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Reaction of Trifluoromethyl Ketones. III.[1] The Aluminum Chloride Assisted Ene Reaction of 1,1,1-Trifluoro-2-hexanone and α,α,α-Trifluoroacetophenone[2]

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In the presence of aluminum chloride, 1,1,1-trifluoro-2-hexanone reacts as an enophile with several allyl compounds to give trifluoromethylated homoallyl alcohols. α,α,α-Trifluoroacetophenone reacts similarly with aliphatic allyl compounds, but its reaction with allylbenzene is too slow to be useful for the synthesis of fluorine compounds.

Keywords——1,1,1-trifluoro-2-hexanone; α,α,α-trifluoroacetophenone; trifluoromethyl; ene reaction; homoallyl alcohol; trifluoromethylcarbinol; Lewis acid-catalyzed reaction; aluminum chloride

For the past few years, we have been examining the ene reaction of trifluoromethyl ketones with the aim of utilizing this reaction for the synthesis of trifluoromethyl compounds. We have already reported the ene reaction of hexafluoroacetone[1a] and 1,1,1-trifluoroacetone.[1b] Hexafluoroacetone was found to react with allyl compounds in the absence of a catalyst, while trifluoroacetone was less reactive and reacted with allyl compounds only in the presence of aluminum chloride as a catalyst. These results are summarized in Chart 1.

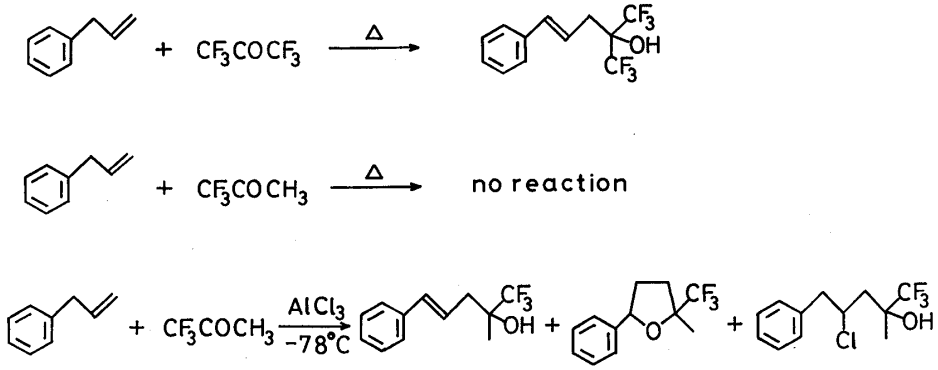
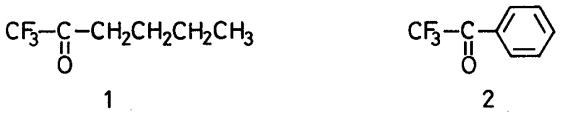


Chart 1

To examine the scope and limitations of this ene reaction of trifluoromethyl ketones, we investigated the effect of the R moiety of CF_3COR on the ene reaction with allyl compounds. We chose 1,1,1-trifluoro-2-hexanone (**1**) as an alkyl trifluoromethyl ketone and α,α,α-trifluoroacetophenone (**2**) as an aryl trifluoromethyl ketone. The ene reaction of these compounds with allyl compounds proceeded in the presence of a Lewis acid, and we found that the nature of the R group had a profound effect on the reaction. The results of the ene reaction of these two ketones are presented in this paper (Fig. 1).

Compound **1** reacted with 1-hexene in the presence of aluminum chloride at −78 °C to



1 2

Fig. 1

give 5-(trifluoromethyl)-7-undecen-5-ol (**3**) in 67% yield, with a small amount of 2-butyl-5-propyl-2-(trifluoromethyl)tetrahydrofuran (**4**). The fluorine-19 nuclear magnetic resonance (^{19}F-NMR) spectrum showed that **3** contained approximately 13% of *Z*-isomer, although the amount was too small to be confirmed definitely by proton nuclear magnetic resonance (^{1}H-NMR). The tetrahydrofuran (**4**) seemed to be formed by the cyclization of **3**, as in the reaction of trifluoroacetone.[1b] In this case, only 9% of the stereoisomer of **4** was detected by ^{19}F-NMR. Namely, this reaction is stereoselective.

