Preparation of Silicon-and Sulfur-Based Fluorinated Methane Derivatives as Versatile Fluoromethylation Reagents

DATASET · DECEMBER 2013

DOI: 10.1002/9781118409466.ch27

CHAPTER 27

Preparation of Silicon- and Sulfur-Based Fluorinated Methane Derivatives as Versatile Fluoromethylation Reagents

G.K. SURYA PRAKASH AND FANG WANG

Despite the fact that fluoromethylated compounds can be derived through C–F bond forming reactions with fluorine gas (F_2), SF_4 derivatives, fluorides, and/or electrophilic fluorinating reagents, the direct introduction of various fluoromethyl groups using fluoromethyl synthons prevails under many synthetic regimes because of their superior efficacy and functional group compatibility [1]. In principle, fluoromethylations can be achieved via nucleophilic, electrophilic, radical, as well as carbene pathways. Although seemingly feasible, the nucleophilic and the electrophilic fluoromethylating reactions, particularly the trifluoromethylations, were indeed quite challenging for many years. For example, the trifluoromethyl anion has been found to possess extreme lability due to the vicinal negative charge–lone pair repulsion, which leads to the rapid decomposition of the anion into fluoride and singlet difluorocarbene [2]. On the one hand, attempts to prepare trifluoromethyl analogs of the organometallic reagents, such as the Grignard or lithium reagents, commonly used in nucleophilic alkylations, have always failed. On the other hand, whereas the trifluoromethyl cation has been frequently observed in mass spectrometric studies [3], electrophilic trifluoromethylation was found to be unproductive using trifluoromethyl iodide and trifluoromethyl sulfonates [4]. This unusual inertness of the CF_3 moiety toward nucleophiles can be attributed to (a) the reverse polarization of the CF_3–halogen and CF_3–O bonds and (b) the steric inaccessibility of the CF_3 group for nucleophilic attack. To address these inherent synthetic challenges, extensive efforts have been made on the development of highly efficient nucleophilic and electrophilic fluoromethylation reagents. Over the past three decades, a series of silicon-based [5]

Efficient Preparations of Fluorine Compounds, First Edition. Edited by Herbert W. Roesky.

and sulfur-based [6] fluorinated methane derivatives have been prepared and applied in fluoromethylations of various organic frameworks as versatile reagents.

27.1 PREPARATION OF (TRIFLUOROMETHYL)TRIMETHYLSILANE ($TMSCF_3$, THE RUPPERT–PRAKASH REAGENT) AS A CF_3^- ANION EQUIVALENT AND A DIFLUOROCARBENE PRECURSOR

(Trifluoromethyl)trimethylsilane ($TMSCF_3$) can be prepared through several synthetic routes. The original procedure involves the reaction of chlorotrimethylsilane (TMSCl) with a complex between trifluoromethyl bromide (CF_3Br) and hexaethylphosphorus triamide [$(Et_2N)_3P$] in benzonitrile [7, 8]. To avoid the use of ozone-depleting CF_3Br, an alternative protocol has been developed, which uses phenyl trifluoromethyl sulfoxide ($PhSOCF_3$) as a trifluoromethyl source to transfer the CF_3 group to TMSCl in the presence of Mg(0) [9]. Other less frequently used methods have also been shown [10].

Route 1. Preparation of $TMSCF_3$ using TMSCl, CF_3Br, and $[(Et_2N)_3P]$ (Scheme 27.1) [7, 8]

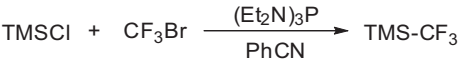
Apparatus A 2-L, three-necked flask fitted with a sealed high-torque mechanical stirrer, a cold-finger condenser (30 cm in length and 8 cm in diameter), a 500-mL Ace dry ice gas condenser trap, a rubber septum, an oil bubbler, a 600-mL pressure-equalizing dropping funnel, a glass stopper, a joint adapter, cooling baths, a 50-mL separatory funnel, a distillation apparatus, a 15-cm column packed with glass helices, safety goggles, laboratory coat, and protective gloves.

Chemicals CF_3Br, TMSCl, anhydrous benzonitrile, hexaethylphosphorus triamide, magnesium sulfate ($MgSO_4$), acetone, potassium hydroxide, and calcium hydride.

Attention! Safety glasses and protective gloves must be used at all times.

Caution! Because of their toxicity and/or volatility, care should be taken to avoid inhalation of CF_3Br, TMSCl, benzonitrile, hexaethylphosphorus triamide, and acetone or contact of their solution with the skin. All reactions should be carried out in a well-ventilated hood. Due the extreme coldness, acetone–dry ice baths should be handled carefully.

Experimental Procedure A 2-L, three-necked flask is oven dried and equipped with an efficient, overhead, sealed mechanical stirrer, a cold-finger condenser, and a rubber septum. The top outlet of the condenser is attached to an oil bubbler. The flask is flushed with dry nitrogen and charged with TMSCl (118.8 g,



SCHEME 27.1 Preparation of $TMSCF_3$ using TMSCl, CF_3Br, and $(Et_2N)_3P$.

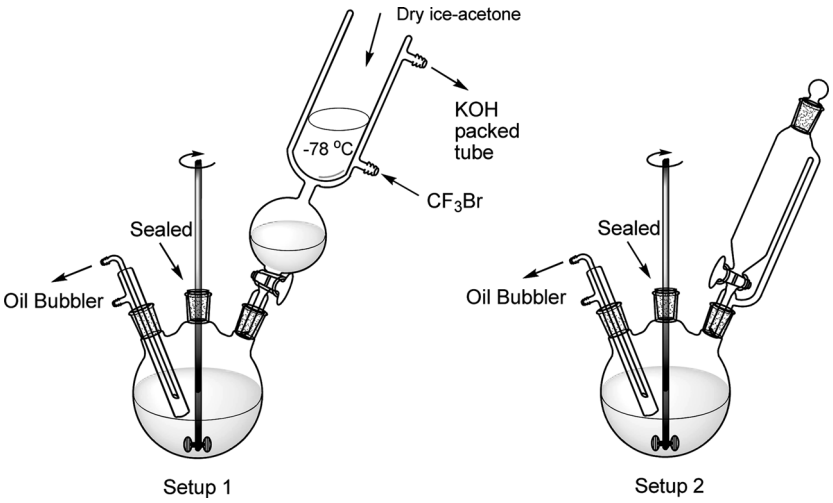


FIGURE 27.1 Reaction setups for the preparation of $TMSCF_3$ using CF_3Br, TMSCl, and hexaethylphosphorus triamide.

1.09 mol), which is distilled over calcium hydride just before use, in 100-mL anhydrous benzonitrile. The septum is quickly replaced with a 500-mL dry ice gas condenser trap under nitrogen protection. The outlet of the trap is connected with a tube filled with potassium hydroxide to protect from moisture, and the inlet is connected with a cylinder of CF_3Br through Tygon tubing. The 2-L flask is immersed in a dry ice–acetone bath (−30 °C), and the condensers are filled with dry ice–acetone mixture maintained at −78 °C (Figure 27.1, Setup 1). CF_3Br (250 mL as liquid, 485 g, 3.25 mol) is condensed into the reservoir, and is gradually added to the reaction pot at −30 °C with rapid mechanical stirring, meanwhile the reservoir is slowly warmed to −45–50 °C. The resulting white slurry is further cooled to −60 °C (the reaction mixture solidifies if the temperature decreases below −60 °C). The dry ice gas condenser trap is then disconnected under nitrogen and quickly replaced with a 600-mL pressure-equalizing dropping funnel containing a solution of hexaethylphosphorus triamide (325.0 g, 1.31 mol, used as received) in 250-mL anhydrous benzonitrile (Figure 27.1, Setup 2). This solution is added to the white slurry mixture with stirring over a period of 2.5 h, and the reaction mixture is maintained at −60 °C. On completion of the addition, the reaction mixture is further stirred at −60 °C for 1 h. The reaction mixture is allowed to warm to room temperature (25 °C) over a period of 14 h, during which time a yellowish mixture can be observed. The condenser and dropping funnel are replaced with a glass stopper and a joint adapter with its glass tube connected to two 250-mL dry ice-acetone-cooled traps. Aspirator vacuum (∼20 mm Hg) is then applied and the reaction mixture is gradually warmed to 50 °C to remove the volatile materials over a period of 3 h. The cooling baths are removed and the

material in the traps is brought to 0 °C. The colorless liquid is rapidly transferred to a 250-mL separatory funnel, and quickly washed with ice-cold water (100 mL × 3). The organic layer is separated (on top). The product is dried over anhydrous $MgSO_4$ (5 g), and the liquid is decanted into a 250-mL Erlenmeyer flask. The product is fractionally distilled through a 15-cm column packed with glass helices. Three fractions are collected. The first minor fraction (bp 45–54 °C) and the second major fraction (bp 54–55 °C) are found to contain the main quantity of $TMSCF_3$. The third minor fraction (bp 55–65 °C) mainly consists of hexamethyldisiloxane with just a small quantity of $TMSCF_3$. The first and second fractions are combined to yield 116.9 g (75%) of clear liquid product, bp 54–55 °C.

Characterization Data ^{1}H NMR (200 MHz, $CDCl_3$, TMS reference): δ 0.25 (s, 9H, $Si(CH_3)_3$) ppm. ^{13}C NMR (50.0 MHz, $CDCl_3$): δ 131.7 (q, $J = 321.9$), −5.2 (CH_3–Si) ppm. ^{19}F NMR (188.0 MHz, $CDCl_3$, $CFCl_3$ reference): δ −66.1 ppm. ^{29}Si NMR (39.7 MHz, $CDCl_3$): δ + 4.7 (q, $^2J(^{29}Si–^{19}F) = 37.9$) ppm. MS (*m*/*z*): 123 ($M^+ - 19$).

Route 2. Preparation of $TMSCF_3$ via Mg(0)-Mediated Reductive Trifluoromethylation of TMSCl and $PhSOCF_3$ (Scheme 27.2)

Apparatus A 250-mL Schlenk flask, a rubber septum, a 10-mL syringe with a needle, a cooling trap (liquid N_2), a magnetic stir bar, an ice bath, a 100-mL separatory funnel, a fractional distillation apparatus, safety goggles, laboratory coat, and protective gloves.

Chemicals TMSCl, $PhSOCF_3$ (commercially available, otherwise can be prepared via a known procedure [11]), Mg turnings, anhydrous dimethylformamide (DMF), and activated 4-Å molecular sieves.

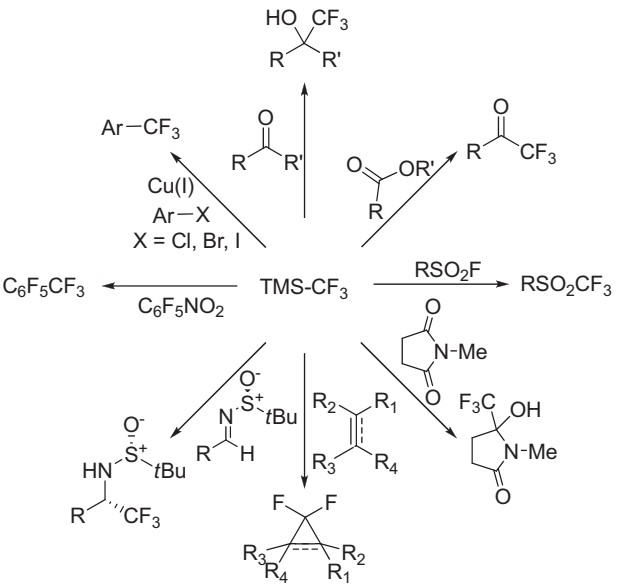
Attention! Safety glasses and protective gloves must be used at all times.

Caution! Because of their toxicity and/or volatility, care should be taken to avoid inhalation of $PhSOCF_3$, TMSCl, and DMF or contact of them. All reactions should be carried out in a well-ventilated hood. Due the extreme coldness, the liquid N_2 trap should be handled carefully.

Experimental Procedure Into a 250-mL, oven-dried, Schlenk flask, Mg turnings (1.14 g, 47.5 mmol) and TMSCl (11.8 g, 109 mmol) in 50-mL DMF were added at 0 °C under inert atmosphere. The reaction mixture was stirred for 2 min before the slow addition of $PhSOCF_3$ (4.62 g, 23.8 mmol) in 5-mL DMF via a syringe. The reaction mixture was stirred at room temperature at 0 °C for 30 min, thereafter at room temperature for another 1.5 h until all the starting material was converted into $TMSCF_3$ (monitored by ^{19}F NMR). The reaction

$$\text{TMSCl} + \text{PhSOCF}_3 \xrightarrow[\text{DMF}]{\text{Mg (0)}} \text{TMS-CF}_3 + \text{PhSSPh}$$

SCHEME 27.2 Reductive trifluoromethylation of TMSCl using $PhSOCF_3$.



SCHEME 27.3 Typical trifluoromethylation using $TMSCF_3$.

flask was then connected to the liquid N_2 trap before the application of vacuum. The low-boiling fractions were collected into the trap followed by warming to room temperature. The volatile fractions were washed with ice water (50 mL × 3) and quickly dried over activated molecular sieves. The organic matter was fractionally distilled using a 30-cm-long column to afford $TMSCF_3$ (2.73 g, 81% yield). Under the similar reaction conditions, other trifluoromethylsilanes can also be prepared.

Applications Prepared by Ruppert in 1984 [8], the synthetic application of $TMSCF_3$ as a trifluoromethyl anion (CF_3^-) was first shown by Prakash and coworkers in the nucleophilic trifluoromethylation of carbonyl compounds [12]. Initiated by catalytic amounts of fluorides, such as cesium fluoride (CsF) and tetra-*n*-butylammonium fluoride (TBAF), $TMSCF_3$ can readily react with ketones and aldehydes to render the corresponding alcohols (from their silyl ethers) in good yields. Since then, a broad spectrum of electrophiles was found to react with $TMSCF_3$, including aldehydes, ketones, esters, imines [13], nitriles [14], nitrones [15], and alkyl halides [6,16] (Scheme 27.3). More importantly, the use of the Ruppert–Prakash reagent further allows the efficient stereoselective synthesis of various chiral trifluoromethylated organic compounds possessing unique biological and pharmaceutical properties [17]. Interestingly, $TMSCF_3$ has also been found to be a versatile difluorocarbene precursor [18]. In the presence of anhydrous fluoride sources, $TMSCF_3$ can release CF_3^- anion, which readily decomposes to fluoride and singlet difluorocarbene. In the presence of alkenes and alkynes, difluorocyclopropanes and difluorocyclopropenes, respectively, can be obtained.

