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Regio- and Stereoselective Reactions of *gem*-Difluorinated Vinyloxiranes with Heteronucleophiles

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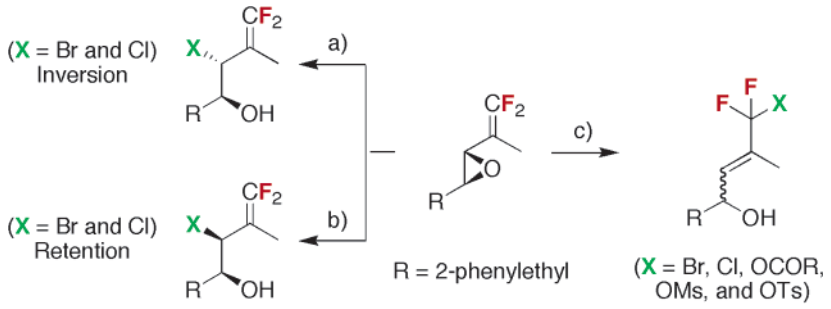

a) $MgBr_2 \cdot Et_2O$; Li_2CuCl_4. b) LiBr/AcOH; BCl_3.
c) $MgBr_2 \cdot Et_2O$ or LiBr/AcOH; LiCl/AcOH or BCl_3; Brønsted acids.

Regio- and stereoselectivity in reactions of *gem*-difluorinated vinyloxiranes with heteronucleophiles were successfully controlled. Halogen atoms were introduced regioselectively at the allylic epoxide carbon with an inversion in stereochemistry using $MgBr_2 \cdot Et_2O$ or Li_2CuCl_4 to produce *anti-vic*-halohydrine. The other diastereomers were obtained selectively using LiBr/AcOH or BCl_3, and S_N2' type products were formed selectively with excellent *E* preference by changing the reaction temperature. Moreover, a further investigation led us to find that a regio- and stereoselective S_N2' addition of several Brønsted acids was dependent on the pK_a values of the acids. Under strong acidic conditions, we exclusively obtained *E* allylic alcohols.

Introduction

Oxiranes are one of the most versatile building blocks in organic synthesis because their ring strain makes them prone to react with a large number of nucleophiles, electrophiles, acids, bases, and reducing and oxidizing reagents.[1] Their availability in optical active form, well-developed in the last two decades,[2] allows impressive access to well-stereodefined compounds with a variety of structures through regio- and stereoselective ring-opening reactions. Among them, regio- and stereoselective reactions of vinyloxiranes were extensively explored,[3] even though they possess three reaction sites for nucleophiles.

Recently, we have established a synthetic method for producing their fluorinated analogue, *gem*-difluorinated vinyloxirane **1** (Chart 1).[4] Systematic investigations of their reactions with nucleophiles were carried out, as high levels of stereocontrolled syntheses of fluorinated compounds with a desired structure are of significant importance for the utilization of the compounds in many fields.[5] Indeed, regio- and stereoselectivity for the reactions were controlled by the various reagents employed (Scheme 1).[4,6] For instance, RLi and monoalkylcopper

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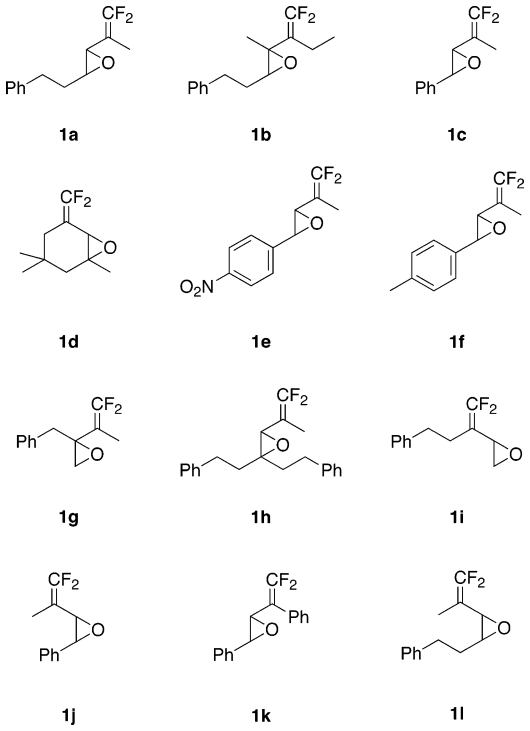
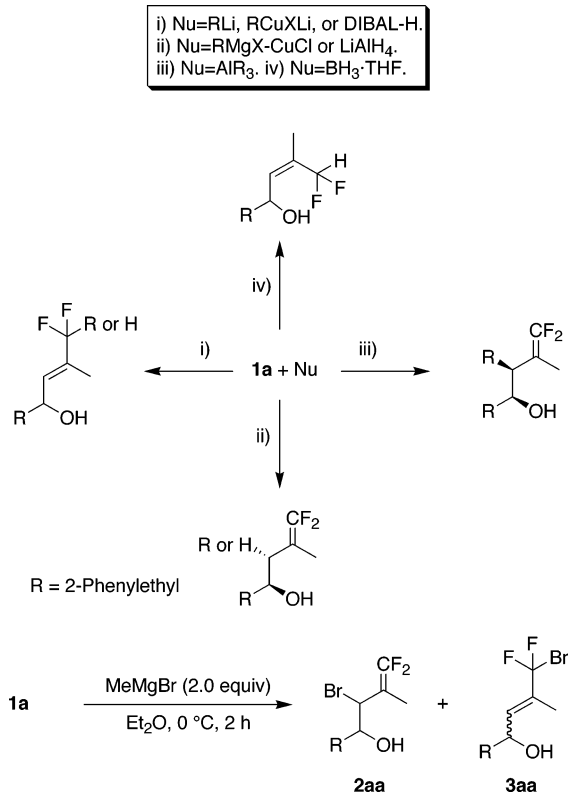
CHART 1. Various Difluorinated Vinyloxirane 1 Compounds



reagents reacted selectively at the terminal-fluorine-attached carbon via an S_N2' pathway to afford the corresponding allylic alcohols with *E* preference. The regio- as well as stereoselective alkyl group introduction through oxirane opening was realized at the allylic epoxide carbon, with retention or inversion in stereochemistry by AlR_3 or cuprates prepared from CuCl and RMgBr in a ratio of 1:3, respectively. Moreover, very recently, regio- and stereoselective reductions were realized using DIBAL-H for *E* allylic alcohols, BH_3·THF for *Z* allylic alcohols, or $LiAlH_4$ for homoallylic alcohols.

On the other hand, introduction of fluorine into molecules often significantly alters the molecules' reactivities as well as reaction outcomes. For instance, the reaction of **1a** with MeMgBr in Et_2O resulted in a complex mixture including brominated compounds (**2aa** and **3aa**), whereas alkylated products were obtained easily using nonfluorinated vinyloxiranes[7] (Scheme 1). In situ-generated $MgBr_2$ from the Schlenk equilibrium of MeMgBr probably acted as a brominating reagent to afford such products.

