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1,2- and 1,3-*O,O*-Silyl Migration Reactions of Fluorine-Containing Monosilylated Diols

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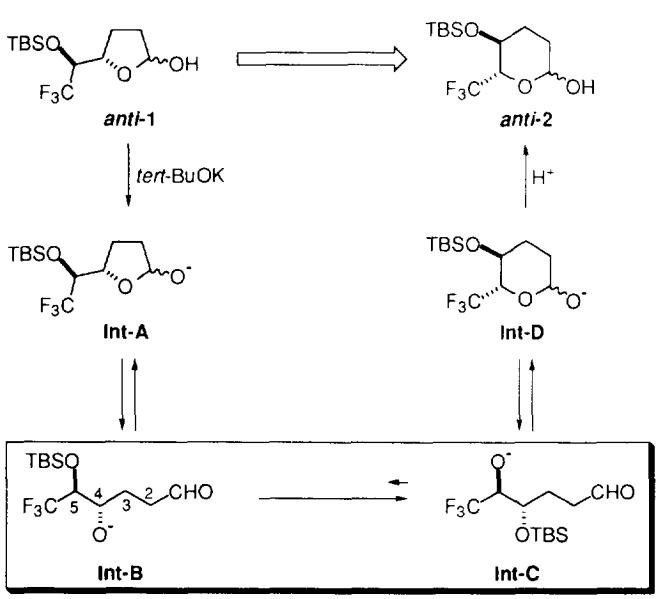
Abstract: 1,2- as well as 1,3-*O,O*-silyl migration was investigated in detail to successfully clarify that these reaction pathways proceeded so as to yield alkoxides stabilized by strongly electronwithdrawing fluorine-containing methyl groups rather than the sterically less demanding counterparts.

Introduction

We have recently developed the efficient routes to access optically active 6-deoxy-6,6,6-trifluoro-sugars from enzymatically resolved secondary alcohols with a trifluoromethyl (CF_3) moiety.[1-3] This process contained such an attractive key process as 1,2-*O,O*-silyl migration reaction playing a significantly important role for successfully reducing the reaction steps (see Scheme 1). Thus, it might take seven steps or more for the conversion of ***anti*-1** to ***anti*-2** via the troublesome protection-deprotection steps, while the present transformation required only the addition of an equimolar amount of *tert*-BuOK to ***anti*-1**. This base might produce the cyclic alkoxide **Int-A**, which would be in equilibrium with the corresponding acyclic form, **Int-B**. At this stage, if migration of a *tert*-butyldimethylsilyl (TBS) group was occurred from the original 5 position to the neighboring 4 position, then the desired pyranose, ***anti*-2** would be produced by recyclization of the resultant alkoxide **Int-C**. This consecutive transformation was expected from the consideration that a CF_3 group is known to display



Scheme 1 1,2-*O,O*-Silyl Migration Employed for the One-pot Conversion of ***anti*-1** to ***anti*-2**

strong electronwithdrawing ability and the report on its steric bulkiness equivalent to a nonfluorinated isopropyl group.[4] Thus, alkoxide at 5 position would be less nucleophilic and more stable than the one at 4 position and the conversion from **Int-B** to **Int-C** would be reasonable under thermodynamically controlled conditions. This was actually the case and the one-pot quantitative conversion of ***anti*-1** to ***anti*-2** was smoothly realized at -78 ℃ in THF for 3 h.[1d]

This interesting reaction has known for more than 20 years for nonfluorinated counterparts (especially the ribose part of nucleosides),[5,6] and Multzer and coworker[7] recently reported their work from the mechanistic point of view. However, to the best of our knowledge, very few examples have been appeared in the literature on the corresponding 1,3-*O*,*O*-silyl migration.[8] Then, we have started our research on the computational analysis of our 1,2-*O*,*O*-silyl migration,[1c,d] and, moreover, this concept was extended to the corresponding 1,3-system, both of these data are reported in detail here.

Calculation methods

Calculations were performed by CAChe MOPAC v. 94.0 based on MOPAC v. 6.0 implemented in CAChe Worksystem (SONY/Tektronix Corporation). Conformers, obtained from the rigid search method with rotating the free single bond in 15° increment, were optimized with CAChe mechanics v. 3.5 and further with CAChe MOPAC (AM1) by the eigenvector following minimization (EF) method with the extra keyword "PRECISE", final gradient norm being less than 0.01 kcal/Å. The obtained conformers were also employed for the vibrational frequency calculation for their confirmation as the stationary points.

In the case of *ab initio* calculations, all geometries were fully optimized without imposing any symmetry constraints at the restricted Hartree-Fock level by using gradient optimization techniques and 6-31G* basis set incorporated in the Gaussian 92 package of program.[9] In addition, single-point second-order Møller-Plesset (MP2[10]) energies as well as vibrational frequencies were calculated for all the optimized conformers with this basis set, the latter clearly demonstrating the obtained conformers as the stationary points.

