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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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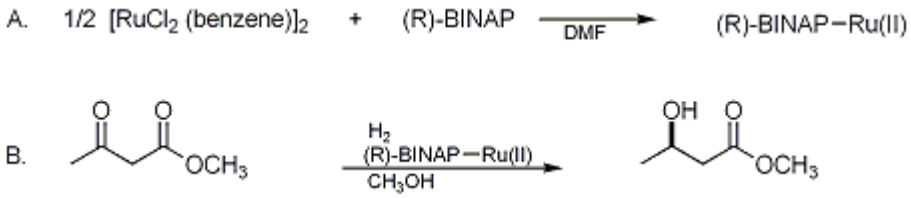
ASYMMETRIC HYDROGENATION OF 3-OXO CARBOXYLATES USING BINAP-RUTHENIUM COMPLEXES: (R)-(−)-METHYL 3-HYDROXYBUTANOATE

[Butanoic acid, 3-hydroxy-, methyl ester, (R)-]



Submitted by Masato Kitamura, Makoto Tokunaga, Takeshi Ohkuma, and Ryoji Noyori[1].
Checked by Jaechul Shim and Larry E. Overman.

1. Procedure

CAUTION! BINAP-Ru complexes are rapidly oxidized in solution in the presence of air and all procedures should be carried out under anaerobic conditions using degassed solvents.

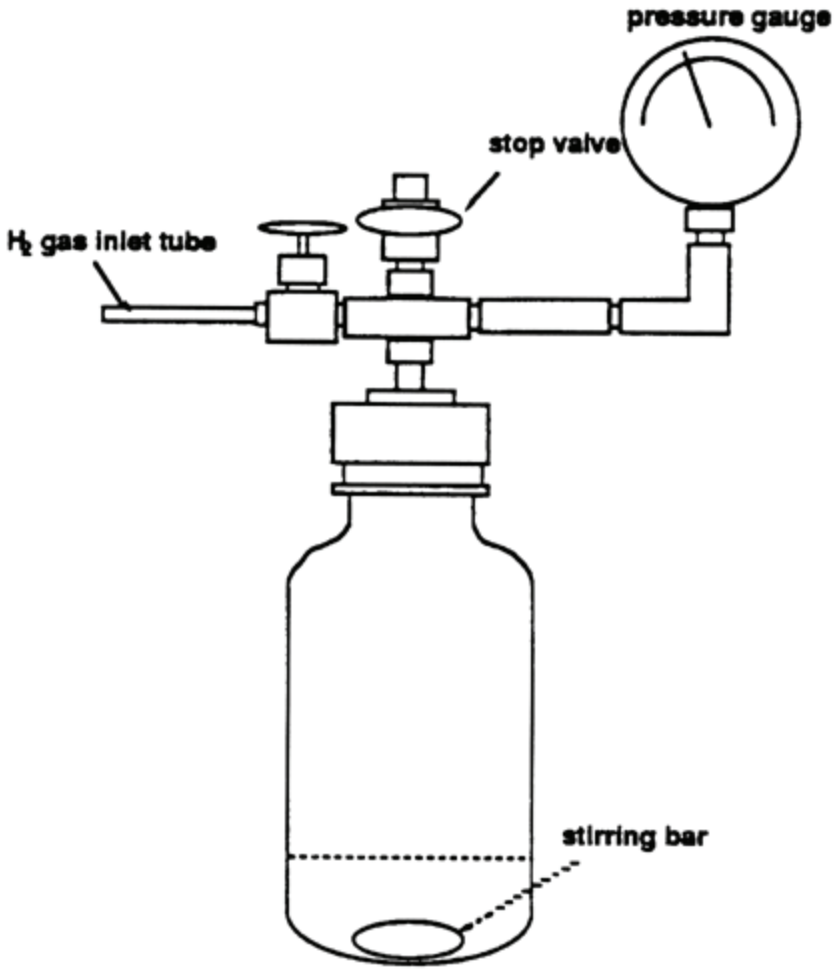
A. *[(R)-2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl]ruthenium(II) complex*. A dry, 80-mL Schlenk tube (Note 1) connected to a supply of argon (Note 2) is equipped with a Teflon-coated magnetic stirring bar and a glass stopper. The flask is charged with $[RuCl_2(benzene)]_2$ (130.5 mg, 0.261 mmol) (Note 3), (R)-BINAP (341 mg, 0.548 mmol) (Note 4), and then is evacuated and filled with argon. N,N-Dimethylformamide (DMF) (9 mL) (Note 5) is introduced with a hypodermic syringe under a stream of argon and the inlet is sealed by a glass stopper using silicon grease. The suspension is stirred at 100°C for 10 min under argon (Note 6), giving a clear reddish brown solution (Note 7). The reaction mixture is cooled and concentrated at 1 mm at 50°C with vigorous stirring and then at 0.1 mm for 1 hr to give 500 mg of (R)-BINAP-Ru(II) complex (Note 8) as a reddish brown solid, which is used as the hydrogenation catalyst.

