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Highly Enantioselective Synthesis of 3-Hydroxy-2-methylpropanoic Acid Esters through Ruthenium-SYNPHOS®-Catalyzed Hydrogenation: Useful Building Blocks for the Synthetic Community

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Abstract: Both enantiomers of 3-hydroxy-2-methylpropanoic acid *tert*-butyl ester were prepared with high enantioselectivity (up to 94%) through a ruthenium-SYNPHOS®-promoted asymmetric hydrogenation reaction using an atom-economic transformation from simple and inexpensive precursors.

Keywords: asymmetric catalysis; hydrogenation; Roche ester; ruthenium

3-Hydroxy-2-methylpropionic acid methyl ester (Figure 1), known as Roche ester (**1a**), represents a major building block in organic synthesis. It is present in a substantial number of both naturally occurring and synthetic biologically relevant molecules.[1]

However, despite the huge number of papers demonstrating its wide potential synthetic value, there are surprisingly only few reports on the synthesis of **1a**,[2–7] which rely on the oxidative degradation of a chiral homoallylic acetate,[2] diastereoselective addition of chiral alcohols to arylketenes,[3] bacterial or microbial oxidation and enzyme-mediated transformations[4] or aldol chemistry.[5] Recently one example of an asymmetric hydrogenation reaction promoted by Rh-DUPHOS or Rh-BeePHOS catalysts was reported, with *ee* values ranging from 7 to 90%.[6] To the best of our knowledge, a method that provides a reliable and stereocontrolled direct access to the Roche ester-type derivatives **1** through Ru-catalyzed asymmetric hydrogenation has not been described, except for one example in a Japanese patent[7] using a Ru-BINAP catalyst and stabilizers to prevent polymerization. Consequently, the development of an efficient large-scale enantioselective synthesis of the Roche ester and its derivatives still remains a challenge and would find significant use in total syntheses.

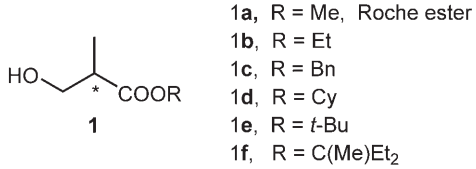
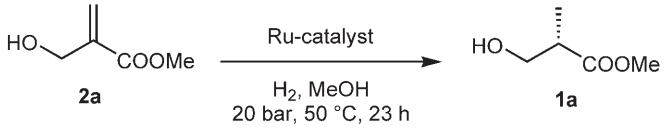


Figure 1. Roche esters type derivatives **1**.

Our interest in the preparation of biologically relevant natural products[8] such as discodermolide and dolabelide A[8b] required large quantities of both enantiomers of 3-hydroxy-2-methylpropanoic acid methyl ester (**1a**). Recently, we succeeded in designing and developing new chiral SYNPHOS ligands.[9] Our group has focused on expanding the versatile applications of SYNPHOS towards the synthesis of key intermediates and the preparation of target molecules of synthetic interest.[8] In this context, we report an efficient, high-yielding synthesis of both enantiomers of Roche ester derivatives **1** using a Ru-SYNPHOS-catalyzed asymmetric hydrogenation of readily available acrylate esters.

The required precursors **2a–f** for the hydrogenation reaction were easily prepared according to published procedures.[10] As outlined in Table 1, initial studies were directed toward the asymmetric hydrogenation of the methyl ester **2a**. A series of chiral Ru-SYNPHOS catalysts was examined to perform the hydrogenation reactions. All the catalytic tests were conducted under 20 bar and 50 °C in methanol for 23 h using 1 mol% of Ru-SYNPHOS complexes.

Table 1. Ru-(*R*)-SYNPHOS-promoted asymmetric hydrogenation of acrylate ester **2a**.



