Chapter 7

Asymmetric Hydrogenation on Preparative Scale using Rhodium Catalysts Based on Monodentate Phosphoramidites

Abstract
The asymmetric hydrogenation of various substrates on a preparative scale is described. This opens a way to rhodium-catalyzed asymmetric hydrogenation with monodentate ligands being applied on preparative scale and even on a pilot plant scale. The obtained products were isolated in high yields with excellent e.e.’s.
7.1 Introduction

7.1.1 Itaconates as prochiral substrates

Multiple examples of rhodium-catalyzed asymmetric hydrogenation have already been discussed in this thesis; however, an important substrate has not been discussed thus far. Asymmetric hydrogenation of substituted $\alpha,\beta$-unsaturated acids is of great current interest as several drug intermediates have structures based on $\alpha$-substituted acids. Typical examples of these unsaturated acids are the itaconate substrates. These itaconates can be hydrogenated using rhodium with bidentate ligands to full conversion within 1 h at pressures ranging from 1 – 5 bar, see Figure 7.1.

![Figure 7.1 Asymmetric Rh-catalyzed hydrogenation of 1 using bisphosphines.](image1)

![Figure 7.2 Phosphoramidite ligands used in the preparative scale experiments.](image2)
Recently, however, it was shown that monodentate ligands can perform equally well in the hydrogenation of itaconates, see Figure 7.3. The products are obtained in high yields and with excellent enantioselectivities.\textsuperscript{5,6,7,8,9,10}

In order to examine the effectiveness of phosphoramidites, itaconic acid and the corresponding ester were subjected to the asymmetric hydrogenation using rhodium and both MonoPhos\textsuperscript{TM} (L\textsubscript{1}) and its piperidine analogue (L\textsubscript{2}), see Figure 7.2.

\textbf{Figure 7.3} E.e.'s obtained using monodentate ligands in the hydrogenation of \textit{I}.\textsuperscript{5,7,8,9,10}

\textbf{Scheme 7.1} Rhodium-catalyzed asymmetric hydrogenation of mono-esters of 2-methylene succinic acid.
Besides the dimethyl ester (1) and acid (2) the hydrogenation of the corresponding mono-esters was recently reported.\textsuperscript{11} Helmchen\textit{ et al.} showed that using mono-methyl esters as substrates in the rhodium-catalyzed asymmetric hydrogenation resulted in a product with high e.e. (Scheme 7.1). This mono-ester could be used as a chiral building block conveniently using the discrimination between the acid and ester functionality in subsequent reactions.

### 7.1.2 Catalysis on preparative scale

Homogeneous rhodium-catalyzed asymmetric hydrogenation has been studied over thirty years now, converting various benchmark substrates with excellent results. Yet, the number of industrial processes that make use of this technology is limited.\textsuperscript{12,13} Since the first industrial enantioselective catalytic process, \textit{i.e.} the production of L-DOPA, has been implemented by Monsanto in the early seventies the number of applications has grown only slowly. The important requirements for these hydrogenations to be implemented in a synthetic route are:\textsuperscript{14}

1) \textit{Can the costs for the overall manufacturing process compete with alternative routes?}  
2) \textit{Can the catalytic step be developed in the given time frame?}

The fast development of a catalytic step in a given time frame is dominated by the time required to find the appropriate ligand for the hydrogenation of a substrate with high enantioselectivity. This fast development can be achieved by using a type of ligand which can be easily prepared and handled, preferably with a modular ligand design. In this way a library of ligands can be synthesized and tested within a relative short time period and the suitable chiral ligand identified for a particular substrate hydrogenation.

