New approaches in asymmetric rhodium-catalyzed hydrogenations with monodentate phosphoramidites
Hoen, Robert

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Chapter 2
Catechol-based Phosphoramidites

In this chapter the synthesis and application of catechol-based phosphoramidites in rhodium-catalyzed hydrogenations are described. Ee’s up to 99% were obtained in the asymmetric hydrogenation of enamides and dehydroamino acids.

Part of this chapter has been published:
Chapter 2

2.1 Introduction

2.1.1 Bidentate ligands for asymmetric rhodium-catalyzed hydrogenations

The rhodium-catalyzed asymmetric hydrogenation of enamides is a key method to synthesize enantiomerically pure amino acids and amines. The majority of successful ligands used in this reaction is bidentate in nature, e.g. DuPhos (L1), DiPAMP (L2), DIOP (L3), BINAP (L4), PennPhos (L5), and ferrocenyl-based ligands, such as JosiPhos (L6), and FerroPhos (L7) (Figure 2.1). With the exception of CAMP (L8), limited success was obtained with monodentate ligands. These ligands were considered not particularly effective since they lack the possibility to form chelating complexes with the metal.

Figure 2.1: Successful bidentate ligands.
2.1.2 Monodentate ligands for asymmetric rhodium-catalyzed hydrogenations

After nearly 30 years of asymmetric hydrogenation it was unequivocally demonstrated in 2000 that bidentate chiral ligands are not a *conditio sine qua non* to reach high enantioselectivities. Three groups showed that monodentate phosphonites (L9), phosphites (L10) and phosphoramidites (L11) can be applied successfully as chiral ligands in the rhodium-catalyzed asymmetric hydrogenation providing excellent enantioselectivities (Figure 2.2). A major advantage of these monodentate ligands is that they can be prepared in one or two steps at low costs, which makes variations easy (see also Scheme 2.1).

![Figure 2.2: Monodentate Phosphonites, Phosphites and Phosphoramidites.](image)

Most successful monodentate ligands recently introduced consist of a chiral diol backbone, with another chiral or achiral moiety attached to phosphorus. The chirality of the backbone dictates in nearly all cases the chirality of the product. The chirality of the other moiety at phosphorus is found to be less important. Illustrative is that one of the most effective monodentate ligands for hydrogenation reactions, the commercially available phosphoramidite MonoPhos™ (L11), consists of only the chiral BINOL part an achiral N,N-dimethyl amine moiety. A few reports on alternative ligands using chiral backbones, such as biphenyls or spiro compounds, have appeared.
2.1.3 Goal of this research

From earlier results it was evident, that in the case of BINOL derived phosphoramidites, a small amine moiety is favored for the hydrogenation of dehydroamino acids. Later results showed that the introduction of a piperidine moiety improved the enantioselectivity of the hydrogenation of a variety of substrates even further. In this chapter a new class of monodentate phosphoramidites, based on an achiral catechol backbone is described. In this case the chirality of the products must be dictated solely by the chirality of the amine moiety. Not only is the chiral moiety an amine instead of the diol, but also the bulkiness of the diol backbone is reduced as a planar catechol is present whereas the size of the amine moiety is increased in the new ligand compared to MonoPhos™ (L11).

2.2 Synthesis of phosphoramidites

2.2.1 Synthesis of BINOL-based phosphoramidites

In general three methods are used to synthesize monodentate phosphoramidites based on BINOL (1) (Scheme 2.1). In the first method BINOL (1) is reacted with PCl₃ to yield the corresponding phosphorochloridite (2). The phosphorochloridite is then reacted with a primary or secondary amine to form the phosphoramidite. In some cases when sterically demanding amines are introduced the more reactive lithium amide of the amine is reacted with the phosphorochloridite (2). The second method converts BINOL in MonoPhos™ (L11) by reacting it with HMPT. Different phosphoramidites can be obtained by amine exchange with MonoPhos™ (L11). The third method is the so-called reversed synthetic approach. In the first step the amine is reacted with PCl₃ to form the corresponding dichlorophosphino amine, which reacts subsequently with the diol to form the corresponding phosphoramidite.

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* The Li-amides were prepared by reaction of the amine with n-BuLi.

† HMPT is hexamethylphosphorus triamide
2.2.2 Synthesis of catechol-based phosphoramidites

Since o-phenylene phosphorochloridite (4) is commercially available, the choice was made to use the first method for synthesizing catechol-based phosphoramidites. Initial attempts using the Li-amide of the corresponding amines afforded the ligands in low yield. A side product was obtained with a $^{31}$P signal at 128 ppm, independent of the amine that was used. Phosphoramidites in general have $^{31}$P signals between 140 and 150 ppm. It is assumed that the formed side-product is pyrophosphate 3, since it’s known from literature that phosphorochloridites can react with water under basic conditions to form pyrophosphites. The reactions were performed in THF, which might have contained traces of water. When the solvent was switched to diethyl ether or methyl t-butyl ether and the base was replaced by Et$_3$N, the desired phosphoramidites could be obtained in moderate yields (21%-48%) after
work up and column chromatography. The catechol-based ligands are in general more sensitive to hydrolysis than BINOL-based phosphoramidites. A considerable lost of product was observed after column chromatography on silica gel presumably due to hydrolysis during chromatography. A variety of easily accessible chiral amines, based on \((S)-(\cdot)-1\)-phenylethylamine, were used in the preparation of ligands \(L_{12}-L_{17}\). The cyclic analogue \(L_{20}\) of ligand \(L_{12}\) was obtained from the corresponding chiral amine \(13\), which could be synthesized in four steps from commercially available \(trans\)-1,2-dibenzoylethylene.\(^{21}\) For comparison also bidentate ligands \(L_{18}\) and \(L_{19}\) were examined (Scheme 2.2). All ligands were obtained as sticky colorless oils, with exception of \(L_{12}\) and \(L_{20}\), which were obtained as white powders. \(^{31}\)P-NMR spectra showed single peaks in the range of 140-150 ppm, typically for phosphoramidites. Additional information was obtained by mass spectroscopy and \(^1\)H- and \(^{13}\)C-NMR spectroscopy.

![Diagram of ligands L12-L20 and amines 5-13, Et\(_3\)N, Et\(_2\)O](image)

**Scheme 2.2:** Synthesis of catechol-based phosphoramidites.
2.3 Catechol-based phosphoramidites in rhodium-catalyzed hydrogenations

2.3.1 Enantioselective hydrogenation of N-acyl dehydrophenylalanine methyl ester (14)

As a benchmark reaction, the ligands were tested in the rhodium-catalyzed asymmetric hydrogenation of N-acyl dehydrophenylalanine methyl ester (14) under standard conditions. Standard conditions are: 0.2 mmol of substrate, 1 mol% of catalyst (L:Rh = 2:1) in 4 ml CH₂Cl₂ at room temperature and 5 bar of H₂ pressure. The results are depicted in Table 2.1.

Table 2.1: Asymmetric hydrogenation of N-acetyl dehydrophenylalanine methyl ester (14) catalyzed by Rh-phosphoramidite ligand systems derived from catechol.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Conversion</th>
<th>E.e.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>L12</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>L13</td>
<td>60</td>
<td>&lt;3</td>
</tr>
<tr>
<td>3</td>
<td>L14</td>
<td>45</td>
<td>&lt;3</td>
</tr>
<tr>
<td>4</td>
<td>L15</td>
<td>100</td>
<td>&lt;3</td>
</tr>
<tr>
<td>5</td>
<td>L16</td>
<td>60</td>
<td>&lt;3</td>
</tr>
<tr>
<td>6</td>
<td>L17</td>
<td>90</td>
<td>&lt;3</td>
</tr>
<tr>
<td>7</td>
<td>L18</td>
<td>100</td>
<td>5&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>8</td>
<td>L19</td>
<td>100</td>
<td>32&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>9</td>
<td>L20</td>
<td>100</td>
<td>92&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

a) Reactions performed under standard conditions; 0.2 mmol of substrate, 1 mol% catalyst (L:Rh = 2:1) in 4 ml CH₂Cl₂ at RT and 5 bar of H₂ pressure; b) Conversions determined by <sup>1</sup>H-NMR, no side products were observed in addition to product and/or starting material; c) E.e. determined by chiral GC (CP Chiralsil-L-Val) d) Product has the R configuration, except when L18 is used (see experimental section for assignment).

