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Preparation and regioselective reactions of novel *gem*-difluorinated vinyloxiranes with some organometallic reagents

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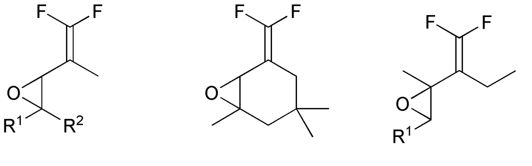
Hitherto unknown, relatively labile *gem*-difluorinated vinyloxiranes were prepared by difluoro-Wittig reactions with α,β-epoxyketones; for these vinyloxiranes alkyl groups were delivered at the fluorine-attached terminal carbon atom in an S_N2' manner by RLi, while Me_3Al and MeMgBr–CuCl (3 : 1) introduced the Me group at the allylic epoxy carbon with retention and inversion of the original stereochemistry, respectively.

Recently, we have reported the construction of chiral aldol structures with variously fluorinated methyl groups at specific positions starting from suitably protected D-glucose derivatives.[1] During our work in this field, installation of the 2,3-epoxy-4-*exo*-difluoromethylene framework into D-glucose was required on the basis of the anticipation that the previous low stereoselection would be effectively modified by imposing this additional three-membered ring strain. However, since our literature search indicated that the targetted 1,1-difluoro-3,4-epoxybutenes had not been reported yet,[2] preparation of such unprecedented molecules and their reactions towards alkylmetal reagents were investigated. This communication describes the preliminary results in this area.

The model materials **1**–**5** (Fig. 1) as shown below were selected as representative examples and prepared by routine methods such as NaOH-promoted H_2O_2 epoxidation of α,β-unsaturated ketones, followed by the difluoromethylenation of the carbonyl moiety using the CBr_2CF_2–HMPT protocol (94, 88, 75, 85 and 91% yields for the latter step for the desired products **1**–**5**, respectively).[3] Compounds thus formed were proved to be relatively unstable especially when concentrated and it was found that argon should be introduced to avoid rapid decomposition of the desired products upon solvent evaporation. In spite of their inherent instability, **1**–**5** as dilute hexane solutions, can be stored at least for a couple of days in a refrigerator under an argon atmosphere.

Among the five compounds synthesized, **1** was selected as a representative material and its reaction with *n*-BuLi was briefly inestigated for finding out the suitable reaction conditions (Table 1). THF and ether as solvents gave comparable yields but the former recorded the better *E*-olefinic preference at the newly formed C–C double bond. In addition, because hexane furnished only 38% yield along with 23% recovery of the starting material **1** and 1,4-dioxane showed almost no olefinic stereoselectivity, we selected THF as the solvent. Further experiments eventually revealed that 2 equiv. of *n*-BuLi was sufficient for the attainment of a good level of conversion at 0 °C. Moreover, the addition of 0.5 equiv. of HMPA dramatically affected the reaction course and the *E* : *Z* ratio was improved to as high as 95 : 5. Interestingly, such improvement was specifically realized by HMPA and almost no (TMEDA and 12-crown-4) or a slight (DMI or DMPU)[4] effect was observed for other familiar chelating agents.



1: R^1=$PhCH_2CH_2$, R^2=H
2: R^1=Ph, R^2=H
5: R^1=H, R^2=Ph

3

4: R^1=$PhCH_2CH_2$

Fig. 1 Representative prepared difluorinated vinyloxiranes.

All the *exo*-difluorinated vinyloxiranes **1**–**5** were reacted with various types of RLi (2 equiv.) in THF in the presence or absence of HMPA (Table 2). In all instances, as was strongly suggested by our *ab initio* calculations,[5] only the S_N2' products were specifically isolated with moderate to excellent *E* preference which was dependent on the bulkiness of the alkyllithium reagents employed. Olefinic stereochemistries of the products were determined by NOE experiments of **6d** and **7e**. Thus, **6d** showed a peak correlation between the vinylic hydrogen (R^4) and the Me group in *tert*-Bu (R) as well as allylic H (R^2) and the Me group (R^3), and **7e** between the Me group (R^3) and allylic H (R^2) or vinylic hydrogen (R^4) for the major or minor isomers, respectively. These facts unambiguously indicated the *E* stereochemistry at the newly formed olefinic bonds for the major isomers.