Reaction of **1** with 1-octene proceeded as in the case of 1-hexene to give 5-(trifluoromethyl)-7-tridecen-5-ol (**5**) and a tetrahydrofuran compound (**6**). Compound **5** was found to be the *E*-isomer from the ^{1}H-NMR spectrum, while its ^{19}F-NMR spectrum showed that it contained a small amount of the *Z*-isomer. The reaction of **1** with allylbenzene gave a trifluoromethylated homoallyl alcohol (**7**) and a tetrahydrofuran compound (**8**) together with another by-product, 2-chloro-1-phenyl-4-(trifluoromethyl)-4-octanol (**9**). Compound **7** was found to be the *E*-isomer, and interestingly, no *Z*-isomer at all was obtained. On the other hand, **8** was a mixture of two diastereoisomers (ratio 3 : 2). Namely, the stereoselectivity of the homoallyl alcohol is much higher and that of the tetrahydrofuran is lower than in the above cases. This may be expalined by the fact that the formation of **8** from **7** becomes reversible due to the electronic effect of the phenyl group, stabilizing the carbonium ion intermediate. Therefore, sterically more stable *E*-**7** was formed preferentially. The steric requirements of a trifluoromethyl group and a butyl group are similar and therefore two isomers of **8** were formed. Compound **9** seemed to be formed not from **7** but directly from the reaction intermediate, as in the case of the reaction of trifluoroacetone.[1b] The reactions are summarized in Chart 2.

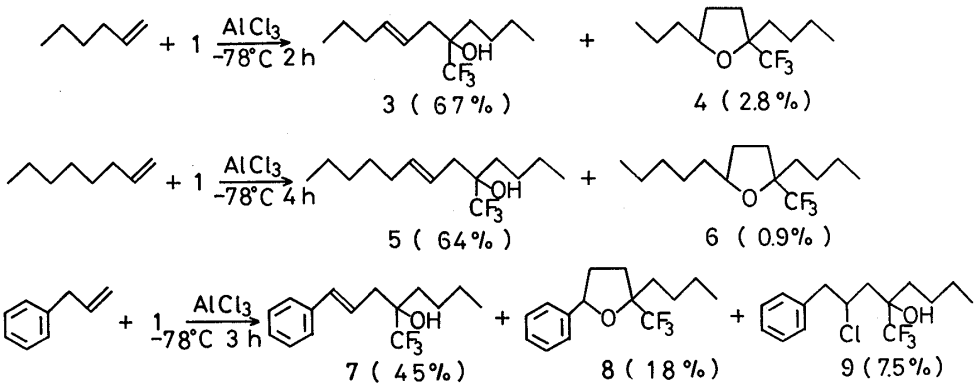
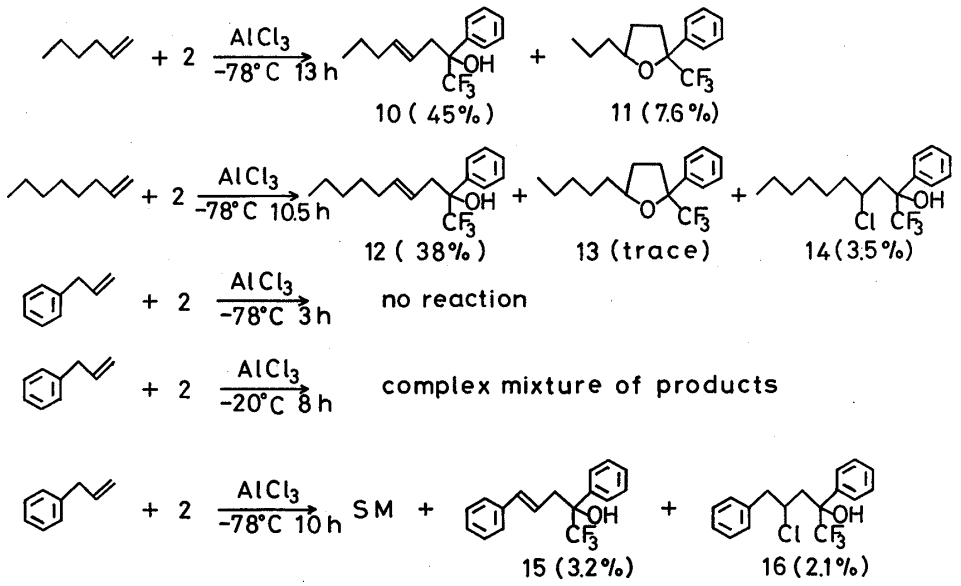


