Chapter 2

The Synthesis of Enantiopure Amino Acids Using Homogeneous Asymmetric Hydrogenation

Abstract

In this chapter the synthesis of several prochiral N-acetyl-2-amino-trans-cinnamic acids and their corresponding methyl esters is described. The results of the subsequent asymmetric hydrogenation reaction of these compounds using a cationic rhodium(I) complex [RhL₂(COD)]BF₄, with chiral phosphoramidites acting as ligands, are presented. The products were obtained with high degrees of enantioselectivity, up to >99% e.e. using monodentate phosphoramidite ligands.
2.1 Introduction

Health care these days is all about the discovery of new drugs for treatment of (new) diseases and drugs to be able to protect us from resistant bacteria like MRSA. Recent developments in biotechnology, such as the human genome project, have led to an increasing demand for protein-based drugs. With investments in the pharmaceutical market still rising, in spite of the current recession, the share of protein-based drugs is expected to grow in the near future.\(^2\) Enantiopure amino acids are important intermediates for the production of these drugs, and the market for these amino acids is therefore expected to experience a strong growth in the near future. Homogeneous asymmetric hydrogenation is a very elegant method of producing enantiopure amino acids. Although a lot of research has been done in this field the majority of processes never leave the laboratories. There are very few industrial processes based on this reaction.\(^3\) One of the problems is ‘time to market’, this is especially the case for the pharmaceutical industry. In the pharmaceutical industry a variety of different building blocks have to be prepared and tested and the hydrogenation catalysts usually have a narrow range of substrates which they can hydrogenate with excellent enantioselectivities. Therefore a catalyst, which usually contains a rhodium or a ruthenium metal with chiral phosphine ligands that can easily be adapted to different substrates, would be ideal. One can test for instance a library of catalysts for every new substrate, which needs to be hydrogenated. The problem with applying this procedure is that bidentate phosphines (Scheme 2.1), which used to be the ligands of choice, are often difficult to prepare and handle (Chapter 1). Also the cost of making a large variety of these ligands would become too high. The costs and availability of these ligands therefore hamper the applicability in industrial processes. These problems could be solved if one could use simpler monodentate phosphoramidites as ligands in the asymmetric hydrogenation.

![Scheme 2.1](image)

**Scheme 2.1** Typical examples of some excellent ligands known to date.\(^4\)
Phosphoramidites are easier to synthesize in one or two steps and are generally less sensitive to oxidation and hydrolysis. Phosphoramidites, due to their modular structure, allow for fine-tuning of the catalyst through modification of the ligands for specific substrates or class of substrates. We therefore started to explore the possibility to perform rhodium-catalyzed asymmetric hydrogenations using chiral phosphoramidite ligands. At the start of this investigation phosphoramidite ligands had not been used in this asymmetric hydrogenation.\textsuperscript{5,6} During our research on the use of phosphoramidite ligands in the asymmetric hydrogenation the groups of Pringle and Reetz simultaneously studied chiral monodentate phosphonites\textsuperscript{7} and phosphites.\textsuperscript{8a,b} After publication of our work\textsuperscript{9} several other groups started working on monodentate phosphites,\textsuperscript{8c,d} phosphoramidites\textsuperscript{10} and phosphines in hydrogenation.\textsuperscript{11} In some cases excellent results were achieved as is shown in Scheme 2.2. This inspired other groups in the field of asymmetric hydrogenation to take a closer look into the monodentate versions of the bidentate ligands used so far.\textsuperscript{12}

\begin{center}
\begin{align*}
\text{Scheme 2.2 Monodentate ligands in highly enantioselective asymmetric hydrogenation.}^{7,8a,9a}
\end{align*}
\end{center}

In this chapter we will describe the synthesis of phosphoramidite ligands; both mono and bidentate in nature. These ligands are used in the rhodium-catalyzed asymmetric hydrogenation of protected amino acid precursors. The rhodium-catalyzed asymmetric hydrogenation reaction using phosphoramidite ligands is optimized by varying several parameters. These parameters include the method of formation of the catalyst, solvent, hydrogen pressure, substrate over catalyst ratio (S/C). To determine whether the catalyst with phosphoramidite ligands is versatile and widely applicable in the hydrogenation various substrates were examined. After the first examples of the use of asymmetric hydrogenation using a homogeneous rhodium catalyst a fine tuning of the phosphoramidite ligands will be described.
2.2 Results and Discussion

2.2.1 Synthesis of phosphoramidite ligands

The phosphoramidite ligands were developed by Feringa et al. which used these ligands in the copper-catalyzed 1,4-addition of dialkylzinc to enones in a highly enantioselective manner.\textsuperscript{13} This expertise led to the joint development of a library of phosphoramidite ligands suitable for the use in the rhodium-catalyzed asymmetric hydrogenation.

The synthesis of these ligands is depicted in Scheme 2.3. There are several different approaches available and they only require a minimum number of steps to give the chiral ligands with yields ranging from 60%-90%.\textsuperscript{14} The most common route used is the first one. This is a suitable way of making relatively pure phosphoramidites from diols and amines. The second route is the method of choice for the preparation of phosphoramidites with hindered amines.\textsuperscript{15} In the first step of the third route MonoPhos\textsuperscript{TM} (L1) was prepared from BINOL and HMPT in toluene with quantitative yield.\textsuperscript{16} MonoPhos\textsuperscript{TM}, a ligand which can be used in the rhodium-catalyzed hydrogenation, can further be used in the synthesis of other phosphoramidites. This reaction of MonoPhos\textsuperscript{TM} with a primary or secondary amine in the presence of a catalytic amount of tetrazole is used to synthesize the more labile phosphoramidite ligands.\textsuperscript{17}
Figure 2.1 Monodentate ligands used in preliminary screening.
2.2.2 Synthesis of the substrates

2.2.2.1 Synthesis of the azlactone

The initial substrates used in the Rh-catalyzed asymmetric hydrogenation with phosphoramidite ligands were N-acetyl dehydroamino acids and the corresponding esters. The products of the asymmetric hydrogenation are useful chiral building blocks in the synthesis of pharmaceuticals. A number of substrates were used as received, without any further purification whereas others were prepared according to (slightly altered) literature procedures. The formation of the azlactone is highly selective towards the Z-isomer.
and final crystallization gave pure Z-isomers of the azlactones. The substrates synthesized were mainly N-acetyl-dehydro-phenylalanines. The synthesis starts with reaction of the properly substituted benzaldehyde (1) with N-acetyl glycine (aceturic acid, 2) to form an azlactone (3) as depicted in Scheme 2.4 also known as the ‘Erlenmeyer azlactone synthesis’.  

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

\[ \begin{align*}
\text{H} & \quad \text{O} \\
\text{NaOAc} & \quad \Delta \\
(36-71\%) &
\end{align*} \]

\[ \text{AcNH} \quad \text{O} \\
\text{O} & \quad \text{R} \\
\text{R} & \quad \text{O} \\
\text{N} & \quad \text{O} \\
\text{O} & \quad \text{R}
\]

\[ \begin{align*}
4) & \text{R} = \text{H} \\
5) & \text{R} = \text{m}-\text{OMe} \\
6) & \text{R} = \text{p}-\text{OMe} \\
7) & \text{R} = \text{p}-\text{F} \\
8) & \text{R} = \text{m}-\text{NO}_2 \\
9) & \text{R} = \text{p}-\text{NO}_2 \\
10) & \text{R} = \text{m}-\text{NO}_2, \text{p}-\text{F} \\
11) & \text{R} = \text{m}-\text{OMe, p-OAc}
\end{align*} \]

Scheme 2.4 Synthesis of azlactones.

2.2.2.2 Synthesis of dehydroamino acid

The azlactone undergoes easily ring opening by heating with water and sodium acetate to provide N-acetyl-2-amino-trans-cinnamic acids (Scheme 2.5).

\[ \begin{align*}
\text{F} & \quad \text{N} \\
\text{N} & \quad \text{O} \\
\text{R} & \quad \text{O} \\
\text{AcNH} & \quad \text{O} \\
\text{OH} & \quad \text{O} \\
\text{O} & \quad \text{R} \\
\text{NH} & \quad \text{O} \\
\text{O} & \quad \text{HO} \\
\text{Ac} & \quad \text{O} \\
\text{NaOAc} & \quad \Delta \\
(64\%) &
\end{align*} \]

\[ \begin{align*}
\text{F} & \quad \text{N} \\
\text{N} & \quad \text{O} \\
\text{R} & \quad \text{O} \\
\text{AcNH} & \quad \text{O} \\
\text{OH} & \quad \text{O} \\
\text{O} & \quad \text{R} \\
\text{NH} & \quad \text{O} \\
\text{O} & \quad \text{HO} \\
\text{Ac} & \quad \text{O} \\
\text{NaOAc} & \quad \Delta \\
(64\%) &
\end{align*} \]

Scheme 2.5 Synthesis of (Z)-2-acetamido-3-(4-fluorophenyl)acrylic acid.