Moreover, $TMSCF_3$ has been used as a trifluoromethyl source for the preparation of $CuCF_3$ and its ligated derivatives, which are capable of trifluoromethylation of aromatic halides (Scheme 27.4, Eqs. 27.2, 27.8 and 27.10) [19], aryl boronic acids (Scheme 27.4, Eq. 27.6) [20], terminal alkynes (Scheme 27.4, Eq. 27.5) [21], and indole derivatives (Scheme 27.4, Eq. 27.9) [22]. In particular, (trifluoromethyl)triethylsilane, an analog of $TMSCF_3$, has also shown significant viability in transition metal-catalyzed–mediated aromatic trifluoromethylation reactions (Scheme 27.4, Eqs. 27.1, 27.3 and 27.4) [23].

27.2 PREPARATION OF TRIFLUOROMETHYL PHENYL SULFONE ($PhSO_2CF_3$) AS A CF_3^- ANION EQUIVALENT

Trifluoromethyl phenyl sulfone ($PhSO_2CF_3$) is usually prepared through the oxidation of trifluoromethyl phenyl sulfide ($PhSCF_3$) using various oxidizing reagents. $PhSCF_3$ can be prepared via several synthetic protocols. The original procedure treated trichloromethyl phenyl sulfide ($PhSCCl_3$) with antimony trifluoride (SbF_3) to yield the titled compound in 70% yield [24]. An improved method used triethylamine trihydrofluoride as the fluoride source, which reacts with $PhSCCl_3$ under microwave irradiation [25]. Alternatively, $PhSCF_3$ can be obtained in 60% yield by direct trifluoromethylthiolation of iodobenzene using methyl fluorosulfonyldifluoroacetate and S_8 [26]. A more feasible preparative method was achieved by reacting CF_3^-, generated from the deprotonation of trifluoromethane (CF_3H) with potassium *tert*-butoxide (*t*BuOK) in DMF, with diphenyl disulfide (PhSSPh) [27]. $PhSO_2CF_3$ can also be directly prepared using $TMSCF_3$ (the Ruppert–Prakash reagent) as a trifluoromethyl source, which reacts with benzenesulfonyl fluoride ($PhSO_2F$) [28] or methyl benzenesulfonate ($PhSO_3Me$) [29] to render the trifluoromethylated product in high yields.

Route 1. Preparation of $PhSO_2CF_3$ using CF_3H and PhSSPh (Scheme 27.5) [27]

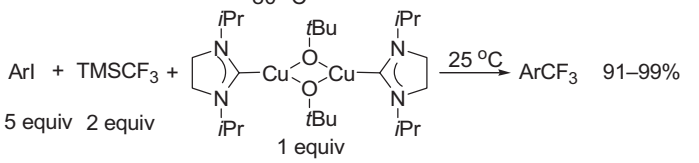
Apparatus A 1-L, three-necked, round-bottomed flask equipped with a dry ice condenser, a magnetic stirring bar, and two rubber septa, a dry ice/ethylene glycol/acetone bath, a long needle for bubbling CF_3H, a vacuum distillation apparatus, a 1-L separatory funnel, a distillation apparatus, a 30-cm-long distillation column, a 250-mL, round-bottomed flask, a reflux condenser, a 250-mL separatory funnel, a filter funnel, safety goggles, laboratory coat, and protective gloves.

Chemicals CF_3H, PhSSPh, *t*BuOK, anhydrous DMF, 30 wt% hydrogen peroxide, acetic acid, dichloromethane, ethyl acetate (EtOAc), acetone, $MgSO_4$, and sodium hydroxide (NaOH), brine.

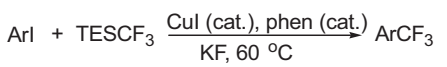
Attention! Safety glasses and protective gloves must be used at all times.

Caution! Because of their toxicity, irritation, and/or volatility, care should be taken to avoid inhalation of CF_3H, PhSSPh, *t*BuOK, hydrogen peroxide, DMF, dichloromethane, EtOAc, acetic acid, acetone, and NaOH or contact of their

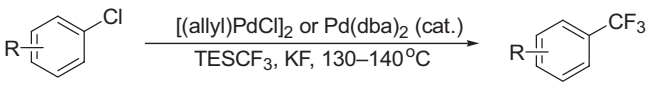
(27.1)



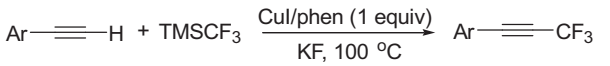
(27.2)



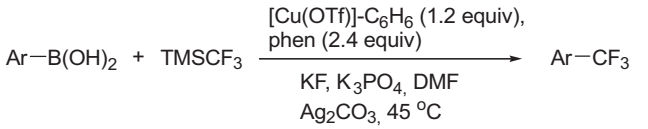
(27.3)



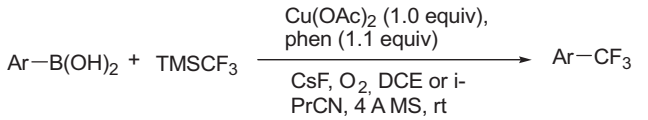
(27.4)



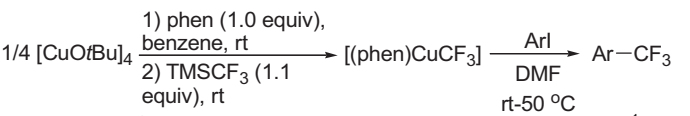
(27.5)



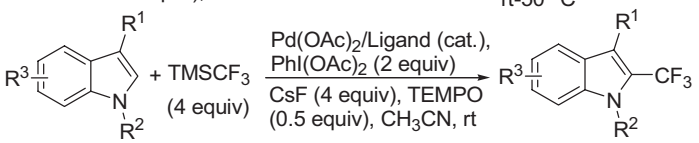
(27.6)



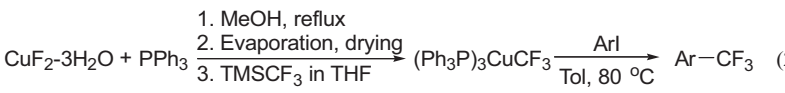
(27.7)



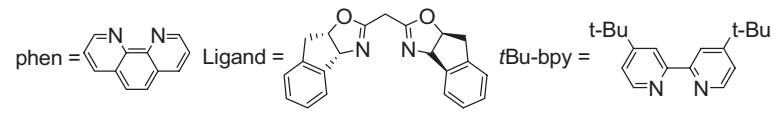
(27.8)



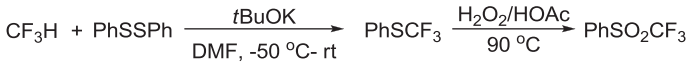
(27.9)



(27.10)



SCHEME 27.4 Transition metal-catalyzed–mediated trifluoromethylation of aromatics, alkenes, and alkynes using $TMSCF_3$ and $TESCF_3$.



SCHEME 27.5 Preparation of $PhSO_2CF_3$ using CF_3H and PhSSPh.

solutions with the skin. All reactions should be carried out in a well-ventilated hood. Due the extreme coldness, the cold bath should be handled carefully.

Experimental Procedure *Step 1: Preparation of $PhSCF_3$*

Into a 1-L, three-necked, round-bottomed flask equipped with a dry ice condenser, a magnetic stirring bar, and two rubber septa, PhSSPh (85 g, 0.39 mol) and *t*BuOK (60 g, 0.53 mol) were added under N_2 protection. After the addition of anhydrous DMF (600 mL), the reaction mixture was cooled to $-40 \sim -50$ °C using a dry ice/ethylene glycol/acetone bath. CF_3H (70 g, 1.0 mol) was then slowly bubbled into the reaction mixture via a needle over a period of 4 h. The flask was gradually warmed to room temperature over a period of 5 h, and the reaction mixture was stirred overnight. Crude products $PhSCF_3$ and DMF were distilled from the reaction mixture under vacuum. The distillate was poured into water (600 mL), and extracted with EtOAc (200 mL $\times$ 2) in a 1-L separatory funnel. The combined organic phase was washed with water and dried over $MgSO_4$. Fractional distillation under vacuum (bp: 55 °C/30 mmHg) using a 30-cm-long column gave $PhSCF_3$ as a colorless liquid (54.3 g, 81% based on PhSSPh used).

Characterization Data ^{1}H NMR (500 MHz, $CDCl_3$, TMS reference): δ 7.40 (t, $J = 7.8$ Hz, 2H) ppm, 7.47 (t, $J = 7.4$ Hz, 1H), 7.65 (d, $J = 7.8$ Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 124.4, 127.7 (q, $J = 309$ Hz), 129.47, 130.81, 136.37 ppm. ^{19}F NMR (470 MHz, $CDCl_3$, $CFCl_3$ reference): δ -43.3. MS (EI, 70 eV): $m/z = 178$.

Step 2: Preparation of $PhSO_2CF_3$

A mixture of $PhSCF_3$ (5 g, 28 mmol) and 30 wt% aqueous hydrogen peroxide (30 mL) in acetic acid (50 mL) was heated at 90 °C for 21 h. After the reaction, brine (40 mL) was added and the reaction mixture was extracted with dichloromethane (50 mL $\times$ 2). The combined organic phase was washed with cold NaOH aqueous solution (10 wt%) twice, followed by washing with brine and water successively. The organic phase was dried over anhydrous $MgSO_4$, and the solvent was removed via rotatory evaporation to give pure $PhSO_2CF_3$ as a colorless liquid (5.28 g, 90%), which can be used without further purification.

Characterization Data ^{1}H NMR (500 MHz, $CDCl_3$, TMS reference): δ 7.69 (t, $J = 7.7$ Hz, 2H), 7.86 (t, $J = 7.6$ Hz, 1H), 8.05 (d, $J = 7.8$ Hz, 2H) ppm. ^{19}F NMR (470 MHz, $CDCl_3$, $CFCl_3$ reference): δ -78.9 ppm.

Route 2. One-Step Synthesis of $PhSO_2CF_3$ using $TMSCF_3$ and $PhSO_2F$ (Scheme 27.6) [28]

Apparatus A 50-mL Schlenk flask equipped with a magnetic stirring bar and a rubber septum, a vacuum distillation apparatus, a 100-mL separatory funnel, a filter funnel, safety goggles, laboratory coat, and protective gloves.

$$TMSCF_3 + PhSO_2F \xrightarrow[\text{Petroleum ether, 25 °C}]{(Me_2N)_3S^+Me_3SiF_2^-} PhSO_2CF_3$$

SCHEME 27.6 One-step synthesis of $PhSO_2CF_3$ using $TMSCF_3$ and $PhSO_2F$.

Chemicals $TMSCF_3$, $PhSO_2F$, tris(dimethylamino)sulfonium difluorotrimethyl siliconate (TASF), petroleum ether (PE), and $MgSO_4$.

Attention! Safety glasses and protective gloves must be used at all times.

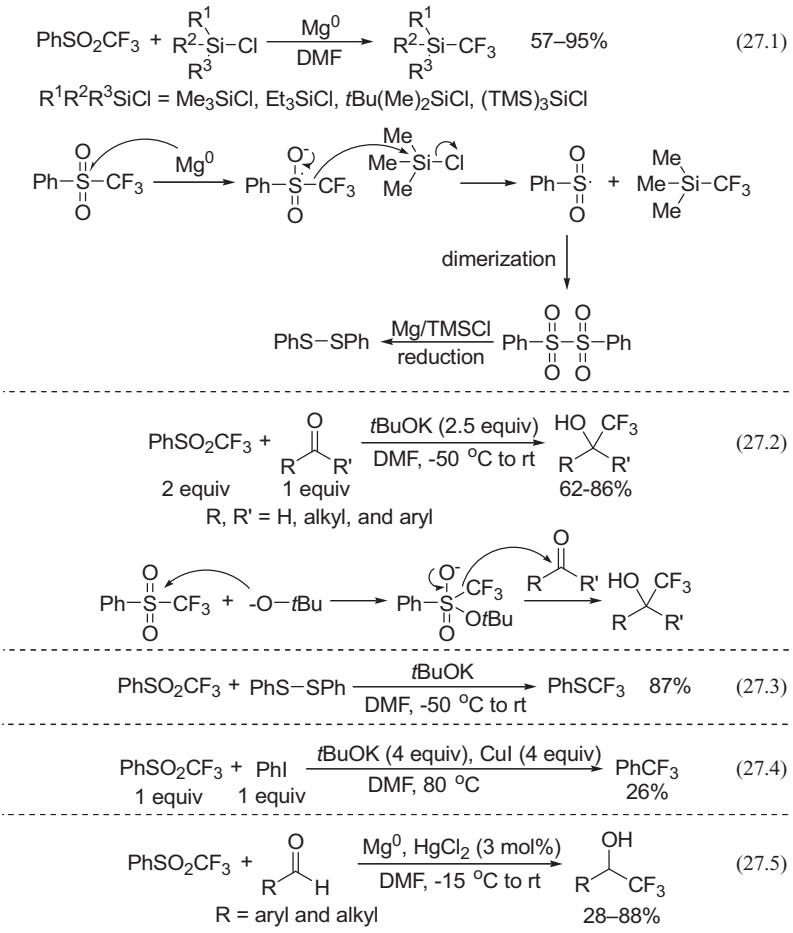
Caution! Because of their toxicity, irritation, and/or volatility, care should be taken to avoid inhalation of $TMSCF_3$, $PhSO_2F$, TASF, and PE or contact of their solutions with the skin. The reaction should be carried out in a well-ventilated hood.