The catalysts based on ligands L13 to L17 gave modest to full conversions, while the ligand L12 based on a sterically demanding amine,
surprisingly, gave no conversion at all. The enantiomeric excesses are in all cases disappointing (entries 1-6, Table 2.1). In sharp contrast however, is the excellent yield and enantioselectivity of >92% reached with ligand \textbf{L20} (entry 9). Although \textbf{L12} and \textbf{L20} have a similar kind of structure, a remarkable difference in activity was observed by introduction of a ring structure in the ligand. The bidentate ligands \textbf{L18} and \textbf{L19} induced full conversion but rather poor e.e.’s although a longer spacer in the ligand resulted in a slightly higher e.e. (entries 7 and 8).

2.3.2 Enantioselective hydrogenation of a variety of substrates

A variety of substrates was tested to expand the scope of the catalytic hydrogenation employing \textbf{L20}. As shown in Table 2.2, other \(\alpha\)-amino acid precursors gave full conversions with modest e.e.’s (entries 1 and 2, Table 2.2). In contrast, \(\beta\)-amino acid precursor \textbf{18} gave no conversion at all using \(\text{CH}_2\text{Cl}_2\) as the solvent (entry 3). When the reaction was performed in \(\text{i-PrOH}\), 80% e.e. was obtained at 40% conversion (entry 4). In earlier studies it was shown that \(\text{i-PrOH}\) is the best solvent for the Rh-phosphoramidite catalyst system in the hydrogenation of \(\beta\)-amino acid precursors with a \(Z\)-configuration.\textsuperscript{22} Elimination of the internal hydrogen bond by \(\text{i-PrOH}\) has been postulated as the origin of this change in reactivity.\textsuperscript{23} Enamides \textbf{19} and \textbf{20} were fully converted and the e.e.’s were good to excellent (entries 5 and 6). As expected, the imines \textbf{21} and \textbf{22} were not converted. Although carbamate \textbf{23} was hardly converted, the selectivity was negligible.

This initial study revealed that \textbf{L20} is comparable to MonoPhos\textsuperscript{TM} (\textbf{L11}) with respect to selectivity in the hydrogenation of \(\alpha\)-amino acid precursors. In the hydrogenation of enamides, however, higher enantioselectivities are observed with a remarkable 99% e.e. for the hydrogenation of \textbf{20}\.\textsuperscript{13,14} Later results revealed that PipPhos (\textbf{L21}) gives in most cases almost perfect selectivity for the \(\alpha\)-amino acid precursors as well as the enamides.\textsuperscript{17a} So far no good results have been obtained for the hydrogenation of imines with monodentate phosphoramidites. Monodentate secondary phosphine oxides, on the other hand, have proved to be much more successful (see also chapter 1).\textsuperscript{24} The results with
Catechol-based Phosphoramidites

carbamate 23 are comparable to those obtained with MonoPhos\textsuperscript{TM} (L11). It appeared that specifically in the hydrogenation of the carbamate the structure of the phosphoramidite is crucial. Introduction of a six-membered ring at the amine moiety raised the rate of the reaction as well as the enantioselectivity.\textsuperscript{25} With these results in hand we decided to screen series of enamides.

Table 2.2 : Asymmetric hydrogenation of a variety of substrates catalyzed by Rh-phosphoramidite (L20) catalyst.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Conversion \textsuperscript{a,b}</th>
<th>E.e. \textsuperscript{c,d}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>16</td>
<td>24</td>
<td>100</td>
<td>89</td>
</tr>
<tr>
<td>2</td>
<td>17</td>
<td>25</td>
<td>100 (&gt;99)</td>
<td>66</td>
</tr>
<tr>
<td>3</td>
<td>18</td>
<td>26</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>4\textsuperscript{e}</td>
<td>18</td>
<td>26</td>
<td>40</td>
<td>80</td>
</tr>
<tr>
<td>5</td>
<td>19</td>
<td>27</td>
<td>100 (&gt;98)</td>
<td>89</td>
</tr>
<tr>
<td>6</td>
<td>20</td>
<td>28</td>
<td>100 (&gt;99)</td>
<td>99</td>
</tr>
<tr>
<td>7</td>
<td>21</td>
<td>29</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>22</td>
<td>30</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>23</td>
<td>31</td>
<td>33</td>
<td>6</td>
</tr>
</tbody>
</table>

\textsuperscript{a) Reactions performed under standard conditions; b) Conversions determined by \textsuperscript{1}H-NMR, no side products were observed in addition to product and/or starting material, isolated yields between brackets; c) E.e.’s determined by chiral GC or HPLC (CP Chiralsil-L-Val, CP Chiralsil-Dex CB, Chiralcel OD); d) All products had the R configuration e) Reaction was performed in i-PrOH.
2.3.3 Synthesis of enamides

The substrates were synthesized, starting from the corresponding oxims,\textsuperscript{26} using methods developed by Zhang\textsuperscript{7b} and Burk (Scheme 2.3).\textsuperscript{27, 28} Although easy synthesis and high yields are claimed, the purification of the compounds is not straightforward. For most compounds extensive column chromatography, washing and recrystallization was needed.

\begin{equation}
\begin{array}{c}
\text{R}^1\text{O} \text{N} \text{OH} \\
\text{EtOH, pyridine} \\
(73-95\%) \\
\end{array}
\end{equation}

\textbf{Scheme 2.3:} Synthesis of enamides.

In no case the reported yields could be reproduced. Substrate 54 was obtained as a 3:2 mixture of E- and Z-isomers which could be separated by column chromatography. Substrate 58 could be made in a one step procedure from the corresponding ketone with p-toluenesulfonic acid and acetamide in good yields.\textsuperscript{29} This method did not work for other substrates as no conversion was observed.
2.3.4 Asymmetric hydrogenations of enamides with a Rh-phosphoramidite (L20) complex

The series of enamides was screened in two solvents at 5 and 25 bar of hydrogen pressure to examine the scope of the asymmetric hydrogenation. The results are depicted in Table 2.3.

Table 2.3: Results of the asymmetric hydrogenation of enamides with Rh-Phosphoramidite (L20) complex.\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>E.e. (^b) CH(_2)Cl(_2) 5 bar</th>
<th>E.e. (^b) CH(_2)Cl(_2) 25 bar</th>
<th>E.e. (^b) EtOAc 25 bar</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>49</td>
<td>59</td>
<td>63</td>
<td>70</td>
<td>26</td>
</tr>
<tr>
<td>2</td>
<td>50</td>
<td>60(^c)</td>
<td>92</td>
<td>93</td>
<td>96.5</td>
</tr>
<tr>
<td>3</td>
<td>51</td>
<td>61</td>
<td>95</td>
<td>94</td>
<td>97</td>
</tr>
<tr>
<td>4</td>
<td>52</td>
<td>62</td>
<td>97</td>
<td>97</td>
<td>97</td>
</tr>
<tr>
<td>5</td>
<td>19</td>
<td>27</td>
<td>89</td>
<td>&gt;99</td>
<td>&gt;99</td>
</tr>
<tr>
<td>6</td>
<td>20</td>
<td>28</td>
<td>99</td>
<td>&gt;99</td>
<td>&gt;99</td>
</tr>
<tr>
<td>7</td>
<td>53</td>
<td>28</td>
<td>90</td>
<td>88</td>
<td>80</td>
</tr>
<tr>
<td>8</td>
<td>54(^e)</td>
<td>28</td>
<td>92</td>
<td>93</td>
<td>84</td>
</tr>
<tr>
<td>9</td>
<td>55</td>
<td>63</td>
<td>9 (3.5)</td>
<td>20 (6)</td>
<td>&lt;3 (14)</td>
</tr>
<tr>
<td>10</td>
<td>56</td>
<td>64</td>
<td>35 (48)</td>
<td>35 (95)</td>
<td>27</td>
</tr>
<tr>
<td>11</td>
<td>58</td>
<td>65</td>
<td>4 (14)</td>
<td>9 (38)</td>
<td>35 (40)</td>
</tr>
</tbody>
</table>

\(^a\) Reactions performed in 4 mL solvent with 0.2 mmol substrate and 1 mol% of catalyst at RT under a H\(_2\) atmosphere for 16 h; \(^b\) Conversions determined by \(^1\)H-NMR, no side products were observed in addition to product and/or starting material; \(^c\) E.e.’s determined by chiral GC (CP Chiralsil-Dex CB); \(^d\) Conversions are between brackets if reactions were not run to completion; \(^e\) In all cases the \(R\) configuration of the product was obtained, except for products 65 and 59; \(^f\) Isolated yield for 60 was >99%; \(^g\) A mixture with a 3:2 ratio of \(E\) and \(Z\) alkene was used.

