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# 12 Asymmetric Hydrogenation of Carbon–Carbon Double Bonds Using Organometallic Catalysts

## CONTENTS

## 12.1 INTRODUCTION

Acrylic acid derivatives were chosen as substrates in the early studies on asymmetric hydrogenation of olefins. The additional coordinating functionality such as an amido, carboxyl, amidomethyl, carbalkoxymethyl or hydrocarbonylmethyl group is a prerequisite for getting higher enantioselectivities. Concerning the synthesis of enantiomerically pure α-amino acids, chiral rhodium–diphosphines[1–3] or ruthenium-[4] catalysts were found to give good results for the enantioselective hydrogenation of α-(acetamido)acrylates α-(enamides) (Figure 12.1). In this section catalytic hydrogenation methods using ligands based on chiral templates, such as [1,2-bis(phospholano)benzene] (DuPHOS), [1,2-(bisphospholano)ethane] (BPE) and 3,6-bis[bis(4-fluorophenyl)-phosphinoxy]-bicyclo[3.2.0]-heptane (B [3.2.0]DPO) will be described.

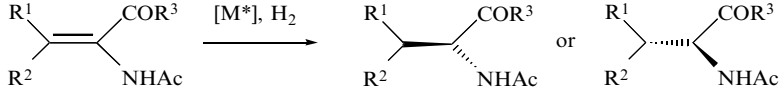



**Figure 12.1** Asymmetric hydrogenation of α-enamides.

One of the possible catalytic cycles (i.e. for olefin hydrogenation) is described in Figure 12.2. The molecular hydrogen is first complexed to the metal. Then the olefin is complexed and inserted into the M–H bond. The alkane is liberated by elimination and the catalyst regenerated.

***Extreme caution must be taken whenever hydrogen gas and active catalyst are used. 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 hydrogenation*** [151].

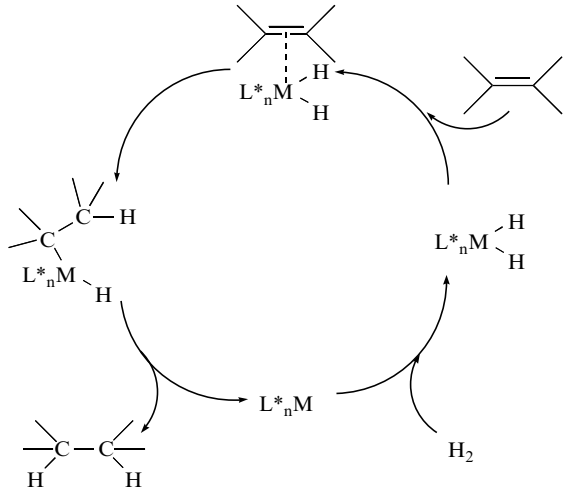
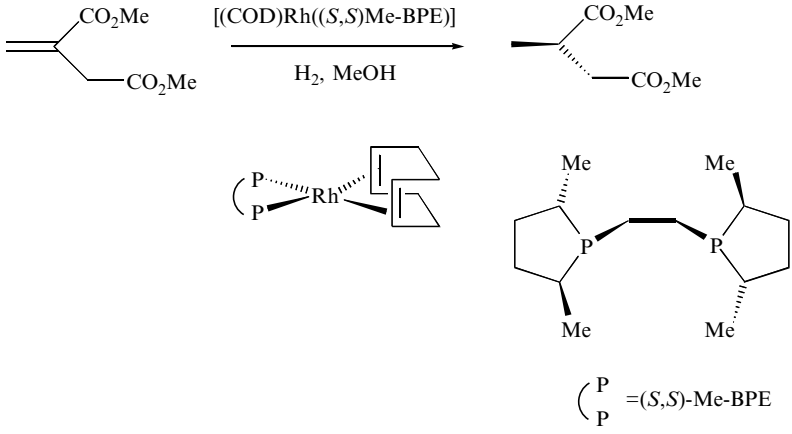



**Figure 12.2** Mechanism of olefin hydrogenation by transition metal complexes.

## 12.2 HYDROGENATION OF DIMETHYL ITACONATE USING [Rh((*S,S*)-Me-BPE)][6]




### Materials and equipment

- Dimethyl itaconate, 177 μL, 200 mg, 1.26 mmol
- (*S,S*)-1,2-bis(1′,4′-Dimethylphospholano)ethane(cyclooctadiene)rhodium(I): [(COD)Rh(*S,S*)-Me-BPE], 0.7 mg, 1.26 μmol, 0.1 mol%*

* *The catalyst [(COD)Rh((S,S)-Me-BPE)] was kindly provided by Dr M. Burk (Chirotech Technology Limited, Cambridge UK).*

- Anhydrous methanol degassed for 20 minutes with nitrogen, 5 mL
- Ethyl acetate, diethyl ether
- Silica gel 60 (0.063–0.04 mm)

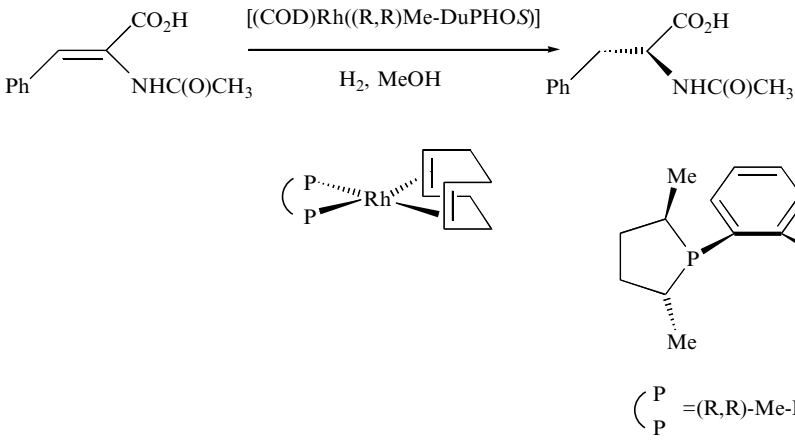
- 10 mL Glass liner adapted to the high pressure reactor
- Magnetic stirrer hot plate with a thermostatically controlled oil-bath and thermometer
- 25 mL High pressure reactor

  The reaction can be performed at atmospheric pressure using a low-pressure hydrogenation apparatus fitted with a gas burette system.

**Procedure**

1. A 10 mL glass liner equipped with a magnetic stirrer bar was dried in an oven at 120 °C overnight, cooled in a desiccator under vacuum and then flushed with nitrogen.
2. The liner was filled under nitrogen with dimethyl itaconate (177 μL, 200 mg) and the catalyst [(COD)Rh(*S,S*)-Me-BPE] (0.7 mg) and then placed in a 25 mL high pressure reactor.
3. The reactor was flushed six times with hydrogen (the bomb was pressurized at 200 psi, then the gas inlet was closed before the hydrogen was slowly vented off). Degassed anhydrous methanol (5 mL) was added and the reactor was pressurized to an initial pressure of 50 psi $H_2$. The reaction was allowed to stir at 20 °C until no further hydrogen uptake was observed (2 hours).
4. The reaction was followed by chiral GC (SE 30, 100 °C isotherm, nitrogen mobile phase). $R_t$ (dimethyl itaconate): 6.8 min; $R_t$ (dimethyl methylsuccinate): 5.7 min.
5. The reaction was then concentrated and the residue was passed through a short column of silica gel eluting with ethyl acetate–diethyl ether (1:1) to remove the catalyst. The (*S*)-dimethyl methylsuccinate does not need any further purification (190 mg, 95 %).
   - The ee (95 %) was determined by chiral GC (Lipodex® E, 25 m, 0.25 mm ID, temperatures: column 75 °C isotherm, injector 250 °C, detector 250 °C, mobile phase helium, sample dissolve in methanol) $R_t$ (*R*)-enantiomer: 39.3 min $R_t$ (*S*)-enantiomer: 41.2 min.
   - $^1$H NMR(200 MHz, $CDCl_3$): δ3.70 (s, 3H, $CO_2CH_3$); 3.69 (s, 3H, $CO_2CH_3$); 2.92 (m, 1H, C*H*); 2.76 (dd, *J* 16.5 Hz, *J* 8.2 Hz, 1H, $CH_aH_b$); 2.42 (dd, *J* 16.5 Hz, *J* 6.0 Hz, 1H, $CH_aH_b$); 1.23 (d, *J* 7.1 Hz, 3H, $CH_3$).
   - IR ($CHCl_3$, $cm^{-1}$): 3031, 2957 (C–H aliphatic), 1727 (C=O), 1463, 1437, 1353, 1280 (C–O), 1167, 1059, 1007.
   - Mass: calculated for $C_7H_{13}O_4$: *m/z* 161.08138; found $[MH]^+$161.08154.

## 12.3 HYDROGENATION OF AN α-AMIDOACRYLATE USING [Rh ((*R,R*)-Me-DuPHOS)][2]




### Materials and equipment

- α-Acetamido cinnamic acid, 259 mg, 1.26 mmol
- (−)-(*R,R*)-1,2-bis(1′,4′-dimethylphospholane)benzene(cyclooctadiene)rhodium (I): [(COD)Rh((*R,R*)Me-DuPHOS)], 0.8 mg, 1.26 μmol, 0.1 mol%*
  This catalyst is commercially available from Strem or Chirotech.
- Anhydrous methanol degassed for 20 minutes with nitrogen, 5 mL
- Ethanol, petroleum ether

- 10 mL Glass liner adapted to the 25 mL high pressure reactor with a magnetic stirrer bar
- 25 mL High pressure reactor
  The reaction can be performed at atmospheric pressure using a low-pressure hydrogenation apparatus fitted with a gas burette system.

### Procedure

1. A 10 mL glass liner equipped with a magnetic stirrer bar was dried in an oven at 120 °C overnight, cooled in a desiccator under vacuum and then flushed with nitrogen.
2. The liner was filled under nitrogen with acetamido cinnamic acid (259 mg), anhydrous methanol (5 mL) and catalyst [(COD)Rh(*R,R*)-Me-DuPHOS] (0.8 mg). The liner was placed in a 25 mL high pressure reactor.
3. The reactor was flushed six times with hydrogen (the bomb was pressurized at 200 psi, then the gas inlet was closed before the hydrogen was slowly vented off) and then pressurized to an initial pressure of 90 psi $H_2$. The

* *The catalyst [(COD)Rh((R,R)Me-DuPHOS)] was kindly provided by Dr M. Burk (Chirotech Technology Limited, Cambridge UK)*

reaction was allowed to stir at 20 °C until no further hydrogen uptake was observed (3 hours).

