Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 707–710

TETRAHEDRON LETTERS

A novel synthesis of functionalized 1,1-difluoro-1-alkenes via isolable 2,2-difluorovinylsilanes

Junji Ichikawa,* Yuichiro Ishibashi and Hiroki Fukui

Department of Chemistry, Graduate School of Science, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

Received 1 November 2002; revised 16 November 2002; accepted 22 November 2002

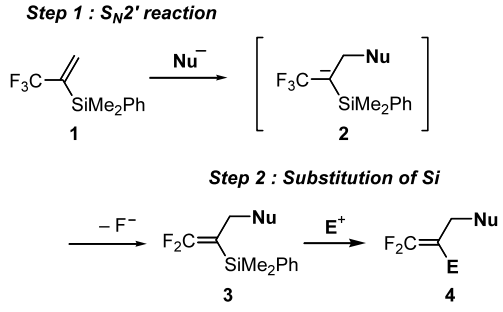
Abstract—Various 1,1-difluoro-1-alkenes such as monosubstituted 1,1-difluoro-1-alkenes, 2-bromo-1,1-difluoro-1-alkenes, and 1,1-difluoro-3-hydroxy-1-alkenes are prepared in two simple steps from 1-trifluoromethylvinylsilane: (i) its S_N2' reaction with nucleophiles to construct 2,2-difluorovinylsilanes and (ii) the subsequent substitution of electrophiles for the vinylic silyl group.

Among fluorine-containing molecules, 1,1-difluoro-1-alkenes are of special interest, due to their diverse utility as building blocks for fluorinated compounds and polymers.[1] The activity of these compounds as new types of enzyme inhibitors has also attracted much attention in recent years.[2] Although a number of examples of the preparation of 1,1-difluoro-1-alkenes have been reported,[1–3] the generality of these methods are limited. The development of general synthetic methods for highly functionalized 1,1-difluoro-1-alkenes still remains a challenge of practical importance.

One straightforward route to their synthesis involves the generation and reaction of 2,2-difluorovinylmetals.[3–5] However, very few 2,2-difluorovinylmetals lacking an α-anion-stabilizing group at the 1-position have been described,[3,6] due to the propensity of 2,2-difluorovinylmetals to undergo β-elimination of a metal fluoride leading to 1-fluoro-1-alkynes.[4,7] As a solution to this problem, we have already developed thermostable 2,2-difluorovinylboron and -zirconium species to achieve the difluoroalkene synthesis via transmetalation to copper and zinc intermediates.[3,6] The corresponding silicon species also attracted our attention. We wish to report herein a novel synthesis of 1,1-difluoro-1-alkenes via 2,2-difluorovinylsilanes, which are quite thermostable, easy to handle and can be stored under air.

For the synthesis of diverse 1,1-difluoro-1-alkenes, it is necessary to prepare a variety of 2,2-difluorovinylsilanes. Since the carbon substituents at the 1-position of reported 2,2-difluorovinylsilanes are limited to phenyl and triphenylsilylmethyl groups,[8] our investigation started with the development of a widely applicable synthetic route to these compounds.

3,3,3-Trifluoropropene derivatives react with nucleophiles in an S_N2' fashion to afford 1,1-difluoro-1-alkenes.[9] The following limitations of this reaction, however, have restricted its applicability: the necessity of (i) an electron-withdrawing group such as a carbonyl or phenyl group on the 2-position of the trifluoropropene framework and/or (ii) highly reactive nucleophiles such as alkyllithiums. We expected that these drawbacks could be overcome by utilizing the α-anion-stabilizing effect of silicon to support the generation of intermediary anion **2** and therefore to promote the S_N2' reaction.[10] The resulting vinylsilanes **3** would allow in turn the introduction of the second substituent by the



Scheme 1.

Keywords: alkenes; fluorine and compounds; silicon and compounds; substitution.

* Corresponding author. Tel./fax: +81-3-5841-4345; e-mail: junji@chem.s.u-tokyo.ac.jp

0040-4039/03/$ - see front matter © 2003 Elsevier Science Ltd. All rights reserved.
PII: S0040-4039(02)02652-7

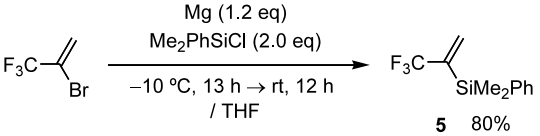
replacement of the silyl group. Thus, as depicted in Scheme 1, the sequence of reactions starting from 1-trifluoromethylvinylsilane **1** could provide a wide variety of 1,1-difluoro-1-alkenes **4** bearing two kinds of substituents (Nu, E).