SCHEME 1



Products such as halohydrine **2** and allyl halide **3** could also be useful synthetic intermediates for constructions of fluorinated compounds, and selective transformations of the compounds such as **3** are especially well-explored. For instance, the *gem*-difluoroallylic metal species, easily derived by treatment with alkyllithium,[8] zinc,[9] or indium,[10] are well-known to react regioselectively with carbonyl compounds. On the other hand, S_N2 or S_N2' nucleophilic substitutions,[11] radical reactions,[12] and other reactions[13] of them are also well-established methods for preparing difluorinated molecules, including biologically active compounds. However, stereoselective syntheses of CF_2X (X = Br, Cl) containing olefins with a variety of substituents such as **3** are not explored in detail. For

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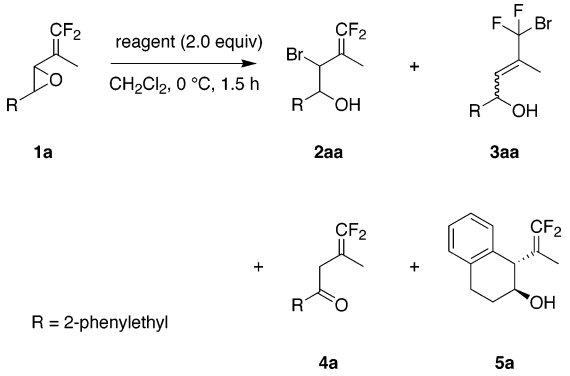
TABLE 1. Reaction of 1a with Brominating Reagents



entry	reagent	yield[a] (%) 2aa	3aa	4a	5a	*syn*/*anti* of **2aa**	*E*/*Z* of **3aa**	recovery of **1a** (%)
1	$MgBr_2$	12	27	3	<1	>99/<1	84/16	58
2	$MgBr_2{\cdot}Et_2O$	2	51	33	3	63/37	66/34	0
3	$ZnBr_2$	<1	26	3	36		98/2	0
4	$SnBr_2$	<1	55	<1	9		>99/<1	0
5	$AlBr_3$	<1	<1	<1	32			0
6	LiBr	<1	<1	<1	<1			>99
7[b]	LiBr	58	4	<1	<1	92/8	58/42	16
8	47% aq HBr	22	18	<1	<1	96/4	95/5	44
9	Br_2	complex mixture						

[a] Yields, ratios, and recoveries were determined by ^{19}F NMR. [b] The reaction was conducted at room temperature in the presence of AcOH (2.0 equiv).

instance, preparations of them by Wittig type olefination often encounter a serious disadvantage in terms of olefinic stereochemistry. Tellier and co-workers reported a stereoselective synthesis of such compounds by way of an S_N2' reaction with thionyl bromide or chloride.[14] However, in their case, the yields are sometimes quite low because of accompanying undesired acid fluorides. Moreover, the substitutions of olefins are restricted; only one example of trisubstituted olefin is reported. From such drawbacks, we turned our attention to the investigation of the selective halogenation of *gem*-difluorinated vinyloxirane **1**, and preliminary results of its selective bromination were reported in a preceding paper.[6b] In this article, besides the investigation of its stability under acidic conditions, we describe full details of the selective halogenation of *gem*-difluorinated vinyloxirane **1**.

Results and Discussion

Selective Bromination of *gem*-Difluorinated Vinyloxiranes. When **1a**, readily prepared from the corresponding α,β-epoxyketone,[4] was treated with $MgBr_2$, the anticipated brominated products were obtained but conversion was low (Table 1, entry 1). However, with $MgBr_2{\cdot}Et_2O$, **1a** was completely consumed to afford the S_N2' product **3aa** along with relatively large amounts of a rearranged compound[15] **4a** (entry 2). Thus, we performed several reactions using other brominating reagents. $ZnBr_2$ and $SnBr_2$ produced the mixture of the S_N2' adduct **3aa** and the intramolecular Friedel−Crafts type product **5a** (entries 3 and 4), whereas **5a** was obtained as a sole product from the reaction with $AlBr_3$ (entry 5). These results clearly indicated that a small difference in the Lewis acidity of brominating reagents would affect the reactivity of **1** as well as the reaction pathway. The use of LiBr by itself resulted in no reaction, whereas in the presence of AcOH *syn*-**2aa** was obtained selectively (entries 6 and 7). Further attempts using HBr and Br_2 resulted in poor selectivity and reactivity (entries 8 and 9). Among brominating reagents employed, $MgBr_2{\cdot}Et_2O$, $SnBr_2$, and the LiBr/AcOH system produced hopeful results. Because of the high toxicity of $SnBr_2$, the other two bromide sources were selected for further optimizations.

For the reaction of **1a** with $MgBr_2{\cdot}Et_2O$ at low temperature, a sufficient decrease in the formation of unfavorable **4a** was observed, although the regioselectivity was decreased and stereoselectivities of the products were unchanged (Table 2, entry 2). Noncoordinating solvents such as *n*-hexane and toluene dominately afforded the S_N2' product accompanied by relatively large amounts of **4a** (entries 3 and 4). In Et_2O the yield of **2aa** increased, but ratios were low (entry 5). The reaction was quite slow in THF, but high regio- and stereoselectivity were observed without any amounts of undesired **4a** and **5a** (entry 6). These different outcomes could be attributable to the donor strength of employed solvents. The donor strengths of solvents are in the order of *n*-hexane < CH_2Cl_2 < Et_2O < CH_3CN < THF.[16] When the reaction was

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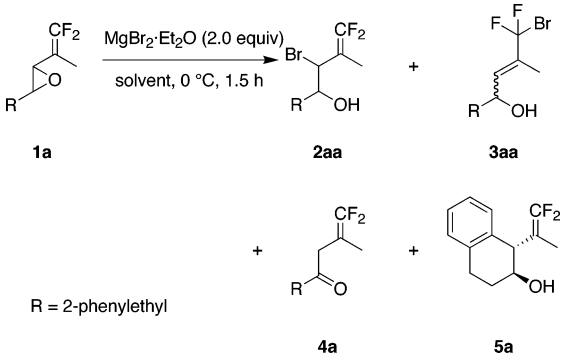
TABLE 2. Reaction of 1a with $MgBr_2 \cdot Et_2O$



		yield[a] (%)						
entry	solvent	**2aa**	**3aa**	**4a**	**5a**	*syn/anti* of **2aa**	*E/Z* of **3aa**	recovery of **1a** (%)
1	CH_2Cl_2	2	51	33	3	63/37	66/34	0
2[b]	CH_2Cl_2	49	31	<1	3	63/37	66/34	0
3	*n*-hexane	<1	41	46	<1		48/52	0
4	toluene	<1	47	43	<1		44/56	0
5	Et_2O	53	27	<1	<1	20/80	75/25	0
6[c]	THF	46	3	<1	<1	<1/>99	>99/<1	51
7	CH_3CN	99[d]	1	<1	<1	1/99	>99/<1	0
8[e]	CH_3CN	54	1	<1	<1	<1/>99	>99/<1	[f]
9[g]	CH_3CN	25	2	<1	<1	<1/>99	>99/<1	[f]
10[c,h]	CH_3CN	<1	89	<1	<1		98/2	0
11[i]	CH_3CN	<1	>99	<1	<1		97/3	0

[a] Yields, ratios, and recoveries were determined by ^{19}F NMR. [b] The reaction was run at −78 °C. [c] The reaction was performed at room temperature. [d] The pure *anti*-**2aa** was isolated in 76% yield. [e] $MgBr \cdot Et_2O$ (1.0 equiv) was used. [f] The remaining **1a** decomposed during workup. [g] $MgBr \cdot Et_2O$ (0.5 equiv) was used. [h] The reaction time was 3 days. [i] The reaction was run at 100 °C.

conducted in a solvent with a weak donating ability, the rearranged products **4a** and **5a** were formed as a result of the strong Lewis acidic aspect of magnesium. The stronger donor strength of a solvent led to the easier release of bromide from $MgBr_2$, affording the *anti*-**2aa** selectively. However, if the donation toward magnesium is too strong, as is the case for THF, low conversion was observed because of the decrease in the Lewis acidity for an activation of the epoxide moiety. Therefore, we performed the reaction in CH_3CN, which has a moderate donor strength, and which resulted in the formation of *anti*-**2aa** in an excellent yield (entry 7). We fixed it as a solvent, and examined the amount of reagent to find that the chemical yield of *anti*-**2aa** decreased according to the amount of $MgBr_2 \cdot Et_2O$ remaining (entries 8 and 9). As far as we know, in the case of halogenation of nonfluorinated vinyloxiranes, usually *vic*-halohydrines such as **2a** were obtained,[17] and quite a few selective S_N2' type halogenations are reported.[18] To our surprise, when we stirred the reaction mixture for a long time in CH_3CN, a

