Asymmetric catalysis with chiral monodentate phosphoramidite ligands
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Chapter 5
The monodentate ligand combination approach

5.1 Introduction

The widespread preference for the use of chiral bidentate ligands over monodentate ones for enantioselective homogeneous catalysis is mainly due to historic reasons.1 Shortly after the pioneering experiments of Knowles and Sabacky,2,3 who employed monodentate phosphane 5.3 as a chiral ligand for the asymmetric hydrogenation of 5.1, Kagan and Dang introduced bidentate phosphane 5.4 (DIOP) as a chiral ligand (Scheme 5.1).4

![Scheme 5.1 Mono- versus bidentate phosphane in asymmetric hydrogenation.](image)

Due to the better results and the more facile synthesis of ligand 5.4 compared to 5.3, the use of (C$_2$-symmetric)5 bidentate ligands became a conditio sine qua non for effective enantioselective hydrogenation and asymmetric catalysis in general. Although for some types of reactions, like the asymmetric conjugate addition, monodentates proved to be the ligands of choice.6 This reasoning eventually led to a large number of very successful bidentate chiral ligands such as DuPhos 5.5 and BINAP (5.5).7,8 The paradigm changed when our group and others demonstrated that monodentate ligands like phosphoramidites (5.6),9 phosphonites (5.7),10 and phosphites (5.8)11 gave comparable or even better results than bidentate ligands for a number of catalytic reactions (Scheme 5.2).

![Scheme 5.2 Privileged chiral bidentate and monodentate ligands.](image)

As outlined in Chapter 1.6, the high levels of stereocontrol exerted by these ligands, combined with the facile synthesis and modular structure of monodentate ligands 5.6-5.8 puts them among the privileged ligands for asymmetric catalysis.12 A unique advantage of

monodentate ligands is the possibility to use two different monodentate ligands instead of one bidentate ligand for the formation of a chiral catalyst; the monodentate ligand combination approach.

5.2 The monodentate ligand combination approach

Transition metal based complexes for enantioselective homogeneous catalysis are generally formed by an in situ complexation of a chiral organic ligand with a metal precursor. In case of the copper- and rhodium-phosphoramidite catalysts employed in the asymmetric conjugate addition (ACA), two coordination sites are occupied by one bidentate or two monodentate phosphoramidite ligands whereas the two other coordination sites remain available for the substrate and reagent (Scheme 5.3).

\[ [M] + PP_2 \rightarrow M(PP)_2 \]

[bidentate] \[ [M] + 2 \cdot P \rightarrow M(P)_2 \]

[monodentate] \[ [M] = Cu(OTf)_2 \text{ or } Rh(acac)(eth)_2 \]

\[ P = \text{phosphoramidite} \]

Scheme 5.3 Catalyst formation with bi- and monodentate phosphoramidite ligands.

In the monodentate ligand combination approach, one equivalent each of two different chiral monodentate phosphoramidite ligands (\( \cdot P_1 \) and \( \cdot P_2 \)) is used. This leads to the simultaneous formation of two homo-complexes, \( M(\cdot P_1)_2 \) and \( M(\cdot P_2)_2 \), and one hetero-complex, \( M(\cdot P_1)(\cdot P_2) \) (Scheme 5.4).

\[ [M] + \cdot P_1 + \cdot P_2 \rightarrow M(\cdot P_1)_2 + M(\cdot P_2)_2 \]

Scheme 5.4 The monodentate ligand combination approach.

The hetero-complex represents a new catalyst, and if it shows higher activity and selectivity than the two homo-complexes simultaneously present in the reaction mixture, it will lead to better results of the reaction as a whole. It is important to note that this approach only leads to improved results when a more selective hetero-complex is also more active than the homo-complexes, or when only minor amounts of homo-complexes are formed. In the form of a simplified rate law, the observed activity (\( k_{obs} \)) of such a mixture of catalysts (with a
The monodentate ligand combination approach

concentration of \([C]_{\text{tot}}\) arises from an addition of the contributions by the three complexes; \(M(P')_2\), \(M(P')_2\) and \(M(P^1P^2)\) (Equation 5.1). As mentioned before, not only the activity of the complexes has to be taken into account, and also the relative amounts (mol fractions \(M\)) have an influence on the contribution of each complex. Next to the activity, the selectivity \((k_R/k_S)\) follows from the overall rate constant \(k\), which is the sum of \(k_R\) and \(k_S\), the rate constants for the formation of product with the \(R\) and \(S\) configuration respectively.

\[
V_{\text{obs}} = k_{\text{obs}} \cdot [C]_{\text{tot}} = k_{M(P')_2} \cdot [C]_{\text{tot}} \cdot M_{M(P')_2} + k_{M(P')_2} \cdot [C]_{\text{tot}} \cdot M_{M(P')_2} + k_{M(P')_2} \cdot [C]_{\text{tot}} \cdot M_{M(P')_2}
\]

Equation 5.1.

The monodentate ligand combination approach is not only limited to the use of two chiral ligands, hetero-complexes arising from the combination of a chiral ligand (not only phosphoramidites) with an achiral ligand (e.g. PPh\(_3\)) or with a ligands having dynamic chirality (e.g. bisphenol based) could also lead to improved results (Figure 5.1).