With the exception of 55, containing a tetrasubstituted alkene, and the bicyclic systems 56 and 58 (entries 9-11, column 4, Table 2.3), all substrates gave full conversion. The enantioselectivity is lower when \(R\) is an alkyl group instead of an aryl group, (compare entries 1 and 2, column 4). This can be due to an increase of steric hindrance, although this seems to be a common feature of this catalytic system, since similar results were observed in the hydrogenation of the \(\alpha\)-amino acid precursors (compare entry 9, Table 2.1 and entry 2, Table 2.2). Favorable \(\pi\)-\(\pi\) interactions between the aromatic moiety of the substrate and the ligand might be another reason for this observation. Different substituents on the aromatic ring seem to have hardly any influence on the enantioselectivity (entries 2-
Chapter 2

5, column 4). Tri-substituted alkenes gave good to excellent enantioselectivities. The best results were obtained with enamides with a Z-configuration (entries 6 and 7, column 4) while an E/Z mixture gave the calculated average of the enantioselectivities for both isomers (entry 8, column 4). Tetra-substituted alkenes and bicyclic systems are not suitable substrates for this new catalytic system. Low conversions and moderate enantioselectivities were obtained (entries 9-11, column 4). High enantioselectivities for these substrates have been obtained with a variety of bidentate phosphines. Reasonable enantioselectivities for alkene 56 were obtained using MonoPhos™ (L11) at –20°C.31

An increase of the pressure to 25 bar had no influence on the enantioselectivity although the conversion did increase. Only in the case of the tetra-substituted alkene and the bicyclic systems derived from β-tetralone the e.e. increased (entries 9 and 11).

The use of EtOAc as solvent resulted in higher enantioselectivities for most of the substrates (Table 2.3, column 6). Surprisingly, the only exceptions are those with R₁ is a t-Bu group (entry 1) or when R₃ (Scheme 2.3) is not hydrogen (entries 7-10).

2.4 Catechol-based monodentate phosphoramidites in the copper-catalyzed conjugate addition of diethylzinc to cyclohexenone

Ligand L12 has been reported to induce 78% e.e. in the copper-catalyzed conjugate addition of Et₂Zn to cyclohexenone (66).18 Ligands L13-L20 were also tested in this reaction. The results are depicted in Table 2.4.

The results from Table 2.4 show that the bulkiness of the ligand is very important. Decreasing the size of the amine in the ligands lowers the e.e. dramatically.

‡ Reactions were run overnight, although in most cases reactions were completed in 4 h at 5 bar and in 2 h at 25 bar of hydrogen pressure.
2.5 A new series of catechol-based phosphoramidites

2.5.1 Synthesis of ligands L22-26

With these results in hand, a new series of catechol-based monodentate phosphoramidites was prepared. Ligand L22, with two \(n\)-propyl substituents on the catechol moiety, was synthesized to investigate the influence of steric hindrance due to alkyl groups at the ortho-positions. Catechol (68) was reacted with 2 equivalents of allyl bromide to form the corresponding diallylether (69). The diallylether was subsequently rearranged to form 70 in only 23% yield. In addition to the desired product, a mixture of side-products was obtained, the composition of which has not been identified. Reduction of the double bonds of the allyl moieties with \(H_2\) and 10% Pd/C yielded 71 quantitatively (Scheme 2.4).
Chapter 2

Scheme 2.4: Synthesis of 71.

\[ \text{L22 could be synthesized by refluxing 71 in PCl}_3 \text{ to provide the corresponding phosphorochloridite (not shown) (Scheme 2.5). The phosphorochloridite was reacted with amine 13 in the presence of Et}_3\text{N to provide L22 in a very low 2.5% yield (not optimized). The low yield is mainly caused by decomposition of L22 on the column during chromatographic purification.} \]

Scheme 2.5: Synthesis of L22.

A series of ligands based on proline esters was synthesized, as an alternative to the rather difficult to synthesize cyclic amine 13 (Scheme 2.6). Amines 72-75 could be synthesized in a one pot procedure from the commercially available (S)-proline by a literature procedure.34 Ligands L23-L26 were synthesized according the procedure described in Scheme 2.2 in 30-60% yield. $^{31}$P-NMR spectra showed single peaks in the range of 140-150 ppm, typically for phosphoramidites. Additional information was obtained by mass spectroscopy and $^1$H- and $^{13}$C-NMR spectroscopy.
A difference between L20 and L23-L26 is the degree of symmetry. L20 based on catechol and symmetrical 2,5-disubstituted pyrolidine is C2-symmetric, while L23-L26 are based on non-symmetrical proline esters which makes these ligands C1-symmetric.

![Scheme 2.6: Synthesis of ligands L23-L26.](image)

**2.5.2 Hydrogenation of benchmark substrates using L22-L26 as ligands**

Monodentate phosphoramidites L22-L26 were tested in the rhodium-catalyzed asymmetric hydrogenation of a set of 4 benchmark substrates *i.e.*, 14, 17, 50 and 76 (*vide infra*). The reactions were run at 10 bar of hydrogen pressure with 1 mol % of catalyst for 16h. The results are depicted in Table 2.5.

Introduction of *n*-propyl groups on the catechol moiety decreases the enantioselectivity as well as the conversion (compare entry 9, Table 2.1; entry 2, Table 2.2; entry 2, Table 2.3 vs. entry 1, Table 2.5). The *e.e.*’s obtained for the hydrogenation of substrate 76 with ligands L22-L26 are very low. In all cases incomplete conversion was obtained (entries 1-5, Table 2.5). The enantioselectivities obtained in the hydrogenation of amino acid derivatives 14 and 17 with ligands L23-L26 are rather poor compared to the results obtained with L20 (entries 2-5, Table 2.5 vs. entry 9, Table 2.1; entry 2, Table 2.2). The best results with L23-L26 were obtained in
the hydrogenation of enamide 50, although the enantioselectivities are still lower than those with L20 (entries 2-5, Table 2.5 vs. entry 2, Table 2.3).

**Table 2.5**: Rh-catalyzed asymmetric hydrogenation with L22-L26.a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>E.e. after hydrogenation of substrateb,c,d,e</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>L22</td>
<td>18 (19) 20 (45) 14 (22) 7 (17)</td>
</tr>
<tr>
<td>2</td>
<td>L23</td>
<td>27 42 69 3 (45)</td>
</tr>
<tr>
<td>3</td>
<td>L24</td>
<td>38 3 65 15 (43)</td>
</tr>
<tr>
<td>4</td>
<td>L25</td>
<td>6 22 69 7 (54)</td>
</tr>
<tr>
<td>5</td>
<td>L26</td>
<td>35 31 60 12 (50)</td>
</tr>
</tbody>
</table>

a) Reactions performed in 4 mL solvent with 0.2 mmol substrate and 1 mol% of catalyst at RT under a H2 atmosphere of 10 bar for 16 h b) Conversions determined by 1H-NMR, besides product and/or starting material no side products were observed c) E.e.’s determined by chiral GC d) Conversions are between brackets if reactions were not run to completion e) In all cases the R enantiomer was obtained, except for product of substrate 76.

The size of the R-group (Scheme 2.6) has hardly any influence on the enantioselectivity of the hydrogenation products. Neither does the introduction of additional stereocenters as in L25 and L26 have a significant effect. The e.e. of the products is mainly defined by the stereocenter of proline, since no pronounced matched/missmatched effect has been observed and the absolute configuration of the products is the same for hydrogenations performed with L25 and L26.
2.6 Conclusion

In this chapter a successful synthesis of catechol-based monodentate phosphoramidites has been described. These ligands showed good results in the rhodium-catalyzed asymmetric hydrogenation of a variety of pro-chiral alkenes. In particular, ligand L20, based on catechol and enantiopure trans-2,5-diphenylpyrrolidine, showed excellent results in the hydrogenation of enamides. Up to 99% of e.e. has been reached in the asymmetric hydrogenation of 20. L20, together with L21, are among the best ligands reported so far for the enantioselective hydrogenation of enamides. 14,17a

The catechol-based ligands have also been tested in the Cu-catalyzed conjugate addition of diethylzinc. Modest e.e.’s have been obtained. The best ligand was L12, which induced an e.e. of 78%.