Recently it was shown that monodentate phosphoramidites (modular, easily prepared and handled) are versatile ligands to be used in the rhodium-catalyzed asymmetric hydrogenation of olefins.\textsuperscript{15} Full conversions could be reached with versatile enantioselectivities for a whole range of benchmark substrates. These results prompted us to investigate the applicability of this catalytic system for the use in a synthetic procedure on a preparative scale, ultimately leading to the use of these ligands in a manufacturing process.
7.2 Results and Discussion

7.2.1 Hydrogenation of itaconates

Substrates 1 and 2 were hydrogenated using a rhodium catalyst with MonoPhos™ as chiral ligand. The catalyst was prepared in situ by mixing [Rh(COD)₂]BF₄ and MonoPhos™ in the appropriate solvent. The reactions were performed at room temperature and at 0°C under a hydrogen pressure of 1 bar. As can be seen from the results summarized in Table 7.1 there is a very strong solvent effect on the hydrogenation of itaconic acid (1).

Table 7.1 Rhodium-catalyzed hydrogenation of itaconates.

<table>
<thead>
<tr>
<th>entry</th>
<th>sub.</th>
<th>T (°C)</th>
<th>solvent</th>
<th>conv. (%)</th>
<th>e.e. (%)</th>
<th>conf.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>20</td>
<td>CH₂Cl₂</td>
<td>100</td>
<td>87</td>
<td>(S)</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>0</td>
<td>CH₂Cl₂</td>
<td>100</td>
<td>94</td>
<td>(S)</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>20</td>
<td>EtOAc</td>
<td>100</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>0</td>
<td>EtOAc</td>
<td>100</td>
<td>6</td>
<td>(S)</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>20</td>
<td>CH₂Cl₂</td>
<td>100</td>
<td>96</td>
<td>(S)</td>
</tr>
<tr>
<td>6</td>
<td>2</td>
<td>20</td>
<td>EtOAc</td>
<td>100</td>
<td>97</td>
<td>(S)</td>
</tr>
</tbody>
</table>

a 5 mol% catalyst, 11 mol% MonoPhos™; in situ prepared catalyst.
b Absolute configurations were determined by comparison of the GC-elution order with an enantiopure sample (see experimental part).

Using ethyl acetate as the solvent in the hydrogenation of 1 the product had an e.e. of only 6% at 0°C. The hydrogenation of 1 in ethyl acetate (entries 3, 4) was independently repeated 4 times to confirm this unexpected result. The low enantioselectivity may be due to the solvent (EtOAc) competing with the ester group of the substrate for ligation at rhodium (Figure 7.4) and presumably hydrogenation takes place via the mono-coordinated substrate complex. This again indicates that a second coordinating functional group is required to reach high e.e.’s. Further research is needed to elucidate this phenomenon. The enantioselectivities
of the hydrogenation of substrate 2 using MonoPhos™, however, are excellent even in ethyl acetate (entry 6).

![Diagram of chemical structures](image)

Figure 7.4 Ethyl acetate competing for ligation with dimethyl 2-methylenesuccinate.

### 7.2.2 Hydrogenations at preparative scale

To study the scalability of the rhodium-catalyzed hydrogenation using monodentate phosphoramidite ligands several substrates were selected. These selected substrates were precursors to protected chiral amino acids, amines, acids and esters. The reactions were initially performed on lab-scale and typically <1 g of substrate was used. These reactions were scaled up to amounts of substrate ranging from 1 – 100 g. This finally led to a reaction at pilot-plant scale converting several hundred kilograms of substrate.

![Chemical structures](image)

Figure 7.5 Substrates used in the preparative scale experiments.
Some of the substrates used were esters or amides while others were carboxylic acids. The carboxylic acids were hydrogenated as a slurry because the amounts used did not completely dissolve in the small amount of solvent used, *i.e.* 3 g of 2 in 5 ml isopropanol. The hydrogenation of the slurries did not lead to many problems; however the conversion was sometimes 97%. The remaining of the starting material was stuck on the walls of the reactor. The reactions performed with a homogeneous solution gave full conversions under the conditions described, *vide infra*. The catalysts used were prepared from the ligands (S)-L1 and (S)-L2 (Figure 7.2) and [Rh(COD)2]BF4 forming the complexes [Rh((S)-L1)2(COD)]BF4 (6) and [Rh((S)-L2)2(COD)]BF4 (7).16

