July 1999 Notes *Chem. Pharm. Bull.* **47**(7) 1013—1016 (1999) 1013

Synthesis of Alkenyl- and Aryldifluoroacetate Using a Copper Complex from Ethyl Bromodifluoroacetate[1)]

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Received January 5,1999; accepted April 5, 1999

Ethyl bromodifluoroacetate reacted with alkenyl or aryl iodides in the presence of copper powder in dimethyl sulfoxide (DMSO) to give the corresponding alkenyl- or aryldifluoroacetates in moderate to good yields.

Key words cross coupling; bromodifluoroacetate; alkenyl iodide; aryl iodide; copper; alkenyldifluoroacetate

Many organic fluorine compounds have been used as medicines based on many interesting characteristics due to high electronegativity and the small van der Waals radius of the fluorine atom.[2)] Therefore, organic fluorine compounds have attracted much attention in biomedicinal and/or agrochemical fields, and many new methodologies for their synthesis have been developed. Some of these compounds possess a difluoromethylene group.[3)] For the introduction of a difluoromethylene group, a Reformatsky reaction[4)] using bromo- or iododifluoroacetate or an aldol type reaction[5)] of enolate or ketene acetal from the above acetate have been widely used. These reactions give α-hydroxydifluoromethylene compounds. However, the α-hydroxy group of a difluoromethylene group is quite unreactive and very difficult to remove due to the high electronegativity of the fluorine atoms. Therefore, synthesis of difluoromethylene compounds without a hydroxy group in the α-position is rather difficult. For this purpose, cross coupling of the above acetate with halogen compounds seemed suitable. One example of this type of reaction was reported by Kobayashi *et al.* using a copper complex from methyl difluoroiodoacetate.[6,7)] This method can be applied to a wide range of halogen compounds. However, methyl difluoroiodoacetate is not commercially available and must be synthesized from bromodifluoroacetate; three moles were used with one mole of halogen compounds. Here, we would like to report the cross coupling reaction of commercially available ethyl bromodifluoroacetate (**1**) with some halogen compounds in the presence of copper powder.

Since Kobayashi *et al.* have reported that hexamethylphosphoric triamide (HMPA) is the best solvent for a coupling reaction of this type,[7)] three equivalents of **1** were reacted with (*E*)-1-iodohexene (**2**) in the presence of Cu powder[8)] in HMPA at 55 °C, and ethyl (*E*)-3,3-difluoro-3-octenoate (**3**) was obtained, but the yield was only 25%, and the formation of a fairly large amount of 1-bromohexene (**4**) was confirmed by GC-MS (Chart 1).

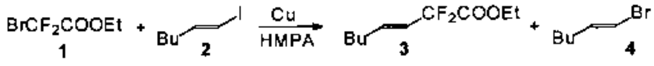

Chart 1

The formation of **4** seemed to be the reason for the low yield of **3**. To lower the formation of **4**, we examined the solvent effect. Dimethyl sulfoxide (DMSO) gave a much better yield (42%) of **3** in a shorter reaction time. However, another byproduct was obtained in this solvent, the structure of which was assigned as diethyl 4-butyl-2,5,5-trifluoro-2-hexenedioate (**5**), based on its spectral data. A large F—H coupling shows the *E* configuration of the double bond. This seemed to be formed by the reaction of **3** with an excess of the copper reagent. To confirm this point, **3** was treated with **1** in the presence of Cu powder, then **5** was obtained (Chart 2).

To avoid the formation of **5**, one equivalent of **1** was used, then **3** was obtained in 64% yield. The results of this reaction in other solvents [*N*,*N*-dimethylformamide (DMF), 1,3-dimethyl-2-imidazolidinone (DMI), dimethoxyethane (DME) and pyridine (Py)] are shown in Table 1.

