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Lewis Acid Catalyzed Aldol-Type Reaction of 1,1-Difluorovinyl Methyl Ether Derivatives

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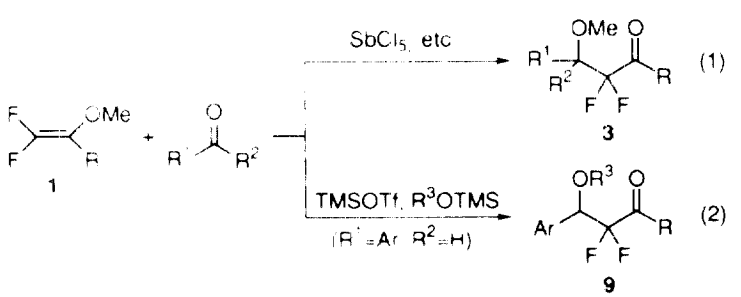
Abstract: In the presence of Lewis acid, such as $SbCl_5$, $SbCl_6$•NAr_3 or $Cu(OTf)_2$, difluorovinyl methyl ether (1,1-difluoro-2-methoxy-1-alkene) **1** reacted with carbonyl compounds to give *O*-methylated aldol-type products **3** in good yields, while Lewis acid, such as TMSOTf, $TiCl_4$ or BF_3•Et_2O, did not work in these reactions. On the other hand, TMSOTf was found an effective catalyst for the reaction of **1** with carbonyl compounds in the presence of alkyl TMS ether **8** to give *O*-alkylated aldol-type products **9** in good yields.

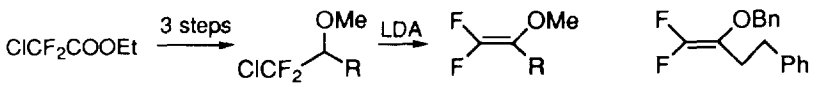
Aldol reaction plays a fundamental role in synthetic organic chemistry, and in particular development of a variety of enolates has opened wide applications of this reaction.[1] It is also the case in fluorinated enolate chemistry in line with a recent recognition of importance of fluorinated compounds in medicinal chemistry and material science due to their unique properties.[2,3] For the synthesis of α,α-difluoro carbonyl compounds, organometallic chemistry using α-halo-α,α-difluoromethyl ketone[4] and halodifluoroacetate[5] has widely been investigated. In general, these methods involve the reaction of electrophiles with *in situ* generated unstable intermediates such as metal enolates or silyl enol ethers and it was often claimed the lack of reproducibility of reported procedures.[6] Contrary to the instability of these reactive species, 1,1-difluorovinyl alkyl ether derivatives are generally readily obtainable and stable enough to store without special caution, although these are expected to be less reactive in the reaction with aldehyde or ketone. Therefore, for the utilization of 1,1-difluorovinyl alkyl ether as a building block, it is needed to find out an effective catalyst or reaction system and to examine the structure of the product obtained. Recently, the corresponding hydrocarbon counterpart, such as 2-methoxy-1-alkene, has been shown to undergo the Lewis acid promoted reaction with aldehydes to give ene-like reaction products.[7] In this paper, we report that an *O*-alkylated aldol-type product **3** or **9**, not the ene-type product, is obtained by the Lewis acid catalyzed reaction of 1,1-difluorovinyl methyl ether **1** with carbonyl compound **2**.



Reaction of 1,1-difluorovinyl methyl ethers 1 with carbonyl and related compounds

As typical 1,1-difluorovinyl alkyl ethers, we chose methyl ethers having *p*-methoxyphenyl, phenyl and phenethyl substituents **1a-1c**, and benzyl ether **1d**. These vinyl ethers were easily prepared through dehydrochlorination of 2-methoxy-1,1-difluoroalkyl chlorides obtained from ethyl chlorodifluoroacetate (Scheme 1).[4a]

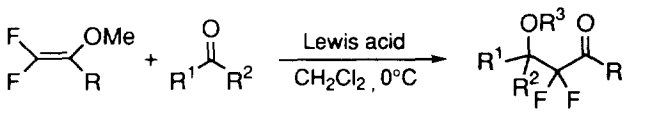
Scheme 1



1a R=C_6H_4OMe-*p* **1d**
1b R=Ph
1c R=CH_2CH_2Ph

Reaction of difluorovinyl ether **1** with carbonyl compounds was conducted in the presence of a catalytic amount of Lewis acid (Scheme 2, Table 1).

Scheme 2



1 **2** **3** R^3=Me **4** R^3=H

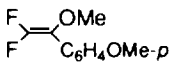
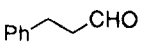
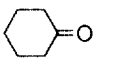
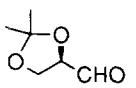
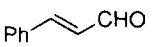
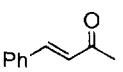
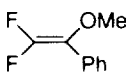
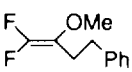
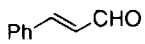
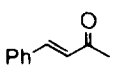
First, we examined the effect of Lewis acid in the reaction of **1a** with benzaldehyde. Among the Lewis acids examined, $SbCl_6$•NAr3,[8] $SbCl_5$ or $Cu(OTf)_2$ was found to work effectively to give *O*-methylated aldol product **3a-1** in high yield, along with a small amount of hydroxyl compound **4a-1** (Runs 1-3). $TiCl_4$, effective in the aldol reaction of *gem*-difluoroenol silyl ethers with aldehyde,[4c,4d] or other Lewis acids such as BF_3•OEt and TMSOTf showed low efficacy for the reaction; most of the starting aldehyde remained unchanged. $SbCl_6$•NAr3, a stable crystalline aminium radical ion complex,[8] effectively mediated the aldol-type reaction of **1a** with not only aromatic aldehyde but also aliphatic aldehyde, ketone or acetal (Runs 4, 6-8). 2,3-*O*-Isopropylideneglyceraldehyde reacted on the acetal moiety, not on the aldehyde group, to give the product **5a** in 48 % yield. Difluorovinyl ethers **1b** and **1c** also reacted with benzaldehyde in the presence of $SbCl_6$•NAr3 or $SbCl_5$ to give the corresponding *O*-methylated aldol products **3** in good yields. It should be noted that the reaction of **1c** having allylic hydrogen with aldehyde gave *O*-methylated aldol-type product **3**, not the ene-type product (Runs 13-15), since nonfluorinated vinyl ether gave the ene-type product.[7] With α,β-unsaturated aldehyde, antimony catalyst did not work well to give a complex mixture, while $Cu(OTf)_2$ effected the reaction to give the aldol-type product (Runs 9, 15). With α,β-unsaturated ketone (benzalacetone), 1,4-addition product **6** was obtained in the presence of antimony catalyst (Runs 10, 16).

Reaction of the benzyl ether derivative **1d** with benzaldehyde under similar conditions as above (catalyst: $SbCl_6$•NAr3) gave the *O*-benzylated aldol-type product **3d** (R^1=Ph, R^2=H, R^3=Bn) in low yield (16 %) in addition to the product **4a-1** (53%). It should be noted that $SbCl_6$•NAr3, showing a highly oxidizing power, can be used as a reagent for cleavage of benzyl ethers *via* single electron transfer (SET) process.[9]

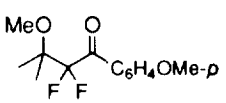
Reaction of 1a with aldehyde mediated by ROTMS and TMSOTf

Reaction of **1** with aldehyde or dimethyl acetal compound leading to *O*-methylated aldol-type product **3** as described above should involve an activation of carbonyl group or acetal moiety by coordination with Lewis acid. Due to low nucleophilicity of **1** by fluorine substituents,[4c] strong Lewis acid was required for

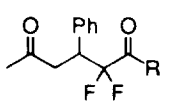
Table 1. Lewis acid catalyzed reaction of **1** with carbonyl and acetal compounds [a)]

Run	1	2	Lewis acid [b)]	3 (Yield %)	4 (Yield %)
1	 **1a**	PhCHO	$SbCl_6$•NAr_3 [c)]	**3a-1** 86	**4a-1** 6
2	**1a**	PhCHO	$SbCl_5$	**3a-1** 74	**4a-1** 13
3	**1a**	PhCHO	$Cu(OTf)_2$ [d)]	**3a-1** 79	**4a-1** 19
4	**1a**	$PhCH(OMe)_2$	$SbCl_6$•NAr_3 [c)]	**3a-1** 95	–
5	**1a**	$PhCH(OMe)_2$	$SbCl_5$	**3a-1** 92	–
6	**1a**		$SbCl_6$•NAr_3 [c)]	**3a-2** 77	–
7	**1a**		$SbCl_6$•NAr_3 [c)]	**3a-3** 90	–
8	**1a**		$SbCl_6$•NAr_3 [c)]	(**5a** 48) [e)]	–
9	**1a**		$Cu(OTf)_2$ [d)]	**3a-4** 20	**4a-4** 17
10	**1a**		$SbCl_6$•NAr_3 [c)]	(**6a** 45) [f)]	–
11	 **1b**	PhCHO	$SbCl_6$•NAr_3 [c)]	**3b** 80	**4b** 10
12	**1b**	$PhCH(OMe)_2$	$SbCl_6$•NAr_3 [c)]	**3b** 20	(**7b** 70) [g)]
13	 **1c**	PhCHO	$SbCl_6$•NAr_3 [c)]	**3c-1** 78	**4c-1** 11
14	**1c**	PhCHO	$SbCl_5$	**3c-1** 72	**4c-1** 9
15	**1c**		$Cu(OTf)_2$ [d)]	**3c-2** 29	**4c-2** 25
16	**1c**		$SbCl_5$	(**6c** 44) [f)]	–

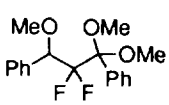
a) Reaction conditions : Lewis acid, 30 mol% ; temperature, 0°C ; solvent, CH_2Cl_2. b) In these reactions, $TiCl_4$, BF_3•Et_2O or TMSOTf was not effective as a Lewis acid. c) Ar = 4-bromophenyl. d) Solvent : CH_3CN. e) Reaction occurred at the acetal moiety to give **5a**. f) 1,4-Addition product **6** was obtained. g) **7b** was isolated as a major product.



