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# A Method for Synthesis of Fluorine Compounds Using Abnormal Grignard Reaction of Halothane. II.[1] Reaction with Aldehydes and Unsaturated Ketones

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**In an abnormal Grignard reaction of halothane, the primary Grignard reagent reacts with another mole of halothane to give 1-bromo-1-chloro-2,2,2-trifluoroethylmagnesium bromide, which in turn reacts with a carbonyl compound to give 1-bromo-1-chloro-2,2,2-trifluoroethyl carbinols and their dehalogenation products, 1-chloro-2,2-difluoroethenyl carbinols. We examined the application of this method to aldehydes and to unsaturated ketones. Aldehydes were much less reactive than ketones, and needed higher reaction temperature. However, elevation of temperature caused dehalogenation of the primary products to 1-chloro-2,2-difluoroethenyl derivatives. These derivatives were treated with hydrogen fluoride to afford 1-chloro-1-(trifluoromethyl)ethene derivatives. The reaction of α,β-unsaturated ketones mainly gave 1,2-addition products of the Grignard reagent, while 3-methyl-2-cyclohexenone gave mainly the 1,4-adducts.**

**Key words** halothane; trifluoromethyl; Grignard reaction; aldehyde; unsaturated ketone; hydrogen fluoride

Organofluorine compounds have attracted much attention in the fields of medicinal and agricultural chemistry.[2] We are engaged in developing new methods for syntheses of bioactive fluorine compounds, and we have reported trifluoromethylation of halogen compounds with trifluoromethyl iodide and copper powder,[3] and an ene reaction of trifluoromethyl carbonyl compounds.[4] As an extension of that research, we used halothane, 2-bromo-2-chloro-1,1,1-trifluoroethane (**1**), as a building block, and found an abnormal Grignard reaction of halothane with ketones (**2**).[1] This reaction affords 1-bromo-1-chloro-2,2,2-trifluoroethyl adducts (**3**) to the carbonyl group and their dehalogenation products, 1-chloro-2,2-difluorovinyl compounds (**4**). The latter compounds were treated with hydrogen fluoride to give 1-chloro-1-(trifluoromethyl)ethene compounds (**5**), as shown in Chart 1.

Now, we would like to report 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. These are discussed in this report.

First, a solution of **1** and octanal (**6**) was added to a suspension of magnesium, as in the case of ketones, but only traces of 2-bromo-2-chloro-1,1,1-trifluoro-3-decanol (**7**) and 2-chloro-1,1-difluoro-1-decen-3-ol (**8**) were obtained, and almost all the starting aldehyde was recovered. The effect of temperature between −53 and 0 °C was examined, but no marked improvement was not observed. Then, a solution of **1** in tetrahydrofuran (THF) was added slowly to a suspension of magnesium at 0 °C. After the start of the reaction was confirmed by evolution of heat, a solution of **1** and **6** in THF was added to the mixture. Analysis of the reaction product by gas-liquid chromatography (GLC) showed that it contained **7** and **8** in a ratio of 2 : 78. Compounds **7** and **8** were isolated by column chromatography in yields of 1% and 49%, respectively. Compound **7** was found to be a 1 : 1 mixture of diastereomers by $^{19}$F-NMR examination. This result showed that prior formation of the organometallic reagent was necessary. At this temperature, the dehalogenation product was mainly obtained. To obtain the primary addition product (**7**), the reaction was carried out at −53 °C, but the reaction hardly proceeded and the aldehyde was recovered nearly quantitatively. Thus, the reaction was examined at higher temperatures. The results of analyses of the reaction mixtures by GLC are shown in Table 1.

At −40 °C, dehalogenation is very slow, but the reaction itself is too slow for practical synthesis. At −20 °C, dehalogenation is marked. At −30 °C, nearly 30% of the desired product (**7**) was formed. These results show that an aldehyde is much less reactive than a ketone in this

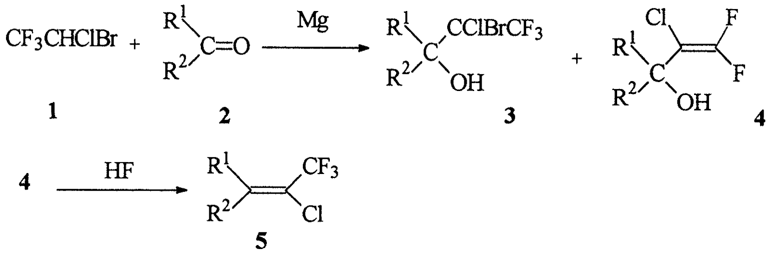

Chart 1

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reaction.