Kobayashi *et al.* obtained a fairly stable univalent copper complex from difluoroiodoacetate in HMPA.[7)] To examine the stability of the complex in our reaction, **1** was stirred with Cu powder in DMSO at 55 °C for 12 h, then **2** was

Table 1. Investigation of Solvent Effect

$BrCF_2COOEt$ (eq)	Solv.	Time (h)[a)]	Yield (%)[b)]	**3** : **4**[c)]
3	HMPA	48	25	100 : 20
3	DMSO	12	42[d)]	100 : 1.8
1	DMSO	12	64	100 : 1.5
1	DMF	36	15	100 : 75
1	DMI	84	2	100 : 200
1	DME	24	No reaction	—
1	Py	24	0[e)]	—

a) Time until the peak of **1** was no longer detected by GC. *b*) Isolation yield of **3**. *c*) Area ratio on GC. *d*) **5** (15%) was isolated. *e*) Formation of **4** was confirmed by GC.

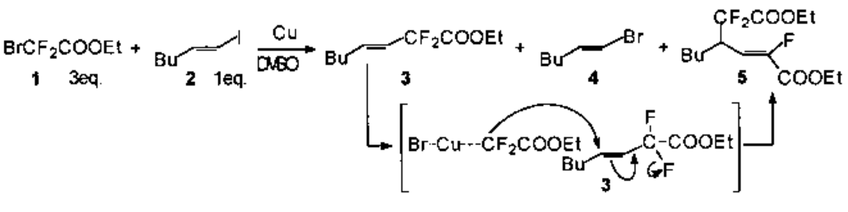

Chart 2

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added and stirred at this temperature for another 12 h, but **3** was not obtained at all. Most of **2** was recovered and the formation of **4** was confirmed by GC-MS. This means the intermediate complex was rather unstable and decomposed to copper bromide, which reacted with **2** to give **4**. On the other hand, **2** was treated with Cu powder, but no decrease in the peak of **2** was observed by GC. By addition of **1** to this mixture, **3** was formed (Chart 3). Namely, **2** did not react with Cu, whereas **1** added later reacted with Cu powder. The complex formed reacted immediately with **2** to give **3**. From these results, we temporarily propose the structure of the complex, which is shown in brackets in Chart 2. Namely, the complex from **1** in DMSO is different from the one in HMPA reported by Kobayashi's group.

Though the mechanism was not clear, we were able to obtain **3** from **1**. We examined the scope and limitation of this method. The results are summarized in Table 2.

As shown in entries 1 and 2, iodides on an sp^2 carbon gave the corresponding ethoxycarbonyldifluoromethyl derivatives stereospecifically in high yields, but iodides on an *sp* carbon (entry 3) or on an sp^3 carbon (entry 4) did not give the expected cross coupling products. Compound **8** afforded a homo coupling product, 5,7-dodecadiyne. Aromatic iodides gave good results (entries 5, 7, 8), while a bromide resulted in the recovery of the starting material (entry 6). Nitro compound **13** gave the highest yield. This suggests that the active complex had a character of carbanion and that it reacted with **13**, having a highly electronegative nitro group. α- Or β-methyl groups did not disturb this reaction (entries 9 and 10), while the presence of a larger trimethylsilyl group in the α-position required longer reaction time and gave **22** in a much lower yield. The coupling constants between the fluorines on the CF$_2$ groups and the methyl (**18**) or the methylene (**20**) protons suggested that these were *cis*. All the products obtained so far were stereoselective, and the structure of **22** was temporarily assigned as *Z*.

