

Transition-Metal-Catalyzed Difluoromethylation, Difluoromethylenation, and Polydifluoromethylenation Reactions

Bo Chen and David A. Vivic

Abstract One way to introduce fluorine into a molecule is through fluoroalkylation reactions. Transition-metal catalysts play an increasing role in selectively incorporating fluoroalkyl groups into organic molecules, especially during the late stages of a synthesis. In this review, we highlight the development of methodologies to incorporate the $[\text{CF}_2\text{H}]$, $[\text{CF}_2\text{R}]$, and $[(\text{CF}_2)_n]$ functionalities into organic substrates by transition-metal complexes. Also discussed are the structural changes that can arise when repeating arrays of $[\text{CF}_2]$ or $[\text{CH}_2\text{CF}_2]$ units are introduced into a single molecule through polydifluoromethylenation reactions.

Keywords Copper • Difluoromethylation • Difluoromethylenation
• Fluoroalkylation • Polydifluoromethylenation

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Abbreviations

bpy	2,2'-Bipyridyl
Bu	Butyl
cat	Catalyst
d	Day(s)
DBU	1,8-Diazabicyclo [5.4.0]undec-7-ene
DCE	1,2-Dichloroethane
DME	1,2-Dimethoxyethane
DMF	Dimethylformamide
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
DMSO	Dimethyl sulfoxide
equiv.	Equivalent(s)
Et	Ethyl
h	Hour(s)
i-Pr	Isopropyl
M	Metal
Me	Methyl
MeCN	Acetonitrile
min	Minute(s)
mol	Mole(s)
NMP	<i>N</i> -Methyl-2-pyrrolidone
Ph	Phenyl
rt	Room temperature
tbpy	4,4'-Di- <i>tert</i> -butyl-2,2'-dipyridyl
<i>t</i> -Bu	<i>tert</i> -butyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TMEDA	<i>N,N,N',N'</i> -Tetramethylethylenediamine
TMS	Trimethylsilyl
Xantphos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene

1 Introduction

Until World War II, there was no commercial production of elemental fluorine, and thus studies on fluorinated molecules and materials were limited. Once it was discovered that UF₆ exhibits a high vapor pressure and could be used to purify isotopically enriched uranium, production of, followed by reserves of, fluorine grew [1]. Scientists were able to tap into these reserves and develop the field of organofluorine chemistry. Organofluorine chemists have been able to parse out the properties and reactivities of various fluorine-containing functional groups, and the development of new methods to incorporate such groups into organic substrates has received considerable attention. The fluoroalkyl family represents one class of

fluorinated functional groups that has grown in significance in recent years. Metal-catalyzed methods to incorporate fluoroalkyl groups into organic substrates can represent an atom economical synthetic approach, but the stabilizing properties of fluoroalkyl groups makes fluoroalkylations difficult because fluoroalkyl ligands can also render a metal catalyst more stable and less reactive [2]. The growth in attention devoted to developing new fluoroalkylation methods can be reflected by the large number of reviews regarding advances in metal-catalyzed trifluoromethylation reactions that have recently appeared in the literature [3–23]. Far fewer accounts describing the roles that transition metals play in the development of difluoromethylation [5, 8, 13, 24–30], difluoromethylenation, and especially polydifluoromethylenation reactions have appeared, so this document attempts to serve as a review of the state of the art in those fields.

Many features contribute to the value of the fluoroalkyl-containing functional group. Ligands [31–33] and counterions [34] that allow metals to operate under oxidative conditions often feature fluoroalkyl substituents due to the chemical inertness of the $[\text{CF}_3]$ and $[\text{CF}_2]$ functional groups. Fluoroalkyl moieties can also serve as isosteres of important organic functional groups. The difluoromethyl group has been described as a lipophilic isostere of the carbinol, thiol, hydroxamic acid, and amide groups that is capable of hydrogen bonding [35, 36] while the difluoromethylene group has been described as an isostere of an oxygen atom functionality [37]. Under such a model, a *gem*-difluorovinyl moiety was reported to act as an isostere for aldehydes and ketones [37]. Such features, together with the fact that the strength of the carbon-fluorine bonds can moderate the metabolism of fluorinated compounds, make the $[\text{CF}_2]$ and $[\text{CF}_2\text{H}]$ important functional groups for drug design and agricultural applications. Indeed, the breadth of applications of these functional groups in the medicinal chemistry field is highlighted by some select drugs shown in Fig. 1.

2 Syntheses of Transition-Metal-Difluoromethyl Complexes

The first reports of a transition-metal-difluoromethyl complex were provided by Calderazzo and co-workers in 1967, who prepared $[(\text{CO})_4\text{Mn}(\text{CF}_2\text{H})]$ through the thermal decarbonylation of $[(\text{CO})_4\text{Mn}(\text{COCF}_2\text{H})]$ [39, 40]. ^{55}Mn NMR data from their group (Table 1) revealed a direct correlation between the degree of fluorination of the Mn-bound methyl ligand with the ^{55}Mn chemical shift from a reference sample. Since Calderazzo and co-workers' initial synthesis of a metal-difluoromethyl complex, the difluoromethyl ligand has exhibited rich coordination chemistry with transition metals, and select examples of well-defined complexes are shown in Fig. 2. Eisenberg and co-workers were the first to publish structurally characterized transition-metal-difluoromethyl complexes in 1973, namely, $[(\text{IrCl}(\text{OCOCF}_2\text{Cl})\text{CF}_2\text{H})(\text{CO})(\text{PPh}_3)_2]$ and $[\text{IrCl}_2(\text{CF}_2\text{H})(\text{CO})(\text{PPh}_3)_2]$ [41].

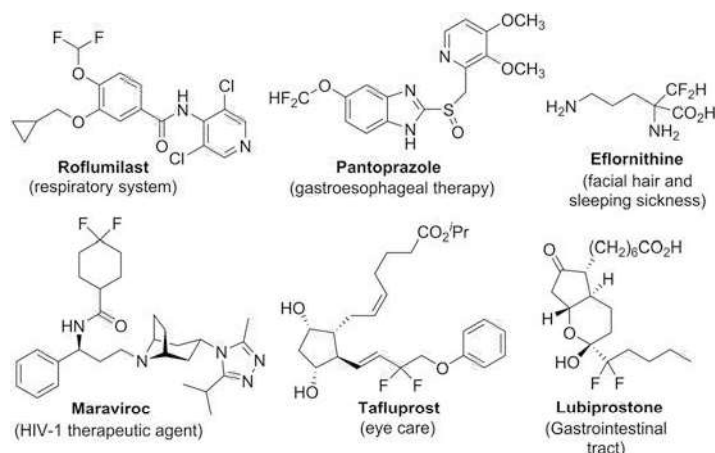


Fig. 1 Select drugs containing the difluoromethyl and difluoromethylene group [28, 38]

Table 1 ^{55}Mn NMR chemical shifts of $[\text{XMn}(\text{CO})_5]$ derivatives (ppm from aqueous $[\text{KMnO}_4]$) [39]

Compound	δ
$\text{H}_3\text{C-Mn}(\text{CO})_5$	2,265
$\text{H}_2\text{FC-Mn}(\text{CO})_5$	2,130
$\text{HF}_2\text{C-Mn}(\text{CO})_5$	1,970
$\text{F}_3\text{C-Mn}(\text{CO})_5$	1,850

The difluoromethyl groups in Eisenberg's iridium complexes were generated by a metal promoted decomposition of the $[\text{CF}_2\text{ClCO}_2]$ anion.