Experimental Procedure To a 50-mL Schlenk flask, $TMSCF_3$ in PE (10 mL) was added to a suspension of $PhSO_2F$ (1.60 g, 10 mmol) and TASF (275 mg, 1 mmol) in PE at 25 °C over a period of 10–15 min under Ar atmosphere. The reaction mixture was further stirred for 0.5 h before quenching with water (30 mL). The reaction mixture was extracted with PE (30 mL), and organic phase was washed with water (50 × 4 mL), dried over $MgSO_4$, and concentrated. The pure product was obtained via vacuum distillation (bp 118–119 °C/1.5 mm Hg).

Applications Due to the extremely electron-deficient nature of the trifluoromethylsulfonyl group ($CF_3SO_2^-$), the sulfur atom in $PhSO_2CF_3$ can readily accept an electron or be attacked by a nucleophile, which leads to the release of the trifluoromethyl anion species. Prakash et al. have described the reductive trifluoromethylation of chlorosilanes using $PhSO_2CF_3$ (Scheme 27.7, Eq. 27.1) [9]. Mediated by Mg^0 in DMF, a series of trifluoromethylsilanes was obtained in moderate to high yields. It has been shown that nucleophilic trifluoromethylation of non-enolizable carbonyl compounds can be achieved through the reaction of carbonyl compounds and $PhSO_2CF_3$ in the presence of excess amounts of *t*BuOK in DMF (Scheme 27.7, Eq. 27.2) [9]. Under similar conditions, trifluoromethylations of iodobenzene and PhSSPh were also shown (Scheme 27.7, Eqs. 27.3 and 27.4) [30]. More recently, Zhao et al. have shown the Mg^0-mediated reductive trifluoromethylation of aldehydes (Scheme 27.7, Eq. 27.5) [31]. Avoiding the use of strong bases, such as *t*BuOK, the protocol was found to be applicable to both non-enolizable and enolizable substrates to render trifluoromethylated alcohols in low to high yields.

27.3 PREPARATION OF DIFLUOROMETHYL PHENYL SULFONE ($PhSO_2CF_2H$) AS A CF_2H^- ANION EQUIVALENT AND A CF_2^{2-} DIANION EQUIVALENT

Difluoromethyl phenyl sulfone ($PhSO_2CF_2H$) is usually prepared through the oxidation of difluoromethyl phenyl sulfide ($PhSCF_2H$), which can be obtained through the reaction between sodium thiophenoxide (PhSNa) and chlorodifluoromethane ($ClCF_2H$, a difluorocarbene precursor) [32,33]. An alternative procedure was shown

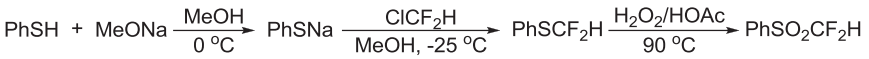


SCHEME 27.7 Typical trifluoromethylation using $TMSCF_3$.

by Chen et al., who prepared the title compound in one step by treating fluorosulfonyldifluoroacetic acid ($FSO_2CF_2CO_2H$, a difluorocarbene precursor) with sodium benzene sulfinate ($PhSO_2Na$) to yield $PhSO_2CF_2H$ in 65% yield [34]. In addition to the above-mentioned methods, another synthetic route has also been reported, however, with fewer efficacies [35].

Preparation of $PhSO_2CF_2H$ using $ClCF_2H$ and PhSNa (Scheme 27.8) [32, 33,36]

Apparatus A 1-L, three-necked flask equipped with a dry ice condenser, a dropping funnel, a rubber septum and a magnetic stirring bar, a dry ice/ethylene glycol/acetone bath, an ice bath, a long needle for bubbling CF_2ClH, a fractional distillation apparatus, a 1-L separatory funnel, a 250-mL, round-bottomed flask,



SCHEME 27.8 Preparation of $PhSO_2CF_2H$ using $ClCF_2H$ and PhSNa.

a reflux condenser, a 250-mL separatory funnel, a filter funnel, safety goggles, laboratory coat, and protective gloves.

Chemicals $ClCF_2H$, thiophenol (PhSH), sodium metal (Na), anhydrous methanol, 30 wt% hydrogen peroxide aqueous solution, acetic acid, dichloromethane, diethyl ether (Et_2O), 5 wt% NaOH aqueous solution, 10 wt% $NaHCO_3$ aqueous solution, saturated Na_2SO_3 aqueous solution, $MgSO_4$, and brine.

Attention! Safety glasses and protective gloves must be used at all times.

Caution! Because of their toxicity, irritation, and/or volatility, care should be taken to avoid inhalation of CF_2ClH, PhSH, Na, hydrogen peroxide, methanol, dichloromethane, Et_2O, acetic acid, NaOH, $NaHCO_3$, and Na_2SO_3 or contact of their solutions with the skin. All reactions should be carried out in a well-ventilated hood. Due the extreme coldness, the cold bath should be handled carefully.

Experimental Procedure *Step 1: Preparation of $PhSCF_2H$*

Under Ar atmosphere, into a 1-L, three-necked flask equipped with a dry ice condenser, a dropping funnel, a rubber septum and a magnetic stirring bar, sodium (65 g, 2.82 mol) was added. Methanol (600 mL) was carefully added into the flask at 0 °C under Ar atmosphere with caution (brisk hydrogen evolution occurred). The mixture was stirred for another 8 h until all the sodium was consumed, and PhSH (100 g, 0.91 mol) was added at 0 °C. The reaction mixture was stirred at room temperature for 3 h and subsequently cooled to −25 °C. $ClCF_2H$ (102 g, 1.18 mol) was slowly bubbled into the reaction mixture via a needle over a period of 7 h. The reaction mixture was gradually warmed to room temperature and stirred overnight before the addition of ice water (30 mL). Volatile materials (methanol and CH_3OCF_2H by-product) were removed through fractional distillation. The residue was washed with water (100 mL) and extracted with dichloromethane (50 mL × 3). The combined organic phase was washed with 5 wt% NaOH aqueous solution (30 mL × 3) and water (30 mL × 3). After being dried over $MgSO_4$, the organic mixture was fractionally distilled to afford $PhSCF_2H$ as a colorless liquid (61.2 g, 42 %).

Characterization Data ^{1}H NMR (500 MHz, $CDCl_3$, TMS reference): δ 7.59 (d, $J = 7.8$ Hz, 2H), 7.41 (m, 3H), 6.83 (t, $J = 56.8$ Hz, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 121.0 (t, $J = 276.6$ Hz), 126.1, 129.4, 129.8, 135.3 ppm. ^{19}F NMR (470 MHz, $CDCl_3$, $CFCl_3$ reference): δ −91.9 (d, $J = 57.2$ Hz) ppm.

Step 2: Preparation of $PhSO_2CF_2H$

A mixture of $PhSCF_2H$ (30 g, 0.19 mol), 30 wt% aqueous hydrogen peroxide (64 mL, 0.63 mol), and acetic acid (80 mL) in a 250-mL, round-bottomed flask was heated at 90 °C. After 20 h, brine (150 mL) was added, and the reaction mixture was extracted with ether (60 mL × 3). The combined organic phase

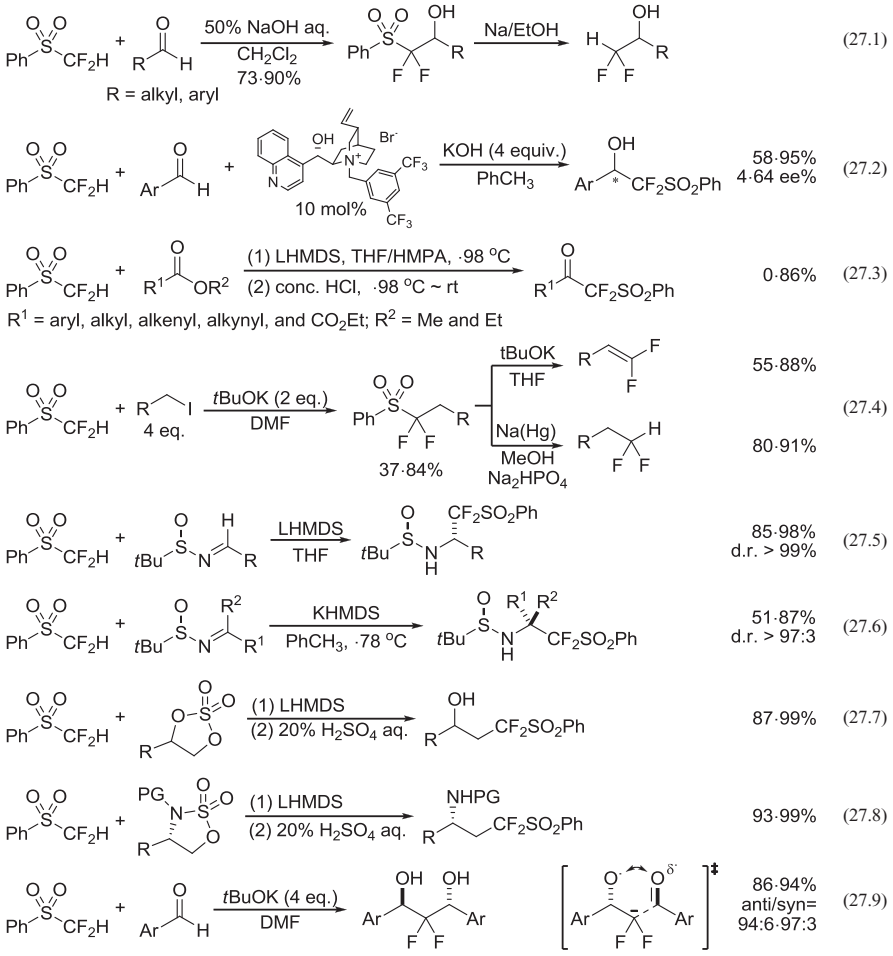
was washed with 10 wt% $NaHCO_3$ aqueous solution (100 mL × 5), saturated Na_2SO_3 aqueous solution (20 mL × 3), and water (20 mL × 3) successively. The organic phase was dried over anhydrous $MgSO_4$, and the solvent was removed to give pure $PhSO_2CF_2H$ as a colorless liquid (36.2 g, 98%).

Characterization Data ^{1}H NMR (500 MHz, $CDCl_3$, TMS reference): δ 8.00 (d, $J = 7.9$ Hz, 2H), 7.81 (t, $J = 7.6$ Hz, 1H), 7.66 (t, $J = 7.8$ Hz, 2H), 6.20 (t, $J = 53.5$ Hz, 1H) ppm. ^{19}F NMR (470 MHz, $CDCl_3$, $CFCl_3$ reference): δ −122.2 (d, $J = 53.4$ Hz) ppm.

Applications Although $PhSO_2CF_2H$ was known as early as 1960 [33], its synthetic applications as CF_2H^- or CF_2^{2-} equivalents were not described until much later. Stahly showed the nucleophilic addition of $PhSO_2CF_2^-$ to various aldehydes rendering the corresponding carbinols, which can be reductively desulfonated into α-difluoromethylated alcohols (Scheme 27.9, Eq. 27.1) [36]. An enantioselective variant of this reaction was facilitated through the application of cinchona alkaloid-derived ammonium salts as chiral catalysts, which gave chiral carbinols with 4–64% enantiomeric excesses (Scheme 27.9, Eq. 27.2) [37]. $PhSO_2CF_2H$ was found to react with a series of esters to yield the corresponding α,α-difluorinated ketones (Scheme 27.9, Eq. 27.3) [38]. $PhSO_2CF_2H$ can also react with primary alkyl iodides to afford substituted products, which can be converted to 1,1-difluoro-1-alkenes and 1,1-difluoromethylalkanes under basic and reductive conditions, respectively (Scheme 27.9, Eq. 27.4) [39]. The reaction between $PhSO_2CF_2H$ and chiral *N*-(*tert*-butylsulfinyl)imines showed high diastereoselectivity (Scheme 27.9, Eq. 27.5) [40]. Similarly, $PhSO_2CF_2H$ can also react with chiral *N*-(*tert*-butylsulfinyl)ketimines to afford the corresponding optically active α-difluoromethyl amines in moderate to high yields (Scheme 27.9, Eq. 27.6) [41]. In addition, $PhSO_2CF_2H$ has been used in the synthesis of β-difluoromethylated or β-difluoromethylenated alcohols and amines through its reactions with 1,2-cyclic sulfates and sulfamidates, respectively (Scheme 27.9, Eqs. 27.7 and 27.8) [42]. Intriguingly, Prakash et al. reported an efficient one-pot synthesis of *anti*-2,2-difluoropropane-1,3-diols using $PhSO_2CF_2H$ as a difluoromethylene dianion (CF_2^{2-}) equivalent (Scheme 27.9, Eq. 27.9) [43].

27.4 PREPARATION OF [(PHENYLSULFONYL)DIFLUOROMETHYL] TRIMETHYLSILANE ($PhSO_2CF_2TMS$) AS A CF_2H^- ANION EQUIVALENT

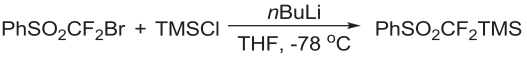
[(Phenylsulfonyl)difluoromethyl]trimethylsilane ($PhSO_2CF_2TMS$) was originally prepared via the oxidation of phenyl (trimethylsilyl)difluoromethyl sulfide ($PhSCF_2TMS$), which can be obtained by Mg^0-mediated trimethylsilylation of bromodifluoromethyl phenyl sulfide ($PhSCF_2Br$) [9]. An improved method was later achieved by treating bromodifluoromethyl phenyl sulfone ($PhSO_2CF_2Br$) with *n*-butyl lithium (*n*BuLi) in the presence of TMSCI (Scheme 27.10) [44].



SCHEME 27.9 Synthetic applications of $PhSO_2CF_2H$.

Preparation of $PhSO_2CF_2TMS$ using $PhSO_2CF_2Br$ and TMSCl [45b]

Apparatus A 250-mL Schlenk flask equipped with a magnetic stirring bar and a rubber septum, an acetone–dry ice bath, a 500-mL separatory funnel, a vacuum distillation apparatus, a filter funnel, safety goggles, laboratory coat, and protective gloves.