**Amount of Rh-catalyst:**
To make these preparative scale reactions more viable the amount of catalyst used should be smaller than the amount typically used for testing the phosphoramidite ligands. These tests were generally performed with 1-5 mol% of catalyst. The costs of the rhodium will become too high to make this asymmetric hydrogenation reaction interesting for large-scale synthesis. The amount of catalyst should be 0.1 mol% or preferably even lower. To maintain a decent reaction rate at these low catalyst loadings the hydrogen pressure was increased, up to 100 bar. As published earlier, this increase in hydrogen pressure does not effect the enantioselectivity of the hydrogenation.15a

**Concentration:**
Another variable that needs attention is the concentration of the substrate. The screening reactions were performed at a concentration in the order of 0.04 - 0.1M. Ideally these concentrations need to be larger than 1M in substrate, *i.e.* the concentrations of the reactions the results of which are compiled in Table 7.2 vary from 1.2 - 4.6 M. Working with these high concentrations and reaction rates heat dissipation becomes a critical issue. The cooling of the reactor must therefore be sufficient enough to remove the heat from the reactor, generated by this exothermic reaction. At lower concentrations and rates this poses fewer problems.

The results obtained are presented in Table 7.2. All reactions reached full conversion unless noted otherwise. From the first entry it is clear that the rhodium-catalyzed asymmetric hydrogenation with phosphoramidites can be performed at gram scale with good isolated yield and excellent e.e. The enantioselectivity was only slightly lower when compared to the enantioselectivity of the reaction performed under the conditions used to screen the ligands (>99% e.e.).15a The first and second entries both show excellent isolated yields when substrate 1 is hydrogenated with either catalyst 6 or catalyst 7. The enantioselectivity on the other hand is considerably higher when catalyst 7 is used. This enhancement in selectivity using catalyst 7 makes it possible to hydrogenate 1 with excellent enantioselectivities at room temperature.
Table 7.2 Rhodium-catalyzed asymmetric hydrogenation using monodentate ligands.

<table>
<thead>
<tr>
<th>entry</th>
<th>sub. cat.</th>
<th>S/C solvent (ml)</th>
<th>pH₂ (bar)</th>
<th>Substrate (g)</th>
<th>Yield (%)</th>
<th>e.e. (%)</th>
<th>conf.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1 6</td>
<td>1000 CH₂Cl₂ (5)</td>
<td>10</td>
<td>2.00</td>
<td>98%</td>
<td>89.9</td>
<td>(S)</td>
</tr>
<tr>
<td>2</td>
<td>1 7</td>
<td>1000 CH₂Cl₂ (5)</td>
<td>10</td>
<td>2.00</td>
<td>98%</td>
<td>99.0</td>
<td>(S)</td>
</tr>
<tr>
<td>3</td>
<td>2 7</td>
<td>1000 2-PrOH (5)</td>
<td>10</td>
<td>2.00</td>
<td>&gt;99%</td>
<td>&gt;99</td>
<td>(S)</td>
</tr>
<tr>
<td>4</td>
<td>2 7</td>
<td>5000 2-PrOH (5)</td>
<td>10</td>
<td>2.00</td>
<td>&gt;99%</td>
<td>98.5</td>
<td>(S)</td>
</tr>
<tr>
<td>5</td>
<td>2 7</td>
<td>10000 2-PrOH (5)</td>
<td>10</td>
<td>3.00</td>
<td>98%</td>
<td>96.9</td>
<td>(S)</td>
</tr>
<tr>
<td>6</td>
<td>3 6</td>
<td>1000 EtOAc (5)</td>
<td>10</td>
<td>1.00</td>
<td>93%</td>
<td>98.1</td>
<td>(R)</td>
</tr>
<tr>
<td>7</td>
<td>4 6</td>
<td>1000 2-PrOH (25)</td>
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<td>5.00</td>
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<td>99.1</td>
<td>(R)</td>
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<td>4.10</td>
<td>76%</td>
<td>98.1</td>
<td>(R)</td>
</tr>
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<td>9</td>
<td>4 6</td>
<td>1000 EtOAc (20)</td>
<td>100</td>
<td>4.10</td>
<td>78%</td>
<td>98.2</td>
<td>(R)</td>
</tr>
<tr>
<td>10</td>
<td>4 6</td>
<td>1000 EtOAc (75)</td>
<td>100</td>
<td>15.38</td>
<td>71%</td>
<td>98.7</td>
<td>(R)</td>
</tr>
<tr>
<td>11</td>
<td>5 7</td>
<td>1000 CH₂Cl₂ (5)</td>
<td>25</td>
<td>1.00</td>
<td>98%</td>
<td>98.4</td>
<td>(R)</td>
</tr>
<tr>
<td>12</td>
<td>5 7</td>
<td>1000 CH₂Cl₂ (80)</td>
<td>100</td>
<td>20.00</td>
<td>88%</td>
<td>98.7</td>
<td>(R)</td>
</tr>
<tr>
<td>13</td>
<td>2 6</td>
<td>100000 2-PrOH (100)</td>
<td>100</td>
<td>100</td>
<td>&gt;99%</td>
<td>97.5</td>
<td>(S)</td>
</tr>
</tbody>
</table>