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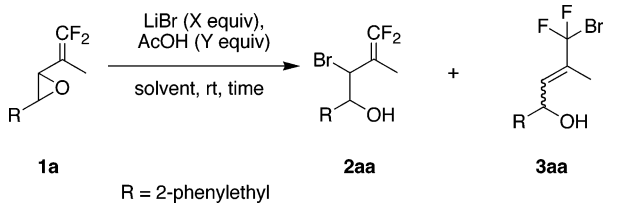
TABLE 3. Reaction of 1a with LiBr in the Presence of AcOH



					yield[a] (%)				
entry	solvent	*X*[b]	*Y*[c]	time	**2aa**	**3aa**	*syn/anti* of **2aa**	*E/Z* of **3aa**	recovery of **1a** (%)
1	*n*-hexane	1.0	1.0	1.5 h	16	6	17/83	>99/<1	55
2	Et_2O	1.0	1.0	1.5 h	26	5	18/82	81/19	33
3	CH_3CN	1.0	1.0	1.5 h	17	11	30/70	83/17	[d]
4	CH_2Cl_2	1.0	1.0	1.5 h	38	4	>99/<1	46/54	41
5	CH_2Cl_2	2.0	2.0	1.5 h	58	4	92/8	58/42	16
6	CH_2Cl_2	3.0	2.0	1.0 h	88	11	97/3	51/49	0
7[e]	CH_2Cl_2	3.0	2.0	1.0 h	95	5	96/4	56/44	0
8	CH_2Cl_2	3.0	3.0	3 days	8	82	51/49	92/8	0
9[f]	CH_3CN	3.0	2.0	1.0 h	<1	91		98/2	0

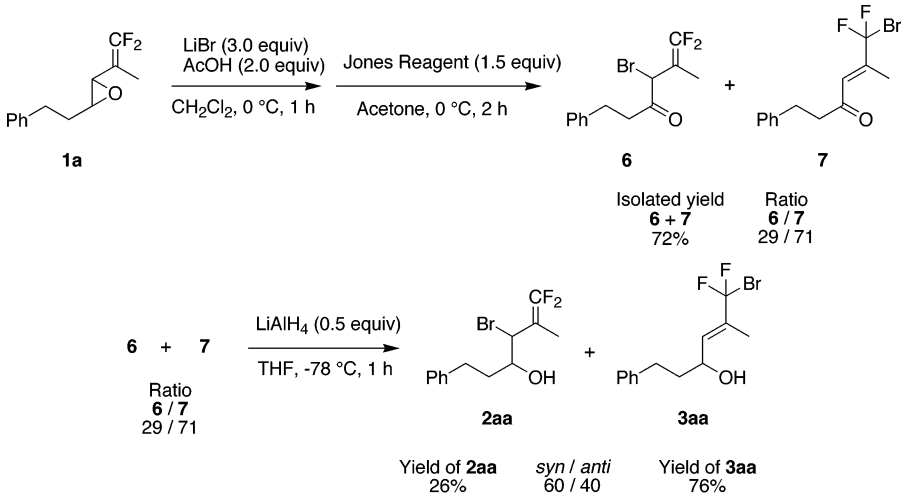
[a] Yields, ratios, and recoveries were determined by ^{19}F NMR. [b] Equivalents of LiBr. [c] Equivalents of AcOH. [d] The remaining **1a** decomposed during workup. [e] The reaction was run at 0 °C. [f] The reaction was run at 100 °C.

further reaction occurred to furnish the S_N2' product **3aa** without forming **2aa** at all (entry 10). This observation implies that **2aa** and **3aa** are kinetically and thermodynamically favored products, respectively, under the current conditions. Thus, we carried out the reaction at a high temperature to accelerate the reaction rate significantly (entry 11). The obtained **3aa** is relatively stable enough to isolate, whereas the bromohydrine *anti*-**2aa** partially decomposed during workup because of its inherent instability.[14a]

Next, we investigated the bromination of **1a** with LiBr in the presence of AcOH. The reactions were performed in several solvents to fix the number of equivalents of the reagents. Although substantial amounts of recovery of the starting material **1a** were observed in any solvent (Table 3, entries 1−4), the excellent *syn*-**2aa** selectivity was realized in CH_2Cl_2. The amounts of the reagents were examined to find out that at least 3.0 equiv of LiBr and 2.0 equiv of AcOH were necessary to consume all the starting **1a** completely in 1 h (entry 6). At a low temperature, although the desired *syn*-**2aa** was formed in an excellent yield (entry 7),the pure *syn*-**2aa** was isolated in 58% because of the inherent instability as in the case of the corresponding anti isomer. Interestingly, lithium cation was crucial for this reaction as both NaBr and KBr in the place of LiBr resulted in no reaction. As in the case with $MgBr_2 \cdot Et_2O$, a longer reaction time or higher temperature produced the *E* isomer of **3aa** selectively (entries 8 and 9). It should be noted that no rearranged products **4a** and **5a** were observed under this LiBr/AcOH system.

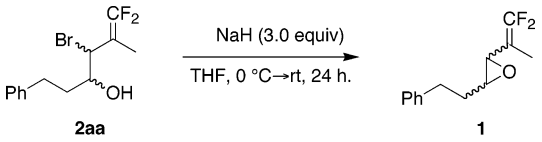
To verify that each **2aa** from $MgBr_2 \cdot E_2O$ and LiBr/AcOH is in the diastereomeric relationship, the crude reaction mixture from the latter conditions was oxidized by Jones reagent. Then, the obtained inseparable corresponding ketones **6** and **7** were reduced with $LiAlH_4$ to afford both diastereomers of **2aa** in a ratio of 60:40 along with **3aa** (Scheme 2). This result led us to conclude that each of them is in the diastereomeric relationship.

SCHEME 2



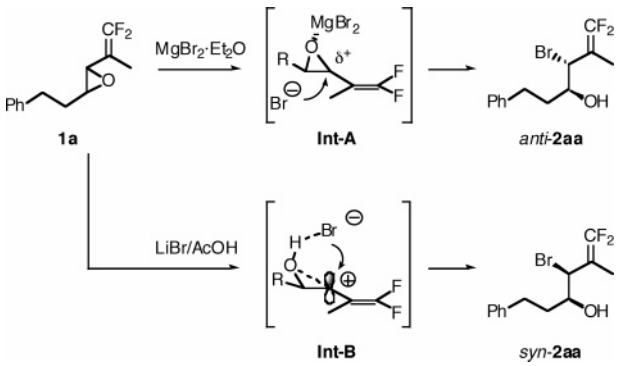
Yields and ratios were determined by ^{19}F NMR.

SCHEME 3



2aa	isolated yield (%)	*trans*/*cis*
2aa from $MgBr_2{\cdot}Et_2O$	>99: **1a**	>99/<1
2aa from LiBr/AcOH	>99: **1l**	<1/>99

SCHEME 4



Thus, to assign the stereochemistry of **2aa**, we performed intramolecular cyclizations of both diastereomerically pure **2aa** (Scheme 3). The **2aa** obtained by the reaction with $MgBr_2{\cdot}Et_2O$ gave **1a**, whereas the corresponding cis isomer **1l** was formed in the reaction using LiBr. This indicates that the *anti*-bromohydrine was obtained dominantly from the reaction with $MgBr_2{\cdot}E_2O$, whereas LiBr/AcOH furnished the corresponding syn isomer.

