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Regio- and Stereoselective Reductions of *gem*-Difluorinated Vinyloxiranes

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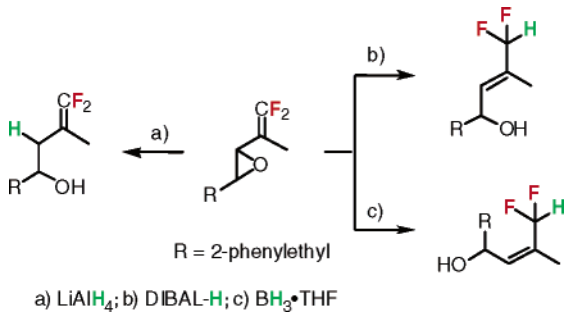
ABSTRACT



***gem*-Difluorinated vinyloxiranes are versatile building blocks for the synthesis of fluorinated compounds. Investigations of their reactions with nucleophiles resulted in highly regio- and stereoselective reductions. In their reactions with $LiAlH_4$, hydride reacted at the allylic epoxide carbon to produce homoallylic alcohols exclusively. Moreover, regio- and stereoselective S_N2' reactions were observed with DIBAL-H and BH_3·THF; the former afforded *E* allylic alcohols, whereas the latter furnished the corresponding *Z* isomers with excellent selectivities.**

Introduction of a fluorine atom into organic compounds greatly alters their physical, chemical, and biological properties,[1] and their unique properties enable us to utilize fluorinated materials in many fields. For instance, fluorinated compounds with difluoromethylene or terminally difluorinated olefin units, which are recognized as mimics of an oxygen atom due to the comparable electronegativity of fluorine and oxygen and the capability of both atoms to serve as hydrogen bond acceptors, recently have attracted attention as potential enzyme inhibitors.[2] However, on the other hand, such changes of properties occasionally prevent us from preparing desired fluorinated compounds by following the protocols for the preparation of the corresponding nonfluorinated hydrocarbons. For instance, Liu and co-workers reported very recently that introduction of fluorine atoms into a substrate can affect the regioselectivity of hydride reduction in an enzymatic reaction.[2c] Therefore, independent synthetic methods are necessary for fluorine-containing materials, and regio- as well as stereoselective construction methods have been developed by many groups.[1a,3]

Recently, we reported[4] the synthetic route for *gem*-difluorinated vinyloxiranes **1**, possessing a strong potential

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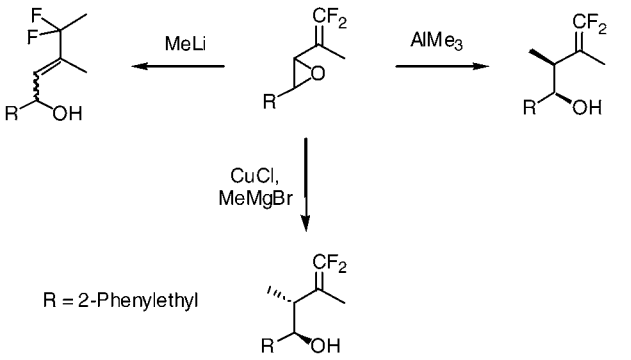
as versatile building blocks for compounds containing terminally difluorinated olefins and difluoromethylene moieties.[5] Indeed, since **1** has three reaction sites for nucleophiles, we have demonstrated[4] their selective alkylations (Scheme 1). For instance, a hard nucleophile like RLi reacted

Scheme 1

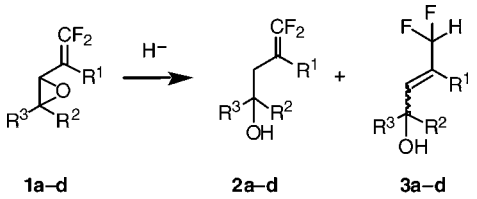


at the terminal-fluorine-attached carbon selectively via an S_N2' pathway to afford the corresponding allylic alcohols with good to excellent *E* selectivity. On the other hand, a regioselective alkylation with retention stereochemistry at the allylic epoxide carbon was observed by an ambiphilic reagent, AlR_3, while cuprates, prepared from CuCl and RMgBr in a ratio 1:3, introduced alkyl groups with inversion stereochemistry at the same carbon.

So far, synthetic strategies for the stereocontrolled synthesis of difluoromethylated materials have not been studied in detail.[6] Among them, the highly geometrically controlled syntheses of trisubstituted alkenes with a difluoromethyl group are not known.[7] Thus, we have devoted our attention to the development of simple and stereocontrolled synthetic methods for the preparation of such compounds utilizing regio- and stereoselective reductions of the versatile building block **1**. The preliminary results of reagent-dependent regio- and stereoselective reductions of *gem*-difluorinated vinyloxiranes **1** are described in this communication.

Several *gem*-difluorinated vinyloxiranes **1a**−**d** were prepared from corresponding α,β-epoxyketones by difluoro Wittig reaction.[4b] At first, reactions of **1a** were performed with various reducing reagents to investigate product distribution (Scheme 2). The results are summarized in Table 1.

