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Enantioselective synthesis of 2,2-difluoro-3-hydroxycarboxylates by rhodium-catalyzed hydrogenation

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Abstract

The highly enantioselective synthesis of 2,2-difluoro-3-hydroxycarboxylates has been achieved by hydrogenating 2,2-difluoro-3-oxocarboxylates in the presence of chiral rhodium-(amidephosphine-phosphinite) complexes. Ethyl 4,4,4-trifluoroacetoacetate can be successfully transformed into the enantiomerically enriched 4,4,4-trifluoro-3-hydroxybutanoate in the same manner. © 2000 Elsevier Science Ltd. All rights reserved.

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 based on the influence of fluorine's unique properties.[1] Fluorine, due to its high electronegativity, has a considerable electronic effect on its neighboring groups in a molecule. The introduction of a difluoromethylene residue into bioactive peptides has led to the discovery of potent protease inhibitors mimicking the transition state for hydrolytic amide bond cleavage,[2] and optically active 2,2-difluoro-3-hydroxycarboxylates are versatile intermediates for the synthesis of these fluorinated peptides. We have previously reported the enantioselective aldol reaction of a difluoroketene silyl acetal catalyzed by chiral Lewis acids to provide 2,2-difluoro-3-hydroxycarboxylates with high enantiomeric excesses.[3] However, this transformation has a drawback such that the decrease in the amount of the catalyst to less than 20 mol% dramatically suppresses the enantioselectivity. This paper discloses herein the catalytic asymmetric hydrogenation of 2,2-difluoro-3-oxocarboxylates (**1**) catalyzed by less than 1 mol% chiral rhodium-(amidephosphine-phosphinite) complexes to provide the corresponding 2,2-difluoro-3-hydroxycarboxylates (**2**) with high enantioselectivity.

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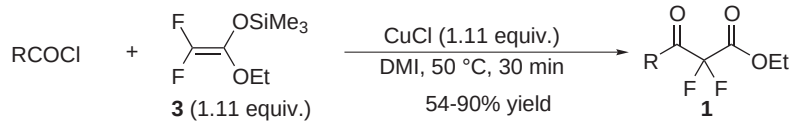
The β-keto ester **1** was prepared using the method developed by Hosomi and collaborators.[4] Difluoroketene silyl acetal **3** was treated with acyl halide in the presence of CuCl in 1,3-dimethyl-2-imidazolidinone (DMI) at 50°C for 30 min to give the β-keto ester **1** in a yield that ranged between 54 and 90% (Scheme 1).

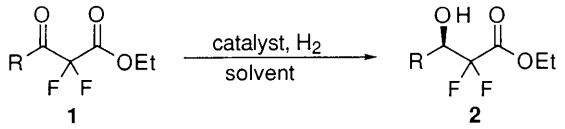


Scheme 1. Preparation of ethyl 2,2-difluoro-3-oxocarboxylate (**1**)

