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HF-mediated equilibrium between fluorinated ketones and the corresponding α-fluoroalcohols

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ABSTRACT

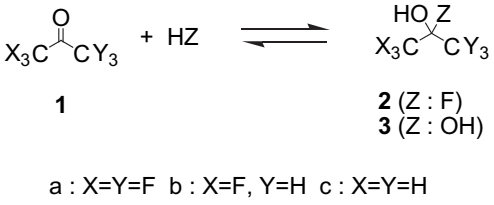
We have successfully obtained the first unambiguous spectroscopic proof of the structure of heptafluoropropan-2-ol by ^{13}C NMR, which has been assumed from early 70s but without unequivocal evidence. Equilibrating relationship between fluorinated ketones and the corresponding hydrates as well as α-fluoroalcohols in anhydrous HF was at least qualitatively supported by our ab initio computation, and moreover, anhydrous HF as a convenient solvent was found to offer an effective new route for production of 1,1,1,3,3,3-hexafluoropropan-2-ol in industrial scales.

1. Introduction

In addition to their low chemical stability, prompt addition–elimination sequence of water or hydrogen halides to carbonyl compounds generally renders isolation of 1,1-diols or 1,1-halohydrins[1] (Scheme 1) difficult, respectively. The strong electron-withdrawing trifluoromethyl groups in hexafluoroacetone (HFA, **1a**) are considered to enable formation of such unique structures by effective electrophilicity enhancement of the carbonyl group, and in fact our computation clearly demonstrated the large LUMO energy difference between **1a** and 1,1,1-trifluoroacetone (TFA, **1b**) or acetone (**1c**) of 1.38 and 2.69 eV, respectively.

The fairly stable *gem*-diol **3a** is known to be readily formed by addition of water to **1a**. However, heptafluoropropan-2-ol **2a**[2] is believed[3] to be obtained[4] by treatment of **1a** with anhydrous HF, to the best of our knowledge, the corresponding α-fluorohydrin **2a** was not isolated from an equilibrium mixture of **1a** and HF[1a] and its structure was not properly confirmed yet.[3,5]

We have envisaged that ^{13}C NMR measurements in an anhydrous HF solvent would provide a clear and straightforward solution on the structure of the adduct obtained by **1a** and HF. In this paper are reported our successful NMR results for clarification of the α-fluorohydrin framework and a novel HF-mediated equilibrium between fluorinated ketones and the corresponding α-fluoroalcohols as well as an alternative process for production of 1,1,1,3,3,3-hexafluoropropan-2-ol **4** (HFIP) and for production of hexafluorobisphenol A using **2a** as the efficient substrate.



Scheme 1. Addition–elimination sequence of water or hydrogen halides to carbonyl compounds.

2. Results and discussion

^{13}C NMR spectrum of **1a** in HF is shown in Fig. 1 along with the ones of tri- and non-fluorinated acetones **1b** and **1c** in HF for comparison, respectively. Two sets of independent peaks were observed for **1a** in HF at δ 98.6 (dsept, J=244.4, 37.4 Hz) and 116.7 (qd, J=285.0, 34.8 Hz) whose (1) ^1J and ^2J doublet coupling patterns, respectively (2) the chemical shift of the former peak, as well as (3) complete disappearance of the HFA C=O peak at 173.0 ppm are the prominent and unanimous indication of HF fluorine attacking the carbonyl carbon atom of **1a** to form a new C^5–F bond in **2a**. On the other hand, only ca. 30% of the HF adduct **2b** was noticed for **1b**[5] with 70% intact, and no HF incorporation was detected for **1c** at all in spite of more

