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Note

Asymmetric synthesis of fluorinated β-hydroxy esters via ruthenium-mediated hydrogenation

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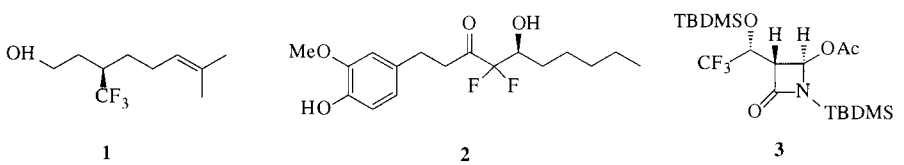
Abstract

The homogeneous asymmetric hydrogenation reactions of fluorinated β-keto esters using ruthenium(II) complexes bearing atropoisomeric diphosphines such as BINAP and MeO–BIPHEP have yielded the corresponding β-hydroxy esters in quantitative yield with ee that ranged between 42 and >95%. © 2000 Published by Elsevier Science S.A. All rights reserved.

Keywords: Ruthenium catalysts; Chiral hydrogenation; Fluoroorganic compounds

In recent years, increased attention in the chemical synthesis of fluorinated compounds has occurred [1], and a large number of fluorinated drugs have been synthesized. Examples include trifluorocitronellol (**1**) [2] prepared recently by Seebach et al. chiral difluorinated gingerol (**2**) [3] and (1′*R*,3*R*,4*R*)-4-acetoxy-3-(2′,2′,2′-trifluoro-1′-hydroxyethyl)-azetidin-2-one (**3**) [4], a key intermediate in the synthesis of fluorocarbapenems (Fig. 1).

Fluorinated β-hydroxy esters are an important class of compounds which serve as chiral building blocks for the synthesis of aminoacids [5], epoxides [6], diols [7] and carbohydrates [8]. However, in the literature there are not many reports available on the synthesis of chiral fluorinated β-hydroxy esters. Enzymatic reduction of ethyl 4,4,4-trifluoro-3-oxobutanoate was reported with an ee of 45% [9] by Seebach et al. about a decade ago. The enantioselective Reformatsky reaction of methyl bromodifluoroacetate has been described, with the formation of methyl (*S*)-2,2-difluoro-3-hydroxy-3-phenylpropanoate in 84% ee [10]. α,α-Difluoro-β-hydroxy esters were obtained more recently by aldol reactions of various aldehydes with α,α-difluoroketene silyl acetal mediated by Lewis acids with ees up to 98% [11]. To the best of our knowledge, only an example of a ruthenium-promoted hydrogenation reaction of fluorinated β-keto ester has been reported by Noyori and his coworkers on ethyl 4,4,4-trifluoro-3-oxobutanoate using RuHCl[(*R*)-BINAP]$_2$ at 80 bar pressure and 30°C. The corresponding β-hydroxy ester was isolated in 95% yield with 46% ee. [12]. As part of our



1 2 3

Fig. 1.

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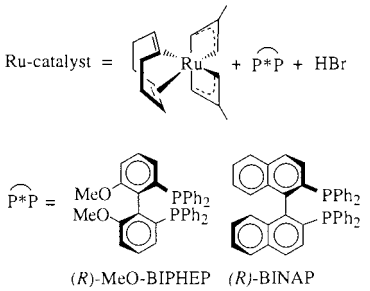
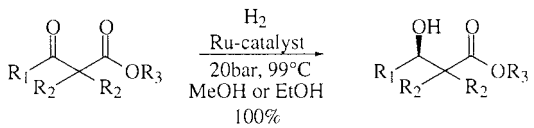


Scheme 1.



4- R_1=CF_3, R_2=H, R_3=Et
5- R_1=C_2F_5, R_2=H, R_3=Et
6- R_1=$C_8F_{17}CH_2CH_2$, R_2=H, R_3=Me
7- R_1=Et, R_2=F, R_3=Me
8- R_1=2, 3, 5-F,F,F-C_6H_2, R_2=H, R_3=Et

9-13

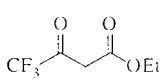
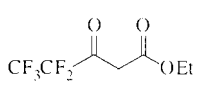
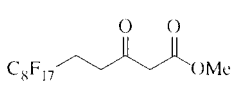
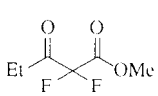
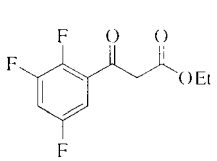
Scheme 2.

continuing interest in the homogeneous ruthenium-promoted hydrogenation reactions [13,14], we herein report the asymmetric hydrogenation of fluorinated β-keto esters using the in situ generated chiral ruthenium catalysts. The ruthenium-catalysts were prepared in situ from (*R*)-BINAP or (*R*)-MeO–BIPHEP and (COD)Ru(η^3-$(CH_2)_2CCH_3)_2$ by addition of methanolic HBr at room temperature [13] (Scheme 1).

