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FLUORINATED ORGANOMETALLICS: PERFLUOROALKYL AND FUNCTIONALIZED PERFLUOROALKYL ORGANOMETALLIC REAGENTS IN ORGANIC SYNTHESIS

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CONTENTS

INTRODUCTION

The use of organometallic reagents in organic synthesis has been a dynamic and growing area in organic chemistry and the degree of sophistication and complexity of the reagents has been remarkable. Unfortunately, the development of fluorinated organometallics has proceeded at a slower pace and has not yet reached the degree of complexity of its hydrocarbon counterparts. This slow growth may have been due to the lack of suitable precursors and in part to the low thermal stability of the early lithium and magnesium analogs which discouraged other investigators. However, in the past decade, a wide variety of precursors have become commercially available, and recent work on copper, mercury and zinc reagents has demonstrated that many of the fluorinated organometallics exhibit excellent thermal stability. Several recent reviews have provided coverage of the preparation of trifluoromethyl organometallics[1] and the reader is referred to these reviews for preparative and structural aspects of these compounds. Several other reviews adequately summarize the older literature[2-5] and most of this material will not be covered in this report except for historical perspective. The main focus of this report is the preparation of perfluoroalkyl and functionalized perfluoroalkyl organometallic reagents and their application in organic synthesis. We plan to prepare a second report later that will review the fluorinated alkenyl, acetylenic and aryl organometallic reagents.

Since the focus of this report is on the application of the reagents in synthesis, literature reports of their preparation without synthetic application generally have not been included. We apologize to authors whose excellent work may not have been documented. In order to keep the review within a manageable size, we have focused on the utility of the reagents and have attempted to present these reagents and their applications in a format easily followed by non-fluorine chemists.

I. Perfluoroalkyl Lithium Reagents:

Although alkyl- and aryllithium reagents can be prepared *via* direct reaction of the corresponding halides with lithium metal, initial attempts to prepare a perfluoroalkyllithium directly from lithium metal and the perfluoroalkyl iodide were unsuccessful.[6,7,8] The products were perfluoroalkenes, traces of monohydroperfluoroalkanes and nonvolatile polymers. However, in the presence of a carbonyl substrate, heptafluoropropyl iodide reacted with a lithium-sodium (2%) alloy to give a low yield of the corresponding carbinol, presumably *via* the perfluoroalkyllithium intermediate.[7]

Halogen-lithium exchange reactions provide the most general method for the preparation of perfluoroalkyllithium compounds.[9,10] Treatment of perfluoroalkyl iodides with organolithium reagents, such as

$$R_FI + RLi \xrightarrow[\text{low temp.}]{Et_2O} R_FLi + RI$$

methyl, butyl or phenyllithium, in diethyl ether at low temperatures affords the perfluoroalkyllithium analogs in reasonable yields. Perfluoroethyl, perfluoropropyl and longer linear chain perfluoroalkyl as well as perfluoroisopropyllithium reagents have been prepared in this manner.[11] Recently, some functionalized fluoroorganolithiums have been reported.[12,13] A notable failure of the halogen-lithium exchange process is iodotrifluoromethane. There has been no successful generation and capture of trifluoromethyllithium. Even at low temperatures CF_3Li is unstable and decomposes to yield tetrafluoroethylene, presumably *via* the following scheme. Mono-fluorinated methyl analogs, such as $CFCl_2Li$, $CFBr_2Li$, and CFHBrLi have been successfully

$$CF_3I + CH_3Li \xrightarrow[-78^{\circ}C]{Et_2O} [CF_3Li] \longrightarrow [:CF_2] \longrightarrow F_2C{=}CF_2$$

generated and utilized as precursors for [:CFCl], [:CFBr] and [:CHF], respectively.[14,15,16]

An analogous dilithioperfluoroalkyl reagent was similarly produced by metal-halogen exchange at -80°C and captured in situ with acetaldehyde.[17] Better results were achieved *via* in situ reaction of 1,6-

$$I(CF_2)_4I + BuLi + CH_3CHO \xrightarrow[Et_2O]{-80^{\circ}C} CH_3CH(OH)(CF_2)_4CH(OH)CH_3$$

18%

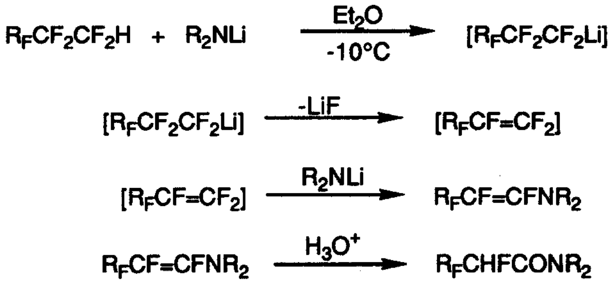
dibromoperfluorohexane with lithium and chlorotrimethylsilane in THF at low temperatures.[18] At -30°C, the yield of the bis silane was only 45%.

$$Br(CF_2)_6Br + Li + Me_3SiCl \xrightarrow[-70\text{ to }-50^{\circ}C]{THF} Me_3Si(CF_2)_6SiMe_3$$

66%

Hydrogen-lithium exchange reactions have been utilized to prepare stable perfluoroalkyllithiums, particularly with 1-hydroperfluorobicyclics.[19] Metallation of 1,1-dichloro-2,2,2-trifluoroethane with butyllithium

at low temperatures also gives the corresponding lithium compound, but only in low to moderate yields.[20] Similarly, 1-hydroperfluoroalkanes react with alkyllithiums[21] or LDA[22] to generate the intermediate perfluoroalkyllithium reagents, which yield fluorinated amides on further reaction as outlined in the following equations.



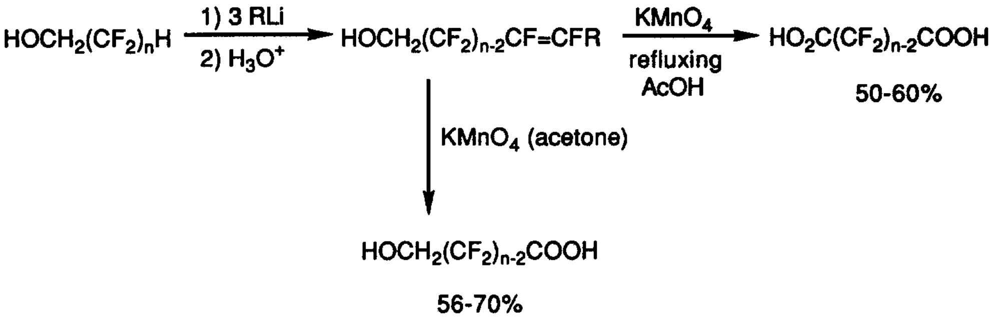
$$R_FCF_2CF_2H + R_2NLi \xrightarrow[-10°C]{Et_2O} [R_FCF_2CF_2Li]$$

$$[R_FCF_2CF_2Li] \xrightarrow{-LiF} [R_FCF{=}CF_2]$$

$$[R_FCF{=}CF_2] \xrightarrow{R_2NLi} R_FCF{=}CFNR_2$$

$$R_FCF{=}CFNR_2 \xrightarrow{H_3O^+} R_FCHFCONR_2$$

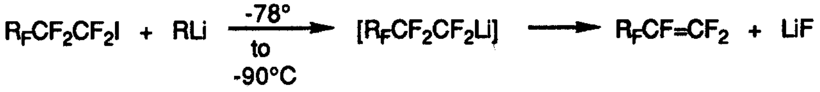
Perfluorocarboxylic acids have been prepared *via* a variant of the above procedure.[23]



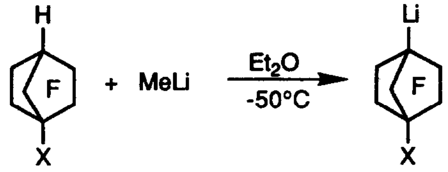
$$HOCH_2(CF_2)_nH \xrightarrow[2)\ H_3O^+]{1)\ 3\ RLi} HOCH_2(CF_2)_{n-2}CF{=}CFR \xrightarrow[\text{refluxing AcOH}]{KMnO_4} HO_2C(CF_2)_{n-2}COOH \quad 50\text{-}60\%$$

$$HOCH_2(CF_2)_{n-2}CF{=}CFR \xrightarrow{KMnO_4\ (acetone)} HOCH_2(CF_2)_{n-2}COOH \quad 56\text{-}70\%$$

Perfluoroalkyllithium reagents are thermally unstable in solution. Perfluoroheptyl and perfluoropropyl lithium are stable in ether at -90°C and decompose very rapidly at -75°C.[10b] Secondary perfluoroalkyllithiums are less stable than the corresponding primary perfluoroalkyllithiums.[11] A recent report indicates that the half-life of pentafluoroethyllithium at -78°C in diethyl ether was eight hours.[24] The instability of the perfluoroalkyllithium is ascribed to rapid β-elimination of lithium fluoride. This proposal is consistent with the greater stability of bridgehead perfluorobicyclolithium reagents relative to acyclic perfluoroalkyllithiums, since β-elimination would form high energy bridgehead alkenes or diradicals. Perfluorobicyclo[2.2.1]hept-1-yllithium and 4-hydroperfluorobicyclo[2.2.1]hept-1-yllithium decompose near room temperature, and 4-trifluoromethylperfluorobicyclo[2.2.1]hept-1-yllithium and perfluorobicyclo[2.2.2]oct-1-yl lithium decompose appreciably only under reflux conditions.[25-29]



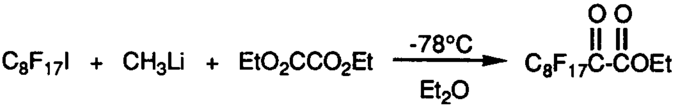
$$R_FCF_2CF_2I + RLi \xrightarrow[\text{to } -90°C]{-78°} [R_FCF_2CF_2Li] \longrightarrow R_FCF{=}CF_2 + LiF$$



X = H, F, CF_3

The perfluoroalkyllithium reagents undergo reactions typical of their hydrocarbon analogs, such as protonation, halogenation, carboxylation, silylation, and addition to aldehydes, ketones, and esters. The marked instability of perfluoroalkyllithiums and the difficulty of controlling the exothermicity of their reactions with electrophiles hamper their synthetic utility. For large scale reactions, addition of the hydrocarbon organolithium compound to the perfluoroalkyl iodide and the substrate in diethyl ether at -78°C to -90°C provides a simpler experimental procedure.[10b]

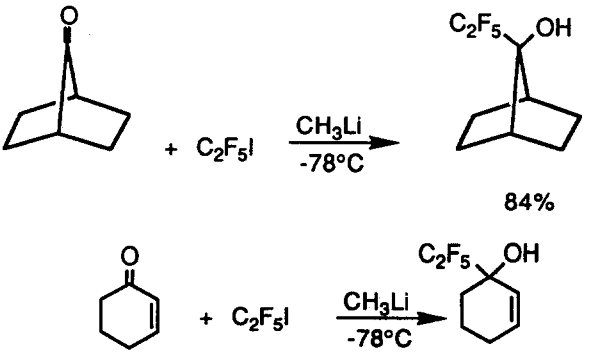
Tamborski utilized such an in situ generation-capture methodology for the reaction of long chain perfluoroalkyllithium reagents with diethyl carbonate and diethyl oxalate.[30]



$$C_8F_{17}I + CH_3Li + EtO_2CCO_2Et \xrightarrow[Et_2O]{-78°C} C_8F_{17}\overset{\overset{O}{\|}}{C}-\overset{\overset{O}{\|}}{C}OEt$$

84%

Subsequently, Gassman demonstrated that pentafluoroethyl iodide reacts with methyllithium at -78°C in the presence of aldehydes and ketones to produce the corresponding secondary and tertiary carbinols and with esters to produce either ketones or tertiary carbinols.[24] Only 1,2-addition was observed with α,β-unsaturated ketones. Temperature, heat dissipation, and reagent concentration were critical to the success of this reaction.



Uno and co-workers utilized similar methodology with longer chain perfluoroalkyl iodides to develop a useful route to perfluoroalkyl ketones.[31,32]

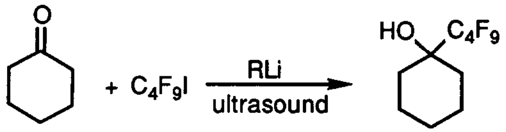
$$\mathrm{PhCH{=}CHCO_2Et} + \mathrm{R_FI} \xrightarrow[-78^\circ\mathrm{C}]{\mathrm{CH_3Li}} \mathrm{PhCH{=}CHCOR_F}$$

$$\mathrm{R_F} = \mathrm{C_4F_9},\ \mathrm{C_6F_{13}},\ \mathrm{C_8F_{17}} \qquad 83\text{-}93\%$$

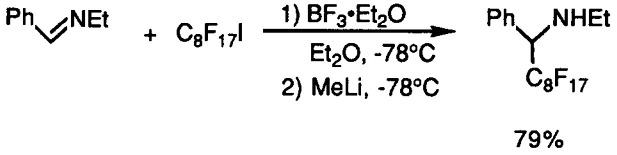
The capture of the perfluoroalkyllithium reagent by the ester can be combined with a sequential 1,4-addition of an organocopper reagent as outlined below:[32]

$$\mathrm{PhCH{=}CHCO_2CH_3} + \mathrm{C_8F_{17}I} \xrightarrow[\substack{\mathrm{Et_2O} \\ -78^\circ\mathrm{C\ to\ rt}}]{\mathrm{MeCu,\ MeLi}} \mathrm{PhCH(Me)CH_2COC_8F_{17}} \quad 75\%$$

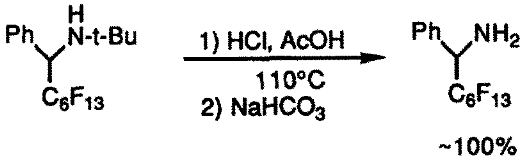
Keese used similar methodology with sonication to add perfluoroalkyllithiums to aldehydes and ketones.[33]



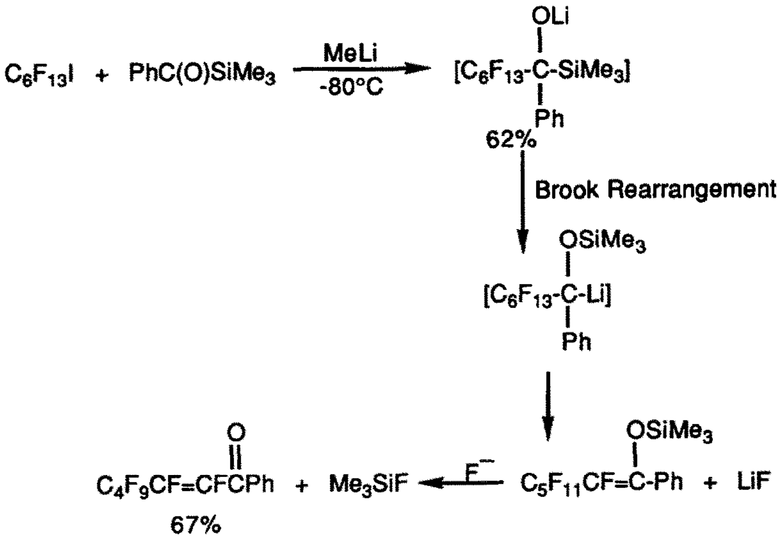
Uno and co-workers also found that perfluoroalkyllithiums react with imines in the presence of boron trifluoride to give secondary amines.[34]



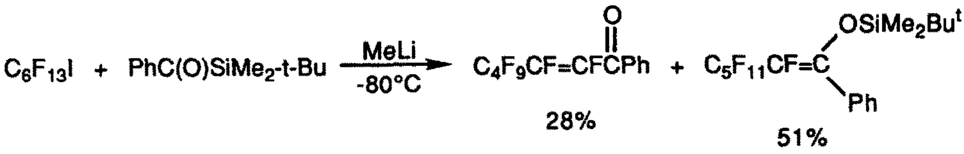
The t-butyl analogs are readily hydrolyzed.



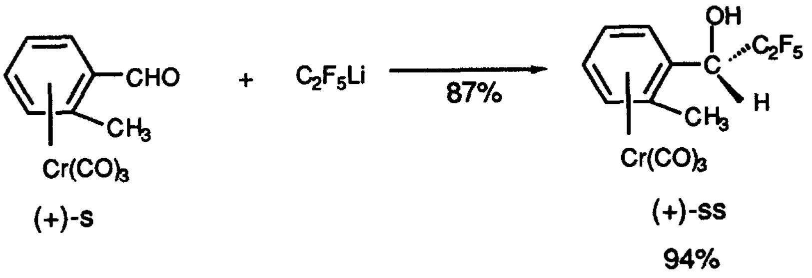
An interesting variation of this *in situ* generation-capture methodology was reported by Pontella. Reaction of benzoyltrimethylsilane and perfluorohexyl iodide with methyllithium in diethyl ether at -80°C gave a fluorinated enone (after hydrolysis). The authors propose that the initial lithium addition product undergoes a Brook rearrangement followed by β-elimination of lithium fluoride as outlined below:[35]



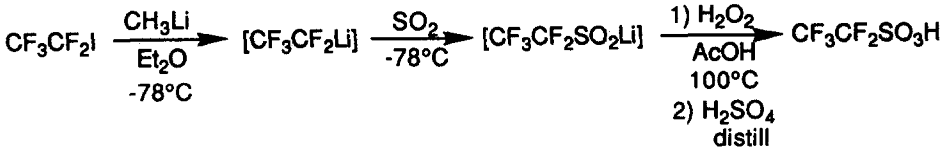
When benzoyl-t-butyldimethylsilane is utilized, the silyl enol ether as well as the enone is formed under the same conditions.



Perfluoroalkyllithiums[36,37,38] or 1,1-dichlorotrifluoroethyllithium[39] readily react with the chromiumtricarbonyl complexes of benzaldehydes. The lithium reagents attack the carbonyl in the direction of the least steric hindrance to produce carbinols in good yields with high asymmetric induction.[38]

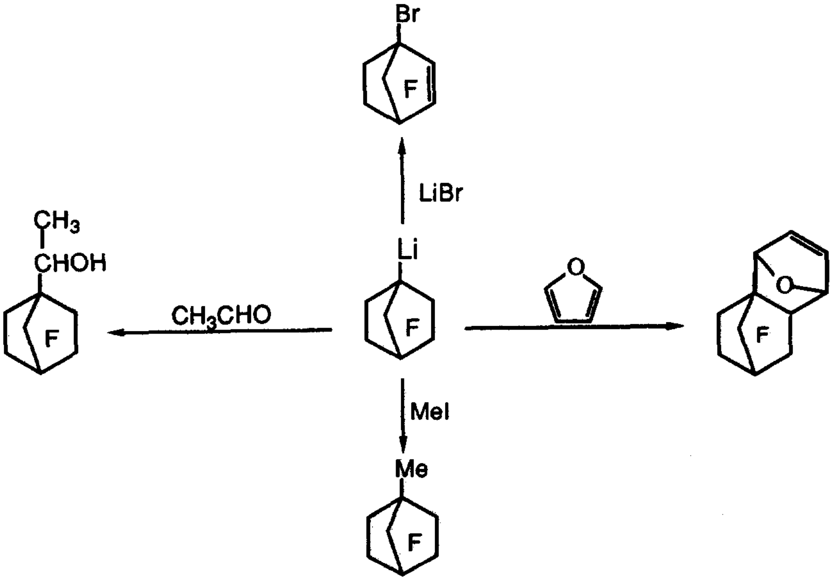


Pentafluoroethyllithium reacts with sulfur dioxide at -78°C to yield lithium pentafluoroethanesulfinate. Oxidation and acidification give a high yield of pentafluoroethanesulfonic (Pentflic) acid.[40] Extension of this procedure to the preparation of homologous perfluoroalkanesulfinates and trifluoromethanesulfinate was unsuccessful.



$$CF_3CF_2I \xrightarrow[\substack{Et_2O \\ -78^\circ C}]{CH_3Li} [CF_3CF_2Li] \xrightarrow[-78^\circ C]{SO_2} [CF_3CF_2SO_2Li] \xrightarrow[\substack{AcOH \\ 100^\circ C \\ 2)\ H_2SO_4 \\ \text{distill}}]{1)\ H_2O_2} CF_3CF_2SO_3H$$

Pregenerated stable perfluorobicyclo[2.2.1]hept-1-yllithium compounds can be used in the synthesis of fluorinated bicyclic compounds.[19,25-28]



II. Perfluoroalkyl Magnesium Reagents:

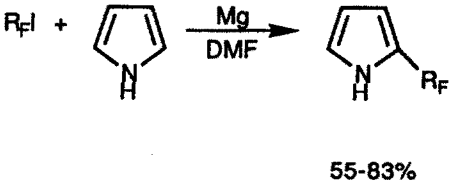
In contrast to the difficulty encountered in the direct reaction of perfluoroalkyl iodides with lithium metal, perfluoroalkylmagnesium reagents can be prepared directly in 40-60% yields by the reaction of perfluoroalkyl iodides with magnesium metal.[41-45] The preparation of perfluoroalkyl Grignard reagents is more sensitive to traces of impurities in the magnesium than are their hydrocarbon analogs, but smooth Grignard reagent formation occurs when spectroscopically pure magnesium, or magnesium that is substantially free from traces of metals such as cobalt, iron, nickel, or manganese is used.[43] The solvent and concentration play important roles in the formation of the perfluoroalkyl Grignard reagents. Although diethyl ether and di-n-butyl ether have been used, improved results were obtained with THF and with tertiary amines. The magnesium reagent is produced in higher yield and is stable at much higher temperatures. In poor coordinating solvents, such as benzene or cyclohexane, no Grignard reagent is formed. The use of concentrated solutions of the perfluoroalkyl iodide causes appreciable side reactions yielding reduction products and polymeric material. The Grignard reagent is much more stable in dilute solution.[43]

$$R_FI + Mg \longrightarrow [R_FMgI]$$

One of the main differences between fluoroalkyl and normal Grignard reagents is the temperature instability of the former. They must be prepared and used at low temperatures (-50 to 0°C). Above 20°C decomposition is rapid, to give the reduced perfluoroalkane (R_FH) or a fluoroolefin *via* β-elimination.[43] Consequently, it has often been found convenient to have the trapping compound (e.g. CO_2 or a carbonyl compound) present throughout the reaction (Barbier conditions) in order to capture the Grignard reagent as it is formed.[43]

$$CF_3CF_2CF_2I + Mg + CO_2 \xrightarrow[Bu_2O]{1)\ -30\ \text{to}\ -10°C} \underset{77\%}{CF_3CF_2CF_2COOH}$$
$$2)\ H^+$$

The role of the solvent in perfluoroalkyl iodide/magnesium reactions has recently been re-examined by Chen and co-workers.[46] In DMF, the perfluoroalkyl radical formed can be regioselectively captured by pyrrole, providing a useful synthesis of 2-fluoroalkylpyrroles. In acetic anhydride or THF, only 1-hydroperfluoroalkane (R_FH) was obtained. Inhibition and trapping experiments support an SET mechanism for the 2-fluoroalkylpyrrole formation.



These same workers discovered that magnesium catalyzed the radical addition of perfluoroalkyl iodides to alkenes or alkynes in DMF, CH_3CN or acetone.[47]

$$R_FI + RCH{=}CH_2 \xrightarrow{Mg} R_FCH_2CHIR$$

58-92%

$$R_FI + HC{\equiv}CR \xrightarrow{Mg} RCI{=}CHR_F \ (E/Z)$$

76-91%

Similar to the perfluoroalkyllithium reagents, the most difficult perfluoroalkyl Grignard reagent to prepare is the trifluoromethyl analog. Initiation of the reaction between CF_3I and magnesium is more difficult than with the longer chain analogs. Decomposition gives mainly polymers and tetrafluoroethylene. However, the trifluoromethyl Grignard reagent has been prepared from either CF_3I[48] or CF_3Br[49] at low temperatures in the presence of a trapping agent. Trifluoromethyl adducts have been isolated, but in low yields. Thus, the trifluoromethyl Grignard reagent can be formed and captured; however the difficulties associated with this reaction have precluded any practical utility.

