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Determination of the absolute configuration of partly fluorinated allylic alcohols; the first synthesis of optically pure 1,2-difluoroallylic alcohols

Yumiko Takagi,[a,*] Takiko Nakatani,[a] Toshiyuki Itoh[b,*] and Toshiyuki Oshiki[c,*]

[a]*Department of Natural Science, Hyogo University of Teacher Education, Yashiro, Hyogo 673-1494, Japan*
[b]*Department of Chemistry, Faculty of Education, Okayama University, Okayama 700-8530, Japan*
[c]*Department of Applied Chemistry, Faculty of Engineering, Okayama University, Okayama 700-8530, Japan*

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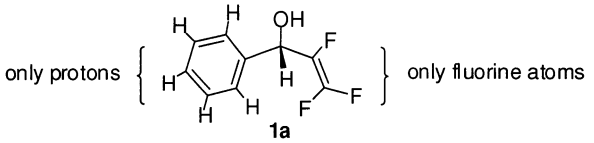
Abstract

Optically active 1,1,2-trifluoro- or 1,2-difluoroallylic alcohols were prepared via a lipase-catalyzed reaction and their absolute configuration was determined by an X-ray crystallographic analysis of the corresponding ferrocene ester along with the refined Mosher method (the Kusumi–Ohtani method).

Keywords: fluorinated allylic alcohol; absolute configuration determination; refined Mosher method; X-ray crystallographic analysis.

Substitution of the fluorine atoms on organic molecules is expected to alter both the chemical reactivity and biological activity due to the strong electron-withdrawing nature of fluorine.[1] We recently reported the preparation of novel 1,1,2-trifluoroallylic alcohols in optically pure form via a lipase-catalyzed reaction[2] and tentatively assigned their absolute configuration by using the refined Mosher method, which is known as the Kusumi–Ohtani method.[3] It was established that this method is applicable for many types of secondary alcohols in which the absolute configuration of the chiral center was determined by comparing the $\Delta\delta$ values of the protons on the molecules. However, our compound, such as (*S*)-1-phenyl-2,3,3-trifluoroprop-2-en-1-ol (**1a**), possesses only protons on the left side and only fluorine atoms at the right side of the molecular frame between the stereo center. There has been no published report to apply the Kusumi–Ohtani method to the determination of the absolute configuration of such types of compound.[3]



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* Corresponding authors. Tel: +81-795-44-2200; e-mail: ytakagi@sci.hyogo-u.ac.jp

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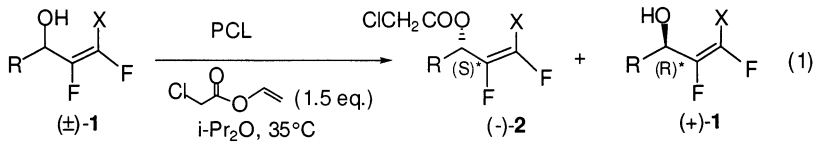
Herein we report that the syntheses of optically active 1,1,2-trifluoro- and 1,2-difluoroallylic alcohols have been accomplished through a lipase-catalyzed reaction and their absolute configuration determined by X-ray crystallographic analysis along with the Kusumi–Ohtani method.

Optically active 1,1,2-trifluoroallylic alcohols[4] and 1,2-difluoroallylic alcohols[5] were prepared by a lipase-catalyzed reaction (Table 1).[2,6] Excellent enantioselectivity was observed for all substrates and high E values[7] were recorded, though it required a longer time for the reactions of the 1,2-difluoroallylic alcohols **1b**[5] and **1d** (entries 2 and 4) than those of the 1,1,2-trifluroallylic alcohols **1a**[2] and **1c**[2] (entries 1 and 3). It was assumed that PCL catalyzed the acylation of these four types of alcohols, **1a**–**d**, with the same enantio-favoritism based on the results of the capillary GC analysis.[6] The absolute configuration of (–)-**2a**, which was obtained by PCL-catalyzed *trans*-acylation, was determined by X-ray crystallographic analysis of the corresponding ferrocenyl ester **4a**. Ester (–)-**2a** (95% ee) was hydrolyzed by LiOH to lead (–)-**1a**, which was then converted to the crystalline ferrocenyl ester **4a** in 87% yield; suitable crystals of **4a** for X-ray analysis were obtained by recrystallization from a mixed solvent of ether and hexane. The ORTEP diagram is shown in Fig. 1. *Flack parameter shows –0.01(2) and the absolute configuration of* ***4a*** *has been determined to be* (*S*).[8,9]