The ability of transition metals to coordinate difluoromethyl groups has sparked substantial interest in learning how to involve such $[\text{M-CF}_2\text{H}]$ species in catalytic cycles affording net transfer of $[\text{CF}_2\text{H}]$ to organic substrates. Historically, structurally simple difluoromethylated organic species can be prepared without the use of transition metals. Reagents such as $\text{FSO}_2\text{CF}_2\text{CO}_2\text{TMS}$, CF_2N_2 , and $\text{HCF}_2\text{SO}_2\text{R}$ are known to generate difluorocarbene in neutral or basic conditions for insertion into O–H, N–H, C=C, C=O, and C≡C bonds, forming difluoromethylated ethers, amines, cyclopropanes, alkenes, and cyclopropenes [42]. These and other reagents for classical organic transformations [13, 27, 28, 35, 43, 44] toward the difluoromethyl and *gem*-difluoromethylene functional groups will not be reviewed here. Rather, our attention will be placed solely on more sophisticated *metal-mediated* transformations involving the $[\text{CF}_2\text{H}]$ or $[\text{CF}_2\text{R}]$ functional groups. Such attention requires first a basic understanding of how to form a $[\text{metal-CF}_2\text{H}]$ complex. Typical synthetic routes to the metal-difluoromethyl functional group are outlined in Scheme 1. Transition metals are known to activate the C–H bond in difluoromethane (Scheme 1, Eq. a) [45] or the C–X bond in a species like difluoriodomethane (Scheme 1, Eq. b) [46] to produce metal-difluoromethyl complexes. As mentioned above, decarbonylation of a $[\text{M-CO-CF}_2\text{H}]$ complex may also lead to well-defined $[\text{M-CF}_2\text{H}]$ species (Scheme 1, Eq. c) [41]. Transition-metal carbenes may also be used as $[\text{M-CF}_2\text{H}]$ precursors, and the $[\text{M}=\text{CF}_2]$

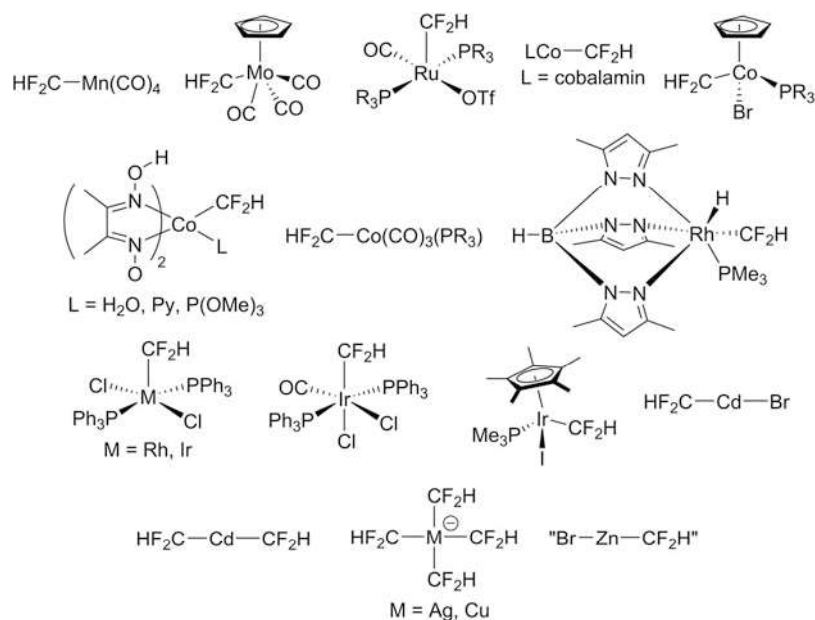


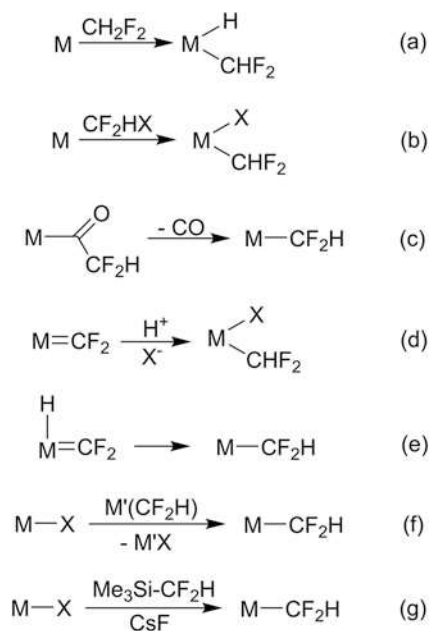
Fig. 2 Selected known transition-metal-difluoromethyl complexes

functionality may react as a formal electrophile (Scheme 1, Eq. e) [47] or as a formal nucleophile (Scheme 1, Eq. f) [48]. Finally, transition metals may react with transmetalating reagents such as $[\text{Cd}(\text{CF}_2\text{H})_2]$ [49], $[\text{Bu}_3\text{Sn}(\text{CF}_2\text{H})]$ [50] (Scheme 1, Eq. f), or the combination of $[\text{Me}_3\text{Si}-\text{CF}_2\text{H}]$ plus an initiator (Scheme 1, Eq. g) [51].

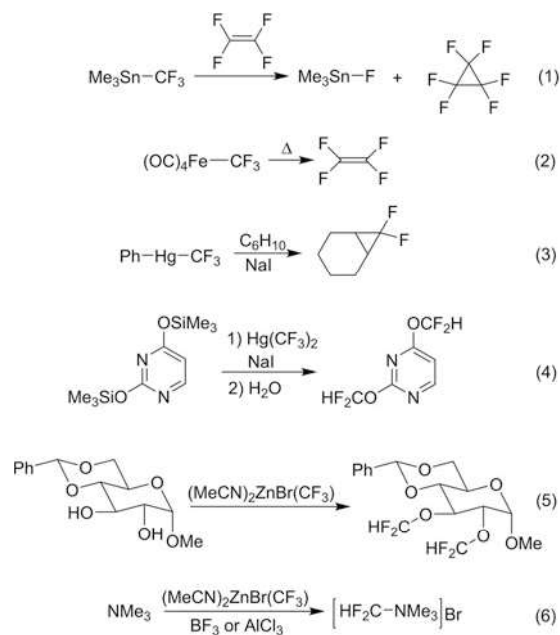
2.1 Metal-Catalyzed Methods for Difluoromethylation and Difluoromethylenation

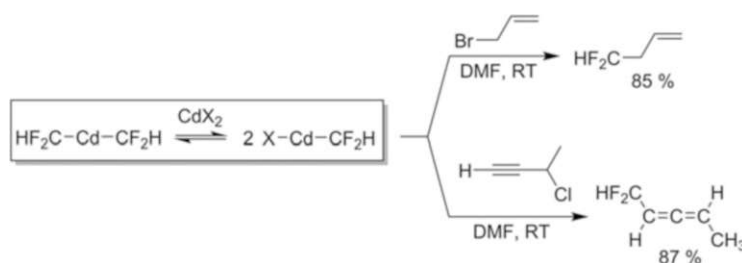
By the 1960s, it was well established that trifluoromethyl-substituted main group metals such as tin could be used as a difluorocarbene source for additions to olefins (Eq. 1) [52]. In 1961 Stone and co-workers provided evidence that similar decomposition reactions could occur for transition metals. They noted that the thermal decomposition of $[(\text{CO})_4\text{Fe}(\text{CF}_3)]$ led to the production of tetrafluoroethylene, presumably by way of difluorocarbene generation (Eq. 2). Seyferth and co-workers in 1969 were the first to show that mercury trifluoromethyl complexes could be used to generate difluorocarbene under mild conditions in the presence of sodium iodide and could subsequently trap the difluorocarbene with acceptor molecules such as cyclohexene (Eq. 3). They suggested the reactions proceeded through nucleophilic displacement of a $[\text{CF}_3]$ anion by iodide, followed by decomposition of the $[\text{CF}_3]$ anion to the difluorocarbene [53]. Such mercury salts could be employed to form difluoromethylated products, and in 1985, Pein and Cech demonstrated that $[\text{Hg}(\text{CF}_3)_2]$ in the presence of sodium iodide could be used to introduce a CF_2H

Scheme 1 Typical methods used to prepare transition-metal-difluoromethyl complexes

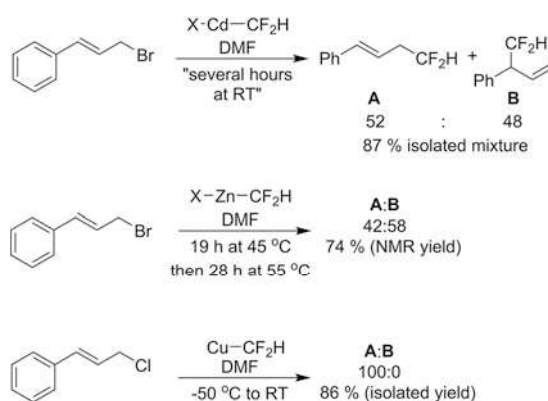


functionality into a more complex organic substrate (Eq. 4) [54, 55]. In a similar vein, less toxic zinc reagents can be used as formal difluorocarbene sources to perform difluoromethylations as described in Eqs 5 and 6 [56, 57].