Chart 2

These results are rather similar to those of the reaction of trifluoroacetone, though the reaction of **1** needed a longer reaction time than that of trifluoroacetone. Therefore, an alkyl group has a small effect on the reactivity of the carbonyl group of trifluoromethyl ketones.

Next, the ene reaction of **2** was examined. A similar reaction of **2** with 1-hexene gave the ene adduct (**10**) and its cyclized by-product (**11**). The ^{19}F-NMR spectrum showed that **10** is a mixture of *E*/*Z* isomers (ratio 7 : 3) and that **11** is a mixture of two diastereoisomers (ratio 3 : 2). Both pairs of isomers were separated by medium pressure column chromatography. The reaction proceeded more slowly than in the case of **1**, and the yields of the products were

lower. These facts show that the phenyl group has a deactivating effect on the ene reaction of trifluoromethyl ketones. The longer reaction time may have been responsible for the lower stereoselectivity. The reaction of 1-octene gave the ene adduct (**12**) with small amounts of a tetrahydrofuran compound (**13**) and 4-chloro-2-phenyl-1,1,1-trifluoro-4-decen-2-ol (**14**). The deactivating effect of the phenyl group became more obvious in the reaction with allylbenzene. The reaction proceeded very slowly, and after 10 h only 3.2% 1,1,1-trifluoro-2,5-diphenyl-4-penten-2-ol (**15**) and 2.1% 4-chloro-1,1,1-trifluoro-2,5-diphenyl-2-pentanol (**16**) were obtained. At −20 °C a complex mixture of products was obtained. The reduced reactivity of **2** may be attributed to the resonance effect of the phenyl group, which compensates for the positive charge on the carbonyl carbon and the steric effect of the phenyl group. The low reactivity of **2** with allylbenzene may be explained by the steric repulsion between the phenyl groups. These results are shown in Chart 3.



SM = starting material

Chart 3

In conclusion, trifluoromethyl ketones were found to react as enophiles in the presence of aluminum chloride. An aryl trifluoromethyl ketone is much less reactive than the alkyl counterpart, though both react with aliphatic allyl compounds to give various types of trifluoromethylated homoallyl alcohols. These alcohols should be useful for the synthesis of a variety of trifluoromethylated analogs of natural compounds, such as terpenoids. Application of this reaction to the synthesis of fluorine analogues of biologically active compounds is in progress and the results will be reported in the near future.

Experimental

Trifluoromethyl ketones, **1** and **2**, were synthesized according to the literature.[3] ^{1}H-NMR spectra were obtained on JNM-FX90Q and JNM-GX400 spectrometers. ^{19}F-NMR spectra were recorded on a JNM-FX90Q spectrometer, using benzotrifluoride as an internal standard (upper field taken as plus).