SCHEME 27.10 Preparation of $PhSO_2CF_2TMS$ using $PhSO_2CF_2Br$ and TMSCl.

Chemicals $PhSO_2CF_2Br$, *n*BuLi (1.6-M hexanes solution), TMSCl, anhydrous THF, aqueous HCl solution (1 M), Et_2O, brine, water, and sodium sulfate (Na_2SO_4).

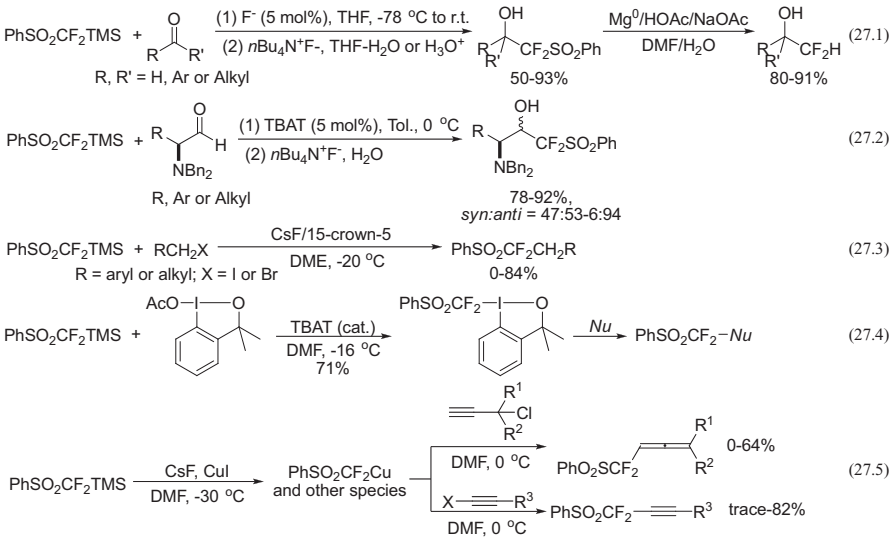
Attention! Safety glasses and protective gloves must be used at all times.

Caution! Because of their toxicity, irritation, and/or volatility, care should be taken to avoid inhalation of $PhSO_2CF_2Br$, *n*BuLi (1.6-M hexanes solution), TMSCl, THF, aqueous HCl solution, Et_2O, and Na_2SO_4 or contact of their solutions with the skin. All reactions should be carried out in a well-ventilated hood. Due the extreme coldness, the cold bath should be handled carefully.

Experimental Procedure Under N_2 atmosphere, to a solution of $PhSO_2CF_2Br$ (6.0 g, 22 mmol) and TMSCl (4.5 mL, 33 mmol) in anhydrous THF (105 mL), *n*BuLi (1.6 M hexanes solution, 15.8 mL, 25 mmol) was added slowly at $-78\ ^\circ C$ over a period of 1.5 h. The reaction mixture was stirred for additional 2 h at same temperature and then carefully transferred into a cold aqueous HCl solution (1 M, 100 mL). The mixture was extracted with Et_2O (70 mL $\times$ 3), and the combined organic phase was washed with brine, water, and then dried over Na_2SO_4. After the removal of the volatile materials under vacuum, crude product was obtained (5.73 g, 98% yield). The crude product was further purified via vacuum distillation to afford $PhSO_2CF_2TMS$ as a colorless liquid (5.10 g, 87%).

Characterization Data ^1H NMR (500 MHz, $CDCl_3$, TMS reference): δ 7.95 (d, $J = 8.0$ Hz, 2H), 7.74 (t, $J = 7.5$ Hz, 1H), 7.61 (t, $J = 7.5$ Hz, 2H), 0.44 (s, 9H) ppm. ^{19}F NMR (470 MHz, $CDCl_3$, $CFCl_3$ reference): δ -112.9 ppm. MS(EI) (*m*/*z*): 175 (M^+).

Applications Although $PhSO_2CF_2H$ can react with enolizable ketones and aldehydes, the reaction suffers from low efficacy and harsh reaction conditions [45]. To overcome these problems, $PhSO_2CF_2TMS$ was developed as a difluoromethyl analog of TMSCF3 [45a]. In the presence of catalytic amounts of fluoride initiators, the reagent can readily react with both enolizable and non-enolizable carbonyl compounds to yield difluoromethylated carbinols in good yields (Scheme 27.11, Eq. 27.1). Under similar reaction conditions, the stereoselective synthesis of α-difluoromethyl-β-amino alcohols was achieved exploiting $PhSO_2CF_2TMS$ as a nucleophilic difluoromethylating reagent (Scheme 27.11, Eq. 27.2) [45b]. An enantioselective difluoromethylation of carbonyl compounds with $PhSO_2CF_2TMS$ has been achieved using cinchonium fluoride catalysts to afford chiral α-difluoromethylated alcohols with low to moderate enantiomeric excesses [37]. Moreover, the nucleophilic substitution reaction between alkyl halides and $PhSO_2CF_2^-$, generated from $PhSO_2CF_2TMS$, was also reported recently (Scheme 27.11, Eq. 27.3) [46]. In addition to the above-mentioned applications, $PhSO_2CF_2TMS$ has also been used as a precursor for preparations of other versatile difluoromethylating reagents. A $PhSO_2CF_2$-iodine(III) reagent (Scheme 27.11, Eq. 27.4) [47] was developed as an electrophilic difluoromethylating reagent, which can be obtained by treating the corresponding acetate-iodine(III) compound with $PhSO_2CF_2TMS$ in the presence of a fluoride initiator [48]. Phenylsulfonyl



SCHEME 27.11 Synthetic applications of $PhSO_2CF_2TMS$.

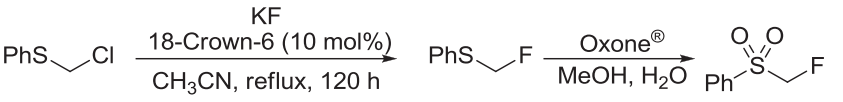
difluoromethylcopper species can be prepared by treating $PhSO_2CF_2TMS$ with CsF and copper iodide (CuI) in DMF (Scheme 27.11, Eq. 27.5). Propargyl chlorides and alkynyl halides can undergo reactions with these species to give $PhSO_2$-containing allenes and alkynes [49].

27.5 PREPARATION OF FLUOROMETHYL PHENYL SULFONE ($PhSO_2CH_2F$) AS A CH_2F^- ANION EQUIVALENT

Fluoromethyl phenyl sulfone ($PhSO_2CH_2F$) is obtained via the oxidation of fluoromethyl phenyl sulfide ($PhSCH_2F$) [50]. The precursor $PhSCH_2F$ can be prepared through the halogen exchange reaction between chloromethyl phenyl sulfide ($PhSCH_2Cl$) and potassium fluoride (KF) [51]. Alternatively, $PhSCH_2F$ can be obtained through the treatment of methyl phenyl sulfoxide with deoxofluorinating reagents, such as diethylaminosulfur trifluoride (DAST) [52] and diethylaminodifluorosulfinium tetrafluoroborate (XtalFluor-E) [53]. Robins and Wnuk have also described the preparation of $PhSCH_2F$ using DAST and methyl phenyl sulfide in quantitative yield [54]. More recently, Zhang et al. reported an efficient synthetic approach toward $PhSCH_2F$ using chlorofluoromethane (CH_2FCl) and sodium thiolate (PhSNa) [55].

Route 1. Preparation of $PhSO_2CH_2F$ via the Halogen Exchange Approach (Scheme 27.12) [50, 51]

Apparatus A 500-mL, three-necked, round-bottomed flask equipped with a magnetic stirring bar and three rubber septa, a reflux condenser fitted with a



SCHEME 27.12 Preparation of $PhSO_2CH_2F$ via the halogen exchange approach.

nitrogen inlet adaptor, a syringe, an oil bath, an ice bath, a 1-L separatory funnel, a 2-L Erlenmeyer flask equipped with a large magnetic stirring bar, a 1-L addition funnel, a 2-L separatory funnel, a chromatographic column, a 500-mL round-bottomed flask, a Büchner funnel, safety goggles, laboratory coat, and protective gloves.

Chemicals Spray-dried KF, $PhSCH_2Cl$, 18-crown-6, Oxone®, anhydrous acetonitrile (CH_3CN), distilled water, dichloromethane (CH_2Cl_2), Na_2SO_4, methanol (MeOH), $MgSO_4$, silica gel (230–400 mesh), and hexanes.

Attention! Safety glasses and protective gloves must be used at all times.

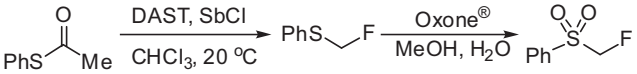
Caution! Because of their toxicity, irritation, and/or volatility, care should be taken to avoid inhalation of KF, $PhSCH_2Cl$, 18-crown-6, Oxone, CH_3CN, CH_2Cl_2, Na_2SO_4, MeOH, $MgSO_4$, silica gel (230–400 mesh), and hexanes or contact of their solutions with the skin. All reactions should be carried out in a well-ventilated hood. Due the extreme heat, the oil bath should be handled carefully.

Experimental Procedure *Step 1: Preparation of $PhSCH_2F$*

In a glove box, a 500-mL, three-necked, round-bottomed flask equipped with a magnetic stirring bar was charged with spray-dried KF (44 g, 0.76 mol, activated under c. 1 mm Hg vacuum at 120 °C for 24 h) and 18-crown-6 (10 g, 37.5 mmol). The flask was sealed with three rubber septa and transferred to a fume hood. A reflux condenser fitted with a nitrogen inlet adaptor was quickly attached to one of the necks of the flask. Anhydrous CH_3CN (250 mL) and $PhSCH_2Cl$ (51 mL, 60 g, 0.38 mol) were successively added to the flask via a syringe under N_2 atmosphere. The reaction mixture was heated to reflux with stirring in an oil bath (100–105 °C) for 120 h, and then cooled in an ice bath. The reaction mixture was diluted with ice water (250 mL) and transferred into a 1-L separatory funnel. The mixture was extracted with CH_2Cl_2 (5 × 100 mL). The combined organic layer was washed with water (150 mL), dried over Na_2SO_4, and filtered. The solvent was removed to give a brownish oily residue (46.5 g, 86%), which was immediately subjected to oxidation.

Characterization Data ^{1}H NMR (500 MHz, $CDCl_3$, TMS reference): δ 7.47–7.50 (m, 2H), 7.28–7.26 (m, 3H), 5.70 (d, $J = 53.1$ Hz, 2H) ppm. ^{19}F NMR (470 MHz, $CDCl_3$, $CFCl_3$ reference): δ −182.0 (t, $J = 52.4$ Hz, 1F) ppm.

Step 2: Oxidation of $PhSCH_2F$ to $PhSO_2CH_2F$ To a 2-L Erlenmeyer flask equipped with a large magnetic stirring bar, Oxone (492 g, 1.6 mol $KHSO_5$) and distilled water (750 mL) were added. The mixture was placed in an ice bath. A solution of $PhSCH_2F$ (45.5 g, c. 0.32 mol) in methanol (750 mL) was added slowly from an addition funnel over a period of c. 1 h. The reaction



SCHEME 27.13 Preparation of $PhSO_2CH_2F$ using $PhSOCH_3$ and DAST.

mixture was then gradually warmed to room temperature and stirred for 12 h. Methanol was removed via rotary evaporation. The residue was extracted with CH_2Cl_2 (5 × 150 mL) in a 2-L separatory funnel. The combined organic layer was dried over $MgSO_4$, filtered, and concentrated to c. 200 mL. The solution was then filtered through a plug of silica gel (230–400 mesh, 500 mL), and washed with CH_2Cl_2 (c. 1 L). The filtrate was concentrated via rotary evaporation and further dried under vacuum to result in slightly yellowish oil, which slowly solidified at room temperature. The solid was stirred with hot hexanes (c. 250 mL, 60–65 °C) for 20 min, which formed two layers. On cooling to 0 °C, the bottom layer gradually crystallized to yield white crystals of $PhSO_2CH_2F$ (44.0 g, 79%), which were collected by filtration on a Büchner funnel and washed with 100 mL cold hexanes.

Characterization Data ^{1}H NMR (300 MHz, $CDCl_3$, TMS reference): δ 7.60–7.80 (m, 5H), 5.15 (d, J = 47.1 Hz, 2H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$, $CFCl_3$ reference): δ −211.2 (t, J = 47.4 Hz, 1F) ppm. MS (EI) (*m*/*z*): 175 (M^+).

Route 2. Preparation of $PhSO_2CH_2F$ via the Reaction Between $PhSOCH_3$ and DAST (Scheme 27.13) [52]

Apparatus A 1-L, three-necked, round-bottomed flask equipped with a magnetic stirring bar, a thermometer, and an air condenser, a cooling bath, a 2-L separatory funnel, a filter funnel, safety goggles, laboratory coat, and protective gloves.

Chemicals Methyl phenyl sulfoxide (PhSOMe), DAST, antimony trichloride ($SbCl_3$), saturated sodium bicarbonate aqueous solution, NaOH, brine, potassium carbonate (K_2CO_3), and chloroform ($CHCl_3$).

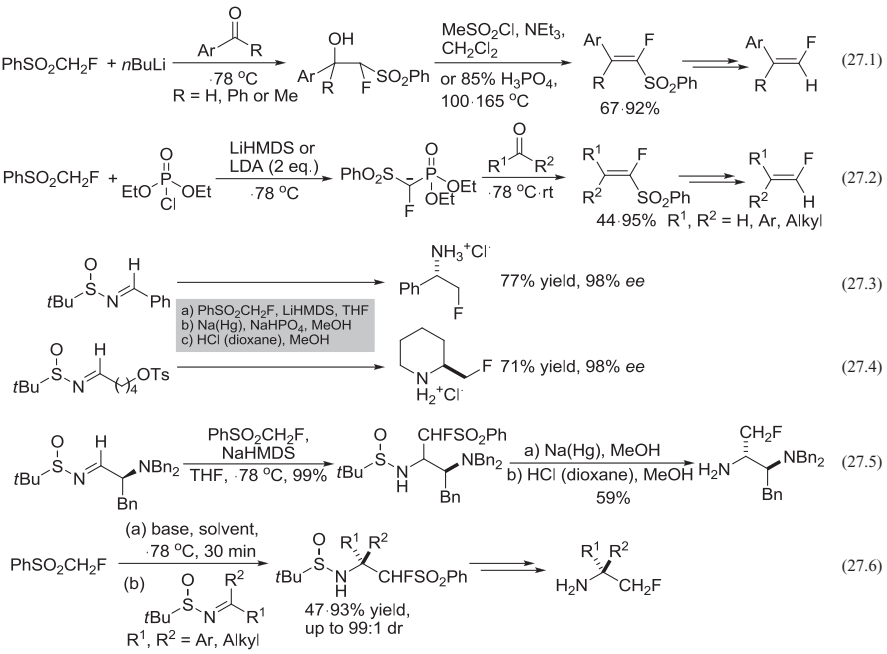
Attention! Safety glasses and protective gloves must be used at all times. Gas evolution can occur during the workup of the reaction.

