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Articles

Chemistry of Trichlorofluoromethane: Synthesis of Chlorofluoromethyl Phenyl Sulfone and Fluoromethyl Phenyl Sulfone and Some of Their Reactions

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It was observed that the reaction of $CFCl_3$ with thiophenoxide gave only 10% of the corresponding thioether. On the other hand, these thioethers could be prepared in excellent yield from diaryl disulfides and $CFCl_3$ in the presence of sodium hydroxymethanesulfinate in aqueous DMF at 4 atm pressure of nitrogen. Dechlorination of the thioether ($PhSCFCl_2$) with different reducing agents were studied. Most of the reducing agents eliminated both fluorine and chlorine functionalities or gave the hydrolyzed products. But its sulfone on treatment with Zinc in methanol gave monochlorofluoromethyl and fluoromethyl phenyl sulfone in good yields. Darzens reaction of these compounds was also studied.

Introduction

Fluorine functionality plays an important role in the biologically active compounds.[1] Several β-fluorophenethylamines,[2] β-fluoroamino acids,[1] 3-fluoroalkylamines,[3] and vinyl fluorides[4] have been proved to be irreversible inhibitors of certain enzymes. Therefore, fluorine chemistry has been the subject of increased research activity in recent years. In continuation of our research on α-mono- and α,α-dihalogenated compounds,[5] we were interested in Darzens condensation reaction of α-halogenated sulfones with various carbonyl compounds. We now report a synthetic method for the preparation of chlorofluoromethyl phenyl sulfone and fluoromethyl phenyl sulfone and their reactions with different carbonyl compounds.

Results and Discussion

Following the literature procedure for the preparation of fluorinated thioethers,[6] we observed that the reaction

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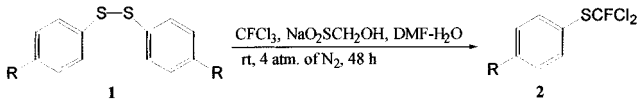
Table 1. Preparation of α-Halothioethers



entry	R	product **2**/yield (%)[a]
a	H	72 (52)
b	CH_3	84 (40)
c	Cl	91 (64)
d	NO_2	45 (16)

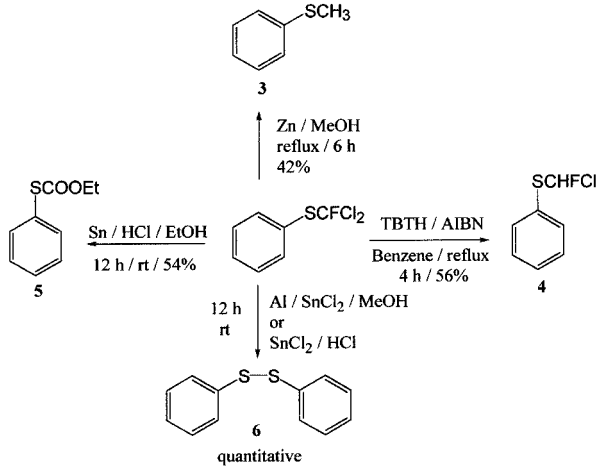
[a] Yield was based on the amount of the starting material consumed, and the yield within the parentheses was the isolated yield.

of $CFCl_3$ with potassium thiophenoxide in DMF under an atmosphere of nitrogen gave only 10% of dichlorofluoromethyl phenyl sulfone. Increasing the pressure up to 2.5 atm of nitrogen also resulted in a low yield (21%). Claude et al.[7] had reported that the reaction of $CFCl_3$ with diphenyl disulfide in the presence of sodium dithionite and sodium dihydrogenphosphate in aqueous DMF yielded 13% of dichlorofluoromethyl phenyl sulfide. We synthesized the thioethers **2** by slightly modifying the Claude's method using sodium hydroxymethanesulfinate in aqueous DMF under 4 atm of nitrogen in 45−91% yield as shown in Table 1.