Stereoisomeric **2** and **5** were found to exhibit a remarkable reactivity difference, the latter *Z*-oxirane only furnishing sluggish results while the former *E*-isomer attained moderate to good yields. This might be mainly stemmed from the severe steric congestion of **5** which would disturb the expected *s-trans*-type conformation where alkyllithiums would approach the terminally fluorinated C^1 atom while retaining interaction with epoxy oxygen.[6] Somewhat lower yields were recorded for **3** probably because of the axially disposed methyl group more or less affecting the access of the nucleophilic species. Moreover, usage of the optimized 0.5 equiv. of HMPA was proved to be effective only for *n*-BuLi and PhLi, and almost no effect was observed for Me-, *sec*-Bu-, and *tert*-BuLi. This tendency would be explained in terms of their inherent aggregation structures in THF which are known to decrease from tetrameric to monomeric in the order of MeLi > *n*-BuLi > PhLi > *tert*-BuLi.[7] So, if the reactive monomeric form is responsible for the present process, HMPA should demonstrate almost no effect for the

Table 1 Reaction of **1** and *n*-BuLi under various conditions

n-BuLi (equiv.)	Solvent	Time/h	Yield[a] (%)	*E* : *Z*
5.0	*n*-Hexane	24	38	66 : 34
5.0	Et_2O	2	52	60 : 40
5.0	THF	2	52	72 : 28
5.0	1,4-Dioxane	24	66	53 : 47
5.0[b]	THF	24	42	81 : 19
2.0	THF	2	63	73 : 27
2.0[c]	THF	2	66	95 : 5

[a] Determined by ^{19}F NMR. [b] Reaction was performed at −78 °C. [c] 0.5 equiv. of HMPA was added.

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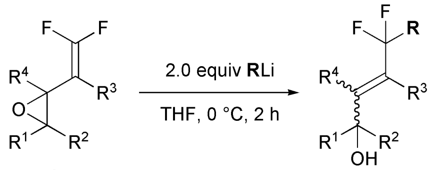
Table 2 Reaction of vinyloxiranes with various alkyllithiums



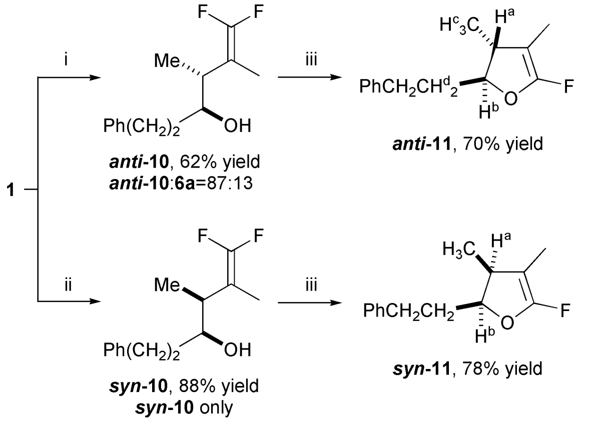
1–5 **6–9**

Sub^a	R	Pro^b	Isolated yield^c (%)	E : Z^c
1	Me	**6a**	84 (78)^d	60 (68) : 40 (32)
	n-Bu	**6b**	51 (61)	74 (95) : 26 (5)
	sec-Bu	**6c**	33 (44)	89 (95) : 11 (5)
	tert-Bu	**6d**	51 (52)	95 (97) : 5 (3)
	Ph	**6e**	58 (76)	71 (94) : 29 (6)
2	Me	**7a**	69	65 : 35
	n-Bu	**7b**	52 (62)	83 (97) : 17 (3)
	tert-Bu	**7d**	49	97 : 3
	Ph	**7e**	50	79 : 21
3	Me	**8a**	65	
	n-Bu	**8b**	63 (75)	
	tert-Bu	**8d**	69	
	Ph	**8e**	81	
4	Me	**9a**	52	63 : 37
	n-Bu	**9b**	31 (27)	95 (65) : 5 (35)
	tert-Bu	**9d**	16	> 99 : < 1
	Ph	**9e**	31	85 : 15
5	Ph^{ef}	**7e**	16	99 : 1

^{a} Substrate. ^{b} Product. ^{c} Result obtained upon the addition of 0.5 equiv. of HMPA is shown in parentheses. ^{d} 5 equiv. of HMPA improved the E : Z ratio to 93 : 7 (67% yield). ^{e} Yield was determined by ^{19}F NMR. ^{f} Only a trace amount of products was detected by the reaction with MeLi, *n*-BuLi or *tert*-BuLi.

originally monomeric *tert*-BuLi and tetrameric MeLi required a larger amount of HMPA for deaggregation.

