Tetrahedron Letters, Vol. 34, No. 3, pp. 415-418, 1993
Printed in Great Britain

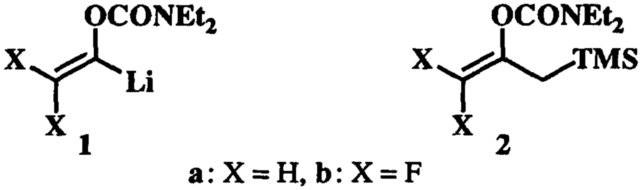
0040-4039/93 $5.00 + .00
Pergamon Press Ltd

FLUORINATED VINYL CARBAMATES AND CARBAMOYLOXY ALLYLSILANES. α-METALATION, ORGANOLITHIUM ADDITION-ELIMINATION, AND FLUORIDE-MEDIATED ELECTROPHILIC REACTIVITY PATTERNS[1]

John Lee, Masao Tsukazaki and Victor Snieckus*
Guelph-Waterloo Centre for Graduate Work in Chemistry
University of Waterloo, Waterloo, Ontario CANADA N2L 3G1

Abstract: LiTMP or LDA-mediated *in situ* generation of α-lithio difluorovinyl carbamate **1b** allows the preparation of silylated derivatives **4a** and **2b** which undergo organolithium addition-elimination and fluoride-mediated condensation reactions respectively to give new functionalized organofluorine derivatives **5a-d** (**Table 2**) and **11a-c** (**Table 3**).

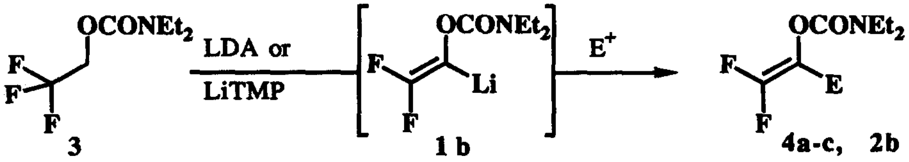
As an extension of exploratory reactivity studies of vinyl carbamate derivatives **1a**[2] and **2a**[3] as new acyl and α,α'-acetone dianion and allene 1,2-dipole equivalents respectively, we turned our attention to the corresponding 2,2-difluorovinyl carbamates **1b**[4] and **2b**. These investigations were stimulated by the rapidly growing interest and demand to incorporate organofluorine units into substances for a diversity of biological and material science applications.[5] Herein we present preliminary results concerned with the addition-elimination and fluoride-mediated electrophilic reactivities of **4a** and **2b** respectively which may foreshadow substantial utility of these organofluorine building blocks in synthesis.[6,7]



Following the lead of Ichikawa and coworkers,[8] who first generated the vinyl tosylate corresponding to **1b**, 2,2,2-trifluoroethyl carbamate **3**,[9] (**Table 1**), was subjected to Martin's conditions (2 equiv LiTMP, 5 equiv TMSCl/THF/-78 °C → rt)[10] to afford the α-silylated product **4a**, (65-70% yield) presumably via the intermediate **1b**. This compound was also obtained (80% yield)[4] using LDA (2.2 equiv)/THF/-78 °C followed by TMSCl quench. Under the latter set of conditions, quench with PhSeBr, MeOTf, and ICH_2TMS afforded compounds **4b**, **4c**, and **2b** respectively in good yields.[11]

In an attempt to probe the enolate chemistry of products **4**, compound **4a** (**Table 2**) was treated with MeLi. This reaction led instead to the formation of **5a** (E:Z mixture) resulting from an addition-elimination process.[12] Similar treatment of **4a** with other organolithiums and super hydride provided the monofluorovinyl carbamates **5b-d** in good yields. While MeLi (entry 1) showed little stereoselectivity in THF solution, sec-