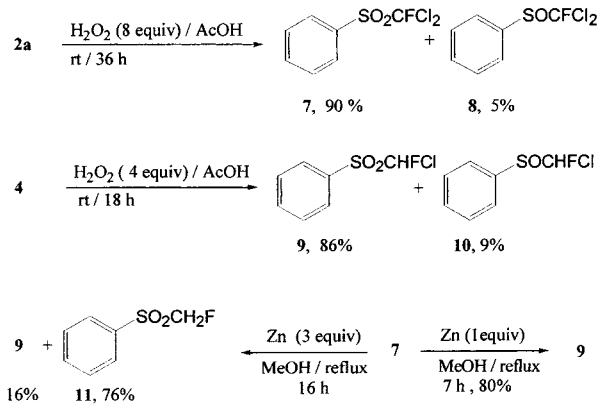
The reduction of the compound **2a** with zinc in methanol[8] gave dehalogenated product, methyl phenyl sulfide (**3**), in 42% yield. On the other hand, the reduction with tributyltin hydride and AIBN[9] afforded the compound **4** in 56% yield. The reduction with tin and hydrochloric acid in ethanol furnished only the hydrolyzed product, ethyl phenyl thiocarbonate (**5**), in 54% yield, whereas the reduction with $SnCl_2$ in hydrochloric acid[10] or Al−$SnCl_2$−MeOH[11] systems afforded disulfide (**6**) quantitatively as shown in Scheme 1.

We observed that when sulfide **2** was initially oxidized with hydrogen peroxide in acetic acid to the corresponding sulfone and then reduced with zinc in methanol, a mixture of chlorofluoromethyl phenyl sulfone ($PhSO_2$-CHClF) and fluoromethyl phenyl sulfone ($PhSO_2CH_2F$) was obtained. Thus, the reaction of **2a** with hydrogen peroxide (8 equiv) in acetic acid afforded the sulfone **7** in 90% yield along with the sulfoxide **8** in 5% yield. Similarly, hydrogen peroxide oxidation of **4** gave 86% of the sulfone **9** and sulfoxide **10** in 9% yield. The compound **10** showed two sets of signals in ^1H and ^{19}F NMR and therefore consists of a pair of diastereomers. Refluxing **7** with 1 equiv of zinc in methanol for 7 h, the sulfone **9** was isolated in 80% yield; however, when 3 equiv of zinc was used in methanol and the reaction was run for 16 h, 76% yield of fluoromethyl phenyl sulfone (**11**) was obtained, along with the compound **9** in 16% yield

Scheme 1. Reduction of α-Halothioethers



Scheme 2. Synthesis of Chlorofluoromethyl and Fluoromethyl Phenyl Sulfone



(Scheme 2). The reason for complete dehalogenation of sulfide (**2a**) is that the lone pairs on sulfur makes the fluorine−carbon bond more labile for elimination.

Darzens Condensation of the Compound 9. Vogt and Tavares[12] prepared epoxy sulfones by treating chloromethyl tolyl sulfone with aldehydes and ketones in the presence of potassium *tert*-butoxide. Makosza[13] and coworkers showed that α,*β*-epoxy sulfones can be simply prepared from α-chlorosulfones and carbonyl compounds under phase-transfer conditions in 60−90% yields. Durst et al.[14] also studied the condensation of α-chlorosulfones with different carbonyl compounds using *n*-BuLi or LDA as a base and obtained halohydrin sulfones in excellent yields which were then cyclized to the corresponding epoxide in the presence of potassium hydroxide. In this paper, some reactions of the sulfone **9** with different aldehydes and ketones were carried out, and the results were summarized in Table 2 and Scheme 3. The reaction of **9** with aromatic aldehydes and ketones under phase-transfer condition using THF as a solvent and benzyltriethylammonium fluoride (TEBA) as catalyst gave rearranged products **11** and **15,** without isolation of the epoxy sulfone **13**. When acetonitrile was used as a solvent, the compound **16** was also obtained in 23% yield. The formation of compounds **11**, **15**. and **16** can be

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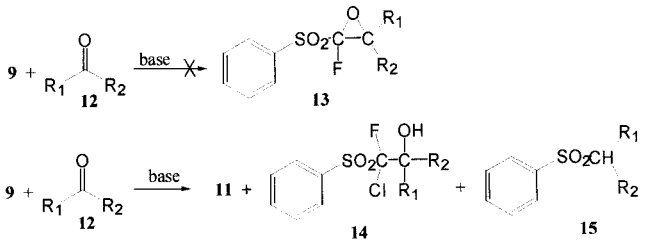
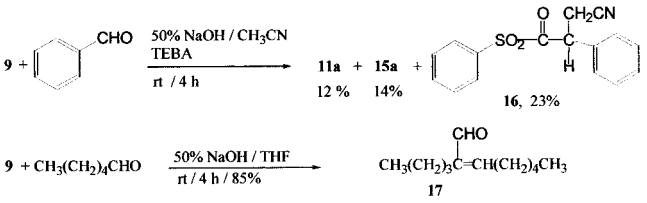
Table 2. Darzens Condensation Products of Sulfone