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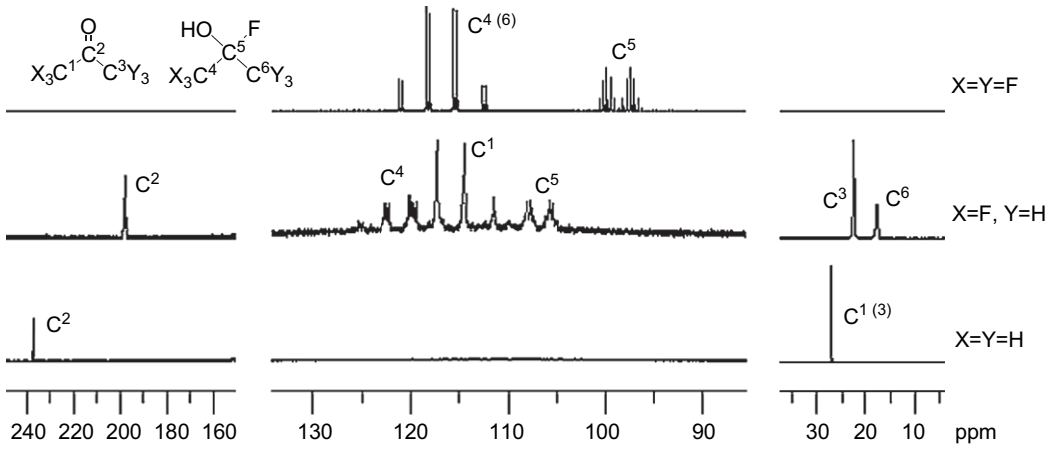
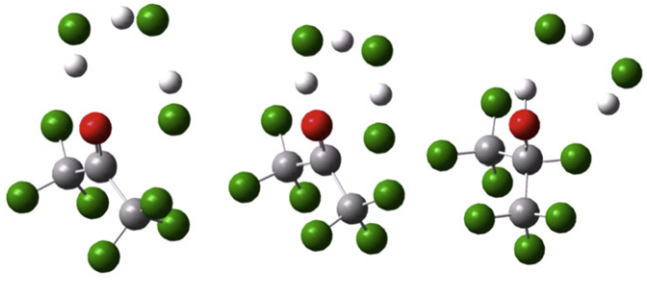


Fig. 1. ^{13}C NMR spectrum of HFA (**1a**), TFA (**1b**), and acetone (**1c**) in anhydrous HF at 24 °C.

than 30 ppm exceeding downfield shift of the C^2 peak[6] possibly by robust HF coordination to the carbonyl oxygen atom.

A part of these trends are qualitatively well elucidated on the basis of the LUMO energy gap between these ketones as depicted above, and for obtaining further theoretical support on such phenomena, extensive computational analysis was carried out for both HF and H_2O addition to the ketones **1a**, **1b**, and **1c**. As shown in Table 1, after a number of attempts, three HF molecules were found to play a pivotal role in this reaction course, and HF coordination to the ketones giving complex was proved to acquire 20–30 kcal/mol energetic stabilization relative to the energetic sum of **1a** and three HF molecules. Magnitude of this gain seemed to be in an inversely proportional to the number of fluorine atoms included in **1**, which would be the reflection of their different HOMO energy levels. After passing through the eight-membered ring transition state (TS) with 16.82 kcal/mol energy barrier, **1a** was transformed into the more stable product **2a**·2HF by 3.96 kcal/mol than the corresponding complex. Considering that this TS was 5.05 kcal/mol lower than the substrate pair of **1a** and 3HF, formation of **2a** by HF addition to **1a** is expected to proceed in a favorably exothermic manner. In the case of **1b**, although the activation energy was found to be almost in a same level (16.02 and 16.83 kcal/mol) as the case of **1a**, the definite discrepancy was the energetic preference of the **1b**·3HF complexes to their products **2b**·2HF by 2.08 and 1.43 kcal/mol. Such trend became more pronounced for acetone **1c**, and the product **2c**·2HF was destabilized by 5.52 kcal/mol. These results led to strong expectation that, different from the case of **1a**, both **1b** and **1c** would be detected at least as the major components in reaction mixtures, which were totally consistent with our NMR observation already shown in Fig. 1.

Table 1
Computational results for the formation of HF as well as H_2O adducts with fluorinated ketones **1a**, **1b**, and **1c**[a,b]



	Relative energy (kcal/mol)		
	Complex	TS	Product
1a+3HF	−21.87	−5.05	−25.83
1b+3HF (*anti*)[c]	−26.27	−10.25	−24.19
1b+3HF (*syn*)[c]	−26.27	−9.44	−24.84
1c+3HF	−31.81	−19.14	−26.29
1a+2HF+H_2O	−22.54	−10.67	−30.89
1b+2HF+H_2O (*anti*)[c]	−24.97	−10.67	−26.22
1b+2HF+H_2O (*syn*)[c]	−24.96	−9.43	−26.84
1c+2HF+H_2O	−29.48	−13.59	−23.52

[a] Computation was carried out by Gaussian 03 W at the B3LYP/6-311++G** level of theory.
[b] Molecular models of **1a**+3HF were shown as the representative examples.
[c] *syn* and *anti* express the relative relationship between a CF_3 group and HF coordinated to the carbonyl oxygen.