4. The reaction was followed by chiral GC (SE 30, 220 °C, nitrogen mobile phase). $R_t$ (α-acetamido cinnamic acid): 3.70 min; $R_t$ (*N*-acetyl-L-phenylalanine): 5.4 min.
5. The reaction was concentrated to give a yellow oil (300 mg) which was crystallized with ethanol and petroleum ether to give slightly yellow crystals (235 mg, 90 %).

   The ee (>98 %) was determined by chiral HPLC (Chiralpak® AD, Hexane-IPA-TFA, 89 %–10 %–1 %, sample dissolved in IPA) $R_t$ (*R*)-enantiomer: 11.9 min, $R_t$ (*S*)-enantiomer: 14.3 min.

   $^1$H NMR(200 MHz, DMSO): δ8.25 (d, *J* 8.2 Hz, 1H, N*H*); 7.26 (m, 5H, Ph); 4.42 (m, 1H, C*H*); 3.07 (dd, *J* 13.7 Hz, *J* 4.9 Hz, 1H, $CH_aH_b$); 2.85 (dd, *J* 13.7 Hz, *J* 9.9 Hz, 1H, $CH_aH_b$); 1.75 (s, 3H, CO-$CH_3$).

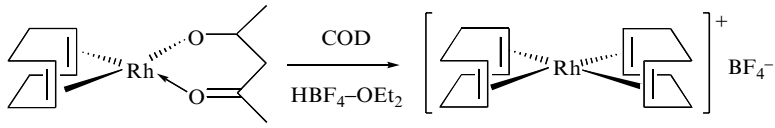
   Mass: calculated for $C_{11}H_{13}O_4N$: *m/z* 207.08954; found $[MH]^+$ 207.08975.

### Conclusion

The procedures using [(COD) Rh (*S*, *S*)-Me-BPE] and [(COD) Rh (*R*,*R*)-Me-DuPHOS] are very similar; they need a hydrogenation bomb and are conducted under an inert atmosphere, as the catalysts are sensitive to oxygen. They give good results (yield and enantiomeric excess) and hydrogenated products do not need lengthy purification, since no secondary products were detected. The reactions can be carried out under atmospheric pressure giving approximately the same results but need a longer time to be complete. The reaction were stopped when no more hydrogen was consumed; they were generally performed overnight (14 hours). Table 12.1 gives some examples of β, β-disubstituted enamides that can be hydrogenated by those catalysts in similar conditions.

## 12.4 HYDROGENATION OF AN α-AMIDOACRYLATE USING [Rh(B[3.2.0]DPO)] COMPLEXES

### 12.4.1 PREPARATION OF $(COD)_2Rh^+BF_4^-$*




### Materials and equipment

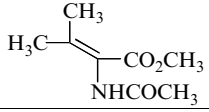
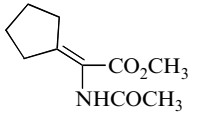
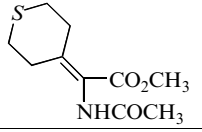
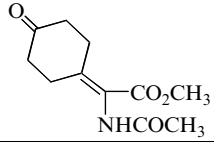
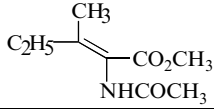
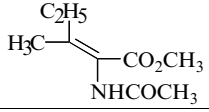
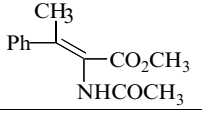
- [(COD)Rh(acac)], 3.1 g, 10 mmol
- Anhydrous tetrahydrofuran, 60 mL

* *Dr. C. Dousson and Dr N. Derrien (University of Liverpool, UK) provided the procedures for the catalyst synthesis and the hydrogenation with Rh(B[3.2.0]DPO)*[7].

- Cycloocta-1,5-diene, 1.30 g, 12 mmol, 1.2 eq
- Tetrafluoroboric acid–diethyl ether complex ($HBF_4.OEt_2$) in diethyl-ether, 54 %, 3.00 g, 2.52 mL, 10 mmol, 1 eq, diluted with tetrahydrofuran, 5 mL
- Dry diethyl ether

- 100 mL Schlenk tube with a magnetic stirrer bar.
- Condenser.
- Magnetic stirrer hot plate with a thermostatically controlled oil-bath and thermometer
- Sinter funnel with an inert gas inlet

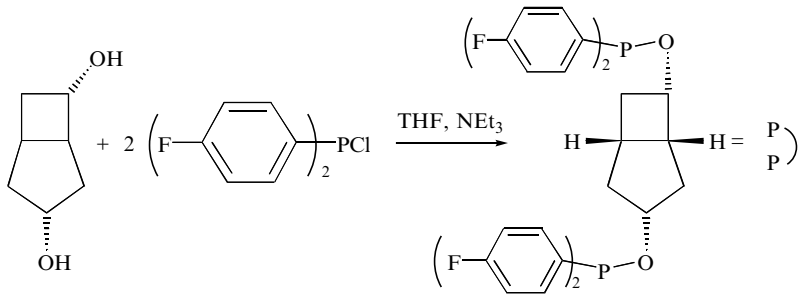
**Table 12.1** Hydrogenation of β, β-disubstituted enamides by [(COD)Rh (*S*,*S*)-Me-BPE] and [(COD)Rh (*R*,*R*)-Me-DuPHOS] catalysts[2] (results according to the literature).

| | [Rh(*S*,*S*)-Me-DuPHOS] ee % (configuration) | [Rh(R,R)-Me-BPE] ee % (configuration) |
|---|---|---|
|  | 96.0 (*S*) | 98.2 (R) |
|  | 96.8 (*S*) | 97.2 (R) |
|  | 95.0 (*S*) | 98.4 (R) |
|  | 93.7 (*S*) | 98.0 (R) |
|  | – | 98.2 (2R,3*S*) |
|  | – | 98.3 (2R,3R) |
|  | 99.4 (2*S*,3R) | 80.1 (2R,3R) |

**Procedure**

1. A 100 mL Schlenk flask equipped with a magnetic stirrer bar and a condenser was dried at 150 °C overnight, cooled under vacuum and then flushed with nitrogen.
2. The Schlenk tube was filled with [(COD)Rh(acac)] (3.1 g) and cycloocta-1,5-diene (1.30 g) which were dissolved in 15 mL of dry tetrahydrofuran. To this orange mixture, the solution of $HBF_4.OEt_2$ in tetrahydrofuran (7.52 mL) was added. A brown precipitate appeared, giving a viscous solution, which was diluted with 40 mL additional tetrahydrofuran to allow the reaction to stir efficiently.
3. The orange solution was heated (80 °C) to reflux under nitrogen for 30 minutes.
4. The brown solution was cooled to room temperature. The brown powder was filtered under nitrogen using a sinter funnel with an inert gas inlet, and then washed with dry diethyl ether (3 × 5 mL).
5. The $[(COD)_2Rh^+BF_4^-]$ complex obtained was used as the catalyst precursor for hydrogenation without further purification.

## 12.4.2 PREPARATION OF THE BISPHOSPHINITE LIGAND




**Materials and equipment**

- (−)-(1*R*,3*R*, 5*R*, 6*S*)-Bicyclo[3.2.0]heptan-3,6-diol, 500 mg, 3.9 mmol
- Anhydrous tetrahydrofuran, 20 mL
- Triethylamine, 0.87 g, 8.6 mmol, 2.2 eq
- Bis(4-fluorophenyl)chlorophosphine, 2.2 g, 8.6 mmol, 2.2 eq

***Chlorophosphines need to be manipulated carefully with gloves and eye protection. They can cause burns, irritation to eyes and irritation to the respiratory system.***

Different chlorophosphines can be synthesised, or are available from Strem or Digital Chemicals.

- Alumina, activated overnight at 150 °C

- Two 100 mL Schlenk tubes with magnetic stirrer bars
- Ice-bath
- Sinter funnel with an inert gas inlet

**Procedure**

1. Two 100 mL Schlenk flasks, each equipped with a magnetic stirrer bar, were dried at 150 °C overnight, cooled under vacuum and then flushed with nitrogen.
2. One of the Schlenk tubes was filled with (−)-(1*R*, 3*R*, 5*R*, 6*S*)-bicyclo [3.2.0] heptan-3,6-diol (500 mg) dissolved in dry tetrahydrofuran (20 mL) under nitrogen, then triethylamine (0.87 g) was added.
3. The solution was cooled to 0 °C in an ice-bath, and then the chlorophosphine (2.2 g) was added dropwise via a syringe over 5 minutes with stirring. A white precipitate of triethylammonium chloride appeared. When the addition was complete, the ice-bath was removed and the stirring was continued at ambient temperature for 15 hours.
4. A sinter funnel with nitrogen inlet connected to the second dry Schlenk tube was filled with a pad of activated alumina which was cooled under vacuum and then flushed with nitrogen. The precipitate was filtered off through the pad of alumina under nitrogen. The solvent was removed under vacuum from the second Schlenk tube.
5. The solvent was removed *in vacuo* to give the bisphosphinite ligand (1*R*, 3*R*, 5*R*, 6*S*)-3,6-bis[bis(4′-fluorophenyl) phosphinooxy] bicyclo [3.2.0] heptane as a white solid (1.99 g, 90 %).

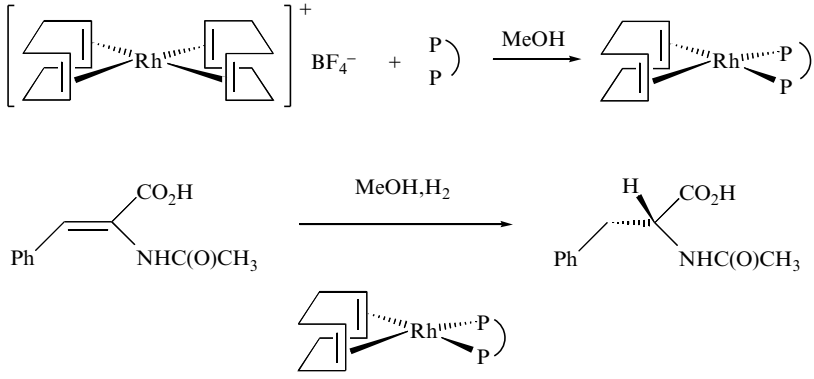
   The ligands prepared by this method were sufficiently pure for use as an *in situ* catalyst preparation.