2.7 Experimental section

General remarks:

All reactions were performed in a dry argon atmosphere using standard Schlenk techniques. Et₂O (Na), CH₂Cl₂ (CaH), EtOAc (boiling chips), toluene (Na) and pentane (boiling chips) were distilled before use. Substrate 14 was made according a literature procedure. Substrates 17 and 76 are commercially available. Michel van den Berg is gratefully acknowledged for substrate 16. Diego Peña is gratefully acknowledged for substrate 18. Xiao-Bin Jiang is gratefully acknowledged for substrates 21-23. Leggy Arnold is gratefully acknowledged for ligand L12 and amines 7 and 8. Amines 8, 9, 11-13 and 72-75 were made according literature procedures. Amine 10 is commercially available. Ketones 32-39 were commercially available.

¹H-NMR, ¹³C-NMR and ³¹P-NMR spectra were recorded on a Varian Gemini-200, Varian VXR-300 or a Varian Mercuri Plus. Chemical shifts are reported in δ units (ppm) relative to the residual deuterated solvent signals of CHCl₃ (¹H-NMR: δ 7.26; ¹³C-NMR: δ 77.0); DMSO (¹H-NMR: δ 2.49; ¹³C-NMR: δ 39.5) or relative to an external standard for ³¹P (H₃PO₄ at δ 0.0). The splitting patterns are designated as follows: s (singlet), d (doublet), t (triplet), q (quartet), b (broad). Optical rotations were measured with a Perkin Elmer 241 polarimeter. Column chromatography was performed using silica gel (Aldrich 60, 230-400 mesh). Mass spectra (HRMS) were recorded on an AEI MS-902.
General procedure for the synthesis of the ligands:

To a solution of 1.5 g (8.60 mmol) of o-phenylenephosphorochloridite (4) and 0.87 g (8.60 mmol) of Et3N in 5 ml of Et2O was added a solution of 8.60 mmol of the appropriate amine in 5 ml Et2O at 0°C. This suspension was warmed to RT and stirred for 1.5 h. The reaction mixture was filtered over Celite. The filtrate was concentrated. The ligand was purified by filtration over a short plug of silica gel (eluents n-pentane:EtOAc 10:1).

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\text{(S,S)-Benzo}[1,3,2]\text{dioxaphosphol-2-yl-bis-(1-phenyl-ethyl)-amine (L12): White solid.} 1^H\text{-NMR} (200 MHz, CDCl}_3 \delta = 7.26-7.14 \text{ (m, 12H)}, 7.01-6.98 \text{ (m, 2H)}, 4.45 \text{ (m, 2H)}, 1.79 \text{ (dd, } J = 1.8 \text{ Hz, 7.1 Hz, 6H}); 13C\text{-NMR} (50.32 MHz, CDCl}_3 \delta = 146.8, 142.0, 129.1, 127.9, 127.7, 126.7, 126.9, 121.7, 53.3, 53.0, 22.4, 22.2; 31P\text{-NMR} (81 MHz, CDCl}_3 \delta = 151.9; \text{HRMS} \text{ calcd. for C}_{22}H_{22}NO_2P 363.138 found 363.138; [\alpha]_D^{20} = -264° \text{ (c= 0.79, CHCl}_3).\]

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\text{(S)-Benzo}[1,3,2]\text{dioxaphosphol-2-yl-benzyl-(1-phenyl-ethyl)-amine (L13): The ligand was obtained as a colorless sticky oil in 25% yield.} 1^H\text{-NMR} (200 MHz, CDCl}_3 \delta = 7.35-7.13 \text{ (m, 10H)}, 6.96-6.78 \text{ (m, 4H)}, 4.34-4.29 \text{ (m, 1H)}, 3.69 \text{ (ddd, } J = 6.8 \text{ Hz, 15.7 Hz, 33.8 Hz, 2H)}, 1.43 \text{ (dd, } J = 1.8 \text{ Hz, 7.1 Hz, 3H}); 13C\text{-NMR} (50.32 MHz, CDCl}_3 \delta = 146.7, 146.6, 146.5, 146.3, 141.9, 138.4, 128.5, 128.3, 128.1, 127.3, 127.2, 121.7, 111.4, 56.2, 55.9, 47.2, 47.1, 22.3, 22.1; 31P\text{-NMR} (81 MHz, CDCl}_3 \delta = 146.1; \text{HRMS} \text{ calcd. for C}_{22}H_{22}NO_2P 349.123 found 349.122; [\alpha]_D^{20} = -21° \text{ (c= 1.17, CHCl}_3).\]

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\text{(S)-Benzo}[1,3,2]\text{dioxaphosphol-2-yl-isopropyl-(1-phenyl-ethyl)-amine (L14): The ligand was obtained as a colorless sticky oil in 37% yield.} 1^H\text{-NMR} (200 MHz, CDCl}_3 \delta = 7.42-7.22 \text{ (m, 5H)}, 7.04-6.95 \text{ (m, 2H)}, 6.90-6.81 \text{ (m, 2H)}, 4.43-4.37 \text{ (m, 1H)}, 3.18-3.05 \text{ (m, 1H)}, 1.54 \text{ (dd, } J = 0.5 \text{ Hz, 7.1 Hz, 3H)}, 1.35 \text{ (d, } J = 6.8 \text{ Hz, 3H}), 0.96 \text{ (d, } J = 6.8 \text{ Hz, 3H}); 13C\text{-NMR} (50.32 MHz, CDCl}_3 \delta = 146.7, 128.2, 127.6, 127.0, 121.6, 111.4, 52.5, 52.4, 46.5, 46.1, 26.3, 26.1, 25.1, 24.9, 20.7, 20.6; 31P\text{-NMR} (81 MHz, CDCl}_3 \delta = 152.5; \text{HRMS} \text{ calcd. for C}_{17}H_{20}NO_2P 301.123 found 301.123; [\alpha]_D^{20} = +214° \text{ (c= 1.02, CHCl}_3).\]
(S)-Benzo[1,3,2]dioxaphosphol-2-yl-ethyl-(1-phenyl-ethyl)-amine (L15): The ligand was obtained as a colorless sticky oil in 36% yield. \(^1\)H-NMR (200 MHz, CDCl\(_3\)) \(\delta = 7.45-7.28\) (m, 5H), 7.06-6.89 (m, 4H), 4.73-4.65 (m, 1H), 2.79-2.64 (m, 2H), 1.69 (dd, \(J = 1.6\) Hz, 7.2 Hz, 3H), 0.89 (t, \(J = 7.1\) Hz, 3H); \(^{13}\)C-NMR (50.32 MHz, CDCl\(_3\)) \(\delta = 146.7, 146.6, 146.4, 142.3, 142.3, 128.4, 127.1, 121.6, 111.2, 55.7, 55.1, 37.2, 37.1, 21.5, 21.2, 17.0, 16.9; \(^{31}\)P-NMR (81 MHz, CDCl\(_3\)) \(\delta = 149.5\); HRMS calcd. for C\(_{16}\)H\(_{18}\)NO\(_2\)P 287.108 found 287.108; \([\alpha]_D^{20} = -65^\circ\) (c= 1.36, CHCl\(_3\)).

(S)-Benzo[1,3,2]dioxaphosphol-2-yl-methyl-(1-phenyl-ethyl)-amine (L16): The ligand was obtained as a colorless sticky oil in 44% yield. \(^1\)H-NMR (200 MHz, CDCl\(_3\)) \(\delta = 7.42-7.26\) (m, 5H), 7.05-6.97 (m, 2H), 6.94-6.87 (m, 2H), 4.79-4.71 (m, 1H), 2.20 (d, \(J = 6.1\) Hz, 3H), 1.59 (dd, \(J = 0.6\) Hz, 7.0 Hz, 3H); \(^{13}\)C-NMR (50.32 MHz, CDCl\(_3\)) \(\delta = 146.7, 141.0, 128.4, 127.1, 121.6, 111.1, 55.0, 54.4, 26.2, 26.1, 18.8, 18.6; \(^{31}\)P-NMR (81 MHz, CDCl\(_3\)) \(\delta = 147.0\); HRMS calcd. for C\(_{15}\)H\(_{16}\)NO\(_2\)P 273.092 found 273.091; \([\alpha]_D^{20} = -28^\circ\) (c= 1.09, CHCl\(_3\)).

(S)-Benzo[1,3,2]dioxaphosphol-2-yl-(1-phenyl-ethyl)-amine (L17): The ligand was obtained as a colorless sticky oil in 38% yield. \(^1\)H-NMR (200 MHz, CDCl\(_3\)) \(\delta = 7.36-6.78\) (m, 9H), 4.21-4.06 (m, 1H), 3.84 (m, 1H), 1.86 (d, \(J = 6.8\) Hz, 3H); \(^{13}\)C-NMR (50.32 MHz, CDCl\(_3\)) \(\delta = 146.0, 144.5, 128.3, 126.9, 125.6, 121.8, 121.7, 111.6, 11.3, 50.0, 25.2, 25.2; \(^{31}\)P-NMR (81 MHz, CDCl\(_3\)) \(\delta = 137.6\); HRMS calcd. for C\(_{14}\)H\(_{14}\)NO\(_2\)P 259.076 found 259.077; \([\alpha]_D^{20} = -205^\circ\) (c= 1.27, CHCl\(_3\)).

