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Atom-transfer Reaction of Difluoroiodoacetate

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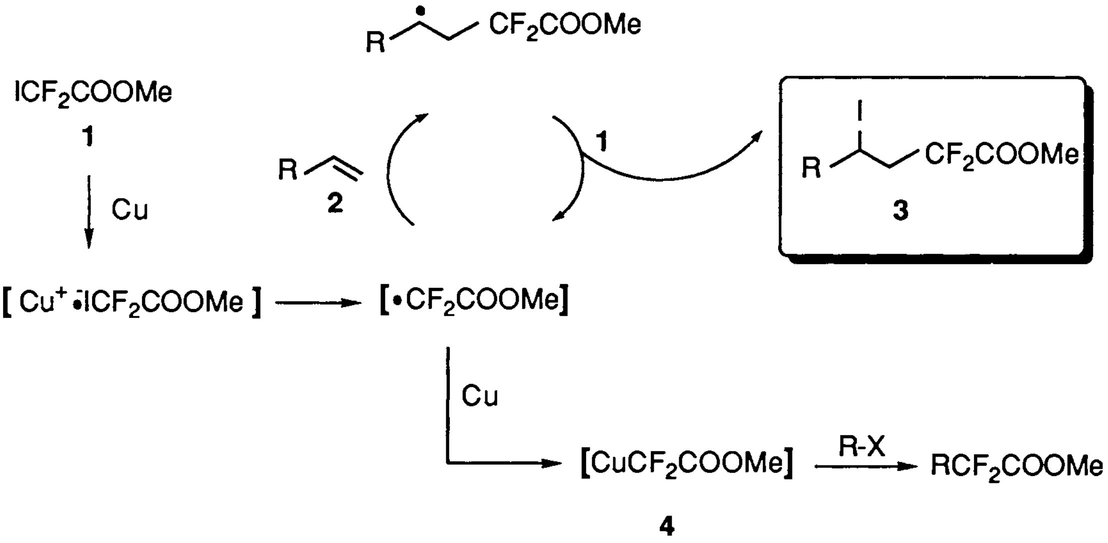
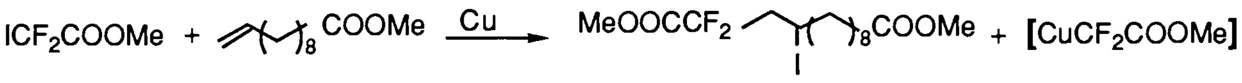
Radical chain reaction of difluoroiodoacetate with olefins catalyzed by copper provided atom-transfer products in good yields.

Fluorinated organic compounds are attracting interest due to the characteristic features of fluorine atom, particulary in the field of medicinal chemistry and material science,[1] and exploration of efficient synthetic methods has been widely required. We reported a new method for the preparation of 2,2-difluoroesters through a coupling reaction of methoxycarbonyldifluoromethylcopper (**4**), formed from methyl difluoroiodoacetate **1** and copper in aprotic polar solvent (DMF, DMSO or HMPA), with organic halides.[2] As a part of our ongoing search for new synthetic reactions using the iodide **1** in organo-fluorine chemistry, we became interested to know whether the expected intermediacy radical can be synthetically usable in atom-transfer reaction with olefins. In this paper, we report atom-transfer reaction of methyl difluoroiodoacetate (**1**) with olefins **2** catalyzed by copper giving good yields of the adduct **3**, which provides a useful process for C-C bond formation of difluoroacetate.[3]



First, we examined the reaction of the iodide **1** with the terminal olefin, methyl 9-dodecenoate (**2a**) in the presence of copper powder[4] in various solvent monitoring the reaction mixture by ^{19}F-NMR (Table 1). In DMF, reaction proceeded at room temperature and only addition product **3a** was identified and isolated in high yield (entry 1), while in HMPA a competitive formation of the copper reagent **4** to some extent was observed (entry 2).5) In nonpolar solvents such as diethyl ether or benzene, **3a** was obtained under refluxing condition in slightly lower yields than that in DMF solvent. The reaction proceeded by a catalytic amount of copper to give **3a** in 88% yield (entry 3), while the use of a slightly excess amount of the iodide **1** and copper resulted in nearly quantitative formation of **3a** (entry 4). From these results, it is concluded that single electron transfer (SET) from copper to the iodide **1** occurs under mild condition and resultant radical reacts with olefin to give the atom-transfer product in high yield, when DMF is used as the solvent.6)