First, the asymmetric hydrogenation reactions of ethyl 3-cyclohexyl-2,2-difluoro-3-oxopropanoate (**1a**) and ethyl 2,2-difluoro-3-oxododecanoate (**1b**), chosen as the model substrates, were carried out using chiral ruthenium and rhodium complexes in order to examine their ability as chiral catalysts (Table 1). A variety of efficient homogeneous transition metal catalysts have been developed for the enantioselective hydrogenation of β-keto esters,[5] and halogen-containing BINAP-Ru(II) complexes are the most useful catalysts for various β-keto esters.[6] However, the hydrogenation of the β-keto ester **1a** using a 0.1 mol% $RuBr_2$((*R*)-binap) (**4**)[7] in EtOH under 100 atm H_2 at 100°C for 24 h afforded ethyl (*R*)-3-cyclohexyl-2,2-difluoro-3-hydroxypropanoate (**2a**) with only 77% ee (entry 1). A 1.0 mol% cationic ruthenium catalyst, [RuCl((*R*)-biphemp)(*p*-cymene)]Cl (**5**),[8] also gave an unsatisfactory enantioselection during the hydrogenation of the β-keto ester **1b** under similar conditions (entry 2, 81% ee).[9,10] A series of amidephosphine-phosphinites derived from homochiral 5-(hydroxymethyl)-2-pyrrolidinone have shown to be highly effective ligands for the rhodium-catalyzed enantioselective hydrogenation reactions of 2-oxo-3,3-dimethyl-γ-butyrolactone and α-keto amides.[11] We have found that the rhodium-(amidephosphine-phosphinite) catalysts give the β-hydroxy ester **2** with high enantioselectivity during the hydrogenation of the β-keto ester **1**.[12] The hydrogenation of **1a** using 0.5 mol% [Rh((*S*)-Cy,Cy-oxoProNOP)$OCOCF_3$]$_2$ (**6**)[11c] was conducted in toluene under 20 atm H_2 at 70°C for 20 h to afford the (*R*)-β-hydroxy ester **2a** in 94% ee and 81% yield (entry 3). The use of 0.1 mol% [Rh((*S*)-Cp,Cp-oxoProNOP)$OCOCF_3$]$_2$ (**7**)[11c] under the same conditions improved the hydrogenation rate without decreasing the enantioselectivity (entry 4, 99% yield and 94% ee). The reaction of **1b** using 0.1 mol% of catalyst **6** was carried out under 20 atm H_2 at 30°C for 20 h to provide ethyl (*R*)-2,2-difluoro-3-hydroxydodecanoate (**2b**) with 97% ee in 98% yield (entry 5). The use of 0.5 mol% [Rh((*S*)-Cy,Cy-oxoProNOP)Cl]$_2$ (**8**) in which the trifluoroacetoxy moiety of catalyst **6** was replaced with a chloride suppressed both the chemical and optical yields (entry 6, 43% yield and 90% ee). Newly prepared catalysts, [Rh((*S*)-C7,C7-oxoProNOP)$OCOCF_3$]$_2$ (**9**)[13] and [Rh((*S*)-*i*-Pr,*i*-Pr-oxoProNOP)$OCOCF_3$]$_2$ (**10**),[13] also gave excellent optical yields although catalyst **9** showed a slightly lower chemical yield (entries 7 and 8).

Table 2 summarizes the results obtained from the hydrogenation of a variety of β-keto esters **1c**–**h** using 0.5 mol% of catalyst **6** in toluene under 20 atm H_2 at 30 or 70°C for 20 h. The hydrogenation reaction of ethyl 2,2-difluoro-3-oxobutanoate (**1c**) proceeded smoothly at 30°C to give the corresponding (*R*)-product **2c** with 96% ee in 93% yield (entry 1). A β-keto ester having a branched alkyl group R (**1d**) was hydrogenated using catalyst **4** at 70°C to afford the (*R*)-product **2d** with an enantiomeric excess of 92% in 95% yield (entry 2). Ethyl 2,2-difluoro-3-oxo-3-phenylpropanoate (**1e**) gave a poor enantioselectivity (entry 3, 84% ee). The hydrogenation of ethyl 2,2-difluoro-3-oxo-4-phenylbutanoate (**1f**) was carried out with an excellent level of

Table 1
Enantioselective hydrogenation reactions of ethyl 2,2-difluoro-3-oxocarboxylates (**1a** and **1b**) in the presence of chiral ruthenium and rhodium complexes



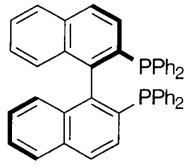
Entry	β-Keto ester **1**		Catalyst[a] (mol%)	H_2 (atm)	Solvent	Temp. (°C)	Time (h)	Product **2**	
	R							Yield (%)[b]	ee (%)[c] (config.)[d]
1	*c*-C_6H_{11}	(**1a**)	**4** (0.1)	100	EtOH	100	24	96	77 (*R*) (**2a**)
2	$CH_3(CH_2)_8$	(**1b**)	**5** (1.0)	100	EtOH	100	5	100	81 (*R*) (**2b**)
3	*c*-C_6H_{11}	(**1a**)	**6** (0.5)	20	Toluene	70	20	81	94 (*R*) (**2a**)
4	*c*-C_6H_{11}	(**1a**)	**7** (0.1)	20	Toluene	70	20	99	94 (*R*) (**2a**)
5	$CH_3(CH_2)_8$	(**1b**)	**6** (0.1)	20	Toluene	30	20	98	97 (*R*) (**2b**)
6	$CH_3(CH_2)_8$	(**1b**)	**8** (0.5)	50	Toluene	30	18	43	90 (*R*) (**2b**)
7	$CH_3(CH_2)_8$	(**1b**)	**9** (0.1)	10	Toluene	30	20	80	96 (*R*) (**2b**)
8	$CH_3(CH_2)_8$	(**1b**)	**10** (0.1)	10	Toluene	30	20	99	97 (*R*) (**2b**)

