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A Method for Synthesis of Fluorine Compounds Using Abnormal Grignard Reaction of Halothane. III.[1)] Simple Synthesis of Trifluoromethylchloroolefins

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We have reported an abnormal Grignard reaction of halothane (1) with carbonyl compounds (2). The reaction afforded 1-bromo-1-chloro-2,2,2-trifluoroethylcarbinols (3) as the major products at -53 °C, while at 0 °C, the main products were the dehalogenation products, 1-chloro-2,2-difluoroethenyl carbinols (4). Treatment of 4 with hydrogen fluoride (HF) afforded 1-chloro-1-(trifluoromethyl)ethene derivatives (5) in good yields. However, this reaction required HF, a dangerous reagent. Here, we describe a much easier and safer synthesis of 5. Thus, treatment of 3 with zinc chloride and acetic anhydride gave acetoxy compounds (6). The acetates were converted to the olefins (5) by reductive debromoacetoxylation with zinc in the presence of a catalytic amount of copper(I) iodide. Application of this reaction to an α,β-unsaturated ketone, benzalacetone, gave the diene bearing a trifluoromethyl group.

Key words halothane; *vic*-chloroacetate; olefin formation; reduction; trifluoromethyl;debromoacetoxylation

Trifluoromethyl compounds have attracted much attention in the fields of medicinal and agricultural chemistry.[2)] We are developing new methods for syntheses of fluorine compounds useful in the biomedicinal field, and we have reported the syntheses of various types of trifluoromethyl compounds.[3,4)] 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 carbonyl compounds (**2**).[1,5)] When this reaction was carried out at -53 °C, 1-bromo-1-chloro-2,2,2-trifluoroethyl adducts (**3**) to the carbonyl group were obtained, while at 0 °C, the dehalogenation products, 1-chloro-2,2-difluorovinyl compounds (**4**), were obtained. Namely, the products expected from the normal Grignard reaction were not obtained. The compounds (**4**) were treated with hydrogen fluoride to give 1-chloro-1- (trifluoromethyl)ethene compounds (**5**), as shown in Chart 1.

Compounds **5** have an important structural unit, the 2-chloro-2-(trifluoromethyl)vinyl group. Some compounds bearing this group are used as agrochemicals. However, this reaction required HF, a dangerous reagent. Here, we would like to report a new synthesis of compounds **5** without using HF. For this purpose, we examined the conversion of **3** into the corresponding acetoxy coumpounds (**6**) followed by the reductive olefin formation with Zn to afford **5**.

First, we tried acetylation of 2-bromo-2-chloro-1,1,1-trifluoro-3-methyl-3-nonanol (**3a**), obtained by the reaction of **1** with 2-octanone (**2a**), under various basic conditions. All the attempted acetylations in the presence of triethylamine and organic bases resulted in recovery of the starting material (**3a**), as shown at the top of Chart 2. Next, **3a** was led to a sodium alkoxide compound with sodium hydride and this was treated with acetyl chloride. At -78 °C the starting material (**3a**) was recovered, and at -20 °C **3a** reverted to 2-octanone (**2a**) through a haloform type reaction, as shown in the second and third equations of Chart 2.

As shown above, attempted acetylations under basic conditions were all unsuccessful. Namely, activation of the hydroxy group with a base did not give a good result. This may be due to the steric hindrance of the large 1-bromo-1-chloro-2,2,2-trifluoroethyl group. Therefore, we tried to activate the acetylating reagent. For this purpose, we examined the acetylation in the presence of a Lewis acid. The acetylation of **3a** using zinc chloride as a Lewis acid gave 3-acetoxy-2-bromo-2-chloro-1,1,1-trifluoro-3-methylnonane (**6a**) in 98.1% yield. These results support our hypothesis. Namely, the hydroxy group of **3a** is so crowded that acetic anhydride cannot acetylate this group even in the presence of strong bases, while an acetyl cation equivalent obtained from acetic anhydride and zinc chloride can attack the hydroxy group. Similarly, 1-(1-bromo-1-chloro-2,2,2-trifluoroethyl)cyclohexanol (**3b**) and 2-bromo-2-chloro-1,1,1-trifluoro-3-phenyl-3-butanol (**3c**) were converted into 1-acetoxy-1- (1-bromo-1-chloro-2,2,2-trifluoroethyl)cyclohexane (**6b**) and 3-acetoxy-2-bromo-2-chloro-1,1,1-trifluoro-3-phenylbutane (**6c**), respectively, by using zinc chloride and acetic anhydride in good yields. These results are shown at the bottom of Chart 2.

