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Synthesis of Fluorine Compounds Using Zinc Complex of Halothane

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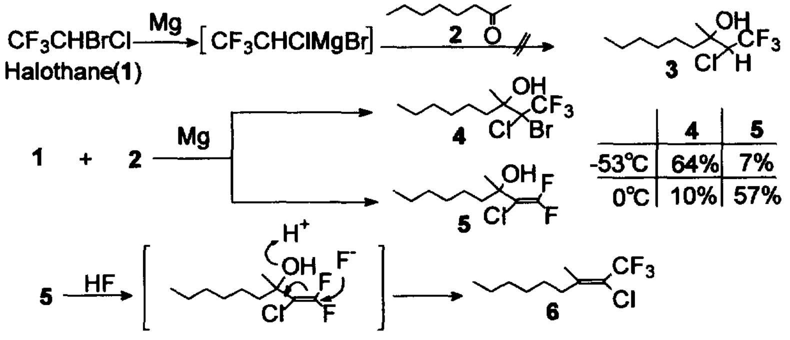
Abstract: We have reported the Grignard reaction of Halothane, 2-bromo-2-chloro-1,1,1-trifluoroethane (**1**), with ketones gave unexpected products, α-(1-bromo-1-chloro-2,2,2-trifluoroethyl)alcohols (**4**) at a low temperature. However, this reaction hardly proceeded with aldehydes. Now, we found the reaction of **1** with aldehydes in the presence of zinc gave not only products of type **4**, but α-(1-chloro-2,2,2-trifluoroethyl)alcohols (**3**), the expected type of products, under mild conditions in good to moderate yields. Copyright © 1996 Elsevier Science Ltd

Organofluorine compounds have attracted much attention in the fields of medicinal and agricultural chemistry. We are engaged in developing new methods for syntheses of bioactive fluorine compounds, and have reported trifluoromethylation of halogen compounds with trifluoromethyl iodide and copper powder,[1] and an ene reaction of trifluoromethyl carbonyl compounds.[2] As an extension of these researches, we examined reactions of Halothane, 2-bromo-2-chloro-1,1,1-trifluoroethane (**1**), as a building block for fluorine compounds. Compound **1** has one hydrogen and two different halogens on one carbon and was expected to show interesting reactivities. The Grignard reaction of **1** with ketones (**2**) gave abnormal results.[3] Thus, the reaction did not afford the expected products, α-(1-chloro-2,2,2-trifluoroethyl)alcohols (**3**), but gave CF_3CBrCl-containing alcohols (**4**) as the major products at -53°C, and at 0°C, the main products were their dehalogenation products, CF_2=CCl-containing allyl alcohols (**5**). The latter compounds were treated with HF to give trifluoromethylated olefins (**6**), as shown in Scheme 1.

Scheme 1



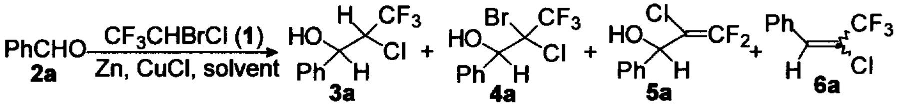
	4	5
-53°C	64%	7%
0°C	10%	57%

Next, we examined the same reaction of **1** with aldehydes. Generally, an aldehyde is more reactive than a ketone in reaction with a nucleophile. However, this reaction did not proceed with aldehydes as smoothly as with ketones, and some improvements in experimental procedure were required. Thus, at first magnesium was treated with **1**, then a mixture of **1** and aldehyde was added to the mixture. By this revised procedure, the reaction gave the products of type **5** in the high yields at 0°C. However, the products of type **4** were not obtained in satisfactory yields by controlling the reaction temperature.[4]

On the other hand, the products from ketones were converted to several types of fluorine compounds, and Halothane was found to be very useful building block for synthesis of fluorine compounds.[5]

To extend the scope of this reaction to aldehydes, we examined the reaction of **1** using other metals. Hiyama[6] and Lang[7] independently reported that 1,1,1-trichloro-2,2,2-trifluoroethane reacts with aldehydes in the presence of zinc in *N,N*-dimethylformamide (DMF) to give 2,2-dichloro-3,3,3-trifluoropropanol derivatives. Thus, we examined the reaction of **1** with zinc in DMF, but the yield of the objective compounds was very low. We examined other metals, but any remarkable improvements were not obtained. However, when pyridine was used as a solvent, **1** reacted with aldehydes in the presence of zinc to give the products of the type **4** with smaller amounts of CF_3CHCl-containing alcohols (**3**). Compounds **3** were not obtained from the Grignard reaction using magnesium. The effects of other solvents and order of addition of the reagents were examined for the reaction of benzaldehyde (**2a**). The results are shown in Table 1.

Table 1. Effect of Solvents on the Reaction of Halothane in the Presence of Zinc.