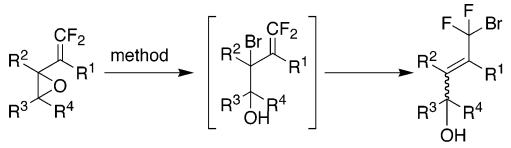
Plausible reaction mechanisms of these selective brominations were depicted in Scheme 4. Usually, oxirane-opening halogenations take place in an S_N2 manner.[17] As noted above, in the case of $MgBr_2{\cdot}Et_2O$, the *anti*-**2aa** was probably produced from **Int-A** by way of an S_N2 type reaction. However, it is proposed that the reaction of oxiranes with LiX/AcOH could involve a reversible-epoxide-opening reaction by a nucleophilic attack of a halide ion, and that a pK_a value of an intermediate alcoxide after opening of an epoxide is important for proceeding with this type of halogenation.[19] Bajwa and Anderson reported that PhOH and dimethylmalonate possess high enough pK_a values for such protonation of the intermediate alcoxide. However, in our case, no reaction was observed with PhOH or dimethylmalonate in the place of AcOH. Moreover, the stronger Brønsted acid *p*-TsOH (*p*-toluenesulfonic acid) afforded the corresponding S_N2' tosylated product (vide infra). Such experimental results clearly indicated that AcOH did not play a role in the protonation for the alcoxide intermediate but acted just for an activation of the epoxide moiety to produce a partially cationic intermediate **Int-B** in our case. This assumption was supported by the result of the reaction without a proton source (LiBr/AcOLi); complete recovery of **1a** was observed even after an extended time period (4 days). Moreover, the nonfluorinated epoxides usually yield only *anti*-halohydrins upon reaction using LiX/AcOH,[17b−d,19] whereas the syn isomer was formed selectively in our case. These different experimental facts indicated that not the reversible-epoxide-opening reaction postulated by Bajwa and Anderson[19a] but another reaction mechanism would be involved in our case; the **Int-B** that is strongly stabilized by the difluoropropylene moiety would be generated, and following bromination in a retention manner could produce *syn*-**2aa**. This hypothesis would be supported by the facts that carbocation intermediates derived from aromatic epoxides have a tendency to furnish corresponding retention-oxirane-opened products.[20]

As noted above, S_N2' type halogenations of vinyloxiranes are extremely rare.[18] Thus, to clarify the mechanism for producing the *E* isomer of **3aa**, the *anti*-**2aa** was stirred at room temperature in CH_3CN in the absence or presence of $MgBr_2{\cdot}Et_2O$ (2.0 equiv) for a few days (Scheme 5). The **3aa** was obtained in 96% yield in the latter case, whereas a quite low yield of **3aa** was observed

(19) (a) Bajwa, J. S.; Anderson, R. C. *Tetrahedron Lett.* **1991**, *32*, 3021. (b) Bartas-Yacoubou, J.-M.; Maduike, N.; Kyere, S.; Doan, L.; Whalen, D. L. *Tetrahedron Lett.* **2002**, *43*, 3781.

(20) Durham, D.; Kingsbury, C. A. *J. Chem. Soc., Perkin Trans. 2* **1986**, 923.

TABLE 4. Selective S_N2' Brominations of 1



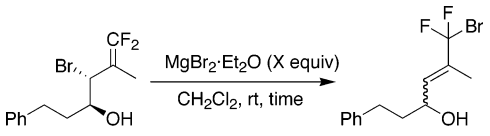
1 **2** **3**

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.

entry	1	method	isolated yield (%)	*E*/*Z*[a]	recovery (%)	entry	1	method	isolated yield (%)	*E*/*Z*[a]	recovery (%)
1	**1a**	A	93 (**3aa**)	97/3	0	11		B	40	97/3	0
2		B	91	98/2	0	12	**1g**	B	complex mixture		0
3	**1b**	A	complex mixture		0	13	**1h**	B	68 (**3ha**)	>99/<1	34
4		B	complex mixture		0	14	**1i**	A	15 (**3ia**)	>99/<1	0
5	**1c**	A	28 **3ca**	95/5	0	15		B	72	94/6	0
6		B	86	97/3	0	16	**1j**	A	22 (**3ca**)	97/3	0
7	**1d**	A	61 (**3da**)		13	17		B	85	98/2	0
8		B	85		0	18	**1k**	A	17 (**3ka**)	87/13	0
9	**1e**	B	96 (**3ea**)	97/3	0	19		B	58	91/9	5
10	**1f**	A	28 (**3fa**)	97/3	0						

[a] *E*/*Z* ratios and recoveries were determined by ^{19}F NMR.

SCHEME 5



anti-**2aa** **3aa**

X=	time	yield of **3aa** (%)	*E*/*Z*	recovery (%)
0	2 d	8	>99/<1	43
2.0	3 d	96	97/ 3	0

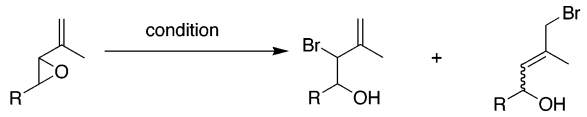
in the former case, implying that a further S_N2' type bromination to the generated **2aa** in the reaction media would take place to furnish **3aa**.

Next, to validate the scope and limitation of the use of **1** as a building block, we adopted various **1** to the standard S_N2' selective conditions (Table 4). Except for **1a** and **1d**, reactions with $MgBr_2{\cdot}Et_2O$ did not produce any fruitful results because of regiorandom reactions and/or rearrangements, whereas the desired **3** was furnished in good yields with excellent *E* preference in most of the cases under the LiBr/AcOH system. It was found that the steric effects of the R^2 moiety decreased the reaction rate for the reaction intermediate *vic*-halohydrine **2**, and brought about undesired reactions (entries 3, 4, and 12). In the case of **1f** (entries 10 and 11), the yield of **3f** was moderate as regiorandom reactions at the first stage of this reaction occurred because of the strong cation stabilizing effect of the 4-Me-C_6H_4 moiety at the benzylic epoxide carbon.

To verify the olefinic stereoselectivity of the S_N2' products, we performed independent NOE experiments with **3ca**, **3fa**, and **3ia**. Both major isomers of **3ca** and **4fa** showed a peak correlation between the allylic H and allylic Me moieties, and a cross-peak was found between the HOCH_2 moiety and R^1 in the case of **3ia**, indicating that the *E* isomer was furnished predominately in the current reaction.

Next, to understand the effect of the fluorine moiety on the reactions, we conducted the four reactions under

SCHEME 6



8 **9** **10**

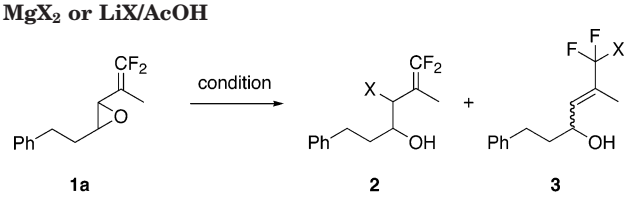
condition A: $MgBr{\cdot}Et_2O$ (2.0 equiv), CH_3CN, 0 °C, 1.5 h
condition B: $MgBr{\cdot}Et_2O$ (2.0 equiv), CH_3CN, 100 °C, 1.5 h
condition C: LiBr (3.0 equiv), AcOH (2.0 equiv), CH_2Cl_2, 0 °C, 1 h
condition D: LiBr (3.0 equiv), AcOH (2.0 equiv), CH_sCN, 100 °C, 1 h

condition	isolated yield (%) **9**	**10**	dr	*E*/*Z*	recovery of **6** (%)
A	17	–	<1/>99		74
B	<2	22	<1/>99	54/46	36
C	68	24	46/54	30/70	5
D	14	67	50/50	72/28	–

standard conditions using corresponding nonfluorinated vinyloxirane **8** (Scheme 6). In all cases, poorer reactivity and selectivities than those found for the fluorinated compound were observed. This difference in the reaction outcome could be attributable to the cation-stabilizing effect at allylic epoxide carbons. The difluoropropylene moiety could have a greater cation-stabilizing ability than that of the nonfluorinated one, which increases the reactivity of the epoxide moiety with the nucleophile. Furthermore, the cation-stabilizing effect could be an important factor for the determination of selectivities at the same time.