Electrostatic characteristics as described above pertinently accounts for in a similar manner why **1a** readily forms the stable and easy-to-handle adduct like **3a**.[7] Ready availability of **3a** led us to confirm its behavior in various equivalents (n) of anhydrous HF whose ^{13}C NMR spectra are collected in Fig. 2.

The peak at δ 88.4 ppm clearly exemplified retention of the *gem*-diol structure of **3a** when n=3, and although the HF adduct **2a** was detected as the minor component with the HF amount of 10 equiv, further introduction of HF until n=30 rendered **2a** as the exclusive species. As shown in Table 1, the adduct **3a**·2HF (product of **1a**+2HF+H_2O) is energetically more stable than the corresponding **2a**·2HF (product of **1a**+3HF), which is reflected to the NMR results when n=3 (Fig. 2). However, increase of the amount of Brønsted acid HF would promote its coordination to water to significantly diminish nucleophilic ability of the latter molecules. Thus, the larger excess HF would result in stronger deactivation of H_2O by effective protonation and give a higher chance for HF to attack at the C=O group, leading to exclusive formation of **2a** when n=30. This method was efficiently applied for dehydration of HFA hydrates[8] and the resultant HF solution of HFA or **2a** was readily reacted with phenol to realize the industrial production of hexafluorobisphenol A (Scheme 2).[8,9]

Until now, a couple of patents have mentioned about the ready preparation of HFIP **4a** by way of the transition metal-catalyzed hydrogenation of HFA hydrate **3a**.[10] We reached to an idea that if this reduction proceeded via the corresponding ketone **1a** generated during equilibration,[11] the HFA–HF adduct **2a** should be also applicable as a substrate to the same protocol. Actually, subjection of **2a** to the standard Pd/C condition under a 1.0 MPa H_2 atmosphere readily afforded **4a** in only 2 h at ambient temperature with perfect product selectivity (Scheme 3).[12,13] On the basis of previous calculations, smaller energy gap between the product **2a**·2HF and the complex **1a**·3HF (3.96 kcal/mol) required less extra energy by

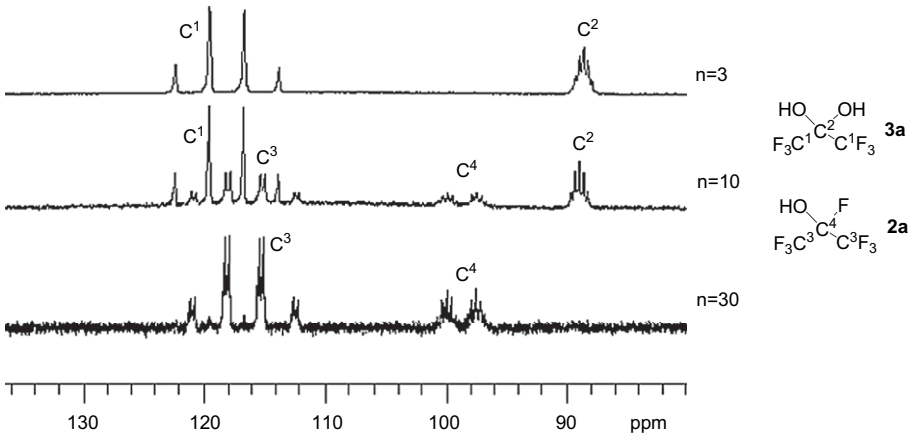
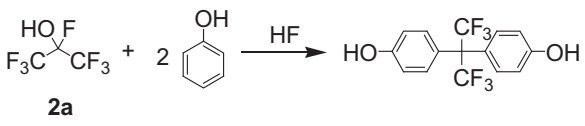
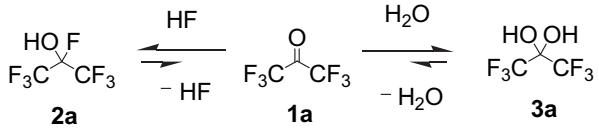


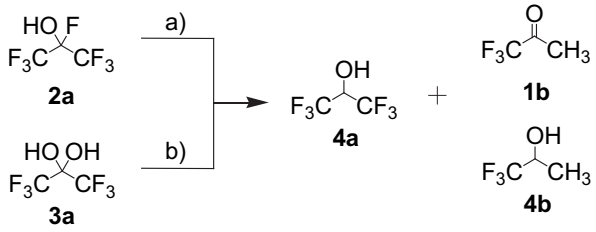
Fig. 2. ^{13}C NMR spectrum of **3a**·$2H_2O$ in HF (*n* equiv) at 24 °C.