Caution! Because of their toxicity, irritation, and/or volatility, care should be taken to avoid inhalation of PhSOMe, DAST, $SbCl_3$, NaOH, K_2CO_3, and $CHCl_3$ or contact of their solutions with the skin. All reactions should be carried out in a well-ventilated hood. Due the extreme heat, the oil bath should be handled carefully.

Experimental Procedure To a 1-L, three-necked, round-bottomed flask, equipped with a magnetic stirring bar, a thermometer, and an air condenser, PhSOMe (25.2 g, 0.18 mol) and trichloromethane (150 mL) were added. The flask was placed in a cooling bath containing 3 L water and kept at 20 °C. DAST (38.5 g, 31.6 mL, 0.24 mol) was added to the flask, followed by $SbCl_3$

(0.50 g, 0.0022 mol), and an additional 50 mL trichloromethane. The light yellow reaction mixture was stirred under Ar atmosphere. An exothermic reaction was observed after 2–8 h, and a dark orange solution was formed. The reaction mixture was carefully poured, with stirring, into saturated sodium bicarbonate aqueous solution containing 10 g (0.25 mol) NaOH (600 mL) at 0 °C (gas evolution occurred). After 10 min, the trichloromethane layer was separated and the aqueous layer was extracted with trichloromethane (3 × 100 mL). The combined organic layers were washed with saturated sodium bicarbonate aqueous solution (250 mL), brine, and dried over potassium carbonate successively. Trichloromethane was removed with a rotary evaporator to result in yellow orange oil as crude $PhSCH_2F$ (c. 29 g). The crude product was used immediately in the oxidation reaction as mentioned in Step 2.

Applications $PhSO_2CH_2F$ can react with ketones and aldehydes to yield the corresponding β-fluoro-alcohols, which can be converted to terminal vinyl fluorides (Scheme 27.14, Eq. 27.1) [53b]. The in situ treatment of $PhSO_2CHF^-$ anion with diethyl chlorophosphate [$ClP(O)(OEt)_2$] led to the formation of diethyl 1-fluoro-1-(phenylsulfonyl)methanephosphonate anion, which readily undergoes reaction with carbonyl compounds to yield the corresponding vinyl fluorides (Scheme 27.14, Eq. 27.2) [56]. In addition, $PhSO_2CH_2F$ has been used in the synthesis of various optically active fluoromethylated amines [57]. In 2006, Li et al. disclosed the stereoselective



SCHEME 27.14 Synthetic applications of $PhSO_2CH_2F$.

monofluoromethylation of homochiral *N*-(*tert*-butylsulfinyl)imines, which could afford chiral β-fluoromethylated amines with high enantiomeric excesses (Scheme 27.14, Eqs. 27.3 and 27.4) [58]. Likewise, $PhSO_2CH_2F$ was also found to react with chiral α-amino *N*-*tert*-butanesulfinimines (Scheme 27.14, Eq. 27.5) [41b] and *N*-(*tert*-butylsulfinyl)ketimines (Scheme 27.13, Eq. 27.6) [59] to render various α-monofluoromethylated amines with high enantiomeric purities.

27.6 PREPARATION OF α-FLUOROBIS(PHENYLSULFONYL) METHANE AS A CH_2F^- ANION EQUIVALENT

Fluorobis(phenylsulfonyl)methane (FBSM) was originally prepared by Shibata and coworkers [60] and Hu and coworkers [61] independently in 2006 as a versatile CH_2F^- anion equivalent through the electrophilic fluorination of bis(phenylsulfonyl)methane using Selectfluor®. Hu and coworkers also described a superior synthetic route based on the sulfoxidation of $PhSO_2CH_2F$ followed by oxidation, which avoids the tedious purification step necessary in the original synthesis [38]. Prakash et al. have designed a practical one-step synthesis of FBSM with $PhSO_2CH_2F$ and less costly $PhSO_2F$, rendering FBSM with high efficacy and purity [62]. In addition to the above-mentioned synthetic protocols, FBSM can also be obtained via electrochemical fluorination approach, which is, however, not frequently used in synthetic organic chemistry laboratories [63].

Route 1. Preparation of FBSM via Electrophilic Fluorination of Bis(phenylsulfonyl)methane (Scheme 27.15) [64]

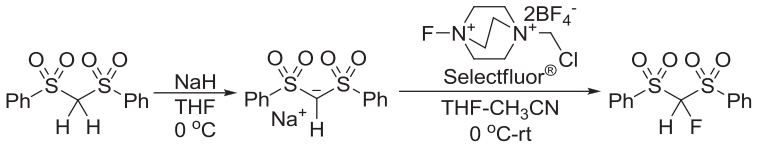
Apparatus A 50-mL Schlenk flask, a rubber septum, a magnetic stir bar, an ice bath, a 100-mL separatory funnel, a chromatography column, safety goggles, laboratory coat, and protective gloves.

Chemicals Bis(phenylsulfonyl)methane, Selectfluor, sodium hydride (NaH, 60% oil dispersion), anhydrous THF, anhydrous CH_3CN, $MgSO_4$, EtOAc, saturated aqueous ammonium chloride, brine, silica gel, hexane, and dichloromethane.

Attention! Safety glasses and protective gloves must be used at all times. NaH reacts violently with water and can ignite in air, and should be handled under inert atmosphere.

Caution! Because of their toxicity, irritation, and/or volatility, care should be taken to avoid inhalation or contact of the chemicals mentioned above. All procedures should be carried out in a well-ventilated hood.

Experimental Procedure To a nitrogen-protected, 50-mL, Schlenk flask containing bis(phenylsulfonyl)methane (2.70 g, 9.0 mmol) in THF (25 mL), NaH (60% oil dispersion that is rinsed with pentane, 240 mg, 6.0 mmol) is added slowly with stirring at 0 °C. The temperature is maintained at 0 °C for 30 min, and a mixture of finely ground Selectfluor powder (2.1 g, 6.0 mmol) and CH_3CN



SCHEME 27.15 Electrophilic fluorination of bis(phenylsulfonyl)methane.

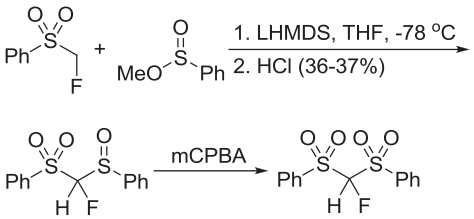
(5 mL) is added at 0 °C. The reaction mixture is warmed to room temperature and stirred for another 12 h. The reaction mixture is quenched by saturated aqueous ammonium chloride. The resulting mixture is then extracted by EtOAc (50 mL × 3). The combined organic layer is washed with brine and dried over anhydrous $MgSO_4$. The solvent is removed under vacuum and the residue is purified by silica gel column chromatography using hexane/dichloromethane as the eluent to afford FBSM (1.6 g, 75%) as a white solid.

Characterization Data Mp 114–114.5 °C (from hexane). ^{1}H NMR (200 MHz, $CDCl_3$, TMS reference): δ 5.70 (1H, d, J = 45.8 Hz, C*H*F), 7.55–7.65 (4H, m, Ar), 7.70–7.80 (2H, m, Ar), 7.95–8.05 (4H, d, J = 7.6 Hz, Ar) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ 105.3 (d, J = 263.4), 129.2, 129.8, 134.9, 135.4 ppm. ^{19}F NMR (188 MHz, $CDCl_3$, $CFCl_3$ reference): δ −167.2 (d, J = 45.8 Hz) ppm. IR (KBr) ν: 1354, 1174 cm^{-1}. MS (ESI-TOF) *(m/z)*: 314 (M^+), 173 ($M^+ - SO_2Ph$), 141 ($M^+ - PhSO_2CHF$).

Route 2. Preparation of FBSM via Oxidation of Sulfoxidated Product of $PhSO_2CH_2F$ (Scheme 27.16) [38]

Apparatus A 20-mL Schlenk tube, a rubber septum, a 3-mL syringe, a magnetic stir bar, a cooling bath (dry ice–acetone), a 50-mL separatory funnel, a chromatography column, a filter funnel, safety goggles, laboratory coat, and protective gloves.

Chemicals Methyl sulfinate, $PhSO_2CH_2F$ (commercially available, and can be prepared via a known procedure [50]), lithium hexamethyldisilazide (LHMDS, 1 M in THF), *m*-chloroperoxybenzoic acid (mCPBA), anhydrous THF, $MgSO_4$, EtOAc, saturated aqueous HCl, saturated aqueous $NaHCO_3$, silica gel, hexane, PE, and dichloromethane.



SCHEME 27.16 Preparation of FBSM via oxidation of sulfoxidated product of fluoromethyl phenyl sulfone.

Attention! Safety glasses and protective gloves must be used at all times. mCPBA is a flammable solid and contact with heat or oxidizable material should be avoided.

Caution! Because of their toxicity, irritation, and/or volatility, care should be taken to avoid inhalation or contact of the chemicals mentioned above. All procedures should be carried out in a well-ventilated hood.

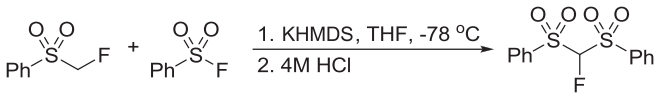
Experimental Procedure Under N_2 atmosphere, methyl sulfinate (187 mg, 1.2 mmol), $PhSO_2CH_2F$ (174 mg, 1.0 mmol), and anhydrous THF (5.0 mL) are added into a Schlenk tube, which is cooled to −78 °C. LHMDS (1.0 M in THF, 2.0 mL, 2.0 mmol) is added drop by drop with vigorous stirring at the same temperature for 30 min. The reaction mixture is quenched with saturated aqueous HCl (36–37%, 2 mL) at this temperature, followed by extraction with EtOAc (20 mL × 3). The combined organic phase is dried over $MgSO_4$ before the removal of the solvents. The crude product is further purified by silica gel column chromatography (PE/EtOAc 3:1 as eluent) to afford the phenylsulfinyl sulfone (285 mg, 95%).

To a solution of the obtained phenylsulfinyl sulfone (298 mg, 1.0 mmol) in CH_2Cl_2 (5 mL), mCPBA (264 mg, 85% purity, 1.3 mmol) is added in one portion at 0 °C. The reaction mixture is warmed to room temperature and stirred for 6 h. The reaction mixture is then diluted with CH_2Cl_2 (50 mL) and washed with saturated aqueous $NaHCO_3$ (20 mL × 3). The organic layer is dried over $MgSO_4$, and the solvents are evaporated under vacuum. The crude product is purified by silica gel column chromatography (PE/EtOAc 1:1–1:2 as eluent) to afford FBSM (304 mg, 96%). Thus, the overall yield of this two-step synthetic protocol is 91%.

Characterization Data [Fluoro (phenylsulfinyl) methylsulfonyl] benzene ($PhSOCHFSO_2Ph$) A mixture of two diastereomers in a ratio of 2:1. ^1H NMR (300 MHz, $CDCl_3$, TMS reference): δ 5.56 (d, $J = 46$ Hz, 0.67H, C*H*F), 5.58 (d, $J = 47$ Hz, 0.33H, C*H*F), 7.52–7.68 (m, 5H, Ar), 7.70–7.82 (m, 3H, Ar), 8.00–8.07 (m, 2H, Ar) ppm. ^{19}F NMR (282 MHz, $CDCl_3$, $CFCl_3$ reference): δ −182.4 (d, $J = 46$ Hz, 0.67F), −167.6 (d, $J = 47$ Hz, 0.33F) ppm. IR (KBr) ν: 1477, 1447, 1336, 1312, 1158 cm^{-1}.

Route 3. Preparation of FBSM via Sulfonation of $PhSO_2CH_2F$ using $PhSO_2F$ (Scheme 27.17) [62]

Apparatus A 20-mL Schlenk tube, a rubber septum, a 10-mL syringe a magnetic stir bar, a cooling bath (dry ice–acetone), a 50-mL separatory funnel, a filter funnel, safety goggles, laboratory coat, and protective gloves.



