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Synthesis of Monofluoromethylcyclopropanes from Alkenes without Using Freons: Novel Synthesis of Chlorofluoromethyl Phenyl Sulfide and Its Application in Cyclopropanation

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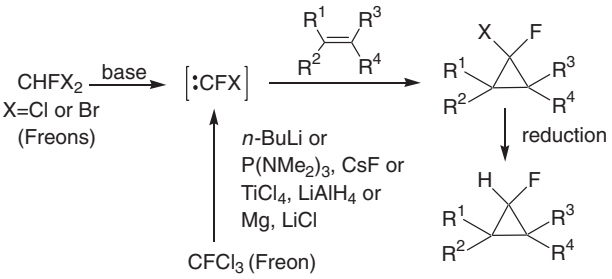
Chlorofluoromethyl phenyl sulfide was prepared from the reaction of chloromethyl phenyl sulfide with Selectfluor™. Monofluorocyclopropanation of an alkene was achieved via cyclopropanation using a fluorocarbene derived from the product chlorofluoromethyl phenyl sulfide, followed by oxidation and desulfurization.

Cyclopropanes are important synthetic intermediates owing to their unique chemical properties. They are also important in the biological sciences and medicinal chemistry. In fact, there are numerous natural products and artificial pharmaceutics containing cyclopropane moieties.[1] A large number of organofluorine compounds are similarly important in material sciences and medicinal chemistry, because the introduction of fluorine atoms into organic compounds results in dramatic physical and chemical changes.[2] Therefore, fluorinated cyclopropanes are important and have received much attention, especially in medicinal chemistry.[3] Among them, monofluorocyclopropane moieties are attractive groups, with one of their most important applications being sitafloxacin, which has a monofluorocyclopropane moiety and is used as an antibacterial pharmaceutical agent.[4]

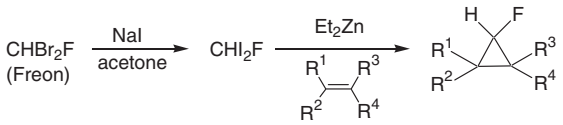
Monofluorocyclopropanes have traditionally been prepared through the halofluorocyclopropanation of alkenes with subsequent reduction of the halogen atom (Scheme 1).[5] Although these methods are reliable, Freons (chlorofluorocarbon and related compounds) are required as reagents.[5] Freons have been heavily regulated because of their destructive effects on the ozone layer.[6] They are no longer commercially available and are thus very difficult to obtain. Therefore, it has become almost impossible to use these standard methods.

Monofluorocyclopropanes can also be synthesized through a Simmons–Smith reaction with alkenes using fluorodiiodomethane (not commercially available) as the reagent.[7] Although fluorodiiodomethane itself is not a Freon, it is typically prepared from dibromofluoromethane (Scheme 2), which is a Freon, and is therefore also impossible to obtain.

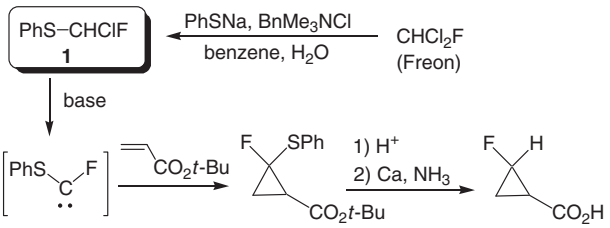
Chlorofluoromethyl phenyl sulfide (**1**) has also been used as a building block for the synthesis of monofluorocyclopropanes from alkenes. The treatment of chlorofluoromethyl phenyl sulfide with a base produces fluoro(phenylthio)carbene, and the resulting carbene reacts with alkenes to afford the corresponding fluoro(phenylsulfanyl)cyclopropanes.[8] Desulfurization of the fluoro(phenylsulfanyl)cyclopropane provides the desired monofluorocyclopropane.[8] Unfortunately, chlorofluoromethyl phenyl sulfide is also not commercially available and has traditionally been prepared through the reaction of sodium phenylthiolate with dichlorofluoromethane, another Freon (Scheme 3).[9]



Scheme 1. Preparations of monofluorocyclopropanes using Freons.



Scheme 2. Simmons–Smith reaction using fluorodiiodomethane.



Scheme 3. Synthesis of a monofluorocyclopropane using **1**.

As described above, because of the use of Freons in the traditional synthetic methods, it has been very difficult lately to synthesize monofluorocyclopropanes from alkenes. To overcome this difficulty, we have developed a novel synthetic route to **1** without the use of Freons, and describe the results in this communication.

