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Different Stereochemistry for the Reduction of Trifluoromethyl Ketones and Methyl Ketones Catalyzed by Alcohol Dehydrogenase from *Geotrichum*

Kaoru Nakamura,*[†] Tomoko Matsuda,[†] Toshiyuki Itoh[††] and Atsuyoshi Ohno[†]

[†] Institute for Chemical Research, Kyoto University, Uji, Kyoto 611, Japan

[††] Department of Chemistry, Faculty of Education, Okayama University, Okayama 700, Japan

Abstract: Reduction of trifluoromethyl ketones by a crude alcohol dehydrogenase from *Geotrichum* affords (*S*)-trifluoromethyl carbinols in excellent ee, whereas the reduction of methyl ketones gives the corresponding alcohols of the opposite configuration in excellent ee.

Optically pure trifluoroalkanols are of great value due to their potential use as ferroelectric liquid crystals,[1] drugs, and tools for metabolic studies.[2] To synthesize chiral fluorinated compounds, chemical[3] and biological[4-6] methods have been developed. For example, yeast reduction of fluoroketones affords the corresponding alcohols in moderate ee.[7,8]

Previously, we found that[9] reduction of methyl ketones by a crude alcohol dehydrogenase (acetone powder) from *Geotrichum candidum* IFO4597 (APG4 system) gives remarkable results. Its advantages are perfect enantioselectivity, easy preparation of the crude enzyme, preservability of the enzyme, recycling of the coenzyme with easily available alcohols and easy experimental operation. Now, we report here the reduction of trifluoromethyl ketones and the corresponding unfluorinated derivatives by the APG4 system.

When 2,2,2-trifluoroacetophenone (**1Fa**) was subjected to the reduction with the APG4 system, the corresponding alcohol, 2,2,2-trifluoro-1-phenylethanol (**2Fa**), was obtained in 98% ee with >99% chemical yield. The absolute configuration of the product was determined to be *S* by comparison of its optical rotational value[10] with the literature value.[11] We have reported that the reduction of acetophenone (**1Ha**), unfluorinated analogue, with the APG4 system affords the corresponding (*S*)-1-phenylethanol ((*S*)-**2Ha**) in excellent ee.[9] Surprisingly, different configurational alcohols were obtained by subjecting the trifluorinated ketone and its unfluorinated analogue to the same reduction system as shown in the scheme. (The absolute configuration of (*S*)-**2Fa** and (*S*)-**2Ha** are opposite according to definition.)

Scheme

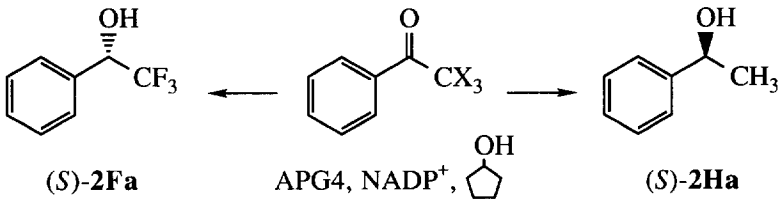


Table 1 shows the results from the reduction of **1Fa** by the APG4 system. According to our previous report,[9] the system for reduction of methyl ketones requires a catalytic amount of a coenzyme which can be recycled by adding excess amount of 2-propanol or cyclopentanol (reducing agent) to the system. Similarly, the reduction of **1Fa** also requires a catalytic amount of a coenzyme and a reducing agent. Combination of $NADP^+$ and cyclopentanol as a coenzyme and a reducing agent, respectively, affords the best result, although the enzyme can also use NAD^+ and 2-propanol as a coenzyme and a reducing agent, respectively.