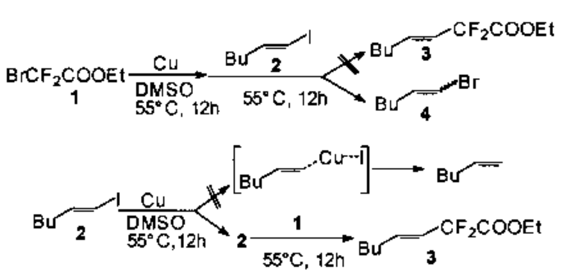


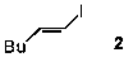
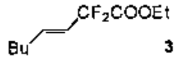
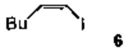
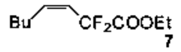
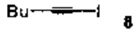
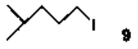
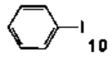
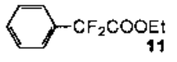
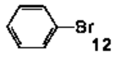
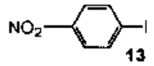
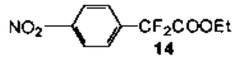
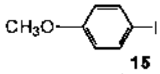
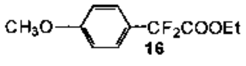
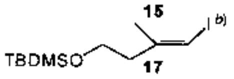
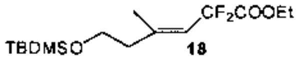
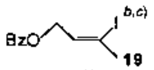
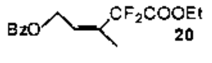
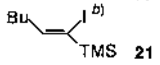
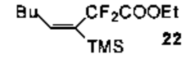
Chart 3

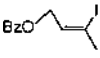
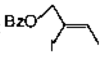
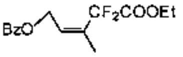
In conclusion, ethyl bromodifluoroacetate (**1**) reacts with iodides on sp^2 carbons in the presence of Cu powder in DMSO to give the corresponding ethoxycarbonyldifluoromethyl derivatives stereospecifically in moderate to good yields, while *sp* or sp^3 analogs or bromides do not react. Thus, this methodology is limited to vinyl or aryl iodides, but **1** is much more easily available than difluoroiodoacetate, and the reaction temperature is easily controllable (55 °C). This method provides another easy access to a special type of difluoromethylene compounds.

Experimental

General Procedures ^{1}H-NMR were recorded on JEOL-FX90Q and JNM-GX400 Spectrometers. Tetramethylsilane was used as an internal standard. ^{19}F-NMR were recorded on Hitachi FT-NMR R-1500 and JEOL-FX90Q Spectrometers. Benzotrifluoride was used as an internal standard.

Table 2. Reaction of **1** with Various Halogen Compounds in the Presence of Cu in DMSO at 55 °C

Entry	R–X	Time (h)	R–CF$_2$COOEt	Yield (%)
1	 **2**	12	 **3**	64
2	 **6**	12	 **7**	69
3	 **8**	—	—	—a)
4	 **9**	6	—	No reaction
5	 **10**	5	 **11**	53
6	 **12**	5	—	No reaction
7	 **13**	9	 **14**	66
8	 **15**	5	 **16**	55
9	 **17** b)	9	 **18**	62
10	 **19** b,c)	8	 **20**	60d)
11	 **21** b)	30	 **22**	21

a) Homo coupling occurred at r.t. *b*) Synthesized according to the literatures (9, 10, 11). *c*)  :  =8.3 : 1. *d*)  isolated yield.

Mass spectra were obtained by JEOL JMS-DX-300. IR spectra were recorded on a Hitachi 270-30 infrared spectrophotometer. The melting point was measured on an Ishii Shoten Melting Point Apparatus. Gas-liquid chromatography (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.