   NMR $^{13}C$ (50 MHz, $CDCl_3$): δ 30.16 (s, $C_1$); 33.80 (d, $^3J_{PC}$ 5.4 Hz, $C_4$), 37.04 (d, $^3J_{PC}$ 6.5 Hz, $C_7$), 40.88 (d, $^3J_{PC}$ 4.8 Hz, $C_2$); 45.43 (d, $^3J_{PC}$ 4.8 Hz $C_5$); 69.98 (d, $^2J_{PC}$ 16.3 Hz, $C_6$); 84.78 (d, $^2J_{PC}$ 17.7 Hz, $C_3$); 115.18–116.88 (m, $C_{3'}, C_{5'}, C_{3''}, C_{5''}$); 131.89–133.87 (m, $C'_2, C'_6, C''_2, C''_6$); 136.99–137.83 (m, $C_{1'}, C_{1''}$); 163.54, 163.63, 163.71, 163.77 (4 × d, $^1J_{FC}$ 247 Hz, $C_{4'}, C_{4''}$).

   NMR $^{31}P$ (162 MHz, $CDCl_3$): δ 103.30 (s), 105.03 (s).

   Mass: calculated for $C_{31}H_{26}F_4O_2P_2$: *m/z* 568.13446; found $[M]^+$ 568.13466.

## 12.4.3 ASYMMETRIC REDUCTION OF α-ACETAMIDO CINNAMIC ACID




### Materials and equipment

- (1*R*, 3*R*, 5*R*, 6*S*)-3, 6-Bis [bis (4′-fluorophenyl) phosphinoxy] bicyclo [3.2.0] heptane, 6.7 mg, 0.012 mmol, 1 mol%
- Anhydrous methanol degassed with nitrogen, bubbling for 1 hour, 30 mL
  $(COD)_2Rh^+BF_4^-$, 5.25 mg, 0.013 mmol, 1.1 mol%
  The catalyst is not stable in solution and cannot be stored for a long time.
- α-Acetamido cinnamic acid, 240 mg, 1.17 mmol

- 25 mL Schlenk tube with a magnetic stirrer bar
- Syringes
- High pressure reactor, 50 mL.
- Glass liner adapted to high pressure reactor with a magnetic stirrer bar

### Procedure

1. A 25 mL Schlenk tube equipped with a magnetic stirrer bar was dried at 150 °C overnight, cooled under vacuum and then flushed with nitrogen.
2. The Schlenk tube was filled with bisphosphinite ligand, (1*R*, 3*R*, 5*R*, 6*S*)-3,6-bis [bis (4′-fluorophenyl) phosphinooxy] bicyclo[3.2.0]heptane (6.7 mg), degassed methanol (3 mL) and $(COD)_2Rh^+BF_4^-$ (5.25 mg). The reaction mixture was stirred at room temperature until all the material was dissolved (10–15 minutes) giving an orange solution.
3. A glass liner of a 50 mL hydrogenation bomb was charged with α-acetamido cinnamic acid (240 mg) and a magnetic stirrer bar. The bomb was then assembled, flushed five times with hydrogen (the bomb was pressurized at 200 psi, then the gas inlet was closed before the hydrogen was slowly vented off).

4. The solution of the catalyst (formed *in situ*) was added via a syringe (3 mL) through the solvent port equipped with a septum, and the mixture stirred.
5. The hydrogenation bomb was pressurized to 200 psi of hydrogen (14 atm). The reaction performed at room temperature was complete after 3 hours (followed by GC/MS). N-Acetyl-L-phenylalanine was obtained in quantitative yield.

   The ee (91 %) was determined by chiral HPLC (Chiralpak® AD, Hexane–IPA–TFA, 89 %–10 %–1 %, sample dissolved in IPA) $R_t$ (*R*)-enantiomer: 11.9 min, $R_t$ (*S*)-enantiomer: 14.3 min.

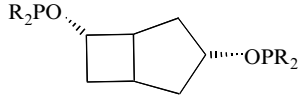
   $^1$H NMR (200 MHz, DMSO): δ 8.22 (d, *J* 8.2 Hz, 1H, N*H*); 7.24 (m, 5H, Ph); 4.40 (m, 1H, C*H*); 3.02 (dd, *J* 13.8 Hz, *J* 5.0 Hz, 1H, $CH_aH_b$); 2.83 (dd, *J* 13.8 Hz, *J* 9.5 Hz, 1H, $CH_aH_b$); 1.78 (s, 3H, CO-$CH_3$).

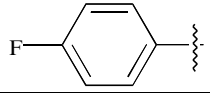
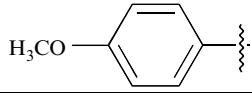
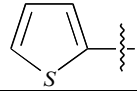
   Other ligands were synthesis by the same methods using different chlorophosphines. The reduction reaction of the α-acetamido cinnamic acid gave good results in term of enantiomeric excess and yield (all the reactions went to completion). The results are summarised in Table 12.2.

## Conclusion

The rhodium–diphosphine catalysts are generally sensitive to oxygen, hence the reactions have to be carried out under strictly inert atmospheric conditions. A decrease in the yield or the enantiomeric excess can be due to a lack of sufficient precaution during the procedure or to the inactivation of the catalyst when exposed to oxygen. However, the reactions using rhodium complexes as catalysts give very good results which correlate well with the published material.

**Table 12.2** Enantiomeric excess resulting from the reduction of α-acetamido cinnamic acid by rhodium (B[3.2.0]DPO) complexes.




| Ligand's substituent, R | ee % |
|---|---|
|  | 91 |
|  | 90.5 |
|  | 87. 5 |

Note that, in contrast, the reactions using [(COD) Rh ((*S*, *S*)Me-BPE)] or [(COD)Rh((*R*, *R*) Me-DuPHOS)] complexes can be performed at atmospheric pressure of hydrogen which avoids the use of heavy-duty hydrogenation apparatus.

## 12.5 HYDROGENATION OF ENOL CARBONATES AND 4-METHYLENE-N-ACYLOXAZOLIDINONE USING [Rh((R)-BiNAP)] COMPLEXES

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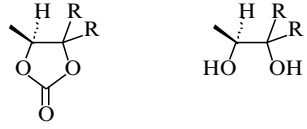
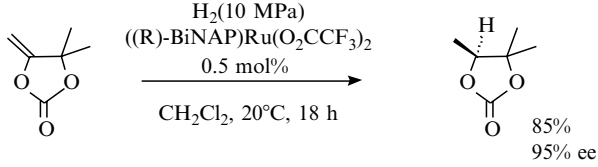



**Figure 12.3** $R = Me, R - R = -(C_2H)_4^-, R - R = -(C_2H)_5^-$.

P.H. Dixneuf, C. Bruneau and P. Le Gendre[8] have reported a straightforward synthesis of optically active cyclic carbonates and 1,2-diols (Figure 12.3) based on the selective hydrogenation of the exocyclic double bond of α-methylene carbonates[8,9] followed by their hydrolysis. By using bis(trifluoroacetate) BiNAP-ruthenium[10] complexes as precatalyst, the asymmetric hydrogenation of α-methylene-1,3-dioxolan-2-ones was carried out in dichloromethane solution under 10 MPa hydrogen pressure. This procedure allowed access to cyclic carbonates with high yields (80–85%) and optical purities (89–95%). The treatment of these carbonates with potassium carbonate in anhydrous methanol for 2.5 hours led to the quantitative conversion of the carbonates into the corresponding diols.

### 12.5.1 SYNTHESIS OF (*S*)-4,4,5-TRIMETHYL-1,3-DIOXOLANE-2-ONE



**Materials and equipment**

- 5-Methylene-1,3-dioxolane-2-one[9], 0.25 g, 1.95 mmol
- ((R)-BiNAP)Ru($O_2CCF_3$)$_2$[10], 9 mg, 0.01 mmol
- Dry and degassed dichloromethane, 15 mL

- 125 mL Stainless steel autoclave with a mechanical stirrer
- 50 mL Round bottomed flask
- Rotary evaporator
- Kugelrohr apparatus

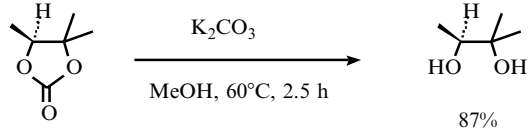
**Procedure**

1. The 125 mL stainless steel autoclave was flushed with nitrogen. The 5-methylene-1,3-dioxolane-2-one, the ruthenium catalyst and dichloromethane (10 mL) were placed in the autoclave under a nitrogen atmosphere.
2. The autoclave was sealed, flushed with hydrogen and pressurized with 10 MPa of hydrogen. The mixture was stirred for 18 hours at 20 °C under 10 MPa of hydrogen.
3. Once the autoclave was depressurized, the solution was poured into a 50 mL round bottomed flask and the autoclave rinsed with dichloromethane (5 mL). The solvent was removed by using a rotary evaporator.
4. The hydrogenated carbonate can be recovered free of ruthenium catalyst by sublimation under reduced pressure using a Kugelrohr apparatus (bp 70 °C, 1.5 mmHg).

   This procedure has been scaled up to provide 2 g of 4,4,5-trimethyl-1,3-dioxolane-2-one.

   The optical purity can be determinated by using GC with a chiral Lipodex capillary column (25 m × 0.25 mm).

## 12.5.2 SYNTHESIS OF (*S*)-2-METHYL-2,3-BUTANEDIOL




**Materials and equipment**

- 4,4,5-Trimethyl-1,3-dioxolane-2-one, 0.17 g, 1.34 mmol
- Potassium carbonate, 0.27 g, 2.0 mmol
- Dry methanol, 10 mL
- Diethyl ether, 10 mL
- Saturated solution of $NH_4Cl$, 5 mL
- Magnesium sulfate

- 50 mL Round bottomed flask with a magnetic stirrer bar
- Reflux condenser
- Magnetic stirrer plate with thermostatically controlled oil bath and thermometer
- Rotary evaporator
- Kugelrohr apparatus

**Procedure**

1. 4,4,5-Trimethyl-1,3-dioxolane-2-one (0.17 g), potassium carbonate (0.27 g) and methanol (10 mL) were placed in 50 mL round bottomed flask equipped with a magnetic stirrer bar and a reflux condenser. The mixture was then stirred at 60 °C for 2.5 hours.
2. The solvent was removed by using a rotary evaporator. The solution was dissolved in a saturated solution of $NH_4Cl$ and extracted with diethyl ether. After the solution was dried with magnesium sulfate, the diethyl ether was removed by using a rotary evaporator.
3. It is noteworthy that this diol has been used as ligand in the molybdenum-mediated kinetic resolution of oxiranes[11].

