



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

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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. © 2000 Elsevier Science Ltd. All rights reserved.

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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

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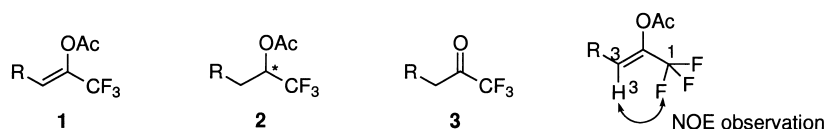


Figure 1.

conducted in MeOH at 50°C and 4 atm H₂ for 18 h to afford (*R*)-2-acetoxyl-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-acetoxyl-1,1,1-trifluorododec-2-ene (**1a**) in the presence of chiral ruthenium and rhodium complexes

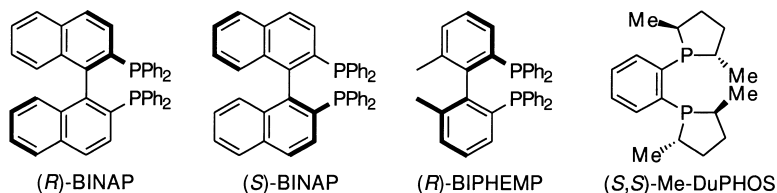
Entry	Catalyst ^a (mol%)	H ₂ (atm)	Solvent	Temp. (°C)	Time (h)	Product 2a	
						Yield (%) ^b	ee (%) ^c (config) ^d
1	4 (1.0)	4	MeOH	50	18	98	>99 (<i>R</i>)
2	4 (1.0)	4	EtOH	50	18	53	>99 (<i>R</i>)
3	4 (1.0)	4	<i>i</i> -PrOH	50	18	5	>99 (<i>R</i>)
4	4 (1.0)	4	MeOH	0	18	0	-
5	4 (0.1)	4	MeOH	50	42	98	>99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

^a **4**: [RuCl((*R*)-binap)(*p*-cymene)]Cl, **5**: RuCl₂((*S*)-binap), **6**: [RuCl((*R*)-biphep)(*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, $\text{RuCl}_2((S)\text{-binap})$ (**5**)¹⁵ and $[\text{RuCl}((R)\text{-biphemp})(p\text{-cymene})]\text{Cl}$ (**6**),¹⁶ also gave excellent optical yields (entries 7 and 8), a cationic rhodium catalyst, $[\text{Rh}(\text{cod})((S,S)\text{-Me-duphos})]\text{OTf}$, (**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**)

$ \begin{array}{c} \text{OR}^1 \\ \\ \text{R} \text{---} \text{C} = \text{C} \text{---} \text{R}_f \\ \mathbf{1} \end{array} \xrightarrow[\text{MeOH, 42 h}]{\text{catalyst (0.1 mol\%), H}_2} \begin{array}{c} \text{OR}^1 \\ \\ \text{R} \text{---} \text{CH}_2 \text{---} \text{CH} \text{---} \text{R}_f \\ \mathbf{2} \end{array} $								
Entry	Enol ester 1			Catalyst ^a	H ₂ (atm)	Temp. (°C)	Yield (%) ^b	Product 2 ee (%) ^c (config) ^d
	R	R ¹	R _f					
1	(CH ₂) ₃ CH ₃	OAc	CF ₃ (1b)	5	10	100	94	98 (<i>S</i>) ¹⁹ (2b)
2	(CH ₂) ₆ CH ₃	OAc	CF ₃ (1c)	5	10	100	94	98 (<i>S</i>) ²⁰ (2c)
3	CH ₂ CH(CH ₃) ₂	OAc	CF ₃ (1d)	4	4	50	100	>99 (2d)
4	<i>c</i> -C ₆ H 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) ₂ CO ₂ Et	OAc	CF ₃ (1g)	4	4	50	71	>99 (<i>R</i>) ²¹ (2g)
7	SPh	OAc	CF ₃ (1h)	6	20	100	83	89 (<i>S</i>) ²² (2h)
8	(CH ₂) ₈ CH ₃	OBz	CF ₃ (1i)	4	4	50	99	99 (<i>R</i>) ¹⁸ (2i)
9	(CH ₂) ₇ CH ₃	OAc	C ₂ F ₅ (1j)	5	10	100	100	98 (2j)

^a **4**: $[\text{RuCl}((R)\text{-binap})(p\text{-cymene})]\text{Cl}$, **5**: $\text{RuCl}_2((S)\text{-binap})$, **6**: $[\text{RuCl}((R)\text{-biphemp})(p\text{-cymene})]\text{Cl}$.

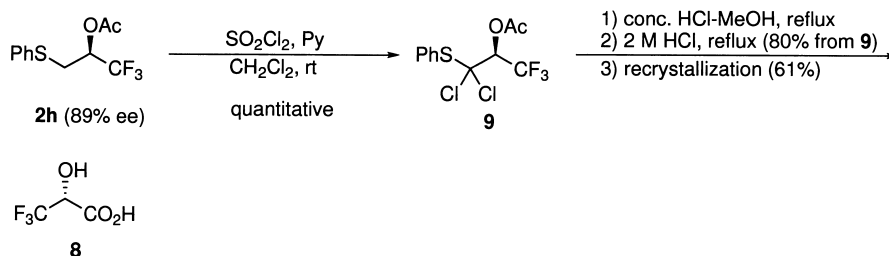
^b Isolated yield.

^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 SO₂Cl₂ and pyridine in CH₂Cl₂ 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 Et₂O–CHCl₃ provided a 61% recovery of the homochiral (*R*)-(+)-**8** {[α]_D²⁵ +21.1 (*c* 0.95, EtOH), lit.²⁴ [α]_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.

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