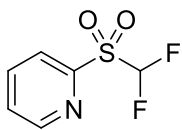
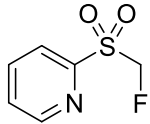
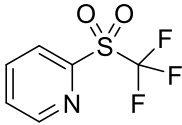
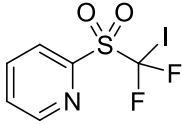
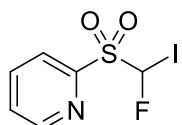
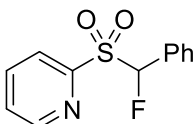
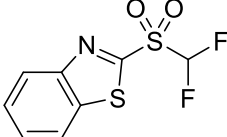


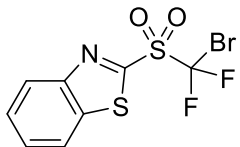
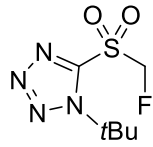
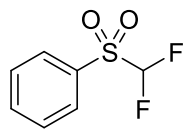
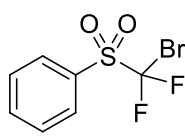
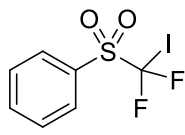
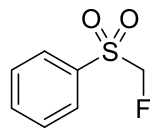
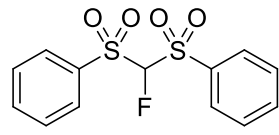
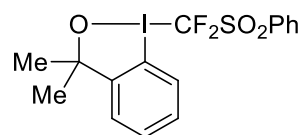
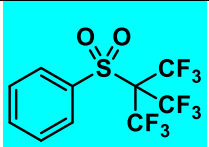
Fluorination Reagents and Applications:

A Review of Hu's Reagents

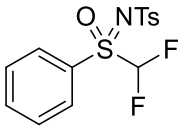
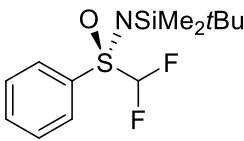
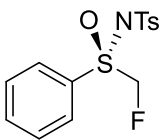
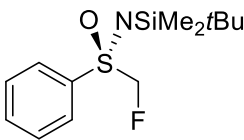
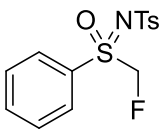
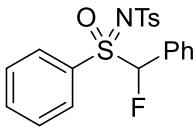
(Feb. 2023)

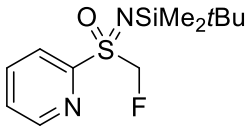
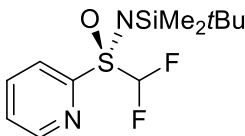
1. Fluorinated sulfones

Reagent No	Chemical Name	Structure Formula	M.P. °C
CAS Reg. No	Acronym		Purity
	MF, MW		(¹ H NMR)
HU-F101	2-Pyridyl difluoromethyl sulfone <i>Hu reagent</i> ; (2-Py)SO ₂ CF ₂ H		45 – 47 (white solid) ≥ 98%
1219454-89-3	C ₆ H ₅ F ₂ NO ₂ S 193.17		
HU-F102	2-Pyridyl fluoromethyl sulfone (2-Py)SO ₂ CH ₂ F		83 – 85 (white solid) ≥ 98%
1365765-53-2	C ₆ H ₆ FNO ₂ S 175.18		
HU-F103 (NEW!)	2-Pyridyl trifluoromethyl sulfone (2-Py)SO ₂ CF ₃		50 – 51 (white solid) ≥ 98%
57830-55-4	C ₆ H ₄ F ₃ NO ₂ S 211.16		
HU-F104	2-Pyridyl difluoroiodomethyl sulfone (2-Py)SO ₂ CF ₂ I		122 – 124 (white solid) ≥ 98%
1621689-73-3	C ₆ H ₄ F ₂ IO ₂ S 319.06		
HU-F105	2-Pyridyl fluoroiodomethyl sulfone (2-Py)SO ₂ CHF ₂ I		68 – 70 (white solid) ≥ 98%
1415115-02-4	C ₆ H ₅ FINO ₂ S 301.08		
HU-F106	2-[[Fluoro(phenyl)methyl]sulfonyl]pyridine		147 – 148 (white solid) ≥ 98%
1689584-09-5	C ₁₂ H ₁₀ FNO ₂ S 251.28		
HU-F107 (NEW!)	2-Benzo[d]thiazolyl difluoromethyl sulfone 2-BTSO ₂ CF ₂ H		155 – 156 (white solid) ≥ 98%
186204-66-0	C ₈ H ₅ F ₂ NO ₂ S ₂ 249.26		

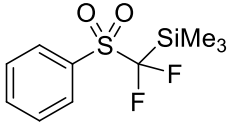
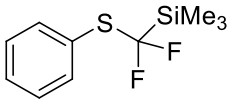
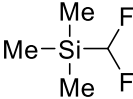
HU-F108 (NEW!) 1230154-56-9	2-Benzo[<i>d</i>]thiazolyl bromodifluoromethyl sulfone <i>2-BTSO₂CF₂Br</i> C ₈ H ₄ BrF ₂ NO ₂ S ₂ 328.16		100 – 102 (white solid) ≥ 98%
HU-F109 1236300-44-9	1- <i>tert</i> -butyl-1 <i>H</i> -tetrazol-5-yl fluoromethyl sulfone <i>1-TBTSO₂CH₂F</i> C ₆ H ₁₁ FN ₄ O ₂ S 222.24		(Colorless oil) ≥ 95%
HU-F110 1535-65-5	Difluoromethyl phenyl sulfone <i>PhSO₂CF₂H</i> C ₇ H ₆ F ₂ O ₂ S 192.18		<i>B.P.</i> 118 – 121 (7 Torr) (Colorless liquid) ≥ 98%
HU-F111 80351-58-2	Bromodifluoromethyl phenyl sulfone <i>PhSO₂CF₂Br</i> C ₇ H ₅ BrF ₂ O ₂ S 271.08		33 – 34 (white solid) ≥ 98%
HU-F112 802919-90-0	Difluoroiodomethyl phenyl sulfone <i>PhSO₂CF₂I</i> C ₇ H ₅ F ₂ IO ₂ S 318.08		66 – 68 (white solid) ≥ 98%
HU-F113 20808-12-2	Fluoromethyl phenyl sulfone <i>PhSO₂CH₂F</i> C ₇ H ₇ FO ₂ S 174.1927		50 – 51 (white solid) ≥ 98%
HU-F114 910650-82-7	Fluorobis(phenylsulfonyl)methane <i>FBSM; (PhSO₂)₂CHF</i> C ₁₃ H ₁₁ FO ₄ S ₂ 314.35		105 – 106 (white solid) ≥ 98%
HU-F115 1052174-67-0	3,3-Dimethyl-1-[difluoro(phenylsulfonyl)methyl]-1,2-benziodoxole C ₁₆ H ₁₅ F ₂ IO ₃ S 452.25		89 – 90 (white solid) ≥ 98%
HU-F116 (NEW!) 68596-36-1	Perfluoro- <i>tert</i> -butyl phenyl sulfone (PF ₇ BS) C ₁₀ H ₅ F ₉ O ₂ S 360.19		55-56 °C (White solid) ≥ 98%

2. Fluorinated Sulfoximines

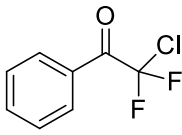
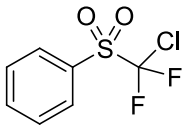
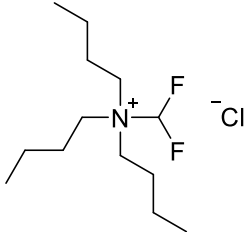
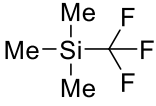
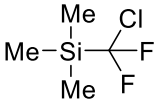
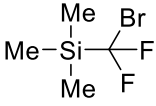
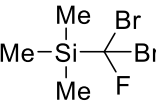
Reagent No	Chemical Name	Structure Formula	M.P. °C
CAS Reg. No	Acronym		Purity
	MF, MW		(¹ H NMR)
HU-F201 1097192-99-8	<i>N</i> -Tosyl- <i>S</i> -difluoromethyl- <i>S</i> -phenyl sulfoximine C ₁₄ H ₁₃ F ₂ NO ₃ S ₂ 345.38		96 – 98 (white solid) ≥ 98%
HU-F202 (NEW!) 1402352-49-1	(<i>R</i>)- <i>N</i> -(<i>tert</i> -Butyl)dimethylsilyl- <i>S</i> -difluoromethyl- <i>S</i> -phenylsulfoximine C ₁₃ H ₂₁ F ₂ NOSSi 305.46		(colorless oil) [α] _D ²⁸ : +54.9 (c = 0.97, CHCl ₃) ≥ 98% > 99% ee
HU-F203 (NEW!) 1422176-84-8	(<i>R</i>)- <i>N</i> -Tosyl- <i>S</i> -fluoromethyl- <i>S</i> -phenylsulfoximine C ₁₄ H ₁₄ FNO ₃ S ₂ 327.39		89 – 91 (white solid) ≥ 98% > 99.5% ee [α] _D ²⁴ : +49.8 (c = 1.00, CHCl ₃)
HU-F204 (NEW!) 825638-25-3	(<i>R</i>)- <i>N</i> -(<i>tert</i> -Butyl)dimethylsilyl- <i>S</i> -fluoromethyl- <i>S</i> -phenylsulfoximine C ₁₃ H ₂₂ FNOSSi 287.47		Colorless oil ≥ 98% > 99% ee [α] _D ²⁶ : 67.5 (c = 0.8, CHCl ₃)
HU-F205 (NEW!) 1097193-08-2	<i>N</i> -Tosyl- <i>S</i> -fluoromethyl- <i>S</i> -phenylsulfoximine C ₁₄ H ₁₄ FNO ₃ S ₂ 327.39		89 – 91 (white solid) ≥ 98%
HU-F206 1260143-68-7	<i>N</i> -{[Fluoro(phenyl)methyl](oxo)(phenyl)-λ-sulfanylidene}-4-methylbenzenesulfonamide C ₂₀ H ₁₈ FNO ₃ S ₂ 403.50		mixture of two isomers, (white solid) ≥ 98%

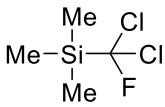
HU-F207 (NEW!) 2050545-76-9	<i>N</i> - <i>tert</i> -Butyldimethylsilyl- <i>S</i> -fluoromethyl- <i>S</i> -(2-pyridyl)sulfoximine		Colorless oil ≥ 98%
	C ₁₂ H ₂₁ FN ₂ OSSi 288.46		
HU-F208 (NEW!)	(<i>R</i>)- <i>N</i> -(<i>tert</i> -Butyl)dimethylsilyl- <i>S</i> -difluoromethyl- <i>S</i> -(2-pyridyl)sulfoximine		68-70 °C (pale yellow solide) [α] _D ²⁴ : +46.4 (c = 1.18, CHCl ₃)
	C ₁₂ H ₂₀ F ₂ N ₂ OSSi 305.46		