For the conversion of the acetoxy compound (**6a**) to the chloro(trifluoromethyl) olefin (**5a**), we examined reductive debromoacetoxylation of **6a** with zinc powder,

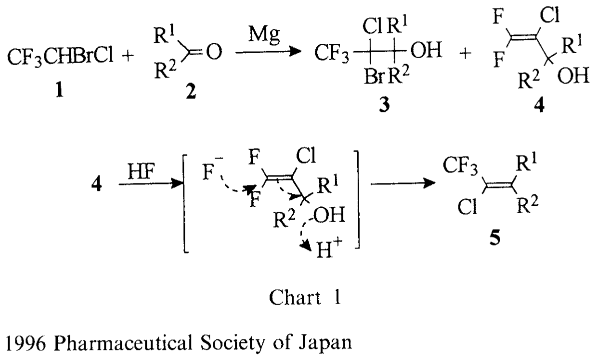

Chart 1

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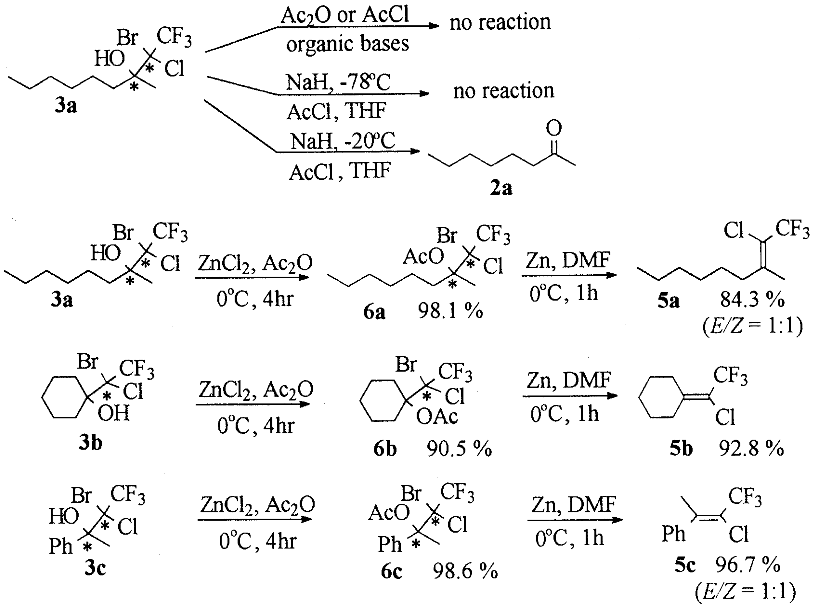