Scheme 2 Reactivity of difluoromethyl cadmium reagents toward organic halides [58, 59]

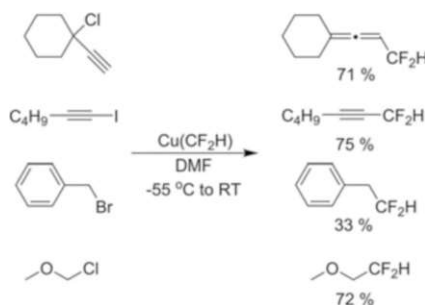


Scheme 3 Reactivity of cadmium, zinc, and copper difluoromethyl complexes with cinnamyl halides

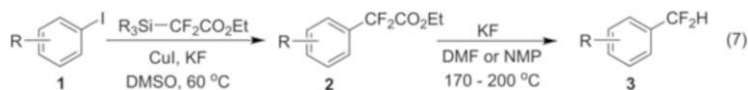
Subsequently, it was shown that metal-bound difluoromethyl complexes could be used to directly transfer the $[\text{CF}_2\text{H}]$ functionality to organic substrates. Burton found that difluoromethyl complexes of cadmium could be prepared by reaction of cadmium metal with $[\text{CF}_2\text{HX}]$, where $\text{X} = \text{Br}$ or I [58]. When prepared as such, the cadmium reagent exists as a 25:75 mixture of $[(\text{CF}_2\text{H})_2\text{Cd}]$ and $[(\text{CF}_2\text{H})\text{CdX}]$ in DMF solution. Notably, this equilibrium mixture of cadmium salts reacted with allylic and propargylic halides to form the difluoromethylated products as described in Scheme 2.

Burton later went on to prepare a zinc difluoromethyl reagent by similarly reacting zinc metal with $[\text{CF}_2\text{HX}]$ [46]. The zinc reagent that formed was thermally stable, but reacted with allylic halides much slower than the analogous cadmium derivative (Scheme 3). A difluoromethyl copper reagent could be prepared by reacting $[\text{XCd}(\text{CF}_2\text{H})]$ with copper halides, but unlike the cadmium and zinc reagents, the copper species was thermally unstable and decomposed rapidly at temperatures above -30°C [46]. Nevertheless, the copper species reacted with allylic halides at -50°C with regioselectivities that were superior to both cadmium and zinc (Scheme 3). Other organic difluoromethylation reactions that are possible with $[\text{Cu}(\text{CF}_2\text{H})]$ as prepared by Burton are outlined in Scheme 4.

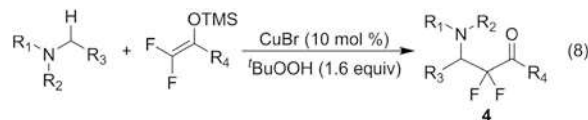
Scheme 4 Reactions of the $[\text{Cu}(\text{CF}_2\text{H})]$ reagent prepared from CuX with $[\text{XCd}(\text{CF}_2\text{H})]$



Because of the reported lack of stability of the $[\text{Cu}(\text{CF}_2\text{H})]$ reagents prepared via Burton's procedure, Amii and co-workers in 2011 developed a new reaction sequence to directly couple difluoroacetates to organic halides [60]. The reaction sequence is believed to involve the generation of a relatively stable $[\text{Cu}(\text{CF}_2\text{CO}_2\text{Et})]$ species that is capable of performing coupling reactions with aryl iodides to afford **2** (Eq. 7) at temperatures of 60°C . Then, under forcing conditions, the resulting difluoroester can be first hydrolyzed then decarboxylated to form product **3** (Eq. 7) in yields ranging from 59 to 89%. The drawback of this method is the high temperatures needed for decarboxylation of the difluoroester.

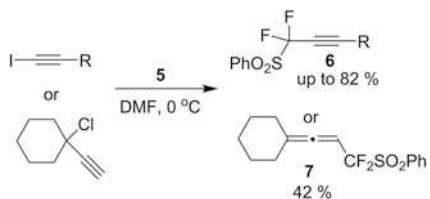


Two years prior to Amii's report on copper difluoroacetates, Qing and co-workers published a CuBr -catalyzed oxidative difluoromethylation of tertiary amines with difluoroenol ethers to afford β -amine- α,α -difluoroketones (Eq. 8). The reaction presumably proceeds through coupling of iminium ions generated in situ with the difluoroenol silyl ethers, which are synthetic equivalents of α,α -difluoroacetyl silanes and can be easily transformed to α,α -difluorocarbonyl compounds such as aldehydes, carboxylic acids, amides, and other derivatives [61]. No attempt was made to convert **4** into $[\text{CF}_2\text{H}]$ derivatives.

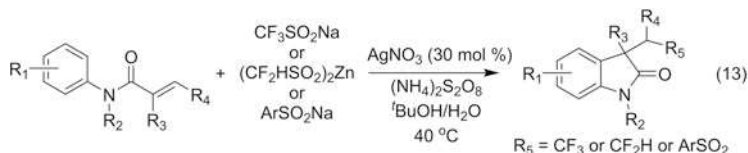


In 2011, Hu and co-workers explored the use of a different fluoroalkyl copper species to perform difluoromethylation reactions [62]. They observed that reaction of $\text{PhSO}_2\text{CF}_2\text{TMS}$ with CsF in the presence of CuI at -30°C generated a $[\text{PhSO}_2\text{CF}_2\text{Cu}]$ species (**5**) that showed two forms in DMF solution (Eq. 9). This

Scheme 5 Difluoromethylenation reactions with $[\text{PhSO}_2\text{CF}_2\text{Cu}]$



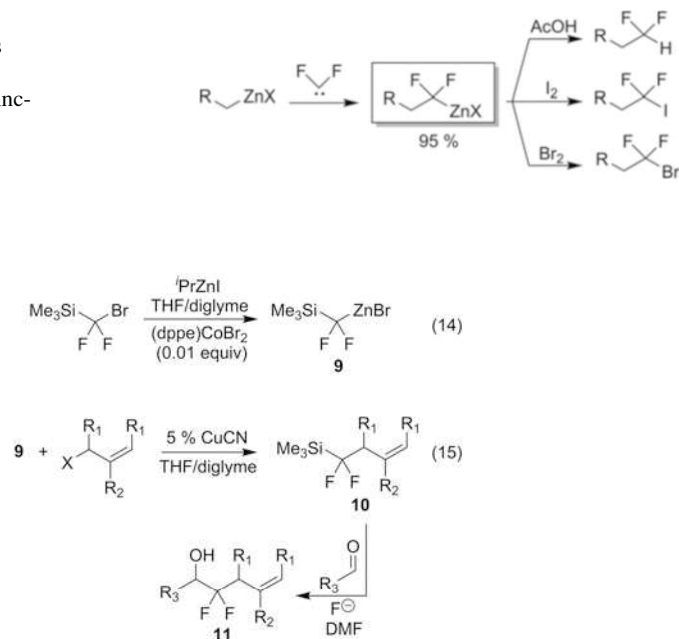
Baran's reagent and Langlois' reagent have also been used in combination with silver salts to prepare difluoromethyl and difluoromethylene substituted oxindoles as described in Eq. 13 [66]. The reactions proceed by addition of the in situ generated difluoromethyl radical to an alkenyl fragment followed by subsequent cyclization with the aromatic ring.



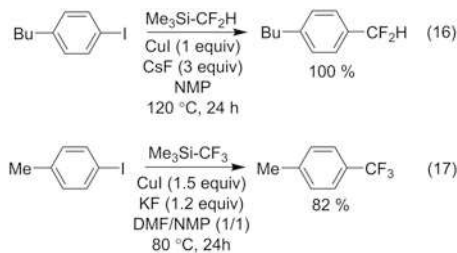
The enhanced stability of fluoroalkyl zinc reagents, together with the relatively low toxicity of zinc, bodes well for its future use and development of fluoroalkylation reactions. Dilman and co-workers have shown that difluoromethylenated compounds can also be prepared by reacting benzyl and alkyl zinc halides with difluorocarbene as described in Scheme 6 [67]. The strategy exploits the fact that difluorocarbene is intrinsically electrophilic and is capable of reacting with nucleophiles like alkyl zinc reagents. The chemistry is versatile in the sense that once the difluorinated organozinc reagents have been synthesized from the organozinc of choice, they can react with electrophiles of choice to form organic products containing the $[\text{CF}_2]$ fragment (Scheme 6). For benzylzinc halides, the yields are high and the reaction tolerates halogen, cyano, ester, and boron groups on the aromatic ring [67]. The yields with aliphatic organozinc reagents were more variable.