Scheme 2. Synthesis of hexafluorobisphenol A.



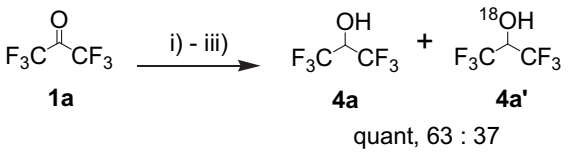
Scheme 5. Equilibrium between **2a** and **3a** via **1a** in HF.



Scheme 3. Preparation of HFIP (**4a**): (a) from **2a** in HF, cat. Pd/C, H_2, 1.0 MPa, 30 °C, 2 h (**4a**: 99.9%, **4b**: none, **1b**: none); (b) from **3a** in H_2O, cat. Pd/C, H_2, 0.5 MPa, 100 °C, 6 h (**4a**: 99.2%, **4b**: 0.6%, **1b**: 0.2%).

heating rather than the case between **3a**·2HF and **1a**+2HF+H_2O (8.35 kcal/mol). This milder conditions would prevent contamination of **1b** as well as its further reduced material, 1,1,1-trifluoropropan-2-ol **4b** (Scheme 3).

At the next stage, for obtaining further fundamental information on the equilibration between **1a** and **2a** in HF, $H_2{}^{18}O$ (1 equiv) was added to a mixture of **1a** in HF (30 equiv). After 2 days at room temperature, only **2a** was observed by ^{13}C was subjected to the similar hydrogenation conditions at 0 °C to furnish a 37/63 mixture of HFIP–^{18}O (**4′a**)/HFIP–^{16}O (**4a**) quantitatively (Scheme 4).[14] 37% incorporation of ^{18}O explicitly demonstrated the direct proof of the equilibrium between **2a** and **3a** via **1a** in an HF solvent. Thus, in spite of strong deactivation of the nucleophilic ability of H_2O (or $H_2{}^{18}O$) by a large excess amount of HF, it appeared that there is still apparent equilibrium between **1a** and **3a** affecting exchange of ^{16}O and ^{18}O (Scheme 5).



Scheme 4. Reduction of **1a** in presence of 30 equiv of HF and 1 equiv of H_2O: (i) HF (30 equiv), 0 °C, 1 h; (ii) $H_2{}^{18}O$ (1 equiv), rt, 2 days; (iii) Pd/C, H_2, 1.0 MPa, 0 °C, 1 h.

3. Conclusions

We have successfully obtained the first and unequivocal spectroscopic proof of the unique structure of **2a** by ^{13}C NMR, which has estimated from early 70s but without decisive evidence. Our ^{13}C NMR spectra and ab initio computation supported equilibration between **1** and **2** as well as **3** in anhydrous HF whose role as a unique and convenient solvent was demonstrated by the effective new production route of **4a** in industrial scales.

4. Experimental section

4.1. General

Caution! Anhydrous HF can cause severe burns and contact with skin must be avoided. Such effect of HF unfortunately prevented us to obtain physical data except for NMR for materials in Section 4.2.

All reagents and solvents were purchased and used without further purification except for hexafluoroacetone (HFA)[15,16] and hydrogen fluoride (HF), both of which produced by ourselves.

^1H NMR (400 MHz), ^{13}C NMR (100 MHz), ^{19}F NMR (376 MHz) spectra were recorded using a JEOL AL-400 spectrometer at ambient temperature using a fluorinated ethylene-propylene copolymer (FEP) tubing without spinning nor deuterated solvent lock. Chemical shifts are reported in parts per million. $CDCl_3$ (7.24 (from $CHCl_3$ as impurity in $CDCl_3$) and 77.0 ppm) and $CFCl_3$ (0.0 ppm) were used as external standards for ^1H, ^{13}C, and ^{19}F NMR spectra, unless otherwise stated. IR spectra were run on a Thermo Nicolet FTIR NEXUS instrument. The electron-impact mass spectra were recorded on a JEOL Automass 150 quadrupol mass spectrometer, and the electron spray ionization mass spectra were recorded on an Appliedbiosystems Mariner time of flight mass spectrometer, and the field ionization mass spectra were recorded on a JEOL T100GC time of flight mass spectrometer.

4.2. NMR measurement of ketones (1) in excess amounts of hydrogen fluoride (HF)

To a 100 mL stainless-steel autoclave cooled in an ice/water bath were charged 30 g of hydrogen fluoride (1.5 mol) and 33.2 g of hexafluoroacetone (0.2 mol) at 0 °C, and 1 mL of the mixture was

transferred to an FEP NMR tubing cooled in an ice/water bath and then the end of the tubing was heat-sealed.

