

## Generation and Reactions of Difluorocyclopropyl Anion

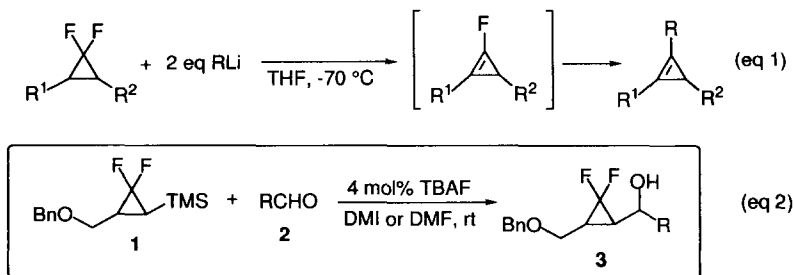
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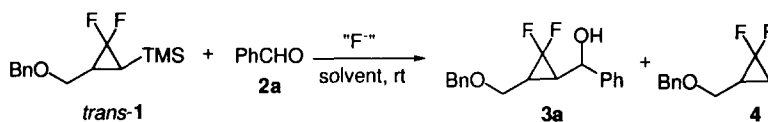
**Abstract:** Reaction of 1-trimethylsilyl-2,2-difluorocyclopropane derivative with aldehydes in the presence of a catalytic amount of TBAF (4 mol%) provides the corresponding cyclopropylcarbinols via cleavage of the carbon-silicon bond. © 1997 Elsevier Science Ltd.

Fluorinated cyclopropanes have attracted interest in the field of medicinal chemistry<sup>1</sup> or in material sciences.<sup>2</sup> Related to our ongoing project on conformationally restricted 3,4-difluoromethanoglutamates<sup>3</sup> to find out a potent and highly specific glutamate receptor-subtype agonist or antagonist and on methylenedifluorocyclopropanes in molecular design of inhibitors for certain enzymes,<sup>4</sup> development of efficient methods for such functionalized difluorocyclopropanes has been carried out. Provided a bond-forming reaction of a difluorocyclopropyl anion with a variety of electrophiles were successfully carried out, this would be useful for the preparation of functionalized difluorocyclopropanes, although such methodology has not been reported so far. It was reported that deprotonation of a difluorocyclopropane derivative by alkyl lithium proceeds at low temperature, while the resultant anion having lithium as a counter ion is so unstable that the product is formed through the facile  $\beta$ -elimination of LiF (eq. 1).<sup>5</sup> In this paper, we report that reaction of 1-trimethylsilyl-2,2-difluorocyclopropane derivative **1** with aldehydes **2** in the presence of a catalytic amount of tetrabutylammonium fluoride (TBAF) provides the corresponding cyclopropylcarbinols **3** via cleavage of the carbon-silicon bond (eq 2).

Scheme 1



First, reaction of the trimethylsilylated difluorocyclopropane (*trans*-1)<sup>6</sup> with benzaldehyde was conducted to examine the fluoride source and solvent effect (Table 1). As a fluoride source, TBAF worked smoothly to cleave the carbon-silicon bond, although the use of equimolar amount of TBAF in THF resulted in the formation of the protodesilylation product **4** as a major product which could not be suppressed by the addition of molecular sieves or by using vacuum-dried TBAF (entries 1, 2). With a catalytic amount of TBAF (4 mol%), a polar solvent such as DMI and DMF was superior to THF with respect to the relative reaction period for the disappearance of *trans*-1 monitored by TLC and the product yield (entries 3, 5, 6). Thus, the desired carbinol **3a** was obtained in 72% yield when the reaction was carried out in the presence of 4 mol% TBAF in DMI at room temperature. TASF in THF (entry 4), tetrabutylammonium triphenyldifluorosilicate ( $\text{Ph}_3\text{SiF}_2^- \cdot \text{Bu}_4\text{N}^+$ )<sup>7</sup> and an alkaline metal fluoride such as CsF in THF, DMF or DMI was ineffective and the starting material was recovered.<sup>8</sup>