Next, we examined the reaction of benzaldehyde (**9**). At 0 °C, the reaction proceeded, and the analysis of the reaction mixture by GLC showed that it contained a 3 : 84 ratio of the primary adduct (**10**) and its dehalogenation product (**11**), while at −53 °C almost all the aldehyde was recovered.

As reported in the previous paper,[1] treatment of the dehalogenation products (**4**) with hydrogen fluoride gave 1-chloro-1-(trifluoromethyl)ethene derivatives (**5**), through dehydroxylation–fluorination with rearrangement of the double bond. Now, we applied this reaction to **8** and **11**, and obtained the chloro(trifluoromethyl)ethene compounds (**12** and **13**) in moderate isolation yields. These results are summarized in Chart 2.

Compounds of this type were synthesized by Hiyama *et al.*[5] They used 1,1,1-trichloro-2,2,2-trifluoroethane, but it is now thought that this compound should not be employed because of its effect on the ozone layer. Further, 1,1-dichloro-2,2,2-trifluoroethylzinc chloride, the intermediate of this reaction, does not react with ketones. Chloro(trifluoromethyl)ethene moiety is an important unit in some bioactive compounds. Thus, our methods should contribute to the synthesis of such compounds.[6]

Next, to explore the scope of this reaction, the reaction of **1** with conjugated ketones in the presence of magnesium was examined. First, the reaction of benzalacetone(4-phenyl-3-buten-2-one, **14**) with **1** in the presence of magnesium was inspected at −53 °C. The reaction mixture was found to contain 2-chloro-1,1-difluoro-3-methyl-5-phenyl-1,4-pentadien-3-ol (**15**), 2-bromo-2-chloro-1,1,1-trifluoro-3-methyl-5-phenyl-4-penten-3-ol (**16**), 5-bromo-5-chloro-6,6,6-trifluoro-4-phenyl-2-hexanone (**17**) and 5-chloro-6,6-difluoro-4-phenyl-5-hexen-2-one (**18**) in a ratio of 2.5 : 63.4 : 19.4 : 11.0 by GLC analysis. The isolation yields by column chromatography from the mixture were 1.9%, 35.8%, 8.6%, and 1.0%, respectively. The structures of these products were determined by mass and nuclear magnetic resonance spectra. Compounds **16** and **17** were found to be mixtures of diastereomers from the $^{19}$F-NMR spectra. This result showed that 1,2-addition to the carbonyl group predominated over 1,4-addition to the olefinic double bond. Some catalysts are reported to promote the 1,4-addition of a Grignard reagent. Therefore, we tried the reaction in the presence of CuI, CuI·SMe$_2$, or some Lewis acids, but analysis of the reaction mixture by GLC showed no appreciable change of product ratios. The reaction of mesityl oxide (**19**) gave 2-bromo-2-chloro-1,1,1-trifluoro-5-methyl-4-hexen-3-ol (**20**) as a product isolated in the yield of 18%, though the yield estimated by GLC was 76%. This low isolation yield is due to the low stability of **20**. The product was a mixture of two diastereomers (ratio 1 : 1).

Table 1. Ratio of Products at Various Temperatures

| Temp. (°C) | Ratio 6 | 7 | 8 |
|---|---|---|---|
| 0 | — | 2 | 78 |
| −20 | 58 | 11 | 26 |
| −30 | 67 | 28 | 5 |
| −40 | 84 | 11 | 1 |

Finally the reaction of 3-methyl-2-cyclohexenone (**21**) was examined. The products were isolated by column chromatography to give 1-(1-bromo-1-chloro-2,2,2-trifluoroethyl)-3-methyl-2-cyclohexen-1-ol (**22**, 10%), 3-(1-bromo-1-chloro-2,2,2-trifluoroethyl)-3-methyl-1-cyclohexanone (**23**, 36%), and a small amount of a mixture of 3-(1-chloro-2,2,2-trifluoroethyl)-3-methyl-1-cyclohexanone (**24**) and 3-(1-chloro-2,2-difluoroethenyl)-3-methyl-1-cyclohexanone (**25**), GLC analysis of which showed the same retention time, and $^{19}$F-NMR of which revealed that it was a mixture of **24**:**25** (0.43 : 1). The ratio of **22**:**23**:(**24**+**25**) was 16.7 : 52.1 : 15.9 by GLC analysis of the reaction mixture. It is noteworthy that **21** gave mainly 1,4-addition products, while other unsaturated ketones gave mainly 1,2-adducts, and that 1-chloro-2,2,2-trifluoroethyl adduct (**24**), a reduction product of **23**, was isolated. This might be due to the greater rigidity of the cyclohexene ring, which makes the steric effect smaller. The results of the reactions of unsaturated ketones are summarized in Chart 3.