B. *(R)-Methyl 3-hydroxybutanoate*. A 200-mL, dry Schlenk tube is charged with methyl 3-oxobutanoate (50.0 g, 0.431 mol) (Note 9) and methanol (50 mL) (Note 10) via hypodermic syringes. To this mixture is added the in situ prepared (R)-BINAP-Ru(II) complex (175 mg) (Note 11) under a stream of argon. The resulting yellowish orange solution (Note 12) is further degassed by two freeze-thaw cycles and then transferred by cannula to a dry, argon-filled, 500-mL glass autoclave equipped with a gas inlet tube, a septa-covered stop valve, and pressure gauge (Note 13). The gas inlet tube is attached to a hydrogen source (Note 14) and the air originally present in this tube and the autoclave is replaced by evacuation (to ca. 20 mm) and refilling with hydrogen five times. Hydrogen is introduced into the reaction vessel until the pressure gauge indicates 3 atm. The pressure is carefully released to 1 atm by opening the stop valve. This procedure is repeated three times, and finally hydrogen is pressurized to 4 atm (Note 15). The yellowish orange solution is vigorously stirred at 100°C for 6 hr during which time the hydrogen cylinder is kept connected. After the main valve of the hydrogen cylinder is closed, the reaction mixture is allowed to cool to room temperature, excess hydrogen is carefully bled off, and the apparatus is disassembled. The deep reddish orange contents (Note 16) are placed in a 300-mL, round-bottomed flask, and the glass autoclave is rinsed with three 20-mL portions of dichloromethane. The solvent is removed by a rotary evaporator, and the residue (Note 17) is distilled to give 47–49 g (92–96% yield) of (R)-(−)-methyl 3-hydroxybutanoate in 97–98% ee as a fraction boiling at 40°C, 2 mm (Note 18).