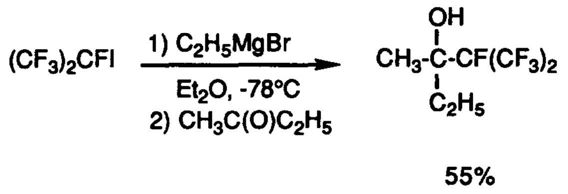
$$CF_3I + Mg + CH_3C(O)CH_3 \xrightarrow[Et_2O]{-65°C} CF_3C(OH)(CH_3)_2$$

14%

The difficulties associated with the direct reaction of perfluoroalkyl iodides with magnesium at low temperatures forced workers in this area to develop an alternative methodology for the preparation of these reagents. McBee and co-workers developed an exchange route to these reagents *via* reaction of the perfluoroalkyl iodide and phenylmagnesium bromide.[50,51] This exchange was shown to be rapid and quantitative even at Dry Ice temperatures. Since the exchange occurred at low temperatures, the perfluoroalkyl Grignard reagent

$$C_3F_7I + C_6H_5MgBr \xrightarrow[Et_2O]{-78°C} [C_3F_7MgBr] + C_6H_5I$$

produced was stable at these temperatures and pregeneration of the reagent could be accomplished. This development was the key to further applications of these reagents and was general for all perfluoroalkyl iodides except trifluoromethyl iodide. Later work demonstrated that alkyllithium reagents functioned equally well in the exchange process. The choice of the hydrocarbon Grignard reagent for the exchange reaction is dictated by the ease of separation of the RI or ArI from the subsequent functionalized product.[52] Chambers utilized this methodology for the preparation of the perfluoroisopropyl Grignard reagent.[11]



$$(CF_3)_2CFI \xrightarrow[\substack{Et_2O,\ -78°C \\ 2)\ CH_3C(O)C_2H_5}]{1)\ C_2H_5MgBr} CH_3\text{-}C(OH)(C_2H_5)\text{-}CF(CF_3)_2$$

55%

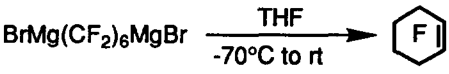
Unlike α,ω-dilithioperfluoroalkanes, the bis magnesium reagents can be readily prepared in quantitative yield by exchange reactions of α,ω-dihaloperfluoroalkanes.[52,53]

$$Br(CF_2)_6Br \ + \ 2\ EtMgBr \xrightarrow[-70°C]{THF} BrMg(CF_2)_6MgBr$$

$$I(CF_2)_nI \ + \ 2\ RMgBr \xrightarrow[-70°C]{Et_2O} BrMg(CF_2)_nMgBr$$

$n = 3,8 \qquad R = Et,\ Ph$

The 1,6-dibromododecafluorohexane exhibits peculiar behavior in the exchange reaction when phenylmagnesium bromide (2 mol) is used in THF. The main exchanged product is the mono Grignard reagent, $Br(CF_2)_6MgBr$. Excess phenyl magnesium bromide does not cause the reaction to proceed to the bis-Grignard reagent. However, when ethyl magnesium bromide (2 mol) is employed, the exchange is quantitative to form the bis-Grignard reagent. Decomposition of the bis-Grignard reagent does not yield a perfluorodiene but gives perfluorocyclohexene in excellent yield, presumably *via* decomposition to $F_2C{=}CF(CF_2)_4MgBr$ followed by intramolecular attack of the Grignard reagent on the perfluoroolefinic group.[53]



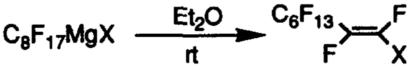
Detailed investigations by Tamborski and co-workers provided more insight into the parameters which control the success in using perfluoroalkyl Grignard reagents.[54] These workers found that the thermal stability of $C_8F_{17}MgBr$ is a function of time, temperature and solvent. This Grignard reagent was more stable in diethyl ether than in THF. For example, after 20 hours at -70°C in ether, perfluorooctylmagnesium bromide had only undergone 3% decomposition, but in THF under the same conditions, 41% of the Grignard reagent had decomposed. Temperature is also critical with these reagents. At -40°C, 39% and 86% of the perfluorooctyl magnesium bromide decomposed in ether and THF, respectively. The decomposition products are dependent on the solvent used. In THF solution, the perfluoroalkyl magnesium reagents undergo β-elimination to form perfluoroalkenes.[55,56] However, in diethyl ether or pentane, an unusual and remarkable decomposition

$$R_FCF_2CF_2I + PhMgBr \xrightarrow[\text{rt to 60°C}]{\text{THF}} R_FCF{=}CF_2$$

95%

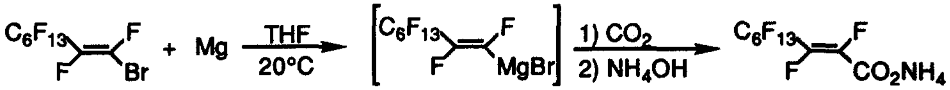
$R_F = C_4F_9, C_5F_{11}, C_6F_{13}$

reaction occurs to give the trans-perfluorovinyl halide as the major product.[54,55,57,58,59] Although several mechanistic rationales have been proposed to explain this unusual decomposition, no satisfactory explanation currently exists.[55,59]



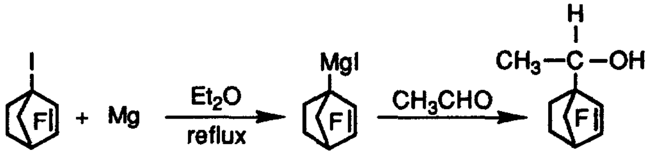
50-60% (X = Cl, Br)
20-30% (X = I)

The trans-perfluorovinyl bromides have been utilized as a synthetic entry to the perfluoro-α,β-unsaturated acids.[60]



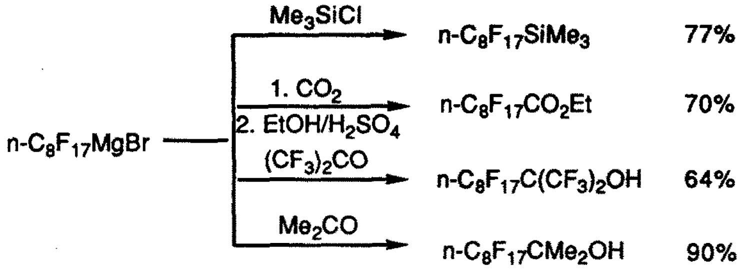
30%

Although perfluoroalkyl Grignard reagents are more thermally stable than the corresponding lithium reagents, they still exhibit low thermal stability. Most perfluoroalkylmagnesium halides rapidly decompose above -30°C. However, like the bridgehead lithium reagents, perfluorobridgehead magnesium reagents exhibit enhanced thermal stability. For example, 1-iodononafluorobicyclo[2.2.1]hept-2-ene gives the corresponding Grignard reagent *via* direct reaction with magnesium metal in "refluxing" ether.[26] Even after reflux in ether at 35°C, 60% of 1-hydrononafluorobicyclo[2.2.1]hept-2-ene was formed on quenching the Grignard reagent with dilute acid.



66%

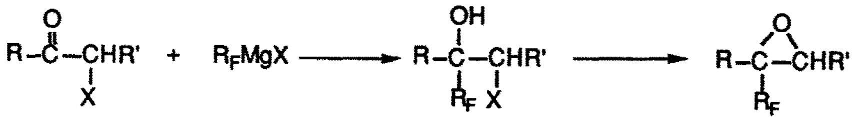
The perfluoroalkyl Grignards reagents participate in a wide variety of functionalization reactions. They react with trimethylsilyl chloride, carbon dioxide and carbonyl compounds at low temperature to give the corresponding perfluoroalkylated products in good yields.[54] With α,β-unsaturated aldehydes, the perfluoroalkylmagnesium bromides afford allylic alcohols as the sole products. No attack on the β-carbon



atom of the carbonyl is detected, even when the reaction is conducted in the presence of cuprous chloride.[59] When α-halocarbonyl compounds are utilized as substrates, diastereomeric halohydrins are obtained, which lead to perfluoroalkyl epoxides by a subsequent cyclization reaction.[61] The configuration of the epoxides may be determined by the value of the coupling constant value ($^4J_{H,F}$) between the epoxide proton and the fluorine of the perfluoroalkyl group.

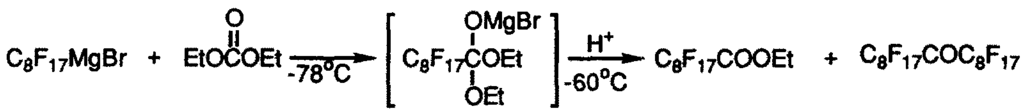
$$\mathrm{RCH{=}CHCHO} \quad + \quad \mathrm{R_FMgBr} \longrightarrow \mathrm{RCH{=}CHCH(OH)R_F}$$

$\mathrm{R_F = C_2F_5, C_6F_{13}, C_8F_{17}}$ 60-70%



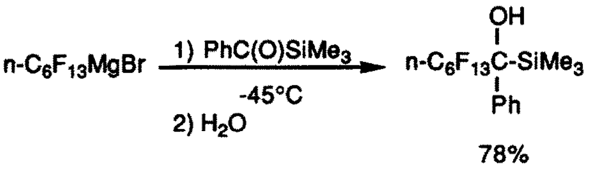
X = halogen

Tamborski has shown that esters of perfluoroalkyl acids can be readily synthesized by the reaction of perfluoroalkylmagnesium bromides with dialkyl carbonates.[30,62] Although ketones are usually obtained as byproducts in this reaction, low reaction temperatures afford almost quantitative yields of esters, due to stabilization of the salt of the hemiketal intermediate. For example, perfluorooctylmagnesium bromide reacts



with diethyl carbonate to give the ester in 96% yield. Only a trace of the ketone is detected at -78 to -60°C. With $FC(CF_3)_2OCF_2CF_2MgBr$, diethyl carbonate gives only the corresponding ester, and no ketone is observed even when excess Grignard reagent is used at -78°C.[30] Raising the temperature to 0°C over three hours gives significant amounts of ketone indicating that the intermediate hemiketal decomposes to give the ester, which then is attacked by a second equivalent of Grignard reagent. With diethyl oxalate, $(CF_3)_2CFOCF_2CF_2MgI$ gave 76% $(CF_3)_2CFOCF_2CF_2C(O)CO_2Et$.

Perfluorohexylmagnesium bromide was reported to give 78% of the alcohol addition product *via* reaction with benzoyltrimethylsilane in ether at -45°C.[35] If the intermediate adduct was allowed to warm to

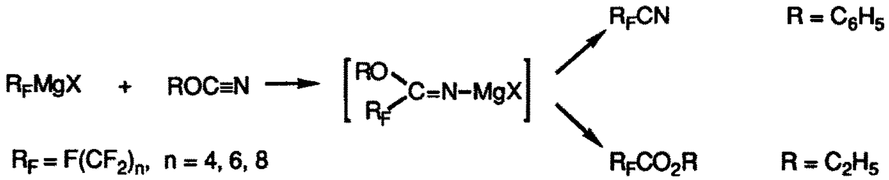


$$n\text{-}C_6F_{13}MgBr \xrightarrow[\substack{-45°C \\ 2)\ H_2O}]{1)\ PhC(O)SiMe_3} n\text{-}C_6F_{13}\overset{\overset{\displaystyle OH}{|}}{\underset{\underset{\displaystyle Ph}{|}}{C}}\text{-}SiMe_3 \quad 78\%$$

room temperature for several hours before hydrolysis, a Brook rearrangement occurred to give the enone, $C_4F_9CF{=}CFC(O)Ph$, in 86% yield in a reaction similar to that observed with the analogous perfluoroalkyllithium reagent.

Perfluoroalkylmagnesium bromide only attacks the sulfur atom of thiocyanates to give the perfluoroalkylated sulfides in good yields.[63] This observation is a striking contrast in behavior between a perfluoroalkylmagnesium halide and its hydrocarbon analog, which exclusively attacks the nitrile part of a thiocyanate. However, only products of attack on the nitrile group are obtained when perfluoroalkyl Grignard reagents react with cyanates.[64] Phenyl cyanate produces the perfluorinated nitrile. Ethyl cyanate, however, gives the corresponding ester. Perfluoroalkyl Grignard reagents have also been reported to react with N-sulfinimines to produce the fluorosulfinamides in good yields.[65]

$$CF_3(CF_2)_3MgBr \quad + \quad RSCN \longrightarrow RS(CF_2)_3CF_3 \quad + \quad MgBrCN$$



$$R_FMgCl \quad + \quad RNSO \xrightarrow[-35°C]{} R_FSONHR \quad 54\text{-}78\%$$

Perfluoroalkylsulfonyl chlorides have been prepared from reaction of perfluoroalkylmagnesium halides and sulfur dioxide, followed by treatment with chlorine.[66]

$$F(CF_2)_nMgBr + SO_2 \longrightarrow F(CF_2)_nSO_2MgBr \xrightarrow{Cl_2} F(CF_2)_nSO_2Cl$$

$$n = 4, 6, 8$$

2,2,2-Trifluorotrihaloethane and organomagnesium halides react with carbonyl substrates to give the carbinols in good to moderate yields at -70°C.[67] However, attempts to prepare the Grignard reagent with magnesium metal leads to the 2,2-difluorodihaloethene, which further reacts with magnesium to produce 2,2-difluoro-1-halomagnesium halide. Under Barbier conditions, a variety of aldehydes treated with three equivalents of CF_3CBr_2Cl and six equivalents of magnesium chips in THF give 1,1-difluoro-2-chloroethenylate alcohols in good yields.[68]

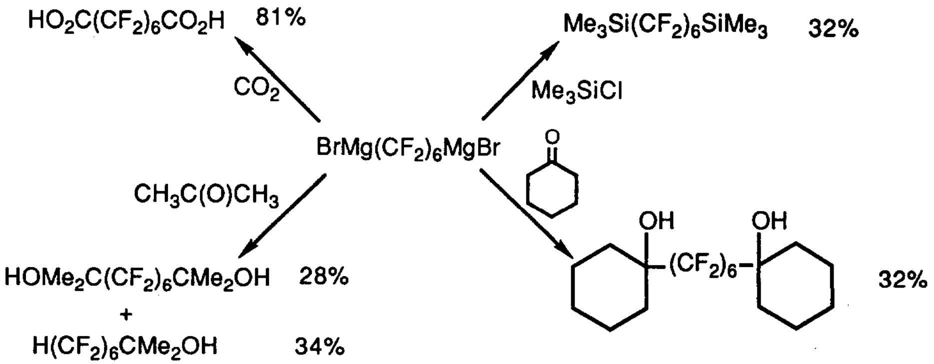
$$CF_3CXYMgBr + RR'C(O) \longrightarrow CF_3CXYC(OH)RR'$$

$$X = F, Cl, Br;\ Y = Cl, Br \qquad 19\text{-}81\%$$

$$3\ CF_3CBr_2Cl + 6\ Mg + RCHO \longrightarrow RCH(OH)CCl{=}CF_2$$

$$42\text{-}77\%$$

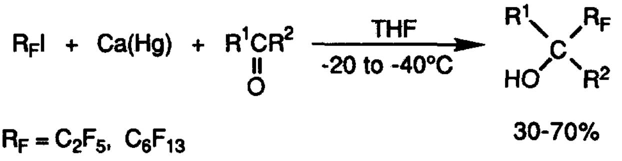
Perfluoroalkylene dimagnesium bromides have been employed to prepare perfluoro bis functionalized compounds. For example,1,6-di-(halomagnesium)perfluorohexane reacts with carbon dioxide, carbonyl substrates and trimethylsilyl chloride to afford the corresponding fluoroalkylated materials.[53]



III. Perfluoroalkyl Calcium Reagents:

Klabunde[69] reacted calcium metal with perfluoro-2-butene at -196°C (*via* co-deposition on a liquid nitrogen cooled surface). Subsequent warming of the reaction mixture to room temperature gave a low yield of perfluoro-2-butyne. No evidence of a stable perfluoroalkyl or alkenyl calcium compound was found. Under similar conditions, perfluoropropane and benzotrifluoride did not react, while perfluoropropene and perfluorocyclobutene gave only polymers.[69]

In an effort to circumvent the low thermal stability of the perfluoroalkyl Grignard reagents, Reiss and co-workers have utilized the reaction of perfluoroalkyl iodides with amalgamated calcium to prepare perfluoroalkyl carbinols.[70] When pure calcium metal was used, the reaction was extremely vigorous at room temperature after an induction period and gave large amounts of 1-hydroperfluoroalkane (R_FH). Dioxane and diethyl ether could also be utilized as solvents; triethylamine, ethylenediamine or tetramethylethylenediamine and benzene failed. The best yields were obtained under Barbier conditions.[71]



Indirect evidence, such as acid quench of the reaction mixture to give R_FH and carbinol addition products, led these authors to propose the formation of a stable perfluoroalkylcalcium reagent. However, no further work on either characterization or applications of the reagent has appeared.

IV. Perfluoroalkyl Tin Reagents:

Although the thermal reaction of dibutyltin dihydride with tetrafluoroethylene was reported to give a fluorocarbon-tin compound, the first practical route to this class of compounds was reported by Clark and Willis, who reacted hexamethylditin with iodotrifluoromethane under pressure at 80°C with excess iodotrifluoromethane as solvent.[72] Later work by Stone[73] and Cullen[74] demonstrated that the reaction could be accomplished with ultraviolet light and other perfluoroalkyl iodides, such as C_2F_5I and $(CF_3)_2CFI$, could be employed. Tetraalkyltin compounds cannot be used in this reaction.[73]

$$(CH_3)_3Sn\text{-}Sn(CH_3)_3 + CF_3I \xrightarrow[\substack{\text{pressure} \\ \text{24 h}}]{80°C} (CH_3)_3SnCF_3 + (CH_3)_3SnI$$

The trifluoromethyl analog can be prepared *via* in situ formation and capture of trifluoromethide by trimethyltin chloride.[75,76]

$$\begin{tikzcd}
\mathrm{Ph_3P} + \mathrm{CF_2Br_2} \arrow[r] & {[\mathrm{Ph_3\overset{+}{P}CF_2Br}]\mathrm{Br}^-} \arrow[d, "\mathrm{(CH_3)_3SnCl}", "\mathrm{KF}"'] \\
 & \mathrm{(CH_3)_3SnCF_3} \\[-20pt]
 & 37\text{-}40\%
\end{tikzcd}$$

Trialkylperfluoroalkyl tin derivatives are also prepared by metathesis of trimethyltin nitrate with bis(trifluoromethyl)cadmium[77] or trialkyltin halides with perfluoroalkyllithium and magnesium reagents.[78]

$$\mathrm{(CH_3)_3Sn(ONO_2)} + \mathrm{(R_F)_2Cd{\bullet}D} \xrightarrow[\mathrm{CH_3CN}]{75°\mathrm{C}} \mathrm{(CH_3)_3SnR_F} + \mathrm{R_FCdONO_2{\bullet}D}$$

$R_F = C_2F_5$, $i\text{-}C_3F_7$

D = diglyme

The difluoromethyl analog has been prepared by insertion of difluorocarbene into the corresponding tin hydride.[74]

$$\mathrm{(CH_3)_3SnH} + \mathrm{(CH_3)_3SnCF_3} \xrightarrow{150°\mathrm{C}} \underset{63\%}{\mathrm{(CH_3)_3SnCF_2H}} + \mathrm{(CH_3)_3SnF}$$

A similar insertion route with hexafluoro-2-diazopropane gave the hexafluoroisopropyl analog.[79]

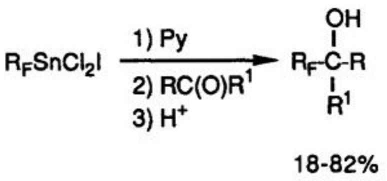
$$\mathrm{(CH_3)_3SnH} + \mathrm{(CF_3)_2CN_2} \longrightarrow \underset{51\%}{\mathrm{(CH_3)_3SnCH(CF_3)_2}}$$

Oxidative addition of perfluoroalkyl iodides to tin (II) halides in DMF gives perfluoroalkyltin halides.[80] The perfluoroalkyltin (IV) dihaloiodide could not be isolated, but in DMF solution, the tin (IV) compound

$$\mathrm{R_FI} + \mathrm{SnX_2} \xrightarrow[\mathrm{RT}]{\mathrm{DMF}} \mathrm{R_FSnX_2I}$$

$X = F,\ Cl;\ R_F = CF_3,\ (CF_3)_2CF,\ CF_3(CF_2)_5$

could be utilized in a pyridine-promoted reaction with aldehydes and ketones to produce perfluoroalkyl carbinols. The reactions work well except when $R_F = CF_3$ (18%) and when X≠F in the tin (IV) precursor.[80]



$$R_FSnCl_2I \xrightarrow[\substack{2)\ RC(O)R^1 \\ 3)\ H^+}]{1)\ Py} R_F\text{-}C(OH)(R^1)\text{-}R$$

18-82%

Morrison has used ligand-exchange reactions of tin halides with bis(trifluoromethyl) mercury to prepare perfluoroalkyltin halides. Mono and bis perfluoroalkyl tin analogs have been prepared, but more fully substituted species, such as $(CF_3)_3SnBr$, rapidly decomposed under the reaction conditions.[81] Subsequently, Morrison utilized bis (trifluoromethyl)cadmium reagents to accomplish the ligand exchange. More highly substituted analogs could be prepared due to the lower temperatures and shorter reaction times used in this route.[82,83] Tetrakis(trifluoromethyl)tin, $Sn(CF_3)_4$, has also been prepared by the reaction of tin (IV) iodide with trifluoromethyl radicals in a radio-frequency discharge.[84]

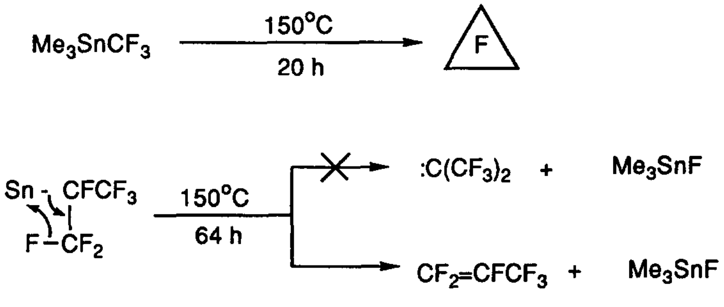
$$(CF_3)_2Hg + SnBr_4 \xrightarrow[42\ h]{112°C} CF_3SnBr_3 + (CF_3)_2SnBr_2$$

46% 3%

$$(CF_3)_2Cd{\bullet}glyme + SnBr_4 \xrightarrow[2\ h]{rt} (CF_3)_4Sn + (CF_3)_3SnBr + CF_3SnBr_3$$

66% 5% 10%

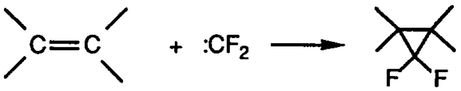
Trimethyl(trifluoromethyl)tin is stable at room temperature. Heating trimethyl(trifluoromethyl)tin at 150°C in a sealed tube in the absence of air for 20 hours converted 90% of the tin reagent quantitatively to perfluorocyclopropane.[72] This finding implies that difluorocarbene is an intermediate. However, trimethylpentafluoroethyltin resists decomposition when heated at 200°C either alone or in the presence of cyclohexene. After 72 hours, only small amounts of pentafluoroethane are detected, and 91% of the tin reagent recovered. This reaction suggests that the pentafluoroethyltin reagent thermally decomposes by homolytic fission of the Sn-C bond rather than by either α- or β-fluorine elimination.[74] Although heptafluoroisopropyltrimethyltin decomposes at 150°C (64 h), no fluorocarbene transfer products are observed in the presence of carbene trapping compounds. Only hexafluoropropene is detected. It has been suggested that decomposition of perfluoroisopropyltin takes place *via* a β- rather than an α-elimination process.[74]



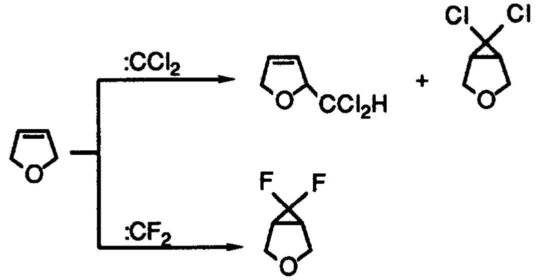
Seyferth and co-workers have found that trimethyl(trifluoromethyl)tin can be utilized as a source of difluorocarbene under mild conditions. In the presence of sodium iodide, trimethyl(trifluoromethyl)tin reacts with cyclohexene to produce 7,7-difluoronorcarane in 73% yield at 80°C. It was proposed that the mechanism of the carbene transfer proceeded *via* the trifluoromethyl anion, followed by decomposition to form difluorocarbene. The carbene adds to a variety of monoalkyl, dialkyl, trialkyl and tetraalkyl substituted alkenes to give good to excellent yields of the difluorocyclopropanes.[85]

$$Me_3SnCF_3 + NaI \longrightarrow NaCF_3 + Me_3SnI$$

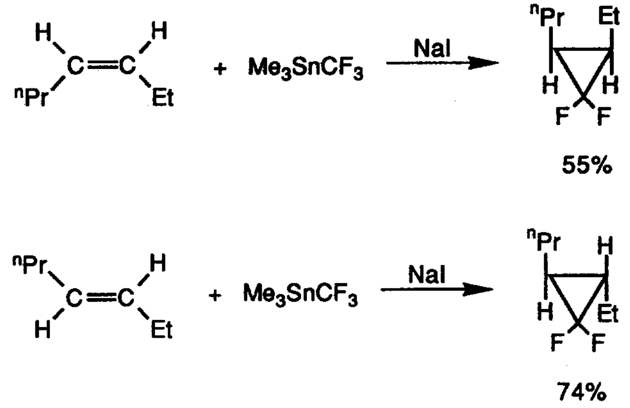
$$NaCF_3 \longrightarrow :CF_2 + NaF$$

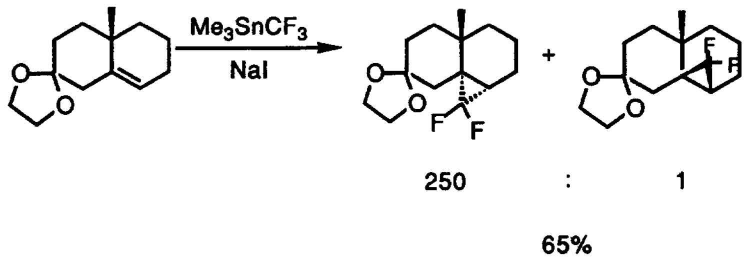


The reaction of the Me_3SnCF_3/NaI reagent with 2,5-dihydrofuran differs from the corresponding reaction of this olefin with dichlorocarbene formed from a variety of precursors. The reaction with 2,5-dihydrofuran gives only the olefin addition product with difluorocarbene, while dichlorocarbene provides both C-H bond insertion and addition products. With cis and trans-2-butene, the difluorocyclopropane compounds are formed



stereospecifically. Deactivated olefins, such as vinyl acetate and vinyl silanes, gave moderate yields (20-50%) of the cyclopropane products.[86] Highly deactivated olefins, such as trichloro- or tetrachloroethylene failed to add [:CF_2]. Moss has utilized this procedure to study difluorocarbene selectivity with model steroidal olefins.[87]





Pyrolysis of trimethyl(trifluoromethyl)tin has been employed as a difluorocarbene precursor for addition to perfluoroalkynyl derivatives of germanium and tin.[88] This pyrolysis route can also be utilized for difluorocarbene addition to olefins and alkynes, but the high temperatures required (150°C) make this route less attractive than the Me_3SnCF_3/NaI reaction at 80°C.