Chart 2

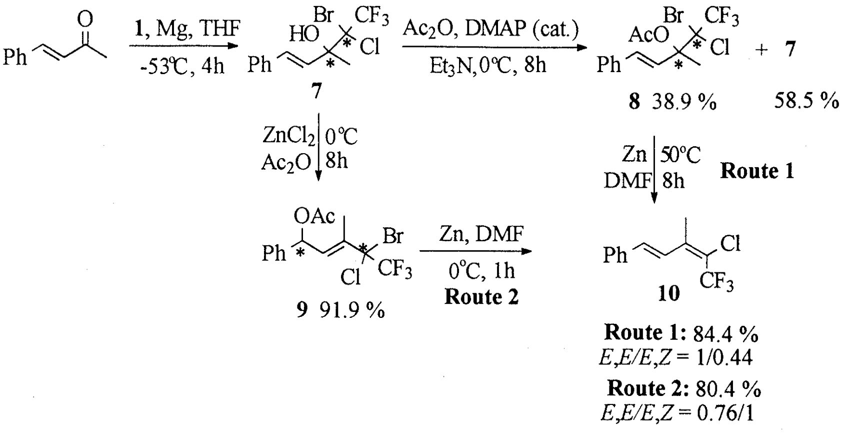

Chart 3

but the starting material was recovered. Next, we tried reduction by zinc in *N,N*-dimethylformamide (DMF) in the presence of copper(I) iodide at 0 °C, and succeeded in obtaining **5a** in 84.3% yield. Application of this reductive olefin formation with zinc in DMF to **6b** and **6c** gave the objective olefins (**5b** and **5c**) in high yields, as shown in Chart 2. Both **5a** and **5c** were mixtures of *E–Z* isomers and the ratios of both compounds were estimated to be 1 : 1 based on ^{19}F-NMR. The products (**3a** and **3c**) from the Grignard reaction[5)] were both 1:1 mixtures of diastereomers. The ratios of the *E–Z* isomers of **5a** and **5c** obtained from **4a** and **4c** were not 1 : 1, probably due to the stability of the transition state of the allylic substitution.[5)] These results suggest that the reductive debromoacetoxylation might be a stereospecific *anti*-elimination.

In the previous paper, we reported that the reaction of **1** with an α,β-unsaturated ketone, benzalacetone, in the presence of magnesium gave a 1,2-adduct (**7**) as a main product.[1)] Thus, we examined the conversion of the main product **7** into the chloro(trifluoromethyl)diene (**10**).

First, we attempted the acetylation with acetic anhydride in the presence of triethylamine and dimethylaminopyridine (DMAP). In this case, the acetoxy compound (**8**) was obtained in only 38.9% yield with recovery of the starting material (**7**) in 58.5% yield. Formation of **8** is interesting, since **5a** could not be acetylated under the same conditions. This might be due to a smaller steric effect of the flat phenylvinyl group of **7** compared with that of the flexible and three-dimensional hexyl group of **5a**. Compound **8** is expected to be a mixture of diastereomers, but we could not confirm this by ^{1}H- or ^{19}F-NMR, or GLC.

As the acetylation of **7** under basic conditions gave only a small amount of **8**, the same procedure used for the transformation of alcohols (**3a**—**c**) to the corresponding acetoxy compounds (**6a**—**c**) was applied to the 1,2-adduct (**7**). On the treatment of **7** with acetic anhydride in the presence of zinc chloride, an acetoxy group was introduced through an allylic rearrangement of the hydroxy group to give an acetoxy compound (**9**) in 91.9% yield.

Finally, the acetoxy compounds (**8** and **9**) were debromoacetoxylated. They were treated with zinc in the presence of copper(I) iodide in DMF to give the chloro(trifluoromethyl)diene (**10**) in a high yield. Compound **10** is a mixture of (*E,E*) and (*E,Z*) isomers, as shown in

Chart 3. The structures of both isomers were estimated from the coupling constants between the methyl hydrogens and the trifluoromethyl fluorine, as described in the experimental section. The larger coupling constant was attributed to the *cis*-relation. It is interesting that the isomers ratios in the two routes are different. Unfortunately, we could not determine the *E*/*Z* ratio of **8**. Thus, we cannot further discuss the stereoselectivity of these reductions.

In conclusion, a new route for the transformation of carbonyl compounds (**2**) into chloro(trifluoromethyl)-olefins (**5**) was developed. In this route, compounds **3**, which were obtained as the main products by the reaction of halothane with **2** at −53 °C, were treated with zinc chloride and acetic anhydride to give acetoxy compounds (**6**). The acetates (**6**) were converted to **5** by reductive debromoacetoxylation with zinc in the presence of copper iodide. This route does not require HF, unlike the method reported previously. In the acetylation of an allyl alcohol derivative (**7**), obtained by the reaction of an α,β-unsaturated ketone, benzalacetone, with **1**, two types of acetates were formed. One was a normal acetate (**8**) and the other was the rearrangement product (**9**). The acetates (**8 and 9**) were both converted to **10** by zinc in the presence of copper(I) iodide. Thus, we suceeded in converting carbonyl compounds into olefins substituted with a chlorine atom and a trifluoromethyl group by making use of the abnormal Grignard reaction of halothane.