Entry	Ru-catalyst[a]	Conversion[b] (yield)[c]	*ee*[d]
1	{Ru[(*R*)-SYNPHOS](*p*-cymene)Cl}$^+$ Cl$^-$	100 (71)	72 (*S*)
2	{[RuCl((*R*)-SYNPHOS)]$_2$(μ-Cl)$_3$}$^-$ [NH_2Me_2]$^+$	100 (74)	77 (*S*)
3	Ru(cod)(η^3-methylallyl)$_2$ + (*R*)-SYNPHOS + HBr (2.2 equivs.)	100 (76)	79 (*S*)
4	Ru(cod)(η^3-methylallyl)$_2$ + (*R*)-SYNPHOS + HBF_4 (1.0 equiv.)	100 (68)	86 (*S*)

[a] 1 mol% of Ru-catalyst. (cod = cycloocta-1,5-diene; cot = cycloocta-1,3,5-triene).
[b] Conversion determined by ^{1}H NMR of crude product.
[c] Isolated yield after flash chromatography.
[d] Measured by HPLC (Chiralcel OD-H). The configuration was determined to be *S* by comparing with commercially available Roche ester **1a.**

Complete conversions were observed for all catalytic systems examined. However, the *ee* values of the Roche ester **1a** were highly dependent on the nature of chiral Ru-SYNPHOS catalysts.[11] The cationic [Ru((*R*)-SYNPHOS)(*p*-cymene)Cl]$^+$Cl$^-$ catalyst exhibited moderate activity and selectivity (Table 1, entry 1, 71% yield, 72% *ee*). An improvement was obtained by using {(RuCl[(*R*)-SYNPHOS])$_2$(μ-Cl)$_3$}$^-$ [NH_2Me_2]$^+$ (Table 1, entry 2, 74% yield, 77% *ee*). Finally, better results were achieved with the *in situ* generated Ru-SYNPHOS complex prepared according to our convenient procedure[12] by mixing Ru(cod)(η^3-methylallyl)$_2$ with SYNPHOS in the presence of methanolic hydrobromic acid (Table 1, entry 3, 76% yield, 79% *ee*). From this initial screening, we were pleased to find that [Ru(H)(η^6-cot)SYNPHOS)]$^+BF_4^-$ (**3**) catalyst[13] prepared by the addition of 1 equiv. of HBF_4 to a mixture of Ru(cod)(η^3-methylallyl)$_2$ and SYNPHOS in dichloromethane gave the best enantioselectivity and satisfactory yield (Table 1, entry 4, 68% yield, 86% *ee*). This cationic Ru-type pre-catalyst was synthesized for the first time in our group,[14a] fully characterized with Me-DuPHOS and used for the key diastereoselective step of a paradisone synthesis.[14] In all cases, Ru-(*R*)-SYNPHOS catalyst provided the desired (*S*)-enantiomer of the product resulting from the coordination of the Ru-catalyst with the alkene and the alcohol function of substrate **2**. Thus, anticipating that a bulkier ester function may induce increased *ee*, we subsequently investigated the hydrogenation of compounds **2a–f** by using [Ru(H)-(η^6-cot)(SYNPHOS)]$^+BF_4^-$ (**3**) catalyst.

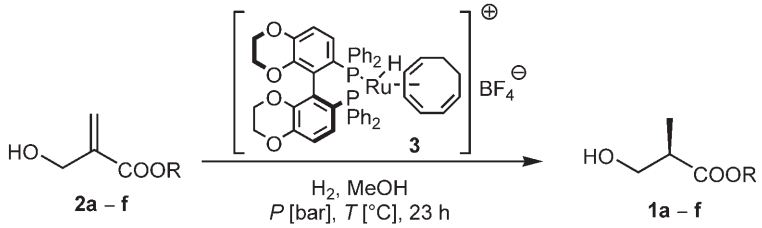
The results are presented in Table 2. Efforts were preliminary focused on the asymmetric hydrogenation of **2a** by varying the temperature and the catalytic amount of HBF_4 (1 to 2 mol%). The reactions were carried out under 5 to 80 bar of hydrogen pressure in methanol for 23 h.

