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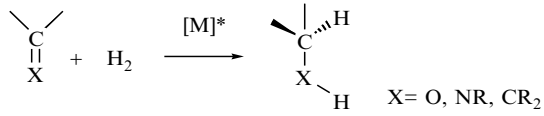
9 Asymmetric Reduction of Ketones Using Organometallic Catalysts

CONTENTS

9.1 INTRODUCTION

Asymmetric catalytic reduction reactions represent one of the most efficient and convenient methods to prepare a wide range of enantiomerically pure compounds (i.e. α-amino acids can be prepared from α-enamides, alcohols from ketones and amines from oximes or imines). The chirality transfer can be accomplished by different types of chiral catalysts: metallic catalysts are very efficient for the hydrogenation of olefins, some ketones and oximes, while nonmetallic catalysts provide a complementary method for ketone and oxime hydrogenation.



Enantioselective catalysis using chiral metal complexes provides a flexible method for asymmetric hydrogenation. The metallic elements possess a variety of catalytic activities and their combination with organic ligands or auxiliaries that direct the steric course can give very efficient catalytic complexes. Well-designed chiral metal complexes can discriminate precisely between enantiotopic groups, or faces, and catalyse the formation of a wide range of natural and unnatural substances with high enantiomeric purity. Asymmetric reduction with a transition metal can use molecular hydrogen (hydrogen gas) as the source of hydrogen or nonhazardous organic molecules as donors of hydrogen such as formic acid or 2-propanol. This last method, hydrogen transfer, can provide a complement to the catalytic reduction using molecular hydrogen[1].

The first enantioselective hydrogenation of unsaturated compounds was using metallic catalysts deposited on chiral supports in the 1930s[2]. In the 1950s, using this method an enantioselectivity exceeding 60% was obtained[3]. Knowles[4] and Horner[5] in 1968 reported homogeneous asymmetric hydrogenation using rhodium–chiral tertiary phosphine complexes.

Nonmetallic systems (Chapter 11) are efficient for catalytic reduction and are complementary to the metallic catalytic methods. For example lithium aluminium hydride, sodium borohydride and borane–tetrahydrofuran have been modified with enantiomerically pure ligands[6]. Among those catalysts, the chirally modified boron complexes have received increased interest. Several ligands, such as amino alcohols[7], phosphino alcohols[8,9] and hydroxysulfoximines[10], complexed with the borane, have been found to be selective reducing agents.

In 1969, Fiaud and Kagan[11] tested ephedrine boranes but achieved only 3.6–5% enantiomeric excess in the reduction of acetophenone. Itsuno *et al.*[12] reported in 1981 an interesting enantioselective reduction of a ketone using an amino alcohol–borane complex as a catalyst. Buono[13] investigated and developed the reactivity of phosphorus compounds as ligands in borane complexes for asymmetric hydrogenation.

Enzyme reductions of carbonyl groups have important applications in the synthesis of chiral compounds (as described in Chapter 10). Dehydrogenases are enzymes that catalyse, for example, the reduction of carbonyl groups; they require co-factors as their co-substrates. Dehydrogenase-catalysed transformations on a practical scale can be performed with purified enzymes or with whole cells, which avoid the use of added expensive co-factors. Bakers' yeast is the whole cell system most often used for the reduction of aldehydes and ketones. Biocatalytic activity can also be used to reduce carbon–carbon double bonds. Since the enzymes for this reduction are not commercially available, the majority of these experiments were performed with bakers' yeast[14].

In summary, the asymmetric hydrogenation of olefins or functionalized ketones catalysed by chiral transition metal complexes is one of the most practical methods for preparing optically active organic compounds. Ruthenium– and rhodium–diphosphine complexes, using molecular hydrogen or hydrogen transfer, are the most common catalysts in this area. The hydrogenation of simple ketones has proved to be difficult with metallic catalysts. However,

asymmetric borane complexes are used as nonmetallic catalysts for the hydrogenation of simple ketones, like acetophenone. They can give the corresponding alcohol in high yield and enantiomeric excess. The use of oxidoreductases contained in bakers' yeast can give good results for reduction of carbonyl and carbon–carbon double bonds.

In contrast to the enantioselective reduction of alkenes or ketones, few catalytic systems have been described for the enantioselective reduction of imines. The nature of the *N*-substituent and the *E/Z*-isomerism caused by the carbon–nitrogen double bond of the substrate are important parameters for the control of the enantioselectivity[15]. The enantioselective hydrogenation of carbon–nitrogen bonds has been reported to occur in the presence of iridium, ruthenium,[1,16,17] titanium,[18–20] zirconium or cobalt[21], with chiral diphosphine ligands. Iridium catalysts have been successfully employed in the hydrogenation of *N*-arylimines.[22–25] Rhodium catalysts have been used for the reduction of imines and nitrones.[26,27] The employment of chiral auxiliaries for the activation of borane reagents in carbon–nitrogen double bond reduction has been shown to induce high enantioselectivities. However, it is quite difficult to maintain the high enantiomeric excesses, obtained by using stoichiometric amounts of such auxiliaries, in a catalytic version of the reduction[28]. The substrates which lead to the best results are oxime ethers. The oxazaborolidine derived from valinol is a very efficient chiral auxiliary for oxime ether reduction with borane. The oxazaphospholidine derived from prolinol (developed by Buono *et al.*) induce enantioselectivity in the reduction of imines[8].

In this chapter and in Chapters 10–12, we will review and validate some methods for asymmetric (transfer) hydrogenation of carbon–oxygen and carbon–carbon double bonds catalysed by non-metallic systems, homogeneous transition metal catalysts and biocatalysts. Reduction of carbon–nitrogen double bond systems will be reported in another volume of this series.