It has been reported that fluoromethyl phenyl sulfide can be synthesized through the reaction of Selectfluor™ with thioanisol,[10] or the reaction of *N*,*N*-diethylaminosulfur trifluoride (DAST) with methyl phenyl sulfoxide in the presence of antimony chloride.[11] We planned to synthesize **1** through the reaction of Selectfluor™ with chloromethyl phenyl sulfide or the reaction of DAST with chloromethyl phenyl sulfoxide. The chlorination of fluoromethyl phenyl sulfide using sulfanyl chloride[12] or *N*-chlorosuccinimide[13] and deoxygenative chlori-

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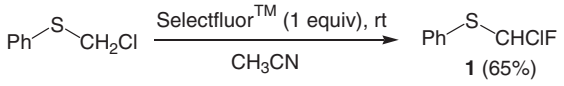
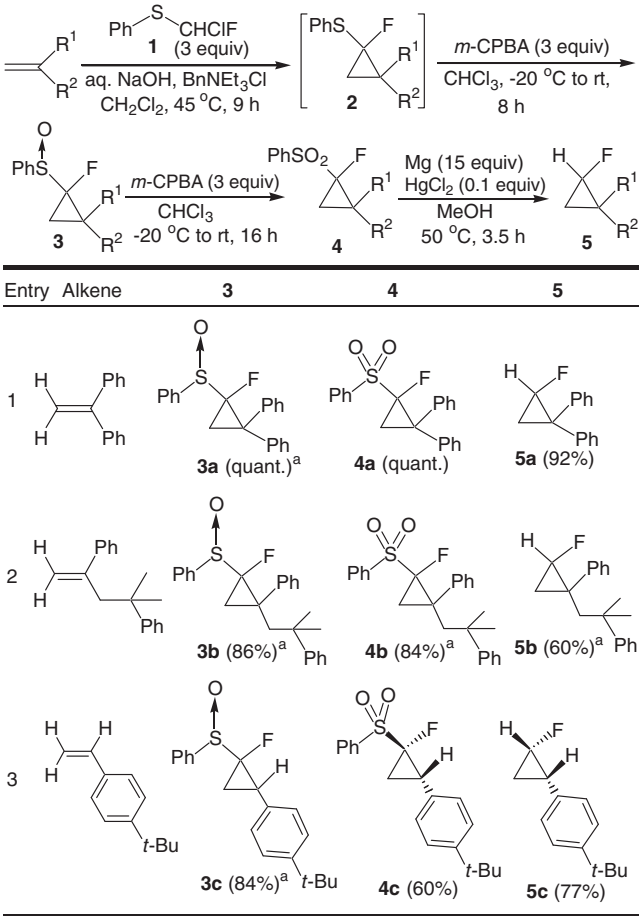


Scheme 4. Synthesis of **1** without using Freons.

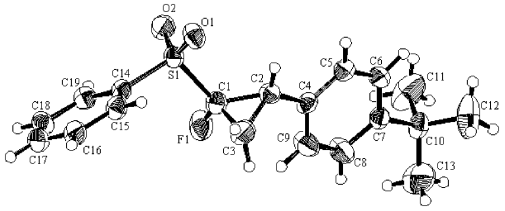
Table 1. Reaction of **1** with 1,1-disubstituted alkenes or a 1-monosubstituted alkene, and further transformation to monofluorocyclopropanes



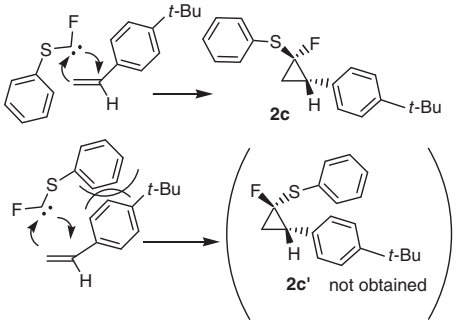
[a]Mixture of stereoisomers.

nation of fluoromethyl phenyl sulfoxide using sulfinyl chloride[14] were also examined. The reaction of chloromethyl phenyl sulfide[13] with Selectfluor™ produced the desired **1** in 65% yield.[15] On the other hand, the other reactions were unsuccessful (Scheme 4).