5a



6a R=C_6H_4OMe-*p*
6c R=CH_2CH_2Ph



7b

Scheme 3

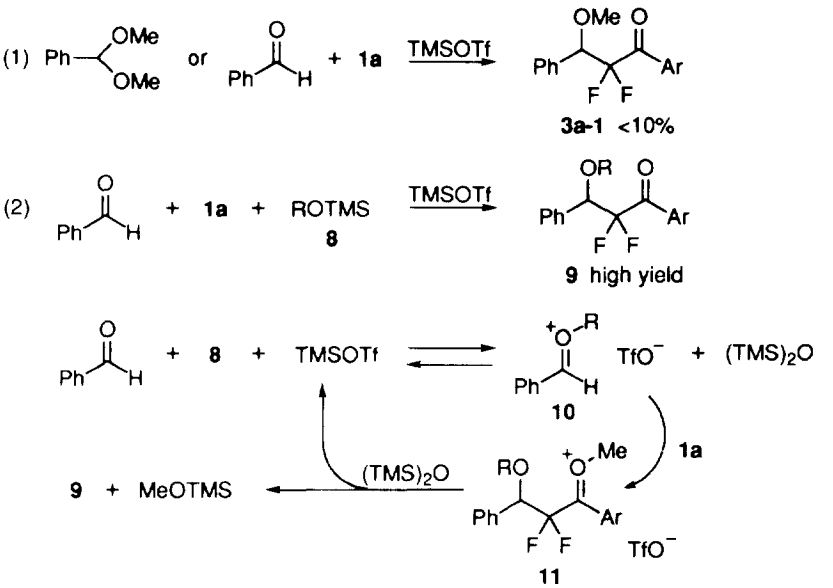
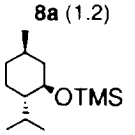


Table 2. Reaction of **1a** with benzaldehyde mediated by alkyl TMS ether **8** and Lewis acid

Run	**8** (equiv.)	Lewis acid	**9** (Yield %)	**3a-1** (Yield %)
1	BnOTMS (5.0) **8a**	TMSOTf	**9a** 71	13
2	**8a** (1.2)	TMSOTf	**9a** 40	24
3	 **8b** (1.2)	TMSOTf	**9b** 73 [b]	16
4	**8b** (1.2)	$SbCl_6{\cdot}NAr_3$ [c]	**9b** 75 [d]	0

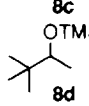
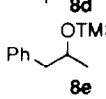
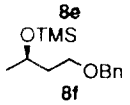
a) Reaction conditions : Lewis acid, 30 mol% ; solvent, CH_2Cl_2 ; temperature, 0°C~rt ; time, 1~2h.
b) Diastereomer ratio was 1.24 : 1. c) Ar = 4-bromophenyl. d) Diastereomer ratio was 1.5 : 1.

the reaction to proceed. That is, with TMSOTf, a Lewis acid weaker than $SbCl_5$ or $Cu(OTf)_2$, the aldol-type product **3a-1** was obtained in low yield (<10%) in the reaction of **1a** with benzaldehyde or its dimethyl acetal [Scheme 3 (1)].[10] On the other hand, we found that in the presence of alkyl trimethylsilyl ether **8** (ROTMS), TMSOTf efficiently catalyzed the reaction of **1a** with aldehyde to give *O*-alkylated aldol-type product **9** in good yield [Scheme 3 (2)].[11] This reaction would be much more practical, because a variety of *O*-alkyl groups, such as benzyl group for protective functionality or a chiral secondary alkyl group for asymmetric reaction, can be incorporated. The *O*-methylated product **3** obtained in the absence of ROTMS **8** may bring about some limitations from the synthetic point of view.

Results of TMSOTf catalyzed reaction of **1a** with benzaldehyde in the presence of benzyl or menthyl TMS ether (**8a** or **8b**) are summarized in Table 2. In the presence of **8a** or **8b**, TMSOTf worked as effectively as $SbCl_6$•NAr_3, but $TiCl_4$ or BF_3•Et_2O did not cause the reaction. These results may suggest that the formation of reactive oxonium intermediate **10** and hexamethyldisiloxane can be achieved efficiently by a Lewis acid TMSOTf.[11] Thus, **1a** reacts with **10** to provide the adduct **11**, which gives rise to the product **9** and methyl TMS ether with the reproduction of TMSOTf, as shown in Scheme 3. The *in situ* formed methyl TMS ether may participate in the competitive formation of the oxonium intermediate **10** (R=Me) leading to the *O*-methylated product **3** as a by-product. Indeed, in the cases of benzyl TMS ether **8a**, a mixture of *O*-benzylated and *O*-methylated products (**9a** and **3a-1**) was obtained and the ratio of **9a** and **3a-1** was dependent on a molar ratio of **1a** and **8a** (Runs 1, 2). With TMS ether **8b** of secondary alcohol, however, the desired *O*-alkylated product **9b** was obtained preferentially even by using a slight excess (1.2 equiv.) of **8b** (Runs 3, 4). In these cases, the diastereomer ratio of **9b** was found 1.24-1.5 : 1.

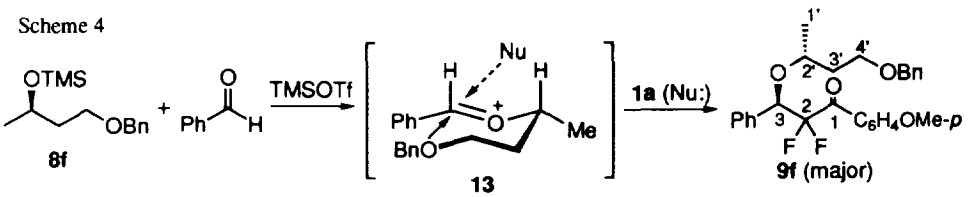
Next, we examined to develop an asymmetric version of the present reaction using TMS ether of a chiral secondary alcohol.[12] Results are summarized in Table 3. When the reaction was carried out using 30 mol% of TMSOTf and 1.2 equimolar amount of **8c-f**, the corresponding **9c-f** were obtained in good yields (69-97%). Regarding the diastereoselectivity, a slightly higher asymmetric induction was observed on using TMS ether of methyl carbinol having benzyl or β-benzyloxyethyl group as another substituent (**8e** or **8f**) than that with *i*-propyl or *t*-butyl derivative (**8c** or **8d**). The relative stereochemistry of the major isomer of **9e** was confirmed to be 3*R**,2'*R** based on X-ray analysis. For the determination of the absolute stereochemistry of **9f** derived from enantiomerically pure TMS ether **8f**[13] of *R* configuration, the major isomer was converted to crystalline *p*-bromobenzoate **12**, whose X-ray analysis revealed the 3*R*,2'*R* configuration (Scheme 4 and Fig. 1).[14] Furthermore, it was confirmed that racemization at the chiral center originated from **8f** (2'-carbon in **9f**) did not occur under the reaction conditions employed. The observed asymmetric induction giving (3*R*,2'*R*)-**9f** as the major isomer is possibly explained by considering the participation of a lone pair electron on β-benzyloxy group to the chair-like oxonium intermediate **13**, in which the methyl group on the chiral center and the phenyl group preferably locate in equatorial positions. Thereby, **1a** attacks from the *si*-face (back site of benzyloxy group) in **13** to give (3*R*,2'*R*)-**9f**. Further experiments should be required to clarify the mechanistic aspects of the present reaction and to achieve a high level of asymmetric induction.