Next, we examined the introduction of other halogen atoms (I, Cl, and F) under the standard conditions (Table 5). Unfortunately, fluorine-adducted products were not obtained under any conditions. It was found that the stability of the halogenated products **2** and **3** was in the order of Cl > Br > I. The iodo-introduced products were too unstable to isolate (entries 1 and 2). The reaction with $MgCl_2$ was extremely slow at an ambient temperature, and under reflux condition almost all **1a** was consumed to afford **2ab** as a main product (entries 3 and 4). However, the cyclization of the obtained **2ab** with a base to epoxide afforded **1l** as a major product, indicating that

TABLE 5. Reaction of 1a with MgX_2 or LiX/AcOH

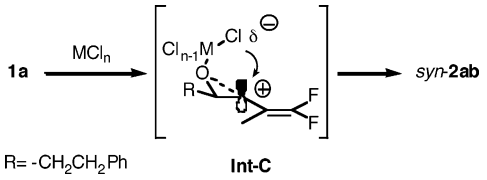


condition A: MgX_2 (2.0 equiv), CH_3CN, 0 °C, time
condition B: MgX_2 (2.0 equiv), CH_3CN, 100 °C, time
condition C: LiX (3.0 equiv), AcOH (2.0 equiv), CH_2Cl_2, 0 °C, time
condition D: LiX (3.0 equiv), AcOH (2.0 equiv), CH_sCN, 100 °C, time

				yield[a] (%)				
entry	reagent	condition	time	**2**	**3**	*syn/anti* of **2**	*E/Z* of **3**	recovery of **1a** (%)
1	MgI_2	A	1.5 h					61
2	LiI	C	10 min					0
3[b]	$MgCl_2$	A	22 h	4 (**2ab**)	<1	>99/<1		90
4	$MgCl_2$	B	1.5 h	70	(23) (**3ab**)	89/11	46/54	5
5	$MgCl_2$	B	9 h	<1	61[c]		85/15	0
6[b]	LiCl	C	20 h	66[c]	16	97/3	70/30	4
7	LiCl	D	24 h	4	71[c]	<1/>99	88/12	0
8[b]	MgF_2	A	24 h	<1	<1			>99
9[b]	LiF	C	24 h	<1	<1			>99

[a] Yields (except where noted), ratios, and recoveries were determined by ^{19}F NMR. [b] The reaction was run at room temperature. [c] These yields were not determined by ^{19}F NMR.

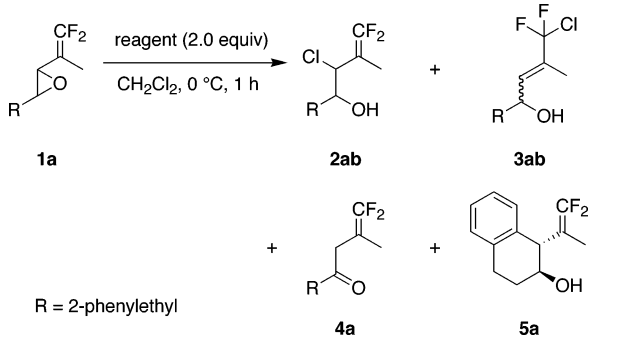
SCHEME 7



syn-**2ab** was the major isomer from this chlorination. In this case, an intramolecular chloride attack from $MgCl_2$ could be the major reaction pathway (Scheme 7). When the reaction time was extended (entry 5), the anticipated S_N2' product was obtained selectively. However, a sharp difference in the reactivity of lithium salts was observed under the LiX/AcOH system (methods C and D). The reactivity of lithium salts was in the order of LiI > LiBr > LiCl ≫ LiF, which coincided well with other reports.[17c,19] Only chlorinations demonstrated moderate results (entries 6 and 7).

Selective Chlorination of *gem*-Difluorinated Vinyloxirane. As noted above, chlorinated products **2ab** and **3ab** are more stable than brominated ones; however, chlorination of **1a** by $MgCl_2$ and LiCl/AcOH resulted in poor selectivities. Such drawbacks prompted us to investigate the chlorination in detail using various chlorinating reagents (Table 6). However, in most of the cases, desired chlorinated products were hardly obtained (entries 1−6). The stronger metal−Cl bond in chlorinating reagents could inhibit chloride's release, leading to low reactivity. Among them, $TiCl_4$ gave the highest yield of a tetrarol derivative **5a**, and further investigation proved that a stoichiometric amount of the reagent was enough to consume all of **1a** (isolated yield of **5a**: 85% in entry 6). Gaseous HCl, which has potential for a selective chlorination from the mechanistic consideration of the above bromination (Scheme 4), resulted in the formation of **2ab** with excellent syn selectivity (entry 7).[21] The *syn*-**2ab** was formed as a major product with BCl_3 (entry 8), and further investigations found a successive decrease

TABLE 6. Chlorination of 1a with Various Chlorinating Reagents

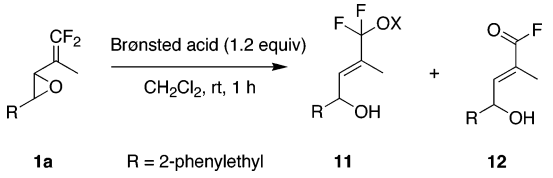


		yield[a] (%)						
entry	reagent	**2ab**	**3ab**	**4a**	**5a**	*syn/anti* of **2ab**	*E/Z* of **3ab**	recovery (%)
1	$ZnCl_2$	1	7	<1	<1	>99/<1	>99/<1	89
2	$SnCl_2$	18	20	<1	2	94/4	>99/<1	47
3	$AlCl_3$	<1	<1	6	21			0
4	$SnCl_4$	<1	<1	<1	34			
5	$TiCl_4$	<1	19	<1	81		90/10	0
6[b]	$TiCl_4$	<1	13	<1	87		>99/<1	0
7	HCl gas	79	21	<1	<1	>99/<1	74/26	0
8	BCl_3	58	9	<1	5	>99/<1	88/12	0
9[c]	BCl_3	86	5	<1	<1	>99/<1	36/64	0
10[c,d]	BCl_3	85	4	<1	<1	>99/<1	45/55	0
11[c,e]	BCl_3	<1	65	<1	<1		94/6	0
12[f]	Li_2CuCl_4	88	3	<1	<1	<1/>99	>99/<1	9

[a] Yields, ratios, and recoveries were determined by ^{19}F NMR. [b] $TiCl_4$ (1.0 equiv) was used. [c] In CH_3CN. [d] BCl_3 (1.0 equiv) was used. [e] The reaction was run at 100 °C for 8 h. [f] The reaction was run in THF at room temperature for 4 days.

in the amount of the reagent and an increase in the chemical yield (isolated yield of *syn*-**2ab**: 77% in entry 10). In this case, BCl_3 could work as an ambiphilic reagent to produce *syn*-**2ab** by way of **Int-C** (Scheme 7). As in the case of the bromination, a further chlorination to **2ab** would be anticipated. However, a longer reaction time at room temperature did not improve the ratio of

TABLE 7. Reaction of 1a with Brønsted Acids



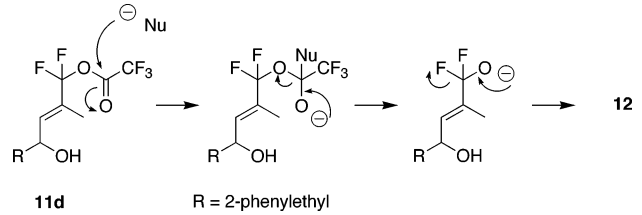
entry	Brønsted acid[a]	pK_a of XOH[b]	isolated yield (%)	recovery of **1a**[d] (%)
1	AcOH	4.756	<1	>99
2	PhCOOH	4.204	<1	>99
3	HCOOH	3.751	39[c] (**11a**)	58
4[d]	HCOOH	3.751	61[c]	0
5	MsOH		94 (**11b**)	0
6	*p*-TsOH·H_2O	2.544[e]	78 (**11c**)	0
7[f]	*p*-TsOH·H_2O	2.544[e]	94	0
8	TFA	0.50	84 (**12**)	0

[a] All reactions of **1a** (0.45 mmol) with Brønsted acids (1.2 equiv) were conducted in 5 mL of CH_2Cl_2. [b] pK_a values in water at 25 °C. [c] Determined by ^{19}F NMR. [d] The reaction time was 8.5 h. [e] The pK_a value is the one of benzenesulfonic acid. [f] The reaction was run in the presence of MS 4 Å.

2:**3** (after 3 days, **2ab**: 75% and **3ab**: 14%), probably because of the stronger C−Cl bond in **2ab**, whereas the S_N2' product **3ab** was formed selectively at a high temperature with higher stereoselectivity than that from LiCl/AcOH (Table 5, entry 7). On the other hand, by treatment with Li_2CuCl_4 prepared from LiCl and $CuCl_2$[17f,22] a selective S_N2 type reaction occurred to furnish *anti*-**2ab** in 83% isolated yield (entry 12). LiCl or $CuCl_2$ by itself did not produce any products, indicating that the copper species was the true reactive form in this reaction.