**Figure 5.1** Hetero-complexes of other ligand combinations

This approach will benefit greatly from combinatorial screening methods, because a relatively small number of monodentate ligands gives rise to a large number of possible hetero-complexes (Figure 5.2). In a mathematical form, \(n\) monodentate ligands give rise to \((n^2-n)/2\) possible hetero-complexes.

**Figure 5.2** Possible number of hetero-complexes from monodentate ligands.
Chapter 5

Since the monodentate ligand combination approach is a new concept in asymmetric catalysis and it dramatically broadens the chiral space for the development of new catalysts, we were eager to apply it in asymmetric conjugate addition reactions.

5.3 Earlier work

Mixtures of ligands have been used before in the formation of chiral catalysts, but this has been limited to bidentate ligands. Examples include ruthenium catalyst 5.9 by the group of Noyori,\textsuperscript{13,14} and titanium catalyst 5.10 by the group of Mikami (Figure 5.3).\textsuperscript{15,17}

![Figure 5.3: Catalysts composed of two different bidentate ligands.](image)

These cases differ, however, with the monodentate ligand combination approach, because these complexes were specifically designed to exist only as the hetero-combination (5.10) or because their corresponding homo-complexes did not form or were catalytically inactive (5.9). Another approach, which also makes use of mixtures of chiral ligands, is the chiral activation of racemic catalysts by the group of Mikami and others (Scheme 5.5).\textsuperscript{18-20}

![Scheme 5.5: The concept and an example of chiral activation of a racemic catalyst.](image)

(S)-catalyst* + Act* \rightarrow (S)-catalyst* activated catalyst

(R)-catalyst* + Act* \rightarrow (R)-catalyst* activated catalyst

rac-5.11, catalyst

(R)-5.12, activator

Ph\(\rightarrow\)H\(\rightarrow\)CO\(_2\)Bu \(\rightarrow\) 10% rac-5.11, toluene, 0°C \(\rightarrow\) Ph\(\rightarrow\)OH\(\rightarrow\)CO\(_2\)Bu

0% (R)-5.12, 6% yield, 0% e.e.
5% (R)-5.12, 52% yield, 90% e.e.
The monodentate ligand combination approach

This chiral activation (or deactivation if the diastereomeric complex is less active) also differs from the monodentate ligand combination approach, because the former is based on diastereomeric interactions, whereas in the latter case there is a competition between three different (not diastereomeric) catalysts.

The first true examples of the monodentate ligand combination approach were reported in the beginning of 2003 simultaneously by our group and the group of Reetz in asymmetric hydrogenation reactions.\textsuperscript{21,22} The e.e. value for $\beta$-amino acid 5.14 is improved when a rhodium catalyst based on the combination of phosphoramidite ligands $L_1$ and $L_2$ is employed, rather than a catalyst based exclusively on $L_1$ or $L_2$ (Scheme 5.6).

\begin{equation}
\begin{array}{c}
\text{O} \\
\text{O}
\end{array}
\begin{array}{c}
\text{P} \\
\text{N}
\end{array}
\begin{array}{c}
\text{(S)}-L_1
\end{array}
\quad
\begin{array}{c}
\text{O} \\
\text{O}
\end{array}
\begin{array}{c}
\text{H}
\end{array}
\begin{array}{c}
\text{(S,R)}-L_2
\end{array}
\end{equation}

\begin{equation}
\text{Ph}
\end{equation}

\begin{equation}
\text{NHAc}
\end{equation}

\begin{equation}
\text{CO}_2\text{Et}
\end{equation}

\begin{equation}
\text{1\% Rh(COD)$_2$BF}_4
\end{equation}

\begin{equation}
\text{1\% L}_x + 1\% L_y
\end{equation}

\begin{equation}
\text{H}_2, \text{CH}_2\text{Cl}_2
\end{equation}

\begin{equation}
\text{5.13}
\end{equation}

\begin{equation}
\text{5.14}
\end{equation}

\begin{equation}
\text{L}_x = \text{L}_y = \text{L}_1 \quad 54\% \text{ e.e.}
\end{equation}

\begin{equation}
\text{L}_x = \text{L}_y = \text{L}_2 \quad 80\% \text{ e.e.}
\end{equation}

\begin{equation}
\text{L}_x = \text{L}_1, \text{L}_y = \text{L}_2 \quad 91\% \text{ e.e.}
\end{equation}

Scheme 5.6 Improved enantioselectivity with a combination of ligands.

This first demonstration of the monodentate ligand combination approach for asymmetric hydrogenation proved to be quite general for a number of phosphoramidite ligands, various substrates, as well as for combinations of phosphonites and phosphites.\textsuperscript{21,22} Improved enantioselectivities for catalytic C-C bond formation by the monodentate ligand combination approach had, however, not been demonstrated.

