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Highly regio- and stereocontrolled brominations of *gem*-difluorinated vinyloxiranes

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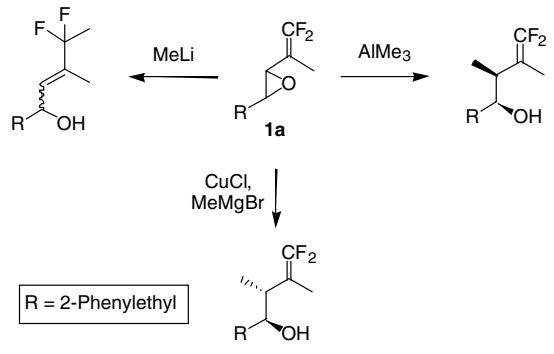
Abstract—*gem*-Difluorinated vinyloxiranes, which are useful synthetic intermediates for difluorinated compounds, were brominated regio- and stereoselectively. Introduction of bromide at the allylic epoxide carbon with inversion of stereochemistry was realized by $MgBr_2{\cdot}Et_2O$ to furnish an *anti vic*-bromohydrine, whereas the reaction with LiBr/AcOH afforded the other diastereomer selectively. Moreover, both reactions at high temperature allowed to obtain, the thermodynamically favored products, *E*-allylic alcohols dominantly.

Exploration of synthetic methods for fluorinated organic compounds with a high level of selectivity is one of the quite important issues because of their significant utilization in many fields.[1] Among fluorinated organic molecules, the incorporation of the CF_2–X (X = Br and Cl) moiety in an allylic position of intermediate synthons is one of the potent tools for the construction of more elaborate molecules. For instance, the *gem*-difluoroallylic metal species, easily derived from them by treatment with alkyllithium,[2] zinc,[3] or indium,[4] are well-known to react with carbonyl compounds regioselectively. On the other hand, S_N2 or S_N2' nucleophilic substitutions,[5] radical reactions,[6] and other reactions[7] of them are also well-established methods to prepare difluorinated molecules including biologically active compounds. However, general methods to synthesize compounds containing bromo- or chlorodifluoromethyl allylic group have not yet been investigated in detail. For instance, preparations of them by Wittg-type olefination sometimes encounter serious disadvantage in terms of olefinic stereochemistry. Tellier et al. reported stereoselective synthesis of such compounds by way of S_N2' reactions with thionyl bromide or chloride, but in their case the substitution of olefins are restricted; especially only one example of tri-substituted olefin is reported.[8]

Recently, we have reported regio- and stereocontrolled constructions of difluorinated compounds by utilization of selective alkylations of readily available *gem*-difluorinated vinyloxiranes **1** (Scheme 1).[9] For instance, a hard nucleophile like RLi reacted 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 of 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 of stereochemistry at the same carbon. Furthermore, very recently, we reported highly regio- and stereocontrolled reductions of them depending on



Scheme 1.

Keywords: Bromination; S_N2' reaction; S_N2 reaction; Inversion; Retention.
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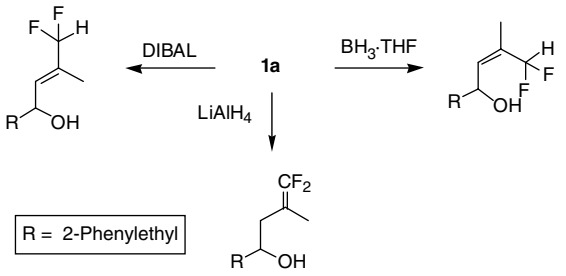
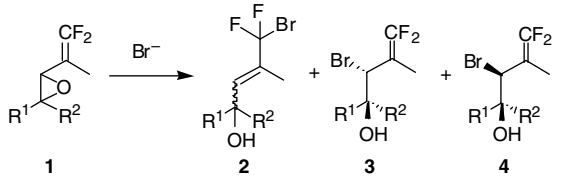
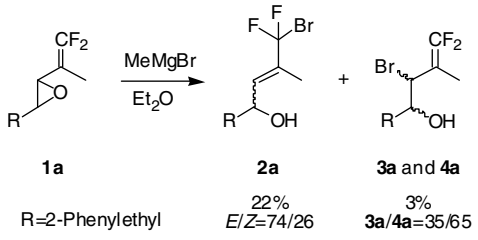


Scheme 2.