9.2 ASYMMETRIC HYDROGENATION USING A METAL CATALYST: [RU((*S*)-BiNAP)]

Few catalysts have been found to produce chiral alcohols from a range of ketones with both high levels of absolute stereocontrol and high catalytic efficiencies[29]. Metallic catalysts are generally used for the asymmetric hydrogenation of functionalized ketones. High enantioselectivities (>98% ee) have been observed in the hydrogenation of a variety of β-keto esters using 2,2′-bis(phosphino)-1,1′-biaryl (BINAP)-derived catalysts such as ruthenium–BINAP[30]. For the hydrogenation of simple ketones, nonmetallic catalysts like chiral borane complexes are often preferred (Chapter 11).[31,32] Biocatalytic reduction with bakers' yeast is used for reduction of ketones such as β-ketoesters, β-diketones, α-hydroxy ketones, aliphatic and aromatic ketones[33] (Chapter 10).

The mechanism of a metal-catalysed reduction is believed to proceed as described in Figure 9.1.

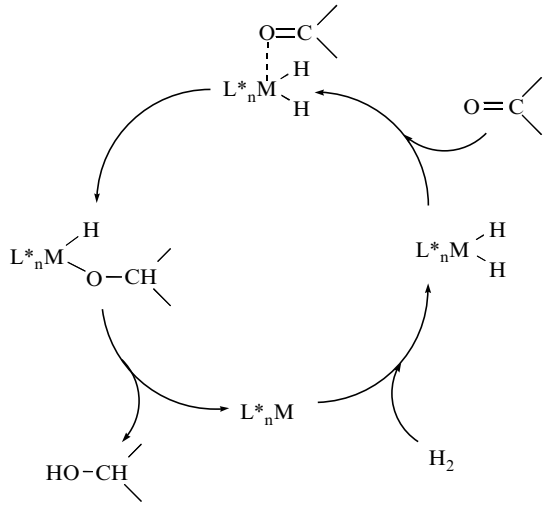
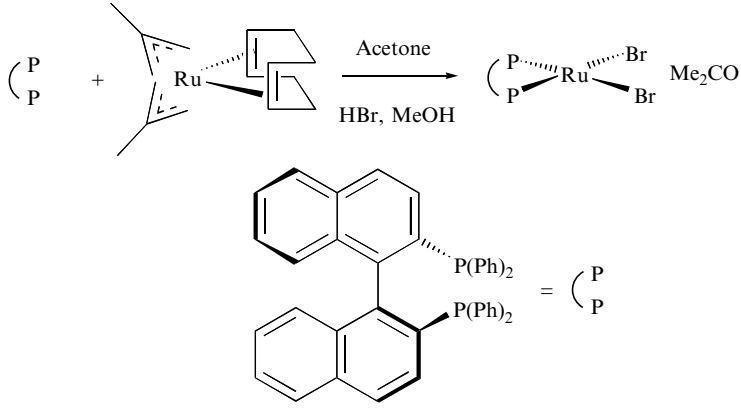


Figure 9.1 Catalytic cycle for hydrogenation of carbonyl compounds.

The method developed by Noyori using $[Ru(BiNAP)Cl_2](NEt_3)$ as catalyst requires high temperatures and/or hydrogen pressures (100 atm)[30]. As this method needs a specific set-up for hydrogenation at high pressure, it was not possible for us to validate this procedure. However, Genêt reported[34, 35] that the catalyst $[Ru(BiNAP)Br_2]$(acetone) can give good results for the hydrogenation of β-ketoesters at atmospheric pressure.



S-BiNAP

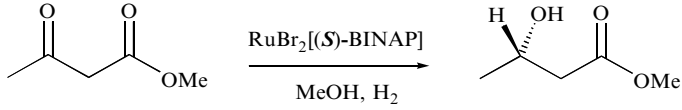
Materials and equipment

- $[Ru(allyl)_2(COD)_n]$, 6 mg, 0.019 mmol, 0.02 eq
- (*S*)-(−)-2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl [(*S*)-BiNAP], 21 mg, 0.033 mmol, 0.035 eq
- Anhydrous acetone degassed (nitrogen) for 30 minutes, 30 mL
- Anhydrous methanol degassed (nitrogen) for 30 minutes, 30 mL

  As the catalyst is very sensitive to oxygen, the solvents were degassed with nitrogen just before use.
- Hydrobromic acid 48 %, 1.0 mL
- Hydrobromic acid solution 0.6 *M* prepared by mixing 9 mL of degassed methanol and 1 mL of hydrobromic acid 48 %
- Methyl acetoacetate, 100 μL, 0.93 mmol

  Methyl acetoacetate was dried with magnesium sulfate which was activated at 500 °C for 2 hours cooled under vacuum and stored under nitrogen.
- Petroleum ether, ethyl acetate, methanol
- Silica gel 60 (0.063–0.04 mm)
- *p*-Anisaldehyde

- 50 mL Schlenk tube
- Egg-shape magnetic stirrer bar
- Low-pressure hydrogenation apparatus fitted with a gas burette system to measure the hydrogen consumed[36]
- Rotary evaporator
- Kugelrohr apparatus



Procedure

1. A 50 mL Schlenk tube was dried overnight in a oven at 150 °C, cooled under vacuum and flushed with nitrogen.
2. The Schlenk tube was filled with $[Ru(allyl)_2(COD)_n]$ (6 mg), ((*S*)-BiNAP) (21 mg) and purged twice using vacuum/nitrogen cycles. Anhydrous acetone was added (2 mL) to give a white suspension. The solution was stirred for 30 minutes at room temperature.
3. To this suspension was added a solution of HBr (0.6 *M*, 0.11 mL). The suspension was stirred for 30 minutes at room temperature. After 15 minutes a yellow precipitate appeared.
4. The solvent was removed by evaporation under high vacuum over 3 hours to give a yellow powder, which was used as the catalyst without any further purification.

5. The Schlenk tube containing the catalyst was filled with degassed methanol (20 mL) and methyl acetoacetate (100 μL); the brown suspension was placed under nitrogen.
6. The Schlenk tube was connected to a low-pressure hydrogenation apparatus fitted with a gas burette system to measure the hydrogen consumed. The Schlenk tube was flushed through three cycles (reduced pressure/hydrogen) and then placed under an atmospheric pressure of hydrogen. The burette was filled with 200 mL of hydrogen.

   Never allow naked flames in the vicinity when hydrogen is being used. Avoid the formation of air–hydrogen mixtures. Any electrical apparatus in the vicinity must be spark-proof. It is far better for the apparatus to be kept in a separate room specially designed for hydrogenations.