In conclusion, halothane (**1**) reacted with aldehydes in the presence of magnesium to give abnormal Grignard reaction products, 2-bromo-2-chloro-3,3,3-trifluoropropanol derivatives, as in the case of ketones, but the reactivity of the aldehydes was much less than that of ketones. Raising the reaction temperature resulted in dehalogenation of the primary products, and 1-chloro-2,2-difluoroethenyl carbinol derivatives were formed preferentially. Treatment of these propenyl alcohols with anhydrous hydrogen fluoride afforded 1-chloro-1-(trifluoromethyl)ethene derivatives in good yields. The reaction of **1** with $\alpha,\beta$-unsaturated ketones gives 1,2-adducts rather than 1,4-adducts, though 3-methyl-2-cyclohexenone (**21**)

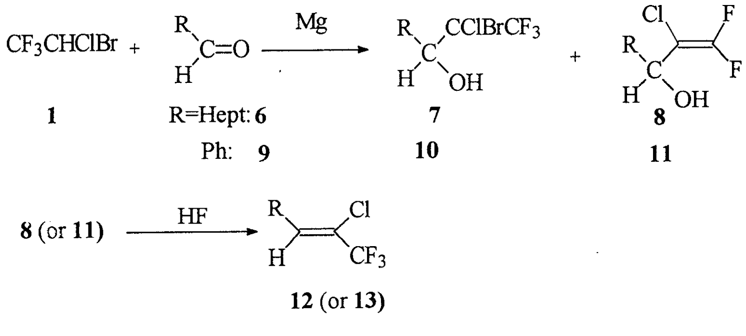
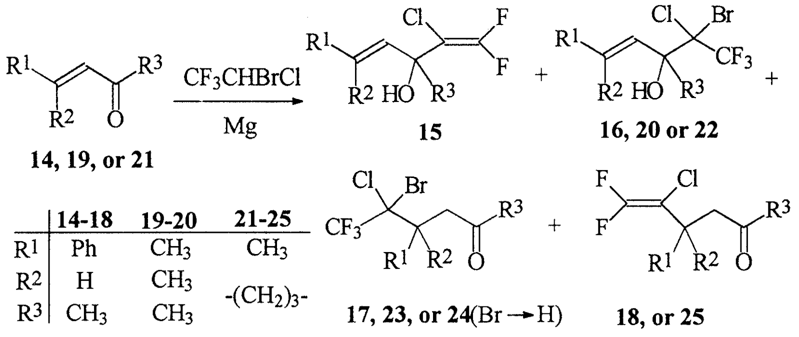


Chart 2



| | 14-18 | 19-20 | 21-25 |
|---|---|---|---|
| R1 | Ph | $CH_3$ | $CH_3$ |
| R2 | H | $CH_3$ | -$(CH_2)_3$- |
| R3 | $CH_3$ | $CH_3$ | |

Chart 3

gave mainly 1,4-adducts. Thus, halothane is a useful synthone for synthesis of fluorine compounds, and this reaction could be applied not only to simple ketones, as reported previously, but also aldehydes and unsaturated ketones.

## Experimental

**General Procedures** Melting points were measured on micro melting point apparatus, Model MP (Yanagimoto, Kyoto, Japan) and a 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 are: s, singlet; d, doublet; m, multiplet; br s, broad singlet; q, quartet. Mass spectra were recorded on a JEOL JMS-DX300. GLC was carried out on a Hitachi 263-50 gas chromatograph (column, 5% SE-30 3 mm × 2 m; carrier, $N_2$ at 30 ml/min). Peak areas were calculated on a Hitachi D-2000 Chromato-integrator.

**Reaction with Octylaldehyde (6)** 1) Addition of Reagents in General Order [Octylaldehyde (**6**) : **1** : Mg = 1 : 3 : 3] at −53 °C: A solution of **1** (6.33 ml, 0.06 mol) and octylaldehyde (**6**, 3.12 ml, 0.02 mol) in THF (20 ml) was added to a suspension of Mg (1.46 g, 0.06 mol) in THF (30 ml) at −53 °C under an atmosphere of Ar. The mixture was stirred at this temperature for 4 h, then poured into ice-water containing 10% HCl, and extracted with $Et_2O$. The $Et_2O$ layer was washed with $H_2O$ and saturated NaCl, and dried over $MgSO_4$. After evaporation of the solvent, the residue was analyzed by GLC and found to contain the starting material (**6**), 2-bromo-2-chloro-1,1,1-trifluoro-3-decanol (**7**) and 2-chloro-1,1-difluoro-1-decen-3-ol (**8**) in a ratio of 98.1 : 0.7 : 0.1. Spectral data for **7** and **8** are given below.