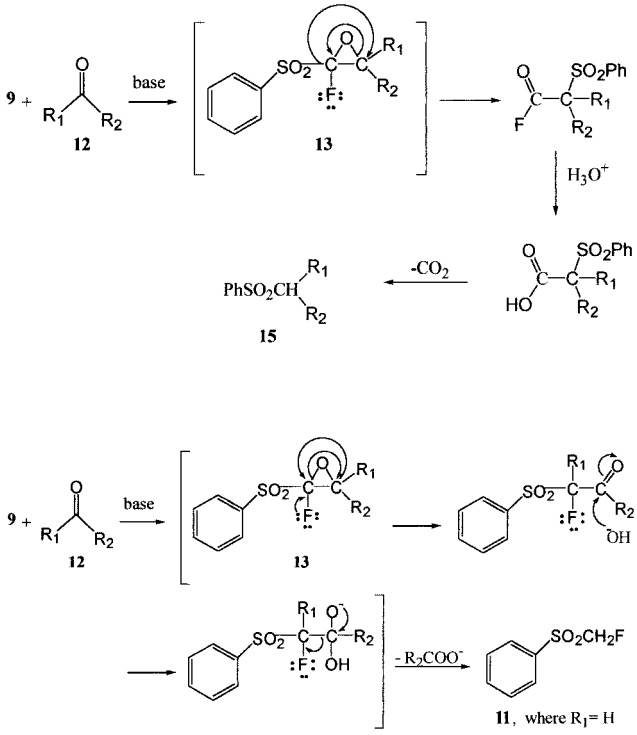
carbonyl compound **12**					products (% yield)		
	R_1	R_2	reaction conditions	reaction time/h	**14**	**11**	**15**
a	C_6H_5	H	50% NaOH/THF/rt[a]	4	---	15	15
b	*p*-$CH_3C_6H_5$	H	50% NaOH/THF/rt[a]	4	---	17	20
c	C_6H_5	C_6H_5-	50% NaOH/THF/rt[a]	4	---	---	60
d	$CH_3(CH_2)_4$	H	50% NaOH/THF/rt[a]	4	aldol product (**17**, 85%)[b]		
a	C_6H_5	H	Bu^{t}OK/THF / −35 °C to rt	16	25	31	30
b	*p*-$CH_3C_6H_5$	H	Bu^{t}OK/THF / −35 °C to rt	16	28	32	31
c	C_6H_5	C_6H_5	Bu^{t}OK/THF / −35 °C to rt	16	---	---	60
d	$CH_3(CH_2)_4$	H	Bu^{t}OK/THF / −35 °C to rt	16	58	---	---
e	$(CH_3)_2CHCH_2$	H	Bu^{t}OK/THF / −35 °C to rt	16	60	---	---

[a] TEBA was used as a phase transfer catalyst [b] See Scheme 3.

Scheme 3



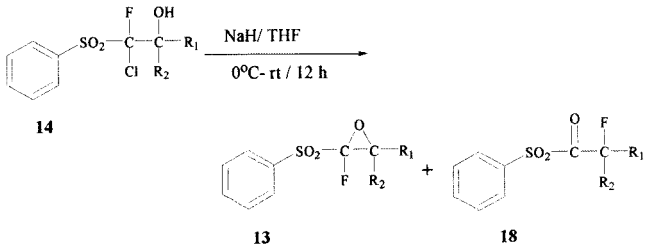
Scheme 4. Mechanism of the Rearrangement Reaction