7. The solution was vigorously stirred to increase the contact area of the reactants with the hydrogen atmosphere. The solution became lighter brown. The reaction was stopped after 48 hours (no more hydrogen was consumed), by removing the hydrogen using reduced pressure.
8. The reaction was monitored by TLC (eluent: petroleum ether–ethyl acetate; 75:25). The methyl acetoacetate was UV active, stained yellow with *p*-anisaldehyde, R_f 0.5. No starting material remained after 48 hours.
9. The solution was filtered through a pad of silica gel to remove the catalyst and the filter residue was washed with methanol. The solvent was removed under reduced pressure using a rotary evaporator (water bath at 30 °C) to give a slightly brown oil.
10. The residue was distilled with a Kugelrohr apparatus under water aspirator vacuum (approximately 20 mbar, 140 °C) to give (*S*)-methyl-(3)-hydroxybutanoate (105 mg, 99 %).

    The ee (>98 %) was determined by chiral GC (Lipodex® E, 25 m, 0.25 mm ID, temperatures: column 90 °C isotherm, injector 250 °C, detector 250 °C, mobile phase helium). R_t (*R*)-enantiomer: 13.5 min; R_t (*S*)-enantiomer: 15.2 min.

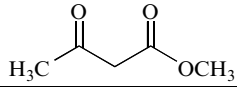
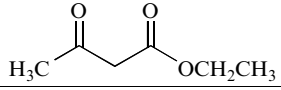
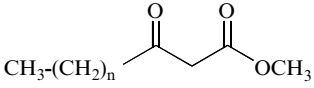
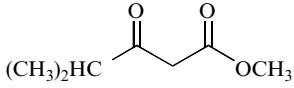
    ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.22 (m, 1H, C*H*OH); 3.72 (s, 3H, OCH_3); 2.56 (br s, 1H, O*H*); 2.46 (d, *J* 6.3 Hz, 2H, CH_2); 1.23 (d, *J* 6.1 Hz, 3H, CH_3CHOH).

    Mass: calculated for $C_5H_{10}O_3$: *m/z* 118.06299, found $[M]^+$ 118.06286.

Conclusion

Hydrogenation with Noyori's catalyst required a customized rig for hydrogenation at high pressure to give good results for a large range of substrates. The Genêt modification does not require pressure and the catalyst can be prepared *in situ* which made the reaction very easy to carry out. Table 9.1 gives examples of the different substrates which can be hydrogenated by Noyori's[37] and Genêt's methods[35].

Table 9.1 Asymmetric hydrogenation of β-keto esters using [Ru(BiNAP)] complexes (results according to the relevant publications).

	[$RuCl_2$((R)-BINAP)][37] 70 to 100 atm. of H_2 Yield %, ee %	[$RuBr_2$((*S*)-BINAP)][35] 1 atm. of H_2 Yield %, ee %
	>99, >99	99, >98*
	99, 99	–
	n=3; 99, 98	n=1; 100, 99 n=14; 100, 96
	99, >99	100, 97

* Rection validated

Alternatively, bis(phospholane) ligands can be very effective for the hydrogenation of carbonyl groups. Using a hydrogen pressure of only 60 psi, the hydrogenation of β-ketoesters by [Ru((*R,R*)–*i*Pr-BPE)Br_2] (0.2 mol%) gives high catalytic efficiency (100 % conversion, 99 % enantiomeric excess) according to the literature[38]. This procedure (not validated in this volume) is similar to the one described later in this chapter for the hydrogenation of olefins using [(COD)Rh(Me-DuPHOS)] and [(COD)Rh(Me-BPE)] catalysts.

9.3 ASYMMETRIC TRANSFER HYDROGENATION OF *β*-KETOESTERS

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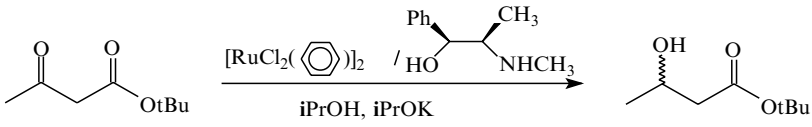


Materials and equipment

- Anhydrous 2-propanol, 19 mL
- *tert*-Butyl acetoacetate (98 %), 316 mg, 2 mmol
- di-μ-Chlorobis[(benzene)chlororuthenium (II)], 5 mg, 0.01 mmol*
- (1*S*,2*R*)-(+)-Ephedrine, 6.6 mg 0.04 mmol
- Potassium 2-propylate solution, 0.12 mol.L^{-1}
- Ethyl acetate, distilled water
- Hydrochloric acid
- Sodium chloride
- Magnesium sulfate

- Two Schlenk tubes
- Magnetic stirrer plate
- Oil bath
- Vacuum line

Procedure

1. In a Schlenk tube equipped with a magnetic stirrer bar were placed under nitrogen $[Ru(benzene)Cl_2]_2$ (5 mg), ephedrine (6.6 mg) and dry 2-propanol (5 mL) previously degassed by three freeze–thaw cycles. The mixture was stirred for 20 minutes at 80 °C to give an orange solution which was allowed to cool to room temperature.
2. In a second Schlenk tube were placed under nitrogen *tert*-butyl acetoacetate and dry 2-propanol (14 mL). The mixture was degassed and added to the first solution. Finally, degassed potassium 2-propylate solution (1 mL) was added. The resulting orange solution was stirred at room temperature.
3. The reaction was monitored by GLC (BPX5 25 m × 0.32 mm column, 0.8 bar N_2, 60 °C).
4. After completion of the reaction (1 hour), the solution was neutralized with dilute hydrochloric acid and the solvent removed *in vacuo*. The residue was diluted with ethyl acetate and the organic solution was washed with saturated aqueous sodium chloride. The organic layer was dried over magnesium sulfate, concentrated under reduced pressure and distilled to afford *tert*-butyl 3-hydroxybutyrate (80 %).

   The ee (44 % in the *S* enantiomer) was determined by GLC (CHIRASIL-DEX CB 25 m × 0.25 mm column, 0.8 bar H_2, 85 °C); (*S*)-enantiomer: R_t 11.7 min, (*R*)-enantiomer: R_t 12.1 min.