Taking into consideration its boiling point and S_N2' reactivity,[11] we adopted dimethylphenylsilyl group for **1**. After some attempts, we found that the in situ generated 1-trifluoromethylvinylmagnesium bromide[12] was efficiently trapped with dimethylphenylsilyl chloride to afford **5** in 80% yield (Scheme 2).[13] Vinylsilane **5** thus obtained was stable enough to be stored at room temperature under air for long periods (no less than 6 months), despite a report on the susceptibility to β-elimination generating 1,1-difluoroallene.[14]

We then investigated the S_N2' reaction of **5** with various nucleophiles. The results are summarized in Table 1. S_N2' Products **6** were obtained in excellent yield for $LiAlH_4$, alkyl- and aryllithiums without further reaction (entries 1–4). Acyl anion equivalents, 2-lithio-1,3-dithianes afforded the corresponding **6e** and **6f** in high yield (entries 5 and 6). In addition, **5** reacted with ketone, ester and amide enolates at the carbon α to their carbonyl groups. Although only limited examples have been reported for the S_N2' reaction of 3,3,3-trifluoropropene derivatives with ester enolates,[9c,f] **5** reacted not only with amide and ketone enolates (entries 7 and 8), but even with the less reactive malonate anion (entry 9). A nitrogen nucleophile also underwent the S_N2' reaction of **5** to give 3,3-difluoroallylamine **6j** in good yield (entry 10).

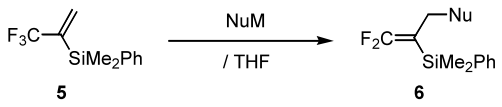
The results of the S_N2' reaction of **5** with various nucleophiles encouraged us to investigate the next step, substitution of the silyl group. It is known that dimethylphenylsilyl–vinylic carbon bonds are cleaved with *n*-Bu_4NF (TBAF) under relatively harsh conditions.[15] The removal of the silyl group in **6c**, however, proceeded very smoothly under mild conditions on treatment with moist THF solution of *n*-Bu_4NF, leading to monosubstituted difluoroalkene **7c** in 99% yield (Scheme 3).

We also examined the substitution of bromine atom for the silyl group. When **6c** was treated with bromine, dibromide **8c** was obtained in low yield due to its instability.[16] Successive treatment of **6c** with bromine and *n*-Bu_4NF without isolation of **8c** smoothly effected dibromination and elimination of a silyl bromide to give 2,2-difluorovinyl bromide **9c**, a useful building block, in 87% yield (Scheme 4).

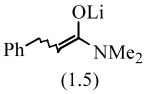
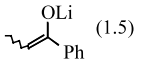
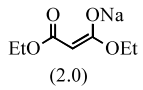


Scheme 2.

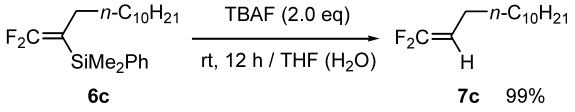
Table 1. S_N2' reaction of **5** with nucleophiles



5 **6**

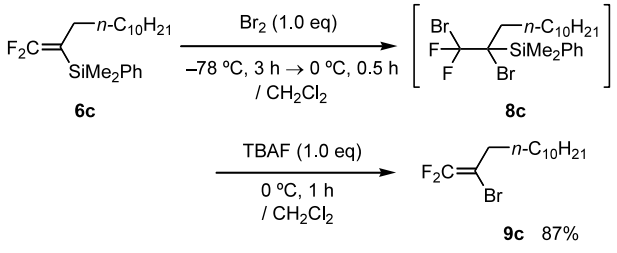
entry	NuM (eq)	conditions	**6** / %
1	$LiAlH_4$ (0.5)	0 °C, 5 h	**6a** 88
2	*n*-C_4H_9Li (1.05)	–78 °C, 40 min	**6b** 93
3	*n*-$C_{10}H_{21}Li$ (1.1)	–78 °C, 1 h	**6c** 99
4	PhLi (1.1)	–78 °C, 2.5 h → 0 °C	**6d** 85[a]
5	 (1.0)	–78 °C, 3 h → 0 °C	**6e** 89
6	 (1.1)	–78 °C, 1 h → rt	**6f** 75
7	 (1.5)	–78 °C, 10 min → 0 °C, 15 min	**6g** 85
8	 (1.5)	–78 °C, 30 min → rt, 1 h → reflux, 8 h	**6h** 59
9	 (2.0)	reflux, 24 h	**6i** 55
10	*i*-Pr_2NLi (1.5)	–78 °C, 10 min → 0 °C, 15 min	**6j** 75

[a] *N,N,N',N'*-Tetramethylethylenediamine (1.0 eq) was used.



