Highly Controlled Ring-Opening of Siloxydifluorocyclopropanes: A Versatile Route to Cyclic Fluoroketones

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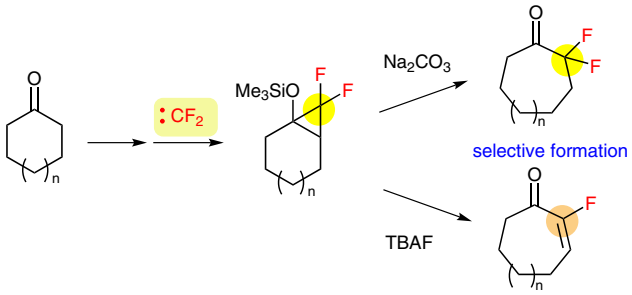

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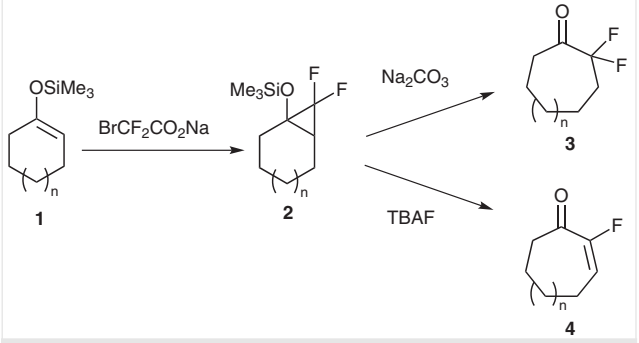
Abstract A convenient access to cyclic fluoroketones that involves base-promoted ring-opening of siloxydifluorocyclopropanes is presented. Selective formation of *gem*-difluorinated cycloalkanones and monofluorinated enones has been achieved.

Key words fluorine, silicon, cyclopropane, ring-opening, ketone

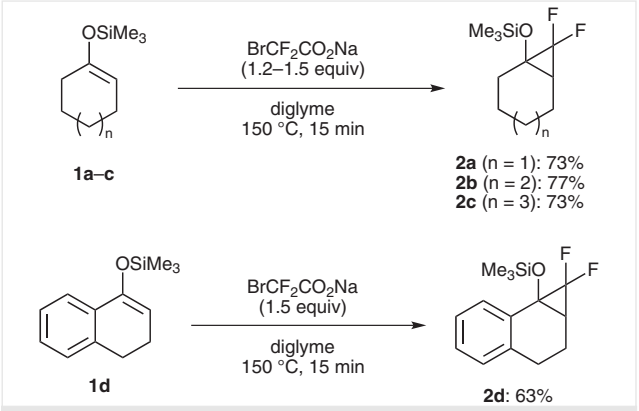
Organofluorine compounds are of considerable interest in various industrial fields,[1,2] and the introduction of fluorine atoms often endows organic molecules with attractive properties. Fluorine is an important element by virtue of the unique properties associated with the atom and its bond to carbon, its high electronegativity and its relatively small size. Given these attractive properties, fluoroorganic compounds find diverse applications in medicinal, agricultural, and material sciences. In particular, difluoromethylene compounds have received a great deal of attention because of their biological activities.[3,4] A difluoromethylene carbon atom mimics the steric and electronic features of an ether oxygen atom or a carbonyl carbon atom. For the synthesis of difluoromethylene compounds, *gem*-difluorocyclopropanes are promising precursors; such compounds are readily prepared by a wide range of convenient synthetic routes.[5,6] The transformations involving selective ring-opening of *gem*-difluorocyclopropanes provides a variety of useful fluoroorganic compounds.[7–13] Meanwhile, siloxycyclopropanes are useful precursors of metal homoenolates in organic synthesis.[14] Siloxydifluorocyclopropanes are considered to be one of the most useful building blocks from which to obtain various difluoromethylene compounds. However, because of the lack of stability of fluorosiloxycyclopropanes,[15] progress in the chemistry of fluorinated homoenolates has been much slower than that of nonfluorinated homoenolates. Herein, we report the ring opening of siloxydifluorocyclopropanes **2** to afford *gem*-difluorinated cycloalkanones **3** and monofluorinated enones **4** selectively (Scheme 1).