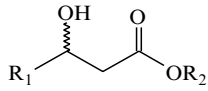
   ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 4.02 (m, *J* 6 Hz, 1H, C<u>H</u>(OH)); 3.5 (s, 1H, O<u>H</u>), 2.2 (d, *J* 6 Hz, 2H, C<u>H</u>$_2$); 1.35 (s, 9H, C(C<u>H</u>$_3$)$_3$); 1.09 (d, *J* 6 Hz, 3H, C<u>H</u>$_3$).

   ^{13}C NMR (300 MHz, $CDCl_3$): δ (ppm) 172.1 (<u>C</u>OO); 80.9 (<u>C</u>(CH$_3$)$_3$); 64.2 (<u>C</u>H(OH)); 43.9 (<u>C</u>H$_2$); 27.9 (C(<u>C</u>H$_3$)$_3$); 22.3 (<u>C</u>H$_3$).[i]

* M. Bennett, A. Smith, *J. Chem. Soc., Dalton Trans.* 1974, 233.

Conclusion

This procedure offers a simple alternative for the reduction of β-ketoesters which does not require the use of an autoclave or hydrogen. The reaction is easily reproducible and leads to virtually quantitative yields of β-hydroxyesters under mild conditions. The use of sterically hindered esters, i.e. *iso*-propyl or *tert*-butyl β-ketoesters, significantly improves the catalytic activity, so that reactions go to completion in a reasonable time at room temperature (see below). When the reaction time is too long, transesterification may occur, giving rise to a mixture of an alkyl β-hydroxyester and the corresponding *iso*-propyl β-hydroxyester. Ephedrine as a chiral ligand affords modest to good enantiomeric excesses according to the nature of the β-ketoester but is essential for good activity of the catalytic system.



R_1	R_2	T(°C)	t (h)	GLC Yield (%)	ee (%)
Me	Et	20	10	100	39 (*S*)
Me	*i*Pr	20	4	100	40 (*S*)
Me	*t*Bu	20	1	100	44 (*S*)
Ph	Et	50	2.5	99	40 (*S*)
Ph	Et	50	15	85	94 (*S*)*

*Catalyst Precursor = $[Ru(p\text{-cymene})Cl_2]_2$

9.4 (S,S)-1,2-BIS(*TERT*-BUTYLMETHYLPHOSPHINO)ETHANE (BisP*)[39]: SYNTHESIS AND USE AS A LIGAND

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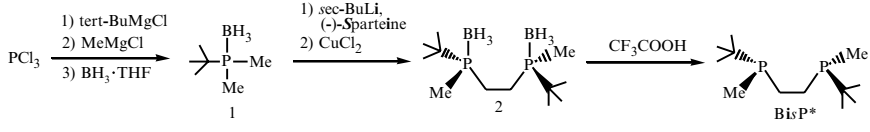
9.4.1 SYNTHESIS OF BisP*



Materials and equipment

- Phosphorus trichloride, 6.4 g
- Dry tetrahydrofuran, 20 mL

- *tert*-Butylmagnesium chloride, 1.0 M THF solution, 52 mL
- Methylmagnesium chloride, 1.0 M THF solution, 112 mL
- Borane–THF complex, 1.0 M, 70 mL
- Hydrochloric acid
- Sodium chloride, sodium sulfate
- Silica gel
- *n*-Hexane, ethyl acetate, diethyl ether, toluene, ethyl alcohol
- (−)-Sparteine, 8.7 g
- *sec*-BuLi 1 M in cyclohexane, 37.1 mL
- Copper(II) chloride, 6.2 g
- Aqueous ammonia
- Trifluoromethanesulfonic acid
- Potassium hydroxide
- Basic alumina
- Argon

- Magnetic stirrer
- 300 mL Round-bottomed flask with a magnetic stirrer bar
- Dropping funnel
- Separatory funnel
- Dry ice
- Schlenk tube
- Oil bath
- Rotary evaporator
- Cannula

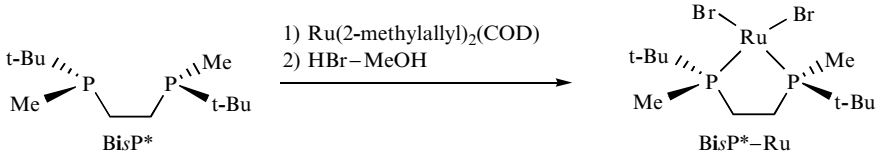
Procedure

1. To a solution of phosphorus trichloride (6.4 g) in dry tetrahydrofuran (20 mL) was added *tert*-butylmagnesium chloride (1.0 M THF solution, 52 mL) at −78°C under an argon atmosphere over a period of 2 hours.
2. After stirring at room temperature for 1 hour, methylmagnesium chloride (1.0 M THF solution, 112 mL) was added at 0 °C over 30 minutes. The reaction mixture was stirred at room temperature for 1 hour. To this solution, borane–THF complex (1.0 M, 70 mL) was added at 0 °C, and the mixture was stirred at the same temperature for 1 hour.
3. The reaction mixture was poured into cold 5% hydrochloric acid (200 mL). The organic layer was separated and aqueous layer was extracted with ethyl acetate (3 × 80 mL). The combined extracts were washed with brine, dried over sodium sulfate, and concentrated in vacuo.
4. The residual pasty solid was purified by column chromatography over silica gel (*n*-hexane : ethyl acetate = 8:1) to afford *tert*-butyl (dimethyl)phosphine–borane (**1**) 5.29 g (86%) as white crystals.
5. To a solution of (−)-sparteine (8.7 g) in diethyl ether (dry, 100 mL) *sec*-butyllithium (1 M in cyclohexane, 37.1 mL) was added at −78 °C under an

argon atmosphere. After stirring for 10 minutes, *tert*-butyl(dimethyl)phosphine–borane (1) (4.9 g) in diethyl ether (40 mL) was added, and the mixture was stirred at −65 °C for 3 hours. Dry copper (II) chloride (6.2 g) was added in one portion, and the mixture was gradually warmed to room temperature over 2 hours.