Dilman also found that a new difluorinated reagent $[\text{Me}_3\text{SiCF}_2\text{ZnBr}]$ (**9**) can be coupled with two different carbon-based electrophiles in a stepwise manner, showing reactivity that could be described as a difluoromethylene bis-carbanion equivalent [68]. The reagent **9** is prepared by a cobalt-catalyzed halogen/zinc exchange reaction [69, 70] as described in Eq. 14. An example of the utility of reagent **9** is the allylation reaction described in Eq. 15. The intermediate allylic silanes (**10**) were obtained in yields from 68 to 88%, and the conditions employed (0 – 20°C for 17 h) were operationally simple. The allyl silanes were then employed as nucleophilic reagents for aldehyde additions to afford the *gem*-difluorinated alcohols **11** in excellent yields.

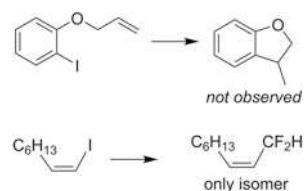
Scheme 6 Difluoromethylenated products through insertion of difluorocarbene into zinc-carbon bonds



Fluoroalkyl-derivatized silanes have also shown great versatility in fluoroalkylation reactions [71], and in 2012, the first copper-mediated difluoromethylation reactions employing $[\text{Me}_3\text{Si-CF}_2\text{H}]$ were reported. Hartwig and co-workers were able to design reaction conditions employing $[\text{Me}_3\text{Si-CF}_2\text{H}]$ that allow copper-mediated difluoromethylations to proceed at higher temperatures (Eq. 16) than any previously reported [51]. The difluoromethyl source was $[\text{Me}_3\text{Si-CF}_2\text{H}]$, which could be prepared on a multigram scale by the reduction of $[\text{Me}_3\text{Si-CF}_3]$ with sodium borohydride. The reaction conditions were amenable for the conversion of a wide range of aryl and vinyl iodides, and electron neutral, electron rich, and sterically hindered aryl iodides reacted in high yields [51]. It is noteworthy to compare the conditions for difluoromethylations reported by Hartwig (Eq. 16) with the conditions similarly used to trifluoromethylate aryl iodides with the $[\text{Me}_3\text{Si-CF}_3]$ reagent (Eq. 17) [72]. The difluoromethylations proceeded at temperatures 40°C higher than the trifluoromethylations, indicating that a stable yet more reactive difluoromethyl source for reactions with copper still remains a desirable synthetic target.

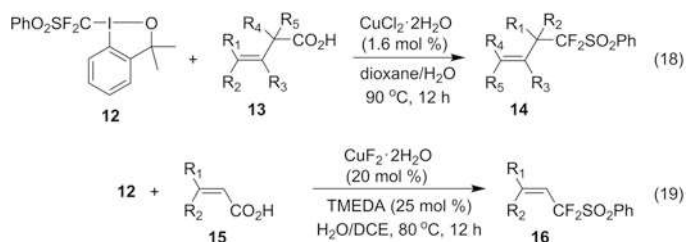


Scheme 7 Support for non-radical processes in the copper-mediated difluoromethylation of aryl and vinyl iodides with $[\text{Me}_3\text{Si}-\text{CF}_2\text{H}]$ [51]

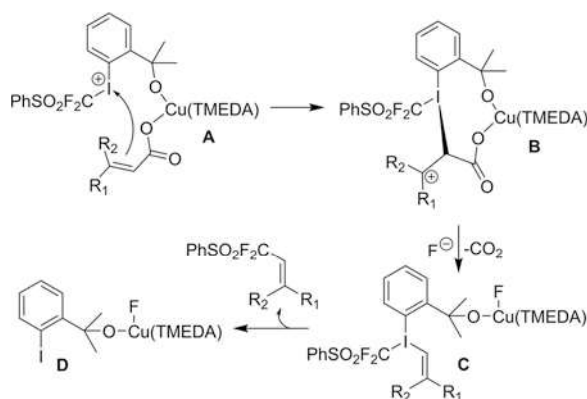


When mixtures of $[\text{CuI}]$, $[\text{CsF}]$, and $[\text{Me}_3\text{Si}-\text{CF}_2\text{H}]$ were heated in the absence of any organo-iodide, ^{19}F NMR evidence for the formation of $[\text{Cu}(\text{CF}_2\text{H})_2]^-$ was observed [51]. The authors suggest that $[\text{Cu}(\text{CF}_2\text{H})_2]^-$ acts as a stable reservoir for the active and neutral $[\text{Cu}(\text{CF}_2\text{H})]$ species. It has recently been reported that perfluoroalkyl cuprates similar to $[\text{Cu}(\text{CF}_2\text{H})_2]^-$ do not react as fast as the neutral copper perfluoroalkyl species [73]. The authors speculate that the low concentration of $[\text{Cu}(\text{CF}_2\text{H})]$ should decrease the rate of bimolecular decomposition, relative to reaction with haloarene [51]. Further experiments to probe the mechanism were performed with radical traps (Scheme 7). No radical cyclizations were observed with [1-(allyloxy)-2-iodobenzene], which rules out the intermediacy of aryl radicals. Moreover, the difluoromethylation of *Z*-1-iodo-1-octene proceeded with complete retention of olefin geometry, which rules out the intermediacy of vinyl radicals.

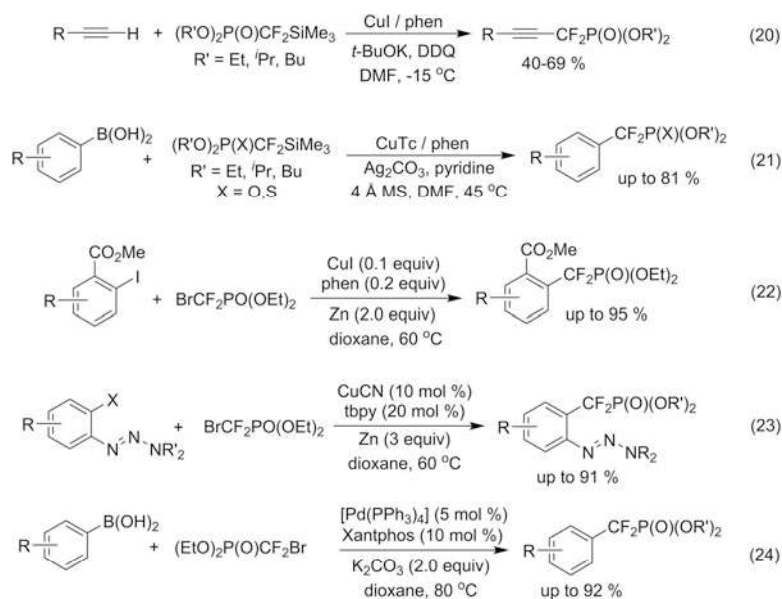
Hypervalent iodine reagents have also been tested for effectiveness in copper-mediated difluoromethylation reactions. High yielding protocols for the synthesis of $\text{C}_{\text{vinyl}}-\text{CF}_2\text{R}$ ($\text{R} \neq \text{F}$) bonds were discovered by Hu and co-workers in 2012 [74, 75]. They observed that the [iodine(III)- $\text{CF}_2\text{SO}_2\text{Ph}$] reagent **12** could be used in combination with copper(II) salts for the regioselective incorporation of allylic difluoromethyl groups by a copper catalyzed decarboxylation of β,γ -unsaturated carboxylic acids (Eq. 18). Functionalizations using this method occurred at the γ -position of **13** only. Gratifyingly, the products **14** can be further transformed into $[\text{R}-\text{CF}_2\text{H}]$ derivatives by reductive desulfonylation with $\text{Mg}/\text{HOAc}/\text{NaOAc}$ in DMF solution at room temperature [74]. The same [iodine(III)- $\text{CF}_2\text{SO}_2\text{Ph}$] reagent could be used to difluoromethylate α,β -unsaturated carboxylic acids as described in Eq. 19 [75]. The proposed mechanism of the decarboxylative functionalization is outlined in Scheme 8. It is believed that intermediate **A** is generated in the course of the reaction, which then undergoes an intramolecular transformation to species **B** which then decarboxylates and liberates product through a reductive elimination at iodine.