6c **7c** 99%

Scheme 3.



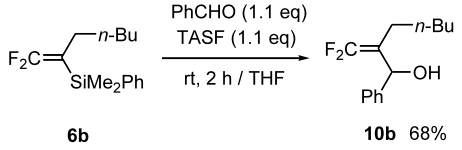
6c **8c** **9c** 87%

Scheme 4.

Furthermore, C–C bond formation was effected by utilizing the vinylic silicon of **6**. Treatment of **6b** with benzaldehyde and *n*-Bu_4NF afforded difluorinated

allylic alcohol **10b** in 22% yield along with 1,1-difluoro-1-heptene (51% yield determined by ^{19}F NMR).[17,18] The yield of **10b** was improved by using tris(diethylamino)sulfonium difluorotrimethylsilycate (TASF)[19] instead of *n*-Bu_4NF up to 68% (Scheme 5).

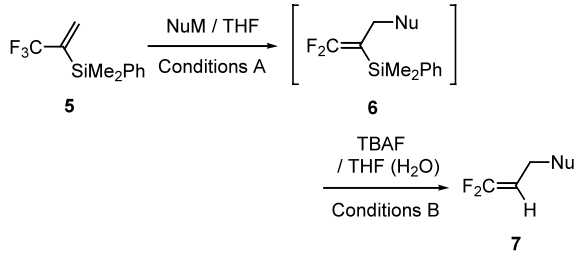
Next, we attempted to combine the S_N2' process and the substitution of silyl group, and eventually accomplished a one-pot synthesis of difluoroalkenes (Table 2). On treatment of **5** with nucleophiles and then with moist *n*-Bu_4NF, the two-step sequence readily proceeded to yield the corresponding monosubstituted difluoroalkenes **7**. This sequence successfully allowed the construction of difluoroalkenes bearing functional groups in a one-pot operation (entries 2 and 3). We also achieved the one-pot synthesis of difluoroallylic alcohol **10b** as shown in Scheme 6.[20]



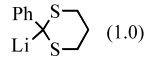
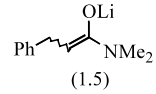
6b **10b** 68%

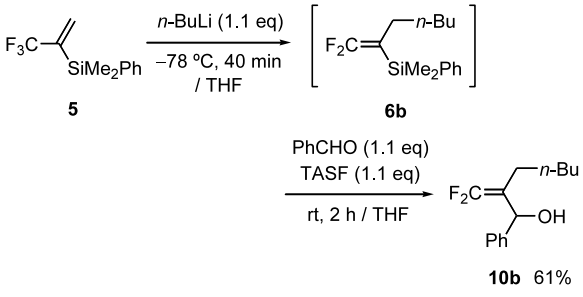
Scheme 5.

Table 2. One-pot synthesis of 1,1-difluoro-1-alkenes **7**



5 **6** **7**

	NuM (eq)	A	TBAF / eq	B	**7** / %
1	*n*-$C_{10}H_{21}Li$ (1.0)	–78 °C, 25 min	2.0	rt 4 h	**7c** 82
2	 (1.0)	–78 °C, 1 h	1.1	rt 2 h	**7e** 80
3	 (1.5)	–78 °C, 30 min → 0 °C	1.1	0°C 10 min	**7g** 64



5 **6b** **10b** 61%

Scheme 6.

We have established a new synthetic method of 1,1-difluoro-1-alkenes with the introduction of two kinds of groups by utilizing the following properties of the silyl group: (i) its α-anion-stabilizing effect promotes the S_N2' reaction of 1-trifluoromethylvinylsilane **5** with nucleophiles to construct 2,2-difluorovinylsilanes **6**, and (ii) the subsequent substitution of electrophiles for the silyl group affords monosubstituted 1,1-difluoro-1-alkenes **7**, 2-bromo-1,1-difluoro-1-alkenes **9** and 1,1-difluoro-3-hydroxy-1-alkenes **10**.

Acknowledgements

We are grateful to TOSOH F-TECH, INC. for a generous gift of 2-bromo-3,3,3-trifluoro-1-propene. This work was supported in part by research fellowship for young scientists from the Japan Society for the Promotion of Science to H.F.