Table 3. Reaction of **1a** with benzaldehyde mediated by *sec*-alkyl TMS ether **8** and TMSOTf

Run	**8**	**9** (Yield %)	Diastereomer ratio	Confign.[b]
1	 **8c**	**9c** 89	1.9 : 1	–[c]
2	 **8d**	**9d** 70[d]	2.7 : 1	–[c]
3	 **8e**	**9e** 97	3.6 : 1	(3R*, 2'R*)
4	**8e**	**9e** 90	4.0 : 1[e]	(3R*, 2'R*)
5	 **8f**	**9f** 69	4.0 : 1	(3R, 2'R)

a) Reaction conditions : molar ratio of **8** / **1a** = 1.2 ; TMSOTf, 30 mol% ; solvent, CH_2Cl_2 ; temperature, 0°C. b) Stereochemistry of the major isomer is shown. c) Not determined. d) **3a-1** was also obtained in 13% yield. e) Reaction was carried out at -78°C.

Scheme 4



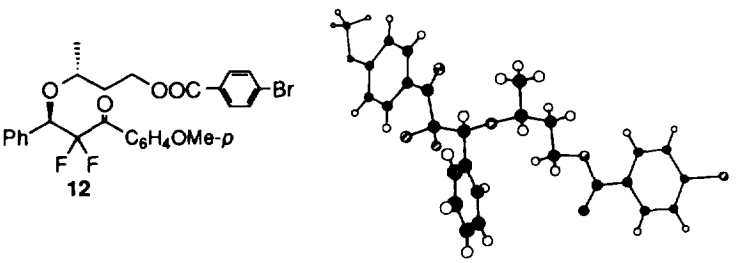


Fig. 1 X-Ray crystal structure of **12**

In summary, we have shown that a stable and storable difluorovinyl methyl ether can react with carbonyl compounds in the presence of alkyl TMS ether and Lewis acid (TMSOTf) to give *O*-alkylated aldol-type products.

EXPERIMENTAL

^{1}H- and ^{13}C-NMR spectra were taken on a Brucker AM400 or a Varian Gemini-300 spectrometer in $CDCl_3$, and the chemical shifts were reported in parts per million (ppm) using $CHCl_3$ (7.26 ppm) for ^{1}H-NMR and $CDCl_3$ (77.01 ppm) for ^{13}C-NMR as an internal standard. ^{19}F-NMR spectra were taken on a Brucker AM400 spectrometer in $CDCl_3$, and chemical shifts were reported in ppm using benzotrifluoride as a standard. Infrared spectra (IR) were recorded on a Perkin-Elmer FTIR-1710 infrared spectrophotometer. Mass spectra (MS) were obtained on a Hitachi M-80 or VG Auto spec. Medium pressure liquid chromatography (MPLC) was performed using prepacked column (silica gel, 50μm) with UV detector.

General procedure for the preparation of vinyl ethers: 1,1-Difluoro-2-methoxy-2-*p*-methoxyphenylethene (1a). To a solution of *p*-methoxyphenylmagnesium bromide, prepared from *p*-methoxybromobenzene (46.8 g) and Mg (6.68 g) in THF, was added ethyl chlorodifluoroacetate (39.7 g) at -78°C. After being stirred for 1 h at the same temperature, the reaction mixture was treated with sat. NH_4Cl aq. Following usual extractive workup and purification of the crude product by distillation gave chlorodifluoromethyl *p*-methoxyphenyl ketone (36.9 g, 67 %). The ketone (12.7 g) thus obtained was treated with $NaBH_4$ (6.4 g) in ethanol to give the corresponding alcohol (12.5 g, 98 %), which was converted to the methyl ether (98 %) by treating with NaH and iodomethane in THF at room temperature. To a solution of LDA prepared from diisopropylamine (4 ml) and butyllithium (1.65 *M* hexane solution, 12 ml) in THF at -78 °C was added the methyl ether (4.4 g), and the mixture was stirred for 6 h at -78 °C. To the mixture was added 5% HCl and it was extracted with Et_2O. The organic layer was washed with sat. $NaHCO_3$ aq., brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (2% AcOEt in hexane) to give **1a** in 77 % yield.

1a: Colorless oil. ^{1}H-NMR δ: 3.60 (3H, s), 3.83 (3H, s), 6.93 (2H, d, *J* =9.0 Hz), 7.39 (2H, d, *J* =9.0 Hz). ^{19}F-NMR δ: -46.95 (1F, d, *J* =63.0 Hz), -37.28 (1F, d, *J* =63.0 Hz). ^{13}C-NMR δ: 55.19, 59.66, 114.06, 119.28 (dd, $J_{C\text{-}F}$ =34.2 and 18.0 Hz), 122.19, 127.80, 154.98 (t, $J_{C\text{-}F}$ =288.8 Hz), 159.50. IR (neat): 2939, 1729, 1612, 1515, 1261, 835 cm^{-1}. EI-MS *m/z*: 200 (M^+). High-resolution MS *m/z*: Calcd for $C_{10}H_{10}F_2O_2$: 200.0643. Found: 200.0649.

1b: 41% yield for dehydrochlorination step. Colorless oil. ^{1}H-NMR δ: 3.63 (3H, s), 7.29 - 7.50 (5H, m). ^{19}F-NMR δ: -44.86 (1F, d, *J* =58.0 Hz), -35.28 (1F, d, *J* =58.0 Hz). ^{13}C-NMR δ: 59.95, 119.54

(dd, J_{C-F}=32.8 and 17.8 Hz), 126.33, 128.12, 128.57, 155.42 (t, J_{C-F} =290.8 Hz). IR (neat): 2939, 1727, 1267, 1145, 769, 696 cm^{-1}. EI-MS *m/z*: 170 (M^+). High-resolution MS *m/z*: Calcd for $C_9H_8F_2O$: 170.0560. Found: 170.0543.

1c: 95% yield for dehydrochlorination step. Colorless oil. ^{1}H-NMR δ: 2.39 - 2.46 (2H, m), 2.80 (2H, t, *J* =7.8 Hz), 3.61 (3H, s), 7.19 - 7.33 (5H, m). ^{19}F-NMR δ: -53.04 (1F, ddd, *J* =80.1, 4.0 and 4.0 Hz), -40.78 (1F, dd, *J* =80.1 and 1.6 Hz). ^{13}C-NMR δ: 27.84, 32.41, 58.81, 117.96 (dd, J_{C-F} =39.5 and 11.3 Hz), 126.13, 128.35, 140.83, 153.96 (dd, J_{C-F} =288.0 and 279.3 Hz). IR (neat): 3029, 2939, 1762, 1497, 1245, 1097, 700 cm^{-1}. EI-MS *m/z*: 198 (M^+), 178. High-resolution MS *m/z*: Calcd for $C_{11}H_{12}F_2O$: 198.0856. Found: 198.0845.

General procedure of Lewis acid catalyzed reaction of 1 with carbonyl and acetal compounds: To a solution of Lewis acid (0.3 mmol) in CH_2Cl_2 (3 ml) was added a mixture of **1** (1.0 mmol) and aldehyde (1.1 mmol) or acetal (1.1 mmol) in CH_2Cl_2 at 0 °C, and the whole was stirred for 1 h at 0 °C. After addition of sat. $NaHCO_3$ aq., the mixture was extracted with Et_2O, and the organic layer was washed with brine, dried over $MgSO_4$, and then concentrated by evaporator. The residue was purified by silica gel column chromatography (hexane-AcOEt as eluent), and further by MPLC if needed, to give the product(s) shown in Table 1.

2,2-Difluoro-3-methoxy-1-*p*-methoxyphenyl-3-phenyl-1-propanone (3a-1): Colorless oil. ^{1}H-NMR δ: 3.30 (3H, s), 3.88 (3H, s), 4.87 (1H, dd, *J* =18.7 and 5.8 Hz), 6.94 (2H, d, *J* =9.0 Hz), 7.39 - 7.50 (5H, m), 8.08 (2H, d, *J* =9.0 Hz). ^{19}F-NMR δ: -53.97 (1F, dd, *J* =273.7 and 18.7 Hz), -41.21 (1F, dd, *J* =273.7 and 5.8 Hz). ^{13}C-NMR δ: 55.38, 57.72, 82.16 (dd, J_{C-F} =29.6 and 22.0 Hz), 113.73, 116.40 (dd, J_{C-F} =265.5 and .253.0 Hz), 126.18, 128.26, 128.73, 129.05, 132.65, 133.01, 164.21, 188.90 (dd, J_{C-F} =30.6 and 25.8 Hz). IR (neat): 2938, 2840, 1687, 1601, 1134, 733 cm^{-1}. EI-MS *m/z*: 306 (M^+), 286. High-resolution MS *m/z*: Calcd for $C_{17}H_{16}F_2O_3$: 306.1068. Found: 306.1075. *Anal.* Calcd for $C_{17}H_{16}F_2O_3$: C, 66.65; H, 5.26. Found: C, 66.36; H, 5.35.