(R,R)-N,N'-Bis-benzo[1,3,2]dioxaphosphol-2-yl-N,N'-bis-(1-phenyl-ethyl)-ethane-1,2-diamine (L18): The ligand was obtained as a colorless sticky oil in 21% yield. \(^1\)H-NMR (200 MHz, CDCl\(_3\)) \(\delta = 7.40-7.15\) (m, 10H), 7.00-6.84 (m, 8H), 4.24-4.13 (m, 2H), 2.74-2.43 (m, 4H), 1.26 (d, \(J = 7.1\) Hz, 6H); \(^{13}\)C-NMR (50.32 MHz, CDCl\(_3\)) \(\delta = 146.6, 141.7, 128.3, 127.2, 121.8, 111.5, 111.3, 55.2, 54.8, 44.5, 44.3, 20.5, 20.3; \(^{31}\)P-NMR (81 MHz, CDCl\(_3\)) \(\delta = 150.1\); HRMS calcd. for C\(_{30}\)H\(_{30}\)N\(_2\)O\(_4\)P\(_2\) 544.168 found 544.168; \([\alpha]_D^{20} = -125^\circ\) (c= 1.06, CHCl\(_3\)).

(S,S)-N,N'-Bis-benzo[1,3,2]dioxaphosphol-2-yl-N,N'-bis-(1-phenyl-ethyl)-propane-1,3-diamine (L19): The ligand was obtained as a colorless sticky oil in 29% yield. \(^1\)H-NMR (200 MHz, CDCl\(_3\)) \(\delta = 7.43-7.25\) (m, 10H), 7.00-6.82
Chapter 2

(S,S)-1-Benzof[1,3,2]dioxaphosphol-2-yl-2,5-diphenylpyrrolidine (L20): The ligand was obtained as colorless crystals in 46% yield. $^1$H-NMR (200 MHz, CDCl$_3$) $\delta$ = 7.26-7.11 (m, 10H), 6.97 (d, $J$ = 7.7 Hz, 1H), 6.75 (dt, $J$ = 1.1 Hz, 7.7 Hz, 1H), 6.51 (dt, $J$ = 1.1 Hz, 7.7 Hz, 1H), 5.95 (d, $J$ = 7.7 Hz, 2H), 2.36-2.25 (m, 2H), 1.67-1.57 (m, 2H); $^{13}$C-NMR (50.32 MHz, CDCl$_3$) $\delta$ = 146.9, 128.1, 126.8, 126.1, 121.6, 121.2, 111.5, 110.3, 63.2, 63.1, 33.7; HRMS calcd. for C$_{22}$H$_{20}$NO$_2$P: 361.122 found 361.123; Anal. Calc. for C$_{22}$H$_{20}$NO$_2$P: C, 73.12 %; H, 5.58 %; N, 3.88 %, found: C, 73.09 %; H, 5.58 %; N, 3.89 %; [α]$_D^{20}$ = -104° (c = 0.79, CHCl$_3$).

General procedure for the synthesis of oximes:

A mixture of 10 g ketone and 10 g (144 mmol) hydroxylamine (HCl salt) in 100 ml EtOH and 10 ml pyridine was refluxed overnight. The reaction mixture was concentrated and poured into 100 ml ice/water. The cooled (0°C) mixture was stirred for 45 min and filtered. The white precipitate was dissolved in 100 ml EtOAc and dried over Na$_2$SO$_4$. The mixture was filtered and concentrated to yield the corresponding oxime in 73-95% yield. The product was used in the next step without any purification.

1-(4-Chloro-phenyl)-ethanone oxime (40): The oxime was obtained as a white solid in 92% yield. $^1$H-NMR (200 MHz, CDCl$_3$) $\delta$ = 9.58 (bs, 1H), 7.56 (d, $J$ = 9.0 Hz, 2H), 7.36 (d, $J$ = 9.0 Hz, 2H), 2.29 (s, 3H); $^{13}$C-NMR (50.32 MHz, CDCl$_3$) $\delta$ = 155.1, 135.3, 128.7, 127.3, 127.3, 127.3, 12.2; HRMS calcd. for C$_8$H$_8$ClNO: 162.029 found 162.028.

3,3-Dimethyl-butan-2-one oxime (41): The oxime was obtained as a white solid in 73% yield. $^1$H-NMR (200 MHz, CDCl$_3$) $\delta$ = 9.39 (bs, 1H), 1.88 (s, 3H), 1.13 (s, 3H); $^{13}$C-NMR (50.32 MHz, CDCl$_3$) $\delta$ = 163.9, 37.2, 27.4, 10.0; MS m/z 116 (M+1), 133.

1-Phenyl-ethanone oxime (42): The oxime was obtained as a white solid in 95% yield. $^1$H-NMR (200 MHz, CDCl$_3$) $\delta$ = 10.09 (bs, 1H), 7.72-7.63 (m, 2H), 7.49-7.35 (m, 3H), 2.36 (s, 3H); $^{13}$C-NMR (50.32 MHz, CDCl$_3$) $\delta$ = 155.9, 136.4, 129.2, 128.5,
Catechol-based Phosphoramidites

126.0, 12.4; HRMS calcd. for C₈H₉NO 135.068 found 135.069.

1-(4-Chloro-phenyl)-ethanone oxime (43): The oxime was obtained as a white solid in 94% yield. ¹H-NMR (200 MHz, CDCl₃) δ = 9.42 (bs, 1H), 7.48 (d, J = 8.1 Hz, 2H), 7.15 (d, J = 8.1 Hz, 2H), 2.33 (s, 3H), 2.25 (s, 3H); ¹³C-NMR (50.32 MHz, CDCl₃) δ = 155.7, 139.1, 133.5, 129.1, 125.8, 21.1, 12.2; HRMS calcd. for C₉H₁₁NO 149.084 found 149.085.

1-(4-Methoxy-phenyl)-ethanone oxime (44): The oxime was obtained as a white solid in 75% yield. ¹H-NMR (200 MHz, CDCl₃) δ = 10.01 (bs, 1H), 7.60 (d, J = 9.0 Hz, 2H), 6.92 (d, J = 9.0 Hz, 2H), 3.82 (s, 3H), 2.30 (s, 3H); ¹³C-NMR (50.32 MHz, CDCl₃) δ = 160.4, 155.3, 128.9, 127.3, 113.8, 55.2, 12.2; HRMS calcd. for C₉H₁₁NO₂ 165.079 found 165.081.

1-Phenyl-butan-1-one oxime (45): The oxime was obtained as a white solid in 95% yield. ¹H-NMR (200 MHz, CDCl₃) δ = 8.92 (bs, 1H), 7.57-7.54 (m, 2H), 7.37-7.21 (m, 3H), 2.75 (t, J = 7.7 Hz, 2H), 1.63-1.47 (m, 2H), 0.94 (t, J = 7.3 Hz, 3H); ¹³C-NMR (50.32 MHz, CDCl₃) δ = 159.4 (s), 135.8 (s), 129.0 (d), 128.4 (d), 126.2 (d), 28.1 (t), 19.7 (t), 14.2 (q); HRMS calcd. for C₁₀H₁₃NO 163.100 found 163.105.

2-Methyl-1-phenyl-propan-1-one oxime (46): The oxime was obtained as a white solid in 79% yield as an 1:1 mixture of syn and anti isomers. ¹H-NMR (200 MHz, CDCl₃) δ = 8.92 (bs, 1H), 7.45-7.21 (m, 10H), 3.56 (m, 1H), 2.80 (m, 1H), 1.18 (d, J = 7.0 Hz, 6H), 1.14 (d, J = 7.0 Hz, 6H); ¹³C-NMR (50.32 MHz, CDCl₃) δ = 164.539, 162.9, 135.6, 133.6, 128.4, 128.3, 128.0, 127.6, 127.4, 34.4, 27.6, 20.0, 19.2; HRMS calcd. for C₁₀H₁₃NO 163.100 found 163.105.