2.2.2.3 Synthesis of dehydroamino acid methyl esters

The azlactones can also be ring opened with methanol (Scheme 2.6) to give the corresponding dehydroamino acid methyl esters.

\[ \begin{align*}
\text{R} & \quad \text{N} \\
\text{N} & \quad \text{O} \\
\text{O} & \quad \text{R} \\
\text{AcNH} & \quad \text{O} \\
\text{O} & \quad \text{R} \\
\text{NH} & \quad \text{O} \\
\text{O} & \quad \text{HO} \\
\text{Ac} & \quad \text{O} \\
\text{NaOAc} & \quad \Delta \\
(11 - 49\%) &
\end{align*} \]

\[ \begin{align*}
14) & \text{R} = \text{H} \\
15) & \text{R} = \text{m}-\text{OMe} \\
16) & \text{R} = \text{p}-\text{OMe} \\
17) & \text{R} = \text{p}-\text{F} \\
18) & \text{R} = \text{m}-\text{NO}_2 \\
19) & \text{R} = \text{p}-\text{NO}_2 \\
20) & \text{R} = \text{m}-\text{NO}_2, \text{p}-\text{F} \\
21) & \text{R} = \text{m}-\text{OMe, p-OAc}
\end{align*} \]

Scheme 2.6 Synthesis of N-acetyl-2-amino-trans-cinnamic acid methyl esters.
The low yields are due to the fact that the substrates have to be recrystallized from ethyl acetate or ethanol two or three times in order to get the required purity according to $^1$H and $^{13}$C NMR analyses. These substrates provide a means of preparing enantiopure amino acids when subjected to asymmetric hydrogenation and subsequent deprotection.$^{19,22}$

### 2.2.3 Preliminary hydrogenation experiments

We started our research in the rhodium/phosphoramidite catalyzed asymmetric hydrogenation by examining various bidentate and monodentate ligands. Following a standard literature procedure we initially examined ligands on the prochiral substrate $N$-acetyl-2-amino-trans-cinnamic acid methyl ester 14 as depicted in Scheme 2.7.$^{23}$ Compound 14 serves as a benchmark substrate in homogeneous asymmetric hydrogenation reactions. We used methanol as the solvent for these hydrogenations as this is the solvent of choice for Rh/diphosphine hydrogenations.$^{24}$

**Scheme 2.7** Standard hydrogenation procedure used in the first screening of phosphoramidite ligands.

These experiments were performed using an *in-situ* prepared catalyst (Scheme 2.8). The procedure is as follows: the cationic rhodium salt $[\text{Rh(COD)}_2]\text{BF}_4$ and ligand were placed in a Schlenk tube. After flushing the setup with nitrogen the solvent, freshly distilled and deoxygenated, was added. The nitrogen atmosphere was replaced by a hydrogen atmosphere and the solution was prehydrogenated for 1h to remove the cyclooctadiene (COD) from the catalyst precursor making the actual active catalyst and cyclooctane (COA) which doesn’t interfere in the catalytic cycle.$^{25}$ After this prehydrogenation a solution containing the substrate was injected into the Schlenk tube.

**Scheme 2.8** Simplified scheme of the *in-situ* formation of the active catalyst.
The results of the hydrogenations are summarized in Table 2.1. From entries 1 to 8 in Table 2.1 it can be noted that higher conversions are obtained when the substituents on the nitrogen atom in the ligand are small. The enantioselectivity is also better when ligands with smaller substituents are used. The rhodium source is also important. Comparing the results of the first two entries one can note that a cationic rhodium precursor gives much better results than to a neutral rhodium complex, containing chloride counter-ions. This result could be explained by the formation of a dimeric complex of the form \([\text{Rh}((S)-\text{MonoPhos}^{\text{TM}})_2\text{Cl}]_2\) (23), which can no longer bind to both substrate and hydrogen.\(^{26}\)

![Scheme 2.9 Proposed formation of complex 23.](image)

Dimerization is also known for the \(\text{RhCl}(\text{PPh}_3)_3\) complex. This complex is in equilibrium in solution with \(\text{RhCl}(\text{PPh}_3)_2\) which can dimerize as is shown in Scheme 2.10.

![Scheme 2.10 Dimeric rhodium complexes.](image)

The results using bidentate ligands (entries 9 – 13) are very disappointing. The conversions are generally lower when compared to the monodentate ligands and the enantioselectivities are also reduced. The influence of the chiral backbone of the ligands shows up when ligands with either a BINOL- or a TADDOL-backbone are compared. The TADDOL derived ligands (entries 14 – 19) in general give better conversions. The highest e.e. in this screening has been obtained with ligand L9 (entry 15), a TADDOL derived ligand. The effect of the size of the amine groups in the ligands are opposite for the two different backbones used. The BINOL derived ligands give higher e.e.’s when the amine moiety is smaller and for the TADDOL derived ligands a larger amine moiety leads to higher e.e.’s. Better results were obtained when 2 equivalents of ligand with respect to rhodium were used instead of 1 equivalent (entries 18 and 19). Both the conversion and enantioselectivity improve upon increasing the amount of ligand relative to Rh, pointing towards a stabilizing effect of the ligand on the catalyst system. When one equivalent is used probably more of the catalyst degrades to form rhodium black, which is also active as a hydrogenation catalyst albeit with a lower activity and of course providing racemic product. Hence, higher enantioselectivity is observed when two equivalents of ligands are used.
Table 2.1 Rh-catalyzed hydrogenation of 14 in methanol, using various ligands.

<table>
<thead>
<tr>
<th>entry</th>
<th>ligand</th>
<th>time (h)</th>
<th>L*/Rh</th>
<th>conversion (%)</th>
<th>e.e. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>L1</td>
<td>24</td>
<td>2.2</td>
<td>100</td>
<td>64</td>
</tr>
<tr>
<td>2</td>
<td>L1</td>
<td>24</td>
<td>2.2</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>L2</td>
<td>24</td>
<td>2.2</td>
<td>16</td>
<td>56</td>
</tr>
<tr>
<td>4</td>
<td>L3</td>
<td>20</td>
<td>2.2</td>
<td>100</td>
<td>21</td>
</tr>
<tr>
<td>5</td>
<td>L4</td>
<td>20</td>
<td>2.2</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>L5</td>
<td>20</td>
<td>2.2</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>7</td>
<td>L6</td>
<td>20</td>
<td>2.2</td>
<td>10</td>
<td>14</td>
</tr>
<tr>
<td>8</td>
<td>L7</td>
<td>20</td>
<td>2.2</td>
<td>13</td>
<td>23</td>
</tr>
<tr>
<td>9</td>
<td>L11</td>
<td>18</td>
<td>1.1</td>
<td>100</td>
<td>22</td>
</tr>
<tr>
<td>10</td>
<td>L12</td>
<td>21</td>
<td>1.1</td>
<td>6</td>
<td>52</td>
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<tr>
<td>11</td>
<td>L13</td>
<td>24</td>
<td>1.1</td>
<td>18</td>
<td>11</td>
</tr>
<tr>
<td>12</td>
<td>L14</td>
<td>21</td>
<td>1.0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>13</td>
<td>L15</td>
<td>24</td>
<td>1.1</td>
<td>40</td>
<td>6</td>
</tr>
<tr>
<td>14</td>
<td>L8</td>
<td>45</td>
<td>2.2</td>
<td>100</td>
<td>2</td>
</tr>
<tr>
<td>15</td>
<td>L9</td>
<td>45</td>
<td>2.2</td>
<td>100</td>
<td>77</td>
</tr>
<tr>
<td>16</td>
<td>L10</td>
<td>45</td>
<td>2.2</td>
<td>100</td>
<td>37</td>
</tr>
<tr>
<td>17</td>
<td>L16</td>
<td>21</td>
<td>1.1</td>
<td>100</td>
<td>14</td>
</tr>
<tr>
<td>18</td>
<td>L17</td>
<td>92</td>
<td>1.1</td>
<td>32</td>
<td>5</td>
</tr>
<tr>
<td>19</td>
<td>L17</td>
<td>21</td>
<td>2.0</td>
<td>40</td>
<td>15</td>
</tr>
</tbody>
</table>

* Reactions were performed with 0.04M substrate solution, 1 mol% of [Rh(COD)2]BF4 (24), 1 bar H2 at room temperature. All systems were prehydrogenated for one hour. [Rh(NBD)Cl]2 (25) was used instead of [Rh(COD)2]BF4 (24).