Table 1. Reduction of 2,2,2-Trifluoroacetophenone (**1Fa**)[a] by APG4[b]

Coenzyme[c]	Reducing Agent[d]	Yield[e] / %	Ee[e] / % (Config.)
none	none	1	81(*S*)
NAD^+	none	4	90(*S*)
none	2-propanol	7	77(*S*)
NAD^+	2-propanol	87	83(*S*)
$NADP^+$	2-propanol	72	87(*S*)
NAD^+	cyclopentanol	96	97(*S*)
$NADP^+$	cyclopentanol	90	98(*S*)
$NADP^+$	cyclopentanol	>99[f]	98(*S*)[f]

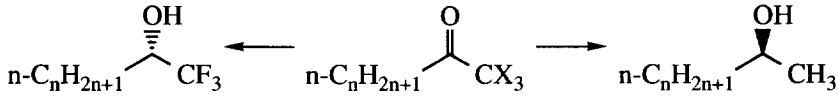
[a] 0.08 mmol. [b] 20 mg. [c] 6 μmol. [d] 50 μL. [e] after 11h. [f] after 23h.

As shown in Table 2, the reduction of other 1,1,1-trifluoro-2-alkanones also gave excellent results. As expected from the difference in the stereochemical course between the reductions of **1Fa** and **1Ha**, the stereochemical course of the reduction of fluorinated compounds is opposite to that of the unfluorinated compounds. For example, the reduction of 1,1,1-trifluoro-2-decanone (**1Fd**) yields (*S*)-1,1,1-trifluoro-2-decanol (**2Fd**) in >99% ee, whereas the reduction of 2-decanone (**1Hd**), the corresponding unfluorinated analogue, yields (*S*)-2-decanol (**2Hd**) also in >99% ee.

Table 2. Reduction of 1,1,1-trifluoro-2-alkanones and 2-alkanones[a]

Trifluoro Substrate	Yield %	ee % (Config.[b])	Unfluorinated Substrate	Yield %	ee % (Config.)
1Fb	>99	96(*S*)	**1Hb**	97	98(*S*)
1Fc	>99	96(*S*)	**1Hc**	88	>99(*S*)
1Fd	>99	>99(*S*)	**1Hd**	87	>99(*S*)
1Fe	>99	98(*S*)	**1He**	84	>99(*S*)

[a] The reaction conditions are described in references and notes.[12]
[b] The absolute configurations were determined by comparison of the GC retention times with those of authentic samples.[6]



(*S*)-**2F** **1** (*S*)-**2H**

2Fb: n=6 **1Fb**: X=F, n=6 **1Hb**: X=H, n=6 **2Hb**: n=6
2Fc: n=7 **1Fc**: X=F, n=7 **1Hc**: X=H, n=7 **2Hc**: n=7
2Fd: n=8 **1Fd**: X=F, n=8 **1Hd**: X=H, n=8 **2Hd**: n=8
2Fe: n=9 **1Fe**: X=F, n=9 **1He**: X=H, n=9 **2He**: n=9

Our finding that the reduction of trifluoromethyl ketones takes place through a completely different stereochemical course from that of the corresponding unfluorinated analogues is indeed noteworthy, but the mechanism of this intriguing stereochemical consequence is not clear at present. There are three plausible explanations for this phenomenon. Firstly, the bulkiness of the trifluoromethyl group affects the stereochemical course of the reduction. The trifluoromethyl group may be recognized by the enzyme as a bulky substituent, since the effective radius[13] of a trifluoromethyl moiety (2.2 Å) is similar to that of an isopropyl moiety (2.2 Å), which is larger than a phenyl moiety (1.62 Å). Secondly, the electronic property of the trifluoromethyl moiety may change the stereochemistry of the reduction. Thirdly, there may exist several dehydrogenases participating in the reduction, and the substrates of different property (trifluoromethyl ketones and methyl ketones) may use different enzymes.

In conclusion, we present here highly stereoselective reduction of ketones by a crude alcohol dehydrogenase(s) from *Geotrichum candidum*. Since the experimental operation is facile, and the enzyme(s) can be stored for more than two years, we believe that the present method is very useful for asymmetric reduction of trifluoromethyl ketones. Isolation of the dehydrogenase(s), investigation of steric and electric effects of the fluorinated compounds in the enzymatic reactions and application of the system to a wide variety of substrates are in progress in our laboratories.