Although no reaction was observed between **1** and Grignard reagents in THF,[8] addition of CuCl[9] in a 3 : 1 stoichiometry (higher-ordered cuprates) led to smooth epoxide opening at the allylic position (Scheme 1). In spite of the concomitant formation of the corresponding S_N2' type product **6a**, the desired material *anti*-**10** was successfully and readily isolated in good yield as a single diastereomer. This epoxy ring-opening was also effected by Me_3Al[10] and entry of the methyl group was realized exclusively at the allylic epoxy carbon atom to afford F_2-homoallylic alcohol *syn*-**10** in excellent yield again as the sole stereoisomer. However, to our astonishment from NMR data, these homoallylic alcohols **10** were *not* identical. Elaboration of *syn*-**10** by the oxidation–reduction sequence led to the exclusive formation of *anti*-**10**, a definite indication of their diastereomeric relationship. Independent NOE studies for *syn*- and *anti*-**11** cyclized by a slightly modified Ichikawa method[11] from *syn*- and *anti*-**10**, respectively, demonstrated explicit NOE correlation between H^a and H^b for *syn*-**11**, and H^a and H^d as well as H^b and H^c for *anti*-**11**. Thus, quite intriguingly, Me_3Al was concluded to deliver the Me group with retention of stereochemistry to form the *syn* configuration[12] and RMgX/CuCl complementarily produced the *anti* isomers.



Scheme 1 *Reagents and conditions*: (i) 2 equiv. CuCl, 6 equiv. MeMgBr/THF, 0 °C, 2 h. (ii) 1.5 equiv. Me_3Al/hexane, 0 °C, 1 h. (iii) 2.5 equiv. NaH/DMF, 100 °C, 3 h. The relative stereochemistry is shown.

As described above, we have succeeded in the preparation of the unprecedented terminally difluorinated vinyloxiranes **1**–**5**. It was further exemplified that judicious choice of the conditions realized the site selective reaction *via* the S_N2' (RLi) or S_N2 (higher ordered cuprates) mechanisms as well as, more interestingly, the epoxide ring opening at the allylic carbon with retention of stereochemistry by Me_3Al. Reactions of **1**–**5** with other heteronucleophiles (hydride, fluoride, alkoxides, and so forth) are underway in this laboratory.

Notes and references

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2 Perfluorinated vinyloxirane was the only example found in the literature containing the requisite framework, see: (*a*) D. Sianesi, G. C. Bernardi and A. Pasetti, *Fr. Pat.* 1,499,094, October 20, 1967; (*b*) L. Stockburger III and J. Heicklen, *J. Am. Chem. Soc.*, 1971, **93**, 3331; (*c*) I. Kaneko, H. Nakamura and K. Oharu, *Jpn. Kokai Tokkyo Koho*, JP 02,040,373, Feb. 9, 1990.

3 W. A. Vinson, K. S. Prickett, B. Spahic and P. R. O. de Montellano, *J. Org. Chem.*, 1983, **48**, 4661.

4 DMI = 1,3-dimethyl-2-imidazolidinone, DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (*N*,*N*′-dimethylpropyleneurea).

5 *Ab initio* (B3LYP/6-31+G*) computation of the unsubstituted 1,1-difluorovinyloxirane and its non-fluorinated counterpart indicated the appreciable polarization of the $C^1F_2{=}C^2H$ moiety than the case of the usual vinyl group with quite similar frontier molecular orbital energy levels, leading to strong anticipation of regioselective reactions of the former especially with hard nucleophiles. Non-fluorinated species usually undergo alkylmetal attack with relatively low regioselectivity. See, for example: R. W. Herr and C. R. Johnson, *J. Am. Chem. Soc.*, 1970, **92**, 4979; for a related review, see: J. A. Marshall, *Chem. Rev.*, 1989, **89**, 1503.

6 Extensive PM3 calculations anticipated such a conformation as the most favorable transition state. Details will be reported elsewhere.

7 E. Weiss, *Angew. Chem., Int. Ed. Engl.*, 1993, **32**, 1501.

8 The $F_2C{=}CX$-moieties were reported to survive in an excess amount of RMgX. See: (*a*) H.-M. Park, T. Uegaki, T. Konno, T. Ishihara and H. Yamanaka, *Tetrahedron Lett.*, 1999, **40**, 2985 (X = F) (*b*) F. Tellier, M. Baudry and R. Sauvêtre, *Tetrahedron Lett.*, 1997, **38**, 5989 (X = H). For the reactions with RLi, see (*c*) S. J. Brown, S. Corr and J. M. Percy, *Tetrahedron Lett.*, 2000, **41**, 5269; (*d*) R. Sauvêtre, D. Masure, C. Chuit and J.-F. Normant, *Synthesis*, 1978, 128.

9 CuI and CuCl showed almost comparable yields and S_N2/S_N2' ratio, while CuCN afforded less satisfactory results.

10 This reaction towards the prototypical vinyloxirane is known to occurred mainly at the allylic epoxy carbon atom C^3 by Lewis-acidic aluminium coordination: I. Mukerji, A. Wayda, G. Dabbagh and S. H. Bertz, *Angew. Chem., Int. Ed. Engl.*, 1986, **25**, 760.

11 J. Ichikawa, Y. Wada, T. Okauchi and T. Minami, *Chem. Commun.*, 1997, 1537.

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