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The cross-aldol reaction of hexafluoroacetone (HFA) with ketones catalyzed by an acid

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Abstract

The cross-aldol reactions of hexafluoroacetone (HFA) and ketones using an acid catalyst are reported. When concentrated sulfuric acid was employed as the catalyst, HFA reacted regioselectively with various ketones at 50–100 °C to give the aldol adducts (**6**) in good yields. The reaction is initiated by an acid-catalyzed transformation of the ketone into the corresponding enol that reacts with HFA. The obtained adducts (**6**) can be reduced with hydrogen under a Ru/C catalyst to lead to the corresponding fluorine-containing diols (**13**).

Keywords: Hexafluoroacetone; Cross-aldol reaction; Ketones; Reduction; Fluorine-containing dioles

1. Introduction

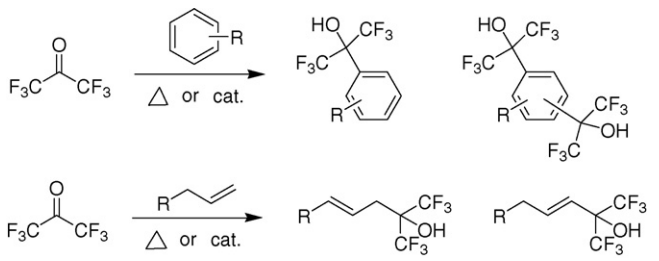
A variety of fluorine-containing organic compounds have been developed in the fields of medicines, agricultural chemicals, and advanced materials that show water repellency, oil repellency, low absorption, heat-resistance, weather resistance, anti-corrosion, transparency, photochemical sensitivity, low refractive index, or low dielectric constant. Thus, many papers have been appearing on the synthetic methods of the fluoro organic compounds. One useful methodology is to derive the target fluoro compounds from a versatile synthetic reagent that contains fluorine atom(s). Hexafluoroacetone (HFA) is one of the most important reagents for this purpose.

HFA is known to undergo Lewis acid-catalyzed or thermal reaction with aromatic compounds [1] or vinylic compounds [2] to give a 1:1 Friedel-Crafts-type adduct together with the corresponding 1:2 adducts (Scheme 1). Of course, the Lewis acid-catalyzed reactions proceed at a lower temperature than the thermal reactions [2b].

Interestingly, a high pressure accelerates the reaction of HFA with ketones. Thus, acetone reacts with HFA at 160 °C under a pressure of about 4 Mpa (Scheme 2) [5]. In this case, 1:2 double-aldol product is also formed as a by-product [6].

It is also known that HFA readily react with lithium enolates [3] or boron enolates as summarized in Scheme 3. In contrast, silyl enolates require the assistance of a Lewis acid [4] in the reaction with HFA leading to the cross-aldol adducts. It should be noted that these methodologies are so difficult to be performed in an industrial scale because the reagents are expensive and not easy to deal with.

Against these background, our investigation was initiated on the reaction of HFA with the enols that can be in equilibrium with the parent ketones (Scheme 4). As known generally, the equilibrium is conveniently achieved by the assistance of an acid.



Scheme 1. .

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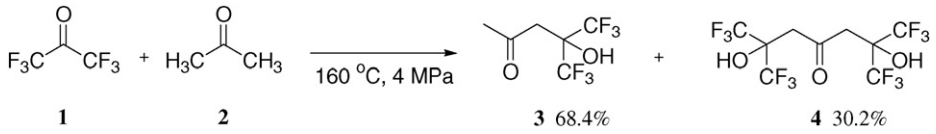
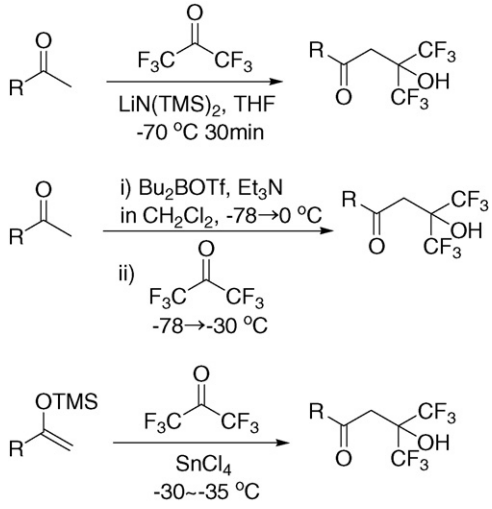
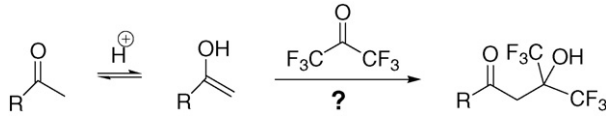


Scheme 2. .



Scheme 3. .



Scheme 4. .

2. Results and discussion

First, the reaction of HFA with acetone was chosen as a typical ketone and various acids were examined for their catalytic activity (Scheme 5). Acetone (0.24 mol) and concentrated sulfuric acid (0.04 g) were placed in a pressure-proof glass reactor and then HFA (0.12 mol) was introduced over 2 h at 50–60 °C under being stirred with a teflon-coated magnetic bar. The reaction was continued at a temperature of 50–60 °C for 3 h. The reaction mixtures were analyzed by gas chromatography. Other acids that are listed in Table 1 were also employed as the catalyst under the same conditions. A 1:2 adduct (**4**) was always produced as a byproduct.

As shown in Table 1 that summarizes the results, concentrated sulfuric acid gave the best result among the acids examined here: the yield of the expected **3** was 86% and the 1:2 adduct (**4**) was formed in a 4% yield (Entry 1). Hence, we decided to employ concentrated sulfuric acid as the catalyst for the reaction of HFA with the ketones. This is also because the concentrated sulfuric acid is one of the cheapest acids.