explained as follows. The epoxide **13** which forms during the reaction is more reactive due to the two electron-withdrawing groups, fluorine and sulfonyl, and consequently in the presence of base, acetonitrile attacks the epoxide **13** as a nucleophile, giving the compound **16** (Scheme 3**).** Compound **15** forms by the migration of sulfonyl group and subsequent decarbonylation as shown in Scheme 4. A similar type of mechanism has also been described by Durst et al.[14] Formation of the compound **11** can be explained by considering the mesomeric effect of fluorine.[15] For this effect, the epoxide ring opens in the opposite direction and migration of hydride presides over that of the phenyl group due to steric hindrance. This is confirmed by the fact that when the reaction was performed with benzophenone only benzhydril phenyl sulfone (**15c**) was obtained and no compound **11** was isolated. In case of aliphatic aldehyde, only aldol product **17** was obtained in 85% yield. When potassium *tert*-butoxide was used as a base, halohydrin sulfone **14** was also obtained along with **11** and **15**. Under this condition, aliphatic aldehyde gave only halohydrin sulfone **14,** and attempt to make an epoxide by treating potassium hydroxide failed, but resulted in the retro-products **9** and **12**. It was observed that treatment of the compound **14** with several organic bases such as triethylamine, pyridine, DBU, and sodium hexamethyldisilazane in anhydrous conditions did not afford the epoxide **13**. In most of the cases, degraded products (**11** and **15a,b**) were obtained, and in some cases starting materials were recovered. On the other hand, the halohydrin sulfone **14** could be converted to the corresponding epoxide **13** by treating with sodium hydride in anhydrous THF. The results were summarized in Table 3. Under this condition, compounds **14a** and **14b** were decomposed to compounds **11** and **15a**,**b**, whereas compound **14e** afforded epoxide **13e** as a diastereomeric mixture **(**1:3**)** in moderate yield (56%). Exposure of compound **14d** to sodium hydride gave epoxide **13d** as a diastereomeric mixture (2:3) which was contaminated with compound **18d (13d**:**18d** = 13:7). The mixture of compounds **13d** and **18d** was inseparable even by HPLC. The existence of the compound **18d** was determined from the ^{1}H NMR, ^{13}C NMR, and IR spectra of the mixture. In the ^{1}H and ^{13}C NMR spectra, the extra peaks at 5.84 and 171.0 ppm indicated the presence of **18d**. It was further confirmed

(15) One reviewer's opinion was that an alternative route of forming **11** from **9** may be due to the reductive properties of aldehydes. But when the same reaction was carried out with compound **7** neither compound **9** nor **11** was formed.

Table 3. Conversion of Halohydrin Sulfone to Epoxide



14 13 18

substrate **14**	R_1	R_2	products (% yield) **13**	**18**
a	C_6H_5-	H	*a*	
b	*p*-$CH_3C_6H_5$	H	*a*	
d	$CH_3(CH_2)_4$	H	34.6	19.2[b]
e	$(CH_3)_2CHCH_2$	H	56	-

[a] Decomposed to compounds **11** and **15a**,**b.** [b] Yield was based on ^{1}H NMR.

from the IR spectrum where a clear band at 1767 cm^{-1} was indicative of a carbonyl group.

Reaction of fluoromethyl phenyl sulfone with various carbonyl compounds has already been studied by Inbasekaran et al.[16] to prepare vinyl fluorides. Fluoromethyl phenyl sulfone has widely been exploited by McCarthy's group in the synthesis of 2′-deoxy-2′-fluoromethylene nucleosides as potential inhibitors of ribonucleoside diphosphate reductase.[4b]

Conclusion

In summary, we have developed a chlorofluoromethylating agent, chlorofluoromethyl phenyl sulfone, and studied its Darzens reaction, which differs from the normal α-halosulfones. Alternatively it is a good method for the preparation of α-fluoro epoxy sulfone. We have also developed an alternative method for the synthesis of fluoromethyl phenyl sulfone which is an important reagent for introduction of fluoromethyl group in bioactive organic molecules[16,4] using relatively cheaper and easily available starting material $CFCl_3$. It is noteworthy that there are two known methods for the preparation of fluoromethyl phenyl sulfone which require costly, explosive reagents, and exceptional dry conditions.[16,17]

Experimental Section

The melting points are uncorrected. All reactions were performed under an atmosphere of dry nitrogen, unless otherwise stated. THF was distilled from sodium/benzophenone ketyl. ^{1}H NMR spectra were recorded in $CDCl_3$ solution at 200 MHz NMR machine using TMS as internal standard. ^{19}F NMR spectra were recorded at 188 MHz using hexafluorobenzene as internal standard.