Results and Discussion

Computational Study: At first, *ab initio* molecular orbital calculations were carried out for alkoxides **3a** to **6a** and silyl ethers **3b** to **6b**. Comparison of **6a** + **3b** and **6b** + **3a** would be considered as the most

Table 1. *Ab initio* Calculation of the Model System

$CH_3CH_2O^-$ + $CH_{3-n}F_nCH_2OSiH_3$ ⟶ $CH_{3-n}F_nCH_2O^-$ + $CH_3CH_2OSiH_3$

6a | **3b** (n=3), **4b** (n=2), **5b** (n=1) | **3a** (n=3), **4a** (n=2), **5a** (n=1) | **6b**

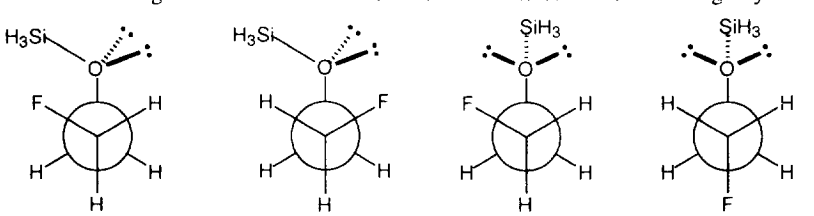
n	Calculated Energy[a] (hartree) $CH_{3-n}F_nCH_2OSiH_3$	$CH_{3-n}F_nCH_2O^-$	ΔE^b (kcal/mol)
0	-444.7116469 (-444.195419)	-153.8789184 (-153.429572)	---
1	-543.7251435 (-543.043187)	-252.9060874 (-252.293268)	8.58 (9.99)
2	-642.7556457 (-641.908142)	-351.9462486 (-351.166932)	14.64 (15.46)
3	-741.7950216 (-740.780757)	-450.9952929 (-450.049465)	20.71 (21.68)

a) Energy was obtained by single point calculation (MP2/6-31G*//HF/6-31G*) of the fully optimized conformers with the HF/6-31G* basis set whose energy values described in the parentheses. b) ΔE=(**6a**+**3**~**5b**) - (**6b**+**3**~**5a**).

simplified form of the 1,2-migration shown in Scheme 1, and other fluorinated materials **4** and **5** were also employed for this calculation to clarify the relationship between the stability difference and the fluorine substitution. It was quite apparent from Table 1 that, as our expectation, difference of the combined calculated energies, ΔE, between the left hand (**6a+3~5b**) and the right hand (**6b+3~5a**) of the scheme was increased in proportion to the number of fluorine (n), and the significant preference of the model migration product was demonstrated in the case of n=3 with more than 20 kcal/mol difference. For other fluorinated alcohols **4** and **5**, successive reduction of a fluorine atom resulted in the loss of ca. 6 kcal/mol energetic preference of the product mixture.

From the structural point of view, one common characteristics was noted for the fluorinated silyl ethers. It has been well documented[11] that the most stable conformations of 1,2-disubstituted ethanes with such electronwithdrawing moieties as halogens,[12] alcohol derivatives,[13] or amines[14] are usually the one these two moieties locating in a *gauche* fashion. Considering that fluorine atom possesses three sets of lone pairs, electronic repulsion between this atom and oxygen lone pair(s) would cause the significant destabilizing interaction, and thus, in the case of silyl ether from monofluoroethanol **5b**, the most stable conformation was expected to be the GG form shown below rather than G'G or sterically less hindered AA (Figure 1). This was really the case in the *ab initio* calculations, and the energy differences between the most stable GG and G'G or AA were calculated to be 2.67 (3.46) or 0.37 (1.81) kcal/mol at HF/6-31G* (MP2/6-31G* result at the HF/6-31G* geometry) level, respectively, and we could not locate the isomer GA as a minimum at HF/6-31G* level. In the case of the corresponding difluorinated counterparts, introduction of the additional fluorine at the antiperiplanar position to oxygen for GG depicted in Figure 1 furnished the energetically most favorable conformation. Two other conformations, GG and GA both with the additional F atom at the other *gauche* positions, were found out as the optimized structures at 1.57 (1.10) and 2.86 (3.32) kcal/mol higher in energy, respectively. Thus, *gauche* relationships between fluorine and oxygen were demonstrated to be best favored in all calculated fluorinated silyl ethers **3-5b** like the previously reported case of the corresponding alcohols[13,15] or methyl ether.[15]

Based on the above fundamental information, we next tried the MOPAC calculations of diastereomeric pair of **7a** and **7c** with both *syn* and *anti* relative stereochemistries which were still model materials of the ones in Scheme 1 but more closely related to the real structures. Prior to employ MOPAC package, the optimization of **3b** was carried out independently with three hamiltonians MNDO, AM1, and PM3 and then these data were compared with ones from *ab initio* calculations with various basis sets to know which hamiltonian was most appropriate for our purpose. Table 2 describes the comparison of the representative bond length and charge data obtained, which clearly showed the significant deviation of the distance between two carbon atoms especially when PM3 was used (the difference was about 0.4 Å and the bond order was calculated to be only 0.42!). In terms of atomic charges on carbons, semiempirical results showed quite different values from the *ab initio* data, and PM3 predicted these charge in a completely opposite manner. Although the data from AM1 seemed still not to be sufficient enough by 0.12 Å