R^1 = 2-phenylethyl, R^2 = H: (**a**), R^1 = Ph, R^2 = H: (**b**),
R^1 = 4-Me-C_6H_4, R^2 = H: (**c**), R^1 = 4-NO_2-C_6H_4, R^2 = H: (**d**),
R^1 = H, R^2 = Ph: (**e**), R^1 = H, R^2 = 2-phenylethyl: (**f**)

Scheme 3.



Scheme 4.

the employed reagents (Scheme 2).[10] Thus, we turned our attention to the synthesis of useful synthon **2** by selective bromination of **1** (Scheme 3). In this letter, regio- and stereoselective brominations of *gem*-difluorinated vinyloxiranes **1** are described.

In the series of investigation of selective alkylations of **1**, we found that the reaction of **1a** with MeMgBr in Et_2O resulted in a complex mixture including brominated compounds **2a**, **3a**, and **4a** (Scheme 4). In situ generated $MgBr_2$ from Schlenk equilibrium of MeMgBr probably acted as a brominating reagent to afford such products.

Thus, at first, we treated **1a** with $MgBr_2$ in CH_2Cl_2 (Table 1, entry 1), and the anticipated brominated products **2a** and **4a** were obtained but low conversion was recorded; the recovery of **1a** was 64%. While complete consumption of **1a** was observed with $MgBr_2{\cdot}Et_2O$ to afford the desired **2a** in moderate yield (entry 2). Main reason responsible for the low yield is rearrangements[11] accompanied in the main process. Further investigation proved out that Lewis basic solvent effectively suppressed such undesired rearrangements and increased

Table 1. Site and stereoselective bromination of **1a** with 2.0 equiv of brominating reagent at 0 °C for 1–1.5 h

Entry	Reagent	Solvent	Yield[a] (%)			*E*/*Z* of **2a**[a]
			2a	**3a**	**4a**	
1	$MgBr_2$	CH_2Cl_2	27	<1	12	84/16
2	$MgBr_2{\cdot}Et_2O$	CH_2Cl_2	51	1	1	66/34
3		CH_3CN	1	99	1	>99/<1
4[b]			89	<1	<1	98/2
5[c]			>99	<1	<1	97/3
6[d]	LiBr/AcOH	CH_2Cl_2	5	4	91	56/44
7[c,d]		CH_3CN	91	<1	<1	98/2

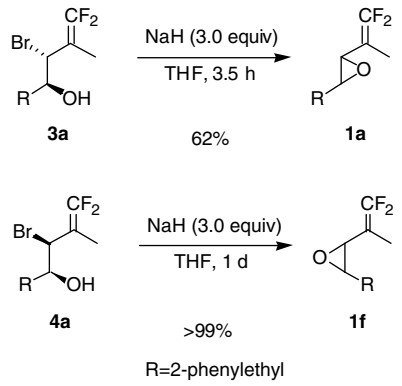
[a] Determined by ^{19}F NMR.
[b] The reaction was performed at rt for 3 days.
[c] The reaction was run at 100 °C.
[d] 3.0 equiv of LiBr and 2.0 equiv of AcOH were used.

the yield of S_N2 product **3a**, and that employment of CH_3CN as a solvent afforded **3a** in an excellent yield (entry 3). As far as we know, in the cases of halogenations of non-fluorinated vinyloxiranes, usually such *anti vic*-halohydrines as **3a** were obtained[12] while quite a few selective S_N2'-type halogenations are reported.[13] However, to our surprise, when the reaction mixture was stirred for a long time (3 days), a further reaction occurred to furnish the desired **2a** in an excellent yield (entry 4), implying that **3a** is kinetically and **2a** is thermodynamically favored product under the current conditions. Therefore, we conducted the reaction at higher temperature to lead a dramatic enhancement of the reaction rate (entry 5).