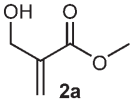
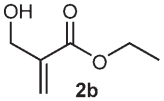
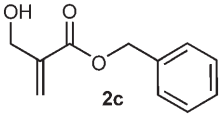
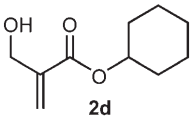
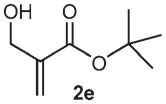
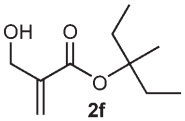
Upon heating to 80 °C and 90 °C, decreased yields were observed mainly due to the polymerization of the substrate (Table 2, entries 2 and 3, 64% and 53% yields), independently of the amount of HBF_4 (1 to 2 mol%). Anticipating that a lower temperature may induce better yield and enantiofacial discrimination, we performed the hydrogenation of **2a** at 20 °C, 15 °C and 5 °C. The yields and enantioselectivities were significantly enhanced (Table 2, entries 4–7, 69 to 92% yield, 86 to 88% *ee*) although a lower yield was obtained by using 1 mol% HBF_4 under the same conditions (Table 2, entry 5, 69% yield). Consequently, all reactions were conducted with 2 mol% of HBF_4. Afterwards, hydrogenation of **2a** was run in the presence of 0.5 mol% of benzoquinone at 15 °C to prevent polymerization and 3-hydroxy-2-methylpropionic acid methyl ester [(*R*)-**1a**] was obtained in 92% yield and 87% *ee* (Table 2, entry 6).

Our next aim was to carry out the hydrogenation on ethyl ester **2b**. In this case, similar results were achieved and 3-hydroxy-2-methylpropanoic acid ethyl ester [(*R*)-**1b**] was synthesized in 82% yield albeit with a slight decrease of the enantioselectivity (Table 2, entry 8, 83% *ee*). Changing the ethyl ester group to a benzyl **2c** or a cyclohexyl group **2d** led to the reaction being more effective in terms of both yield and selectivity (Table 2, entries 9 and 10). Especially in the case of the cyclohexyl ester group **2d**, the yield was increased to 96% with an *ee* value of 90%.

These results suggest that the stereochemical outcome of the reaction is greatly affected by the nature of the ester functionality: due to greater steric hindrance, a higher enantioselectivity was achieved. As expected, the use of the sterically hindered *tert*-butyl ester **2e** induced both an increase of yield and selectivity, with no influence of hydrogen pressure (Table 2, entries 11–16, 5 to 80 bar, 94% *ee*). It should be noted that the use of benzoquinone as stabilizer

Table 2. Enantioselective hydrogenation of substrates **2** using Ru-(*S*)-SYNPHOS catalyst **3**.[a]



Entry	Substrate	$HBF_4 \cdot Me_2O$ [mol%]	*P* [bar]	*T* [°C]	Yield[b] [%]	*ee*[c] [%]
1		1	20	50	68	86 (*R*)-**1a**
2		1	20	80	64	77 (*R*)-**1a**
3	 **2a**	2	20	90	53	76 (*R*)-**1a**
4		2	20	20	83	87 (*R*)-**1a**
5		1	20	20	69	86 (*R*)-**1a**
6		2	20	15	92[d]	87 (*R*)-**1a**
7		2	20	5	75	88 (*R*)-**1a**
8	 **2b**	2	20	20	82	83 (*R*)-**1b**
9	 **2c**	2	20	20	91	87 (*R*)-**1c**
10	 **2d**	2	20	20	96	90 (*R*)-**1d**
11		2	20	20	94	94 (*R*)-**1e**
12		2	80	20	93[d]	94 (*R*)-**1e**
13		2	50	20	95[d]	94 (*R*)-**1e**
14		2	5	20	94[e,d]	94 (*R*)-**1e**
15	 **2e**	2	5	20	98[e]	94 (*R*)-**1e**
16		2	5	20	95[e,f]	94 (*S*)-**1e**
17	 **2f**	2	5	20	95	94 (*R*)-**1f**