GG (*gauche-gauche*) G'G (*gauche'-gauche*) GA (*gauche-anti*) AA (*anti-anti*)

Fig. 1. Representative Conformers of Silyl Ether from Monofluoroethanol, **5b**

Table 2. *Ab initio* and MOPAC Calculation Data of Alkoxide Derived from Trifluoroethanol, **3b**

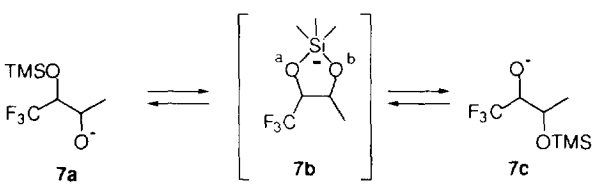
Method	Bond length[a] (Å) C-C	C-O	$C-F_a$	$C-F_b$	C-H	Charge[b] F_3C	C-O	O
MOPAC								
MNDO	1.735	1.266	1.368	1.362	1.137	0.360	0.384	-0.634
AM1	1.654	1.287	1.381	1.373	1.136	0.237	0.210	-0.643
PM3	1.918	1.249	1.357	1.351	1.104	-0.040	0.405	-0.624
ab initio								
HF/3-21G	1.523	1.345	1.377	1.361	1.117	1.094	-0.139	-0.916
HF/6-31G*	1.529	1.306	1.352	1.335	1.122	1.239	-0.026	-1.010
HF/6-31+G*	1.532	1.317	1.354	1.334	1.113	1.192	-0.031	-1.037
MP2/6-31G*	1.529	1.318	1.383	1.362	1.141	1.240	-0.035	-1.001

a) F_a and F_b are the fluorine atoms possessing the *antiperiplanar* and *gauche* relationship with oxygen atom, respectively.
b) Natural population analysis was carried out for the obtained geometry in the case of *ab initio* calculations.

difference at the C-C bond and from viewpoint of the atomic charges, we decided to use this hamiltonian because of the best results among the three and cost of calculations.

Results of MOPAC AM1 calculations of model compounds **7a** and **7c** both with *anti* and *syn* relationships, was summarized in Table 3 and was suggested the existence of the similar intermediates **7b** containing pentavalent silicon atoms, whose mechanism was previously postulated by several research groups[5a,5b,6a,7b] (Table 3). The next step of the present 1,2-*O*,*O*-silyl migration process would be the preferential cleavage of Si-O^a bond to Si-O^b bond and this trend was assumed from the calculated bond orders of these bonds of 0.46 for Si-O^a and 0.61 for Si-O^b (the same value was obtained for both diastereomers). From the energetic point of view, **7c** was proved to be at least 10 kcal/mol more stable than the regioisomeric **7a** and this seemed to be enough difference for quantitatively converting the latter to the former under thermodynamically controlled conditions. Thus, exclusive formation of **7c** over **7a** was strongly supported from the MOPAC calculations which apparently explained our previous results depicted

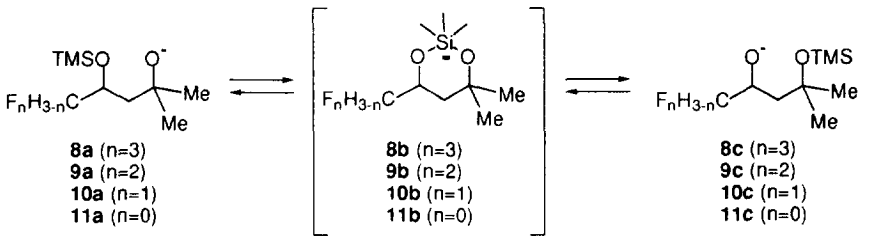
Table 3. MOPAC Calculations of Model 1,2-*O*,*O*-Silyl Migration Systems



	Free energy G at -78 °C[a] (kcal/mol) **7a**	**7b**	**7c**	ΔG^b (kcal/mol)
anti	-348.219 (-320.439)	-377.272 (-349.690)	-358.807 (-330.632)	10.59 (10.19)
syn	-346.695 (-319.188)	-380.642 (-352.857)	-359.567 (-331.099)	12.87 (11.91)

a) In the parentheses were shown the calculated heat of formation, H. b) ΔG=G(7a)-G(7c) and in the parentheses were shown the corresponding ΔH, H(7a)-H(7c).