Scheme 8 Key steps in the proposed mechanism of the decarboxylative fluoroalkylation of α,β -unsaturated carboxylic acids [75]



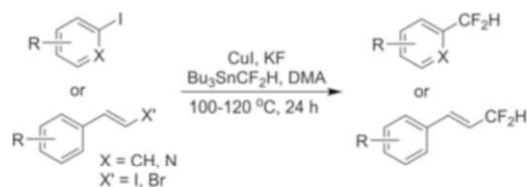
Another *gem*-difluorinated functional group which has received much attention is the difluorophosphonate group [76–83]. Organodifluoromethylphosphonates are an important class of compounds because of their significant bioactivities as protein tyrosine phosphatase (PTP) inhibitors [77]. Burton and co-workers prepared the first transition-metal difluorophosphonate in 1981 by the reaction of $[(\text{EtO})_2\text{P}(\text{O})\text{CF}_2\text{Br}]$ with cadmium metal to produce the stable $[(\text{EtO})_2\text{P}(\text{O})\text{CF}_2\text{CdBr}]$ [81]. They showed that $[(\text{EtO})_2\text{P}(\text{O})\text{CF}_2\text{CdBr}]$ reacted with a variety of electrophiles (e.g., with allyl bromide to afford allyl difluorophosphonate) to form new organic difluorophosphonates. Selected recent advances in this area are shown in Eqs 20–24. In 2012, Qing and co-workers showed that terminal alkynes react with $[(\text{RO})_2\text{P}(\text{O})\text{CF}_2\text{SiMe}_3]$ through a copper-mediated oxidative cross-coupling reaction to afford α,α -difluoropropargylphosphonates in moderate to good yields with excellent functional group compatibility (Eq. 20) [76]. Their group subsequently extended their oxidative coupling method to include aryl boronic acids (Eq. 21) [78]. Also in 2012, Zhang and co-workers demonstrated an operationally simple protocol whereby copper difluorophosphonates can be generated in situ and then reacted with iodobenzoates to afford aryl difluorophosphonates in excellent yields (Eq. 22) [83]. Their group extended this method to include iodo- and bromo-triazenes coupling partners (Eq. 23) [77]. Within the triazene family, aryl bromides could be coupled with copper difluorophosphonates for the first time in yields up to 69%. Zhang and co-workers also developed a palladium-catalyzed method to prepare aryl difluoromethylated phosphonates from aryl boronic acids and $[(\text{EtO})_2\text{P}(\text{O})\text{CF}_2\text{Br}]$ (Eq. 24) [79]. The palladium method also worked for coupling aryl boronic acids with $[\text{EtCO}_2\text{CF}_2\text{Br}]$ and $[\text{R}_2\text{NCOCF}_2\text{Br}]$ and was compatible with late-stage functionalization of scaffolds present in bioactive molecules [79].



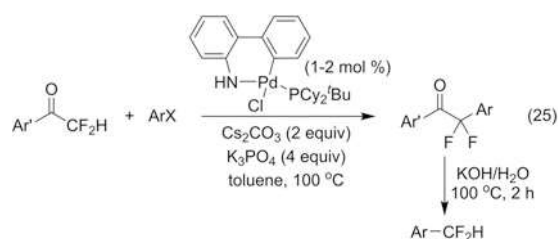
Prakash and co-workers developed a copper protocol using $[n\text{-Bu}_3\text{SnCF}_2\text{H}]$ to difluoromethylate aryl, heteroaryl, and vinyl halides (Scheme 9). One of their motivations for using a tin reagent was that the Hartwig procedure for difluoromethylation, which uses $[\text{Me}_3\text{Si-CF}_2\text{H}]$ as the difluoromethyl source (Eq. 16), is not compatible with aldehydes and ketones owing to competitive nucleophilic addition reactions [50]. Indeed, reactions with iodo-substituted benzaldehydes and acetophenones afforded excellent yields of difluoromethylated products [50]. $[n\text{-Bu}_3\text{SnCF}_2\text{H}]$ is benchtop stable and can be stored in air for weeks to months without any apparent decomposition. The use of tin reagents for the formation of vinyl difluoromethylated complexes also outperformed Baran's reagent in decarboxylative protocols [65].

Other metals besides copper have shown promise in fluoroalkylation chemistry. A recent breakthrough in difluoromethylenation chemistry was the ability to perform palladium-catalyzed α -arylations with α,α -difluoroketones. In 2014, Hartwig and co-workers found that a palladacycle precatalyst that releases $[\text{Pd}(\text{PCy}_2)_2\text{Bu}]$ as the active component was able to couple α,α -difluoroacetophenone derivatives with aryl bromides and aryl chlorides to generate α -aryl- α,α -difluoroketones in excellent yields (Eq. 25) [84]. The formation of product presumably arises from reductive elimination at a $[\text{Pd}(\text{Ar})(\text{CF}_2\text{COAr}')]_2$ center, which is noteworthy because reductive eliminations of perfluoroalkyl groups at palladium have previously been limited to complexes of bulky ligands or with large bite angles [84]. The ability to incorporate a carbonyl atom next to the difluoromethylene group is synthetically attractive, due to the wide range of transformations that could be performed in subsequent derivatizations. In the course of these studies, the authors also found that the C-C bond adjacent to the carbonyl group in the α -aryl- α,α -difluoroketones

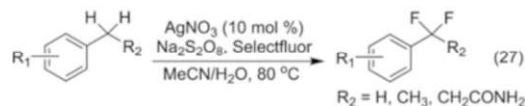
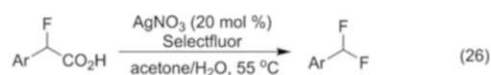
Scheme 9 Copper-mediated difluoromethylation of heteroaryl iodides and β -styryl halides with tributyl (difluoromethyl)stannane



could be readily cleaved to form difluoromethylarenes (Eq. 25) [84]. The pathway to the difluoromethylarenes could be done in a stepwise fashion as shown in Eq. 25 or in a single pot procedure.



Two unconventional methods to prepare difluoromethyl and difluoromethylenated arenes using the combination of silver and Selectfluor were recently reported. In 2013, Gouverneur and co-workers found that silver could promote the decarboxylative fluorination outlined in Eq. 26 in yields up to 91% [85]. Importantly, the authors demonstrated that if ^{18}F -labeled Selectfluor was used, the successful radiosynthesis of difluoromethyl arenes could be performed for the first time. The radiochemical yield of [*para*-Ph-C₆F₄-CF₂H] using this method was $8.6 \pm 2.6\%$ [85]. Tang and co-workers found that the combination of silver salts with Selectfluor was able to mediate a quite different transformation, namely, the fluorination of benzylic C–H bonds (Eq. 27) [86]. The procedure tolerates a variety of functional groups, and gram-scale syntheses of functionalized difluoromethyl and difluoromethylenated arenes could be realized. This procedure is interesting because no C–C bond coupling is required to generate fluoroalkylated products from nonfluorinated substrates.



3 Polydifluoromethylenation

There are interesting considerations for the preparation and use of molecules containing repeating difluoromethylene groups. It is well known that molecules containing CF_2 groups exhibit geometric parameters that are dissimilar to their nonfluorinated congeners [26, 87]. O'Hagan and co-workers analyzed crystallographically determined molecular structures bearing the $\text{CH}_2\text{CF}_2\text{CH}_2$ motif and found that the average $\text{C}-\text{CF}_2-\text{C}$ angle was 118° and the average $\text{F}-\text{C}-\text{F}$ angle was 104° [26]. These angles are significantly wider and narrower than those counterparts found in $\text{CH}_2\text{CH}_2\text{CH}_2$ motifs. Less appreciated, however, is the fact that structural differences become more complex when there are repeating arrays of CF_2 or CH_2CF_2 units in a single molecule. Consider the structural differences between *n*-hexane (**A**) and *n*-perfluorohexane (**E**, Fig. 3). Density functional theory (DFT) calculations predict (Figs. 3 and 4) that in the gas phase, the interior $\text{CH}_2\text{CH}_2\text{CH}_2$ and $\text{CF}_2\text{CF}_2\text{CF}_2$ angles are nearly identical, at 113.7° and 113.9° , respectively. The calculated bond angle of 113.9° in **E** matches well with the experimentally determined bond angles of $113.8(1)^\circ$ and $113.9(1)^\circ$ for the two innermost difluoromethylenes in perfluorohexane [88].

Figure 3 also shows that when there are repeating arrays of $\text{CH}_2\text{CF}_2\text{CH}_2$ motifs like in all-*trans* 1,1,1,3,3,5,5-heptafluorohexane (**C**₁), the interior $\text{CH}_2\text{CF}_2\text{CH}_2$ bond angle may actually be less than that calculated for *n*-hexane. The angle for this motif, however, is highly dependent on the chain structure, and when the *trans*-gauche or "zigzag" conformation (**C**₂) is accessed, the calculated $\text{CH}_2\text{CF}_2\text{CH}_2$ bond angles become larger than the corresponding angles in *n*-hexane (Fig. 3). The only two known examples of molecules containing repeating arrays of CH_2CF_2 moieties that were characterized by single crystal X-ray diffraction exhibit the *trans*-gauche configurations (Fig. 5) [89].

