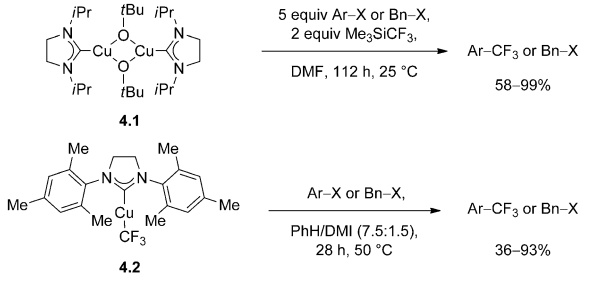
Copper has been used stoichiometrically and also as a catalyst with various reagents: dibromodifluoromethane,[352] sodium trifluoroacetate,[353] methyl trifluoroacetate,[354] fluorosulfonyldifluoromethyl iodide,[355] ethyl chlorodifluoroacetate/KF,[356] bis(trifluoromethyl)mercury,[357] and *S*-(trifluoromethyl)diphenylsulfonium triflate.[358] The use of *S*-(trifluoromethyl)diphenylsulfonium triflate is interesting because an electrophilic crystalline trifluoromethylating reagent can be reduced in situ to a nucleophilic copper–trifluoromethyl complex to afford trifluoromethylated heteroarenes from the corresponding iodides. Electrochemical reduction methods with a copper anode and $CF_3Br$[359] as well as generation of a copper–trifluoromethyl complex by the cupration of fluoroform[360] have both been explored for the trifluoromethylation of aryl halides. In some cases, co-catalysis with silver(I) has also been used to facilitate trifluoromethylation (Scheme 76[353d]).[353d,361]

Trifluoromethylorganosilanes, first reported by Ruppert et al.,[362] are the most commonly used nucleophilic trifluoromethylation reagent in cross-coupling reactions and addition



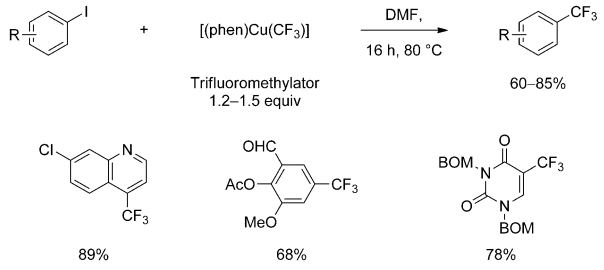

***Scheme 76.*** Cu and Ag co-catalyzed trifluoromethylation of aryl iodides with sodium trifluoroacetate.

reactions. Trifluoromethylorganosilanes such as trimethylsilyltrifluoromethane ($TMSCF_3$) and triethylsilyltrifluoromethane ($TESCF_3$) can be desilylated with fluoride to give the trifluoromethyl anion. The first report of the copper-mediated trifluoromethylation of aryl iodides with $TMSCF_3$/KF[363] by Urata and Fuchikami laid the foundation for trifluoromethylation/cross-coupling with trifluoromethyltrialkylsilanes. Aryl halides in conjunction with trifluoromethylorganosilanes can react with the copper carbene complexes **4.1** and **4.2** described by Vicic and co-workers (Scheme 77),[364] copper/silver co-

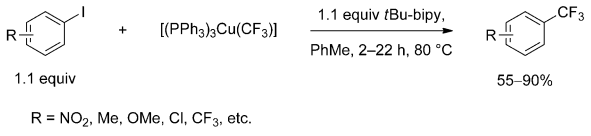



***Scheme 77.*** Cu-mediatated trifluoromethylation of organic halides with $TMSCF_3$. DMI = 1,3-dimethyl-2-imidazolidinone.

catalysts by Weng et al.,[361] copper–nitrogenous ligand catalysts by Amii and co-workers,[365] isolated stoichiometric copper–phenanthroline complexes by Hartwig and co-workers (Scheme 78),[366] and stoichiometric copper–phosphine complexes by Grushin and co-workers (Scheme 79)[367] to afford trifluoromethylated arenes. The method of Hartwig and co-workers is the most functional-group tolerant and



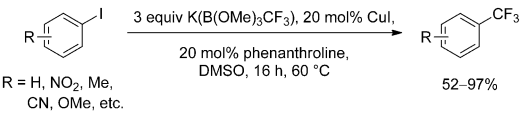

***Scheme 78.*** Trifluoromethylation of aryl halides with Trifluoromethylator. BOM = benzyloxymethyl.




***Scheme 79.*** Trifluoromethylation of aryl halides with a copper/phosphine trifluoromethyl complex. bipy = bipyridine.

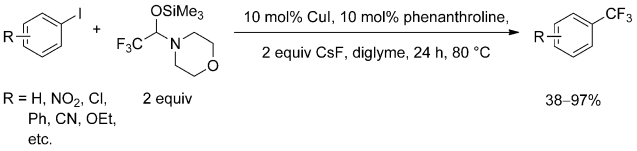
allows the trifluoromethylation of electron-poor, electron-rich, and even *ortho*,*ortho*-disubstituted arenes, while the catalytic system of Amii and co-workers utilizes only 10 mol% of the copper catalyst to afford trifluoromethylated arenes in 44–99% yield.

Copper-catalyzed trifluoromethylations of aryl iodides with trifluoromethylborate salts (Scheme 80)[368] and with α-trifluoromethylmorpholinotrimethyl silyl ether (fluoral hemi-




***Scheme 80.*** Cu-catalyzed trifluoromethylation of aryl halides with potassium trifluoromethyltrimethoxyborate.

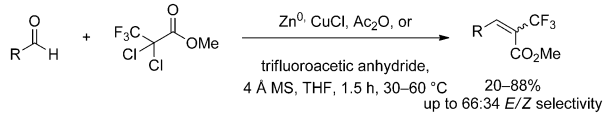
aminal; Scheme 81)[369] have been established in efforts to replace the use of volatile and moisture-sensitive trifluoromethyltrialkylsilanes. Trifluoromethylborate salts are crystalline, air-stable, storage-stable reagents that can act as




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

a trifluoromethyl anion donor in the presence of copper salts.[368] Similarly, fluoral hemiaminal has been shown to be a stable and inexpensive source of the trifluoromethyl anion; however, two equivalents of the reagent relative to the substrate are required.[370] This necessity is postulated to arise from dimerization of the reagent to a silicate species that then acts as the reactive trifluoromethyl anion donor.[370b]

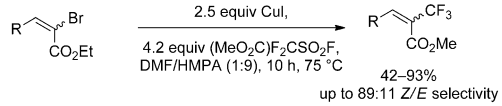
A Reformasky/elimination reaction sequence between methyl α-trifluoromethyl-α,α-dichloroacetate with aldehydes mediated by zinc and copper(I) in acetic or trifluoroacetic anhydride afforded trifluoromethyl olefins (Scheme 82).[371]




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

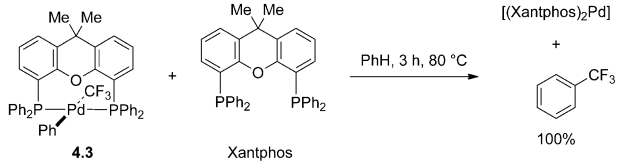
Additionally, alkenyl bromides treated with nucleophilic trifluoromethyl–copper complexes generated from fluorosulfonyldifluoroacetate (Scheme 83),[372] mercury bis(trifluoromethyl),[373] and $TMSCF_3$[374] can afford the desired trifluoromethyl alkenes.

The strong Pd–$CF_3$ bond in trifluoromethyl–palladium complexes renders the reductive elimination of trifluoromethyl arenes difficult compared to the reductive elimination



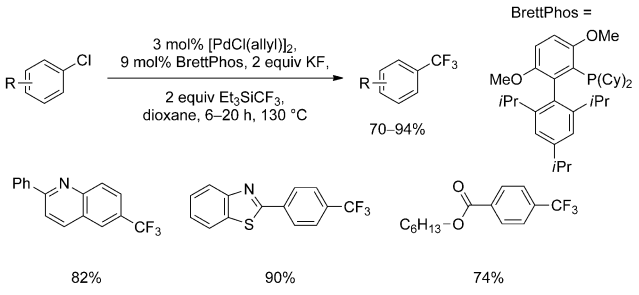

***Scheme 83.*** Cu-mediated trifluoromethylation of alkenyl bromides.

from arylmethyl–palladium complexes, which readily undergo reductive elimination to afford toluene.[375] The viability of reductive elimination from $Pd^{II}$–aryl complexes to form C(aryl)–$CF_3$ bonds was established by Grushin et al. by using the chelating ligand XantPhos at 80 °C (Scheme 84,




***Scheme 84.*** Reductive elimination of trifluoromethyl arenes from a $Pd^{II}$ complex.

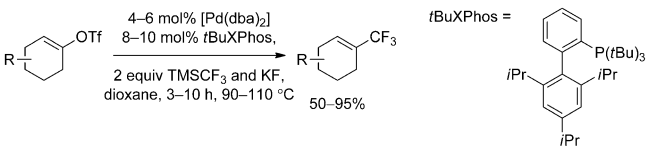
complex **4.3**).[376] The palladium-catalyzed cross-coupling of aryl chlorides with $TESCF_3$ was achieved by Buchwald and co-workers using BrettPhos, a bulky monodentate phosphine, which allows reductive elimination to occur from the T-shaped trifluoromethyl aryl palladium phosphine complex (Scheme 85).[377] While protic functional groups are not



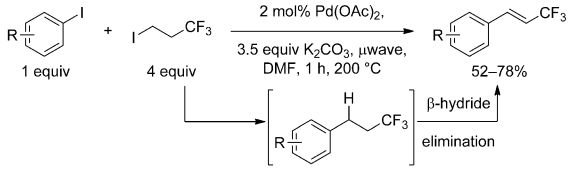

***Scheme 85.*** Pd-catalyzed cross-coupling of aryl halides with $TMSCF_3$.

tolerated, possibly because of protonation of the trifluoromethyl anion to generate fluoroform, electron-rich and poor aryl chlorides as well as heteroaryl chlorides can be trifluoromethylated.