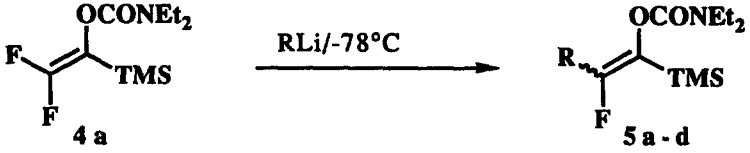
Table 1



E^+	Product	E	Yield, %
TMSCl	4 a	TMS	80
PhSeBr	4 b	SePh	58
MeOTf	4 c	Me	71
$TMSCH_2OTf$	2 b	CH_2TMS	91

BuLi (entry 2), PhLi (entry 4), and, overwhelmingly, Et_3BHLi (entry 6) gave ratios of products favoring the Z-isomers. Inversion of stereochemical outcome was observed in addition of sec-BuLi (entry 3) and PhLi (entry 5) in Et_2O solution. The stereochemical assignments are inferred on the basis of desilylation (TBAF/THF/rt) of **5b** (E:Z mixture) to the chromatographically separated isomers **E-6b** and **Z-6b** (90% yield) which showed coupling constants consistent with the indicated geometrical isomers (**Scheme 1**). In the absence of precedent, we tentatively rationalize the observed solvent-dependent stereoselectivity by assuming *cis* addition of an RLi aggregate, **7** → **8** and the predominant population of dipole-stabilized conformer **10** over **9** in the solvent of higher dielectric constant (THF).

Table 2



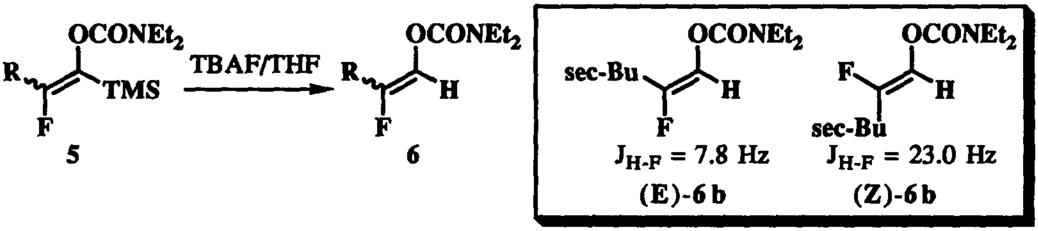
Entry	RLi	Solvent	Product	R	Yield, %	E:Z[a]
1	MeLi	THF	5 a	Me	67	64 : 36
2	sec-BuLi	THF	5 b	sec-Bu	85	9 : 1
3		Et_2O			90	1 : 9
4	PhLi	THF	5 c	Ph	63	85 : 15
5		Et_2O			75	7 : 93
6	$LiBEt_3H$	THF	5 d	H	87	99 : 1

[a] Ratio established by ^1H, ^{19}F NMR and HPLC

To demonstrate fluoride-induced electrophilic allylsilane reactivity, **2b** was protonated and treated with representative aldehydes in the presence of TBAF to afford masked fluorinated aldols **11a-c** (**Table 3**).

In summary, our results and those of Percy[4] provide evidence for the generation and utility of a new fluorinated acyl anion equivalent **1b**. We further demonstrate that fluorinated vinyl carbamates **4a** and carbamoyloxy allylsilane **2b** undergo organolithium addition-elimination and fluoride-mediated electrophilic reactions respectively. Synthetic manipulation of the derived multifunctional compounds **4**, **5**, and **11** may add to our evolving knowledge of the unexpected and invariably unique reactivity of simple organofluorine derivatives.[13,14,15]