2) At −30° C: A similar reaction was carried out at −30 °C, but no marked improvement was observed. The ratio of **6** : **7** : **8** of the product was 92.6 : 0.1 : 3.7 on GLC analysis.

3) At 0 °C: A similar reaction at 0 °C gave little improvement. The ratio of **6** : **7** : **8** of the product was 93.6 : 0.5 : 1.7 on GLC analysis.

4) Addition of Reagents in Modified Order [Octylaldehyde (**6**) : **1** : Mg = 1 : 3 : 3] at 0 °C: Compound **1** (*ca.* 1 ml) was added to a suspension of Mg (0.73 g, 0.03 mol) in THF (15 ml) under an atmosphere of Ar at 0 °C with stirring. After the start of reaction was confirmed by increase of the temperature of the mixture and coloration, the remainder of **1** (3.16 ml, 0.03 mol in total) and **6** (1.56 ml, 0.01 mol) in THF (10 ml) was added, keeping the temperature below 10 °C. The mixture was stirred at 0 °C for 4 h, poured into ice-water containing 10% HCl, and extracted with $Et_2O$. The $Et_2O$ layer was washed with $H_2O$ and saturated NaCl, and dried over $MgSO_4$. After evaporation of the solvent, the residue (2.141 g) was analyzed by GLC and found to contain **7** and **8** in a ratio of 1.6 : 77.8. This residue was separated by column chromatography ($SiO_2$, hexane–$CH_2Cl_2$, 7 : 3—1 : 1) and the products were distilled to give 2-bromo-2-chloro-1,1,1-trifluoro-3-decanol (**7**, 0.023 g, 0.71%) and 2-chloro-1,1-difluoro-1-decen-3-ol (**8**, 1.098 g, 48.6%). Compound **7** was shown to be a mixture of two diastereomers from the $^{19}$F-NMR spectrum (ratio 1 : 1). **7**: A colorless oil, bp 115—120 °C (21 mmHg) (bulb-to-bulb distillation). MS *m/z*: 323 ($M^+$). HRMS Calcd for $C_{10}H_{17}BrClF_3O$ ($M^+$): 323.002. Found: 323.002. $^{19}$F-NMR ($CDCl_3$) ppm: 9.22 (3F, s), 9.75 (3F, s), (peak ratio: 1 : 1). $^1$H-NMR of one diastereomer ($CDCl_3$) $\delta$: 0.89 (3H, t, $J$=7.0 Hz), 1.20—1.50 (9H, m), 1.55—1.70 (2H, m), 1.95—2.10 (1H, m), 2.20 (1H, d, $J$=7.9 Hz), 3.90 (1H, dd, $J$=8.6, 7.9 Hz). $^1$H-NMR of the other diastereomer ($CDCl_3$) $\delta$: 0.89 (3H, t, $J$=7.0 Hz), 1.20—1.50 (9H, m), 1.55—1.70 (2H, m), 1.95—2.10 (1H, m), 2.28 (1H, d, $J$=7.6 Hz), 4.05 (1H, dd, $J$=8.9, 7.6 Hz). **8**: A colorless oil, bp 120 °C (18 mmHg) (bulb-to-bulb distillation). MS *m/z*: 226 ($M^+$). HRMS Calcd for $C_{10}H_{17}ClF_2O$ ($M^+$): 226.093. Found: 226.093. $^1$H-NMR ($CDCl_3$) $\delta$: 0.88 (3H, t, $J$=7.0 Hz), 1.18—1.38 (10H, br s), 1.58—1.78 (2H, m), 1.88 (1H, br s), 4.52 (1H, dddd, $J$=7.5, 6.9, 2.7, 2.5 Hz). $^{19}$F-NMR ($CDCl_3$) ppm: 25.1 (1F, dd, $J$=40.5, 2.5 Hz), 29.55 (1F, dd, $J$=40.5, 2.7 Hz).

5) The Same Order of Addition at −20 °C: Compound **1** (*ca.* 2 ml) was added slowly to a suspension of Mg (1.46 g, 0.06 mol) in dry THF (30 ml) at −20 °C in an atmosphere of Ar. After the start of the reaction was confirmed by evolution of heat, the remainder of **1** (6.33 ml, 0.06 mol) and **6** (3.12 ml, 0.02 mol) in THF (20 ml) was added, keeping the temperature below −14 °C. The mixture was stirred at −20 °C for 4 h, then treated as above. It was found to contain the aldehyde (**6**), **7** and **8** in a ratio of 58.1 : 10.7 : 26.3.