Cross-coupling with $TMSCF_3$ and alkenyl sulfonates has been developed with palladium catalysts to afford trisubstituted trifluoromethyl alkenes (Scheme 86).[378] An unconventional approach to installing trifluoromethylalkenyl groups on arenes makes use of palladium-catalyzed cross-coupling and β-hydride elimination to selectively afford disubstituted *E*-trifluoromethyl alkenes (Scheme 87).[379] The electrophilic trifluoromethylation of alkynes with Togni reagent II mediated by copper iodide can afford trisubstituted trifluoromethyl alkenyl carbonates.[380] For the synthesis of β-trifluoromethyl styrenes, aryl iodides underwent cross-coupling with (*E*)-trimethylsilyl-3,3,3-trifluoropropene with retention of the double-bond geometry.[381]




***Scheme 86.*** Pd-catalyzed trifluoromethylation of alkenyl triflates. dba = dibenzylidineacetone.

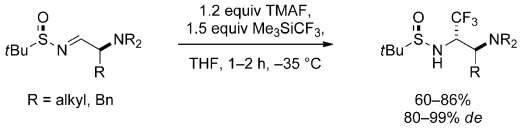



***Scheme 87.*** Pd-catalyzed cross-coupling of aryl iodides and 1,1,1-trifluoro-3-iodopropane with sequential β-hydride elimination.

### *4.2.2. Nucleophilic Methods for the Synthesis of Trifluoromethylated $sp^3$ Carbon Centers*

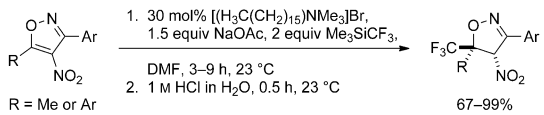
Trifluoromethylating reagents based on mecury,[382] zinc,[226a,c,383] and cadmium,[226a,384] have been explored, but difficulties and inefficient processes for their generation have made their use impractical. Currently, trifluoromethylorganosilanes are the most commonly used nucleophilic trifluoromethyl reagents in the laboratory.

Trifluoromethyltrimethylsilane ($TMSCF_3$) after desilylation with tetrabutylammonium fluoride (TBAF) or tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF) can react with aldehydes,[385] esters,[386] *N*-(*tert*butylsulfinyl)imines,[387] amino *N*-(*tert*butylsulfinyl)imines (Scheme 88),[388]




***Scheme 88.*** Diastereoselective addition of $TMSCF_3$ to *N*-(*tert*-butylsulfinyl)imines.

*N*-tosylaldimines,[389] diketo compounds,[390] α,β-unsaturated carbonyls,[391] imines/iminiums,[392] and isoxazoles (Scheme 89).[393] The fluoride source is integral for a constructive trifluoromethylation reactivity especially for enolizable substrates. Basic metal fluorides can α-deprotonate enolizable substrates, and so tetraalkylammonium fluorides have been used because they exhibit the right amount of nucleophilicity and basicity. Other nucleophilic methods for the

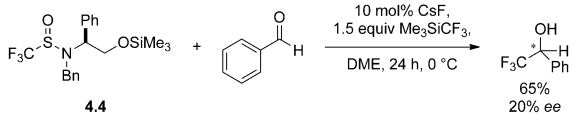



***Scheme 89.*** Diasteroselective addition of $TMSCF_3$ to isoxazoles.

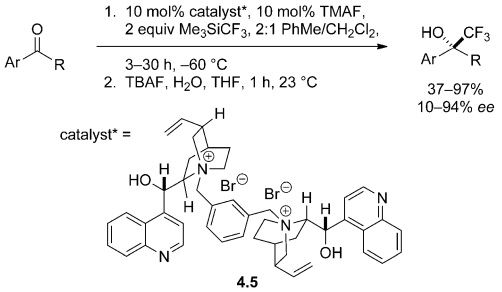
trifluoromethylation of carbonyl compounds and carbonyl derivatives have been accomplished with Lewis acids and bases,[258e,394] as well as tri-*tert*-butylphosphine as the desilylating reagent.[395]

Preliminary efforts toward the enantioselective addition of a trifluomethyl group involved chiral amine auxiliaries such as **4.4** (Scheme 90)[396] or asymmetric induction with chiral




***Scheme 90.*** Synthesis of enantioenriched trifluoromethylated alcohols with a chiral amine auxiliary.

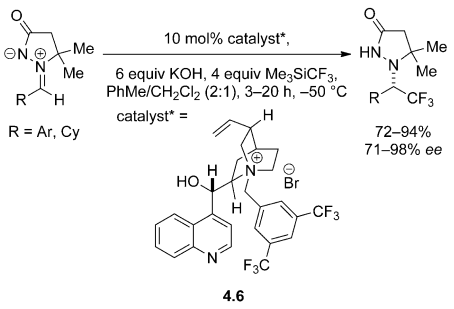
sulfinyl directing groups.[397] The enantioselective addition of the trifluoromethyl anion to carbonyl electrophiles has been challenging because tight ion pairing between the chiral catalyst and the substrate has been hard to achieve. The use of chiral ammonium catalysts such as **4.5** based on the cinchona alkaloid has enabled the asymmetric trifluoromethylation of aromatic aldehydes and ketones,[398] cyclic electron-neutral aromatic ketones (Scheme 91),[399] and alkynyl ketones.[400]




***Scheme 91.*** Enantioselective addition of $TMSCF_3$ to aryl ketones by phase-transfer catalysis. TMAF = tetramethylammonium fluoride, TBAF = tetrabutylammonium fluoride.

Chiral ammonium bromides with exogenous potassium fluoride can be employed in place of the hydroscopic chiral ammonium fluoride salts;[401] however, because potassium fluoride is sparingly soluble in polar aprotic solvents, phenoxide was investigated as the desilylating agent for $TMSCF_3$.[402] Besides carbonyl substrates, activated azomethine imines have similarly been reported as viable substrates for enantioselective trifluoromethylation with the chiral ammonium bromide catalyst **4.6** (Scheme 92).[403]

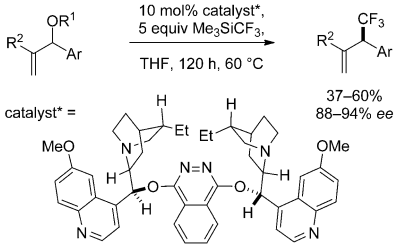
Other nucleophilic trifluoromethylating reagents such as α-trifluoromethylmorpholinotrimethyl silyl ether,[370b] α-trifluoromethylpiperazinotrimethyl silyl ether,[370a,404] and potassium trifluoromethylborates[405] have been utilized for trifluoromethylation reactions. Trifluoroiodomethane reduced with TDAE[406] as well as copper in conjunction with methyl fluorosulfonyldifluoroacetate,[407] chloro difluoroacetate,[408] methyl chlorodifluoroacetate,[356,409] bromotrifluoromethane,[410] and sodium trifluoroacetate[411] have been used to




***Scheme 92.*** Enantioselective addition of $TMSCF_3$ to azomethine imines by phase-transfer catalysis.

generate nucleophilic trifluoromethylating reagents. While many copper-based methods exist, further development of these copper reagents for substitution and addition reactions would need to be developed for practical and efficient applications. More recently, $[(Ph_3P)_3CuCF_3]$ complexes have been treated with propargyl halides to afford halide-displaced trifluoromethylation products,[412] and copper salts in conjunction with $TMSCF_3$ and CsF have also been used for the trifluoromethylation of α-diazo esters.[413]

Enantioenriched trifluoromethyl allyl compounds can be synthesized by enantioselective trifluoromethylation of Baylis–Hilman adducts of allylic acetates (Scheme 93)[414]




***Scheme 93.*** Enantioselective synthesis of allylic trifluoromethylated products with a cinchona alkaloid catalyst.

and carbonates.[415] The substrate scope is limited to compounds containing an ester group in the β position to the allylic acetate or carbonate moiety.

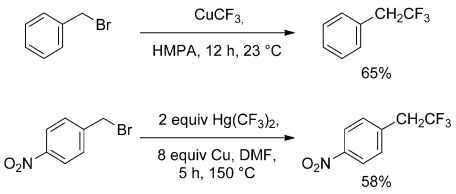
## 5. Trifluoroethylation and Perfluoroalkylation

The direct introduction of trifluoroethyl groups for the synthesis of compounds, many of which find applications as pharmaceuticals,[416] can be accomplished with trifluoromethylhalomethane by using either nucleophilic (i.e. cross-coupling of aryl iodides with trifluoromethyliodomethane) or electrophilic methods (i.e. cross-coupling of aryl boronic acids with trifluoromethyliodomethane). 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 perfluoroalkyliodonium salts or nucleophilic perfluoroalkylating

reagents synthesized by reduction of perfluoroalkyl halides with copper, zinc, or organic reductants.