Reaction of 1,1,1-Trifluoro-2-hexanone (1) with 1-Hexene——Compound **1** (770 mg, 5.0 mmol) was added to a solution of aluminum chloride (660 mg, 5.0 mmol) in CH_2Cl_2 (15 ml) at −78 °C under stirring. The mixture was allowed to warm up to room temperature and stirring was continued for a few minutes, until the aluminum chloride dissolved to form a complex with **1**. The solution was cooled to −78 °C, and 1-hexane (421 mg, 5.0 mmol) was added at this temperature under stirring. The mixture was stirred for 4 h, then poured into ice-water containing hydrochloric acid and extracted with Et_2O. The extract was dried over $MgSO_4$ and the solvent was evaporated under vacuum. Column chromatography of the residue on silica gel in CH_2Cl_2–hexane (1 : 5) gave 2-butyl-5-propyl-2-(trifluoromethyl)tetrahydrofuran (**4**, 33 mg, 2.8%) and 5-(trifluoromethyl)-7-undecen-5-ol (**3**, 797 mg, 67%) in that

order. **3**: Colorless oil. Mass spectrum (MS) *m/e*: 238 (M^+). High resolution MS (HRMS) Calcd for $C_{12}H_{21}F_3O$: 238.154. Found: 238.154. ^{1}H-NMR ($CDCl_3$) δ: 0.72—1.08 (6H, m), 1.08—1.85 (8H, m), 2.04 (2H, td, J=7.1, 5.7 Hz), 2.17 (1H, s), 2.28—2.64 (2H, m), 5.16—5.55 (1H, m), 5.58 (1H, dt, J=15.1, 5.7 Hz). ^{19}F-NMR ($CDCl_3$) ppm: 16.39 (s), 16.74 (s) (relative intensity 7/1). These results show that **3** is the *E* isomer, but the product contains a small amount of the *Z* isomer. **4**: Colorless oil, bp 90 °C/20 mmHg (bulb-to-bulb distillation). MS *m/e*: 237 (M−1). HRMS Calcd for $C_{12}H_{20}F_3O$: 237.147. Found: 237.149. *Anal.* Calcd $C_{12}H_{21}F_3O$: C, 60.48; H, 8.88. Found: C, 60.44; H, 9.14. ^{1}H-NMR ($CDCl_3$) δ: 0.62—2.55 (20H, m), 3.83—4.21 (1H, m). ^{19}F-NMR ($CDCl_3$) ppm: 17.35 (s), 17.26 (s) (relative intensity 10/1).

Reaction of 1 with 1-Octene——1-Octene (1.12 g, 10.0 mmol) was added to a solution of **1** (1.54 g, 10 mmol) and $AlCl_3$ (1.12 g, 8.5 mmol) in CH_2Cl_2 (30 ml) under stirring at −78 °C. After being stirred at this temperature for 2 h, the reaction mixture was poured into ice and conc. HCl, extracted with ether, washed with water and dil. $NaHCO_3$, and dried over $MgSO_4$. After the evaporation of the solvent, the residue was separated by column chromatography on an SiO_2 column with CH_2Cl_2–hexane (1 : 4) as the solvent to give 2-butyl-5-pentyl-2-(trifluoromethyl)tetrahydrofuran (**6**) (25 mg, 0.9%) and 5-(trifluoromethyl)-7-tridecen-5-ol (**5**) (1.689 g, 64%). **5**: Colorless oil. MS *m/e*: 266 (M^+). HRMS Calcd for $C_{14}H_{25}F_3O$: 266.186. Found: 266.185. ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, t, J=7.1 Hz), 0.92 (3H, t, J=7.3 Hz), 1.20—1.50 (10H, m), 1.61—1.71 (2H, m), 2.05 (2H, td, J=7.0, 7.0 Hz), 2.14 (1H, s), 2.34 (1H, dd, J=14.4, 8.4 Hz), 2.44 (1H, dd, J=14.4, 6.7 Hz), 5.41 (1H, ddd, J=15.6, 8.4, 6.7 Hz), 5.60 (1H, dt, J=15.6, 7.0 Hz). ^{19}F-NMR ($CDCl_3$) ppm: 16.36 (s), 16.74 (s) (intensity ratio 8 : 1). This result shows that **5** contains a small amount of the *Z*-isomer, but it was too small an amount for signals to be assignable in the ^{1}H-NMR spectrum. It was not detectable by gas liquid chromatography (GLC), either. **6**: Colorless oil. MS *m/e*: 266 (M^+). HRMS Calcd for $C_{14}H_{25}F_3O$: 266.186. Found: 266.185. ^{1}H-NMR ($CDCl_3$) δ: 0.65—2.34 (24H, m), 3.78—4.25 (1H, m). ^{19}F-NMR ($CDCl_3$) ppm: 17.35 (s), 17.26 (relative intensity 10 : 1).