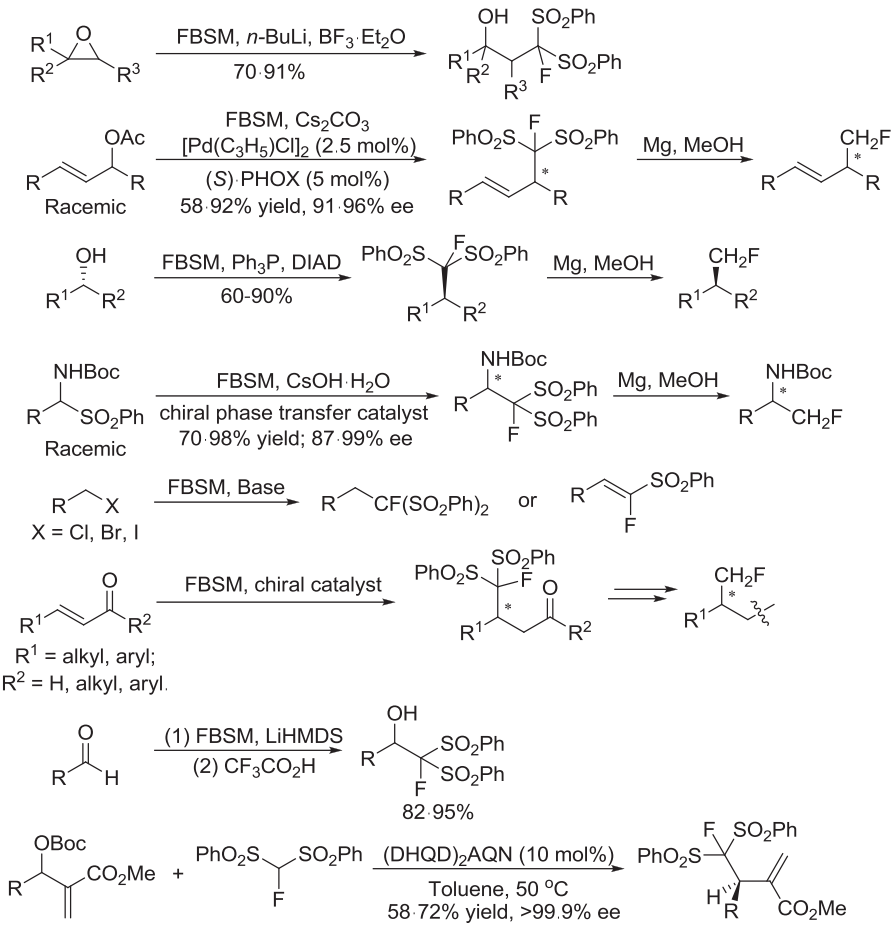
SCHEME 27.17 One-step preparation of FBSM using $PhSO_2CH_2F$ and $PhSO_2F$.

Chemicals $PhSO_2F$, $PhSO_2CH_2F$, potassium hexamethyldisilazide (KHMDS), anhydrous THF, $MgSO_4$, aqueous HCl (4 M), and dichloromethane.

Attention! Safety glasses and protective gloves must be used at all times.

Caution! Because of their toxicity, irritation, and/or volatility, care should be taken to avoid inhalation or contact of the chemicals mentioned above. All procedures should be carried out in a well-ventilated hood.

Experimental Procedure $PhSO_2CH_2F$ (348 mg, 2 mmol) and $PhSO_2F$ (320 mg, 2 mmol) are dissolved in anhydrous THF (10 mL) in a Schlenk tube under inert atmosphere. The solution is cooled to −78 °C. KHMDS (499 mg, 5 mmol, in 5 mL anhydrous THF) is added drop by drop to the Schlenk flask. The reaction mixture is stirred for 30 min at −78 °C before being poured into 4 M HCl aqueous solution (20 mL). The resulting mixture is washed with water and



SCHEME 27.18 Monofluoromethylations using α-fluorobis(phenylsulfonyl)methane (FBSM).

extracted with CH_2Cl_2 (15 mL × 3). The combined organic layer is dried over $MgSO_4$, and the solvents are evaporated to afford an oily product, which slowly solidifies after standing over a period of time (598 mg, 95%). ^1H NMR and ^{19}F NMR spectroscopy show the product is highly pure (>95%).

Applications FBSM has been developed as a versatile nucleophilic monofluoromethylating reagent (a CH_2F^- anion equivalent). Owing to the presence of the two phenylsulfonyl groups, FBSM is more acidic than $PhSO_2CH_2F$, thereby undergoing feasible deprotonation to render rather stable α-fluorocarbanion [65]. Thus, a variety of nucleophilic monofluoromethylation reactions has been achieved using FBSM, such as the ring-opening reaction of epoxides and aziridines [61], the allylic monofluoromethylation reaction [66], the Mitsunobu reaction [67], conjugate addition reactions [68], the Mannich reaction [69], the aldol reaction [70], the Morita–Baylis–Hillman reaction [71], as well as many other reactions (Scheme 27.18) [57, 72]. In particular, the facile reductive removal of the sulfonyl groups allows the introduction of unfunctionalized CH_2F motif using FBSM, thereby prevailing over many other monofluoromethylating reagents. In addition, FBSM can be further converted to fluoroiodobis(phenylsulfonyl)methane, which has been used as a viable radical monofluoromethylating reagent [73].

27.7 PREPARATION OF *S*-(DIFLUOROMETHYL)-*S*-PHENYL-2,3,4,5-TETRAMETHYLPHENYLSULFONIUM TETRAFLUOROBORATE (DPTPT) AS A CF_2H^+ CATION EQUIVALENT

S-(Difluoromethyl)-*S*-phenyl-2,3,4,5-tetramethylphenylsulfonium tetrafluoroborate (DPTPT) [74] is an electrophilic difluoromethylating reagent, which is analogous to the electrophilic trifluoroemethylating reagents developed by Yagupolskii and Umemoto [75]. DPTPT was obtained through a two-step procedure. The triflate salt of DPTPT was prepared via the reaction of difluoromethyl phenyl sulfoxide ($PhSOCF_2H$) with 1,2,3,4-tetramethylbenzene in the presence of triflic anhydride (Tf_2O). The product was then subjected to an anion exchange reaction with sodium tetrafluoroborate ($NaBF_4$), rendering DPTPT in 51% overall yield.

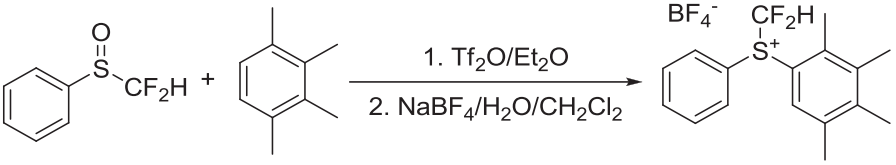
Preparation of DPTPT using $PhSOCF_2H$ and 1,2,3,4-Tetramethylbenzene (Scheme 27.19) [74]

Apparatus A 150-mL Schlenk flask equipped with a magnetic stirring bar and a rubber septum, an ice bath, a syringe with a needle, a 250-mL separatory funnel, a filter funnel, safety goggles, laboratory coat, and protective gloves.

Chemicals $PhSOCF_2H$, 1,2,3,4-tetramethylbenzene, Tf_2O, anhydrous Et_2O, dichloromethane, $NaBF_4$ aqueous solution (1 M), and anhydrous $MgSO_4$.

Attention! Safety glasses and protective gloves must be used at all times.

Caution! Because of their toxicity, irritation, and/or volatility, care should be taken to avoid inhalation of $PhSOCF_2H$, 1,2,3,4-tetramethylbenzene, Tf_2O,



SCHEME 27.19 Preparation of DPTPT using $PhSOCF_2H$ and 1,2,3,4-tetramethylbenzene.

Et_2O, dichloromethane, $NaBF_4$ aqueous solution, and anhydrous $MgSO_4$ or contact of their solutions with the skin. All reactions should be carried out in a well-ventilated hood. Due the extreme coldness, the cold bath should be handled carefully.

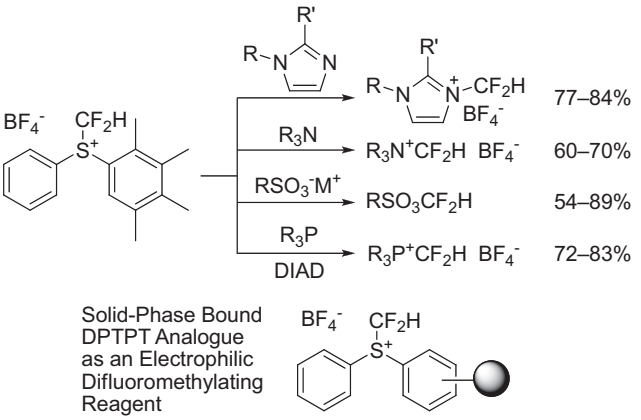
Experimental Procedure To a stirred solution of $PhSOCF_2H$ (4.00 g, 25 mmol) and 1,2,3,4-tetramethylbenzene (3.35 g, 25 mmol) in anhydrous Et_2O (60 mL) at 0 °C under Ar, Tf_2O (7.0 g, 25 mmol) was added in small portions over a period of 2 h. The reaction mixture was stirred for 20 min at the same temperature, and the formed oil was separated from the Et_2O phase under nitrogen. Then, anhydrous Et_2O (30 mL) was added to the oil and the reaction mixture was stirred again. This procedure was repeated four times. The resulting oil was dissolved in dichloromethane (50 mL). The dichloromethane solution was extracted with $NaBF_4$ aqueous solution (1 M, 5 × 100 mL), and the organic layer was dried over anhydrous $MgSO_4$. The drying agent was filtered off and the dichloromethane was removed in vacuum. The product was obtained as a brown semisolid (5.9 g, 51%).

Characterization Data ^{1}H NMR (400 MHz, $CDCl_3$, TMS reference): δ 8.12 (t, $J = 47.4$ Hz, 1H), 7.65–7.95 (m, 5H), 7.49 (s, 1H), 2.57 (s, 3H), 2.40 (s, 3H), 2.32 (s, 3H), 2.31 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, TMS reference): 17.0, 17.1, 18.0, 21.1, 113.0, 118.90 (t, $J = 297.5$ Hz), 119.0, 129.0, 131.6, 131.9, 135.5, 138.9, 139.1, 140.0, 145.3 ppm. ^{19}F NMR (376 MHz, $CDCl_3$, $CFCl_3$ reference): δ −99.9 (d, $J = 53.4$ Hz, 1F), −100.6 (d, $J = 53.4$ Hz, 1F), −152.0 (s, 1F), −152.1 (s, 3F) ppm. HRMS (FAB) m/z: Calcd for $C_{17}H_{19}F_2S^+$, 293.1170; found, 293.1170.

Applications DPTPT was found to be a versatile reagent enabling electrophilic difluoromethylation of various nucleophiles, including CD_3OD, triflates, tertiary amines, phosphines, and imidazole derivatives (Scheme 27.20) [74]. Noticeably, an analogous solid-phase-bound electrophilic difluoromethylating reagent has also been synthesized, which facilitates the purification-free difluoromethylations of triflates and imidazoles [76].

27.8 PREPARATION OF *S*-(FLUOROMETHYL)-*S*-PHENYL-2,3,4,5-TETRAMETHYLPHENYLSULFONIUM TETRAFLUOROBORATE (FPTPT) AS A CH_2F^+ CATION EQUIVALENT

S-(Fluoromethyl)-*S*-phenyl-2,3,4,5-tetramethylphenylsulfonium tetrafluoroborate (FPTPT) was prepared by Prakash et al. as a novel electrophilic fluoromethylating



SCHEME 27.20 Synthetic applications of DPTPT in electrophilic difluoromethylations.

reagent [77]. Similar to its difluoromethyl counterpart, the reagent was synthesized through the treatment of fluoromethyl phenyl sulfoxide ($PhSOCH_2F$) with 1,2,3,4-tetramethylbenzene in the presence of triflic anhydride (Tf_2O) and the subsequent anion exchange.

Preparation of FPTPT using $PhSOCH_2F$ and 1,2,3,4-Tetramethylbenzene (Scheme 27.21) [77]

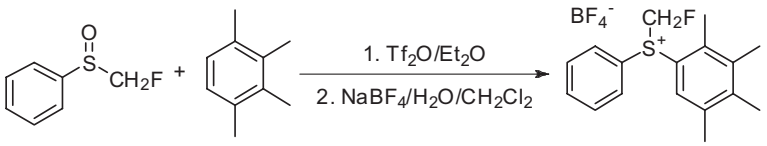
Apparatus A 150-mL Schlenk flask equipped with a magnetic stirring bar and a rubber septum, an ice bath, a syringe with a needle, a 250-mL separatory funnel, a filter funnel, safety goggles, laboratory coat, and protective gloves.

Chemicals $PhSOCH_2F$, 1,2,3,4-tetramethylbenzene, Tf_2O, anhydrous Et_2O, dichloromethane, $NaBF_4$ aqueous solution (1 M), and anhydrous $MgSO_4$.

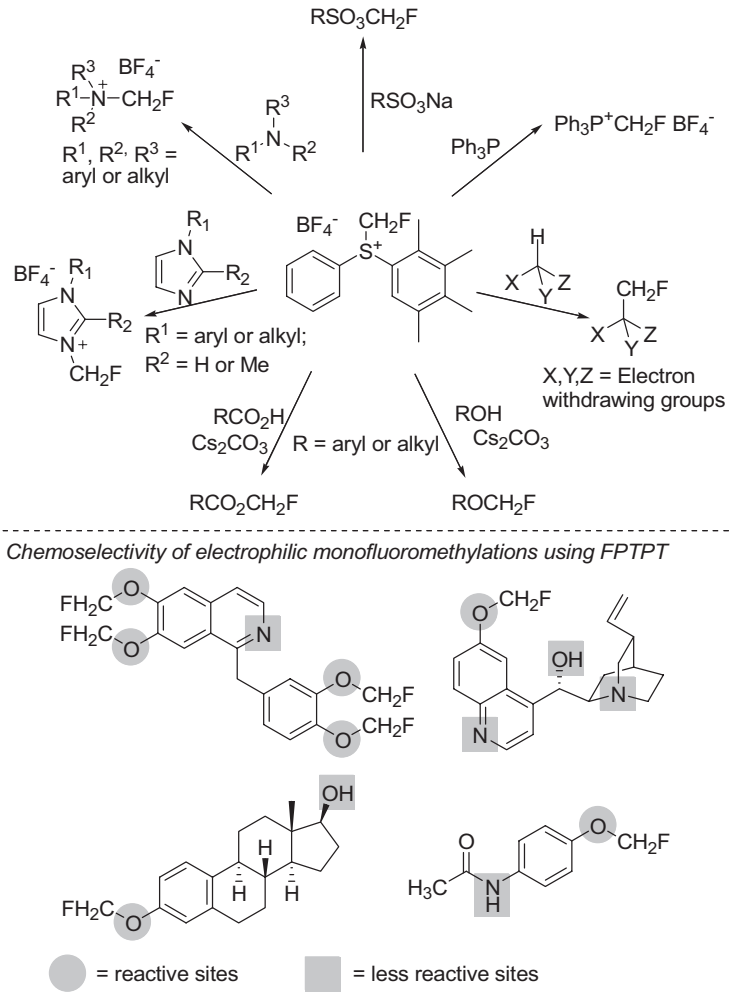
Attention! Safety glasses and protective gloves must be used at all times.