As an alternative method, we found that LiBr/AcOH system[12b–d,14] was effective for the selective bromination of **1**. Interestingly, although LiBr itself would not produce any product, the other diastereomer of **3a**, *syn vic*-bromohydrine **4a** was obtained as a major product under such system (entry 6). This stereochemical outcome could be accounted by the reaction going through a carbocationic intermediate.[15] Furthermore, as in the case of $MgBr_2{\cdot}Et_2O$, higher temperature produced *E*-**2a** as a main product (entry 7). It should be noted that **3a** and **4a** are relatively unstable; 20–30% of these products decomposed during purification by silica gel column chromatography.[8a]

To assign the stereochemistries of **3a** and **4a**, independent reactions of diastereomerically pure **3a** and **4a** with NaH (3.0 equiv) were performed. The former gave **1a**, while the corresponding *cis*-substituted *gem*-difluorinated vinyloxirane **1f** was formed quantitatively in the latter case (Scheme 5). These results led us to conclude unambiguously that the *anti* isomer **3a** was obtained dominantly from the reaction with $MgBr_2{\cdot}Et_2O$ and that the selective formation of the *syn* isomer **4a** was realized by LiBr/AcOH system.

Next, we investigated the generality of the selective brominations. Since **3** and **4** are not stable enough,[8a] other substrates **1b–e** were applied only to the S_N2' selective conditions (Table 2). Except for **1a**, bromination by $MgBr_2{\cdot}Et_2O$ (method A) did not give fruitful results presumably because both epoxide carbons are activated by



Scheme 5.

Table 2. Selective S_N2' bromination of **1** with $MgBr_2{\cdot}Et_2O$ or LiBr/AcOH

Entry	Substrate	Method[a]	Yield[b] (%)	Product	*E*/*Z*[c]
1	**1a**	A	93	**2a**	97/3
2		B	91		98/2
3	**1b**	A	28	**2b**	95/5
4		B	86		97/3
5	**1c**	A	28	**2c**	97/3
6		B	40		97/3
7	**1d**	B	96	**2d**	97/3
8	**1e**	A	22	**2b**	97/3
9		B	85		98/2

[a] Method A: $MgBr_2{\cdot}Et_2O$ (2.0 equiv)/CH_3CN, 100 °C, 1.5 h. Method B: LiBr (3.0 equiv), AcOH (2.0 equiv)/CH_3CN, 100 °C, 1 h.
[b] Isolated yield.
[c] Determined by ^{19}F NMR.

adjacent sp^2 system to bring about accompanying unfavorable rearrangement and regio- as well as stereorandom reactions (entries 3, 5, and 8). On the other hand, LiBr/AcOH system (method B) demonstrated superior results that excellent regio- and stereoselective bromination were realized to furnish bromodifluoromethylated allylic alcohols **2** in good to excellent yields (entries 2, 4, 7, and 9). However, the reaction of **1c** resulted in poor yield even by method B (entry 6). At the first stage of these S_N2' reactions, *vic*-bromohydrines **3** and **4** could be formed, and following S_N2'-type bromination or rearrangement would lead to the formation of the thermodynamically favored final product **2**. In the case of **1c**, regiorandom reaction at the first stage due to the strong cation stabilizing effect of 4-Me–C_6H_4 moiety at the benzylic epoxide carbon could decrease the yield of **2c**.

To assign the olefinic stereochemistry, independent NOE experiments of **2b** and **c** were performed. The results, in which both major isomer showed a peak correlation between the allylic H and allylic Me moiety, indicated that the *E* isomer was obtained predominantly in the current selective S_N2' brominations.

In summary, we found a highly regio- and stereoselective S_N2'-type bromination of *gem*-difluorinated vinyloxiranes **1** by LiBr/AcOH to afford synthetically useful bromodifluoromethylated olefines **2** with, in general, good *E* selectivity. At the same time, judicious choice of reagents and reaction conditions enabled the selective formation of S_N2 (either retention and inversion manner) products. Further investigations (other halogen introductions as well as the reactions with hetero-nucleophiles) are underway in our laboratory.

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