2.2.4 Solvent screening

We have shown that phosphoramidite ligands can be used in the rhodium-catalyzed asymmetric hydrogenation with promising preliminary results with several ligands yielding moderate enantioselectivities and full conversions.
The next step is to elaborate further on these results and test different conditions. We started by screening several solvents in order to determine the effects on the enantioselectivity and conversion.

The most striking outcome of the results listed in Table 2.2 is a dramatic increase in e.e. (70% → 95%) by changing the solvent from methanol to dichloromethane. This has also been reported for some bidentate phosphine ligands, which give better results in dichloromethane than in methanol. 27,28,29 1,2-Dichloroethane was also able to improve the enantioselectivity when compared to methanol but not to the same extent as dichloromethane. Because chlorinated solvents are not the ideal solvents from an environmental point of view other solvents were explored. Since ethyl acetate is often a replacement for dichloromethane in synthesis this solvent was tested in the catalytic hydrogenation. We were very pleased with the outcome of this venture as ethyl acetate turned out to be an excellent solvent for hydrogenation and it is as good as dichloromethane. The results with tetrahydrofuran were comparable to those with the chlorinated solvents; the enantioselectivity being slightly lower.
Toluene on the other hand gave low conversion for all the substrates investigated; this is possibly due to the poor solubility of the catalyst precursor/ligand system in this solvent. Another reason of the low reactivity could be that toluene can form $\eta^6$-arene-RhI complexes. These complexes are not active in asymmetric hydrogenation thus lowering the overall activity. Acetone provided good results although there was some self-condensation product of the solvent present in the crude reaction mixture.

2.2.5 Effects of pressure and substrate over catalyst ratios (S/C)

The standard substrate 14 was hydrogenated using different substrate to catalyst ratios besides changing the hydrogen pressure. From Table 2.3 entries 1 to 3 it is noted that upon increasing the S/C ratio and at the same time increasing the hydrogen pressure the reaction becomes faster due to an increase in the hydrogen concentration in the solution. However, the enantioselectivity remains constant. This behavior is in contrast too most of the rhodium-catalyzed asymmetric hydrogenations reported using bidentate ligands where the e.e. decreases with increasing hydrogen pressure. It is also known that e.e.’s can increase with increasing hydrogen pressure. Considering entry 4 we conclude that using 0.015 mol% of catalyst brings us to the limits of our catalyst system with this substrate in dichloromethane. The conversion did not go to completion, even after a prolonged hydrogenation period. Surprisingly, when changing the catalyst-precursor to ligand ratio from 2.0 to 1.0 the effect seems to be beneficial. The enantioselectivity remains constant however; the turnover frequency is increased (entries 4 and 7). Probably the active catalyst needs to be formed from $[\text{Rh(COD)}_2]\text{BF}_4$ (24) by displacement of one cyclooctadiene by two ligand molecules and followed by the hydrogenation of the remaining cyclooctadiene on the rhodium. When a small part of the catalyst precursor is converted there is still an excess of ligand present in the solution. This excess of ligand can also coordinate to the active catalyst forming the $[\text{Rh}((S)\text{-MonoPhos™})_4]\text{BF}_4$ (26). This complex is inactive in the hydrogenation reaction and therefore a smaller amount of initially free ligand gives rise to decreased formation of inactive complex 26. After formation of 26 the exchange of ligands between 26 and 24 is negligible (Chapter 7). Another variable, which greatly enhances the reaction rate, is the hydrogen pressure. This can be concluded from the calculated turnover frequencies (TOF). These values increase from about 3 (mol/mol·h) at 1 bar hydrogen pressure to 1667 (mol/mol·h) at 60 bar. The fact that the enantioselectivity is not affected with changing hydrogen pressures, *vides supra*, gives the advantage that the reaction rate can be enhanced considerably at higher hydrogen pressures to make this catalyst more attractive for industrial application.
Table 2.3 Variation in S/C and pressure.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Rh (mol%)</th>
<th>L1/Rh</th>
<th>solvent</th>
<th>pH2</th>
<th>time</th>
<th>e.e. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5.0</td>
<td>2.2</td>
<td>CH2Cl2</td>
<td>1 bar</td>
<td>3 h</td>
<td>95</td>
</tr>
<tr>
<td>2</td>
<td>0.5</td>
<td>2.2</td>
<td>CH2Cl2</td>
<td>5 bar</td>
<td>40 min</td>
<td>95</td>
</tr>
<tr>
<td>3</td>
<td>0.1</td>
<td>2.2</td>
<td>CH2Cl2</td>
<td>15 bar</td>
<td>2 h</td>
<td>95</td>
</tr>
<tr>
<td>4</td>
<td>0.015</td>
<td>2.0</td>
<td>CH2Cl2</td>
<td>5 bar</td>
<td>16 h</td>
<td>95&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>5</td>
<td>0.9</td>
<td>2.2</td>
<td>EtOAc</td>
<td>60 bar</td>
<td>4 min</td>
<td>97</td>
</tr>
<tr>
<td>6</td>
<td>5.0</td>
<td>1.1</td>
<td>EtOAc</td>
<td>1 bar</td>
<td>2 h</td>
<td>96</td>
</tr>
<tr>
<td>7</td>
<td>0.015</td>
<td>1.0</td>
<td>CH2Cl2</td>
<td>5 bar</td>
<td>16 h</td>
<td>95&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Conversions are quantitative, unless noted otherwise. <sup>b</sup> 81% conversion; TOF = 338 h<sup>-1</sup>. <sup>c</sup> 90% conversion; TOF = 375 h<sup>-1</sup>. <sup>d</sup> As reaction times are not optimised, TOF’s are indicative.

2.2.6 Substrates with different substitution patterns

![Figure 2.3 Dehydroamino acids and corresponding methyl esters.](image-url)
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After having established the solvents of choice for our catalyst system in the hydrogenation of the substrate 14 we investigated substrates with different substitution patterns. These substrates with substituents at the phenyl moiety were subjected to varying hydrogenation conditions. The results are summarized in Table 2.4. From these data it is evident that it does not make a difference if these substituents are at the meta- or para-position, as e.e.’s only vary from 94 - 97 %. Comparison of the reaction rates is difficult from these results, because the reaction all went to full completion within the given time for hydrogenation.

It also shows that the enantioselectivity is very similar for both electron withdrawing and electron donating substituents (Table 2.4, entries 1 - 8).

Interestingly, the solvent can be changed to the environmentally more benign ethyl acetate providing similar results (e.e.) as with the reactions performed in dichloromethane (entries 3 and 11, see also Table 2.3 entries 5 and 6). The final two entries 11 and 12 illustrate that the enantioselectivity is not only determined by the electronic properties of the double bond. Steric hindrance of the substituent at the β-position of the substrate also plays an important role. The β-unsubstituted substrates 28 and 29 (Figure 2.3) give rise to excellent enantioselectivities at full conversions.

<table>
<thead>
<tr>
<th>Substrate (R,R’)</th>
<th>Rh mol%</th>
<th>L1/Rh</th>
<th>solvent</th>
<th>pH₂</th>
<th>time</th>
<th>e.e. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 12 p-F-Ph, H</td>
<td>2.0</td>
<td>2.2</td>
<td>CH₂Cl₂</td>
<td>27 bar</td>
<td>0.17 h</td>
<td>93</td>
</tr>
<tr>
<td>2 15 m-MeO-Ph, Me</td>
<td>1.0</td>
<td>1.1</td>
<td>CH₂Cl₂</td>
<td>5 bar</td>
<td>2 h</td>
<td>97</td>
</tr>
<tr>
<td>3 16 p-MeO-Ph, Me</td>
<td>1.0</td>
<td>1.1</td>
<td>CH₂Cl₂</td>
<td>5 bar</td>
<td>2 h</td>
<td>94</td>
</tr>
<tr>
<td>4 17 p-F-Ph, Me</td>
<td>1.0</td>
<td>1.1</td>
<td>CH₂Cl₂</td>
<td>5 bar</td>
<td>0.42 h</td>
<td>96</td>
</tr>
<tr>
<td>5 18 m-NO₂-Ph, Me</td>
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<td>1.1</td>
<td>CH₂Cl₂</td>
<td>5 bar</td>
<td>2 h</td>
<td>95</td>
</tr>
<tr>
<td>6 19 p-NO₂-Ph, Me</td>
<td>1.0</td>
<td>1.1</td>
<td>CH₂Cl₂</td>
<td>5 bar</td>
<td>2 h</td>
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<td>1.1</td>
<td>CH₂Cl₂</td>
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<td>2 h</td>
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</tr>
<tr>
<td>8 21 m-MeO-p-AcO-Ph, Me</td>
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<td>2.2</td>
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<td>2.2</td>
<td>CH₂Cl₂</td>
<td>5 bar</td>
<td>3 h</td>
<td>97</td>
</tr>
<tr>
<td>11 28 H, H</td>
<td>5.0</td>
<td>2.2</td>
<td>EtOAc</td>
<td>1 bar</td>
<td>3 h</td>
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<td>12 29 H, Me</td>
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<td>CH₂Cl₂</td>
<td>5 bar</td>
<td>2 h</td>
<td>&gt;99</td>
</tr>
</tbody>
</table>

