A novel fluorine–metal exchange reaction of pentafluorocrotonate with organocuprate. Generation of β-metallated tetrafluorocrotonate and its cross-coupling reaction†

Shigeyuki Yamada, Toshio Takahashi, Tsutomu Konno and Takashi Ishihara*

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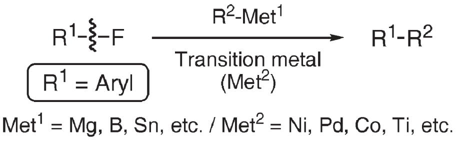
Fluorine–metal exchange reaction of 2,3,4,4,4-pentafluorocrotonates with organocuprate derived from Grignard reagent and CuCN takes place efficiently to generate the β-metallated tetrafluorocrotonate intermediate, which reacts with various electrophiles to give β-substituted 2,4,4,4-tetrafluorocrotonates.

The cleavage of a carbon–fluorine (C–F) bond and the subsequent carbon–carbon (C–C) bond formation has been one of the most challenging subjects in organic chemistry. Much effort has been made for the development of such chemical transformations thus far (Scheme 1). The cross-coupling reactions of aryl fluorides with various organometallic reagents have been accomplished *via* the activation of a C–F bond in the presence of a transition metal catalyst (nickel,[1] palladium,[2] cobalt,[3] titanium[4] and so on[5]), in which the C–F bond cleavage occurs *via* an oxidative addition process. Examples for the transition metal-catalyzed cross-coupling reactions using aliphatic fluorides have also appeared in the literature.[6]

Very recently, we reported that the reaction of α,β,β-trifluoroacrylate with various types of Grignard reagents in the presence of a catalytic amount of CuBr gave the corresponding addition–elimination products in a highly *Z*-selective manner (Scheme 2).[7] During the course of our continuous studies on the reactions of fluorine-containing alkenes having an electron-withdrawing group with organocopper reagents, we found that the treatment of benzyl pentafluorocrotonate (**1**) with Grignard reagents in the presence of copper(I) salt caused the vinylic fluorine–metal exchange reaction, leading to the corresponding β-metallated product **2** (Scheme 2). To our knowledge there has been only one previously reported example related to this vinylic fluorine–metal exchange reaction, and that was observed for the reaction of β,β-difluorovinyl ethers with low-valent zirconocene.[8] In this communication we wish to disclose preliminary results on the quite novel vinylic fluorine–metal exchange reaction and the subsequent cross-coupling reaction with various carbon electrophiles.

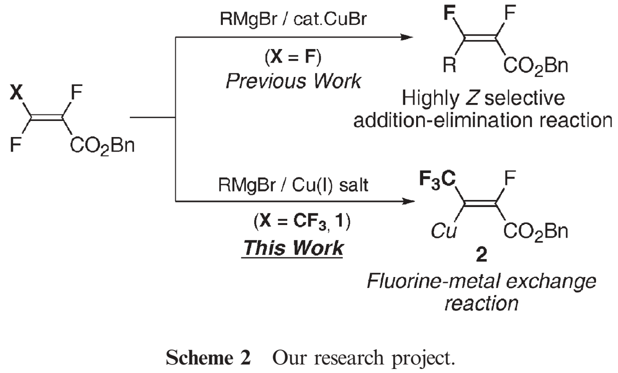


Scheme 1 The activation of a C–F bond for cross-coupling reaction.

Initially, we examined the reaction of pentafluorocrotonate **1**, which was prepared by slight modifications of the previously reported methods,[9] with various organocuprates generated from Grignard reagents and Cu(I) salt, as summarized in Table 1.