Table 4. MOPAC Calculations of Model 1,3-*O*,*O*-Silyl Migration Systems



8a (n=3) **8b** (n=3) **8c** (n=3)
9a (n=2) **9b** (n=2) **9c** (n=2)
10a (n=1) **10b** (n=1) **10c** (n=1)
11a (n=0) **11b** (n=0) **11c** (n=0)

	Free energy (G) at -78 ℃[a] (kcal/mol)						
n[b]	a		b		c		ΔG^c (kcal/mol)
3 (**8**)	-358.668	(-328.576)	-380.383	(-350.759)	-368.876	(-337.896)	10.21 (9.32)
2 (**9**)	-302.443	(-273.023)	-322.437	(-293.507)	-304.903	(-276.112)	2.46 (3.09)
1 (**10**)	-247.049	(-218.399)	-266.091	(-238.560)	-245.612	(-217.582)	-1.44 (-0.82)
0 (**11**)	-193.919	(-166.399)	-212.367	(-185.383)	-188.050	(-160.999)	-5.87 (-5.40)

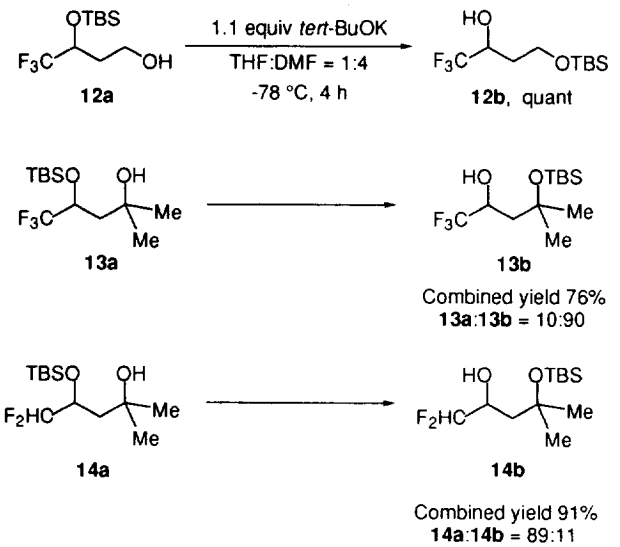
a) In the parentheses were shown the calculated heat of formation, H. b) In the parentheses were described the compound number. c) ΔG=G(**8a**)-G(**8c**) and in the parentheses were shown the corresponding ΔH, H(**8a**)-H(**8c**).

in Scheme 1.[1d]

At the next stage, we have planed the extension of the 1,2-*O*,*O*-silyl migration to the corresponding 1,3 version, especially migration of a silyl group from a secondary hydroxy moiety to the sterically more biased tertiary alcohol because i) 1,3-migration seemed to readily form the six-membered cyclic structure similar to **7b**,[8] and, moreover, ii) in the case of 1,2-shift (migration from secondary alcohol to another secondary alcohol), the calculated energy difference was more than 10 kcal/mol in favor of the migration product **7c** and if this was also the case, the imposed steric factor would be possibly overcome. Then, we decided to use model compounds **8** to **11** for confirming the possibility of this pathway as well as the relationship between energy difference ΔE and the number of fluorine atoms.

The most striking result was the energy difference between **8a** and **8c** with a CF_3 group. In spite of imposing the additional steric hindrance around the oxygen where the silyl group was migrated, **8c** was still energetically 10 kcal/mol more favorable than the substrate **8a**. However, removal of one fluorine atom significantly affected the ΔE value and **9c** was found to be only 2.5 kcal/mol more stable than **9a**, and in the case of n=1 or 0, such methyl groups only possessed very weakly electronwithdrawing nature, and thus no migration would be occurred.

For the verification of the above calculation results, the similar type of materials **13a** and **14a** to the model compounds **8** and **9** were prepared. At first, reaction conditions were optimized by using primary alcohol **12a**, and usage of 1.1 equiv of *tert*-BuOK in a mixed solvent of THF and DMF in a ratio of 1:4 at -78 ℃ for 4 h were found to be the conditions of choice, and the migration product **12b** was isolated in a quantitative yield with perfect conversion (Scheme 2). The required substrates **13a** and **14a** were synthesized from the corresponding 4,4,4-trifluoro- and 4,4-difluoro-3-hydroxybutanoates, respectively, via the silylation with *tert*-butyldimethylsilyl chloride and reaction with methyllithium. Subjection of **13a** to the above standard conditions led to the formation of the desired 1,3-migration products **13b** in a ratio of **13a**:**13b** = 10:90, while the corresponding difluorinated material **14a** attained only 10% conversion by the same procedure, both of which would be attained by the ΔG of only 0.85 kcal/mol (in favor of the product **13b** in the case of CF_3 compound, while the substrate **14a** should be more stable for the



Scheme 2 1,3-*O,O*-Silyl Migartion

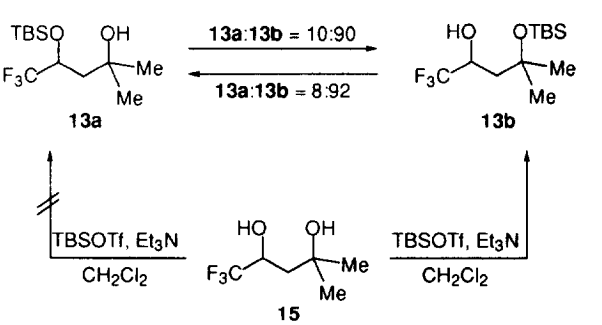
difluorinated molecule). Unfortunately, MOPAC could not provide the exact energetics, but the tendency of ready migration of **13a** over **14a** was correct.