1 **2a** **3a** **4**

Table 1. Solvent Effect on Cu-Catalized Atom-Transfer Reaction

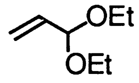
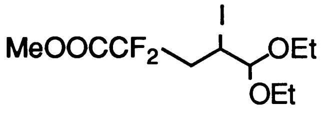
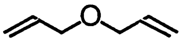
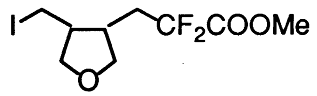
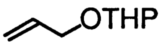
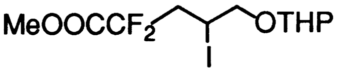
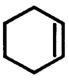
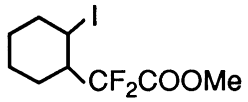
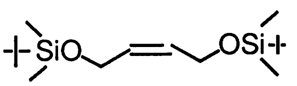
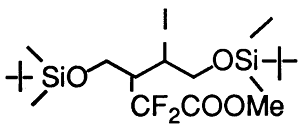
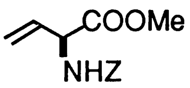
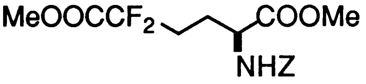
Entry	Solvent	**1** : **2a** : Cu	Temp	Time/h	**3** Yield/%[a]	**4** Yield/%[b]
1	DMF	1 : 1 : 1	rt,	6	85	—[c]
2	HMPA	1 : 1 : 1	rt,	4	75	13[d]
3	DMF	1.3 : 1 : 0.3	rt,	4	88	—
4	DMF	1.5 : 1 : 1.5	rt,	6	96	—
5	benzene	1.5 : 1 : 1.5	reflux,	24	79	—
6	ether	1.5 : 1 : 1.5	reflux,	20	87	—

a) Isolated yield. b) Determined by ^{19}F-NMR based on internal benzotrifluoride.
c) Recovery of **2a**, 7%. d) Recovery of **2a**, 18%.

Reaction of the iodide **1** with various olefins catalyzed by copper in DMF are summarized in Table 2. It is noteworthy that 1) reaction proceeds under mild conditions; 2) atom-transfer products are obtained in good yield not only with terminal olefins (entries 1-3), but also with internal ones (entries 4, 5); 3) olefins having functional group such as acetal, ester or amide can be applicable; 4) formation of the tetrahydrofuran derivative by the reaction of the iodide **1** with diallyl ether also supports that the present reaction involves a radical chain mechanism (entry 2).7)

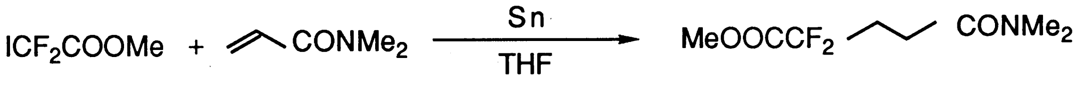
Since the atom-transfer product obtained by the reaction of **1** with vinylglycine derivative8) was labile on silica gel, the crude adduct was further treated with Zn in AcOH-Et_2O to give 5,5-difluorohomoglutamic acid derivative (entry 6).

Table 2. Cu-Catalyzed Reaction of Difluoroiodoacetate **1** with Olefins[a)]

Entry	Olefin **2**	Time /h	Product **3**	Yield/%[b)]
1		13		58
2		15		72
3		5		72
4		6		79[c)]
5		7.5		69
6		20		42[d)]

a) Solvent, DMF. b) Isolated Yield. c) trans:cis = 5:3 d) see Text.