Ethyl (*E*)-2,2-Difluoro-3-octenoate (3) 1) Using 3 eq of Ethyl Bromodifluoroacetate (**1**) in HMPA: In an atmosphere of Ar, ethyl bromodifluoroacetate (**1**, 0.77 ml, 6.0 mmol) and (*E*)-1-iodo-1-hexene (420 mg, 2.0 mmol) were added to a suspension of activated Cu powder (353 mg, 5.6 mmol) in HMPA (10 ml), and the mixture was stirred at 55 °C for 24 h. After this time, **1** was not detected by GLC. The mixture was poured into a mixture of ice and saturated NH_4Cl, then extracted with Et_2O. The Et_2O layer was washed with saturated NH_4Cl and saturated NaCl, then dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by column chromatography (SiO_2, Et_2O : hexane=1 : 9) to give **3** (105 mg, 25%). **3**: Colorless oil, MS *m/z*: 206 (M^+); HRMS Calcd $C_{10}H_{16}F_2O_2$: 206.112 (M^+). Found: 206.112. IR (neat) cm^{-1}: 2968, 2936, 2880, 1772, 1678, 1302, 1230, 1084. ^1H-NMR ($CDCl_3$) δ: 6.27 (dtt, 1H, J=15.9, 7.0, 2.5 Hz), 5.67 (dtt, 1H, J=15.9, 11.0, 1.5 Hz), 4.32 (q, 2H, J=7.0 Hz), 2.15 (m, 2H), 1.28—1.46 (m, 4H), 1.34 (t, 3H, J=7.0 Hz), 0.90 (t, 3H, J=7.0 Hz). ^{19}F-NMR ($CDCl_3$) ppm: −40.1 (dq, 2F, J=11.0, 2.5 Hz).

2) In DMSO: In an atmosphere of Ar, **1** (0.77 ml, 6.0 mmol) and **2** (420 mg, 2.0 mmol) were added to a suspension of activated Cu powder (353 mg, 5.6 mmol) in DMSO (10 ml), then the mixture was stirred at 55 °C. After 12 h, the peak of **1** on GLC was no longer observed. The mixture was worked up as in 1). After concentration of the extract, the residue was separated by column chromatography (SiO_2, Et_2O : hexane=1 : 9) to give **3** (175 mg, 42%) and diethyl 4-butyl-2,5,5-trifluoro-2-hexenedioate (**5**, 93 mg, 15%). **5**: Colorless oil; MS *m/z*: 310 (M^+), HRMS Calcd $C_{14}H_{21}F_3O_4$: 310.139 (M^+) Found: 310.139. IR (neat) cm^{-1}: 2968, 2880, 1774, 1742, 1688, 1398, 1376, 1322, 1254, 1208, 1132, 1096, 1018. ^1H-NMR ($CDCl_3$) δ: 5.97 (dd, 1H, J=31.1, 11.0 Hz), 4.33 (q, 2H, J=7.0 Hz), 4.31 (q, 2H, J=7.0 Hz), 3.40 (m, 1H), 1.15—1.52 (m, 6H), 1.35 (t, 3H, J=7.0 Hz), 1.34 (t, 3H, J=7.0 Hz), 0.89 (t, 3H, J=7.0 Hz). ^{19}F-NMR ($CDCl_3$) ppm: −47.7 (dd, 1F, J=14.3, 2.4 Hz), −47.9 (dd, 1F, J=13.4, 2.4 Hz), −61.8 (d, 1F, J=31.1 Hz).

3) Using 1 eq of **1** in DMSO: In an atmosphere of Ar, **1** (0.25 ml, 2.0 mmol) and **2** (420 mg, 2.0 mmol) were added to a suspension of activated Cu powder (353 mg, 5.6 mmol) in DMSO (10 ml), and the mixture was stirred at 55 °C for 12 h. The mixture was worked up as above, and the product was purified by column chromatography (SiO_2, Et_2O : hexane=1 : 9) to give **3** (263 mg, 64%).

4) In Other Solvents: The same reaction as above using DMF, DMI, DME or pyridine were examined. Amount of **4** was estimated by GLC. The results are shown in Table 2.