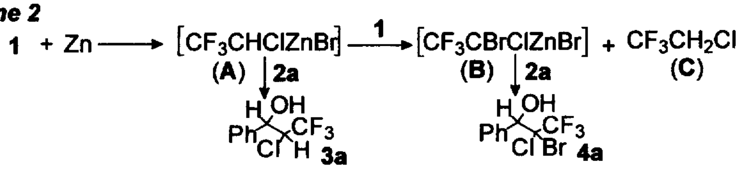


Solvent	Temp (°C)	Time (h)	Method	Yield (%)				
				3a	4a	5a	6a	2a (recovered)
Pyridine	0	2	A	8	69	6	3	6
			B	23	43	7	3	11
DMF	0	2	A	2	3	trace	trace	62
			B	31	2	5	trace	37
NMP	0	2	A	22	8	16	trace	51
			B	38	trace	12	trace	47
DMI	R.T.	2	A	6	trace	3	-	70
			B	18	trace	5	-	60
HMPA	R.T.	2	A	21	-	11	trace	55
			B	30	trace	13	trace	22

2a : **1** : Zn = 1 : 3 : 3.
Method A: **1** was added to a suspension of Zn and CuCl in the solvent, then **2a** was added.
Method B: **2a** was added to a suspension of Zn and CuCl in the solvent, then **1** was added.

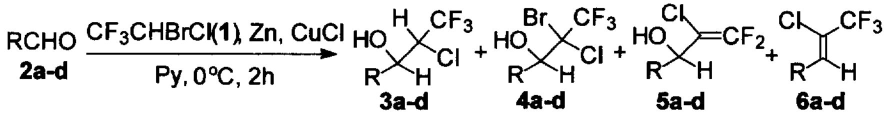
As shown in Table 1, when pyridine was used as a solvent, the reaction proceeded most smoothly to give compound (**4a**) as a main product and compound (**3a**) as a byproduct. When **1** was added to a suspension of zinc and a catalytic amount of cuprous chloride in pyridine then **2a** was added, **4a** was isolated in the yield of 69% with 8% of **3a**. When **1** was added in the presence of **2a**, the yield of **3a** was increased. Compounds (**3a** and **4a**) were mixtures of diastereomers. The ratio of diastereomers of **4a** was approximately same as that from the reaction with magnesium. These results may be explained by a similar mechanism as in the reaction with magnesium[3] as shown in Scheme 2.

Scheme 2



Thus, CF_3CHCl-ZnBr (**A**) was formed first, and then this reacted with the aldehyde (**2a**) to give a CF_3CHCl-containing alcohol (**3a**). If **A** reacted with another mole of **1** to give the CF_3CBrCl-ZnBr reagent (**B**), it would add to the aldehydes to give the CF_3CBrCl-containing alcohol (**4a**). The above mechanism is supported by the fact that the yield of **3a** was increased by the change of the order of addition of reagents as shown in the method B in Table 1. However, the yield of **3a** was not satisfactory in pyridine. To improve this, effects of several solvents were examined. *N,N*-Dimethylformamide (DMF), 1-methyl-2-pyrrolidinone (NMP), 1,3-dimethyl-2-imidazolidinone (DMI) or hexamethylphosphoramide (HMPA) gave **3a** as the main product, but in low yields. Lowering of reaction temperature or change of the reaction time did not improve the yields. This suggests that the zinc complexes are stabilized by the solvation with pyridine and that conversion of **A** to **B** is fast in pyridine. Other solvents do not have these effects. Absence of cuprous chloride decreased the yield of reaction considerably, but we could not tell its effect clearly at this stage. From the results in Table 1, synthesis of type **4** products in pyridine seemed to be most useful. Thus, we examined the reaction of other aldehydes in pyridine. The results are shown in Table 2.

Table 2. Reactions of Aldehydes



Aldehydes	Reaction method	Yield % 3	4	5	6	Recovered(**2**) %
2a: R = Ph	A	8	69	6	3	6
	B	23	43	7	3	11
2b: R = *n*-C_7H_{15}	A	8	55	8	9	15
	B	18	45	9	13	14
2c: R = $PhCH_2CH_2$	A	8	50	10	4	9
	B	15	33	12	6	5
2d: R = PhCH=CH	A	8	69	8	7	2
	B	6	66	3	5	11

2 : **1** : Zn = 1 : 3 : 3.

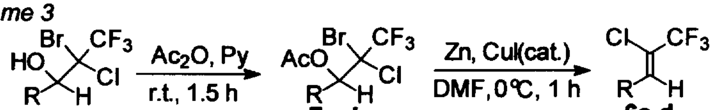
Method A: **1** was added to a suspension of Zn and CuCl in the solvent, then **2** was added.

Method B: **2** was added to a suspension of Zn and CuCl in the solvent, then **1** was added.

In method A, where zinc powder was treated with Halothane (**1**) first, then aldehydes were added to the mixture, α-(1-bromo-1-chloro-2,2,2-trifluoroethyl)alcohols (**4**) were obtained in moderate to good yields. The change in the order of addition of the reagents slightly increased the yields of α-(1-chloro-2,2,2-trifluoroethyl)-alcohols (**3**), but the yields were not of practical use and not examined any more. Formation of the compounds (**5** and/or **6**) may be due to the presence of excess zinc.

As mentioned before, the reaction of **1** with carbonyl compounds in the presence of magnesium at 0°C gave α-(1-chloro-2,2-difluorovinyl)alcohols (**5**) in good yields, and treatment of **5** with HF afforded 1-chloro-1-(trifluoromethyl)ethene derivatives (**6**) in good yields. However, this reaction required HF, a dangerous reagent. We have described a much easier and safer synthesis of **6** from **4** obtained by the reaction of ketones in the presence of magnesium at -53°C. Thus, treatment of **4** with acetic anhydride and zinc chloride gave acetoxy compounds (**7**), which were converted to the olefins (**6**) by reductive deacetoxybromination with zinc in the presence of a catalytic amount of copper (I) iodide.[5b] The products (**4**) from the aldehydes through the above procedure were much more easily acetylated with acetic anhydride and pyridine to the acetoxy compounds (**7**) in almost quantitative yields, and **7** were transformed to **6** by treatment with Zn in very high yields, as shown in Scheme 3.

