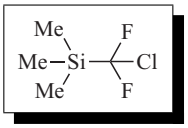
(Chlorodifluoromethyl)trimethylsilane

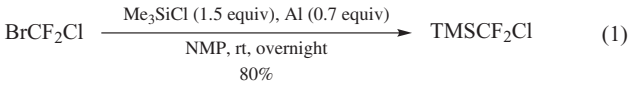


[115262-00-5] $C_4H_9ClF_2Si$ (MW 158.65)
InChI = 1S/C4H9ClF2Si/c1-8(2,3)4(5,6)7/h1-3H3
InChIKey = DGLFKUGPLIRHCC-UHFFFAOYSA-N

(nucleophilic chlorodifluoromethylation reagent for aldehydes, ketones, and oxalates;[1,2] difluoromethylenation reagent for alkynes and alkenes[3])

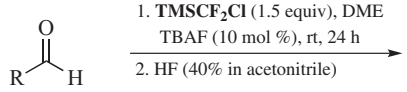
Physical Data: bp 80–82 °C.[1]
Solubility: insoluble in H_2O; soluble in organic solvents.
Form Supplied in: colorless liquid; often prepared by aluminum-induced reduction of bromochlorodifluoromethane ($BrCF_2Cl$) with chlorotrimethylsilane (Me_3SiCl).[1]
Handling, Storage, and Precautions: (chlorodifluoromethyl)-silane (Me_3SiCF_2Cl) is stable in 98% sulfuric acid at 0 °C, but has high reactivity with bases and reducing metals; store under anhydrous, neutral conditions; use in a fume hood.

Preparation of (Chlorodifluoromethyl)trimethylsilane. (Chlorodifluoromethyl)trimethylsilane ($TMSCF_2Cl$) is often prepared from bromochlorodifluoromethane ($BrCF_2Cl$) and chlorotrimethylsilane (Me_3SiCl) in the presence of a reducing agent.[1,3] Initially, $TMSCF_2Cl$ was prepared by the reduction of $BrCF_2Cl$ with tris(diethylamino)phosphane [$P(NEt_2)_3$] in only 20% yield.[4] Later an efficient method was developed applying an aluminum-induced reductive synthesis of $TMSCF_2Cl$ in *N*-methylpyrrolidinone (NMP) solvent (eq 1),[1] avoiding the use of the carcinogenic $P(NEt_2)_3$. The unavoidable by-product disiloxane can be quantitatively removed by washing the mixture with 98% sulfuric acid without affecting $TMSCF_2Cl$.[1] Although halogen exchange reaction between $TMSCF_2Br$ and TMSCl also leads to the formation of Me_3SiCF_2Cl,[1] this method is seldom used due to the poor commercial availability of Me_3SiCF_2Br.



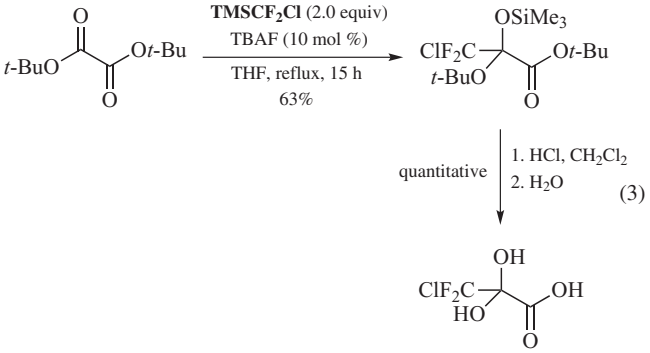
(1)

Nucleophilic Addition to Carbonyl Groups. The $TMSCF_2Cl$ reagent can be used as a nucleophilic chlorodifluoromethylating agent for aldehydes, ketones, and oxylates (eq 2).[1,2] Although $TMSCF_2Cl$ is less reactive than the Ruppert–Prakash reagent ($TMSCF_3$), the chlorodifluoromethylation of carbonyls can proceed smoothly in strong polar solvents or at elevated temperatures.[1] Using tetra(*n*-butyl)ammonium fluoride (TBAF) as an initiator, both aromatic and aliphatic aldehydes are chlorodifluoromethylated in dimethoxyethane (DME) at room temperature in good yields (eq 2).[1] Ketones, such as benzophenones, also react with $TMSCF_2Cl$ at room temperature in presence of TBAF as an initiator furnishing the chlorodifluoromethylated adducts in low yields.[1] At an elevated temperature, di(*tert*-butyl) oxalate reacts with $TMSCF_2Cl$ in THF giving a siloxy product in moderate yield that is converted by HCl into 3,3,3-chlorodifluoro-2-oxopropanoic acid monohydrate quantitatively (eq 3).[2]