2. Notes

1. All the apparatus is dried overnight in a 120°C oven before use.
2. Argon gas (99.998%) is purified by passing through the BASF catalyst R3-11 column at 80°C and then through 4 Å molecular sieves.
3. $[RuCl_2(benzene)]_2$, available from Aldrich Chemical Company, Inc., is used without purification.
4. BINAP is 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl.[2]
5. Guaranteed grade DMF, available from NACALAI TESQVE, Inc. (the checkers used DMF, Certified A.C.S., from Fisher Scientific Company), is distilled over 4 Å molecular sieves under argon before use and stored in a 100-mL Schlenk tube. It is degassed by three freeze-thaw cycles.
6. Reaction at a higher temperature for a longer period leads to formation of the ruthenium carbonyl complex [IR(KBr) 1964 cm^{-1}]. This undesired reaction is suppressed under the present conditions. Use of commercial $[RuCl_2(1,5\text{-cyclooctadiene})]_n$ or readily available $RuCl_2[Sb(C_6H_5)_3]_3$[3] gives similar results on heating in DMF at 160°C for 20 min or in o-dichlorobenzene at 160°C for 10 min. N,N-Dimethylacetamide can be used in place of DMF.
7. The solution is probably a crude mixture of cationic BINAP-Ru(II) complexes such as $[RuCl(BINAP)(DMF)_3]Cl$ and $[Ru(BINAP)(DMF)_4]Cl_2$. The physical properties are as follows: conductivity 27 Scm^2/mol (DMF); ^{31}P NMR (4:1 DMF-$CDCl_3$) δ: 60.6 (d, J = 46), 61.4 (d, J = 46), 61.8 (s). The DMF solution can be used directly for hydrogenation although the reactivity is one-half that of the dried material (Note 8).
8. This complex is probably a mixture of neutral BINAP-Ru(II) complexes such as $RuCl_2(BINAP)(DMF)_2$ and $[RuCl_2(BINAP)(DMF)]_n$. The physical properties are as follows: conductivity 0.4 Scm^2/mol (CH_2Cl_2); ^{31}P NMR ($CDCl_3$) δ: 53.7 (d, J = 41), 54.5 (d, J = 42), 54.8 (d, J = 39), 57.4 (d, J = 41), 59.7 (d, J = 42), 61.5 (d, J = 39).
9. Methyl 3-oxobutanoate, available from NACALAI TESQVE, Inc. (the checkers used ester purchased from Aldrich Chemical Company, Inc.), is distilled over 4 Å molecular sieves under argon and stored in a 200-mL Schlenk tube. It is degassed by three freeze-thaw cycles before use.
10. Guaranteed-grade methanol is dried and degassed at refluxing temperature over magnesium methoxide (from magnesium turnings) under a stream of argon for 6 hr and distilled into a 2-L Schlenk flask. It is further degassed by three freeze-thaw cycles before use.
11. The complex is weighed quickly in the air.
12. The ruthenium complex is moderately soluble in methanol. Suspension in an ultrasonic cleaning bath is employed to achieve complete solution.
13. The glass autoclave is evacuated and filled with argon five times before use. The apparatus is shown in Figure 1. Inside diameter and length are 7 and 14 cm. A Teflon-coated stirring bar of ca. 2 by 4 cm is recommended. The submitters report that vigorous stirring and use of a wide-shaped autoclave (Figure 1) are important in obtaining high yields.

Figure 1. A low-pressure hydrogenation apparatus.



14. Hydrogen of 99.99999% purity (Nippon Sanso) is used. The checkers employed 99.99% grade hydrogen.
15. Satisfactory results are not obtained at atmospheric hydrogen pressure, with slow conversion even at 100°C.
16. The color changes gradually to dark green in the air.
17. Gas chromatographic analysis indicates that the yield of methyl 3-hydroxybutanoate is 98%: column, PEG-20M on Chromosorb WAW (Stainless steel 3 m × 3 φ, Gasukuro Kogyo); column temperature, 120°C; injector temperature, 160°C, carrier nitrogen pressure, 1.2 kg/cm^2; t_R of methyl 3-oxobutanoate, methyl 3,3-dimethoxybutanoate, and methyl 3-hydroxybutanoate are 31.5, 34.0 and 41.7 min, respectively.
18. The product has the following spectral properties: ^{1}H NMR (270 MHz, $CDCl_3$) δ: 1.24 (d, 3, J = 6.3, CH_3CHOH), 2.43 (dd, 1, J = 8.3 and 16.5, CHH), 2.52 (dd, 1, J = 4.3 and 16.5, CHH), 3.01 (br s, 1, OH), 3.72 (s, 3, CH_3O), 4.2–4.3 (m, 1, CHOH); IR ($CHCl_3$) cm^{-1}: 3450, 2980, 1735, 1440, 1380, 1285, 1180, 1070, 1005; $[\alpha]_D^{25}$ −23.1° to −23.6° (neat) [lit.[4] $[\alpha]_D^{22}$ −23.5° (neat)]. The enantiomeric excess is determined to be 97–98% by HPLC analysis after converting an aliquot of the product to the (R)-α-methoxy-α-trifluoromethylphenylacetate [(R)-MTPA ester]. An aliquot of the crude reaction product (17.5 mg, 148 μmol) is dissolved in dichloromethane (0.5 mL). To this solution are added (S)-MTPACI (75.0 mg, 297 μmol) (Note 19) and pyridine (50 μL) and the mixture is kept at 20°C for 12 hr. To this are added ether (2 mL) and water (1 mL) and the mixture is vigorously stirred for 15 min. The aqueous layer is extracted with two 2-mL portions of ether and the combined organic layers are successively washed with 1 N hydrochloric acid (3 mL), 1 N sodium hydroxide (3 mL), water (3 mL), and brine (3 mL). Drying over anhydrous sodium sulfate, evaporation of the solvent under reduced pressure, and purification by flash chromatography [silica gel (Fuji Davison BW 300), 2 g; eluent, 1:20 and then 1:7 ether-hexane mixture] afford 45 mg (91% yield) of the (R)-MTPA ester. ^{1}H NMR (270 MHz, $CDCl_3$) δ:

1.34 (d, 3, J = 6.3, CH_3), 2.57 (dd, 1, J = 4.6 and 16.2, CHH), 2.74 (dd, 1, J = 8.6 and 16.2, CHH), 3.53 (br s, 3, J = 1.3, CH_3OCCF_3), 3.67 (s, 3, CH_3OCO), 5.55 (ddq, 1, J = 4.6 and 8.6 and 6.3, CHOCO), 7.3–7.6 (m, 5, aromatic). HPLC analysis of this ester [column, YMC 003-3 SIL (250 mm × 4.6 mm) and 002-3 SIL (150 mm × 4.6 mm); eluent, 1:5 ether-hexane mixture] shows two signals with t_R of 18.6 and 20.7 min in a 98.9:1.1 ratio assignable to the (R,R-) and (R,S)-diastereomers, indicating 98% ee. The checkers used a SUPELCOCIL LC-SI column (250 mm × 4.6 mm); eluent 7:1 hexane-ethyl acetate with RI detection and observed two signals (t_R, 13.7 and 15.0 min) with 98.6:1.4 ratio, indicating 97% ee.

19. The (S)-MTPACI is prepared by Mosher's method[5] from (R)-α-methoxy-α-(trifluoromethyl) phenylacetic acid purchased from Aldrich Chemical Company, Inc.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Optically pure alkyl (R)-3-hydroxybutanoates can be obtained by alcoholysis of poly-(R)-3-hydroxybutanoate, a fermentation product of fructose by *Alcaligenes eutrophus*.[4] (S)-Ethyl 3-hydroxybutanoate in 84–87% ee can be synthesized in 57–67% yield on a decagram-scale by an *Organic Syntheses* procedure[6] using bakers' yeast reduction of ethyl 3-oxobutanoate with the aid of sucrose.[7] In order to obtain enantioselectivity as high as 95–97% ee, the substrate concentration should be kept below 1 g/L.[8]