Reaction with Brønsted or Lewis Acids. As noted above, **1** did not react with a weak Brønsted acid such as AcOH whereas the S_N2' tosylated product was obtained by a strong acid TsOH. This different reaction outcome prompted us to examine the stability of **1** under Brønsted acidic conditions. We selected **1a** as a model substrate, and treated it with several Brønsted acids in CH_2Cl_2 (Table 7). Under relatively weak acidic conditions by AcOH or PhCOOH, no reaction occurred after 1 h of stirring (entries 1 and 2), and in the former case, complete recovery was observed even after 1 day. HCOOH decomposed some amount of **1a** in 1 h, affording the S_N2' product **11a** in moderate yield. A longer reaction time led to consumption of all the starting **1a**, but it was not easy to isolate **11a** from its partially decomposed product **12** (entries 3 and 4). With methanesulfonic acid (MsOH) and TsOH·H_2O (entries 5 and 6), a highly regio- and stereoselective S_N2' type reaction was observed to furnish difluoroallylsulfonate **11b**,**c**, whose utility as a building block was reported by us recently.[23] The moderate yield in the latter case could be attributable to decomposition of the product **11c** by H_2O from the employed reagent.

SCHEME 8



Thus, when the reaction was performed in the presence of MS 4 Å, the desired product was obtained in an excellent yield (entry 7). The stronger acid TFA (trifluoroacetic acid) demonstrated a higher reactivity for **1a**; however, only the acid fluoride **12** was isolated after the purification. It could be generated from decomposition of the desired product by nucleophilic attack at the highly activated carbonyl moiety (Scheme 8). The olefinic stereochemistry of **11** as *E* isomer was assigned by the NOESY spectroscopy of **11c**, which showed a peak correlation between the Me group and vinylic H. These results clearly indicated that **1** is not stable enough under strong acidic conditions to furnish S_N2' adducts of Brønsted acids smoothly, and relatively weak Brønsted acids whose pK_a are higher than 4.0 will not react with **1**.

On the other hand, a complex mixture was obtained when the reaction of nonfluorinated vinyloxirane **8** with MsOH was conducted. The selective S_N2' reaction of **1a** with Brønsted acids could be rationalized by the highly positive polarization at the terminal-fluorine-attached carbon in a carbocationic intermediate easily capturing the conjugated base of XOH.

1 is relatively unstable not only under Brønsted but also under Lewis acidic conditions. Thus as a comparison, in CH_2Cl_2 **1a** was treated with several Lewis acids: Sc(OTf)$_3$, Yb(OTf)$_3$, Zn(OTf)$_3$, and $LiClO_4$, whose strength as Lewis acids are in this order.[24] Under strong Lewis acidic conditions by Sc(OTf)$_3$, **1a** decomposed easily even in the presence of a catalytic amount of the Lewis acid. It was found that the rate of the decomposition of **1a** was clearly dependent on the strength of the employed Lewis acids, and **1a** was stable for a long time in the presence of $LiClO_4$. The above information with respect to the stability of *gem*-difluorinated vinyloxirane under Brønsted and Lewis acidic conditions will help us select reagents for avoiding unfavorable decomposition of **1** in reaction media.

Conclusion

In summary, reagent-dependent regio- and stereoselective reactions of *gem*-difluorinated vinyloxiranes **1** were realized. An S_N2 type halogenation at the allylic epoxide carbon occurred with $MgBr_2$·Et_2O for the bromination and Li_2CuCl_4 for the chlorination to afford the *anti-vic*-halohydrines, whereas the corresponding syn isomers were obtained selectively by LiBr/AcOH for the bromohydrine and BCl_3 for the chlorohydrine. The thermodynamically favored *E* allylic alcohols were formed selectively by way of a further bromination or chlorina-

(21) Oxirane-opening halogenations with retention of stereochemistry by gaseous HCl are reported. See: (a) Gilmore, A.; Lauret, C.; Roberts, S. M. *Tetrahedron* **2003**, *59*, 4363. (b) Adger, B. M.; Barkley, J. V.; Bergeron, S.; Cappi, M. W.; Flowerdew, B. E.; Jackson, M. P.; McCague, R.; Nugent, T. C.; Roberts, S. M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3501. (c) Berti, G.; Macchia, B.; Macchia, F.; Monti, L. *J. Chem. Soc. C* **1971**, 3371.

(22) Ciaccio, J. A.; Addess, K. J.; Bell, T. W. *Tetrahedron Lett.* **1986**, *27*, 3697.

(23) Yamazaki, T.; Hiraoka, S.; Sakamoto, J.; Kitazume, T. *Org. Lett.* **2001**, *3*, 743.

(24) (a) Fukuzumi, S.; Ohkubo, K.; Okamoto, T. *J. Am. Chem. Soc.* **2002**, *124*, 14147. (b) Fukuzumi, S.; Ohkubo, K. *J. Am. Chem. Soc.* **2002**, *124*, 10270. (c) Ohkubo, K.; Suenobu, T.; Imahori, H.; Orita, A.; Otera, J.; Fukuzumi, S. *Chem. Lett.* **2001**, 978. (d) Fukuzumi, S.; Ohkubo, K. *Chem.—Eur. J.* **2000**, *6*, 4532.

tion to the *vic*-halohydrine in an S_N2' manner. The reaction of **1a** with several Brønsted acids led us to find that Brønsted acids whose pK_a is lower than 4.0 can smoothly react regio- and stereoselectively at the fluorine-attached-terminal sp^2 carbon. These results indicate that **1** is one of the quite useful and versatile building blocks for synthesizing fluorine-containing compounds. Moreover, the products obtained by their highly regio- and stereocontrolled reactions possess further utilizations as synthetic intermediates through selective transformations.

Experimental Section

General Procedure for the Bromination of 1 with $MgBr_2$·Et_2O. The reaction of (*E*)-3,4-epoxy-1,1-difluoro-2-methyl-6-phenylhex-1-ene (**1a**) is described as a representative example. To a solution of **1a** (0.10 g, 0.45 mmol) in 5 mL of CH_3CN was added $MgBr_2$·Et_2O (0.23 g, 0.89 mmol) at 0 °C under argon. After stirring the mixture for 1.5 h at that temperature, we quenched the reaction with water, and the organic layer was extracted with Et_2O three times and dried over anhydrous $MgSO_4$. Removal of the solvents and purification with silica gel column chromatography (*n*-hexane:AcOEt = 4:1) afforded the desired pure *anti*-**2aa** in 76% yield.

3aa was obtained in 93% yield when the reaction was run at 100 °C for 1.5 h.

4-Bromo-6,6-difuruoro-5-methyl-1-phenylhex-5-en-3-ol (*anti*-2aa): ^{1}H NMR δ 1.75 (3 H, dd, J = 3.30, 3.02 Hz), 1.73−1.86 (1 H, m), 2.04 (1 H, dddd, J = 13.7, 9.61, 6.87, 3.02 Hz), 2.70 (1 H, ddd, J = 13.7, 9.34, 6.87 Hz), 2.88 (1 H, ddd, J = 13.8, 9.61, 5.21 Hz), 3.87 (1 H, ddd, J = 9.34, 6.32, 3.02 Hz), 4.82 (1 H, ddd, J = 6.31, 2.47, 0.82 Hz), 7.18−7.34 (5 H, m); ^{19}F NMR δ 71.7 (1 F, dquint, J = 37.3, 3.02 Hz), 73.4 (1 F, dq, J = 37.9, 3.45 Hz); ^{13}C NMR δ 9.32 (t, J = 1.15 Hz), 32.0, 35.6, 54.4 (dd, J = 6.01, 0.86 Hz), 73.2 (dd, J = 1.72, 1.71 Hz), 86.0 (dd, J = 21.5, 14.6 Hz), 126.0, 128.3, 128.4, 141.1, 153.1 (dd, J = 289.7, 288.0 Hz); IR (neat) ν 700, 747, 856, 911, 1106, 1227, 1288, 1388, 1455, 1496, 1603, 1734, 1803, 2341, 2360, 2862, 2931, 3027, 3063, 3086, 3453 cm^{-1}.