3. Fluoroalkylsilanes

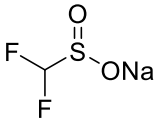
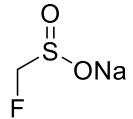
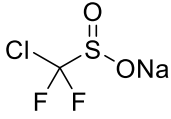
<i>Reagent No</i>	Chemical Name	Structure Formula	<i>B.P.</i> °C
<i>CAS Reg. No</i>	<i>Acronym</i>		<i>Purity</i>
	MF, MW		(¹ H NMR)
HU-F301 536975-50-5	[Difluoro(phenylsulfonyl)methyl]trimethylsilane <i>TMSCF₂SO₂Ph</i>		112 – 114 (1 Torr) (colorless liquid) ≥ 98%
	C ₁₀ H ₁₄ F ₂ O ₂ SSi 264.36		
HU-F302 536975-49-2	[Difluoro(phenylthio)methyl]trimethylsilane <i>TMSCF₂SPh</i>		86 – 87 (4 Torr) (colorless liquid) ≥ 98%
	C ₁₀ H ₁₄ F ₂ SSi 232.37		
HU-F303 65864-64-4	(Difluoromethyl)trimethylsilane <i>TMSCF₂H</i>		86 – 87 (colorless liquid) ≥ 98%
	C ₄ H ₁₀ F ₂ Si 124.20		

4. Difluorocarbene reagents

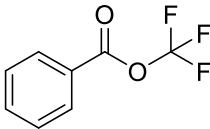
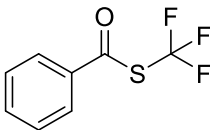
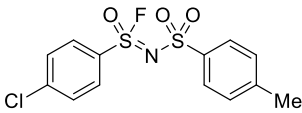
Reagent No CAS Reg. No	Chemical Name Acronym MF, MW	Structure Formula	B.P. °C Purity (¹ H NMR)
HU-F401 384-67-8	2-Chloro-2,2-difluoro-1-phenylethane none <i>PhCOCF₂Cl</i> C ₈ H ₅ ClF ₂ O 190.57		94 – 96 (35 Torr) ≥ 97%
HU-F402 930836-30-9	Chlorodifluoromethyl phenyl sulfone <i>PhSO₂CF₂Cl</i> C ₇ H ₅ ClF ₂ O ₂ S 226.63		<i>M.P.</i> 32 – 33 (White solid) ≥ 97%
HU-F403 1004517-48-9	Difluoromethyltributylammonium chloride C ₁₃ H ₂₈ ClF ₂ N 271.82		<i>M.P.</i> 91 – 93 (White solid) ≥ 95%
HU-F404 81290-20-2	Trimethyl(trifluoromethyl)silane <i>Ruppert-Prakash reagent, TMSCF₃</i> (作为二氟卡宾试剂) C ₄ H ₉ F ₃ Si 142.19		55 – 55.5 (colorless liquid) ≥ 98%
HU-F405 115262-00-5	(Chlorodifluoromethyl)trimethylsilane <i>TMSCF₂Cl</i> C ₄ H ₉ ClF ₂ Si 158.65		80 – 82 (colorless liquid) ≥ 98%
HU-F406 115262-01-6	(Bromodifluoromethyl)trimethylsilane <i>TMSCF₂Br</i> C ₄ H ₉ BrF ₂ Si 203.10		106 – 108 (colorless liquid) ≥ 98%
HU-F407 151479-64-0	(Dibromofluoromethyl)trimethylsilane <i>TMSCFBr₂</i> C ₄ H ₉ Br ₂ FSi 264.00		Colorless liquid) ≥ 95%

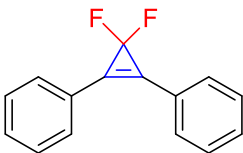
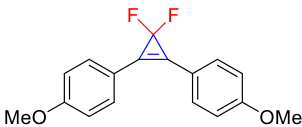
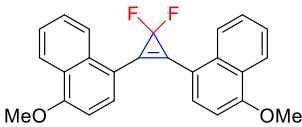
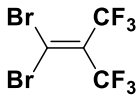
HU-F408	(Dichlorofluoromethyl)trimethylsilane		Colorless liquid) ≥ 95%
90503-30-3	<i>TMSCFCl₂</i> C ₄ H ₉ Cl ₂ FSi 175.10		

5. Fluorinated sulfinate salts

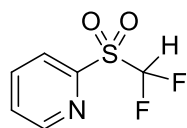
<i>Reagent No</i>	Chemical Name	Structure Formula	<i>M.P. °C</i>
<i>CAS Reg. No</i>	<i>Acronym</i>		<i>Purity</i>
	MF, MW		(¹ H NMR)
HU-F501	Sodium difluoromethanesulfinate		(white solid) ≥ 97%
275818-95-6	CHF ₂ NaO ₂ S 138.07		
HU-F502	Sodium fluoromethanesulfinate		(white solid) ≥ 97%
1661836-10-7	CH ₂ FNaO ₂ S 120.08		
HU-F503	Sodium chlorodifluoromethanesulfinate		(white solid) ≥ 97%
	CClF ₂ NaO ₂ S 172.51		

6. Fluorination and trifluoromethoxylation reagents

<i>Reagent No</i>	Chemical Name	Structure Formula	<i>M.P. °C</i>
<i>CAS Reg. No</i>	<i>Acronym</i>		<i>Purity</i>
	MF, MW		(¹ H NMR)
HU-F601	Trifluoromethyl benzoate		(colorless liquid) ≥ 98%
(NEW!) 1035797-66-0	<i>TFBz</i> C ₈ H ₅ F ₃ O ₂ 190.12		
HU-F602	S-(trifluoromethyl) benzothioate		(colorless liquid) ≥ 98%
(NEW!) 175400-81-4	<i>TFBT</i> C ₈ H ₅ F ₃ OS 206.18		
HU-F603	4-Chloro- <i>N</i> -tosylbenzenesulfonimide		110 – 112 (White solid) ≥ 98%
(NEW!) 2143892-50-4	doyl fluoride <i>SulfoxFluor</i> C ₁₃ H ₁₁ ClFNO ₃ S ₂ 347.80		

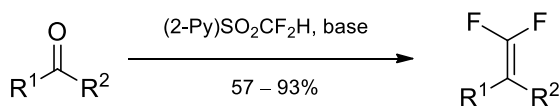
HU-F604 (NEW!) 172747-57-8	(3,3-Difluorocycloprop-1-ene-1,2-diyl)dibenzene <i>CpFluor-Ph</i> $C_{15}H_{10}F_2$ 228.24		58 – 59 (White solid) $\geq 98\%$
HU-F605 (NEW!) 2061959-86-0	4,4'-(3,3-Difluorocycloprop-1-ene-1,2-diyl)bis(methoxybenzene) <i>CpFluor-MP</i> $C_{17}H_{14}O_2F_2$ 288.29		112 – 114 (White solid) $\geq 98\%$
HU-F606 (NEW!) 2061959-93-9	4,4'-(3,3-Difluorocycloprop-1-ene-1,2-diyl)bis(1-methoxynaphthalene) <i>CpFluor-MN</i> $C_{25}H_{18}O_2F_2$ 388.41		210 – 212 (Bright yellow solid) $\geq 98\%$
HU-F607 (NEW!) 56152-73-9	1,1-Dibromo-2,2-bis(trifluoromethyl)ethylene <i>DBBF</i> $C_4Br_2F_6$ 321.84		Colorless liquid (b.p. 45°C/50 Torr) $\geq 95\%$

Technical Notes of HU-F101



Difluoromethyl 2-pyridyl sulfone, also known as *Hu reagent*, is a novel and efficient *gem*-difluoroolefination reagent for preparing *gem*-difluoroalkenes from both aldehydes and ketones. The fluorinated sulfinate intermediates during the *gem*-difluoroolefination is relatively stable, and can be halogenated in situ to afford bromo- and iododifluoromethyl compounds. It can also act as nucleophilic difluoro(sulfonato)methylation reagent for the synthesis of α,α -difluorosulfonates from aldehydes, and alkyl halides and triflates.

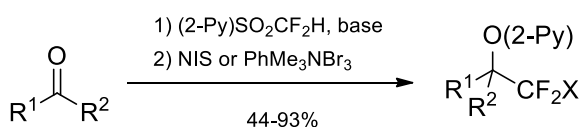
(1) *gem*-Difluoroolefination of aldehydes and ketones.



R¹, R² = H, alkyl, allyl, aryl

Refs. *Org. Lett.* **2010**, *12*, 1444 – 1447; *Org. Chem. Front.* **2015**, *2*, 163–168

(2) Halodifluoromethylation of aldehydes and ketones.

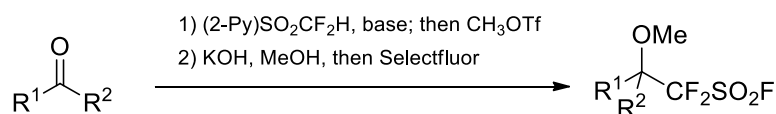


R¹, R² = H, alkyl, allyl, aryl

X = Br, I

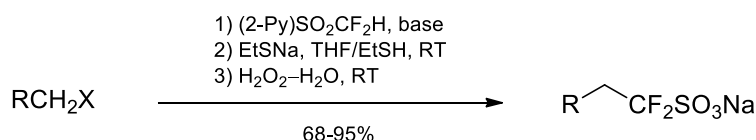
Refs. *J. Am. Chem. Soc.* **2012**, *134*, 5790 – 5793; *Org. Lett.* **2016**, *18*, 2766–2769.

(3) (Fluorosulfonyl)difluoromethylation of aldehydes and ketones.



Ref. *Sci. Sin. Chim.* **2011**, *41*, 1833 – 1839.

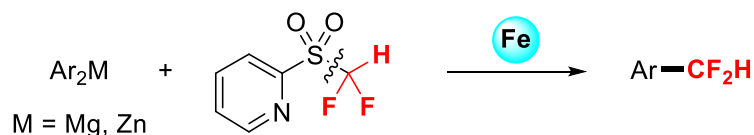
(4) Difluoro(sulfonato)methylation of alkyl halides and triflates.



R = H, alkyl, allyl, aryl
X = Br, I, OTf

Refs. *Angew. Chem. Int. Ed.* **2011**, *50*, 2559 – 2563; *Angew. Chem. Int. Ed.* **2013**, *52*, 3949 – 3952.

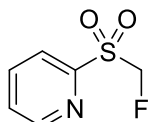
(5) Aromatic difluoromethylation



selective C–S bond cleavage

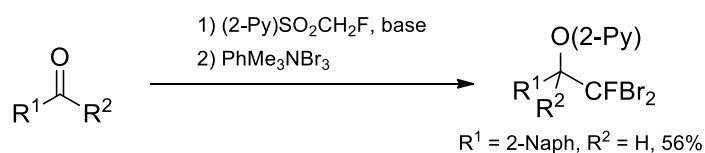
Ref. *J. Am. Chem. Soc.* **2018**, *140*, 880–883.