3,4-Dihydro-2H-naphthalen-1-one oxime (47): The oxime was obtained as a brown solid in 92% yield. ¹H-NMR (400 MHz, CDCl₃) δ = 10.0 (bs, 1H), 7.89 (d, J = 7.7 Hz, 1H), 7.29-7.19 (m, 2H), 7.15 (d, J = 7.3 Hz, 1H), 2.86 (t, J = 6.5 Hz, 2H), 2.75 (t, J = 6.0 Hz, 2H), 1.86 (m, 2H); ¹³C-NMR (50.32 MHz, CDCl₃) δ = 155.2 (s), 139.8 (s), 130.3 (s), 129.2 (d), 128.6 (d), 126.4 (d), 123.9 (d), 29.7 (t), 23.9 (t), 21.2 (t); HRMS calcd. for C₁₀H₁₁NO 161.084 found 161.086.
Chapter 2

General procedure for the synthesis of enamides:

Method A: A mixture of 55.6 mmol of oxime, 12 ml (166 mmol) acetic anhydride, 6.2 g (111 mmol) Fe-powder (325 mesh) and 9.5 ml (166 mmol) acetic acid in 40 ml toluene was stirred for 4 h at 70°C. The mixture was cooled and filtered through Celite® and the residue was washed with toluene. The filtrates were washed with 2M NaOH (aq), dried over Na₂SO₄, filtered and concentrated. The crude enamides were purified by column chromatography and thoroughly washing with hexane.

Method B: A mixture of 13.2 mmol oxime, 2.20 g (39.4 mmol) Fe-powder (325 mesh) and 0.95 ml (16.6 mmol) acetic anhydride in 100 ml DMF was stirred at RT for 6 h. The reaction was initiated by a few drops of TMSCl. The reaction mixture was diluted with water and extracted with 200 ml of ether. The organic layer was washed with water (2x 200 ml), brine (1x 200 ml), dried over Na₂SO₄, filtered and concentrated. The crude enamides were purified by column chromatography and thoroughly washing with hexane.

\( N-[1-(4\text{-Chloro-phenyl}-\text{vinyl})-\text{acetamide} \quad (19) \): The enamide was obtained as a white solid in 17% yield. \( ^1\text{H-NMR} \) (200 MHz, CDCl₃) \( \delta = 7.32-7.28 \text{ (m, 5H)}, 5.71 \text{ (s, 1H)}, 5.07 \text{ (s, 1H)}, 2.06 \text{ (s, 3H)} \); \( ^{13}\text{C-NMR} \) (50.32 MHz, CDCl₃) \( \delta = 169.5 \text{ (s)}, 139.6 \text{ (s)}, 136.5 \text{ (s)}, 136.3 \text{ (s)}, 128.6 \text{ (d)}, 127.3 \text{ (d)}, 103.6 \text{ (t)}, 24.2 \text{ (q)}; \text{ HRMS calcd. for } C_{10}H_{10}ClNO 195.045 \text{ found 195.044.} \)

\( N-(1\text{-Phenyl-but-1-etyl})-\text{acetamide} \quad (20) \): The Z-isomer was isolated from a 3:2 mixture of E- and Z-isomers by column chromatography. (SiO₂, pentane / EtOAc, 4:1), \( R_f = 0.13 \). The Z-enamide was obtained as a white solid in a 3:1 mixture of rotamers in 21% yield. \( ^1\text{H-NMR} \) (200 MHz, CDCl₃) \( \delta = 7.41-7.19 \text{ (m, 5H)}, 7.10 \text{ (bs, 0.75H)}, 6.89 \text{ (bs, 0.25H)}, 5.93 \text{ (t, } J = 7.6 \text{ Hz, 0.25H}), 5.80 \text{ (t, } J = 7.1 \text{ Hz, 0.75H}), 2.31-2.09 \text{ (m, 2H)}, 2.08 \text{ (s, 2.25H)}, 1.76 \text{ (s, 0.75H)}, 1.11 \text{ (t), 2.25H)}, 1.61 \text{ (t), 1.01 (m, 3H)}; \text{ HRMS calcd. for } C_{12}H_{15}NO 189.115 \text{ found 189.116.} \)

\( N-(2,2\text{-Dimethyl-1-methylene-propyl})-\text{acetamide} \quad (49) \): The enamide was obtained as colorless crystals in 36% yield. \( ^1\text{H-NMR} \) (300 MHz, CDCl₃) \( \delta = 6.38 \text{ (bs, 1H)}, 5.61 \text{ (s, 1H)}, 4.79 \text{ (s, 1H)}, 2.08 \text{ (s, 3H)}, 1.11 \text{ (s, 9H)}; \text{ HRMS calcd. for } C_{8}H_{15}NO 141.115 \text{ found 141.115.} \)
**N-(1-Phenyl-vinyl)-acetamide (50):** The enamide was obtained as a white solid in 17% yield. $^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ = 7.38 (m, 5H), 7.06 (bs, 1H), 5.83 (s, 1H), 5.08 (s, 1H), 2.08 (s, 3H); $^{13}$C-NMR (50.32 MHz, CDCl$_3$) $\delta$ = 169.5, 140.6, 138.0, 128.3, 125.9, 102.7, 24.0; HRMS calcd. for C$_{10}$H$_{11}$NO 161.084 found 161.088.

**N-(1-p-Tolyl-vinyl)-acetamide (51):** The enamide was obtained as a white solid in 44% yield. $^1$H-NMR (200 MHz, CDCl$_3$) $\delta$ = 7.31 (d, $J$ = 8.1 Hz, 2H), 7.20 (d, $J$ = 8.1 Hz, 2H), 6.99 (bs, 1H), 5.79 (s, 1H), 5.05 (s, 1H), 2.35 (s, 3H), 2.09 (s, 3H); $^{13}$C-NMR (50.32 MHz, CDCl$_3$) $\delta$ = 169.1 (s), 140.4 (s), 135.5 (s), 129.2 (d), 125.8 (d), 101.8 (t), 24.4 (q), 21.1 (q); HRMS calcd. for C$_{11}$H$_{13}$NO 175.100 found 175.100.

**N-[1-(4-Methoxy-phenyl)-vinyl]-acetamide (52):** The enamide was obtained as a yellow solid in 39% yield. $^1$H-NMR (200 MHz, CDCl$_3$) $\delta$ = 7.32 (d, $J$ = 8.4 Hz, 2H), 6.95 (bs, 1H), 5.69 (s, 1H), 4.99 (s, 1H), 3.79 (s, 3H), 2.06 (s, 3H); $^{13}$C-NMR (50.32 MHz, CDCl$_3$) $\delta$ = 169.1 (s), 159.8 (s), 140.1 (s), 130.8 (s), 127.2 (d), 113.8 (d), 101.4 (t), 55.2 (q), 24.3 (q); HRMS calcd. for C$_{11}$H$_{13}$NO$_2$ 191.095 found 191.096.

**N-(1-Phenyl-but-1-enyl)-acetamide (53):** The E-isomer was isolated from a 3:2 mixture of E and Z by column chromatography. (SiO$_2$, pentane / EtOAc, 4:1), R$_f$ = 0.0.26. The E-enamide was obtained as a white solid in 28% yield. $^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ = 7.42 (bs, 1H), 7.34-7.23 (m, 5H), 6.11 (t, $J$ = 7.8 Hz, 1H), 2.11-1.96 (m, 2H), 1.76 (s, 3H), 0.96 (t, $J$ = 7.4 Hz, 3H); $^{13}$C-NMR (50.32 MHz, CDCl$_3$) $\delta$ = 167.7, 135.5, 131.9, 127.1, 126.7, 126.3, 120.9, 22.4, 20.0, 13.3; HRMS calcd. for C$_{12}$H$_{15}$NO 189.115 found 189.116.