5.4 Copper-catalyzed asymmetric conjugate addition

As a first example of an enantioselective C-C bond forming reaction, the copper-phosphoramidite catalyzed ACA of diethylzinc to acyclic enones 5.15 and 5.16 was investigated (Scheme 5.7).

\begin{equation}
\text{5.15}
\end{equation}

\begin{equation}
\text{5.16}
\end{equation}

\begin{equation}
\text{Et}_2\text{Zn}
\end{equation}

\begin{equation}
\text{2\% Cu(OTf)$_2$}
\end{equation}

\begin{equation}
\text{2\% L}_x + 2\% L_y
\end{equation}

\begin{equation}
\text{toluene, \text{-45\degree C}}
\end{equation}

\begin{equation}
\text{5.17}
\end{equation}

\begin{equation}
\text{5.18}
\end{equation}

Scheme 5.7 Cu-catalyzed ACA of diethylzinc.
In a one-pot multi-substrate experiment (Chapter 2.4), benzylidene acetone (5.15) and 3-nonen-2-one (5.16) were allowed to react with diethylzinc. The monodentate ligand combination approach was used for the formation of the copper-phosphoramidite catalysts with the ligands shown in Figure 5.4.

Figure 5.4 Phosphoramidite ligands used in the Cu-catalyzed ACA.

The e.e. values obtained for 5.17 and 5.18 are shown in Table 5.1, where the homo-combinations (Lx = Ly) of phosphoramidites can be found on the diagonal and the hetero-combinations (Lx ≠ Ly) off-diagonal. In all cases complete conversion was reached.

Table 5.1 E.e. values obtained with the monodentate ligand combination approach.

<table>
<thead>
<tr>
<th>Lx</th>
<th>L3</th>
<th>L4</th>
<th>L5</th>
<th>L6</th>
<th>L7</th>
</tr>
</thead>
<tbody>
<tr>
<td>L3</td>
<td>80</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
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<td>L4</td>
<td>77</td>
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<td>78</td>
<td>76</td>
<td>78</td>
<td></td>
<td></td>
</tr>
<tr>
<td>L6</td>
<td>69</td>
<td>65</td>
<td>73</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td>L7</td>
<td>65</td>
<td>65</td>
<td>67</td>
<td>55</td>
<td>56</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lx</th>
<th>L3</th>
<th>L4</th>
<th>L5</th>
<th>L6</th>
<th>L7</th>
</tr>
</thead>
<tbody>
<tr>
<td>L3</td>
<td>67</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L4</td>
<td>-25</td>
<td>-47</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L5</td>
<td>-69</td>
<td>-67</td>
<td>-67</td>
<td></td>
<td></td>
</tr>
<tr>
<td>L6</td>
<td>-62</td>
<td>-65</td>
<td>-68</td>
<td>-63</td>
<td>-67</td>
</tr>
<tr>
<td>L7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*a* Determined by chiral GC, + value = (R)-configuration, - value = (S)-configuration.
The monodentate ligand combination approach

The homo-complex based on phosphoramidite ligand \( L_3 \) is the most effective catalyst for substrate \( 5.15, 5.17 \) was formed in 80% e.e. The other homo-combinations resulted in similar (78-75%) or lower (56-55%) e.e. values, all with the same absolute configuration \((R)\) for the major enantiomer. Unfortunately, the combination of phosphoramidite ligands does not lead to improved e.e. values compared to the homo-combinations. The obtained e.e. values are close to the average of the two individual homo-complexes. This means that the hetero-complex, if it is formed at all, has a lower selectivity and/or activity than the homo-complexes also present in the solution. The situation for substrate \( 5.16 \) is slightly more complicated, because the catalysts based on homo-combinations of the ligands do not all lead to the same absolute configuration for the major enantiomer of \( 5.18 \). Phosphoramidite ligands \( L_4, L_5 \) and \( L_7 \) give \( 5.18 \) with the \( S \)-configuration as the major enantiomer, while \( L_3 \) and \( L_6 \) give the \( R \)-configuration as the major enantiomer. However, the hetero-combinations of ligands do not perform better than the homo-combinations. It is also clear that the e.e. values obtained with hetero-combinations of ligands \( L_5 \) and \( L_7 \) closely resemble the values for their corresponding homo-combinations. The homo-complexes of \( L_5 \) and \( L_7 \) are more active (100% conv. in <30 min) than the homo-complexes of the other ligands (100% conv. in ~60min). Therefore they might also be more active than the hetero-complexes that could be formed when the monodentate ligand combination approach is used, and therefore no improvement in e.e. values is found.

The use of the other enantiomer of one of the phosphoramidite ligands in the hetero-combination, leads to the formation of a hetero-complex that is a diastereomer of the original hetero-complex. Since diastereomers have different chemical properties it might be a more active and selective catalyst than the original hetero-complex. Therefore the hetero-combination of \((S)\)\(-L_3\) and \((S,R,R)\)-\(L_5\), which is a diastereomer of the catalyst based on \((S)\)-\(L_3\) and \((R,S,S)\)-\(L_5\), was also tested (Scheme 5.8).

![Scheme 5.8](image)

Scheme 5.8 The diastereomeric hetero-combination.

This diastereomeric hetero-combination is also not able to improve the e.e. values obtained with the corresponding homo-combinations. In the case of \( 5.16 \) the high catalytic activity of the homo-complex formed with ligand \((R,S,S)\)-\(L_5\) again determines the e.e. value of \( 5.18 \).
5.5 Rhodium-catalyzed asymmetric conjugate addition

5.5.1 Combinations of chiral ligands

Like the copper-phosphoramidite catalyzed ACA of diethylzinc, the rhodium-phosphoramidite catalyzed ACA of phenylboronic acid is also a suitable C-C bond forming reaction for the application of the monodentate ligand combination approach. Inspired by the earlier successes of the rhodium-based hydrogenation catalysts in this approach (Section 5.3), the conjugate addition of phenylboronic acid to 4-methylnitrostyrene (5.19, Chapter 4.4) was used as a model reaction (Scheme 5.9).