[a] **4**: $RuBr_2$[(*R*)-binap], **5**: [RuCl((*R*)-biphemp)(*p*-cymene)]Cl, **6**: $[Rh((S)\text{-Cy,Cy-oxoProNOP})OCOCF_3]_2$, **7**: $[Rh((S)\text{-Cp,Cp-oxoProNOP})OCOCF_3]_2$, **8**: $[Rh((S)\text{-Cy,Cy-oxoProNOP})Cl]_2$, **9**: $[Rh((S)\text{-C7,C7-oxoProNOP})OCOCF_3]_2$, **10**: $[Rh((S)\text{-}i\text{-Pr,}i\text{-Pr-oxoProNOP})OCOCF_3]_2$.

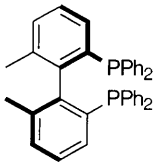
[b] Isolated yield.

[c] Determined by HPLC using a chiral column (CHIRALCEL® OD-H, Daicel Chemical Industries, Ltd.).

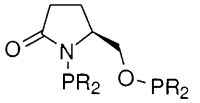
[d] The absolute configuration was assigned using the modified Mosher method. See reference 14.



(*R*)-BINAP

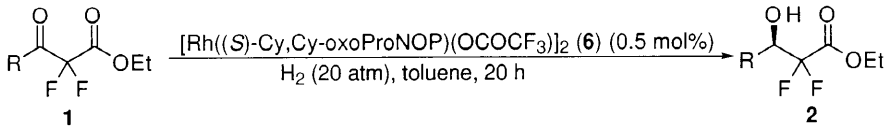


(*R*)-BIPHEMP



(*S*)-Cy,Cy-oxoProNOP: R = cyclohexyl
(*S*)-Cp,Cp-oxoProNOP: R = cyclopentyl
(*S*)-C7,C7-oxoProNOP: R = cycloheptyl
(*S*)-*i*-Pr,*i*-Pr-oxoProNOP: R = isopropyl

Table 2
Enantioselective hydrogenation of various β-keto esters **1c–h** catalyzed by chiral rhodium complex **6**



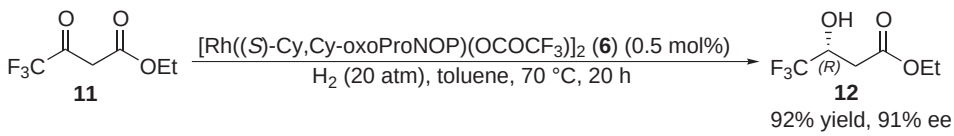
1 **2**

Entry	β-Keto ester **1**		Temp. (°C)	Product **2**	
	R			Yield (%)[a]	Ee (%)[b] (config.)
1	CH_3	(**1c**)	30	93	96 (*R*)[c] (**2c**)
2	$(CH_3)_2CHCH_2$	(**1d**)	70	95	92 (*R*)[c] (**2d**)
3	Ph	(**1e**)	30	97	84 (*R*)[d] (**2e**)
4	$PhCH_2$	(**1f**)	30	63	94 (*R*)[c] (**2f**)
5	$PhCH_2CH_2$	(**1g**)	30	100	96 (*R*)[c] (**2g**)
6	$PhCH_2OCH_2$	(**1h**)	30	95	95 (*R*)[c] (**2h**)

[a] Isolated yield.
[b] Determined by HPLC using a chiral column (CHIRALCEL® OD-H or OB-H, Daicel Chemical Industries, Ltd.).
[c] The absolute configuration was assigned using the modified Mosher method. See reference 14.
[d] The β-hydroxy ester **2e** was shown to have the (*R*)-configuration by conversion to the known corresponding methyl ester. See reference 15.

enantioselectivity although the chemical yield was not very good (entry 4, 94% ee and 63% yield). Two β-keto esters, **1g** and **1h**, bearing a phenyl moiety, were hydrogenated at 30°C and gave the corresponding products in excellent chemical and optical yields (entries 5 and 6). In all cases, the rhodium-((*S*)-amidephosphine-phosphinite) complexes gave predominantly the (*R*)-enantiomers (Table 1, entries 3–8 and Table 2).