Scheme 3



4a-d	**7a-d** Yield %	**6a-d** Yield % (*E*/*Z*)
4a: R = Ph	**7a**: 100	**6a**: 88 (0.12/1)
4b: R = n-C_7H_{15}	**7b**: 99	**6b**: 95 (0.23/1)
4c: R = $PhCH_2CH_2$	**7c**: 97	**6c**: 99 (0.26/1)
4d: R = PhCH=CH	**7d**: 95	**6d**: 95 (0.19/1)

In conclusion, we succeeded in the synthesis of CF_3CBrCl-containing alcohols (**4**) from aldehydes using zinc in the place of magnesium, which were difficult to obtain using magnesium. This widened the usefulness of Halothane (**1**) as a building block. Dichloro analogs of **4** and type **6** compounds were obtained by the reaction of 1,1,1-trichloro-2,2,2-trifluoroethane[6,7] and used for synthesis of fluorine analogs of pyrethroids and other types of compounds, but this chlorofluorocarbon is now inhibited to use because of ozone layer problem. Our method uses easily available Halothane, and provides a new ecologically safe route for synthesis of these types of compounds.

Experimental

General Procedures.

Melting points were measured on micro melting point apparatus, Model MP, Yanagimoto, Kyoto, Japan, and Melting Point Apparatus, Ishii Shoten, Tokyo, Japan, without correction. ^{1}H-NMR spectra were recorded on JEOL FX90Q and JNM-GX400 spectrometers. ^{19}F-NMR spectra were measured on Hitachi R-1500 and JEOL- FX90Q spectrometers. Benzotrifluoride (BTF) was used as an internal standard and 64 ppm was added to convert to a common standard scale from $CFCl_3$. Abbreviations: s, singlet; d, doublet; m, multiplet; bs, broad singlet; q, quartet. Mass spectra were recorded on a JEOL JMS-DX300. Gas-liquid chromatography (GLC) was carried out on a Hitachi 263-50 gas chromatograph (column, 5% SE-30 3 mm x 2 m; carrier, N_2 at 30 ml/min). Peak areas were calculated on a Hitachi D-2000 Chromato-integrator to estimate approximate yields

Zinc powder was washed successively with dilute hydrochloric acid, water, ethanol and diethyl ether, and dried under vacuum. Typical procedures for method A and B are exemplified in the reaction of benzaldehyde in pyridine.

Reaction with Benzaldehyde (2a).

Method A: Halothane (**1**, 0.32 ml, 3 mmol) was added to a suspension of Zn (196 mg, 3 mmol) and CuCl (3 mg, 0.03 mmol) in pyridine (3 ml) over 15 min at 0°C under an Ar atmosphere. To the mixture was added benzaldehyde (**2a**, 0.10 ml, 1 mmol) over 5 min at 0°C. After being stirred for 2 h at this temperature, the mixture was poured into 10% HCl and ice, then extracted with ether. The ether layer was washed with saturated $NaHCO_3$ and saturated NaCl, and dried over $MgSO_4$. After the evaporation of the solvent, the residue was analyzed GLC (from 80 to 200°C by 20°C/min) and found to contain 2-chloro-1,1,1-trifluoro-3-phenyl-2-propene (**6a**), 2-bromo-2-chloro-1,1,1-trifluoro-3-phenylpropan-3-ol (**4a**), **2a** and {2-chloro-1,1,1-trifluoro-3-phenylpropan-3-ol (**3a**) and 2-chloro-1,1-difluoro-3-phenyl-1-propen-3-ol (**5a**)} in a ratio of 2.0:75.2:8.7:13.9. The residue was separated by column chromatography (SiO_2, hexane-CH_2Cl_2, 7:3) to give **6a** (2.6 %), **4a** (207 mg, 68.5 %), **2a** (6 mg, 5.7 %), **3a** (17 mg, 7.6 %) and **5a** (13 mg, 6.4 %). The yield of **6a** was decided by ^{19}F-NMR (the ratio of *E/Z*=0.32/1). The structures of **4a** were determined by the comparison of spectral data,[4] which showed that **4a** was a mixture of diastereomers. The ratio was approximately 1:1 and same as that from the reaction with magnesium. ^{19}F-NMR spectrum of **3a** showed that it was a 1:1 mixture of two diastereomers. This was separated by medium pressure column chromatography to give two diastereomers. One diastereomer of **3a**: A colorless oil. Bp 85°C/0.8 mmHg (bulb-to-bulb distillation). MS *m/z*: 224 (M^+). HRMS Calcd for $C_9H_8ClF_3O$: 224.021. Found: 224.021. ^1H-NMR ($CDCl_3$) δ: 2.63 (1H, d, J=5.93 Hz), 4.34 (1H, q-d, J=6.81, 3.29 Hz), 5.25 (1H, d-d, J=5.93, 3.29 Hz), 7.38 (5H, bs). ^{19}F-NMR ($CDCl_3$) ppm: 7.51 (3F, d, J=6.81 Hz). The other diastereomer of **3a**: A colorless oil. Bp 95°C/0.3 mmHg (bulb-to-bulb distillation). MS *m/z*: 224 (M^+). HRMS Calcd for $C_9H_8ClF_3O$: 224.021. Found: 224.021. ^1H-NMR ($CDCl_3$) δ: 2.61 (1H, d, J=4.18 Hz), 4.37 (1H, q-d, J=7.03, 6.80 Hz), 5.04 (1H, d-d, J=7.03, 4.18 Hz), 7.64 (5H, bs). ^{19}F-NMR ($CDCl_3$) ppm: 6.15 (3F, d, J=6.80 Hz). The structures of **5a** and **6a** were determined by comparison of spectral data.[4]