Technical Notes of HU-F102



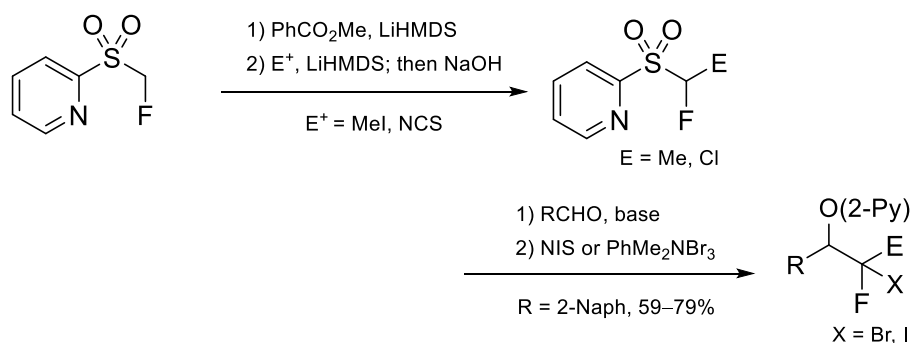
Fluoromethyl 2-pyridyl sulfone and its derivatives can be used as novel monofluoromethylation reagents. The monofluorinated sulfinate intermediates during the monofluoroolefination of aldehydes and ketones can be halogenated in situ to afford mono- and dihalofluoroalkyl compounds. The coupling reaction between iodofluoromethyl 2-pyridyl sulfone and aryl iodides mediated by copper can be used to prepare monofluoromethyl arenes and heteroarenes.

(1) Dihalofluoromethylation of aldehydes and ketones.



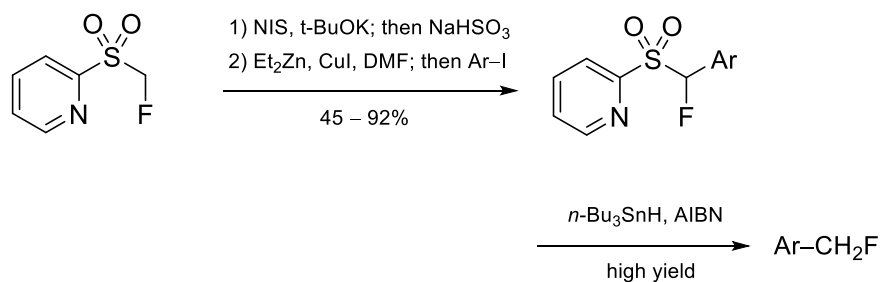
Ref. *J. Am. Chem. Soc.* **2012**, *134*, 5790 – 5793.

(2) Halofluoroalkylation of aldehydes.



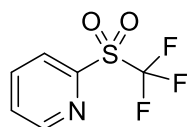
Ref. *J. Am. Chem. Soc.* **2012**, *134*, 5790 – 5793.

(3) Monofluoromethylation of arenes and heteroarenes.



Ref. *Org. Lett.* **2012**, *14*, 6080 – 6083.

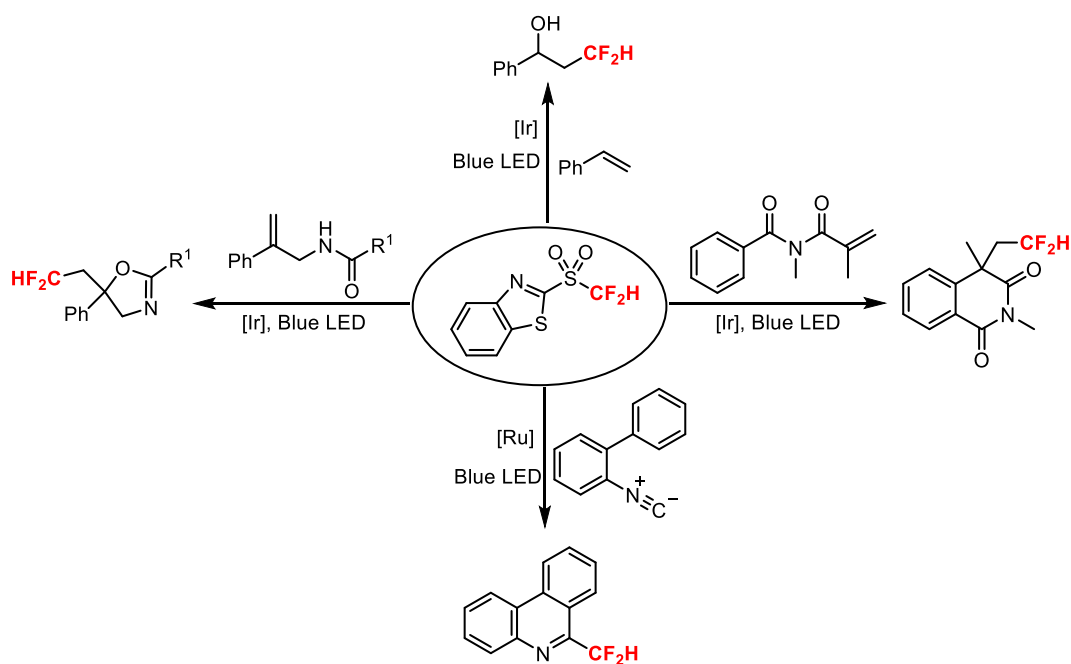
Technical Notes of HU-F103



A CF₃ radical source.

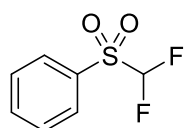
Refs: *Angew. Chem. Int. Ed.* **2016**, *55*, 2743; *Angew. Chem. Int. Ed.* **2022**, *61*, e202114048;

Technical Notes of HU-F107



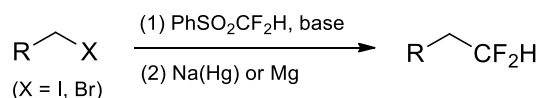
Ref. *Angew. Chem. Int. Ed.* **2016**, *55*, 2743.

Technical Notes of HU-F110



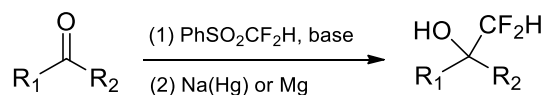
Difluoromethyl phenyl sulfone is a powerful nucleophilic difluoromethylation reagent due to the high reactivity of the sulfonyl-stabilized difluoromethyl anion towards many electrophiles including carbonyls, imines, alkyl halides, and cyclic sulfates and sulfamidates. In the nucleophilic reaction step, depending on the substrate structure, strong bases are used to generate the nucleophilic (phenylsulfonyl)difluoromethyl anion in situ. In the desulfonylation step, sodium/mercury amalgam and magnesium are the commonly used reductive reagents. Besides, the (phenylsulfonyl)difluoromethylated compounds can undergo β -elimination to afford *gem*-difluoroalkenes.

(1) Difluoromethylation of alkyl halides.



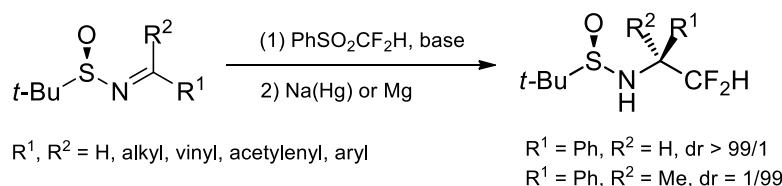
Ref. *Org. Lett.* **2004**, *6*, 4315 – 4317.

(2) Difluoromethylation of aldehydes and ketones.



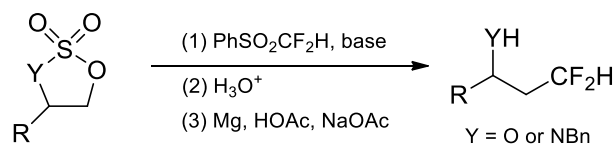
Ref. *Eur. J. Org. Chem.*, **2005**, 2218 – 2223

(3) Difluoromethylation of aldimines and ketimines.



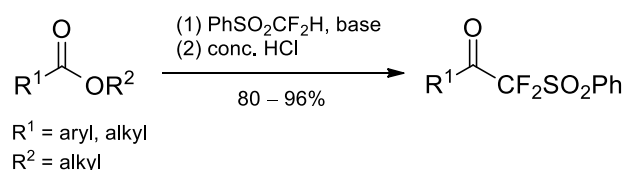
Refs. 1) *Angew. Chem. Int. Ed.*, **2005**, *44*, 5882 – 5886; 2) *J. Org. Chem.*, **2007**, *72*, 3119 – 3121; 3) *Chem. Eur. J.* **2010**, *16*, 11443 – 11454.

(4) Difluoromethylation of cyclic sulfates and sulfamidates.



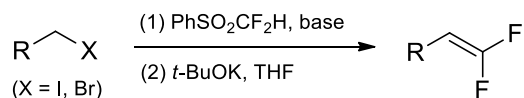
Ref. *Angew. Chem. Int. Ed.* **2007**, *46*, 786 – 789.

(5) (Phenylsulfonyl)difluoromethylation of carboxylic acid esters.



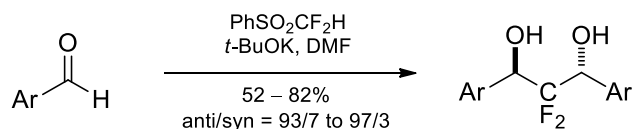
Ref. *J. Org. Chem.* **2009**, *74*, 3767–3771.

(6) Difluoromethylenation of alkyl halides.



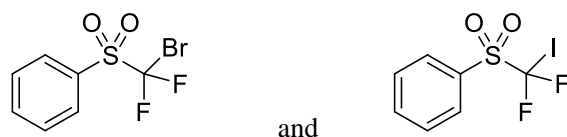
Refs. 1) *Angew. Chem. Int. Ed.*, **2004**, *43*, 5203 – 5206; 2) *Angew. Chem. Int. Ed.* 2007, *46*, 786 –789.

(7) Difluoromethylenation of aromatic aldehydes.



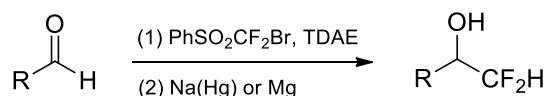
Ref. *Angew. Chem. Int. Ed.*, 2003, *42*, 5216 – 5219.

Technical Notes of HU-F111 and HU-F112



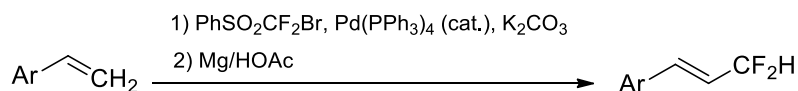
The nucleophilic reactions of bromodifluoromethyl phenyl sulfone with electrophiles such as aldehydes in the presence of TDAE affords (phenylsulfonyl)difluoromethyl-containing synthetically useful intermediates. Palladium-mediated reactions of styrene derivatives, vinyl ethers, and heteroaromatics with bromodifluoromethyl phenyl sulfone in the presence of potassium carbonate affords the (phenylsulfonyl)difluoromethylated products. Iododifluoromethyl phenyl sulfone can be used for the difluoromethylation of alkenes and alkynes initiated by triethylborane/air or arenediazonium salt/titanium chloride in moderate to good yields.

(1) Difluoromethylation of aldehydes.