The screening tests were carried out on a 1 mmol scale in methanol or ethanol under 20 bar of hydrogen pressure at 99°C using the in situ generated ruthenium dibromide catalysts. Catalytic activity in the hydrogenation of fluorinated β-keto esters was excellent. In all cases, complete conversions were achieved (Scheme 2).

Hydrogenation of ethyl 4,4,4-trifluoro-3-oxobutanoate (**4**) was carried out using both enantiomers of MeO–BIPHEP leading to (*S*)-**9** and (*R*)-**9** with 42% ee (entries 1 and 2). For the hydrogenation of ethyl 5,5,5,4,4,-pentafluoro-3-oxopentanoate (**5**), promoted by the in situ generated ruthenium complexes, both ruthenium–BINAP and MeO–BIPHEP complexes lead

Table 1

Entry	Substrate	Ligands	Conditions [a]	(Configuration)/ee
1		(*R*)-MeO–BIPHEP	20 bar, 99°C, 1 h	(*S*)-**9**/42% [b]
2		(*S*)-MeO–BIPHEP	20 bar, 99°C, 1 h	(*R*)-**9**/42% [b]
	4			
3		(*R*)-BINAP	20 bar, 99°C, 18 h	(*S*)-**10**/48% [b]
4		(*R*)-MeO–BIPHEP	20 bar, 99°C, 20 h	(*S*)-**10**/61% [b]
	5			
5		(*R*)-BINAP	20 bar, 99°C, 24 h	(*R*)-**11**/>95% [c]
6		(*R*)-MeO–BIPHEP	20 bar, 99°C, 24 h	(*R*)-**11**>95% [c]
	6			
7		(*R*)-BINAP	20 bar, 99°C, 18 h	(*R*)-**12**/>95% [b]
8		(*R*)-MeO–BIPHEP	20 bar, 99°C, 20 h	(*R*)-**12**/>95% [b]
	7			
9		(*R*)-BINAP	20 bar, 99°C, 18 h	(*S*)-**13**/88% [b]
10		(*R*)-MeO–BIPHEP	20 bar, 99°C, 20 h	(*S*)-**13**/86% [b]
	8			

[a] Reactions times are not optimized.
[b] The enantiomeric excesses were measured by gas chromatography using a lipodex A column (Macherey–nagel).
[c] Determined by ^{1}H-NMR spectroscopy of the corresponding (*R*)-methoxy(trifluoromethyl)phenylacetyl (MTPA) ester.

to the formation of fluorinated β-hydroxy ester (**10**) in moderate enantioselectivities (48 and 61%, entries 3 and 4). On the other hand, the same atropoisomeric ligands promoted highly enantioselective hydrogenations of the methyl 5-perfluorooctyl-3-oxopentanoate (**6**) (entries 5 and 6) under the same reaction conditions affording fluorinated alcohol **11** as the only detectable product with enantiomeric excesses higher than 95% (determined by ^{1}H-NMR spectroscopy of the corresponding (*R*)-methoxy(trifluoromethyl)phenylacetyl (MTPA) ester (Table 1).

The same conditions were applied to methyl-2,2-difluoro-3-oxopentanoate (**7**) (entries 7 and 8) and the corresponding α,α-difluoro-β-hydroxy ester (**12**) was obtained quantitatively with excellent ee ($>95\%$ ee). Finally, we examined the hydrogenation of ethyl 3-oxo-3-(2,3,5-trifluoro)phenyl propanoate (**8**) (entries 9 and 10) which proceeded in good enantioselectivities affording **13** (88 and 86% ee). The absolute configurations of the hydrogenated derivative **9** has been established by comparison with literature data. Consequently, we assumed that the other hydrogenation reactions follow the same stereochemical course as this was described with the BINAP and atroposisomeric ligands Ru-mediated hydrogenation of β-keto esters [15].

In conclusion, a practical synthesis of several fluorinated β-hydroxy esters [16] has been described with significant levels of enantioselectivities. Applications to the synthesis of fluorinated biologically active molecules are under investigation.

Acknowledgements

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[16] General procedure for asymmetric hydrogenation: (*R*)-MeO–BIPHEP (7 mg, 0.012 mmol) and (COD)Ru(η^3-$(CH_2)_2CCH_3$) (3.2 mg, 0.01 mmol) were placed in a 10 ml glass tube and 1 ml of anhydrous acetone were added dropwise. A methanolic solution of HBr (122 μl, 0.18 M) was added dropwise to the suspension. The reaction mixture was stirred at room temperature for about 30 min and a resulting yellow suspension was observed. The solvent was removed under vacuum. The yellow solid residue was used as catalyst for the hydrogenation reaction. Methanol or ethanol (2 ml) and appropriate substrate (1 mmol) were added and the reaction vessel were placed then in a 500 ml stainless steel autoclave under argon. The autoclave was then pressurized to the desired hydrogen pressure and the reaction was allowed to proceed until complete conversion.