Scheme 2



1a–d **2a–d** **3a–d**

1a: R_1=Me, R_2=H, R_3=2-phenylethyl
1b: R_1=Me, R_2=H, R_3=Ph
1c: R_1=Me, R_2=Ph, R_3=H
1d: R_1=Ph, R_2=H, R_3=Ph

Reactions with several borohydrides ($NaBH_4$ in MeOH as well as in DMSO, $LiBH_4$ in THF, Me_4NBH_4 in THF, and $NaBH_3CN$ in MeOH) resulted in no reaction at room temperature after 24 h, and poor conversion was recorded even at high temperatures (entry 1). The stronger reducing reagent $LiAlH_4$ afforded **2a** exclusively both in Et_2O (^{19}F NMR yield of **2a**, 55%; recovery of **1a**, 19%) and in THF, and almost all **1a** was consumed at higher temperatures (entries 2 and 3). On the other hand, despite low reactivities of other borohydrides, when $Zn(BH_4)_2$, possessing more coordinating ability to activate the substrate,[8] was employed, a highly regioselective S_N2'-type reaction with an exclusive *Z* selectivity was observed (entry 4). This encouraging result prompted us to investigate the reaction with electrophilic reducing reagents such as diisobutylaluminum hydride (DIBAL-H) and BH_3. In the former case, the selective S_N2' reaction, without any formation of the regioisomer **2a**, occurred to furnish **3a** in several solvents (benzene, Et_2O, CH_2Cl_2, and *n*-hexane).[9] Among them, the best yield of **3a** was attained in *n*-hexane, while CH_2Cl_2 showed a superior result from the point of the olefinic stereochemistry of the product (entries 5 and 6). When the reaction was performed with less than 2 equiv of DIBAL-H, only the S_N2' product **3a** was obtained, but the yield was lower. At lower temperatures (entries 7 and 8), only the *E* isomer was furnished in both solvents, whereas, in nonfluorinated cases,[9c] significant *Z* selectivity was observed under a similar condition. On the other hand, only the *Z* isomer of **3a** was obtained in a better yield in BH_3·THF (entry 9) than in $Zn(BH_4)_2$. Moreover, by decreasing the amount of the reagent, the unfavorable defluorination was suppressed (entry 10).

The NOESY experiment of the product **3a** (*E*/*Z* = 67/33) was performed for the determination of the olefinic stereo-

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(7) For example, preparation by Hörner−Wadsworth−Emmonds reaction demonstrated poor *E*/*Z* selectivities. See: Dolence, J. M.; Poulter, C. D. *Tetrahedron* **1996**, *52*, 119.

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(9) In nonfluorinated vinyloxirane cases, regio- and stereoselectivities were greatly affected by the solvents employed. See: (a) Bloodworth, A. J.; Curtis, R. J.; Spencer, M. D.; Tallant, N. A. *Tetrahedron* **1993**, *49*, 2729. (b) Lee, E.; Paik, Y. H.; Park, S. K. *Tetrahedron Lett.* **1982**, *23*, 2671. (c) Lenox, R. S.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1973**, *95*, 957.

Table 1. Reaction of **1a** with Various Reducing Reagents[a]

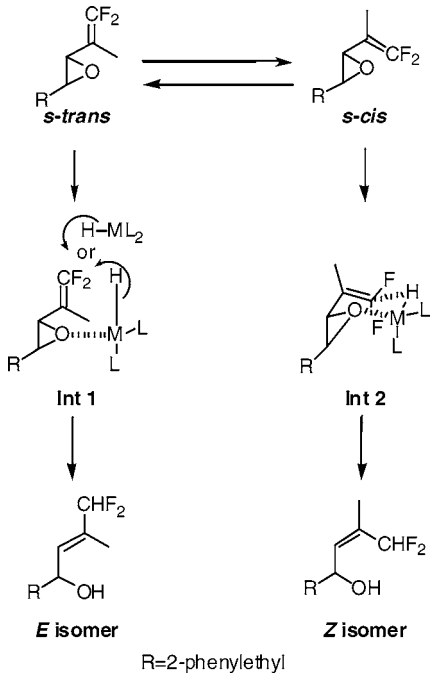
entry	conditions	yield (%) 2a	yield (%) 3a	*E*/*Z* of **3a**	recovery of **1a** (%)
1	$NaBH_4$ (0.5 equiv)/DMSO, 100 °C, 1 day	24	9	>99/<1	*b*
2	$LiAlH_4$ (0.5 equiv)/THF, rt, 24 h	28	<1		63
3	$LiAlH_4$ (0.5 equiv)/THF, reflux, 2 h	78	<1		4
4	$Zn(BH_4)_2$ (0.5 equiv)/THF, reflux, 5 h	<1	60	<1/>99	0
5	DIBAL-H (2.0 equiv)/*n*-hexane, 0 °C, 1 h	<1	74	67/33	0
6	DIBAL-H (2.0 equiv)/CH_2Cl_2, 0 °C, 1 h	<1	58	84/16	0
7	DIBAL-H (2.0 equiv)/*n*-hexane, −78 °C, 1 h	14	64	>99/<1	*b*
8	DIBAL-H (2.0 equiv)/CH_2Cl_2, −78 °C, 1 h	<1	77	>99/<1	*b*
9	BH_3·THF (1.0 equiv)/THF, rt, 1 h	<1	72	<1/>99	0
10	BH_3·THF (0.75 equiv)/THF, rt, 1 h	<1	94	<1/>99	0