2,2-Difluoro-3-hydroxy-1-*p*-methoxyphenyl-3-phenyl-1-propanone (4a-1): Colorless crystals. mp 116.0 - 117.0 °C [hexane-AcOEt (20 : 1)]. ^{1}H-NMR δ: 3.38 (3H, s), 5.37 (1H, dd, *J* =19.0 and 5.1 Hz), 6.94 (2H, d, *J* =9.1 Hz), 7.38 - 7.52 (5H, m), 8.02 (2H, d, *J* =9.1 Hz). ^{19}F-NMR δ: -53.00 (1F, dd, *J* =293.0 and 19.0 Hz), -41.38 (1F, dd, *J* =293.0 and 5.1 Hz). ^{13}C-NMR δ: 55.52, 73.34 (dd, J_{C-F} =28.6 and 23.2 Hz), 113.96, 115.91 (dd, J_{C-F} =264.7 and .257.0 Hz), 128.12, 128.18, 128.85, 132.86, 134.90, 164.73, 189.11 (t, J_{C-F} =30.0 Hz). IR (KBr): 3427, 3011, 1719, 1665, 1593, 1268, 1121 cm^{-1}. EI-MS *m/z*: 292 (M^+). High-resolution MS *m/z*: Calcd for $C_{16}H_{14}F_2O_3$: 292.0911. Found: 292.0893. *Anal.* Calcd for $C_{16}H_{14}F_2O_3$: C, 65.75; H, 4.83. Found: C, 65.78; H, 4.89.

2,2-Difluoro-3-methoxy-1-*p*-methoxyphenyl-5-phenyl-1-pentanone (3a-2): Colorless oil. ^{1}H-NMR δ: 1.96 - 2.06 (2H, m), 2.74 (1H, ddd, *J* =14.0, 9.3 and 7.2 Hz), 2.92 (1H, ddd, *J* =14.0, 9.3 and 6.0 Hz), 3.45 (3H, s), 3.81 (1H, m), 6.96 (2H, d, J =8.6 Hz), 7.18 - 7.33 (5H, m), 8.09 (2H, d, *J* =8.6 Hz). ^{19}F-NMR δ: -49.75 (1F, dd, *J* =275.5 and 14.2 Hz), -44.12 (1F, dd, *J* =275.5 and 9.4 Hz). ^{13}C-NMR δ: 30.28, 31.45, 55.49, 60.39, 80.19 (dd, J_{C-F} =25.7 and 23.4 Hz), 113.88, 118.25 (dd, J_{C-F} =261.1 and 257.6 Hz), 126.06, 128.41, 128.47, 132.66, 132.69, 132.72, 141.14, 164.40, 188.86 (t, J_{C-F} =28.4 Hz). IR (neat): 3027, 2937, 2840, 1686, 1601, 1267, 1116, 701 cm^{-1}. EI-MS *m/z*: 334 (M^+). *Anal.* Calcd for $C_{19}H_{20}F_2O_3$: C, 68.24; H, 6.03. Found: C, 68.27; H, 6.19.

2,2-Difluoro-3-methoxy-1-*p*-methoxyphenyl-3,3-pentamethylene-1-propanone (3a-3): Colorless oil. ^{1}H-NMR δ: 1.20 (1H, m), 1.37 - 1.67 (7H, m), 1.95 (2H, bd, *J* =12.5 Hz), 3.36 (3H, s), 3.88 (3H, s), 6.78 (2H, d, *J* =9.0 Hz), 8.08 (2H, d, *J* =9.0 Hz). ^{19}F-NMR δ: -45.12 (2F, s). ^{13}C-NMR δ: 21.05, 25.05, 27.97, 51.73, 55.46, 77.75 (t, J_{C-F} =22.2 Hz), 113.72, 120.53 (t, J_{C-F} =263.5 Hz), 127.73, 132.64, 132.68, 132.73, 164.03, 189.17 (t, J_{C-F} =28.3 Hz). IR (neat): 2940, 1684, 1601, 1266, 1176, 1104 cm^{-1}. EI-MS *m/z*: 298 (M^+). High-resolution MS *m/z*: Calcd for $C_{16}H_{20}F_2O_3$: 298.1381. Found: 298.1407. *Anal.* Calcd for $C_{16}H_{20}F_2O_3$: C, 64.41; H, 6.78. Found: C, 64.34; H, 6.84.

2,2-Difluoro-3-methoxy-1-*p*-methoxyphenyl-5-phenyl-3-penten-1-one (3a-4): Colorless crystals. mp 35.5-37.0 °C. ^{1}H-NMR δ: 3.38 (3H, s), 3.89 (3H, s), 4.43 (1H, ddd, *J* =16.3, 7.7 and 6.8 Hz), 6.23 (1H, dd, *J* =16.1 and 7.7 Hz), 6.81 (1H, d, *J* =16.1 Hz), 6.96 (2H, d, *J* =8.8 Hz), 7.29 - 7.47 (5H, m), 8.11 (2H, d, *J* =8.8 Hz). ^{19}F-NMR δ: -52.61 (1F, dd, *J* =274.5 and 16.3 Hz), -42.05 (1F, dd, *J* =274.5 and 6.8 Hz). ^{13}C-NMR δ: 55.49, 57.52, 81.80 (dd, $J_{C\text{-}F}$ =29.8 and 23.6 Hz), 113.83, 116.79 (dd, $J_{C\text{-}F}$ =263.2 and 254.0 Hz), 120.69, 126.89, 128.44, 128.64, 132.72, 135.81, 137.37, 164.31, 188.67 (dd, $J_{C\text{-}F}$ =29.9 and 26.4 Hz). IR (KBr): 2944, 2834, 1677, 1604, 1264, 1143, 1117, 755 cm^{-1}. EI-MS *m/z*: 332 (M^+), 312. High-resolution MS *m/z*: Calcd for $C_{19}H_{18}F_2O_3$: 332.1224. Found: 332.1224.

2,2-Difluoro-3-hydroxy-1-*p*-methoxyphenyl-5-phenyl-3-penten-1-one (4a-4): Colorless crystals. mp 100.5-101.5 °C. ^{1}H-NMR δ: 2.89 (1H, d, *J* =5.8 Hz, OH), 3.90 (3H, s), 4.94 (1H, m), 6.34 (1H, dd, *J* =15.7 and 6.4 Hz), 6.85 (1H, d, *J* =15.7 Hz), 6.98 (2H, d, *J* =9.1 Hz), 7.25 - 7.45 (5H, m), 8.13 (2H, d, *J* =9.1 Hz). ^{19}F-NMR δ: -51.99 (1F, dd, *J* =293.7 and 15.8 Hz), -42.80 (1F, dd, *J* =293.7 and 6.8 Hz). ^{13}C-NMR δ: 55.56, 72.71 (dd, $J_{C\text{-}F}$ =26.9 and 26.1 Hz), 114.33, 116.08 (dd, $J_{C\text{-}F}$ =262.5 and 258.1 Hz), 122.21, 125.10, 126.80, 128.09, 128.44, 132.53, 135.26, 136.02, 164.82, 188.63 (t, $J_{C\text{-}F}$ =30.1 Hz). IR (KBr): 3470, 2928, 2850, 1693, 1605, 1262, 1174, 1039 cm^{-1}. EI-MS *m/z*: 318 (M^+), 298. High-resolution MS *m/z*: Calcd for $C_{18}H_{16}F_2O_3$: 318.1068. Found: 318.1068.

2,2-Difluoro-3-methoxy-1-*p*-methoxyphenyl-3-methyl-1-butanone (5a): Colorless oil. ^{1}H-NMR δ: 1.38 (6H, bs), 3.21 (3H, s), 3.87 (3H, s), 6.29 (2H, d, *J* =9.2 Hz), 8.10 (2H, d, *J* =9.2 Hz). ^{19}F-NMR δ: -47.76 (s). ^{13}C-NMR δ: 18.79, 49.78, 55.40, 77.61 (t, $J_{C\text{-}F}$ =25.3 Hz), 113.33, 119.00 (t, $J_{C\text{-}F}$ =259.8 Hz), 127.37, 133.29, 163.87, 189.90 (t, $J_{C\text{-}F}$ =28.0 Hz). IR (neat): 2992, 2953, 1683, 1602, 1264, 1142, 1116, 899 cm^{-1}. EI-MS *m/z*: 258 (M^+).

2,2-Difluoro-1-*p*-methoxyphenyl-3-phenyl-1,5-hexanedione (6a): Colorless crystals. mp 83.0 - 84.5°C. ^{1}H-NMR δ: 2.11 (3H, s), 3.06 (1H, dd, *J* =17.8 and 8.5 Hz), 3.23 (1H, dd, *J* =17.8 and 4.6 Hz), 3.83 (3H, s), 4.28 (1H, dddd, *J* =18.8, 13.9, 8.5 and 4.6 Hz), 6.91 (2H, d, *J* =8.6 Hz), 7.25 (5H, bs), 7.95 (2H, d, *J* =8.6 Hz). ^{19}F-NMR δ: -42.70 (1F, dd, *J* =269.1 and 18.8 Hz), -38.46 (1F, dd, *J* =269.1 and 13.9 Hz). IR (KBr): 2943, 2850, 1720, 1693, 1600, 1270, 1165, 1067, 917 cm^{-1}. EI-MS *m/z*: 332 (M^+), 312, 292. High-resolution MS *m/z*: Calcd for $C_{19}H_{18}F_2O_3$: 332.1224. Found: 332.1203.

