Pergamon

Tetrahedron Letters 41 (2000) 4603–4607

TETRAHEDRON LETTERS

Enantioselective synthesis of 1,1,1-trifluoroalkan-2-ols by ruthenium-catalyzed hydrogenation

Yoshichika Kuroki, Daisuke Asada, Yuko Sakamaki and Katsuhiko Iseki*

MEC Laboratory, Daikin Industries, Ltd., Miyukigaoka, Tsukuba, Ibaraki 305-0841, Japan

Received 22 March 2000; accepted 14 April 2000

Abstract

The highly enantioselective synthesis of 1,1,1-trifluoroalkan-2-ols has been achieved by hydrogenating 1,1,1-trifluoroalkan-2-one enol acetates in the presence of chiral ruthenium catalysts. An enol acetate, 2-acetoxy-3,3,3-trifluoro-1-(phenylthio)propene, can be successfully transformed into enantiomerically pure trifluorolactic acid.

Keywords: asymmetric synthesis; catalysts; fluorine and compounds; hydrogenation.

The catalytic asymmetric synthesis of chiral fluoroorganic compounds has played an important role in the development of medicines and materials in consideration of the influence of fluorine's unique properties.[1] Homochiral α-trifluoromethyl alcohols are versatile intermediates for the synthesis of anti-ferroelectric liquid crystalline molecules.[2] A variety of asymmetric catalyses for preparing the alcohols have been reported.[3–7] However, their synthesis has drawbacks such as insufficient levels of enantioselectivity, low catalytic efficiencies and limited scope of the substrates. This paper discloses herein the catalytic asymmetric hydrogenation of 1,1,1-trifluoroalkan-2-one enol acetates (**1**) catalyzed by ruthenium–chiral ligand complexes to provide 1,1,1-trifluoroalkan-2-ol acetates (**2**) with high enantioselectivity.

The enol acetate **1** was prepared in yields greater than 90% by treatment of 1,1,1-trifluoroalkan-2-one (**3**) with acetic anhydride and pyridine at room temperature. The NOE observation between the fluorine atoms and the olefinic proton H-3 disclosed that the (*Z*)-olefin **1** was obtained as the sole product (Fig. 1).[8]

The asymmetric hydrogenation reactions of (*Z*)-2-acetoxy-1,1,1-trifluorododec-2-ene (**1a**), chosen as the model substrate, were carried out using four ruthenium and rhodium complexes in order to examine their ability as chiral catalysts.[9,10] The results are summarized in Table 1. The reaction using a 1.0 mol% cationic ruthenium catalyst, [RuCl((*R*)-binap)(*p*-cymene)]Cl (**4**),[11] was

* Corresponding author. Tel: +00 81 298 58 5060; fax: +00 81 298 5082; e-mail: katsuhiko.iseki@daikin.co.jp

0040-4039/00/$ - see front matter
PII: S0040-4039(00)00643-2

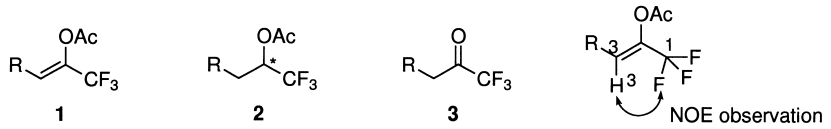
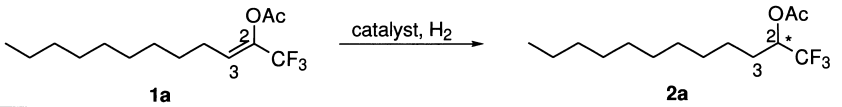


Figure 1.

conducted in MeOH at 50°C and 4 atm H_2 for 18 h to afford (*R*)-2-acetoxy-1,1,1-trifluorododecane (**2a**) in >99% ee and 98% yield (entry 1). Use of EtOH and *i*-PrOH in place of MeOH did not affect the enantioselectivity but remarkably suppressed the hydrogenation rate (entries 2 and 3),[12] suggesting that protons from protic solvents are incorporated into the C-2 and C-3 positions.[13,14] The incorporation may be sluggish in EtOH and *i*-PrOH. Decreasing the reaction temperature to 0°C completely disturbed the hydrogenation (entry 4). The catalyst **4** mediated the hydrogenation without the loss of either enantioselectivity or activity with a catalyst loading as low as 0.04 mol% although a prolonged reaction time was necessary (entries 5 and 6).