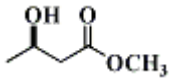
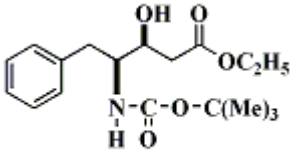
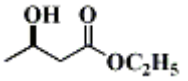
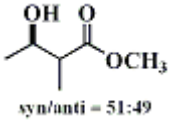
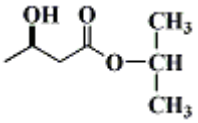
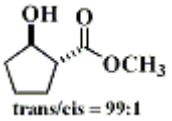
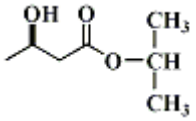
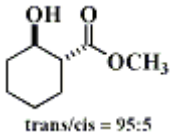
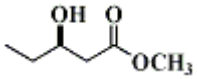
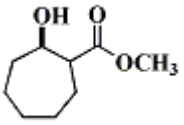
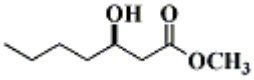
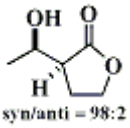
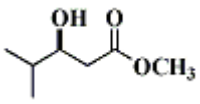
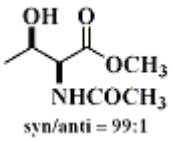
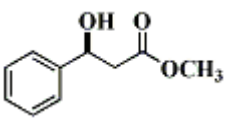
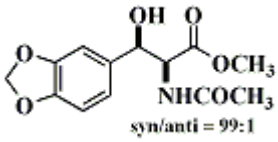
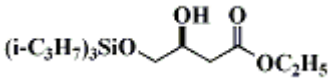
Among some syntheses of optically active 3-hydroxy carboxylates including optical resolution,[9] enantioselective aldol reactions between aldehydes and chirally-modified enolates,[10] cinchona alkaloid-catalyzed [2+2] cycloaddition between aldehydes and ketene,[11] enantioselective hydride reduction[12] or hydrogenation[13,14] of 3-oxo carboxylic acid derivatives, the most simple and most desirable would be asymmetric hydrogenation of 3-oxo carboxylates aided by chiral metal catalysts. Methyl 3-oxobutanoate can be hydrogenated by using a homogeneous chiral phosphine rhodium complex[13] and heterogeneous Raney nickel catalyst modified by tartaric acid and sodium bromide,[14] affording methyl 3-hydroxybutanoate in up to 71% ee and 87% ee, respectively.

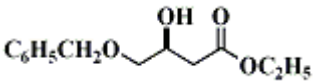
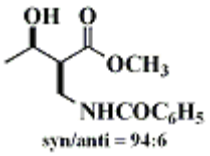
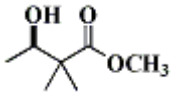
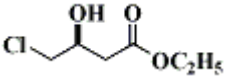
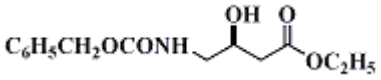
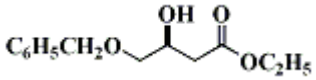
Hydrogenation of 3-oxobutanoic acid esters catalyzed by $Ru(OCOCH_3)_2$ [(R)-BINAP][15] proceeds slowly and in very low optical yield. However, addition of two equivalents of hydrogen chloride to the ruthenium complex facilitates the hydrogenation of methyl 3-oxobutanoate in methanol under the 100-atm, room temperature conditions to give the corresponding (R)-hydroxy ester in 97% isolated yield and in greater than 99% ee. RuX_2(BINAP) (empirical formula, X = Cl, Br, or I),[16] is prepared by mixing Ru $(OCOCH_3)_2$ (BINAP) and hydrogen chloride, hydrogen bromide, hydrogen iodide, or iodotrimethylsilane in a 1:2 mole ratio followed by removal of the solvent. [RuCl(benzene)(BINAP)]Cl[17] or $Ru_2Cl_4(BINAP)_2[N(C_2H_5)_3]$[18] are also usable as catalyst precursor. The present crude BINAP-Ru (II) complexes prepared by high-temperature ligand exchange[19] possess reactivities and selectivities comparable to these materials. In research laboratories, one may conduct relatively small-scale reactions in a Parr apparatus or an ordinary thickwalled glass vessel equipped with a Young's tap under pressure as low as 4 atm and at 80–100°C.[20] Large-scale reactions are performed conveniently under high pressure by using a stainless steel autoclave at room temperature.