Preparation of α-Halothioethers: Synthesis of Dichlorofluoromethyl Phenyl Sulfide (2a). A mixture of diphenyl disulfide (1.0 g, 4.58 mmol), sodium hydroxymethanesulfinate (1.0 g, 8.47 mmol), $CFCl_3$ (1.47 g, 10.8 mmol), DMF (10 mL), and water (5 mL) was stirred at 4 atm of nitrogen for 48 h in a pressure bomb. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with 5% hydrochloric acid and then with 10% sodium bicarbonate solution and dried over $MgSO_4$. Solvent was removed under reduced pressure and purified by column chromatography to obtain 0.93 g (52%, 72% on the basis of 73% conversion) of the product **2a** as an oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.33 (m, 3 H), 7.53 (m, 2 H); ^{19}F NMR (188 MHz, $CDCl_3$, C_6F_6): δ 141.62 (s, 1 F, $CFCl_2$); GC/MS (EI, 70 eV) *m*/*z* 210 (M^+), 177, 175, 109, 77, 65.

Reduction of 2a with Zinc in Methanol. A mixture of **2a (**0.048 g, 0.23 mmol), and powdered zinc (0.84 g) in methanol (1.0 mL) was refluxed for 6 h. The solid material was filtered and the filtrate evaporated to dryness and purified by column chromatography to give 0.012 g (42%) of the product as an oil which was identified as methyl phenyl sulfide (**3**); ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.4 (s, 3 H), 7.27 (m, 5H); GC/MS (EI, 70 eV) *m*/*z* 124 (M^+), 109, 77.

Reduction of 2a with $SnCl_2$ and HCl. A mixture of **2a** (0.11 g, 0.52 mmol), $SnCl_2{\cdot}2H_2O$ (0.09 g, 0.52 mmol) and concd HCl (0.5 mL) was heated to 90 °C and kept for 12 h. The mixture was filtered with suction to remove the solid material. The humus on the filter was washed with water and finally with ethyl acetate. The aqueous phase was extracted with ethyl acetate, and the combined filtrate and extract was washed with sodium bicarbonate and water and then dried ($MgSO_4$). After evaporation of the solvent, the product was purified by column chromatography. The compound was identified as diphenyl disulfide. The spectral data were identical with the authentic sample.

Reduction of 2a with Al and $SnCl_2$ in MeOH. A mixture of **2a** (0.14 g, 0.67 mmol), $SnCl_2{\cdot}2H_2O$ (0.13 g, 0.7 mmol), and Al (0.019 g) was stirred in MeOH at room temperature for 14 h. The mixture was filtered and the residue washed with ethyl acetate. The combined filtrate and washings were washed with water and dried ($MgSO_4$). After evaporation of the solvent and column chromatography, the isolated compound was identified as diphenyl disulfide.

Reduction of 2a with Sn in HCl and EtOH. To a solution of **2a** (0.09 g, 0.43 mmol) in EtOH (1 mL) was added concentrated HCl (0.1 mL, 1.0 mmol) and granulated tin (0.10 g), and the mixture was refluxed for 4 h. The reaction mixture was filtered hot, and the residue was washed with ethyl acetate. The combined filtrate and washings were treated with sodium bicarbonate solution, dried ($MgSO_4$), and then evaporated to give the crude product, which was further purified by column chromatography and characterized as ethyl phenyl thiocarbonate (0.042 g, 54%). Colorless oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.32 (t, J = 7.4 Hz, 3 H), 4.30 (q, J = 7.4 Hz, 2 H), 7.42 (m, 3 H), 7.53 (m, 2 H); GC/MS (EI, 70 eV) *m*/*z* 182 (M^+), 123, 110, 109, 77, 65.