6) The Same Order of Addition at −30 °C: Compound **1** (*ca.* 1 ml) was added to suspension of Mg (0.73 g, 0.03 mol) in THF (15 ml) at −30 °C. After the start of the reaction was confirmed by evolution of heat, the remainder of **1** (3.16 ml, 0.03 mol in total) and **6** (1.56 ml, 0.01 mol) in THF (10 ml) was added, keeping the temperature below −22 °C. The mixture was stirred at −30 °C for 4 h and treated as above. It was found to contain the aldehyde (**6**), **7** and **8** in a ratio of 66.5 : 27.6 : 4.5.

7) The Same Order of Addition at −40 °C: Compound **1** (*ca.* 1 ml) was added slowly to a suspension of Mg (0.73 g, 0.03 mol) in dry THF (15 ml) at −40 °C. After the start of reaction was confirmed, the remainder of **1** (3.16 ml, 0.03 mol in total) and **6** (1.56 ml, 0.01 mol) in THF (10 ml) was added, keeping the temperature below −32 °C. The mixture was stirred at −40 °C for a further 4 h then treated as above. It was found to contain the aldehyde (**6**), **7** and **8** in a ratio of 84.4 : 11.1 : 0.7.

8) The Same Order of Addition at −53 °C: Compound **1** (*ca.* 2 ml) was added slowly to a suspension of Mg (1.46 g, 0.06 mol) in dry THF (15 ml) at −53 °C. After the start of reaction was confirmed, the remainder of **1** (6.33 ml, 0.06 mol in total) and **6** (3.12 ml, 0.02 mol) in THF (20 ml) was added, keeping the temperature below −50 °C. The mixture was stirred at −50 °C for a further 4 h then treated as above. It was found to contain the aldehyde (**6**), **7** and **8** in a ratio of 98.5 : 1.4 : 0.0.

**Reaction of Benzaldehyde (9)** Compound **1** (*ca.* 2 ml) was added to a suspension of Mg (1.46 g, 0.06 mol) in dry THF (30 ml) under an atmosphere of Ar at 0 °C with stirring. After the start of reaction was confirmed by an increase of temperature of the mixture and coloration, the remainder of **1** (6.33 ml, 0.06 mol in total) and benzaldehyde (**9**, 2.03 ml, 0.02 mol) in THF (20 ml) was added, keeping the temperature under 15 °C. The mixture was stirred at 0 °C for 4 h, poured into ice-water containing 10% HCl, and extracted with $Et_2O$. The $Et_2O$ layer was washed with $H_2O$ and saturated NaCl, and dried over $MgSO_4$. After evaporation of the solvent, the residue was analyzed by GLC and found to contain **10** and **11** in a ratio of 2.6 : 84.3. This residue was separated by column chromatography ($SiO_2$, hexane–$CH_2Cl_2$, 7 : 3—1 : 1) and the products were distilled to give 2-bromo-2-chloro-1,1,1-trifluoro-3-phenyl-3-propanol (**10**, 0.148 g, 2.5%) and 2-chloro-1,1-difluoro-3-phenyl-1-propen-3-ol (**11**, 1.371 g, 33.6%). Compound **11** was shown to be a mixture of two diastereomers by $^{19}$F-NMR analysis (ratio 1 : 1). **10**: A colorless oil, bp 105 °C (2 mmHg) (bulb-to-bulb distillation). MS *m*/*z*: 302 (M$^+$). HRMS Calcd for $C_9H_7BrClF_3O$ (M$^+$): 301.932. Found: 301.932. $^{19}$F-NMR (CDCl$_3$) ppm: 9.24 (3F, s), 9.68 (3F, s), (peak ratio 1 : 1). $^1$H-NMR of one diastereomer (CDCl$_3$) $\delta$: 2.90 (1H, d, $J$=4.9 Hz), 5.15 (1H, d, $J$=4.9 Hz), 7.33—7.44 (3H, m), 7.50—7.58 (2H, m). $^1$H-NMR of the other diastereomer (CDCl$_3$) $\delta$: 2.92 (1H, d, $J$=4.9 Hz), 5.20 (1H, d, $J$=4.9 Hz), 7.33—7.44 (3H, m), 7.50—7.58 (2H, m). **11**: A colorless oil, bp 105—110 °C (8 mmHg) (bulb-to-bulb distillation). MS *m*/*z*: 204 (M$^+$). HRMS Calcd for $C_9H_7ClF_2O$ (M$^+$): 204.015. Found: 204.016. $^1$H-NMR (CDCl$_3$) $\delta$: 2.40 (1H, br s), 5.73 (1H, dd, $J$=2.7, 2.3 Hz), 7.38 (5H, br s). $^{19}$F-NMR (CDCl$_3$) ppm: 24.72 (1F, dd, $J$=38.1, 2.3 Hz), 28.89 (1F, dd, $J$=38.1, 2.7 Hz).