Method B: **2a** (0.10 ml, 1 mmol) was added to a suspension of Zn (0.196 mg, 3 mmol) and CuCl (3 mg, 0.03 mmol) in pyridine (3 ml) at 0°C under an Ar atmosphere. **1** (0.32 ml, 3 mmol) was added to the mixture over 30 min at 0°C. After being stirred for 1 h at this temperature, the mixture was poured into 10% HCl and ice, then extracted with ether. The ether layer was washed with saturated $NaHCO_3$ and saturated NaCl, and dried over $MgSO_4$. After the evaporation of the solvent, the residue was analyzed GLC (from 80 to 200°C by 20°C/min), and found to contain **6a**, **4a**, **2a** and (**3a** and **5a**) in ratio of 3.5:46.0:12.3:38.1. The residue was separated by column chromatography (SiO_2, hexane-CH_2Cl_2, 7:3-1:1) to give **6a** (3.1 %), **4a** (130 mg, 43.0 %), **2a** (12 mg, 11.3 %), **3a** (51 mg, 22.8 %) and **5a** (15 mg, 7.4 %). The yield of **6a** was decided by ^{19}F-NMR (the ratio of *E/Z*=0.43/1). The ratio of diastereomers of **4a** was 1:1 based on peak areas on ^{19}F-NMR. ^{19}F-NMR spectrum of **3a** showed that it was a 1:1 mixture of two diastereomers. The *E/Z* ratio of **6a** was estimated to be 0.43/1 based on by ^{19}F-NMR.

Reaction with Octylaldehyde (2b).

Method A: After **1** (0.32 ml, 3 mmol) was added to a suspension of Zn (196 mg, 3 mmol) and CuCl (3 mg, 0.03 mmol) in pyridine (3 ml) over 15 min at 0°C under an Ar atmosphere, **2b** (0.16 ml, 1 mmol) was added, and treated as in the case of **2a**. After the concentration of the ether extract, the residue was analyzed GLC (from 80 to 200°C by 20°C/min) and found to contain 2-chloro-1,1,1-trifluoro-2-decene **(6b)**, 2-bromo-2-chloro-1,1,1-trifluorodecan-3-ol **(4b)**, **2b** and {2-chloro-1,1,1-trifluorodecan-3-ol **(3b)** and 2-chloro-1,1-difluoro-1-decen-3-ol **(5b)**} in ratio of 10.2:58.5:13.6:10.2. The residue was separated by column chromatography (SiO_2, hexane-CH_2Cl_2, 9:1-7:3) to give **6b** (20 mg, 8.8 %), **4b** (187 mg, 54.7 %), **2b** (19 mg, 14.8 %), **3b** (19 mg, 7.7 %) and **5b** (19 mg, 8.4 %). **3b**: A colorless oil. Bp 80°C/0.5 mmHg (bulb-to-bulb distillation). MS *m/z*: 228 (M^+-H_2O). HRMS Calcd for $C_{10}H_{16}ClF_3$: 228.089. Found: 228.089. ^1H-NMR ($CDCl_3$) δ: 0.89 (3H, t, J=6.87 Hz), 1.28-1.97 (12H, m), 1.84 (0.5H, d, J=8.24 Hz), 1.97 (0.5H, d, J=7.32 Hz), 4.15-4.01 (1.5H, m), 4.24 (0.5H, q-d, J=7.08, 4.74 Hz). ^{19}F-NMR ($CDCl_3$) ppm: 6.45 (1.5F, d, J=7.08 Hz), 7.71 (1.5F, d, J=7.08 Hz). ^{19}F-NMR spectrum of **3b** showed that it was a 1:1 mixture of two diastereomers. The *E/Z* ratio of **6b** was estimated to be 0.64/1 based on by ^{19}F-NMR. The structures of **4b** were determined by the comparison of spectral data,[4] which showed that **4b** was a mixture of diastereomers. The ratio is approximately 1:1 and same as that from the reaction with magnesium.

Method B: After **2b** (0.16 ml, 1 mmol) was added to a suspension of Zn (0.196 mg, 3 mmol) and CuCl (3 mg, 0.03 mmol) in pyridine (3 ml) at 0°C under an Ar atmosphere, **1** (0.32 ml, 3 mmol) was added to the mixture, and treated as in the case of **2a**. Analysis of the residue by GLC (from 80 to 200°C by 20°C/min) showed it contained **6b**, **4b**, **2b** and **(3b** and **5b)** in ratio of 13.9:45.1:12.1:28.7. This residue was separated by column chromatography (SiO_2, hexane-CH_2Cl_2, 9:1-7:3) to give **6b** (30 mg, 13.2 %), **4b** (145 mg, 44.8 %), **2b** (18 mg, 14.0 %), **3b** (45 mg, 18.3 %) and **5b** (20 mg, 8.8 %). The *E/Z* ratio of **6b** was estimated to be 0.63/1 based on by ^{19}F-NMR. ^{19}F-NMR spectra of **3b** and **4b** showed that they were 1:1 mixtures of the two diastereomers.