ᵃ Conversions are quantitative, unless noted otherwise. ᵇ not determined. ᵇ e.e.’s were determined by chiral GC.
2.2.7 Examples of the application of enantiopure non-natural amino acids

The production of enantiopure non-natural amino acids provides building blocks for new or improved drugs. Illustrative examples are the teicoplanin aglycon 41,34 in Figure 2.4, and vancomycin analogs.34 Vancomycin and teicoplanin are members of a family of glycopeptide antibiotics.35 These two glycopeptides are the only ones from this family that are used clinically for the treatment of methicillin-resistant Staphylococcus aureus (MRSA) infections and are used as a last resort against Gram-positive pathogens.36 Considering its clinical importance it is a serious issue that vancomycin-resistant S. aureus have emerged37,38 and are likely to spread. This finding has prompted investigations into the total synthesis of these molecules and their analogs in order to elucidate the structural requirement of the active part of the drug. Both in the total synthesis34,39,40 and the structure/activity relationship41 studies protected amino acid 37 plays an important role providing the desired functional groups on the phenyl ring of the amino acid.42,43,44 This protected amino acid can be made via asymmetric hydrogenation as depicted in Scheme 2.11, vide supra.

Scheme 2.11 Synthesis of a building block of teicoplanin (41) using rhodium-catalyzed asymmetric hydrogenation.

Figure 2.4 Molecule 37 incorporated in the total synthesis of teicoplanin (41).
Noteworthy is the fact that using the phosphoramidite based homogeneous rhodium-catalyst the nitro moiety is not reduced to an amine moiety as is the case when using a heterogeneous catalyst like palladium on carbon. Olefin 20 was obtained from 4-fluoro-3-nitrobenzaldehyde and N-acetyl glycine as described in paragraphs 2.2.2.1 and 2.2.2.3.

Another example of the use of rhodium-catalyzed asymmetric hydrogenation is the production of various protected α-amino acids on large scale. The synthesis of one example is depicted in Scheme 2.12. The manufacture of N-Boc-(S)-3-fluorophenylalanine according to the outlined route has been performed on 200 kg scale.

![Scheme 2.12 Route used for large scale manufacture of N-Boc-(S)-3-fluorophenylalanine.](image)

This route was also used for the production of other α-amino acids with different substituents on the phenyl moiety. With the appropriate solvent changes for each substrate this route has been widely used for producing pilot quantities (10-200kg) of many derivatives.

![Figure 2.5 Examples of protected α-amino acids manufactured on a 10-200kg scale.](image)

2.2.8 Further ligand optimization

We tried to improve our results by further screening a variety of ligands. The hydrogenation procedure was also changed by excluding the prehydrogenation step of the catalyst followed by the addition of the substrate, because the results did not improve with the prehydrogenation procedure. In addition, the formation of rhodium-black seems to increase
by the prehydrogenation of the catalyst. Also the formation of rhodium-black after the reaction has finished indicated that the catalyst is not very stable especially if there is a lack of substrate.

Henceforth the substrate 14 or 29 (0.2 mmol), catalyst precursor (1 mol%), ligand (2.1 mol%) and solvent (5ml) were all placed in an autoclave and after purging with nitrogen a hydrogen atmosphere of 5 bar was applied. The first ligand that was compared to L1 was ligand L18, which is based on a primary amine instead of a secondary one connected to the phosphorus (Table 2.5, entry 2). This ligand gave already improved results when compared to L4, which has two alpha methyl benzyl groups attached to the nitrogen and did not gave any conversion. However, as expected a lower e.e. than with MonoPhos™ (L1) was obtained (entries 1, 2). This result prompted us to make a smaller version of MonoPhos™ with only one methyl on the nitrogen as in L19. This ligand also performed well; unfortunately the expected increase in enantioselectivity compared to the catalyst based on L1 was not observed (entry 3). Consequently we tested ligands with smaller backbones changing the binaphthol to a biphenol moiety in ligands L20 and L21. These ligands also gave promising results (entries 4, 5 and 10).

The use of either of these biphenol-based ligands resulted in full conversions and high enantioselectivities. Taking into account that only the dimethylamino variant was tested it seems an interesting class of ligands to be used in the screening of ligands in the rhodium-catalyzed asymmetric hydrogenation of new and more challenging substrates.

In ligand L22 the electronic properties were changed by the introduction of a methoxy group on the nitrogen. The results of the hydrogenation using this ligand showed a little decrease in enantioselectivity, but again the effect is not very dramatic. With these results in mind it might be better to increase the steric bulk a little bit as in ligands L23 and L24. The ligand derived from pyrrolidine was the one expected to give a better result because it resembles MonoPhos™ quite well compared to the ligand derived from piperidine. It turned out that the results obtained with L24 were superior to L23 and even better than MonoPhos™ itself.
Table 2.5 Extended exploration into monodentate phosphoramidite ligands.

<table>
<thead>
<tr>
<th>entry</th>
<th>ligand</th>
<th>substrate</th>
<th>e.e. (%)&lt;sup&gt;c&lt;/sup&gt;</th>
<th>entry</th>
<th>ligand</th>
<th>substrate</th>
<th>e.e. (%)&lt;sup&gt;c&lt;/sup&gt;</th>
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<td>73</td>
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<td>L20</td>
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<td>14</td>
<td>99</td>
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</tbody>
</table>

<sup>a</sup> 1 mol% \([\text{Rh(COD)}_2]\text{BF}_4\), 2.1 mol% Ligand, DCM (5ml; 0.04M), 5 bar H₂, r.t.  
<sup>b</sup> Conversions were quantitative within 24h.  
<sup>c</sup> e.e.’s were determined by chiral GC.

2.3 Conclusions

The results described in this chapter clearly demonstrate the usefulness of monodentate phosphoramidite ligands in the rhodium-catalyzed asymmetric hydrogenation reaction of prochiral dehydroamino acids yielding the protected chiral amino acids with high enantioselectivity. From the initial screening of ligands we conclude that the monodentate ligands performed no less or even better than their bidentate counterparts. These monodentate ligands seemed to give better results with smaller substituents at the nitrogen atom as in the ligand L1, however after fine tuning of the ligand a more sterically demanding group on the nitrogen give even better results (L24). The electronic effects we have introduced in ligands with only a secondary amine or a protected hydroxylamine moiety did not gave a clear picture of the influence of the difference in the electronic nature of the ligand. The rate of the reaction can be greatly enhanced by applying a higher hydrogen pressure hence increasing
the hydrogen concentration in solution. This increase in hydrogen concentration does not lower the enantioselectivity of the hydrogenation and therefore offers an excellent opportunity to develop a process with high turnover frequencies and enantioselectivities.

The enantioselectivity or rate of the hydrogenation reaction was not influenced significantly by electron withdrawing or electron donating substituents on the substrate.

The catalyst also hydrogenates the carboxylic acids substrates and their corresponding methyl esters equally well, even when these free acids are hydrogenated as slurry. Lack of a substituent on the β-position of the double bond does not diminish the enantioselectivity; on the contrary these substrates were hydrogenated with higher rates as well as with higher selectivity.

2.4 Experimental

General remarks:
All solvents were reagent grade and were dried and distilled, if necessary, following standard procedures. Reagents were purchased from Aldrich, Acros Chimica, Merck or Fluka and used as received unless stated otherwise. \(^1\)H NMR, \(^1\)C NMR, \(^3\)P\(^{\{1\}}\)H and \(^{19}\)F NMR spectra were recorded on a Varian VXR-200 spectrometer (at 200 MHz, 50 MHz, 81 MHz and 188 MHz, respectively). Chemical shifts are reported in \(\delta\) units (ppm) relative to the solvent signals of CHCl\(_3\) (\(^1\)H: 7.27 ppm, \(^1\)C: 77.0 ppm), DMSO-\(d_6\) (\(^1\)H: 2.49 ppm, \(^1\)C: 39.5 ppm) or to external references 85\% aq. H\(_3\)PO\(_4\) (\(^3\)P: 0 ppm) and CFCl\(_3\) (\(^{19}\)F: 0 ppm). Mass spectra were recorded by A. Kiewiet on an AEI-MS-902 mass spectrometer. GC measurements were performed on either a HP 5890A 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 or Pd on carbon. Carboxylic acids were transformed into their methyl ester analogues using (trimethylsilyl)diazomethane before GC analysis.