* Reactions were performed at room temperature using preformed catalysts. b Purified by kugelrohr distillation. c No purification. d Purified by recrystallization from EtOAc/EtOH 10:1. e Purified by column chromatography. f Purified by trituation with EtOAc/pentane. g E.e. of isolated material. h 98% conversion. i 97% conversion. j Conversions were determined by ¹H NMR and e.e.’s were determined by chiral GC.

In the hydrogenation of substrate 2 isopropanol was used as solvent, because it gave better results compared to dichloromethane or ethyl acetate which gave lower conversions and/or e.e.’s. Carboxylic acid 2 was hydrogenated as a slurry in isopropanol with excellent results. With this substrate the amount of catalyst could even be lowered further to 0.01 mol%, albeit with a slight loss of e.e., entries 3-5. The conversions and yields remained the same. The asymmetric hydrogenation of amino acid precursor 4 was successfully performed in several different solvents.

The difference in isolated yield is due to the workup procedure. The solvent of choice for this substrate (4) turns out to be ethyl acetate, because of its environmentally benign nature and the ease of workup. The e.e.’s of the crude reaction product only differ 1-2% depending on the solvent used. As can be noted from entry 10 product 6 can be obtained in more than 10 g quantities. Catalyst 7 even allowed us to hydrogenate enamide 5 with excellent results up to 20 g scale (entries 11-12). The isolated yield is dependent of the method of isolating the product. These results ultimately led to, an experiment in which substrate 2 was hydrogenated with only 0.01 mol% of catalyst 6 on a 100 g scale in isopropanol. On this scale removal of generated heat becomes an issue to deal with. Sufficient cooling should be applied to maintain a constant temperature for the duration of the hydrogenation. The product was isolated with >99% yield after removing the solvent under vacuum, leaving the product with a rhodium content of 100 ppm. The rhodium can be removed using activated carbon to a level.
of <10 ppm, which is the limit for pharmaceuticals. At 100 bar of hydrogen pressure the reaction went to completion with a TOF$_{av}$ of 6667 (h$^{-1}$), yielding the product with an e.e. of 97.5%.

The applicability of this catalyst system was also shown by DSM N.V. A reaction at pilot-plant scale, several hundred kilograms, was successfully performed using a rhodium catalyst with a MonoPhos™ type ligand and this technology is now used on multi-ton scale.

