ELSEVIER

Journal of Fluorine Chemistry 117 (2002) 131–135

JOURNAL OF FLUORINE CHEMISTRY

www.elsevier.com/locate/jfluchem

Synthesis and X-ray information of substituted *gem*-difluoroallenyl amines

Qilong Shen, Chbun-Hsing Chen, Gerald B. Hammond*

Department of Chemistry and Biochemistry, University of Massachusetts Dartmouth, 285 Old Westport Road, North Dartmouth, MA 02747, USA

Received 25 April 2002; received in revised form 13 May 2002; accepted 15 May 2002

Dedicated to Professor Lev M. Yagupolskii on the occasion of his 80th birthday.

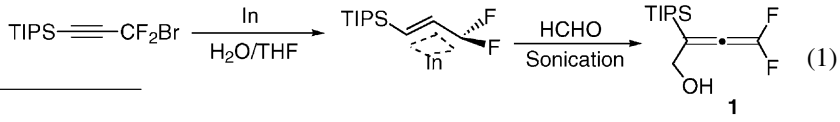
Abstract

An O to N substitution in 4,4-difluorobutadiene-2,3-ol-1 has been accomplished in very satisfactory yields, and without compromising the *gem*-difluoroallenyl integrity, using modified Mitsunobu conditions. Recrystallization of the resulting tosyl-substituted amines furnished the first X-ray crystallographic analysis of difluoroallenes.

Keywords: Fluoroallenes; Recrystallization; Nucleophiles

1. Introduction

In recent years, considerable attention has been given to the development of new methodologies for the introduction of fluorine into organic molecules, since this modification can bring dramatic changes in physical properties, chemical reactivity and biological activity [1]. Fluoroallenes, despite their potential as synthons in the preparation of alicyclic fluorinated compounds, remain largely unexplored [2]. With minor exceptions, most of the work involving the synthesis and chemistry of fluorinated allenes, namely, tetrafluoroallene, trifluoroallene, 1,1-difluoroallene, and 1,3-difluoroallene, has been carried out in Dolbier's group [3]. As mechanistic probes, these fluoroallenes were extensively investigated toward cycloaddition reactions. Xu has reported the synthesis of alkyl-substituted *gem*-difluoroallenes, however, harsh reaction conditions were needed [4]. Recently, the first functionalized *gem*-difluoroallenol **1** was synthesized in our laboratory by treating a room-temperature stable difluoroallenyl indium with aqueous formaldehyde [5] (Eq. (1)). The readily available starting materials and mild reaction conditions will make this process valuable for the synthesis of other functionalized *gem*-difluoroallenes. Herein, we report a convenient synthesis of *gem*-difluoroallenyl amines **2** and provide selected X-ray data for some of them.



1 (1)

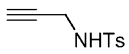
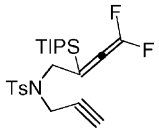
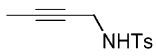
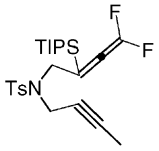
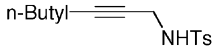
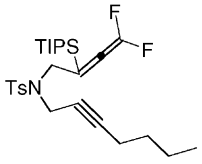
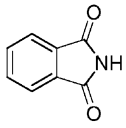
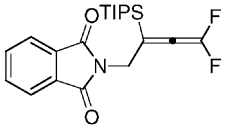
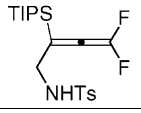
2. Results and discussion

Being interested in the synthesis of difluoroallenyl amines, we turned our attention to the Mitsunobu reaction (Eq. (2)). This reaction is a useful tool for replacing a hydroxyl group with nucleophiles [6]. Various nitrogen nucleophiles have been utilized in this procedure to afford amino derivatives [7]. The starting *gem*-difluoroallenyl alcohol **1** was obtained by reacting TIPS-difluoropropargyl bromide with indium in H_2O/THF, followed by sonication with excess aqueous formaldehyde at room temperature overnight. The standard Mitsunobu redox system, diethyl azodicarboxylate (DIAD)/triphenylphosphine, was tested first, with disappointingly low yields. By decreasing the temperature, switching to diisopropyl azodicarboxylate

* Corresponding author. Tel.: +1-508-999-8865; fax: +1-508-910-6918.
E-mail address: ghammond@umassd.edu (G.B. Hammond).