**N-(2-Methyl-1-phenyl-propenyl)-acetamide (55):** The enamide was obtained as a white solid in 42% yield as a 3:1 mixture of rotamers. $^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ = 7.30-7.14 (m, 5H), 6.91 (bs, 0.75H), 6.86 (bs, 0.25H), 1.94 (s, 2.25H), 1.81 (0.75H), 1.78 (s, 0.75H), 1.74 (s, 0.75H), 1.72 (s, 4.50H), 1.67 (s, 0.75H); $^{13}$C-NMR (50.32 MHz, CDCl$_3$) $\delta$ = 173.8 (s), 168.2(s), 138.7 (s), 130.0 (s), 129.0 (d), 128.1 (d), 127.8 (d), 127.4 (d), 127.0 (d), 23.1 (q), 21.1 (q), 21.0 (q), 20.6 (q); HRMS calcd. for C$_{12}$H$_{15}$NO 189.115 found 189.116.
**N-(3,4,4a,8a-Tetrahydro-naphthalen-1-yl)-acetamide (56):**
Mixture of rotamers (3:1); \( ^1H\)-NMR (400 MHz, CDCl\(_3\)) \( \delta = 7.21-7.11 \ (m, \ 4H), \ 6.76 \ (bs, \ 0.75H), \ 6.65 \ (bs, \ 0.25H), \ 6.46 \ (bt, \ 0.75H), \ 5.97 \ (bt, \ 0.25H), \ 2.87-2.73 \ (m, \ 2H), \ 2.43-2.33 \ (m, \ 2H), \ 2.18 \ (s, \ 0.25H), \ 1.96 \ (s, \ 0.75H); \ ^{13}C\)-NMR (50.32 MHz, CDCl\(_3\)) \( \delta = 169.2 \ (s), \ 136.7 \ (s), \ 131.5 \ (s), \ 127.8 \ (d), \ 127.5 \ (d), \ 126.3 \ (d), \ 120.6 \ (d), \ 119.6 \ (d), \ 27.6 \ (t), \ 24.1 \ (q), \ 22.1 \ (t); \) HRMS calcd. for C\(_{12}\)H\(_{13}\)NO \( 187.100 \) found 187.101.

**N-(3,4,4a,8a-Tetrahydro-naphthalen-2-yl)-acetamide (58):**
A solution of 3.69 g (25.2 mmol) of \( \beta \)-tetralone, 7.45 g (126 mmol) acetamide and 0.96 g (5.04 mmol) \( p \)-toluenesulfonic acid in 150 ml toluene was refluxed under Dean-Stark conditions under an inert atmosphere for 20h. After cooling to RT, 250 ml of saturated NaHCO\(_3\)(aq) was added, and the mixture was warmed to 60°C for 30 min. After cooling to RT, the organic layer was extracted and washed with water (3x 150 ml), dried over Na\(_2\)SO\(_4\), filtered and concentrated. The enamide was purified by column chromatography (SiO\(_2\), ether/pentane (1:2)). The enamide was obtained as a white solid, 3.74g (20.0 mmol; 80%); \( ^1H\)-NMR (300 MHz, CDCl\(_3\)) \( \delta = 7.12-7.02 \ (m, \ 5H), \ 6.61 \ (bs, \ 1H), \ 2.89 \ (dd, \ J = 8.4 \ Hz, 7.7 \ Hz, \ 2H), \ 2.44 \ (dd, \ J = 8.4 \ Hz, 7.7 \ Hz, 2H), \ 2.12 \ (s, \ 3H); \ ^{13}C\)-NMR (50.32 MHz, CDCl\(_3\)) \( \delta = 113.7, \ 100.2, \ 100.0, \ 99.2, \ 96.9, \ 96.8, \ 96.5, \ 96.4, \ 90.7, \ 57.4, \ 57.1, \ 56.0; \) HRMS calcd. for C\(_{12}\)H\(_{13}\)NO \( 187.100 \) found 187.101.

**1,2-Bis-allyloxy-benzene (69):** A solution of 22.0 g (0.20 mol) catechol, 34.8 ml (0.40 mol) allylbromide and 60.8 g (0.45 mol) in 300 ml acetone was refluxed overnight. The reaction mixture was diluted with water and extracted with ether. The combined organic layers were washed with water, 5% NaOH(aq) and dried on Na\(_2\)SO\(_4\). The solution was filtered and concentrated. The product was purified by distillation. Yield 33.1 g (0.17 mol; 85%); \( ^1H\)-NMR (200 MHz, CDCl\(_3\)) \( \delta = 6.92 \ (s, \ 4H), \ 6.11 \ (ddt, \ J = 17.3 \ Hz, 10.5 \ Hz, 5.2 \ Hz, 2H), \ 5.44 \ (ddt, \ J = 10.5 \ Hz, 2.9 \ Hz, 1.5 \ Hz, 2H), \ 5.29 \ (ddt, \ J = 17.3 \ Hz, 3.3 \ Hz, 1.5 \ Hz, 2H), \ 4.62 \ (ddd, \ J = 5.2 \ Hz, 1.5 \ Hz, 1.5 \ Hz, 4H); \ ^{13}C\)-NMR (50.32 MHz, CDCl\(_3\)) \( \delta = 148.5, \ 133.4, \ 121.1, \ 117.4, \ 114.2, \ 69.8; \) HRMS calcd. for C\(_{12}\)H\(_{14}\)O\(_2\) \( 190.099 \) found 190.100.

**3,6-Diallyl-benzene-1,2-diol (70):** 33.1 g (0.17 mol) of 69 was heated at 200°C for 4 h. The dark red reaction mixture was distilled. A yellow oil was obtained at 88-90°C and 0.3 mbar. The oil was purified by column chromatography (SiO\(_2\); CH\(_2\)Cl\(_2\)) to obtain a yellowish oil, which solidified in a white solid after standing. Yield: 7.5 g (39.5 mmol; 23%) \( ^1H\)-NMR (200 MHz, CDCl\(_3\)) \( \delta = 6.70 \ (s, \ 2H), \ 6.13-5.99 \ (m, \ 2H), \ 5.60 \ (bs, \ 2H), \ 5.25-5.17 \ (m,
Catechol-based Phosphoramidites

3,6-Dipropyl-benzene-1,2-diol (71): A mixture of 6.6 g (34.7 mmol) of 70 and 0.73 g 10% Pd/C in 70 ml of EtOH was stirred under H₂ (1 bar) for 2 d. The reaction mixture was filtered and the remaining solution was dried on Na₂SO₄ and concentrated to give a grey solid. Yield: 6.7 g (34.7 mmol: 100%).

1H-NMR (200 MHz, CDCl₃) δ = 6.60 (s, 2H), 5.15 (bs, 2H), 2.50 (t, $J = 7.7$ Hz, 4H), 1.63-1.57 (m, 4H), 0.94 (t, $J = 7.3$ Hz, 6H); 13C-NMR (50.32 MHz, CDCl₃) δ = 141.4, 126.2, 121.0, 31.7, 22.9, 14.0; HRMS calcd. for C₁₂H₁₈O₂ 194.131 found 194.130.

(S,S)-1-(4,7-Dipropyl-benzo[1,3,2]dioxaphosphol-2-yl)-2,5-diphenyl-pyrrolidine (L22): 0.93 g (4.80 mmol) of 71 was refluxed in 5 ml of PCl₃ overnight. The excess PCl₃ was removed by distillation. The resulting oil was dissolved in 5 ml of Et₂O and 0.65 ml (4.80 mmol) Et₃N. To the cooled solution (0°C) was added dropwise a solution of 1.07 g (4.80 mmol) 13 in 5 ml Et₂O. The mixture was stirred for 2h at RT. The suspension was filtered over Celite and the filtrate was concentrated. The remaining oil was purified by column chromatography (Si₄O; pentane:EtOAc 10:1). The obtained solid was recrystallized to give colorless crystals. Yield 55 mg (0.12 mmol; 2.6%).

1H-NMR (200 MHz, CDCl₃) δ = 7.34-7.15 (m, 10H), 6.60 (d, $J = 7.7$ Hz, 1H), 6.38 (d, $J = 7.7$ Hz, 1H), 4.89 (d, $J = 7.1$ Hz, 2H), 2.82-2.60 (m, 2H), 2.39-2.23 (m, 2H), 1.86-1.51 (m, 6H), 1.31-1.13 (m, 2H), 1.07 (t, $J = 7.1$ Hz, 3H), 0.73 (t, $J = 7.3$ Hz, 3H), 0.73 (t, $J = 7.1$ Hz, 3H); 13C-NMR (50.32 MHz, CDCl₃) δ = 145.6, 145.5, 128.9, 128.1, 127.8, 126.7, 126.1, 124.6, 121.8, 121.2, 63.0, 62.9, 62.5, 52.5, 48.0, 33.4, 33.4, 32.0, 30.6, 23.2, 22.1, 18.6, 14.1, 13.9; 31P-NMR (81 MHz, CDCl₃) δ =143.2; HRMS calcd. for C₂₈H₃₂NO₂P 445.217 found 445.216; [α]D₂₀ = -29° (c= 0.43, CHCl₃).