Table 1
Acid-mediated reaction of HFA with acetone

Entry	Acid	Temperature (°C)[a]	Conversion (%) of HFA	Yield (%)[b]	
				3	**4**
1	H_2SO_4	50	100	86	4
2	$(C_2H_5)_2O{\cdot}BF_3$	50	100	63	24
3	CF_3SO_3H	50	100	65	1
4[c]	CF_3CO_2H	80	100	66	32
5	$TiCl_3$	70	92	77	18.5
6	$TiCl_4$	70	95	70	19
7	$ZnCl_2$	90	1	–	–

[a] Reaction time was 3 h.
[b] Determined by GC.
[c] The pressure was reached to 0.5 MPa.

When an excess amount of acetone was used in the reaction with HFA in the presence of concentrated sulfuric acid, the yield of **3** remained unchanged as shown in Table 2. In these cases, a self condensation product of acetone was slightly increased.

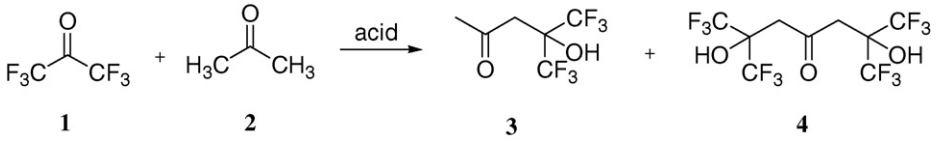
Therefore, we selected the reaction conditions using a slight excess of acetone and a catalytic amount (0.2 wt%) of concentrated sulfuric acid for the reaction of HFA with various ketones (Scheme 6). The results are given in Table 3.

In the reaction of HFA with alkyl methyl ketones (Entries 1–3), these methyl groups were always the most reactive. Thus, treatment of 2-butanone with HFA gave **6** (R^1 = H, R^2 = Et) in 85% yield along with a small amount (8% yield) of 4-hydroxy-

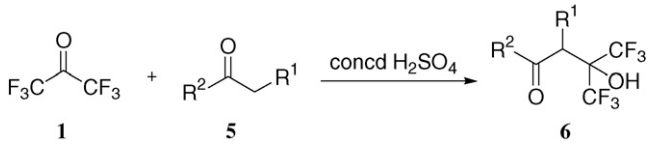
Table 2
Reaction of HFA with various amounts of acetone[a]

Entry	Acetone (**2**) equiv	Conversion (%) of **1**	Yield (%)[b]	
			3	**4**
1	1.0	90	88	2
2	1.5	100	87	3
3	2.0	100	86	4

[a] 50–60 °C, 3 h, max. 0.5 MPa.
[b] Determined by GC.



Scheme 5. .



1 5 6

Scheme 6. .

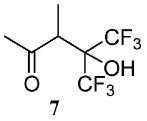
Table 3
Reaction of HF A with various ketones in the presence of concentrated sulfuric acid[a]

Entry	5		Yield(%)[b] of 6
	R^1	R^2	
1	H	Et	85[c] (52)
2	H	*i*-Pr	90 (73)
3	H	*i*-Bu	99 (80)
4	H	Ph	95 (80)
5[d]	Me	Et	98 (55)
6	$-(CH_2)_3-$		87 (82)
7	$-(CH_2)_4-$		56 (48)

[a] The reaction using 1.2 equiv of the ketone and 0.2 wt% of concentrated sulfuric acid was performed at 50–60 °C for 5 h.

[b] The yield was determined by GC. The value in parenthesis means the isolated yield.

[c] A byproduct (**7**) was formed in a 8% yield.



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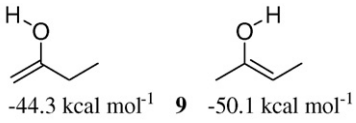
[d] Reaction temperature: 50–100 °C and reaction time was 10 h.

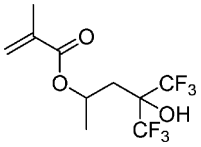
3-methyl-4-(trifluoromethyl)-5,5,5-trifluoro-2-pentanone (**7**) (Entry 1). When 3-methyl-2-butanone and 4-methyl-2-butanone were employed as **5**, we could not observe the formation of the products that were derived by the reaction of the isopropyl and isobutyl parts (Entries 2 and 3). As a matter of course, acetophenone (**5**; R^1 = H, R^2 = Ph) gave the corresponding **6** in 95% yield (Entry 4). Since the reaction of diethyl ketone became somewhat slow, a higher reaction temperature and a longer reaction time were required to complete the reaction (Entry 5). The reaction at 100 °C for 10 h resulted in the formation of **6** (R^1 = Me and R^2 = Et) in a 98% yield. Cyclic ketones, cyclopentanone and cyclohexanone, also reacted with of HFA to afford the corresponding aldols in 87% and 56% yields, respectively (Entries 6 and 7). The low yield in the latter case was attributable to the formation of the self condensation product of cyclohexanone.

As mentioned in the Section 1, the present aldol reaction is thought to proceed via an enol (**5′**) of the ketone (**5**), which reacts with HFA to give the aldol adduct (**6**) (Scheme 7).



8 -44.3 kcal mol^{-1} 9 -50.1 kcal mol^{-1}

Fig. 1. Heat of formation for the geometry-optimized enols of ethyl methyl ketone.