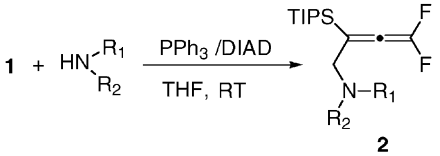
0022-1139/02/$ – see front matter
PII: S0022-1139(02)00158-6

Table 1
Mitsnobou reaction of TIPS–difluoroallyl alcohol 1[a]

Entry	Substituted amine	Product	Yield[b]
1			**2a** (83%)
2			**2b** (43%)
3			**2c** (44%)
4			**2d** (32%)
5			**2e** (51%)[c]

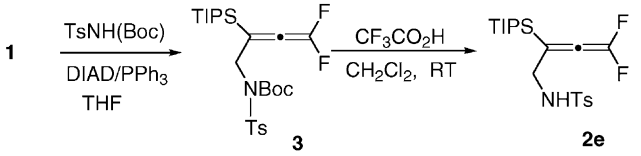
[a] All reaction were carried out with TIPS–difluoroallenyl alcohol (1 mmol) and PPh_3 (1 eq.) and DIAD (1 eq.) in THF at 0 °C.
[b] Isolated yields.
[c] PPh_3 (2 eq.) and DIAD (4 eq.) were used.

(DIAD)/triphenylphosphine, and controlling the order of addition of reactants, we were able to get the desired *gem*-difluoroallenyl amine in very good yield. A typical experiment consisted in the dropwise addition of a solution of DIAD in THF at 0 °C to a mixture of *gem*-difluoroallenyl alcohol **1**, triphenyl phosphine, and propargyl amine; the reaction was left to stir at 0 °C for 2 h, after which standard work-up and purification by flash chromatography afforded **2a** in 83% yield.



(2)

We conducted the reaction of **1** with other amines in a similar fashion (Table 1). As shown in the table, whereas, an unsubstituted *N*-tosyl propargyl amine afforded the product **2a** in high yield (entry 1), alkyl substitution on the triple bond decreased the yield (entries 2 and 3). Use of an imide substrate (entry 4) decreased the yield even further. When the same Mitsunobu conditions were applied to a protected sulfonamide (Eq. (3)) the ^{19}F-NMR spectrum of crude **3** showed a very complicated mixture. After experimenting with different amounts of the reagents, we obtained the desired product **3** in 61% yield using the conditions described in the table footnote. The Boc-group in **3** was easily removed using an excess of trifluoroacetic acid [8] to yield **2e** (entry 5).



(3)

The ^{19}F-NMR chemical shifts of all products were observed in the range δ: 104–108 ppm. The recrystallization of *gem*-difluoroallenyl amines **2a–c**, **e** and their X-ray analysis secured the difluoroallene structure (Table 2). As shown in boldface, the bond lengths of carbons C(1), C(2) and C(3) and its torsion angle provides evidence for the allene presence, whereas the C–F bond length and F–C–F angle lent experimental support to previous calculations on the nature of bonds and bond angles in *gem*-difluoroallene (recently, the X-ray of tetrafluorobutatriene was reported by [9]) (Figs. 1 and 2).

