J. Am. Chem. Soc. **2001,** *123,* 6947−6948

New, General, and Stereoselective Synthesis of CF_3-Containing Tri- and Tetrasubstituted Oxiranes and Tetrasubstituted Alkenes

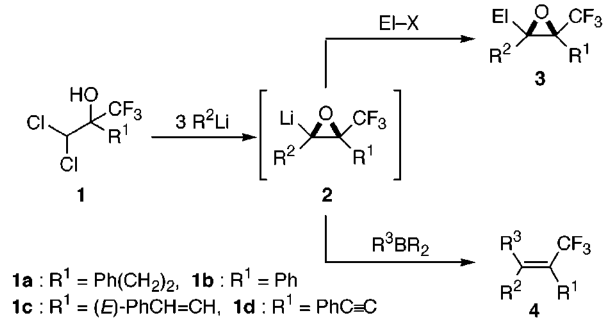
Masaki Shimizu,* Takuya Fujimoto, Hiroshi Minezaki,
Takeshi Hata, and Tamejiro Hiyama

Department of Material Chemistry
Graduate School of Engineering, Kyoto University
Yoshida, Sakyo-ku, Kyoto 606-8501, Japan

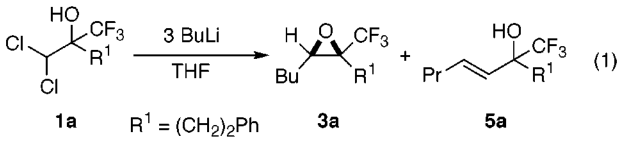
Received April 24, 2001
Revised Manuscript Received June 9, 2001

We report that treatment of 2-substituted 3,3-dichloro-1,1,1-trifluoropropan-2-ol **1**[1] with an organolithium reagent R^2Li in THF at −98 °C produces 2,3-disubstituted 2-lithio-3-trifluoromethyloxirane **2** stereoselectively that reacts with an electrophile El-X or an organoborane R^3BR_2 stereospecifically to give CF_3-containing tri- and tetrasubstituted oxirane **3** or tetrasubstituted alkene **4**, respectively, with high selectivities (Scheme 1).

Scheme 1



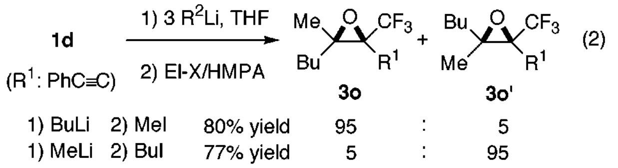
It is well-established that the rearrangement of *β*-oxido carbenoids generated from dihalohydrins is useful for homologation of aldehydes as well as acyclic and cyclic ketones,[2] while there is no precedent regarding CF_3-substituted *β*-oxido carbenoids. We became interested in the carbenoids in view of novel synthesis of CF_3-containing organic molecules that are receiving much attention in pharmaceutical and material sciences.[3]



We first treated **1a** with 3 molar amounts of BuLi at −78 °C and then warmed the reaction mixture to room temperature before quenching with MeOH. Workup and purification by column chromatography (silica gel) unexpectedly gave (*E*)-allylic alcohol **5a** as the sole product in 58% yield. No products derived from the expected CF_3 or R^1 rearrangement were detected. The same reaction with quenching at −78 °C afforded **5a** (58% yield) and 2-butyl-3-(2-phenylethyl)-3-trifluoromethyloxirane (**3a**, 33% yield). When the reaction was effected and quenched at −98 °C, **3a** was solely obtained in 85% yield as a single diastereomer.

Formation of oxirane of type **3** in Scheme 1 is general irrespective of R^1 and R^2 (Table 1).[4] Thus, the reaction of dichlorohydrins **1b**−**d** (R^1 = phenyl, styryl, or phenylethynyl) with BuLi produced the corresponding oxiranes **3b**−**d** in good yields with good to high stereoselectivity (runs 2−4). In addition to BuLi, MeLi, PhLi, and vinyllithium also reacted with **1d** to give **3e**−**g** stereoselectively (runs 5−7).[5] Furthermore, we found that treatment of **1** with BuLi and then with electrophiles gave tetrasubstituted oxiranes **3h**−**n** with similar high selectivity (runs 8−14).