Scheme 1



Scheme 2

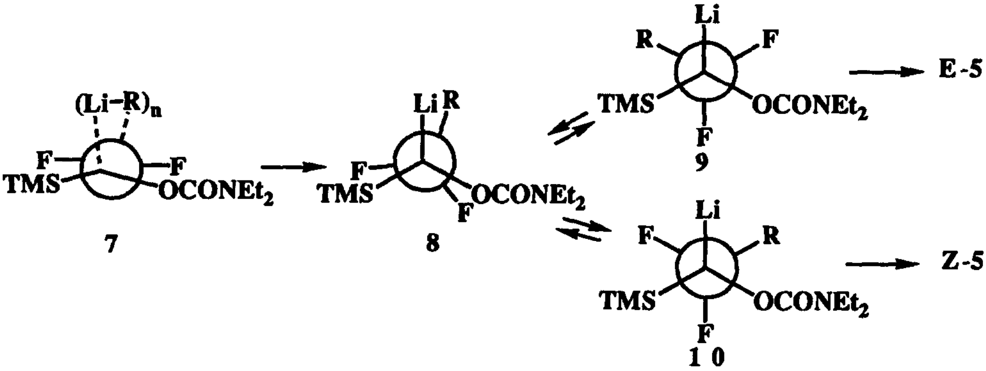
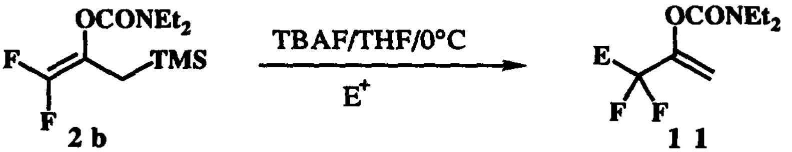


Table 3



E$^+$	Product	E	Yield, %
H_2O	11a	H	79
PhCHO	11b	PhCH(OH)	64
i-PrCHO	11c	i-PrCH(OH)	38

References and Footnotes

1. Tsukazaki, M., Snieckus, V. *Abstracts of Papers*, 203rd National Meeting of the American Chemical Society, San Francisco, CA; American Chemical Society: Washington, DC, 1992; Abstract ORGN 248.
2. Sengupta, S.; Snieckus, V. *J. Org. Chem.* **1990**, *55*, 5680.
3. Tsukazaki, M.; Snieckus, V. *Tetrahedron Lett.* preceding communication in this issue.
4. During the course of our work, Percy reported the generation and electrophile quenching experiments of **1b** (Bennett, A.J.; Percy, J.M.; Rock, M.H. *Synlett* **1992**, 483). We therefore exclude overlapping results on **1b** and disclose only those which are complementary and illustrate new reactivity patterns of **4a** and **2b** thereby enhancing the synthetic value of these substances.
5. General: Welch, J.T. Ed. *Selective Fluorination in Organic and Bioorganic Chemistry* ; ACS Symposium Series 456; American Chemical Society: Washington, D.C., 1991; Welch, J.T.; Eswarakrishnan, S. *Fluorine in Bioorganic Chemistry*; Wiley: New York, 1990; Liebman, J.F.; Greenberg, A.; Dolbier, Jr., W.R., Eds. *Fluorine-Containing Molecules - Structure, Reactivity, Synthesis and Applications*; VCH Publishers: New York, 1988; Hudlicky, M. *Chemistry of Organic Fluorine Compounds*, 2nd Ed.; Ellis Horwood: Chichester, 1976. Fluorine introduction: Mann, J. *Chem. Soc. Rev.* **1987**, *16*, 381. Synthesis of fluorinated bioactive compounds: Welch, J.T. *Tetrahedron* **1987**, *43*, 3123. Fluoropeptides: Imperiali, B. *Adv. Biotechnol. Processes* **1988**, *10*, 97. Mechanism-based enzyme inhibitors: McCarthy, J.R.; Matthews, D.P.; Stemerick, D.M.; Huber, E.W.; Bey, P.; Sunkara, P.S. *J. Am. Chem. Soc.* **1991**, *113*, 7439 and references cited therein.
6. For a list of citations on the synthesis of 1,1-difluoro-1-alkenes, see Ichikawa, J.; Minami, T.; Sonoda, T.; Kobayashi, H. *Tetrahedron Lett.* **1992**, *33*, 3779.
7. For other $F_2C = C(OZ)R$ and RfRC=C(OZ)R systems, see: Z = Li, Na: Nakai, T.; Qian, C. *Tetrahedron Lett.* **1988**, *29*, 4119; Z = $PO(OR)_2$, AlR_2: Ishihara, T.; Yamaguchi, K.; Kuroboshi, M. *Chem. Lett.* **1989**, 1191; Z = MEM: Percy, J.M. *Tetrahedron Lett.* **1990**, *31*, 3931; Z = SiR_3: Jin, F.; Jiang, B.; Xu, Y. *Tetrahedron Lett.* **1992**, *33*, 1221.
8. Ichikawa, J.; Moriya, T.; Sonoda, T.; Kobayashi, H. *Chem. Lett.* **1991**, 961.
9. Prepared in 73% yield by sequential treatment of 2,2,2-trifluoroethanol with NaH and $ClCONEt_2$ in DMF, O °C → rt. See also ref 4.
10. Martin, J.C.; Krizan, T.D. *J. Am. Chem. Soc.* **1983**, *105*, 6155.
11. Treatment of **4a** with TBAF/THF/-25 °C followed by aqueous quench led to the parent system **4**, E = H (85-90% yield). See also ref 4 for its direct formation from **3**.
12. For reactions of difluoroolefins with RLi reagents, see Ishikawa, N.; Nakai, T.; Hayashi, S. *Chem. Lett.* **1980**, 935.
13. The following procedures are representative. Compound **5a**: To a solution of **4a** (300 mg, 1.2 mmol) in THF (5 mL) at -78 °C was added MeLi (1.6 mL, 1.5 M solution, 2.4 mmol) and the mixture was stirred for 40 min and quenched with satd NH_4Cl solution. Removal of THF under reduced pressure followed by extraction with Et_2O, drying (Na_2SO_4), concentration, and flash chromatography afforded 200 mg (67%) of **5a**, oil, IR υ(max) 1722 cm^{-1}: ^1H NMR (200 MHz, $CDCl_3$) δ 0.19 (s, 9H), 1.14 (m, 6H), 1.92 (d, J = 17.3 Hz, 1.5H), 1.97 (d, J = 17.8 Hz, 1.5H), 3.30 (m, 4H); ^{13}C NMR ($CDCl_3$) δ -1.63, -1.22, 13.5, 14.0, 14.3, 15.1, 41.7, 42.1, 131.8, 139.3, 154.6, 161.9, 165.8; ^{19}F NMR ($CDCl_3$) δ -95.9, -117.1; MS m/e 247.1 (M^+).