## 12.5.3 PREPARATION OF OPTICALLY ACTIVE N-ACYLOXAZOLIDINONES

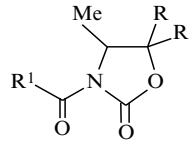
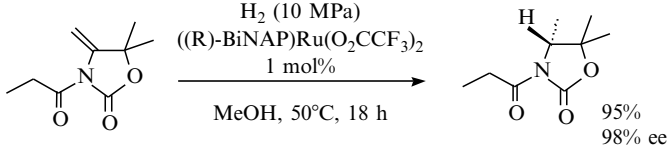



**Figure 12.4** $R^1$ = Me, Et, Ph; R = Me, R-R= -($C_2H_5$).

Whereas optically active acyloxazolidinones are usually prepared by acylation of oxazolidinone arising from optically active natural amino acids via multistep synthesis[12], Dixneuf's research group[13] recently described a novel route to both enantiomers of optically active N-acyloxazolidinones (Figure 12.4) via asymmetric hydrogenation of 4-methylene-N-acyloxazolidinones[13,14]. The enantioselective hydrogenation of the latter was performed under 10 MPa of hydrogen in MeOH at 50 °C for 18 hours in the presence of 1 mol% of ((R)-BiNAP)Ru($O_2CCF_3$)$_2$[10] as catalyst and led to optically active N-acyloxazolidinones with very high yields (> 85 %) and enantioselectivities (> 98 %).

## 12.5.4 SYNTHESIS OF (*R*)-N-PROPIONYL-4,5,5-TRIMETHYL-1,3-OXAZOLIDIN-2-ONE




### Materials and equipment

- N-Propionyl-5,5-dimethyl-4-methylene-1,3-oxazolidin-2-one [13,14], 0.2 g, 1.2 mmol
- ((R)-BiNAP)Ru($O_2CCF_3$)$_2$[10]. 11 mg, 0.012 mmol
- Dry and degassed methanol, 15 mL

- 125 mL Stainless steel autoclave with mechanical stirrer, thermostatically controlled oven and thermocouple
- 50 mL Round bottomed flask
- Rotary evaporator
- Kugelrohr apparatus

### Procedure

1. The 125 mL stainless steel autoclave was flushed with nitrogen.
2. The N-propionyl-5,5-dimethyl-4-methylene-1,3-oxazolidin-2-one, the ruthenium catalyst and methanol (10 mL) were placed in the autoclave under nitrogen atmosphere.
3. The autoclave was sealed, flushed with hydrogen and pressurized with 10 MPa of hydrogen. The mixture was stirred for 18 hours at 50 °C under 10 MPa of hydrogen.
4. Once the autoclave had cooled to room temperature, the autoclave was carefully depressurized, the solution was poured into a 50 mL round bottomed flask and the autoclave was rinsed with methanol (5 mL). The solvent was removed by using a rotary evaporator.
5. The hydrogenated carbamate can be recovered free of ruthenium catalyst by sublimation under reduced pressure using a Kugelrohr apparatus (bp 80 °C, 1.5 mmHg).

   This procedure has been scaled up to provide 1.5 g of 4,4,5-trimethyl-1,3-dioxolane-2-one.

   The optical purity can be determinated by using HPLC equipped with a chiral (S,S)-WHELK 0–1 column (250 × 4.6 mm) eluted with a hexane-2-propanol (95/5) mixture.

## 12.6 ENANTIOSELECTIVE RUTHENIUM-CATALYZED HYDROGENATION OF VINYLPHOSPHONIC ACIDS

VIRGINIE RATOVELOMANANA-VIDAL, JEAN-PIERRE GENÊT

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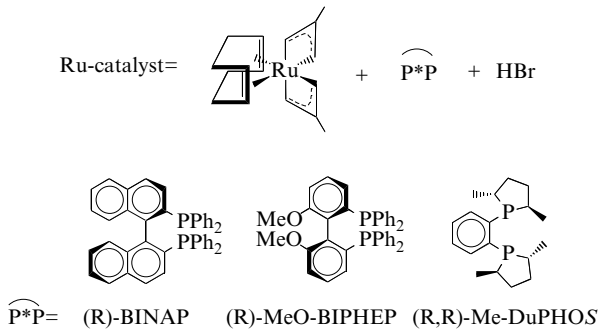
### 12.6.1 SYNTHESIS OF CHIRAL RU(II) CATALYSTS




**Materials and equipment**

- [(COD)Ru(2-(methylallyl)$_2$], 22 mg
- (*R*)-MeO-BIPHEP, 48 mg
- Distilled acetone, 2 mL
- Methanolic hydrobromic acid (0.2 N), 0.72 mL

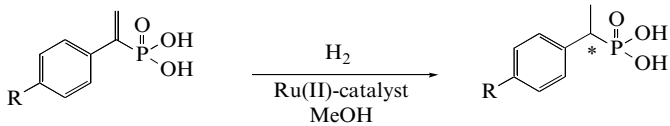
- Glass tube (10 mL) with a magnetic stirrer bar
- Magnetic stirrer

**Procedure**

All reactions were carried out under argon in solution in dry solvents.

1. The ruthenium catalyst was prepared at room temperature by reaction of [(COD)Ru(2-(methylallyl)$_2$] with ligand P*P in this case (*R*)-MeO-BIPHEP (1.2 eq) in acetone (2 mL).
2. Methanolic HBr (2.2 eq) was added dropwise to the solution which was subsequently stirred for 30 minutes at room temperature. A yellow precipitate was formed and the solvent was then evaporated *in vacuo*.

## 12.6.2 ASYMMETRIC HYDROGENATION OF VINYLPHOSPHONIC ACIDS CARRYING A PHENYL SUBSTITUENT AT $C_2$




R=H, Cl, Me

### Materials and equipment

- Ru(II)-catalyst 1 mol%
- Vinyl phosphonic acid, 1 mmol to 6 mmol
- Methanol, 2 mL to 5 mL

- Autoclave (500 mL)
- Magnetic stirrer

### Procedure

All reactions were carried out in solution under argon.

1. A solution of the appropriate substrate (1 mmol or 6 mmol) in degassed methanol (2 mL to 5 mL) was added to the Ru(II) catalyst.
2. The glass vessel was placed under argon in a stainless steel autoclave, which was then pressurized with hydrogen.
3. The reaction proceeded at 10 bar and 80 °C.

   The enantiomeric excesses of the phosphonic acids were measured using $^{31}$P NMR after treatment with (1S, 2S)-(−)-N,*N*′-dimethyl(diphenylethylene)-diamine in $CDCl_3$ and a catalytic amount of $CD_3OD$.

*1-Phenylethenylphosphonic acid (R = H):*

$^1$H NMR (200 MHz, $CDCl_3$): δ 9.2 (sl, 2H); 7.3 (s, 5H); 3.0 (qd, J 8.5 Hz, J 24.5 Hz, 1H); 1.5 (dd, J 6.5 Hz, J 18.4 Hz, 3H).

$^{31}$P NMR (101 MHz, $CDCl_3$): δ 35.3 ppm.

The ee was measured by $^{31}$PNMR (101 MHz, $CDCl_3$) in the presence of 1 equivalent of (1S, 2S)-(−)-N, N′-diphenyl-ethylenediamine and 4% (vol.) of $CD_3OD$.

δ (ppm) 26.8 (R,S,S) and 26.4 ppm (S,S,S). Methyl ester $[\alpha]_D = +4.5$ (c 1.3., $CHCl_3$) for ee 71% (R).

*1-para-Chlorophenylethenylphosphonic acid (R = Cl)*

$^1$H NMR (200 MHz, $CDCl_3$): δ8.9 (sl, 2H); 7.3–7.2 (d, *J* 7.6 Hz, 2H); 7.2–7.1 (d, *J* 7.6 Hz, 2H); 3.0 (qd, *J* 7.3 Hz, *J* 23.2 Hz, 1H); 1.4 (dd, *J* 7.2 Hz, *J* 18.4 Hz, 3H).

$^{31}$P NMR (101 MHz, $CDCl_3$): δ 32.9 ppm.

The ee was measured by $^{31}$P NMR (101 MHz, $CDCl_3$) in the presence of 1 equivalent of (1*S*, 2*S*)-(−)-*N*, *N*′-dimethyl(diphenylethylene)diamine and 1 % (vol.) of $CD_3OD$.

δ (ppm) 26.4 (*R,S,S*) and 25.9 ppm (*S,S,S*). Methyl ester $[\alpha]_D = 7.0$ (*c* 1.3, $CHCl_3$) for ee 80 % (*S*).

*1-para-Methylphenylethenylphosphonic acid (R = Me)*

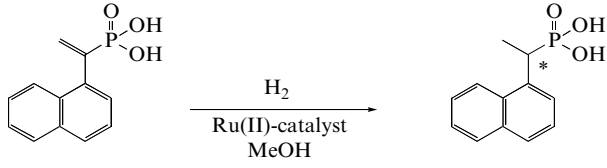
$^1$H NMR (200 MHz, $CDCl_3$): δ 8.5 (sl, 2H); 7.2 (d, *J* 7.8 Hz, 2H); 7.1 (d, *J* 7.8 Hz, 2H); 2.9 (qd, *J* 8.0 Hz, *J* 19.0, 1H); 2.3 (s, 3H); 1.4 (dd, *J* 6.0 Hz, *J* 18.1 Hz, 3H).

$^{31}$P NMR (101 MHz, $CDCl_3$): δ 35.3 ppm.

The ee was measured by $^{31}$ P NMR (101 MHz, $CDCl_3$) in the presence of 1 equivalent of (1*S*, 2*S*)-(−)-*N*,*N*′-dimethyl-diphenylethylene)diamine and 4 % (vol.) of $CD_3OD$.

δ (ppm) 27.6 (*R,S,S*) and 27.3 ppm (*S,S,S*). Methyl ester $[\alpha]_D = -7.5$ (*c* 1.0, $CHCl_3$) for ee 78 % (*S*).

## 12.6.3 ASYMMETRIC REDUCTION OF A VINYLPHOSPHORIC ACID CARRYING A NAPHTHYL SUBSTITUENT AT $C_2$




**Materials and equipment**

- Ru(II)-catalyst, 1 mol %
- Vinyl phosphonic acid, 1 mmol to 6 mmol
- Methanol, 2 mL to 5 mL

- Autoclave (500 mL)
- Magnetic stirrer

**Procedure**

All reactions were carried out under argon in solution as above. Thus:

1. A solution of the appropriate substrate (1 mmol or 6 mmol) in degassed methanol (2 mL to 5 mL) was added to the Ru(II) catalyst.
2. The glass vessel was placed under argon in a stainless steel autoclave, which was then pressurized with hydrogen.
3. The reaction proceeded at 10 bar and 80 °C.