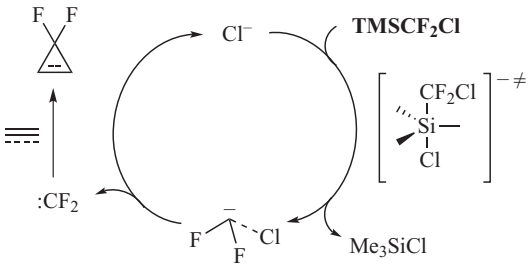
(2)

R = Ph,	yield = 75%;
= CH_2Ph,	yield = 85%;
= n-C_6H_{13},	yield = 64%;



(3)

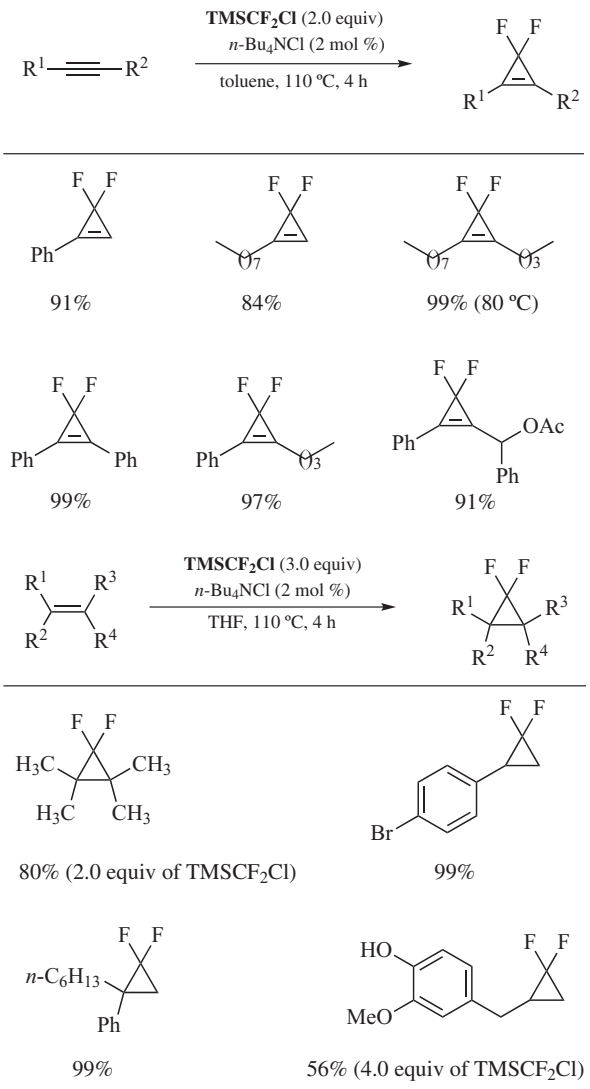
Difluoromethylenation of Alkynes. The title compound can also be used as a difluorocarbene precursor under neutral conditions (eq 4).[3] It has been found that the difluoromethylenation of various alkynes catalyzed by tetra(*n*-butyl)ammonium chloride (n-Bu_4NCl) afforded *gem*-difluorocyclopropenes in good to excellent yields (eq 5).[3] The reaction is usually conducted in toluene at 110 °C and is amenable to both alkyl- and aryl-substituted alkynes. Even the propargyl acetate could be difluoromethylenated in high yields (eq 5).[3] In the cases of the dialkylated alkynes, the reaction was performed at 80 °C due to the thermal instability of the *gem*-difluorocyclopropene products (eq 5).[3]



(4)

Difluoromethylenation of Alkenes. The title reagent can difluoromethylenate a variety of structurally diverse alkenes under the catalysis of n-Bu_4NCl, giving *gem*-difluorocyclopropanes in moderate to good yields (eq 6).[3] To achieve the best result, the reaction was carried out in a sealed system at 110 °C with THF as the solvent. The reaction not only works for multisubstituted electron-rich alkenes, but also works well with many monosubstituted

alkenes. Among the monosubstituted alkenes, aryl-substituted alkenes generally provided higher yields than alkyl-substituted substrates. Moreover, for the alkene bearing a reactive phenoxyl group, *gem*-difluorocyclopropane was also obtained in 56% yield (eq 6).[3]