[a] *Conditions:* all reactions were performed using 1 mmol of substrate **2** in methanol for 23 h, catalyst loading, 1 mol%. In all cases, complete conversions were achieved.
[b] Isolated yield after flash chromatography.
[c] Measured by HPLC analysis (see Supporting Information).
[d] 0.5 mol% of benzoquinone is used.
[e] Hydrogenation carried out on a 5-gram scale.
[f] (*R*)-SYNPHOS was used instead of (*S*)-SYNPHOS.

had a positive effect only on substrates with a high tendency for polymerization, such as methyl ester **1a**. In all other cases, its use did not really change the chemical outcome of the reaction (see Table 2). With this encouraging result in hand, and keeping in mind that a bulky ester substituent is essential for obtaining high selectivity, we then turned our attention to the hydrogenation of the even more hindered 3-methylpentyl ester (Mpe)[15] **2f**. Disappointingly, the two added methyl groups have no impact on the course of the reaction and comparable results to those of the *tert*-butyl ester **2e** were obtained (Table 2, entry 17, 95% yield, 94% *ee*). Finally, we were pleased to find that under the optimized reaction conditions (5 bar, 20°C), hydrogenation of substrate **2e** with the Ru-SYNPHOS catalyst **3** afforded the desired (*R*)-**1e** product on a 5-gram scale with excellent isolated yield (98%) and an highly reproducible *ee* up to 94%.

In conclusion, highly efficient syntheses of Roche ester derivatives were successfully achieved with excellent isolated yields and enantioselectivities through ruthenium catalytic hydrogenation. To the best of our knowledge, this is one of the first reported uses of a chiral cationic Ru-catalyst based upon SYNPHOS ligand to effect this reaction in a simple way, with great atom-efficiency and under very mild conditions. Moreover, this transformation can be carried out with no stabilizers on a multigram scale.

Experimental Section

General Remarks

Unless otherwise stated, all reagents were used as purchased without further purification. All solvents were reagent grade and distilled under positive pressure of argon prior to use. CH_2Cl_2 was distilled from calcium hydride. Thin layer chromatography (TLC) was carried out on commercial 0.25 mm precoated plates Merck silica gel 60 PF 254 and visualized with either an ultraviolet lamp ($\lambda = 254$ nm) or a potassium permanganate solution. Flash column chromatography was performed on Merck silica gel (0.040–0.063 mesh). ^{1}H- and ^{13}C NMR spectra were recorded either at 300 MHz and 75 MHz, respectively, on a Bruker AC300 spectrometer. Mass spectra (MS) were measured on a Nermag R10–10C instrument by chemical ionization with ammonia (DCI/NH_3) or by electrospray (ESI) on a API 3000 PE Sciex instrument. High resolution mass spectra (HR-MS) were performed on a Varian MAT311 instrument at the Ecole Normale Supérieure (Paris). Optical rotation values were recorded on a Perkin–Elmer 241 polarimeter at 589 nm (sodium lamp) and are given in 10^{-1} deg cm^2 g^{-1}.

General Procedure for the Asymmetric Hydrogenation of Baylis–Hillman Adducts 2a–f

Chiral diphosphine (0.011 mmol) and (1,5-cyclooctadiene)Ru(2-methylallyl)$_2$ (3.2 mg, 0.010 mmol, commercially available from Acros), were placed in a round-bottomed tube, degassed by three vacuum/argon cycles at room temperature, and dissolved in degassed dichloromethane (1 mL). To this suspension was added dropwise at 0 °C, a freshly prepared solution of HBF_4·Me_2O in dichloromethane (130 μL, 0.022 mmol, 0.17 N). The reaction mixture was stirred at room temperature for 30 min and a resulting orange suspension was observed. After evaporation of the solvent under vacuum, a solution of the desired substrate **2a–f** (1 mmol) in 3 mL of MeOH was added to the ruthenium catalyst. The resulting mixture was placed under the desired hydrogen pressure and temperature for 23 h. After removal of the solvent, the residue was purified by flash chromatography on silica gel to afford the hydrogenated product **1a–f**.

Supporting Information

Characterization data for products **1a–f** are given in the Supporting Information.

Acknowledgements

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