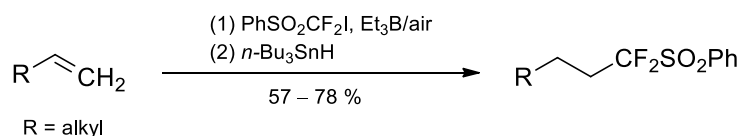
Ref. *J. Fluorine Chem.* **2005**, *126*, 1361–1367.

(2) Difluoromethylation of styrenes, vinyl ethers, and heteroaromatics.



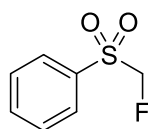
Ref. *Eur. J. Org. Chem.* **2012**, 5943–5952.

(3) Difluoromethylation of terminal alkenes and alkynes.



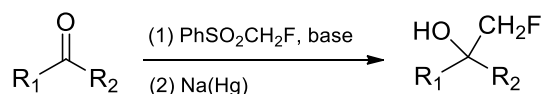
Refs. 1) *J. Org. Chem.*, **2007**, *72*, 5824; 2) *Tetrahedron*, **2009**, *65*, 478.

Technical Notes of HU-F113



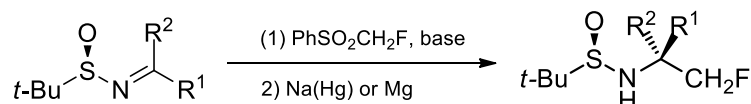
Fluoromethyl phenyl sulfone is a useful nucleophilic monofluoromethylation reagent for the synthesis of fluoromethyl alcohols and amines. In the nucleophilic reaction step, strong bases such as LiHMDS and *n*-BuLi are used to generate the nucleophilic (phenylsulfonyl)fluoromethyl anion. In the desulfonylation step, sodium/mercury amalgam and magnesium are the commonly used reductive reagents. Besides, the addition reaction between fluoromethyl phenyl sulfone and carbonyls can be used to prepare monofluoroalkenes via acylation–elimination.

(1) Monofluoromethylation of aldehydes and ketones.



Ref. *J. Org. Chem.* 2008, *73*, 5699.

(2) Monofluoromethylation of aldimines and ketimines.

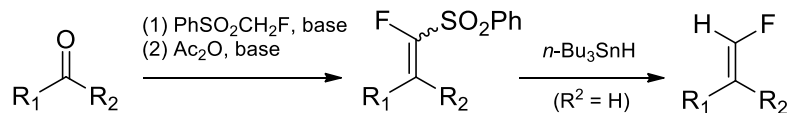


R¹, R² = H, alkyl, vinyl, acetylenyl, aryl

R¹ = Ph, R² = H, dr = 99/1
R¹ = 4-MeOC₆H₄, R² = Me, dr = 1/99

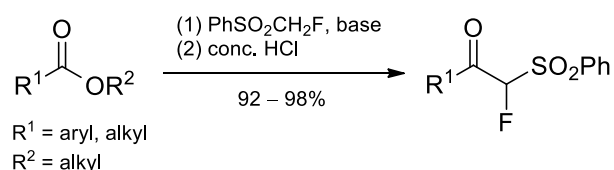
Refs. 1) *Org. Lett.* 2006, *8*, 1693; 2) *Org. Lett.* 2008, *10*, 5377.

(3) Monofluoromethylation of aldehydes and ketones.



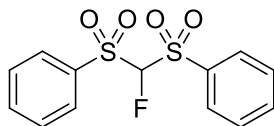
Ref. *J. Chem. Soc., Chem. Commun.* 1985, 678.

(4) (Phenylsulfonyl)fluoromethylation of esters.



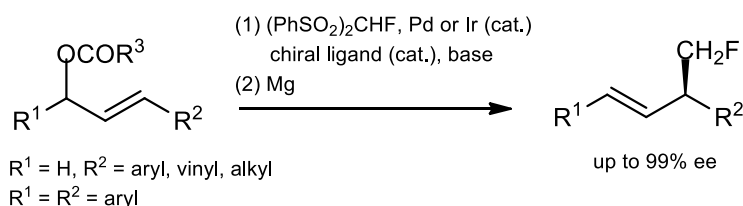
Ref. J. Org. Chem. 2009, 74, 3767–3771.

Technical Notes of HU-F114



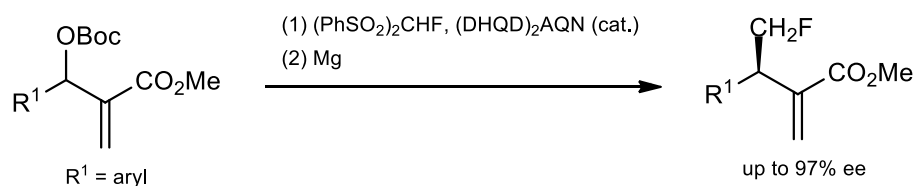
Fluorobis(phenylsulfonyl)methane (FBSM), can be deprotonated under much milder basic conditions than those required for the deprotonation of fluoromethyl phenyl sulfone, and thus has been used as an excellent nucleophilic fluoromethylation reagent in many catalytic asymmetric reactions with allyl esters, imines, and α,β -unsaturated compounds. Stereoselective nucleophilic substitution reaction between chiral alcohols and FBSM under Mitsunobu conditions gives the fluoromethylated products with full inversion of the configuration. Nucleophilic substitution reaction of epoxides and aziridines with FBSM gives the precursors of β -fluoromethylated alcohols and amines in high yields. As a carbon acid, FBSM can also be used in cross dehydrogenative coupling reaction.

(1) Monofluoromethylation of allyl esters.



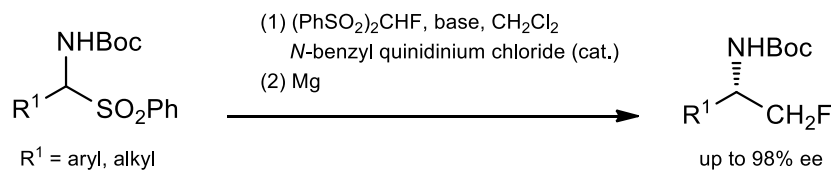
Refs. 1) Angew. Chem. Int. Ed. 2006, 45, 4973-4977; 2) Chem. Commun. 2009, 6604-6606.

(2) Monofluoromethylation of Morita–Baylis–Hillman carbonates.



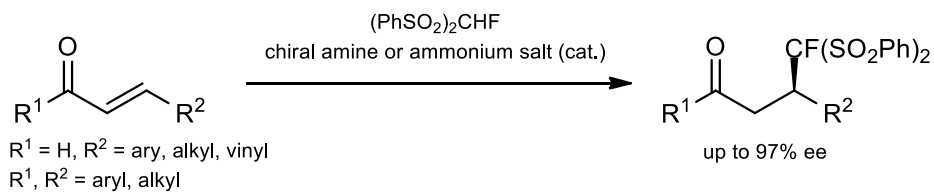
Ref. Angew. Chem. Int. Ed. 2011, 50, 9684

(3) Monofluoromethylation of imines.



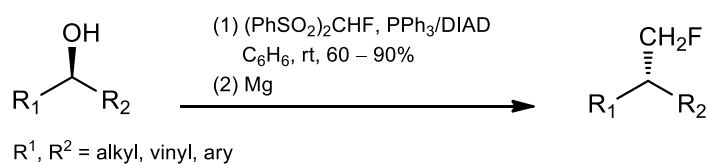
Ref. J. Am. Chem. Soc. 2007, 129, 6394-6395.

(4) Monofluoromethylation of α,β -unsaturated ketones and aldehydes.



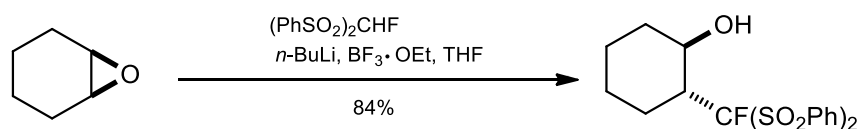
- Refs.** 1) *Angew. Chem. Int. Ed.* **2008**, *47*, 8051-8054;
 2) *Chem. Eur. J.* **2009**, *15*, 7035;
 3) *Tetrahedron Lett.* **2009**, *50*, 4896-4898.

(5) Monofluoromethylation of α,β -unsaturated ketones and aldehydes.



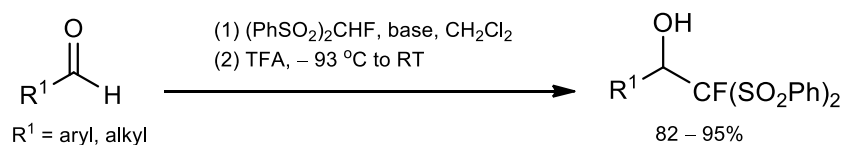
Ref. *Angew. Chem. Int. Ed.* **2007**, *46*, 4933.

(6) Monofluoromethylation of epoxides.



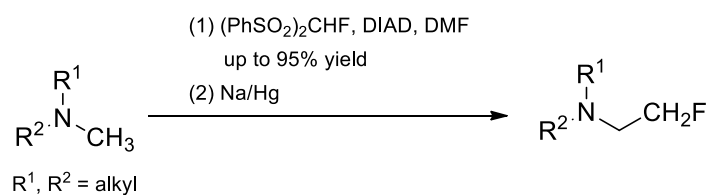
Ref. *J. Org. Chem.* **2006**, *71*, 6829-6833.

(7) Monofluoromethylation of aldehydes.



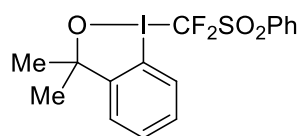
Ref. *Angew. Chem. Int. Ed.* **2011**, *50*, 2588 –2592

(8) Monofluoromethylation of tertiary amines.



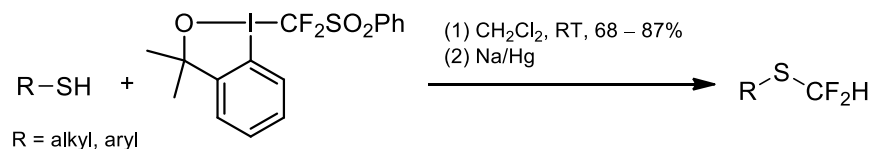
Ref. *New J. Chem.* **2013**, *42*, 10.1039/C2NJ40842B.

Technical Notes of HU-F115



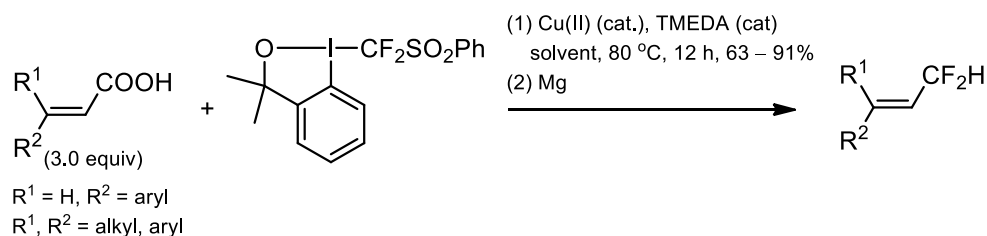
A novel electrophilic difluoromethylation reagent prepared from $\text{TMSCF}_2\text{SO}_2\text{Ph}$, which can efficiently transfer the PhSO_2CF_2 moiety to nucleophiles such as thiols under mild reaction conditions. Copper(II)-catalyzed decarboxylative difluoro(phenylsulfonyl)methylation of α,β - or β,γ -unsaturated carboxylic acids with this reagent can afford vinylic and allylic difluoromethylation products.