Scheme 5.9 Rh-catalyzed ACA of phenylboronic acid.

Phenylboronic acid was generated in situ from phenylboroxine and water (one equivalent with respect to boron), because this provides mild reaction conditions that are beneficial for the stability of the catalyst. Several chiral phosphoramidite ligands were used for the combinations, based on small (catechol) and large (BINOL) diol moieties as well as small, medium and large amine moieties (Figure 5.5).

Figure 5.5 Phosphoramidite ligands used in the Rh-catalyzed ACA.

The results of the use of these ligands in the monodentate ligand combination approach for the reaction in Scheme 5.9 are shown in Table 5.2. The e.e. as well as the conversion was measured over a period of 3 hours. Again the homo-combinations (Lx = Ly) of the ligands can be found on the diagonal and the hetero-combinations (Lx ≠ Ly) off-diagonal.
The monodentate ligand combination approach

Table 5.2 E.e. values for 5.20 and (conversions) of 5.19.

<table>
<thead>
<tr>
<th>ligand</th>
<th>L3</th>
<th>L5</th>
<th>L6</th>
<th>L7</th>
<th>L8</th>
<th>L9</th>
<th>L10</th>
</tr>
</thead>
<tbody>
<tr>
<td>L3</td>
<td>23 (11)</td>
<td>47 (4)</td>
<td>28 (4)</td>
<td>41 (100)</td>
<td>-</td>
<td>45 (100)</td>
<td>-</td>
</tr>
<tr>
<td>L5</td>
<td>41 (100)</td>
<td>-</td>
<td>31 (94)</td>
<td>24 (97)</td>
<td>-</td>
<td>31 (94)</td>
<td>22 (100)</td>
</tr>
<tr>
<td>L6</td>
<td>-2 (13)</td>
<td>-</td>
<td>-</td>
<td>0 (13)</td>
<td>19 (100)</td>
<td>-7 (69)</td>
<td>-</td>
</tr>
<tr>
<td>L7</td>
<td>-31 (92)</td>
<td>37 (45)</td>
<td>29 (100)</td>
<td>-2 (13)</td>
<td>-</td>
<td>4 (29)</td>
<td>52 (15)</td>
</tr>
<tr>
<td>L8</td>
<td>-</td>
<td>-</td>
<td>22 (100)</td>
<td>-</td>
<td>19 (100)</td>
<td>-7 (69)</td>
<td>-</td>
</tr>
<tr>
<td>L9</td>
<td>-</td>
<td>-</td>
<td>22 (100)</td>
<td>-</td>
<td>19 (100)</td>
<td>-7 (69)</td>
<td>-</td>
</tr>
<tr>
<td>L10</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>4 (29)</td>
<td>52 (15)</td>
<td>-</td>
</tr>
</tbody>
</table>

aDetermined by chiral HPLC, b determined by GC, - = not determined.

Although not all possible combinations were tested, we were able to demonstrate for the first time that the monodentate ligand combination approach led to improved catalytic asymmetric C-C bond formation. The three hetero-combinations of ligands L3 with L5, L3 with L9 and L5 with L9 all resulted in higher e.e. values than their corresponding homo-combinations. In addition, it was found that in the case of L3 with L9, even the conversion increased from 69% to 92%. This indicates that the hetero-complex is formed, and that it is more active and selective than the two homo-complexes. Two diastereomeric hetero-combinations of (S,S)-L9, with (R)-L3 and (R,S,S)-L5, were much less successful. They led to -33% e.e. at 24% conversion and -23% e.e. at 18% conversion, respectively. The combination of a relatively small phosphoramidite, e.g. L9, with a bulky phosphoramidite such as L3 or L5 seems essential in this case in order to create a more selective hetero-complex. Homo-complexes of the bulky ligands have a very low activity and give moderate enantioselectivities, whereas the homo-complex of the small phosphoramidite ligand has a moderate activity and gives a low e.e. A combination of these two types of ligands gives a hetero-complex that combines the two best properties of both, a moderate activity and enantioselectivity.

In order to broaden the scope of this approach, other substrates were used. Benzylidene acetone (5.15) was considered to be an attractive substrate (Table 5.3). β-Aryl-substituted enones have not been used before as substrates in the ACA of arylboronic acids and offer the attractive feature that they lead to a benzydrylic stereogenic center.23 As in the case of nitrostyrenes (Chapter 4.4), this is a frequent motif in natural products and pharmaceuticals.24
Table 5.3 Results for benzylidene acetone.

\[ \text{Table 5.3 Results for benzylidene acetone.} \]

![Chemical Structure](attachment:image.png)

\[
\begin{array}{l|c|c|l|c|c}
\text{Lx / Ly conv. (%)a e.e. (%)b} & \text{Lx / Ly conv. (%)a e.e. (%)b} \\
\hline
\text{L9 / L9} & 27 & 33 & \text{L9 / L3} & 33 & -36 \\
\text{L3 / L3} & 23 & -30 & \text{L9 / L5} & 30 & 12 \\
\text{L5 / L5} & 0 & - & \text{L3 / L5} & 15 & -45 \\
\end{array}
\]

*aDetermined by GC, b determined by chiral HPLC, absolute configurations were not determined.