Finally, the asymmetric hydrogenation of ethyl 4,4,4-trifluoroacetoacetate (**11**) using 0.5 mol% of catalyst **6** was examined in toluene under 20 atm H_2 at 70°C for 20 h, and ethyl (*R*)-4,4,4-trifluoro-3-hydroxybutanoate (**12**) was obtained in 91% ee and 92% yield (Scheme 2).[16]



11 **12**
92% yield, 91% ee

Scheme 2. Enantioselective hydrogenation of ethyl 4,4,4-trifluoroacetoacetate (**11**) catalyzed by **6**

The enantioface differentiation cannot be simply explained by the coordination of the rhodium atom with two carbonyl oxygens of the β-keto ester (**1** and **11**). Interestingly, the 2,2-difluoro-3-oxocarboxylate **1** is hydrogenated on the under surface (α-side), while the reaction of the 4,4,4-trifluoroacetoacetate **11** occurs on the upper surface (β-side), suggesting that the fluorine atoms exert a pronounced influence on the enantiotopic face selection (Fig. 1).[17]

In conclusion, we have described the highly enantioselective hydrogenation of 2,2-difluoro-3-oxocarboxylates mediated by chiral rhodium-(amidephosphine-phosphinite) catalysts. Ethyl 4,4,4-trifluoro-3-hydroxybutanoate of 91% ee was obtained from the 4,4,4-trifluoroacetoacetate in the same manner. The origin of the enantiofacial selection and application of this method to the synthesis of versatile chiral fluorinated molecules is currently under investigation.

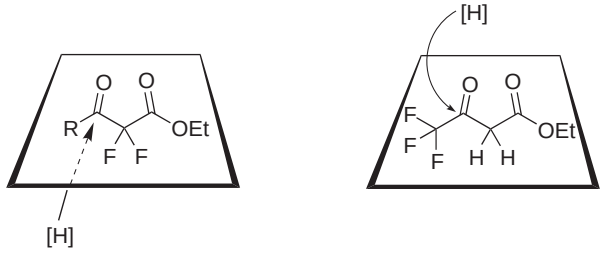


Figure 1. Stereochemical course of the hydrogenation catalyzed by **6**

General procedure for the 2,2-difluoro-3-hydroxycarboxylates. Toluene was distilled from sodium ketyl. A solution of $[Rh(COD)OCOCF_3]_2$ (6.5 mg, 0.01 mmol) and (*S*)-Cy,Cy-oxo-ProNOP (11.2 mg, 0.022 mmol) in toluene (1 mL) was stirred for 15 min in a glove box. The resulting catalyst solution (150 μL) was transferred to a 100 mL stainless steel autoclave. A solution of the 2,2-difluoro-3-hydroxycarboxylate (3.0 mmol) in toluene (4 mL) was transferred to the autoclave, hydrogen (20 atm) was introduced, and the reaction mixture was stirred magnetically at 30 or 70°C. After the desired reaction time, hydrogen was removed and the solution was concentrated in vacuo. The crude residue was analyzed by GLC and chromatographed to furnish the hydrogenation product.

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8. The ruthenium catalyst **5** 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 [RuCl((*R*)-

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12. However, these catalysts are not useful for the hydrogenation of β-keto esters other than **1**. The hydrogenation of ethyl 3-oxohexanoate using 0.5 mol% $[Rh((S)\text{-Cy,Cy-oxoProNOP})OCOCF_3]_2$ (**6**) was conducted in toluene under 20 atm H_2 at 30°C for 20 h to give the corresponding β-hydroxy ester with 32% ee in 47% yield. The hydrogenation of methyl 3-oxo-2,2-dimethylbutanoate under the same conditions gave the product with 12% ee and only a 2% yield.
13. The catalyst was prepared using (*S*)-C7,C7-oxoProNOP or (*S*)-*i*-Pr,*i*-Pr-oxoProNOP according to the procedure given for **6**–**8**. See reference 11c.
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17. The fluorine atom in **1** and **11** may make five-membered chelate rings with the rhodium atom to determine the enantioface selection.