(1) Difluoromethylation of thiols.



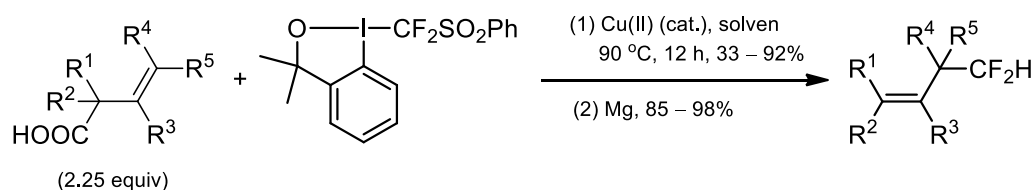
Ref. Tetrahedron Lett. 2008, 49, 5006.

(2) Difluoromethylation of β,γ -unsaturated carboxylic acids.



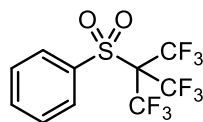
Ref. Angew. Chem. Int. Ed. 2012, 51, 3944–3947.

(3) Difluoromethylation of α,β -unsaturated carboxylic acids.

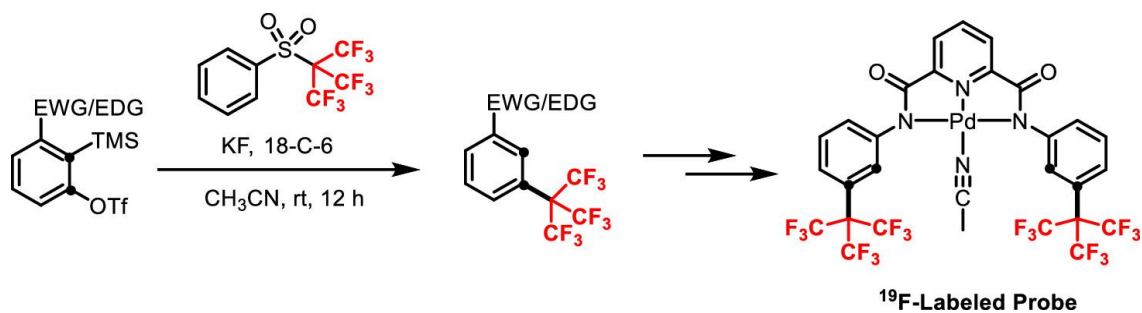


Ref. Angew. Chem. Int. Ed. 2012, 51, 11545–11547.

Technical Notes of HU-F116

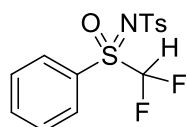


The selective introduction of perfluoro-*tert*-butyl group (PFtB, the bulkier analogue of CF_3 group) into arenes has long been sought after but remains a formidable task. We herein report the first general synthetic protocol to realize aromatic perfluoro-*tert*-butylation. The key to the success is the identification of PFtB phenyl sulfone as a new source of PFtB anion, which reacts with arynes in a highly regioselective manner to afford perfluoro-*tert*-butylated arenes in high yields. The application of the method is demonstrated by the preparation of sensitive ^{19}F -labeled NMR probes with an extraordinary resolving ability.



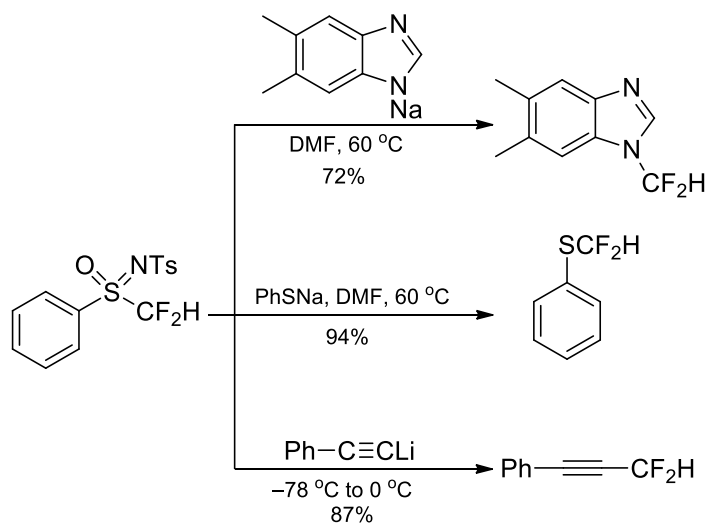
Ref.: *J. Am. Chem. Soc.* **2022**, *144*, 22281-22288.

Technical Notes of HU-F201



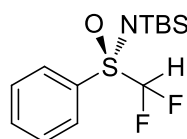
A novel and efficient difluoromethylation reagent for transferring the CF₂H group to *S*-, *N*-, and *C*-nucleophiles under water-free conditions.

(1) Difluoromethylation of *S*-, *N*-, and *C*-nucleophiles.



Ref. *Org. Lett.*, 2009, *11*, 2109-2112.

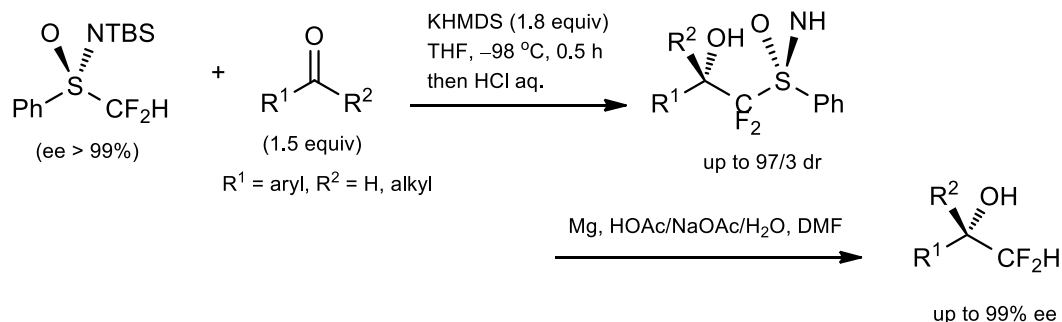
Technical Notes of HU-F202



A novel chiral difluoromethylation reagent towards electrophiles such as aldehydes and ketones. Reductive desulfonimidoylation of the addition products with magnesium can afford difluoromethyl alcohols with high enantiopurity. This reagent is useful for the synthesis of

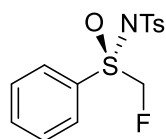
enantioenriched difluoromethyl alcohols, especially the tertiary alcohols.

(1) Difluoromethylation of aldehydes and ketones.



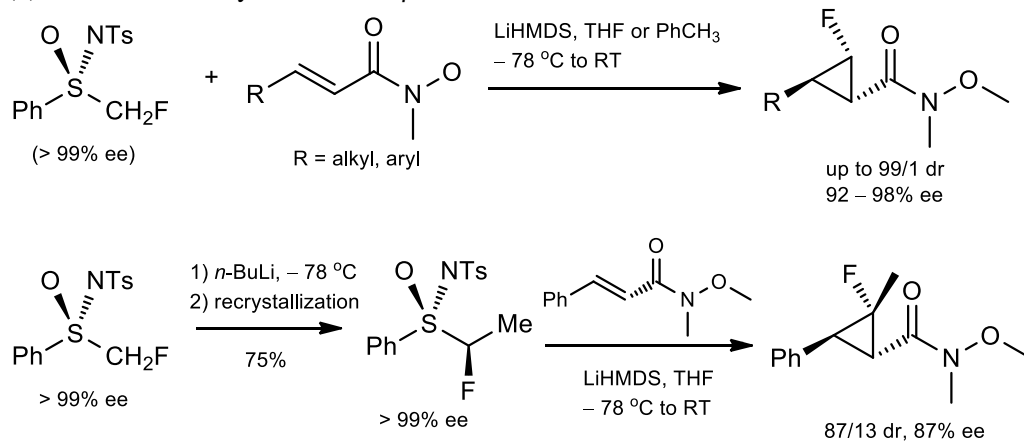
Ref. J. Am. Chem. Soc. 2012, 134, 16999–17002.

Technical Notes of HU-F203



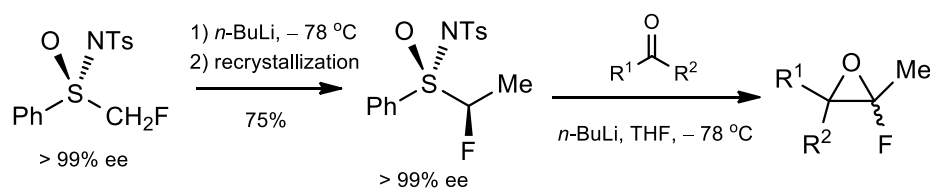
A novel chiral monofluoromethylation reagent towards electrophiles such as α,β -unsaturated Weinreb amides. The reaction is general and a variety of structurally diverse α,β -unsaturated Weinreb amides can be monofluoromethylated to give the corresponding monofluorinated cyclopropanes in good yield, with good diastereoselectivity, and with excellent enantioselectivity.

(1) Monofluoromethylation of α,β -unsaturated Weinreb amides.



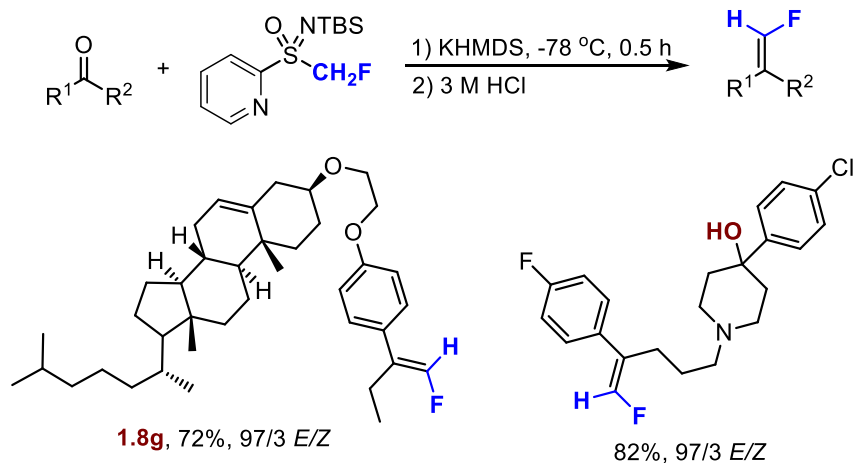
Ref. Angew. Chem. Int. Ed. 2012, 51, 6966 – 6970.

(2) Monofluoromethylation of ketones.