The use of hetero-combinations of ligands has a beneficial effect on the enantioselectivity of 5.21, although it is not as pronounced as for 5.20, and the conversion remains nearly the same. A diastereomeric hetero-combination of (S,S)-L9 with (R)-L3 did not improve the results (25% conversion, 0% e.e.).

Cyclic enones such as 2-cyclohexenone (5.22) have been extensively studied as substrates in the rhodium-catalyzed ACA of arylboronic acids and their derivatives, and can be seen as benchmark substrates (Table 5.4).25-28

Table 5.4 Results for 2-cyclohexenone.

![Chemical Structure](attachment:image.png)

\[
\begin{array}{l|c|c|l|c|c}
\text{Lx / Ly conv. (%)a e.e. (%)b} & \text{Lx / Ly conv. (%)a e.e. (%)b} \\
\hline
\text{L9 / L9} & 26 & 33 & \text{L9 / L3} & 93 & 75 \\
\text{L3 / L3} & 22 & -27 & \text{L9 / L5} & 40 & 77 \\
\text{L5 / L5} & 18 & -16 & \text{L3 / L5} & 16 & -60 \\
\text{L11 / L11} & 21 & 4 & \text{L3 / L5 / L9} & 47 & 75 \\
\end{array}
\]

*aDetermined by chiral GC, absolute configurations were not determined.
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For this substrate, the trend of decreased activity with increasing steric bulk of the phosphoramidite ligands is also present. In contrast to 5.20, the e.e. values also decrease with an increase of steric bulk of the ligand. However, the advantage of using hetero-combinations of monodentate phosphoramidite ligands is considerably more pronounced. In case of the combination of L9 with L3, the conversion almost quadruples from 26 to 93% and the e.e. more than doubles from 33 to 75%. This higher activity and selectivity is also observed for the hetero-combination of L9 with L5, where a small and bulky phosphoramidite are combined. It even holds for the combination of the three phosphoramidite ligands L3, L5 and L9. Surprisingly, combinations with L11, which is similar in size to L9, do not lead to improved e.e. values or conversions. The abovementioned results clearly demonstrate that the hetero-complex is formed when two different monodentate phosphoramidite ligands are combined, and it is frequently a better catalyst than the two parent homo-complexes. It remains unclear, however, what the relative amounts of homo- and hetero-complex are.

5.5.2 31P-NMR of rhodium-phosphoramidite complexes

In order to get an idea of the relative amounts of homo- and hetero-complex formed when two different phosphoramidite ligands are added to the catalyst precursor Rh(acac)(eth)₂, 31P-NMR spectra of the homo- and hetero-combinations were recorded (Figure 5.6).
Figure 5.6 $^{31}$P-NMR spectra of homo- and hetero-combinations (overlap of signals at 161.350 ppm as evident from integration).
The monodentate ligand combination approach

The homo-combination of L5 gives a doublet with signals at 161.3 and 157.6 ppm, corresponding with a homo-complex of L5 (Rh(acac)(L5)2) with a Rh-P coupling of 300 Hz. The absence of a P-P coupling indicates that the two phosphoramidite ligands are aligned in an antiparallel way, leading to a C2-symmetric complex. The homo-combination of L9 leads to an identical situation with a doublet at 159.1 and 155.6 ppm ($J_{Rh,P} = 282$ Hz). The minor doublet at 153.5 and 150.1 ppm ($J_{Rh,P} = 279$ Hz) arises from the mono-complex where only one phosphoramidite ligand is bound to the rhodium (Rh(acac)(eth)(L9)), which was proven by an NMR-titration experiment. The 31P-NMR spectrum of the hetero-combination of ligands L5 and L9 shows the presence of both the homo- and the hetero-complexes, as was expected based on Scheme 5.4. Integration of the signals gives the ratio of the homo- and hetero-complexes. The homo-complexes of L5 and L9, including the L9 mono-complex, are present in small amounts of about 5%. The hetero-complex is with 85% the major species. It appears as two double doublets originating from 160.1 and 158.1 ppm. The double doublet of L5 (at 162.5, 161.3, 158.9 and 157.7 ppm) is due to a Rh-P coupling of 289 Hz and a P-P coupling of 96 Hz. The double doublet of L9 (at 160.5, 159.3, 156.9 and 155.8 ppm) is due to a Rh-P coupling of 286 Hz and a P-P coupling of 96 Hz. Additional proof was provided by a simulation of the 31P-NMR of the hetero-complex by the group of Van Leeuwen. This simulation corresponds adequately with the observed spectrum (Figure 5.7).

By integration of the 31P-NMR signals of the homo- and hetero-complexes, observed by combining two different phosphoramidite ligands and Rh(acac)(eth)2, their ratios were readily determined (Table 5.5).

Table 5.5 Ratios of homo- and hetero-complexes.