One point of attention still is the removal of the catalyst from the product. Besides the conventional methods like column chromatography or recrystallization, other methods can be useful as well. One of these methods is to immobilize the ligand on a solid support (Figure 7.6, L4 and L5). The ligands which are bound to the solid support bind to the rhodium forming the catalyst. After the hydrogenation is finished the catalyst is removed from the reaction mixture via filtration and the product is isolated without any catalyst. The results obtained with these supported catalysts are generally lower compared to the non-supported analog of these catalysts (Table 7.3).

![Figure 7.6 Immobilized monodentate phosphoramidite ligands L4, L5, L6 and L7.](image-url)
Ding et al. demonstrated the use of bidentate ligands like L6 to create a polymer type catalyst. This catalyst does not need a support material and can be filtered from the reaction mixture to remove the catalyst.\textsuperscript{21} The results obtained using this self-supporting catalyst were comparable or better than those obtained using the analogues homogeneous catalysts. The reusability of the catalyst was tested and it was shown to work for at least seven cycles. The enantioselectivity only dropped slightly from 95.0\% to 89.5\% in the hydrogenation of 3. An alternative way of retaining the catalyst is the synthesis of dendrimer-supported ligands. Based on the readily modified BICOL-backbone dendrimer-ligand L7 was prepared that has a performance comparable to MonoPhos\textsuperscript{TM} (L1) in the hydrogenation of methyl N-acyl dehydrophenylalanine that was obtained with 95\% e.e.\textsuperscript{22}

**Table 7.3 Rhodium-catalyzed asymmetric hydrogenation using monodentate ligands.**

<table>
<thead>
<tr>
<th>entry</th>
<th>sub.</th>
<th>L*</th>
<th>conv. (%)</th>
<th>e.e. (%)</th>
<th>conf.</th>
</tr>
</thead>
<tbody>
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<td>1</td>
<td>1</td>
<td>L3</td>
<td>100</td>
<td>95</td>
<td>(S)</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>L4</td>
<td>100</td>
<td>67</td>
<td>(R)</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>L5</td>
<td>57</td>
<td>49</td>
<td>(S)</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>L3</td>
<td>100</td>
<td>84</td>
<td>(R)</td>
</tr>
<tr>
<td>5</td>
<td>3</td>
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<td>100</td>
<td>75</td>
<td>(R)</td>
</tr>
<tr>
<td>6</td>
<td>3</td>
<td>L5</td>
<td>96</td>
<td>65</td>
<td>(R)</td>
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<td>95.8</td>
<td>(R)</td>
</tr>
<tr>
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<td>98</td>
<td>75</td>
<td>(R)</td>
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<tr>
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<td>4</td>
<td>L5</td>
<td>100</td>
<td>49</td>
<td>(R)</td>
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<tr>
<td>11</td>
<td>5</td>
<td>L6</td>
<td>100</td>
<td>97.3</td>
<td>(R)</td>
</tr>
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</table>

\textsuperscript{a} Reactions were performed at room temperature under ambient H\textsubscript{2} pressure for 20h. [Substrate (0.2mmol), 0.04M):Rh(COD)\textsubscript{2}BF\textsubscript{4}:L* = 1:0.05:0.05].

Another solution may be to immobilize the catalyst by exchanging the counter ion (BF\textsubscript{4}\textsuperscript{−}) for a ‘solid support’ counter ion. Functionalized TUD-1 which is a well-defined mesoporous siliceous oxide can be used for this purpose.\textsuperscript{23} It has a large surface area and easily tunable pore size distribution with three dimensional connectivity. This TUD-1 can be functionalized with heteropoly acids which act as the actual counter ions to bind the catalyst. Immobilization can also be achieved by using two liquid phases that mix under reaction conditions and separate under the appropriate conditions. This facilitates separation of the catalyst from the products.\textsuperscript{24}
7.3 Conclusions

From the results presented here it is evident that monodentate phosphoramidite ligands are very useful in the rhodium-catalyzed asymmetric hydrogenation. Because of the ease of ligand modification, these ligands provide an excellent opportunity finding the right ligand for the substrate which needs to be hydrogenated. Once the appropriate ligand is identified it can be used in the synthesis of enantiopure building blocks on a preparative scale as was described.