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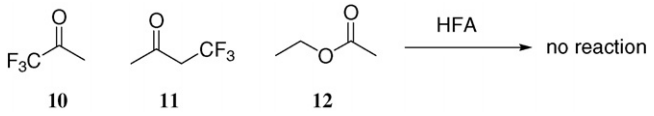
If **5′** reacts with the parent ketone (**5**) itself, the self condensation product would be formed. The alkyl methyl ketones form two types of enol that have the newly formed C=C bond in methyl and alkyl sites. It is generally known that the enol having the C=C bond in the alkyl site is thermodynamically favorable. The heat of formation was calculated with PM3 for two geometry-optimized enols of ethyl methyl ketone (Fig. 1): the enol (**9**) having the C=C bond at the ethyl side is more stable than another one (**8**). In the reaction of HFA with the alkyl methyl ketone (Entries 1–3 in Table 1), the major product is always derived from the enol that has a C=C bond in the methyl site. This suggests that the reaction of HFA with the enol occurs favorably at the less hindered site.

When an electron-withdrawing group is introduced into the ketone (**5**), the resulting enol is thought to become less reactive to HFA. Indeed, fluorine-substituted ketones (**10** and **11**) did not react with HFA. It is noteworthy that no adduct was obtained in the reaction of ethyl acetate (**12**) with HFA (Scheme 8).

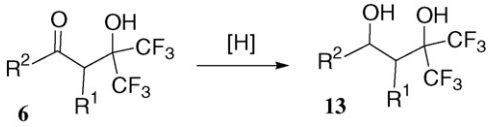
Since the aldol-type adducts are so unstable that they undergo either dehydration to give α,β-unsaturated ketones or the retro-aldol reaction to go back to the parent ketones. Hence, we tried the reduction of the aldol adducts (**6**) to lead to the corresponding diols (Scheme 9).

This is also because the diol (**13**; R^1 = H, R = Me) derived from the acetone-HFA aldol (**6**; R^1 = H, R = Me) is utilized as a



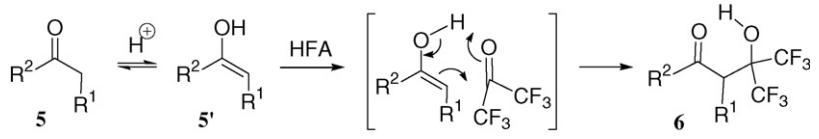
10 11 12

Scheme 8. .



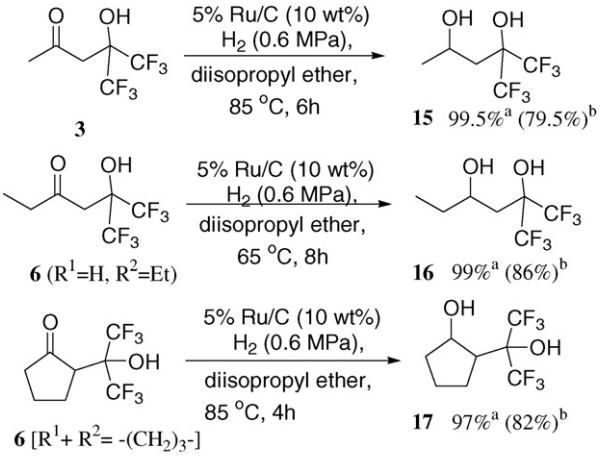
6 13

Scheme 9. .



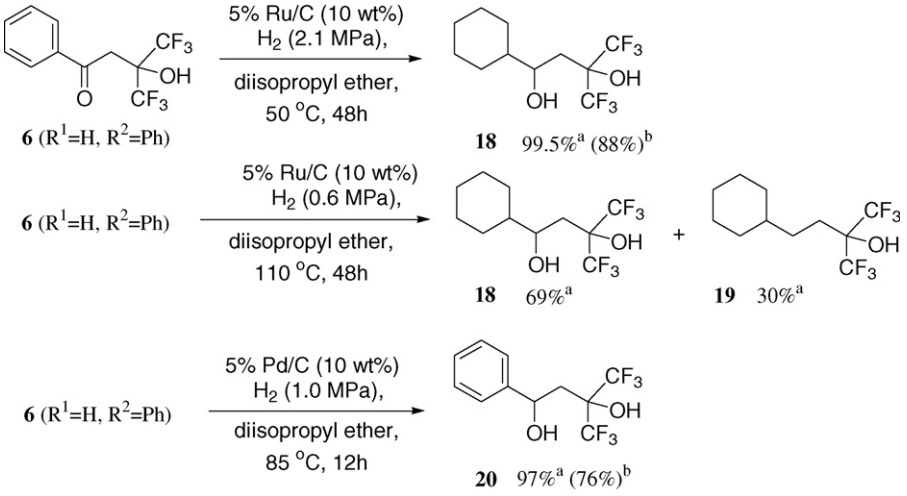
5 5′ 6

Scheme 7. .



[a]The yield was determined by GC anaqlysis.
[b]The value in parenthesis means the isolated yield.

Scheme 10. (a) The yield was determined by GC anaqlysis. (b)The value in parenthesis means the isolated yield.



[a]The yield was determined by GC analysis.
[b]The value in parenthesis means the isolated yield.

Scheme 11. (a) The yield was determined by GC analysis. (b) The value in parenthesis means the isolated yield.

raw material for the methacrylate (**14**) that is a monomer of photolithography resin [7].