Caution! Because of their toxicity, irritation, and/or volatility, care should be taken to avoid inhalation of $PhSOCH_2F$, 1,2,3,4-tetramethylbenzene, Tf_2O, Et_2O, dichloromethane, $NaBF_4$ aqueous solution, and anhydrous $MgSO_4$ or contact of their solutions with the skin. All reactions should be carried out in a well-ventilated hood. Due the extreme coldness, the cold bath should be handled carefully.

Experimental Procedure To a stirred solution of $PhSOCH_2F$ (3.00 g, 19 mmol) and 1,2,3,4-tetramethylbenzene (2.54 g, 19 mmol) in anhydrous Et_2O (45 mL)



SCHEME 27.21 Preparation of FPTPT using $PhSOCH_2F$ and 1,2,3,4-tetramethylbenzene.



SCHEME 27.22 Synthetic applications of FPTPT in electrophilic fluoromethylations.

at 0–5 °C under Ar, Tf_2O (5.36 g, 19 mol) was added drop by drop over a period of 30 min. The reaction mixture was stirred at the same temperature range for 1 h. The precipitated triflate salt was filtered off and washed with Et_2O five times. The triflate salt was then dissolved in 60 mL dichloromethane and washed with $NaBF_4$ aqueous solution (1 M, 5 × 80 mL). The organic layer was dried over $MgSO_4$ and the solvent was evaporated under vacuum. The resulting solid was further dried under vacuum to give FPTPT as a white powder (6.88 g, 81%).

Characterization Data ^{1}H NMR (400 MHz, $CDCl_3$, TMS reference): δ 7.76 (m, 3H), 7.67 (m, 2H), 7.43 (s, 1H), 6.55 (dd, J = 47.0, 9.7 Hz, 1H), 6.46 (dd, J = 47.0, 9.6 Hz, 1H), 2.50 (s, 3H), 2.39 (s, 3H), 2.31 (s, 3H), 2.29 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, TMS reference): 17.1, 17.2, 17.9, 21.4, 89.9 (d,

$J = 242$ Hz), 116.4, 121.4, 121.4, 128.6, 128.6, 131.1, 131.6, 134.6, 137.7, 138,4, 139.6, 144.2 ppm. ^{19}F NMR (376 MHz, $CDCl_3$, $CFCl_3$ reference): δ 207.8 (t, $J = 47.1$ Hz, 1F), −152.1 (s, 3F), −152.0 (s, 1F). HRMS (FAB) m/z: Calcd for $C_{17}H_{20}FS^+$, 275.1264; found, 275.1257. Elemental analysis: Calcd: C, 56.37%; H, 5.57%. Found: C, 56.23%; H, 5.43%.

Applications FPTPT can react with a variety of nucleophiles to afford the corresponding monofluoromethylated products (Scheme 27.22) [77]. Compared with the substrate scope of electrophilic difluoromethylations using DPTPT, a broader spectrum of nucleophiles was found to readily react with FPTPT, including alkoxides, acetate, triflates, tertiary amines, phosphines, imidazole derivatives, and carbon nucleophiles. Noticeably, the protocol also showed remarkable chemoselectivity, which preferentially monofluoromethylates phenolic groups over many other nucleophiles (Scheme 27.22).

REFERENCES

1. (a) Uneyama K. *Organofluorine Chemistry*. Oxford: Blackwell; 2006, chapter 7. (b) Kirsch P. *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*. Weinheim. Wiley-VCH; 2004, chapter 2.
2. Adolph HG, Kamlet MJ. Fluoronitroaliphatics. I. The effect of α fluorine on the acidities of substituted nitromethanes. *J Am Chem Soc* 1966;88:4761–4763.
3. Olah GA, Heiliger L, Prakash GKS. Stable carbocations. Part 276. Trihalomethyl cations. *J Am Chem Soc* 1989;111:8020–8021.
4. Umemoto T. Electrophilic perfluoroalkylating agents. *Chem Rev* 1996;96:1757–1777, and reference therein.
5. (a) Prakash GKS, Hu J. New nucleophilic fluoroalkylation chemistry. In: *Fluorinated Synthons*; Soloshonok VA, editor; ACS Symposium Series 911; Washington, DC: American Chemical Society, 2005. (b) Prakash GKS, Hu J. Selective fluoroalkylations with fluorinated sulfones, sulfoxides and sulfides. *Acc Chem Res* 2007;40:921–930. (c) Hu J. Nucleophilic, radical, and electrophilic (phenylsulfonyl) difluoromethylations. *J Fluorine Chem* 2009;130:1130–1139. (d) Hu J, Zhang W, Wang F. Selective difluoromethylation and monofluoromethylation reactions. *Chem Commun* 2009:7465.
6. (a) Prakash GKS, Yudin AK. Perfluoroalkylation with organosilicon reagents. *Chem Rev* 1997;97:757–786. (b) Singh RP, Shreeve JM. Nucleophilic trifluoromethylation reactions of organic compounds with (triflluoromethyl)trimethylsilane. *Tetrahedron* 2000;56:7613–7632. (c) Prakash GKS, Mandal M. Nucleophilic trifluoromethylation tamed. *J Fluorine Chem* 2001;112:123–131. (d) Shibata N, Mizuta S, Kawai H. Recent advances in enantioselective trifluoromethylation reactions. *Tetrahedron: Asymmetry* 2008;19:2633–2644.
7. Ramaiah P, Krishnamurti R, Prakash GKS. 1-trifluoromethyl-1-cyclohexanol. *Org Synth* 1995;72:232–236.
8. Ruppert I, Schlich K, Volbach W. Die ersten CF_3-substituierten organyl (chlor)silane. *Tetrahedron Lett* 1984;25:2195–2198.
9. Prakash GKS, Hu J, Olah GA. Preparation of tri- and difluoromethylsilanes via an unusual magnesium metal-mediated reductive tri- and difluoromethylation of chlorosilanes using tri- and difluoromethyl sulfides, sulfoxides, and sulfones. *J Org Chem* 2003;68:4457–4463.

10. (a) Pawelke GJ. Tetrakis (dimethylamino)ethylene/trifluoroiodomethane. A specific novel trifluoromethylating agent. *J Fluorine Chem* 1989;42:429–433. (b) Prakash GKS, Deffieux D, Yudin AK, Olah GA. Convenient ands afe electrochemical synthesis of (trifluoromethyl) trimethylsilane. *Synlett* 1994:1057–1058. (c) Aymard F, Nédélec J-Y, Périchon J. An efficient inexpensive electrochemical preparation of Ruppert's reagent. *Tetrahedron Lett* 1994;35:8623–8624. (d) Grobe J, Hegge J. Facile aluminum induced synthesis of (trifluoromethyl) trimethylsilane. *Synlett* 1995:641–642. (e) Prakash GKS, Yudin AK, Deffieux D, Olah GA. Facile preparation of (trifluoromethyl) tributyltin and transtrifluoromethylation of disilyl sulfides to the corresponding trifluoromethylsilanes. *Synlett* 1996: 151–153.
11. Russell J, Roques N. Effective nucleophilic trifluoromethylation with fluoroform and common base. *Tetrahedron* 1998;54:13771–13782.
12. (a) Prakash GKS, Krishnamurti R, Olah GA. Synthetic methods and reactions. 141. Fluoride-induced trifluoromethylation of carbonyl compounds with trifluoromethyltrimethylsilane (TMS-CF3). A trifluoromethide equivalent. *J Am Chem Soc* 1989;111:393–395. (b) Krishnamurti R, Bellew DR, Prakash GKS. Preparation of trifluoromethyl and other perfluoroalkyl compounds with (perfluoroalkyl)trimethylsilanes. *J Org Chem* 1991;56:984–989.
13. Blazejewski J-C, Anselmi E, Wilmshurst MP. Extending the scope of Ruppert's reagent: Trifluoromethylation of imines. *Tetrahedron Lett* 1999;40:5475–5478.
14. Huang A, Li H-Q, Massefski W, Saiah E. Direct trifluoromethylation of nitriles promoted by tetrabutylammonium bifluoride. *Synlett* 2009;2518–2520.
15. Nelson DW, Easley RA, Pintea BNV. Nucleophilic perfluoroalkylation of nitrones. *Tetrahedron Lett* 1999;40:25–28.
16. (a) Kim J, Shreeve JM. The first Cu(I)-mediated nucleophilic trifluoromethylation reactions using (trifluoromethyl) trimethylsilane in ionic liquids. *Org Biomol Chem* 2004;2: 2728–2734. (b) Tyrra W, Naumann D, Quadt S, Buslei S, Yagupolskii YL, Kremlev MM. Fluoride-mediated selective cross-coupling reactions of alkyl halides and trimethyl(perfluoroalkyl)silanes, Me3SiRf (Rf = CF_3, C_2F_5) in the absence of any catalysts. *J Fluorine Chem* 2007;128:813–817.
17. Ma J-A, Cahard D. Update 1 of: Asymmetric fluorination, trifluoromethylation, and perfluoroalkylation reactions. *Chem Rev* 2008;108:PR1–PR43.
18. (a) Prakash GKS. Nucleophilic perfluoroalkylation of organic compounds using perfluoroalkyltrialkylsilanes. In: Olah GA, Chambers RD, Prakash GKS, editors. *Synthetic Fluorine Chemistry*. New York: Wiley; 1992, chapter 10. (b) Wang F, Luo T, Hu J, Wang Y, Krishnan HS, Jog PV, Ganesh SK, Prakash GKS, Olah GA. Synthesis of gem-difluorinated cyclopropanes and cyclopropenes: Trifluoromethyltrimethylsilane as a difluorocarbene source. *Angew Chem, Int Ed* 2011;50:7153–7157.
19. (a) Dubinina GG, Furutachi H, Vicic DA. Active trifluoromethylatinga gents from well-defined copper(I)–CF_3 complexes. *J Am Chem Soc* 2008;130:8600–8601. (b) Tomashenko OA, Escudero-Adán EC, Belmonte MM, Grushin VV. Simple, stable, and easily accessible well-defined CuCF3 aromatic trifluoromethylating agents. *Angew Chem, Int Ed* 2011;50:7655–7659. (c) Morimoto H, Tsubogo T, Litvinas ND, Hartwig JF. A broadly applicable copper reagent for trifluoromethylations and perfluoroalkylations of aryl iodides and bromides. *Angew Chem, Int Ed* 2011;50:3793–3798.
20. (a) Chu L, Qing F-L. Copper-mediated oxidative trifluoromethylation of boronic acids. *Org Lett* 2010;12:5060–5063. (b) Senecal TD, Parsons AT, Buchwald SL. Room temperature

aryl trifluoromethylation via copper-mediated oxidative cross-coupling. *J Org Chem* 2011;76:1174–1176.

21. Chu L, Qing F-L. Copper-mediated aerobic oxidative trifluoromethylation of terminal alkynes with Me_3SiCF_3. *J Am Chem Soc* 2010;132:7262–7263.
22. Mu X, Chen S, Zhen X, Liu G. Palladium-catalyzed oxidative trifluoromethylation of indoles at room temperature. *Chem Eur J* 2011;17:6039–6042.
23. (a) Urata H, Fuchikami T. A novel and convenient method for trifluoromethylation of organic halides using $CF_3SiR'3$/KF/Cu(I) system. *Tetrahedron Lett* 1991;32:91–94. (b) Oishi M, Kondo H, Amii H. Aromatic trifluoromethylation catalytic in copper. *Chem Commun* 2009:1909–1911. (c) Cho DJ, Senecal TD, Kinzel T, Zhang Y, Watson DA, Buchwald SL. The palladium-catalyzed trifluoromethylation of aryl chlorides. *Science* 2010;328:1679–1681.
24. Yagupol'skii LM, Marenets MS. Phenyl trifluoromethyl sulfides and phenyl trifluoromethyl sulfones with substituents in the p-position. *Russ J Gen Chem* 1954;24:885–891.
25. Kremsner JM, Rack M, Pilger C, Kappe CO. Microwave-assisted aliphatic fluorinechlorine exchange using triethylamine trihydrofluoride (TREAT-HF). *Tetrahedron Lett* 2009;50:3665–3668.
26. Chen Q-Y, Duan J-X. Direct trifluoromethylthiolation of aryl halides using methyl fluorosulfonyldifluoroacetate and sulfur. *J Chem Soc, Chem Commun* 1993:918–919.
27. (a) Hu J. Ph.D. Thesis, Investigations in selective fluorinations: novel synthetic methodologies and material syntheses. University of Southern California, Los Angeles, USA, 2002.
28. Kolomeitsev AA, Movchun VN, Kondratenko NV, Yagupolski YL. A convenient route to aryl trifluoromethyl sulfones by fluoride-catalyzed cross-coupling of arenesulfonyl fluorides with (trifluoromethyl) trimethylsilane and (trifluoromethyl) trimethylstannane. *Synthesis* 1990:1151–1152.
29. Singh RP, Cao G, Kirchmeier RL, Shreeve JM. Cesium fluoride catalyzed trifluoromethylation of esters, aldehydes and ketones with (trifluoromethyl) trimethylsilane. *J Org Chem* 1999;64:2873–2876.
30. Prakash GKS, Hu J, Olah GA. Alkoxide- and hydroxide-induced nucleophilic trifluoromethylation using trifluoromethyl sulfone or sulfoxide. *Org Lett* 2003;5:3253–3256.
31. Zhao Y, Zhu J, Ni C, Hu J. Magnesium metal-mediated reductive trifluoromethylation of aldehydes with phenyl trifluoromethyl sulfone. *Synthesis* 2010:1899–1904.
32. Hine J, Porter JJ. Methylene derivatives as intermediates in polar reactions. VIII. Difluoromethylene in the reaction of chlorodifluoromethane with sodium methoxide. *J Am Chem Soc* 1957;79:5493–5496.
33. Hine J, Porter JJ. The formation of difluoromethylene from difluoromethyl phenyl sulfone and sodium methoxide. *J Am Chem Soc* 1960;82:6178–6181.
34. Chen Q-Y, Wu S-W. Perfluoro- and polyfluorosulfonic acids. 21. Synthesis of difluoromethyl esters using fluorosulfonyldifluoroacetic acid as a difluorocarbene precursor. *J Org Chem* 1989;54:3023–3027.
35. Walkowiak J, Campo T, Ameduri B, Gouverneur V. Syntheses of mono-, di-, and trifluorinated styrenic monomers. *Synthesis* 2010:1883–1890.
36. Stahly GP. Nucleophilic addition of difluoromethyl phenyl sulfone to aldehydes and various transformations of the resulting alcohols. *J Fluorine Chem* 1989;43:53–66.