Reaction of 1 with Allylbenzene——Allylbenzene (1.18 g, 10.0 mmol) was added to a solution of $AlCl_3$ (1.32 g, 10.0 mmol) and **1** (1.54 g, 10.0 mmol) in CH_2Cl_2 (25 ml) at −78 °C under stirring. Stirring was continued at this temperature for 3 h, then the reaction mixture was worked up as above and the products were separated on an SiO_2 column in CH_2Cl_2–hexane (1 : 2) to give 2-butyl-5-phenyl-2-(trifluoromethyl)tetrahydrofuran (**8**) (483 mg, 18%), 1-phenyl-4-(trifluoromethyl)-1-octen-4-ol (**7**) (1.218 g, 45%), and 2-chloro-1-phenyl-4-(trifluoromethyl)-4-octanol (**9**) (230 mg, 7.5%). **7**: Colorless oil, bp 120 °C/16 mmHg (bulb-to-bulb distillation). MS *m/e*: 272 (M^+). HRMS Calcd for $C_{15}H_{19}F_3O$: 272.139. Found: 272.138. ^{1}H-NMR ($CDCl_3$) δ: 0.58—1.88 (9H, m), 2.12 (1H, s), 2.33—2.90 (2H, m), 6.22 (1H, ddd, J=15.9, 6.3, 8.5 Hz), 6.49 (1H, d, J=15.9 Hz), 7.19—7.49 (5H, m). ^{19}F-NMR ($CDCl_3$) ppm: 16.40 (s). The large coupling constant in the ^{1}H-NMR spectrum suggests that this compound is an *E*-isomer. The ^{19}F-NMR spectrum shows that **7** does not contain the *Z*-isomer. **8**: Colorless oil. MS *m/e*: 272 (M^+). HRMS Calcd for $C_{15}H_{19}F_3O$: 272.139. Found: 272.139. This was found to be a mixture of diastereoisomers (ratio 3 : 2), which were separated by medium-pressure column chromatography on SiO_2. One isomer: ^{1}H-NMR ($CDCl_3$) δ: 0.75—2.59 (13H, m), 4.88—5.22 (1H, m), 7.06—7.68 (5H, m). ^{19}F-NMR ($CDCl_3$) ppm: 16.79 (s). The other isomer; ^{1}H-NMR ($CDCl_3$) δ: 0.68—2.50 (13H, m), 4.78—5.18 (1H, m), 6.98—7.63 (5H, m). ^{19}F-NMR ppm: 16.88 (s). **9**: Colorless oil. MS *m/e*: 308 (M^+; the presence of a strong M+2 peak shows that **9** contains one chlorine atom). HRMS Calcd for $C_{15}H_{20}ClF_3O$: 308.116. Found: 308.116. ^{1}H-NMR ($CDCl_3$) δ: 0.72—1.93 (10H, m), 2.08—2.26 (2H, m), 2.94 (1H, s), 3.08 (2H, d, J=7.1 Hz), 4.45 (1H, tdd, J=7.1, 7.1, 4.3 Hz), 7.12—7.45 (5H, m). ^{19}F-NMR ($CDCl_3$) ppm: 16.36 (s).