Although the aldol adducts can be reduced with the aluminum isopropoxide in isopropyl alcohol (the Meerwein–Pondolf–Verley reduction) [5], this method disadvantageously uses a large quantity of aluminum isopropoxide, which is undesirable in an industrial process. Therefore, the catalytic reduction with hydrogen was examined. First, we examined the reduction of the acetone-HFA aldol (**3**) in the presence of Pd/C (10 wt%). At 0.6 Mpa pressure of hydrogen and 100 °C, the reduction was performed in THF containing a catalytic amount of Pd/C. However, the reduction did not occur even after 9 h and the starting **3** remained unchanged. Next, Ru/C was employed as a catalyst, **3** in diisopropyl ether was contacted with 0.6 Mpa of hydrogen in the presence of 10 wt% of Ru/C. Delightedly, the reaction proceeded so smoothly at 85 °C to finish after 6 h and give the expected diol (**15**) in 99.5% yield. Under the similar conditions, **6** (R^1 = H, R^2 = Et) and **6** [$R^1 + R^2$ = –$(CH_2)_3$–] were reduced, the reaction yields were as high as 99%, and 97%, respectively (Scheme 10).

When **6** (R^1 = H, R^2 = Ph) is reduced by 0.5 Mpa of hydrogen in the presence of Ru/C (10 wt%) at 110 °C for 48 h, the over-reduction to saturate the benzene ring occurred to give a 4,4,4-trifluoro-3-trifluoromethyl-1-cyclohexylbutane-1,3-diol (**18**) along with 1,1,1-trifluoro-2-trifluoromethyl-4-cyclohexyl-l-butanol (**19**). The reduction at 2.1 MPa hydrogen pressure and 50 °C required a long period of reaction time (48 h), but the yield of **18** became high (99.5%). We again examined the reduction of **6** (R^1 = H, R^2 = Ph) using Pd/C as a catalyst. To our surprise, the desired **20** was selectively obtained (Scheme 11). When the hydrogen pressure was 1.0 MPa, in the presence of 10 wt% of Pd/C in diisopropyl ether at 85 °C the reaction was completed within 12 h to give the reduction product **20** in 97% yield.

3. Conclusion

We found out that the reactions of ketones with HFA proceeds by the assistance of an acid. Concentrated sulfuric acid works as the catalyst that smoothly achieves the conversion of the ketones to the corresponding enols that react with FIFA to give the aldol-type 1:1 adduct (**6**). The obtained compounds (**6**) can be reduced with hydrogen under a Ru/C-catalyzed conditions to produce the corresponding fluorine-containing diols (**13**).

4. Experimental

4.1. General methods

^{1}H NMR and ^{19}F NMR spectra were recorded at 400 MHz on a JEOL α-400 and JEOL AL-400. ^{1}H NMR data were given in a parts per million (ppm) downfield from tetramethylsilane (TMS) as internal standard. ^{19}F NMR data were given in ppm upfield from CCl_3F as the internal standard. The abbreviations used are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Coupling constants (*J* values) are given in hertz (Hz). MS analyses were performed using a Shimadzu GCMS-QP2010 (EI at 70 eV) and a JEOL Automass II 150 (CI at 150 eV). Gas chromatography (GC) analyses were performed on a Shimadzu GC17A equipped with J & W DB-1 capillary column (30 m) and a FID detector.

4.2. Preparation of 5,5,5-trifluoro-4-hydroxy-4-(trifluoromethyl)pentan-2-one (*3*)

4.2.1. With concentrated sulfuric acid

To a 100 mL pressure-proof glass reactor equipped with a pressure gauge, a thermometer, and a gas introducing tube, a stirring magnet covered with tetrafluoroethylene resin was placed. After 14.1 g (0.24 mol) of acetone and 0.04 g of concentrated sulfuric acid were added, 20.0 g (0.12 mol) of 1,1,1,3,3,3-hexafluoroacetone (HFA) was introduced over 2 h under being stirred at 50–60 °C. The pressure was kept to be 0.4 MPa. The resultant mixture was stirred at 50–60 °C for 3 h. A small aliquot was analyzed by gas chromatography (GC), which showed that the target 5,5,5-trifluoro-4-hydroxy-4-(trifluoromethyl)pentan-2-one (**3**) and 1,1,1,7,7,7-hexafluoro-2,6-dihydroxy-2,6-bis(trifluoromethyl)heptan-4-one (**4**) were present in the reaction mixture in 86% and 4% yields, respectively. By distillation (68–70 °C/5.3 kPa; 1.0 kPa = 7.5 Torr), the reaction mixture (34.1 g) was purified to give 5,5,5-trifluoro-4-hydroxy-4-(trifluoromethyl)pentan-2-one (**3**; 17.0 g, purity: 99.5%, 63% yield) as a colorless oil together with 1,1,1,7,7,7-hexafluoro-2,6-dihydroxy-2,6-bis(trifluoromethyl)heptan-4-one. 5,5,5-Trifluoro-4-hydroxy-4-(trifluoromethyl)pentan-2-one (**3**): ^{1}H NMR ($CDCl_3$) δ 6.78 (1H, s), 2.96 (2H, s), 2.34 (3H, s); ^{19}F NMR ($CDCl_3$) δ −78.9 (6F, s); EI-MS *m/z* (rel. int.): 225 $[M+1]^+$ (0.4), 209 $[M\text{-}CH_3]^+$ (2.5), 181 $[M\text{-}CH_3CO]^+$ (1.9), 155 $[M\text{-}CF_3]^+$ (1.5), 43 $[CH_3CO]^+$ (100). Anal. Calcd for $C_6H_6F_6O_2$: C, 32.16; H, 2.70. Found: C, 32.16; H, 2.75. 1,1,1,7,7,7-Hexafluoro-2,6-dihydroxy-2,6-bis(trifluoromethyl)heptan-4-one(**4**): ^{1}H NMR acetone-d_6) δ 7.21 (2H, s), 3.45 (4H, s); ^{19}F NMR (acetone-d_6) δ −76.8 (12F, s); EI-MS *m/z* (rel. int.): 391 $[M+1]^+$ (1), 321 $[M\text{-}CF_3]^+$ (1), 209 $[M\text{-}C_4H_3OF_6]^+$ (100), 191 $[M\text{-}C_4H_3OF_6\text{–}H_2O]^+$ (4), 181 $[C_4H_3OF_6]^+$ (9), 161 $[C_4H_2OF_5]^+$ (4), 69 $[CF_3]^+$ (1.2), 43 $[CH_3CO]^+$ (4). Anal. Calcd for $C_9H_6F_{12}O_3$: C, 27.71; H, 1.55. Found: C, 27.58; H, 1.31.