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 higher field is shown by +. 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.

3-Acetoxy-2-bromo-2-chloro-1,1,1-trifluoro-3-methylnonane (6a) Acetic anhydride (1 ml) was added to zinc chloride (96% $ZnCl_2$, 0.426 g, 3 mmol) under an atmosphere of argon at room temperature and the mixture was stirred for 30 min. Then a solution of 2-bromo-2-chloro-1,1,1-trifluoro-3-methyl-3-nonanol (**3a**, 0.324 g, 1 mmol) in CH_2Cl_2 (5 ml) was added slowly at 0 °C. The reaction mixture was stirred for 4 h at this temperature, then poured into ice-water, and extracted with CH_2Cl_2. The CH_2Cl_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 by GLC (from 80 to 200 °C by 20 °C/min); it contained 98.6% of a major product. This residue was separated by column chromatography (SiO_2, hexane–CH_2Cl_2, 4 : 1) to give **6a** (0.359 g, 98.1%). This was a mixture of two diastereomers (ratio 1 : 1), as judged from the ^{19}F-NMR spectrum. **6a**: A colorless oil. MS *m*/*z*: 309 ($M^+ - C_4H_9$). HRMS Calcd for $C_6H_6BrClF_3O_2$ ($M^+ - C_6H_{13}$): 280.919. Found: 280.918. ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, t, *J* = 6.56 Hz), 1.30 (6H, br s), 1.40—1.59 (2H, m), 1.93 (1.5H, q, *J* = 1.22 Hz), 1.95 (1.5H, q, *J* = 0.92 Hz), 2.00—2.17 (4H, m), 2.21—2.35 (1H, m). ^{19}F-NMR ($CDCl_3$) ppm: 5.06 (1.5F, br s), 5.15 (1.5F, br s).

1-Acetoxy-1-(1-bromo-1-chloro-2,2,2-trifluoroethyl)cyclohexane (6b) 1-(1-Bromo-1-chloro-2,2,2-trifluoroethyl)cyclohexanol (**3b**, 0.294 g, 1 mmol) was acetylated by a similar method to that used in the case of **6a** to give 98.2% of a crude product. This was purified by column chromatography (SiO_2, hexane–CH_2Cl_2, 4 : 1) to give **6b** (0.304 g, 90.5%). **6b**: A colorless oil. MS *m*/*z*: 240 ($M^+ - C_2H_3OCl$). HRMS Calcd for $C_8H_{10}BrF_3O$ ($M^+ - C_2H_3OCl$): 239.976. Found: 239.975. ^{1}H-NMR ($CDCl_3$) δ: 0.84—2.12 (11H, m), 2.64—3.02 (2H, m). ^{19}F-NMR ($CDCl_3$) ppm: 5.08 (3F, s).

3-Acetoxy-2-bromo-2-chloro-1,1,1-trifluoro-3-phenylbutane (6c) 2-Bromo-2-chloro-1,1,1-trifluoro-3-phenyl-3-butanol (**3c**) was acetylated by a similar method to that used in the case of **6a** to give a crude product, which was found to contain 98.5% of a major product by GLC analysis (from 80 to 200 °C by 20 °C/min). It was purified by column chromatography (SiO_2, hexane–CH_2Cl_2, 7 : 3) to give **6c** (0.353 g, 98.6%). This was a mixture of two diastereomers (ratio 1 : 1) as judged from the ^{19}F-NMR spectrum. **6c**: A colorless oil. MS *m*/*z*: 358 (M^+). HRMS Calcd for $C_{12}H_{11}BrClF_3O_2$ (M^+): 357.958. Found: 357.959. One diastereomer: ^{1}H-NMR ($CDCl_3$) δ: 2.173 (3H, s), 2.342 (3H, q, *J* = 1.53 Hz), 7.279—7.476 (5H, m). ^{19}F-NMR ($CDCl_3$) ppm: 4.04 (3F, q, *J* = 1.53 Hz). The other diastereomer: ^{1}H-NMR ($CDCl_3$) δ: 2.168 (3H, s), 2.366 (3H, q, *J* = 1.22 Hz), 7.279—7.476 (5H, m). ^{19}F-NMR ($CDCl_3$) ppm: 4.12 (3F, q, *J* = 1.22 Hz).