**Reaction of 2-Chloro-1,1-difluoro-1-decen-3-ol (8) with HF** A solution of **8** (3.006 g, 13.3 mmol) in $CH_2Cl_2$ (5 ml) cooled at 0 °C was treated with HF (liquid, 15 ml) and the mixture was stirred at 0 °C for 8 h, then allowed to warm to temperature under stirring. After evaporation of HF during overnight stirring, the mixture was poured into ice-water containing $NaHCO_3$ (30 g) and $CH_2Cl_2$ (15 ml), and extracted with $CH_2Cl_2$. The $CH_2Cl_2$ layer was washed with $H_2O$ and dried over $MgSO_4$. After evaporation of the solvent at atmospheric pressure, the residue was found by GLC to contain 87.5% of the product. It was distilled under vacuum to give 2-chloro-1,1,1-trifluoro-2-decene (**12**, 1.687 g, 55.6%). **12**: A colorless oil, bp 80°C (2.0 mmHg) (bulb-to-bulb distillation). MS *m*/*z*: 228 (M$^+$). HRMS Calcd for $C_{10}H_{16}ClF_3$ (M$^+$): 228.089. Found: 228.089. $^1$H-NMR (CDCl$_3$) $\delta$: 6.44 (1H, tq, $J$=7.37, 0.90 Hz), 2.23 (2H, qq, $J$=7.37, 1.85 Hz), 1.56 (10H, br s), 0.84 (3H, t, $J$=7.02 Hz). $^{19}$F-NMR (CDCl$_3$) ppm: 5.75 (td, $J$=1.85, 0.90 Hz). The structure of **12** was determined to be *Z*-form, since a coupling between the hydrogen on C-3 and the fluorines was observed on $^{19}$F-NMR.

**Reaction of 2-Chloro-1,1-difluoro-3-phenyl-1-propen-3-ol (11)** In a similar manner to that described for the preparation of **12** from **8**, reaction of **11** (0.972 g, 14.8 mmol) in $CH_2Cl_2$ (5 ml) with HF (liquid, 15 ml) was carried out. After evaporation of the solvent at atmospheric pressure, the residue was found by GLC to contain 92.9% of the product. It was distilled under vacuum to give 2-chloro-1,1,1-trifluoro-3-phenyl-2-propene (**13**, 0.549 g, 56.0%). **13**: A colorless oil, bp 70°C (0.5 mmHg) (bulb-to-bulb distillation). MS *m*/*z*: 206 (M$^+$). HRMS Calcd for $C_9H_6ClF_3$ (M$^+$): 206.011. Found: 206.011. $^1$H-NMR (CDCl$_3$) $\delta$: 7.27—7.30 (1H, m), 7.39—7.45 (3H, m), 7.68—7.73 (2H, m). $^{19}$F-NMR (CDCl$_3$) ppm: −6.15 (d, $J$=0.98 Hz). The stereochemistry of **13** was determined to be *Z*-form, since a coupling between the hydrogen at C-3 and the fluorines was observed.