4.2.2. Reaction with BF_3 etherate

To the same glass reactor mentioned above, 13.3 g (0.23 mol) of acetone and 0.04 g (0.28 mmol) of BF_3 etherate were added. Then, 19.0 g (0.11 mol) of HFA was introduced over 1 h under being stirred at 50–60 °C. The pressure was maintained at 0.5 MPa. The mixture was further stirred at 50–60 °C for 3 h. As a result, 32.3 g of a reaction mixture was obtained. The reaction mixture was analyzed by GC to contain **3** and **4** in 63% and 24% yields, respectively.

4.2.3. Reaction with trifluoromethanesulfonic acid

The same procedure mentioned in Section 4.2.2 was performed except that BF_3 etherate was replaced with 0.04 g (0.27 mmol) of trifluoromethanesulfonic acid. It was shown by GC analysis that the reaction mixture (32.3 g) contains **3** and **4** in 65% and 1% yields, respectively.

4.2.4. Reaction with trifluoroacetic acid

The same procedure mentioned in Section 4.2.2 was performed using 0.04 g (0.35 mmol) of trifluoroacetic acid instead of BF_3. GC analysis of the reaction mixture (32.3 g) revealed that the yields of **3** and **4** were 66% and 32% yields, respectively.

4.2.5. Reaction with titanium trichloride

The same procedure mentioned in Section 4.2.2 was repeated by using 0.04 g (0.26 mmol) of titanium trichloride instead of BF_3 etherate. GC analysis of the reaction mixture (30.7 g) showed that the yields of **3** and **4** were 77% and 18.5% yields, respectively.

4.2.6. Reaction with titanium tetrachloride

Similarly, 0.04 g (0.21 mmol) of titanium tetrachloride was employed instead of BF_3 etherate. The reaction mixture (31.5 g) was shown by GC to contain **3** and **4** in 70% and 19% yields, respectively.

4.3. Reaction of HFA with the ketone (*5*) in the presence of concentrated sulfuric acid

4.3.1. Preparation of 6,6,6-trifluoro-5-hydroxy-5-(trifluoromethyl)-3-hexanone (*6*; R^1 = H, R^2 = Et). A typical procedure

After 10.0 g (0.14 mol) of 2-butanone and 0.04 g of concentrated sulfuric acid were placed in the same apparatus mentioned in Section 4.2.1, 20.0 g (0.12 mol) of HFA was introduced over 2 h under being stirred at 50–60 °C. The pressure was also kept to be 0.5 MPa. Then, the mixture was stirred at a temperature of 50–60 °C for 3 h. It was found by GC that the reaction mixture (27.5 g) contained 6,6,6-trifluoro-5-

hydroxy-5-(trifluoromethyl)hexan-3-one (**6**; R^1 = H, R^2 = Et) and 5,5,5-trifluoro-4-hydroxy-3-methyl-4-(trifluoromethyl)-pentan-2-one (**7**) in 85% and 8% yields, respectively. The reaction mixture was purified by distillation (75–76 °C/6.7 kPa) to give 15.5 g (52% yield) of **6** (R^1 = H, R^2 = Et).

6,6,6-Trifluoro-5-hydroxy-5-(trifluoromethyl)-3-hexanone (**6**; R^1 = H, R^2 = Et): a colorless oil; bp 75–76 °C/6.7 kPa; ^{1}H NMR ($CDCl_3$) δ 6.86 (1H, s), 2.92 (2H, s), 2.61 (2H, q, J = 7.2 Hz), 1.11 (3H, t, J = 7.2 Hz); ^{19}F NMR ($CDCl_3$) 5–78.8 (6F, s); EI-MS m/z (rel. int.): 239 $[M+1]^+$ (0.2), 209 $[M\text{-}C_2H_5]^+$ (20), 181 $[M\text{-}C_2H_5CO]^+$ (7.7), 69 $[CF_3]^+$ (16), 57 $[C_2H_5CO]^+$ (1 0 0), 29 $[C_2H_5]^+$ (39). Anal. Calcd for $C_7H_8F_6O_2$: C, 35.31; H, 3.39. Found: C, 34.83; H, 3.09.

5,5,5-Trifluoro-4-hydroxy-3-methyl-4-(trifluoromethyl)-2-pentanone (**7**): ^{1}H NMR ($CDCl_3$) δ 6.86 (1H, s), 2.92 (2H, s), 2.61 (2H, q, J = 7.2 Hz), 1.11 (3H, t, J = 7.2 Hz); ^{19}F NMR ($CDCl_3$): δ −78.8 (6F, s); EI-MS m/z (rel. int.): 223 $[M\text{-}CH_3]^+$ (0.1), 69 $[CF_3]^+$ (5), 43 $[CH_3CO]^+$ (100), 28 $[CO]^+$ (1.9), 18 $[H_2O]^+$ (41), 17 $[OH]^+$ (9), 15 $[CH_3]^+$ (3).

Similarly, various ketones were subjected to the reaction with HFA in the presence of concentrated sulfuric acid. Their yields were given in Table 3. The physical properties of the obtained **6** were shown in the following.