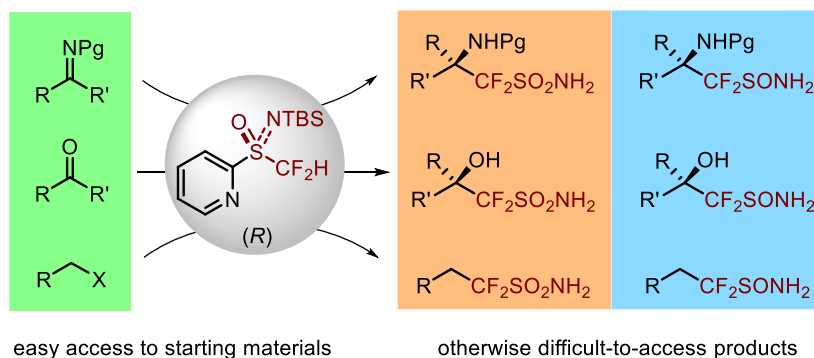
Ref. Adv. Synth. Catal. 2010, 352, 2799 – 2804.

Technical Notes of HU-F207



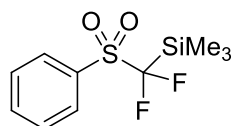
Ref. Angew. Chem. Int. Ed. 2017, 56, 619.

Technical Notes of HU-F208



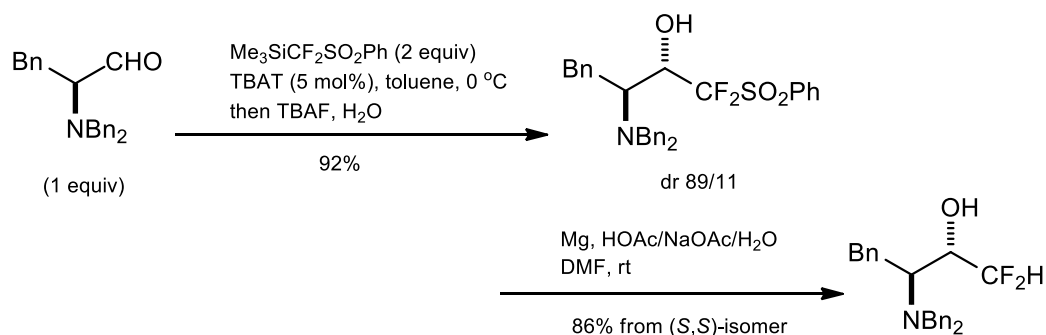
Ref. CCS Chem. 2022, DOI: 10.31635/ccschem.022.202101634.

Technical Notes of HU-F301



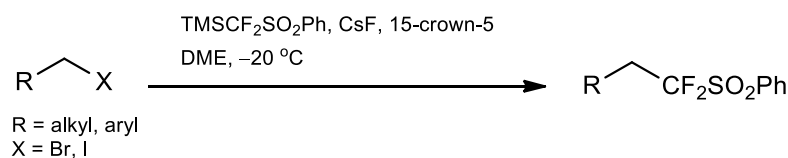
A much milder difluoro(phenylsulfonyl)methylation reagent than difluoromethyl phenyl sulfone. Under the action of Lewis bases such as tetrabutylammonium triphenyldifluorosilicate (TBAT), potassium fluoride, potassium hydrodifluoride, and potassium carbonate, difluoro(phenylsulfonyl)methyl can be transferred to aldehydes, ketones, alkyl halides, and non-activated imines.

(1) Difluoromethylation of aldehydes and ketones.



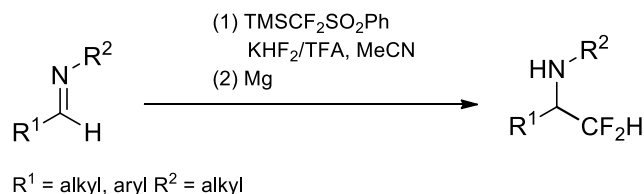
Ref. Tetrahedron Lett. 2008, 49, 1605 – 1608.

(2) Difluoromethylation of alkyl halides.



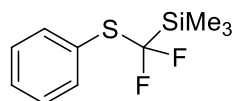
Ref. Tetrahedron Lett. 2010, 51, 6150 – 6152.

(3) Difluoromethylation of imines and enamines.



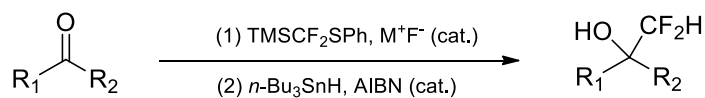
Ref. J. Org. Chem. 2012, 77, 2080–2086.

Technical Notes of HU-F302



An effective reagent to introduce difluoromethyl groups into carbonyls, imines, enamines, and alkyl halides. Not only various simple aldehydes and ketones, but also functionalized carbonyls such as α - and γ -ketoesters and cyclic imides can be difluoro(phenylthio)methylated in high yields under the activation of a catalytic amount of Lewis bases. The substitution reaction proceeds well with primary alkyl bromides and iodides as the limiting reactant when cesium fluoride/15-crown-5 is used as the fluoride source/additive. Under radical conditions, the difluoro(phenylthio)methyl compounds containing vinyl functional groups can form 5- or 6-membered rings via intramolecular cyclization.

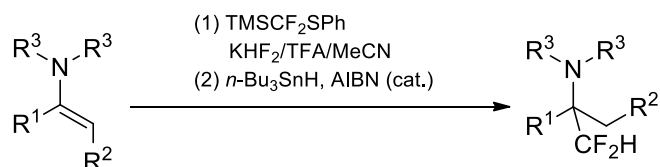
(1) Difluoromethylation of aldehydes and ketones.



R¹, R² = H, alkyl, vinyl, aryl

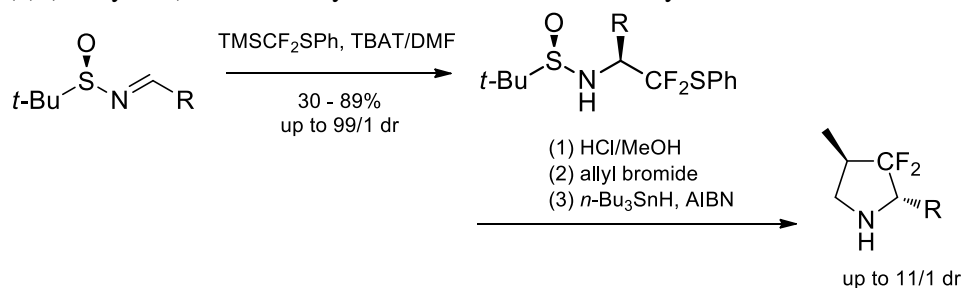
Ref. J. Org. Chem. 2009, 74, 3798–3805

(2) Difluoromethylation of imines and enamines.



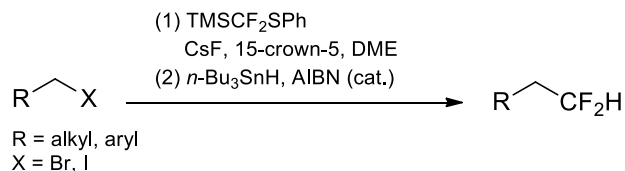
Ref. J. Org. Chem. 2012, 77, 2080–2086.

(3) (Phenylthio)difluoromethylation of imines for further cyclizations.

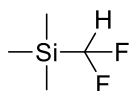


Ref. Angew. Chem., Int. Ed. 2007, 46, 2489–2492.

(4) Difluoromethylation of alkyl halides.

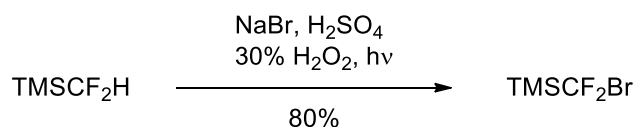


Technical Notes of HU-F303



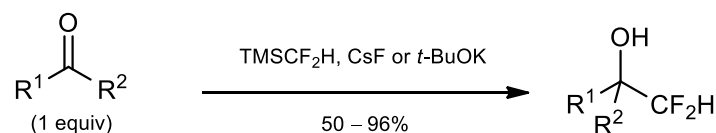
A direct nucleophilic difluoromethylation reagent. The nucleophilic activation of the silicon center with Lewis base initiators allows transfer of the difluoromethyl moiety to electrophiles such as aldehydes, ketones, and aldimines. The copper-mediated difluoromethylation of halides using TMSCF₂H tolerates amine, ether, amide, ester, aromatic bromide, and protected alcohol functionalities in aryl iodides and occurs in high yield and stereoselectivity with vinyl iodides.

(1) Direct bromination to prepare TMSCF₂Br



Ref. *J. Org. Chem.* **2012**, *77*, 5850 – 5855.

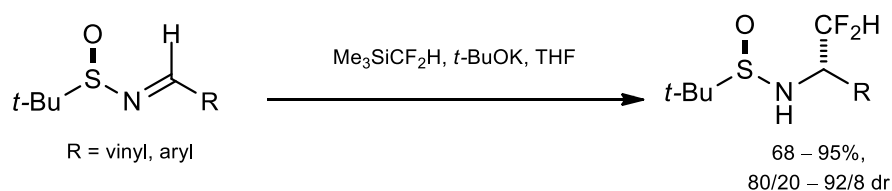
(2) Difluoromethylation of aldehydes and ketones.



R¹, R² = H, alkyl, vinyl, aryl

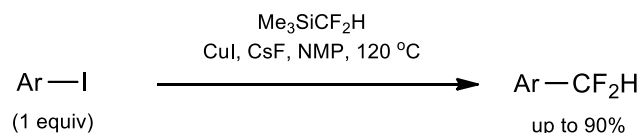
Ref. *Org. Lett.*, **2011**, *13*, 5342 – 5345.

(3) Difluoromethylation of aldimines.



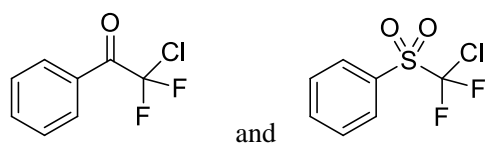
Ref. *Org. Lett.*, **2011**, *13*, 5342 – 5345.

(4) Difluoromethylation of aryl and vinyl iodides.



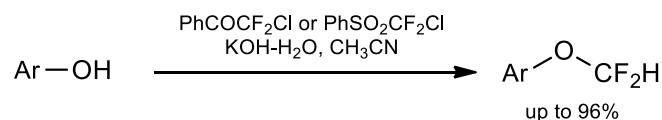
Ref. *J. Am. Chem. Soc.* **2012**, *134*, 5524–5527.

Technical Notes of HU-F401 and Hu-F402



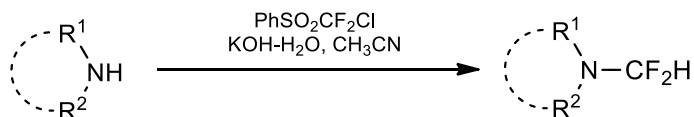
Novel and non-ODS-based (ODS = ozone-depleting substance) difluorocarbene reagents for *O*- and *N*-difluoromethylation. PhCOCF₂Cl reacts with a variety of structurally diverse phenol derivatives to produce aryl difluoromethyl ethers in good yields. PhSO₂CF₂Cl can react with a variety of structurally diverse phenol derivatives and *N*-heterocyclic compounds.

(1) *O*-difluoromethylation.