### 5.1. Trifluoroethylation

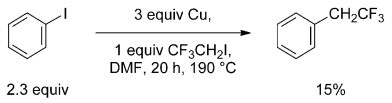
Trifluoroethylated arenes were first synthesized by nucleophilic substitution of the corresponding benzyl bromide with trifluoromethylcopper or bis(trifluoromethyl)mercury reagents (Scheme 94).[364,417] A new operationally facile




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

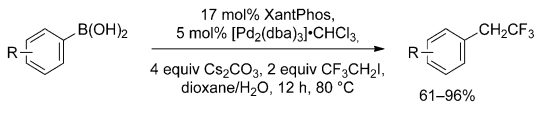
approach for the generation of a trifluoromethylcopper complex is the reduction of *S*-(trifluoromethyl)diphenylsulfonium triflate with copper metal at 60 °C to afford the trifluoroethylated arene products in 36–83 % yield.[418]

The direct trifluoroethylation of iodobenzene was first reported by McLoughlin and Thrower through copper-mediated nucleophilic trifluoroethylation with 1-iodo-2,2,2-trifluoroethane (Scheme 95).[417a] The drawbacks of this




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

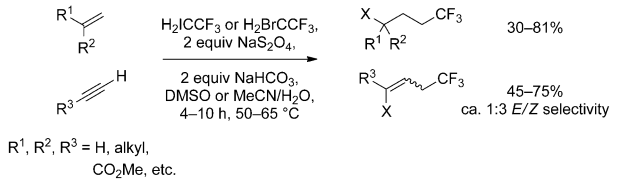
method include the need for excess aryl iodide and the low yields of the trifluorethylated arenes. Subsequently, Culkin and Hartwig reported the reductive elimination of *para*-trifluoroethyltoluene from an aryl trifluoroethyl $Pd^{II}$ complex, thus demonstrating that the C(aryl)–$CH_2CF_3$ bond could be formed by reductive elimination.[419] The palladium-catalyzed cross-coupling of trifluoromethyliodomethane with aryl and alkenyl boronic acids and esters (Scheme 96)[420] or alkenyl stannanes[324] affords trifluoroethylated arenes or alkenes. This cross-coupling method displays broad substrate scope and functional-group tolerance, and allows for the trifluoroethylation of *meta*-aminophenylboronic acid with no *N*-trifluoroethylated by-products. Moreover, the cross-coupling of boronic acids and esters with trifluoromethyliodomethane is complimentary to trifluoroethylations with aryl halides.



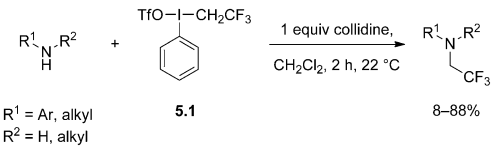

***Scheme 96.*** Pd-catalyzed trifluoroethylation of aryl boronic acids.

Trifluorodihaloethylzinc nucleophiles generated by the one-electron reduction of 1,1,1-trihalo-2,2,2-trifluoroethane reagents with zinc powder were used in aldehyde addition reactions.[421] Electrophilic trifluoroethylation can occur through radical pathways with alkenes[422] and alkynes[422b] by using halogenated trifluoroethane reagents and radical initiators such as copper salts[422a] or sodium dithionite (Scheme 97).[422b]

Nitrogenous nucleophiles such as aniline, amines (Scheme 98), imidazoles, and pyridines as well as phenols,




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

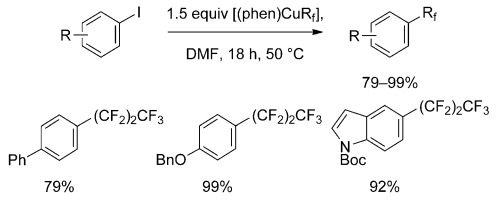



***Scheme 98.*** Trifluoroethylation of amines with an electrophilic trifluoroethylating hypervalent iodine reagent.

alcohols, carboxylic acids, and thiols can be trifluoroethylated using trifluoroethyliodonium salts,[423] which act as sources of electrophilic trifluoroethyl groups.[423b,c,424] Carbon-based nucleophiles afford trifluoroethylated products in 25–36 % yield, although the α-trifluoroethylation of silylenol ethers is possible in 49–92 % yield.[425] A broader range of non-aromatic N, O, and S nucleophiles than previously reported can react with reagent **5.1** by trifluoroethylation of the heteroatom.[424c]

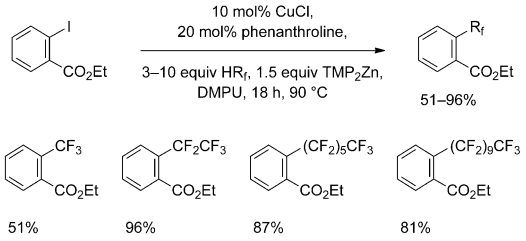
### 5.2. Perfluoroalkylation

Nucleophilic perfluoroalkyl copper reagents were first used to generate perfluoroalkyl arenes from aryl halides[417a] and perfluoroalkyl-substituted alkenes from alkenyl halides.[426] When ionic liquids were used as the solvent for the perfluoroalkylation of aryl halides, the reaction temperature could be lowered from 150 °C to 75 °C.[427] The perfluoroalkylation of alkenyl and aryl halides has been investigated with discrete phenanthroline-ligated perfluoroalkyl copper complexes by Hartwig and co-workers (Scheme 99),[366] and with palladium catalysts and zinc metal under ultrasonic irradiation by Kitazume and Ishikawa.[428] Chambers and co-workers used sodium perfluoroalkyl carboxylates[429] and




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

Daugulis and co-workers 1*H*-perfluoroalkanes[343] in lieu of perfluoroalkyl halides as the sources of perfluoroalkyl groups to accomplish the perfluoroalkylation. The method reported by Hartwig and co-workers affords electron-rich and electron-poor perfluoroalkyl arenes and heteroarenes in 88–99% yield at 50 °C, while the method developed by Daugulis and co-workers can afford perfluoroalkylated products from 1*H*-perfluoroalkanes ranging from trifluoromethane to 1*H*-perfluorodecane (Scheme 100).[343] Aryl boronic acids undergo

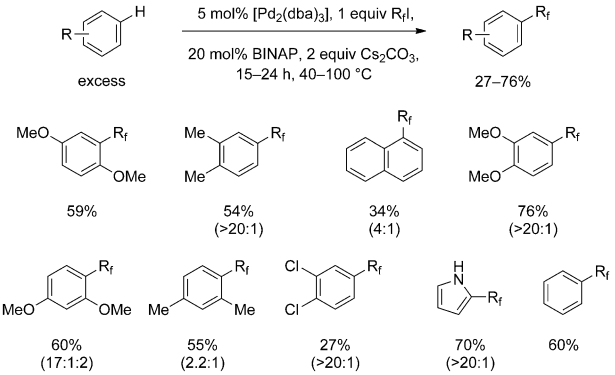



***Scheme 100.*** Cu-catalyzed perfluoroalkylation of aryl iodides. DMPU = 1,3-dimethyltetrahydropyrimidin-2(1H)-one.

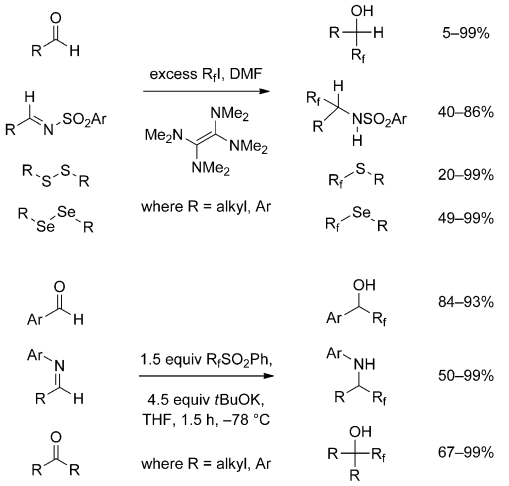
electrophilic perfluoroalkylation with perfluoroalkyl halide and copper under ambient atmosphere.[242] This room-temperature perfluoroalkylation method developed by Shen and co-workers yields perfluoroalkylated arenes in 29–65% yield.

A general strategy for the perfluoroalkylation of arenes has been reported by Hartwig and co-workers through a one-pot borylation/perfluoroalkylation sequence.[296b] Arenes can be perfluoroalkylated with a palladium–binap catalyst and perfluoroalkyl halide, as described by Sanford; solvent quantities of the arene are needed (Scheme 101).[430]

Radical addition of haloperfluoroalkylsulfonyl halides to alkenes can be accomplished with benzoyl peroxide[431] and ruthenium(II) catalysts.[432] Perfluoroalkyl transition metal complexes can react with alkynes,[433] dienes, and allylic halides,[434] as well as propargyl halides[435] to afford the corresponding perfluoroalkylated alkenes and allenes. Nucleophilic reagents, such as perfluoroalkyl lithium,[436] -magnesium bromide,[437] calcium,[438] tin,[439] trimethylsilane[440] and zinc (with a palladium or nickel catalyst),[434,441] were used prior to the development of the TDAE/perfluoroalkyl halide combination by Dolbier and co-workers, which is a straightforward and practical method for the perfluoroalkylation of aldehydes, ketones, imines, disulfides, and diselenides (Scheme 102),[442] and affords nonafluorobutylation products in 20–98% yield. Similarly, Prakash et al. reported the




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

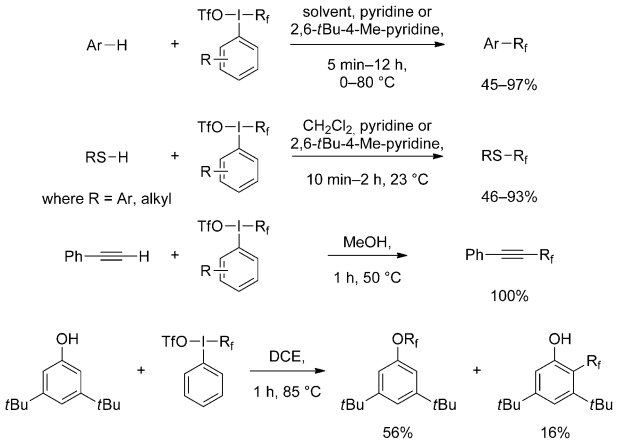



***Scheme 102.*** Two methods for the addition of perfluoroalkyl groups to carbonyl compounds and carbonyl derivatives.

alkoxide-induced release of perfluoroalkyl anions from pentafluoroethylphenylsulfone reagents which reacts with carbonyl compounds and imines in 50–99% yield (Scheme 102).[443]