2,2-Difluoro-3-methoxy-1,3-diphenyl-1-propanone (3b): Colorless oil. ^{1}H-NMR δ: 3.30 (3H, s), 4.88 (1H, dd, *J* =19.0 and 5.7 Hz), 7.40 - 7.51 (7H, m), 7.51 - 7.55 (1H, m), 8.06 (2H, d, *J* =8.5 Hz). ^{19}F-NMR δ: -54.96 (1F, dd, *J* =274.2 and 19.0 Hz), -44.17 (1F, dd, *J* =274.2 and 5.7 Hz). ^{13}C-NMR δ: 57.75, 82.15 (dd, $J_{C\text{-}F}$ =30.1 and 21.9 Hz), 116.13 (dd, $J_{C\text{-}F}$ =266.0 and 252.7 Hz), 128.34, 128.42, 128.76, 129.17, 129.98, 132.81, 133.87, 191.06 (dd, $J_{C\text{-}F}$ =31.5 and 25.6 Hz). IR (neat): 2937, 1698, 1450, 1276, 1137, 700 cm^{-1}. EI-MS *m/z*: 276 (M^+), 256, 244. High-resolution MS *m/z*: Calcd for $C_{16}H_{14}F_2O_2$: 276.0962. Found: 276.0978. *Anal.* Calcd for $C_{16}H_{14}F_2O_2$: C, 69.56; H, 5.11. Found: C, 69.53; H, 5.15.

2,2-Difluoro-1-methoxy-1,5-diphenyl-3-pentanone (3c-1): Colorless oil. ^{1}H-NMR δ: 2.90 - 3.15 (4H, m), 3.23 (3H, s), 4.64 (1H, dd, *J* =18.7 and 6.2 Hz), 7.19 - 7.42 (10H, m). ^{19}F-NMR δ: -62.83 (1F, dd, *J* =263.5 and 18.7 Hz), -47.49 (1F, dd, *J* =263.5 and 6.2 Hz). ^{13}C-NMR δ: 28.39, 39.90, 57.57, 81.97 (dd, $J_{C\text{-}F}$ =30.1 and 22.7 Hz), 114.68 (dd, $J_{C\text{-}F}$ =263.7 and 253.2 Hz), 126.17, 128.34, 128.42, 128.51, 129.17, 132.48, 140.29, 201.16 (dd, $J_{C\text{-}F}$ =33.4 and 24.5 Hz). IR (neat): 3031, 2937, 1742, 1497, 1455, 1113, 700 cm^{-1}. EI-MS *m/z*: 304 (M^+), 272. *Anal.* Calcd for $C_{18}H_{18}F_2O_2$: C, 71.04; H, 5.96. Found: C, 71.03; H, 6.08.

2,2-Difluoro-1-hydroxy-1,5-diphenyl-3-pentanone (4c-1): Colorless needles. mp 61.5 - 62.0 °C (hexane). ^{1}H-NMR δ: 2.60 (1H, d, J =4.6 Hz, -OH), 2.85 - 3.01 (4H, m), 5.15 (1H, ddd, *J* =16.3, 7.7 and 4.6 Hz), 7.12 - 7.42 (5H, m). ^{19}F-NMR δ: -59.90 (1F, dd, *J* =269.1 and 16.3 Hz), -50.66 (1F,

dd, J =269.1 and 7.7 Hz). ^{13}C-NMR δ: 28.37, 39.78, 73.20 (dd, $J_{C\text{-}F}$ =27.7 and 24.5 Hz), 114.84 (dd, $J_{C\text{-}F}$ =261.5 and 255.8 Hz), 126.30, 127.69, 128.29, 128.45, 128.51, 129.17, 134.66, 140.05, 201.45 (dd, $J_{C\text{-}F}$ =31.7 and 27.7 Hz). IR (KBr): 3425, 3029, 2936, 1737, 1207, 1085, 699 cm^{-1}. EI-MS m/z: 290 (M^+), 272. *Anal.* Calcd for $C_{17}H_{16}F_2O_2$: C, 70.33; H, 5.56. Found: C, 70.18; H, 5.64.

4,4-Difluoro-5-methoxy-1,7-diphenyl-6-heptene-3-one (3c-2): Colorless crystals. mp 53.0 - 54.0 °C (hexane). ^{1}H-NMR δ: 2.96 (2H, m), 3.08 (2H, m), 3.29 (3H, s), 4.21 (1H, ddd, J =16.8, 7.9 and 6.0 Hz), 6.11 (2H, dd, J =15.9 and 7.9Hz), 6.74 (1H, d, J =15.9 Hz), 7.18 - 7.46 (10H, m). ^{19}F-NMR δ: -61.65 (1F, dd, J =264.0 and 16.8 Hz), -47.69 (1F, dd, J =264.0 and 6.0 Hz). ^{13}C-NMR δ: 28.41, 39.90, 57.25, 81.61 (dd, $J_{C\text{-}F}$ =30.5 and 23.7 Hz), 115.05 (dd, $J_{C\text{-}F}$ =262.0 and 253.6 Hz), 120.03, 126.21, 126.89, 128.33, 128.46, 128.55, 128.65, 135.60, 137.73, 140.30, 201.00 (dd, $J_{C\text{-}F}$ =32.1 and 25.2 Hz). IR (KBr): 2932, 2907, 2831, 1741, 1120, 1098, 977, 698 cm^{-1}. EI-MS m/z: 330 (M^+), 298. *Anal.* Calcd for $C_{20}H_{20}F_2O_2$: C, 72.71; H, 6.10. Found: C, 72.63; H, 6.27.

4,4-Difluoro-5-hydroxy-1,7-diphenyl-6-heptene-3-one (4c-2): Colorless needles. mp 80.5 - 81.5 °C (hexane). ^{1}H-NMR δ: 2.44 (1H, bs, -OH), 2.96 (2H, t, J =6.9 Hz), 3.09 (2H, t, J =6.9 Hz), 4.75 (1H, m), 6.22 (2H, dd, J =15.9 and 6.6Hz), 6.78 (1H, d, J =15.9 Hz), 7.17 - 7.43 (10H, m, aromatic). ^{19}F-NMR δ: -59.97 (1F, dd, J =272.0 and 15.0 Hz), -50.54 (1F, dd, J =272.0 and 7.3 Hz). ^{13}C-NMR δ: 28.39, 39.65, 72.32 (dd, $J_{C\text{-}F}$ =28.3 and 25.8 Hz), 114.92 (dd, $J_{C\text{-}F}$ =260. 5 and 256.4 Hz), 121.63, 126.33, 126.85, 128.28, 128.50, 128.65, 135.73, 140.06, 201.06 (dd, $J_{C\text{-}F}$ =30.4 and 28.6 Hz). IR (KBr): 3467, 3028, 1734, 1395, 1089, 749, 698 cm^{-1}. EI-MS m/z: 316 (M^+). High-resolution MS m/z: Calcd for $C_{19}H_{18}F_2O_2$: 316.1275. Found: 316.1249.

5,5-Difluoro-4,9-diphenyl-2,7-nonanedione (6c): Colorless crystals. mp 44.5 - 45.5 °C (hexane- AcOEt , 20 : 1). ^{1}H-NMR δ: 2.09 (3H, s), 2.49 (1H, m), 2.61 - 2.79 (3H, m), 3.01 (1H, dd, J =17.6 and 4.7 Hz), 3.13 (1H, dd, J =17.6 and 8.8 Hz), 4.03 (1H, dddd, J =21.0, 11.6, 8.8 and 4.7 Hz), 7.01 (2H, d, J =7.1 Hz), 7.15 - 7.32 (8H, m). ^{19}F-NMR δ: -52.99 (1F, dd, J =256.6 and 21.0 Hz), -43.37 (1F, dd, J =256.6 and 11.6 Hz). ^{13}C-NMR δ: 28.36, 30.12, 39.65, 42.09, 43.99 (t, $J_{C\text{-}F}$ =22.0 Hz), 117.88 (t, $J_{C\text{-}F}$ =257.8 Hz), 126.24, 128.18, 128.23, 128.48, 128.80, 129.42, 134.78, 140.07, 200.66 (dd, $J_{C\text{-}F}$ =32.7 and 27.2 Hz). IR (KBr): 3033, 2896, 1737, 1715, 1279, 1171, 1082 cm^{-1}. EI-MS m/z: 330 (M^+), 310. High-resolution MS m/z: Calcd for $C_{20}H_{20}F_2O_2$: 330.1431. Found: 330.1408.