For obtaining mechanistic insight, **13b**, separated from a small amount of **13a** (10%) after 1,2-*O,O*-silyl migration, was subjected again to the same condition to yield a mixture of **13a** and **13b** basically in a same ratio of 8:92, which was explicitly demonstrated the both reaction occurred via the same intermediate (Scheme 3). Interesting discrimination between two hydroxy groups in **15** was observed by the silylation of this compound with *tert*-butyldimethylsilyl trifluoromethanesulfonate in the presence of triethylamine to furnish sterically more congested tertiary silyl ether **13b** as a single product and the formation of the corresponding less sterically demanding secondary ether **13a** was not detected at all. This selection could be recognized as the reflection of the significantly different nucleophilic ability of two hydroxy groups in **15**, and well supported our present calculation.

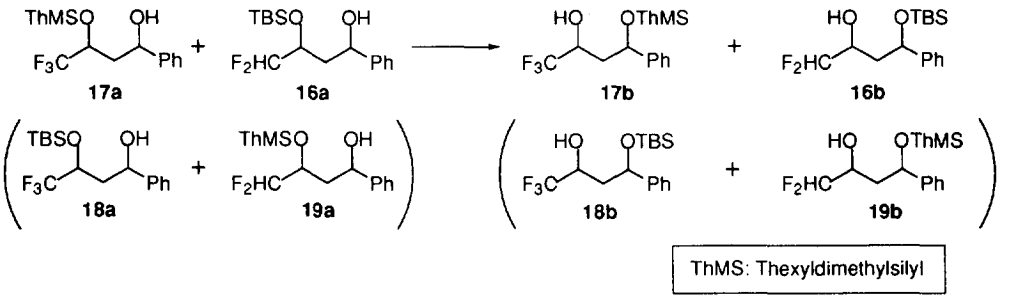
We have also tried the cross-over experiment by using tri- or difluorinated 1,3-diols, **17a** or **16a**, with thexyldimethylsilyl or *tert*-butyldimethylsilyl groups as the protection of a hydroxy moiety close to the fluorinated terminus, respectively. If this migration was occurred in an intermolecular manner, not only the usual products **16b** and **17b** but also the cross-over products **18b** and **19b** and their less favorable migration products, **18a** or **19a** would be produced. This mixture was subjected to the above conditions[16] and the reaction mixture was analyzed by capillary gas chromatography to detect no trace amount of **18** nor **19**, which, in sharp contrast to the corresponding nonfluorinated systems,[7b] unambiguously manifested this reaction path proceeding in an intramolecular manner.

Conclusion

As described above, we have studied 1,2- as well as 1,3-*O,O*-silyl migration reactions both from theoretical and experimental points of view, and it was clearly demonstrated that the both pathways proceeded very smoothly especially when strongly electronwithdrawing trifluoromethylated materials were employed, in good accordance with the prediction from molecular orbital calculations. Employment of this thermodynamically



Scheme 3 Mechanistic Study of 1,3-*O,O*-Silyl Migration (1)



Scheme 4 Mechanistic Study of 1,3-*O*,*O*-Silyl Migration (2)

controlled isomerization process would effectively reduce the reaction pathways for the appropriately designed molecules by avoiding troublesome protection-deprotection steps.[1]

Experimental

General Methods. Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. All manipulations involving air-sensitive materials were performed under nitrogen, with such materials being exposed only to thoroughly dried and degassed solvents. Ether and THF were distilled from sodium/benzophenone under a nitrogen atmosphere immediately prior to use. CH_2Cl_2 and DMF was similarly distilled from calcium hydride.

^1H NMR and ^{13}C NMR spectra were recorded with a Varian Gemini-200 (200 MHz), or a Varian VXR-500 (500 MHz), in $CDCl_3$ unless otherwise noted. Chemical shifts were recorded in parts per million (ppm), downfield from internal tetramethylsilane (Me_4Si). ^{19}F NMR spectra were recorded with a Hitachi R-1200F (56.45 MHz), or a Varian VXR-500 (500 MHz), in CH_2Cl_2 or $CDCl_3$ unless otherwise noted. Chemical shifts were reported in ppm downfield from external trifluoroacetic acid (TFA). Data were tabulated in the following order: number of protons, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; quint, quintet; sex., sextet; sep., septet; m, multiplet; br, broad peak), coupling constants (in hertz). For minor isomers were shown only the chemical shifts for the representative peaks. Infrared (IR) spectra were obtained on a JASCO A-102 spectrometer and all spectra were reported in wave numbers (cm^{-1}). Gas liquid chromatography (GLC), was performed on a Shimadzu GC-8A or a Shimadzu GC-14A chromatograph equipped with a flame ionization detector and nitrogen carrier gas using Silicone GE XE-60 or ULBON HR-20M on Chromosorb W, 30 m x 3 mm.