$R = CH_3$; $M = Ge, Sn$; $R_F = CF_3, C_2F_5, CF(CF_3)_2$; $n = 2,3$

V. Perfluoroalkyl Lead Reagents:

Thermal or photochemical reaction of tetraalkyllead compounds with perfluoroalkyl iodides has been reported to give trialkylperfluoroalkyllead, but only details for the preparation of trimethylpentafluoroethyllead are available.[73] The exchange reaction of trimethyllead(trifluoroacetate) with bis(perfluoroalkyl)cadmium gives the corresponding trimethyl(perfluoroalkyl)lead in good yields.[89] Synthesis of tetrakis(trifluoromethyl)lead has been achieved by a radio frequency discharge reaction between hexafluoroethane and lead (II) chloride.[90] In the presence of carbonyl substrates, the reaction of trichlorotrifluoroethane with lead affords 1,1-difluoro-2-chloroethenyl carbinols, presumably involving fluorinated organolead intermediates.[91]

$$(CH_3)_4Pb + C_2F_5I \xrightarrow[150°C]{} \underset{28\%}{(CH_3)_3PbC_2F_5}$$

$$CF_3CCl_3 + RCHO + Pb \longrightarrow RCH(OH)CCl{=}CF_2$$

VI. Perfluoroalkyl Zinc Reagents:

The reaction of perfluoroalkyl iodides with zinc in ethereal solvents affords solvated perfluoroalkylzinc compounds.[92,93] The yield of the zinc reagent is dependent on the reaction temperature and concentration of the zinc reagent. In the case of perfluoropropylzinc iodide, the maximum yield occurs in dioxane near 0°C and in dilute solution with an iodide-solvent ratio of at least 1:5. At higher temperatures, the yield of the dimerized product, perfluoro-n-hexane, increases. The solvated organozinc compound containing one mole of dioxane can be converted into the pure heptafluoropropylzinc iodide by vacuum sublimation. Heating of the unsolvated

$$n\text{-}C_3F_7I + Zn \xrightarrow{\text{dioxane}} \underset{50\text{-}75\%}{n\text{-}C_3F_7ZnI} \xrightarrow{180°C} F_2C{=}CFCF_3$$

heptafluoropropylzinc iodide gives hexafluoropropene. Perfluoroisopropylzinc iodide can be similarly prepared from perfluoroisopropyl iodide and zinc in dioxane.[94] Perfluoro-n-pentyl iodide behaved similarly, but trifluoroiodomethane failed to give detectable quantities of the organozinc compound under these conditions.[93] Peroxide-free solvents are required, otherwise significant amounts of 1-hydroperfluoroalkane (R_FH) is produced. If dilute solutions were not employed, the amount of dimerized product [$(R_F)_2$] increased. The perfluoroalkylzinc reagents do not readily react with carbonyl substrates, carbon dioxide, or oxygen.

Tarrant has reported the cross-coupling of primary chlorofluorocarbon iodides in ethyl acetate-methylene chloride mixed solvent as a route to α,ω-perfluorodiene precursors.[95,96] Similar couplings had been reported in acetic anhydride-methylene chloride mixed solvent system by Henne.[97] These cross-coupling reactions give

$$CF_2ClCFClI + Zn \xrightarrow[CH_2Cl_2]{Ac_2O} \underset{51\%}{CF_2ClCFClCFClCF_2Cl}$$

$$CF_2ClCFClI + CF_2ClCFClCF_2CFClI \xrightarrow[Ac_2O,\ CH_2Cl_2]{Zn} \underset{46\%}{CF_2ClCFClCFClCF_2CFClCF_2Cl} + \text{others}$$

mixtures, which seriously restricts the utility of this reaction.[98] Reaction of 1,2-dihaloperfluoroalkanes with zinc gives only the α,β-elimination product, perfluoroalkenes.[99]

The importance of solvent effects in the formation of perfluoroalkylzinc reagents is further illustrated by the reaction of perfluoroalkyl iodides with zinc-copper couple in DMSO, DMF or HMPA. In these solvents, the main product is the fluoroolefin.[100] Potassium thiocyanate was reported to facilitate olefin formation.

$$C_nF_{2n+1}I \xrightarrow[KSCN\ \ DMSO]{Zn/Cu} \underset{80\%}{C_nF_{2n}\text{ isomers}} + C_nF_{2n+1}H$$

Mixtures of isomeric olefins were obtained in all cases. When the reactions in DMF or DMSO were carried out in the presence of an organic halide, the reaction took an alternative course and gave either 1-hydroperfluoroalkane, perfluoroalkylzinc reagents or alkylated products depending on the organic halide utilized.[101]

$$3\,CH_2Br_2 \xrightarrow[\substack{Zn/Cu\\ DMSO\\ 20°C}]{C_6F_{13}I} \underset{50\%}{C_6F_{13}CH_2CH_2I} + \underset{20\%}{C_{12}F_{26}} + \underset{30\%}{C_6F_{13}H}$$

Solvated perfluoroalkylzinc reagents are also prepared by the reaction of perfluoroalkyl iodides with dialkylzincs in a Lewis base solvent. Reaction of trifluoromethyl iodide with dialkylzincs gives bis(trifluoromethyl)zinc quantitatively. However, pentafluoroethyl and heptafluoropropyl iodides do not yield pure compounds.[102]

$$R_FI + R_2Zn \longrightarrow (R_F)_2Zn + RI$$

$$R_F = CF_3, C_2F_5, i\text{-}C_3F_7, C_6F_5$$

Trifluoromethylzinc reagent has also been prepared from dihalodifluoromethane and zinc in DMF by Burton and Wiemers.[103] In this remarkable reaction, DMF functions both as a solvent and reactant. Inhibition and trapping experiments support an SET mechanism to produce difluorocarbene, which on

$$Zn + CF_2X_2 \xrightarrow[RT]{DMF} CF_3ZnX + (CF_3)_2Zn$$

$$X = Br, Cl \qquad\qquad 80\text{-}85\%$$

further reaction with fluoride formed by reaction of difluorocarbene with DMF, eventually leads to the trifluoromethylzinc reagent.

$$Zn + CF_2XY \longrightarrow Zn^{+} + [CF_2X_2]^{\dot{-}}$$

$$[CF_2X_2]^{\dot{-}} + Zn^{+} \longrightarrow Zn^{+2} + [CF_2X]^{-} + X^{-}$$

$$[CF_2X]^{-} \rightleftharpoons [:CF_2] + X^{-}$$

$$[:CF_2] + Me_2NCHO \longrightarrow Me_2NCF_2H + CO$$

$$Me_2NCF_2H + [:CF_2] \longrightarrow [CF_3]^{-} + [Me_2\overset{+}{N}{=}CFH]$$

$$[CF_3]^{-} + [ZnX]^{+} \longrightarrow CF_3ZnX$$

Zinc and difluorodibromomethane in THF have been utilized as a difluorocarbene source for the synthesis of gem-difluorocyclopropane derivatives.[104]

Non-solvated trifluoromethylzinc iodide has been prepared by Klabunde *via* the reaction of zinc atoms with trifluoromethyl iodide. This non-solvated zinc reagent decomposed at temperatures above -80°C, indicative of the high reactivity and low stability of non-solvated zinc reagents compared to the perfluoroalkylzinc reagents prepared in solution.[105]

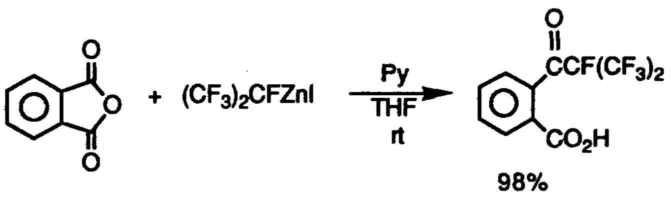
Ligand exchange reactions have also been utilized in the preparation of perfluoralkylzinc reagents. Solvated trifluoromethyl zinc compounds have been synthesized from the reaction of dialkylzincs with bis(trifluoromethyl)mercury or bis(trifluoromethyl) cadmium in DMF or pyridine. Mixed alkylperfluoroalkylzincs were prepared using different reactant ratios.[106,107]

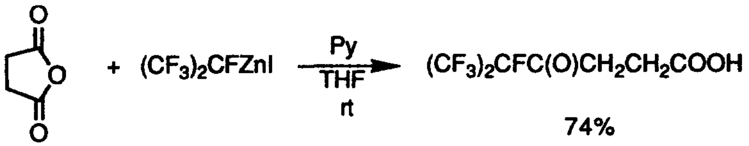
$$(CH_3)_2Zn + (CF_3)_2M \xrightarrow{\text{solvent}} (CF_3)_2Zn{\bullet}Solv + (CH_3)_2M$$

$$M = Cd,\ Hg$$

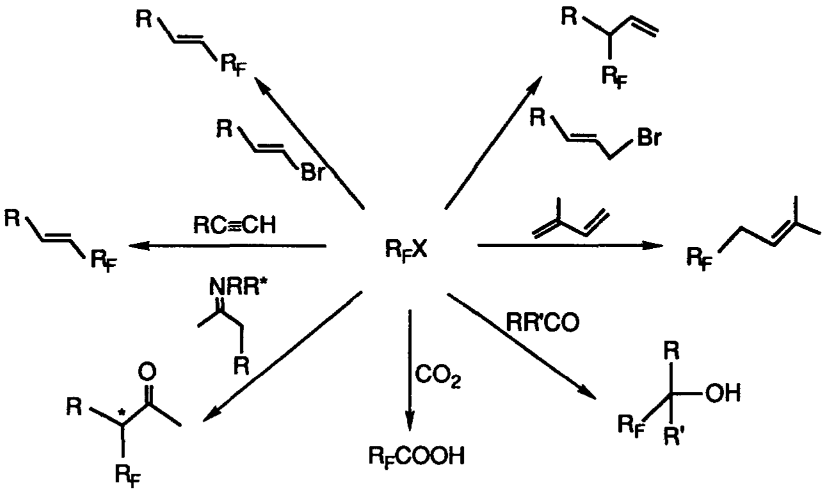
Generally, solvated perfluoroalkylzinc reagents are too stable to be of synthetic value. Solutions of heptafluoropropylzinc iodide in dioxane do not react with aldehydes, ketones and non-fluorinated acyl chlorides, and give only low yields of perfluoroalkyl ketones with perfluoroacyl chlorides.[93] Ishikawa, however, has demonstrated that in the presence of pyridine, acylation of perfluoroisopropyl zinc iodide with benzoyl fluoride or chloride gives the corresponding perfluoroisopropyl ketone.[108] Aliphatic acyl fluorides and chlorides gave perfluoroisopropyl ketones in lower yields than the aroyl halides. With benzoyl chloride, an equimolar amount of zinc fluoride (ZnF_2) was added to convert the benzoyl chloride in situ to benzoyl fluoride to give the ketone in 89% yield. Triethylamine, N-methylpiperidine, and N,N-dimethylaniline did not catalyze the reaction. n-Heptafluoropropylzinc iodide gave no reaction under these conditions. Phthalic anhydride and succinic anhydride were successfully acylated with perfluoroisopropylzinc iodide.[108]

$$PhC(O)F + (CF_3)_2CFZnI \xrightarrow[\substack{THF \\ rt}]{Py} \underset{\sim 100\%}{PhC(O)CF(CF_3)_2} + ZnIX$$





With sonication, the reaction of perfluoroalkyl iodides with zinc under Barbier conditions has been utilized by Ishikawa to effect perfluoroalkylation of a variety of organic substrates.[109-112] Although detailed mechanistic studies were not carried out, these authors propose radical intermediates as the reactive species.

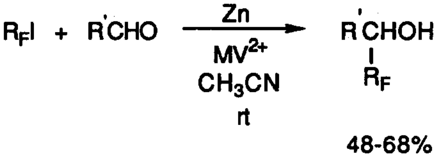


X = I, Br

Although the carbinols are obtained in only moderate yields when ketones are used as substrates, the yields could be improved by the utilization of a titanium(II) complex as catalyst. Ultrasound promotes the coupling reaction of perfluoroalkyl iodides with vinyl and allyl halides in the presence of zinc and palladium catalysts. Reaction of perfluoroalkyl halides with alkynes or dienes with copper salts or a titanium complex as a catalyst gives iodine-free perfluoroalkylated alkenes in constrast to SET or radical induced addition reactions. Perfluoroalkylation of chiral enamines, derived from S-proline and S-glutamic acid, results in moderate asymmetric induction. The product ketones have optical purities of 64-76%. Although palladium and nickel complexes were used as catalysts in these asymmetric induction perfluoroalkylations, the best catalyst was Cp_2TiCl_2.

Although ultrasound-promoted perfluoroalkylation provides a novel and unique approach to fluorinated compounds under mild conditions, this reaction has only been carried out on a small scale. This limitation may restrict further application of this procedure in organic synthesis.

In related work, the combination of zinc and methyl viologen (MV^{2+}) has been demonstrated to effectively serve as an electron mediator for the conversion of perfluoroalkyl iodides to α-perfluoroalkyl carbinols in a Barbier-type reaction.[113]

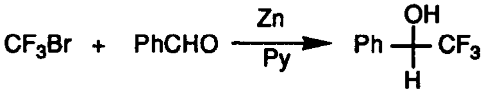


$$R_FI + R'CHO \xrightarrow[\substack{MV^{2+} \\ CH_3CN \\ rt}]{Zn} R'\underset{\substack{| \\ R_F}}{C}HOH$$

48-68%

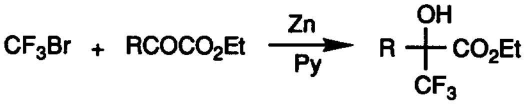
Perfluoroalkyl halides react with electrophiles in the presence of zinc under Barbier conditions. Trifluoromethyl bromide has been reported to react with aldehydes and zinc to give carbinols.[114-116] Addition of pyridine significantly facilitates the reaction and high yields of the alcohols are formed. Although ketones react sluggishly, carbinols can be obtained in reasonable yields with an α-keto ester.

Esters activated by an electron-withdrawing group and anhydrides also react with trifluoromethyl bromide and zinc to yield the trifluoromethyl ketone. However, ethyl benzoate and acetone induce the formation of trifluoromethylzinc reagents, which do not react with carbonyl compounds. It is proposed that the reaction involved nascent organometallics reacting near the zinc surface rather than the perfluoroalkylzinc compound.



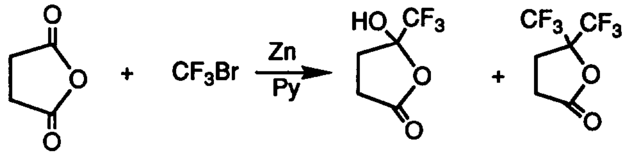
$$CF_3Br + PhCHO \xrightarrow[Py]{Zn} Ph\text{-}C(OH)(H)\text{-}CF_3$$

52%



$$CF_3Br + RCOCO_2Et \xrightarrow[Py]{Zn} R\text{-}C(OH)(CF_3)\text{-}CO_2Et$$

30-35%



18% 40%

$$RCO_2Et + CF_3Br \xrightarrow[Py]{Zn} RC(O)CF_3$$

$R = CO_2Et, CF_3$ 38-54%

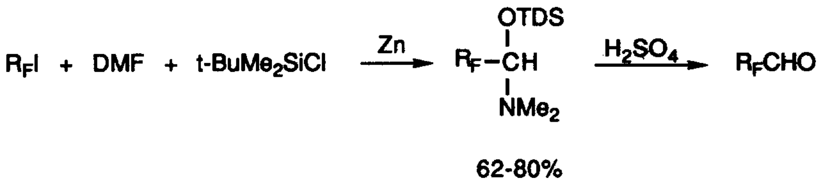
Perfluoroalkylation of aldehydes can be accomplished with perfluoroalkyl iodides and zinc catalyzed by palladium or nickel in DMF. Similar reactions with ketones, epoxides, acetals and acid chlorides were unsuccessful.[117]

$$R_FI + RCHO + Zn \xrightarrow{M(PPh_3)_2Cl_2} RCH(OH)R_F$$

$M = Pd, Ni$

$R_F = CF_3, C_2F_5, i\text{-}C_3F_7, C_4F_9, C_6F_{13}, C_8F_{17}$

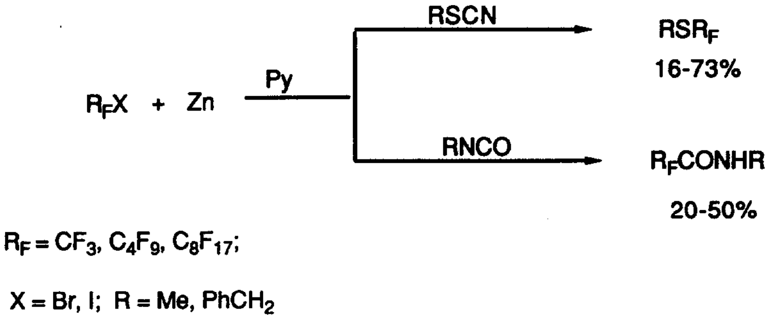
In the presence of a trialkylsilyl chloride, zinc mediated reaction of perfluoroalkyl halides with DMF, followed by hydrolysis with acid, yield perfluoroaldehydes.[118] Thiocyanates and isocyanates can also be



$$R_FI + DMF + t\text{-}BuMe_2SiCl \xrightarrow{Zn} R_F-\underset{NMe_2}{\overset{OTDS}{CH}} \xrightarrow{H_2SO_4} R_FCHO$$

62-80%

used as substrates to give perfluoroalkyl sulfides and perfluoroalkyl acetamides, respectively.[119]



In the presence of zinc, perfluoroalkyl iodides react with carbon tetrachloride or bromotrichloromethane in methylene chloride to give 1,1,1-trichloroperfluoroalkanes.[120]

$$R_FI + CCl_3X \xrightarrow[CH_2Cl_2]{Zn} R_FCCl_3$$

X = Cl, Br 30-50%

$R_F = C_4F_9,\ C_8F_{17}$

Reaction of trifluoromethyl bromide with sulfur dioxide and zinc leads to trifluoromethanesulfinate.[121] A perfluoroalkyl radical has been proposed as an intermediate, which can be trapped by enamines and electron-rich aromatics to form perfluoroalkylated products.[122] Oxidation leads to triflic acid. Radical addition of

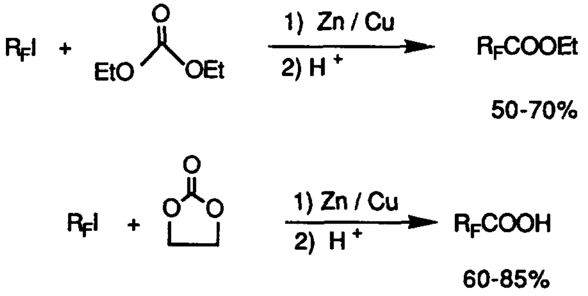
$$CF_3Br + Zn + SO_2 \xrightarrow[3\ atm.]{DMF} (CF_3SO_2)_2M \xrightarrow[\substack{2)\ H_2O_2 \\ 3)\ H_2SO_4}]{1)\ NaOH} CF_3SO_3H{\cdot}H_2O$$

perfluoroalkyl iodides to alkenes initiated by zinc has also been reported.[123]

$$R_FI + H_2C{=}CHR \xrightarrow{Zn} R_FCH_2CHIR$$

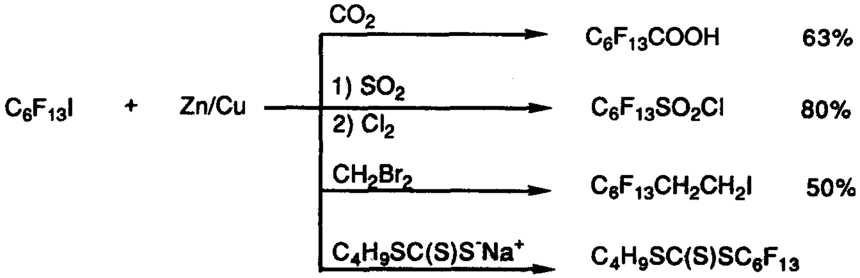
$$60\text{-}96\%$$

When the more active Zn-Cu couple is employed, the reaction of perfluoroalkyl iodides with alkyl carbonates and pyrocarbonates gives fluorocarboxylic esters and fluorocarboxylic acids, respectively.[124] Extension of this procedure for the preparation of phosphono-fluorinated compounds such as phosphinates, phosphine oxides, and phosphines *via* reaction with alkyl phosphites was also successful.[125] Chen has utilized zinc to induce the SET reaction of perfluoroalkyl iodides with pyrrole in DMSO or DMF to give 2- perfluoroalkyl pyrroles regioselectively.[126]



$$R_FI + PO(OR)_3 + Zn/Cu \xrightarrow{60^\circ C} (R_F)_2PO(OR)$$

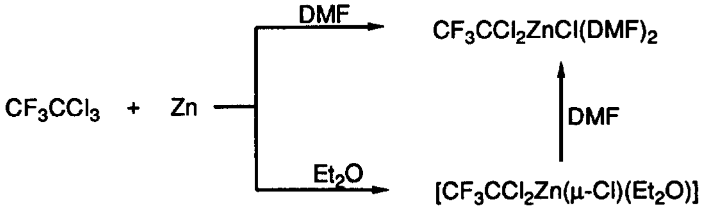
Reaction of perfluoroalkyl iodides with zinc-copper couple and carbon dioxide or sulfur dioxide in DMSO produces the corresponding perfluorocarboxylic acids and sulfonyl chlorides in 40-80% yield, respectively.[127] When dibromomethane is used as substrate, reaction of perfluoroalkyl iodides with Zn/Cu affords the double methylene inserted products in reasonable yields.[101] With sodium alkyl trithiocarbonate, the preparation of perfluoroalkyl alkyl thiocarbonates can be realized.[128]



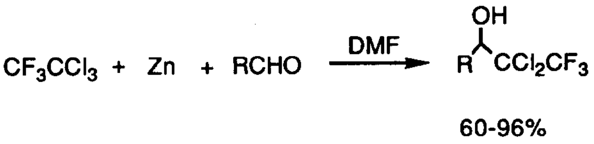
VII. 1,1-Dichlorotrifluoroethylzinc Chloride:

A fluorine-containing zinc reagent that has recently received significant attention is 1,1-dichlorotrifluoromethylzinc chloride because of its ease of preparation and utility in the synthesis of potentially industrially important products. Thus, this reagent and its application will be treated separately from perfluoroalkylzinc reagents.

This reagent was first reported in 1972 by Posta and Paleta *via* the reaction of 1,1,1-trifluorotrichloroethane with zinc in ethereal solvents, such as dioxane, 1,2-dimethoxyethane, diethylene glycol diethyl ether, and tetrahydrofuran.[129] Several of the ether complexes of 1,1-dichlorotrifluoroethylzinc were isolated and characterized by elemental analysis. Lang was able to prepare the DMF complex of CF_3CCl_2ZnCl by either direct reaction of CF_3CCl_3 with zinc in DMF or by a ligand exchange reaction from the diethyl ether complex with DMF. The structure of the DMF complex, $CF_3CCl_2ZnCl(DMF)$, was determined by ^{13}C NMR and by x-ray diffraction and was shown to be monomeric.[130]

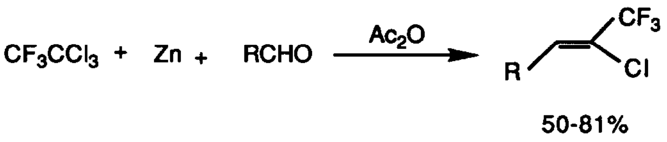


The synthetic utility of CF_3CCl_2ZnCl has been demonstrated by addition to aldehydes[131,132] and α-keto esters. Although the pregenerated zinc reagent does undergo addition to aldehydes, Barbier conditions were found more efficient. The reaction with aromatic aldehydes proceeds smoothly to give carbinols in good yields.

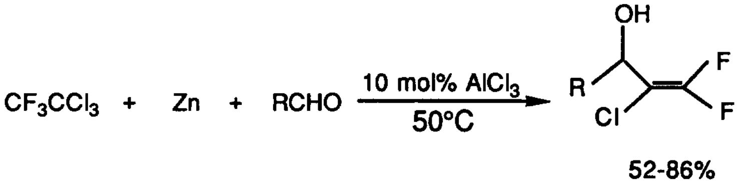


Although reaction with aliphatic or α,β-unsaturated aldehydes affords moderate yields of the 1,2-addition products, either addition of cuprous chloride, bis(triphenylphosphine)palladium dichloride, bis(triphenylphosphine)nickel dichloride or sonication improved the yields significantly.[133] However, treatment of CF_3CBr_3 and CF_3CBr_2Cl with aldehydes and zinc gives only low yields (23-27%) of the desired products, even with ultrasonic irradiation.[133] Unlike alkylzinc reagents, reaction of CF_3CCl_2ZnCl, complexed with optically pure ligands, with aldehydes gave no optically pure alcohols.[134]

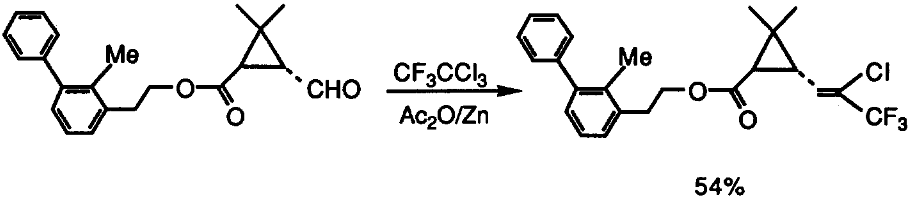
In the presence of excess zinc and acetic anhydride, CF_3CCl_3 reacts stereoselectively with aldehydes to form trifluoromethyl substituted Z-alkenes at room temperature to 50°C.[135] The reaction works well with aromatic, aliphatic and α,β-unsaturated aldehydes.[136] Lewis acids such as $TiCl_4$, $SiCl_4$ or acetyl chloride were also used to mediate this reaction.