General procedure for the preparation of methyl esters using trimethylsilyl diazomethane.\(^\text{46}\) A 2-fold excess of trimethylsilyl diazomethane (2M in hexane) was added to a sample of the reaction mixture followed by addition of a few drops of methanol. After the evolution of nitrogen has ceased the solution was filtered over a short plug of silica to remove excess trimethylsilyl diazomethane and rhodium-complex to provide a colorless GC-sample.

Phosphoramidite ligands were synthesized according to literature procedures: \(L10^{47}\), \(L11^{48}\), \(L12^{51}\), \(L13^{49}\), \(L14^{49}\), \(L15^{49}\), \(L16^{49}\), \(L17^{49}\), \(L23^{50}\). Ligands \(L2^{51}\), \(L3^{51}\), \(L4^{51}\), \(L5^{52}\), \(L6^{51}\), \(L7^{51}\), \(L8^{53}\) and \(L9^{53}\) were kindly provided by Dr. A. Arnold while ligands \(L20^{54}\), \(L21^{54}\) and \(L22^{54}\) were kindly provided by Dr. J.-G. Boiteau.
Chapter 2

(S)-3,5-Dioxa-4-phospha-cyclohepta[2,1-a;3,4-a']dinaphthalen-4-yl)-dimethyl-amine (L1)

A mixture of (S)-bis-β-naphthol (2.35 g, 8.2 mmol), hexamethyl phosphorous triamide (3.08 g, 12.5 mmol) and anhydrous toluene (50 mL) was heated under reflux for 9 h under a nitrogen atmosphere. After cooling to room temperature, the solvent was removed under reduced pressure. The crude pale yellow product was purified through flash column chromatography (silica gel 200–300), gradient elution with petroleum ether/ethyl acetate afforded product (S)-L1 (2.80 g, 88%). 1H NMR (CDCl3) δ 2.75 (d, 3J = 9.2 Hz, 6H), 7.25-8.00 (m, 12H). 13C NMR (CDCl3, APT) δ 35.8 (d, 3J = 22.0 Hz), 121.8 (d, 3J = 1.0 Hz), 123.0 (d, 3J = 84.0 Hz), 124.5 (d, 4J = 15.1 Hz), 125.9 (s), 126.8 (d, 4J = 6.0 Hz), 128.1 (d, 7J = 6.0 Hz), 130.0 (d, 6J = 36.0 Hz), 130.8 (d, 4J = 47.4 Hz), 132.7 (d, 3J = 2.0 Hz), 149.5 (d, 2J = 38.3 Hz). 31P NMR (CDCl3) δ 148.7. HRMS (EI +) calculated for C22H18NO2P: 359.107, found: 359.108. [α]D = +579º.

(S)-3,5-Dioxa-4-phospha-cyclohepta[2,1-a;3,4-a']dinaphthalen-4-yl)-(1-(R)-phenyl-ethyl)-amine (L18)

A solution of (S)-MonoPhos™ (718 mg, 2 mmol), 1H-tetrazole (140 mg, 2 mmol) and (R)-(+)−1-phenylethylamine (645 µl, 5 mmol) in toluene (12 mL) was heated under reflux and a slightly stream of nitrogen during 6 h. The mixture was filtered over a small plug of silica and concentrated to afford L18 as a white foam (836 mg, 96%). Further purification is possible by crystallization from toluene. 1H NMR (CDCl3) δ 1.53 (d, 4J = 10.2 Hz, 3H), 3.42 (d, 3J = 15.3 Hz, 1H), 4.55 (m, 1H), 6.78 (d, 2J = 13.6 Hz, 1H), 7.20-7.45 (m, 1H), 7.53 (d, 2J = 13.2 Hz, 1H), 7.78 (d, 2J = 13.2 Hz, 1H), 7.87-7.99 (m, 3H). 31P NMR (CDCl3) δ 151.5. EI-MS m/z = 435 (85) [M]+; HRMS (EI+) calculated for C28H22NO2P: 435.1388, found: 435.1397. [α]D = +155º.

(S)-3,5-Dioxa-4-phospha-cyclohepta[2,1-a;3,4-a']dinaphthalen-4-yl)-methyl-amine (L19)

Diethyl ether (5ml) was cooled to -30ºC and methyamine was bubbled through. At the same time a solution of 4-chloro-3,5-dioxa-4-phospha-cyclohepta[2,1-a;3,4-a']dinaphthalene (2.54 g, 7.2 mmol) in Et2O (13ml) was added dropwise in 15 min. Stirring was continued for 30 min before toluene (10ml) was added and the mixture was slowly warmed to r.t. After filtration the volatiles were removed in vacuo to give 1.95 g (79 %) of a white solid. 1H NMR (CDCl3) δ 2.54 (dd, 3J = 11.5 Hz, 3J = 9.9 Hz, 3H), 2.87-2.99 (m, 1H), 7.23-7.56 (m, 8H), 7.87-8.01 (m, 4H). 13C NMR (CDCl3, APT) δ 26.6 (d, 2J = 14.1 Hz), 121.8 (s), 122.2 (s), 124.7 (s), 124.8 (s), 126.1 (s), 126.8 (s), 126.9 (s), 128.2 (s), 128.3 (s), 129.7 (s), 130.2 (s), 130.8 (s), 131.3 (s), 132.7 (s), 149.4. 31P NMR (CDCl3) δ 151.4. EI-MS m/z = 239 (36), 268 (41), 313 (68), 345 (100) [M]+; HRMS (EI+) calculated for C21H16NO2P: 345.0919, found: 345.0904. [α]D = +372º.
The Synthesis of Enantiopure Amino Acids Using Homogeneous Asymmetric Hydrogenation

(S)-1-(3,5-Dioxa-4-phospha-cyclohepta[2,1-a;3,4-a']dinaphthalen-4-yl)-piperidine (L24)

(S)-Bis-β-naphthol (10 g, 35 mmol) in 40 ml of PCl₃ was heated under reflux for 8 h. Excess of PCl₃ was removed by distillation in vacuo (20 mbar). The residual solid was subjected to azeotropic distillation with toluene (2x 10 ml) and dried in vacuo until a white foam resulted. (12.2 g, 100 %). The residue was dissolved in toluene to afford 50 ml of a chlorophosphite stock solution. A 10 ml aliquot of the above prepared chlorophosphite stock solution was added at 0°C to a solution of 2.13 ml (15.4 mmol, 2.2 eq.) of triethylamine and 0.76ml (7.7 mmol, 1.1 eq.) of piperidine in 15 ml of dry THF. The reaction mixture was allowed to warm to r.t. and stirred overnight. The mixture was diluted with diethyl ether (50 ml) and filtered over a plug of silica, washed with 50 ml of diethyl ether, and the solvent was removed in vacuo. Column chromatography on silica with pentane/ethyl acetate as eluent was used to purify the ligand (65%). 1H NMR (CDCl₃) δ 1.36-1.61 (m, 6H), 2.88-3.11 (m, 4H), 7.21-7.56 (m, 8H). 13C NMR (CDCl₃, APT) δ 24.9, 26.9, 27.0, 45.1, 45.5, 122.1, 122.2, 122.7, 123.9, 124.1, 124.5, 124.7, 126.0, 127.0, 128.3, 129.8, 130.2, 130.7, 131.3, 132.6, 149.3, 149.9. 31P NMR (CDCl₃) δ 145.5. HRMS (EI⁺) calculated for C₂₅H₂₃NO₂P: 400.147, found: 400.147.51

The different azlactones were synthesized according to (slightly modified) literature procedures.¹⁸,²¹

4-Benzylidene-2-methyl-4H-oxazol-5-one (6)¹⁸

A mixture of N-acetyl glycine (29.0 g, 248 mmol), benzaldehyde (37.5 mL, 370 mmol) and sodium acetate (15.0 g, 183 mmol) in acetic anhydride (59 mL) was refluxed for 1 h and subsequently cooled in a cold room overnight. The mixture was poured into ice water (60 mL) while stirred. The precipitate was collected by filtration using a glass filter (P4) and washed with ice water (3 x 20 mL). After washing with a little amount of cold ethanol the product was recrystallized from ethyl acetate to yield a yellow solid (20.02 g, 44 %). 1H NMR data was in good agreement with the data in literature.⁵⁶

4-(3-Methoxy-benzylidene)-2-methyl-4H-oxazol-5-one (7)

