A Unique Chelating Effect of $Sc(OTf)_3$ to Organofluorine Compounds

Hiroshi Kajiro,† Atsunori Mori,* Yasushi Nishihara, and Tamejiro Hiyama#
Research Laboratory of Resources Utilization, Tokyo Institute of Technology, Nagatsuta, Yokohama 226-8503

(Received March 5, 1999; CL-990149)

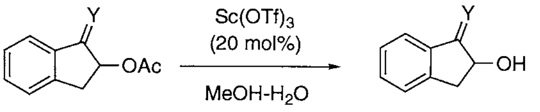
The scandium trifluoromethanesulfonate-catalyzed cleavage of acetate bearing two or three fluorine atoms at a position β to an acetoxy group proceeds exceptionally rapidly. The high efficiency of the hydrolysis is caused by a chelating effect of scandium with the fluorine atoms and an acetate moiety.

The marked effect by the introduction of fluorine atoms into an organic molecule has attracted much attention in biological and material science.[1] In particular, the interaction of a fluorine atom to a certain metal is of great interest due to the strong affinity of fluorine to the metal.[2] Hence, a proper design of chelation involving the metal-fluorine interaction, if successful, would lead to highly selective and/or facile synthetic reactions.

We herein disclose that the $Sc(OTf)_3$-catalyzed cleavage of acetate that bears a neighboring fluorine atom is accelerated by the chelating effect. The interaction of a fluorine atom with several main group metallic species such as lithium and aluminum is proposed;[2] however, the chelation of rare earth metals involving fluorine atom has not yet been designed.

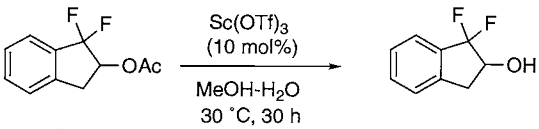
We recently reported the $Sc(OTf)_3$-catalyzed hydrolysis of esters, in which an oxo- or methoxy group adjacent to the ester group played a significant role for the rapid and selective reactions.[3-5] For example, the reaction of 2-acetoxyindanone (**1**) catalyzed by $Sc(OTf)_3$ proceeded much faster than that of 2-acetoxyindan (**2**) as shown in Eq. 1. Therefore, the cleavage of an ester neighboring to fluorine has turned to our further interest.

The reaction of 1,1-difluoro-2-acetoxyindan (**3**) was performed in the presence of 10 mol% of $Sc(OTf)_3$ in aqueous methanol at 30 °C for 30 h to furnish 1,1-difuluoro-2-hydroxyindan (**4**) in 93% yield (Eq. 2).



(1)

1: 95% (Y=O)
2: 21% ($Y=H_2$)



(2)

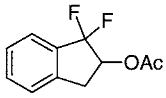
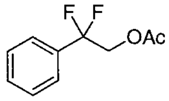
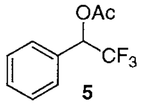
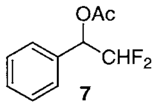
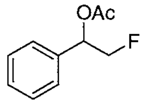
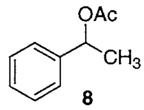
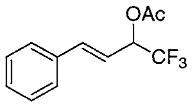
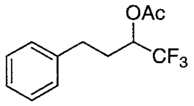
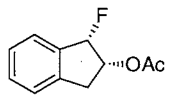
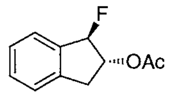
3

4 (93%)

Since the scandium-catalyzed reaction of **3** is found much faster than that of **2**, the result suggests that the neighboring fluorine facilitates the reaction. It should also be noted that the fluorine effect appears to be comparable to the carbonyl effect as observed in the reaction of **1**.

The similar reaction also proceeded with several esters bearing fluorine atom(s). As summarized in Table 1, a variety of acetates that bear fluorine atom(s) at a position β to the acetoxy

Table 1. $Sc(OTf)_3$ catalyzed cleavage of fluoro acetates[a]

Entry	Substrate	Time/h	Yield/%[b]
1	 **3**	30	93
2		5	82
3	 **5**	8 28 30	76[c] 97[c] 89
4	 **7**	8 28 48	56[c] 84[c] 90
5		8 28 48	25[c] 48[c] 57[c]
6	 **8**	48	21
7		20	91
8		46	86
9[d]		48	36[c, e]
10[d]		48	29[c, e]