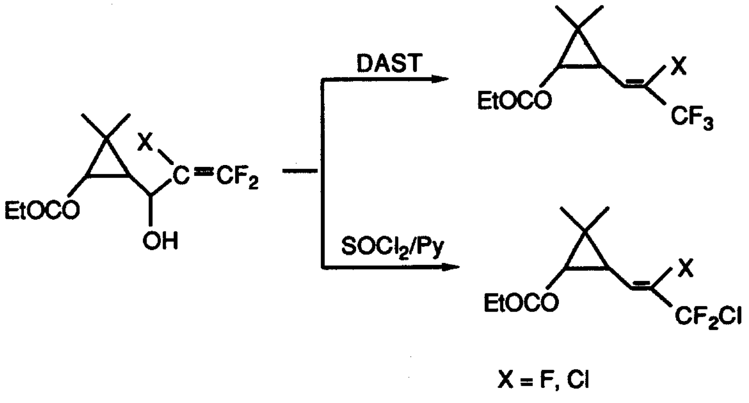
In striking contrast, in the presence of 10 mol% of $AlCl_3$, the zinc reagent reacts with aldehydes to produce 2-chloro-3,3-difluoro-2-propen-1-ols in good yields.[135,136] These compounds previously have been obtained *via* addition of the labile $LiCCl{=}CF_2$ to carbonyl substrates below -100°C. This $CF_3CCl_3/Zn/AlCl_3$ methodology avoids this difficult reaction.

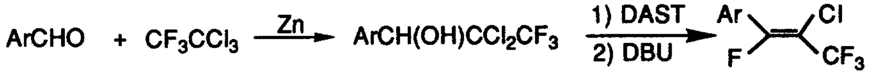


These approaches have led to the preparation of artificial pyrethroids containing the $CH{=}C(Cl)CF_3$ moiety.[136,137]



Modification of the above mentioned addition or addition-elimination adducts has provided new routes to some fluorinated alkenes and aryl trifluoropropynes as outlined below.[138,139]



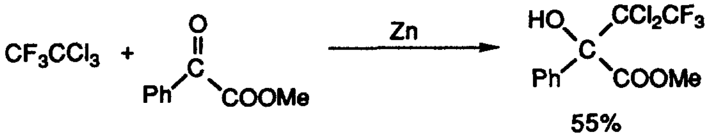


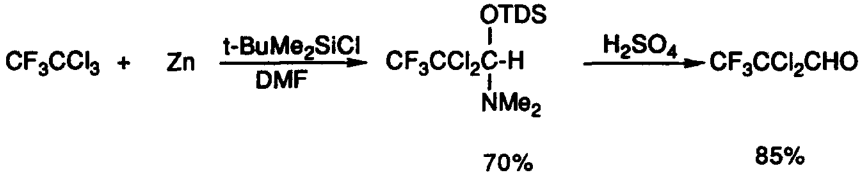
78-96%

$$\text{ArCHO} + \text{CF}_3\text{CCl}_3 \xrightarrow[\text{Ac}_2\text{O}]{\text{Zn}} \text{ArCH}=\text{CClCF}_3 \xrightarrow[\text{t-BuOH}]{\text{NaNH}_2} \text{ArC}\equiv\text{CCF}_3$$

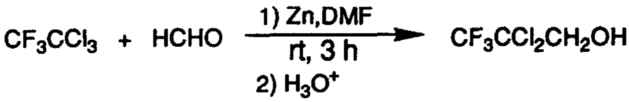
51-95%

Although the CF_3CCl_2ZnCl reagent does not add to ketones, the zinc reagent does react with ketoesters. The yields of the adducts are moderate even in the presence of large excess of the zinc reagent.[133] In the presence of a chlorosilane, CF_3CCl_2ZnCl reacts with DMF to give α-silyloxy N,N-dimethylamine. Treatment with acid produces CF_3CCl_2CHO in good yield.[118] Reaction of CF_3CCl_3/Zn/DMF with formaldehyde provides a useful preparation of 2,2-dichloro-3,3,3-trifluoropropanol.[118] Fluoropropionic acids of the general formula $CF_3CXYCOOH$ (X = F,Cl,Br; Y = F,Cl,Br,H) have been prepared by the ultrasonic promoted reaction of fluorohalogenoethanes, CF_3CXYZ (Z = Cl,Br), with zinc and carbon dioxide.[140]



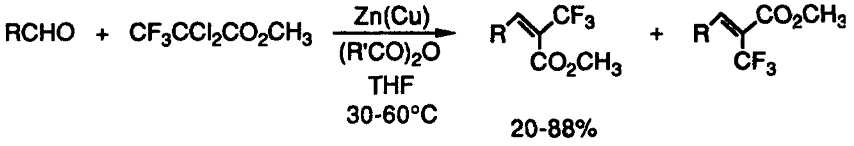


$$CF_3CCl_3 + Zn \xrightarrow[DMF]{t\text{-}BuMe_2SiCl} CF_3CCl_2C(OTDS)(H)NMe_2 \; (70\%) \xrightarrow{H_2SO_4} CF_3CCl_2CHO \; (85\%)$$



$$CF_3CCl_3 + HCHO \xrightarrow[\substack{rt,\ 3\ h \\ 2)\ H_3O^+}]{1)\ Zn,DMF} CF_3CCl_2CH_2OH$$

Recent work by Lang demonstrates that the readily available methyl 2,2-dichloro-3,3,3-trifluoropropionate undergoes the Reformatsky reaction with aldehydes and provides a useful synthetic entry for the synthesis of methyl α-trifluoromethyl-α,β-unsaturated carboxylates.[141]



VIII. Perfluoroalkyl Cadmium Reagents:

Perfluoroalkylcadmium reagents were first prepared by Dyatkin et. al. *via* metathesis between dialkylcadmiums and bis(trifluoromethyl) mercury in pyridine or diglyme.[142] As expected, an equilibrium mixture of all possible cadmium and mercurial compounds was rapidly established and the equilibrium could be shifted toward the formation of bis(trifluoromethyl) cadmium by use of excess bis(trifluoromethyl) mercury. A

$$(CF_3)_2Hg + (CH_3)_2Cd \longrightarrow (CF_3)_2Cd + (CH_3)_2Hg$$

decade later, Naumann prepared other analogs in essentially quantitative yields *via* the direct reaction of primary and secondary perfluoroalkyl iodides with dialkylcadmium in Lewis basic solvents such as glymes, TMED,

$$2\ R_FI + R_2Cd \longrightarrow (R_F)_2Cd + 2\ RI$$

$R_F = CF_3,\ C_2F_5,\ n\text{-}C_3F_7,$ $i\text{-}C_3F_7,\ n\text{-}C_4F_9,\ CF_3CH_2$ $\qquad R = CH_3,\ C_2H_5$

pyridine and acetonitrile.[143,144] The cadmium reagents were isolated as Lewis base adducts and characterized by IR, Raman and NMR spectroscopy and hydrolysis to the 1-hydroperfluoroalkane. Although the Naumann

$$(R_F)_2Cd + 2\ ROH \longrightarrow 2\ R_FH + Cd(OR)_2$$

$R = H, CH_3$

procedure gives excellent yields of the perfluoroalkylcadmiums, it necessitates the prior preparation and handling of toxic dialkylcadmiums. Perfluoroalkylcadmiums are often employed as precursors to other perfluoroalkyl organometallic reagents *via* metathetical processes. It is only necessary to generate them in situ. The in situ production of perfluoroalkylcadmiums can be readily accomplished *via* the direct reaction of perfluoroalkyl iodides with acid-washed cadmium powder in DMF at room temperature as reported by Burton and Heinze.[145] The exothermic reaction occurs rapidly and generally is complete in one hour. A mixture of the mono and bis perfluoroalkylcadmium reagents is obtained which can be readily identified by ^{19}F and ^{113}Cd NMR. When n = 1-3, the perfluoroalkylcadmiums are produced in good to excellent yields. When n > 3 the yields are

$$R_FI + Cd \xrightarrow[\text{rt}]{\text{DMF}} R_FCdI + (R_F)_2Cd$$

$R_F = C_nF_{2n+1};\quad n = 1 \text{ to } 8$

somewhat reduced. The yields are significantly improved when the reaction is carried out under degassed conditions.[146] Partially fluorinated alkylcadmiums can be prepared similarly.[147] The perfluoroalkylcadmiums are stable (indefinitely) at room temperature in solution in the absence of moisture.

$$CHF_2X + Cd \xrightarrow[\text{RT-50°C}]{\text{DMF}} CHF_2CdX + (CHF_2)_2Cd$$

$X = Br, I$

$X = Br,\ 65\text{-}75\%$

$X = I,\ 91\%$

The difluoromethylcadmium is stable at room temperature for several weeks. At temperatures above 105°C it rapidly decomposes to CF_2H_2.

The solvent plays a significant role in the direct reaction between cadmium metal and perfluoroalkyl iodides. When this reaction is carried out in DMF, perfluoroalkylcadmiums are obtained. However, as reported by Tamborski, when similar reactions are carried out in acetonitrile, the major product of the reaction results from dimerization of the perfluoroalkyl iodide.[148] As expected, ICF_2CF_2I and $ClCF_2CFClI$ gave only

$$R_FI + Cd \xrightarrow{CH_3CN} \underset{72\text{-}90\%}{R_F\text{-}R_F}$$

$$R_F = F(CF_3)_2C(CF_2CF_2)_3,\quad n\text{-}C_6F_{13},\quad F(CF_3)_2COCF_2CF_2,$$

$$F(CF_3)_2CO(CF_2CF_2)_4,\quad C_2H_5OC(O)(CF_2CF_2)_2OCF_2CF_2$$

dehalogenation products. Similar coupling reactions have also been observed in our laboratory in acetonitrile and are not totally unexpected. As in other SET reactions, the donor number of the solvent plays a significant role in the fate of the initially formed perfluoroalkyl radical.

Under electrochemical conditions, trifluoromethyl iodide reacts with cadmium to form a trifluoromethyl cadmate.[149] Recently, Naumann and co-workers have prepared a series of trifluoromethyl cadmates *via* reaction of bis(trifluoromethyl) cadmium complexes with alkali metal halides.[150] The anions have been identified by ^{19}F and ^{113}Cd NMR spectroscopy. The chemical shifts and coupling constants exhibit a strong dependence on the number of trifluoromethyl groups bound to cadmium. The first trifluoromethylargenate, $[Ag(CF_3)_4]^-$, was also prepared *via* this route.[151]

$$(CF_3)_2Cd + MX \longrightarrow [(CF_3)_2CdX]^-M^+ \longrightarrow M_2[(CF_3)_4Cd]$$

M = Cs, Rb

X = Cl, Br, I

One of the most significant contributions to this class of organometallic reagents was made by Morrison, who reported the preparation and isolation of bis(trifluoromethyl) cadmium•glyme.[152,153] This stable cadmium complex has been utilized in a variety of exchange processes and is a useful reagent for the introduction of

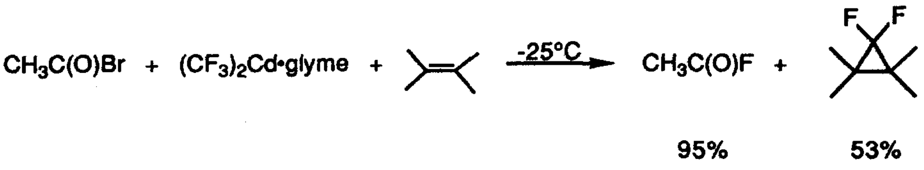
$$(CF_3)_2Hg + (CH_3)_2Cd \xrightarrow{\text{glyme}} (CF_3)_2Cd{\cdot}\text{glyme} + (CH_3)_2Hg\uparrow$$

air stable, white solid

trifluoromethyl groups into inorganic compounds such as $(CF_3)_3Au$[154], $CpCo(CO)(CF_3)_2$,[155] $(CF_3)_4Te$[156] and R_FSnR_3.[157] Dialkyl and diarylcadmium reagents are useful alternatives to the more reactive Grignard reagents

$$CH_3CdX + RC(O)Cl \longrightarrow RC(O)CH_3 + CdXCl$$

in the preparation of ketones from acyl or aroyl halides. Unfortunately, bis(trifluoromethyl) cadmium•glyme does not yield trifluoromethyl ketones when reacted with acyl halides. Instead, the acyl halide promotes the decomposition of bis(trifluoromethyl) cadmium•glyme to tetrafluoroethylene. If this reaction is carried out in the presence of an olefin, the difluorocyclopropane derivative is formed, indicating that the decomposition proceeds *via* a difluorocarbene intermediate.[158] This mild, low temperature production of [$:CF_2$]



provides an alternative to other modes of [$:CF_2$] generation. Its main limitation is the prior preparation of $(CF_3)_2Cd{\cdot}$glyme.

Naumann has reported a new synthesis of CF_3NO utilizing the bis(trifluoromethyl) cadmium•glyme complex.[159] With the higher homologous perfluoroalkylcadmium complexes, a metathetical reaction at

$$(CF_3)_2Cd{\cdot}\text{glyme} + (CH_3)_3Sn(ONO_2) \xrightarrow[\text{rt}]{CH_3CN} \underset{60\%}{CF_3NO}$$

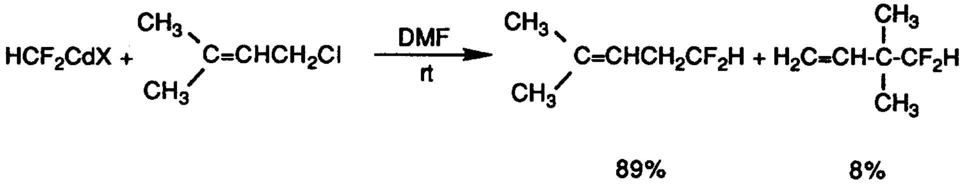
75°C in acetonitrile gives $(CH_3)_3SnR_F$ ($R_F = C_2F_5$, i-C_3F_7).

Perfluoroalkylcadmium reagents are thermally stable and react readily with acid or halogens to give the hydro- and haloperfluoroalkanes, respectively. They react sluggishly with allyl halides. However, difluoromethylcadmium reacts readily with allyl halides in DMF at room temperature.[147] With substituted

$$HCF_2CdX + H_2C{=}CHCH_2Br \xrightarrow[rt]{DMF} H_2C{=}CHCH_2CF_2H$$

$X = Br, I, CF_2H$ 85%

allyl halides, products of both α and γ-attack are obtained with preference for attack at the less hindered position.[147]



$$HCF_2CdX + (CH_3)_2C{=}CHCH_2Cl \xrightarrow[rt]{DMF} (CH_3)_2C{=}CHCH_2CF_2H + H_2C{=}CH\text{-}C(CH_3)_2\text{-}CF_2H$$

89% 8%

The fluoroalkylcadmium compounds also readily exchange with copper (I) halides or copper (I) cyanide and provide a useful low temperature entry to the fluoroalkyl copper reagents. The copper reagent produced depends upon the copper (I) salt utilized and the stoichiometry employed.[160,161] When R_F is CF_3, oxidation

$$R_FCdX + CuY \xrightarrow{rt} R_FCu \text{ and/or } [(R_F)_2Cu^-]\overset{+}{C}dX$$

$Y = Cl, Br, I, CN$

$R_F = CF_3, C_2F_5, CHF_2$

of the copper reagent readily occurs and leads to the formation of a stable Cu (III), $[(CF_3)_4Cu^-]$, compound.[162]

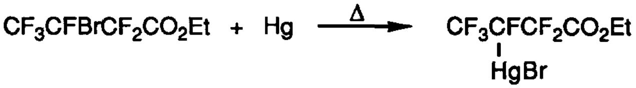
IX. Perfluoroalkyl Mercury Reagents:

Emeleus and co-workers reported the first synthesis of a perfluoroalkylmercury compound *via* the photochemical reaction of trifluoromethyl iodide with mercury or *via* the reaction of the trifluoromethyl iodide with cadmium amalgam.[163] Higher homologs[164] and functionalized analogs have also

$$CF_3I + Hg \xrightarrow[\text{sealed tube}]{h\nu} CF_3HgI$$

$$CF_3I + Cd\text{-}Hg \xrightarrow[\text{sealed tube}]{h\nu} (CF_3)_2Hg$$

been prepared by this route.[165,166] An excellent preparation of bis(trifluoromethyl) mercury is described in Inorganic Synthesis.[167]



$$CF_3CFBrCF_2CO_2Et + Hg \xrightarrow{\Delta} CF_3\underset{\displaystyle HgBr}{\underset{|}{C}}FCF_2CO_2Et$$

50-60%

A more convenient preparation of higher homologs is the reaction of mercuric fluoride and fluoroolefins. Krespan carried out the addition of mercuric fluoride to fluoroethylenes to obtain bis(fluoroalkyl) mercurials.[168] Mercuric fluoride reacts explosively with tetrafluoroethylene (TFE). However, controllable reactions of TFE readily occur at 50-100°C when arsenic trifluoride or hydrogen fluoride was employed as solvent. Subsequent

$$F_2C{=}CF_2 + HgF_2 \xrightarrow{100°C} (CF_3CF_2)_2Hg$$

56%

$$F_2C{=}CH_2 + HgF_2 \xrightarrow{100°C} (CF_3CH_2)_2Hg$$

66%

reports by Miller[169] and DuPont workers[170] expanded the scope of this preparation and demonstrated the utility of anhydrous hydrogen fluoride as a solvent. Mercuric fluoride is soluble in hydrogen fluoride at 100°C and autogeneous pressure in an autoclave. Mercuric fluoride adds regiospecifically to olefins with more than two carbons to give either secondary or tertiary perfluoroorganomercurials.[169,170,171] In the absence of HF, very little reaction is observed. Addition of mercuric fluoride to the internal double bond of compounds such as octafluoro-2-butene,hexafluorocyclobutene, and 2,3-dichloro-1,1,1,4,4,4-hexafluoro-2-butene failed. When a

$$CF_3CF{=}CF_2 + HgF_2 \xrightarrow[\Delta]{HF} [(CF_3)_2CF]_2Hg$$

60-68%

$$(CF_3)_2C{=}CF_2 + HgF_2 \xrightarrow[\Delta]{HF} [(CF_3)_3C]_2Hg$$

33%

$$F_2C{=}CCl_2 + HgF_2 \xrightarrow[\Delta]{HF} (CF_3CCl_2)_2Hg$$

69%

mixture of mercuric fluoride and mercuric chloride was utilized, perfluoroisopropylmercuric chloride was preferentially formed.[69]

$$CF_3CF{=}CF_2 + HgF_2 + HgCl_2 \xrightarrow[82^\circ]{HF} [(CF_3)_2CF]HgCl$$

54%

Miller proposed a mechanism involving electrophilic attack on the fluorinated alkene by a mercury cation to explain these results. These mercurials are cleaved by halogen providing a route to secondary and tertiary perfluoroalkyl halides. They also react with nitrosyl chloride to yield perfluoroalkyl nitroso compounds.[172]

$$[(CF_3)_2CF]_2Hg + 2\,NOCl \xrightarrow[rt]{DMF} 2\,(CF_3)_2CFNO + HgCl_2$$

64%

Although the addition of mercuric fluoride to fluoroolefins exhibits a reasonable scope, it requires the use of autoclaves and the handling of anhydrous hydrogen fluoride. Dyatkin has reported an alternative to the preparation of many of these mericurials *via* the reaction of fluoroolefins and mercury salts in the presence of alkali metal fluorides in aprotic polar solvents.[173,174] Depending on reaction conditions either completely substituted or mixed perfluoroalkyl mercury derivatives are obtained. Phenylmercuric fluoride and perfluoroisobutene gives phenylperfluoro-t-butyl mercury in 61% yield. Perfluorocyclobutene, which does not react with HgF_2/HF, gave 33% of the bis mercurial.

$$CF_3CF{=}CF_2 + KF + HgCl_2 \xrightarrow{DMF} [(CF_3)_2CF]_2Hg$$

65%

$$(CF_3)_2C{=}CF_2 + KF + HgF_2 \xrightarrow{DMF} [(CF_3)_3C]_2Hg$$

67%

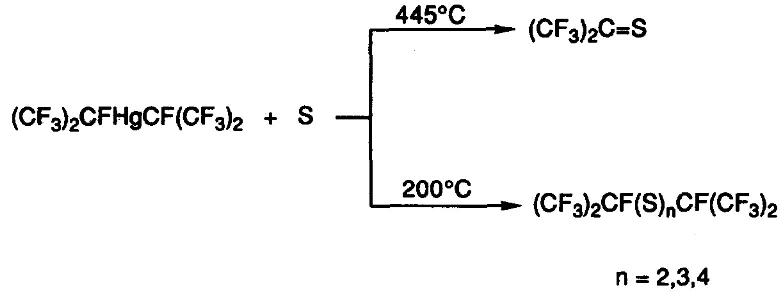
Mechanistically, the reaction involves mercuration of fluoroolefins *via* capture of the intermediate fluorocarbanion by the mercury salt. The regiochemistry observed is consistent with intermediate fluorocarbanion formation. Capture of the carbanion by the mercury salt is consistent with previously reported work by Miller with silver fluoride.[175] Other fluorocarbanion precursors such as $(CF_3)_2CHCN$[176a,176b] and 1-hydroperfluorobridgehead precursors[176c] give the corresponding mercurials by reaction with base and

$$CF_3CF{=}CF_2 + F^- \rightleftharpoons (CF_3)_2CF^- \xrightarrow{HgF_2} [(CF_3)_2CF]_2Hg$$

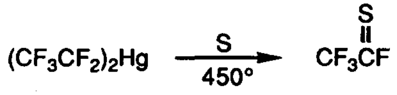
mercury chloride or acetate. Perfluoroalkylmercurials are readily prepared from a variety of other perfluoroalkyl elemental or metal reagents and mercury halides. Perfluoroalkyllithium and magnesium compounds have frequently been employed for this purpose, but this approach requires pregeneration of the unstable perfluorometal reagents at low temperature with the exception of perfluorobicyclobridgehead lithium and Grignard reagents.[176c] Some stable perfluoroalkylmetal reagents such as Me_3SnCF_3, $PhTlCF_3$ and $P(CF_3)_3$ have been used to prepare the mercury derivatives.[177,178] The reaction of mercury vapor with trifluoromethyl radicals in a radio frequency glow discharge has been reported.[179]

Perfluoroalkylmercurials are thermally stable and sublime from concentrated H_2SO_4 without decomposition. They are not easily cleaved by electrophiles and some are stable in aqueous solution. Treatment with halides forms complex anions such as $[(CF_3)_2HgX_2]_2^-$ or $[R_FHgIX]^-$ which implies that the perfluoroalkyl group exhibits pseudohalogen character.[180,181] However, secondary perfluoroalkylmercurials give hydroperfluoroalkanes under the same conditions. Although bis(trifluoromethyl) mercury has been widely used as a trifluoromethylating reagent in the synthesis of trifluoromethyl element compounds,[182] perfluoroalkylmercurials do not function readily as perfluoroalkylating reagents in the preparation of organofluorine molecules. However, organo(fluorohalomethyl)mercurials have been demonstrated to be efficient fluorohalocarbene reagents. Preparation and application of these carbenes will not be discussed in this report since several reviews are available.[183-187]

Perfluoroalkylmercurials react with sulfur at elevated temperature.[188] Hexafluorothioacetone is obtained by heating a mixture of bis(perfluoroisopropyl)mercury and sulfur at 445°C. However, when the reaction is



carried out at 200°C, perfluoroisopropyl disulfide and polysulfides are formed. The reaction of perfluoroalkyl mercurials with sulfur is also applicable to the synthesis of thio acid fluorides. In the presence of fluoride,



$$(CF_3CF_2)_2Hg \xrightarrow[450°]{S} CF_3\overset{S}{\overset{\|}{C}}F$$

bis(perfluoroisopropyl)mercury reacts smoothly in aprotic solvents to give the thiomercurial at 70°C.[189] The proposed mechanism involves attack of fluoride on mercury to produce the perfluoroalkyl anion, which reacts with sulfur to give the fluorinated thiomercury derivative.

$$[(CF_3)_2CF]_2Hg + S + KF \longrightarrow [(CF_3)_2CFS]_2Hg \xrightarrow{Cl_2} [(CF_3)_2CFS]_2$$

X. Perfluoroalkyl Copper Reagents:

[A]: Perfluoroalkylation:

Perfluoroalkylcopper reagents have received more attention than perhaps any other perfluorinated organometallic compounds. They have been prepared by three main methods: (1) reaction of a perfluoroalkyl halide with copper metal in a coordinating solvent at elevated temperatures; (2) decarboxylation of perfluorocarboxylates in the presence of Cu (I) halides; and (3) metathesis of perfluoroalkylorganometallic reagents with copper metal or copper (I) salts. The various approaches will be discussed in detail in this section.

The initial preparation of R_FCu reagents was disclosed in the comprehensive paper by McLoughlin and Thrower in 1969.[190] These workers found that when perfluoroalkyl iodides are heated with copper metal in DMSO at 110-120°C for one to three hours, perfluoroalkyl copper reagents are formed in good yields. Although the stoichiometry requires two equivalents of copper, best results were obtained with 2.5-3.0 equivalents of the copper metal. Perfluoroalkyl bromides can also be used as precursors, but generally higher temperatures are necessary and lower yields are obtained. Although DMSO is the most generally employed solvent, other coordinating solvents such as dimethylsulfide, DMF, HMPA and pyridine have been utilized. The coordinating ability of the solvent is important. In an elegant study, Chen and co-workers have demonstrated that the mechanism of the reaction of fluoroalkyl iodides with copper depends on the donor number (DN)

$$R_FI + 2\,Cu \xrightarrow[110\text{-}120°C]{DMSO} R_FCu + CuI$$

of the solvent used.[191] When a $R_FI/Cu°/C_6H_5I$/olefin reaction was carried out in solvents with DN less than 19, such as hexane, benzene, acetic anhydride, acetonitrile, and dioxane, the perfluoroalkyl radical was formed and could be trapped by olefins. The perfluoroalkylated benzene was not detected. In solvents with DN greater than 31, such as DMF, DMSO, pyridine or HMPA, the major product was the perfluoroalkylated

$$Cl(CF_2)_4I + Cu + H_2C{=}CHC_5H_{11} + C_6H_5I \xrightarrow{110°C} Cl(CF_2)_4CH_2CHIC_5H_{11}$$
$$+ \ Cl(CF_2)_4C_6H_5$$

benzene. Consequently, the mechanism for R_FCu formation appears to involve initial single electron transfer to form an ion pair within the solvent cage. In solvents of low DN, diffusional control of the caged ion pair produces the perfluoroalkyl radical. However, in solvents with large DN the ion pair collapses to give

$$R_FI + Cu \longrightarrow [R_F^{\dot{-}}\ Cu^{+}] \xrightarrow[\substack{DN\\ \text{solvent}}]{\text{low}} R_FI^{\dot{-}} + Cu^{+} \longrightarrow R_F\bullet + CuI$$

a radical in a solvent cage which is adsorbed on the surface of the copper metal to form R_FCu *via* a second electron transfer. Chen found a linear relationship between the differences of the chemical shift of the $-CF_2I$

$$\begin{tikzcd}
{[R_FI^{\dot{-}}\ Cu^{+}]} \arrow[r, "\text{large}", "\substack{DN\\ \text{solvent}}"'] & R_F\bullet + CuI \arrow[d, "Cu°"] \\
 & R_FCu
\end{tikzcd}$$

group and the DN of various solvents, which may be of value for prediction of the usefulness of solvents not yet studied in detail in the R_FI/Cu reaction. In any event, solvents of high DN should be employed for successful generation of R_FCu.