(5)

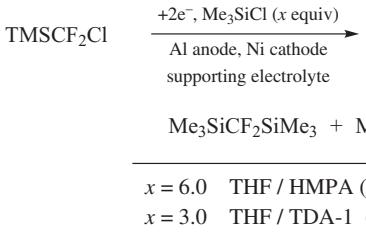
(6)

Reduction with tributylstannane. The C–Cl bond of $TMSCF_2Cl$ reagent can be cleaved under radical initiating condition. The reduction of $TMSCF_2Cl$ with tributylstannane (*n*-Bu_3SnH) produces difluoromethyltrimethylsilane ($TMSCF_2H$) in 81% isolated yield (eq 7).[4] The improved difluoromethylation reactions of carbonyl compounds and imines with $TMSCF_2H$ reagent have been reported.[5]

$$TMSCF_2Cl + n\text{-}Bu_3SnH \xrightarrow[50\ ^\circ C,\ 5\text{–}6\ h]{neat} TMSCF_2H + Bu_3SnCl \quad (7)$$

81%

Electroreduction with Chlorotrimethylsilane. The $TMSCF_2Cl$ reagent can also undergo electroreduction. Electroreduction of $TMSCF_2Cl$ in the presence of chlorotrimethylsilane (TMSCl) using the sacrificial aluminum anode technique gives a mixture of $TMSCF_2TMS$ and $TMSCF_2CF_2TMS$ (eq 8).[1] A mixed solvent system of THF and hexamethylphosphoramide (HMPA) strongly favors the generation of $TMSCF_2TMS$, while a combination of THF and tris(3,6-dioxaheptyl)amine (TDA-1) favors $TMSCF_2CF_2TMS$. Formation of the homocoupling product $TMSCF_2CF_2TMS$ indicates the formation of radicals in the course of the reduction (eq 9).[1] Both $TMSCF_2TMS$ and $TMSCF_2CF_2TMS$ can be used as selective fluoroalkylating or fluorovinylating agents.[1]



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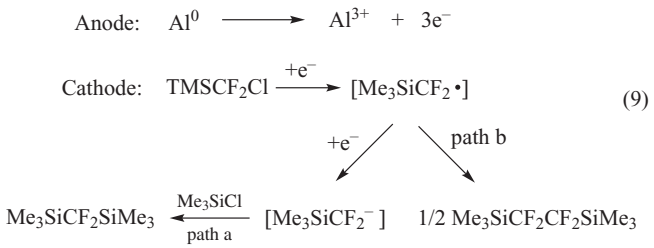
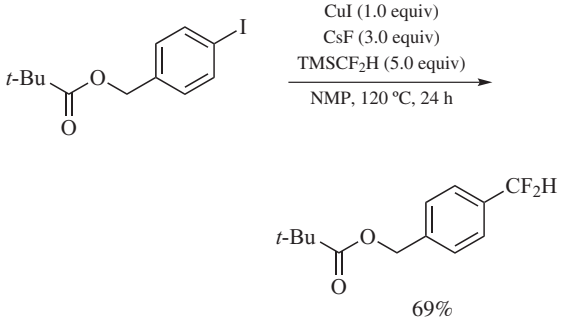


(9)

Difluoromethylation of Aryl- and Vinyl Iodides. The combination of CuI, CsF, and $TMSCF_2H$ enables the difluoromethylation reaction of electron-neutral, electron-rich, and sterically hindered aryl- and vinyl iodides (eqs 10 and 11).[6] High yields and excellent chemoselectivity are observed for this reaction.



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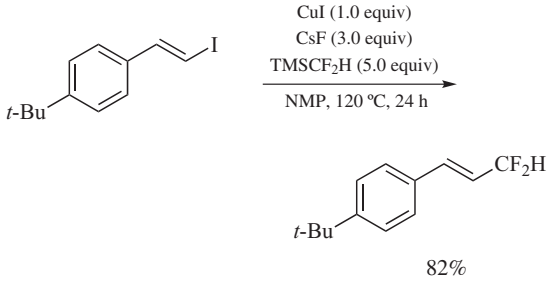

(11)

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