Reaction with 3-Phenylpropionaldehyde (2c).

Method A: After **1** (0.32 ml, 3 mmol) was added to a suspension of Zn (196 mg, 3 mmol) and CuCl (3 mg, 0.03 mmol) in pyridine (3 ml), **2c** (0.16 ml, 1 mmol) was added, and treated as in the case of **2a**. After the evaporation of the solvent, the residue was analyzed GLC (from 80 to 200°C by 20°C/min) and found to contain 2-chloro-1,1,1-trifluoro-5-phenyl-2-pentene **(6c)**, 2-bromo-2-chloro-1,1,1-trifluoro-5-phenylpentan-3-ol **(4c)**, **2c** and 2-chloro-1,1,1-trifluoro-5-phenylpentan-3-ol **(3c)** and 2-chloro-1,1-difluoro-5-phenyl-1-penten-3-ol **(5c)** in ratio of 11.6:7.6:61.1:7.0:12.6. The residue was separated by a column chromatography (SiO_2, hexane-CH_2Cl_2, 1:1) to give **6c** (10 mg, 4.3 %), **4c** (167 mg, 49.7 %), **2c** (12 mg, 8.9 %), **3c** (19 mg, 7.5 %) and **5c** (24 mg, 10 %). ^{19}F-NMR spectrum of **3c** showed that it was a 1:1 mixture of two diastereomers, which were separated by a medium pressure column chromatography. One diastereomer of **3c**: A colorless oil. Bp 85°C /0.2 mmHg (bulb-to-bulb distillation). MS *m/z*: 252 (M^+). HRMS Calcd for $C_{11}H_{12}ClF_3O$: 252.053. Found: 252.052. ^1H-NMR ($CDCl_3$) δ: 1.87 (1H, d-d-d-d, J=14.04, 9.16, 7.32, 4.28 Hz), 1.97 (1H, d, J=8.24 Hz), 2.04 (1H, d-d-d-d, J=14.04, 9.15, 8.85, 5.50 Hz), 2.72 (1H, d-d-d, J=13.73, 9.15, 7.32 Hz), 2.84 (1H, d-d-d, J=13.73, 9.16, 5.50 Hz), 4.07-4.14 (2H,m), 7.19-7.32 (5H, m). ^{19}F-NMR ($CDCl_3$) ppm: 8.19 (3F, d-d, J=6.96, 0.24 Hz). The other diastereomer of **3c**: A colorless oil. Bp 90°C/0.2 mmHg (bulb-to-bulb distillation). MS *m/z*: 252 (M^+). HRMS Calcd for $C_{11}H_{12}ClF_3O$: 252.053. Found: 252.054. ^{1}H-NMR ($CDCl_3$) δ: 1.95 (1H, d-d-d-d, J=14.34, 9.46, 9.16, 5.19 Hz), 2.01-2.15 (2H, m), 2.72 (1H, d-d-d, J=14.04, 9.16, 7.33 Hz), 2.90 (1H, d-d-d, J=14.04, 9.46, 5.19 Hz), 4.04 (1H, d-d-d-d, J=9.46, 7.65, 4.88, 2.75 Hz), 4.23 (1H, q-d, J=7.02, 4.88 Hz), 7.20-7.32 (5H, m). ^{19}F-NMR ($CDCl_3$) ppm: 6.89 (3F, d-d, J=7.08, 0.24 Hz). **6c**: A colorless oil. GC-MS (5%SE30, 4 m, carrier gas He, 80-220°C, 20°C/min) *m/z*: 234. GC-HRMS Calcd for $C_{11}H_{10}ClF_3$: 234.042. Found: 234.042. ^{1}H-NMR ($CDCl_3$) δ: 2.58-2.69 (2H, m), 2.74-2.80 (2H, m), 6.21 (0.5H, t, J=7.94 Hz), 6.48 (0.5H, t-q, J=7.17, 0.92 Hz), 7.16-7.33 (5H, m). ^{19}F-NMR ($CDCl_3$) ppm: -0.40 (1.5F, t, J=1.71 Hz), 6.28 (1.5F, t-d, J=1.71, 0.92 Hz). The *E/Z* ratio of **6c** was estimated to be 0.56/1 based on by ^{19}F-NMR. The structures of **4c** were determined by the comparison of spectral data,[4] which showed that **4c** was a mixture of diastereomers. The ratio is approximately 1:1 and same as that from the reaction with magnesium.

Method B: After **2c** (0.13 ml, 1 mmol) was added to a suspension of Zn (0.196 mg, 3 mmol) and CuCl (3 mg, 0.03 mmol) in pyridine (3 ml) at 0°C, **1** (0.32 ml, 3 mmol) was added to the mixture, and treated as in the case of **2a**. After concentration of the ether extract, analysis of the residue by GLC (from 80 to 200°C by 20°C/min) and showed it contained **6c**, **4c**, **2c**, **3c** and **5c** in ratio of 24.8:39.0:4.8:15.3:16.0. The residue was separated by column chromatography (SiO_2, hexane-CH_2Cl_2, 1:1) to give **6c** (14 mg, 5.9 %), **4c** (109 mg, 33.0 %), **2c** (6 mg, 4.5 %), **3c** (37 mg, 14.7 %) and **5c** (28 mg, 12.1 %). ^{19}F-NMR spectrum of **3c** and **4c** showed that they were 1:1 mixtures of two diastereomers. The *E/Z* ratio of **6c** was estimated to be 0.58/1 based on by ^{19}F-NMR.