4.3.2. 6,6,6-Trifluoro-5-hydroxy-2-methyl-5-(trifluoromethyl)-3-hexanone (**6**: R^1 = H, R^2 = i-Pr)

A colorless oil: bp 52–54 °C/4.0 kPa; ^{1}H NMR ($CDCl_3$) δ 7.03 (1H, s), 2.96 (1H, s), 2.70 (1H, sep, J = 7.1 Hz), 1.17 (6H, d, J = 7.1 Hz); ^{19}F NMR ($CDCl_3$): δ −78.3 (6F, s); EI-MS m/z (rel. int.) 253 $[M+1]^+$ 0.2, 209 $[M\text{-}C_3H_7]^+$ (18), 181 $[M\text{-}C_3H_7CO]^+$ (4), 71 $[C_3H_7CO]^+$ (100), 43 $[C_3H_7]^+$ (64). Anal. Calcd for $C_8H_{10}F_6O_2$: C, 38.11; H, 4.00. Found: C, 38.27; H, 4.24.

4.3.3. 1,1,1-Trifluoro-2-hydroxy-6-methyl-2-(trifluoromethyl)-4-heptanone (**6**: R^1 = H, R^2 = i-Bu)

A colorless oil: bp 75–78 °C/2.9 kPa; ^{1}H NMR ($CDCl_3$) δ 6.93 (1H, broad s), 2.90 (2H, s), 2.46 (2H, d, J = 6.6 Hz), 2.16 (1H, sep, J = 6.6 Hz), 0.95 (6H, d, J = 6.6 Hz); ^{19}F NMR ($CDCl_3$): δ −78.7 (6F, s); EI-MS m/z (rel. int.) 266 $[M]^+$ (0.9), 251 $[M\text{-}CH_3]^+$ (9), 224 $[M\text{-}C_3H_6]^+$ (22), 209 $[M\text{-}C_2H_5CO]^+$ (22), 181 $[M\text{-}C_4H_9CO]^+$ (7), 85 $[C_4H_9CO]^+$ (72), 69 $[CF_3]^+$ (22), 57 $[C_2H_5CO]^+$ (100), 43 $[C_3H_7]^+$ (49), 41 $[C_3H_5]^+$ (44). Anal. Calcd for $C_9H_{12}F_6O_2$: C, 40.61; H, 4.54. Found: C, 40.78; H, 4.90.

4.3.4. 4,4,4-Trifluoro-3-hydroxy-1-phenyl-3-(trifluoromethyl)-1-butanone (**6**: R^1 = H, R^2 = Ph)

A colorless viscous oil: bp 135–137 °C/2.9 kPa; ^{1}H NMR ($CDCl_3$) δ 7.95 (2H, m), 7.68 (1H, m), 7.52 (1H, m), 7.21 (1H, s), 3.46 (2H, s); ^{19}F NMR ($CDCl_3$): δ −78.5 (6F, s); EI-MS m/z (rel. int.): 286 $[M]^+$ (1), 217 $[M\text{-}CF_3]^+$ (0.4), 105 $[C_6H_5CO]^+$ (100), 77 $[C_6H_5]^+$ (46), 69 $[CF_3]^+$ (6), 51 (15). Anal. Calcd for $C_{11}H_8F_6O_2$: C, 46.17; H, 2.82. Found: C, 46.06; H, 2.19.

4.3.5. 6,6,6-Trifluoro-5-hydroxy-4-methyl-5-(trifluoromethyl)-3-hexanone (6: R^1 = Me, R^2 = Et)

A colorless oil: bp 97–99 °C/12.0 kPa; ^{1}H NMR ($CDCl_3$): δ 6.58 (1H, s), 3.17 (1H, q, J = 7.1 Hz), 2.66 (2H, q, J = 7.1 Hz), 1.32 (3H, d, J = 7.1 Hz), 1.10 (3H, t, J = 7.1 Hz); ^{19}F NMR ($CDCl_3$): δ −79.1 (6F, s); EI-MS m/z (rel. int.): 253 $[M+1]^+$ (4), 223 $[M\text{-}C_2H_5]^+$ (12), 175 $[M\text{-}C_2H_5CO\text{-}HF]^+$ (10), 125 $[M\text{-}C_2H_5CO\text{-}HCF_3]^+$ (30), 97 (7), 69 $[CF_3]^+$ (12), 57 $[C_2H_5CO]^+$ (1 0 0). Anal. Calcd for $C_8H_{10}F_6O_2$: C, 38.11; H, 4.00. Found: C, 38.05; H, 3.84.

4.3.6. 2-(1,1,1,3,3,3-Hexafluoro-2-hydroxypropan-2-yl)cyclopentanone [**6**: $R^1 + R^2 = -(CH_2)_3-$]

A colorless oil: bp 81–83 °C/2.9 kPa (1.0 kPa = 7.5 Torr); ^{1}H NMR ($CDCl_3$) δ 7.01 (1H, s), 2.33 (6H, m), 1.77 (1H, m); ^{19}F NMR ($CDCl_3$) δ −72.5 (3F, q, J = 9.2 Hz), −78.3 (3F, q, J = 9.2 Hz); EI-MS m/z (rel. int.): 250 $[M]^+$ (14), 190 $[M\text{-}C_3H_6\text{-}H_2O]^+$ (3), 163 (4), 125 $[M\text{-}C_2H_3CO\text{-}HCF_3]^+$ (4), 83 $[C_4H_7CO]^+$ (2), 55 $[C_2H_3CO]^+$ (1 0 0). Anal. Calcd for $C_8H_8F_6O_2$: C, 38.41; H, 3.22. Found: C, 38.10; H, 3.15.