General Procedure for the Bromination of 1 with LiBr in the Presence of AcOH. The reaction of (*E*)-3,4-epoxy-1,1-difluoro-2-methyl-6-phenylhex-1-ene (**1a**) is described as a representative example. To a solution of **1a** (0.10 g, 0.45 mmol) and LiBr (0.12 g, 1.34 mmol) in 5 mL of CH_2Cl_2 was added AcOH (0.05 mL, 0.89 mmol)at 0 °C under argon. After 1 h of stirring, we quenched the reaction with saturated aq $NaHCO_3$, and the organic layer was extracted with CH_2Cl_2 three times and dried over anhydrous $MgSO_4$. Removal of the solvents and purification with silica gel column chromatography (*n*-hexane:AcOEt = 4:1) afforded the desired pure *syn*-**2aa** in 58%.

3aa was obtained in 91% yield when the reaction in CH_3CN was run at 100 °C for 1.0 h.

4-Bromo-6,6-difuruoro-5-methyl-1-phenylhex-5-en-3-ol (*syn*-2aa): ^{1}H NMR δ 1.56 (3 H, dd, J = 3.30, 3.02 Hz), 1.58−1.83 (2 H, m), 2.72 (1 H, ddd, J = 13.7, 8.52, 7.97 Hz), 2.89 (1 H, ddd, J = 13.7, 9.07, 5.22 Hz), 3.71 (1 H, tdd, J = 9.06, 3.29, 1.10 Hz), 4.87 (1 H, ddd, J = 9.06, 2.20, 1.10 Hz), 7.17−7.35 (5 H, m); ^{19}F NMR δ 71.7 (1 F, dquint, J = 35.3, 3.02 Hz), 74.5 (1 F, dq, J = 35.3, 3.44 Hz); ^{13}C NMR δ 8.41 (t, J = 1.15 Hz), 31.9, 34.8, 60.1 (dd, J = 6.02, 0.86 Hz), 72.0 (dd, J = 2.77, 1.44 Hz), 86.3 (dd, J = 22.3, 15.5 Hz), 126.0, 128.4, 128.4, 141.1, 152.8 (t, J = 289.4 Hz); IR (neat) ν 700, 749, 778, 856, 925, 971, 1030, 1071, 1109, 1228, 1287, 1388, 1455, 1496, 1603, 1739, 1802, 1869, 1943, 2346, 2363, 2863, 2930, 3027, 3063, 3086, 3447 cm^{-1}.

6-Bromo-6,6-difuruoro-5-methyl-1-phenylhex-4-en-3-ol (3aa): IR (neat) ν 700, 748, 853, 903, 967, 1030, 1129, 1249, 1387, 1455, 1496, 1603, 1669, 1700, 1802, 1943, 2861, 2929, 3027, 3063, 3086, 3338 cm^{-1}. Anal. Calcd for $C_{13}H_{15}BrF_2O$: C, 51.17; H, 4.95. Found: C, 50.91; H, 4.70. ***E* isomer:** ^{1}H NMR δ 1.75−1.88 (1 H, m), 1.82 (3 H, d, J = 1.37 Hz), 1.99 (1 H, dddd, J = 14.0, 8.79, 7.69, 6.59 Hz), 2.69 (1 H, ddd, J = 14.0, 9.07, 6.59 Hz), 2.75 (1 H, ddd, J = 13.7, 8.80, 6.32 Hz), 4.39 (1 H, m), 6.00 (1 H, dsex, J = 8.25, 1.37 Hz), 7.17−7.34 (5 H, m); ^{19}F NMR δ 111.5 (1 F, d, J = 147.4 Hz), 112.2 (1 F, d, J = 147.4 Hz); ^{13}C NMR δ 12.2 (dd, J = 2.00, 1.43 Hz), 31.3, 38.1 (t, J = 0.86 Hz), 67.2, 119.5 (t, J = 304.3 Hz), 126.0, 128.2, 128.4, 131.9 (t, J = 7.15 Hz), 133.4 (dd, J = 20.0, 19.8 Hz), 140.9. ***Z* isomer:** ^{1}H NMR δ 1.73−2.06 (2 H, m), 1.90 (3 H, s), 2.59−2.85 (2 H, m), 4.72 (1 H, m), 5.50 (1 H, m), 7.17−7.34 (5 H, m); ^{19}F NMR δ 117.9 (1 F, d, J = 152.5 Hz), 120.4 (1 F, dd, J = 154.5, 2.59 Hz); ^{13}C NMR δ 18.6 (t, J = 3.72 Hz), 31.5, 38.2 (m), 67.2 (dd, J = 4.29, 4.01 Hz), 118.4 (dd, J = 306.0, 304.9 Hz), 125.8, 128.3, 132.7 (dd, J = 21.5, 21.2 Hz), 136.0 (dd, J = 3.15, 2.00 Hz), 141.3.

Synthesis of *syn*-4-Chloro-6,6-difuruoro-5-methyl-1-phenylhex-5-en-3-ol (*syn*-2ab). BCl_3 (0.45 mmol) was added to a mixture of **1a** (0.10 g, 0.45 mmol) and 5 mL of CH_3CN, and the reaction mixture was stirred at 0 °C for 1 h. The reaction was then quenched with water, and the organic layer was extracted with Et_2O three times and dried over anhydrous $MgSO_4$. Removal of the solvents and purification with silica gel column chromatography (*n*-hexane:AcOEt = 4:1) afforded the desired pure *syn*-**2ab** in 77%.

3ab was obtained in 65% yield when the reaction in CH_3CN was run at 100 °C for 8 h.

***syn*-4-Chloro-6,6-difuruoro-5-methyl-1-phenylhex-5-en-3-ol (*syn*-2ab):** ^{1}H NMR δ 1.53 (3 H, dd, J = 3.30, 3.02 Hz), 1.60−1.81 (2 H, m), 2.71 (1 H, ddd, J = 13.7, 8.24, 7.97 Hz), 2.89 (1 H, ddd, J = 13.7, 8.52, 5.50 Hz), 3.69 (1 H, tdd, J = 8.79, 3.84, 1.10 Hz), 4.69 (1 H, ddd, J = 8.79, 2.48, 1.10 Hz), 7.17−7.34 (5 H, m); ^{19}F NMR δ 71.4 (1 F, dquint, J = 39.2, 3.02 Hz), 73.1 (1 F, dq, J = 39.2, 3.02 Hz); ^{13}C NMR δ 7.59 (dd, J = 1.43, 1.15 Hz), 31.7, 34.7, 65.3 (dd, J = 6.29, 1.43 Hz), 72.1 (dd, J = 2.86, 1.43 Hz), 85.4 (dd, J = 21.8, 15.5 Hz), 126.0, 128.4, 128.4, 141.1, 153.4 (dd, J = 288.9, 288.3 Hz); IR (neat) ν 669, 700, 749, 781, 926, 973, 1030, 1073, 1091, 1115, 1227, 1286, 1389, 1455, 1497, 1604, 1746, 1870, 2345, 2364, 2929, 3028, 3063, 3447, 3568 cm^{-1}. Anal. Calcd for $C_{13}H_{15}ClF_2O$: C, 59.89; H, 5.80. Found: C, 60.01; H, 6.25.