References

1. (a) Tozer, M. J.; Herpin, T. F. *Tetrahedron* **1996**, *52*, 8619; (b) Percy, J. M. *Contemporary Org. Synth.* **1995**, *2*, 251.
2. (a) Bey, P.; McCarthy, J. R.; McDonald, I. A. In *Selective Fluorination in Organic and Bioorganic Chemistry*, ACS Symp. Ser. No. 456; Welch, J. T., Ed.; Am. Chem. Soc.: Washington. DC, 1991; p. 104; (b) *Biomedical Frontiers of Fluorine Chemistry*, ACS Symp. Ser. No. 639; Ojima, I.; McCarthy, J. R.; Welch, J. T., Eds.; Am. Chem. Soc.: Washington. DC, 1996.
3. Ichikawa, J. *J. Fluorine Chem.* **2000**, *105*, 257 and references cited therein.
4. For reviews, see: (a) Brisdon, A. K.; Banger, K. K. *J. Fluorine Chem.* **1999**, *100*, 35; (b) Coe, P. L. *J. Fluorine Chem.* **1999**, *100*, 45; (c) Burton, D. J.; Yang, Z.-Y.; Morken, P. A. *Tetrahedron* **1994**, *50*, 2993; (d) Normant, J. F. *J. Organomet. Chem.* **1990**, *400*, 19.
5. (a) Anilkumar, R.; Burton, D. J. *Tetrahedron Lett.* **2002**, 2731; (b) Shigeoka, T.; Kuwahara, Y.; Watanabe, K; Sato, K.; Omote, M.; Kumadaki, I. *J. Fluorine Chem.* **2000**, *103*, 99; (c) Bainbridge, J. M.; Brown, S. J.; Ewing, P. N.; Gibson, R. R.; Percy, J. M. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2541 and references cited therein.
6. For thermostable 1-unsubstituted 2,2-difluorovinylzinc reagents, see: Nguyen, B. V.; Burton, D. J. *J. Org. Chem.* **1997**, *62*, 7758.
7. Runge, A.; Sander, W. W. *Tetrahedron Lett.* **1990**, *31*, 5453.
8. (a) Okano, T.; Ito, K.; Ueda, T.; Muramatsu, H. *J. Fluorine Chem.* **1986**, *32*, 377; (b) Xu, Y.; Jin, F.; Huang, W. *J. Org. Chem.* **1994**, *59*, 2638.
9. For the S_N2' reaction of 3,3,3-trifluoropropene derivatives [CH_2=C(Y)CF_3], see: Y = CO_2R (CO_2H): (a) Kitazume, T.; Ohnogi, T., Miyauchi, H.; Yamazaki, T. *J. Org. Chem.* **1989**, *54*, 5630; (b) Fuchikami, T.; Shibata, Y.; Suzuki, Y. *Tetrahedron Lett.* **1986**, *27*, 3173. Y = SPh,

SePh: (c) Feiring, A. E. *J. Org. Chem.* **1980**, *45*, 1962. Y = Ph: (d) Bégué, J.-P.; Bonnet-Delpon, D.; Rock, M. H. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1409. Y = H (Me): (e) Hiyama T.; Obayashi, M.; Sawahata, M. *Tetrahedron Lett.* **1983**, *24*, 4113; (f) Kendrick, D. A.; Kolb, M. *J. Fluorine Chem.* **1989**, *45*, 265; (g) Bergstrom, D. E.; Ng, M. W.; Wong, J. J. *J. Org. Chem.* **1983**, *48*, 1902.

