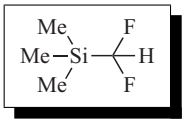
(Difluoromethyl)trimethylsilane



[65864-64-4] $C_4H_{10}F_2Si$ (MW 124.20)
InChI = 1S/C4H10F2Si/c1-7(2,3)4(5)6/h4H,1-3H3
InChIKey = OOKFLLNDYNWCHK-UHFFFAOYSA-N

(nucleophilic difluoromethylation reagent for carbonyl compounds,[1,2,10] imines,[1] and iodides[3]; important precursor to prepare $TMSCF_2Br$[4])

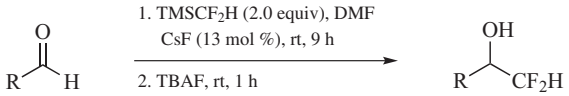
Physical Data: bp 51–53 °C.[5]
Solubility: insoluble in H_2O; soluble in organic solvents.
Form Supplied in: colorless liquid; often prepared by hydrodefluorination of (trifluoromethyl)trimethylsilane ($TMSCF_3$) with sodium borohydride ($NaBH_4$).[6]
Handling, Storage, and Precautions: (difluoromethyl)trimethylsilane ($TMSCF_2H$) has moderate reactivity with nucleophilic bases; store under anhydrous, neutral conditions; use in a fume hood.

Preparation of (Difluoromethyl)trimethylsilane. (Difluoromethyl)trimethylsilane ($TMSCF_2H$) is easily prepared from the commercially available Ruppert–Prakash reagent ($TMSCF_3$) and sodium borohydride ($NaBH_4$) by slowly adding the former into a diglyme solution of the latter at room temperature (eq 1).[6] Initially, $TMSCF_2H$ was prepared by fluorination of tetramethylsilane with diluted fluorine gas, and was isolated using gas chromatography for characterization.[7] The radical-mediated monodehalogenation of (bromodifluoromethyl)trimethylsilane ($TMSCF_2Br$) or (chlorodifluoromethyl)trimethylsilane ($TMSCF_2Cl$) with tributylstannane (n-Bu_3SnH) provided the first synthetically useful method to produce $TMSCF_2H$.[5] However, this method is less attractive in modern organic synthesis, not only because of the use of large amount of toxic n-Bu_3SnH, but also because of the less ready availability of dibromodifluoromethane (CF_2Br_2) and bromochlorodifluoromethane ($BrCF_2Cl$) that are used to prepare $TMSCF_2Br$ and $TMSCF_2Cl$, respectively. The reductive desulfonylation of difluoromethyl phenyl sulfone ($PhSO_2CF_2H$) with magnesium (Mg) in the presence of chlorotrimethylsilane (TMSCl) can also afford $TMSCF_2H$ (eq 2),[8] which is an important alternative to the monodefluorination of $TMSCF_3$.[6]

$$TMSCF_3 \xrightarrow[\text{diglyme, 20–25 °C}]{NaBH_4} TMSCF_2H \quad (1)$$
70%

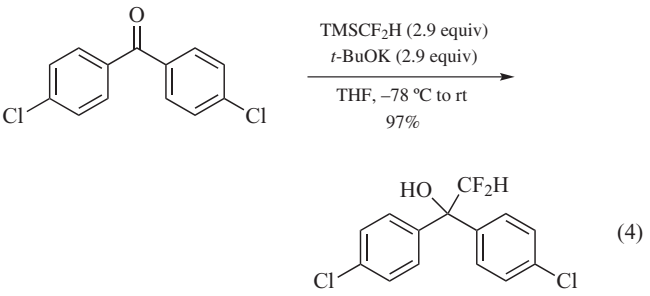
$$PhSO_2CF_2H \xrightarrow[\text{DMF, 0 °C, 1.5 h}]{Mg/Me_3SiCl} TMSCF_2H \quad (2)$$
76%