General procedure of reaction of 1a with benzaldehyde mediated by ROTMS 8 and TMSOTf; preparation of *O*-alkylated aldol-type compounds (9a-9f): TMSOTf (0.3 mmol) was added to a mixture of **1a** (1.1 mmol), benzaldehyde (1.2 mmol) and **8** (1.3 mmol) in CH_2Cl_2 (10 ml) at 0 °C. After 1-2 h, the reaction was quenched by addition of sat. $NaHCO_3$ aq. and extracted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane-AcOEt as eluent) and further by MPLC to give **9** shown in Table 2 and Table 3.

3-Benzyloxy-2,2-difluoro-1-*p*-methoxyphenyl-3-phenyl-1-propanone (9a): Colorless oil. ^{1}H-NMR δ: 3.89 (3H, s), 4.34 (1H, d, J =11.6 Hz), 4.56 (1H, d, J =11.6 Hz), 5.02 (1H, dd, J =19.0 and 5.8 Hz), 6.92 (2H, d, J =9.0 Hz), 7.08 (2H, m), 7.22 (3H, m), 7.41 - 7.52 (5H, m), 8.07 (2H, d, J =9.0 Hz). ^{19}F-NMR δ: -53.83 (1F, dd, J =270.0 and 19.0 Hz), -41.05 (1F, dd, J =270.0 and 5.8 Hz). ^{13}C-NMR δ: 55.41, 71.40, 79.38 (dd, $J_{C\text{-}F}$ =30.5 and 22.6 Hz), 113.69, 116.49 (dd, $J_{C\text{-}F}$ =265.3 and 252.3 Hz), 126.23, 127.77, 128.04, 128.19, 128.93, 129.15, 132.67, 132.70, 133.02, 136.57, 164.18, 188.83 (dd, $J_{C\text{-}F}$ =29.9 and 25.3Hz). IR (neat): 3032, 2936, 1686, 1601, 1265, 1133, 700 cm^{-1}. EI-MS m/z: 381 (M^+-1). *Anal.* Calcd for $C_{23}H_{20}F_2O_3$: C, 72.24; H, 5.27. Found: C, 72.39; H, 5.32.

2,2-Difluoro-3-menthyloxy-1-*p*-methoxyphenyl-3-phenyl-1-propanone (9b): major isomer: ^{1}H-NMR δ: 0.45 (3H, d, J =7.1 Hz), 0.54 (1H, m), 0.73 (2H, m), 0.83 (3H, d, J =6.4 Hz), 0.84 (3H, d, J =6.4 Hz), 1.01 - 1.19 (2H, m), 1.48 - 1.55 (2H, m), 2.00 (1H, bd, J =11.7 Hz), 2.36 (1H, m), 3.02 (1H, ddd, J =10.4, 10.4 and 4.3 Hz), 3.89 (3H, s), 5.10 (1H, dd, J =19.2 and 6.2 Hz),

6.94 (2H, d, J =8.8 Hz), 7.37 - 7.52 (5H, m), 8.10 (2H, d, J =8.8 Hz). ^{19}F-NMR δ: -53.66 (1F, dd, J =261.7 and 18.9 Hz), -41.26 (1F, dd, J =261.7 and 6.2 Hz). ^{13}C-NMR δ: 15.54, 21.22, 22.20, 22.56, 24.87, 31.14, 34.14, 38.52, 48.19, 55.48, 75.49, 76.49 (dd, $J_{C\text{-}F}$ =31.1 and 22.0 Hz), 113.51, 117.10 (dd, $J_{C\text{-}F}$ =265.3 and 251.8 Hz), 126.92, 128.14, 129.10, 129.49, 132.88, 132.93, 133.69, 164.06, 190.17 (dd, $J_{C\text{-}F}$=30.8 and 25.1 Hz). IR (neat): 2959, 1689, 1601, 1263, 1134, 733, 702 cm^{-1}. EI-MS m/z: 431 (M^++1), 410 (M^+-HF). High-resolution MS m/z: Calcd for $C_{26}H_{32}F_2O_3$: 430.2320. Found: 430.2327. **minor isomer**: ^{1}H-NMR δ: 0.57 (3H, d, J =6.9 Hz), 0.61 - 0.77 (2H, m), 0.71 (3H, d, J =6.4 Hz), 0.73 (3H, d, J =6.4 Hz), 0.88 (1H, m), 1.18 (2H, m), 1.53 (2H, bd, J =11.0 Hz), 1.64 (1H, bd, J =12.4 Hz), 2.00 (1H, m), 3.33 (1H, ddd, J =10.4, 10.4 and 4.1 Hz), 3.89 (3H, s), 5.07 (1H, dd, J =18.4 and 6.5 Hz), 6.92 (2H, d, J =8.7 Hz), 7.33 - 7.50 (5H, m), 8.05 (2H, d, J =8.7 Hz). ^{19}F-NMR δ: -52.85 (1F, dd, J =273.2 and 18.4 Hz), -40.10 (1F, dd, J =273.2 and 6.5 Hz). ^{13}C-NMR δ: 15.55, 21.12, 22.14, 22.74, 24.74, 31.41, 34.20, 41.99, 48.77, 55.45, 79.19 (dd, $J_{C\text{-}F}$ =28.1 and 21.8 Hz), 81.41, 113.65, 116.94 (dd, $J_{C\text{-}F}$ =265.6 and 254.5 Hz), 126.36, 127.89, 128.52, 128.67, 132.71, 132.76, 136.28, 164.23, 189.21 (dd, $J_{C\text{-}F}$=30.5 and 26.3 Hz). IR (neat): 2955, 2870, 1686, 1601, 1264, 1124, 731, 701 cm^{-1}. EI-MS m/z: 431 (M^++1), 410 (M^+-HF). High-resolution MS m/z: Calcd for $C_{26}H_{32}F_2O_3$: 430.2320. Found: 430.2312.

2,2-Difluoro-3-(2-propyloxy)-1-*p*-methoxyphenyl-3-phenyl-1-propanone (9c): major isomer: ^{1}H-NMR δ: 0.73 (6H, d, J =6.8 Hz), 0.88 (3H, d, J =6.2 Hz), 1.61.(1H, d of sept, J =6.8 and 4.8 Hz), 3.23 (1H, dq, J =6.2 and 4.8 Hz), 3.90 (3H, s), 5.01 (1H, dd, J =19.5 and 5.8 Hz), 6.92 - 6.97 (2H, m), 7.36 - 7.52 (5H, m), 8.08 - 8.12 (2H, m). ^{19}F-NMR δ: -54.51 (1F, dd, J =262.1 and 19.5 Hz), -40.41 (1F, dd, J =262.1 and 5.8 Hz). IR (neat): 2966, 2936, 1687, 1602, 1264, 1127, 731 cm^{-1}. EI-MS m/z: 361 (M^+-1). *Anal.* Calcd for $C_{21}H_{24}F_2O_3$: C, 69.59; H, 6.68. Found: C, 69.41; H, 6.72. **minor isomer**: ^{1}H-NMR δ: 0.67 (3H, d, J =6.9 Hz), 0.72 (3H, d, J =6.9 Hz), 0.86 (3H, d, J =6.4 Hz), 1.72.(1H, dsept, J =6.9 and 4.2 Hz), 3.35 (1H, dq, J =6.4 and 4.2 Hz), 3.89 (3H, s), 5.04 (1H, dd, J =19.4 and 5.6 Hz), 6.92 - 6.97 (2H, m), 7.36 - 7.52 (5H, m), 8.08 - 8.12 (2H, m). ^{19}F-NMR δ: -54.17 (1F, dd, J =267.5 and 19.4 Hz), -40.05 (1F, dd, J =267.5 and 5.6 Hz).

2,2-Difluoro-3-*tert*-butoxy-1-*p*-methoxyphenyl-3-phenyl-1-propanone (9d): major isomer: ^{1}H-NMR δ: 0.77 (9H, s), 0.80 (3H, d, J =6.3 Hz), 3.31 (1H, q, J =6.3 Hz), 3.88 (3H, s), 5.04 (1H, dd, J =19.2 and 5.9 Hz), 6.93 (2H, d, J =9.0 Hz), 7.35 - 7.50 (5H, m), 8.05 (2H, d, J =9.0 Hz). ^{19}F-NMR δ: -53.48 (1F, dd, J =274.0 and 19.2 Hz), -39.40 (1F, dd, J =274.0 and 5.9 Hz). ^{13}C-NMR δ: 15.44, 25.95, 35.30, 55.50, 79.75 (dd, $J_{C\text{-}F}$ =29.0 and 21.6 Hz), 85.33, 113.73, 116.81 (dd, $J_{C\text{-}F}$ =266.2 and 254.1 Hz), 126.50, 127.94, 128.58, 128.82, 132.78, 136.15, 164.20, 189.42 (dd, $J_{C\text{-}F}$=31.6 and 26.4 Hz). IR (neat): 2964, 1690, 1601, 1513, 1264, 1180, 1122, 726, 701 cm^{-1}. EI-MS m/z: 377 (M^++1), 356 (M^+-HF). *Anal.* Calcd for $C_{22}H_{26}F_2O_3$: C, 70.19; H, 6.96. Found: C, 70.32; H, 6.95. **minor isomer:** ^{1}H-NMR δ: 0.73 (9H, s), 0.87 (3H, d, J =6.1 Hz), 3.05 (1H, q, J =6.1 Hz), 3.90 (3H, s), 5.03 (1H, dd, J =19.9 and 5.7 Hz), 6.96 (2H, d, J =9.0 Hz), 7.40 - 7.53 (5H, m), 8.13 (2H, d, J =9.0 Hz). ^{19}F-NMR δ: -54.67 (1F, dd, J =260.7 and 19.9 Hz), -40.09 (1F, dd, J =260.7 and 5.7 Hz). ^{13}C-NMR δ: 12.06, 25.98, 34.74, 55.48, 77.70 (dd, $J_{C\text{-}F}$ =31.9 and 22.3 Hz), 79.74, 113.62, 117.13 (dd, $J_{C\text{-}F}$ =265.7 and 250.5 Hz), 126.83, 128.10, 129.09, 129.62, 132.88, 133.34, 164.10, 190.12 (dd, $J_{C\text{-}F}$=30.4 and 24.1 Hz). IR (neat): 2965, 2872, 1687, 1602, 1512, 1264, 1133, 702 cm^{-1}. EI-MS m/z: 376 (M^+), 356 (M^+-HF). *Anal.* Found: C, 70.31; H, 6.93.