The perfluoroalkylcopper reagents exhibit versatile chemical reactivity and participate in a wide variety of coupling reactions. Specific examples are shown below. The coupling reactions can be carried out either by pregenerated perfluoroalkylcopper or in situ *via* heating a mixture of organic halides with perfluoroalkyl iodides and copper metal.[192]

$$\mathrm{C_7F_{15}I + ICH{=}CHCl \xrightarrow[\substack{Py\\100^\circ C}]{Cu} C_7F_{15}CH{=}CHCl}$$

65%

$$\mathrm{PhCH{=}CHBr + C_3F_7I \xrightarrow[\substack{Py\\100^\circ C}]{Cu} C_3F_7CH{=}CHPh}$$

82%

Note that both vinyl bromides and iodides participate in the coupling reaction. When α,ω-perfluoroalkyl diiodides are used in this reaction, α,ω-dienes are produced.[193]

$$\mathrm{I(CF_2)_3I + ICH{=}CHCl \xrightarrow[\substack{Py\\100^\circ C}]{Cu} ClHC{=}CH(CF_2)_3CH{=}CHCl}$$

96%

When 1,2-diiodoethylene was employed, both mono or bis coupling could be selectively achieved.[193,194,195]

$$\mathrm{C_7F_{15}I + \underset{(excess)}{(E)\text{-}CHI{=}CHI} \xrightarrow[\substack{DMF\\120^\circ C}]{Cu} (E)\text{-}C_7F_{15}CH{=}CHI}$$

$$\mathrm{C_7F_{15}I + (E)\text{-}CHI{=}CHI \longrightarrow (E)\text{-}C_7F_{15}CH{=}CHC_7F_{15}}$$

50%

As expected, the couplings with haloethylenes proceeded stereospecifically. An interesting anomoly was reported by DePasquale in the attempted coupling of a secondary perfluoroalkylene ether iodide. Only decomposition products involving scission at the C-O bond of the fluoro ether presumably producing perfluoroethylcopper were detected. When iodides of the type $\mathrm{R_FOCF_2CF_2I}$ were used, the expected coupling product was obtained.[196]

$$\mathrm{C_3F_7O(CF(CF_3)CF_2O)_2CFICF_3 + PhCH{=}CHBr \xrightarrow[\substack{DMF\\80^\circ C}]{Cu} CF_3CF_2CH{=}CHPh}$$

With active halides such as allyl, propargyl and acyl halides, the pregenerated perfluoroalkylcopper route gives the best results. Hudlicky prepared an α-diketone *via* capture of R_FCu with an α-ketoaroyl halide.[197]

$$C_3F_7Cu + C_6H_5C(O)COCl \xrightarrow{CH_3CN} \underset{49\%}{C_3F_7C(O)C(O)C_6H_5}$$

However, other α-diketones were prepared *via* capture of R_FCu with α-ketoacyl halides in low yields (<5%). Coe and Milner obtained low yields of allene in an extremely violent exothermic reaction of perfluoroheptylcopper with propargyl bromide.[198]

$$C_7F_{15}Cu + HC{\equiv}CCH_2Br \longrightarrow \underset{<10\%}{C_7F_{15}CH{=}C{=}CH_2}$$

Later work by Burton and Hartgraves demonstrated that the allene synthesis could be successfully accomplished with propargyl chlorides or tosylates in DMF or DMSO.[199] Similar methodology

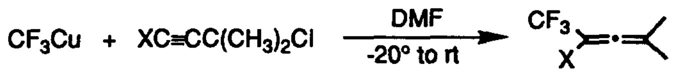
$$R_FCu + HC{\equiv}CR^1R^2X \xrightarrow[\substack{\text{or} \\ \text{DMSO} \\ 0°\text{C-rt}}]{\text{DMF}} \underset{30\text{-}73\%}{R_FCH{=}C{=}CR^1R^2} + CuX$$

$R_F = CF_3,\ C_3F_7;\ C_6F_{13},\ C_8F_{17}$ $R^1, R^2 = H,\ CH_3,\ \text{-}(CH_2)_5\text{-}$

$X = Cl,\ OTs$

$$CHF_2Cu + HC{\equiv}CC(CH_3)_2Cl \xrightarrow[-55°C]{DMF} \underset{78\%}{CF_2HCH{=}C{=}C(CH_3)_2}$$

with difluoromethyl copper gives the analogous difluoromethyl allenes.[200] The methodology is also applicable to the preparation of functionalized perfluoroalkyl substituted allenes.[199] Similar work by Hung with perfluoroalkylene dicopper reagents with propargyl bromides gave perfluorodiallenes in high yield and high regioselectivity.[201]



$X = CO_2Et$ (57%)

$X = Me_3Si$ (52%)

$$Cu(CF_2)_nCu + HC{\equiv}CCH_2Br \xrightarrow[15\text{-}20^\circ C]{DMSO} H_2C{=}C{=}CH(CF_2)_6CH{=}C{=}CH_2$$

$n = 6,8$ 27-32%

$$C_6F_{13}Cu + (i\text{-}Pr)_3SiC{\equiv}CCH_2Br \xrightarrow[15\text{-}20^\circ C]{DMSO} C_6F_{13}CH_2C{\equiv}CSi(i\text{-}Pr)_3$$

50%

Coupling of the pregenerated perfluoroalkylcopper reagent with 1-iodo-2-phenylacetylene gave the expected perfluoroalkyl phenyl alkyne.[198a] The reaction was complicated by formation of 1,4-diphenylbutadiyne. This side reaction was rapid at 100°C, but could be almost completely supressed by working at the temperature where the DMSO solution of the perfluoroalkylcopper reagent began to solidify. Similar coupling to an alkyne derivative was noted with 3-hydroxy-1-iodo-3-methyl-1-butyne. When 1-iodoperfluoroalkyl acetylene is used, exchange processes are rapid and only the perfluorodiyne was detected.[198b] No perfluoroacetylene coupled product was observed.

$$C_6F_{13}Cu + IC{\equiv}CPh \longrightarrow C_6F_{13}C{\equiv}CPh$$

Both pregeneration and in situ conditions have been employed in the R_FI/Cu reaction with olefins. Presumably, these reactions occur *via* perfluoroalkyl radicals generated from decomposition of the perfluoroalkyl copper reagent.[202] 1-Dodecene, cycloheptene and cyclohexene behaved similarly. Reactions with allyl alcohol, norbornadiene, 1,2-dihydropyran and methyl acrylate resulted only in polymerization or complex mixtures. Related work by Riess with perfluoroalkylethylenes gave polyfluorinated dienes.[203]

$$C_7F_{15}Cu + H_2C{=}CHC_5H_{11} \xrightarrow[DMSO]{110^\circ C} C_7F_{15}CH_2CH_2C_5H_{11} + C_7F_{15}CH_2CH{=}CHC_4H_9$$

1 : 2

$$R_FCF_2CH{=}CH_2 + R_F'CF_2I + Cu \xrightarrow[150^\circ C]{DMF} R_FCF{=}CHCH{=}CFR_F'$$

50-73%

Similar thermal reactions of perfluoroalkylcoppers with aromatic hydrocarbons gave the perfluoroalkylated aromatic hydrocarbons.[204] The products from toluene were the ortho and para isomers in a 1:2 ratio. In later work, Ojima investigated this reaction in detail with functionalized benzenes and concluded that the *in situ* reaction may involve an "active species" other than the perfluoroalkylcopper reagent.[205] Functional groups such as OH, NH_2, OR, CO_2R, halogen, and $NHCO_2R$ were unaffected. Whether this "active species" is the perfluoroalkyl radical was not determined.

$$C_7F_{15}Cu + C_6H_6 \xrightarrow[\text{110°C}]{\text{DMSO}} C_7F_{15}C_6H_5$$

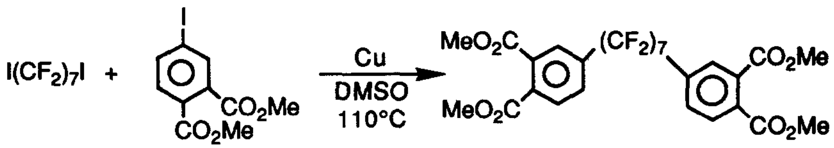
The most widely studied reaction of perfluorocopper reagents has been their coupling reaction with aromatic halides. As expected, aryl iodides work better than aryl bromides. Recent work by Tamborski with functionalized mono and dibromobenzenes indicates that the aryl bromides can be cost effective in some cases.[206] Tamborski has employed bromoheterocyclic compounds as a route to perfluoroalkylated pyridine and pyrimidines as well as perfluoroalkylated furans and thiophenes.[207]

In the pioneering work of McLoughlin and Thrower,[190] the reactions were generally carried out *in situ* with the perfluoroalkyl iodide, the functionalized iodoaromatic compound and copper metal in a polar aprotic solvent at 110-130°C to give good yields of fluoroalkyl aromatic compounds. α,ω-Diiodoperfluoroalkanes could be reacted to give the α,ω-diarylperfluoroalkanes. Some typical examples are outlined below:

$$C_7F_{15}I + C_6H_5I \xrightarrow[\substack{\text{DMSO} \\ \text{110°C}}]{\text{Cu}} \underset{70\%}{C_7F_{15}C_6H_5}$$

$$(CF_3)_2CFI + C_6H_5I \xrightarrow[\substack{\text{DMSO} \\ \text{110°C}}]{\text{Cu}} \underset{40\%}{(CF_3)_2CFC_6H_5}$$

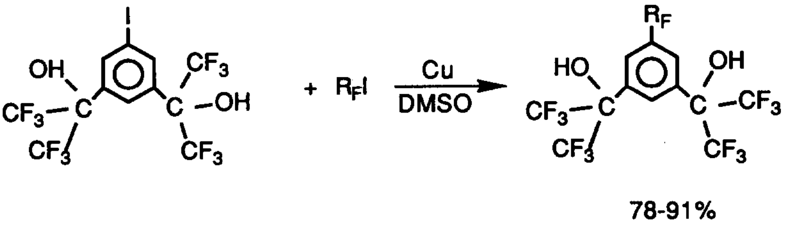
$$HO_2C(CF_2)_3I + C_6H_5I \xrightarrow[\substack{\text{Cu} \\ \text{110°C}}]{\text{DMSO}} C_6H_5(CF_2)_3COOH$$



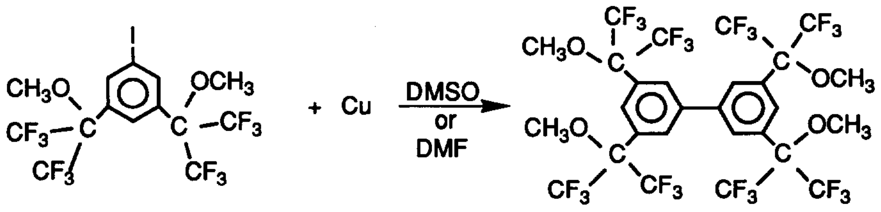
85%

Heterocyclic analogs, such as 3-iodopyridine and 2-iodothiophene give 52% and 25% of the coupled products, respectively, with $I(CF_2)_3I$.

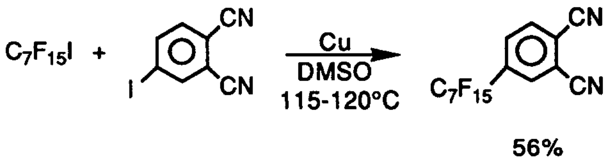
Griffith, Soulen and co-workers have employed this type of coupling in the synthesis of 1,3-bis[2-hydroxyhexafluoro-2-propyl]-5-perfluoroalkylbenzene, a precursor of interest for polymeric materials with low critical surface tension.[208] The diol product forms stable complexes with DMSO.[209] Homocoupling of the iododiol precursor with copper failed. However, the dimethyl ether derivative of the iododiol reacted smoothly with copper to give the biphenyl tetrol in good yield.[210]



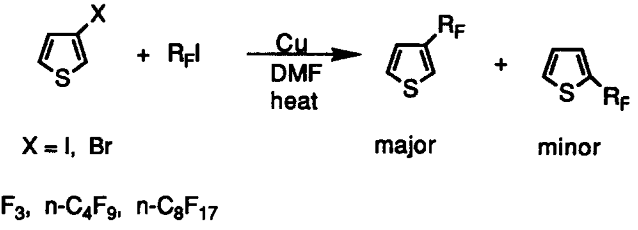
$R_F = C_3F_7,\ C_6F_{13},\ C_7F_{15},\ C_8F_{17},\ (CF_3)_2CF$



Similar couplings with 4-iodophthalonitrile gives a convenient route to fluorinated phthalonitriles which readily form phthalocyanines in the presence of stannous chloride hydrate.[211]



In the coupling reaction of halothiophenes with perfluoroalkyl iodide and copper, an unusual rearrangement occurred. A mixture of 3- and 2-perfluoroalkylated isomers was obtained from the 3-halothiophene.[212]



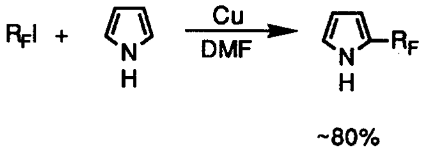
A similar rearrangement has been previously observed by Kobayashi in the coupling of 3-bromobenzofuran with trifluoromethyl iodide and copper in pyridine.[21] The extent of the rearrangement depended on the halogen substituent. When X = Br, 18% of the rearranged product was obtained; when X = I, only 2%. Although no definitive mechanistic studies were done, Wakselman proposed a transient carbenoid species to account for the rearranged product.

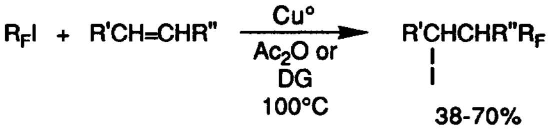
Perfluoroalkylcopper reagents react readily with allyl halides[202] or thiocyanates[63] to give perfluoroalkyl substituted olefins and sulfides, respectively.

$$C_7F_{15}Cu + H_2C{=}CHCH_2Br \longrightarrow C_7F_{15}CH_2CH{=}CH_2$$

$$C_4F_9Cu + PhCH_2SCN \longrightarrow C_4F_9SCH_2Ph$$

Chen[214] has reported the preparation of 2-perfluoroalkylated pyrroles *via* direct reaction of perfluoroalkyl iodides and pyrroles with stoichiometric amounts of copper metal. Similarly, these workers utilized copper metal to initiate the addition of perfluoroalkyl iodides to olefins.[215] When tetrafluoroethylene





$$R_FI + R'CH{=}CHR'' \xrightarrow[\substack{Ac_2O\text{ or}\\ DG\\ 100^\circ C}]{Cu^\circ} \underset{\substack{|\\ I}}{R'CHCHR''R_F}$$

38-70%

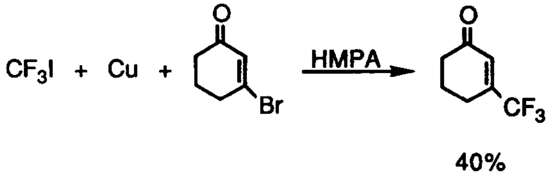
(TFE) was utilized as the substrate, telomerization of the TFE occurred.[216]

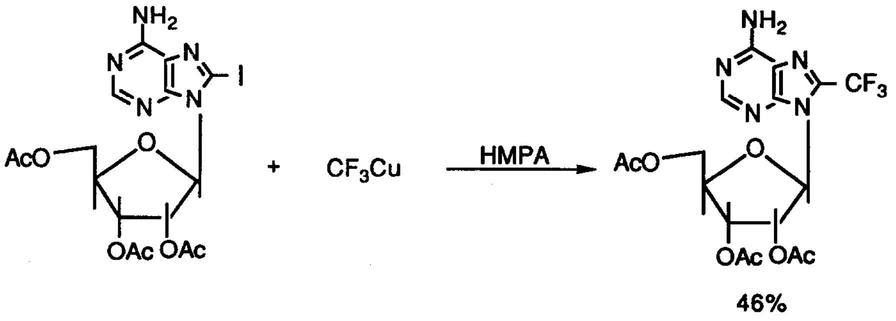
$$CF_3CF_2I + F_2C{=}CF_2 \xrightarrow[100°C]{Cu°} CF_3CF_2(CF_2CF_2)_nI$$

[B]: Trifluoromethylation

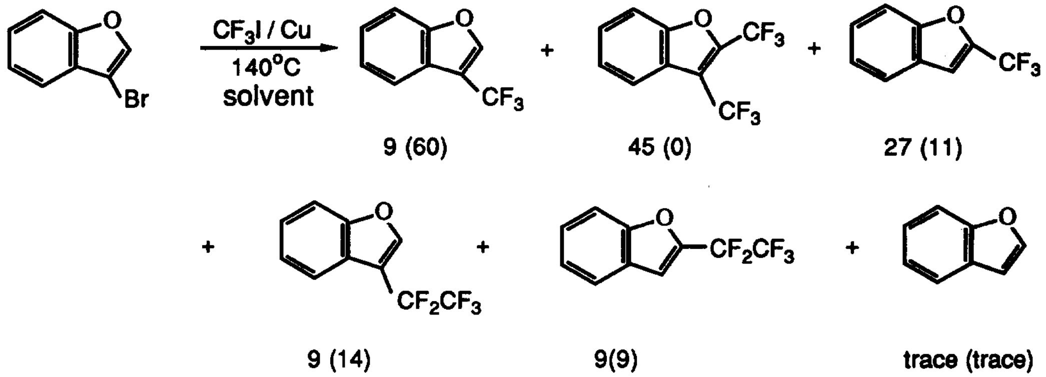
Trifluoromethylation is the most important perfluoroalkylation reaction, since pharmaceutical and agricultural chemicals which contain the trifluoromethyl group often exhibit enhanced reactivity. Concomitant with these applications have been increased efforts to develop cheaper and more efficient methodologies for the introduction of the trifluoromethyl group into a variety of molecules. This has resulted in numerous investigations to incorporate the trifluoromethyl group directly into molecules *via* in situ generation and coupling of trifluoromethylcopper.

The pioneering studies for the in situ generation of trifluoromethylcopper were performed by Kobayashi and co-workers who reported the trifluoromethylation of aryl, vinyl, alkyl, and heterocyclic halides with trifluoromethyl iodide or bromide in the presence of copper powder in aprotic solvents at elevated temperatures (120-150°C).[217,218] This method has been applied to pyrimidine and purine nucleosides.[219,220] In some cases the reaction is more complex than simple coupling to give the trifluoromethylated product. For example, 3-bromobenzofuran produces at least seven products with CF_3I/Cu. The amount of each product is dependent on the solvent employed. The yields are shown for pyridine and DMF as solvents





(yields in DMF are given in parentheses).[213] The pentafluoroethyl compounds were postulated to arise from

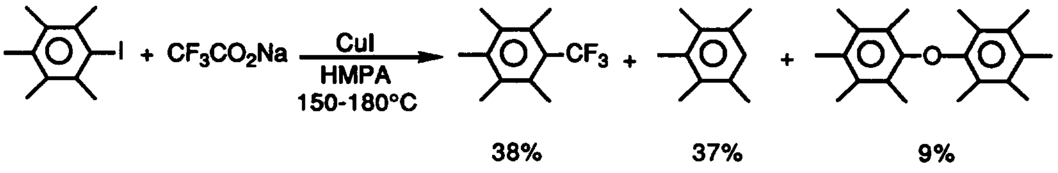


decomposition of trifluoromethylcopper to form pentafluoroethylcopper. The formation of the 2-substituted benzofurans was explained by addition of trifluoromethyl anion to the delocalized double bond between the 2- and 3-position, followed by migration of hydride ion and elimination of bromide anion. Similar phenomena have been observed by Wakselman in the reaction of perfluoroalkyl iodides with 3-iodothiophene in the presence of copper.[212]

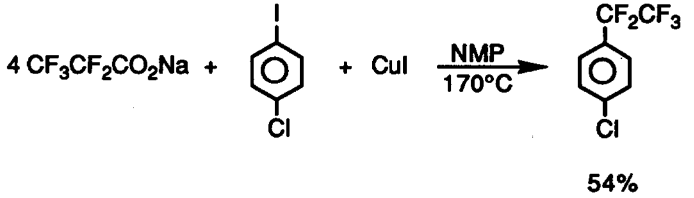
In addition to the high temperatures necessary in the CF_3I/Cu route for trifluoromethylation, another major drawback is the cost of the trifluoromethyl iodide. Consequently, cheaper sources of the trifluoromethyl groups have been pursued by several groups. In 1981, Matsui reported that regiospecific trifluoromethylation by substitution of halogen in aromatic halides could be achieved by the use of sodium trifluoroacetate and copper (I) iodide in dipolar aprotic solvents.[221] Reaction with aromatics containing electron-withdrawing groups such as NO_2 and Cl or electron-releasing groups such as OCH_3 and CH_3 were successful. Similarly, 2-bromopyridine

$$\mathrm{ArI} + \mathrm{CF_3CO_2Na/CuI} \xrightarrow[\text{140-160°C}]{\text{NMP}} \underset{\text{40-78\%}}{\mathrm{ArCF_3}}$$

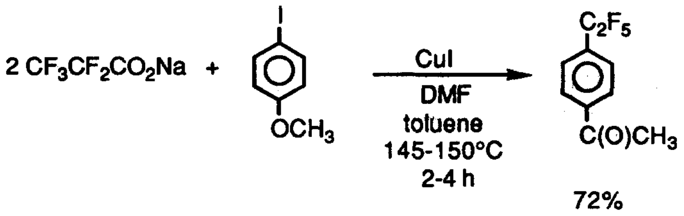
gave 2-trifluoromethylpyridine. Suzuki reacted polymethyliodobenzenes with CF_3CO_2Na/CuI in HMPA at 150-180°C to give the corresponding polymethylbenzotrifluoride in 35-37% yields.[222] Byproducts included the parent hydrocarbon from reductive dehalogenation and bis-polymethylphenyl ether. No trifluoromethylation occurred without the Cu(I) salt. Attempts to extend the perfluoroalkylation reaction to higher perfluoroalkanoates were unsuccessful under these conditions.

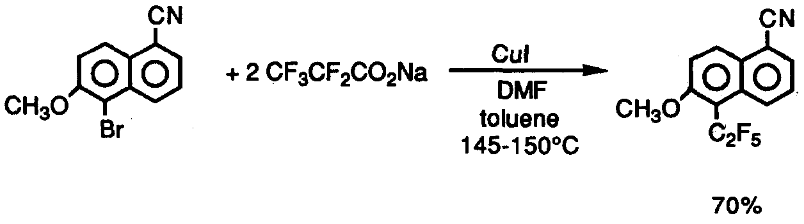


Chambers has also studied the Matsui route to trifluoromethyl aromatics[223] and applied it to some heterocyclic and vinyl halides. They found that sodium pentafluoropropionate worked well in this reaction to give the corresponding pentafluoroethyl derivatives. Sodium heptafluorobutyrate was also investigated, but transfer of the heptafluoropropyl group was inefficient and only a 30% GLPC yield of heptafluoropropylbenzene was obtained from iodobenzene. Although the mechanism of the Matsui reaction has not been studied in detail, Chambers was able to exclude the decarboxylation of the aryl ester ($ArCO_2CF_3$) as the reaction pathway. A crude Hammett study with substituted iodobenzenes revealed a ρ value of + 0.46, indicative of a reactive species that is nucleophilic in character. Consequently, Chambers concluded that the potential reactive intermediate might be $[CF_3CuI^-]$ rather than $[CF_3CuI^\bullet]$. The CF_3CO_2Na/CuI approach does not avoid the elevated temperatures of the CF_3I/Cu method. In addition, a four-fold excess of sodium trifluoroacetate was needed to achieve reasonable yields, thus negating some of the cost effectiveness of this approach.