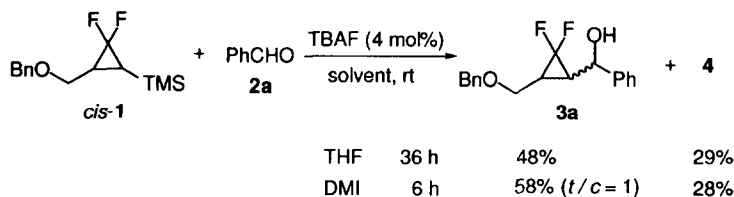


**Table 1.** Reaction of *trans*-1 with benzaldehyde.

| Entry | Solvent          | F <sup>-</sup>             | Time(h) | <b>3a</b> (%) <sup>a, b</sup> | <b>4</b> (%) <sup>a</sup> | <i>trans</i> -1 (%) |
|-------|------------------|----------------------------|---------|-------------------------------|---------------------------|---------------------|
| 1     | THF              | TBAF (100 mol%)            | 4       | 12                            | 83                        | 0                   |
| 2     | THF              | TBAF (100 mol%)<br>MS 4A   | 4       | 18                            | 80                        | 0                   |
| 3     | THF              | TBAF (4 mol%)<br>MS 4A     | 4       | 26                            | 12                        | 47                  |
| 4     | THF              | TASF <sup>c</sup> (4 mol%) | 4       | 0                             | 0                         | 100                 |
| 5     | DMF              | TBAF (4 mol%)<br>MS 4A     | 10      | 74                            | 26                        | 0                   |
| 6     | DMI <sup>d</sup> | TBAF (4 mol%)              | 6       | 72                            | 0                         | 0                   |

a) Isolated yield. b) In all cases, **3a** was obtained as a mixture of *trans* and *cis* isomers. c) TASF : tris(diethylamino)sulfonium difluorotrimethylsilicate. d) DMI : 1,3-dimethyl-2-imidazolidinone.

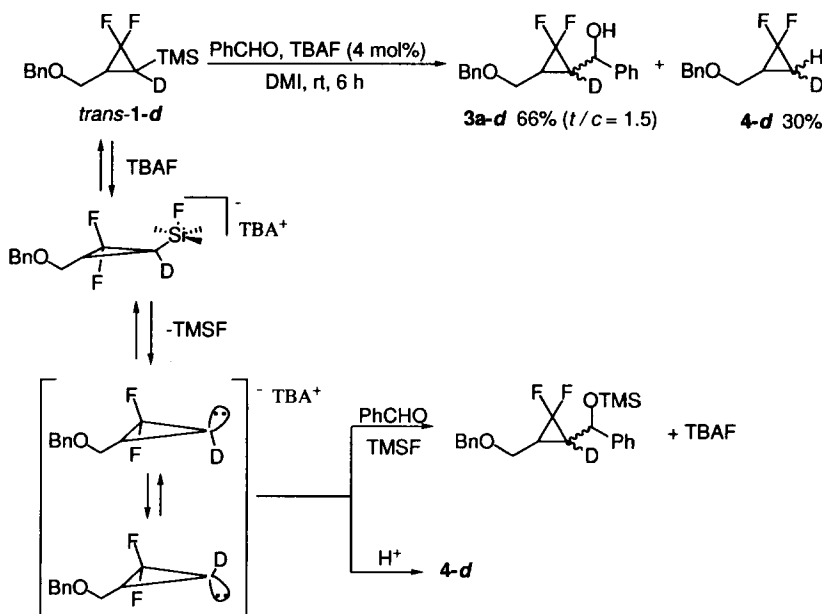
In all cases shown in Table 1, the carbinol **3a** was obtained as a mixture of *trans* and *cis* isomers in a ratio of 4~3 : 1, both consisted of a mixture of two diastereomers. For example, in DMI the ratio of *trans* and *cis* isomer **3a** was 4 : 1.<sup>9</sup> Similar reaction of *cis*-1 with benzaldehyde in DMI gave **3a** in a ratio of *trans* : *cis* = 1 : 1.



These results may indicate that, under the above reaction conditions, fluoride attacks the silicon atom to form a hypervalent silicate intermediate which, in turn, generates the difluorocyclopropyl anion having a

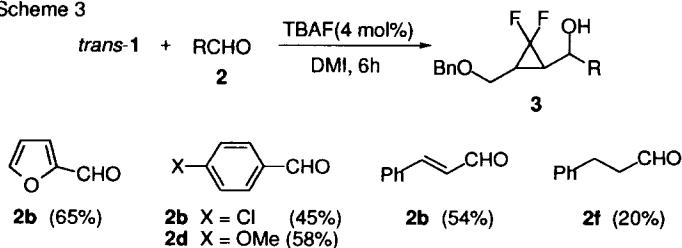
tetrabutylammonium counter ion.<sup>10</sup> While this step possibly proceeds in a stereospecific manner (retention of the cyclopropyl anion configuration), the anion, thus formed, is stable enough to react with aldehyde accompanying the configurational isomerization of the initially formed anion to some extent, giving rise to a mixture of *trans* and *cis* isomers.<sup>11</sup> The reaction pathway mentioned here is shown as in the case of the deuterated substrate **1-d** (Scheme 2). Thus, the reaction of the deuterated substrate **1-d** with benzaldehyde in the presence of 4 mol% TBAF provided the carbinol **3a-d** and **4-d**, both as a mixture of *trans* and *cis* isomers without deuterium-proton exchange, respectively. This may indicate that in this reaction TBAF does not act as a base.