Acknowledgement

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References and Notes

1. Nohira, H. *J. Synth. Org. Chem. Jpn.* **1991**, 49, 467-474.
2. Tanaka, Y.; DeLuca, H. F.; Kobayashi, Y.; Ikekawa, N. *Arch. Biochem. Biophys.* **1984**, 229, 348-354.
3. Ojima, I.; Kato, K.; Nakahashi, K.; Fuchikami, T.; Fujita, M. *J. Org. Chem.* **1989**, 54, 4551-4522.
4. Yamazaki, T.; Okamura, N.; Kitazume, T. *Tetrahedron: Asymm.* **1990**, 1, 521-524.
5. Fujisawa, T.; Ichikawa, K.; Shimizu, M. *Tetrahedron: Asymm.* **1993**, 4, 1237-1240.
6. Hamada, H.; Shiromoto, M.; Funahashi, M.; Itoh, T.; Nakamura, K. *J. Org. Chem.* **1996**, 61, 2332-2336.
7. Servi, S. *Synthesis*, **1990**, 1-25.
8. Csuk, R.; Glänzer, B. I. *Chem. Rev.* **1991**, 91, 49-97.
9. Nakamura, K.; Kitano, K.; Matsuda, T.; Ohno, A. *Tetrahedron Lett.* **1996**, 37, 1629-1632.
10. The acetone powder of *Geotrichum candidum* IFO4597(APG4) was prepared as follows. The cells were mixed with cold acetone (-20 °C), and the resulting suspension was filtered. The procedure was repeated three times, then the powder was dried under reduced pressure. On a preparative scale, **1Fa** (1.18 mmol, 205 mg), cyclopentanol (1.0 mL), $NADP^+$ (100 mg) and APG4 (400 mg) were added to 60 ml of MES (2-(*N*-morpholino)ethanesulfonic acid) buffer (0.1 M, pH=7.0). The mixture was stirred at room temperature for 16 h under an argon atmosphere in the dark, and filtered through Extrelut which was washed with ether. The filtrate was extracted with ether, and the combined ether solution was concentrated under reduced pressure. The yield and ee were determined to be 99% and 98% (*S*), respectively, from GC analysis (G-TA, 0.25 mm x 40 m, He: 2 mL/min). The crude product was purified by silica gel column chromatography (eluent, hexane : ethyl acetate = 2 : 1), and distillation by a Kugelrohr apparatus (110°C/17mmHg), giving (*S*)-**2Fa** (175 mg, 84%): $[\alpha]_D^{24}$ +25.1°(*c* 0.81, CCl_4)(ref[11] $[\alpha]_D^{20}$-25.1°, (*c* 3, CCl_4) >99% ee(*R*)). ^1H NMR d 2.63 (*d*, 1H, OH, *J* = 4.6 Hz), 5.02 (*dq*, 1H, CH, *J* (*d*)= 4.5 Hz, *J* (*q*)= 6.8 Hz) and 7.37-7.59 (*m*, 5H, Ph). Anal. Calcd. for $C_8H_7OF_3$: C, 54.55; H, 4.01%. Found: C, 54.24%; H, 4.09%.
11. Holzwarth, G.; Hsu, E. C.; Mosher, H. S.; Faulkner, T. R.; Moscowitz, A. *J. Am. Chem. Soc.* **1974**, 96, 251-252.
12. In a typical experiment, a ketone (0.08 mmol), NAD^+ (6 μmol) and cyclopentanol (50 μL) were added to a suspension of APG4 (20 mg) in MES buffer (pH 7.0, 0.1 M, 3 mL). The mixture was shaken at 130 rpm at 30 °C for 20h, and the mixture was put on Extrelut and eluted with ether. Chemical yield and ee were determined by GC analyses.
13. Bott, G.; Field, L.; Sternhell, S. *J. Am. Chem. Soc.* **1980**, 102, 5618-5626.

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