6. After stirring for 1 hour, 25% aqueous ammonia (50 mL) was added dropwise. The organic layer was separated and aqueous layer was extracted with ethyl acetate (200 mL, twice). The combined extracts were washed with 5% aqueous ammonia (100 mL), 2 M hydrochloric acid, and brine, and then dried over sodium sulfate, and concentrated *in vacuo*.
7. The residual solid was recrystallized from toluene twice to afford (*S,S*)-1,2-bis(boranato(*tert*-butyl)methylphosphino)ethane (**2**) 1.89 g (39%) as white crystals $[\alpha]^{27}_{D} = -9.1°$(*c* 1.0, $CHCl_3$).
8. In a Schlenk tube equipped with a magnetic stirrer bar were placed (*S,S*)-1,2-bis(boranato(*tert*-butyl)methylphosphino)ethane (**2**) (131 mg) and dry toluene (4 mL) under an argon atmosphere at 0 °C. To this solution, trifluoromethanesulfonic acid (0.22 mL) was added over a period of 5 minutes.
9. After stirring at 0 °C for 30 minutes and at room temperature for 1 hour, the solvent was removed *in vacuo*. The resulting pasty oil was dissolved in degassed ethanol/water (10/1) containing potassium hydroxide (280 mg), and stirred at 50 °C for 90 minutes. After cooling to room temperature, degassed diethyl ether (5 mL) was added, and the upper layer was collected through a cannula. The extraction was repeated three times. The combined extracts were dried over sodium sulfate. The solution was passed through a column of basic alumina (13 g) using degassed diethyl ether (30 mL) under an argon atmosphere.
10. The resulting solution was concentrated in vacuo to afford (*S,S*)-1,2-bis(*tert*-butylmethylphosphino)ethane (BisP*) as a solid or an oil.

9.4.2 SYNTHESIS OF 1,2-BIS(*TERT*-BUTYLMETHYLPHOSPHINO)ETHANERUTHENIUM BROMIDE[40](BisP*−Ru)



Materials and equipment

- (*S,S*)-1,2-Bis(*tert*-butylmethylphosphino)ethane (BisP*), 77 mg
- Bis(2-methylallyl)cyclooctadieneruthenium, 105 mg
- Argon

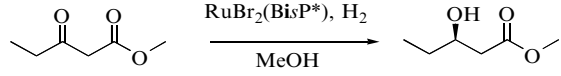
- *n*-Hexane (degassed) 2.5 ml
- Acetone (degassed) 11 ml
- 1.45 M HBr/Methanol

- Schlenk tube
- Magnetic stirrer
- Magnetic stirrer bar
- Oil bath
- Cannula
- Rotary evaporator

Procedure

1. In a Schlenk tube, equipped with a magnetic stirrer bar, were placed BisP* (77 mg), bis(2-methylallyl)cyclooctadieneruthenium (II) (105 mg), and degassed *n*-hexane (2.5 mL) under an argon atmosphere. The mixture was stirred at 60 °C for 10 hours.
2. To the reaction mixture, degassed *n*-hexane 5 mL was added. The solution was passed through a cannula capped with a filter paper, and concentrated *in vacuo*.
3. The resulting solid was dissolved in degassed acetone (11 mL). To this solution, 1.45 M methanolic hydrogen bromide (0.384 mL) was added dropwise. The mixture was stirred for two hours.
4. The mixture was filtered by passing through a cannula capped with a filter paper, and the solvent was removed *in vacuo* to afford 1,2-bis(*tert*-butylmethylphosphino)ethaneruthenium(II) bromide.

9.4.3 SYNTHESIS OF (*R*)-(−)-METHYL 3-HYDROXYPENTANOATE[40] USING (BisP*−Ru)



Materials and equipment

- Methanol–distilled water (10:1), 200 mL
- BisP*–$RuBr_2$ 52 mg,
- Methyl 3-oxopentanoate 10.7 g
- Argon, hydrogen
- Silica gel
- Chloroform, acetone

- Low pressure hydrogenator equipped with a 500 mL glass autoclave, a heater, and a magnetic stirrer

- Magnetic stirrer bar
- Rotary evaporator
- Chromatography column (200 mL)

Procedure

1. In a glass autoclave equipped with a magnetic stirrer bar were placed BisP*–$RuBr_2$ (52 mg), methyl 3-oxopentanoate (10.7 g), and degassed methanol/water (10/1) 200 mL under an argon atmosphere.
2. Then argon gas was replaced with hydrogen. The hydrogenation was performed at 70 °C under 6 kg/cm^2 of hydrogen for 10 hours.
3. The solvent was removed under reduced pressure and the residue was purified by chromatography on silica gel (chloroform:acetone = 3:1) to afford (*R*)-(−)-methyl 3-hydroxypentanoate (10.4 g, 96%, 98% ee) as a colourless oil.

   The ee (98%) was determined by HPLC (CHIRALCEL OD, flow rate 0.5 mL/min, eluent *n*-hexane/2-propanol = 95/5); (*R*)-enantiomer: R_t 13.8 min, (*S*)-enantiomer: R_t 28.4 min.

   ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.97 (3H, t, *J* 7.4 Hz), 1.48–1.58 (2H, m), 2.41 (1H, dd, *J* 9.1 and 16.4 Hz), 2.53 (1H, dd, *J* 3.0 and 16.4 Hz), 2.91 (1H, br s), 3.72 (3H, s), 3.95 (1H, m).

   IR (neat, cm^{-1}): 3443 (OH), 2965, 2881, 1738 (C=O), 1439, 1284, 1172, 1113, 1068, 1015, 983.

Conclusion

The asymmetric hydrogenation with BisP*–$RuBr_2$ may be applied to a wide range of β-ketoesters, β-ketoamides, and β-ketophosphonates. Table 9.2 shows typical examples.