7.4 Experimental

General remarks:
For general information, see Chapter 2. Glassware used for the preparation of the metal complexes was flame-dried under vacuum. Both dichloromethane (from CaH₂) and ethyl acetate were distilled and stored under nitrogen. Isopropanol was purchased from Labscan (p.a.) and used without further purification. ¹H NMR, ³¹P{¹H} NMR spectra were recorded on a Varian MERCURYplus 400 spectrometer (400 MHz and 162 MHz, respectively). Chemical shifts are reported in δ units (ppm) relative to the solvent signals of CHCl₃ (¹H: 7.27 ppm) or to an external reference H₃PO₄ (³¹P: 0 ppm). Mass spectra were recorded on a Sciex API 3000™ LC/MS/MS. GC measurements were performed on either a HP 5890 A or a HP 6890 gas chromatograph using a flame ionization detector. To ensure accurate determination of e.e.’s, racemic mixtures of all products were prepared employing the hydrogenation using Wilkinson’s catalyst (RhCl(PPh₃)₃) or Pd on carbon. The absolute configurations were assigned by comparing the GC elution order of the product with those in literature.¹⁵c Carboxylic esters were transformed into there methyl esters analogues using (trimethylsilyl)diazomethane before GC analysis.²⁵ Substrates 2, 3 and 4 were purchased from Fluka (>99%), Aldrich (97%) and Fluka (>99%), respectively, and used as received without further purification. Substrates 1²⁶,²⁷ and 5²⁸ were synthesized according to (slightly altered) literature procedures.

Warnings:
1) Always be careful when working with high pressures, especially when working with exothermic reactions under pressure. Use specialized equipment.
2) Make sure the dissipation of heat is sufficient when a reaction is scaled-up.
3) Hydrogen should be handled with care especially at high pressures. Explosive mixtures in air are in the range from 4% (LEL) to 74% (UEL). Venting excess hydrogen can cause an explosion.

Ligands L1 and L2 are described in Chapter 2.
Bis((S)-1-(3,5-dioxa-4-phospha-cyclohepta[2,1-a;3,4-a']dinaphthalen-4-yl)-piperidine)-(cyclooctadiene)rhodium (I) tetrafluoroborate (7). To a solution of [Rh(COD)₂]BF₄ (150 mg, 0.369 mmol) in dichloromethane (20 mL) was added dropwise while stirring a solution of (S)-L₂ (295.1 mg, 0.739 mmol) dissolved in dichloromethane (20 mL). After addition the solution was left stirring for one hour before the mixture was reduced in volume under vacuum to about 5 mL. To this concentrated mixture pentane (15 mL) was added and stirring was continued for one hour to obtain a fine yellow precipitate. This precipitate was filtered off under nitrogen and dried under low vacuum. A yellow powder was obtained in 95 % yield (385 mg). This was a mixture of two dynamically interconverting diastereomeric complexes which was used without further purification.²⁹ ¹H NMR (400 MHz, CDCl₃) δ 1.14 (bp), 1.55 (bp), 1.85 (bp), 2.14 (bp), 2.50-2.66 (bm), 2.93-3.31 (bm), 4.86 (bp), 5.31 (bp), 5.59 (bp), 5.79 (bp), 5.86 (bp), 6.22 (bp), 7.00-8.47 (m); ³¹P NMR (162 MHz, CDCl₃) δ 139.47 (d, ¹JRh-P = 237 Hz), 138.23 (d, ¹JRh-P = 243 Hz), 130.97 (dd, ¹JRh-P = 235 Hz, ²JP-P = 28 Hz); ESI-MS m/z 1009.3 [M]+; calcd for C₅₂H₄₈N₂O₄P₂Rh: 1009.95.