[a] The reactions were carried out using 10 mol% of $Sc(OTf)_3$ at 30 °C in $MeOH-H_2O$ (4:1) unless otherwise noted. [b] Isolated yield unless otherwise noted. [c] HPLC yield. [d] *cis/trans*-Stereochemistry was not assigned. [e] Consumption of the starting material.

group was examined. The scandium-catalyzed cleavage of difluoro- or trifluoroalkoxy acetates proceeded highly efficiently to furnish the corresponding alcohol in excellent yields, whereas the monofluoro ester (entry 5) was found to be less effective as well as the non-fluorinated one (entry 6). In addition, the reactions using the diastereomer of the monofluorinated derivatives of 2-acetoxyindan, whose relative stereochemistries were not assigned (entries 9 and 10), resulted in giving the corresponding products in 36% and 29% yield, respectively. The results suggest that a single sterically preferred fluorine atom does not facilitate the scandium-catalyzed reaction but geminal two fluorine atoms, at least, at the β-position seem to be a requisite for the efficient cleavage.[2b]

Subsequently, the observed rapid reaction appears to be specific in the use of $Sc(OTf)_3$ as a catalyst, while such rate enhancement was not observed in the Brønsted acid-catalyzed hydrolysis of **5** under similar conditions. Figure 1 shows the results of time-conversion curve from **5** to **6** catalyzed by $Sc(OTf)_3$ and trifluoromethanesulfonic acid (TfOH). In contrast with the increasing conversion by the catalysis of the scandium, the reaction in the presence of 10 mol% of TfOH proceeded in only 5% after 48 h.[6] The results indicate that the rate enhancement of hydrolysis is not due to the electron-withdrawing nature of a fluorine atom. Taken together with the result that the $Sc(OTf)_3$-catalyzed reaction of non-fluorinated acetate **7** (Table 1, entry 6) is sluggish, we may conclude that the fluorine effect in the cleavage of acetates is specifically observed in the scandium-catalyzed reactions.

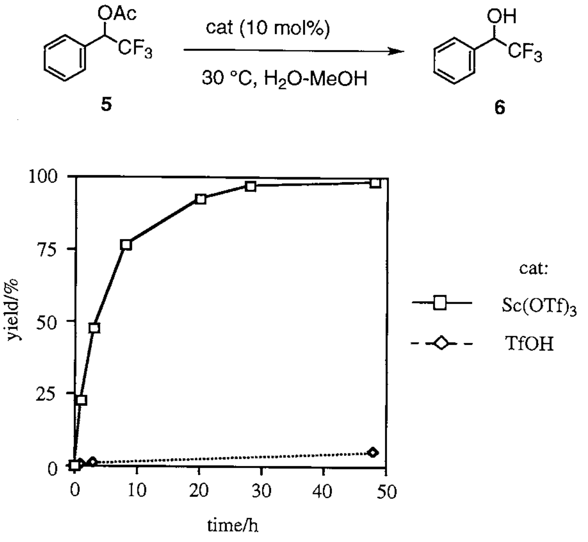


Figure 1. Time course of deacetylation of **5** catalyzed by $Sc(OTf)_3$ or TfOH.

Thus, we consider that strong chelation of the scandium would facilitate the reaction. Furthermore, the concept could also be applied to a variety of $Sc(OTf)_3$-catalyzed synthetic reactions[5] as well as the present deacetylation.

The experimental procedure is representative for the deacetylation of 1,1-difluoro-2-acetoxyindan (**3**): To a solution of $Sc(OTf)_3$ (25 mg, 50 μmol) in methanol-water (4:1 v/v, 5 mL) was added **3** (106 mg, 0.50 mmol) at 30 °C for 30 h. The reaction mixture was poured into water and extracted with ether. The organic layer was dried over anhydrous magnesium sulfate and concentrated in vacuo to leave a crude oil. Purification by column chromatography on silica gel (hexane : EtOAc = 3 : 1, R_f = 0.5) afforded 79 mg of **4** (93%) as a colorless solid. Mp 46.0-47.5 °C; IR (KBr) 3351, 1619, 1470, 1321, 1304, 1275, 1233, 1169, 1059, 982, 926, 762 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 2.32 (br.s, 1 H, OH), 2.86-2.93 (m, 1 H, CH_2), 3.35 (dd, J = 7.0, 16.0 Hz, 1 H, CH_2), 4.51-4.61 (m, 1 H, C$\underline{H}$OH), 7.26-7.29 (m, 1 H, ArH), 7.35 (t, J = 7.5 Hz, 1 H, ArH), 7.43-7.48 (m, 1 H, ArH), 7.55-7.58 (m, 1 H, ArH); ^{13}C NMR (75.5 MHz, $CDCl_3$): _ = 140.04 (t, J = 7.5 Hz), 134.11 (t, J = 26.0 Hz), 131.89, 127.72 (t, J = 1.5 Hz), 125.65 (t, J = 125.0 Hz), 125.60, 123.60, 74.82 (dd, J = 22.0, 28.0 Hz), 36.59; ^{19}F NMR (188 MHz, $CDCl_3$): δ = -103.33 (dd, J = 13.5, 250.5 Hz), -108.08 (dd, J = 7.0, 250.5 Hz); HRMS (EI) found [M^+]:170.0547; calcd for $C_9H_8F_2O$: 170.0543.