Aryl perfluoroalkyliodonium chloride reagents were developed for the perfluoroalkylation of thio and seleno nucleophiles by Yagupolskii et al.[444] The chloride was subsequently exchanged for the less-coordinating triflate counterion, thereby resulting in the more electrophilic FITS (perfluoroalkylphenyliodonium trifluoromethanesulfonate) reagent for the perfluoroalkylation (Scheme 103) of carbanion nucleophiles,[445] arenes,[446] thiophenols and thiols at the sulfur atoms,[335] substituted phenols at the oxygen atoms,[447] alkynes,[448] and alkylenol ethers at the carbon atoms[449] as described by Umemoto et al. Additionally, alkenes can be perfluoroalkylated with the FITS reagent to afford perfluoroalkyl olefins.[450] The α-perfluoroalkylation of silylenol ethers with perfluoroalkyl halides can be initiated with the radical promoter triethylborane.[451] Another approach for the *O*- and *S*-perfluoroalkylation of phenolates and thiophenolates involves the use of tetrafluorodihaloethane and perfluorodihaloalkanes.[452] This process is proposed to occur by




***Scheme 103.*** Perfluoroalkylation of arenes, sulfides, terminal alkynes, and 3,5-di*tert*-butylphenol with electrophilic perfluoroalkyl hypervalent iodine reagents.

the in situ conversion of the perfluoroalkylating reagent to a perfluorinated alkene intermediate; this hypothesis is supported by separate reports of *O*-perfluoroalkylation of phenol with perfluoropropylene[453] and *N*-perfluoroalkylation with tetrafluoroethylene.[454]

In addition to perfluoroalkyl substituents, the pentafluorosulfanyl substituent has received increased attention recently. Pentafluorosulfanyl substituents are chemically inert, increase the lipophilicity, and could develop in to useful groups for pharmaceuticals and agrochemicals.[455] Simple pentafluorosulfanyl-substituted compounds are commercially available, but the difficulty of synthesis and the requirement for toxic reagents is currently a drawback for the development of new methods for the incorporation of the $SF_5$ group into more complex substrates.

## 6. Trifluoromethyl Ethers, Sulfides, and Amines

Trifluoromethoxylated and trifluoromethylthiolated molecules have been used as agrochemicals, pharmaceuticals, and electrooptical materials.[456] The increase in lipophilicity[457] resulting from incorporation of the trifluoromethoxy and trifluoromethylthiol groups 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,[2a] in contrast to a methoxy group, which normally rests in the plane of the arene, can be beneficial for obtaining additional binding affinity. Trifluoromethylamines have applications as fluorinating reagents;[458] these compounds are prone to fluoride ionization followed by hydrolysis of the resulting iminium or imine, which renders many trifluoromethylamines difficult to isolate and store.

The difficulty of trifluoromethylating heteroatoms is dependent on the nucleophilicity of the heteroatom; trifluoromethylation at the nitrogen and oxygen atoms is more difficult to accomplish than at a sulfur atom.[459] Consequently, the synthesis of trifluoromethyl ethers and amines has classically involved prefunctionalization at the oxygen or nitrogen atoms with carbonyl or thiocarbonyl functional groups followed by introduction of fluorine. Many approaches for the synthesis of trifluoromethyl ethers and amines have low functional group tolerance because of the use of hydrogen fluoride, Lewis acids, or thermally unstable, reactive trifluoromethylating reagents. Trifluoromethylsulfides 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 of cross-coupling methods for the synthesis of trifluoromethyl sulfides.

### 6.1. Preparation of Trifluoromethyl Ethers

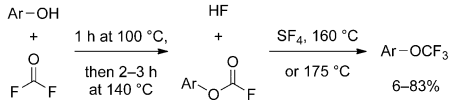
The formation of the O–$CF_3$ bond as well as the C–$OCF_3$ bond has been difficult to accomplish for two main reasons: the reactivity of the trifluoromethylating reagents with carbon sites of the oxygenated nucleophile leads to the formation of by-products and the thermal instability of many trifluoromethoxide salts. Many nucleophilic fluorodesulfurizations and fluorodeoxygenations of functionalized alcohols and phenols have been established for the synthesis of trifluoromethyl ethers, whereas fewer methods for the formation of O–$CF_3$ and C–$OCF_3$ bonds have been successfully accomplished. The synthesis of aryl trifluoromethyl ethers by the *O*-trifluoromethylation of phenols is currently of limited synthetic use as a result of carbon trifluoromethylation or the need for impractical reaction conditions with thermally unstable *O*-(trifluoromethyl)dibenzofuranium reagents. In contrast, the *O*-trifluoromethylation of primary and secondary alcohols with the thermally stable Togni reagent affords the desired trifluoromethyl ethers.[460]

#### 6.1.1. Preparation of Aryl Trifluoromethyl Ethers

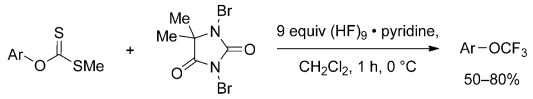
The nucleophilic fluorination of aryl trichloromethyl ethers,[461] aryl chlorothionoformates,[461b,462] phenyl fluoroformates,[463] and aryl xanthates[464] are the most frequently used methods for the synthesis of trifluoromethyoxyarenes. A general, practical, functional group tolerant trifluoromethylation of phenols is not yet available. Aryl trichloromethyl ethers[461b,d] synthesized in situ[461e] or prior to the reaction by chlorination of the aryl methyl ether[461a,c,f] or aryl chlorothionoformates[461b,462] can be fluorinated nucleophilically with hydrogen fluoride,[461e,465] $SbF_5$,[461g] $SbF_3$ in the presence of $SbF_5$,[461a,b,466] or molybdenum hexafluoride.[462,467] Likewise, phenol fluoroformates can be treated with $SbF_3$ or $SF_4$/HF to afford trifluoromethoxyarenes (Scheme 104).[463] Aryl xanthates were used as substrates for fluorodesulfurization with HF/pyridine and dibrominated hydantoin (Scheme 105).[464a]

Umemoto et al. reported that phenol derivatives can undergo trifluoromethylation with *O*-(trifluoromethyl)dibenzofuranium reagents in the presence of alkyl amine bases to afford trifluoromethoxyarenes (Scheme 106).[459] The reagent

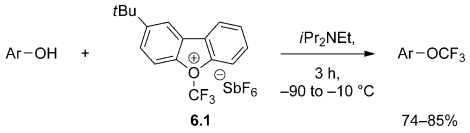
  




***Scheme 104.*** Synthesis of aryl trifluoromethyl ethers via fluoroformate intermediates.

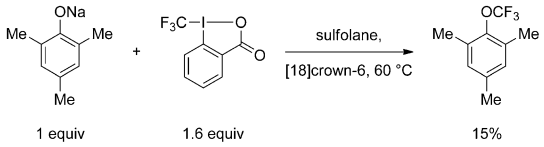



***Scheme 105.*** Synthesis of aryl trifluoromethyl ethers by fluorodesulfurization of aryl xanthates.



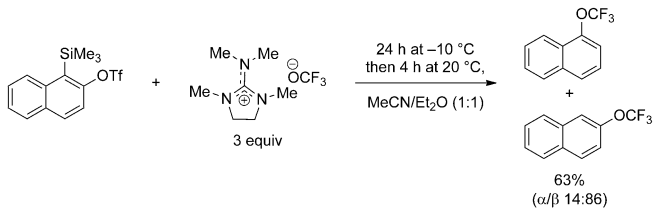

***Scheme 106.*** *O*-Trifluoromethylation of phenols to afford aryl trifluoromethyl ethers.

needs to be generated prior to use by photochemical decomposition of the trifluoromethyoxybiaryl diazonium salt at −100 to −90 °C to yield the active *O*-(trifluoromethyl)dibenzofuranium reagent **6.1**. The 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).[273b]




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

The use of the trifluoromethoxide anion to form the C(aryl)–O bond has not been as widely explored as other approaches. The $S_NAr$ reaction with trifluoromethoxide was attempted, but products from an $S_NAr$ reaction with fluoride are observed instead, likely because of degradation of the trifluoromethoxide into volatile carbonyl difluoride and fluoride.[468] Kolomeitsev et al. reported that formation of a C(phenyl)–$OCF_3$ and C(naphthyl)–$OCF_3$ bond occurred when the trifluoromethoxide anion was added to benzynes to afford aryl trifluoromethyl ethers (Scheme 108).[468] Aryl stannanes and aryl boronic acids can undergo silver-mediated cross-coupling with tris(dimethylamino)sulfonium trifluoromethoxide to afford functionalized aryl trifluoromethyl ethers (Scheme 109).[469] This method

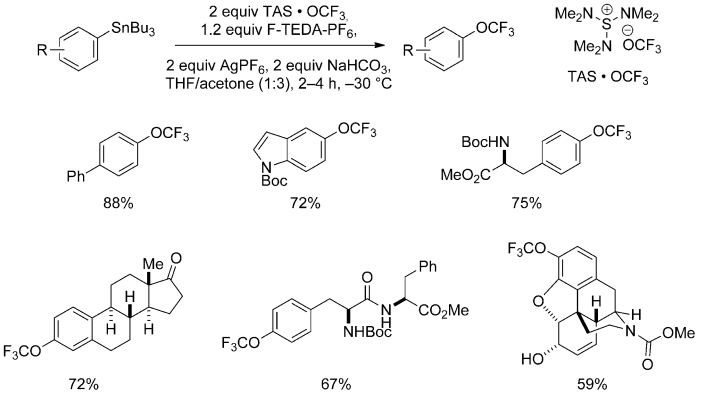



***Scheme 108.*** Addition of the trifluoromethoxide anion to *ortho*-trimethylsilylnaphthyl triflate via an aryne intermediate.