Scheme 1

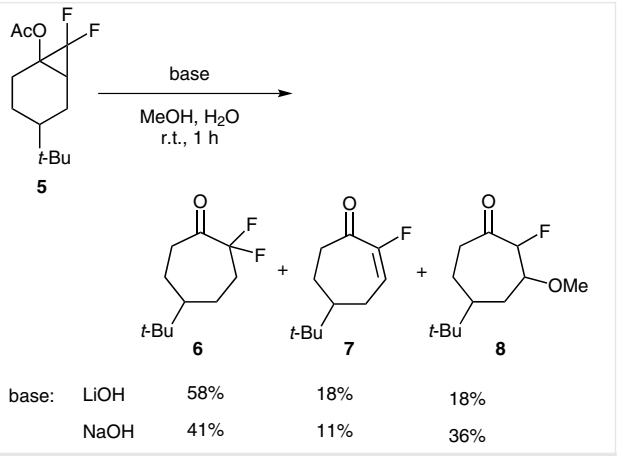
Our initial studies focused on exhaustive formation of *gem*-difluorinated cycloalkanones **3**. Previously, we demonstrated that sodium bromodifluoroacetate ($BrCF_2CO_2Na$) acts as a powerful difluorocarbene source to give difluorinated cyclopropanes and cyclopropenes.[16,17] The use of $BrCF_2CO_2Na$ was found to be effective for the selective formation of siloxydifluorocyclopropanes (Scheme 2).[18]

In related pioneering work, in 1979, Kobayashi and Taguchi reported base-promoted ring-opening reactions of acetoxycyclopropane **5** (Scheme 3).[8a] Under their reaction conditions, a mixture of difluoroketone **6**, monofluoro-



Scheme 2

enone **7**, and its methanol adduct **8** were obtained due to the use of the strong bases such as LiOH and NaOH for deacetylation.



Scheme 3

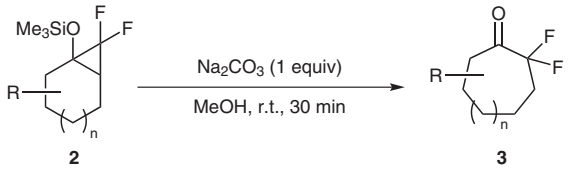
Taking advantage of the readily removable trimethylsilyl (TMS) protecting group, we have developed highly controlled ring-opening reactions of siloxydifluorocyclopropanes **2**, which provide versatile synthetic routes to cyclic fluoroketones. To a stirred solution of siloxydifluorocyclopropane **2a** in methenol was added sodium carbonate. After the reaction mixture was stirred at room temperature for 30 min, ring opening of **2a** proceeded smoothly to provide difluorinated cycloheptanone **3a** in 71% yield (Table 1, entry 1).[19] Gratifyingly, no contamination by dehydrofluorinated product was observed (<1%) under the present conditions.

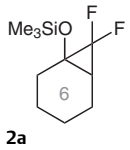
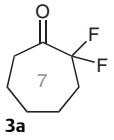
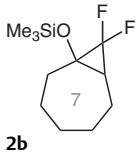
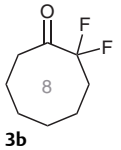
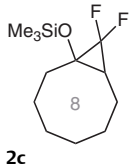
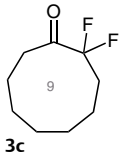
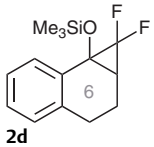
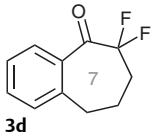
Other examples of the formation of *gem*-difluorinated cycloalkanones **3** are given in Table 1. By the use of alkaline metal carbonates (Na_2CO_3 or K_2CO_3), siloxydifluorocyclopropanes **2** underwent ring opening to give medium-sized difluorocycloalkanones **3** in moderate to good yields.

In contrast, through the use of fluoride such as tetrabutylammonium fluoride (TBAF) as a base, ring-opening dehydrofluorination of **2** took place predominantly. After a survey of suitable reaction conditions, treatment of **2** with TBAF in THF at –78 °C led to the formation of monofluorinated enones **4** (Scheme 4).[20,21]

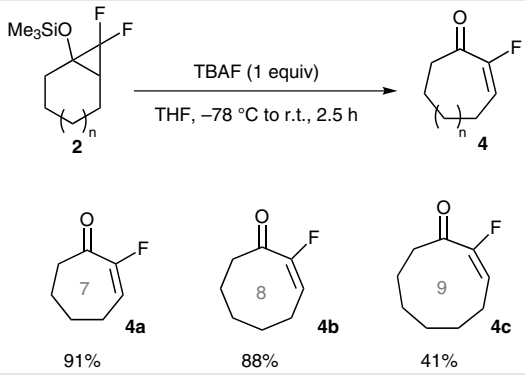
In summary, we have demonstrated a convenient and highly controlled route to *gem*-difluorinated cycloalkanones and monofluorinated enones. In the net transformations, one-carbon ring-enlargement and insertion of fluorinated methylene groups into the α-C–C bond in cycloalkanones **9** was achieved (Scheme 5). Further utilization of siloxydifluorocyclopropanes **2** as homoenolates is underway to explore other useful applications.