10. The favorable effect of an α-silyl group in α,β-unsaturated enones on the Michael reaction is well documented: Stork, G.; Ganem, B. *J. Am. Chem. Soc.* **1973**, *95*, 6152.
11. Kishi, N.; Imma, H.; Mikami, K.; Nakai, T. *Synlett* **1992**, 189.
12. The Grignard reagent was prepared from 2-bromo-3,3,3-trifluoro-1-propene, see: Jiang, B.; Wang, Q.-F.; Yang, C.-G.; Xu, M. *Tetrahedron Lett.* **2001**, *42*, 4083.
13. **Dimethylphenyl(1-trifluoromethylvinyl)silane (5)**. To a suspension of magnesium turnings (292 mg, 12.0 mmol) and chlorodimethylphenylsilane (3.36 mL, 20.0 mmol) in THF (10 mL) was added 2-bromo-3,3,3-trifluoro-1-propene (1.04 mL, 10.0 mmol) over 8 h at −10°C under argon. The reaction mixture was stirred at −10°C for 5 h and then at rt for an additional 12 h. The reaction was quenched with phosphate buffer (pH 7), and organic materials were extracted with Et_2O (10 mL×3). The combined extracts were washed with brine and then dried over $MgSO_4$. After removal of the solvent under reduced pressure (30 kPa), the residue was purified by column chromatography (pentane) to give **5** (1.84 g, 80%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.32 (6H, s), 5.32 (1H, s), 5.84 (1H, bs), 7.33–7.41 (3H, m), 7.46–7.51 (2H, m). ^{13}C NMR (126 MHz, $CDCl_3$) δ −2.9, 125.7 (q, J_{CF} = 274 Hz), 128.0, 129.7, 134.0, 134.2 (q, J_{CF} = 17 Hz), 135.6, 140.9 (q, J_{CF} = 30 Hz). ^{19}F NMR (471 MHz, $CDCl_3/C_6F_6$) δ_F 101.9 (s). IR (neat) 2967, 1614, 1413, 1255, 1120, 975, 836, 811 cm^{-1}. Anal. calcd for $C_{11}H_{13}F_3Si$: C, 57.37; H, 5.69. Found: C, 57.43; H, 5.53.
14. Drakesmith, F. G.; Stewart, O. J.; Tarrant, P. *J. Org. Chem.* **1968**, *33*, 472.
15. Oda, H.; Sato, M.; Morizawa, Y.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1983**, *24*, 2877.
16. Sayferth, D.; Wada, T.; Maciel, G. E. *Inorg. Chem.* **1962**, *1*, 232.
17. While the reaction of fluorinated vinylsilanes with aldehydes are known, all of these vinylsilanes have a halogen at the position α to the silicon: (a) Hanamoto, T.; Harada, S.; Shindo, K.; Kondo, M. *Chem. Commun.* **1999**, 2397; (b) Yudin, A. K.; Prakash, G. K. S.; Deffieux, D.; Bradley, M.; Bau, R.; Olah, G. A. *J. Am. Chem. Soc.* **1997**, *119*, 1572; (c) Fujita, M.; Obayashi, M.; Hiyama, T. *Tetrahedron* **1988**, *44*, 4135; (d) Martin, S.; Sauvêtre, R.; Normant, J.-F. *J. Organomet. Chem.* **1984**, *264*, 155.
18. For reports on the utility of difluoroallylic alcohols, see: Patel, S. T.; Percy, J. M.; Wilkens, R. D. *J. Org. Chem.* **1996**, *61*, 166 and references cited therein.
19. Fujita, M.; Hiyama, T. *Org. Synth.* **1990**, *69*, 44.
20. **3,3-Difluoro-2-pentyl-1-phenyl-2-propen-1-ol** (**10b**). To a solution of **5** (268 mg, 0.400 mmol) in THF (4 mL) was added *n*-BuLi (0.27 mL, 1.63 M in hexane, 0.44 mmol) over 10 min at −78°C under argon. After the reaction mixture was stirred for 30 min, benzaldehyde (46 mg, 0.44 mmol) and tris(diethylamino)sulfonium difluorotrimethylsilycate (0.44 mL, 1.0 M in THF, 0.44 mmol) was added. The reaction mixture was stirred for 2 h at rt. The reaction was quenched with phosphate buffer (pH 7), and organic materials were extracted with AcOEt (10 mL×3). The combined extracts were washed with brine and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by PTLC (hexane–AcOEt, 5:1) to give **10b** (59 mg, 61%) as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.80 (3H, t, J = 7.1 Hz), 1.08–1.23 (5H, m), 1.25–1.34 (1H, m), 1.79–1.86 (1H, m), 1,87 (1H, d, J = 3.7 Hz), 1.89–1.97 (1H, m), 5.69 (1H, ddd, J = 3.7 Hz, J_{HF} = 1.6, 1.6 Hz), 7.35–7.39 (5H, m). ^{13}C NMR (126 MHz, $CDCl_3$) δ 13.9, 22.2, 22.8, 28.5 (dd, J_{CF} = 2, 2 Hz), 31.6, 69.5 (dd, J_{CF} = 6, 1 Hz), 93.3 (dd, J_{CF} = 16, 11 Hz), 125.5, 127.5, 128.3, 141.4 (dd, J_{CF} = 2, 2 Hz), 154.5 (dd, J_{CF} = 288, 288 Hz). ^{19}F NMR (471 MHz, $CDCl_3/C_6F_6$) δ_F 69.2 (1F, d, J_{FF} = 49 Hz), 69.6 (1F, d, J_{FF} = 49 Hz). IR (neat) 3388, 2956, 2931, 1739, 1452, 1261, 1211, 1130, 1009, 700 cm^{-1}. Anal. calcd for $C_{14}H_{18}F_2O$: C, 69.98; H, 7.55. Found: C, 70.08; H, 7.51.