**Reaction of 1 with Benzalacetone (14)** A solution of **1** (0.63 ml, 6 mmol) and benzalacetone (**14**, 0.292 ml, 2 mmol) in THF (2 ml) was added to a suspension of Mg (0.146 g, 6 mmol) in THF (3 ml) cooled at −53 °C under an atmosphere of Ar, keeping the temperature below −45 °C. The mixture was stirred at 4 h at −53 °C, poured into a mixture of ice-saturated $NH_4Cl$, and extracted with $Et_2O$. The $Et_2O$ layer was washed with saturated NaCl, and dried over $MgSO_4$. After evaporation of the solvent under vacuum, the residue (0.607 g) was analyzed by GLC (80—200 °C, 20 °C/min) and found to contain **15** : **16** : **17** : **18** = 2.5 : 63.4 : 19.4 : 11.0. It was separated by a column chromatography ($SiO_2$, hexane–$CH_2Cl_2$, 7 : 3—1 : 1) to give 2-chloro-1,1-difluoro-3-methyl-5-phenyl-1,4-pentadien-3-ol (**15**, 14 mg, 1.9%), 2-bromo-2-chloro-1,1,1-trifluoro-3-methyl-5-phenyl-4-penten-3-ol (**16**, 245 mg, 35.8%), 5-bromo-5-chloro-6,6,6-trifluoro-4-phenyl-2-hexanone (**17**, 59 mg, 8.6%) and 5-chloro-6,6-difluoro-4-phenyl-5-hexen-2-one (**18**, 5 mg, 1.0%). Compounds **15** and **18** were very labile. They were analyzed by $^1$H-NMR, $^{19}$F-NMR and GLC-MS after column chromatography. Compound **16** was purified by vacuum distillation, and **17** was recrystallized from EtOH. Compounds **16** and **17** are mixtures of diastereomers (ratio 1 : 1). The spectral data of these products are as follows. **15**: A colorless oil. GLC-MS (column, 5% SE-30 4 m; column temperature, 80—220 °C, at 16 °C/min; carrier, He, 25 ml/min) *m*/*z*: 244 (M$^+$). $^1$H-NMR (CDCl$_3$) $\delta$: 1.67 (3H, d, $J$=3.52 Hz), 2.41 (1H, br s), 6.27 (1H, dd, $J$=15.99, 2.08 Hz), 6.72 (1H, d, $J$=15.99 Hz), 7.28—7.42 (5H, m). $^{19}$F-NMR (CDCl$_3$) ppm: 17.9 (1F, d, $J$=41.09 Hz), 20.1 (1F, dm, $J$=41.09 Hz). **16**: A colorless oil, bp 129 °C (0.3 mmHg). MS *m*/*z*: 342 (M$^+$). HRMS Calcd $C_{12}H_{11}BrClF_3O$ (M$^+$): 341.963. Found: 341.962. $^1$H-NMR (CDCl$_3$) $\delta$: 1.78 (3H, s), 2.602 (0.5H, br s), 2.604 (0.5H, br s), 6.54 (0.5H, d, $J$=15.87 Hz), 6.58 (0.5H, d, $J$=15.87 Hz), 6.838 (0.5H, d, $J$=15.87 Hz), 6.844 (0.5H, d, $J$=15.87 Hz), 7.25—7.45 (5H, m). $^{19}$F-NMR (CDCl$_3$) ppm: 5.15 (1.5F, br s), 5.21 (1.5F, br s). **17**: Colorless crystals, mp 59 °C. MS *m*/*z*: 342 (M$^+$). HRMS Calcd $C_{12}H_{11}BrClF_3O$ (M$^+$): 341.964. Found: 341.964. $^1$H-NMR (CDCl$_3$) $\delta$: 2.09 (3H, s), 3.22—3.52 (2H, m), 4.08—4.44 (1H, m), 7.16—7.57 (5H, m). $^{19}$F-NMR (CDCl$_3$) ppm: 8.50 (1.5F, br s), 8.69 (1.5F, br s). **18**: A colorless oil. MS *m*/*z*: 244 (M$^+$). HRMS Calcd $C_{12}H_{11}ClF_2O$ (M$^+$): 244.047. Found: 244.046. $^1$H-NMR (CDCl$_3$) $\delta$: 2.18 (3H, s), 2.94 (1H, dd, $J$=17.39, 5.65 Hz), 3.19 (1H, dd, $J$=17.39, 8.85 Hz), 4.46 (1H, ddd, $J$=8.85, 5.65, 2.31 Hz), 7.21—7.38 (5H, m). $^{19}$F-NMR (CDCl$_3$) ppm: 23.88 (1F, d, $J$=41.48 Hz), 27.25 (1F, dd, $J$=41.48, 2.31 Hz).

**Reaction with Mesityl Oxide (19)** In a similar manner to that described for the reaction of **14**, **1** (1.90 ml, 18 mmol) and mesityl oxide (**19**, 0.69 ml, 6 mmol) were treated with Mg (0.437 g, 18 mmol) in THF at −53 °C. After evaporation of the solvent, the residue (1.107 g) was analyzed by GLC and found to contain a main product (75.8%). This was purified by column chromatography ($SiO_2$, hexane–$CH_2Cl_2$, 9 : 1—7 : 3) to give 2-bromo-2-chloro-1,1,1-trifluoro-5-methyl-4-hexen-3-ol (**20**, 0.313 g, 17.7%), which was a mixture of two diastereomers (ratio 1 : 1). **20**: A colorless oil, bp 60 °C (5 mmHg) (bulb-to-bulb distillation). MS *m*/*z*: 294 (M$^+$). HRMS Calcd $C_8H_{11}BrClF_3O$ (M$^+$): 293.963. Found: 293.963. $^1$H-NMR (CDCl$_3$) $\delta$: 1.72 (3H, br s), 1.77 (1.5H, br s), 1.79 (1.5H, br s), 1.92 (1.5H, br s), 1.93 (1.5H, br s), 2.42 (1H, br s), 5.69 (1H, br s). $^{19}$F-NMR (CDCl$_3$) ppm: 5.06 (1.5F, br s), 5.13 (1.5F, br s).