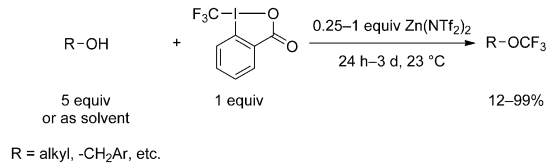
affords the cross-coupling products of functionalized aryl stannanes and boronic esters with trifluoromethoxide; heteroaryl nucleophiles and nucleophilic amines cannot currently be used in this reaction. More recently, oxygen-bound trifluoromethoxide copper and gold complexes have been prepared and characterized in efforts to provide a better understanding of the transition-metal interactions with the trifluoromethoxide anion.[470] Preliminary efforts toward the direct C–H functionalization of arenes with trifluoromethylhypofluorite has been reported to give mixtures consisting mainly of fluorinated arenes in addition to trifluoromethoxylated arenes.[471]

### 6.1.2. *Preparation of Alkyl Trifluoromethyl Ethers*

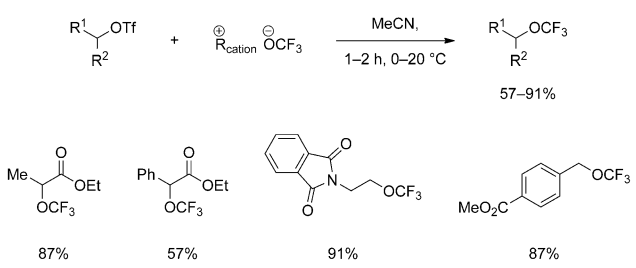
Alkyl trifluoromethyl ethers can be synthesized by the trifluoromethylation of alcohols or the displacement of a leaving group on alkyl electrophiles by the trifluoromethoxide anion. Primary and secondary alcohols can be trifluoromethylated with the Togni reagent in the presence of Zn-$(NTf_2)_2$ (Scheme 110).[460a] The soluble zinc catalyst with nonnucleophilic triflimide anions is proposed by Togni and coworkers 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[460b] and reacts with sulfonic acids to afford *O*-trifluoromethylated sulfonic acids.[340] 2-Phenylethanol, *n*-decanol, and (2-naphthyl)methanol were reported by Umemoto et al. to react with *O*-(trifluoromethyl)dibenzofuranium reagents (shown in Scheme 106 with phenols) to afford the




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




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

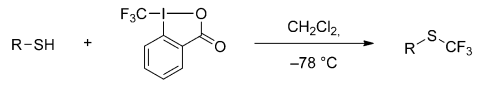



***Scheme 111.*** Synthesis of trifluoromethyl ethers by displacement of alkyl triflates with trifluoromethoxide salts.

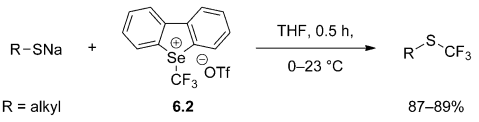
corresponding alkyl trifluoromethyl ethers.[459] Analogous to the fluorination of aryl xanthates,[464a] alkyl xanthates were treated with $BrF_3$ to afford alkyl trifluoromethyl ethers,[464b] while alkyl triflates were substituted with the trifluoromethoxide anion (Scheme 111).[468]

### 6.2. Preparation of Trifluoromethyl Sulfides

The 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)[273a] and *S*-hydrogen phosphorothiolates[472] by using Togni reagent II was reported by Togni and co-workers, and later applied to the trifluoromethylation of cysteine residues in peptide substrates.[473] *Se*-(trifluoromethyl)dibenzoselenophenium reagent **6.2** can likewise afford *S*-trifluoromethylated thiols, as demonstrated by Umemoto and Ishihara (Scheme 113).[271b]

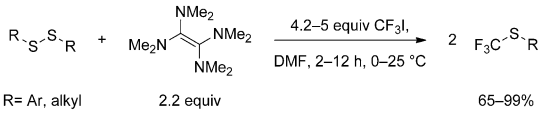



***Scheme 112.*** *S*-Trifluoromethylation of thiols with Togni reagent II.



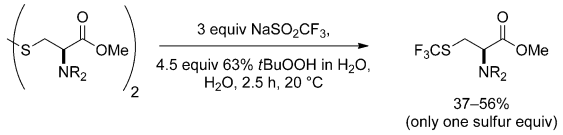

***Scheme 113.*** *S*-Trifluoromethylation of sodium thiolates with *S*-(trifluoromethyl)dibenzoselenophenium triflate.

Trifluoromethylsulfides can be synthesized by photolysis of aryl and alkyl trifluoromethylthiosulfonates[474] to promote desulfonylation and radical recombination or trifluoromethylation of disulfides[475] with $TMSCF_3$, as reported by Langlois and co-workers. Similarly, disulfides can be trifluoromethylated with a mixture of TDAE and iodotrifluoromethane (Scheme 114).[476] The $CF_3I$/TDAE method developed by

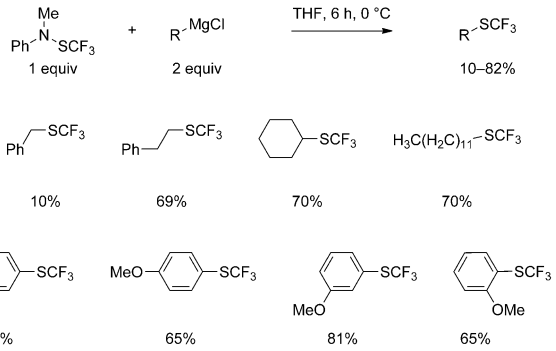



***Scheme 114.*** *S*-Trifluoromethylation of disulfides.

Dolbier and co-workers 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).[477] Trifluoromethanesulfanamide reagents have also been used as the electrophilic source of "$SCF_3$" groups with aryl and alkyl Grignard nucleophiles for the synthesis of trifluoromethyl sulfides (Scheme 116).[478]



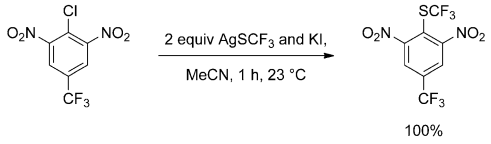

***Scheme 115.*** *S*-Trifluoromethylation of cysteine derivatives.



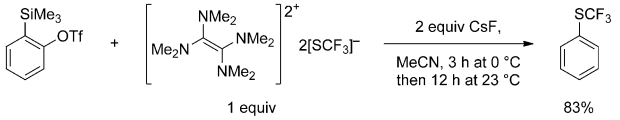

***Scheme 116.*** Grignard reaction with a trifluoromethanesulfanamide reagent to afford trifluoromethylsulfides.

The displacement of chloride through $S_NAr$ reactions of electron-poor chloroarenes with silver trifluoromethylthiolate is limited in substrate scope but affords the desired aryl trifluoromethylsulfide (Scheme 117).[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 phenyltrifluoromethyl sulfide (Scheme 118).[468] Although both approaches give rise to trifluoromethyl sulfides in high yield, the reported methods



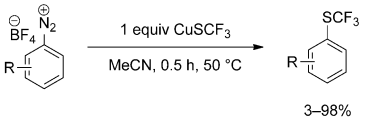

***Scheme 117.*** Nucleophilic aromatic substitution with silver trifluoromethylthiolate.



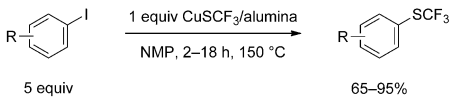

***Scheme 118.*** Addition of the trifluoromethylthiolate anion to *ortho*-trimethylsilylphenyl triflate via an aryne intermediate.

are biased toward electron-poor arenes or unfunctionalized *ortho*-trimethylsilylaryl triflates.

Aryl trifluoromethyl sulfides have been synthesized from aryl diazonium salts (Scheme 119)[480] and electron-poor aryl iodides (Scheme 120)[481] by Clark and co-workers by reaction



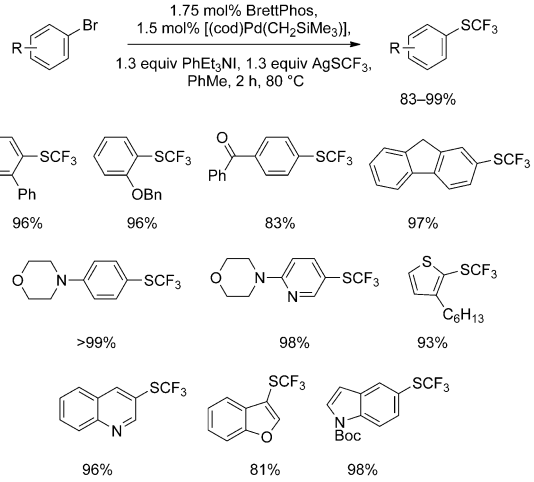

***Scheme 119.*** Synthesis of aryl trifluoromethyl thioethers from aryl diazonium salts and copper trifluoromethylthiolate.