In the case of alkylation, both diastereomers of tetrasubstituted oxiranes **3** can be prepared by proper choice of R^2Li and El-X as illustrated in eq 2. Thus, **3o** was obtained from **1d** using BuLi and MeI, whereas the other diastereomer **3o′** was produced by MeLi-induced generation of **2** followed by trapping with BuI.



Stereochemistry of **3** was determined by X-ray crystallographic analysis of benzophenone adducts **3k** and **3m** and CF_3 and El were shown to be cis.[6] These results indicate that oxiranyllithiums **2** were stereoselectively generated as intermediates with CF_3 and Li being cis in all cases.[7]

Stereoselective generation of **2** can be tentatively explained by assuming a lithium−fluorine chelation model (Scheme 2).[8] At first, **1** would react with 2 molar amounts of BuLi to produce *β*-oxidocarbenoid **6**. We assume that the conformation of **6** in which a CF_3 group and a lithium atom connecting a carbenoid carbon are arranged *synclinal* is favored due to Li−F chelation. Substitution of chlorine in **6** with BuLi from the OLi side followed by intramolecular cyclization would generate **2** that was stable at −98 °C and reacted with an electrophile producing **3**. Alternatively, cyclization of **6** might take place at first to give a

---

[1] Dichlorohydrin **1** were prepared from R^1MgBr and 3,3-dichloro-1,1,1-trifluoropropan-2-one kindly provided by Central Glass Co. Ltd. For the detail, see Supporting Information.

[2] (a) Concise review of rearrangement of *β*-oxido carbenoids: Wovkulich, P. M. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 1, pp 873−877. (b) Boche, G.; Lohrenz, J. C. W. *Chem. Rev.* **2001**, *101*, 697−756. For pioneering works, see (c) Villieras, J.; Bacquet, C.; Normant, J. F. *J. Organomet. Chem.* **1972**, *40*, C1−C4. (d) Köbrich, G.; Grosser, J. *Tetrahedron Lett.* **1972**, 4117−4120. (e) Taguchi, H.; Yamamoto, H.; Nozaki, H. *Tetrahedron Lett.* **1972**, 4661−4662. (f) Köbrich, G.; Grosser, J. *Chem. Ber.* **1973**, *106*, 2626−2635. (g) Villieras, J.; Bacquet, C.; Normant, J. F. *J. Organomet. Chem.* **1975**, *97*, 325−354. (h) Taguchi, H.; Yamamoto, H.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 1592−1595.

[3] (a) *Fluorine-containing molecules: Structure, Reactivity, Synthesis, and Applications*; Liebman, J. F.; Greenberg, A.; W. R. Dolbier, J., Eds.; VCH: New York, 1988. (b) *Organofluorine Chemistry: Principles and Commercial Applications*; Banks, R. E.; Smart, B. E.; Tatlow, J. C., Eds.; Plenum Press: New York, 1994. (c) *Chemistry of Organic Fluorine Compounds II A Critical Review*; Hudlicky, M.; Pavlath, A. E., Eds.; ACS Monograph 187; American Chemical Society: Washington, DC, 1995. (d) *Organofluorine Chemistry: Fluorinated Alkenes and Reactive Intermediates*, Chambers, R. D., Ed.: Top. Curr. Chem. Vol 192; Springer: Berlin, 1997. (e) *Organofluorine Chemistry: Techniques and Synthons*, Chambers, R. D., Ed.: Top. Curr. Chem. Vol 193; Springer: Berlin, 1997. (f) Hiyama, T. *Organofluorine Compounds-Chemistry and Applications*; Springer: Berlin, 2000. (g) Begue, J.-P.; Bonnet-Delpon, D. *Tetrahedron* **1991**, *47*, 3207−3258. (h) McClinton, M. A.; McClinton, D. A. *Tetrahedron* **1992**, *48*, 6555−6666.

[4] Treatment of $PhMeC(OLi)CHCl_2$ or $Ph_2C(OH)CHCl_2$ with excess BuLi or PhLi was reported to produce respectively $MeCOCH(Cl)Ph$ or $Ph_2CHCOPh$ in ref 2f. It is not clear why no rearrangement took place in **1**. The fluorine atoms may destabilize the positively charged transition state for a migration of either the trifluoromethyl group or R^1, as one of the referees suggested.

[5] *s*-BuLi and *t*-BuLi gave complex mixtures; PhC≡CLi, no reaction.

[6] For the detail, see Supporting Information.