*4.2.1. NMR of hexafluoroacetone (HFA, **1a**) in HF.* ^{1}H NMR: δ 7.43 (s, *H*F). ^{13}C NMR: δ **2a** 98.6 (septd, J=34.7, 244.4 Hz, CF_3C), 116.7 (dq, J=34.7, 285.0 Hz, CF_3). ^{19}F NMR: δ −197.9 (H*F*), −85.4 (s, **2a**).

*4.2.2. NMR of 1,1,1-trifluoroacetone (TFA, **1b**)[5] in HF.* Colorless liquid. Bp 22 °C. ^{1}H NMR δ 1.8 (CH_3, **2b**), 2.7 (CH_3, **1b**·HF), 8.2 (s, *H*F). ^{13}C NMR: δ **1b**·HF 15.4 (s, J=24.8 Hz, CH_3), 113.7 (q, J=286.9 Hz, CF_3), 196.7 (q, J=38.1 Hz, C=O). Compound **2b** 20.3 (d, CH_3), 104.7 (qd, J=37.8, 229.0 Hz, CF_3C), 118.9 (dq, J=39.7, 267.3 Hz, CF_3). ^{19}F NMR: δ −190.2 (H*F*), −90.0 (s, **2b**), −83.1 (s, **1b**·HF).

*4.2.3. NMR of acetone (**1c**)[6] in HF.* ^{1}H NMR: δ **1c**·HF 3.3 (s, CH_3), 9.1 (s, *H*F). ^{13}C NMR: δ **1c**·HF 27.0 (CH_3), 237.0 (C=O).

4.3. HFA (1a) in excess amounts of H_2O

^{1}H NMR: δ **3a** 4.50 (s, O*H*). ^{13}C NMR: δ **3a** 88.4 (sept, J=33.2 Hz, CF_3C), 118.9 (q, J=88.3 Hz, CF_3). ^{19}F NMR: δ **3a** −83.4 (s). IR (ATR, germanium): 3700–3000, 1629, 1227, 1168, 1092 cm^{-1}. HRMS (ESI): $[M-H]^-$, found 182.9865. $C_3H_1F_6O_2$ requires 182.9881.

4.4. Dehydration of hexafluoroacetone hydrate

To a 1 L PTFE (polytetrafluoroethylene) bottle with a PTFE distillation column (3 cm ID, 45 cm length) packed with PTFE Raschig rings (4 mm) and a PTFE ice-water cooler on the top of the column, was charged 220 g (1 mol) of hexafluoroacetone trihydrate ($HFA\cdot 3H_2O$) and the bottle was cooled in dry-ice/acetone bath to freeze $HFA\cdot 3H_2O$, and then 272 g of hydrogen fluoride (13.6 mol) was charged. The mixture was agitated by a magnetic stirrer and was allowed to stand in a water bath, and then heated. From the top of the column, a solution containing **2a** and HF was distilled off at the range of 14–20 °C. The temperature of the still pot was raised gradually and when it reached to 111 °C, distillation was stopped. The weight calculation, the acid titration, and the result of Kirl–Fischer Test showed that 389 g of the distillate contained 166 g (1 mol) of HFA and 223 g (11.15 mol) of HF without water, and 96 g of the residual liquid contained 54 g of water and 42 g of HF. The yield was 98.6%. The identical NMR data to the one in Section 4.2.1 were obtained for the obtained material.

4.5. Preparation of hexafluorobisphenol A[17]

To a 1 L stainless-steel autoclave were charged 188 g (2 mol) of phenol and 375 g of the distillate obtained in Section 4.4 consisting of 160 g (0.96 mol) of HFA and 215 g (10.75 mol) of HF. The reaction mixture was agitated and heated in an oil bath up to 110 °C (0.95 MPa) and kept for 6 h. The reaction mixture was poured onto crashed ice, and precipitates are collected, filtered, washed with water, and then dried to afford of hexafluorobisphenol A as a white powder (265 g, 82% yield, 99.1% purity). Mp 162 °C. ^{1}H NMR (CD_3OD): δ 4.88 (2H, s, O*H*), 6.76 (2H, d, J=8.5 Hz, Ph), 7.16 (2H, d, J=8.5 Hz, Ph). ^{13}C NMR (CD_3OD): δ 64.9 (sept, J=25.2 Hz, $(CF_3)_2C$), 115.9, 125.5, 132.6, 158.9 (all s, aromatic), 125.9 (q, J=286.3 Hz, CF_3). ^{19}F NMR (CD_3OD): δ −63.8 (s, CF_3). IR (ATR, germanium): 1516, 1245, 1211, 1171, 1139 cm^{-1}. MS (EI) m/z (% rel int.): 336 (M^+, 21), 267 (100), 227 (9), 199 (15), 197 (12), 169 (6), 99 (28). HRMS (FI): M^+, found 336.0565. $C_{15}H_{10}F_6O_2$ requires 336.0585.