Table 1
Results of PCL-catalyzed *trans*-esterification of fluorinated allylic alcohols (±)-**1**



Entry	R	X	Time (h)	%conv.	%ee of 2 (%yield)[a]	E[7]	Relative rate[b]	$[\alpha]_D$ of **1** (c ca. 1)
1	Ph	F	22	33	95 (32)	62	1.5	+30 (>99% ee)
2	Ph	H	128	23	99 (23)	265	0.18	+4.3 (>99% ee)
3	$PhCH_2CH_2$	F	36	29	97 (24)	99	0.81	+15 (91% ee)
4	$PhCH_2CH_2$	H	63	36	98 (27)	170	0.57	+5.3 (>99% ee)

[a] Isolated yield.
[b] %conv./time (h).

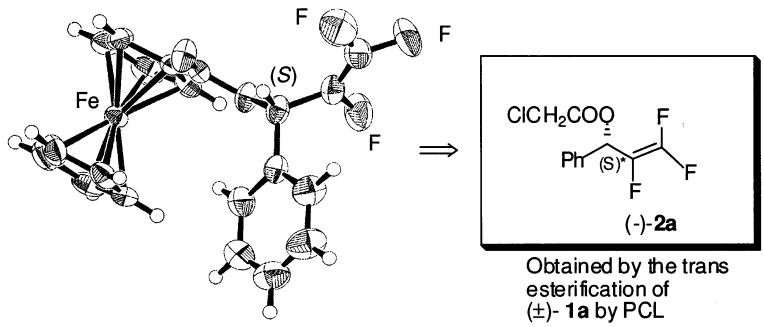


Figure 1. ORTEP view of 1-phenyl-2,3,3-trifluoroprop-2-en-1-yl ferrocenecarboxylate (**4a**)

We then tried to determine the absolute configuration of these optically active compounds by the Kusumi–Ohtani method. The produced acetates, (−)-**2a–d**, and the unreacted alcohols, (+)-**1a–d**, were converted to the corresponding (*S*)-α-methoxy-α-trifluoro-α-phenylacetates (MTPA) and (*R*)-MTPA esters **3**, respectively. The $\Delta\delta$ values for the protons were calculated from the results of the 500 MHz ^{1}H NMR analyses, and those for the fluorine atoms were calculated from the 188 MHz ^{19}F NMR analyses. All the products, (−)-**2a–d**, which were obtained by the lipase-catalyzed reaction were assigned to be (*S*) by the Kusumi–Ohtani rule (Fig. 2).[3] Although a single exception was found for compounds (*S*)-**3b** and (*R*)-**3b**, in which both the $\Delta\delta$ values for the 1-protons showed opposite signs suggested by the Kusumi–Ohtani rule (see the underlined part). However, this exception might be ruled out because these $\Delta\delta$ values were too small to apply the rule by comparing with other signals. It was thus confirmed that the results of the Kusumi–Ohtani method for (−)-**2a** definitely agreed with the X-ray crystallographic analysis.

In conclusion, new types of partly fluorinated allylic alcohols were synthesized in an optically active form via the lipase-catalyzed reaction and their absolute configuration was determined by X-ray crystallographic analysis and the Kusumi–Ohtani method. This is not only the first synthesis of 1,2-difluoroallylic alcohols in optically active form, but also the first example to