Table 2
Bond lengths and angles measured for allenes **2a–d**

Atom–atom	Bond length (Å)			
	2a	**2b**	**2c**	**2d**
F(1)–C(1)	1.347 (5)	1.339 (6)	1.311 (7)	1.327 (3)
F(2)–C(1)	1.292 (6)	1.287 (5)	1.308 (6)	1.327 (3)
C(1)–C(2)	**1.270 (5)**	**1.277 (5)**	**1.280 (6)**	**1.286 (3)**
C(2)–C(3)	**1.299 (3)**	**1.294 (3)**	**1.299 (5)**	**1.305 (3)**
C(3)–C(4)	1.518 (3)	1.515 (3)	1.517 (4)	1.513 (3)
C(3)–Si(1)	1.905 (2)	1.906 (2)	1.898 (3)	1.9059 (2)
Atom–atom–atom	Bond angle (°)			
F(1)–C(1)–F(2)	**108.9 (4)**	**107.69 (4)**	**107.5 (4)**	**108.16 (18)**
F(1)–C(1)–C(2)	123.9 (4)	127.1 (4)	126.3 (5)	126.2 (2)
F(2)–C(1)–C(2)	127.2 (4)	125.3 (4)	126.2 (5)	125.7 (2)
C(1)–C(2)–C(3)	**178.4 (3)**	**173.6 (3)**	**178.4 (4)**	**175.2 (2)**
C(2)–C(3)–C(4)	119.3 (2)	121.1 (2)	120.3 (3)	120.71 (18)
C(2)–C(3)–Si(1)	120.24 (17)	118.92 (16)	119.6 (2)	117.72 (15)
C(4)–C(3)–Si(1)	120.48 (14)	119.96 (16)	120.1 (2)	121.35 (14)

3. Conclusion

We have successfully synthesized substituted *gem*-difluoroallenyl amines using Mitsunobu conditions. In addition, X-ray crystallographic analysis of the difluroroallenyl amine products demonstrated, for the first time, the validity of theoretical predictions regarding the nature of bonds and bond angles in fluoroallenes.

4. Experimental

The solvents are reagent grade and used without purification. The indium metal powder (100 mesh) and all other commercial reagents were purchased from Aldrich and used, as received. The reaction progress were monitored using one of the following techniques: ^{19}F-NMR, TLC and GC–MS. Analytical TLC was performed using Macherey–Nagel Polygram Sil G/UV$_{254}$ precoated plastic plates and visualized using phosphomolybdic acid (5% in methanol). Flash chromatography (eluant: hexane/ethyl acetate) was performed using silica gel 230–400 mesh, 40–63 μm (Lagand Chemicals). IR spectra were recorded on a Bruker Vector, 22 FT–IR spectrophotometer. ^{1}H, ^{19}F and ^{13}C-NMR spectra were recorded in $CDCl_3$ at 300, 282 and 75 MHz, respectively. ^{19}F-NMR spectra were referenced against external $CFCl_3$ and were broadband decoupled from hydrogen nuclei. Elemental analyses were performed by Atlantic Microlab Inc., Norcross, GA.

4.1. Typical procedure for the synthesis of allenylamines *2a–d*

To the solution of TIPS-α-hydroxy difluoroallene **1** (0.262 g, 1 mmol) in THF (2 ml) were added tosyl propargyl amine (0.209 g, 1 mmol) and triphenylphosphine (0.262 g, 1 mmol) at 0 °C under argon. A solution of diisopropyl azodicarboxylate (0.202 g, 1 mol) in THF (1 ml) was added dropwise and the reaction mixture was stirred overnight, concentrated in vacuo and the product was purified by flash chromatography on silica gel (20/1, hexane/ethyl acetate).

4.2. N-Tosyl-1,1-difluoro-3-triisopropylsilyl-5-aza-octa-1,2-dien-7-yne *2a*

^{1}H-NMR ($CDCl_3$) δ: 7.70 (d, $^{3}J_{HH} = 8.3$ Hz, 2H), 7.28 (d, $^{3}J_{HH} = 8.4$ Hz, 2H), 4.21 (t, $^{5}J_{HF} = 5.8$ Hz, 2H), 4.21 (d, $^{4}J_{HH} = 2.4$ Hz, 2H), 2.42 (s, 3H), 2.10 (t, $^{4}J_{HH} = 2.6$ Hz, 1H), 1.21 (m, 3H), 1.07 (d, $^{3}J_{HH} = 6.6$ Hz, 18H) ppm; ^{19}F-NMR ($CDCl_3$) δ: −107.47 (s, 2F) ppm; ^{13}C-NMR ($CDCl_3$,