Nucleophilic Addition to Carbonyls. (Difluoromethyl)trimethylsilane ($TMSCF_2H$), as a more readily available reagent than (difluoromethyl)dimethyl(phenyl)silane ($PhMe_2SiCF_2H$),[9] can be used for the nucleophilic difluoromethylation of aldehydes and ketones.[1,2,10] Although $TMSCF_2H$ is less reactive than the Ruppert–Prakash reagent ($TMSCF_3$), the difluoromethylation reaction initiated by a catalytic amount of Lewis base can proceed in a strongly polar solvent.[1,2,10] If the initiating agent is less soluble in the solvent used, a high reaction temperature is necessary.[10] However, the difluoromethylation in a less polar solvent requires a stoichiometric amount of soluble Lewis base to activate $TMSCF_2H$. The reaction of aldehydes, even enolizable aldehydes, with $TMSCF_2H$ initiated by a catalytic amount of cesium fluoride (CsF) in NMP can afford the difluoromethyl-substituted carbinols in moderate to excellent yields (eq 3).[1] The enolizable ketones were also reported to be reactive under similar reaction conditions.[2] Sometimes, an alkoxide-based reagent are more efficient than fluoride to initiate the reaction. The reactions with diaryl ketones initiated by a stoichiometric amount of potassium *tert*-butoxide (*t*-BuOK) give CF_2H-containing carbinols in excellent yields (eq 4), whereas the reactions with enolizable methyl ketones failed to give the corresponding products. This is probably due to the labile enolization of these substrates under the basic reaction conditions.[1] The requirement of a stoichiometric amount of *t*-BuOK indicates that *tert*-butoxide anion possesses better activating ability for silicon–carbon bond cleavage than the in situ generated difluoromethyl carbinolate species.[1]



(3)

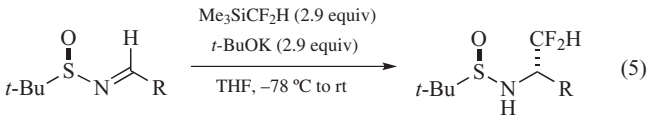
R	Yield (%)
4-$MeOC_6H_4$	91
3-$NO_2C_6H_4$	77
(*E*)-styryl	78
CH_2CH_2Ph	53



(4)

Nucleophilic Addition to Imines. The $TMSCF_2H$ reagent can also be used as a nucleophilic difluoromethylating agent for activated aldimines.[1] The direct addition of $TMSCF_2H$ to non-*aza*-enolizable *N*-*tert*-butylsulfinyl aldimines initiated by a stoichiometric amount of *t*-BuOK in THF gives the difluoromethyl-containing sulfinamides in good to excellent yields with good diastereoselectivity (eq 5).[1] The observed slightly lower diastereoselectivity (compared with the corresponding nucleophilic trifluoromethylation using $TMSCF_3$)[11] was attributed to the decreased steric hindrance of the difluoromethyl group (CF_2H) relative to the trifluoromethyl group (CF_3).[1] As the two diastereomers are separable, this reaction is useful for the synthesis of optically active

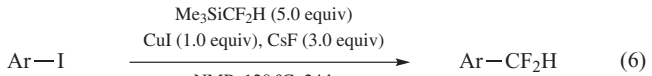
α-difluoromethyl amines after the removal of the *tert*-butylsulfinyl group.



(5)

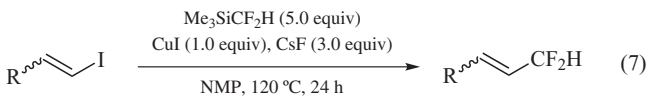
R	Yield (%)	dr
4-$MeOC_6H_4$	91	92:8
3-pyridyl	68	90:10
t-Bu	90	92:8
2-furyl	90	91:9

Difluoromethylation of Aryl and Vinyl Iodides. The cross coupling of electron-rich and electron-neutral aryl iodides with $TMSCF_2H$ promoted by a stoichiometric amount of copper iodide (CuI) and CsF can provide difluoromethylated arenes in moderate to excellent yields (eq 6).[3] The reactive species that undergoes this coupling reaction is believed to be (difluoromethyl)copper ($CuCF_2H$) that is in situ generated from $TMSCF_2H$ and CuI under the action of CsF. The progress of this difluoromethylation requires DMF and a temperature as high as 120 °C.[3] The reaction tolerates amine, ether, amide, ester, aromatic bromide, and protected alcohol functionalities; however, electron-deficient aryl iodides are not proper coupling partners in this difluoromethylation reaction.[3] The cross-coupling of vinyl iodides with $TMSCF_2H$ under similar reaction conditions gives difluoromethylated alkenes in moderate to good yields (eq 7).[3] This reaction proceeds stereospecifically, that is, no *Z*/*E* isomerization of the C–C double bond occurs.[3] In contrast to $TMSCF_2H$, tributyl(difluoromethyl)stannane (n-Bu_3SnCF_2H) is much more suitable for the copper-mediated difluoromethylation of electron-deficient aryl iodides.[12]