Reaction of α,α,α-Trifluoroacetophenone (2) with 1-Hexene——1-Hexene (252 mg, 3.0 mmol) was added to a solution of $AlCl_3$ (336 mg, 2.5 mmol) and **2** (522 mg, 3.0 mmol) in CH_2Cl_2 (15 ml) at −78 °C under stirring. Stirring was continued for 10.5 h at this temperature, then the mixture was worked up as usual and the products were separated by column chromatography on SiO_2 in hexane to give 2-phenyl-5-propyl-2-(trifluoromethyl)tetrahydrofuran (**11**) (65 mg, 7.6%) and 2-phenyl-1,1,1-trifluoro-4-octen-2-ol (**10**) (319 mg, 45%). **10**: Colorless oil. MS *m/e*: 240 ($M-H_2O$), 175 ($C_6H_5C(OH)CF_3$), 84 ($M-C_6H_5COCF_3$). This was found to be a mixture of *E*/*Z* isomers (ratio 7 : 3) from the ^{19}F-NMR data, and it was separated by medium-pressure column chromatography on SiO_2 in CH_2Cl_2–hexane (1 : 10). *Z*-isomer: ^{1}H-NMR ($CDCl_3$) δ: 0.90 (3H, t, J=7.1 Hz), 1.07—1.63 (2H, m), 2.04 (2H, td, J=7.1, 7.1 Hz), 2.55 (1H, s), 2.93 (2H, d, J=7.3 Hz), 5.19 (1H, dt, J=10.7, 7.3 Hz), 5.64 (1H, dt, J=10.7, 7.1 Hz), 7.21—7.72 (5H, m). ^{19}F-NMR ($CDCl_3$) ppm: 16.45 (s). *E*-isomer: ^{1}H-NMR ($CDCl_3$) δ: 0.83 (3H, t, J=7.1 Hz), 1.33 (2H, qt, J=7.1, 7.1 Hz), 1.96 (2H, td, J=7.1, 7.1 Hz), 2.64 (1H, s), 2.82 (1H, dd, J=12.1, 7.1 Hz), 2.89 (1H, dd, J=12.1, 7.1 Hz), 5.19 (1H, dt, J=15.2, 7.1 Hz), 5.65 (1H, dt, J=15.2 Hz, 7.1 Hz), 7.20—7.76 (5H, m). ^{19}F-NMR ($CDCl_3$) ppm: 16.19 (s). **11**: Colorless oil, bp 115—120 °C/15 mmHg (bulb-to-bulb distillation). MS *m/e*: 258 (M^+). HRMS Calcd for $C_{14}H_{17}F_3O$: 258.123. Found: 258.123. ^{1}H-NMR ($CDCl_3$) δ: 0.81—1.13 (3H, m), 1.18—2.92 (8H, m), 3.87—4.50 (1H, m), 7.20—7.68 (5H, m). ^{19}F-NMR ($CDCl_3$) ppm: 15.78 (s), 16.28 (s), (ratio 2 : 3).

Reaction of 2 with 1-Octene——1-Octene (560 mg, 5.0 mmol) was added to a solution of $AlCl_3$ (660 mg, 5.0 mmol) and **2** (870 mg, 5.0 mmol) in CH_2Cl_2 (15 ml) at −78 °C under stirring. Stirring was continued at this temperature for 13 h, then the solution was worked up as usual, and the products were separated by column chromatography on SiO_2 in CH_2Cl_2–hexane (1 : 10) to give 5-pentyl-2-phenyl-2-(trifluoromethyl)tetrahydrofuran (**13**) (trace), 1,1,1-trifluoro-2-phenyl-4-decen-2-ol (**12**) (542 mg, 38%), and 4-chloro-1,1,1-trifluoro-2-phenyl-2-