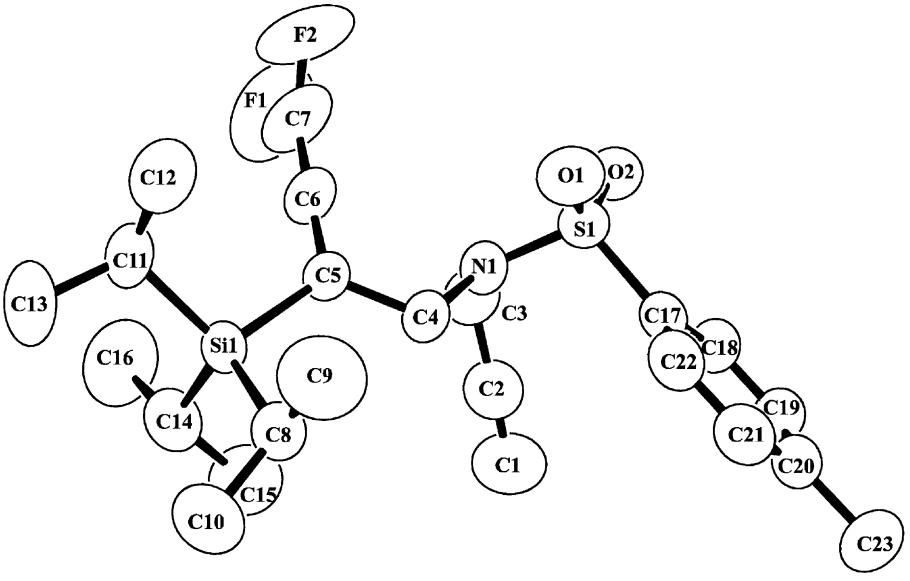


Fig. 1. ORTEP view of **2a**. Displacement ellipsoids are shown at the 50% probability level.

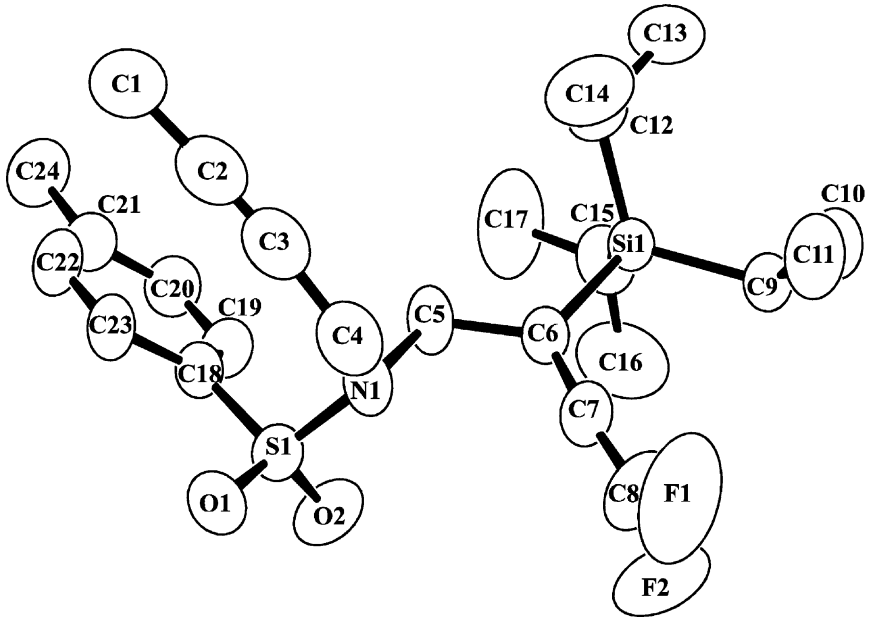


Fig. 2. ORTEP view of **2b**. Displacement ellipsoids are shown at the 50% probability level.