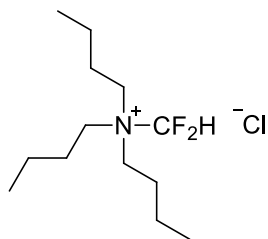
Refs. 1) Chem. Commun., 2007, 5149–5151; 2) J. Org. Chem. 2006, 71, 9845–9848.

(2) *N*-difluoromethylation.



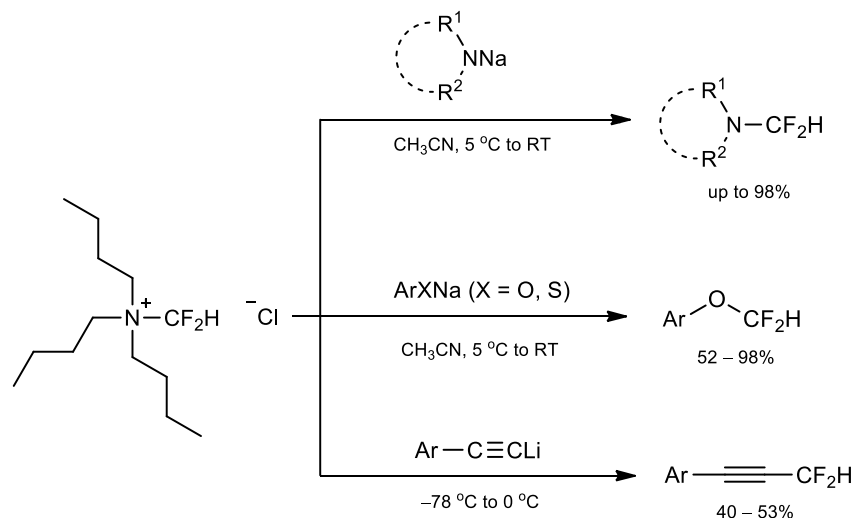
Ref. 1) Chem. Commun., 2007, 5149–5151.

Technical Notes of HU-F403



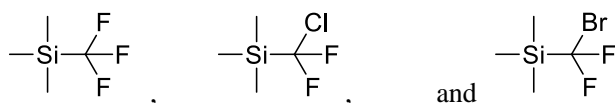
A novel and effective difluorocarbene reagent for *O*-, *S*-, *N*-, *C*-difluoromethylation under mild conditions. When only 1.2 equivalent of the reagent is used, the difluoromethylated products can be obtained in moderate to excellent yields at low temperatures.

(1) *O*-, *S*-, *N*-, *C*-difluoromethylation



Ref. Chin. J. Chem. 2011, 29, 2717–2721.

Technical Notes of HU-F404, HU-F405 and HU-F406

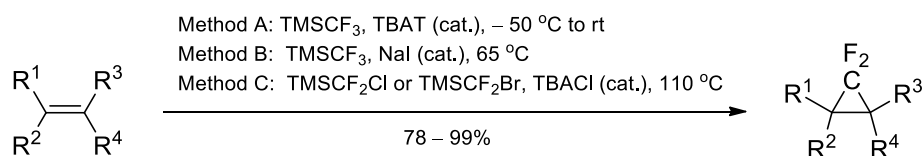


For a recent review, see: Ispizua-Rodriguez, C. Barrett, V. Krishamurti, G.K.S. Prakash. Silicon-based difluoromethylations, difluoromethylenations, pentafluoroethylations, and related fluoroalkylations. In: The Curious World of Fluorinated Molecules Molecules Containing Fluorine

(Volume 6 in Progress in Fluorine Science). Elsevier, 2021, Pages 117-218.

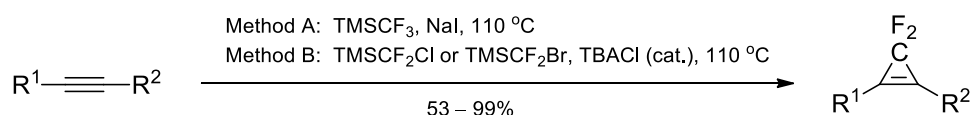
Novel difluorocarbene reagents for the synthesis of gem-difluorinated cyclopropanes and cyclopropenes from alkenes and alkynes. TMSCF_3 can be used to generate difluorocarbene at low temperatures using TBAT as the initiator or at higher temperatures using NaI as the initiator. TMSCF_2Cl and TMSCF_2Br can be used to generate difluorocarbene at higher temperatures catalyzed by chloride ion. Reactions of difluorocarbene generated from TMSCF_2Br with TMSCN , and benzyl and alkylzinc halides leading to new difluorinated organometallic reagents.

(1) Difluoromethylenation of alkenes.



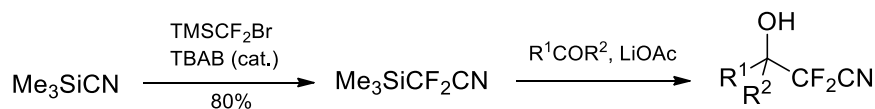
Refs. 1) *Angew. Chem. Int. Ed.* 2011, 50, 7153–7157; 2) *Chem. Commun.* 2011, 47, 2411–2413.

(2) Difluoromethylenation of alkynes.



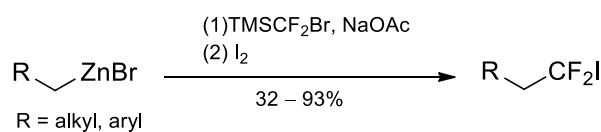
Refs. 1) *Angew. Chem. Int. Ed.* 2011, 50, 7153–7157; 2) *Chem. Commun.* 2011, 47, 2411–2413.

(3) Difluoromethylenation of TMSCN .



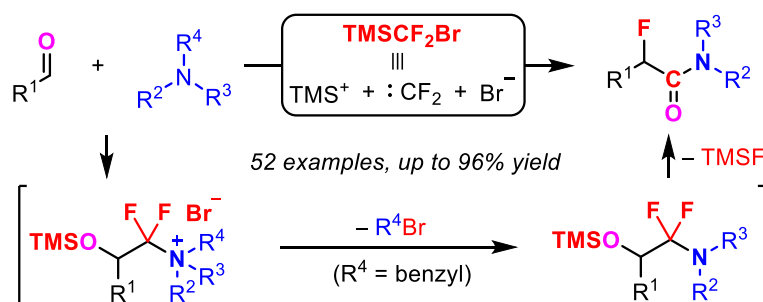
Ref. *J. Org. Chem.* 2012, 77, 5850–5855.

(4) Difluoromethylenation of benzyl and alkylzinc halides.

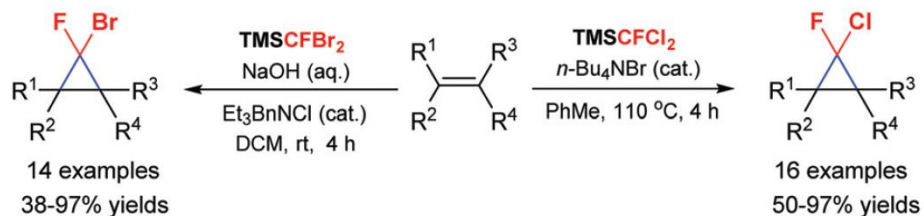


Ref. *Org. Lett.* 2013, 15, 917–919.

(5) Fluorination aminocarbonylation of aldehydes

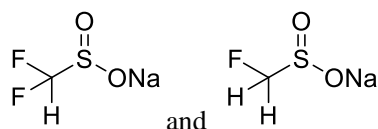


Technical Notes of HU-F407 and HU-F408

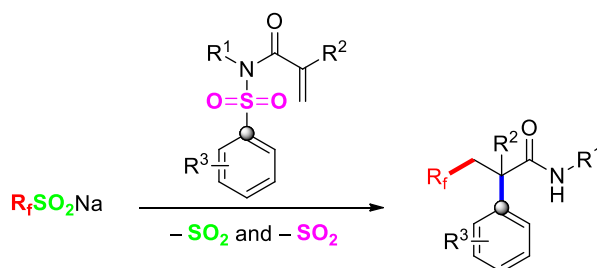


Ref. Chen, D.; Fan, Z.; Huang, L.; Gao, K.; Xiao, P.; Ni, C.; Hu, J. C TMSCFX₂ (X = Cl, Br) as Halofluorocarbene Sources for the Synthesis of Halofluorocyclopanes. *Chem. Commun.* **2021**, 57, 319-322.

Technical Notes of HU-F501 and HU-F502



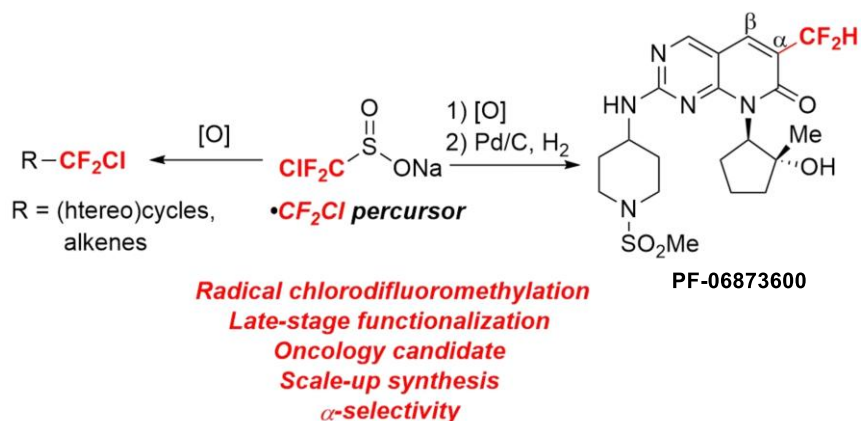
Our group recently demonstrated the utility of these reagents as efficient radical fluoroalkylating reagents able to react with conjugated N-arylsulfonated amides to yield the desired fluoroalkylamides in good to high yields.