Despite the similarity of $\text{C}-\text{C}-\text{C}$ bond angles in *n*-hexane versus *n*-perfluorohexane, the interior $\text{C}-\text{C}-\text{C}-\text{C}$ dihedral angles vary significantly (calculated difference of 17.6° between **A** and **E**). Repeating CF_2 groups are known to impart a significant twist along the carbon chain into a helix with dihedral angles reported near 17° [90]. The variation in twisting for the nonfluorinated versus fluorinated structures is graphically illustrated for **A**, **C**₁, **C**₂, and **E** in Fig. 4 as well as for the phenyl capped species **B** and **F** (Figs. 6 and 7). Such twisting is clearly exhibited in the experimentally determined crystal structure for 4,4''-(perfluorohexane-1,6-diyl)di-1,1'-biphenyl (Fig. 7) [91]. Figure 6 illustrates how both the changes in $\text{C}-\text{C}-\text{C}$ and dihedral angles in fluorinated versus nonfluorinated hexyl derivatives influence the distance between the C1 and C6 termini. The general observed trend is that for all-*trans* geometries, fluorination has the effect of increasing the C1-C6 distance largely in part due to the changes in dihedral angles of the hexyl carbon chain. Once the *trans*-gauche conformation has been obtained for derivatives bearing repeating CF_2CH_2 linkages (**C**₂ and **D**₂, Figure 6), the distance between termini drastically shortens. Such geometric

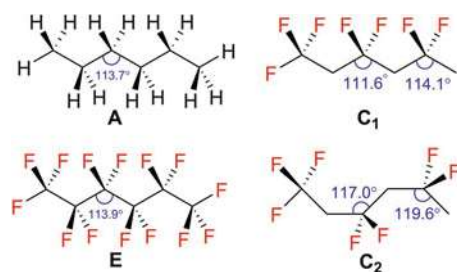


Fig. 3 Calculated (6-31++G(d,p)) bond angles in fluorinated hexane derivatives

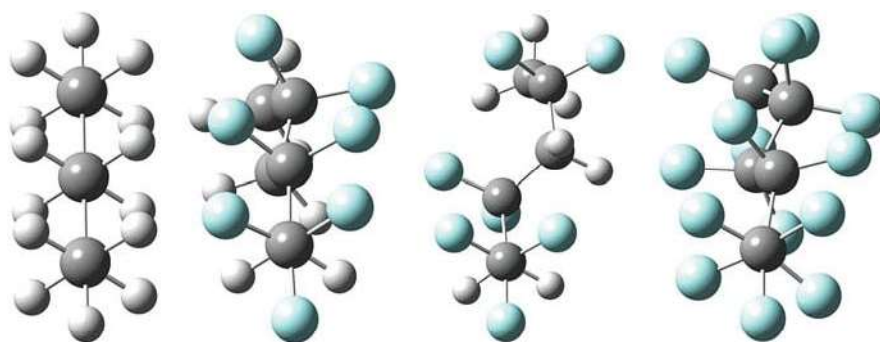


Fig. 4 Optimized geometries of, from left to right, A, C₁, C₂, and E from Fig. 3 projected down the C1–C2 bond axis

considerations play an important practical role in the applications and ferroelectric properties of molecules like poly(vinylidene fluoride) [92].

Having multiple repeating difluoromethylene groups in an organic molecule can also largely affect its hydrophobicity. Here, it is important to understand the difference between the lipophilic character of a molecule from the hydrophobic character. In simple aromatic molecules, addition of fluorine or fluorinated groups tends to increase the lipophilicity of the molecule [93]. For aliphatic molecules or molecules containing large perfluoroalkyl chains, fluorination can actually induce a decrease in lipophilicity while enhancing the hydrophobic character [94]. This leads to the phenomenon where highly fluorinated compounds may form a third phase from water and organic solvents. Bégué and Bonnet-Delphon note that the confusion about hydrophobicity and lipophilicity comes from the way we measure lipophilicity, by taking the logarithm of the partition coefficient between 1-octanol and water ($\log P$) [94]. They note that it is often considered that the higher the $\log P$ value, the more lipophilic a compound is perceived to be. However, it must be kept in mind that the $\log P$ value is only a measure of relative solubility. Bégué and Bonnet-Delphon go on to state that “considering that the solubility of a fluorinated substance decreases more in water than in octanol, this measurement leads one to think that fluorinated compounds are more ‘lipophilic’. Actually, this represents the

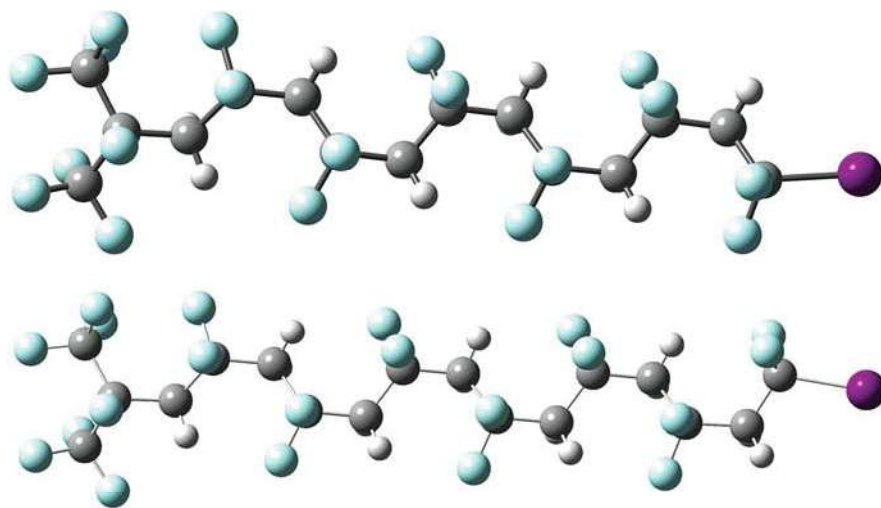


Fig. 5 Experimentally obtained X-ray crystal structures of $(\text{CF}_3)_2\text{CF}-(\text{CH}_2\text{CF}_2)_6\text{-I}$ (top) and $(\text{CF}_3)_2\text{CF}-(\text{CH}_2\text{CF}_2)_7\text{-I}$ (bottom), demonstrating the zigzag geometry in the solid state [89]

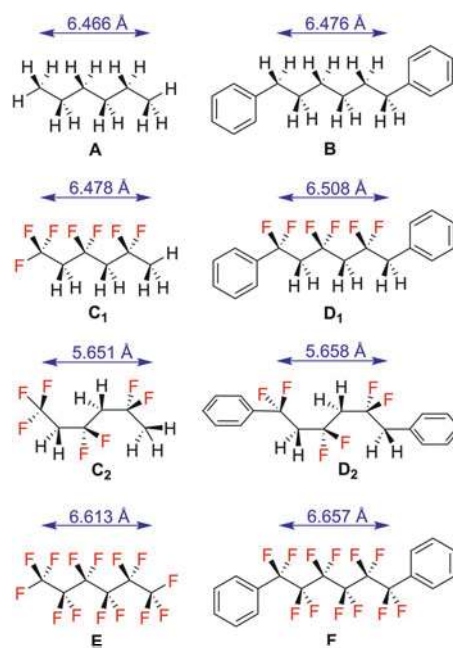


Fig. 6 Calculated (6-31++G(d,p)) bond distances of the terminal carbon atoms of the fluorocarbon chain in hexyl and dodecafluorohexyl linkages for selected conformations

relative lack of affinity of fluorinated compounds for both phases.” For these reasons and the complicated dependence of $\log P$ values on the reference solvent [94], observed $\log P$ values are often difficult to interpret. Therefore, caution should be taken when referring to a polydifluoromethylenated molecule as more lipophilic