<table>
<thead>
<tr>
<th>Lx / Ly</th>
<th>Rh(acac)(Lx)2</th>
<th>Rh(acac)(Lx)(Ly)</th>
<th>Rh(acac)(Ly)2</th>
</tr>
</thead>
<tbody>
<tr>
<td>L3 / L9</td>
<td>17</td>
<td>78</td>
<td>5</td>
</tr>
<tr>
<td>L5 / L9</td>
<td>6</td>
<td>89</td>
<td>5</td>
</tr>
<tr>
<td>L3 / L5</td>
<td>27</td>
<td>54</td>
<td>19</td>
</tr>
<tr>
<td>L5 / L11</td>
<td>25</td>
<td>45</td>
<td>30</td>
</tr>
</tbody>
</table>
The imbalance in homo-complex ratios is due to errors in weighing and the fact that mono-complexes were not included since they do not give stable catalysts. In cases where the hetero-combination of ligands is based on a small and a bulky phosphoramidite, such as L3 or L5 with L9, the hetero-complex is also the most abundant one and improved results are found in the asymmetric C-C bond formation. It even exceeds the statistical distribution of 25:50:25 as expected on the basis of Scheme 5.4. This distribution is approximately found for hetero-combinations that are based on two bulky phosphoramidite ligands (such as L3 with L5), and, although they sometimes give improved e.e. values, they do not lead to more active catalysts.

5.5.3 Combinations of chiral and achiral ligands

If the hetero-combination of a small ligand with a bulky ligand is essential for the formation of a hetero-complex with a higher activity and selectivity, it should be possible to replace one of the two chiral ligands by an achiral ligand and still observe these improvements. For that purpose achiral phosphorus ligands with different donating and steric properties were screened in the ACA of phenylboronic acid to 5.19 (Table 5.6).

Table 5.6 Rh-catalyzed ACA with a combination of chiral and achiral ligands.

<table>
<thead>
<tr>
<th>Lx / Ly</th>
<th>conv. (%)a</th>
<th>e.e. (%)b</th>
<th>Lx / Ly</th>
<th>conv. (%)a</th>
<th>e.e. (%)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>L3 / L3</td>
<td>11</td>
<td>23</td>
<td>L5 / L12</td>
<td>12</td>
<td>9</td>
</tr>
<tr>
<td>L5 / L5</td>
<td>4</td>
<td>28</td>
<td>L3 / L13</td>
<td>97</td>
<td>0</td>
</tr>
<tr>
<td>L7 / L7</td>
<td>0</td>
<td>-</td>
<td>L5 / L13</td>
<td>73</td>
<td>0</td>
</tr>
<tr>
<td>L12 / L12</td>
<td>8</td>
<td>0</td>
<td>L7 / L13</td>
<td>78</td>
<td>0</td>
</tr>
<tr>
<td>L13 / L13</td>
<td>83</td>
<td>0</td>
<td>L3 / L14</td>
<td>4</td>
<td>55</td>
</tr>
<tr>
<td>L14 / L14</td>
<td>0</td>
<td>-</td>
<td>L7 / L14</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>L15 / L15</td>
<td>100</td>
<td>0</td>
<td>L3 / L15</td>
<td>94</td>
<td>7</td>
</tr>
<tr>
<td>L5 / L15</td>
<td>83</td>
<td>-30</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

aDetermined by GC, b determined by chiral HPLC, absolute configurations were not determined.
The monodentate ligand combination approach

The use of triphenylphosphine (L12) as a ligand leads to catalysts with a very low activity, in the homo- as well as the hetero-combination. The less basic triphenylphosphite (L13) is a surprisingly good ligand for this reaction, considering the easy hydrolysis of phosphites under these conditions. Hetero-combinations of achiral L13 with bulky optically active phosphoramidites unfortunately result in high conversions to racemic products, indicating that the homo-complex of L13 is the most active catalyst. This demonstrates that chiral phosphites might be effective ligands for the rhodium-catalyzed ACA of arylboronic acids. Phosphite ligand L14, due to its steric bulk, is much more stable towards hydrolysis, but also leads to almost inactive catalysts in homo- as well as hetero-combinations. The e.e. value in combination with L3 is very promising. Achiral phosphoramidite L15 proved to be the most suitable achiral ligand, resulting in complete conversion to the racemic product in the case of the homo-combination. The hetero-combination of this simple achiral ligand with L3 does not lead to improved results, but the combination with L5 leads to a drastic improvement of conversion from 4% to 83% with a reversed and slightly higher e.e. value.

These results prompted us to apply the combination of bulky chiral phosphoramidites with the small achiral phosphoramidite L15 in the ACA of phenylboronic acid to 5.20 (Table 5.7).

**Table 5.7 Rh-catalyzed ACA with achiral ligand combinations.**

<table>
<thead>
<tr>
<th>Lx / Ly</th>
<th>conv. (%)a</th>
<th>e.e. (%)a</th>
<th>Lx / Ly</th>
<th>conv. (%)a</th>
<th>e.e. (%)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>L3 / L3</td>
<td>22</td>
<td>-27</td>
<td>L3 / L15</td>
<td>100</td>
<td>5</td>
</tr>
<tr>
<td>L5 / L5</td>
<td>18</td>
<td>-16</td>
<td>L5 / L15</td>
<td>79</td>
<td>31</td>
</tr>
<tr>
<td>L7 / L7</td>
<td>0</td>
<td>-</td>
<td>L7 / L15</td>
<td>98</td>
<td>-22</td>
</tr>
<tr>
<td>L15 / L15</td>
<td>100</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

aDetermined by chiral GC, absolute configurations were not determined.