9.5 (1*S*, 3*R*, 4*R*)-2-AZANORBORNYLMETHANOL, AN EFFICIENT LIGAND FOR RUTHENIUM CATALYSED ASYMMETRIC TRANSFER HYDROGENATION OF AROMATIC KETONES

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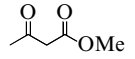
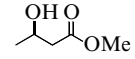
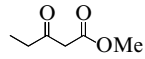
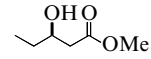
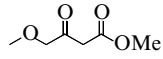
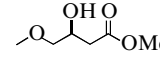
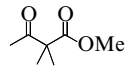
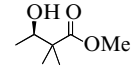
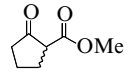
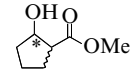
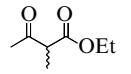
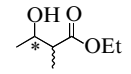
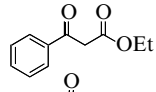
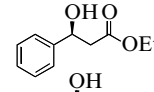
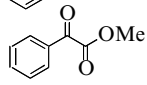
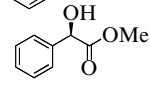
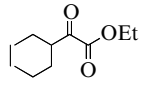
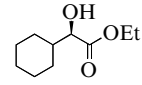
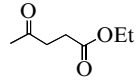
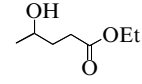
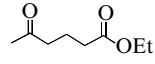
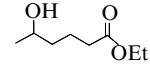
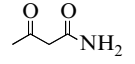
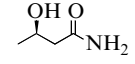
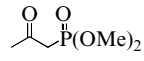
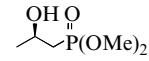
Asymmetric ruthenium-catalysed hydrogen transfer from 2-propanol to ketones is an efficient method for the preparation of optically active secondary alcohols[41]. Very recently, a new catalytic system has been developed based on ruthenium complexes having 2-azanorbornylmethanol as the chiral ligand (Figure 9.2), and their efficiency as catalysts for the enantioselective transfer hydrogenation of aromatic ketones has been demonstrated, affording the corresponding secondary alcohols with high rates and excellent ee's[42].

Table 9.2 Asymmetric hydrogenation of keto esters with BisP*–Ru(II) catalysts.

Entry	Substrate	BisP*	Product		Yield(%)	% ee
1		a			86	97
2[b)]		a			96	98
3		b			18	87
4		a			100	81
5		a			81	98
6[c)]		a		(*syn*) (anti)	13 70	91 96
7		a		(*syn*) (anti)	39 45	96 97
8		a			100	89
9		a			90	70
10		a			77	50
11		a			No reaction	
12		a			No reaction	
13[d)]		a			100	89
14[e)]		a			51	85

a) Reaction conditions: substrate 2 mmol, catalyst/substrate = 0.005, 70 °C, 6 kg/cm^2.
b) Substrate 82 mmol, catalyst/substrate = 0.0013.
c) At 50 °C.
d) Substrate 0.7 mmol, catalyst/substrate = 0.014, at 50 °C.
e) At 60 °C.

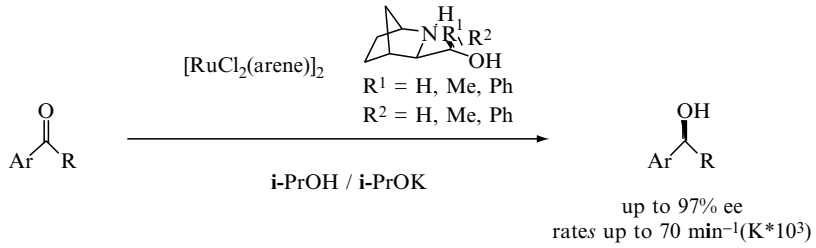
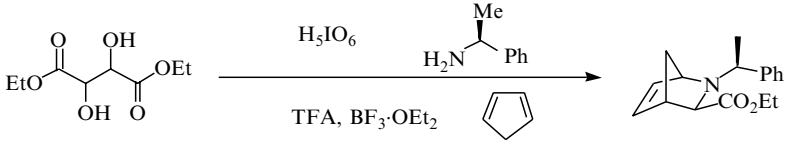


Figure 9.2 Transfer hydrogenation of ketones catalyzed by Ru(II)(2-azanorbornylmethanol) complexes.

9.5.1 SYNTHESIS OF ETHYL (1*S*,3*R*,4*R*)-2-[(*S*)-1-PHENYLETHYLAMINO]-2-AZABICYCLO [2.2.1] HEPT-5-ENE-3-CARBOXYLATE



Materials and equipment

- Diethyl L-tartrate (98 %), 10 g, 47.5 mmol
- *Ortho*-periodic acid (>99 %), 10.8 g, 47.5 mmol
- (*S*)-(−)-α-Methylbenzylamine, (98 %, 99 % ee/GLC), 12.4 mL, 95 mmol
- Trifluoroacetic acid (99 %), 7.4 mL, 95 mmol
- Boron trifluoride etherate (99 %), 12.1 mL, 95 mmol
- Cyclopentadiene, 6.2 g, 95 mmol
- Triethylamine, 45 mL
- Dry diethyl ether, 30 mL
- Dry methylene chloride, 150 mL
- Pentane, diethyl ether
- Methylene chloride, 400 mL
- Saturated solution of sodium bicarbonate
- Anhydrous magnesium sulfate
- Activated molecular sieves, 3 Å, 0.4–0.8 mm beads, 17 g
- Celite®, 20 g
- Silica gel (Matrex 60 Å, 37–70 μm), 250 g
- TLC plates, SIL G-60 UV_{254}

- 100 mL and 250 mL round-bottomed flasks with magnetic stirrer bars
- Magnetic stirrer plate
- One glass sintered funnel, diameter 7 cm

- One 500 mL Erlenmeyer flask
- One Büchner funnel, diameter 10 cm
- One Büchner flask, 500 mL
- Filter paper
- One 500 mL separatory funnel
- One glass column, diameter 7 cm
- One Dewar flask
- Rotary evaporator