Reduction of 2a with TBTH (Bu_3SnH) and AIBN. A mixture of **2a** (0.21 g, 1 mmol), tributyltin hydride (0.29 g, 1 mmol), AIBN (0.01 g), and benzene (10 mL) was refluxed under nitrogen for 3 h. The mixture was evaporated under reduced pressure and the residue was washed with aqueous $NaHCO_3$ solution, extracted with ethyl acetate, dried ($MgSO_4$), and evaporated. The product was purified by column chromatography to give 0.1 g (56% yield) of the reduced product **4** as an oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.07 (d, J = 55.8 Hz, 1 H, −CHFCl), 7.4 (m, 3 H), 7.61 (m, 2 H); ^{19}F NMR (188 MHz, $CDCl_3$, C_6F_6): δ 62.6 (d, J = 55.8 Hz, 1 F, −CHFCl); GC/MS (EI, 70 eV) *m*/*z* 176 (M^+), 141, 125, 109, 77.

Oxidation of 2a with H_2O_2 and AcOH. A mixture of **2a** (0.50 g, 2.38 mmol), 30% H_2O_2 (2.57 mL, 22.7 mmol), and acetic acid (2 mL) was stirred at room temperature for 36 h. The reaction mixture was diluted with water, extracted with ethyl acetate, washed with 10% sodium bicarbonate solution, dried ($MgSO_4$), and evaporated. Finally the product was purified by column chromatography to give sulfone **7** (0.52 g, 90%) as white solid; mp 32 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.59 (m, 3 H), 7.83 (m, 2H); ^{19}F NMR (188 MHz, $CDCl_3$, C_6F_6): δ 99.29 (s, 1 F, $-CFCl_2$); ^{13}C NMR (50 MHz, $CDCl_3$): δ 121.94 (d, J = 335.0 Hz), 129.44, 130.15, 131.79, 136.14; GC/MS (EI, 70 eV) *m*/*z* 242 (M^+), 141, 109, 77, 51 and sulfoxide (**8**) (0.03 g, 5%) as a gum; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.61 (m, 3 H), 7.84 (m, 2 H); ^{19}F NMR (188 MHz, $CDCl_3$, C_6F_6): δ 99.47 (s, 1 F, $-CFCl_2$); GC/MS (EI, 70 eV) *m*/*z* 226 (M^+), 143, 125, 109, 97, 77.

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Oxidation of 4 with H_2O_2 and AcOH. A mixture of **4** (0.5 g, 2.84 mmol), 30% H_2O_2 (0.52 mL, 5.68 mmol), and acetic acid (1 mL) was stirred at room temperature for 12 h. The reaction mixture was diluted with water, extracted with ethyl acetate, washed with 10% sodium bicarbonate solution, dried ($MgSO_4$), and evaporated. Finally the product was purified by column chromatography to give sulfone **9** (0.51 g, 86%) as a gum; ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.54 (d, J = 49.0 Hz, 1 H, −CHFCl), 7.61−7.80 (m, 3 H), 8.01 (m, 2 H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 104.4 (d, J = 282.5 Hz), 129.45, 130.77, 132.01, 135.66; ^{19}F NMR (188 MHz, $CDCl_3$, C_6F_6): δ 25.24 (d, J = 49.1 Hz, 1 F, CHFCl); GC/MS (EI, 70 eV) m/z 208 (M^+), 141, 125, 109, 77, 65; and sulfoxide **10** (diastereomeric mixture (1:2) as determined by ^{19}F NMR analysis, 0.05 g, 9%) as a gum; ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.47 (d, J = 50.6 Hz, 1 H, CHFCl), 6.46 (d, J = 50.8 Hz, 1F, CHFCl), 7.53−7.64 (m,3 H), 7.75 (m, 2 H); ^{19}F NMR (188 MHz, $CDCl_3$, C_6F_6): δ 23.68 (d, J = 50.19 Hz, 1 F, CHFCl), 23.49 (d, J = 50.76 Hz, 1 F, CHFCl); GC/MS (EI, 70 eV) m/z 192 (M^+), 109, 77, 65.

Reduction of 7 with Zinc and MeOH. A mixture of **7** (1.1 g, 4.54 mmol) and powdered zinc (0.86 g, 13.6 mmol) in methanol (10 mL) was refluxed for 16 h. The solid material was filtered and washed with ethyl acetate, and the combined filtrate and washings were evaporated to dryness and purified by column chromatography to give 0.60 g (76%) of sulfone **11** as a gum; ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.13 (d, J = 47.14 Hz, 1 H, $-CH_2F$), 7.57−7.78 (m, 3 H), 7.94−7.98 (m, 2 H); ^{19}F NMR (188 MHz, $CDCl_3$, C_6F_6): δ −48.97 (t, J = 46.43 Hz, 1 F, CH_2F); GC/MS (EI, 70 eV) m/z 174 (M^+), 141, 77, 51; and sulfone **9** (0.15 g, 16%) as a gum.