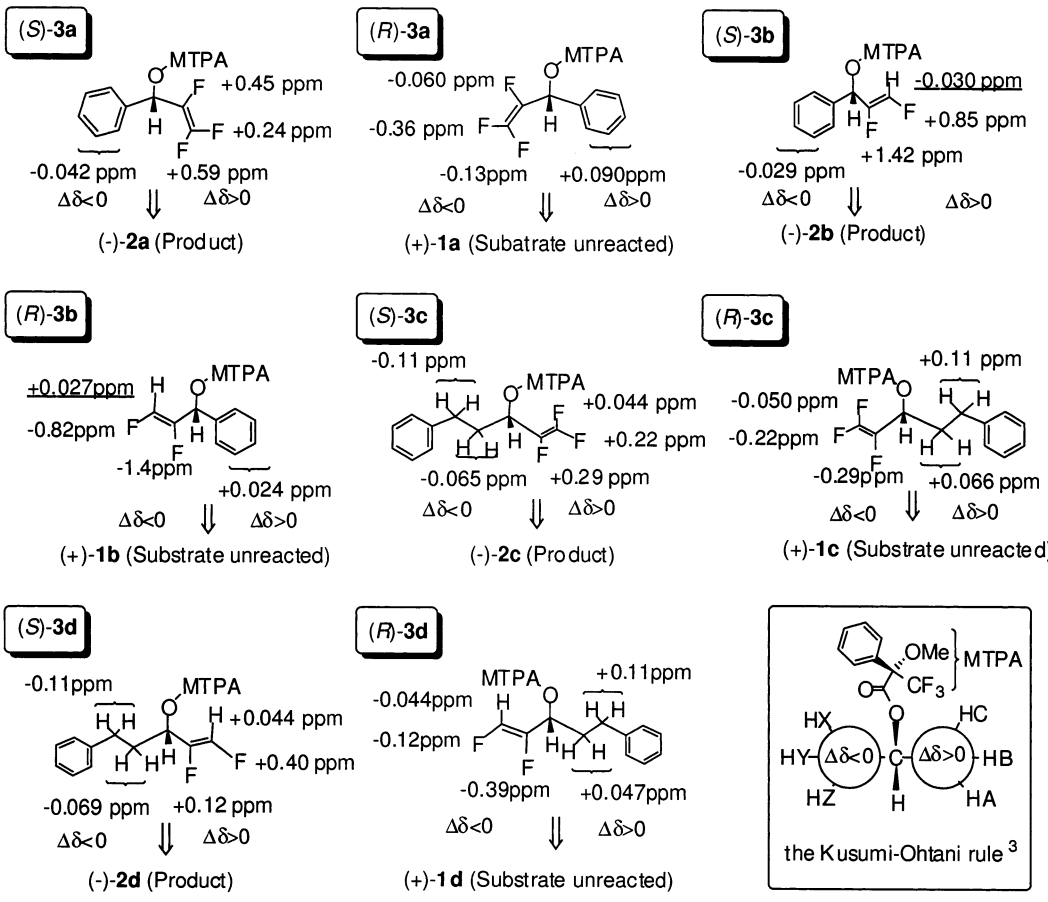


Figure 2. Determination of the absolute configuration of **3a–d** by the Kusumi–Ohtani rule. $\Delta\delta = (\delta S - \delta R)$ were calculated by the results for (*R*)- and (*S*)-MTPA esters of 500 MHz ^{1}H- and 188 MHz ^{19}F NMR analysis

verify the Kusumi–Ohtani rule in which the method is applicable to partly fluorinated molecules, such as 1,2,2-trifluoroallylic alcohols.