The enantiomeric excesses of the phosphonic acid was measured using $^{31}P$ NMR after treatment with (1S, 2S)-(−)-N,N′-dimethyl(diphenyl-ethylene)-diamine in $CDCl_3$ and a catalytic amount of $CD_3OD$.

*1-Naphthylethenylphosphonic acid (R = naphthyl)*

$^1H$ NMR (200 MHz, $CDCl_3$): δ 9.0 (sl, 2H); 7.9–7.8 (m, 2H); 7.74–7.71 (d, *J* 7.7 Hz, 1H); 7.748–7.34 (m, 4H) 3.7 (qd, *J* 7.2 Hz, *J* 25.1, 1H); 1.3 (dd, *J* 7.1 Hz, *J* 18.7 Hz, 3H).

$^{31}P$ NMR (101 MHz, $CDCl_3$): δ 32.2 ppm

The ee was measured by $^{31}P$ NMR (101 MHz, $CDCl_3$) in the presence of 1 equivalent of (*1S, 2S*)-(−)-*N*,*N*′-dimethyl(diphenylethylene)-diamine and 4% (vol.) of $CD_3OD$.

δ (ppm) 26.7 (*R,S,S*) and 26.3 ppm (*S,S,S*). Methyl ester $[\alpha]_D = +94.2$ (*c* 1.0, $CHCl_3$) for ee 86% (*S*).

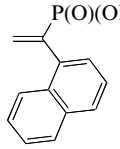
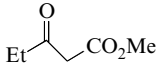
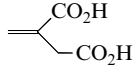
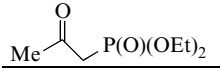
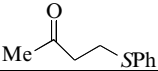
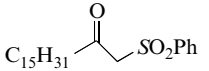
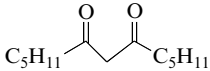
## 12.6.4 SCOPE OF THE HYDROGENATION REACTION

The enantioselective ruthenium-catalysed hydrogenation reaction, which is applied above to vinylphosphonic acid derivatives[15], has a much larger scope. It has been shown that a number of olefins and functionalized carbonyl compounds can be hydrogenated with very high selectivity by using the '*in situ*' generated ruthenium catalyst[16]. For instance, β-ketoesters[16], phosphonates[17], sulfides[18], sulfones[19], sulfoxides and β-diketones[20] have been reduced to the corresponding alcohols in enantiomeric excesses approaching 100%. Atropoisomeric ligands (BINAP, BIPHEMP, MeO-BIPHEP) but also DuPHOS, DIOP, SKEWPHOS[21], CnrPHOS[22] etc... can be used as chiral auxiliaries. Selected results are given in the following table. Dynamic kinetic resolution of α-chloro and α-acetamido-β-ketoesters have also been performed by this method, leading to *anti*-α-chloro[23] and *syn*-α-acetamido-β-hydroxyesters[24] in 99% enantiomeric excess.

All these hydrogenation reactions are quantitative, easy to perform on a large scale, and thus represent an highly convenient approach to a number of optically pure compounds. In most cases, it compares favourably with

enzyme-promoted reductions which have more limited scope with respect to substrates. The enantioselective hydrogenations have been applied to the synthesis of natural products of biological interest[25].

**Table 12.3** Asymmetric ruthenium-catalysed hydrogenations.

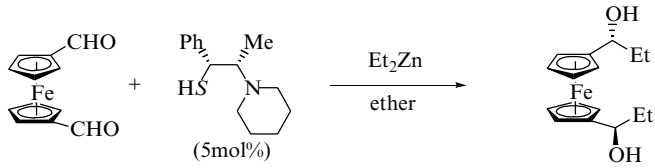
| *S*ubstrate | [Ru]/(P*P) | e.e.(%) | Ref. |
|---|---|---|---|
|  | (R)-MeO-BIPHEP | 86(*S*) | 15 |
|  | (R)-MeO-BIPHEP | 99(R) | 16 |
|  | (R)-BINAP | 98(R) | 16 |
|  | (R)-BINAP | 99(R) | 17 |
|  | (*S*)-MeO-BIPHEP | 98(*S*) | 18 |
|  | (*S*)-MeO-BIPHEP | >95(*S*) | 19 |
|  | (R)-MeO-BIPHEP | 99(R,R) (anti) | 20 |

## 12.7 SYNTHESIS OF A CYLINDRICALLY CHIRAL DIPHOSPHINE AND ASYMMETRIC HYDROGENATION OF DEHYDROAMINO ACIDS

Jahyo Kang and Jun Hee Lee

*Department of Chemistry, Sogang University, Seoul 121–742, Korea*

## 12.7.1 PREPARATION OF (R,R)-1,1′-BIS (α-HYDROXYPROPYL) FERROCENE




### Materials and equipment

- 1,1′-Ferrocenedicarboxaldehyde, 8.30 g[26,27]
- Diethylzinc (1.1 M in toluene), 28.7 mL
- (1*R*,2*S*)-1-Phenyl-2-(1-piperidinyl)propane-1-thiol, 400 mg
- Diethyl ether, 115 mL
- 1 M Hydrochloric acid
- Diethyl ether
- Brine
- Magnesium sulfate
- Silica gel (230–400 mesh)

- 250 mL Round-bottomed flask with a magnetic stirring bar
- Magnetic stirrer
- Temperature controller
- Separatory funnel, 250 mL
- Glass filter (3G3)
- Rotatory evaporator
- Glass column

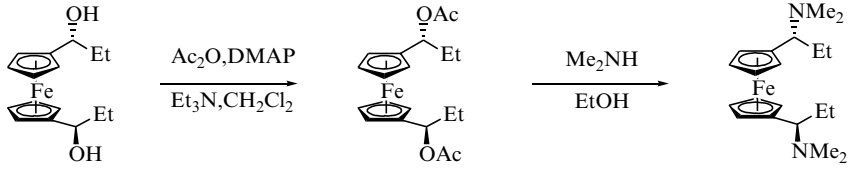
### Procedure

1. In a degassed 250 mL round-bottomed flask equipped with a magnetic stirring bar were placed 1,1′-ferrocenedicarboxaldehyde (8.30 g), (1*R*,2*S*)-1-phenyl-2-(1-piperidinyl)propane-1-thiol (400 mg) and dry diethyl ether (115 mL). Diethylzinc in toluene (1.1 M, 28.7 mL) was added dropwise to the mixture at 0 °C. The reaction mixture was stirred at 0 °C for 10 hours.
2. After the period, the reaction was quenched by adding a solution of 1 M HCl with vigorous stirring at 0 °C until no more ethane gas was generated. The white inorganic material was removed by filtration over a glass filter.
3. The organic layer was separated and the aqueous layer was extracted with ether (3 × 30 mL). The combined organic layer was washed with brine, dried over magnesium sulfate, filtered and concentrated using a rotatory evaporator to give a crude black residue.

4. The residue was chromatographed on silica gel (eluent: *n*-hexane–ethyl acetate, 3:1) to afford the (*R,R*)-1,1′-bis(α-hydroxypropyl)ferrocene as an orange solid (9.83 g, 95 %).

   The ee (99.9 %) was determined by HPLC (Daicel Chiralcel OJ column, eluent 2-propanol-*n*-hexane 2:98, flow 0.5 mL/min); (*S,S*)-enantiomer: $R_t$ 20.0 min, (*R,S*)-*meso* isomer: $R_t$ 24.8 min, (*R,R*)-enantiomer: $R_t$ 35.6 min; the (*S,S*)-isomer was not detected); (*R,R*)-isomer: (*R,S*)-*meso* isomer = 98.3:1.7.

## 12.7.2 PREPARATION OF (R,R)-1,1′-BIS[α-(DIMETHYLAMINO) PROPYL]FERROCENE[28]




**Materials and equipment**

- Dichloromethane, 54 mL
- 4-Dimethylaminopyridine
- Triethylamine, 36.4 mL
- Acetic anhydride, 12.2 mL
- 50 % Aqueous dimethylamine, 22.2 mL
- Absolute ethyl alcohol, 90 mL
- 10 % Phosphoric acid solution
- 10 % Sodium hydroxide solution
- Diethyl ether
- Magnesium sulfate, potassium carbonate

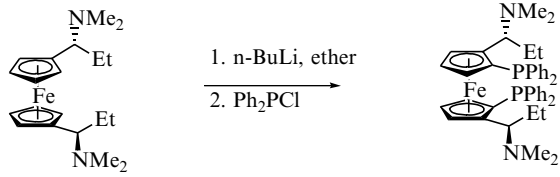
- 250 mL Round-bottomed flask with a magnetic stirring bar
- Magnetic stirrer
- Separatory funnel, 250 mL, 1 L
- Rotatory evaporator

**Procedure**

1. In a 250 mL round-bottomed flask equipped with a magnetic stirring bar were placed dichloromethane (54 mL), (*R,R*)-1,1′-bis(α-hydroxypropyl)ferrocene (9.84 g) and a catalytic amount of 4-(dimethylamino)pyridine (39.8 mg) under nitrogen. Triethylamine (36.4 mL) and acetic anhydride (12.2 mL) were

added to the mixture successively at 0 °C, and the resulting mixture was stirred at room temperature for 8 hours.
2. Cold water (ice–water, 50 mL) was added, and the mixture was extracted with dichloromethane (3 × 30 mL). The combined extracts were dried over magnesium sulfate, filtered and concentrated using a rotatory evaporator to afford the diacetate as a dark-brown residue.
3. To the residue in a 250 mL round-bottomed flask equipped with a magnetic stirring bar were added 50 % aqueous dimethylamine (22.2 mL) and absolute ethyl alcohol (90 mL), the mixture was stirred at room temperature for 48 hours. During this time, an orange solid was formed.
4. The solvent was removed using a rotatory evaporator, and the resulting residue was diluted with ether (50 mL). The diamine was extracted with 10 % phosphoric acid (3 × 15 mL), after which the aqueous layer was made alkaline (pH 9) with 10 % sodium hydroxide solution (100 mL). The resulting mixture was extracted with ether (5 × 50 mL). The combined ethereal extracts were dried over anhydrous potassium carbonate, filtered and concentrated *in vacuo* to afford the pure (*R,R*)-1,1′-bis [α-(dimethylamino) propyl]ferrocene as an orange solid (11.4 g, 98.0 %).