[7] Trapping of oxiranyllithium with such an electrophile as D_2O, Me_3SiCl, MeI, aldehydes, or ketones was reported to proceed with retention of configuration at the lithiated carbon. (a) Eisch, J. J.; Galle, J. E. *J. Organomet. Chem.* **1988**, *341*, 293−313. (b) Molander, G. A.; Mautner, K. *J. Org. Chem.* **1989**, *54*, 4042−4050. (c) Lohse, P.; Loner, H.; Acklin, P.; Sternfeld, F.; Pfaltz, A. *Tetrahedron Lett.* **1991**, *32*, 615−618.

[8] For Li−F interaction, see ref 3f, p 129. One of the referees kindly suggested the possibility of dipole effects responsible for the cis selectivity.

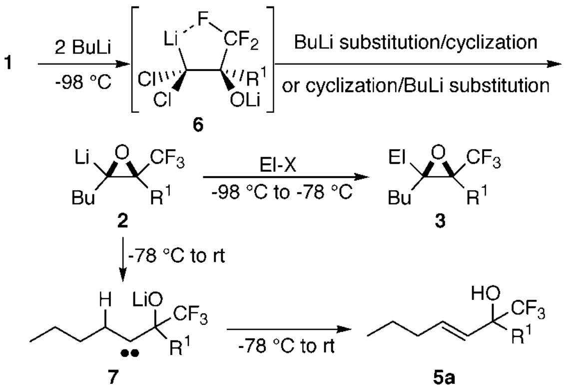
10.1021/ja016077k CCC: $20.00

Table 1. Synthesis of Tri- and Tetrasubstituted Oxiranes[a]

run	R^1	R^2	El[b]	3	yield (%)[c]	isomer ratio[d]
1	$Ph(CH_2)_2$	Bu	H	**3a**	85	>95:<5
2	Ph	Bu	H	**3b**	83	89:11
3	(*E*)-PhCH=CH	Bu	H	**3c**	74	83:17
4	PhC≡C	Bu	H	**3d**	84	>95:<5
5	PhC≡C	Me	H	**3e**	85	>95:<5
6	PhC≡C	Ph	H	**3f**	95	>95:<5
7	PhC≡C	C_2H_3	H	**3g**	67	>95:<5
8	PhC≡C	Bu	Me_3Si	**3h**	79	>95:<5
9	PhC≡C	Bu	PhCH(OH)	**3i**	82	*e*
10	PhC≡C	Bu	$Et_2C(OH)$	**3j**	71	>95:<5
11	PhC≡C	Bu	$Ph_2C(OH)$	**3k**	68	>95:<5
12	$Ph(CH_2)_2$	Bu	$Ph_2C(OH)$	**3l**	57	>95:<5
13	(*E*)-PhCH=CH	Bu	$Ph_2C(OH)$	**3m**	55	89:11
14	PhC≡C	Bu	C_3H_5	**3n**	70	>95:<5

[a] To a solution of **1** (1.0 mmol) in THF (5 mL) was added R^2Li (3 mmol) at −98 °C and the mixture was stirred at −98 °C for 15 min before adding MeOH or El-X (1.5 mmol). As for runs 8−14, the resulting solution was gradually warmed to −78 °C and quenched with MeOH. [b] The El-X employed were as follows: runs 1−7, MeOH; run 8, Me_3SiCl; run 9, PhCHO; run 10, Et_2CO; runs 11−13, Ph_2CO; run 14, allyl bromide. [c] Isolated yield. [d] Determined by ^1H and ^{19}F NMR analysis. [e] Two of four possible diastereomers were obtained in a ratio of 60:40.

Scheme 2



chlorolithiooxirane. Subsequently, the remaining chlorine might be substituted stereoselectively by the third BuLi to give rise to **2**.[9] At temperatures above −78 °C, **2** would cause ring-opening via α-elimination followed by adjacent C−H bond insertion of intermediate carbene **7** to give **5a**.