A mixture of N-acetyl glycine (3.04 g, 26 mmol), m-methoxy-benzaldehyde (3.7 mL, 30 mmol) and sodium acetate (1.64 g, 20 mmol) in acetic anhydride (30 mL) was refluxed for 2 h and subsequently cooled in an ice-water bath. The mixture was poured into ice water (70 mL) while stirred. The precipitate was collected by filtration using a glass filter (P4) and washed with ice water (3 x 20 mL). After washing with a little amount of cold ethanol the product was dried in a vacuum oven at 60 °C. The product was obtained as a yellow solid (2.03 g, 36 %). 1H NMR and 13C NMR data were in good agreement with the data in literature.⁵⁷
4-(4-Methoxy-benzylidene)-2-methyl-4H-oxazol-5-one (8)

A mixture of N-acetyl glycine (15.20 g, 130 mmol), p-methoxy-benzaldehyde (18.2 mL, 150 mmol) and sodium acetate (8.20 g, 100 mmol) in acetic anhydride (150 mL) was refluxed for 70 min and subsequently cooled in an ice-water bath. The mixture was poured into ice water (70 mL) while stirred. The precipitate was collected by filtration using a glass filter (P4) and washed with ice water (3 x 20 mL). After washing with a little amount of cold ethanol the product was dried in a vacuum oven at 60 °C. The product was obtained as a yellow solid (20.02 g, 71 %). \(^1\)H NMR and \(^{13}\)C NMR data were in good agreement with the data in literature.\(^{58}\)

4-(4-Fluoro-benzylidene)-2-methyl-4H-oxazol-5-one (9)

A mixture of N-acetyl glycine (7.60 g, 65 mmol), p-fluoro-benzaldehyde (10.6 mL, 98 mmol) and sodium acetate (3.94 g, 48 mmol) in acetic anhydride (14 mL) was refluxed for 90 min and subsequently cooled in an ice-water bath. The mixture was poured into ice water (16 mL) while stirred. The precipitate was collected by filtration using a glass filter (P4) and washed with ice water (3 x 20 mL). After washing with a little amount of cold ethanol the product was dried in a vacuum oven at 60 °C. The product was obtained as a yellow solid (6.99 g, 71 %). \(^1\)H NMR (CDCl3) \(\delta\) 2.42 (s, 3H), 7.10 (s, 1H), 7.16 (t, \(^3J = 9\) Hz, 2H), 8.13 (dd, \(^3J = 10\) Hz, \(^3J = 9\) Hz, 2H). \(^{13}\)C NMR (DMSO-d\(_6\), APT) \(\delta\) 14.3 (s), 114.7 (d, \(^2J = 20\) Hz), 127.3 (s), 128.4 (s), 130.8 (s), 133.1 (s), 149.4 (d, \(^1J = 32\) Hz), 159.6 (s), 164.6 (s). EI-MS \(m/z\) = 57 (6), 83 (6), 108 (22), 135 (100), 177 (24), 205 (86) [M]+; HRMS (EI+) calculated for C\(_{11}\)H\(_8\)NO\(_2\)F: 205.0539, found: 205.0533.

2-Methyl-4-(3-nitro-benzylidene)-4H-oxazol-5-one (10)

A mixture of N-acetyl glycine (1.03 g, 8.8 mmol), m-nitro-benzaldehyde (1.96 g, 13 mmol) and sodium acetate (0.53 g, 6.5 mmol) in acetic anhydride (3.8 mL) was refluxed for 90 min and subsequently cooled in an ice-water bath. The mixture was poured into ice water (16 mL) while stirred. The precipitate was collected by filtration using a glass filter (P4) and washed with ice water (3 x 20 mL). After washing with a little amount of cold diethyl ether the product was dissolved in acetone and precipitated by adding water. The precipitate was filtered off and dried in a vacuum oven at 60 °C. The product was obtained as a yellow solid (1.57 g, 52%). \(^1\)H NMR data was in good agreement with the data in literature.\(^{56}\)

2-Methyl-4-(4-nitro-benzylidene)-4H-oxazol-5-one (11)

A mixture of N-acetyl glycine (1.03 g, 8.8 mmol), p-nitro-benzaldehyde (1.96 g, 13 mmol) and sodium acetate (0.53 g, 6.5 mmol) in acetic anhydride (3.8 mL) was refluxed for 50 min and subsequently cooled in an ice-water bath. The mixture was poured into ice water (16 mL) while stirred. The precipitate was collected by filtration using a glass
filter (P4) and washed with ice water (3 x 20 mL). After washing with a little amount of cold diethyl ether the product was dissolved in acetone and precipitated by adding water. The precipitate was filtered off and dried in a vacuum oven at 60 °C. The product was obtained as a yellow solid (2.08 g, 69 %). \textsuperscript{1}H NMR data was in good agreement with the data in literature.\textsuperscript{56}

4-(4-Fluoro-3-nitro-benzylidene)-2-methyl-4H-oxazol-5-one (12)

A mixture of \textit{N}-acetyl glycine (15.2 g, 130 mmol), \textit{p}-fluoro-\textit{m}-nitro-benzaldehyde (25.64 g, 150 mmol) and sodium acetate (8.15 g, 100 mmol) in acetic anhydride (150 mL) was heated at reflux for 90 min and subsequently cooled in an ice-water bath. The mixture was poured into ice water (70 mL) while stirred. The precipitate was collected by filtration using a glass filter (P4) and washed with ice water (3 x 20 mL). After washing with a little amount of cold ethanol the precipitate was filtered off and dried in a vacuum oven at 60 °C. The product was obtained as a brownish solid (20.64 g, 55 %). \textsuperscript{1}H NMR (CDCl\textsubscript{3}) \(\delta\) 2.45 (s, 3H), 7.06 (s, 1H), 7.37 (t, \(3J = 6.4\) Hz, 2H), 8.30-8.33 (m, 1H), 8.88 (d, \(4J = 3.4\) Hz). \textsuperscript{19}F NMR (CDCl\textsubscript{3}) \(\delta\) 96 (s). EI-MS \(m/z\) = 57 (13), 83 (37), 107 (18), 149 (22), 180 (6), 222 (8), 250 (100) [M]\textsuperscript{+}; HRMS (EI\textsuperscript{+}) calculated for C\textsubscript{11}H\textsubscript{7}N\textsubscript{2}O\textsubscript{4}F: 250.0390, found: 250.0400.

Acetic acid 2-methoxy-4-(2-methyl-5-oxo-oxazol-4-ylidenemethyl)-phenyl ester (13)

A mixture of \textit{N}-acetyl glycine (8.7 g, 75 mmol), \textit{m}-methoxy-\textit{p}-hydroxy-benzaldehyde (11.4 g, 75 mmol) and sodium acetate (4.5 g, 55 mmol) in acetic anhydride (25 mL) was refluxed for 2 h and subsequently cooled. After an overnight period of precipitation the mixture was filtered over a glass filter with the aid of water. The solids were washed with water and diethyl ether before being dried using the rotary evaporator. The product was obtained as a brownish solid (16.16 g, 78%). \textsuperscript{1}H NMR data was in good agreement with the data in literature.\textsuperscript{56}

\((\textit{Z})\)-2-Acetamido-3-(4-fluorophenyl)acrylic acid (15)

A mixture of oxazolone 9 (2.0 g, 9.75 mmol), water (8.0 mL), acetone (19.0 mL) and sodium acetate (0.82 g, 20 mmol) was refluxed for 30 min and subsequently the acetone was removed under vacuum. The precipitate was collected by filtration using a glass filter (P4) and washed with ice water (3 x 15 mL). The isolated solid was dissolved in a sodium hydroxide solution (0.5M, 50 mL) and extracted three times with 20 mL of diethyl ether. The water layer was acidified with hydrochloric acid (35%) until the product precipitated. After filtration the water layer was extracted tree times with 20 mL of diethyl ether. The solvents were evaporated under vacuum. The collected solids were recrystallized from water and dried in a vacuum oven at 60 °C. The product was obtained as a white solid (1.40 g, 64 %). \textsuperscript{1}H NMR and \textsuperscript{13}C NMR data were in good agreement with the data in literature.\textsuperscript{59}
(Z)-Methyl 2-acetamido-3-phenylacrylate (16)

A mixture of oxazolone 6 (1.14 g, 6.08 mmol) and methanol (50 mL) was refluxed for 48 h and after cooling to room temperature the methanol was removed under vacuum. The remaining solids were recrystallized from ethyl acetate. The product was obtained as a white solid (0.65 g, 49 %). $^1$H NMR and $^{13}$C NMR and MS data were in good agreement with the data in literature.\(^{60,61}\)

(Z)-Methyl 2-acetamido-3-(3-methoxyphenyl)acrylate (17)

A mixture of oxazolone 7 (1.69 g, 7.77 mmol), sodium methoxide (0.02 g), sodium acetate (0.02 g) and methanol (35 mL) was stirred at room temperature for 2.5 h and after the methanol was removed under vacuum a little amount of cold acetone was added and the remaining salts were filtered off. The acetone was removed under vacuum before the product was recrystallized from ethyl acetate. The product was obtained as a white solid (0.69 g, 38 %). $^1$H NMR (CDCl$_3$) $\delta$ 2.04 (s, 3H), 3.75 (s, 3H), 3.79 (s, 3H), 6.83-7.27 (m, 5H), 7.51 (s, 1H). $^{31}$C NMR (CDCl$_3$) $\delta$ 23.0, 52.5, 55.0, 114.7, 115.1, 122.1, 124.7, 129.4, 132.2, 134.7, 159.4, 165.6, 169.2. EI-MS $m/z$ = 51 (2), 77 (5), 121 (6), 147 (36), 174 (4), 207 (100), 249 (37) [M]$^+$; HRMS (EI$^+$) calculated for C$_{13}$H$_{15}$NO$_4$: 249.1001, found: 249.1012.