Table 1 Selective Formation of *gem*-Difluorinated Cycloalkanones **3**

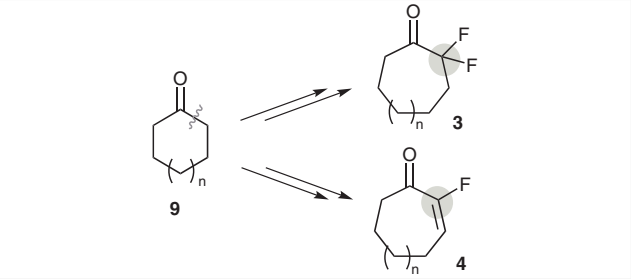


Entry	2	3	Yield (%)[a]
1	 **2a**	 **3a**	71
2	 **2b**	 **3b**	51
3	 **2c**	 **3c**	81
4	 **2d**	 **3d**	39

[a] Isolated yield of **3**.



Scheme 4



Scheme 5

Acknowledgment

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1379599.

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(17) Sodium bromodifluoroacetate is available from Tokyo Chemical Industry Co., Ltd. Otherwise, this reagent is prepared by the reaction of bromodifluoroacetic acid (available from SynQuest Laboratories, Inc.) with NaOH; see ref. 16.

(18) **Formation of Siloxydifluorocyclopropanes 2; General Procedure:** To a solution of silyl enol ether **1a** (851 mg, 5.0 mmol) in diglyme (20 mL), was added a diglyme solution (20 mL) of sodium bromodifluoroacetate (1.48 g, 7.5 mmol) at 150 °C. The reaction mixture was stirred for 10 min at 150 °C, then, after cooling to room temperature, the reaction was quenched by the addition of water. Organic materials were extracted three times with hexane and the combined organic layers were washed with brine and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by silica gel

column chromatography (hexane–EtOAc, 50:1) to give **2a**[15,16] (800 mg, 73%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 2.22–2.10 (m, 1 H), 1.96–1.78 (m, 2 H), 1.64–1.40 (m, 2 H), 1.38–1.20 (m, 4 H), 0.17 (s, 9 H). ^{19}F NMR (376 MHz, $CDCl_3$, C_6F_6): δ = 25.9 (dd, J_{F-F} = 161.7, J_{H-F} = 23.3 Hz, 1 F), 15.4 (d, J_{F-F} = 161.7 Hz, 1 F). GC-MS: *m*/*z* (%) = 220 (4) $[M]^+$, 205 (10), 81 (31), 73 (100).

(19) **Formation of *gem*-Difluorinated Cycloalkanones 3; General Procedure:** A mixture containing siloxydifluorocyclopropane **2a** (594 mg, 2.7 mmol) and Na_2CO_3 (286 mg, 2.7 mmol) in MeOH (30 mL) was stirred at room temperature under an atmosphere of argon for 30 min. Organic materials were extracted three times with Et_2O, and the combined organic layers were washed with brine and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by silica gel column chromatography (hexane–EtOAc, 5:1) to give **3a** (283 mg, 71%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 2.70–2.64 (m, 2 H), 2.15–2.03 (m, 2 H), 1.88–1.80 (m, 2 H), 1.76–1.68 (m, 2 H), 1.67–1.60 (m, 2 H). ^{19}F NMR (376 MHz, $CDCl_3$, C_6F_6): δ = 56.9 (s, 2 F). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 201.3 (t, *J* = 24.9 Hz), 118.6 (t, *J* = 249.2 Hz), 38.8, 33.7 (t, *J* = 23.7 Hz), 27.5, 23.6, 22.8 (t, *J* = 5.7 Hz). GC-MS: *m*/*z* (%) = 148 (3) $[M]^+$, 119 (15), 84 (61), 55 (100). IR (NaCl): 1739 cm^{-1}. Anal. Calcd for $C_7H_{10}F_2O$: C, 56.75; H, 6.80. Found: C, 56.41; H, 6.89.

(20) **Formation of Fluorinated Cyclic Enones 4; General Procedure:** To a solution of siloxydifluorocyclopropane **2a** (66.0 mg, 0.3 mmol) in diglyme (3.0 mL) was added TBAF (1 M in THF, 0.3 mL, 0.3 mmol) at –78 °C under an atmosphere of argon. The reaction mixture was then stirred for 150 min at room temperature. Organic materials were extracted three times with Et_2O and the combined organic layers were washed with brine and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by silica gel column chromatography (hexane–EtOAc, 5:1) to give **4a**[21] (34.9 mg, 91%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 6.25 (dt, J_{H-F} = 21.6, 6.6 Hz, 1 H), 2.70–2.64 (m, 2 H), 1.89–1.87 (m, 2 H), 1.74–1.62 (m, 4 H). ^{19}F NMR (282 MHz, $CDCl_3$, C_6F_6): δ = 43.0 (d, J_{H-F} = 21.6 Hz, 1 F). GC-MS: *m*/*z* (%) = 128 (4) $[M]^+$, 85 (64), 72 (100). IR (NaCl): 1698 cm^{-1}.

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