## 12.7.3 PREPARATION OF (R,R$_p$*S*,$_p$*S*)-1,1′-BIS [α-(DIMETHYLAMINO) PROPYL]-2,2′-BIS(DIPHENYL-PHOSPHINO)FERROCENE




**Materials and equipment**

- Diethyl ether, 22 mL
- *n*-BuLi (1.68 M in hexanes), 21.3 mL
- Chlorodiphenylphosphine, 10.3 mL
- Saturated sodium bicarbonate solution
- Diethyl ether
- Brine
- Magnesium sulfate
- Silica gel (230–400 mesh)

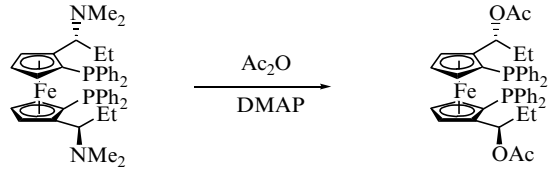
- 250 mL Round-bottomed flask with a magnetic stirring bar
- Magnetic stirrer
- Syringe pump

- Separatory funnel, 250 mL
- Rotatory evaporator

**Procedure**

1. (*R*,*R*)-1,1′ -Bis[α-(dimethylamino)propyl]ferrocene (5.10 g) was placed in a 250 mL round-bottomed flask equipped with a magnetic stirring bar under nitrogen; dry diethyl ether (22 mL) was then added. To the mixture was added dropwise *n*-BuLi in hexanes (1.68 M, 34.0 mL) within 10 minutes at room temperature. After 30 minutes the colour of the mixture changed from yellow to red.
2. After 6 hours, chlorodiphenylphosphine (18 mL) was added over 2 hours with the help of a syringe pump. After the addition was complete, the resulting suspension was stirred at room temperature for 3 hours and aqueous sodium bicarbonate was slowly added to hydrolyse the excess chlorodiphenylphosphine with cooling in an ice bath.
3. The reaction mixture was extracted with diethyl ether (3 × 30 mL). The combined organic layer was washed with brine, dried over magnesium sulfate, filtered and concentrated using a rotatory evaporator. The resulting residue was chromatographed (eluent: *n*-hexane–ethyl acetate, 97:3) on silica gel predeactivated with triethylamine: *n*-hexane (2:98) to afford the (*R*, *R*, $_{p}S$, $_{p}S$)-1,1′-bis[α-(dimethylamino)propyl]-2,2′-bis(diphenylphosphino)ferrocene as an orange solid (8.07 g, 78.0 %).

## 12.7.4 PREPARATION OF (*R*, *R*, $_{p}S$, $_{p}S$)-1,1′-BIS (α-ACETOXYPROPYL)-2,2′-BIS (DIPHENYLPHOSPHINO)FERROCENE[29]




**Materials and equipment**

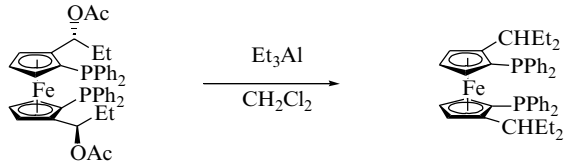
- Acetic anhydride, 4.00 mL
- 4-Dimethylaminopyridine
- Silica gel (230–400 mesh)

- 25 mL Schlenk-type flask with a magnetic stirring bar
- Magnetic stirrer
- Rotatory evaporator

**Procedure**

1. ($R$, $R$, $_pS$, $_pS$)-1,1′-bis [α-(Dimethylamino)propyl]-2,2′-bis(diphenylphosphino)ferrocene (1.55 g) and 4-dimethylaminopyridine were placed in a 25 mL degassed Schlenk flask equipped with a magnetic stirring bar; acetic anhydride (4.00 mL) was then added.
2. The reaction mixture was heated at 100 °C for 20 hours, after which time the excess acetic anhydride was removed under high vacuum at 50 °C.
3. The resulting residue was chromatographed (eluent: *n*-hexane–ethyl acetate, 95:5) on silica gel pre-deactivated with triethylamine: *n*-hexane (2:98) to afford the ($R$, $R$, $_pS$, $_pS$)-1,1′-bis(α-acetoxypropyl)-2,2′-bis(diphenylphosphino)ferrocene as an orange solid (1.26 g, 78.0 %).

## 12.7.5 PREPARATION OF ($_pS$, $_pS$)-1,1′-BIS(DIPHENYLPHOSPHINO)-2,2′-BIS(1-ETHYLPROPYL)FERROCENE [(S,S)-3-PT-FERROPHOS]




**Materials and equipment**

- Dichloromethane, 16.6 mL
- Triethylaluminium (1.35 M in toluene), 6.14 mL
- Saturated sodium bicarbonate solution
- Saturated sodium potassium tartrate solution
- Diethyl ether, 30 mL
- 1 M Hydrochloric acid
- Brine
- Magnesium sulfate

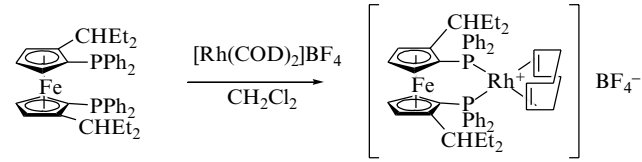
- 100 mL Round-bottomed flask with a magnetic stirring bar
- Magnetic stirrer
- Separatory funnel, 125 mL
- Rotatory evaporator

**Procedure**

1. In a 100 mL round-bottomed flask equipped with a magnetic stirring bar were placed dichloromethane (16.6 mL) and ($R$, $R$, $_pS$, $_pS$)-1,1′-bis (α-acetoxypropyl)-2,2′-bis(diphenylphosphino)ferrocene (1.25 g) under nitrogen. Triethylaluminium in toluene (1.35 M, 6.14 mL) was added to the mixture

at −20 °C. The cold bath was removed immediately and the reaction mixture was warmed to room temperature.
2. After stirring at room temperature for 20 minutes, the reaction mixture was cooled to 0 °C and transferred via a cannula into saturated aqueous $NaHCO_3$ (15 mL). Saturated aqueous sodium potassium tartrate was added (15 mL).
3. The dichloromethane was removed by rotatory evaporation and dry ether (30 mL) was added. The mixture was stirred vigorously for 15 minutes and then acidified with 1 N HCl (15 mL).
4. The organic layer was separated, and the aqueous layer was extracted with ether (3 × 20 mL). The combined organic layer was washed with brine, dried over magnesium sulfate, filtered and concentrated using a rotatory evaporator. The crude orange solid was recrystallized from hot ethanol to give the ($_pS$, $_pS$)-1,1′-bis(diphenylphosphino)-2,2′-di-γ-pentylferrocene [(*S*,*S*)-3-Pt-FerroPHOS] as yellow crystals (519 mg, 45.0 %).

## 12.7.6 PREPARATION OF [(COD)RH(($_pS$, $_pS$)-1,1′-BIS (DIPHENYLPHOSPHINO)-2,2′-BIS(1-ETHYLPROPYL) FERROCENE)]$^+BF_4^-$




(*S*,*S*)-3-Pt-FerroPHO*S* [Rh((*S*,*S*)-3-Pt-FerroPHO*S*)(COD)]$BF_4$

### Materials and equipment

- Dichloromethane
- Bis(1,5-cyclooctadiene)rhodium(I) tetrafluoroborate, 111 mg

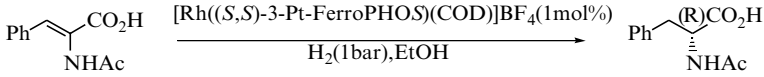
- 25 mL Schlenk-type flask with a magnetic stirring bar
- 10 mL pressure-equalized dropping funnel
- Magnetic stirrer
- Glass filter (3G4)

### Procedure

1. In a 25 mL Schlenk-type flask, equipped with a 10 mL pressure equalized dropping funnel and a magnetic stirring bar, were placed bis(1,5-cyclooctadiene)rhodium(I) tetrafluoroborate (111 mg) and dichloromethane (5 mL) under nitrogen.

2. A solution of (*S*,*S*)-3-Pt-FerroPHOS (200 mg) in dichloromethane (5 mL) was added dropwise over 20 minutes to the above mixture from the dropping funnel at 23 °C. The resulting deep red homogeneous solution was stirred for 3 hours at that temperature.
3. During this time, a red orange coloured solution was formed. The solvent was carefully removed by a stream of nitrogen gas to afford a gold creamy solid. The creamy solid was recrystallized from $CHCl_3/Et_2O$, filtered, washed with ether and dried *in vacuo* to afford a Rh complex as orange crystals (230 mg, 84.6 %).

## 12.7.7 ASYMMETRIC HYDROGENATION OF α-ACETAMIDO CINNAMIC ACID




**Materials and equipment**

- {Rh(COD)[(*S*,*S*)-3-Pt-FerroPHOS]}$BF_4$, 9.9 mg
- Absolute ethyl alcohol, 3.3 mL
- α-Acetamido cinnamic acid, 205 mg
- Degassed ethanol (3.3 mL)

- Dry box
- 25 mL Schlenk-type flask with a magnetic stirring bar
- Magnetic stirrer

**Procedure**

1. In a dry box, a 25 mL Schlenk-type flask with a magnetic stirring bar was charged with {Rh(COD)[(*S*,*S*)-3-Pt-FerroPHOS]}$BF_4$ (9.9 mg), α-acetamido cinnamic acid (205 mg) and degassed ethanol (3.3 mL). After sealing, the flask was removed from the dry box.
2. With stirring of the mixture at 20–23 °C, the flask was then freeze–pump–thaw–degassed (3 cycles) and stirred under hydrogen gas (*ca.* 1 bar) for 2 hours.

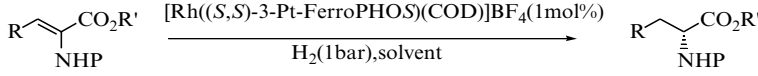
   The enantiomeric excess (98.9 %) was determined by GC (Chrompack Chiralsil-L-Val column)

   The reaction depends on various factors including solvent, initial pressure, catalyst precursor and the N-protecting group. Due to the high stability of (S,S)-3-Pt-FerroPHOS towards air, it may be used in an industrial process.

## Conclusion

The cylindrically chiral diphosphine neither changed, nor lost its reactivity and selectivity in hydrogenation reactions even after long exposure to air. In a $^{31}P$-NMR study, no detectable air-oxidation was observed even after a long exposure (3 weeks) to the atmosphere. The procedures for the synthesis of the chiral ligand and the asymmetric reaction described above are very simple, giving high enantioselectivity with many dehydroamino acids (Table 12.4).