3-(*tert*-Butyldimethylsilyloxy)-4,4,4-trifluorobutanol (12a). A solution of DIBALH (48.00 mL of a 1.0 M solution in hexanes, 48.0 mmol) was added at -78 ℃ to a THF (20 mL) solution of ethyl 3-(*tert*-butyldimethylsilyloxy)-4,4,4-trifluorobutanoate (6.01 g, 20.0 mmol), obtained from usual silylation conditions of ethyl 4,4,4-trifluoro-3-hydroxybutanoate with TBSCl and imidazole, and the resulting solution was stirred for additional 1 h. The reaction mixture was quenched with 1 *N* HCl aq., followed by extraction with ether three times. Combined organic layers were dried ($MgSO_4$), concentrated in vacuo, and the crude product was purified by column chromatography (14% EtOAc/hexanes) to afford **12a** in 69% yield. ^1H NMR δ 0.10 (6 H, s), 0.89 (9 H, s), 1.45-1.65 (1 H, br), 1.79 (1 H, ddt, *J* = 4.7, 8.5, 14.3 Hz), 1.88-2.01 (1 H, m), 3.77 (2 H, dd, *J* = 4.8, 8.2 Hz), 4.26 (1H, ddq, *J* = 3.7, 6.7, 8.5 Hz). ^{13}C NMR δ -5.1, 18.1, 25.6, 33.4, 57.9, 68.2 (q, *J* = 31.0 Hz), 125.2 (q, *J* =281.2 Hz). ^{19}F NMR δ

0.69 (d, J = 6.2 Hz). IR (neat) ν 3360, 2960, 2940, 2900, 2860. HRMS calc. for $C_{10}H_{21}F_3O_2Si$ 258.1262, found 258.1274.

4-(*tert*-Butyldimethylsilyloxy)-5,5,5-trifluoro-2-methylpentan-2-ol (13a). To a solution of ethyl 3-(*tert*-butyldimethylsilyloxy)-4,4,4-trifruorobutanoate (0.60 g, 2.00 mmol) in Et_2O (4 mL) at -78 ℃ was added MeLi (3.10 ml of a 1.4 M solution in Et_2O, 4.34 mmol), and the resulting solution was stirred for 1 h. The reaction mixture was quenched with aqueous 1 *N* HCl, followed by usual work-up and purification by column chromatography (30% EtOAc/hexanes) to afford **13a** in 40% yield. ^{1}H NMR δ 0.14 (3 H, q, J = 1.3 Hz), 0.17 (3 H, s), 0.92 (9 H, s), 1.27 (6 H, s), 1.80 (1 H, dd, J = 3.7, 14.7 Hz), 1.86 (1 H, dd, J = 8.1, 15.0 Hz), 2.49 (1 H, s), 4.30 (1 H, ddq, J = 3.7, 6.5, 8.2 Hz). ^{13}C NMR δ -4.8 (q, J = 2.6 Hz), -4.6, 18.2, 25.7, 28.5, 30.9, 42.5 (q, J = 1.6 Hz), 69.5 (q, J = 30.8 Hz), 69.6, 124.9 (q, J = 281.3 Hz). ^{19}F NMR δ -0.48 (d, J = 6.9 Hz). IR (neat) ν 3460, 2970, 2940, 2900, 2865. HRMS calc. for $C_{12}H_{25}F_3O_2Si$ 286.1574, found 286.1588.

4-(*tert*-Butyldimethylsilyloxy)-5,5-difluoro-2-methylpentan-2-ol (14a). Yield 40%. ^{1}H NMR δ 0.16 (6 H, s), 0.91 (9 H, s), 1.26 (3 H, s), 1.28 (3 H, s), 1.67-1.88 (2 H, m), 2.85 (1 H, bs), 4.15 (1 H, m), 5.66 (1 H, dt, J = 3.9, 55.9 Hz). ^{13}C NMR δ -4.8, -4.2, 18.1, 25.7, 28.9, 30.9, 42.0 (t, J = 3.2 Hz), 69.9, 70.7 (t, J = 23.5 Hz), 116.0 (t, J = 245.5 Hz). ^{19}F NMR δ 33.4 (ddd, J = 9.5, 56.1, 283.4 Hz), 35.3 (ddd, J = 11.3, 56.9, 283.6 Hz). IR (neat) ν 3450, 2970, 2940, 2900, 2870. HRMS calc. for $C_{12}H_{26}F_2O_2Si$ 268.1669, found 268.1682.