(3*R,2'*R**)-2,2-Difluoro-1-*p*-methoxyphenyl-3-phenyl-3-(1'-phenyl-2'-propyl)oxy-1-propanone (major isomer of 9e):** Colorless crystals. mp 71.5 -72.5 °C (MeOH). ^{1}H-NMR δ: 0.99 (3H, d, J =5.9 Hz), 2.56 (1H, dd, J =13.7 and 5.8 Hz), 2.69 (1H, dd, J =13.7 and 7.3 Hz), 3.62 (1H, m), 3.91 (3H, s), 5.03 (1H, dd, J =19.1 and 5.8 Hz), 6.94 - 7.32 (12H, m), 8.09 (2H, d, J =8.0 Hz). ^{19}F-NMR δ: -54.36 (1F, dd, J =264.4 and 19.1 Hz), -40.64 (1F, dd, J =264.4 and 5.8 Hz). ^{13}C-NMR δ: 18.04, 43.73, 55.49, 75.09, 78.05 (dd, $J_{C\text{-}F}$ =30.7 and 22.8 Hz), 113.62, 116.74 (dd, $J_{C\text{-}F}$ =265.5 and

251.8 Hz), 126.13, 126.76, 128.03, 128.10, 128.80, 128.88, 129.56, 132.83, 133.57, 138.40, 164.13, 189.86 (dd, $J_{C\text{-}F}$ =30.6 and 24.6 Hz). IR (KBr): 3029, 2978, 1687, 1605, 1293, 1134, 730, 700 cm^{-1}. CI-MS *m/z*: 410 (M^+), 319 (M^+ - $PhCH_2$). *Anal.* Calcd for $C_{25}H_{24}F_2O_3$: C, 73.13; H, 5.89. Found: C, 73.42; H, 5.82.

(3*R,2'*S**)-9e (minor isomer of 9e):** Colorless crystals. mp 75.5 -77.0 °C (MeOH). ^{1}H-NMR δ: 0.94 (3H, d, *J* =6.3 Hz), 2.45 (1H, dd, *J* =13.3 and 7.9 Hz), 2.85 (1H, dd, *J* =13.3 and 5.0 Hz), 3.69 (1H, m), 3.90 (3H, s), 5.06 (1H, dd, *J* =19.0 and 5.8 Hz), 6.94 (2H, d, *J* =7.1 Hz), 7.01 (2H, m), 7.13 - 7.21 (3H, m), 7.36 - 7.50 (5H, m), 7.64 (2H, d, *J* =8.1 Hz). ^{19}F-NMR δ: -53.97 (1F, dd, *J* =269.1 and 19.2 Hz), -40.65 (1F, dd, *J* =269.1 and 5.8 Hz). ^{13}C-NMR δ: 20.25, 42.19, 55.52, 76.97, 78.99 (dd, $J_{C\text{-}F}$ =26.9 and 22.0 Hz), 113.68, 116.65 (dd, $J_{C\text{-}F}$ =265.8 and 253.1 Hz), 126.15, 128.18, 128.21, 128.81, 128.92, 129.41, 132.82, 134.72, 138.05, 164.20, 189.44 (dd, $J_{C\text{-}F}$ =30.7 and 25.9 Hz). IR (KBr): 2974, 1680, 1599, 1572, 1267, 1077, 741 cm^{-1}. CI-MS *m/z*: 319 (M^+ - $PhCH_2$). *Anal.* Calcd for $C_{25}H_{24}F_2O_3$: C, 73.13; H, 5.89. Found: C, 73.22; H, 5.98.

(3*R*,2'*R*)-2,2-Difluoro-3-(4'-benzyloxy-2'-butyl)oxy-1-*p*-methoxyphenyl-3-phenyl-1-propanone (major isomer of 9f): Colorless needles. mp 41.5 - 43.5 °C (hexane). $[\alpha]_D^{26}$ -105.3 (c 1.01, $CHCl_3$). ^{1}H-NMR δ: 0.99 (3H, d, *J* =6.1 Hz), 1.57 - 1.76 (2H, m), 3.43 (2H, t, *J* =6.3 Hz), 3.64 (1H, m), 3.89 (3H, s), 4.30 (1H, d, *J* =11.7 Hz), 4.33 (1H, d, *J* =11.7 Hz), 5.04 (1H, dd, *J* =19.0 and 6.0 Hz), 6.94 (2H, d, *J* =9.1 Hz), 7.17 - 7.50 (10H, m), 8.09 (2H, d, *J* =9.1 Hz). ^{19}F-NMR δ: -53.99 (1F, dd, *J* =264.9 and 19.0 Hz), -40.99 (1F, dd, *J* =264.9 and 6.0 Hz). ^{13}C-NMR δ: 18.46, 37.11, 55.49, 66.74, 71.40, 72.87, 78.05 (dd, $J_{C\text{-}F}$ =30.6 and 22.3 Hz), 113.64, 116.84 (dd, $J_{C\text{-}F}$ =265.3 and 252.2 Hz), 126.70, 127.48, 127.59, 128.19, 128.27, 129.06, 132.77, 133.91, 138.37, 164.13, 189.73 (dd, $J_{C\text{-}F}$ =30.4 and 25.4 Hz). IR (KBr): 2964, 2869, 1688, 1608, 1279, 1088, 732, 703 cm^{-1}. EI-MS *m/z*: 454 (M^+), 434 . *Anal.* Calcd for $C_{27}H_{28}F_2O_4$: C, 71.35; H, 6.21. Found: C, 71.58; H, 6.25.

(3*S*,2'*R*)-9f (minor isomer of 9f): Colorless oil. $[\alpha]_D^{26}$ 67.2 (c 1.01, $CHCl_3$). ^{1}H-NMR δ: 0.99 (3H, d, *J* =6.3 Hz), 1.60 (1H, m), 1.79 (1H, m), 3.37 (2H, m), 3.72 (1H, tq, *J* =6.3 and 6.3 Hz), 3.87 (3H, s), 4.33 (1H, d, *J* =11.8 Hz), 4.40 (1H, d, *J* =11.8 Hz), 5.05 (1H, dd, *J* =18.9 and 6.0 Hz), 6.93 (2H, d, *J* =9.0 Hz), 7.26 - 7.51 (10H, m), 8.08 (2H, d, *J* =9.0 Hz). ^{19}F-NMR δ: -53.70 (1F, dd, *J* =268.9 and 18.9 Hz), -40.72 (1F, dd, *J* =268.9 and 6.0 Hz). ^{13}C-NMR δ: 21.03, 36.01, 55.43, 66.64, 72.79, 74.04, 79.27 (dd, $J_{C\text{-}F}$ =30.0 and 22.3 Hz), 113.68, 116.69 (dd, $J_{C\text{-}F}$ =265.4 and 253.2 Hz), 126.46, 127.42, 127.71, 128.05, 128.26, 128.80, 132.73, 134.98, 138.46, 164.17, 189.44 (dd, $J_{C\text{-}F}$ =30.7 and 25.7 Hz). IR (neat): 2933, 1686, 1601, 1265, 1127, 700, 613 cm^{-1}. EI-MS *m/z*: 454 (M^+), 363 . *Anal.* Calcd for $C_{27}H_{28}F_2O_4$: C, 71.35; H, 6.21. Found: C, 71.52; H, 6.21.