(Z)-Methyl 2-acetamido-3-(4-methoxyphenyl)acrylate (18)

A mixture of oxazolone 8 (5.00 g, 23 mmol), sodium methoxide (0.06 g, 1.1 mmol) and methanol (100 mL) was stirred for 4 h. The methanol was removed under vacuum. To the remaining solids a small amount of cold acetone was added and after filtration diethyl ether was added to the filtrate to precipitate the product. After filtration over a glass filter (P4) it was further purified by recrystallization from ethanol. The product was obtained as a white solid (0.63 g, 11 %). $^1$H NMR and $^{13}$C NMR data were in good agreement with the data in literature.\(^{62}\)

(Z)-Methyl 2-acetamido-3-(4-fluorophenyl)acrylate (19)

A mixture of oxazolone 9 (0.94 g, 4.60 mmol) and methanol (30 mL) was refluxed for 4 h and after cooling to room temperature the methanol was removed under vacuum. The remaining solids were dissolved in a small amount of cold acetone and diethyl ether was added to precipitate the product. After filtration over a glass filter (P4) it was further purified by column chromatography (SiO$_2$; EtOAc). The product was obtained as a white solid (0.38 g, 35 %). $^1$H NMR and $^{13}$C NMR data were in good agreement with the data in literature.\(^{63}\)
(Z)-Methyl 2-acetamido-3-(3-nitrophenyl)acrylate (20)

A mixture of oxazolone 10 (1.50 g, 6.45 mmol) and methanol (20 mL) was refluxed for 2 h and after cooling to room temperature the methanol was removed under vacuum. The remaining solids were recrystallized from ethyl acetate and after another recrystallization from chloroform the product was obtained as a white solid (0.52 g, 32 %). \(^1\)H NMR and \(^1^3\)C NMR data were in good agreement with the data in literature.\(^{64}\)

(Z)-Methyl 2-acetamido-3-(4-nitrophenyl)acrylate (21)

A mixture of oxazolone 11 (2.00 g, 8.60 mmol) and methanol (20 mL) was refluxed for 2 h and after cooling to room temperature the methanol was removed under vacuum. The remaining solids were recrystallized from ethyl acetate and after another recrystallization from chloroform the product was obtained as a white solid (0.75 g, 35 %). \(^1\)H NMR and \(^1^3\)C NMR data were in good agreement with the data in literature.\(^{65}\)

(Z)-Methyl 2-acetamido-3-(4-fluoro-3-nitrophenyl)acrylate (22)

A mixture of oxazolone 12 (0.91 g, 3.67 mmol) and methanol (30 mL) was refluxed for 3 h and after cooling to room temperature the methanol was removed under vacuum. The remaining solids were dissolved in a small amount of cold acetone and diethyl ether was added to precipitate the product. After filtration over a glass filter (P4) it was further purified by recrystallization from ethyl acetate. The product was obtained as a white solid (0.41 g, 40 %). \(^1\)H NMR and \(^1^3\)C NMR data were in good agreement with the data in literature.\(^{39}\)

(Z)-Methyl 2-acetamido-3-(4-acetoxy-3-methoxyphenyl)acrylate (23)

A mixture of oxazolone 13 (16 g, 58 mmol), sodium acetate (0.2 g) and methanol (40 mL) was stirred at room temperature for 3 h before the amount of methanol was reduced under vacuum. Water was added to the mixture water followed by the addition of ethyl acetate. The organic layer was separated from the water layer. After washing this organic layer with a sodium bicarbonate solution the organic layer was dried over magnesium sulphate. The product was purified by recrystallization from ethyl acetate. The product was obtained as a yellowish solid (4.28 g, 24 %). \(^1\)H NMR and \(^1^3\)C NMR data were in good agreement with the data in literature.\(^{66}\)
2-Acetamido-3-phenylpropanoic acid (26)

Method A: Hydrogenations at ambient hydrogen pressure.

Hydrogenation reactions were performed using standard Schlenk techniques. All solvents were distilled and deoxygenated before use. Glassware was flame dried in vacuo.

To a Schlenk tube equipped with septum and stirring bar 4.061 mg (10.00 µmol) of [Rh(COD)2]BF4, 7.906 mg (22.00 µmol) of ligand and 200 µmol of substrate were added. After three vacuum/nitrogen cycles followed by two vacuum/hydrogen cycles, 5 mL of solvent was added through the septum and the reaction was left stirring at room temperature under ambient H2 pressure. Samples were taken which were filtered over a short silica column and subjected to e.e. determination by GC or HPLC. Conversions were determined by means of 1H NMR and GC analysis. 1H NMR data were in good agreement with the data in literature.67

E.e. determination by GC analysis: CP Chirasil-L-Val (25 m × 250 µm × 0.12 µm), N2-flow: 1.3 mL/min., 160 °C isothermal, T_r = 6.2 min. (R), T_r = 6.7 min. (S).

Method B: Experiments at 5 bar of hydrogen pressure.

In a Schlenk tube equipped with a septum 8.8 µmol of (S)-(−)-1 and 4.0 µmol of [Rh(COD)2]BF4 were dissolved in 5 mL of dichloromethane under an inert atmosphere and added by syringe into a glass Büchi Miniclave containing a magnetic stirring bar. In the case of ethyl acetate as solvent, the dichloromethane was evaporated under vacuum and 5 mL of ethyl acetate was added. The inert atmosphere was replaced by 5 bar of hydrogen, stirring was started and 15 mL of solvent containing 800 µmol of substrate was added. Samples were taken (1 mL) which were filtered over a short silica column and subjected to e.e. determination by GC or HPLC. Conversions were determined by means of 1H NMR and GC analysis.

Method C: Experiments at 5-60 bar of hydrogen pressure in a Parr autoclave mini reactor series 4560 (Hastelloy C). The autoclave was charged with 240 mg of methyl 2-acetamidocinnamic acid (1090 µmol). 4.0 mg (9.9 µmol, 0.9 mol% compared to the substrate) of [Rh(NBD)2]BF4 and 8.6 mg (23.93 µmol) of ligand and 50 mL of degassed ethyl acetate. After purging the autoclave three times with nitrogen a hydrogen pressure of 60 bar was applied. After 4 min. the reactor pressure was released and samples were taken which were filtered over a short silica column and subjected to e.e. determination by GC or HPLC. Conversions were determined by means of 1H NMR and GC analysis.

Method D: Experiments in the Endeavor™.

The Endeavor is an autoclave with eight reactors equipped with glass reaction vessels. Into these reaction vessels 1000 µmol of substrate, 10 µmol (1 mol%) of [Rh(COD)2]BF4 and 22 µmol of ligand L1 were weighed in. The vessels were placed in the reactors and 5 mL of dichloromethane was added to each of the reactors. The reactors were then purged for 30 min with N2 before applying a hydrogen atmosphere of 5 bar. The pressure was kept constant.
during the reaction and the hydrogen uptake was monitored. After completion of the reaction, the reactors were opened and samples were taken which were filtered over a short silica column and subjected to e.e. determination by GC or HPLC. Conversions were determined by means of $^1$H NMR and GC analysis.

**2-Acetamido-3-(4-fluorophenyl)propanoic acid (27)**

This product was obtained after hydrogenation of substrate 15 using method D. $^1$H NMR and $^{19}$F NMR data were in good agreement with the data in literature. $^{68,69}$ E.e. determination by GC analysis: CP Chirasil-L-Val (25 m × 250 µm × 0.12 µm), N$_2$-flow: 1.3 mL/min., 160 °C isothermal, $T_r = 7.5$ min. (R), $T_r = 8.0$ min (S).

**Methyl 2-acetamido-3-phenylpropanoate (28)**

This product was obtained after hydrogenation of substrate 16 using methods A, B, C and D. $^1$H NMR and $^{13}$C NMR data were in good agreement with the data in literature. $^{70}$ E.e. determination by GC analysis: CP Chirasil-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).