6-Chloro-6,6-difuruoro-5-methyl-1-phenylhex-4-en-3-ol (3ab): IR (neat) ν 669, 699, 715, 748, 865, 922, 973, 1071, 1131, 1251, 1388, 1454, 1496, 1604, 1803, 1870, 1943, 2346, 2363, 2862, 2930, 3028, 3063, 3337 cm^{-1}. Anal. Calcd for $C_{13}H_{15}ClF_2O$: C, 59.89; H, 5.80. Found: C, 60.33; H, 5.61. ***E* isomer:** ^{1}H NMR δ 1.75−2.09 (2 H, m), 1.81 (3 H, d, J = 1.38 Hz), 2.63−2.85 (2 H, m), 4.40 (1 H, m), 6.02 (1 H, dsex, J = 7.14, 1.37 Hz), 7.16−7.35 (5 H, m); ^{19}F NMR δ 105.5 (1 F, ddd, J = 156.4, 1.72, 1.30 Hz), 106.3 (1 F, ddd, J = 156.0, 1.72, 1.29 Hz); ^{13}C NMR δ 11.8 (dd, J = 2.00, 1.72 Hz), 31.3, 38.2 (t, J = 0.86 Hz), 67.2, 125.9, 126.6 (dd, J = 290.0, 289.3 Hz), 128.2, 128.3, 131.6 (t, J = 22.9 Hz), 132.6 (dd, J = 6.87, 6.58 Hz), 140.9. ***Z* isomer:** ^{1}H NMR δ 1.75−2.09 (2 H, m), 1.91 (3 H, d, J = 1.37 Hz), 2.63−2.85 (2 H, m), 4.73 (1 H, m), 5.56 (1 H, m), 7.16−7.35 (5 H, m); ^{19}F NMR δ 112.6 (1 F, d, J = 159.0 Hz), 114.4 (1 F, dd, J = 159.8, 2.58 Hz); ^{13}C NMR δ 18.8 (dd, J = 3.72, 3.44 Hz), 31.5, 38.4, 67.2, 125.8, 126.1 (dd, J = 294.9, 289.2 Hz), 128.3, 128.3, 131.1 (dd, J = 24.6, 24.3 Hz), 136.5 (dd, J = 2.87, 2.01 Hz), 141.3.

Intramolecular Cyclization of 1a with $TiCl_4$. $TiCl_4$ (0.049 mmol, 0.45 mmol) was added to a mixture of **1a** (0.10 g, 0.45 mmol) and 5 mL of CH_2Cl_2, and the reaction mixture was stirred at 0 °C for 1 h. The reaction was then quenched with aqueous 3 N HCl, and the organic layer was extracted with CH_2Cl_2 three times and dried over anhydrous $MgSO_4$. Removal of the solvents and purification with silica gel column chromatography (*n*-hexane:AcOEt = 4:1) afforded the desired pure **5a** in 85%.

***trans*-2-Hydroxy-1-(1,1-difluoroprop-1-en-2-yliden)-1,2,3,4-tetrahydronaphthalene (5a):** ^{1}H NMR δ 1.44 (3 H, dd, J = 3.29, 3.18 Hz), 1.86 (1 H, dddd, J = 12.3, 11.2, 9.37, 7.44 Hz), 2.24 (1 H, m), 2.88−2.98 (2 H, m), 3.71 (1 H, brd, J = 8.54 Hz), 3.86 (1 H, td, J = 8.55, 2.17 Hz), 7.03−7.24 (4 H,

m); ^{19}F NMR δ 66.1 (1 F, dq, J = 51.1, 3.81 Hz), 70.5 (1 F, dquint, J = 51.1, 3.05 Hz); ^{13}C NMR δ 8.56 (dd, J = 3.43, 1.71 Hz), 28.5, 31.2, 47.3 (d, J = 2.86 Hz), 68.8 (dd, J = 2.42, 1.56 Hz), 84.6 (t, J = 17.2 Hz), 126.2, 126.4, 128.0, 128.6, 134.3, 136.3, 155.4 (dd, J = 284.9, 282.9 Hz); IR (neat) ν 744, 768, 789, 841, 863, 886, 906, 956, 976, 1037, 1072, 1107, 1157, 1184, 1215, 1270, 1388, 1438, 1451, 1488, 1754, 1923, 2346, 2362, 2931, 3020, 3062, 3366 cm^{-1}. Anal. Calcd for $C_{13}H_{14}F_2O$: C, 69.63; H, 6.29. Found: C, 69.15; H, 6.68.

Synthesis of *anti*-4-Chloro-6,6-difuruoro-5-methyl-1-phenylhex-5-en-3-ol (*anti*-2ab). After 30 min of stirring the mixture of LiCl (0.076 g, 1.78 mmol) and $CuCl_2$ (0.120 g, 0.89 mmol) in 2 mL of THF at room temperature under an Ar atmosphere to generate Li_2CuCl_4, we added **1a** (0.10 g, 0.45 mmol) to the flask with the aid of 3 mL of THF, and the reaction mixture was stirred at room temperature for 4 days. The reaction was then quenched with aq NH_4Cl, and the organic layer was extracted with Et_2O three times and dried over anhydrous $MgSO_4$. Removal of the solvents and purification with slica gel column chromatography (*n*-hexane:AcOEt = 4:1) afforded the desired pure *anti*-**2ab** in 83%.

***anti*-4-Chloro-6,6-difuruoro-5-methyl-1-phenylhex-5-en-3-ol (*anti*-2ab):** ^{1}H NMR δ 1.54−1.69 (1 H, m), 1.56 (3 H, dd, J = 3.30, 3.02 Hz), 1.77−1.93 (2 H, m), 2.55 (1 H, ddd, J = 13.7, 9.61, 7.14 Hz), 2.73 (1 H, ddd, J = 13.7, 9.89, 5.22 Hz), 3.65 (1 H, ddd, J = 9.34, 6.32, 3.02 Hz), 4.49 (1 H, dd, J = 6.32, 2.48 Hz), 7.02−7.20 (5 H, m); ^{19}F NMR δ 71.5 (1 F, dquint, J = 41.2, 3.05 Hz), 73.0 (1 F, ddd, J = 41.2, 6.89, 3.82 Hz); ^{13}C NMR δ 8.34 (t, J = 1.15 Hz), 31.9, 35.1, 61.0 (dd, J = 6.01, 1.15 Hz), 72.9 (dd, J = 1.72, 1.72 Hz), 85.1 (dd, J = 21.2, 14.6 Hz), 126.0, 128.3, 128.4, 141.1, 153.7 (dd, J = 287.3, 287.2 Hz); IR (neat) ν 698, 748, 768, 922, 1030, 1072, 1111, 1227, 1288, 1389, 1454, 1497, 1605, 1748, 2342, 2365, 2662, 2932, 3028, 3063, 3445, 3464, 3568 cm^{-1}. Anal. Calcd for $C_{13}H_{15}ClF_2O$: C, 59.89; H, 5.80. Found: C, 60.03; H, 6.24.

General Procedure of the Reaction of 1a with Brønsted Acids. The reaction with MsOH is described as a representative example. To the flask containing 4 mL of dry CH_2Cl_2 and **1a** (0.10 g, 0.45 mmol) was added MsOH (0.035 mL, 0.53 mmol) at room temperature under argon, and the mixture was kept stirring for 1 h. The reaction was then quenched with saturated aq $NaHCO_3$. The organic layer was extracted with CH_2Cl_2 three times, and the combined organic layer was dried over anhydrous $MgSO_4$. After removal of solvents and purification by silica gel column chromatography (*n*-hexane:AcOEt = 4:1), the desired **11b** was obtained in 94%.

***(E)*-1,1-difluoro-4-hydroxy-2-methyl-6-phenylhex-2-enyl methanesulfonate (11b):** ^{1}H NMR δ 1.73−1.88 (1 H, m), 1.77 (3 H, d, J = 1.37 Hz), 1.98 (1 H, m), 2.69 (1 H, ddd, J = 14.0, 8.51, 6.86 Hz), 2.76 (1 H, ddd, J = 14.0, 9.34, 6.32 Hz), 3.25 (3 H, s), 4.42 (1 H, m), 6.11 (1 H, dq, J = 8.52, 1.38 Hz), 7.15−7.35 (5 H, m); ^{19}F NMR δ 90.1 (s); ^{13}C NMR δ 11.3 (dd, J = 2.00, 1.72 Hz), 31.2, 38.0, 41.1, 67.0, 121.9 (t, J = 272.8 Hz), 125.8, 127.1 (t, J = 26.6 Hz), 128.2, 128.3, 135.5 (dd, J = 6.30, 6.01 Hz), 141.0; IR (neat) ν 702, 733, 779, 845, 891, 961, 1030, 1049, 1142, 1200, 1238, 1265, 1335, 1381, 1416, 1454, 1497, 1605, 1709, 2365, 2862, 2940, 3028, 3406, 3553 cm^{-1}. Anal. Calcd for $C_{14}H_{18}F_2O_4S$: C, 52.49; H, 5.66. Found: C, 52.26; H, 5.53.

Supporting Information Available: Reactions of **1a** with Lewis acids (Table S1), 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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