75 Hz) δ: 179.41 (t, $^2J_{CF} = 36.3$ Hz), 159.61 (t, $^1J_{CF} = 260.4$ Hz), 143.91, 136.66, 130.42 (t, $^3J_{CF} = 5.9$ Hz), 129.82, 127.73, 76.93, 74.18, 49.45, 36.17, 21.74, 18.65, 11.53. Anal. Calc. for $C_{23}H_{33}F_2NO_2SSi$: C, 60.89; H, 7.33. Found: C, 61.11; H, 7.27.

4.3. *N-Tosyl-1,1-difluoro-3-triisopropylsilyl-5-aza-nona-1,2-dien-7-yne* ***2b***

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 7.70 (d, $^3J_{HH} = 7.5$ Hz, 2H), 7.29 (*d*, $^3J_{HH} = 8.2$ Hz, 2H), 4.19 (t, $^5J_{HF} = 5.7$ Hz, 2H), 4.21 (q, $^5J_{HH} = 2.2$ Hz, 2H), 2.42 (s, 3H), 1.60 (t, $^5J_{HH} = 2.4$ Hz, 1H), 1.21 (m, 3H), 1.07 (d, $^3J_{HH} = 6.6$ Hz, 18H) ppm; ^{19}F-NMR ($CDCl_3$, 282MHz) δ: −107.70 (s, 2F) ppm; ^{13}C-NMR ($CDCl_3$, 75 Hz) δ: 179.40 (t, $^2J_{CF} = 35.2$ Hz), 159.61 (t, $^1J_{CF} = 260.1$ Hz), 143.59, 136.83, 130.57 (t, $^3J_{CF} = 5.8$ Hz), 129.64, 127.76, 82.18, 72.03, 49.45, 36.69, 21.69, 18.67, 11.30, 3.48. Anal. Calc. for $C_{24}H_{35}F_2NO_2SSi$: C, 61.63; H, 7.54. Found: C, 61.80; H, 7.61.

4.4. *N-Tosyl-1,1-difluoro-3-triisopropylsilyl-5-aza-undeca-1,2-dien-8-yne* ***2c***

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 7.70 (d, $^3J_{HH} = 7.5$ Hz, 2H), 7.28 (d, $^3J_{HH} = 8.2$ Hz, 2H), 4.18 (t, $^5J_{HF} = 5.8$ Hz, 2H), 4.10 (t, $^5J_{HH} = 2.1$ Hz, 2H), 2.41 (s, 3H), 1.92 (tt, $^3J_{HH} = 7.0$ Hz, $^4J_{HH} = 2.2$ Hz, 2H), 1.30 (m, 2H), 1.17 (m, 3H), 1.06 (d, $^3J_{HH} = 6.6$ Hz, 18H), 0.82 (t, $^3J_{HH} = 7.4$ Hz, 3H) ppm; ^{19}F-NMR ($CDCl_3$, 282MHz) δ: −107.73 (s, 2F) ppm; ^{13}C-NMR ($CDCl_3$, 75 Hz) δ: 179.54 (t, $^2J_{CF} = 36.4$ Hz), 159.63 (t, $^1J_{CF} = 260.4$ Hz), 143.58, 136.85, 130.50 (t, $^3J_{CF} = 6.0$ Hz), 129.71, 127.75, 86.65, 72.80, 49.30, 36.65, 21.95, 21.68, 20.69, 18.65, 13.57, 11.53.

4.5. *N-(2-triisopropylsilyl-4,4-difluoro-2,3-butyldienyl) phthalimide* ***2d***

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 7.87 (m, 2H), 7.74 (m, 2H), 4.52 (t, $^5J_{HF} = 5.8$ Hz, 2H), 1.28 (m, 3H), 1.16 (d, $^3J_{HH} = 6.6$ Hz, 18H) ppm; ^{19}F-NMR ($CDCl_3$, 282 MHz) δ: −106.96 (s, 2F) ppm; ^{13}C-NMR ($CDCl_3$, 75MHz) δ: 177.05 (t, $^2J_{CF} = 33.8$ Hz), 167.55, 159.33 (t, $^1J_{CF} = 261.8$ Hz), 134.35, 132,13, 130.98 (t, $^3J_{CF} = 6.3$ Hz), 123.60, 41.78 (t, $^4J_{CF} = 4.1$ Hz), 18.52, 11.37.