Ethyl (*Z*)-2,2-Difluoro-3-octenoate (7) In an atmosphere of Ar, **1** (0.25 ml, 2.0 mmol) and (*Z*)-1-iodo-1-hexene (**6**, 420 mg, 2.0 mmol) were added to a suspension of activated Cu powder (353 mg, 5.6 mmol) in DMSO (10 ml), then the mixture was stirred at 55 °C for 12 h. The mixture was worked up as in the case of **2**, and the product was purified by column chromatography (SiO_2, Et_2O : hexane=1 : 9) to give **7** (284 mg, 69%). **7**: Colorless oil, bp 77 °C/8 mmHg, MS *m/z*: 206 (M^+), HRMS Calcd $C_{10}H_{16}F_2O_2$: 206.112 (M^+). Found: 206.111. IR (neat) cm^{-1}: 2964, 2936, 2876, 1770, 1662, 1302, 1090. ^1H-NMR ($CDCl_3$) δ: 5.93 (dtt, 1H, J=11.6, 7.9, 1.8 Hz), 5.58 (tdt, 1H, J=14.3, 11.6, 1.5 Hz), 4.32 (q, 2H, J=7.0 Hz), 2.29 (m, 2H), 1.28—1.44 (m, 4H), 1.34 (t, 3H, J=7.0 Hz), 0.90 (t, 3H, J=7.0 Hz). ^{19}F-NMR ($CDCl_3$) ppm: −36.0 (dd, 2F, J=14.3, 1.8 Hz).

Ethyl 2,2-Difluoro-2-phenylacetate (11) In an atmosphere of Ar, **1** (0.10 ml, 0.8 mmol) and iodobenzene (**10**, 0.09 ml, 0.8 mmol) were added to a suspension of activated Cu powder (140 mg, 2.2 mmol) in DMSO (4.0 ml), then the mixture was stirred at 55 °C for 5 h. The mixture was worked up as above, and the product was purified by column chromatography (SiO_2, Et_2O : hexane=1 : 9) to give **11** (84 mg, 53%). **11**: Colorless oil, MS *m/z*: 200 (M^+), HRMS Calcd $C_{10}H_{10}F_2O_2$: 200.065 (M^+). Found: 200.064. IR (neat) cm^{-1}: 2992, 1768, 1374, 1268, 1104. ^1H-NMR ($CDCl_3$) δ: 7.61 (m, 2H), 7.47 (m, 3H), 4.30 (q, 2H, J=7.0 Hz), 1.30 (t, 3H, J=7.0 Hz). ^{19}F-NMR ($CDCl_3$) ppm: −41.1 (s, 2F).

Ethyl 2,2-Difluoro-2-(4-nitrophenyl)acetate (14) In an atmosphere of Ar, **1** (0.25 ml, 2.0 mmol) was added to a suspension of activated Cu powder (353 mg, 5.6 mmol) and 4-nitroiodobenzene (**13**, 500 mg, 2.0 mmol) in DMSO (10 ml), then the mixture was stirred at 55 °C for 9 h. The mixture was worked up as above, and the product was purified by column chromatography (SiO_2, Et_2O : hexane=1 : 9) to give **14** (321 mg, 66%). **14**: Pale yellow crystals, mp 47—48 °C, MS *m/z*: 245 (M^+), HRMS Calcd $C_{10}H_9F_2NO_4$: 245.050 (M^+) Found: 245.050. IR (KBr) cm^{-1}: 3128, 3096, 3068, 2996, 2948, 2872, 1770, 1528, 1348, 1298, 1268, 1142, 1122, 1104. ^1H-NMR ($CDCl_3$) δ: 8.32 (m, 2H), 7.82 (m, 2H), 4.32 (q, 2H, J=7.0 Hz), 1.32 (t, 3H, J=7.0 Hz). ^{19}F-NMR ($CDCl_3$) ppm: −41.6 (s, 2F).

Ethyl 2,2-Difluoro-2-(4-methoxyphenyl)acetate (16) In an atmosphere of Ar, **1** (0.25 ml, 2.0 mmol) was added to a suspension of activated Cu powder (353 mg, 5.6 mmol) and 4-iodoanisole (**15**, 468 mg, 2.0 mmol) in DMSO (10 ml), then the mixture was stirred at 55 °C for 5 h. The mixture was worked up as above, and the product was purified by column chromatography (SiO_2, Et_2O : hexane=1 : 9) to give **16** (255 mg, 55%). **16**: Colorless oil, MS *m/z*: 230 (M^+), HRMS Calcd $C_{11}H_{12}F_2O_3$: 230.075 (M^+). Found: 230.076. IR (neat) cm^{-1}: 2988, 2944, 2848, 1770, 1618, 1520, 1256, 1180, 1140, 1102, 1022. ^1H-NMR ($CDCl_3$) δ: 7.53 (m, 2H), 6.95 (m, 2H), 4.29 (q, 2H, J=7.0 Hz), 3.83 (s, 3H), 1.30 (t, 3H, J=7.0 Hz). ^{19}F-NMR ($CDCl_3$) ppm: −39.8 (s, 2F).

