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Bromo(*t*-butyldimethylsilyl)fluoromethyllithium: A Fluorinated Nucleophilic Carbenoid Reagent Stabilized by a Silyl Substituent

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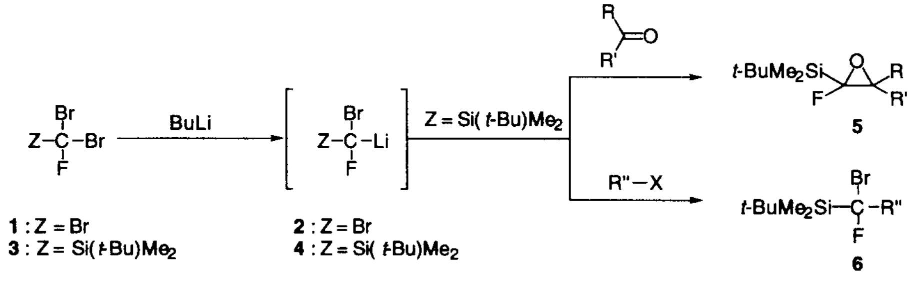
Abstract: The title carbenoid reagent was generated by treatment of dibromofluoromethyl(*t*-butyl)dimethylsilane with butyllithium in THF at -78 °C and was allowed to react with aldehydes and ketones to give 1-fluoro-1-silyloxiranes in good yields. Alkylation of the silyl-substituted carbenoid was also achieved efficiently in good yields. © 1997 Elsevier Science Ltd.

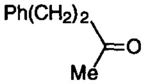
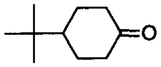
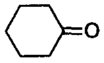
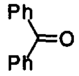
For the synthesis of organofluorine compounds, fluorohalomethylmetals are valuable reagents which are readily accessible from fluorohalohydrocarbons.[1] We recently reported that the treatment of tribromofluoromethane (**1**) with butyllithium at -130 °C generates the lithium carbenoid **2**, which reacted with aldehydes and ketones to give the corresponding fluorinated alcohols in good yields.[2] However, since the carbenoid **2** is thermally labile, the generation of **2** should be carried out at -130 °C *in the presence of* an electrophile. We envisioned that the replacement of one bromine in **2** with silicon[3] would enhance the stability of **4** due to the α-anion-stabilizing effect of silicon[4] to allow us to add an electrophile *after* the generation of **4**.[5] Furthermore, the presence of a silyl substituent in the initial products would extend the synthetic utility of the fluorinated products. We report herein that the silicon-containing lithium carbenoid **4**[6] is successfully generated from dibromofluoromethyl(*t*-butyl)dimethylsilane (**3**) with butyllithium, and reacts with carbonyl compounds to give 1-fluoro-1-silyloxiranes **5** or with alkyl halides to afford the alkylated products **6** in good yields.



Scheme 1

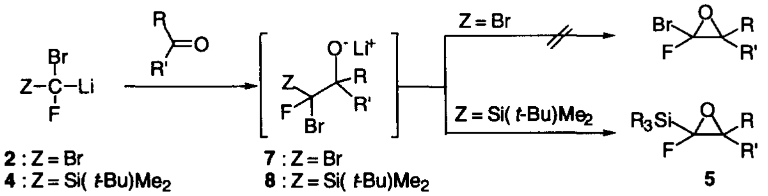
A THF solution of dibromofluoromethyl(*t*-butyl)dimethylsilane[7] (**3**) and a carbonyl compound was treated with butyllithium at -78 °C. The resulting solution was stirred for 30 min at -78 °C and allowed to warm up to room temperature. The reaction mixture was quenched with sat. aq. NH_4Cl solution. Workup and purification by silica gel column chromatography gave **5** as summarized in Table 1.[8]

Table 1. Carbonyl Addition of Lithium Carbenoid **4**

Entry	RR'C=O	R	R'	Product	Yield (%)[a]	Diastereomeric ratio[b]
1	$Ph(CH_2)_2CHO$	H	$Ph(CH_2)_2$	**5a**	73	55 : 45
2	*n*-$C_7H_{15}CHO$	H	*n*-C_7H_{15}	**5b**	97	56 : 44
3		Me	$Ph(CH_2)_2$	**5c**	94	64 : 36
4[c]					16	68 : 32
5[d]					86	67 : 33
6		$-(CH_2)_2CH(t\text{-}Bu)(CH_2)_2-$		**5d**	98	73 : 27
7		$-(CH_2)_5-$		**5e**	97	———
8		Ph	Ph	**5f**	89	———

a) Isolated yield. b) The diastereomeric ratio was determined on the basis of ^1H and ^{19}F NMR spectroscopy. The stereochemistry was not determined. c) 4-Phenyl-2-butanone was added to the reaction mixture after the generation of **4** at -78 °C. d) The carbenoid **4** was generated at -98 °C before the addition of 4-phenyl-2-butanone.