**Reaction with 3-Methyl-2-cyclohexen-1-one (21)** In a similar manner to that described for the reaction of **14**, **1** (1.90 ml, 18 mmol) and 3-methyl-2-cyclo-hexenone (**21**, 0.69 ml, 6 mmol) was treated with Mg (0.437 g, 18 mmol) in THF (10 ml) at −53 °C. After evaporation of the solvent, the residue (1.648 g) was analyzed by GLC and found to be a mixture of products, **22** : **23** : (**24** + **25**) = 16.7 : 52.1 : 15.9. This was separated by column chromatography ($SiO_2$, hexane–$CH_2Cl_2$, 7 : 3—1 : 1). The product from the first eluate was purified by vacuum distillation to give 1-(1-bromo-1-chloro-2,2,2-trifluoroethyl)-3-methyl-2-cyclohexen-1-ol (**22**, 0.189 g, 10.3%). The product from the second eluate was recrystallized from EtOH to give 3-(1-bromo-1-chloro-2,2,2-trifluoroethyl)-3-methyl-1-cyclohexanone (**23**, 0.668 g, 36.4%). 3-(1-Chloro-2,2,2-trifluoroethyl)-3-methyl-1-cyclohexanone (**24**) and 3-(1-chloro-2,2-difluoroethenyl)-3-methyl-1-cyclohexanone (**25**) were obtained as a mixture (0.137 g), and showed a same retention time on GLC. $^{19}$F-NMR showed the mixture to consist of **24** + **25** (0.43 : 1). GLC-MS (column, 5% SE-30 4 m; column temperature, 90—250 °C at 20 °C/min; carrier: He, 20 ml/min) of this mixture showed two M$^+$ ions corresponding to **24** (*m*/*z*: 228) and **25** (*m*/*z*: 208). No olefinic or hydroxylic proton was observed in the $^1$H-NMR and IR spectra, which suggested that both were 1,4-addition products. Carbonyl absorption was observed at 1726 cm$^{-1}$. **22**: A colorless oil, bp 85 °C (0.3 mmHg) (bulb-to-bulb distillation). MS *m*/*z*: 306 (M$^+$). HRMS Calcd for $C_9H_{11}BrClF_3O$ (M$^+$): 305.963. Found: 305.964. $^1$H-NMR (CDCl$_3$) $\delta$: 1.54—2.16 (9H, m), 2.38 (1H, br s), 5.75 (1H, br s). $^{19}$F-NMR (CDCl$_3$) ppm: 4.70 (1.5F, br s), 4.76 (1.5F, br s). **23**: Colorless crystals, mp 42 °C. MS *m*/*z*: 306 (M$^+$). HRMS Calcd $C_9H_{11}BrClF_3O$ (M$^+$): 305.963. Found: 305.963. $^1$H-NMR (CDCl$_3$) $\delta$: 1.30 (3H, br s), 1.48—2.99 (8H, m). $^{19}$F-NMR (CDCl$_3$) ppm: 3.40 (3F, br s). Compounds **24** and **25** were obtained as an inseparable mixture. The structures were proposed based on the following spectral data. **24**: $^1$H-NMR (CDCl$_3$) $\delta$: 4.03 (0.5H, q, $J$=7.47 Hz), 4.07 (0.5H, q, $J$=7.47 Hz). $^{19}$F-NMR (CDCl$_3$) ppm: 2.24 (1.5F, d, $J$=7.47 Hz), 2.33 (1.5F, d, $J$=7.47 Hz). M$^+$ was consistent with the proposed structure and alpha protons to the $CF_3$ groups were observed as two quartets, and the $CF_3$ groups as two doublets of equal intensity. Therefore, this is a mixture of two diastereomers (1 : 1). The mass-pattern of M$^+$ showed that it contained one chlorine atom. **25**: $^{19}$F-NMR (CDCl$_3$) ppm: 16.94 (1F, d, $J$=46.88 Hz), 22.92 (1F, d, $J$=46.88 Hz). The chemical shifts and a large coupling constant suggested the presence of a terminal difluorovinyl group. The mass-pattern of M$^+$ was consistent with the presence of one chlorine atom.

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