- Ref. 1) He, Z.; Tan, P.; Ni, C.; Hu, J. *Org. Lett.* **2015**, 17, 1838 –1841. (The invention of HCF₂SO₂Na and H₂CF₂SO₂Na as radical fluoroalkylation reagents)
- 2) Dai, P.; Yu, X.; Teng, P.; Zhang, W.-H.; Deng, C. *Org. Lett.* **2018**, 20, 6901–6905.
- 3) Zhang, W. et al. *Nat. Commun.* **2020**, 11, art. no. 638. (HCF₂SO₂Na was referred to as Hu's reagent)

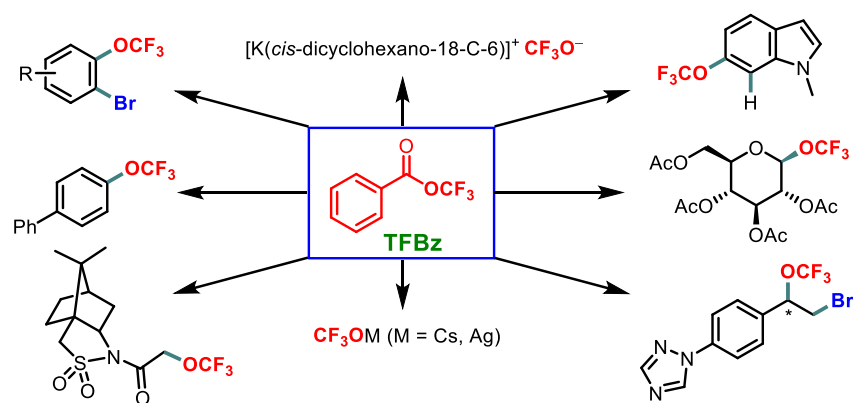
Technical Notes of HU-F503

(masked difluoromethyl radical precursor)



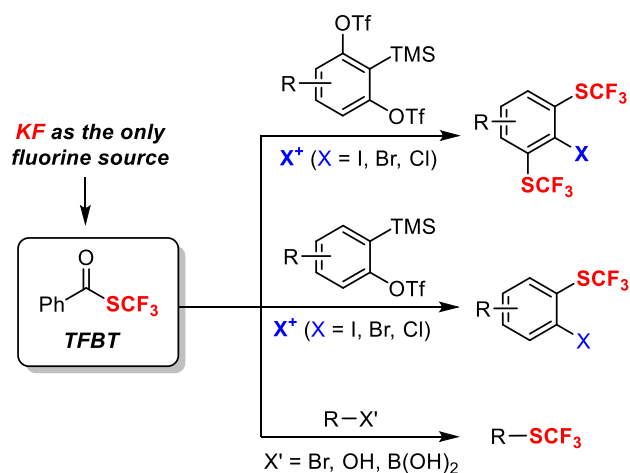
Ref. *Cell Rep. Phys. Sci.* **2021**, 2, 10.1016/j.xcrp.2021.100394

Technical Notes of HU-F601



Ref. *J. Am. Chem. Soc.* **2018**, 140, 6801–6805

Technical Notes of HU-F602

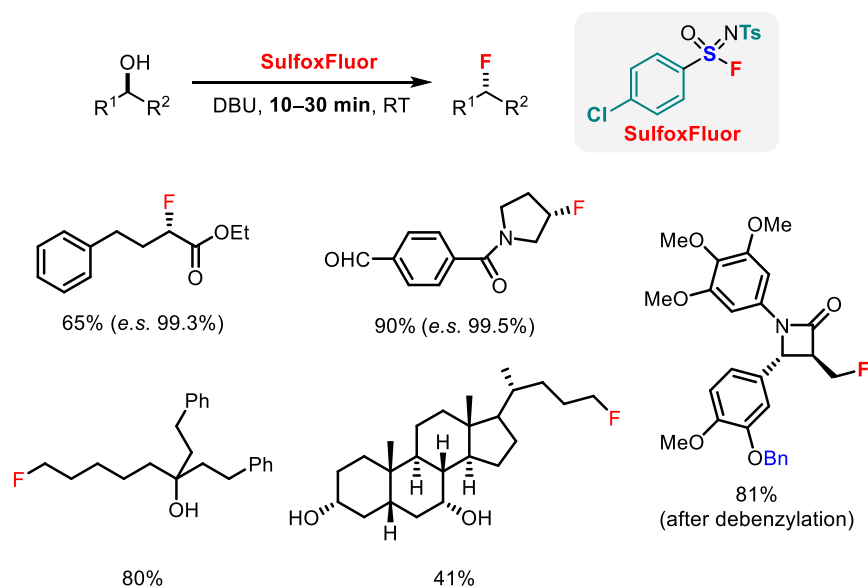


Ref. *Chem. Eur. J.* **2022**, 28, e202104395 (VIP)

Technical Notes of HU-F603

(1) Deoxyfluorination of alcohols

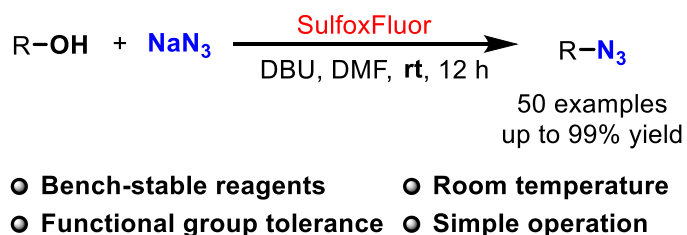
The deoxyfluorination of alcohols is a fundamentally important approach to access alkyl fluorides, and thus the development of shelf-stable, easy-to-handle, fluorine-economical, and highly selective deoxyfluorination reagents is highly desired. This work describes the development of a crystalline compound, N-tosyl-4-chlorobenzenesulfonimidoyl fluoride (SulfoxFluor), as a novel deoxyfluorination reagent that possesses all of the aforementioned merits, which is rare in the arena of deoxyfluorination. Endowed by the multi-dimensional modulating ability of the sulfonimidoyl group, SulfoxFluor is superior to 2-pyridinesulfonyl fluoride (PyFluor) in fluorination rate, and is also superior to perfluorobutanesulfonyl fluoride (PBSF) in fluorine-economy. Its reaction with alcohols not only tolerates a wide range of functionalities including the more sterically hindered alcoholic hydroxyl groups, but also exhibits high fluorination/elimination selectivity.



- Ref.** 1) Guo, J.; Kuang, C.; Rong, J.; Li, L.; Ni, C.; Hu, J. *Chem.-Eur. J.* **2019**, *25*, 7259 – 7264.
(The invention of SulfoxFluor as deoxyfluorination reagent)
- 2) Tang, H.; Cheng, J.; Liang, Y.; Wang Y. *Eur. J. Med. Chem.* **2020**, *197*, art. no. 112323.

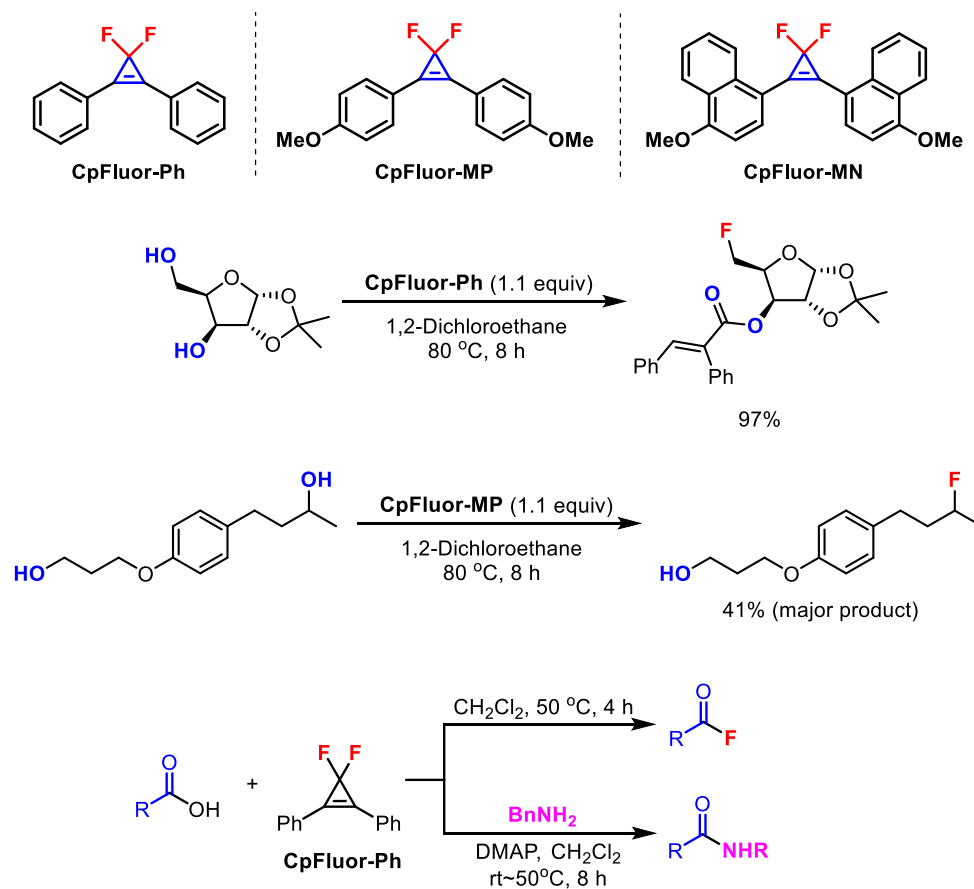
(2) Deoxyazidation of Alcohols with NaN_3

Direct deoxyazidation of alcohols with NaN_3 is a straightforward method for the synthesis of widely used alkyl azides in organic chemistry. However, known methods have some limitations such as high reaction temperatures and narrow substrate scope. Herein, a general and practical method for the preparation of alkyl azides from alcohols using NaN_3 has been developed. N-tosyl-4-chlorobenzenesulfonimidoyl fluoride (SulfoxFluor) plays an important role in this deoxyazidation process, which converts a broad range of alcohols into alkyl azides at room temperature. The power of this deoxyazidation protocol has been demonstrated by successful late-stage deoxyazidation of natural products and pharmaceutically relevant molecules.



Ref. *Nat. Commun.* **2022**, *13*, 2752. DOI: 10.1038/s41467-022-30132-x

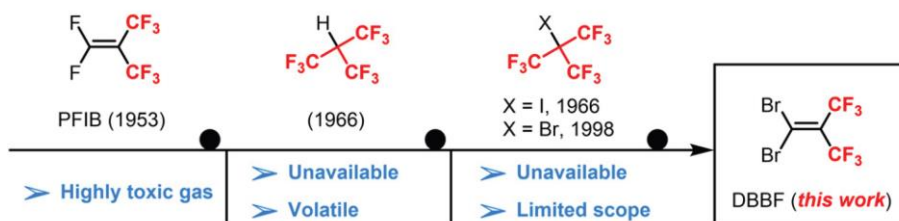
Technical Notes of HU-F604, HU-605 and HU-F606



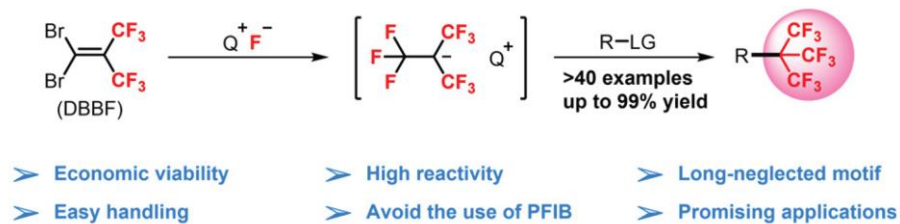
- Ref. 1) Li, L.; Ni, C.; Wang, F.; Hu, J. Deoxyfluorination of alcohols with 3,3-difluoro-1,2-diarylcyclopropenes. *Nat. Commun.* **2016**, *7*, art. no. 13320.
- 2) Wang, X.; Wang, F.; Huang, F.; Ni, C.; Hu, J. Deoxyfluorination of Carboxylic Acids with CpFluor: Access to Acyl Fluorides and Amides. *Org. Lett.* **2021**, *23*, 1764.

Technical Notes of HU-F607 (DBBF)

(a) Development of perfluoro-*tert*-butylation reactions



(b) Perfluoro-*tert*-butylation with DBBF in the presence of fluoride ions (*this work*)



Ref. *Angew. Chem. Int. Ed.* **2021**, *60*, 27318.