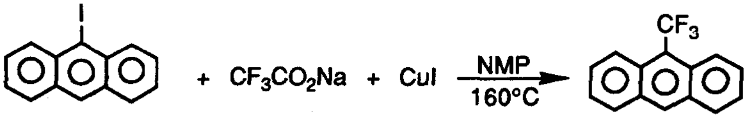


An improvement to this methodology was reported by Frekos for the synthesis of pentafluoroethyl substituted aromatics.[224] Chambers noted that much of the excess of R_FCO_2Na formed significant amounts of R_FH, indicating the presence of water in the perfluorocarboxylate. Frekos employed a DMF/toluene solvent mixture to remove any water present as a toluene azeotrope before raising the temperature to the decarboxylation temperature. With this approach, only two equivalents of the perfluorocarboxylate were required and the yields of the perfluoroethylated products were significantly higher. Aryl bromides could also be perfluoroalkylated, although perfluoroalkylation is slower than with aryl iodides. The corresponding anthracene

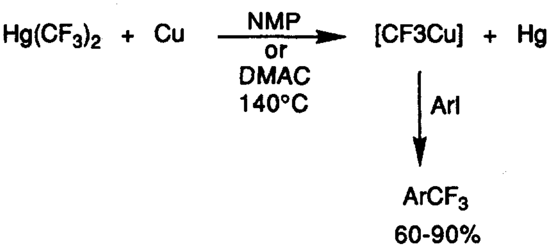




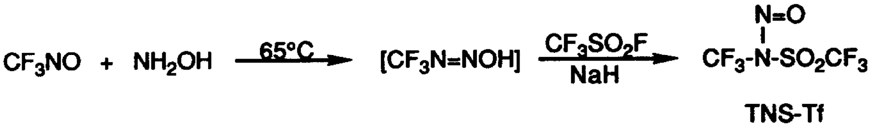
analog was prepared by Mintas.[225] Irradiation of the 9-trifluoromethylanthracene gives the anti [4+4] dimer whose structure was determined by ^{1}H and ^{13}C NMR spectroscopy, and confirmed by x-ray crystallography.[225]



Yagupolskii employed the reaction of bis(trifluoromethyl) mercury with copper powder in N-methylpyrrolidone (NMP) or dimethylacetamide (DMAC) at elevated temperatures (140°C) to produce a solution of trifluoromethylcopper, which could be utilized for the trifluoromethylation of benzyl, aromatic, and heterocyclic halides.[226] The main drawback to this approach is the use of toxic bis(trifluoromethyl) mercury. Other workers have not employed this route.



Umemoto has also developed a pregeneration route to trifluoromethylcopper from N-trifluoromethyl-N-nitrosotrifluoromethanesulfonamide (TNS-Tf), prepared as follows:[227]



$$CF_3NO + NH_2OH \xrightarrow{65°C} [CF_3N{=}NOH] \xrightarrow[NaH]{CF_3SO_2F} CF_3\text{-}\overset{\overset{\displaystyle N{=}O}{|}}{N}\text{-}SO_2CF_3$$

TNS-Tf

TNS-Tf reacted vigorously with activated copper in acetonitrile, HMPA, NMP and DMF at room temperature to give a homogeneous brown solution, presumably a trifluoromethylcopper complex, which reacted with iodoaromatic compounds to give ~60% yields of the trifluoromethylated aromatics. This route appears to be a

$$\text{TNS-Tf} \xrightarrow[\substack{rt \\ \text{solvent}}]{Cu} [CF_3Cu{\bullet}\text{solvent}] \xrightarrow[100°C]{ArI} ArCF_3$$

useful pregeneration route to trifluoromethylcopper. However, the necessary preparation of CF_3NO and the thermal lability of TNS-Tf have deterred its use for the preparation of trifluoromethylated compounds.

A unique and useful pregenerative route has been reported by Burton and Wiemers, who discovered that dihalodifluoromethanes readily reacted with acid-washed cadmium or zinc powders in DMF at room temperature to give stable solutions of trifluoromethylcadmium and zinc, respectively.[103] The trifluoromethylcadmium

$$CF_2XY + M \xrightarrow[\substack{rt \\ \text{(exothermic)}}]{DMF} [CF_3MX + (CF_3)_2M]$$

80-95%

X = Br, Cl M = Cd, Zn
Y = Br, Cl

reagent readily undergoes a metathesis reaction with copper (I) salts at -40°C to give a solution of trifluoromethylcopper.[228] The analogous zinc reagent also exchanges with copper (I) salts, but only slowly at

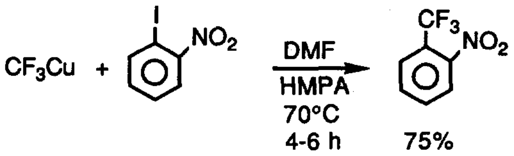
$$[CF_3CdX + (CF_3)_2Cd] \xrightarrow[-40°C]{CuY} [CF_3Cu]$$

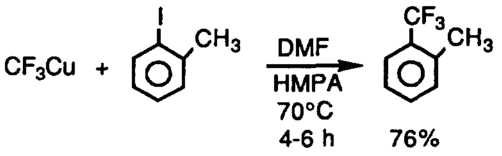
Y = I, Br, Cl, CN 90-100%

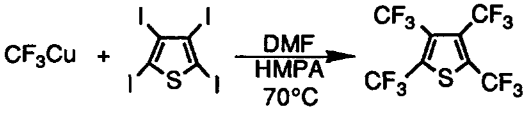
room temperature. Surprisingly, two different copper species can be formed depending on the copper (I) salt used and the stoichiometry of the metathesis reaction. These copper species have been tentatively assigned as $CF_3Cu{\bullet}L$ (L = metal halide) and $CdI^+[(CF_3)_2Cu]^-$. The cuprate species, $CdI^+[(CF_3)_2Cu]^-$ is easily oxidized by oxygen, iodine or bromine to a *stable* copper (III) compound. An analog of this stable trifluoromethylcopper (III) complex has been isolated and the structure was confirmed by an x-ray analysis.[229]

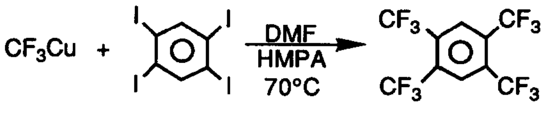
The solution of trifluoromethylcopper in DMF, prepared *via* metathesis from trifluoromethyl cadmium, slowly decomposes to pentafluoroethylcopper at room temperature, a process observed previously in low yield by Kobayashi in the CF_3I/Cu system. However, addition of an equivalent volume of HMPA to the CF_3Cu/DMF solution inhibits the formation of pentafluoroethylcopper and permits the reagent to be utilized for the trifluoromethylation of aryl iodides even at elevated temperatures.[228,230] Polytrifluoromethylation can be readily achieved with polyiodinated aryl compounds.[231] The ability to pregenerate trifluoromethylcopper permits trifluoromethylation of temperature sensitive halogen-containing analogs that would not survive the previously noted in situ methods.

$$CF_3Cu \xrightarrow[DMF]{rt} CF_3CF_2Cu$$









Other trifluoromethylation reactions occur readily at room temperature or below and do not require the use of HMPA to stabilize the trifluoromethylcopper solution.[199,228,231,232] Some typical examples are outlined below:

$$CF_3Cu + H_2C{=}CHCH_2Cl \xrightarrow[rt]{DMF} CF_3CH_2CH{=}CH_2$$

$$CF_3Cu + HC{\equiv}CCH_2OTs \xrightarrow{DMF} CF_3CH{=}C{=}CH_2$$

$$CF_3Cu + (E)\text{-}CF_3C(Ph){=}CFI \xrightarrow[-50^\circ \text{ to rt}]{DMF} (Z)\text{-}CF_3C(Ph){=}CFCF_3$$

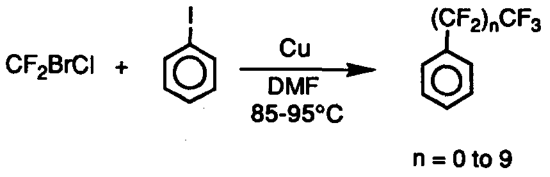
$$CF_3Cu + ClCH_2C{\equiv}CCH_2Cl \xrightarrow[rt]{DMF} H_2C{=}C(CF_3)C(CF_3){=}CH_2$$

Later work by Easdon demonstrated that oligomerization of trifluoromethylcopper occurred when a solution of trifluoromethylcopper in DMF is heated.[233] A similar distribution of perfluoroalkylcoppers can be obtained *via* the direct reaction of copper metal with dihalodifluoromethanes in DMF at 85-95°C.[233] When the the CF_2XY/Cu reaction was carried out in the presence of iodobenzene, a mixture of perfluoroalkylbenzenes was

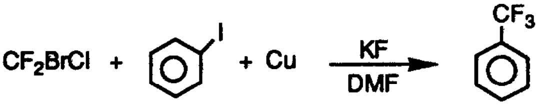
$$CF_3Cu \xrightarrow[90\text{-}100^\circ C]{DMF} CF_3(CF_2)_nCu \qquad n = 1 \text{ to } 14$$

$$CF_2XY + Cu \xrightarrow[85\text{-}95^\circ C]{DMF} CF_3(CF_2)_nCu \qquad n = 1 \text{ to } 14$$

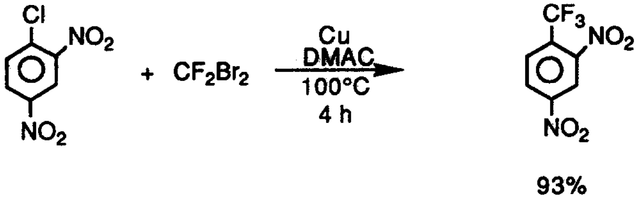
$X = Br, Cl$
$Y = Br$



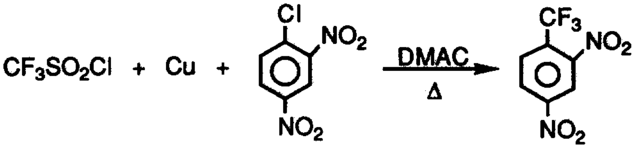
obtained, indicating that oligomerization of the perfluoroalkylcopper reagents was competitive with trapping of trifluoromethylcopper by iodobenzene. However, Easdon found that addition of potassium fluoride to the reaction mixture effectively supressed the oligomerization process and permitted efficient trapping of the initially formed trifluoromethylcopper by iodobenzene. Only 5% of pentafluoroethyl benzene was formed in this reaction.[233]



Clark utilized this reaction in DMAC to carry out the trifluoromethylation of activated aryl chlorides possessing ortho groups capable of interacting with the metal.[234] With less activated substrates the formation of higher perfluoroalkyl substituted products occurred (cf. Easdon[233]). To circumvent this problem, Clark added charcoal to the CF_2Br_2/Cu/DMAC solution or utilized a CuI-charcoal supported reagent.[235] This resulted in the effective trifluoromethylation of activated aryl chlorides with very little higher perfluoroalkylated products. Later work by Clark also explored the effects of ring substituents on the efficiency of this reaction.[236]



The activated aryl chlorides may also be trifluoromethylated *via* generation of the trifluoromethylcopper from trifluoromethylsulfonyl chloride. Full details of this approach have not yet appeared.[237]



Mechanistically[103] the CF_2XY/M reaction involves the formation of difluorocarbene *via* radical anion formation (cf. perfluoroalkylcadmium reagent section) followed by reaction of the difluorocarbene with fluoride ion formed from [$:CF_2$] and DMF to form trifluoromethide. The methide reacts with the in situ formed metal

$$\mathrm{CF_2XY + M(Zn,Cd,Cu) \longrightarrow MXY + [:CF_2]}$$

$$\mathrm{[:CF_2] + Me_2NCHO \longrightarrow Me_2NCHF_2 + CO}$$

$$\mathrm{Me_2NCHF_2 \rightleftharpoons [Me_2\overset{+}{N}{=}CHF]F^-}$$

$$\mathrm{F^- + [:CF_2] \rightleftharpoons CF_3^-}$$

$$\mathrm{CF_3^- + MXY \longrightarrow CF_3MX + (CF_3)_2M}$$

halide to give the trifluoromethylorganometallic reagent. Other difluorocarbene precursors could potentially be utilized to accomplish the same overall transformation. Chen has successfully used methyl fluorosulphonyldifluoroacetate and fluorosulphonyldifluoromethyl iodide with copper (I) iodide or copper metal to produce and capture in situ trifluoromethylcopper.[238,239] The mechanism of the reaction is similar to that outlined above.

$$\mathrm{CuI + FO_2SCF_2CO_2Me \xrightarrow[60\text{-}80°C]{DMF} MeI + [FO_2SCF_2CO_2Cu]}$$

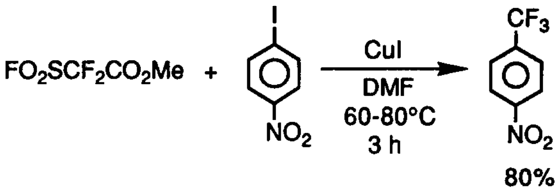
$$\mathrm{[FO_2SCF_2CO_2Cu] \longrightarrow CO_2 + SO_2 + Cu^+ + [:CF_2] + F^-}$$

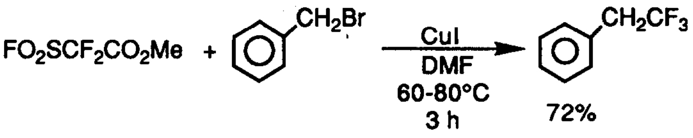
$$\mathrm{[:CF_2] + F^- \rightleftharpoons CF_3^-}$$

$$\mathrm{CF_3^- + CuI \longrightarrow [CF_3CuI]^-}$$

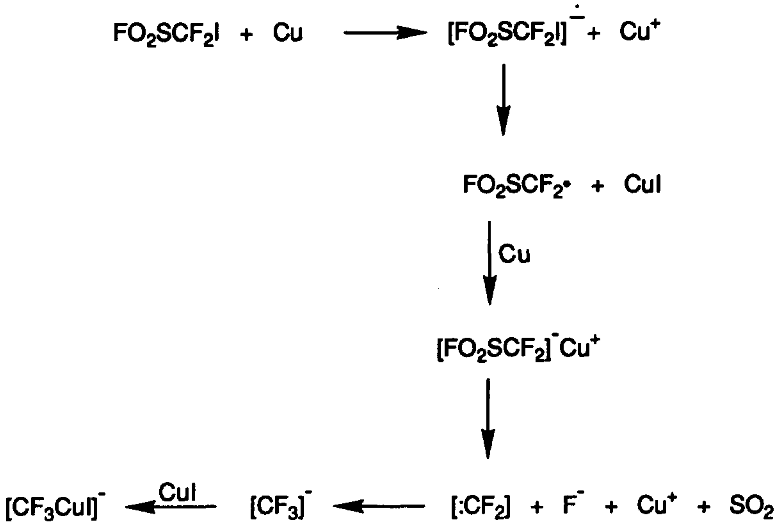
$$\mathrm{[CF_3CuI]^- + RX \longrightarrow CF_3R + CuX + I^-}$$

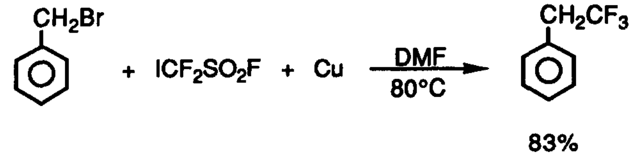
Typical applications of this approach are outlined below:





With fluorosulfonyldifluoromethyl iodide, the reaction with copper produces difluorocarbene *via* an SET reaction. Capture of the intermediates, fluorosulfonyldifluoromethyl radical and difluorocarbene, with 2,3-dimethylbut-2-ene is consistent with the SET mechanism. Both ICF_2SO_2F and $FO_2SCF_2CO_2Me$ are obtained from FO_2SCF_2COF, which is prepared *via* ring opening of the β-sultone formed by reaction of tetrafluoroethylene and sulfur trioxide. The hazards associated with the preparation of the β-sultone may deter some researchers from utilizing this route.

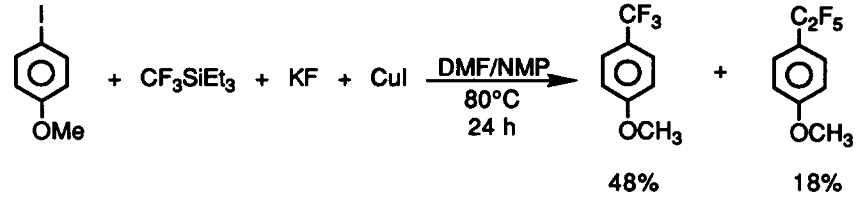




Fuchikami has reported an interesting approach to the in situ generation and capture of trifluoromethylcopper from trifluoromethyltrialkylsilanes.[240] Aryl, vinyl iodides, allyl halides and benzyl

$$RX + CF_3SiR'_3 \xrightarrow[\substack{CuI \\ DMF/NMP \\ 60\text{-}80°C}]{F^-} R\text{-}CF_3$$

bromide were successfully trifluoromethylated *via* this procedure. Some pentafluoroethyl by-products were also formed. Presumably the trifluoromethyltrialkylsilane/F⁻/CuI reaction produces [CF_3Cu] in situ which can be



captured or which can form [CF_3CF_2Cu] as noted earlier in the CF_2XY/M reactions. Similar reactions with pentafluoroethyltrialkylsilanes gave the pentafluoroethylation products in a stereospecific and chemoselective

$$R\text{-}X + C_2F_5SiMe_3 \xrightarrow[\text{DMF}\ 60°\text{C}]{\text{KF/CuI}} RC_2F_5$$

reaction. One example of a perfluoropropylation reaction with $C_3F_7SiMe_3$ was noted. This approach is dependent on the availability or synthesis of the requisite perfluoroalkyltrialkylsilane, R_FSiR_3. These silanes are usually prepared *via* the Ruppert reaction from perfluoroalkyl iodides or bromides.[241] Consequently, researchers wishing to employ this method will need to prepare these precursors (where $R_F \neq CF_3$) which may inhibit their choice of this procedure.

$$R_FI + (Et_2N)_3P + R_3SiCl \longrightarrow R_FSiR_3$$

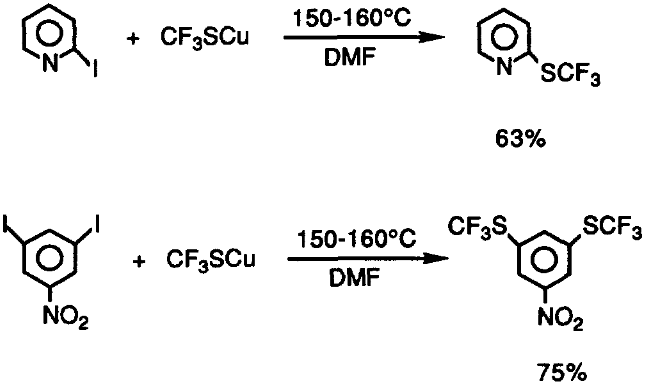
[C]: Perfluoroalkylthio and Perfluoroalkylseleno Copper Reagents:

The incorporation of a perfluoroalkylthio group into organic compounds often results in products with useful biological activity. Thus, methodology for the introduction of this useful substituent has stimulated researchers to develop procedures for its introduction into organic molecules. One important method for CF_3S-incorporation has been *via* perfluoroalkylthiocopper reagents.

Yagupolskii prepared the trifluoromethylthiocopper reagent *via* metathesis of trifluoromethylthiosilver with copper (I) halides in acetonitrile or tetrahydrofuran.[242] Subsequent reaction with aryl and heterocyclic iodides

$$AgSCF_3 + CuBr \longrightarrow [CuSCF_3] + AgBr$$

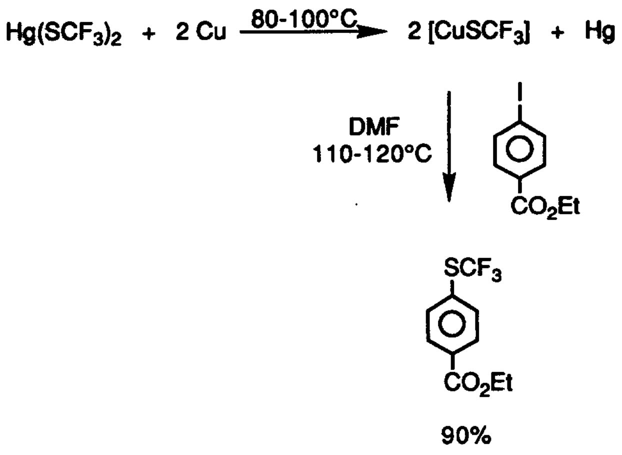
gave trifluoromethylthio derivatives. These derivatives can be oxidized to the corresponding trifluoromethylsulfones. The difficulty with this approach is that the trifluoromethylthiosilver is expensive to prepare and requires reactions using an autoclave. However, Clark has recently reported the *in situ* formation of CF_3SAg at atmospheric pressure and its conversion to CF_3SCu supported on alumina for the trifluoromethylthioalkylation of aryl iodides.[243] Consequently, alternative syntheses of this copper reagent were investigated.



$$CS_2 + AgF \xrightarrow[\text{autoclave}]{140°C} CF_3SAg$$

$$\begin{tikzcd}
AgF + CS_2 \arrow[r, "CH_3CN", "80°C"'] & {[CF_3SAg]} \arrow[r, "CuBr"] & {[CF_3SCu]} \arrow[d, "CH_3CN"', "Al_2O_3"] & \\
 & & {[CF_3SCu\cdot Al_2O_3]} \arrow[r, "ArI", "150°C"'] & ArSCF_3
\end{tikzcd}$$

Remy prepared the reagent from bis(trifluoromethylthio)mercury.[244] It can also be generated *in situ* and reacts with both aryl iodides and bromides. The main drawback of this procedure is the necessity to prepare and handle the toxic bis(trifluoromethylthio)mercury.



Yagupolskii generated the reagent from bis(trifluoromethyl)disulfide with copper powder in DMF, NMP or HMPA.[245] The reaction is exothermic and is complete within one hour when activated copper is used. Temperatures of 50-60°C are required with unactivated copper. A similar reaction with bis(pentafluorophenyl)

$$CF_3S\text{-}SCF_3 + 2\,Cu \xrightarrow{DMF} 2\,CF_3SCu$$

disulfide at 70°C gives the analogous pentafluorophenylthiocopper in quantitative yield.[245] Perfluoroalkylthioalkylation occurs with aryl iodides in good yields. Although this procedure is operationally simple, it requires the use of the toxic bis(trifluoromethyl) disulfide. Munavalli and co-workers have also prepared CF_3SCu from CF_3SSCF_3 and isolated the stable copper reagent. They utilized the reagent to prepare mixed disulfides.[246]

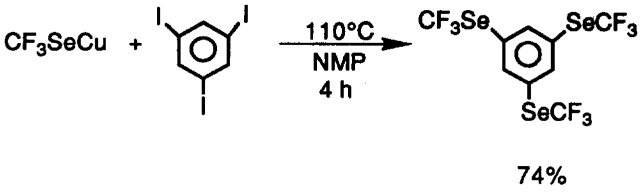
$$CF_3SCu + RSSR \longrightarrow CF_3SSR$$

$$R = Ph,\ 74\%$$

An analogous route can be employed with bis(trifluoromethyl) diselenides to give the trifluoromethylselenocopper reagent which reacts with aryl iodides to give the corresponding trifluoromethylseleno

$$CF_3Se\text{-}SeCF_3 + 2\,Cu \longrightarrow 2\,CF_3SeCu$$

derivatives.[245] Similar reaction with bis(pentafluorophenyl) diselenide with copper powder gives the pentafluorophenylselenocopper reagent, C_6F_5SeCu, which couples readily with aryl iodides.[245]



XI. Perfluoroalkyl Silver Reagents:

In 1968, Miller and Burnard prepared the first perfluoroalkylsilver reagent *via* the reaction of a perfluoroalkene with silver fluoride in acetonitrile.[247] Solutions of this silver reagent could also be prepared in tetraglyme, DMF and benzonitrile using sealed ampoules. Hexafluoropropene, 1-chloropentafluoropropene and

$$CF_3CF{=}CF_2 + AgF \xrightarrow[\substack{25°C \\ 2\,h}]{CH_3CN} (CF_3)_2CFAg$$

perfluoro-2-methyl-2-pentene readily gave secondary or tertiary silver reagents. These reagents were stable and could be isolated as an acetonitrile solvate by removal of excess solvent under reduced pressure. Acetonitrile solutions of the perfluoroalkylsilver reagents gave the hydroperfluoroalkanes when treated with HCl or H_2O.

$$CF_3CFBrCF_3 \xleftarrow{Br_2} (CF_3)_2CFAg \xrightarrow[\substack{or \\ H_2O}]{HCl} CF_3CFHCF_3$$

Reaction with bromine gave the bromoperfluoroalkane. Thermolysis of the acetonitrile solvate gave mainly the dimerized perfluoroalkane. The silver reagent from 2-chloropentafluoropropene gave $(CF_3)_2CClCClCF(CF_3)_2$

$$(CF_3)_2CFAg{\cdot}CH_3CN \xrightarrow[1.5\,h]{100°C} (CF_3)_2CFCF(CF_3)_2$$

66%

at 100°C. A similar addition of silver fluoride to tetrafluoroallene was reported by Banks.[248]

$$F_2C{=}C{=}CF_2 + AgF \longrightarrow CF_3C(Ag){=}CF_2$$

The 2-hydrohexafluoroisopropylsilver was prepared by Knunyants *via* decarboxylation of the pyridine complex of the silver salt of 2-hydroperfluoroisobutyric acid.[249] Acid hydrolysis, bromination, NMR, and

$$(CF_3)_2CHCOOH + Ag_2CO_3 \longrightarrow (CF_3)_2CHCO_2Ag \xrightarrow[\text{2) 40-50°C}\atop\text{MeCN}]{\text{1) Py}} (CF_3)_2CHAg$$

mass-spectral data were consistent with the formation of the silver reagent. Although Miller noted that the perfluoroalkylsilver reagents did not readily transfer perfluoroalkyl groups, Knunyants found that

$$(CF_3)_2CHAg + HgCl_2 \xrightarrow{CH_3CN} [(CF_3)_2CH]_2Hg$$

$$49\%$$

2-hydrohexafluoroisopropylsilver underwent a metathesis reaction with mercuric chloride to give bis(2-hydrohexafluoroisopropyl) mercury. Normant later reported functionalization of the perfluorosilver reagent with carbon dioxide or allyl bromide.[250]