General Procedure for the Darzens Condensation under Phase-Transfer Conditions. Compound **9** (0.16 g, 0.76 mmol), THF (5 mL), TEBA (0.01 g), 50% NaOH (0.4 mL), and benzaldehyde (0.08 g, 0.76 mmol) were stirred at room temperature for 4 h. The product was isolated and purified by column chromatography to give compound **11** (0.021 g, 15.0%) and the compound **15a** (0.028 g, 15.0%) as a white solid; mp 143 °C (lit.[18] 144.5−146 °C); ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.21 (s, 2 H), 7.57−7.78 (m, 3 H), 7.94−7.98 (m, 2 H).

General Procedure for the Darzens Condensation with Bu^{t}OK. To a solution of sulfone **9** (0.15 g, 0.72 mmol) in dry THF (1 mL) was added potassium *tert*-butoxide (0.11 g, 1.0 mmol) at −30 °C and stirred for 10 min, and then benzaldehyde (0.07 g, 0.7 mmol) was added and allowed to warm to room temperature. After being stirred for 16 h, the reaction mixture was poured into water, extracted with ethyl acetate, and purified by column chromatography to give compound **11** (0.039 g, 31%), and **14a** (0.056 g, 25%) as a diastereomeric mixture (2:3) as determined by ^{1}H NMR analysis; ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.40 (d, J = 3.2 Hz, 0.4 H), 3.57 (d, J = 4.0 Hz, 0.6 H), 5.45 (dd, J = 20.6 and 3.2 Hz, 0.6 H), 5.58 (br, 0.4 H,), 7.12−7.94 (m, 10 H); ^{19}F NMR (188 MHz, $CDCl_3$, C_6F_6): δ −33.8 (d, J = 20.68 Hz, CClF), −50.44 (s, CClF); GC/MS (EI, 70 eV) m/z 315 (M^+ +1), 107, 79, 77, 51, and the compound **15a** (0.05 g, 30%).

General Procedure for the Preparation of Epoxide. To a solution of halohydrine sulfone **14e** (0.10 g, 0.34 mmol) in dry THF (2 mL) was added sodium hydride (60% oil suspension, 0.20 g, 0.5 mmol) at 0 °C and allowed to warm to room temperature. After being stirred for 12 h, the reaction mixture was filtered to remove a small amount of insoluble material. Evaporation of the filtrate at reduced pressure and purification of the residue on silica gel column gave 0.20 g (56%) of the compound **13**e as a diastereomeric mixture (1:3) as determined by ^{1}H NMR analysis; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.97 (m, 6 H), 1.5−2.2 (m, 3 H), 4.34 (m, 0.25 H, C*H*F), 4.48 (m, 0.75 H, C*H*F), 7.57−8.0 (m, 5 H); ^{19}F NMR (188 MHz, $CDCl_3$, C_6F_6): δ 52.26 (s, 0.58 F, OC*F*), 56.29 (d, J = 5.45, 0.42F, OC*F*), ^{13}C NMR (50 MHz, $CDCl_3$): δ 22.04, 22.96, 23.19, 24.12, 24.21, 24.36, 40.30, 40.46, 77.79, 77.24, 128.05, 128.99, 129.06, 129.12, 131.31, 135.15.

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Supporting Information Available: ^{19}F NMR spectra of compounds **2a**−**d**, **7**, **8**, **9**, **10**, **11**, **13e**, **14a**, **14d**, **14e**; ^{13}C NMR spectra of compounds **7**, **9**, **13d**, **14b**, **14d**, **14e**, **16**; ^{1}H NMR spectra of compounds **9**, **11**, **13d**, **13e**, **14a**, **14b**, **14d**, **14e**, **16**; IR spectra of compounds **13d** and **18d** (as a mixture) and spectral data of the compounds **2b**, **2c**, **2d**, **13d**, **14b**, **14d**, **14e**, **15b**, **15c**, **16**, **17**, and **18d** (**13d** and **18d** as a mixture). This material is available free of charge via the Internet at http://pubs.acs.org.

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