37. Ni C, Wang F, Hu J. Enantioselective nucleophilic difluoromethylation of aromatic aldehydes with Me3SiCF2SO2Ph and $PhSO_2CF_2H$ reagents catalyzed by chiral quaternary ammonium salts. *Beilstein J Org Chem* 2008;4(21).

38. Ni C, Zhang L, Hu J. Synthesis of fluorinated β-ketosulfones and gem-disulfones by nucleophilic fluoroalkylation of esters and sulfinates with di- and monofluoromethyl sulfones. *J Org Chem* 2009;74:3767–3771.

39. (a) Prakash GKS, Hu J, Wang Y, Olah GA. Difluoromethyl phenyl sulfone, a difluoromethylidene equivalent: Use in the synthesis of 1,1-difluoro-1-alkenes. *Angew Chem, Int Ed* 2004;43:5203–5206. (b) Prakash GKS, Hu J, Wang Y, Olah GA. Nucleophilic difluoromethylation of primary alkyl halides using difluoromethyl phenyl sulfone as a difluoromethyl anion equivalent. *Org Lett* 2004;6:4315–4317.

40. (a) Li Y, Hu J. Facile synthesis of chiral alpha-difluoromethyl amines from N-(tert-butylsulfinyl) aldimines. *Angew Chem, Int Ed* 2005;44:5882–5886. (b) Liu J, Li Y, Hu J. Stereoselective synthesis of di- and monofluoromethylated vicinal ethylenediamines with di- and monofluoromethyl sulfones. *J Org Chem* 2007;72:3119–3121.

41. Liu J, Hu J. Highly diastereoselective synthesis of alpha-difluoromethyl amines from N-tert-butylsulfinyl ketimines and difluoromethyl phenyl sulfone. *Chem Eur J* 2010;16:11443–11454.

42. Ni C, Liu J, Zhang L, Hu J. A remarkably efficient fluoroalkylation of cyclic sulfates and sulfamidates with $PhSO_2CF_2H$: Facile entry into beta-difluoromethylated or beta-difluoromethylenated alcohols and amines. *Angew Chem, Int Ed* 2007;46:786–789.

43. Prakash GKS, Hu J, Mathew T, Olah GA. Difluoromethyl phenyl sulfone as a selective difluoromethylene dianion equivalent: One-pot stereoselective synthesis of anti-2,2-difluoropropane-1,3-diols. *Angew Chem, Int Ed* 2003;42:5216–5219.

44. (a) Ni C, Hu J. Nucleophilic difluoromethylation of carbonyl compounds using $TMSCF_2SO_2Ph$ and Mg-0-mediated desulfonylation. *Tetrahedron Lett* 2005;46:8273–8277. (b) Liu J, Ni C, Wang F, Hu J. Stereoselective synthesis of alpha-difluoromethyl-beta-amino alcohols via nucleophilic difluoromethylation with Me(3)SiCF(2)SO(2)Ph. *Tetrahedron Lett* 2008;49:1605–1608.

45. Prakash GKS, Hu J, Wang Y, Olah GA. Convenient synthesis of difluoromethyl alcohols from both enolizable and non-enolizable carbonyl compounds with difluoromethyl phenyl sulfone. *Eur J Org Chem* 2005:2218–2223.

46. Zhu L, Li Y, Zhao Y, Hu J. Nucleophilic (phenylsulfonyl)difluoromethylation of alkyl halides using $PhSO_2CF_2SiMe_3$: Preparation of gem-difluoroalkenes and trifluoromethyl compounds. *Tetrahedron Lett* 2010;51:6150–6152.

47. (a) Eisenberger P, Gischig S, Togni A. Novel 10-I-3 hypervalent iodine-based compounds for electrophilic trifluoromethylation. *Chem Eur J* 2006;12:2579–2586. (b) Kieltsch I, Eisenberger P, Togni A. Mild electrophilic trifluoromethy-lation of carbon- and sulfur-centered nucleophiles by a hypervalent iodine(III)-CF_3 reagent. *Angew Chem, Int Ed* 2007;46:754–757. (c) Eisenberger P, Kieltsch I, Armanino N, Togni A. Mild electrophilic trifluoromethylation of secondary and primary aryl- and alkylphosphines using hypervalent iodine(III)-CF_3 reagents. *Chem Commun* 2008;1575–1577.

48. Zhang W, Zhu J, Hu J. Electrophilic (phenylsulfonyl)difluoromethylation of thiols with a hypervalent iodine(III)-CF_2SO_2Ph reagent. *Tetrahedron Lett* 2008;49:5006–5008.

49. Zhu J, Wang F, Huang W, Zhao Y, Ye W, Hu J. Copper-mediated fluoroalkylation reactions with [(phenylsulfonyl)-difluoromethyl]trimethylsilane: Synthesis of $PhSO_2CF_2^-$ containing allenes and alkynes. *Synlett* 2011:899–902.

50. McCarthy JR, Matthews DP, Paolini JP. Reaction of sulfoxides with diethylaminosulfur trifluoride: fluoromethyl phenyl sulfone, a reagent for the synthesis of fluoroalkenes. *Org Synth* 1995;72:209–215.
51. More KM, Wemple J. The synthesis of aryl fluoromethyl sulfoxides. *Synthesis* 1977;791–792.
52. (a) McCarthy JR, Peet NP, LeTourneau ME, Inbasekaran M. (Diethylamino) sulfur trifluoride in organic synthesis. 2. The transformation of sulfoxides to .alpha.-fluoro thioethers. *J Am Chem Soc* 1985;107:735–737. (b) Inbasekaran M, Peet NP, McCarthy JR, LeTourneau ME. A novel and efficient synthesis of fluoromethyl phenyl sulphone and its use as a fluoromethyl Wittig equivalent. *Chem Commun* 1985;678–679.
53. L'Heureux A, Beaulieu F, Bennett C, Bill DR, Clayton S, LaFlamme F, Mirmehrabi M, Tadayon S, Tovell D, Couturier M. Aminodifluorosulfiniumsalts: Selective fluorination reagents with enhanced thermal stability and ease of handling. *J Org Chem* 2010;75:3401–3411.
54. Robins MJ, Wnuk SF. Nucleic acid related compounds. 79. Efficient conversions of thioethers to .alpha.-fluoro thioethers with DAST or DAST/antimony(III) chloride. *J Org Chem* 1993;58:3800–3801.
55. Zhang W, Zhu L, Hu J. Electrophilic monofluoromethylation of O-, S-, and N-nucleophiles with chlorofluoromethane. *Tetrahedron* 2007;63:10569–10575.
56. (a) McCarthy JR, Matthews DP, Edwards ML, Stemerick DM, Jarvi ET. A new route to vinyl fluorides. *Tetrahedron Lett* 1990;31:5449–5452. (b) McCarthy JR, Matthews DP, Stemerick DM, Huber EW, Bey P, Lippert BJ, Snyder RD, Sunkara PS. Stereospecific method to (E) and (Z) terminal fluoroolefins and its application to the synthesis of 2′-deoxy-2′-fluoromethylenenucleosides as potential inhibitors of ribonucleoside diphosphate reductase. *J Am Chem Soc* 1991;113:7439–7440.
57. (a) Hu J, Zhang W, Wang F. Selective difluoromethylation and monofluoromethylation reactions. *Chem Commun* 2009:7465–7478. (b) Ni C, Hu J. Selective nucleophilic fluoroalkylations facilitated by removable activation groups. *Synlett* 2011:770–782.
58. Li Y, Ni C, Liu J, Zhang L, Zheng J, Zhu L, Hu J. Stereoselective nucleophilic monofluoromethylation of N-(tert-butanesulfinyl)imines with fluoromethyl phenyl sulfone. *Org Lett* 2006;8:1693–1696.
59. Liu J, Zhang L, Hu J. Stereoselective monofluoromethylation of N-tert-butylsulfinyl ketimines using pregenerated fluoro(phenylsulfonyl) methyl anion. *Org Lett* 2008;10:5377–5380.
60. Fukuzumi T, Shibata N, Sugiura M, Yasui H, Nakamura S, Toru T. Fluoro-bis (phenylsulfonyl) methane: As a fluoromethide equivalent and palladium-catalyzed enantioselective allylic monofluoromethylation. *Angew Chem, Int Ed* 2006;45:4973–4977.
61. Ni C, Li Y, Hu J. Nucleophilic fluoroalkylation of epoxides with fluorinated sulfones. *J Org Chem* 2006;71:6829–6833.
62. Prakash GKS, Wang F, Ni C, Thomas TJ, Olah GA. Efficient synthesis of α-(fluoro/chloro/methoxy) disulfonylmethane derivatives as tunable substituted methyl synthons via a new CS bond forming strategy. *J Fluorine Chem* 2010;131:1007–1012.
63. Nagura H, Fuchigami T. Regioselective electrochemical monofluorination of α-sulfonyl sulfides. *Synlett* 2008:1714–1718.
64. Ni C, Zhang L, Hu J. Nucleophilic fluoroalkylation of alpha,beta-enones, arynes, and activated alkynes with fluorinated sulfones: Probing the hard/soft nature of fluorinated carbanions. *J Org Chem* 2008;73:5699–5713.

65. Prakash GKS, Wang F, Shao N, Mathew T, Rasul G, Haiges R, Stewart T, Olah GA. A persistent α-fluorocarbanion and its analogues: Preparation,characterization, and computational study. *Angew Chem, Int Ed* 2009;48:5358–5363.
66. (a) Liu W-B, Zheng S-C, He H, Zhao X-M, Dai L-X, You S-L. Iridium-catalyzed regio- and enantioselective allylic alkylation of fluorobis (phenylsulfonyl) methane. *Chem Commun* 2009:6604–6606. (b) Zhao X, Liu D, Zheng S, Gao N. Highly regioselective Pd-catalyzed allylic alkylation of fluorobis (phenylsulfonyl)methane. *Tetrahedron Lett* 2011;52:665–667.
67. Prakash GKS, Chacko S, Alconcel S, Stewart T, Mathew T, Olah GA. Stereoselective monofluoromethylation of primary and secondary alcohols using a fluorocarbon nucleophile in Mitsunobu reaction. *Angew Chem, Int Ed* 2007;46:4933–4936.
68. (a) Prakash GKS, Zhao X, Chacko S, Wang F, Vaghoo H, Olah GA. Efficient 1,4-addition of α-substituted fluoro(phenylsulfonyl)methane derivatives to α,β-unsaturated compounds. *Beilstein J Org Chem* 2008:4(17). (b) Moon HW, Cho MJ, Kim DY. Enantioselective conjugate addition of fluorobis(phenylsulfonyl)methane to α,β-unsaturated ketones catalyzed by chiral bifunctional organocatalysts. *Tetrahedron Lett* 2009;50:4896–4898. (c) Alba A-N, Companyó X, Moyano A, Rios R. Formal highly enantioselective organocatalytic addition of fluoromethyl anion to α,β-unsaturated aldehydes. *Chem Eur J* 2009;15:7035–7038. (d) Zhang S, Zhang Y, Ji Y, Li H, Wang W. Catalytic enantioselective conjugate addition of fluorobis (phenylsulfonyl) methane to enals: Synthesis of chiral monofluoromethyl compounds. *Chem Commun* 2009;4886–4888.
69. Mizuta S, Shibata N, Goto Y, Furukawa T, Nakamura S, Toru T. Cinchona alkaloid-catalyzed enantioselective monofluoromethylation reaction based on fluorobis (phenylsulfonyl) methane chemistry combined with a mannich-type reaction. *J Am Chem Soc* 2007;129:6394–6395.
70. Shen X, Zhang L, Zhao Y, Zhu L, Li G, Hu J. Nucleophilic fluoromethylation of aldehydes with fluorobis (phenylsulfonyl) methane: The importance of strong LiO coordination and fluorine substitution for C-C bond formation. *Angew Chem, Int Ed* 2011;50:2588–2592.
71. Yang W, Wei X, Pan Y, Lee R, Zhu B, Liu H, Yan L, Huang K-W, Jiang Z, Tan C-H. Highly enantio- and diastereoselective synthesis of β-methyl-γ-monofluoromethyl-substituted alcohols. *Chem Eur J* 2011;17:8066–8070.
72. (a) Prakash GKS, Chacko S. Novel nucleophilic and electrophilic fluoroalkylation methods. *Curr Opin Drug Discovery Dev* 2008;11:793–802. (b) Valero G, Companyo X, Rios R. Enantioselective organocatalytic synthesis of fluorinated molecules. *Chem Eur J* 2011;17:2018–2037.
73. Prakash GKS, Ledneczki I, Chacko S, Ravi S, Olah GA. Stereoselective synthesis of fluorobis (phenylsulfonyl) methyl-substituted alkenes using free radical fluoroalkylation. *J Fluorine Chem* 2008;129:1036–1040.
74. Prakash GKS, Weber C, Chacko S, Olah GA. New electrophilic difluoromethylating reagent. *Org Lett* 2007;9:1863–1866.
75. (a) Shibata N, Matsnev A, Cahard D. Shelf-stable electrophilic trifluoromethylating reagents: A brief historical perspective. *Beilstein J Org Chem* 2010;6(65).
76. Prakash GKS, Weber C, Chacko S, Olah GA. New solid-phase bound electrophilic difluoromethylating reagent. *J Comb Chem* 2007;9:920–923.
77. Prakash GKS, Ledneczki I, Chacko S, Olah GA. Direct electrophilic monofluoromethylation. *Org Lett* 2008;10:557–560.