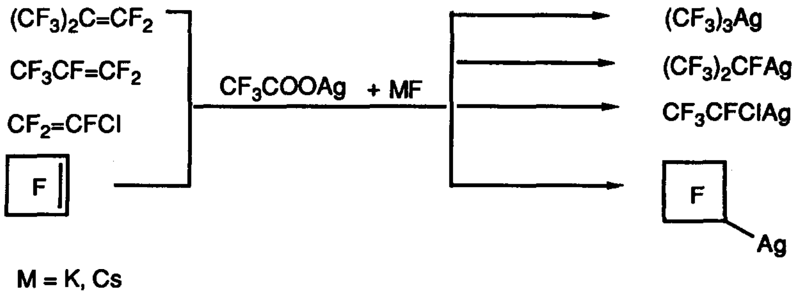
$$(CF_3)_2CFAg{\bullet}CH_3CN + CH_2{=}CHCH_2Br \longrightarrow (CF_3)_2CFCH_2CH{=}CH_2$$

$$50\%$$

$$(CF_3)_2CFAg \xrightarrow[\text{2) } PhCH_2Br]{\text{1) } CO_2} (CF_3)_2CFCO_2CH_2Ph$$

$$60\%$$

Dyatkin demonstrated that perfluoroolefins could react with silver trifluoroacetate in the presence of fluoride to give perfluoroalkylsilver reagents in a manner similar to the preparation of perfluoroalkylmercurials.[251] This method avoids the tedious preparation of silver fluoride. DMF, CH_3CN or 1,2-dimethoxyethane have been employed as solvents in this method with olefins such as hexafluoropropene, trifluorochloroethene and perfluorocyclobutene. Cesium fluoride and potassium fluoride were used. Cesium fluoride exhibited higher reactivity. This approach produces primary, secondary, and tertiary perfluoroalkylsilver reagents. The reaction

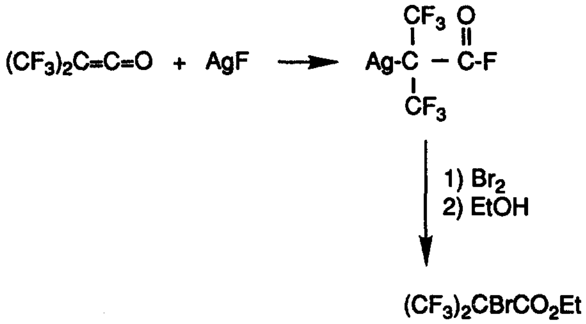


presumably proceeds *via* formation of an intermediate perfluorocarbanion followed by displacement of silver from the silver trifluoroacetate. The regiochemistry of the reaction is consistent with this mechanism. With

$$>C{=}CF_2 + F^- \rightleftharpoons R_F^-$$

$$R_F^- + AgO_2CCF_3 \longrightarrow AgR_F + {}^-O_2CCF_3$$

strong electrophiles catalysis involving fluoride ion is not necessary, and bis(trifluoromethyl) ketene readily adds silver fluoride in DMF to give the α-silver perfluoroisobutyryl fluoride. As noted in previous work, the



$$(CF_3)_2C{=}C{=}O + AgF \longrightarrow Ag\text{-}C(CF_3)_2\text{-}C(O)F \xrightarrow[2)\ EtOH]{1)\ Br_2} (CF_3)_2CBrCO_2Et$$

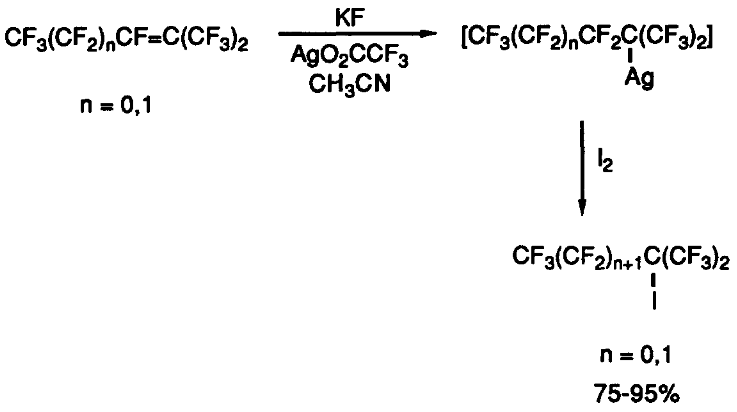
perfluoroalkylsilver reagents react with halogens, bromine and iodine. The silver reagents are oxidized by dioxygen.

$$(CF_3)_2CFAg + O_2 \longrightarrow (CF_3)_2C{=}O$$

Banks employed the Dyatkin methodology to prepare heptafluoro-2-nitrosopropane.[252]

$$CF_3CF{=}CF_2 + KF + CF_3CO_2Ag \xrightarrow[rt]{CH_3CN} [(CF_3)_2CFAg] \xrightarrow{NOCl} \underset{85\%}{(CF_3)_2CFNO}$$

Von Werner and co-workers also utilized this approach to prepare novel perfluoro-tert-alkyl iodides *via* the indirect addition of iodine fluoride to perfluoroalkenes.[253]

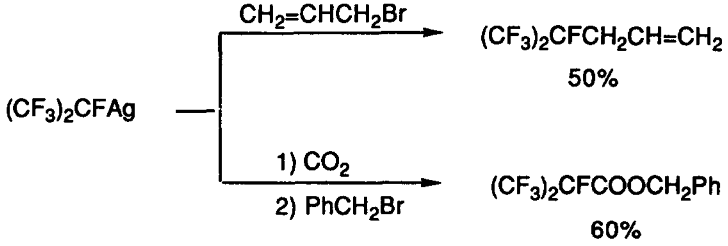


Burch and Calabrese[254] found that the heptafluoroisopropylsilver acetonitrile complex exists in dynamic equilibrium in solution with solvated Ag^+ and the anionic perfluoroalkylsilver complex $Ag[CF(CF_3)_2]_2^-$. Addition of tetraalkylammonium salts gave isolable tetraalkylammonium salts of $Ag[CF(CF_3)_2]_2^-$· The photochemical and thermal instability of these tetraalkylammonium salts precluded elemental analyses and structure determination by x-ray crystallography. The rhodium (I) salt of $Ag[CF(CF_3)_2]_2^-$ was isolated and the structure was determined by x-ray diffraction. The overall geometry is essentially linear and the two isopropyl groups are rotated about the C-Ag-C axis so that the C-F bonds are nearly perpendicular. The trifluoromethyl silver complex $[Ag(CF_3)_4]^-$ can be prepared by the reaction of silver nitrate with bis(trifluoromethyl)cadmium in acetonitrile.[151]

Perfluoroalkylsilver compounds react with halogens[247,251] to give perfluoroalkyl halides. The silver reagents, when treated with elemental sulfur[251] or carbon dioxide[250] form perfluoroalkylthiosilvers or the salt of a perfluoro carboxylic acid, respectively. These react with organic halides to produce fluorinated sulfides or perfluoroesters. Direct reaction with allyl halides gives the fluorinated alkenes.

$$(CF_3)_3CAg \quad + \quad S_8 \longrightarrow (CF_3)_3SAg \longrightarrow (CF_3)_3CSCH_2CH{=}CH_2$$

46%



Emeleus reported the preparation of trifluoromethylthiosilver.[255]

$$3\,AgF + CS_2 \longrightarrow AgSCF_3 + Ag_2S$$

XII. Functionalized Fluorinated Organometallics:

Carboalkoxydifluoromethylene Organometallics:

[A]: Carboalkoxydifluoromethylene Zinc Reagents:

In 1984, Fried reported that reaction of bromodifluoroacetate with carbonyl substrates in the presence of zinc gave the α,α-difluoro-β-hydroxyester.[256,257] Although a two step procedure was used, the intermediate zinc reagent need not be isolated. The zinc reagent could either be carbon- or oxygen-metallated.

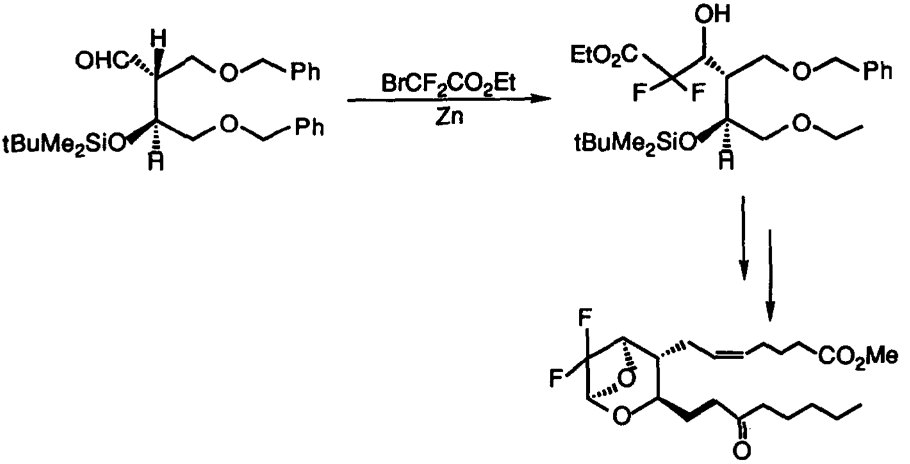
Burton and Easdon generated the reagent from zinc amalgam and ethyl difluorobromoacetate in triglyme or THF. The structure was demonstrated to be the carbon-metallated reagent *via* ^{19}F and ^{13}C NMR analysis.[258] Subsequently, Kobayashi prepared this zinc reagent from iododifluoroacetates and zinc in

$$BrCF_2CO_2Et + Zn(Hg) \xrightarrow[\text{rt}]{\text{Triglyme}} \underset{77\%}{[BrZnCF_2CO_2Et]} + \underset{4\%}{(CF_2CO_2Et)_2} + \underset{1\%}{HCF_2CO_2Et}$$

various solvents (THF, dioxane, DMF, DME and CH_3CN). Best results were obtained in acetonitrile. Only the succinate was observed when diethyl ether was employed as the solvent.[259]

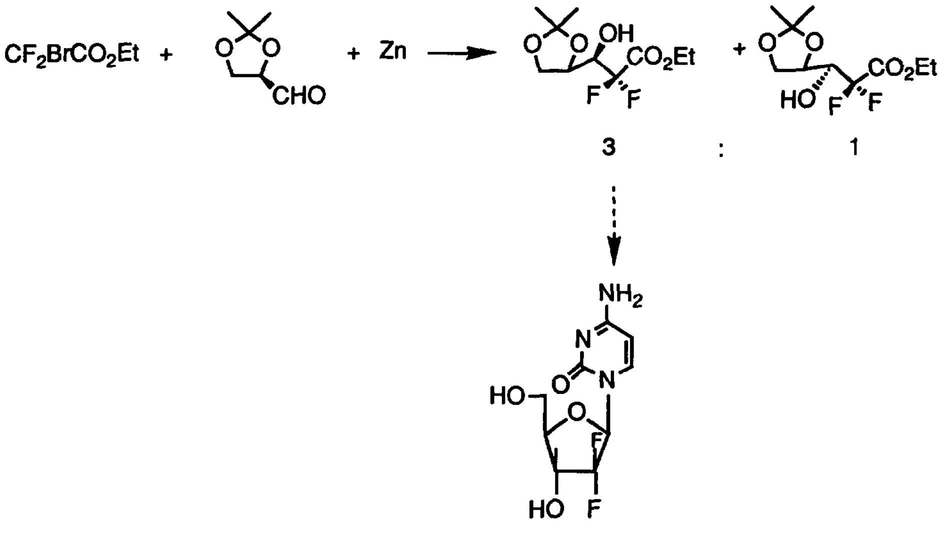
$$ICF_2CO_2Me + Zn \longrightarrow \underset{75\text{-}85\%}{[IZnCF_2CO_2Me]} + \underset{10\%}{(CF_2CO_2Me)_2} + \underset{5\text{-}7\%}{HCF_2CO_2Me}$$

The main application of the α,α-difluoro Reformatsky reagent has been for the incorporation of the $-CF_2C(O)-$ group or its derivatives, since this functionality often confers enhanced biological activity. Fried has prepared the 7,7-difluoro derivatives of the 2,6-dioxa[3.1.1]bicycloheptane ring system present in thromboxane A_2 *via* the reaction of the difluoro Reformatsky reagent with a chiral β-protected hydroxyaldehyde.[256,260]



Further elaboration gave the 10,10-difluorothromboxane A_2. The rate of hydrolysis of the 2,6-dioxadifluoro-[3.1.1]bicycloheptane system was 10^8 times slower than that of thromboxane A_2.[260]

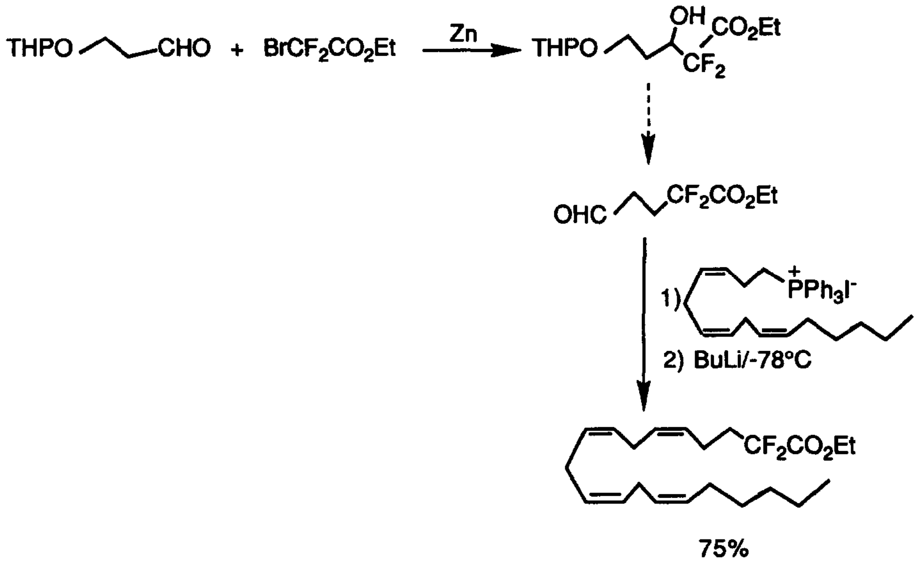
Hertel and co-workers employed this reagent to stereoselectively prepare a difluoro-γ-lactone intermediate that was subsequently converted to 1-(2-deoxy-2,2-difluororibofuranosyl) pyrimidine nucleosides.[261] These



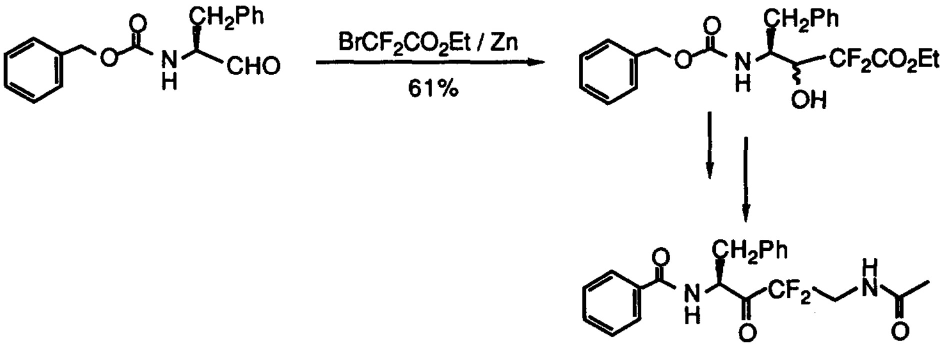
3 : 1

workers also prepared uridine nucleoside analogues *via* 2,2-difluoroketene silyl acetal in the condensation step.

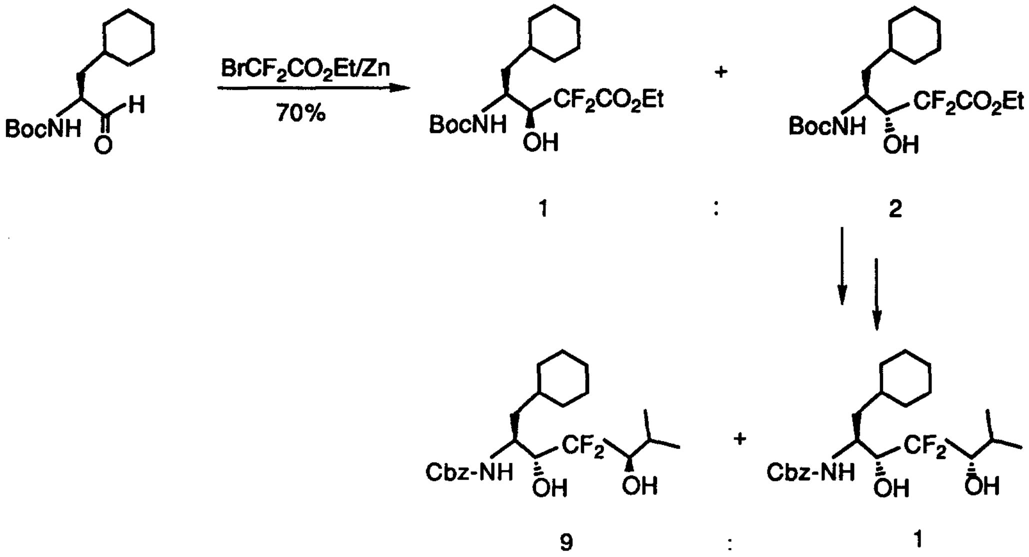
Matsuda employed the difluoro Reformatsky reagent in the preparation of 14,14-difluoro-4-demethoxydaunorubicin.[262] This anthracycline was found to exhibit prominent *in vitro* cytotoxicity and *in vivo* antitumor activity against P388 murine leukemia. Kobayashi used the difluoro Reformatsky reagent as a key step in the preparation of 2,2-difluoroarachidonic acid.[263]



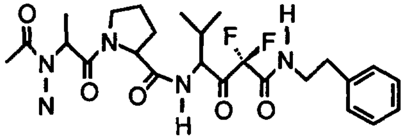
The difluoro Reformatsky reagent has been widely used for the introduction of the difluoromethylene unit to yield dipetidyl difluoromethyl ketones, which are potent enzyme inhibitors.[264,265] The preparation of a dipeptide isostere precursor reported by Schirlin[266] is outlined below:



Sham and co-workers employed this reagent in the synthesis of 6(S)-amino-7-cyclohexyl-4,4-difluoro-3(R),5(R)-dihydroxy-2-methylheptane.[267] This compound was coupled with Boc-Phe-Leu-OH to give a potent inhibitor of human renin. Hoover[268] also prepared a ketodifluoromethylene dipeptide isostere by ylide methodology. The crystal structure of a precursor of (2S,5S,4R)-2,5-diamino-3,3-difluoro-1,6-diphenylhydroxyhexane has recently been published.[269] The introduction of the difluoromethylene unit was

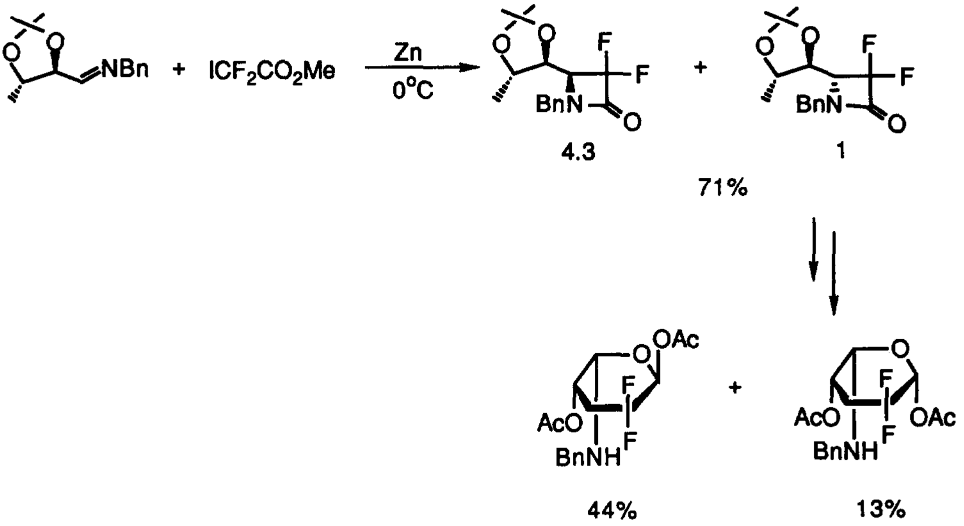


accomplished with the difluoro Reformatsky reagent. Incorporation of this compound as the core unit of a small molecule resulted in a very potent inhibitor of HIV-1 proteinase. The crystal structure of the covalent complex formed by the peptidyl α,α-difluoro-β-keto amide, below, with porcine pancreatic elastase has shown that the

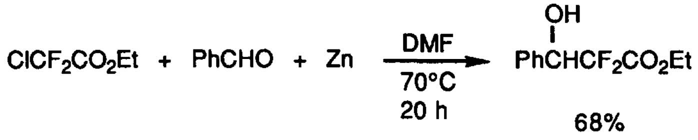


lightly bound inhibitor forms a hemiketal complex with the $O\gamma$ atom of the catalytic Ser-195 and is stabilized by five intermolecular hydrogen bonds and optimal Van der Waals' surface interactions.[270]

The Reformatsky reaction of iodo- or bromodifluoroacetates with imines has been used by Taguchi to prepare 3,3-difluoro-2-azetidinone derivatives.[271] Imines derived from aromatic aldehydes (66-87%) afforded the lactam in good yields as compared to crotonaldehyde imine (35%). With chiral aldehydes, syn-selectivity (syn/anti = 3.1-4.7/1) was observed. The 3,3-difluoro-2-azetidinones could be transformed to 2,3-dideoxy-2,2-difluoro-3-amino sugar derivatives.

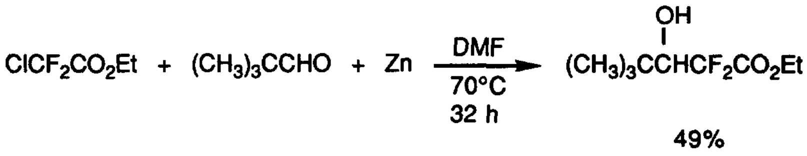


Elegant work by Lang demonstrated that the cheaper precursor, ethyl chlorodifluoroacetate, could also be converted to a Reformatsky reagent in dry DMF.[272] Ethereal solvents were ineffective. In-situ trapping of the reagent with aldehydes using Barbier conditions with aldehydes gave the β-hydroxy-α,α-difluoroesters. The corresponding chlorodifluoroamide gave low yields (>20%) in the analogous reaction with



$$\mathrm{ClCF_2CO_2Et + PhCHO + Zn \xrightarrow[70^\circ C,\ 20\ h]{DMF} Ph\overset{OH}{\overset{|}{C}}HCF_2CO_2Et}$$

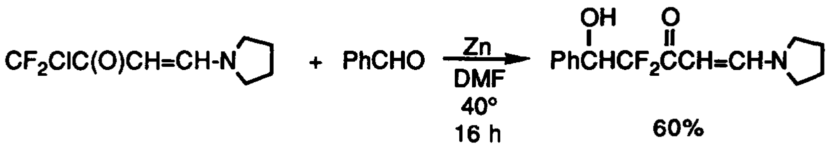
68%



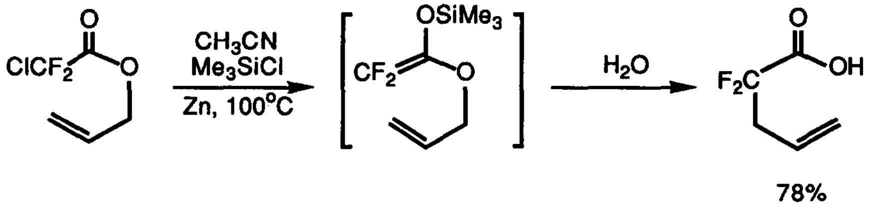
$$\mathrm{ClCF_2CO_2Et + (CH_3)_3CCHO + Zn \xrightarrow[70^\circ C,\ 32\ h]{DMF} (CH_3)_3C\overset{OH}{\overset{|}{C}}HCF_2CO_2Et}$$

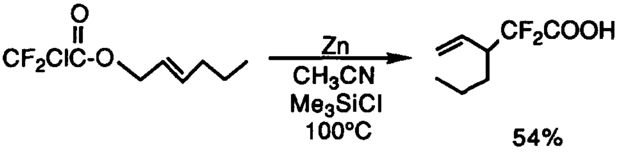
49%

benzaldehyde. Interestingly, the vinylogous esters and amides both reacted. The vinylogous amide gave the expected addition product, but the primary product from the vinylogous ester underwent spontaneous cyclization to give 3,3-difluoro-2-phenyl-2,3-dihydro-4-pyrone.

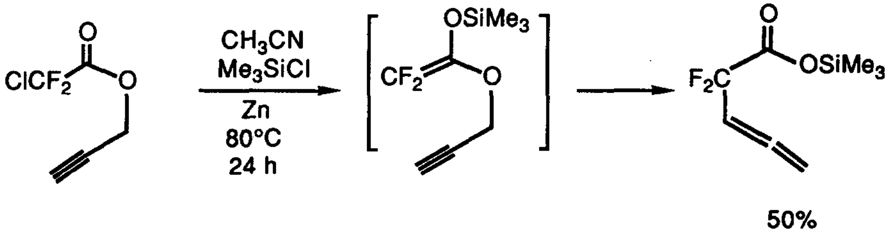


In a subsequent paper, Lang demonstrated that a silicon-induced Reformatsky-Claisen reaction of allyl chlorodifluoroacetate in the presence of zinc and trimethylsilyl chloride gives the 2,2-difluoro-4-pentenoic acid after hydrolysis of the silyl ester.[273] This reaction sequence was applicable to a wide variety of alkyl substituted





allyl chlorodifluoroacetates. These acids are useful precursors to α-amino ketones which can be utilized in the preparation of protease inhibitors. Reaction with propargylic esters gives the allenic esters.