Procedure

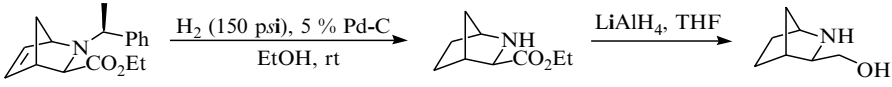
1. Diethyl tartrate (10 g, 47.5 mmol) was placed in a 100 mL round-bottomed flask equipped with a magnetic stirrer bar, under nitrogen. Dry diethyl ether (30 mL) was then added and the mixture was cooled at 0 °C. To this solution, *ortho*-periodic acid (10.8 g, 47.5 mmol) was added carefully, portionwise, over 20 minutes and the resulting mixture was vigorously stirred for 1 hour under nitrogen at the same temperature.
2. Activated molecular sieves (7 g) were added to the reaction and stirring continued for 20 minutes.
3. The mixture was carefully filtered into a 250 mL round-bottomed flask through a thin pad of Celite. The filtration was completed by rinsing the packing with diethyl ether (50 mL).
4. The solvent was removed from the filtrate using a rotary evaporator to afford the corresponding ethyl glyoxylate (9.7 g, 95 mmol)
5. In the 250 mL round-bottomed flask equipped with a magnetic stirrer bar, the resulting ethyl glyoxylate (9.7 g) was placed under nitrogen. Dry methylene chloride (125 mL) was added followed by activated molecular sieves (10 g). The mixture was then cooled at 0 °C under nitrogen.
6. To this solution (*S*)-(−)-phenylethylamine (12.4 mL, 95 mmol) was added dropwise and when the addition was complete, stirring was continued for 1 hour at 0 °C.
7. The mixture was cooled to −78°C in a dry ice–acetone bath and trifluoroacetic acid (7.4 mL, 95 mmol), boron trifluoride etherate (12.1 mL, 95 mmol) and freshly distilled cyclopentadiene (6.2 g, 95 mmol) were added in that order over a 20 minute period. The mixture was stirred at −78°C for 5 hours before it was allowed to warm to room temperature.
8. The reaction was hydrolysed and neutralized (pH = 8) in a 500 mL Erlenmeyer flask with a saturated aqueous solution of sodium bicarbonate.
9. The resulting mixture was filtered into a Büchner funnel with the aid of a water aspirator and transferred to a 500 mL separatory funnel where the phases were separated. The aqueous layer was extracted with methylene chloride (2 × 150 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated using a rotary evaporator to give the corresponding mixture of crude Diels–Alder adducts (minor *exo*-isomer + major *endo*-isomer + major *exo*-isomer. *Exo/endo* ratio: 98/2).

10. The major *exo* diastereoisomer was easily isolated from the crude reaction mixture by column chromatography (deactivated silica gel[43], pentane/Et_2O: 99/1 to 80/20) to give, 14.1 g, 55 % yield.

    ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.34–7.19 (5H, m), 6.36–6.33 (1H, m), 6.22–6.18 (1H, m), 4.37 (1H, s), 3.87 (2H, q, *J* 6.8 Hz), 3.10 (1H, q, *J* 6.5 Hz), 2.96 (1H, s), 2.27 (1H, s), 2.20 (1H, d, *J* 8.4 Hz), 1.48 (3H, d, *J* 6.5 Hz), 1.01 (3H, d, *J* 7.0 Hz), 1.00 (1H, d, *J* 8.4 Hz).

    This procedure has been scaled up to provide 28 g of the major Diels–Alder adduct.

9.5.2 SYNTHESIS OF (1*S*,3*R*,4*R*)-3-HYDROXYMETHYL-2-AZABICYCLO[2.2.1]HEPTANE



Materials and equipment

- Ethyl (1*S*,3*R*,4*R*)-2-[(*S*)-1-phenylethylamino]-2-azabicyclo[2.2.1]hept-5-ene-3-carboxylate, 10 g, 36.9 mmol
- 5 % Pd–C, 2 g, 20 wt%
- Absolute ethanol (99 %), 60 mL
- 95 % Ethanol, 75 mL
- Hydrogen pressure (150 psi)
- Benzoyl chloride
- Triethylamine
- Lithium aluminium hydride, (97 %), 8.4 g, 215 mmol
- Dry tetrahydrofuran, 130 mL
- 15 wt% NaOH aqueous solution, 8.4 mL
- Celite®, 20 g
- TLC plates, SIL G-60 UV_{254}

- One Büchner flask, 250 mL
- One glass sintered funnel, diameter 7 cm
- Two 250 mL round bottomed flasks, one equipped with a magnetic stirrer bar
- Magnetic stirrer
- Hydrogen pressure reactor vessel, 250 mL with stirrer
- Water aspirator
- Kugelrohr distillation equipment

Procedure

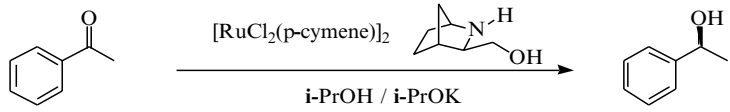
1. A solution of ethyl (1*S*,3*R*,4*R*)-2-[(*S*)-1-phenylethylamino]-2-azabicyclo [2.2.1]hept-5-ene-3-carboxylate (major *exo*-Diels–Alder adduct) (10 g, 36.9 mmol) in absolute ethanol (60 mL) was stirred under a hydrogen pressure of 150 psi at room temperature for 48 hours in the presence of activated 5% Pd–C (2 g, 20 wt%).
2. The Pd–C catalyst was then removed by filtration through Celite in a sintered glass funnel with the aid of a water aspirator. The filtration was completed by rinsing the packing with 95% ethanol (75 mL). **Attention: due to the pyrophoric properties of hydrogen-saturated palladium, it is important to keep the filter plug under a layer of ethanol**.
3. The filtrate was transfered to a 250 mL round bottomed flask and the solvent was removed using a rotary evaporator to afford the corresponding pure amino ester as a pale yellowish oil (6.11 g, 98% yield).

   The ee (98%) of the ligand was determined at this point as its *N*-benzoyl derivative [44] by HPLC (ChiralCelOD-H, 254 nm UV detector, flow 0.4 mL/min, eluent hexane/*i*-PrOH: 80/20); R_t (minor) 15.0 min, R_t (major) 22.9 min.

   ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.21 (1 H, br d, *J* 9.8 Hz), 1.25 (3 H, t, *J* 7.1 Hz), 1.34–1.66 (5 H, m), 2.18 (1 H, br s), 2.59, 3.27, 3.50 (1 H each, 3 br s) and 4.15 (2 H, q, *J* 7.1 Hz).
4. Lithium aluminium hydride (8.4 g, 215 mmol) was placed in a 250 mL round bottomed flask equipped with a magnetic stirrer bar and flushed with nitrogen. Dry tetrahydrofuran (120 mL) was added and the suspension was cooled with the aid of an ice-bath.
5. A solution of the amino ester (6.11 g, 36.2 mmol) in dry tetrahydrofuran (10 mL) was carefully, dropwise added to this supension. When the addition was complete, the mixture was stirred for 30 minutes at room temperature.
6. After completion according to TLC, the reaction was quenched adding consecutively 8.4 mL of water, 8.4 mL of 15% NaOH solution and 25.2 mL of water. The mixture was then stirred for 30 min at room temperature.
7. The aluminates were removed by filtration through a sintered glass funnel with the aid of the water aspirator. The filtration was completed by rinsing the packing with tetrahydrofuran (75 mL).
8. Solvent evaporation in a rotary evaporator afforded the amino alcohol product (4.14 g, 90% yield). The purity of the crude product is high enough to be used in the catalysis experiments, but it can be purified further by vacuum distillation in a Kugelrohr [90–100 °C, 0.030–0.035 mbar] cooling the recipient flask with dry ice (84% yield from the amino ester, as white needles).

   ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.15 (1 H, dt, *J* 9.8, 1.4 Hz), 1.40–1.30 (2 H, m), 1.72–1.53 (3 H, m), 2.17 (1 H, m), 2.89–2.79 (3 H, m), 3.17 (1 H, dd, *J* 10.7, 8.2 Hz), 3.40 (1 H, dd, *J* 10.7, 5.4 Hz) and 3.43 (1 H, br s).

9.5.3 RUTHENIUM-CATALYZED ASYMMETRIC TRANSFER HYDROGENTION OF ACETOPHENONE



Materials and equipment

- Anhydrous isopropanol, 20 mL
- Acetophenone (99 %), 235 μl, 2 mmol
- $[RuCl_2(p\text{-cymene})]_2$, 3.06 mg, 0.005 mmol (0.25 mol%)
- (1*S*,3*R*,4*R*)-3-Hydroxymethyl-2-azabicyclo[2.2.1]heptane, 5.08 mg, 0.04 mmol (2 mol%)
- 1 M Solution of *i*-PrOK in *i*-PrOH, 50 μl, 0.05 mmol
- 1 M solution of HCl, two drops
- Ethyl acetate, pentane
- Celite®, 5 g
- Silica gel (Matrex 60 Å, 37–70 μm), 13 g

- One 10 mL two-necked round-bottomed flask equipped with magnetic stirrer bar
- Magnetic stirrer with thermostatically controlled oil bath and thermometer
- Reflux condenser
- One 30 mL Schlenk flask equipped with magnetic stirrer bar
- Magnetic stirrer
- Glass sintered funnel, diameter 3.5 cm
- One 50 mL filter flask
- Rotary evaporator
- Chromatography column, diameter 2.5 cm

Procedure

1. The 10 mL two-necked round-bottomed flask, equipped with a magnetic stirrer bar, was dried in a oven at 120 °C for 10 hours. The flask was removed, sealed, cooled under vacuum and flushed with nitrogen.
2. The ruthenium complex dimer (3.06 mg, 0.25 mol%) and the chiral ligand (5.08 mg, 2 mol%) were then weighed into the round-bottomed flask and any moisture was azeotropically removed *via* evaporation of benzene (5 × 5 mL) at reduced pressure.
3. A condenser was attached to the flask which was sealed under vacuum and flushed with nitrogen. The residue was dissolved in dry (freshly distilled from $CaCl_2$) *i*-PrOH (5 mL). The solution was refluxed under nitrogen for 30 minutes before it was cooled to room temperature.

4. Once the clear reddish solution of the catalyst had cooled to room temperature, it was transferred under a gentle stream of nitrogen to a Schlenk flask containing a solution of the ketone (235 μL, 2 mmol) and potassium isopropoxide (0.05 mmol, 2.5 mol%) in *i*-PrOH (15 mL). The resulting solution was then stirred for 1.5 hours at room temperature under nitrogen (monitored by GC and/or ^{1}H NMR).
5. After completion, the reaction was neutralized with a 1 M solution of HCl (2 drops) and concentrated *in vacuo* to give the crude product. After dilution with ethyl acetate and removal of the catalyst by filtration over a thin pad of Celite, the sample was analysed.

   The ee of the alcohol (94 %) was determined by HPLC analysis (ChiralCel OD-H) using a 254 nm UV detector and a flow rate of 0.5 mL/min of 5 % of *i*-PrOH in hexane. (*S*)-α-Methylbenzyl alcohol (major): R_t 20.65 min; (*R*)-α-methylbenzyl alcohol (minor): R_t 17.72 min.
6. Finally, the crude product was purified by flash chromatography (eluent: pentane/ethyl acetate: 85/15) to afford 224.5 mg of pure alcohol (92 % yield).

Conclusion

The procedure is very easy to reproduce and the asymmetric transfer hydrogenation may be applied to a wide range of aromatic ketones. Table 9.3 gives different substrates that can be reduced with the Ru(II)-(2-azanorbornylmethanol) complex in *iso*-propanol

Table 9.3 Hydrogen transfer reduction of ketones using Ru (II)-(*1S, 3R, 4R)-3*-hydroxymethyl-2-azabicyclo [2.2.1]heptane as catalyst.

			Product	
Entry	Ar	R	Yield (%)	ee %
1	Naphthyl	Me	98	97 (*S*)
2	Ph	*n*-C_4H_9	80	95 (*S*)
3	*m*-Tol	Me	94	94 (*S*)
4	*m*-MeO-C_6H_4	Me	96	94 (*S*)
5	*m*-NH_2-C_6H_4	Me	100	93 (*S*)

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43. When mentioned, deactivated silica gel means that it was treated with 5% triethylamine in pentane and the column was eluted with the same solvent mixture until the outflowing eluent was basic according to pH paper.
44. The NH ester was *N*-benzoylated in methylene chloride by reaction with benzoyl chloride in the presence of triethylamine.