3-(*tert*-Butyldimethylsilyloxy)-4,4-difluoro-1-phenylbutanol (16a). Yield 92%. ^{1}H NMR δ 0.13 (3 H, q, J = 1.0 Hz), 0.13 (3 H, s), 0.94 (9 H, s), 1.83 (1 H, dddd, J = 0.7, 2.8, 8.6, 14.3 Hz), 2.06 (dddd, J = 1.8, 5.7, 9.1, 14.8 Hz), 3.9-4.0 (1 H, m), 4.98 (1 H, dd, J = 3.7, 9.3 Hz), 5.78 (ddd, J = 5.0, 55.3, 57.3 Hz), 7.3-7.4 (5 H, m). ^{13}C NMR δ -5.0, -4.7 (d, J = 2.7 Hz), 18.1, 25.7, 40.5 (dd, J = 2.0, 4.7 Hz), 70.7 (dd, J = 22.7, 261 Hz), 70.8, 116.3 (t, J = 243.1 Hz), 125.5, 125.7, 127.6, 127.7, 128.6, 144.2. ^{19}F NMR δ major isomer 33.3 (ddd, J = 7.3, 55.3, 283.4 Hz), 36.5 (ddd, J = 12.2, 58.0, 283.9 Hz): minor isomer 33.7 (ddd, J = 8.8, 56.1, 283.4 Hz), 35.1 (ddd, J = 11.5, 55.8, 283.1 Hz). IR (neat) ν 3440, 2960, 2930, 2900, 2860. HRMS calc. for $C_{16}H_{26}F_2O_2Si$ 316.1669, found 316.1676.

4,4,4-Trifluoro-1-phenyl-3-(thexyldimethylsilyloxy)butanol (17a). Yield 94%. ^{1}H NMR δ 0.17 (3 H, s), 0.19 (3 H, s), 0.8-1.0 (12 H, m), 1.66 (1 H, sep, J = 6.9 Hz), 1.9-2.2 (2 H,m), 2.21 (1 H, d, J = 3.0 Hz), 4.18 (1 H, sex., J = 6.4 Hz), 4.8-5.0 (1 H, m), 7.3-7.5 (5 H, m). ^{13}C NMR δ -3.1 (q, J = 1.7 Hz), -2.8, 18.4, 18.6, 20.0, 20.1 (q, J = 1.5 Hz), 25.0, 34.0, 41.0 (q, J = 1.5 Hz), 69.1 (q, J = 31.1 Hz), 71.1 (q, J = 1.4 Hz), 125.2 (q, J = 281.3 Hz), 125.5-144.4 (m). ^{19}F NMR δ major isomer 83.9 (d, J = 6.1 Hz): minor isomer 83.7 (d, J = 6.1 Hz). IR (neat) ν 3422, 2915. HRMS calc. for $C_{18}H_{29}F_3O_2Si$ 362.1887, found 362.1895.

4-(*tert*-Butyldimethylsilyloxy)-1,1,1-trifluorobutan-2-ol (12b). **12a** in a mixed solvent of THF and DMF (1:4, 0.5 mol/L solution) was reacted with 1.1 equiv of *tert*-BuOK at -78 ℃. After stirring for 4 h at that temperature, the reaction was quenched with aqueous NH_4Cl, followed by usual work-up and purification by column chromatography (14% EtOAc/hexanes) to afford **12b** in quantitative yield. ^{1}H NMR δ 0.09 (6 H, s), 0.90 (9 H, s), 1.87 (1 H, ddq, J = 4.3, 6.9, 14.5 Hz), 1.83-2.00 (1 H, m), 3.80-4.04 (2H, m), 3.95 (1 H, d, J = 3.8 Hz). ^{13}C NMR δ -5.6, 18.1, 25.8, 31.0 (q, J = 1.8 Hz), 61.0, 70.3 (q, J = 31.4 Hz), 125.0 (q, J = 281.1 Hz). ^{19}F NMR -2.01 (d, J = 6.9 Hz). IR (neat) ν 3450, 2960, 2940, 2900, 2870. HRMS calc. for $C_{10}H_{21}F_3O_2Si$ 258.1262, found 258.1280.

4-(*tert*-Butyldimethylsilyloxy)-1,1,1-trifluoro-4-methylpentan-2-ol (13b). Yield 79%. ^{1}H NMR δ 0.16 (3 H, s), 0.17 (3 H, s), 0.82 (9 H, s), 1.38 (6 H, s), 1.65 (1 H, dd, J = 2.2, 14.3 Hz), 1.88 (1 H, dd, J = 10.9, 14.4 Hz), 4.30 (1 H, dddq, J = 1.5, 2.2, 6.7, 11.0 Hz), 4.56 (1 H, d, J = 1.6 Hz). ^{13}C NMR δ -2.1, -2.1, 17.8, 27.7, 31.5, 42.1 (q, J = 1.8 Hz), 68.5 (q, J = 31.1 Hz), 75.1, 125.0 (q, J

= 279.0 Hz). ^{19}F NMR δ -2.20 (d, *J* = 7.6 Hz). IR (neat) ν 3470, 2980, 2950, 2900, 2875. HRMS calc. for $C_{12}H_{25}F_3O_2Si$ 286.1574, found 286.1582.