Acknowledgements

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2. Takagi, Y.; Kashiwagi, M.; Kihara, H.; Itoh, T. *Tetrahedron Lett.* **1999**, *40*, 2801.
3. Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092. Generally, this rule is applied to compounds that possess the same nuclear species in the vicinity of the stereo center, because the response of magnetic anisotropy depends on the nuclides.
4. Racemic 2,2,3-trifluoroalk-2-en-1-ols, **1a** and **1c**, were synthesized according to Percy's method; Patel, S. T.; Percy, J. M.; Wilkes, R. D. *Tetrahedron* **1995**, *51*, 9201.
5. Racemic alcohols, **1b** and **1d**, were synthesized according to the method of Funabiki et al.; Funabiki, K.; Fukushima, Y.; Inagaki, T.; Murata, E.; Matsui, M.; Shibata, K. *Tetrahedron Lett.* **1998**, *39*, 1913. These compounds were so unstable under distillation that they were immediately subjected to the lipase-catalyzed reaction after simple purification by silica gel flash column chromatography. 5-Phenyl-1,2-difluoropent-1-en-3-ol (**1d**): R_f 0.6 (hexane/ethyl acetate = 3:1); ^{1}H NMR (200 MHz, $CDCl_3$, δ) 1.69 (1H, s, OH), 1.96 (2H, q, J = 7.5), 2.67 (2H, dt, J = 8.8, 6.6 Hz), 3.97 (1H, ddt, J = 19.1, 6.8, 1.7 Hz), 6.34 (1H, dd, J = 72.6, 17.7 Hz), 7.10–7.27 (5H, m); ^{13}C NMR (50 MHz, $CDCl_3$, ppm) 31.29, 34.64 (d, J_{C-F} = 2.3 Hz), 66.84 (dd, J_{C-F} = 24.5, J_{C-F} = 2.0 Hz), 126.20, 128.40, 128.54, 131.67, 134.34 (dd, J_{C-F} = 257.3, J_{C-F} = 6.0 Hz); ^{19}F NMR (188 MHz, $CDCl_3$, C_6F_6) −3.03 (1F, dd, J = 72.74, 10.0 Hz); IR (neat, cm^{-1}) 3300, 2900, 1720, 1600, 1490, 1440, 1320, 1190, 1110, 1000 and 860.
6. Typically the enzymatic reaction was performed as follows; to a mixture of *Pseudomonas cepacia* lipase (PCL) (50 wt.% towards the substrate) was added 2.5 ml of diisopropyl ether (i-Pr_2O), a solution of racemic alcohol (±)-**1** (0.5 mmol) and vinyl chloroacetate (1.5 equiv.) as acyl donor and the resulting mixture was stirred at 35°C. Because separation of two enantiomers was insufficient for chloroacetate **2** or alcohol **1** by capillary GC analysis using a chiral column (Chiraldex G-TA), the enantiomeric excess of the produced chloroacetate (−)-**2** and the remaining alcohol (+)-**1** was determined as for acetates **5**.[2] Retention times on GC analyses of acetates, **5a**–**d**, are summarized as follows: Chiraldex G-Ta, ϕ 0.25 mm×20 m, carrier gas: He 40 ml/min. 100°C, inlet pressure: 1.35 kg/cm^2, amount 400 ng, detection: FID; **5a**: R$t_{(R)}$ = 8.97 min, R$t_{(S)}$ = 10.0 min (80°C); **5b**: R$t_{(S)}$ = 20.9 min, R$t_{(R)}$ = 24.8 min (80°C); **5c**: R$t_{(S)}$ = 16.2 min., R$t_{(R)}$ = 17.4 min (100°C); **5d**: R$t_{(S)}$ = 20.1 min, R$t_{(R)}$ = 24.6 min (100°C). Here, **5a** was derived from **2a** or **1a**, **5b** was from **2b** or **1b**, **5c** was from **2c** or **1c** and **5d** was from **2d** or **1d**, respectively.
7. Chen, C.-S.; Fujimoto, Y.; Girdauskas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1982**, *102*, 7294.
8. Initially, we synthesized the naproxen ester **4b** and *p*-bromobenzoate **4c** and attempted to recrystallize it using various solvent systems. However, all our efforts to obtain good crystals of **4b** and **4c** suitable for X-ray analysis proved unsuccessful.
9. Crystal and refinement data: $C_{20}H_{15}F_3FeO_2$, monoclinic, space group $P21$ (#4) a = 7.572(3), b = 10.577(3), c = 10.667(3) Å, β = 92.002(3)°, V = 853.7(4), Z = 2, fw = 400.18, D_{calcd} = 1.56 g/cm^3, Mo Kα, u = 9.2 cm^{-1}, 4446 reflections measured, 2068 were unique (R_{int} = 0.022), R (all data) = 0.087, wR_2 (all data) = 0.101, reflection parameter ratio = 18.78, GOF = 1.12. Measurements were made on a Rigaku AFC5R diffractometer at the X-ray Laboratory of Okayama University. Crystallographic calculations were performed on SGI workstation at Venture Business Laboratory, Graduate School of Okayama University. Crystallographic data have been deposited with the Cambridge Crystallographic Center.

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