4.3.7. 2-(1,1,1,3,3,3-Hexafluoro-2-hydroxypropan-2-yl)cyclohexanone [**6**: $R^1 + R^2 = -(CH_2)_4-$]

A colorless oil: bp 98–100 °C/2.2 kPa; ^{1}H NMR ($CDCl_3$) δ 7.25 (1H, s), 3.02 (1H, m), 2.11 (8H, m); ^{19}F NMR ($CDCl_3$) δ −72.6 (3F, q, J = 10.2 Hz), −76.8 (3F, q, J = 10.2 Hz); EI-MS m/z (rel. int.): 264 $[M]^+$ (4), 195 $[M\text{-}CF_3]^+$ (6), 125 $[M\text{-}C_3H_5CO\text{-}HCF_3]^+$ (5), 97 $[C_5H_9CO]^+$ (21), 83 $[C_4H_7CO]^+$ (8), 69 $[CF_3]^+$ (26), 55 $[C_2H_3CO]^+$ (1 0 0), 41 $[C_3H_5]^+$ (28). Anal. Calcd for $C_9H_{10}F_6O_2$: C, 40.92; H, 3.82. Found: C, 40.73; H, 3.68.

4.4. Reduction of 5,5,5-trifluoro-4-hydroxy-4-(trifluoromethyl)-2-pentanone (**3**)

A stirring magnet coated with tetrafluoroethylene resin was placed in a 100 mL pressure-proof glass reactor equipped with a pressure gauge, and a thermometer. After 20 mL of diisopropyl ether, 20.0 g (0.089 mol) of 5,5,5-trifluoro-4-hydroxy-4-(trifluoromethyl)pentan-2-one (**3**: purity 99.5%) and 2.0 g of 5% Ru/C (water content: 50%; made by N.E. CHEMCAT CORPORATION, Japan) were successively introduced, the atmosphere of the reactor was replaced with hydrogen, and then the hydrogen pressure was adjusted to 0.6 MPa. The reactor was heated at 85 °C (internal temperature) for 6 h. It was shown by GC analysis the reaction mixture contained 99.5% 1,1,1-trifluoro-2-(trifluoromethyl)pentane-2,4-diol (**13**: R^1 = H, R^2 = Me) and 0.5% of by-products. After the ruthenium catalyst was filtered off, the filtrate was purified by distillation (85–87 °C/4.6 kPa) to give 16.0 g (79.5% yield) 1,1,1-trifluoro-2-(trifluoromethyl)pentane-2,4-diol (**15**; purity: 99.2%,).

A colorless viscous oil: ^{1}H NMR ($CDCl_3$) δ 6.62 (1H, s), 4.44 (1H, m), 2.79 (1H, d, J = 3.9 Hz), 2.04 (2H, m), 1.30 (3H, d, J = 6.1 Hz); ^{19}F NMR ($CDCl_3$) δ −76.2 (3F, q, J = 10.7 Hz), −80.0 (3F, q, J = 10.7 Hz); EI-MS m/z (rel. int.): 227 $[M+1]^+$ (0.04), 211 $[M\text{-}CH_3]^+$ (6), 145 (6), 139 $[M\text{-}H_2O\text{-}CF_3]^+$ (4), 123 (2.9), 91 (8), 69 $[CF_3]^+$ (17), 45 $[C_2H_4OH]^+$ (100), 41 $[C_3H_5]^+$ (7). Anal. Calcd for $C_6H_8F_6O_2$: C, 31.87; H, 3.57. Found: C, 31.91; H, 3.36.

4.5. Hydrogenation of 6,6,6-trifluoro-5-hydroxy-5-(trifluoromethyl-3-hexanone (**6**: R^1 = H, R^2 = Et)

In the manner similar to Section 4.4, **6** (R^1 = H, R^2 = Et) was reduced to give 1,1,1-trifluoro-2-(trifluoromethylhexane-2,4-diol (**16**) in 86% yield (GC yield: 99%).

A colorless oil: bp 88–92 °C/2.0 kPa; ^{1}H NMR ($CDCl_3$) δ 6.69 (1H, s), 4.15 (1H, m), 2.95 (1H, s), 2.04 (2H, m), 1.55 (2H, m), 0.96 (3H, t, J = 7.6 Hz); ^{19}F NMR ($CDCl_3$): δ −76.1 (3F, q, J = 10.2 Hz), −79.9 (3F, q, J = 10.2 Hz); EI-MS *m/z* (rel. int.): 241 $[M+1]^+$ (0.6), 211 $[M\text{-}C_2H_5]^+$ (77), 145 (38), 69 $[CF_3]^+$ (22), 59 $[C_3H_6OH]^+$ (1 0 0), 31 $[CH_2OH]^+$ (48). Anal. Calcd for $C_7H_{10}F_6O_2$: C, 35.01; H, 4.20. Found: C, 34.79; H, 4.02.

4.6. Hydrogenation of 2-[1-hydroxr-2,2,2-trifluorol-1(trifluoromethyl)ethyl])cyclopentanone [**6**: $R^1 + R^2 = -(CH_2)_3-$]

In the manner similar to 4.4, **6** [$R^1 + R^2 = -(CH_2)_3-$] was reduced to give 2-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)cyclopentanol (**17**) in 82% yield (GC yield: 97%).