Reaction with Cinnamaldehyde (2d).

Method A: After **1** (0.32 ml, 3 mmol) was added to a suspension of Zn (196 mg, 3 mmol) and CuCl (3 mg, 0.03 mmol), **2d** (0.13 ml, 1 mmol) was added to the mixture, and treated as in the case of **2a**. After the evaporation of the solvent, analysis of the residue by GLC (from 80 to 200°C by 20°C/min) showed it contained 2-chloro-1,1,1-trifluoro-5-phenyl-2,4-pentadiene (**6d**), 2-bromo-2-chloro-1,1,1-trifluoro-5-phenyl-4-penten-3-ol (**4d**) and {2-chloro-1,1,1-trifluoro-5-phenyl-4-penten-3-ol (**3d**) and 2-chloro-1,1-difluoro-5-phenyl-1,4-pentadien-3-ol (**5d**)} in ratio of 8.4:76.3:15.3. The residue was separated by a column chromatography (SiO_2, hexane-CH_2Cl_2, 7:3-1:1) to give **6d** (16 mg, 6.9 %), **4d** (225 mg, 68.6 %), **3d** (21 mg, 8.4 %) and **5d** (8.4 %). The yield of **5d** was decided by ^{19}F-NMR. ^{19}F-NMR spectrum of **3d** showed that it was a 1:1 mixture of two diastereomers, which were separated by a medium pressure column chromatography. One diastereomer of **3d**: A colorless oil. Bp 100°C/0.4 mmHg (bulb-to-bulb distillation). MS *m/z*: 250 (M^+). HRMS Calcd for $C_{11}H_{10}ClF_3O$: 250.037. Found: 250.037. ^{1}H-NMR ($CDCl_3$) δ: 2.22 (1H, d, J=7.32 Hz), 4.26 (1H, q-d, J=6.84, 3.06 Hz), 4.81-4.85 (1H, m), 6.22 (1H, d-d, J=15.87, 6.26 Hz), 6.77 (1H, d-d, J=15.87, 1.22 Hz), 7.27-7.42 (5H, m). ^{19}F-NMR ($CDCl_3$) ppm: 7.84 (3F, d-d, J=6.84, 0.50 Hz). The other diastereomer of **3d**: Colorless crystals. Mp 38-39°C. MS *m/z*: 250 (M^+). HRMS Calcd for $C_{11}H_{10}ClF_3O$: 250.037. Found: 250.038. ^{1}H-NMR ($CDCl_3$) δ: 2.26 (1H, d, J=6.11 Hz), 4.40 (1H, d-d, J=6.91, 4.27 Hz), 4.72-4.80 (1H, m), 6.31 (1H, d-d-q, J=15.87, 6.72, 0.78 Hz), 6.74 (1H, d, J=15.87 Hz), 7.27-7.42 (5H, m). ^{19}F-NMR ($CDCl_3$) ppm: 7.32 (3F, d-d, J=6.91, 0.78 Hz).

^{19}F-NMR spectrum of **4d** showed that it was a 1:1 mixture of two diastereomers, which were separated by a medium pressure column chromatography. One diastereomer of **4d**: Colorless crystals. Mp 40-40.5°C. MS *m/z*: 328 (M$^+$). HRMS Calcd for $C_{11}H_9BrClF_3O$: 327.948. Found: 327.948. ^{1}H-NMR (CDCl$_3$) δ: 2.48 (1H, d-d, J=7.32, 0.61 Hz), 4.70 (1H, d-d-q, J=7.32, 6.72, 1.07 Hz), 6.36 (1H, d-d-q, J=15.87, 6.72, 0.61 Hz), 6.84 (1H, d, J=15.87 Hz), 7.29-7.45 (5H, m). ^{19}F-NMR (CDCl$_3$) ppm: 9.58 (3F, bs). The other diastereomer of **4d**: A colorless oil. Bp 120°C/0.2 mmHg (bulb-to-bulb distillation). MS *m/z*: 328 (M$^+$). HRMS Calcd for $C_{11}H_9BrClF_3O$: 327.948. Found: 327.948. ^{1}H-NMR (CDCl$_3$) δ: 2.52 (1H, d, J=7.02 Hz), 4.78 (1H, d-d-q, J=7.02, 6.71, 0.92 Hz), 6.36 (1H, d-d-q, J=15.87, 6.71, 0.92 Hz), 6.83 (1H, d, J=15.87 Hz), 7.29-7.45 (5H, m). ^{19}F-NMR (CDCl$_3$) ppm: 9.18 (3F, bs). **5d**: MS *m/z*: 230 (M$^+$). HRMS Calcd for $C_{11}H_9ClF_2O$: 230.031. Found: 230.031. ^{1}H-NMR (CDCl$_3$) δ: 2.14 (1H, d, J=6.10 Hz), 5.23-5.29 (1H, m), 6.26 (1H, d-d, J=15.87, 5.95 Hz), 6.72 (1H, d-d, J=15.87, 0.92 Hz), 7.26-7.42 (5H, m). ^{19}F-NMR (CDCl$_3$) ppm: 23.86 (1F, d-d, J=37.75, 2.20 Hz), 25.26 (1F, d-d, J=37.75, 2.57 Hz). **6d**: MS *m/z*: 232 (M$^+$). HRMS Calcd for $C_{11}H_8ClF_3$: 232.027. Found: 232.027. ^{1}H-NMR (CDCl$_3$) δ: 6.81 (0.32H, d, J=11.59 Hz), 6.76 (0.32H, d, J=15.26 Hz), 6.92-7.10 (2.04H, m), 7.11 (0.32H, d-d-q, J=15.26, 11.59, 1.83 Hz), 7.30-7.51 (5H, m). ^{19}F-NMR (CDCl$_3$) ppm: -1.07 (0.96F, d, J=1.83 Hz), 1.98 (2.04F, bs). The *E/Z* ratio of **6d** was estimated to be 0.47/1 based on by ^{19}F-NMR.