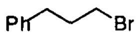
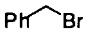
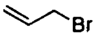
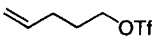
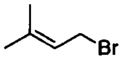
Aldehydes and ketones gave the corresponding 1-fluoro-1-silyloxiranes **5**[9] in good to excellent yields (except for entry 4) with moderate diastereoselectivity (55 : 45 ~ 73 : 27).[10] Oxirane **5** was apparently produced by carbonyl addition of **4** to give alkoxide **8** followed by cyclization (Scheme 2).[5f,g] Noteworthy is that the substitution reaction took place at the fluorine-substituted carbon. The substitution is generally considered to be difficult to carry out.[11] Indeed, the lithium alkoxide **7** derived from **2** did not cyclize even at the refluxing temperature of THF.[2] The ring-closure of **8** to give **5** should be attributed to the interaction of the Si-C σ* orbital with the *p*-orbital to stabilize the transition state of the nucleophilic substitution.[12] Thus, the silicon accelerating effect for the nucleophilic substitution at the α-carbon surpasses the fluorine retarding effect.



Scheme 2

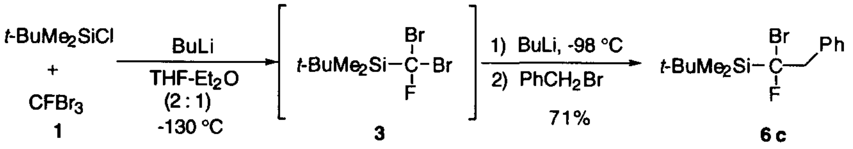
The augmented stability of **4** was apparently confirmed by the fact that the generation and reaction of **4** with a coexisting electrophile could be carried out at -78 °C. Moreover, at -98 °C, an electrophile could be added *after* the generation of the carbenoid reagent (Table 1, entry 5). This observation suggests that **4** can be reacted with an electrophile which may competetively react with butyllithium. For example, alkylation was carried out by generation of **4** at -98 °C followed by the addition of an alkylating reagent. The results are shown in Table 2. The relatively reactive alkyl halides and sulfonates as well as chlorotrimethylsilane gave the alkylated (silylated) products in good yields.[13,14]

Table 2. Alkylation of Lithium Carbenoid **4**

R"—X	Product	Yield (%)[a)]	R"—X	Product	Yield (%)[a)]
MeI	**6a**	70[b)]		**6f**	trace
EtI	**6b**	85[b)]		**6f**	81
	**6c**	62		**6f**	83
	**6d**	69		**6g**	90
	**6e**[c)]	66	Me_3SiCl	**6h**	74

a) Isolated yield. b) Yields were determined by ^1H NMR using 1,1,2-trichloroethylene as an internal standard. c) α-Alkylated product only.

The utility of the silicon-substituted carbenoid approach for monofluoro compounds is demonstrated by the sequential reactions involving preparation of **3**, generation, and alkylation of **4** in one pot (Scheme 3). Thus, **1** (1.5 mol) was treated with butyllithium (1.5 mol) in the presence of *t*-butylchlorodimethylsilane (1.5 mol) in THF-Et_2O (2 : 1) at -130 °C. To the mixture, additional butyllithium (1.2 mol) and benzyl bromide (1 mol) were added successively at -98 °C to give rise to **6c** in 71% yield.



Scheme 3

In summary, we have demonstrated that the introduction of a silyl group into a fluorine-containing lithium carbenoid enhances the stability of the reagent to react with carbonyl compounds, 1-fluoro-1-silyloxiranes being produced in good yields through carbonyl addition followed by intramolecular cyclization. Alkylation of the fluorinated carbenoid with alkyl halides afforded the corresponding products in yields of synthetic value. The present reagent provides a convenient way for the synthesis of monofluoro compounds. Further synthetic applications of 1-fluoro-1-silyloxiranes and alkylated products are under investigation in our laboratory.