[a] Yields, ratios, and recoveries were determined by ^{19}F NMR. [b]Remaining starting **1a** decomposed during workup.

chemistries. Peak correlations between the vinylic H and the CF_2-H moiety as well as the allylic H and the allylic Me moiety for the major isomer and, at the same time, a cross-peak between the CF_2-H moiety and the allylic H for the minor isomer led us to conclude unambiguously that the *E* isomer is the main product in the DIBAL-H cases while an exclusive *Z* selectivity occurs with BH_3.

The mechanism for the stereoselective reductions is suggested as follows. DIBAL-H and BH_3 could activate the oxirane moiety strongly to lead an intramolecular hydride shift to the fluorine-attached-terminal carbon.[9c,10] To account for the current olefinic stereochemical outcome of **3a**, which depends on the kind of reagent employed, a plausible reaction mechanism is described in Scheme 3.

Scheme 3



The *E* isomer would be furnished from the *s*-trans conformer by way of **Int 1**, while **Int 2** could be generated from the *s*-cis conformer to afford the *Z* isomer. The chairlike six-membered ring conformation of **Int 2** would be favorable in the case of reducing reagents with relatively small ligands (Ls) such as BH_3·THF to produce the *Z* product easily. On the other hand, as for DIBAL-H whose Ls are relatively

Table 2. Reaction of **1** with $LiAlH_4$, DIBAL-H, and BH_3·THF[a]

method A: $LiAlH_4$ (0.5 equiv) / THF, reflux, 2 h
method B: DIBAL-H (2.0 equiv) / *n*-hexane, -78 °C, 1 h
method C: DIBAL-H (2.0 equiv) / CH_2Cl_2, -78 °C, 1 h
method D: BH_3·THF (0.75 equiv) / THF, rt, 1 h

entry	**1**	method	yield[b] (%) **2**	yield[b] (%) **3**	*E*/*Z* of **3**	recovery (%)
1	**1a**	A	78: **2a**	(<1)		*c*
2		B	(14)	(64): **3a**	>99/<1	*c*
3		C	(<1)	66	>99/<1	*c*
4		D	(<1)	95	<1/>99	0
5	**1b**	A	(39): **2b**	(10): **3b**	94/6	
6		B	(14)	(39)	>99/<1	0
7		C	(6)	62	>99/<1	0
8		D	(<1)	71	<1/>99	13
9	**1c**	A	61: **2b**	(<1)		*c*
10		B	87	(2): **3b**	>99/<1	7
11		C	78	(4)	>99/<1	0
12		D	(<1)	(13)	23/77	87
13	**1d**	A	(<1)	(<1)		0
14		B		66: **3d**	92/8	0
15		C		66	92/8	0
16		D	(<1)	91	<1/>99	*c*

[a] Yields in parentheses, ratios, and recoveries were determined by ^{19}F NMR. [b]Isolated yields after purification using column chromatography. [c]Remaining starting **1** decomposed during workup.

large, steric repulsion between L and the epoxide moiety in **Int 2** could inhibit the reaction pathway to the *Z* product.

Then, successful regio- and stereoselective reductions of **1a** described above prompted us to investigate the scope and the limitation of their reactions (Table 2). Other *gem*-difluorinated vinyloxiranes **1b**−**d** were reduced by $LiAlH_4$, DIBAL-H, and BH_3·THF under standard conditions. Stereoisomeric **1b** and **1c** were found to exhibit remarkably different reaction outcomes (entries 5−12). In the (*E*)-oxirane case (entries 5−8), stereoselective S_N2' reactions were realized; however, concomitant formation of the regioisomer was observed in the reaction with $LiAlH_4$ and DIBAL-H. These regiorandom reactions would be explained by the activation of both epoxide carbons by the adjacent sp^2 systems. On the other hand, when the corresponding (*Z*)-oxirane **1c** was used as a substrate (entries 9−12), the S_N2 product **2b** was formed selectively with $LiAlH_4$ and DIBAL-H. The S_N2' product **3b** was hardly obtained by DIBAL-H as well as by BH_3. This observation could be attributable to the disturbance of the formation of *s*-trans and *s*-cis conformers because of steric congestion of the cis-substituted epoxide. **1d** demonstrated selective reactions (entries 13−16), except for the reaction with $LiAlH_4$ showing unfavorable defluorination.

In summary, we have accomplished reagent-dependent reductions of **1**, in general, with high levels of regio- and stereocontrol. Thus, judicious choice of reagents enabled us to introduce a hydride in a regio- and stereoselective manner to obtain compounds either by way of S_N2 or S_N2' mechanisms, the latter of which includes the selective formation of *E* as well as *Z* isomers. These highly selective S_N2' reactions make it possible to synthesize geometrically controlled trisubstituted alkenes with a difluoromethyl group.

Supporting Information Available: Details of experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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