**Table 12.4** Rh-Catalyzed asymmetric hydrogenation of α-(acylamino)acrylic acids and esters.




| R | R′ | P | Solvent | % ee | Config |
|---|---|---|---|---|---|
| Ph | H | Ac | EtOH | 98.7 | **R** |
| Ph | H | Ac | EtOH | 98.9 | *R* |
| Ph | Me | Ac | EtOH | 97.6 | *R* |
| Ph | Me | Cbz | MeOH | 85.3 | *R* |
| H | H | Ac | MeOH | 98.2 | *R* |
| H | Me | Ac | MeOH | 97.5 | *R* |
| 2-Np | H | Ac | MeOH | 95.7 | *R* |

## 12.8 SYNTHESIS AND APPLICATION OF DIAMINO FERRIPHOS AS A LIGAND FOR ENANTIOSELECTIVE Rh-CATALYSED PREPARATION OF CHIRAL α-AMINO ACIDS

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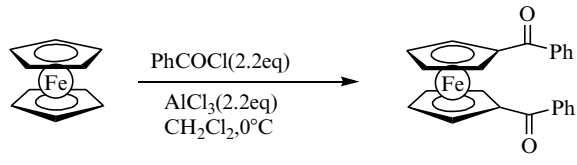
### 12.8.1 SYNTHESIS OF 1,1′-DI(BENZOYL)FERROCENE



**Materials and equipment**

- Ferrocene, 9.30 g, 50.0 mmol
- Benzoyl chloride, 12.77 mL, 110.0 mmol
- Aluminum (III) chloride, 14.67 g, 110.0 mmol
- Dry dichloromethane, 210 mL
- Water
- Brine
- Saturated potassium carbonate solution
- *n*-Pentane, *t*-butyl methyl ether
- Silica gel (60, 0.063–0.0200 mm, 70–200 mesh ASTM, Merck)

- 250 mL Two neck round-bottomed flask with an argon inlet
- 250 mL Dropping funnel
- Magnetic stirring bar
- Magnetic stirrer
- Syringe (20 mL)
- Separatory funnel, 500 mL
- Chromatography column

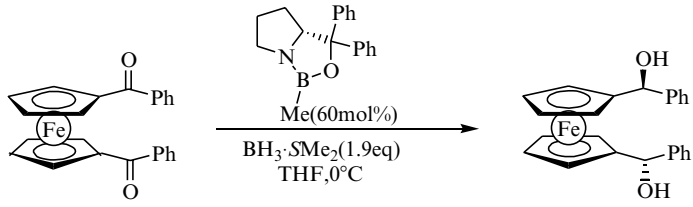
**Procedure**

1. In a 250 mL two-necked round-bottomed flask with an argon inlet, equipped with a dropping funnel and a magnetic stirring bar, aluminium (III) chloride (14.67 g) was suspended under argon in dichloromethane (60 mL) and cooled to 0 °C in an ice bath. Via a syringe, benzoyl chloride (12.77 mL) was added. Ferrocene (9.30 g), dissolved in dichloromethane (50 mL), was added dropwise within 30 minutes. The reaction was allowed to warm to room temperature and stirred overnight.
2. The work-up was done by dropwise addition of ice-cold water (50 mL; **caution: gas evolution**!). The reaction mixture was diluted with dichloromethane (100 mL) and washed with saturated potassium carbonate solution (2 × 50 mL) and brine (2 × 50 mL). The organic layer was dried over magnesium sulfate, filtrated and concentrated using a rotatory evaporator.
3. The crude product was purified by column chromatography (*n*-pentane: *t*-butyl methyl ether: dichloromethane 5:4:1) yielding 1,1′-di(benzoyl)ferrocene (16.16 g, 41.0 mmol, 82 %) as a dark red solid (mp 97–100 °C).

   $^{1}$H-NMR (200 MHz, $CDCl_3$): δ 7.77–7.72 (m, 4 H), 7.50–7.38 (m, 6 H), 4.88 (t, *J* 1.8 Hz, 4 H), 4.53 (t, *J* 1.8 Hz, 4 H).

   $^{13}$C-NMR (50 MHz, $CDCl_3$): δ 197.71, 138.94, 131.76, 128.18, 127.95, 79.36, 74.46, 72.95.

## 12.8.2 SYNTHESIS OF (S,S)-1,1′-BIS (α-HYDROXYPHENYLMETHYL)FERROCENE




### Materials and equipment

- 1,1′Di(benzoyl)ferrocene, 3.00 g, 11.1 mmol
- CBS-catalyst[30]: B-methyl oxazaborolidine (prepared from (*R*)-2-(diphenyl-hydroxy-methyl)pyrrolidine and methyl boronic acid)[31], 1.85 g, 6.7 mmol
- Borane dimethyl sulfide-complex, 2.00 mL, 21.1 mmol
- Dry tetrahydrofuran, 50 mL
- Methanol, 3 mL
- Saturated ammonium chloride solution, 150 mL
- *t*-Butyl methyl ether
- Diethyl ether
- Brine
- Magnesium stirrer
- Silica gel (60, 0.063–0.0200 mm, 70–200 mesh ASTM, Merck)

- 250 mL Round-bottomed flask with an argon inlet
- Magnetic stirring bar
- Magnetic stirrer
- Ice bath
- Two syringes (20 mL)
- Separatory funnel, 500 mL
- Rotatory evaporator
- Chromatography column

### Procedure

1. In a 250 mL round-bottomed flask with an argon inlet equipped with a magnetic stirring bar the CBS-catalyst (1.85 g) was dissolved in tetrahydrofuran (10 mL) and cooled to 0 °C in an ice bath. From a syringe filled with borane dimethyl sulfide-complex (2.00 mL dissolved in 10 mL THF) 20 % of the volume (2.40 mL) were added and the solution was stirred for 5 minutes. A solution of the diketone (3.00 g dissolved in 30 mL THF) was added from a second syringe simultaneously with the rest of the borane dimethyl sulfide-complex over 2 hours. The resulting yellow solution was stirred for another

10 minutes at 0 °C and the excess borane dimethyl sulfide-complex was destroyed by dropwise addition of methanol (**caution: gas evolution!**).

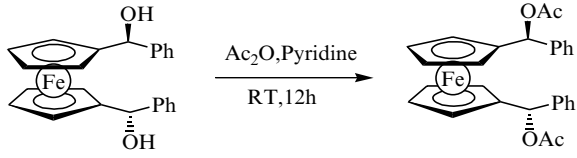
2. After no further gas evolution could be detected, the reaction mixture was poured into saturated ammonium chloride solution (150 mL) and transferred into a separatory funnel. The aqueous layer was extracted with *t*-butyl methyl ether (3 × 70 mL), the combined organic layers were washed with water (2 × 100 mL) and brine (100 mL) and dried over magnesium sulfate. After filtration the solvent was removed using a rotatory evaporator (bath temperature <30 °C) to give a yellow oil.
3. The crude product was purified by column chromatography (*n*-pentane: diethyl ether 1:1) and dried under vacuum yielding (*S*,*S*)-1,1′-bis(α-hydroxyphenyl-methyl)ferrocene (2.93 g, 10.7 mmol, 96 %) as a yellow solid (mp 128–130 °C).

   The ee (> 99 %) was determined by HPLC (Daicel® OD column, flow 0.6 mL/min, 215 nm, eluent 2-propanol/*n*-heptane 5/95); (*SS* and *RS*): $R_t$ 26.53 min, (*RR*): $R_t$ 30.70 min.

   $^1$H-NMR (300 MHz, $CDCl_3$): δ 7.27–7.17 (m, 10 H), 5.45 (s, br, 4 H), 4.42 (s, br, 2 H), 4.22 (s, br, 2 H), 4.16 (s, br, 2 H), 4.11 (s, br, 2 H).

   $^{13}$C-NMR (75 MHz, $CDCl_3$): δ 144.08, 128.17, 127.40, 126.19, 93.45, 72.59, 68.10, 67.89, 66.70, 66.66.

## 12.8.3 SYNTHESIS OF (*S,S*)-1,1′-BIS (α-ACETOXYPHENYLMETHYL)FERROCENE




### Materials and equipment

- (*S*,*S*)-1,1′-Bis (α-hydroxyphenylmethyl)ferrocene, 2.50 g, 6.3 mmol
- Acetic anhydride, 2 mL
- Pyridine, 4 mL

- 50 mL Round-bottomed flask
- Magnetic stirring bar
- Magnetic stirrer

### Procedure

1. In a 50 mL round-bottomed flask equipped with a magnetic stirring bar (*S*,*S*)-1,1′-bis(α-hydroxyphenylmethyl)ferrocene (2.50 g) was dissolved in

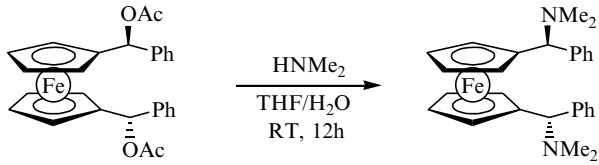
pyridine (4 mL) and acetic anhydride (2 mL) was added. The reaction mixture was stirred for 12 hours at room temperature.

2. All volatile material was evaporated under vacuum (1 mmHg, 3 hours) yielding (*S*,*S*)-1,1′-bis(α-acetoxyphenylmethyl)ferrocene in quantitative yield as a brown oil.

   $^{1}$H-NMR (300 MHz, $CDCl_3$): δ 7.30–7.20 (m, 10 H), 6.57 (s, 2 H), 4.25–4.23 (m, 2 H), 4.03–4.02 (m, 2 H), 3.98–3.97 (m, 2 H), 3.85–3.84 (m, 2 H), 2.04 (s, 6 H).

   $^{13}$C-NMR (75 MHz, $CDCl_3$): δ 169.91, 139.97, 128.27, 128.03, 127.17, 88.46, 74.06, 69.32, 69.27, 68.58, 68.37, 21.26.

## 12.8.4 SYNTHESIS OF (S,S)-1,1′-BIS(α-N,N-DIMETHYLAMINOPHENYLMETHYL)FERROCENE




**Materials and equipment**

- (*S*,*S*)-1,1′-Bis(α-acetoxyphenylmethyl)ferrocene, 3.00 g, 6.2 mmol
- Tetrahydrofuran
- Distilled water
- Dimethylamine (40 % in water), 10 mL
- *t*-Butyl methyl ether
- Diethyl ether
- Brine
- Magnesium sulfate
- *n*-Pentane
- Triethylamine
- Silica gel (60, 0.063–0.0200 mm, 70–200 mesh ASTM, Merck)

- 50 mL Round-bottomed flask
- Magnetic stirring bar
- Magnetic stirrer
- Chromatography column

**Procedure**

1. In a 50 mL round-bottomed flask equipped with a magnetic stirring bar (*S*, *S*)-1,1′-bis(α-acetoxyphenylmethyl)ferrocene (3.00 g) was dissolved in tetra-

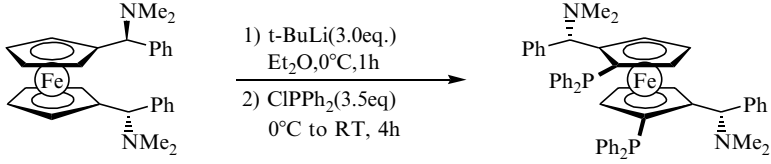
hydrofuran and dimethylamine (10 mL, 40 % in water) was added. Then water was added dropwise until a yellow solid started to precipitate, whereupon the solid was dissolved again by addition of tetrahydrofuran and the suspension was stirred for 12 hours at room temperature.