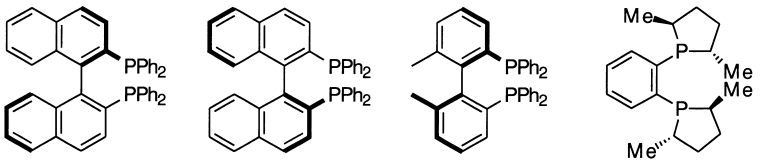
Table 1
Enantioselective hydrogenation reactions of 2-acetoxy-1,1,1-trifluorododec-2-ene (**1a**) in the presence of chiral ruthenium and rhodium complexes



1a **2a**

Entry	Catalyst[a] (mol%)	H_2 (atm)	Solvent	Temp. (°C)	Time (h)	Product **2a** Yield (%)[b]	ee (%)[c] (config)[d]
1	**4** (1.0)	4	MeOH	50	18	98	>99 (*R*)
2	**4** (1.0)	4	EtOH	50	18	53	>99 (*R*)
3	**4** (1.0)	4	*i*-PrOH	50	18	5	>99 (*R*)
4	**4** (1.0)	4	MeOH	0	18	0	-
5	**4** (0.1)	4	MeOH	50	42	98	>99 (*R*)
6	**4** (0.04)	20	MeOH	50	90	99	>99 (*R*)
7	**5** (0.1)	10	MeOH	100	42	94	99 (*S*)
8	**6** (0.1)	4	MeOH	50	42	98	98 (*R*)
9	**7** (0.4)	4	MeOH	50	42	99	92 (*S*)

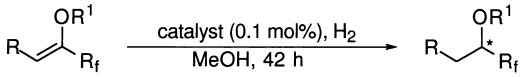
[a] **4**: [RuCl((*R*)-binap)(*p*-cymene)]Cl, **5**: $RuCl_2$((*S*)-binap), **6**: [RuCl((*R*)-biphemp)(*p*-cymene)]Cl, **7**: [Rh(cod)((*S*,*S*)-Me-duphos)]OTf.
[b] Isolated yield.
[c] Determined by HPLC and GLC analyses using chiral columns (CHIRALCEL® OD-H, Daicel Chemical Industries, Ltd., and CP-Cyclodex-β-236M, CHROMPACK).
[d] The absolute configuration was assigned using the modified Mosher method. See reference 18.



Although two other ruthenium catalysts, $RuCl_2$((*S*)-binap) (**5**)[15] and [RuCl((*R*)-biphemp)(*p*-cymene)]Cl (**6**),[16] also gave excellent optical yields (entries 7 and 8), a cationic rhodium catalyst, [Rh(cod)((*S*,*S*)-Me-duphos)]OTf, (**7**)[3b,17] showed a slightly lower enantioselectivity (92% ee, entry 9). The nearly enantiopure **2a** was deacetylated without racemization by treatment with K_2CO_3 in MeOH at room temperature to quantitatively give the corresponding α-trifluoromethyl alcohol.

Table 2 summarizes the results obtained from the hydrogenation of a variety of enol acetates **1b–j** using a 0.1 mol% ruthenium catalyst, either **4**, **5**, or **6**, in MeOH at 50 or 100°C for 42 h. The hydrogenation reactions of (*Z*)-2-acetoxy-1,1,1-trifluorohept-2-ene (**1b**) and (*Z*)-2-acetoxy-1,1,1-trifluorodec-2-ene (**1c**) proceeded in the presence of the catalyst **5** at 100°C and 10 atm H_2 to give the corresponding products, **2b** and **2c**, with 98% ee in 94% yield (entries 1 and 2). Enol acetates having the branched alkyl group R (**1d** and **1e**) were hydrogenated using the catalyst **4** at 50°C and 4 atm H_2 to afford the (*R*)-acetates with enantiomeric excesses of >99% and 95%, respectively (entries 3 and 4). However, the attachment of a phenyl group at the olefinic carbon failed in the reaction under the same conditions (entry 5). The hydrogenation of an ethoxycarbonyl-containing substrate **1g** was carried out in EtOH with an excellent level of enantioselectivity although the chemical yield was not very good (entry 6). The enol acetate **1h** bearing a phenylthio moiety at the olefinic carbon was hydrogenated using the catalyst **6** at 100°C and 20 atm H_2, and gave the corresponding product **2h** in 83% yield and 89% ee (entry 7). Replacement of the acetyl of **1a** with a benzoyl group did not affect the yield and enantioselectivity (Table 1, entry 5 vs Table 2, entry 8). The enol acetate **1j** having a pentafluoroethyl group in place of the CF_3 is also a good substrate for the hydrogenation (entry 9).