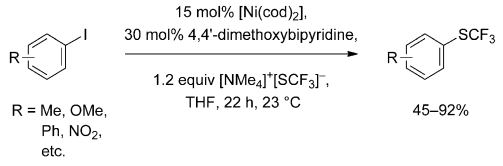

***Scheme 120.*** Synthesis of aryl trifluoromethyl thioethers from aryl iodides and copper trifluoromethylthiolate.

with pregenerated copper trifluoromethylthiolate. Chen and Duan have reported the in situ generation of copper trifluoromethylthiolate at 100 °C from copper, sulfur ($S_8$), and fluorosulfonyldifluoroester for the trifluoromethylthiolation of aryl iodides.[482]

Palladium-catalyzed synthesis of aryl trifluoromethyl thioethers was developed by Buchwald and co-workers by using a silver trifluoromethylthiolate nucleophile and aryl bromide electrophiles for the synthesis of a variety of aromatic and heteroaromatic trifluorothiolates (Scheme 121).[483] A combination of a nickel catalyst with tetramethylammonium trifluoromethylthiolate was described by the Vicic research group to convert aryl iodides into aryl trifluoromethylsulfides (Scheme 122).[484] This method was later extended to boronic acid substrates by using a copper catalyst.[485] While the 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




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




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

palladium-catalyzed reaction developed by the Buchwald research group. Qing and co-workers established the cross-coupling of aryl boronic acids with sulfur ($S_8$) in the presence of $TMSCF_3$ and two equivalents of silver carbonate catalyzed by copper(I) salts 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] An amide-directed C–H functionalization of arenes with trifluorosulfenyl groups was recently accomplished by Daugulis and co-workers through copper catalysis with trifluoromethyl disulfide (Scheme 123).[488]

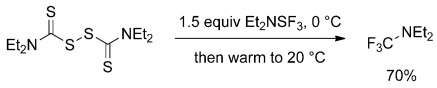

***Scheme 123.*** Cu-catalyzed *N*-directed C–H functionalization of arenes with trifluoromethylsulfenyl groups.

### *6.3. Preparation of Trifluoromethylamines*

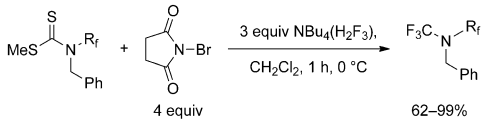
Primary and secondary alkyl trifluoromethyl amines have been difficult to synthesize due to their facile decomposition, mostly by elimination of fluoride, while tertiary alkyl trifluoromethyl amines can be synthesized but are difficult

to isolate.[458] Nitrogenous nucleophiles with less nucleophilic lone pairs on the nitrogen atom such as anilines, pyridine, and azoles can be successfully trifluoromethylated and isolated.[459,489]

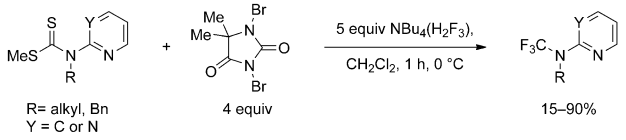
The main approaches for the synthesis of trifluoromethylamines involve nucleophilic fluorination of thiocarbonyl-functionalized amines and *N*-trifluoromethylation of amines. Amines are first derivatized to thiuramide sulfides (Scheme 124)[107c],[107c,490] *N*-alkyl dithiocarbamates (Scheme 125),[491] or formamides[458,492] 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 $SF_4$. This functionalization/fluorination reaction sequence was also reported with *N*-perfluoroalkyl dithiocarbamates[493] and *N*-heteroaryl dithiocarbamates (Scheme 126).[494]




***Scheme 124.*** Fluorodesulfurization of thiuramide sulfides.

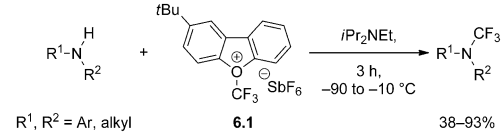



***Scheme 125.*** Fluorodesulfurization of dithiocarbamates.

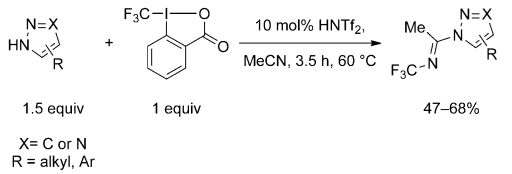



***Scheme 126.*** Fluorodesulfurization of *N*-heteroaryl dithiocarbamates.

Although *S*-(trifluoromethyl)dibenzothiophenium salts react with nitrogenous nucleophiles to afford *C*-trifluoromethylated products,[271b] *O*-(trifluoromethyl)dibenzoxonium reagent **6.1** reacts with nitrogenous nucleophiles to afford *N*-trifluoromethylated anilines, primary, secondary, and tertiary alkyl amines, and nitrogenous heteroarenes (Scheme 127).[459] The *O*-(trifluoromethyl)dibenzofuranium reagent **6.1** applied by Umemoto et al. is the same, thermally unstable, reagent used for the *O*-trifluoromethylation of phenols. *N*-Trifluoromethylation of nitriles after a Ritter-type reaction with azoles has been reported by Togni and coworkers (Scheme 128).[495] Subsequently, the same research group reported the direct *N*-trifluoromethylation of azoles in 13–66% yield.[489] Additionally, primary phosphines can undergo *P*-trifluoromethylation with Togni reagent II.[496]




***Scheme 127.*** Electrophilic *N*-trifluoromethylation of amines.



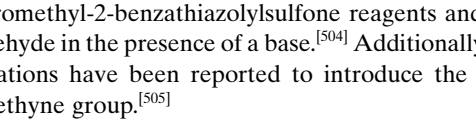

***Scheme 128.*** *N*-Trifluoromethylation of Ritter-type reaction products.

## 7. Fluorinated Alkenes

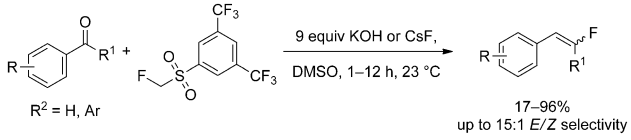
Fluoroalkenes find applications as peptide mimics[497] and as monomers in polymerization reactions, for example, for the synthesis of teflon.[498] As the fluoroalkene moiety has a size and dipole moment similar to an amide bond while being difficult to hydrolyze,[499] molecules containing the fluoroalkene motif have been used as inhibitors of peptidases.[500]

### 7.1. Preparation of Monofluoroalkenes

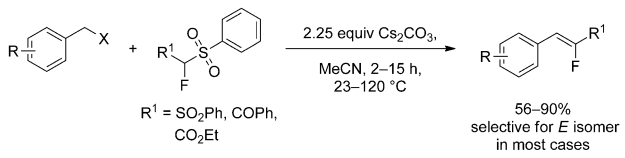
Monofluoroalkenes can be synthesized by Wittig olefination of carbonyl compounds with triphenylphosphonium monofluoromethylide (Scheme 129),[501] by Peterson-type olefination of aldehydes with α-fluoro-α-trialkylsilyl esters with 50:1 *Z*/*E* stereoselectivity,[502] and by modified Julia–Kocienski conditions for the fluoromethylenation of ketones[503] in up to 15:1 *E*/*Z* stereoselectivity (Scheme 130).[503a] α-Fluorostyrenes can be synthesized from α,α-arylfluoromethyl-2-benzathiazolylsulfone reagents and paraformaldehyde in the presence of a base.[504] Additionally, aldol condensations have been reported to introduce the monofluoromethyne group.[505]




***Scheme 129.*** Synthesis of monofluoroalkenes by Wittig olefination of carbonyl compounds.

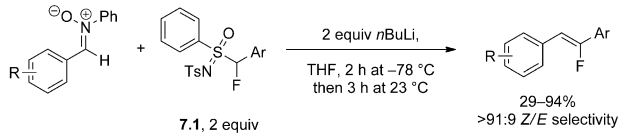



***Scheme 130.*** Synthesis of monofluoroalkenes by a Julia–Kocienski reaction with carbonyl compounds.




***Scheme 131.*** Synthesis of monofluoroalkenes by a Julia–Kocienski-type reaction with benzyl halides.

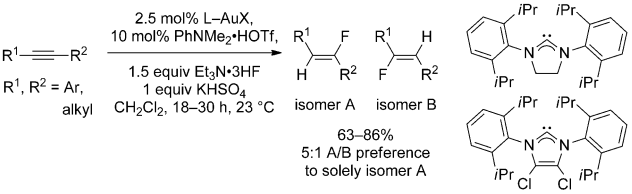
An addition/elimination sequence of fluorobis(phenylsulfonyl)methane with alkyl halides was used to afford monofluoroalkenes (Scheme 131).[194] The selectivity for the *E* isomer is proposed to arise from neighboring group participation by the aryl group during the elimination step. The stereoselective synthesis of (*Z*)-fluoroalkenes was achieved by addition of fluorosulfoximine **7.1** to nitrones followed by elimination of nitrosobenzene (Scheme 132).[506]




***Scheme 132.*** Synthesis of monofluoroalkenes by nitrone addition to a fluoromethyl pronucleophile.

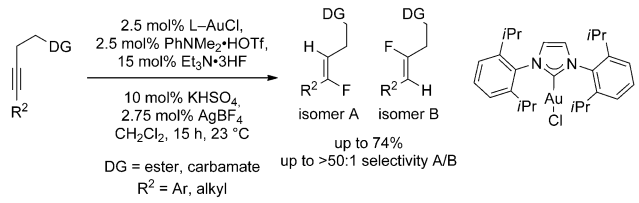
In the proposed transition state, the two aryl groups are positioned gauche for the formation of the disfavored *E* isomer; therefore, a preference for the *Z* isomers would be predicted.

Monofluoroalkene synthesis by alkyne hydrofluorination was first accomplished with polymer-supported dihydrogen trifluoride[507] and tetrabutylammonium dihydrogen trifluoride.[508] Transition-metal-mediated hydrofluorination was demonstrated by Sadighi and co-workers by a reversible gold-mediated hydrofluorination of substituted alkynes with triethylamine/hydrogen fluoride (Scheme 133).[509] Subsequently, a gold-catalyzed *N*-directed synthesis of fluoroalkenes from disubstituted alkynes and triethylamine/hydrogen fluoride was shown to yield > 50:1 regioselectivity by Miller and co-workers (Scheme 134).[510] The reaction can also be directed by the ester, but the regioselectivity is lower: 1:1.5 in favor of isomer B in some cases (see Scheme 134).

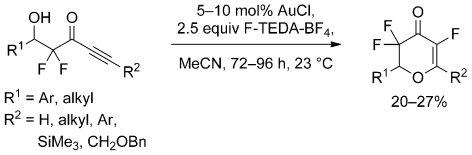



***Scheme 133.*** Au-catalyzed hydrofluorination of alkynes.

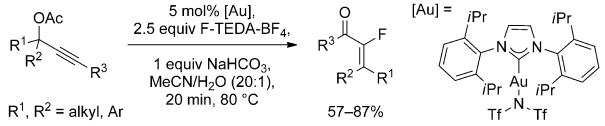
Silver-mediated electrophilic fluorodestannylation of alkenyl stannanes reported by Tius et al. demonstrated that the synthesis of fluoroalkenes could be accomplished by electrophilic fluorination.[34i,46] Gouverneur and co-workers reported the gold-catalyzed cyclization/fluorination of propargyl ketones with F-TEDA-$BF_4$ to afford cyclic α-fluoro vinylogous esters (Scheme 135)[511] with the protodeaurated product accounting for most of the by-product. Intermediates of the gold-carbene-catalyzed rearranged proparyl acetates can also be fluorinated electrophilically to afford α-fluoroenones, as describe by de Haro and Nevado (Scheme 136).[512] Only alkyl- or phenyl-functionalized propargyl acetates were reported to undergo this rearrangement.