Copper catalyzed reaction proceeded favorably with electron-rich olefins as described above, but with electron-deficient olefin such as acrylamide we obtained the iodine-free adduct **6** in 5% yield. When the reaction was conducted using Sn in THF, the adduct **6** was obtained in 40% yield.[9)]



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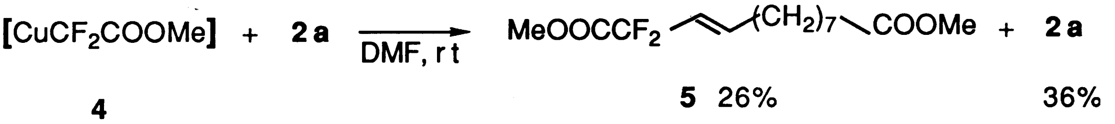
In conclution, atom-transfer reaction of difluoroiodoacetate **1** with olefins described here provides an efficient method for the preparation of functionalized molecules containing the difluoromethylene group.

We are grateful to Asahi Glass Co., for providing the iodide **1**.[2)]

References

1) R. Filler and Y. Kobayashi, "Biomedicinal Aspects of Fluorine Chemistry," Elsevier Biomedical Press and Kodansha Ltd., (1982); J. T. Welch, *Tetrahedron*, **43**, 3123 (1987).

2) T. Taguchi, O. Kitagawa, T. Morikawa, T. Nishiwaki, H. Uehara, H. Endo, and Y. Kobayashi, *Tetrahedron Lett.*, **27**, 6103 (1986); O. Kitagawa, T. Taguchi, and Y. Kobayashi, *Chem. Lett.*, **1989**, 389.
3) A part of this work was reported at the 109th Annual Meeting of the Pharmaceutical Society of Japan, Nagoya, Japan, April 1989.
4) R. Q. Brewster and T. Groening, *Org. Synth.*, Coll. Vol.II, 455(1948).
5) Q-Y. Chen, Z-Y, Yang, and Y-B. He, *J. Fluorine Chem.*, **37**, 171 (1987).
6) It is noteworthy that the reaction of the copper reagent **4**2) formed in DMF with **2a** proceeded very slowly to give the iodine-free olefinic compound **5** in 26% yield along with the recovery of the starting olefin **2a**. Moreover, the copper reagent **4** did not react with α,β-unsaturated carbonyl compounds.



7) Atom-transfer reactions of fluoroalkyl iodide with olefins were reported. For example: N. O. Brace, *J. Org. Chem.*, **31**, 2879 (1966); M. Kuroboshi and T. Ishihara, *J. Fluorine Chem.*, **39**, 299 (1988); Q-Y. Chen, Z-Y. Yang, C-X. Zhao, and Z-M. Qui, *J. Chem. Soc., Perkin Trans.* 1, **1988**, 563 and references cited therein; Z-Y. Yang and D. J. Burton, *J. Fluorine Chem.*, **45**, 4817 (1989).
8) A. Afzali-Ardakani and H. Rapoport, *J. Org. Chem.*, **45**, 4817 (1980).
9) It was found that reaction of the iodide **1** with Sn in THF produced a tin compouns as a major product (80% yield), whose structure was tentatively assigned as $I_2Sn(CF_2COOMe)_2$ from its NMR spectra and MS spectrum, [^{19}F-NMR ($CDCl_3$, benzotrifluoride as an internal standard) -37.3ppm ($^2J_{F\text{-}^{117}Sn}$=426, $^2J_{F\text{-}^{119}Sn}$=448Hz), ^{13}C-NMR ($CDCl_3$) δ 164.5 (t,$^2J_{C\text{-}F}$=24Hz,CO), 124.2 (t,$^1J_{C\text{-}F}$=308Hz,CF_2), 54.3 (s,CH_3)] along with $Sn(CF_2COOMe)_4$. These tin compounds did not react with acrylamide.
10) Aldol and related reactions of zinc reagent and 2,2-difluoroketene silyl acetal generated from the iodide **1** were reported by us. O. Kitagawa, T. Taguchi, and Y. Kobayashi, *Tetrahedron Lett.*, **29**, 1803 (1988); T. Taguchi, O. Kitagawa, Y. Suda, S. Ohkawa, A. Hashimoto, Y. Iitaka, and Y. Kobayashi, *ibid.*, **29**, 5291 (1988).

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