The hetero-combination with L5 gives a high conversion, and in addition to a reversal, a large increase in e.e. from -16 to 31%. But the most striking results are obtained with the combination of L7 with L15. Whereas the homo-complex of L7 is inactive and the homo-complex of L15 not enantioselective, the hetero-complex of L7 with L15 is both an active and enantioselective catalyst.

Integration of the signals in the $^{31}$P-NMR spectra of the hetero-combinations showed that also here the most successful combinations of ligands (L15 with L5 or L7) correspond with a high proportion of the hetero-complex (92% and 86% respectively). It also demonstrates that the lack of enantioselectivity obtained with mixtures of L13 are not due to the absence
of a hetero-complex, but to the fact that the homo-complex of \( \text{L13} \) is a more active catalyst (Table 5.8).

### Table 5.8 Ratios of homo- and hetero-complexes with achiral ligands based on \(^{31}\text{P-NMR.}\)

<table>
<thead>
<tr>
<th>( \text{Lx} / \text{Ly} )</th>
<th>( \text{Rh(acac)}(\text{Lx})_2 )</th>
<th>( \text{Rh(acac)}(\text{Lx})(\text{Ly}) )</th>
<th>( \text{Rh(acac)}(\text{Ly})_2 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{L3} / \text{L13} )</td>
<td>13</td>
<td>49</td>
<td>38</td>
</tr>
<tr>
<td>( \text{L5} / \text{L13} )</td>
<td>14</td>
<td>61</td>
<td>25</td>
</tr>
<tr>
<td>( \text{L3} / \text{L15} )</td>
<td>13</td>
<td>69</td>
<td>18</td>
</tr>
<tr>
<td>( \text{L5} / \text{L15} )</td>
<td>5</td>
<td>92</td>
<td>3</td>
</tr>
<tr>
<td>( \text{L7} / \text{L15} )</td>
<td>8</td>
<td>86</td>
<td>6</td>
</tr>
</tbody>
</table>

### 5.6 Further developments

Shortly after the publication of our results,\(^{30}\) the group of Reetz also reported the use of combinations of chiral and achiral ligands in the hydrogenation of dehydro \( \alpha \)-amino ester \( \text{5.24} \) (Scheme 5.10).\(^{31}\)

```
\[
\begin{array}{cccc}
\text{Lx} = \text{Ly} = \text{L12} & 0\% \text{ e.e.} \\
\text{Lx} = \text{Ly} = \text{L16} & 92\% \text{ e.e. (S)} \\
\text{Lx} = \text{L12}, \text{Ly} = \text{L16} & 20\% \text{ e.e. (R)}
\end{array}
\]
```

Scheme 5.10 The combination of a chiral and achiral ligand in hydrogenation.

Although they were not able to improve the e.e. or conversion in this way, they observed a reversal of enantioselectivity for \( \text{5.25} \). Recently two strategies for the exclusive synthesis of a hetero-complex of two different monodentate ligands appeared. They differ from the monodentate ligand combination approach because the homo-complexes of the two ligands are not formed. This is achieved by modifying the ligands with complementary binding sites in such a way that in fact a bidentate is formed. The group of Takács has synthesized hetero-complexes of two different monodentate phosphite ligands, \( \text{P}^1 \) and \( \text{P}^2 \) (\( \text{5.26} \)), coordinated to palladium via the complexation of two bisoxazoline linkers with zinc (Scheme 5.11).\(^{32}\)
Scheme 5.11 Bidentate hetero-complex of chiral phosphites.

In the palladium-catalyzed allylic amination of 5.27 this bidentate ligand, were P1 and P2 are TADDOL based phosphites, resulted in 97% e.e. for 5.28. The group of Reek used the binding of nitrogen containing phosphate ligands like 5.30 to zinc(II)porphyrins such as 5.29 in order to obtain mixed bidentate ligands. In the palladium catalyzed allylic alkylation of 5.31 this led to an e.e. value of 60% for 5.32 (Scheme 5.12).

Scheme 5.12 Allylic alkylation with a bidentate hetero-complex of a phosphine-phosphite.

5.7 Conclusions

The monodentate ligand combination approach is a new concept in asymmetric catalysis. By using a mixture of two different monodentate phosphoramidite ligands for the in situ catalyst formation, three different catalysts are obtained. The two homo-complexes contain two identical ligands and could also be prepared separately by using two equivalents of identical ligands. But the hetero-complex, which contains two different ligands, is a new catalyst. These three catalysts are simultaneously present in the reaction mixture, but if the hetero-complex has a higher activity and/or selectivity than the two homo-complexes it will lead to improved results. This principle has now been shown for enantioselective C-C bond forming reactions. The initial experiments focused on the copper-catalyzed ACA of diethylzinc to acyclic enones, but combinations of monodentate ligands did not lead to
improved results. This might be due to the fact that the hetero-complex is not formed at all, because the e.e. values for the ethyl-adduct of benzylidene acetone are close to the average values obtained with the parent homo-complexes. An alternative explanation is that the homo-complexes are much more active than the hetero-complex, like in the case of 3-nonen-2-one. On the other hand, the monodentate ligand combination approach did lead to improved results in the rhodium-catalyzed ACA of arylboronic acids. The combination of a small and a bulky phosphoramidite ligand led to an increase of conversion as well as e.e. for three different substrates. The ratios of homo- and hetero-complexes that were formed when the ligands were added to the catalyst precursor Rh(acac)(eth)$_2$ could be determined with $^{31}$P-NMR. It turned out that the hetero-complex was indeed formed, and moreover, that it was the most abundant species, present in over 90% in the most successful cases. Although these measurements do not show the catalytically active species under the reaction conditions, they provide, in combination with the obtained conversions and e.e. values, a good insight into the monodentate ligand combination approach. This approach can even lead to improved results when combinations of chiral with achiral ligands are employed. In the most striking case the homo-complexes do not function as enantioselective catalysts whereas the hetero-complex does. The advantage of the monodentate ligand combination approach over other methods for the formation of hetero-complexes lies in the fact that it makes use of unmodified monodentate ligands. This not only profits from facile synthesis of the individual ligands, and also leads to a larger number of possible hetero-complexes when there are no complementary binding sites that have to be taken into account. Due to these large numbers, the monodentate ligand combination approach is highly suitable for, and actually requires, screening in a high throughput fashion.