4.6. *N-Tosyl-N-Boc-1,1-difluoro-3-triisopropylsilyl-1,2-butadienyl-4-amine 3*

To the solution of *N*-(*t*-Butoxycarbonyl)-*p*-toluenesulfonamide (0.44 g, 1.6 mmol) in THF (10 ml) was added PPh_3 (0.85 g, 3.2 mmol). Followed by the addition of **1** (0.44 g, 1.6 mmol), and then DIAD (1.344 g, 6.7 mmol). The resulted mixture was stirred at room temperature overnight. Standard work-up gave a pale yellow oil, which was purified by flash chromatography to give a solid in 60.5% yield.

4.7. *Cleavage of Boc-protected group*

To a solution of **3** (0.483 g, 0.94 mmol) in CH_2Cl_2 (15 ml) was added trifluoroacetic acid (0.321 g, 2.8 mmol) at room temperature. The mixture was stirred for 3 h. Standard work-up gave a pale yellow crude product, which was then purified by flash chromatography (Hex:E-Ac = 30:1) to give **2e** as a solid in (0.323 g, 83%). Colorless crystals were obtained by

recrystallization from a mixture of hexane and ethyl acetate. ^{1}H-NMR ($CDCl_3$) δ: 7.72 (d, $^3J_{HH} = 8.4$ Hz, 2H), 7.29 (d, $^3J_{HH} = 8.0$ Hz, 2H), 4.75 (s, 1H), 3.85 (t, $^5J_{HF} = 5.7$ Hz, 2H), 2.41 (s, 3H), 1.18 (m, 3H), 0.97 (d, $^3J_{HH} = 6.7$ Hz, 18H) ppm; ^{19}F-NMR ($CDCl_3$) δ: −104.81 (s, 2F) ppm; ^{13}C-NMR ($CDCl_3$) 159.61 (t, $^1J_{CF} = 263.2$ Hz), 143.92, 136.78, 132.05 ($^3J_{CF} = 5.8$ Hz),, 129.99, 127.40, 46.00 (t, $^4J_{CF} = 3.5$ Hz), 21.69, 18.38, 10.98. Anal. Calc. for $C_{20}H_{31}F_2NO_2SSi$: C, 57.80; H, 7.52. Found: C, 57.67; H, 7.53.

4.8. Crystal structure data

4.8.1. Crystal data for compound **2a**

$C_{23}H_{33}F_2NO_2SSi$, $M = 453.67$, triclinic, space group P1 (no. 2), $a = 9.88819(2)$, $b = 10.8511$ (2), $c = 12.9294$ (3) Å; $\alpha = 108.1280(7)$, $\beta = 90.8731$ (7), $\gamma = 103.5254$ (11); $V = 1276.03$ (5) Å^3; $Z = 2$; $D_{calc} = 1.181$ g cm^{-3}; λ(Mo Kα) = 0.71073 Å; $T = 293.0$ K; prismatic crystal 0.08 mm × 0.22 mm × 0.30 mm, R, wR, S 0.0512, 0.1417, 1.03.

4.8.2. Crystal data for compound **2b**

$C_{24}H_{35}F_2NO_2SSi$, $M = 467.70$, triclinic, space group P1 (no. 2), $a = 9.2423$ (1), $b = 11.3980$ (1), $c = 14.1375$ (2) Å; $\alpha = 98.7602$ (5), $\beta = 108.9314$ (6), $\gamma = 105.8472$ (6); $V = 1306.70$ (5) Å^3; $Z = 2$; $D_{calc} = 1.189$ g cm^{-3}; λ(Mo Kα) = 0.71073 Å; $T = 293.0$ K; prismatic crystal 0.40 mm × 0.50 mm × 0.50 mm. R, wR, S 0.0493, 0.1429, 1.05.