**Methyl 2-acetamido-3-(3-methoxyphenyl)propanoate (29)**

This product was obtained after hydrogenation of substrate 17 using method C. $^1$H NMR (CDCl$_3$) $\delta$ 1.87 (s, 3H), 2.92 (dd, $^2$J = 13.7 Hz, $^3$J = 6.0 Hz, 1H), 3.00 (dd, $^2$J = 13.2 Hz, $^3$J = 5.1 Hz, 1H), 3.62 (s, 3H), 3.67 (s, 3H), 4.73-4.79 (m, $^1$H), 6.32 (d, $^3$J = 7.3 Hz, 1H), 6.57 (s, 1H), 6.59 (d, $^3$J = 11.7 Hz, 1H), 6.68 (d, $^3$J = 8.4 Hz, 1H), 7.10 (t, $^3$J = 8.4 Hz, 1H). $^{13}$C NMR (CDCl$_3$, APT) $\delta$ 22.5 (s), 37.4 (s), 51.9 (s), 53.0 (s), 54.7 (s), 112.0 (s), 114.6 (s), 121.10 (s), 129.1 (s), 137.3 (s), 159.3 (s), 169.8 (s), 172.0 (s). EI-MS $m/z$ = 88 (24), 192 (100), 251 (15) [M$^+$]; HRMS (EI$^+$) calculated for C$_{13}$H$_{17}$NO$_4$: 251.1157, found: 251.1170. E.e. determination by GC analysis: CP Chirasil-L-Val (25 m × 250 µm × 0.12 µm), N$_2$-flow: 1.3 mL/min., 160 °C isothermal, $T_r = 14.8$ min. (R), $T_r = 15.4$ min. (S).

**Methyl 2-acetamido-3-(4-methoxyphenyl)propanoate (30)**

This product was obtained after hydrogenation of substrate 18 using method C. $^1$H NMR data was in good agreement with the data in literature. $^{71}$ E.e. determination by GC analysis: CP Chirasil-L-Val (25 m × 250 µm × 0.12 µm), N$_2$-flow: 1.3 mL/min., 160 °C isothermal, $T_r = 15.8$ min. (R), $T_r = 16.4$ min. (S).
Methyl 2-acetamido-3-(4-fluorophenyl)propanoate (31)

This product was obtained after hydrogenation of substrate 19 using method D. ¹H NMR and ¹³C NMR data were in good agreement with the data in literature. E.e. determination by GC analysis: CP Chirasil-L-Val (25 m × 250 µm × 0.12 µm), N₂-flow: 1.3 mL/min., 160 °C isothermal, Tᵣ = 7.5 min. (R), Tᵣ = 8.0 min. (S).

Methyl 2-acetamido-3-(3-nitrophenyl)propanoate (32)

This product was obtained after hydrogenation of substrate 20 using method D. ¹H NMR (CDCl₃) δ 1.99 (s, 3H), 3.16 (dd, ²J = 13.9 Hz, ³J = 5.9 Hz, 1H), 3.25 (dd, ²J = 13.8 Hz, ³J = 5.8 Hz, 1H), 3.74 (s, 3H), 4.85-4.94 (m, 1H), 6.30 (d, ³J = 7.1 Hz, 1H), 7.45-7.48 (m, 2H), 7.97 (s, 1H), 8.06-8.12 (m, 1H). ¹³C NMR (CDCl₃, APT) δ 21.5 (s), 36.0 (s), 51.2 (s), 51.5 (s), 120.7 (s), 122.7 (s), 128.0 (s), 134.0 (s), 136.7 (s), 146.1 (s), 168.5 (s), 170.1 (s). E.e. determination by HPLC analysis: Daicel Chiralcel-OD (250 × 4.6 mm), heptane/2-PrOH, 90:10, flow rate 1.0 mL/min., UV detector (254 nm); Tᵣ = 23.4 min. (R), Tᵣ = 36.0 min. (S).

Methyl 2-acetamido-3-(4-nitrophenyl)propanoate (33)

This product was obtained after hydrogenation of substrate 21 using method D. ¹H NMR (CDCl₃) δ 1.98 (s, 3H), 3.14 (dd, ²J = 14 Hz, ³J = 5.9 Hz, 1H), 3.24 (dd, ²J = 14 Hz, ³J = 5.4 Hz, 1H), 4.85-4.93 (m, 1H), 6.14 (d, ³J = 6.9 Hz, 1H), 7.43-7.47 (m, 2H), 7.95 (s, 1H), 8.06-8.11 (m, 1H). ¹³C NMR (CDCl₃, APT) δ 22.6 (s), 38.3 (s), 52.1 (s), 52.4 (s), 121.8 (s), 123.6 (s), 128.9 (s), 135.1 (s), 138.1 (s), 148.0 (s), 169.6 (s), 171.3 (s). E.e. determination by GC analysis: CP Chirasil-L-Val (25 m × 250 µm × 0.12 µm), N₂-flow: 1.3 mL/min., 160 °C isothermal, Tᵣ = 14.0 min. (R), Tᵣ = 16.1 min. (S).

Methyl 2-acetamido-3-(4-fluoro-3-nitrophenyl)propanoate (34)

This product was obtained after hydrogenation of substrate 22 using method D. ¹H NMR and ¹³C NMR data were in good agreement with the data in literature. E.e. determination by HPLC analysis: Daicel Chiralcel-OD (250 × 4.6 mm), heptane/2-PrOH, 90:10, flow rate 1.0 mL/min., UV detector (254 nm); Tᵣ = 21.0 min. (R), Tᵣ = 24.6 min. (S).
Methyl 2-acetamido-3-(4-acetoxy-3-methoxyphenyl)propanoate (35)

This product was obtained after hydrogenation of substrate 23 using method B. \(^1\)H NMR data was in good agreement with the data in literature.\(^{71}\) E.e. determination by HPLC analysis: Daicel Chiralcel-OD (250 × 4.6 mm), heptane/2-PrOH, 90:10, flow rate 1.0 mL/min., UV detector (254 nm); \(T_r = 19.0\) min. (R), \(T_r = 21.1\) min. (S).

2-Acetamidopropanoic acid (36)

This product was obtained after hydrogenation of substrate 24 using method A. \(^1\)H NMR and \(^{13}\)C NMR data were in good agreement with the data in literature.\(^{72}\) E.e. determination by GC analysis: CP Chirasil-L-Val (25 m × 250 \(\mu\)m × 0.12 \(\mu\)m), N\(_2\)-flow: 1.3 mL/min., 110 °C isothermal, \(T_r = 3.3\) min. (R), \(T_r = 3.8\) min. (S).

Methyl 2-acetamidopropanoate (37)

This product was obtained after hydrogenation of substrate 25 using methods A, B, C and D. \(^1\)H NMR and \(^{13}\)C NMR data were in good agreement with the data in literature.\(^{73}\) E.e. determination by GC analysis: CP Chirasil-L-Val (25 m × 250 \(\mu\)m × 0.12 \(\mu\)m), N\(_2\)-flow: 1.3 mL/min., 110 °C isothermal, \(T_r = 3.3\) min. (R), \(T_r = 3.8\) min. (S).

2.5 References and Notes

1 Michel Leeman (BSc) is gratefully acknowledged for carrying out part of the experiments of the research described in this chapter.
5 QUINAPHOS which is a mixed phosphine-phosphoramidite bidentate ligand was recently reported: G. Franciò, F. Faraone, W. Leitner, Angew. Chem., Int. Ed. 2000, 39, 1428.
6 One publication has appeared in which palladium-phosphoramidite complexes were used in the asymmetric hydrogenation of itaconic acid, albeit with low (5%, bidentate) or no e.e. (monodentate phosphoramidite): E.E. Nifantyev, S.A. Rumyantseva, M.P.Koroteyev, E.M. Abbasov, A.T. Teleshev, V.A. Pavlov, E.I. Klabunovsky, Phosphorus & Sulfur 1981, 12, 27.
17 It is not recommended to scale this method up to 10g scale or above because of shock sensitivity of tetrazole. An alternative catalyst is benzimidazolium triflate. See also ref. 14 for more alternatives and references.
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33 The exchange between [Rh(MonoPhos™)4]BF4 (41) and [Rh(COD)2]BF4 (38) was studied in an NMR experiment and provided evidence that on the timescale of the hydrogenation reaction no significant changes were observed.
42 The functionalities incorporated within molecule 34 are otherwise introduced using a Schöllkopf alkylation of a bromide using a chiral auxiliary to get the desired stereochemistry.
48 This ligand was kindly provided by Drs M. Hettinga who made this ligand while he was an undergraduate student in the group of Prof. dr. J.H. Teuben.