2. The tetrahydrofuran was removed under vacuum (1 mmHg), water was added (50 mL) and the solution was transferred into a separatory funnel. After extraction with *t*-butyl methyl ether (3 × 100 mL) the combined organic layers were washed with water (2 × 50 mL) and brine (2 × 50 mL) and dried over magnesium sulfate. After filtration the solvent was removed using a rotatory evaporator to give a yellow oil.
3. The crude product was purified by column chromatography (*n*-pentane: diethyl ether 3:1, 1 % triethylamine) and dried under vacuum yielding (*S*, *S*)-1,1′-bis(α-*N*,*N*-dimethylaminophenylmethyl)ferrocene (2.45 g, 5.41 mmol, 87 %) as a brown solid (48–49 °C).

   $^{1}$H-NMR (300 MHz, $CDCl_3$): δ 7.43–7.28 (m, 10 H), 3.89–3.88 (m, 2 H), 3.61 (s, br, 2 H), 3.56–3.55 (m, 2 H), 3.50–3.49 (m, 4 H), 1.98 (s, 12 H).

   $^{13}$C-NMR (75 MHz, $CDCl_3$): δ 143.34, 128.40, 127.97, 127.00, 90.38, 72.39, 71,39, 70.07, 67.74, 67.67, 44.48.

## 12.8.5 SYNTHESIS OF (αS, α′*S*)-1,1′-BIS (α-N, N-DIMETHYLAMINOPHENYLMETHYL)-(R,R)-1,1′-BIS(DIPHENYLPHOSPHINO)FERROCENE




diamino FERRIPHO*S*

### Materials and equipment

- (*S*,*S*)-1,1′-Bis(α-*N*,*N*-dimethylaminophenylmethyl)ferrocene, 480 mg, 1.06 mmol
- *t*-BuLi (1.60 M in pentane), 1.99 mL, 3.18 mmol
- Chlorodiphenylphosphine, 0.67 mL, 3.71 mmol
- Dry diethyl ether
- *n*-Pentane
- Saturated sodium hydrogen carbonate solution
- Magnesium sulfate
- Silica gel (60, 0.063–0.0200 mm, 70–200 mesh ASTM, Merck)

- 100 mL Round-bottomed flask with an argon inlet
- Two syringes (5 mL, 1 mL)
- Separatory funnel, 500 mL
- Magnetic stirring bar
- Magnetic stirrer
- Rotatory evaporator
- Chromatography column

**Procedure**

1. In a 100 mL round-bottomed flask with an argon inlet equipped with a magnetic stirring bar (*S*,*S*)-1,1′-bis(α-*N*,*N*-dimethylaminophenylmethyl)ferrocene (480 mg) was dissolved in diethyl ether (20 mL) under argon and cooled in an ice bath to 0 °C. *t*-BuLi (1.60 M in pentane, 1.99 mL) was added within 10 minutes via a syringe (after a few minutes the colour of the solution turned from yellow to dark red). After 1 hour of stirring, chlorodiphenylphosphine (0.67 mL) was added at 0 °C via a syringe and the resulting mixture was stirred for 4 hours at room temperature.
2. After addition of saturated sodium hydrogen carbonate solution (20 mL) the organic layer was separated and the aqueous layer extracted with diethyl ether (3 × 70 mL). The combined organic layers were dried over magnesium sulfate, filtrated and the solvent removed using a rotatory evaporator to give a yellow oil.
3. The crude product was purified by column chromatography (*n*-pentane: diethyl ether 1:1) immediately after isolation and dried under vacuum yielding (α*S*, α′*S*)-1,1′-bis(α-*N*,*N*-dimethylaminophenyl-methyl)-(*R*,*R*)-1,1′-bis(diphenylphosphino)-ferrocene (392 mg, 0.48 mmol, 45 %) as a yellow solid (mp 245–246 °C).

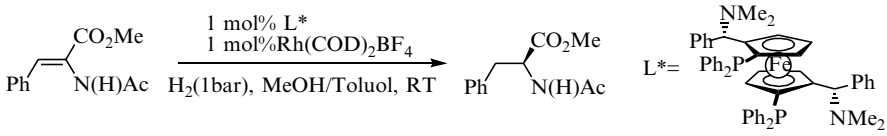
   It is important that the crude product is purified as quickly as possible, because in the crude reaction mixture it tends to become oxidized and/or degrade with time.

   $^{1}$H-NMR (300 MHz, $CDCl_3$): δ 7.35–7.10 (m, 30 H), 4.52 (s, br, 2 H), 4.39 (s, br, 2 H), 3.29 (s, br, 2 H), 3.15 (s, br, 2 H), 1.51 (s, 12 H).

   $^{13}$C-NMR (75 MHz, $CDCl_3$): δ 139.99, 139.68 (d, *J* 6.8 Hz), 137.84 (d, *J* 10.1 Hz), 134.77 (d, *J* 23.0 Hz), 132.38 (d, *J* 13.4 Hz), 128.55, 128.49, 127.97 (d, *J* 8.0 Hz), 127.92, 127.44 (d, *J* 7.0 Hz), 127.30, 126.59, 98.09 (d, *J* 22.5 Hz), 76.51 (d, *J* 10.0 Hz), 73.13, 72.88 (d, *J* 5.2 Hz), 71.57, 68.27 (d, *J* 10.1 Hz), 42.00.

   $^{31}$P-NMR (81 MHz, $CDCl_3$): δ − 23.89.

## 12.8.6 ASYMMETRIC HYDROGENATION OF METHYL-(Z)-3-PHENYL-2-METHYL-CARBOXAMIDO-2-PROPENOATE USING (S)-(R)-DIAMINO FERRIPHOS AS THE CHIRAL LIGAND




### Materials and equipment

- $Rh(COD)_2BF_4$, 4.1 mg, 0.01 mmol
- ($\alpha S, \alpha' S$)-1,1′-Bis(α-*N*,*N*-dimethylaminophenyl-methyl)-(*R,R*)-1,1′-bis(diphenylphosphino)ferrocene, 8.2 mg, 0.01 mmol
- Methyl-(Z)-3-phenyl-2-methylcarboxamido-2-propenoate, 219 mg, 1.0 mmol
- Dry methanol, 9 mL
- Dry toluene, 1 mL
- *t*-Butyl methyl ether
- Silica gel (60, 0.063–0.0200 mm, 70–200 mesh ASTM, Merck)

- 25 mL Schlenk tube
- Magnetic stirring bar
- Magnetic stirrer
- Balloon, filled with hydrogen
- Chromatography column

### Procedure

1. In a 25 mL Schlenk tube equipped with a magnetic stirring bar, under argon, $Rh(COD)_2BF_4$ (4.1 mg) and the ferrocenyl ligand (8.2 mg) were dissolved in methanol/toluene (5:1, 5 mL). After complete solubilization of the rhodium complex, the α-acetamido acrylate (219 mg) was added (dissolved in 5 mL methanol). The Schlenk tube was connected to a hydrogen balloon and the inert gas atmosphere was replaced by hydrogen.
2. The reaction was monitored by $^1$H-NMR. When complete conversion was obtained, the solvent was removed and the crude reaction was filtered through a short silica gel column using *t*-butyl methyl ether as eluent. The resulting solution was concentrated using a rotatory evaporator to give N-acetylphenylalanine methyl ester in quantitative yield as a white solid.

   The enantiomeric excess (97.5 %) was determined by GC (25 m × 0.2 mm fused silica WCOT Chirasil-L-Val (0.12 μm) using hydrogen (100 kPa) as the mobile phase, 140 °C); (*R*): $R_t$ 10.13 min, (*S*): $R_t$ 11.67 min.

$^1$H-NMR (300 MHz, $CDCl_3$): δ 7.25–7.18 (m, 3H), 7.04–7.00 (m, 2H), 5.96 (d, *J* 7.1 Hz, 1 H), 4.85–4.78 (m, 1 H), 3.65 (s, 3 H), 3.11–2.97 (m, 2H), 1.90 (s, 3 H).

$^{13}$C-NMR (75 MHz, $CDCl_3$): δ 172.07, 169.52, 135.85, 129.18, 128.51, 127.06, 53.10, 52.21, 37.83, 23.02.

## Conclusion

The straightforward synthesis of the diamino FERRIPHOS ligand offers a convenient access to this class of ferrocenyl ligands[32] and makes this ligand well suited for applications in asymmetric hydrogenation.

Table 12.5 shows some examples of α-acetamidoacrylates that were hydrogenated with (*S*)-(*R*)-diamino FERRIPHOS as ligand[33].

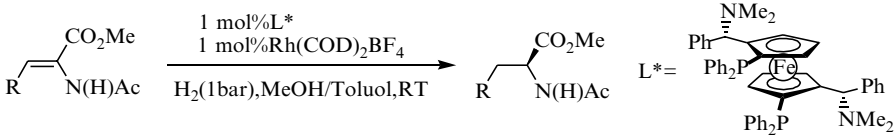



**Table 12.5** Asymmetric hydrogenation of α-acetamidoacrylates using the (*S*)-(*R*)-diamino FERRIPHOS ligand.

| Substrate | Conversion [%] | *ee* [%] |
|---|---|---|
| R = H | 100 | 97.8 (*S*) |
| R = Ph | 100 | 97.5 (*S*) |
| R = 2-Naphthyl | 100 | 97.7 (*S*) |
| R = *p*-Cl-Ph | 100 | 98.7 (*S*) |
| R = *p*-F-Ph | 100 | 97.2 (*S*) |

Furthermore FERRIPHOS ligands bearing alkyl groups instead of dimethylamino substituents proved to be excellent ligands in the asymmetric hydrogenation of α-acetamidoacrylic acids[34] and acetoxy acrylic esters[35]. Their air stability and the easy modification of their structure make the FERRIPHOS ligands particularly useful tools for asymmetric catalysis.

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