***Scheme 134.*** Au-catalyzed ester-directed hydrofluorination of alkynes.

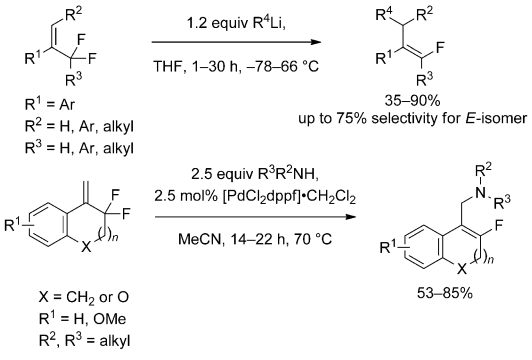



***Scheme 135.*** Au-catalyzed fluorocyclization of propargyl ketones.




***Scheme 136.*** Synthesis of α-fluoroenones by an Au-catalyzed 1,3-acyloxy rearrangement of propargyl acetates.

Nucleophilic $S_N2'$ additions of 3,3-difluoropropenes with cuprates,[513] organolithium reagents,[514] and amines[515] have been used by Paquin and co-workers to synthesize fluorinated allylic products with transposed double bonds (Scheme 137). In contrast to the nucleophilic organolithium compounds,




***Scheme 137.*** Addition of an alkyl lithium and Pd-catalyzed allylic alkylation of amines of 3,3-difluoropropenes.

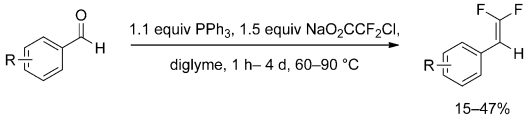
neutral amine nucleophiles required the use of palladium complexes to first activate 3,3-difluoropropenes as an allyl fragment. With organolithium reagents monoiodoalkenes are lithiated and fluorinated with *N*-fluoro-*N*-*tert*-butylphenylsulfonamide, thereby affording the same double-bond geometry;[516] trifluoromethyl tosylhydrazones, on the other hand, rearrange to monofluoroalkenes with an excess of alkyl lithium reagents.[517]

The palladium-catalyzed cross-coupling of terminal alkynes with iodofluoroalkenes affords fluorinated enyne products,[518] while fluorovinyl tosylate undergoes cross-coupling with boronic acids to yield terminal fluoroalkenes.[519] The copper-catalyzed reaction of Freon-113 (1,1,1-difluorochloro-2,2,2-dichlorofluoroethane) with aryl hydrazones produces fluorinated alkene derivatives with release of $N_2$.[520]

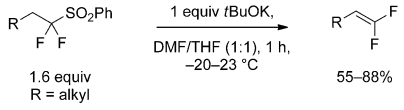
### 7.2. Preparation of α,α-Difluoroalkenes and 1,2-Difluoroalkenes

#### 7.2.1. Preparation of α,α-Difluoroalkenes

Approaches used to synthesize difluoroalkenes are similar to those of monofluoroalkenes, and include Wittig (Scheme 138)[501b,c,521] and Horner–Wadsworth–Emmons olefination[522] as well as difluoromethylenation with bis(trifluoromethyl) mercury,[523] copper and difluorodibromomethane,[524] and difluorophenylsulfenyltrimethylsilane.[525] In general, difluoromethylenation reactions of carbonyl compounds with difluoromethylenating reagents give rise to yields below 70%. The addition/elimination sequence used to synthesize monofluoroalkenes from alkyl halides and fluoromethyl phenyl sulfone[526] was adapted to the synthesis of difluoroalkenes through the use of difluoromethyl phenyl sulfone and alkyl halides (Scheme 139).[526b] Although the method by Prakash and co-workers shown in Scheme 139 makes use of a slight excess of starting material relative to base, it provides access to aliphatic and aryl difluoroolefins in a synthetically practical manner.

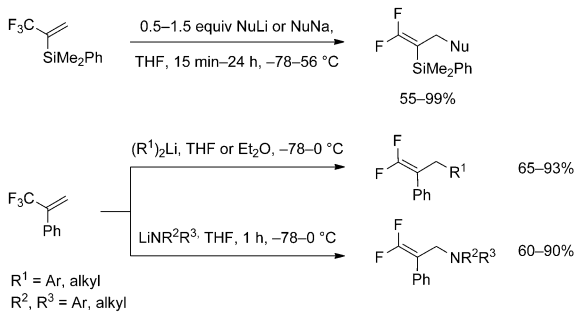



***Scheme 138.*** Synthesis of difluoroalkenes by a Wittig-type olefination of aldehydes.

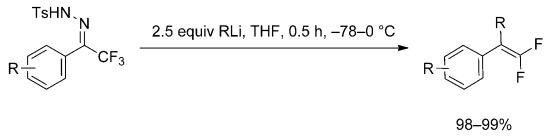



***Scheme 139.*** Elimination of fluoromethyl alkylated products to afford difluoroalkenes.

Geminally substituted trifluoromethyldimethylphenylsilyl alkenes can be transformed to the 1,1-difluoroalkenes by the $S_N2'$ addition of various nucleophiles. such as LAH, organolithium reagents, and lithium enolates (Scheme 140).[527] Similarly, trifluoromethylstyrene derivatives can rearrange to geminal difluoroalkenyl amines[528] after the addition of lithium amide or allylic alkyl difluoroalkenes[529] or organolithium reagents (Scheme 140). More recently, the addition of substituted hydrazine nucleophiles to trifluoromethylstyrene followed by intramolecular cyclization was shown to yield various 3-fluoropyrazole products.[530] Trifluoromethyl tosylhydrazones rearrange to difluoroalkenes with 2.5 equivalents of *n*BuLi or methyllithium through extrusion of $N_2$ gas and tolylsulfinate (Scheme 141).[517] Similarly, *n*BuLi induces the opening of chlorodifluoromethyl epoxides to afford 1,1-difluoroallylic alcohols.[531]

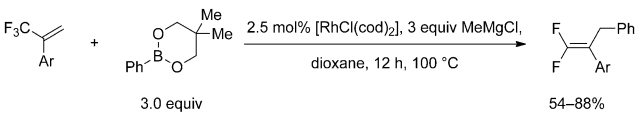



***Scheme 140.*** $S_N2'$ addition of various nucleophiles to 3,3,3-trifluoropropene.




***Scheme 141.*** Alkyl lithium induced rearrangement of aryl trifluoromethyl tosylhydrazones to terminal 1,1-difluorostyrenes.

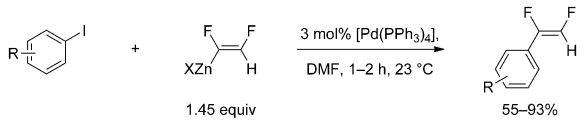
Cross-coupling methods provide an expedient route for the installation of difluoroalkenyl groups from commercially available arene precursors. Trifluoromethyl groups of α-trifluoromethylstyrenes undergo β-fluoride elimination in the presence of rhodium catalysts and then participate in a cross-coupling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



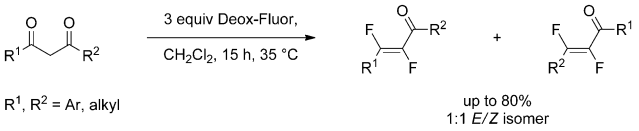

***Scheme 142.*** Rh-catalyzed coupling of 3,3,3-trifluoropropene and aryl boronic ester with β-fluoride elimination.

#### 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,[535] as well as by protodesilyation of 1,2-difluoro-1-silylalkene.[536] 1,2-Difluoroolefins can additionally be synthesized by cross-coupling of the fluorinated alkenylzinc reagent with aryl iodides (Scheme 143),[537] thereby allowing for the late-stage introduction of vicinal difluoroalkenyl groups into arenes. Treatment of α-keto carbonyl compounds with Deoxo-Fluor yields α,β-difluoroenone (Scheme 144).[538]




***Scheme 143.*** Pd-catalyzed cross-coupling of aryl iodides with a 1,2-difluoroalkenylzinc reagent.




***Scheme 144.*** Synthesis of α,β-difluoroenones by nucleophilic fluorination with Deoxo-Fluor.

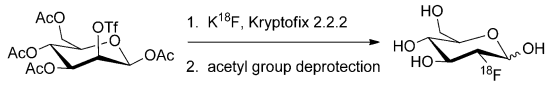
## 8. Fluorination with $^{18}$F for Positron Emission Tomography (PET)

Positron emission tomography (PET) is widely recognized as a clinical tool for cancer diagnosis, with other applications emerging in medical research and patient care.[5c,d] PET relies on the use of radiotracers that bear a radionuclide which decays by positron emission, such as $^{18}$F. Simple radiotracers containing $^{18}$F can be synthesized by conventional fluorination methods. However, these methods typically have low functional group tolerance and cannot afford complex, biomedically relevant molecules as PET tracers. Seeing as $^{18}$F has a half-life of only 110 min, the synthesis of radiotracers requires that the introduction of $^{18}$F occurs 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 the introduction of $^{18}$F 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–$^{18}$F bond formation; comprehensive reviews are available.[5a–e,552]

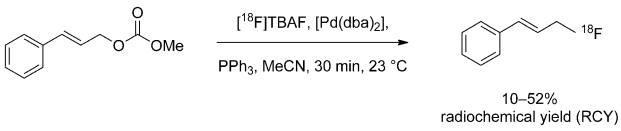
### 8.1. Nucleophilic Methods for the Incorporation of $^{18}$F