4-(*tert*-Butyldimethylsilyloxy)-1,1-difluoro-4-methylpentan-2-ol (14b). Conversion 10%. ^{1}H NMR δ 0.16 (6 H, s), 0.87 (9 H, s), 1.37 (6 H, s), 1.59 (1 H, ddd, *J* = 1.3, 2.3, 14.4 Hz), 1.79 (1 H, dd, *J* = 10.8, 14.2 Hz), 4.1-4.5 (1 H, m), 4.5-4.9 (1 H, br), 5.63 (1 H, dt, *J* = 4.0, 56.2 Hz). ^{13}C NMR δ -2.1, -2.0, 25.7, 27.9, 31.7, 42.1 (t, *J* = 3.5 Hz), 69.0 (t, *J* = 24.6 Hz), 116.3 (t, *J* = 243.2 Hz). ^{19}F NMR δ 29.8 (ddd, *J* = 12.2, 56.5, 285.4 Hz), 32.8 (ddd, *J* = 9.6, 55.3, 285.0 Hz). IR (neat) ν 3470, 2960, 2940, 2860. HRMS calc. for $C_{12}H_{26}F_2O_2Si$ 268.1669, found 268.1678.

4-(*tert*-Butyldimethylsilyloxy)-1,1-difluoro-4-phenylbutan-2-ol (16b). Yield 79%. ^{1}H NMR δ -0.22 (3 H, s), 0.06 (3 H, s), 0.91 (9 H, s), 1.91-2.07 (2 H, m), 3.53 (1 H, bs), 3.93 (1 H, m), 4.95 (1 H, dd, *J* = 4.6, 8.8 Hz), 5.68 (1 H, dt, *J* = 4.8, 55.0 Hz), 7.3-7.4 (5 H, m). ^{19}F NMR δ major isomer 30.1 (ddd, *J* = 12.2, 56.5, 286.9 Hz), 32.5 (ddd, *J* = 9.9, 55.7, 286.1 Hz); minor isomer 31.1 (ddd, *J* = 11.5, 55.7, 285.4 Hz), 32.2 (ddd, *J* = 11.8, 56.1, 285.0 Hz). IR (neat) ν 3460, 2970, 2940, 2900, 2860. HRMS calc. for $C_{16}H_{26}F_2O_2Si$ 316.1669, found 316.1649.

1,1,1-Trifluoro-4-phenyl-4-(thexyldimethylsilyloxy)butan-2-ol (17b). Yield 72%. ^{1}H NMR δ -0.22 (3 H, s), 0.13 (3 H, s), 0.83 (3 H, s), 0.86 (3 H, s), 0.88 (3 H, d, *J* = 6.8 Hz), 0.90 (3 H, d *J* = 7.1 Hz), 1.63 (1 H, sep., *J* = 6.8 Hz), 1.99 (1 H, ddd, *J* = 2.2, 4.9, 14.4 Hz), 2.11 (1 H, ddd, *J* = 8.8, 10.3, 14.4 Hz), 3.42 (1 H, d, *J* = 2.7 Hz), 4.0-4.2 (1 H, m), 4.93 (1 H, dd, *J* = 4.9, 8.8 Hz), 7.3-7.4 (5 H, m). ^{13}C NMR δ -3.2, -2.3, 18.4, 18.6, 20.0, 20.3, 24.9, 34.0, 39.7 (q, *J* = 1.8 Hz), 69.7 (q, *J* = 31.5 Hz), 124.7 (q, *J* = 279.2 Hz), 125.8, 126.1. ^{19}F NMR δ major isomer 81.5 (d, *J* = 6.1 Hz): minor isomer 81.8 (d, *J* = 7.7 Hz). IR (neat) ν 3448, 2915. HRMS calc. for $C_{18}H_{29}F_3O_2Si$ 362.1887, found 362.1901.

1,1,1-Trifluoro-4-methylpentane-2,4-diol (15). To a THF (6 mL) solution of ethyl 4,4,4-trifluoro-3-hydroxybutanoate (0.56 g, 3.0 mmol) was added 7.0 mL of methyllithium (1.4 mol/L, 9.9 mmol), and the mixture was stirred overnight. The usual work-up and purification furnished **15** in 60% yield. ^{1}H NMR (with a few drop of D_2O) δ 1.36 (3 H, s), 1.37 (3 H, s), 1.74 (1 H, dd, *J* = 2.0, 14.6 Hz), 1.90 (1 H, dd, *J* = 11.2, 14.4 Hz), 4.32 (1 H, ddq, *J* = 2.2, 11.2, 6.6 Hz). ^{13}C NMR δ 27.4, 31.6, 39.9 (q, *J* = 1.6 Hz), 68.5 (q, *J* = 31.4 Hz), 124.9 (q, *J* = 281.0 Hz). ^{19}F NMR δ -5.1 (d, *J* = 6.1 Hz). IR (neat) ν 3390, 2970, 2940. HRMS calc. for $C_6H_{11}F_3O_2$ 172.0710, found 172.0723.

This compound was treated with 1 equiv of TBSOTf and 2 equiv of triethylamine in CH_2Cl_2 at room temperature afforded **13b** as a single product.

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16. Both **16a** and **17a** were independently subjected to the migration conditions to attain 87% and >99% conversions to the corresponding **16b** and **17b**, respectively.

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