Thus, the reaction of **1** with PhMgBr in the absence of copper(I) salt in THF at −78 °C for 1 h did not proceed at all, the starting ester **1** being recovered nearly quantitatively (Entry 1). The reactions in the presence of various copper(I) salts, such as CuBr, CuI and CuCN, were examined (Entries 2–4). CuBr and CuI were ineffective, the ester **1** being recovered in 76–87% yields. In sharp contrast, the use of CuCN was found to give the β-reduction product **4-*H*** in 34% yield after hydrolysis, together with 64% recovery of **1**, and any trace of the addition–elimination product **3** was not detected at all. Interestingly, the reaction at −20 °C for 1 h gave benzyl 4,4,4-trifluorobutynoate (**6**) in 31% yield, along with 35% of the starting ester **1** (Entry 5). Eventually, it was found that the reaction of **1** with 2.2 equiv. of organocuprate at −78 °C for 1 h proceeded smoothly to afford the β-reduction product **4-*H*** in 66% yield as a sole stereoisomer, together with 18% yield of benzyl 3-phenyl-4,4,4-trifluorocrotonate (**5**) (Entry 6).[10] On the other hand, the reaction at higher temperature (−20 °C) gave **5** in 80% yield as a mixture of the *E* and *Z* isomers (*E*/*Z* = *ca.* 50/50) (Entry 7).

As shown in Entries 8, 9 and 11, aryl Grignard reagents having an electron-donating group, such as methoxy or methyl group, at the *p*- or *m*-position of benzene ring could also participate nicely in the reaction to afford the corresponding β-reduction product **4-*H*** in 61–65% yields. In the case of 2-methoxyphenylmagnesium bromide, the reaction proceeded reluctantly to form **4-*H*** in 23% yield, the starting ester **1** being recovered in 73% yield (Entry 10). On the other hand, aryl Grignard reagent bearing an



Scheme 2 Our research project.

Department of Chemistry and Materials Technology, Kyoto Institute of Technology, Matsugasaki, Sakyo-ku, Kyoto 606-8585, Japan. E-mail: ishihara@kit.ac.jp; Fax: (+81)-75-724-7580; Tel: (+81)-75-724-7504

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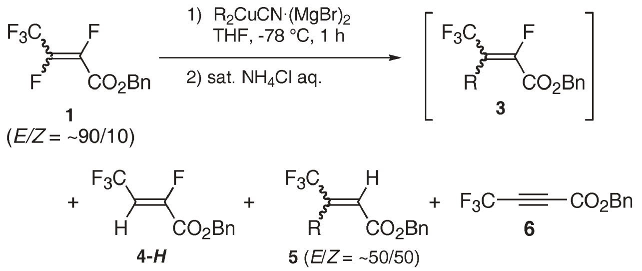
Table 1 Reaction of **1** with various organocuprates



Entry	R	Equiv. of cuprate	Yield[a]/% of **3**	Yield[a]/% of **4-*H***	Yield [a]/% of **5**	Recovery [a]/% of **1** [*E*/*Z*]
1[b]		1.1	0	0	0	91
2[c]		1.1	0	0	0	87
3[d]		1.1	0	0	0	76[78/22]
4	Ph	1.1	0	34	0	64[80/20]
5[e,f]		1.1	0	5	0	35[60/40]
6		2.2	0	66 (50)	18	0
7[e]		2.2	0	0	80(79)	0
8	4-$MeOC_6H_4$		0	61(53)	25	trace
9	3-$MeOC_6H_4$		0	62(54)	23	trace
10	2-$MeOC_6H_4$		0	23	0	73[90/10]
11	4-MeC_6H_4		0	65(56)	0	0
12	4-$CF_3C_6H_4$	2.2	0	27	0	0
13	*n*-Bu		0	59(40)	0	9
14	Me		0	60(38)	0	10
15[g]	$PhCH_2$		51(36)[h]	15	0	8
16[g]	Allyl		62(32)[h]	0	0	10

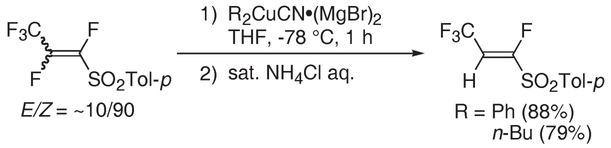
[a] Determined by ^{19}F NMR. Values in parentheses are of isolated yield. [b] Without Cu(I) salt. [c] CuBr was used as a Cu(I) salt. [d] CuI was used as a Cu(I) salt. [e] Carried out at −20 °C. [f] Alkynoate **6** was obtained in 31% yield. [g] Benzyl- or allylmagnesium chloride was used as a Grignard reagent. [h] In entries 15 and 16, the ratio of the *E*/*Z* isomers of **3** was 29/71 and 32/68, respectively.

electron-withdrawing group on benzene ring gave rise to the β-reduction product **4-*H*** in only 27% yield, along with many unidentified products (Entry 12). As shown in Entries 15–20, *n*-butyl- and methylmagnesium bromide were also found to be effective, giving rise to **4-*H*** in 59% and 66% yields, respectively (Entries 13 and 14). Interestingly, when benzyl- or allylmagnesium chloride was employed as a Grignard reagent, the starting ester **1** was almost consumed and the corresponding addition–elimination product **3** was obtained in 51% or 62% yield, respectively (Entries 15 and 16).