$^{18}$F is synthesized by bombardment of $^{18}$O-enriched water with protons to afford aqueous [$^{18}$F]fluoride with 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.[6] $^{18}$F-enriched fluorine gas is generally of lower specific activity than the [$^{18}$F]fluoride, but recent advances have increased the specific activity that can be obtained for [$^{18}$F]$F_2$.[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 of substitution reactions of alkyl or aryl electrophiles functionalized with appropriate leaving groups. Alkali salts are typically used along with cryptands to increase the fluoride nucleophilicity.[5d] Reaction solvents are chosen such that $S_N$2-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. *Tert*-butanol may be used to temper the basicity of the [$^{18}$F]fluoride for aliphatic substitution reactions.[105] The most commonly used radiotracer for imaging, 2-deoxy-2-[$^{18}$F]fluoro-D-glucose ([$^{18}$F]FDG), is made by nucleophilic substitution of a triflate leaving group on a mannose triflate derivative with [$^{18}$F]fluoride (Scheme 145).[540] Gouverneur and co-workers reported the first palladium-catalyzed fluorination reaction with [$^{18}$F]fluoride during the synthesis of $^{18}$F-functionalized allylic fluorides (Scheme 146).[167]



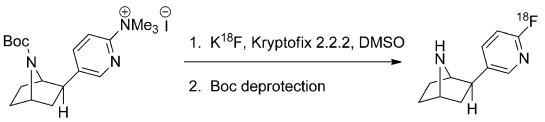

***Scheme 145.*** Nucleophilic radiochemical fluorination with [$^{18}$F]fluoride to afford [$^{18}$F]FDG.



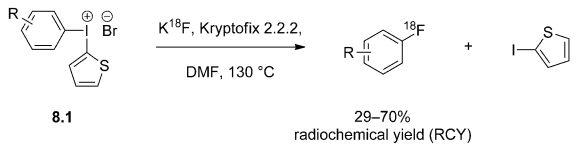

***Scheme 146.*** Pd-catalyzed allylic fluorination with [$^{18}$F]fluoride.

Nucleophilic aromatic substitution with [$^{18}$F]fluoride can be used to synthesize $^{18}$F-labeled arenes.[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, trialkylammonium, halide, or sulfonate group. Nicotinic acetylcholine receptor radioligands have been synthesized by nucleophilic aromatic substitution (Scheme 147).[542]

Diaryliodonium salts **8.1** can be fluorinated with [$^{18}$F]fluoride to yield radiolabeled aryl fluorides.[543] The selectivity for fluorination between the two arenes attached




***Scheme 147.*** Nucleophilic aromatic substition with [$^{18}$F]fluoride.




***Scheme 148.*** Nucleophilic radiochemical fluorination of aryl(2-thienyl)-iodonium bromides.

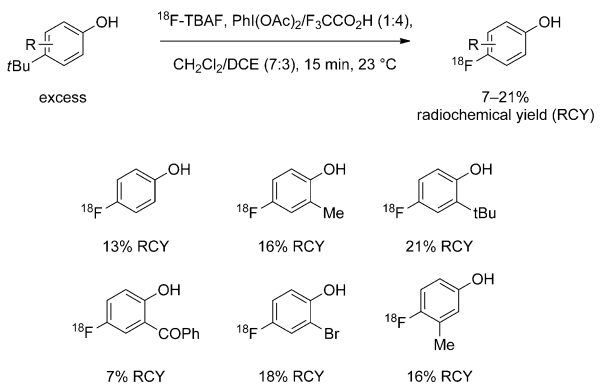
to iodine is based on the electronic structure of the arenes (the more-electron-poor arene is fluorinated) and the steric bulk near the iodine atom (*ortho*-substituted arenes are more susceptible to fluorination because of the *ortho* effect[544]; Scheme 148). Electron-rich 2-thiophene can be used to advantage as a dummy ligand on the iodine atom.[543b] The counterion of the iodonium salts also has a large effect on the yield of fluorination, with the more dissociative and non-nucleophilic counteranions 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 diaryl iodonium salts would increase the utility of the method and its use for the synthesis of PET tracers. Current syntheses of aryl iodonium salts often employ strong Lewis or Brønsted acids.[545]

### 8.2. Electrophilic Methods for the Incorporation of $^{18}F$

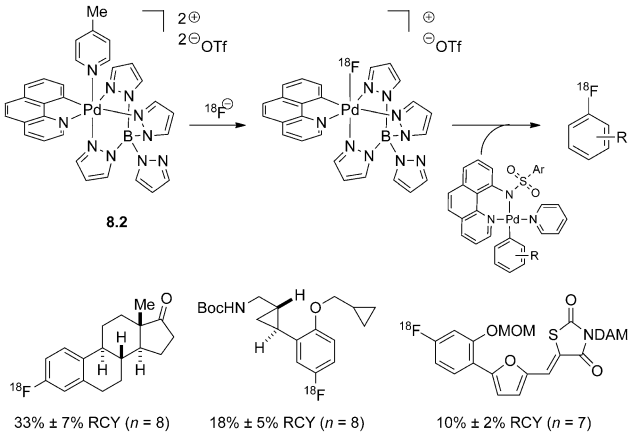
Several $^{18}F$-labeled electrophilic fluorinating reagents have been synthesized from [$^{18}F$]fluorine gas such as [$^{18}F$]acetyl hypofluorite,[546] [$^{18}F$]xenon difluoride,[546a,547] $^{18}F$-labeled *N*-fluorosulfonamide or imide reagents,[548] [$^{18}F$]*N*-fluoropyridinium salts,[549] and [$^{18}F$]TEDA salts.[539b] Electrophilic radiofluorination by direct fluorination of substrates such as alkenes[550] for the synthesis of [$^{18}F$]FDG and related sugars, as well as arenes[551] for the synthesis of [$^{18}F$]fluoro-3,4-dihydroxyphenylalanine ([$^{18}F$]F-DOPA) can lead to multiple fluorinated products and typically are not functional-group tolerant. Radiochemical fluorodemetalation has been used for aryl organometallic reagents,[548a] aryl silanes,[37c,d] and aryl stannanes,[34a,c,546b] and can afford selective fluorination.

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

An electrophilic radiofluorination for the synthesis of aryl fluorides with high specific activity makes use of $Pd^{IV}$ complex **8.2** to incorporate [$^{18}F$]fluoride into complex arenes (Scheme 150).[553] The $Pd^{IV}$ complex captures fluoride and then functions as an electrophilic $^{18}F$-fluorination reagent. Direct $S_N2$ transfer and an electron-coupled fluoride transfer have both been proposed as possible reaction pathways. An




***Scheme 149.*** Oxidative radiochemical fluorination of *para-tert*-butylphenols with [$^{18}F$]fluoride and iodobenzene diacetate.




***Scheme 150.*** Synthesis of an electrophilic [$^{18}F$]-$Pd^{IV}$ fluorinating reagent from [$^{18}F$]fluoride for the synthesis of $^{18}F$-labeled aryl fluorides.

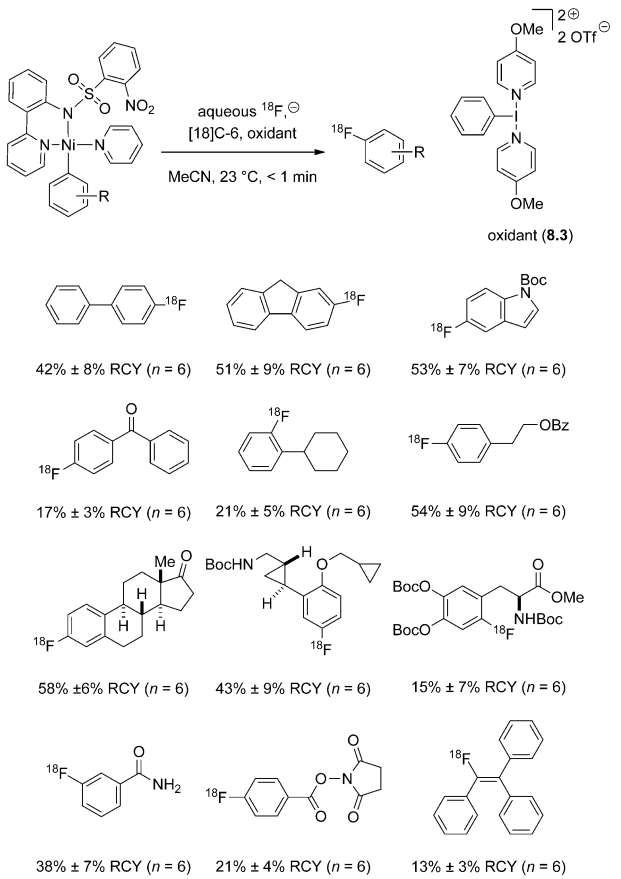
advantage of using this method is that [$^{18}F$]fluoride can be incorporated into functionalized arenes at a late stage. Additionally, the $Pd^{IV}$-[$^{18}F$] complex is thermally stable and insensitive to water.

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

## 9. Outlook

The most significant, conceptual advances over the past decade in the area of fluorination, broadly defined, were made in the reactions that led to the formation of C–F and C–$CF_3$ bonds, most prominently by organo- and transition-metal catalysis. The most challenging transformation remains the formation of the parent C–F bond, primarily due to the high hydration energy of fluoride, strong metal–fluorine bonds, and the highly polarized nature of bonds to fluorine.




***Scheme 151.*** Synthesis of $^{18}$F-labeled aryl fluorides from $Ni^{II}$ complexes, oxidant, and aqueous [$^{18}$F]fluoride.

Fluorination reactions still lack general predictability and practicality. For example, commonly employed electrophilic fluorinating and trifluoromethylating reagents are often not cost efficient on a 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 fluorination methods have made fluorinated molecules more readily available than ever before. In particular, the modern methods have started to have an impact on 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, and use fluoride and a readily available, inexpensive catalyst.

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