References and Notes

† On leave from Nippon Steel Corporation, Kawasaki.

Present address: Department of Material Chemistry, Graduate School of Engineering, Kyoto University, Yoshida, Kyoto 606-8501.

1 a) R. Filler and Y. Kobayashi, "Biomedical Aspects of Fluorine Chemistry," Kodansha, Tokyo (1982). b) R. E. Banks, "Preparation, Properties, and Industrial Applications of Organofluorine Compounds," Wiley, New York (1982). c) T. A. O'Donnell, "The Chemistry of Fluorine," Pergamon, Oxford (1975).

2 a) T. Ooi, Y. Kondo, K. Kon-i, and K. Maruoka, *Chem. Lett.*, **1998**, 403. b) C.-P. Quian and T. Nakai, *J. Am. Chem. Soc.*, **112**, 4602 (1990). c) T. Ooi, M. Furuya, and K. Maruoka, *Chem. Lett.*, **1998**, 817. d) T. Ooi, N. Kagoshima, and K. Maruoka, *J. Am. Chem. Soc.*, **119**, 5754 (1997). e) G. H. Posner and S. R. Haines, *Tetrahedron Lett.*, **26**, 1823 (1985). f) T. Hanamoto and T. Fuchikami, *J. Org. Chem.*, **55**, 4969 (1990). g) K. C. Nicolaou, R. E. Dolle, A. Chucholowski, and J. L. Randall, *J. Chem. Soc., Chem. Commun.*, **1984**, 1153. For reviews: h) H. Pletino, *Chem. Rev.*, **97**, 3363 (1997). i) E. F. Murphy, R. Murugavel, and H. W. Roesky, *Chem. Rev.*, **97**, 3425 (1997). j) T. Yamazaki and T. Kitazume, *J. Synth. Org. Chem. Jpn.*, **54**, 665 (1996). k) J. W. Smith in "The Chemistry of the Carbon-Halogen Bond Part I," ed by S. Patai, Wiley, New York (1973), pp. 292-297, and references therein.

3 a) H. Kajiro, S. Mitamura, A. Mori, and T. Hiyama, *Synlett*, **1998**, 51. b) H. Kajiro, S. Mitamura, A. Mori, and T. Hiyama, *Tetrahedron Lett.* **40**, 1689, (1999).

4 a) B. K. Shull, T. Sakai, and M. Koreeda, *J. Am. Chem. Soc.*, **118**, 11690 (1996). b) K. Ishihara, M. Kubota, H. Kurihara, and H. Yamamoto, *J. Org. Chem.*, **61**, 4560 (1996). c) R. Yanada, N. Negoro, K. Bessho, and K. Yanada, *Synlett*, **1995**, 1261. d) M. Yashiro, T. Takarada, S. Miyama, and M. Komiyama, *J. Chem. Soc., Chem. Commun.*, **1994**, 1757. e) J. Inanaga, Y. Yokoyama, and T. Hanamoto, *J. Chem. Soc., Chem. Commun.*, **1993**, 1090. f) M. Komiyama, K. Matsumura, and Y. Matsumoto, *J. Chem. Soc., Chem. Commun.*, **1992**, 640, and references therein.

5 For reviews: a) R. W. Marshman, *Aldrichimica Acta*, **28**, 77 (1995). b) S. Kobayashi, *Eur. J. Org. Chem.*, **1999**, 15.

6 The reaction catalyzed by 10 mol% of H_2SO_4 was also sluggish; 5% yield after 48 h.