Our interest was next directed toward to the coupling reaction of *in-situ* formed intermediate **2** with various electrophiles. The results are tabulated in Table 2.

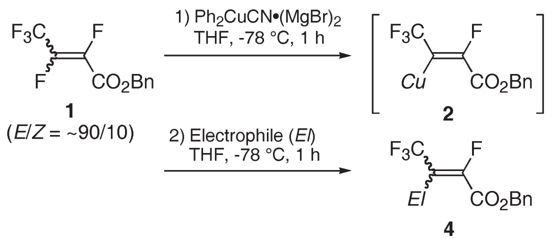
When **1** was allowed to react with diphenylcyanocuprate (2.2 equiv.), prepared from CuCN (2.2 equiv.) and PhMgBr (4.4 equiv.), followed by treatment with I_2 (5.0 equiv.) at −78 °C for 1 h, benzyl 2,4,4,4-tetrafluoro-3-iodo-2-butenoate was obtained in 82% yield as a mixture of the *E* and *Z* isomers (*E*/*Z* = 79/21) (Entry 1). As shown in Entries 2–4, allyl bromide, methallyl bromide and crotyl bromide could also participate well in the coupling reaction to give the corresponding β-allylated, β-methallylated and β-crotylated[11] products in 67%, 66% and 65% yields, respectively. However, other electrophiles, such as propargyl bromide, benzyl bromide and trimethylsilyl chloride, were ineffective for the cross-coupling reaction,[12] the β-reduction product **4-*H*** being provided in 43%, 59% and 41% yields, respectively.

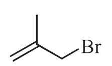
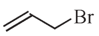
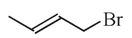
It was found, moreover, that 1,2,3,3,3-pentafluoropropen-1-yl 4-methylphenyl sulfone underwent the present fluorine–metal exchange reaction with diphenyl- or di-*n*-butylcyanocuprate under similar conditions, leading to the corresponding 1,3,3,3-tetrafluoropropen-1-yl sulfone in good yield (eqn (1)).



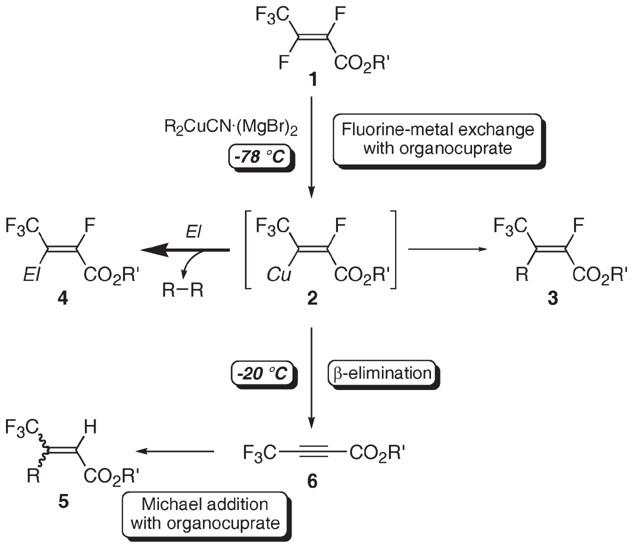
(1)

Table 2 Cross-coupling reaction with various electrophiles



Entry	Electrophile	Yield[a]/% of **4** [*E*/*Z*]	Entry	Electrophile	Yield[a]/% of **4** [*E*/*Z*]
1	I_2	82(78) [79/21]	3	 Br	66(62) [18/82]
2	 Br	67(42) [0/100]	4	 Br	65(58) [0/100]

[a] Determined by ^{19}F NMR. Values in parentheses are of isolated yield.