Scheme 2



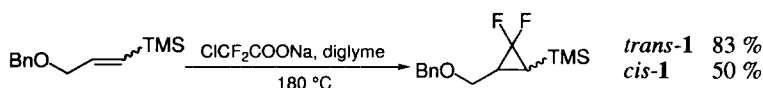
Results with various aldehydes are shown below (Scheme 3). Aromatic aldehydes generally gave the products **3** in fairly good yields, while the yield with aliphatic aldehyde was low. Similar to the case of benzaldehyde, the products **3** were obtained as a mixture of *trans* and *cis* isomers, both consisted of a mixture of diastereomers due to the newly formed chiral center bearing the hydroxyl group. Although several improvements are still needed at this moment, the present results show for the first time a method for generation of the difluorocyclopropyl anion and its reaction with electrophile.

Scheme 3



## References and notes

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- The 1-trimethylsilyl-2,2-difluorocyclopropane derivatives, *trans*-**1** and *cis*-**1**, were prepared by the addition of difluorocarbene to the corresponding *E*- and *Z*-olefin, respectively.



- trans*-**1**: <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 0.11 (9H, s), 0.52 (1H, dddd, *J* = 17.9, 9.3, 8.0, 1.2 Hz), 1.75 (1 H, dm, *J* = 7.1 Hz), 3.53 (1 H, dd, *J* = 10.7, 7.5 Hz), 3.63 (1 H, dm, *J* = 10.7 Hz), 4.50 (1 H, d, *J* = 12.1 Hz), 4.60 (1 H, d, *J* = 12.1 Hz), 7.26 - 7.45 (5 H, m). <sup>19</sup>F-NMR (376.5 MHz, CDCl<sub>3</sub>): δ -70.4 (1F, dd, *J* = 152.4, 17.5 Hz), -64.6 (1F, ddd, *J* = 152.4, 9.3, 8.6 Hz). *cis*-**1**: <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 0.14 (9H, s), 0.86 (1H, dddd, *J* = 16.8, 13.2, 10.6, 0.9 Hz), 2.09 (1 H, dm, *J* = 7.6 Hz), 3.50 - 4.80 (2 H, m), 4.51 (1 H, d, *J* = 11.6 Hz), 4.57 (1 H, d, *J* = 11.6 Hz), 7.26 - 7.55 (5 H, m). <sup>19</sup>F-NMR (376.5 MHz, CDCl<sub>3</sub>): δ -78.1 (1F, dd, *J* = 149.0, 9.5 Hz), -55.9 (1F, ddd, *J* = 149.0, 14.2, 12.9 Hz).
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  - In DMF or DMI, TASF (4 mol%) promoted the reaction of *trans*-**1** with benzaldehyde very slowly to give **3a** in low yield along with recovery of *trans*-**1**.
  - Diastereomeric ratio of *trans*-**3a** was 1 : 1 and that of *cis*-**3a** was 2 : 1 as determined by <sup>19</sup>F-NMR.
  - Generation of α- and/or β-fluorinated carbanions through fluoride-mediated cleavage of carbon-silicon bonds and their reactions with electrophiles were reported. For examples: (a) Hiyama, T.; Obayashi, M.; Sawahata, M. *Tetrahedron Lett.* **1983**, *24*, 4113. (b) Fujita, M.; Hiyama, T. *J. Am. Chem. Soc.* **1985**, *107*, 4085. (c) Fujita, M.; Obayashi, M.; Hiyama, T. *Tetrahedron* **1988**, *44*, 4135. (d) Martin, S.; Sauvetre, R.; Normant, J. F. *J. Organomet. Chem.* **1984**, *264*, 155. (e) Prakash, G. S. K.; Krishnamurti, R.; Olah, G. *J. Am. Chem. Soc.* **1989**, *111*, 393.
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