Table 2
Enantioselective hydrogenation of various enol esters **1b–j** catalyzed by chiral ruthenium complexes (**4–6**)

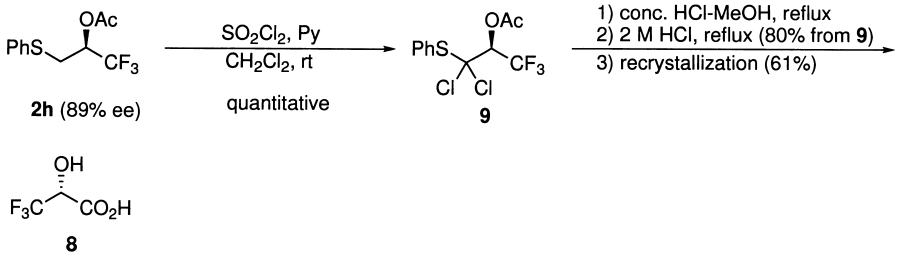


1 **2**

Entry	Enol ester **1**				Catalyst[a]	H_2	Temp.	Product **2**		
	R	R^1	R_f			(atm)	(°C)	Yield (%)[b]	ee (%)[c] (confign)[d]	
1	$(CH_2)_3CH_3$	OAc	CF_3	(**1b**)	**5**	10	100	94	98 (*S*)[19]	(**2b**)
2	$(CH_2)_6CH_3$	OAc	CF_3	(**1c**)	**5**	10	100	94	98 (*S*)[20]	(**2c**)
3	$CH_2CH(CH_3)_2$	OAc	CF_3	(**1d**)	**4**	4	50	100	>99	(**2d**)
4	*c*-C_6H_{11}	OAc	CF_3	(**1e**)	**4**	4	50	81	95	(**2e**)
5	Ph	OAc	CF_3	(**1f**)	**4**	4	50	0	-	(**2f**)
6[e]	$(CH_2)_2CO_2Et$	OAc	CF_3	(**1g**)	**4**	4	50	71	>99 (*R*)[21]	(**2g**)
7	SPh	OAc	CF_3	(**1h**)	**6**	20	100	83	89 (*S*)[22]	(**2h**)
8	$(CH_2)_8CH_3$	OBz	CF_3	(**1i**)	**4**	4	50	99	99 (*R*)[18]	(**2i**)
9	$(CH_2)_7CH_3$	OAc	C_2F_5	(**1j**)	**5**	10	100	100	98	(**2j**)

[a] **4**: [RuCl((*R*)-binap)(*p*-cymene)]Cl, **5**: $RuCl_2$((*S*)-binap), **6**: [RuCl((*R*)-biphemp)(*p*-cymene)]Cl.
[b] Isolated yield.
[c] Determined by HPLC and GLC analyses using chiral columns (CHIRALCEL® OD-H, Daicel Chemical Industries, Ltd., and CP-Cyclodex-β-236M, CHROMPACK).
[d] The absolute configuration was assigned by comparing the sign of the optical rotations with literature data. See references 18-22.
[e] The reaction was carried out in EtOH.