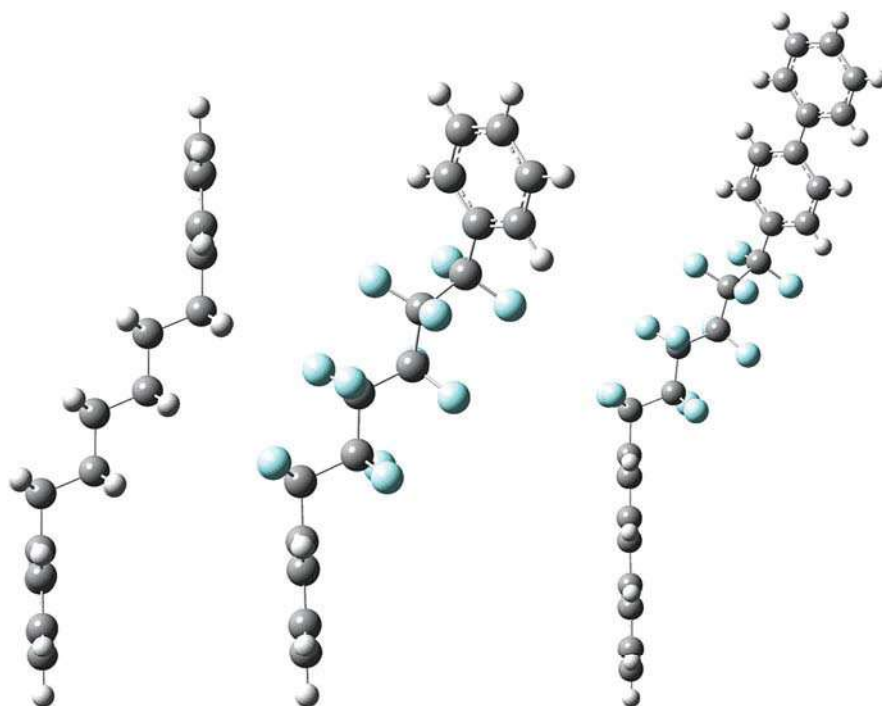


Fig. 7 Optimized geometries of **B** (left) and **F** (middle), with the plane of the lower aryl ring set perpendicular to the page. Note the twisting of the upper aryl ring caused by changes in the dihedral angles in the perfluoroalkyl linker. Shown to the right is the experimentally determined structure of 4,4''-(perfluorohexane-1,6-diyl)di-1,1'-biphenyl [91]

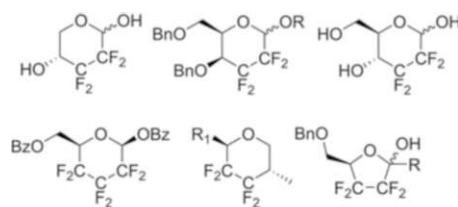
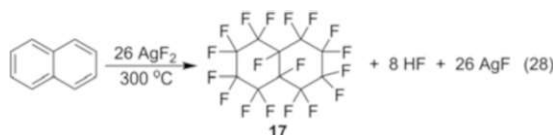


Fig. 8 Examples of sugar molecules containing repeating difluoromethylene groups

than its unsubstituted derivative. The hydrophobic nature of fluorocarbons, however, remains less controversial [95]. One important field that exploits the “polar hydrophobicity” [96] of repeating difluoromethylene groups is the pharmaceutical field. For instance, heavily fluorinated sugars, like those shown in Fig. 8, have been targeted as probes for protein-carbohydrate interactions and as carbohydrate-based therapeutics [96–102]. Incorporating repeating difluoromethylene groups into organic molecules through metal-mediated processes is quite challenging, however, and is discussed below.

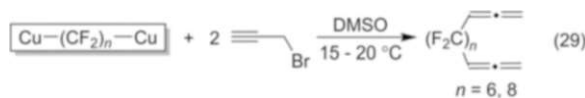
3.1 Transition-Metal-Mediated Polydifluoromethylenation

Early syntheses of molecules containing polydifluoromethylene linkages were often performed under forcing conditions in the gas phase. In 1947, McBee and Bechtol reported that fused ring fluorocarbons such as perfluoronaphthalene (**17**) could be prepared by reaction of silver difluoride with naphthalene at temperatures up to 300°C [103]. The resulting products were *perfluorinated*, limiting the application of the procedure to prepare molecules with other functionalities.

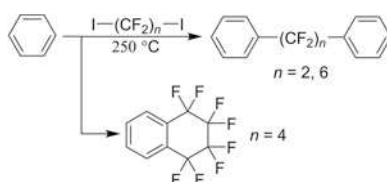


Partially difluoromethylenated molecules could also be prepared under metal-free conditions, given the appropriate fluoroalkylated reagents. In 1967, Knunyants and co-workers showed that the thermolysis of α,ω -diiodoperfluoroalkanes in the presence of benzene led either to diarylated products or to fluoroalkyl-containing ring formation, depending on the size of the diiodoperfluoroalkane (Scheme 10) [104]. Such methodology was later exploited by Boltalina to form C_4F_8 -annulated corannulene derivatives [105]. These radical and metal-free processes require temperatures above 250°C, at which point the reactions take place in the gas phase.

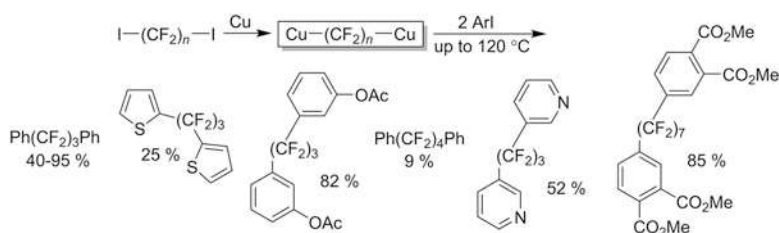
In 1969, McLoughlin and Throrer reported that α,ω -diiodoperfluoroalkanes could be doubly cuprated to form a $[\text{Cu}-(\text{CF}_2)_n-\text{Cu}]$ species which react with aryl iodides at temperatures much lower than the metal-free systems described above (Scheme 11) [106]. With iodobenzene as the substrate, $[\text{Ph}(\text{CF}_2)_3\text{Ph}]$ could be formed in 40–95% yield, depending on the choice of solvent. The milder reaction conditions were amenable to functionalized aromatics and heterocycles, producing products in moderate to good yields (Scheme 11). However, superstoichiometric amounts of copper (up to 13 equivalents) were required [106]. Such dicopper perfluoroalkyl reagents, prepared using copper powder, were later used to prepare fluorinated allenes as described in Eq. 29 [107]. However, the diallene products were formed in only 27–32% yield.



Chen and co-workers developed a stepwise protocol to cyclize α,ω -difunctionalized perfluoroalkanes onto aromatic rings [108–110]. The procedure first involves coupling $[\text{I}(\text{CF}_2)_n\text{Cl}]$ with aryl iodides in the presence of copper metal to form an $[\text{Ar}-(\text{CF}_2)_n\text{Cl}]$ such as **18** (Eq. 30). Then, the aryl perfluoroalkyl chloride was activated using a sulfinate dehalogenation system, inducing a radical cyclization to afford **19**. The protocol is compatible with functionalized aromatics

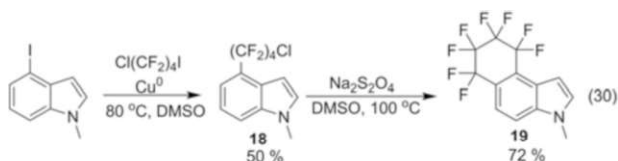


Scheme 10 Reaction of diiodoperfluoroalkanes with benzene under metal-free conditions

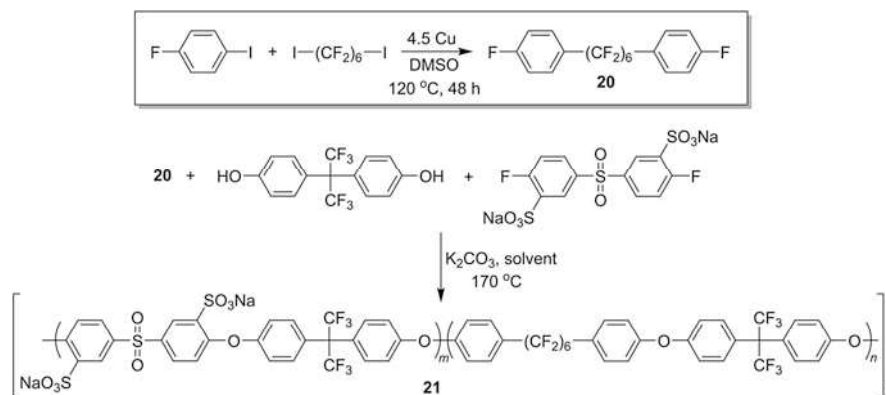


Scheme 11 Routes to fluoroalkyl-substituted aromatics using copper metal

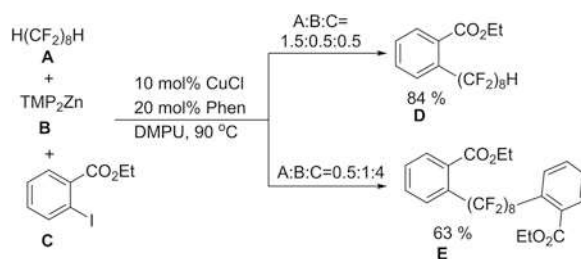
and even porphyrins [109] and was ultimately performed under purely metal-free and radical conditions since the two-step process involving copper leads to somewhat low overall yields based on starting organic iodide.