The present catalytic, asymmetric hydrogenation using BINAP-Ru(II) complexes is the first practical chemical procedure for the preparation of (R)- or (S)-3-hydroxybutanoates. Characteristic features of this method include high chemical and optical yields, high efficiency of chiral multiplication (a substrate to catalyst mol ratio of >1000), easy access to both antipodes, clean reactions with high (up to 50%) substrate concentrations, and simple isolation of products by distillation. Some examples of the high-pressure, enantioselective hydrogenation of 3-oxo carboxylates using halogen-containing preformed BINAP-Ru(II) complexes are given in the Table.[21]

TABLE

OPTICALLY ACTIVE 3-HYDROXY CARBOXYLATES OBTAINED BY (R)-BINAP-Ru-CATALYZED ASYMMETRIC HYDROGENATION OF 3-OXO CARBOXYLATES[a]

Product	% ee	Product	%ee
	>99	 syn/anti = >99:1	99
	99	 syn/anti = 51:49	syn, 97 anti, 98
	98	 trans/cis = 99:1	92[c]
	98		
 trans/cis = 95:5	100		90[c]
 trans/cis = 93:7	98		93[c]
 syn/anti = 98:2	>99		
	85	 syn/anti = 99:1	94
	95	 syn/anti = 99:1	98[c]
	98[b]		

	97[b]	 syn/anti = 94:6	94[c]
	88		98[c]
	99		96

[a]Hydrogenation catalyzed by performed RuX_2 (BINAP) (X = Cl, Br, or I) at room temperature at 100 atm of hydrogen. [b]100° C. [c]In CH_2Cl_2.

This method has been used to effect practical asymmetric syntheses of carnitine[22] and statine,[23] important, unusual amino acids. Highly stereoselective hydrogenation via dynamic kinetic resolution has been realized with chirally-labile, racemic, 2-substituted 3-oxo carboxylic esters,[24,25,26] allowing stereocontrolled synthesis of natural and unnatural threonine, DOPS (anti-Parkinsonian agent), a useful intermediate for the synthesis of compounds such as carbapenems or carbocyclic analogues of prostacyclin. This methodology can be further extended to a variety of functionalized ketones that have directive groups such as dialkylamino, hydroxyl, alkoxyl, siloxyl, keto, alkoxycarbonyl, alkylthiocarbonyl, (dialkylamino)-carbonyl, carboxyl, dialkoxyphosphoryl, and halogen.[27]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 9, 169
- Org. Syn. Coll. Vol. 9, 483
- Org. Syn. Coll. Vol. 9, 487

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

BINAP

(R)-(−)-Methyl 3-hydroxybutanoate

[(R)-2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl]ruthenium(II) complex

(R)-BINAP

(R)-BINAP-Ru(II) complex

hydrogen chloride,
hydrochloric acid (7647-01-0)

ethyl acetate (141-78-6)

methanol (67-56-1)

ether (60-29-7)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

magnesium turnings (7439-95-4)

hydrogen bromide (10035-10-6)

sodium bromide (7647-15-6)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

sucrose

Raney nickel (7440-02-0)

pyridine (110-86-1)

hydrogen iodide (10034-85-2)

tartaric acid (87-69-4)

ethyl 3-oxobutanoate (141-97-9)

magnesium methoxide

dichloromethane (75-09-2)

fructose (57-48-7)

N,N-dimethylformamide (68-12-2)

hexane (110-54-3)

methyl 3-oxobutanoate (105-45-3)

threonine (72-19-5)

argon (7440-37-1)

3-oxobutanoic acid (541-50-4)

ruthenium (7440-18-8)

N,N-dimethylacetamide (127-19-5)

Iodotrimethylsilane (16029-98-4)

o-dichlorobenzene (95-50-1)

methyl 3-hydroxybutanoate

2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (76189-56-5)

(R)-Methyl 3-hydroxybutanoate,
Butanoic acid, 3-hydroxy-, methyl ester, (R)- (3976-69-0)

(S)-Ethyl 3-hydroxybutanoate (56816-01-4)

phosphine rhodium

carnitine

(R)-α-methoxy-α-(trifluoromethyl)phenylacetic acid,
(R)-α-methoxy-α-trifluoromethylphenylacetate (20445-31-2)

methyl 3,3-dimethoxybutanoate