A colorless viscous oil: bp 110–115 °C/2.8 kPa; ^{1}H NMR ($CDCl_3$) δ 6.32 (1H, s), 4.73 (1H, m), 2.33 (1H, d, J = 2.9 Hz), 1.96 (7H, m); ^{19}F NMR ($CDCl_3$) δ −75.1 (3F, q, J = 12.2 Hz), −75.8 (3F, q, J = 12.2 Hz); EI-MS *m/z* (rel. int.): 252 $[M]^+$ (0.5), 234 $[M\text{-}H_2O]^+$ (9), 183 $[M\text{-}CF_3]^+$ (2), 165 $[M\text{-}H_2O\text{-}CF_3]^+$ (9), 147 (5), 127 (7), 85 $[C_5H_7OH]^+$ (3), 71 (8), 69 $[CF_3]^+$ (22), 67 $[C_5H_7]^+$ (17), 57 $[C_3H_5O]^+$ (1 0 0), 44 $[C_2H_4O]^+$ (43). Anal. Calcd for $C_8H_{10}F_6O_2$: C, 38.11; H, 4.00. Found: C, 37.92; H, 3.80.

4.7. Hydrogenolysis of 4,4,4-trifluoro-3-hydroxy-1-phenyl-3-(trifluoromethyl)butan-1-one (**6**, R^1 = H, R^2 = Ph)

4.7.1. With Ru/C catalyst

In a 100 mL pressure-proof stainless steel (SUS316) reactor equipped with a thermometer and a pressure gauge, a stirring magnet coated with tetrafluoroethylene resin was placed and 10.4 g (0.036 mol) of **6** (R^1 = H, R^2 = Ph), 1.0 g of 5% Ru/C, and 20 mL of diisopropyl ether were added. The atmosphere of the reactor was replaced with hydrogen, and then the hydrogen pressure was adjusted to 2.1 MPa. The reactor was heated at 50 °C (internal temperature) in an oil bath for 48 h under being magnetically stirred. The analysis by GC showed that the yield of l-cyclohexy1-4,4,4-trifluoro-3-(trifluoromethyl)butane-l,3-diol (**18**) was 99.5%. The ruthenium catalyst was filtered off and the filtrate was concentrated in vacuo.

The residue was purified by recrystallization from hexane to give 1-cyclohexyl-4,4,4-trifluoro-3-(trifluoromethyl)butane-l,3-diol (**18**, 9.33 g: 88% yield).

Similarly, the hydrogenolysis of **6** (R^1 = H, R^2 = Ph) was performed at 110 °C under the hydrogen pressure of 0.6 MPa. The reaction time was 48 h to form **18** in 69% yield (GC) along with 4-cyclohexyl-1,1,1-trifluoro-2-(trifluoromethyl)-2-butanol (GC yield: 30%).

18: colorless crystals: mp 58–60 °C; ^{1}H NMR ($CDCl_3$) δ 6.31 (1H, s), 4.01 (1H, s), 2.2 (1H, m), 2.06 (3H, m), 1.60 (6H, m), 1.21 (3H, m); ^{19}F NMR ($CDCl_3$) δ −75.9 (3F, d, J = 10.7 Hz), −72.9 (3F, d, J = 9.2 Hz); CI-MS *m/z* (rel. int.) 277 $[M\text{–OH}]^+$ (1 0 0), 211 $[M\text{-}C_6H_{11}]^+$ (26), 83 $[C_6H_n]^+$ (56). Anal. Calcd for $C_{11}H_{16}F_6O_2$: C, 44.90; H, 5.48. Found: C, 44.88; H, 5.41.

19: a colorless oil; ^{1}H NMR ($CDCl_3$) δ 2.86 (1H, s), 1.92 (2H, m), 1.70 (5H, m), 1.39 (2H, m), 1.18 (4H, m), 0.93 (2H, m); ^{19}F NMR ($CDCl_3$) δ −77.1 (6F, s); CI-MS *m/z* (rel. int.): 278 $[M]^+$ (1), 83 $[C_6H_{11}]^+$ (1 0 0), 69 $[CF_3]^+$ (10), 55 $[C_4H_7]^+$ (64), 41 $[C_3H_5]^+$ (24), 18$[H_2O]^+$(9).

4.7.2. With Pd/C catalyst

In the same glass reactor mentioned in 4.7.1, 20 mL of diisopropyl ether, 10.4 g (0.036 mol) of **6** (R^1 = H, R^2 = Ph), and 1.0 g of 5% Pd/C (water content: 50%; made by N.E. CHEMCAT CORPORATION, Japan) were placed. The atmosphere of the reactor was replaced with hydrogen, and then the hydrogen pressure was adjusted to 1.0 MPa. The reactor was heated at 40 °C by an oil bath for 12 h. It was found by GC analysis that l-phenyl-4,4,4-trifluoro-3-(trifluoromethyl)butane-l,3-diol (**20**) was formed in 97% yield. The palladium catalyst was filtered off and the filtrate was purified by distillation to give **20** (7.97 g, 76% yield).

20: a colorless viscous oil; bp 140–143 °C/2.0 kPa; ^{1}H NMR ($CDCl_3$) δ 7.29 (5H, m), 6.41 (1H, s), 5.24 (1H, d, J = 11.7 Hz), 2.91 (1H, s), 2.29 (2H, m); ^{19}F NMR ($CDCl_3$): δ −75.8 (3F, q, J = 9.9 Hz), −79.7 (3F, q, J = 9.9 Hz); EI-MS *m/z* (rel. int.): 288 $[M]^+$ (1), 107 $[C_7H_6OH]^+$ (100), 79 $[C_6H_7]^+$ (63), 77 $[C_6H_5]^+$ (35), 69 $[CF_3]^+$ (9), 51 (12). Anal. Calcd for $C_{11}H_{10}F_6O_2$: C, 45.84; H, 3.50. Found: C, 45.78; H, 3.55.

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