Finally, the optically active 2-acetoxy-1,1,1-trifluoro-3-(phenylthio)propane (**2h**) was shown to be a useful intermediate for preparing the enantiomerically pure trifluorolactic acid (**8**) in Scheme 1. The treatment of (*S*)-**2h** (89% ee) with SO_2Cl_2 and pyridine in CH_2Cl_2 at room temperature for 3 h afforded the α,α-dichlorosulfide **9** in quantitative yield.[23] The hydrolysis of **9** by refluxing in a mixture of 12 M HCl and MeOH (3:20) for 40 h and in 2 M HCl for 18 h gave the acid **8** in 80% yield. A single recrystallization of this material from Et_2O–$CHCl_3$ provided a 61% recovery of the homochiral (*R*)-(+)-**8** {$[\alpha]_D^{25}$ +21.1 (*c* 0.95, EtOH), lit.[24] $[\alpha]_D^{rt}$ +21.0 (*c* 1.98, EtOH)}.



Scheme 1. Preparation of enantiomerically pure (*R*)-(+)-trifluorolactic acid (**8**)

In conclusion, we have described the highly enantioselective hydrogenation of 1,1,1-trifluoroalkan-2-one enol acetates mediated by chiral ruthenium catalysts. Applications of this method to the synthesis of versatile chiral fluorinated molecules are now being carried out.

References

1. (a) Bravo, P.; Resnati, G. *Tetrahedron: Asymmetry* **1990**, *1*, 661–692. (b) *Enantiocontrolled Synthesis of Fluoro-Organic Compounds*; Hayashi, T.; Soloshonok, V. A., Eds. Tetrahedron: Asymmetry, Special Issue; *Tetrahedron: Asymmetry* **1994**, *5*, issue N 6. (c) Iseki, K. *Tetrahedron* **1998**, *54*, 13887–13914. (d) *Enantiocontrolled Synthesis of Fluoro-Organic Compounds*; Soloshonok, V. A., Ed. John Wiley: New York, 1999. (e) *Asymmetric Fluoroorganic Chemistry: Synthesis, Applications, and Future Directions* (ACS Symposium Series 746); Ramachandran, P. V., Ed. American Chemical Society: Washington DC, 2000.
2. (a) Suzuki, Y.; Hagiwara, T.; Kawamura, I.; Okamura, N.; Kitazume, T.; Kakimoto, M.; Imai, Y.; Ouchi, Y.; Takezoe, H.; Fukuda, A. *Liq. Cryst.* **1989**, *6*, 167. (b) Mikami, K. In *Asymmetric Fluoroorganic Chemistry: Synthesis, Applications, and Future Directions* (ACS Symposium Series 746); Ramachandran, P. V., Ed.; American Chemical Society: Washington DC, 2000; pp. 255–269.
3. For the enantioselective hydrogenation reactions of 2-acetoxy-3,3,3-trifluoropropene, see: (a) Koenig, K. E.; Bachman, G. L.; Vineyard, B. D. *J. Org. Chem.* **1980**, *45*, 2362–2365. (b) Burk, M. J. *J. Am. Chem. Soc.* **1991**, *113*, 8518–8519.
4. For the enantioselective reduction of α,α,α-trifluoroacetophenones, see: (a) Corey, E. J.; Bakshi, R. K. *Tetrahedron Lett.* **1990**, *31*, 611–614. (b) Ohkuma, T.; Koizumi, M.; Doucet, H.; Pham, T.; Kozawa, M.; Murata, K.; Katayama, E.; Yokozawa, T.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1998**, *120*, 13529–13530.
5. For the catalytic asymmetric reactions with fluoral, see: (a) Mikami, K.; Yajima, T.; Terada, M.; Uchimaru, T. *Tetrahedron Lett.* **1993**, *34*, 7591–7594. (b) Ishii, A.; Mikami, K. The International Conference on Fluorine Chemistry 1999 Tokyo, Yokohama, 1999, Abstr., No. P50. (c) Poras, H.; Matsutani, H.; Yaruva, J.; Kusumoto, T.; Hiyama, T. *Chem. Lett.* **1998**, 665–666.
6. For the asymmetric dihydroxylation of α-(trifluoromethyl)styrene, see: Bennani, Y. L.; Vanhessche, K. P. M.; Sharpless, K. B. *Tetrahedron: Asymmetry* **1994**, *5*, 1473–1476.
7. For the catalytic asymmetric trifluoromethylation of aldehydes and ketones with (trifluoromethyl)trimethylsilane, see: (a) Iseki, K.; Nagai, T.; Kobayashi, Y. *Tetrahedron Lett.* **1994**, *35*, 3137–3138. (b) Kuroki, Y.; Iseki, K. *Tetrahedron Lett.* **1999**, *40*, 8231–8234.