Ethyl (*E*)-2,2-Difluoro-4-methyl-6-(*tert*-butyldimethylsilyloxy)-3-hexenoate (18) In an atmosphere of Ar, **1** (0.25 ml, 2.0 mmol) and (*E*)-4-(*tert*-butyldimethylsilyloxy)-1-iodo-2-methyl-1-butene[9] (**17**, 653 mg, 2.0 mmol) were added to a suspension of activated Cu powder (353 mg, 5.6 mmol) in DMSO (10 ml), then the mixture was stirred at 55 °C for 9 h. The mixture was worked up as above, and the product was purified by column chromatography (SiO_2, Et_2O : hexane=1 : 9) to give **18** (402 mg, 62%). **18**: Colorless oil, MS *m/z*: 277 ($M^+-C_2H_5O$), 265 ($M^+-{}^t$Bu). HRMS Calcd $C_{13}H_{23}F_2O_2Si$: 277.144 ($M^+-C_2H_5O$), $C_{11}H_{19}F_2O_3Si$: 265.107 ($M^+-{}^t$Bu) Found: 277.143 ($M^+-C_2H_5O$), 265.107 ($M^+-{}^t$Bu). IR (neat) cm^{-1}: 2960, 2864, 1770, 1676, 1298, 1258, 1200, 1102. ^1H-NMR ($CDCl_3$) δ: 5.47 (ttq, 1H, J=14.0, 1.2, 1.2 Hz), 4.32 (q, 2H, J=7.0 Hz), 3.72 (t, 2H, J=6.4 Hz), 2.28 (ttd, 2H, J=6.4, 2.1, 1.2 Hz), 1.88 (td, 3H, J=2.7, 1.2 Hz), 1.34 (t, 3H, J=7.0 Hz), 0.88 (s, 9H), 0.04 (s, 6H). ^{19}F-NMR ($CDCl_3$) ppm: −36.0 (dqt, 2F, J=14.0, 2.7, 2.1 Hz).

Ethyl (*Z*)-5-Benzoyloxy-2,2-difluoro-3-methyl-3-pentenoate (20) In an atmosphere of Ar, **1** (0.25 ml, 2.0 mmol) and (*Z*)-2-iodo-2-butenyl benzoate[10] (**19**, 604 mg, 2.0 mmol) were added to a suspension of activated Cu powder (353 mg, 5.6 mmol) in DMSO (10 ml), and the mixture was stirred at 55 °C for 8 h. The mixture was worked up as above, and the product was purified by column chromatography (SiO_2, Et_2O : hexane=1 : 9) to give **20** (358 mg, 60%). **20**: Colorless oil, MS *m/z*: 298 (M^+), HRMS Calcd. $C_{15}H_{16}O_4F_2$: 298.101 (M^+) Found: 298.102. IR (neat) cm^{-1}: 3072, 2992, 1772, 1724, 1606, 1270, 1118, 1072, 1040, 1028. ^1H-NMR ($CDCl_3$) δ: 8.05 (m, 2H), 7.57 (tt, 1H, J=7.4, 1.2 Hz), 7.44 (m, 2H), 5.88 (tqt, 1H, J=6.1, 1.5, 0.6 Hz), 5.07 (dtq, 2H, J=6.1, 3.1, 1.5 Hz), 4.35 (q, 2H, J=7.0 Hz), 1.91 (q, 3H, J=1.5 Hz), 1.35 (t, 3H, J=7.0 Hz). ^{19}F-NMR ($CDCl_3$) ppm: −36.9 (td, 2F, J=3.1, 0.6 Hz).