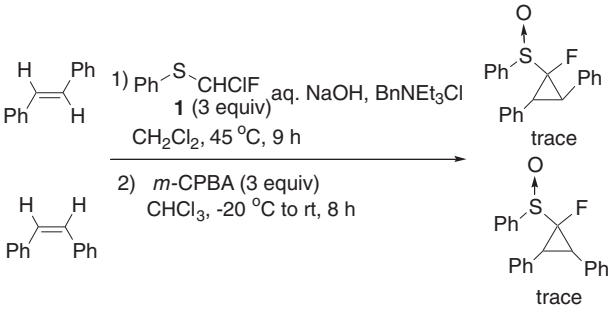
1 synthesized by this method was pure enough to be used for the cyclopropanation of an alkene without further purification (Table 1). Treatment of 1,1-disubstituted alkenes or a 1-monosubstituted alkene with **1** in aqueous base in the presence of a phase-transfer catalyst provided the 1-fluoro-1-(phenylsulfanyl)cyclopropanes **2**. Since these cyclopropanes were not stable enough to be purified, they were subsequently oxidized with *m*-chloroperbenzoic acid (*m*-CPBA) to afford the corresponding sulfoxides **3**.[16] The sulfoxides **3** have two or three stereogenic centers (one chiral sulfur, and one or two chiral



Scheme 5. Stereochemistry of **4c**.



Scheme 6. Origin of the stereoselectivity.



Scheme 7. The reaction with 1,2-disubstituted alkenes.

carbons of the cyclopropane ring), so they were obtained as a mixture of diastereomers. They were then oxidized further by using *m*-CPBA to produce the corresponding sulfones **4**.[17] Desulfurization of **4** was achieved by using magnesium metal in the presence of a catalytic amount of mercury chloride[19] to provide the desired monofluorocyclopropanes **5**.[20] For the monofluorocyclopropanes **4c** and **5c**, a single stereoisomer was obtained in each case (Entry 3). The stereochemistry of **4c** was determined to be as depicted in Scheme 5 according to the X-ray crystallography results.[21] Additionally, the desulfurization of a 2-substituted-1-fluoro-1-sulfonylcyclopropane using metallic magnesium has been found to proceed with retention of configuration.[24] As a result, **5c** may be a *cis*-isomer, but further spectroscopic elucidation is necessary.

The fluoro(phenylsulfanyl)carbene, which was produced from **1**, attacked (4-*t*-butylphenyl)ethylene from a less hindered site to afford **2c** stereoselectively, as shown in Scheme 6.

In contrast to the reaction of 1,1-disubstituted alkenes, 1,2-disubstituted alkenes are almost inert to the fluoro(phenylsulfanyl)carbene derived from **1**, forming trace amounts of the cyclopropanes under the same conditions (Scheme 7), presumably owing to steric hindrance.

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In conclusion, a synthetic method for the preparation of chlorofluoromethyl phenyl sulfide without using Freons has been developed. The chlorofluoromethyl phenyl sulfide prepared through this method can be used for the synthesis of monofluorocyclopropane from 1-monosubstituted alkenes or 1,1-disubstituted alkenes. This method is the sole Freons-free procedure for the synthesis of monofluorocyclopropanes from alkenes.[25,26]

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15 **Preparation of chlorofluoromethyl phenyl sulfide (1)**: To a stirred solution of chloromethyl phenyl sulfide[13] (353 mg, 2.00 mmol) in acetonitrile (2 mL) was added a solution of Selectfluor™ (1062 mg, 3.00 mmol) in acetonitrile (20 mL) at 0 °C under a nitrogen atmosphere, and the mixture was stirred for 25 min under the same condition. The reaction mixture was evaporated in vacuo to remove the solvent, and carbon tetrachloride (20 mL) was added to the residue. The resulting suspension was filtered through a glass filter and the filtrate was evaporated in vacuo to provide chlorofluoromethyl phenyl sulfide (228.0 mg, 65%) as a colorless oil. Chlorofluoromethyl phenyl sulfide (**1**):[9] ^{1}H NMR ($CDCl_3$): δ 7.30 (1H, d, $J = 57$ Hz), 7.36–7.39 (3H, m), 7.56–7.79 (2H, m); ^{19}F NMR ($CDCl_3$): δ −99.44 (1F, d, $J = 57$ Hz); IR (neat) cm^{-1}: 2400, 1443, 762.