4.8.3. Crystal data for compound **2d**

$C_{21}H_{27}F_2NO_2SSi$, $M = 391.53$, triclinic, space group P1 (no. 2), $a = 7.9802$ (2), $b = 9.0863$ (2), $c = 16.3280$ (4) Å; $\alpha = 76.0452$ (9), $\beta = 84.9547$ (8), $\gamma = 76.2805$ (9)°; $V = 1115.63$ (5) Å^3; $Z = 2$; $D_{calc} = 1.166$ g cm^{-3}; λ(Mo Kα) = 0.71073 Å; $T = 293.0$ K; prismatic crystal 0.40 mm × 0.90 mm × 1.00 mm, R, wR, S 0.1053, 0.3258, 1.06.

4.8.4. Crystal data for compound **2e**

$C_{20}H_{31}F_2NO_2SSi$, $M = 415.62$, monoclinic, space group P21/n (no. 14), $a = 10.6123$ (2), $b = 12.9595$ (2), $c = 17.3623$ Å; $\alpha = 90$, $\beta = 105.3074$ (7), $\gamma = 90°$; $V = 2303.32$ (8) Å^3; $Z = 4$; $D_{calc} = 1.199$ g cm^{-3}; λ(Mo Kα) = 0.71073 Å; $T = 293.0$ K; prismatic crystal 0.10 mm × 0.35 mm × 0.75 mm, R, wR, S 0.0487, 0.1360, 1.04.

Acknowledgements

The financial support of the Petroleum Research Fund (PRF no. 36602-AC1) is acknowledged with gratitude. The authors are grateful to Drs. James A. Golen, Department of Chemistry and Biochemistry (UMass Dartmouth) and A. Chandrasekaran (UMass Amherst), for supplying the crystallographic data.

References

[1] D. Lentz, S. Willemsen, Angew. Chem. Int. Ed. 40 (2001) 2087–2091;
R.E. Banks, Fluorine Chemistry at the Millennium: Fascinated by Fluorine, 1st Edition, Elsevier, Amsterdam, 2000;
T. Hiyama, Organofluorine Compounds, Chemistry and Applications, Springer, Berlin, 2000;
D.P. Curran, S. Hadida, S.-Y. Kim, Z. Luo, J. Am. Chem. Soc. 121 (1999) 6607–6615;
M. Schlosser, Angew. Chem. Int. Ed. 37 (1998) 1496–1513;
D. O'Hagan, H.S. Rzepa, J. Chem. Soc. Chem. Commun. (1997) 645–652;
S. Moran, R.X.-F. Ren, S. Rumney Jr, E.T. Kool, J. Am. Chem. Soc. 119 (1997) 2056–2057;
I. Ojima, J.R. McCarthy, J.T. Welch (Eds.), Biomedical Frontiers of Fluorine Chemistry, Vol. 639, American Chemical Society, Washington, DC, 1996.
[2] A.B. Shtarov, P.J. Krusic, B.E. Smart, W.R. Dolbier Jr, J. Am. Chem. Soc. 123 (2001) 9956–9962.
[3] W.R. Dolbier Jr, Acc. Chem. Res. 24 (1991) 63–69.
[4] G. Shi, Y. Xu, J. Fluorine Chem. 44 (1989) 161–166.
[5] Z. Wang, G.B. Hammond, J. Org. Chem. 65 (2000) 6547–6552;
Q. Shen, G.B. Hammond, Org. Lett. 3 (2001) 2213–2215.
[6] O. Mitsunobu, Synthesis (1981) 1–28.
[7] M.L. Edwards, D.M. Stemerick, J.R. McCarthy, Tetrahedron Lett. 131 (1990) 3417–3420.
[8] G.L. Stahl, R. Walter, C.W. Smith, J. Org. Chem. 43 (1978) 2285.
[9] D. Dixon, B. Smart, J. Phys. Chem. 93 (1989) 7772–7780;
A. Bash, D. Lentz, P. Luger, M. Messerschmidt, C. Olesch, M. Patzschke, Angew. Chem. Int. Ed. 41 (2002) 296–299.