Method B: After **2d** (0.13 ml, 1 mmol) was added to a suspension of Zn (0.196 mg, 3 mmol) and CuCl (3 mg, 0.03 mmol) in pyridine (3 ml), **1** (0.32 ml, 3 mmol) was added to the mixture, and treated as in the case of **2a**. After the evaporation of the solvent, the residue was analyzed GLC (from 80 to 200°C by 20°C/min interval) and found to contain **6d**, **4d**, (**3d** and **5d**) and **2d** in ratio of 8.9:73.7:13.7:3.6. The residue was separated by a column chromatography (SiO$_2$, hexane-CH$_2$Cl$_2$, 7:3-1:1) to give **6d** (11 mg, 4.7 %), **4d** (216 mg, 65.9 %), **3d** (18 mg, 6.4 %), **5d** (3.0 %) and **2d** (14 mg, 10.6 %). The yield of **5d** was decided by ^{19}F-NMR. ^{19}F-NMR spectrum of **3d** showed that it was a 1:1 mixture of two diastereomers. ^{19}F-NMR spectrum of **4d** showed that it was a 1:1 mixture of two diastereomers.The *E/Z* ratio of **6d** was estimated to be 0.48/1 based on by ^{19}F-NMR.

Reaction with Benzaldehyde (2a) in various solvents.

All the reactions were carried out using 1 mmol of **2a** and 3 ml of solvents designated in Table 1. Amounts of other reagents were same as in the reaction using pyridine as a solvent. Reaction temperatures and times are as shown in Table 1. Yields are isolation yields by column chromatography.

Acetylation of 4a.

Acetic anhydride and pyridine were added to **4a** (302 mg, 1 mmol) at 0°C. The mixture was stirred for 1 h at room temperature, then poured into 10% HCl and ice, and extracted with CH$_2$Cl$_2$. The CH$_2$Cl$_2$ layer was washed with saturated NaHCO$_3$ and saturated NaCl, and dried over MgSO$_4$. After the evaporation of the solvent, the residue was analyzed GLC (from 80 to 200°C by 20°C/min), it contained 99.6 % of a major product. The residue was separated by a column chromatography (SiO$_2$, hexane-CH$_2$Cl$_2$, 7:3) to give **7a** (343 mg, 99.7 %). **7a**: Colorless crystals. Mp 35.0-35.5°C. MS *m/z*: 344 (M$^+$). HRMS Calcd for $C_{11}H_9BrClF_3O_2$:

343.943. Found: 343.942. ^{1}H-NMR ($CDCl_3$) δ: 2.15 (1.5H, s), 2.16 (1.5H, s), 6.30 (0.5H, s), 6.39 (0.5H, s), 7.35-7.45 (3H, m), 7.54-7.61 (2H, m). ^{19}F-NMR ($CDCl_3$) ppm: 9.75 (1.5F, s), 10.04 (1.5F, s).

Acetylation of 4b.

4b (323 mg, 1 mmol) was acetylated as in the case of **4a** at 0°C. After the evaporation of the solvent, the residue was found to contain 99.7 % of a major product by GLC. The residue was separated by column chromatography (SiO_2, hexane-CH_2Cl_2, 7:3) to give **7b** (362 mg, 99.2 %). **7b**: A colorless oil. Bp 120°C /0.6 mmHg (bulb-to-bulb distillation). MS *m/z*: 351 (M^+-CH_3). HRMS Calcd for $C_{11}H_{16}BrClF_3O_2$: 350.998. Found: 350.998. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J=6.87 Hz), 1.20-1.43 (10H, m), 1.79-1.91 (1H, m), 1.99-2.20 (1H, m), 2.13 (3H, s), 5.40 (0.5H, d-d, J=10.38, 2.14 Hz), 5.54 (0.5H, d-d, J=10.37, 2.14 Hz). ^{19}F-NMR ($CDCl_3$) ppm: 9.94 (1.5F, s), 10.38 (1.5F, s)

Acetylation of 4c.

4c (299 mg, 0.91 mmol) was acetylated as in the case of **4a**. After the evaporation of the solvent, the residue was found to contain 99.7 % of a major product by GLC. The residue was separated by column chromatography (SiO_2, hexane-CH_2Cl_2, 7:3) to give **7c** (362 mg, 99.2 %). **7c**: A colorless oil. Bp 140°C /0.8 mmHg (bulb-to-bulb distillation). MS *m/z*: 372 (M^+). HRMS Calcd for $C_{13}H_{13}BrClF_3O_2$: 371.974. Found: 371.974. ^{1}H-NMR ($CDCl_3$) δ: 2.11 (3H, s), 2.15-2.27 (1H, m), 2.37-2.51 (1H, m), 2.61-2.73 (2H, m), 5.48 (0.5H, d-d, J=10.07, 2.14 Hz), 5.62 (0.5H, d-d, J=10.07, 2.14 Hz), 7.19-7.32 (5H, m). ^{19}F-NMR ($CDCl_3$) ppm: 9.96 (1.5F, s), 10.41 (1.5F, s)

Acetylation of 4d.