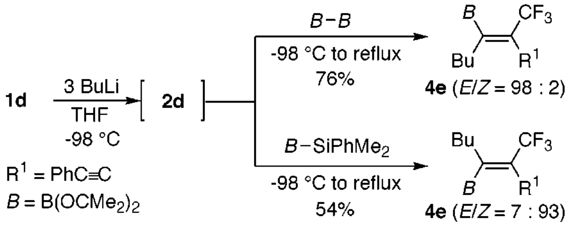
With stereochemically defined **2** being formed at −98 °C, we next studied the reaction of **2** with an organometallic reagent to develop a novel method for CF_3-containing tetrasubstituted alkenes **4** (Scheme 1).[10] Although **2** did not react with BuLi any more,[11] tetrasubstituted alkenes **4** were produced in low yields when **2** was treated with Me_3Al or Et_2Zn. For this transformation, organoboron compounds were found appropriate. For example, **2d** reacted with Et_3B to give **4a** in 45% yield with excellent selectivity (Table 2).[12] (Pinacolato)borane showed better reactivity, and thus aryl, alkenyl, alkynyl, and alkyl groups were applicable to this stereospecific alkene formation as a R^3 substituent (runs 2−5). Stereochemical assignment was effected by X-ray analysis of **4b** to reveal CF_3 and phenyl being cis.[6] Noteworthy is that appropriate combination of R^2 and R^3 allows us to selectively prepare either stereoisomer of **4** at will as demonstrated in runs 2 and 5.

Table 2. Synthesis of Tetrasubstituted Alkenes (R^1 = PhC≡C)[a]

run	R^2	R^3BR_2	4	yield (%)[b]	isomer ratio[c]
1	Bu	$EtBEt_2$	**4a**	45	>95:<5
2	Bu	$PhB(OCMe_2)_2$	**4b**	66	97:3
3	Bu	(*E*)-BuCH=CHB$(OCMe_2)_2$	**4c**	56	>95:<5
4	Bu	PhC≡CB$(OCMe_2)_2$	**4d**	74	>95:<5
5	Ph	$BuB(OCMe_2)_2$	**4b**	84	4:96

[a] To a solution of **1d** (1.0 mmol) in THF (5 mL) was added R^2Li (3 mmol) at −98 °C and the mixture was stirred at −98 °C for 15 min before R^3BR_2 (2.0 mmol) was added. The resulting solution was gradually warmed to room temperature and refluxed for 4 h. [b] Isolated yield. [c] Determined by ^1H and ^{19}F NMR analysis.

Scheme 3



Furthermore, it is remarkable that stereodivergent synthesis of β-CF_3-substituted alkenylborane **4e** can be achieved, using bis(pinacolato)diboron or (dimethyphenysilyl)(pinacolato)borane as the organoboron reagent (Scheme 3).[13]

In summary, we have developed stereoselective synthesis of a variety of CF_3-containing tetrasubsituted oxiranes and alkenes in one pot from readily available dichlorohydrins, which would serve as highly valuable intermediates for stereoselective construction of CF_3-containing complex organic molecules. Further study on β-oxido carbenoids bearing a CF_3 group is in progress.

Acknowledgment. We thank the Ministry of Education, Culture, Sports, Science, and Technology, Japan, for the Grand-in-Aid for COE Research on Element Science, No. 12CE2005, and the Central Glass Co. Ltd. for a generous gift of dichlorotrifluoroacetone.

Supporting Information Available: Typical procedures, spectral data for new compounds, and X-ray crystallographic data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA016077K

---

(9) Molines, H.; Normant, J.-M.; Wakselman, C. *Tetrahedron Lett.* **1974**, 951−954.

(10) Reviews on oxiranyllithiums: (a) Satoh, T. *Chem. Rev.* **1996**, *96*, 3303−3325. (b) Molander, G. A.; Mautner, K. *Pure Appl. Chem.* **1990**, *62*, 707−712. Such an organometalic compound as RLi, R_3A_l, R_2Zn, or R_4CeLi reportedly reacted with oxiranyllithiums to afford alkylated alkenes.

(11) The results contrast sharply to those obtained by Mioskowski and coworkers: Doris, E.; Dechoux, L.; Mioskowski, C. *Tetrahedron Lett.* **1994**, *35*, 7943−7946. See also, Eisch, J. J.; Galle, J. E. *J. Org. Chem.* **1976**, *41*, 2615−2621. Ukaji, Y.; Yoshida, A.; Fujisawa, T. *Chem. Lett.* **1990**, 157−160.

(12) The reactivity of **2d** towards organoboranes contrasts to that of oxiranyllithium generated from triphenylsilyloxirane: Taniguchi, M.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **1991**, *32*, 2783−2786.

(13) Hata, T.; Kitagawa, H.; Masai, H.; Kurahashi, T.; Shimizu, M.; Hiyama, T. *Angew. Chem., Int. Ed.* **2001**, *40*, 790−792.