(S)-1-Benzo[1,3,2]dioxaphosphol-2-yl-pyrrolidine-2-carboxylic acid methyl ester (L23): The ligand was obtained as a colorless sticky oil in 30% yield. 1H-NMR (200 MHz, CDCl₃) δ = 7.05-6.87 (m, 4H), 4.28-4.24 (m, 1H), 3.70 (s, 3H), 3.06-2.98 (m, 2H), 2.09-2.01 (m, 2H), 1.84-1.73 (m, 2H); 13C-NMR (50.32 MHz, CDCl₃) δ = 174.1, 145.9, 145.8, 121.8, 121.7, 111.3, 111.1, 59.4, 59.1, 52.3, 44.6, 44.5, 30.7, 30.6, 24.8; 31P-NMR (81 MHz, CDCl₃) δ =141.8; HRMS calcd. for C₁₂H₁₄NO₄P 267.066 found 267.067; [α]D₂₀ = -2° (c= 1.03, CHCl₃).
(S)-1-Benzol[1,3,2]dioxaphosphol-2-yl-pyrrolidine-2-carboxylic acid benzyl ester (L24): The ligand was obtained as a colorless sticky oil in 60% yield. $^1$H-NMR (200 MHz, CDCl$_3$) $\delta = 7.42-7.33$ (m, 5H), 7.05 (dd, $J = 2.4$ Hz, 6.8 Hz, 1H), 6.97-6.87 (m, 3H), 5.19 (d, $J = 12.1$ Hz, 1H), 5.12 (d, $J = 12.1$ Hz, 1H), 4.34-4.30 (m, 1H), 3.12-3.00 (m, 2H), 2.16-2.00 (m, 2H), 1.80-0.88 (m, 2H); $^{13}$C-NMR (50.32 MHz, CDCl$_3$) $\delta = 173.4$, 146.0, 145.9, 145.8, 145.7, 135.4, 128.4, 128.2, 128.1, 121.8, 121.7, 111.2, 111.1, 66.9, 59.4, 59.2, 44.5, 44.4, 30.6, 30.5, 24.6; $^{31}$P-NMR (81 MHz, CDCl$_3$) $\delta = 141.9$; HRMS calcd. for C$_{18}$H$_{18}$NO$_4$P 343.097 found 343.096; $[\alpha]_D^{20} = -4^\circ$ (c= 1.42, CHCl$_3$).

(S,1R,2S,5R)-1-Benzol[1,3,2]dioxaphosphol-2-yl-pyrrolidine-2-carboxylic acid 2-isopropyl-5-methyl-cyclohexyl ester (L25): The ligand was obtained as a colorless sticky oil in 36% yield. $^1$H-NMR (200 MHz, CDCl$_3$) $\delta = 6.97-6.94$ (m, 1H), 6.92-6.89 (m, 1H), 6.84-6.80 (m, 2H), 4.62 (dt, $J = 4.4$ Hz, 10.6 Hz, 1H), 4.21-4.17 (m, 1H), 2.99-2.88 (m, 2H), 2.07-1.82 (m, 4H), 1.73-1.62 (m, 5H), 1.58-1.42 (m, 2H), 1.16-0.90 (m, 2H), 0.86 (dd, $J = 4.4$ Hz, 5.7 Hz, 6H), 0.70 (d, $J = 7.0$ Hz, 3H); $^{13}$C-NMR (50.32 MHz, CDCl$_3$) $\delta = 173.2$, 146.2, 146.1, 146.0, 145.9, 121.7, 121.6, 111.2, 111.1, 60.1, 59.8, 46.9, 44.2, 44.2, 40.6, 34.1, 31.3, 30.8, 30.7, 26.0, 24.7, 23.1, 21.9, 20.8, 15.9; $^{31}$P-NMR (81 MHz, CDCl$_3$) $\delta = 142.5$; HRMS calcd. for C$_{21}$H$_{30}$NO$_4$P 391.191 found 391.192; $[\alpha]_D^{20} = +54^\circ$ (c= 0.98, CHCl$_3$).

(S,1S,2R,5S)-1-Benzol[1,3,2]dioxaphosphol-2-yl-pyrrolidine-2-carboxylic acid 2-isopropyl-5-methyl-cyclohexyl ester (L26): The ligand was obtained as a colorless sticky oil in 47% yield. $^1$H-NMR (200 MHz, CDCl$_3$) $\delta = 7.06-6.86$ (m, 4H), 4.70 (dt, $J = 4.4$ Hz, 10.8 Hz, 1H), 4.28-4.24 (m, 1H), 3.01-2.90 (m, 2H), 2.09-1.85 (m, 3H), 1.84-1.67 (m, 6H), 1.51-1.40 (m, 2H), 1.26-0.95 (m, 2H), 0.91 (d, $J = 6.2$ Hz, 6H), 0.76 (d, $J = 7.0$ Hz, 3H); $^{13}$C-NMR (50.32 MHz, CDCl$_3$) $\delta = 173.2$, 146.2, 146.1, 146.0, 145.9, 121.7, 121.6, 111.2, 111.0, 60.0, 59.8, 46.8, 44.1, 40.6, 34.1, 31.3, 30.6, 30.6, 26.1, 24.6, 23.2, 22.0, 20.8, 16.1; $^{31}$P-NMR (81 MHz, CDCl$_3$) $\delta = 142.7$; HRMS calcd. for C$_{21}$H$_{30}$NO$_4$P 391.191 found 391.192; $[\alpha]_D^{20} = -25^\circ$ (c= 0.99, CHCl$_3$).
Catechol-based Phosphoramidites

General procedure for hydrogenations:

In a glass tube, 0.81 mg (2 µmol) of Rh(COD)₂BF₄, 4 µmol of ligand (2 µmol in case of the bidentate ligands L₈ and L₉), 200 µmol of the substrate and 4 ml of solvent, was added. This small glass tube was placed in a semi-automated autoclave with eight reactors (Endeavor™) that was purged 4 times with nitrogen and once with hydrogen. Then, the autoclave was pressurized with 5 or 25 bar of hydrogen. The reaction mixture was stirred for 16 h. A sample of the resulting mixture was filtered over a silica plug and subjected to conversion (¹H-NMR) and e.e. determination (capillary GC). Full conversion was observed in most cases. As typical examples the isolated yields for 2₅, 2₇, 2₈ and 5₉ were determined. The complete reaction mixtures were filtered over a short silica plug (EtOAc) to yield the corresponding products in 99% yield. Absolute configurations were determined by comparison with reference compounds (5₉, 6₀, 6₄), literature values (GC or HPLC injections; 1₅, 2₄, 2₅, 2₆, 2₇, 2₈, 6₂), optical rotation (6₁) or assigned by analogy through chiral GC elution order (6₃, 6₅).

Table 2.6: E.e. determination for compounds 1₅, 2₄-3₁, 5₉-6₅ and 7₇.

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<th>Entry</th>
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<th>Retention time (min)</th>
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</table>

ᵃ) Absolute configuration is not known

Method A: CP Chiral-L-Val from Chrompack (30 m x 0.25 mm x 0.12 µm), 160°C
Method B: Chiralcel-OD (0.46 cm x 25 cm), iPrOH: heptane 1:9
Method C: CP Chiral-L-Val from Chrompack (30 m x 0.25 mm x 0.12 µm), 110°C
Chapter 2

Method D: CP Chiralsil-Dex CB from Chrompack (25m x 0.25mm x 0.25µm), 160°C
Method E: CP Chiralsil-Dex CB from Chrompack (25m x 0.25mm x 0.25µm), 170°C
Method F: CP Chiralsil-Dex CB from Chrompack (25m x 0.25mm x 0.25µm), 130°C
Method G: CP Chiralsil-Dex CB from Chrompack (25m x 0.25mm x 0.25µm), 100°C
Method H: CP Chiralsil-Dex CB from Chrompack (25m x 0.25mm x 0.25µm), 140°C
Method I: CP Chiralsil-Dex CB from Chrompack (25m x 0.25mm x 0.25µm), 150°C
Method J: CP ChiralDex G-TA from Altrack (30m x 0.25 mm x 0.125µm), 80°C
Method K: Chiralcel-OD (0.46 cm x 25 cm), i-ProOH: heptane S-95
Method L: CP Chiralsil-L-Val from Chrompack (30m x 0.25mm x 0.125µm), 100°C

2.8 References


Catechol-based Phosphoramidites

15 MonoPhos is commercially available from Strem Chemicals.
26 The oximes were prepared according to a method from Vogel: Vogel, A. Vogel’s practical organic chemistry 4th edition, Longman Group Limited 1978, 1113.
29 Dupau, P.; Le Gendre, P.; Bruneau, C.; Dixneuf, P.H. Synlett 1999, 11, 1832.
Chapter 2