   Compound **11b**: TBAF (0.15 mL, 1.0 M THF solution, 0.15 mmol) was added to a THF (2 mL)-HMPA (2 mL) solution containing molecular sieves and the mixture was stirred for 2 hr at rt. After cooling to 0 °C, PhCHO (0.18 mL, 1.80 mmol) and a solution of allylsilane **2b** (398 mg, 1.50 mmol) in THF (0.5 mL) were added successively. The reaction mixture was stirred for 3 hr at 0 °C and quenched with 1N HCl. Workup followed by column chromatography (Et_2O: hex = 1:2) afforded 273 mg (64%) of **11b**, oil: IR υ(max) 3414, 1712 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.18 (t, J = 7.1 Hz, 3H), 1.19 (t, J = 7.1 Hz, 3H), 3.31 (t, J = 7.1 Hz, 2H), 3.35 (t, J = 7.1 Hz, 2H), 4.42 (bs, 1H), 4.81 (dd, J = 4.0, 20.1 Hz, 1H), 5.29 (m, 1H), 5.60 (m, 1H), 7.32-7.53 (m, 5H).
14. All reported yields are those of chromatographed materials. All compounds show spectroscopic (^1H, ^{13}C, and ^{19}F NMR, MS) data consistent with the assigned structures. Wherever feasible, analytical data have also been obtained on the purified oily materials.
15. We are grateful to NSERC Canada for continued support of our synthetic programs via Operating (Research) and Industrial Research Chair grants.

(Received in USA 9 October 1992)