16 **General procedure of the reaction of a carbene derived from chlorofluoromethyl phenyl sulfide (1) with an alkene, and subsequent oxidation**: To a stirred solution of **1** (3.50 mmol) and benzyltriethylammonium chloride (98.5 mg, 0.40 mmol) in dichloromethane (1.2 mL) was added a solution of sodium hydroxide (600 mg, 15 mmol in 1.2 mL of water). A solution of an alkene (1.10 mmol) in dichloromethane (5 mL) was added to the mixture at 45 °C, and the resulting suspension was stirred under the same condition for 9 h. Water (10 mL) was added to the reaction mixture, and the mixture was extracted with dichloromethane (10 mL × 3). The extract was washed with brine, dried over magnesium sulfate, and the solvent was evaporated. The resulting residue was dissolved in chloroform (7 mL), and the solution was cooled to −20 °C. A solution of *m*-chloroperbenzoic acid (579.8 mg, 3.30 mmol) in dichloromethane (7 mL) was added dropwise to the solution over 5 min, and the resulting mixture was stirred at −20 °C for 2 h, and then the reaction mixture was warmed to room temperature and stirred for an additional 5 h. Saturated aqueous sodium hydrogen carbonate (10 mL) was added, and the resulting mixture was extracted with chloroform (10 mL × 3). The combined extract was washed with brine, and dried over magnesium sulfate. The solvent was evaporated and the residue was purified by silica gel column chromatography with *n*-hexane–ethyl acetate as eluent to afford 1-fluoro-1-(phenylsulfinyl)cyclopropane **3** as a mixture of diastereomers.

17 **General procedure of the oxidation of 3 with *m*-chloroperbenzoic acid**: A solution of *m*-chloroperbenzoic acid (262.3 mg, 1.50 mmol) in chloroform (5 mL) was added dropwise over 5 min to a stirred solution of **3** (a mixture of diastereomers, 0.6 mmol) in chloroform (10 mL) at −20 °C under a nitrogen atmosphere. The resulting mixture was stirred under the same conditions for 2 h, and then the reaction mixture was warmed to room temperature and stirred for an additional 14 h. Saturated aqueous sodium hydrogen carbonate (10 mL) was added, and the resulting mixture was extracted with chloroform (10 mL × 3). The combined extract was washed with brine, and dried over magnesium sulfate. The solvent was evaporated and the residue was purified by silica gel column chromatography with *n*-hexane–ethyl acetate as eluent to afford the 1-fluoro-1-phenylsulfonylcyclopropane **4**.[18] As we mentioned in Table 1, **4a** and **4c** were obtained as a single compound. Either stereoisomer of **4b** could not be obtained in a pure form at this stage.

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20 **Desulfurization of 4**: To a stirred solution of **4** (1.00 mmol) in methanol, magnesium powder (365.3 mg, 15.0 mmol) and mercury chloride (30.7 mg, 0.11 mmol) were added at 50 °C under a nitrogen atmosphere, and stirred for 3.5 h. The reaction mixture was poured into hydrochloric acid (0.5 M, 100 mL), and the resulting mixture was extracted with ethyl acetate (5 mL × 3). The extract was washed with saturated aqueous sodium hydrogen carbonate (7 mL) and brine (7 mL). Then, the extract was dried over anhydrous magnesium sulfate, and the solvent was evaporated. The residue was purified by silica gel column chromatography with *n*-hexane–ethyl acetate as eluent to afford the monofluorocyclopropane **5**.[18] As we mentioned in Table 1, **5a** and **5c** were obtained as a single compound. One of the stereoisomer of **5b** was obtained in a pure form.

21 **Single-crystal X-ray analysis**: All measurements were made on a RIGAKU R-AXIS RAPID imaging plate area detector graphite monochromated Cu Kα radition. The data were collected at a temperature of −100 °C. The structure was solved by direct method SIR92[22] and expanded using Fourier techniques. The non-hydrogen atoms were refined anisotropically. All calculations were performed using Crystal Structure (CrystalStructure 4.0[23]) crystallographic software package.
Crystal data for 4c: $C_{19}H_{21}O_2SF$: mp 125–126 °C, $M_r = 332.43$, Cu Kα ($\lambda = 1.54187$ Å), monoclinic, $P2_1/c$, colorless prism 0.30 × 0.15 × 0.05 mm^3, crystal dimensions $a = 6.0428(2)$ Å, $b = 14.6851(3)$ Å, $c = 19.1851(4)$ Å, $\alpha = 90°$, $\beta = 99.550(2)°$, $\gamma = 90°$, $T = 173$ K, $Z = 4$, $V = 1702.41(6)$ Å^3, $D_{calcd} = 1.297$ g cm^{-3}, μCu Kα = 18.324 cm^{-1}, $F_{000} = 704.00$, GOF = 1.859, $R_{int} = 0.0382$, $R_1 = 0.0608$, $wR_2 = 0.1894$. CCDC-963046.

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25 Recently, Hu et al. reported an enantioselective monofluorocyclopropanation of α,β-unsaturated amides using (*S*)-*N*-tosyl-*S*-methyl-*S*-phenylsulfoximine.[26] This method is also Freon-free, and enantioselectively provides monofluorocyclopropanes in high yields. This reaction proceeds through a Michael-type addition–elimination reaction, therefore, it can be applicable only to electronic deficient alkenes such as α,β-unsaturated amides.

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