2-Chloro-1,1,1-trifluoro-3-methyl-2-nonene (5a) A solution of **6a** (0.359 g, 0.98 mmol) in DMF (3 ml) was added to a suspension of Zn (71 mg, 1.08 mmol) and CuI (1 mg) in DMF (2 ml) at 0 °C. After having been stirred for 1 h at this temperature, the solution was poured into 10% HCl and ice, and then 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); it contained 84.3% of a major product. This residue was separated by column chromatography (SiO_2, pentane) to give **5a** (0.182 g, 81.3%).[5] This compound (**5a**) was a mixture of *E*/*Z* isomers (ratio 1 : 1), as judged from the ^{19}F-NMR spectrum.

2-Chloro-1,1,1-trifluoroethylidenecyclohexane (5b) A solution of **6b** (0.324 g, 0.96 mmol) in DMF (3 ml) was treated with Zn (69 mg, 0.96 mmol) and CuI (1 mg) in DMF (2 ml) as in the case of **5a** to give a crude product, which was found to contain 92.8% of a major product. This was purified by column chromatography (SiO_2, pentane) to give **5b** (0.176 g, 92.1%).[5]

2-Chloro-1,1,1-trifluoro-3-phenyl-2-butene (5c) A solution of **6c** (0.322 g, 0.90 mmol) in DMF (3 ml) was treated with Zn (65 mg, 0.99 mmol) and CuI (1 mg) in DMF (2 ml) similarly as in the case of **5a** to give a crude product, which was found to contain 96.7% of a major product by GLC. This was purified by column chromatography (SiO_2, pentane) to give **5c** (0.176 g, 88.9%). This product was a mixture of *E*/*Z* isomers (ratio 1 : 1), as judged from the ^{19}F-NMR spectrum. **5c**: A colorless oil. MS *m*/*z*: 220 (M^+). HRMS Calcd for $C_{10}H_8ClF_3$ (M^+): 220.027. Found: 220.026. *E* isomer: ^{1}H-NMR ($CDCl_3$) δ: 2.27 (3H, q, *J* = 2.03 Hz), 7.12—7.44 (5H, m). ^{19}F-NMR ($CDCl_3$) ppm: −3.28 (3F, q, *J* = 2.03 Hz). *Z* isomer: ^{1}H-NMR ($CDCl_3$) δ: 2.88 (3H, q, *J* = 2.03 Hz), 7.12—7.44 (5H, m). ^{19}F-NMR ($CDCl_3$) ppm: −2.88 (3F, q, *J* = 2.65 Hz).

3-Acetoxy-4-bromo-4-chloro-5,5,5-trifluoro-3-methyl-1-phenyl-1-pentene (8). Acetylation of 7 with Ac_2O in the Presence of Et_3N and DMAP Et_3N (0.14 ml, 1 mmol), Ac_2O (0.10 ml, 1 mmol) and 2,6-dimethyl-4-aminopyridine (DMAP, 8 mg, 0.07 mmol) were added to a solution of **7** (0.228 g, 0.67 mmol) in CH_2Cl_2 (0.67 ml) at 0 °C. The mixture was stirred for 8 h at this temperature, then poured into 10% HCl and ice, and extracted with CH_2Cl_2. The CH_2Cl_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 by GLC (from 80 to 200 °C by 20 °C/min) and found to contain **8** and **7** in a ratio of 37.2 : 58.2. The residue was separated by column chromatography (SiO_2, hexane–CH_2Cl_2, 7 : 3) to give **8** (0.100 g, 38.9%) and **7** (0.134 g, 58.5%). **8**: A colorless oil. MS *m*/*z*: 384 (M^+). HRMS Calcd for $C_{14}H_{13}BrClF_3O_2$ (M^+): 383.974. Found: 383.974. ^{1}H-NMR ($CDCl_3$) δ: 2.12 (3H, s), 2.16 (3H, br s), 6.31 (1H, d, *J* = 16.25 Hz), 6.68 (1H, d, *J* = 16.25 Hz), 7.16—7.52 (5H, m). ^{19}F-NMR ($CDCl_3$) ppm: 4.42 (3F, br s).