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[¶] JSPS Research Fellow

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6. An example of the reagent bearing a CF(SiR$_3$)Li moiety : (EtO)$_2$P(O)CF(SiMe$_3$)Li which could be prepared at -78 °C and was alkylated with alkyl iodides in good yields. a) Patois, C.; Savignac, P. *J. Chem. Soc., Chem. Commun.* **1993**, 1711-1712; b) Patois, C.; Savignac, P. *Synth. Commun.* **1994**, *24*, 1317-1322; c) Nieschalk, J.; Batsanov, A. S.; O'Hagan, D.; Howard, J. A. K. *Tetrahedron* **1996**, *52*, 165-176.
7. The silane **3** was prepared by silylation of **2** with *t*-BuMe$_2$SiCl at -130 °C in 74% yield.
8. Physical properties of **5f**: a colorless oil. ^{1}H NMR (CDCl$_3$, 200 MHz) δ -0.37 (s, 3H), -0.12 (s, 3H), 1.01 (s, 9H), 7.20-7.55 (m, 10H); ^{13}C NMR (CDCl$_3$, 50 MHz) δ -7.4 (d, *J* = 4.2 Hz), -7.0 (d, *J* = 2.3 Hz), 17.1 (d, *J* = 1.9 Hz), 26.8 (d, *J* = 1.9 Hz), 67.3 (d, *J* = 17.8 Hz), 100.5 (d, *J* = 299.4 Hz), 127.2 (d, *J* = 1.1 Hz), 127.6 (d, *J* = 1.5 Hz), 127.7, 127.9, 128.1, 128.2, 137.6 (d, *J* = 4.2 Hz), 137.9 (d, *J* = 3.8 Hz); ^{19}F NMR (CDCl$_3$, 188 MHz) δ -132.5; IR (neat) 3063, 3033, 2932, 2861, 1813, 1497, 1472, 1449, 1364, 1254, 1051, 926, 905, 876, 839, 808, 783, 754, 702 cm^{-1}; MS (70 eV) *m/z* (rel intensity) 329 (M$^+$+1, 0.3), 328 (M$^+$, 0.8), 253 (0.4), 214 (0.2), 194 (19), 166 (100), 77 (39). Anal. Calcd for $C_{20}H_{25}FOSi$: C, 73.13; H, 7.67. Found: C, 73.09; H, 7.73.
9. Although 1,2-difluoro-1-silyloxiranes and 1,2,2-trifluoro-1-silyloxirane were reportedly prepared by epoxidation of the corresponding fluorosilylethenes (*vide infra*), the synthesis of 1-fluoro-1-silyloxiranes **5** has never been reported, to the best of our knowledge. a) Dubuffet, T.; Sauvetre, R.; Normant, J.-F. *J. Organomet. Chem.* **1988**, *354*, 1-6; b) Arnone, A.; DesMarteau, D. D.; Novo, B.; Petrov, V. A.; Pregnolato, M.; Resnati, G. *J. Org. Chem.* **1996**, *61*, 8805-8810.
10. No product resulting from the Peterson elimination or the Brook rearrangement of **8** was observed.
11. Smart, B. E. In *Organofluorine Chemistry-Principles and Commercial Applications*; Banks, R. E.; Smart, B. E., Tatlow, J. C., Eds.; Plenum Press: New York, 1994; pp 57-88.
12. a) Fleming, I. In *Comprehensive Organic Chemistry*; Barton, D., Ollis, W. D., Eds.; Pergamon Press: Oxford, 1979; Vol. 3; pp 541-686 (especially pp 545-546); b) Ref. 4a; pp.951-955.
13. Physical properties of **6f**: a colorless oil. ^{1}H NMR (CDCl$_3$, 200 MHz) δ 0.16 (s, 3H), 0.22 (s, 3H), 0.99 (d, *J* = 0.6 Hz, 9H), 1.90-2.35 (m, 4H), 2.68 (t, *J* = 6.6 Hz, 2H), 7.05-7.35 (m, 5H); ^{13}C NMR (CDCl$_3$, 50 MHz) δ -6.6 (d, *J* = 3.0 Hz,), -6.5 (d, *J* = 1.9 Hz), 17.9, 26.0 (d, *J* = 5.7 Hz), 27.5 (d, *J* = 0.8 Hz), 35.4, 41.9 (d, *J* = 19.0 Hz), 116.9 (d, *J* = 266.5 Hz), 125.9, 128.4 (2 peaks), 141.7; ^{19}F NMR (CDCl$_3$, 188 MHz) δ -123.9 (dd, *J* = 6.6, 30.5 Hz); IR (neat) 3029, 2959, 2932, 2861, 1605, 1497, 1472, 1464, 1366, 1254, 1084, 1007, 955, 839, 810, 777, 747 cm^{-1}. Anal. Calcd for $C_{16}H_{26}BrFSi$: C, 55.64; H, 7.59. Found: C, 55.51; H, 7.63.
14. When *i*-propyl iodide or *i*-butyl iodide was used, protonated product *t*-BuMe$_2$SiCFBrH formed which might have resulted from a proton abstraction from the iodide.

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