Ethyl 2,2-Difluoro-3-trimethylsilyl-3-octenoate (22) In an atmosphere of Ar, **1** (0.25 ml, 2.0 mmol) and (*Z*)-(1-iodo-1-hexenyl)trimethylsilane[11] (**21**, 532 mg, 2.0 mmol) were added to a suspension of activated Cu powder (353 mg, 5.6 mmol) in DMSO (10 ml), then the mixture was stirred at 55 °C for 30 h. The mixture was worked up as above, and the product was purified by column chromatography (SiO_2, Et_2O : hexane=1 : 9) to give **22** (118 mg, 21%). **22**: Colorless oil, MS *m/z*: 263 (M^+-CH_3), HRMS Calcd $C_{12}H_{21}F_2O_2Si$: 263.128 (M^+-CH_3). Found: 263.128 (M^+-CH_3). IR (neat) cm^{-1}: 2968, 2876, 1766, 1618, 1288, 1252, 1182, 1132, 1092. ^1H-NMR ($CDCl_3$) δ: 6.10 (t, 1H, J=7.3 Hz), 4.28 (q, 2H, J=7.0 Hz), 2.24 (m, 2H), 1.25—1.40 (m, 4H), 1.32 (t, 3H, J=7.0 Hz), 0.89 (t, 3H, J=7.0 Hz), 0.17 (s, 9H). ^{19}F-NMR ($CDCl_3$) ppm: −28.1 (s, 2F).

References and Notes

1) Part of this work was presented in the 22nd Fluorine Conference of Japan, Osaka, 1998.
2) "Fussokagakunyumon," edited by Nihon Gakujutu Shinkokai, Nikkankogyoshimbunsha, Osaka, 1997, 311—340.
3) *a*) Nakano T., Makino M., Morizawa Y., Matsumura Y., *Angew. Chem., Int. Ed. Engl.*, **35**, 1019—1021 (1996); *b*) Hertel L. W., Korin J. S., Misner J. W., Tustin J. M., *J. Org. Chem.*, **53**, 2406—2409 (1988).
4) *a*) Hallinan E. A., Fried J., *Tetrahedron Lett.*, **25**, 2301—2302 (1984); *b*) Lang R. W., Schaub B., *ibid.*, **29**, 2943—2946 (1988); *c*) Braun M., Vonderhagen A., Waldmhller D., *Liebigs Ann.*, **1995**, 1447—1450.
5) a) Kitagawa O., Taguchi T., Kobayashi Y., *Tetrahedron Lett.*, **29**, 1803—1806 (1988); *b*) Iseki K., Kuroki Y., Asada D., Kobayashi Y. , *ibid.*, **38**, 1447—1448 (1997); *c*) Iseki K., *Tetrahedron*, **54**, 13887—13914 (1998).

6) Taguchi T., Kitagawa O., Morikawa T., Nishiwaki T., Uehara H., Endo H., Kobayashi Y., *Tetrahedron Lett.*, **27**, 6103—6106 (1986).

7) Kitagawa O., Taguchi T., Kobayashi Y., *Chem. Lett.*, **1989**, 389—392.

8) Cu powder was formed according to the following reference. Brewster R. Q., Groening T., “Org. Synthesis,” Coll. Vol. II, **1948**, 445—446.

9) Rand C. L., Van Horn D. E., Moore M. W., Negishi E., *J. Org. Chem.*, **46**, 4096—4097 (1981).

10) Corey E. J., Katzenellenbogen J. A., Posner G. H., *J. Am. Chem. Soc.*, **89**, 4245—4247 (1967).

11) Zweifel G., Lewis W., *J. Org. Chem.*, **43**, 2739—2744 (1978).