4d (197 mg, 0.60 mmol) was acetylated as in the case of **4a**. After the evaporation of the solvent, the residue was found to contain 95.9 % of a major product by GLC. The residue was separated by column chromatography (SiO_2, hexane-CH_2Cl_2, 7:3) to give **7d** (211 mg, 95.0 %). **7d**: A colorless oil. Bp 180°C /8.0 mmHg (bulb-to-bulb distillation). MS *m/z*: 370 (M^+). HRMS Calcd for $C_{13}H_{11}BrClF_3O_2$: 369.959. Found: 369.958. ^{1}H-NMR ($CDCl_3$) δ: 2.16 (1.5H, s), 2.17 (1.5H, s), 5.96 (0.5H, d, J=7.63 Hz), 6.04 (0.5H, d, J=7.93 Hz), 6.26 (0.5H, d-d, J=15.83, 7.63 Hz), 6.27 (0.5H, d-d, J=15.83, 7.93 Hz), 6.85 (1H, d, J=15.83 Hz), 7.29-7.47 (5H, m). ^{19}F-NMR ($CDCl_3$) ppm: 2.90 (1.5F, s), 3.16 (1.5F, s).

Deacetoxybromination of 7a.

A solution of **7a** (343 mg, 1.0 mmol) in DMF (2 ml) was added to a suspension of Zn (72 mg, 1.1 mmol) and CuI (1 mg) in DMF (3 ml) at 0°C. The mixture was stirred for 1 h at this temperature, then poured into 10% HCl and ice, and extracted with pentane. The pentane layer was washed with saturated $NaHCO_3$ and saturated NaCl, and dried over $MgSO_4$. After a careful evaporation of the solvent at 0°C under reduced pressure, the residue was analyzed by GLC (from 80 to 200°C by 20°C/min) and found to contain **6a** and **7a** in ratio of 95.9:1.4. The residue was separated by column chromatography (SiO_2, pentane~pentane-CH_2Cl_2, 7:3) to give **6a** (182 mg, 88.3 %) and **7a** (4 mg, 1.2 %). The *E/Z* ratio of **6a** was estimated to be 0.12/1 based on ^{19}F-NMR.

Deacetoxybromination of 7b.

A solution of **7b** (281 mg, 0.77 mmol) in DMF (2 ml) was added to a suspension of Zn (54 mg, 0.85 mmol) and CuI (1 mg) in DMF (3 ml) at 0°C, and treated as in the case of **7a** to give **6b** (167 mg, 94.9 %) and **7b** (13 mg, 4.6 %). The *E/Z* ratio of **6b** was estimated to be 0.23/1 based on by ^{19}F-NMR.

Deacetoxybromination of 7c.

A solution of **7c** (372 mg, 1.0 mmol) in DMF (2 ml) was added to a suspension of Zn (72 mg, 1.1 mmol) and CuI (1 mg) in DMF (3 ml) at 0°C, and treated as in the case of **7a** to give **6c** (222 mg, 94.9 %). The *E/Z* ratio of **6c** was estimated to be 0.26/1 based on by ^{19}F-NMR.

Deacetoxybromination of 7d.

A solution of **7d** (211 mg, 0.57 mmol) in DMF (2 ml) was added to a suspension of Zn (41 mg, 0.63 mmol) and CuI (1 mg) in DMF (3 ml) at 0°C, and treated as in the case of **7a** to give **7d** (4 mg, 1.9 %) and **6d** (125 mg, 94.7 %). The *E/Z* ratio of **6d** was estimated to be 0.19/1 based on by ^{19}F-NMR.

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REFERENCES

1. a) Kobayashi, Y.; Kumadaki, I. *Tetrahedron Lett.* **1969**, 4095-6: b) Kobayashi, Y.;Kumadaki, I.; Sato, S.; Hara, N.; Chikami, E. *Chem. Pharm. Bull.* **1970**, 18, 2334-2339.
2. Review: Kumadaki, I. *Reviews Heteroatom Chem.* **1993**, 9, 181-204.
3. Takagi, T.; Takesue, A.; Koyama, M.; Ando, A.; Miki, T.; Kumadaki, I. *J. Org. Chem.* **1992**, 57, 3921-3923.
4. Takagi, T.; Takesue, A.; Isowaki, A; Koyama, M.; Ando, A.; Kumadaki, I. *Chem.Pharm. Bull.* **1995**, 43, 1107-1110.
5. a) Takagi, T.; Okikawa, N.; Johnoshita,S.; Koyama, M.; Ando, A.; Kumadaki, I. *Synnlett.* **1996**, 82-84.
   b) Takagi, T.; Takahashi, J.; Nakatsuka, H.; Koyama, M.; Ando, A.; Kumadaki, I. *Chem.Pharm. Bull.* **1996**, 44, 280-283.
6. Fujita, M.; Hiyama, T. *Tetrahedron Lett.* **1986**, 27, 3655-3658.
7. Lang, R. W. *Helv. Chim. Acta* **1986**, 69, 881-886.

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