8. 2-Acetoxy-3,3,3-trifluoropropene [$CF_3(OAc)C{=}CH_2$] showed the NOE between the fluorine atoms and one of the olefinic protons, while the other proton did not have any NOE on the fluorines.
9. For the first successful asymmetric hydrogenation of functionalized prochiral olefins using chiral ruthenium complexes, see: Ikariya, T.; Ishii, Y.; Kawano, H.; Arai, T.; Saburi, M.; Yoshikawa, S.; Akutagawa, S. *J. Chem. Soc., Chem. Commun*. **1985**, 922–924.
10. For a recent enantioselective hydrogenation of enol esters with chiral rhodium catalysts, see: Burk, M. J.; Kalberg, C. S.; Pizzano, A. *J. Am. Chem. Soc*. **1998**, *120*, 4345–4353.
11. (a) Mashima, K.; Kusano, K.; Ohta, T.; Noyori, R.; Takaya, H. *J. Chem. Soc., Chem. Commun*. **1989**, 1208–1210. (b) Mashima, K.; Kusano, K.; Sato, N.; Matsumura, Y.; Nozaki, K.; Kumobayashi, H.; Sayo, N.; Hori, Y.; Ishizaki, T.; Akutagawa, S.; Takaya, H. *J. Org. Chem*. **1994**, *59*, 3064–3076.
12. The hydrogenation did not occur at all in THF, CH_2Cl_2, or CH_3CN.
13. When **1a** reacted in the presence of 1 mol% **4** in CD_3OD at 50°C and 4 atm H_2, **2a**-2*d* and **2a**-3*d* were obtained.
14. Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; John Wiley: New York, 1994; pp. 49–54.
15. Noyori, R.; Ohkuma, T.; Kitamura, M.; Takaya, H.; Sayo, N.; Kumobayashi, H.; Akutagawa, S. *J. Am. Chem. Soc*. **1987**, *109*, 5856–5858. The catalyst **5** was purchased from AZmax Co., Ltd., Chiba, Japan.
16. The ruthenium catalyst **6** was prepared using (*R*)-BIPHEMP (Schmid, R.; Cereghetti, M.; Heiser, B.; Schönholzer, P.; Hansen, H.-J. *Helv. Chim. Acta* **1988**, *71*, 897–929) according to the procedure given for **4**.
17. Burk, M. J.; Feaster, J. E.; Nugent, W. A.; Harlow, R. L. *J. Am. Chem. Soc*. **1993**, *115*, 10125–10138.
18. (a) Xiao, L.; Yamazaki, T.; Kitazume, T.; Yonezawa, T.; Sakamoto, Y.; Nogawa, K. *J. Fluorine Chem*. **1997**, *84*, 19–23. (b) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc*. **1991**, *113*, 4092–4096.
19. Yonezawa, T.; Sakamoto, Y.; Nogawa, K.; Yamazaki, T.; Kitazume, T. *Chem. Lett*. **1996**, 855–856.
20. Ramachandran, P. V.; Teodorovic, A. V.; Brown, H. C. *Tetrahedron* **1993**, *49*, 1725–1738.
21. Seebach, D.; Renand, P. *Helv. Chim. Acta* **1985**, *68*, 2342–2349.
22. Shimizu, M.; Sugiyama, K.; Fujisawa, T. *Bull. Chem. Soc. Jpn*. **1996**, *69*, 2655–2659.
23. Fortes, C. C.; Fortes, H. C.; Goncalves, D. C. R. G. *J. Chem. Soc., Chem. Commun*. **1982**, 857–858.
24. von dem Bussche-Hünnefeld, C.; Cescato, C.; Seebach, D. *Chem. Ber*. **1992**, *125*, 2795–2802.