Catalytic Hydrogenation:

Method A: Experiments performed in a Parr autoclave mini reactor series 4561 (Hastelloy C), nominal size 300 ml cooled in a water bath. In the autoclave were placed 2-methylene-succinic acid (2, 100g, 0.77 mol), [Rh((S)-L₁)₂(COD)]BF₄ (6, 78.0 mg, 76.9 µmol), and isopropanol (100 mL) and the system was purged five times with nitrogen and once with hydrogen. A hydrogen pressure (100 bar) was applied and the overhead pitched blade turbine stirrer was switched on. The reaction was allowed to run for 1.5 h before the system was vented and a sample was taken for GC analysis. The volatiles were removed under reduced pressure isolating 101g of product (>99% yield).

Method B: Experiments performed in the Endeavor™, an autoclave with eight reactors equipped with glass liners and stirring paddles. Into a reaction vessel were placed, 2-acetylamino-acrylic acid methyl ester (3, 1.00 g, 6.99 mmol), and [Rh((S)-L₁)₂(COD)]BF₄ (6, 7.06 mg, 6.96 µmol) and ethyl acetate (5 mL). The reactors were then purged for 10 min. with nitrogen before applying a hydrogen atmosphere of 10 bar. The pressure was kept constant during the reaction and the hydrogen uptake was monitored. After completion of the reaction, the reactors were vented and a sample was taken which was filtered over a short silica column and subjected to e.e. determination by means of chiral GC. The product was isolated, after Kugelrohr purification, as a white solid (0.94 g, 93%).

2-Methyl-succinic acid dimethyl ester (8)

¹H NMR and ¹³C NMR data were in good agreement with those in the literature.³⁰ E.e. determination by GC analysis: Chiraldex G-TA (30 m × 250 µm × 0.125 µm), N₂-flow: 1.0 mL/min, 80°C isothermal, Tᵣ = 19.3 min (S), Tᵣ = 21.3 min (R).
2-Methyl-succinic acid (9)

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{OH} & \quad \text{OH}
\end{align*}
\]

\(^1\)H NMR and \(^{13}\)C NMR data were in good agreement with those in the literature.\(^{31}\)

2-Acetylamino-propionic acid methyl ester (10)

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{NH} & \\
\end{align*}
\]

\(^1\)H NMR and \(^{13}\)C NMR data were in good agreement with those in the literature.\(^{32}\) E.e. determination by GC analysis: CP Chirasil-L-Val (25 m × 250 µm × 0.12 µm), N\(_2\)-flow: 1.3 mL/min, 110°C isothermal, \(T_r = 3.3\) min (\(R\)), \(T_r = 3.8\) min (\(S\)).

2-Amino-3-phenyl-propionic acid methyl ester (11)

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{H} & \quad \text{N} \\
\end{align*}
\]

\(^1\)H NMR and \(^{13}\)C NMR data were in good agreement with those in the literature.\(^{33}\) E.e. determination by GC analysis: CP Chiralsil-L-Val (25 m × 250 µm × 0.12 µm), N\(_2\)-flow: 1.3 mL/min, 160°C isothermal, \(T_r = 6.2\) min (\(R\)), \(T_r = 6.7\) min (\(S\)).

N-(1-Phenylethyl)acetamide (12)

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{H} & \quad \text{N} \\
\end{align*}
\]

\(^1\)H NMR and \(^{13}\)C NMR data were in good agreement with those in the literature.\(^{34}\) E.e. determination by GC analysis: CP Chiralsil Dex CB (25 m × 250 µm × 0.25 µm), N\(_2\)-flow: 1.0 mL/min, 140°C isothermal, \(T_r = 13.5\) min (\(R\)), \(T_r = 14.6\) min (\(S\)).

7.5 References and Notes


16. For analysis of the rhodium complexes, see experimental sections in Chapter 6 and 7.


18. Personal communication with Prof. Dr. J.G. de Vries.


29 As is described in Chapter 6 the complex [Rh(MonoPhos™)2(COD)]BF4 has two configurations which are in equilibrium with each other at room temperature.