decanol (**14**) (56 mg, 3.5%). **12**: Colorless oil. MS *m/e*: 268 ($M-H_2O$), 175 ($C_6H_5C(OH)CF_3$). This was found to be a mixture of *E*/*Z* isomers (8 : 3) from the ^{19}F-NMR data. The isomers were separated by medium-pressure column chromatography on SiO_2 in CH_2Cl_2–hexane (1 : 4). *Z*-isomer: ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, t, J=6.2 Hz), 1.10—1.82 (6H, m), 1.82-2.42 (2H, m), 2.53 (1H, s), 2.75—2.97 (2H, m), 4.95—5.50 (1H, m), 5.50—5.84 (1H, m), 6.89—7.75 (5H, m). ^{19}F-NMR ($CDCl_3$) ppm: 16.45 (s). *E*-isomer: ^{1}H-NMR ($CDCl_3$) δ: 0.85 (3H, t, J=5.7 Hz), 0.99—1.67 (6H, m), 1.75—2.18 (2H, m), 2.66 (1H, s), 2.66—3.08 (2H, m), 5.14 (1H, ddd, J=15.1, 7.4, 7.4 Hz), 5.67 (1H, dt, J=15.1, 6.3 Hz), 7.18—7.78 (5H, m). ^{19}F-NMR ($CDCl_3$) ppm: 16.19 (s). **13**: Colorless oil. MS *m/e*: 286 (M^+). HRMS Calcd for $C_{16}H_{21}F_3O$: 286.154. Found: 286.155. This was a mixture of two diastereoisomers, which were separated as above in CH_2Cl_2–hexane (1 : 10). One isomer: ^{1}H-NMR ($CDCl_3$) δ: 0.76—2.47 (14H, m), 2.58—2.91 (1H, m), 3.84—4.22 (1H, m), 7.20—7.70 (5H, m). ^{19}F-NMR ($CDCl_3$) ppm: 16.22 (s). The other isomer: ^{1}H-NMR ($CDCl_3$) δ: 0.55—2.85 (15H, m), 3.98—4.47 (1H, m), 7.12—7.69 (5H, m). ^{19}F-NMR ($CDCl_3$) ppm: 15.75 (s). **14**: Colorless oil. MS *m/e*: 322 (M^+) (the presence of a chlorine atom was confirmed by a peak at (M+2)). ^{1}H-NMR ($CDCl_3$) δ: 0.70—1.04 (3H, t, J= 5.7 Hz), 1.04—2.81 (12H, m), 2.52 (1H, s), 3.64—4.11 (1H, m), 7.27—7.85 (5H, m). ^{19}F-NMR ($CDCl_3$) ppm: 17.40 (s), 17.69 (s) (ratio 1 : 1). The ^{19}F-NMR spectrum shows that **14** is a mixture of two diastereoisomers.

Reaction of 2 with Allylbenzene——Allylbenzene (427 mg, 4.0 mmol) was added to a solution of **2** (348 mg, 2.0 mmol) and $AlCl_3$ (264 mg, 2.0 mmol) in CH_2Cl_2 (10 ml) at −78 °C under stirring. Stirring was continued at this temperature for 10 h, then the reaction mixture was worked up as usual, and the products were separated by column chromatography on SiO_2 in CH_2Cl_2–hexane (1 : 2) to give 2,5-diphenyl-1,1,1-trifluoro-4-penten-2-ol (**15**) (18 mg, 3.2%) and 4-chloro-2,5-diphenyl-1,1,1-trifluoro-2-pentanol (**16**) (14 mg, 2.1%). **15**: Colorless oil. MS *m/e*: 292 (M^+). HRMS Calcd for $C_{17}H_{15}F_3O$: 292.107. Found: 292.108. ^{1}H-NMR ($CDCl_3$) δ: 2.64 (1H, s), 2.78—3.34 (2H, m), 5.95 (1H, dt, J=15.8, 7.4 Hz), 6.56 (1H, d, J=15.8 Hz), 6.91—7.71 (10H, m). ^{19}F-NMR ($CDCl_3$) ppm: 16.21 (s). This spectrum shows a small peak at 16.31 ppm (s) due to the *Z*-isomer. **16**: Colorless oil. MS *m/e*: 328 (M^+) (presence of a chlorine was shown by a peak at M+2). HRMS Calcd for $C_{17}H_{16}ClF_3O$: 328.084. Found: 328.085. ^{1}H-NMR ($CDCl_3$) δ: 2.43 (1H, dd, J=15.5, 9.6 Hz), 2.73 (1H, dd, J=15.5, 2.2 Hz), 2.91 (1H, dd, J=13.7, 8.1 Hz), 3.04 (1H, dd, J=13.7, 6.3 Hz), 3.60 (1H, s), 3.73—4.07 (1H, m), 6.94—7.40 (10H, m). ^{19}F-NMR ($CDCl_3$) ppm: 18.45 (s).

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References and Notes

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