(6)

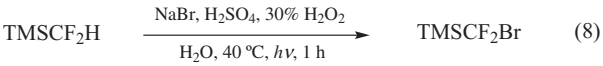
R	Yield (%)
4-*t*-BuC_6H_4	90
3-$MeOC_6H_4$	81
4-(4-$BrC_6H_3CH_2$)C_6H_4	77
4-(BocOCH_2)C_6H_4	52



(7)

R	Yield (%)
(*E*)-4-*t*-BuC_6H_4	80
(*E*)-C_6H_{13}	91
(*Z*)-C_6H_{13}	42

Radical Bromination. The F_2C–H bonds of difluoromethyl silanes can readily undergo radical reactions.[9] Bromination of $TMSCF_2H$ using hydrogen bromide/aqueous hydrogen peroxide system irradiated with household incandescent light bulb afforded $TMSCF_2Br$ in a good yield (eq 8).[4] Considering the ready availability of $TMSCF_2H$,[6,8] this is a very practical protocol to prepare the synthetically useful $TMSCF_2Br$. As a source of difluorocarbene or difluorocarbenoid species, $TMSCF_2Br$ has been used to synthesize *gem*-difluorocyclopropenes,[13] α-difluorinated alkylzinc reagents (RCF_2ZnX),[14] and difluoro(trimethylsilyl)acetonitrile ($TMSCF_2CN$)[4] from alkynes, alkylzinc reagents (RZnX), and trimethylsilyl cyanide (TMSCN), respectively.



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1. Zhao, Y.; Huang, W.; Zheng, J.; Hu, J., *Org. Lett.* **2011**, *13*, 5342.
2. Tyutyunov, A. A.; Boyko, V. E.; Igoumnov, S. M., *Fluorine Notes* **2011**, *78*, 5.
3. Fier, P. S.; Hartwig, J. F., *J. Am. Chem. Soc.* **2012**, *134*, 5524.
4. Kosobokov, M. D.; Dilman, A. D.; Levin, V. V.; Struchkova, M. I., *J. Org. Chem.* **2012**, *77*, 5850.
5. Broicher, V.; Geffken, D., *J. Organomet. Chem.* **1990**, *381*, 315.
6. Tyutyunov, A. A.; Boyko, V. E.; Igoumnov, S. M., *Fluorine Notes* **2011**, *74*, 1.
7. Liu, E. K. S.; Lagow, R. J., *J. Organomet. Chem.* **1978**, *145*, 167.
8. Prakash, G. K. S.; Hu, J.; Olah, G. A., *J. Org. Chem.* **2003**, *68*, 4457.
9. Fuchikami, T.; Ojima, I., *J. Organomet. Chem.* **1981**, *212*, 145.
10. Hagiwara, T.; Fuchikami, T., *Synlett* **1995**, 717.
11. Prakash, G. K. S.; Mandal, M.; Olah, G. A., *Angew. Chem., Int. Ed.* **2001**, *40*, 589.
12. Prakash, G. K. S.; Ganesh, S. K.; Jones, J.-P.; Kulkarni, A.; Masood, K.; Swabeck, J. K.; Olah, G. A., *Angew. Chem., Int. Ed.* **2012**, *51*, 12090.
13. Wang, F.; Zhang, W.; Zhu, J.; Li, H.; Huang, K.-W.; Hu, J., *Chem. Commun.* **2011**, *47*, 2411.
14. Levin, V. V.; Zemtsov, A. A.; Struchkova, M. I.; Dilman, A. D., *Org. Lett.* **2013**, *15*, 917.

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