One application of the copper-mediated polydifluoromethylenation chemistry is the design of new fuel cell membranes. It has been reported that when sulfonated poly(arylene ether sulfone) (SPAES) ionomer membranes possess a high degree of sulfonation, in particular above 50%, they tend to deliver relatively high methanol permeability and water uptake which results in the low selectivity (a ratio of proton conductivity to methanol permeability) and poor cell performance [111]. To combat these problems, the effect of polydifluoromethylenation on the membrane properties and membrane-electrode assembly performance for direct methanol fuel cell applications was investigated comprehensively and compared with the non-difluoromethylenated derivative as well as with Nafion membranes. The synthesis of the new SPAES involved as a key step the copper catalyzed coupling of $[I-(CF_2)_6-I]$ with 4-fluoro-iodobenzene to afford **20** (Scheme 12). 1,6-Bis(4-fluorophenyl)-perfluorohexane and 2,2-bis(4-hydroxyphenyl) hexafluoropropane were designed to replace diphenyl sulfone and bisphenol groups, respectively. The resulting copolymer membrane (**21**) presented higher selectivity than Nafion®117 as well as pristine SPAES membranes [111].



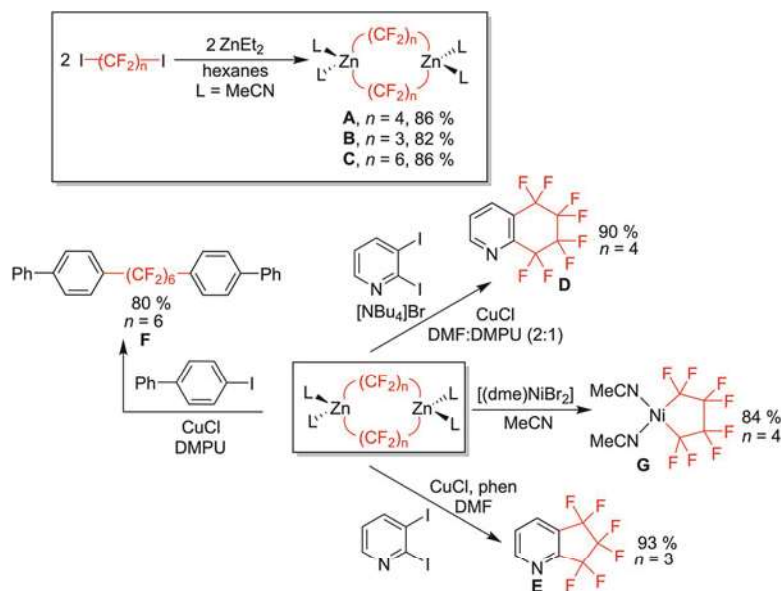
Scheme 12 Synthesis of partially fluorinated copolymers for fuel cell applications



Scheme 13 Polydifluoromethylation catalytic in copper

A method to incorporate polydifluoromethylene linkages that was catalytic in copper was developed in 2011. Daugulis and co-workers demonstrated that zinc bis-2,2,6,6-tetramethylpiperidide [(TMP)₂Zn] could be used to generate perfluoroalkyl zinc reagents directly from α -*H*- and α,ω -*H*-perfluoroalkanes (Scheme 13) [112]. The resulting bis(perfluoroalkyl)zinc reagents were then used in situ for a copper-catalyzed perfluoroalkylation (Scheme 13). DMPU solvent was key for high yields. When [H-(CF₂)₈-H] was used as the perfluoroalkane, reaction with ethyl 2-iodobenzoate afforded either monosubstituted product **D** or dimeric product **E**, depending on the ratio of reagents used. The work was significant not only because the method was catalytic in copper but also because α -*H*-perfluoroalkanes could be used in the coupling reactions, instead of the commonly employed and expensive R_f-SiMe₃ reagents. Only one example of polydifluoromethylation using α,ω -*H*-perfluoroalkanes was tested in this work, however (Scheme 13).

In 2013, Vicić and co-workers developed synthetic routes to perfluoroalkyl dizinc reagents by reacting α,ω -diiodoperfluoroalkanes with diethylzinc (Scheme 14) [91]. Complexes **A** and **B** were structurally characterized to confirm



Scheme 14 Synthesis and utility of perfluoroalkyl dizinc reagents

the dimeric nature of those derivatives. The $n=3$ and $n=6$ derivatives **B** and **C** display enhanced stabilities relative to the $n=4$ derivative **A**, which is prone to decompose to form $[\text{H}-(\text{CF}_2)_4-\text{H}]$. Nevertheless, **A** could be used in combination with CuCl and $[\text{NBu}_4]\text{Br}$ to afford novel perfluoroalkyl-containing ring systems like octafluoroquinoline (**D**) from diiodoarenes in good yields. Interestingly, routes to hexafluorocyclopentapyridine (**E**) did not require the use of $[\text{NBu}_4]\text{Br}$ to afford high yields of product. It was determined that formation of the unusual bis-cuprate species $[\text{Cu}_2(\text{C}_4\text{F}_8)_2]^{2-}$ was competitive with perfluoroalkylation of organic diiodides in the case of reagent **A**. It should be mentioned that the large-scale synthesis of $[\text{Me}_3\text{Si}(\text{CF}_2)_4\text{SiMe}_3]$ (**22**) has recently been reported [113]. Importantly, it was shown that **22** could not be used as a perfluoroalkylating agent under standard conditions. Such results reinforce the utility of the dizinc reagent **A** for transferring the C_4F_8 fragment. For the dizinc reagent bearing six difluoromethylene groups (**C**), reactions with diiodoarenes did not afford ring structures, but instead led to dimeric compounds like **F** in good yields.

The dizinc reagent **A** also reacts with nickel dihalides to form perfluoroalkyl-metallacyclopentanes such as **G**. Monomer/dimer preferences are likely due to the fact that zinc(II) complexes prefer tetrahedral geometries while nickel(II) complexes prefer square planar ones, and the angles to accommodate such geometries with a perfluoroalkyl chain are more optimal in one or the other form. Bickelhaupt and co-workers suggested that metal electronegativities also play a role in monomer/dimer preferences in similar reactions [114] and that the geometric forms are also governed by Bent's rule [115, 116]. The ability to form

perfluoroalkyl metallacycles like **G** was significant, because all previous synthetic routes to perfluoroalkyl-metallacyclopentanes involved the oxidative coupling of tetrafluoroethylene (TFE) [91]. TFE has become increasingly unavailable to acquire in a small laboratory setting because of the explosion hazards associated with its use [91]. It is expected that the new dizinc reagents will be useful for laboratories that want to explore the chemistry of perfluoroalkyl metallacycles and are less equipped to handle or generate perfluorinated gases.

Summary, Conclusions, and Outlook

Fluoroalkylation reactions are becoming increasingly important in the chemical, biological, and materials fields. While the methodology for *perfluoroalkylations* has matured significantly in the past decade, relatively fewer studies have focused on the historically less common difluoromethylation, difluoromethylenation, and polydifluoromethylenation reactions. The design of new reagents such as $[\text{PhSO}_2\text{CF}_2\text{Cu}]$, $[\text{Me}_3\text{Si-CF}_2\text{H}]$, $[\text{Zn}(\text{SO}_2\text{CF}_2\text{H})_2]$, $[n\text{-Bu}_3\text{SnCF}_2\text{H}]$, $[\text{HCF}_2\text{Cu}]$, and $[\text{L}_2\text{Zn}((\text{CF}_2)_n)_2\text{ZnL}_2]$ is further enabling new methods development in these areas. The ability to tailor the amount of fluorine in *small molecules* continues to be important for drug design, biological probes and imaging, and ligands for transition-metal catalysts operating under oxidative conditions. Tailoring the amount of difluoromethylene linkages in *large molecules* will also allow for better control of the unique optical, electronic, processing, environmental stability, and surface properties of new materials [117].

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