1-Acetoxy-4-bromo-4-chloro-5,5,5-trifluoro-3-methyl-1-phenyl-2-pentene (9). Acetylation of 7 using $ZnCl_2$ and Ac_2O Acetic anhydride (1 ml) was added to zinc chloride (96% $ZnCl_2$, 0.426 g, 3 mmol) under an atmosphere of argon at room temperature and the mixture was stirred for 30 min. A solution of **7** (0.342 g, 1 mmol) in CH_2Cl_2 (5 ml) was slowly added at 0 °C. The mixture was stirred for 8 h at this temperature, then poured into ice-water and extracted with CH_2Cl_2. The CH_2Cl_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 by GLC (from 80 to 200 °C by 20 °C/min); it contained 98.3%

of a major product. This was purified by column chromatography (SiO_2, hexane–CH_2Cl_2, 7 : 3) to give **9** (0.353 g, 91.9%). This compound was a mixture of two diastereomers, as judged from the ^{19}F-NMR spectrum (ratio 1 : 1). **9**: A colorless oil. MS *m/z*: 384 (M^+). HRMS Calcd for $C_{12}H_{10}BrClF_3$ ($M^+ - C_2H_3O_2$): 324.961. Found: 324.961. ^{1}H-NMR ($CDCl_3$) δ: 2.12 (6H, br s), 6.49 (2H, br s), 7.40 (5H, br s). ^{19}F-NMR ($CDCl_3$) ppm: 9.97 (1.5F, br s), 10.13 (1.5F, br s).

4-Chloro-5,5,5-trifluoro-3-methyl-1-phenyl-1,3-pentadiene (10) from 8 A solution of **8** (0.248 g, 0.65 mmol) in DMF (3 ml) was added to a suspension of Zn (46 mg, 0.71 mmol) and CuI (1 mg) in DMF (3 ml) at 0 °C. The mixture was stirred for 8 h at 50 °C, 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 careful evaporation of the solvent at 0 °C under reduced pressure, the residue was analyzed by GLC, which showed that it contained 99.5% of a major product. This was purified by column chromatography (SiO_2, pentane) to give **10** (0.135 g, 84.4%). This compound (**10**) was a mixture of (*E*,*E*)- and (*E*,*Z*)-isomers (ratio 1 : 0.43), as judged from the ^{19}F-NMR spectrum. **10**: A colorless oil. MS *m/z*: 246 (M^+). HRMS Calcd for $C_{12}H_{10}ClF_3$ (M^+): 246.042. Found: 246.042. (*E*,*E*) compound: ^{1}H-NMR ($CDCl_3$) δ: 2.25 (3H, q, $J=2.13$ Hz), 6.88 (1H, d, $J=15.87$ Hz), 7.26—7.54 (6H, m). ^{19}F-NMR ($CDCl_3$) ppm: −5.76 (3F, qd, $J=2.13$, 1.95 Hz). (*E*,*Z*) compound: ^{1}H-NMR ($CDCl_3$) δ: 2.21 (3H, q, $J=2.32$ Hz), 6.96 (1H, d, $J=16.18$ Hz), 7.26—7.54 (5H, m). ^{19}F-NMR ($CDCl_3$) ppm: −4.79 (3F, q, $J=2.32$ Hz).

10 from 9 A solution of **9** (0.318 g, 0.83 mmol) in DMF (3 ml) was added to a suspension of Zn (60 mg, 0.91 mmol) and CuI (1 mg) in DMF (2 ml) at 0 °C. The reaction mixture was stirred for 1 h at this temperature, 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 careful evaporation of the solvent at 0 °C under reduced pressure, the residue was analyzed by GLC; it contained 95.9% of a major product. This was purified by column chromatography (SiO_2, pentane) to give **10** (0.164 g, 80.4%). This compound (**10**) was a mixture of (*E*,*E*) and (*E*,*Z*), as judged from the ^{19}F-NMR spectrum (ratio 0.76 : 1).

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