4.6. Catalytic hydrogenation of hexafluoroacetone[18]

To a 500 mL stainless-steel autoclave were charged 4.5 g of a 5% ruthenium on carbon catalyst (50% wet, 1 wt %, 1.1 mmol), 139 g of hydrogen fluoride (6.95 mol), and 86 g of hexafluoroacetone (0.52 mol) at 0 °C, and the mixture was cooled in an ice/water bath. The reaction vessel was flushed with nitrogen once and then with hydrogen twice. The reaction mixture was stirred under 1.0 MPa of hydrogen with controlling the temperature between 0 and 25 °C, whose ^{19}F NMR with an FEP tubing clarified quantitative conversion of HFA after 1 h (100% conversion and 99.9% selectivity by ^{19}F NMR). The resultant hexafluoropropan-2-ol was isolated by filtration of a catalyst, neutralization of an aqueous solution by inorganic bases followed by distillation (76% yield). ^{1}H NMR ($CDCl_3$): δ 6.46 (s, O*H*). ^{13}C NMR ($CDCl_3$): δ 70.3 (sept, J=34.2 Hz, C–OH), 122.0 (q, J=289.1 Hz, CF_3). ^{19}F NMR ($CDCl_3$): δ −76.0 (s). IR (ATR, germanium): 1377, 1286, 1180, 1103 cm^{-1}. MS (EI) m/z (% rel int.): 129 (25), 101 (29), 99 (100), 79 (28), 69 (21). HRMS (FI): M^+, found 168.0019. $C_3H_2F_6O$ requires 168.0010.

4.7. Catalytic hydrogenation of hexafluoroacetone with heavy-oxygen water

To a 100 mL stainless-steel autoclave, 2.74 g (0.137 mol) of $H_2{}^{18}O$ was charged and was frozen in a dry ice bath. A mixture of 82.2 g (4.11 mol) of HF and 22.74 g (0.137 mol) of HFA was then added and the vessel was allowed to warm to room temperature with stirring. This $HFA/HF/H_2{}^{18}O$ mixture (molar ratio: 1/30/1) was kept for 2 days at room temperature and a small amount of the mixture was used for measurement of NMR. In another 100 mL stainless-steel autoclave, 1 g of 5% palladium on carbon (50% wet, 0.5 wt %, 0.23 mmol) was placed and evacuated. To this reaction vessel, 99.6 g of the $HFA/HF/H_2{}^{18}O$ mixture was charged and was cooled in an ice/water bath. The reaction vessel was flushed with nitrogen once and with hydrogen twice. The reaction mixture was stirred and hydrogen was introduced so as to attain a pressure of 1.0 MPa and the temperature was kept between 0 and 10 °C throughout the hydrogenation reaction. Observation of the reaction mixture by ^{19}F NMR in an FEP tubing clarified that the conversion of HFA and the selectivity of the hydrogenation reaction were quantitative at the end of the 1 h reaction period. The reaction mixture was poured onto ice and was extracted with diisopropyl ether (IPE). An IPE solution containing HFIP was used for GC/MS analysis. HRMS (FI): M^+, found 167.9998. $C_3H_2F_6{}^{16}O$ requires 168.0010. M^+, found 170.0032. $C_3H_2F_6{}^{18}O$ requires 170.0052.

4.8. Computational methods

All calculations were performed with Gaussian03W[19] (revision B.03) at the B3LYP/6-311++G** level of theory, and 0 (complex and product) and 1 (TS) negative engenvalues were confirmed by frequency calculation.

Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2011.01.087.

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15. Colorless gas. Bp −28 °C ^{13}C NMR ($CDCl_3$): δ 114.2 (q, J=289.9 Hz, CF_3), 172.9 (sept, J=41.4 Hz, C=O). ^{19}F NMR ($CDCl_3$): δ −76.2 (s). IR (gas): 1807, 1341, 1273, 1218 cm^{-1}. HRMS (FI): M^+, found 165.9864. C_3F_6O requires 165.9853.
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