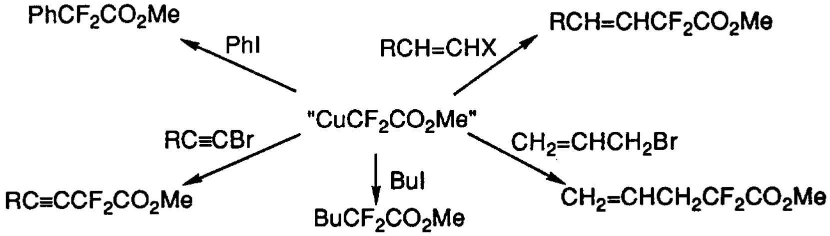
[B]: Carboalkoxydifluoromethylene Copper Reagents:

Reaction of methyl iododifluoroacetate with copper in DMF, DMSO or HMPA gives the methoxycarbonyldifluoromethylcopper reagent.[274] Although different species of the copper reagent in solution were detected by ^{19}F NMR spectroscopy (cf. CF_3Cu), the structure of each species has not been determined.[275]

$$ICF_2COMe + Cu \longrightarrow \text{"}CuCF_2CO_2Me\text{"}$$

The thermal stability of the copper reagent is solvent dependent. The half lives of the copper reagents at room temperature in HMPA, DMF and DMSO are 40 hours, 20 hours and 5 hours, respectively. The major decomposition product detected in DMSO and HMPA is difluorofumurate. In DMF, the major product is difluoroacetate.[275]

The copper reagent couples with aryl, alkenyl and allyl halides to give the corresponding α,α-difluoroesters in good yield.[274,275] However, with haloacetylenes in DMF, very poor yields of the desired products are obtained because of a preferential halogen-metal exchange reaction. When DMF is replaced with HMPA, the copper reagent reacts smoothly with a bromoacetylene derivative to afford the alkynylated α,α-difluoroester.[275] Halogen metal exchange is still observed with iodoacetylene derivatives even if HMPA is used as the solvent. Reaction with an alkyl iodide in HMPA gave the alkylated product in moderate yield.



Dialkoxyphosphinyldifluoromethylene Organometallics:

[A]: Dialkoxyphosphinyldifluoromethyllithium Reagents:

Diethyl difluoromethylphosphonate is readily prepared from chlorodifluoromethane.[276] Although the

$$(EtO)_2P(O)^-Na^+ + CHF_2Cl \longrightarrow (EtO)_2P(O)CF_2H + NaCl$$

reaction appears to be an S_N2 type of displacement, the mechanism involves generation and capture of difluorocarbene.[277] When difluoromethylphosphonate is treated with lithium diisopropylamide in THF

$$(EtO)_2P(O)^-Na^+ + CHF_2Cl \longrightarrow (EtO)_2P(O)H + [:CF_2] + Cl^- + Na^+$$

$$(EtO)_2P(O)^-Na^+ + [:CF_2] \rightleftharpoons (EtO)_2P(O)\overset{-}{C}F_2Na^+$$

$$(EtO)_2P(O)\overset{-}{C}F_2Na^+ + (EtO)_2P(O)H \longrightarrow (EtO)_2P(O)CF_2H + (EtO)_2P(O)^-Na^+$$

at -78°C, dialkoxyphosphinyldifluoromethyllithium is produced and can be captured by a variety of electrophiles.[278] The dialkoxylphosphinyldifluoromethyl anion is unstable and rapidly dissociates to give difluorocarbene.[277,279] Thus the generation of this lithium reagent is best conducted at -78 to -90°C.

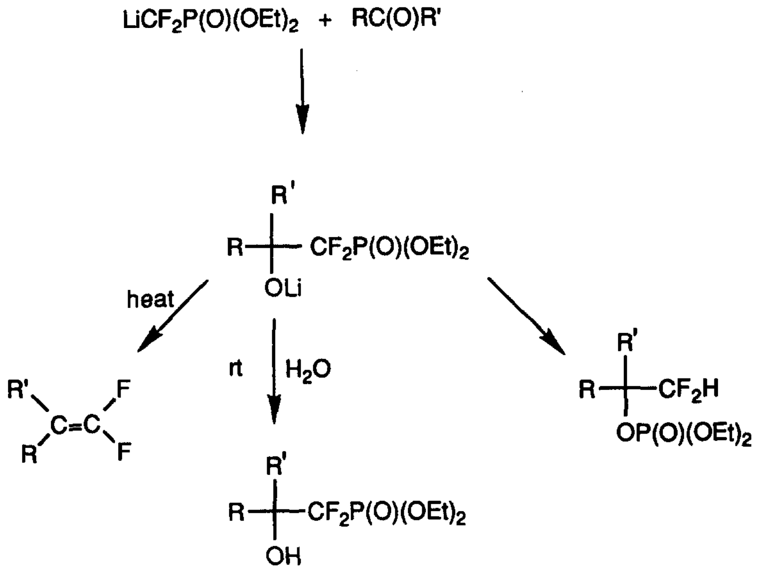
$$HCF_2P(O)(OEt)_2 \xrightarrow[-78^\circ C \atop THF]{LDA} LiCF_2P(O)(OEt)_2 \xrightarrow{EX} ECF_2P(O)(OEt)_2$$

EX = Me_3SiCl, $n\text{-}Bu_3SnCl$, $(EtO)_2P(O)Cl$, EtBr,

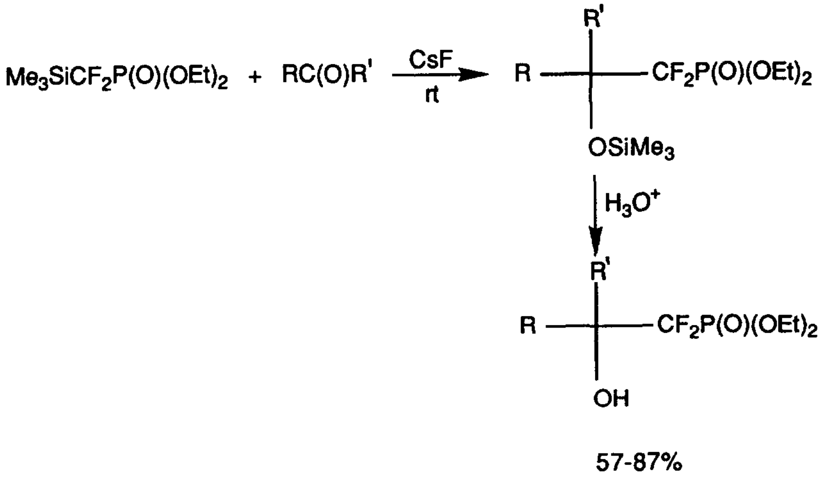
$C_6H_{13}Br$, $H_2C{=}CHCH_2Br$, PhC(O)Cl

$$(EtO)_2P(O)\overset{-}{C}F_2Li^+ \rightleftharpoons [:CF_2] + (EtO)_2P(O)Li$$

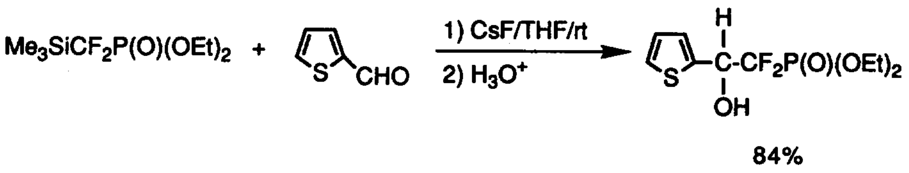
Aldehydes and ketones react with the dialkoxyphosphinyldifluoromethyllithium. Work-up at room temperature produced diethyl 2,2-difluoro-3-hydroxyalkylphosphonates. Heating the THF solution of the intermediate adduct derived from aldehydes and ketones induced the Wadsworth-Emmons reaction to give 1,1-difluoroolefins.[278] Although this procedure is generally applicable to various aldehydes and ketones, those having a nitro group or a pyridine ring gave none of the desired products or underwent rearrangement to give phosphates.



An improved procedure for the above transformation was accomplished *via* the reaction of diethyl difluoro(trimethylsilyl)methylphosphonate with arene carbaldehydes and aryl methyl ketones in the



presence of cesium fluoride.[280] Both p-nitrobenzaldehyde and 4-pyridinecarbaldehyde as well as highly enolizable acetophenone derivatives are viable substrates. An improved preparation of the trimethylsilyl

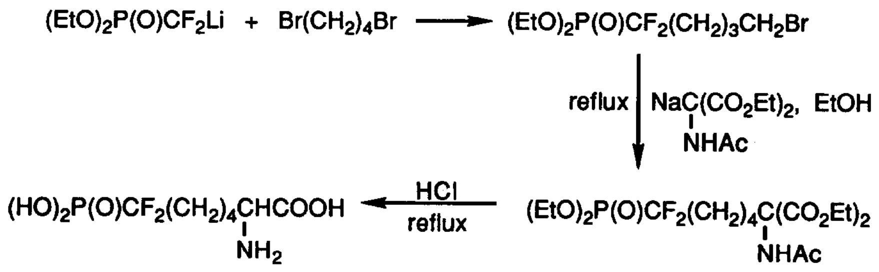


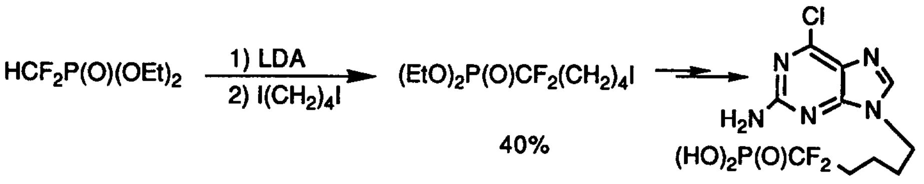
analog on a 0.5 mole scale has been reported by Sprague *via* in situ generation and capture of the unstable dialkoxyphosphinyldifluoromethyllithium with trimethylsilyl chloride.[281]

$$(EtO)_2P(O)CF_2Br + BuLi + Me_3SiCl \xrightarrow{-78°C} (EtO)_2P(O)CF_2SiMe_3$$

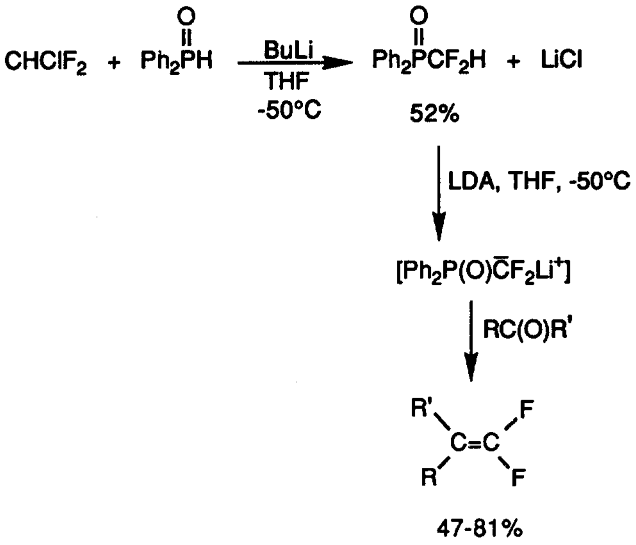
51%

This lithium reagent has been used in the preparation of biologically active compounds. For example, Johnson and co-workers utilized the lithium reagent to give an intermediate difluoromethylene phosphonate which could be converted to 2-amino-7,7-difluoro-7-phosphonoheptanoic acid for evaluation in an N-methyl-D-aspartic acid binding assay.[282] Similarly, Danzin employed this reagent to prepare 9-(5,5-difluoro-5-phosphonopentyl)quanine as a multisubstrate analogue inhibitor of purine nucleoside phosphorylase.[283]





Edwards reported an analog of the above described reagent *via* similar methodology.[284] Reaction of difluoromethyldiphenylphosphine oxide with LDA in THF at -50°C gave a solution of the anion which could be captured by aldehydes and ketones.

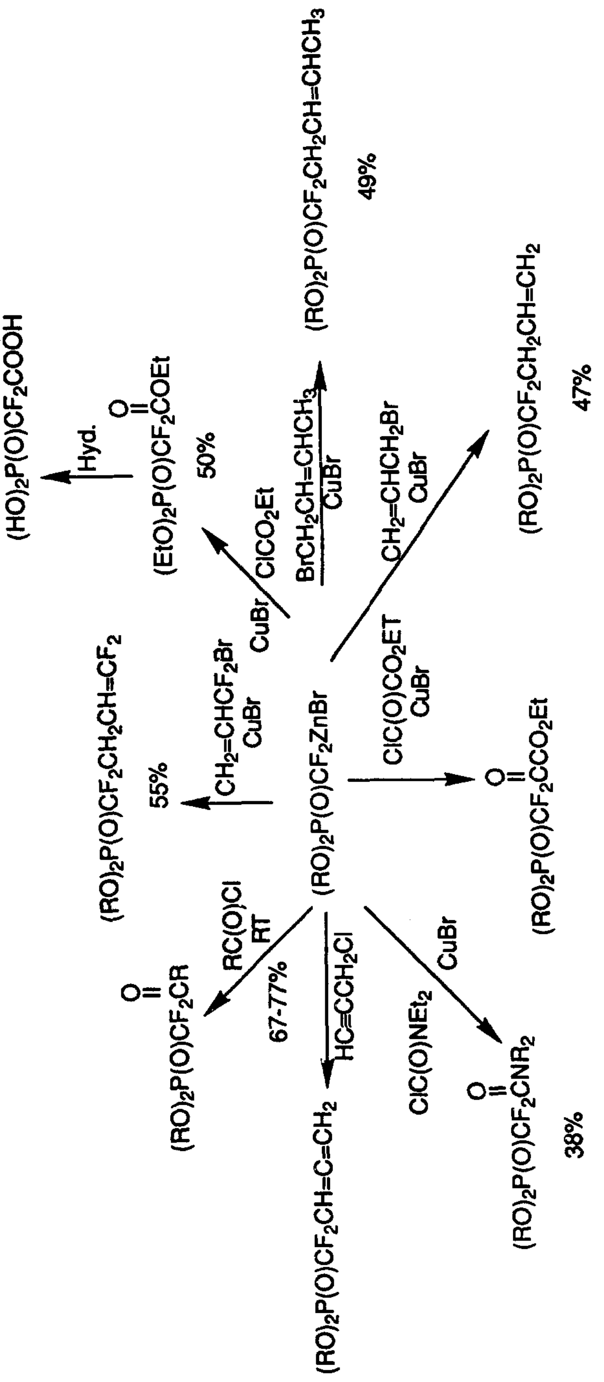


[B] Dialkoxyphosphinyldifluoromethylzinc Reagents

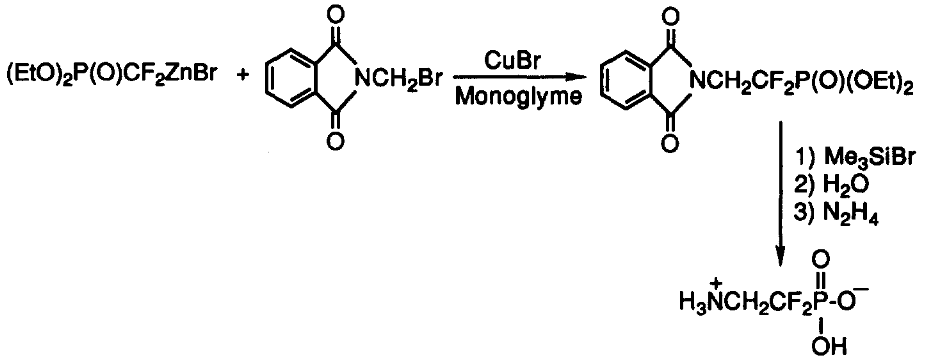
Treatment of dialkyl bromodifluoromethylphosphonates with acid washed zinc dust or powder in ethereal solvents such as dioxane, THF, monoglyme or triglyme at room temperature to 60°C gives the dialkoxyphosphinyldifluoromethylzinc reagents in good yields.[285] The zinc reagent forms a homogeneous solution in these ethereal solvents and can be stored at room temperature for several months without change. This zinc reagent also exhibits excellent thermal stability. For example, only 49% of the zinc reagent decomposed when dibutoxyphosphinyldifluoromethylzinc bromide was heated at 100°C for four hours. Aqueous hydrolysis of the zinc reagent is slow at room temperature. Consequently, the dialkoxyphosphinyldifluoromethylzinc reagent is significantly more stable than the corresponding lithium reagent. As expected, the zinc reagent is not as reactive as the lithium reagent, but it does react with strong electrophilic reagents. It is the method of choice when either of the reagents can be employed, especially for larger scale reactions. Some typical applications of this stable reagent are illustrated on the following page.[286,287,288]

$$(RO)_2P(O)CF_2Br + Zn \xrightarrow{rt} (RO)_2P(O)CF_2ZnBr$$

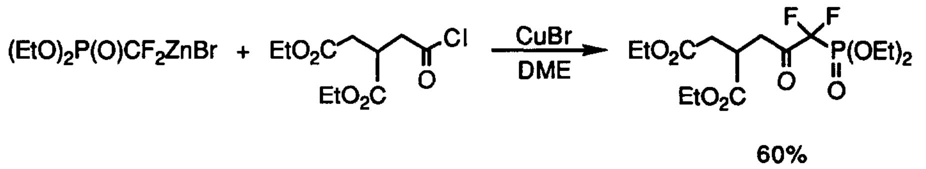
R = Et, *i*-Pr, n-Bu stable


(RO)$_2$P(O)CF$_2$ZnBr
(HO)$_2$P(O)CF$_2$COOH
Hyd.
(EtO)$_2$P(O)CF$_2$C(O)OEt
50%
ClCO$_2$Et
CuBr
BrCH$_2$CH=CHCH$_3$
CuBr
(RO)$_2$P(O)CF$_2$CH$_2$CH$_2$CH=CHCH$_3$
49%
CH$_2$=CHCH$_2$Br
CuBr
(RO)$_2$P(O)CF$_2$CH$_2$CH$_2$CH=CH$_2$
47%
CH$_2$=CHCF$_2$Br
CuBr
(RO)$_2$P(O)CF$_2$CH$_2$CH$_2$CH=CF$_2$
55%
ClC(O)CO$_2$ET
CuBr
(RO)$_2$P(O)CF$_2$C(O)CO$_2$Et
RC(O)Cl
RT
67-77%
(RO)$_2$P(O)CF$_2$C(O)R
HC≡CCH$_2$Cl
(RO)$_2$P(O)CF$_2$CH=C=CH$_2$
ClC(O)NEt$_2$
CuBr
(RO)$_2$P(O)CF$_2$C(O)NR$_2$
38%

With less reactive electrophiles cuprous bromide catalyzes and improves the reaction with the zinc reagent. This methodology was used in the preparation and x-ray structure determination of 2-amino-1,1-difluoroethylphosphonic acid, a phosphate mimic.[289]



Similarly, Lindell prepared functionalized difluoromethylene phosphonates for evaluation as inhibitors of the enzyme aspartate transcarbamoylase.[290]



As noted, cuprous halide catalysis is effective in reactions of the dialkoxyphosphinyldifluoromethylzinc reagent. Presumably, the functionalizations proceed through an intermediate dialkoxyphosphinyldifluoromethylcopper species. In the absence of a trapping electrophile and in a poor coordinating solvent, copper (I) halide mediated reactions of dialkoxyphosphinyldifluoromethylzinc bromide give the (E) and (Z)-1,2-difluoroethenediylbisphosphonates.[291] Presumably, these bisphosphonates are formed from either fluoro(diethoxyphosphinyl)carbene dimerization or a dialkoxyphosphinyldifluoromethyl copper carbenoid. However, attempts to trap $[(EtO)_2P(O)\ddot{C}F]$ with alkenes were unsuccessful.

The zinc reagent can undergo metathesis with metal halides, such as copper (I) halides and mercuric halides.

$$(EtO)_2P(O)CF_2ZnBr + PhHgCl \longrightarrow (EtO)_2P(O)CF_2HgPh$$

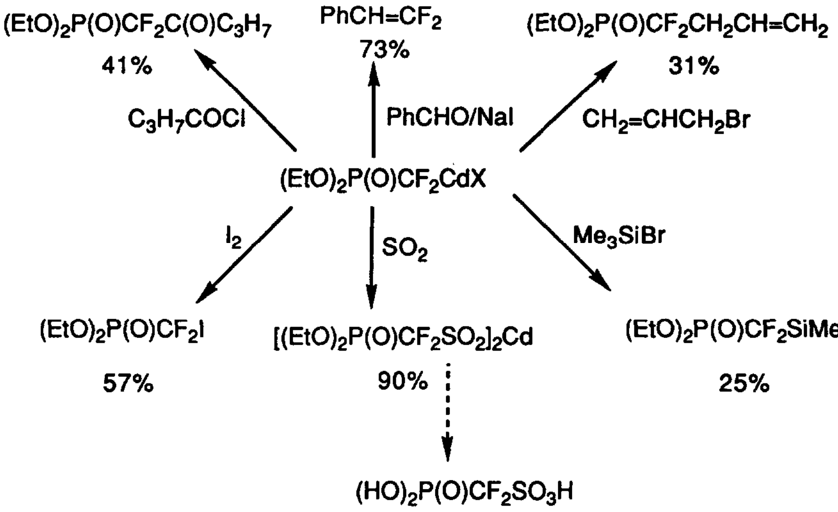
61%

[C]: Dialkoxyphosphinyldifluoromethylcadmium Reagents:

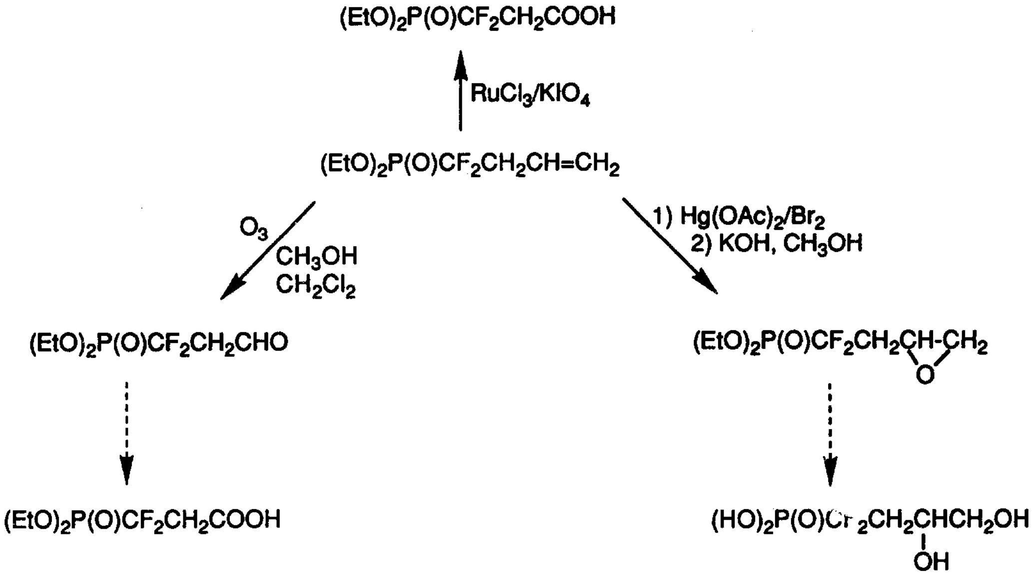
Dialkoxyphosphinyldifluoromethylcadmium reagent can be readily prepared *via* reaction of diethyl bromodifluoromethylphosphonate with acid-washed cadmium powder in solvents such as triglyme, dioxane, DMF, HMPA and THF.[292] The cadmium reagent is remarkably stable. In the absence of moisture it is stable at room temperature for days to months and can be heated at 70-100°C for a few hours without significant decomposition. Moisture rapidly hydrolyzes the cadmium reagent to $(EtO)_2P(O)CF_2H$.

$$(EtO)_2P(O)CF_2Br + Cd \xrightarrow{\text{rt-70°C}} (EtO)_2P(O)CF_2CdBr + [(EtO)_2P(O)CF_2]_2Cd$$

The cadmium reagent exhibits versatile chemical reactivity. Halogenation and acylation occur readily with bromine, iodine and acid halides, respectively. Reaction with sulfur dioxide, followed by oxidation and hydrolysis, provides (sulfodifluoromethyl)phosphonic acid.[293] The cadmium reagent reacts with trimethylsilyl bromide to give the carbon silylated product. Interestingly, in the presence of sodium iodide, the cadmium reagent reacts with benzaldehyde to produce the Wittig product.



The difluoromethylenephosphonate produced by alkylation of the cadmium reagent with allyl halides has been demonstrated to be a versatile intermediate in the preparation of complex difluoromethylenephosphonates of biological importance.[294,295]

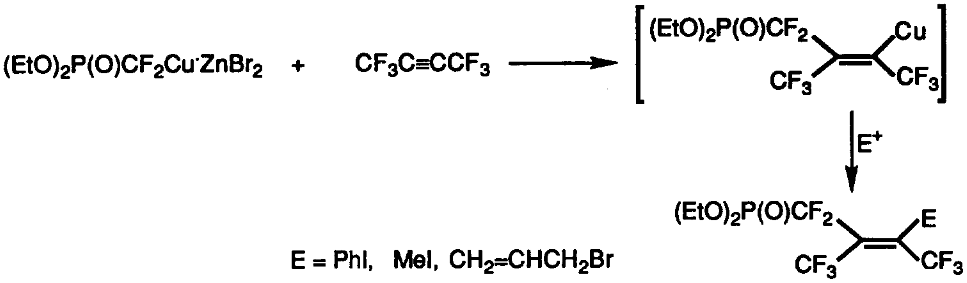


[D]: Dialkoxyphosphinyldifluoromethylcopper Reagents:

As noted in [B] above, copper (I) halide catalysis of the dialkoxyphosphinyldifluoromethylzinc reagents enhances reaction of this reagent with electrophiles. Generally, the reactions of the zinc reagent are carried out in glyme or other ethereal solvents in which an analogous copper reagent would not be expected to exhibit high stability. However, if either the zinc or cadmium reagent is exchanged with copper (I) bromide in DMF, a stable dialkoxyphosphinyldifluoromethylcopper reagent is produced.[296] The copper reagent in DMF undergoes a syn addition to hexafluoro-2-butyne to give the functionalized vinyl copper reagent, which reacted further with allyl bromide, methyl iodide and iodobenzene.[297] Future study of this functionalized difluoromethyl organometallic

$$(EtO)_2P(O)CF_2MX + CuBr \longrightarrow (EtO)_2P(O)CF_2CuMBr_2$$

$$M = Cd,\ Zn$$



should provide new methodology for the introduction of the difluoromethylphosphonate group.

Acknowledgement

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