Scheme 3 A possible reaction mechanism.

A possible reaction mechanism is described in Scheme 3. The starting ester **1** undergoes the vinylic fluorine–copper exchange reaction with organocuprate to form the corresponding vinyl copper species **2**, which is stabilized due to the strong electron-withdrawing effect of a CF_3 group[13] and is not susceptible to the reductive elimination leading to **3** at −78 °C. By subsequent treatment with various electrophiles including H_2O, the vinyl copper species **2** is converted to the corresponding tetrafluorocrotonates **4**, along with the formation of homo-coupling product (R–R). On the other hand, raising the reaction temperature from −78 to −20 °C promotes the elimination of *Cu*–F[14] in **2**, giving rise to the corresponding alkynoate **6**, which may undergo Michael addition of an excess amount of cuprate to afford 3-substituted -4,4,4-trifluorocrotonate **5**.

In summary, we have found that the fluorine–metal exchange reaction of 2,3,4,4,4-pentafluorocrotonate **1** with Grignard reagents in the presence of copper(I) salt takes place efficiently to generate the β-metallated tetrafluorocrotonate intermediate, of which hydrolysis gives the β-reduction product **4-*H*** in good yield. Treatment of the organocopper intermediate with various electrophiles, such as iodine, allyl bromide, methallyl bromide and crotyl bromide, gave the corresponding 3-substituted 2,4,4,4-tetrafluorocrotonates **4** in good yields (65–82%).[15] Further study of the scope, mechanistic implications, and synthetic applications of the reactions is currently ongoing in our laboratory.

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10 Other esters, such as 2-phenylethyl and (*E*)-3-phenyl-2-propen-1-yl ester, also underwent the similar reaction to give the corresponding β-reduction products in 64% and 50% yields, respectively.

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15 A typical procedure for the preparation of benzyl 2,4,4,4-tetrafluoro-3-iodo-2-butenoate **4** (*El* = I) is as follows: A 30 mL two-necked round-bottomed flask equipped with a magnetic stirrer bar, a rubber septum and an inlet tube for argon was charged with a suspended solution of CuCN (0.037 g, 0.418 mmol) in THF (1 mL). To this solution was slowly added a solution of phenylmagnesium bromide (0.836 mmol) in THF *via* a syringe at −78 °C. The whole was warmed up at −20 °C and stirred for 15 min. To the resulting solution was added benzyl 2,3,4,4,4-pentafluoro-2-butenoate (**1**, 0.050 g, 0.190 mmol) *via* a syringe at −78 °C. After being stirred at −78 °C for 1 h, the reaction mixture was treated with iodine (0.241 g, 0.950 mmol) in THF at −78 °C for 1 h. After stirring for 1 h, the reaction mixture was poured into ice-cooled saturated aqueous NH_4Cl (30 mL), followed by extraction with ether (30 mL × 5). The organic layers were dried over anhydrous sodium sulfate, filtered and concentrated with a rotary evaporator. Column chromatography of the residue using hexane/benzene (2 : 1) yielded pure benzyl 2,4,4,4-tetrafluoro-3-iodo-2-butenoate (0.055 g, 78%). **4** (*El* = I): ^1H NMR ($CDCl_3$) δ 5.35 (s, 2H), 7.35–7.50 (m, 5H); ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ −80.78 (q, J = 24.4 Hz, 1F), −58.25 (d, J = 24.4 Hz, 1F); ^{13}C NMR ($CDCl_3$) δ 68.81, 74.01 (dq, J = 38.1, 38.1 Hz), 120.87 (q, J = 274.9 Hz), 128.73, 128.74, 128.97, 133.89, 150.89 (dq, J = 294.1, 2.8 Hz), 158.51 (d, J = 33.6 Hz); IR (neat) 3069 (w), 2962 (w), 1743 (vs), 1627 (m), 1498 (m), 1312 (vs), 1237 (vs), 1187 (vs), 1147 (vs), 956 (s) cm^{-1}; HRMS (FAB) Calcd for (M+) $C_{11}H_7IF_4O_2$: 373.9427, Found 373.9438. Anal. Calcd for $C_{11}H_7F_4IO_2$: C, 35.32: H, 1.89. Found: C, 35.50; H, 1.92.