(3*R*,2'*R*)-*p*-Bromobenzoate (12). After a mixture of **(3*R*,2'*R*)-9f** (695 mg, 1.53 mmol) and iodotrimethylsilane (0.3 ml, 2.1 mmol) in $CHCl_3$ (20 ml) was stirred for 1 h at room temperature, the mixture was diluted with Et_2O and washed successively with $Na_2S_2O_3$ aq., sat. $NaHCO_3$ aq. and brine. The organic layer was dried over $MgSO_4$ and concentrated to give crude debenzylated compound (485 mg) after the residue was passed through a short column. The crude alcohol (220 mg, 0.61 mmol) was treated with *p*-bromobenzoyl chloride (180 mg, 0.82 mmol) in a mixture of pyridine (4.5 ml) and CH_2Cl_2 (8 ml) at room temperature for 12 h. The reaction mixture was extracted with Et_2O after addition of 5% HCl and the extract was washed with sat. $NaHCO_3$ aq. and brine, dried over $MgSO_4$ then concetrated *in vacuo*. The residue was purified by prep. TLC (hexane-AcOEt = 3:1) to give **12** (304 mg). **(3*R*,2'*R*)-12:** Colorless crystals. mp 87.0 -88.0 °C (hexane-AcOEt, 20:1). $[\alpha]_D^{28}$ -3.35 (c 1.07, $CHCl_3$). ^{1}H-NMR δ: 1.07 (3H, d, *J* =6.1 Hz), 1.80 (2H, dt, *J* =6.5 and 6.2 Hz), 3.64 (1H, tq, *J* =6.2 and 6.1 Hz), 3.89 (3H, s), 4.31 (2H, m), 5.07 (2H, dd, *J* =19.2 and 5.8 Hz), 6.95 (2H, d, *J* =9.0 Hz), 7.28 - 7.33 (4H, m), 7.47 - 7.52 (4H, m), 7.66 (2H, d, *J* =6.7 Hz), 8.09 (2H, d, *J*=9.0 Hz). ^{19}F-NMR δ: -54.24 (1F, dd, *J* =268.0 and 19.2 Hz), -40.92 (1F, dd, *J* =268.0 and 5.8 Hz). ^{13}C-NMR δ: 18.32, 35.90, 55.46, 61.51, 70.03, 77.76 (dd, $J_{C\text{-}F}$ =31.2 and 22.4 Hz), 113.69, 116.68 (dd, $J_{C\text{-}F}$ =265.6 and 252.0 Hz), 126.48, 127.83,

128.26, 129.05, 129.09, 130.95, 131.50, 132.68, 132.72, 133.49, 164.18, 165.53, 189.40 (dd, $J_{C\text{-}F}$ =30.5 and 25.1 Hz). IR (KBr): 1716, 1600, 1267, 1121, 736 cm^{-1}. EI-MS *m/z*: 547 (M^+), 527. *Anal.* Calcd for $C_{27}H_{25}BrF_2O_5$: C, 59.24; H, 4.60. Found: C, 59.29; H, 4.69.

References and Notes

1. a) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1. b) Mukaiyama, T. *Org. React.* **1982**, *28*, 203. c) Mukaiyama, T. *Pure Appl. Chem.* **1983**, *55*, 1749. d) Heathcock, C. H. In *Comprehensive Carbanion Chemistry*, Buncel, E.; Durst, T. Eds.; Elsevier: Amsterdam, 1984, part B. e) Evans, D. A. *Aldrichimica Acta* **1982**, *15*, 23. f) Masamune, S.; Choy, W. *ibid.* **1982**, *15*, 47.
2. a) Welch, J. T.; Eswarakrishnan, S. In *Fluorine-Containing Molecules; Structure, Reactivity, Synthesis*, Liebman, J. F.; Greenberg, A.; Dolbier, Jr., W. R. Eds.; VCH Publisher: New York, 1988, p123. b) Ishihara, T. *J. Synth. Org. Chem. Jpn.* **1992**, *50*, 347 and references cited therein.
3. a) Welch, J. T. *Tetrahedron* **1987**, *43*, 3123. b) "*Selective Fluoronation in Organic and Bioorganic Chemistry*", Welch, J. T. Ed.; ACS Symposium Series 456, ACS: Washington DC, 1991.
4. a) Kuroboshi, M.; Ishihara, T. *Tetrahedron Lett.* **1987**, *28*, 6481. b) *idem. Bull. Chem. Soc. Jpn.* **1990**, *63*, 428. c) Yamana, M.; Ishihara, T.; Ando, T. *Tetrahedron Lett.* **1983**, *24*, 507. d) Jin, F.; Jiang, B.; Xu, Y. *ibid.* **1992**, *33*, 1221.
5. a) Lang, R. W.; Schaub, B. *Tetrahedron Lett.* **1988**, *29*, 2943. b) Hallinan, E. A.; Fried, J. *ibid.* **1984**, *25*, 2301. c) Taguchi, T.; Kitagawa, O.; Suda, Y.; Ohkawa, S.; Hashimoto, A.; Iitaka, Y.; Kobayashi, Y. *ibid.* **1988**, *29*, 5291. d) Burton, D. J.; Easdon, J. C. *J. Fluorine Chem.* **1988**, *38*, 125. e) Kitagawa, O.; Taguchi, T.; Kobayashi, Y. *Tetrahedron Lett.* **1988**, *29*, 1803. f) Kitagawa, O.; Hashimoto, A.; Kobayashi, Y.; Taguchi, T. *Chem. Lett.* **1990**, 1307. g) Takahashi, L. H.; Radhakrishnan, R.; Rosenfield, Jr., R. E.; Meyer, Jr., E. F.; Trainor, D. A. *J. Am. Chem. Soc.* **1989**, *111*, 368.
6. Howarth, J. A.; Owton, W. M.; Percy, J. M. *J. Chem. Soc., Chem. Commun.* **1995**, 757.
7. a) Deaton, M. V.; Ciufolini, M. A. *Tetrahedron Lett.* **1993**, *34*, 2409. b) Shoda, H.; Nakamura, T.; Tanino, K.; Kuwajima, I. *ibid.* **1993**, *34*, 6281. c) Carreira, E. M.; Lee, W.; Singer, R. A. *J. Am. Chem. Soc.* **1995**, *117*, 3649.
8. a) Bell, F. A.; Ledwith, A.; Sherrington, D. C. *J. Chem. Soc. (C)* **1969**, 2719. b) Schmidt, W.; Steckhan, E. *Chem. Ber.* **1980**, 577.
9. a) Schmidt, W.; Steckhan, E. *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 801. b) Bauld, N. L.; Bellville, D. J.; Harirchian, B.; Lorenz, K. T.; Pabon, Jr., R. A.; Reynolds, D. W.; Wirth, D. D.; Chiou, H. -S.; Marsh, B. K. *Acc. Chem. Res.* **1987**, *20*, 371.
10. Efficacy of TMSOTf as a Lewis acid catalyst is demonstrated in the aldol-type reaction of acetals with enol silyl ether and in the allylation reaction of acetals with allylsilanes. a) Murata, S.; Suzuki, M.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 3248. b) *idem. Tetrahedron* **1988**, *44*, 4259 and references cited therein. c) Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 71.
11. Similar activation process is postulated in the preparation of homoallylic ethers from TMS ethers, allyltrimethylsilane and carbonyl compounds under TMSOTf catalyzed reaction and the related intramolecular version. a) Mekhalfia, A.; Markó, I. E. *Tetrahedron Lett.* **1991**, *32*, 4779. b) Mekhalfia, A.; Markó, I. E.; Adams, H. *ibid.* **1991**, *32*, 4783. c) Markó, I. E.; Mekhalfia, A. *ibid*, **1992**, *33*, 1799. d) Markó, I. E.; Mekhalfia, A.; Bayston, D. J.; Adams, H. *J. Org. Chem.* **1992**, *57*, 2211. See also, e) Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett*, **1979**, 4679. f) Hatakeyama, S.; Mori, H.; Kitano, K.; Yamada, H.; Nishizawa, M. *ibid.* **1994**, *35*, 4367.
12. A higly diastereoselective addition of allylsilane to carbonyl compounds in the presence of TMS ether of chiral *N*-trifluoroacetylaminoalcohol derivative has been reported. a) Thietze, L. F.; Dolle, A.; Schiemann, K. *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 1372. b) Thietze, L. F.; Schiemann, K.; Wengner, C. *J. Am. Chem. Soc.* **1995**, *117*, 5851.
13. Mori, K.; Tanida, K. *Tetrahedron* **1981**, *37*, 3221.
14. Crystal structure analysis of **(3*R*,2*R'*)-12**. A total 1597 reflections out of 2207 within the 2θ range of 6° through 120° were collected on a Rigaku AFC7R diffractometer using Cu Kα radiation (λ = 1.54178 Å). Crystal data of **(3*R*,2*R'*)-12**: mol formula = $C_{27}H_{25}BrF_2O_5$, M_r = 547.39, orthorhombic, space group $P2_12_12_1$, a = 12.572(1) Å, b = 19.694(2) Å, c = 10.345(2) Å, V = 2561.3(5) $Å^3$, Z = 4, D_x = 1.42 g cm^{-3}, μ = 2.62 mm^{-1}, $F(000)$ =1120. The final R factor was 0.037.

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