5.8 Experimental section

For general information see Chapters 2 and 4. Phosphoramidite ligands (L$_3$,$^{34}$ L$_4$,$^{35}$ L$_5$,$^{34}$ L$_6$,$^{36}$ L$_7$,$^{37}$ L$_8$,$^{38}$ L$_{10}$,$^{39}$ L$_{11}$,$^{35}$ L$_{15}$) were synthesized according to literature procedures,$^{25,36}$ which are discussed in detail in Chapter 7. Phosphoramidite ligand L$_9$,$^{30}$ was kindly provided by Rob Hoen. Spectral data for ligands L$_3$-L$_{11}$ can be found in the given references.

![1-Benzol[1,3,2]dioxaphosphol-2-yl-pyrrolidine (L$_{15}$).](image)

To a solution of 1.74 g (10 mmol) of 1,2-phenylene phosphorochloridite in 10 ml of anhydrous THF at 0 °C was added a solution of 711 mg (10 mmol) of pyrrolidine and 1.01 g (10 mmol) triethylamine in 5 ml of anhydrous THF. The resulting white turbid mixture was stirred at 0 °C for 1 h. The solvent was removed under reduced pressure and the product was purified with column chromatography (pentanes:diethyl ether 10:1, R$_f$ 0.9) to give 82 mg (0.4 mmol, 4% yield) of L$_{15}$ as a colorless oil. $^1$H-NMR $\delta$: 6.93 (m, 4H), 3.06 (m, 4H), 1.73 (m, 4H); $^{13}$C-NMR $\delta$: 144.7 (d, $J_\text{C}^\text{P}=8$ Hz), 120.1 (s), 109.5 (s), 43.5 (d, $J_\text{C}^\text{C}=15$ Hz), 24.5 (d, $J_\text{C}^\text{C}=3$ Hz); $^{31}$P-NMR $\delta$: 141.5. HRMS calcd for C$_{10}$H$_{12}$NO$_2$P 209.060 found 209.060.
General procedure A. Monodentate ligand combination approach of the copper-phosphoramidite catalyzed ACA of diethylzinc.

In a Schlenk tube 3.6 mg (0.01 mmol, 2 mol%) of Cu(OTf)$_2$ was flame-dried, and together with two (0.01 mmol, 2 mol%) portions of phosphoramidite dissolved in 2 ml of dry toluene. After 30 min of stirring at room temperature, 36 mg (0.25 mmol) of $\text{5.15}$, 35 mg (0.25 mmol) of $\text{5.16}$ and 10 µl of n-tridecane (internal standard) were added to the clear solution. An initial sample was taken before the reaction mixture was cooled to -45 °C and 0.6 ml (0.6 mmol) of diethylzinc (1.0M in hexanes) was added. The reaction mixture was stirred at -45 °C and during the reaction samples of 0.1 ml were taken from the reaction mixture with a glass pipette and added to 1 ml of a rigorously stirred mixture of diethyl ether : saturated aqueous NH$_4$Cl (1:1). The organic layer was decanted, filtered over Na$_2$SO$_4$, and subjected to GC analysis.

4-Phenyl-hexan-2-one (5.17). According to general procedure A, spectral data were in accordance with literature.$^{40}$ Enantiomer separation on a Chiraldex G-TA column, 30m x 0.25 mm x 0.25 µm, 105°C for 10 min then with 10°C/min to 110°C for 15 min, 22.8 / 23.8 min (GC).

4-Ethyl-nonan-2-one (5.18). According to general procedure A, spectral data were in accordance with literature.$^{41}$ Enantiomer separation on a Chiraldex G-TA column, 30m x 0.25 mm x 0.25 µm, 105°C for 10 min then with 10°C/min to 110°C for 15 min, 9.4 / 9.6 min (GC).

General procedure B. Monodentate ligand combination approach of the rhodium-phosphoramidite catalyzed ACA of arylboronic acids.

In a Schlenk tube 2.58 mg (0.01 mmol, 2 mol%) of Rh(acac)(eth)$_2$ and two 0.012 mmol (2.5 mol%) portions of phosphoramidite ligand were dissolved in 1 ml of anhydrous dioxane and stirred at room temperature for 15 min. 0.5 mmol of the Michael acceptor, 0.67 mmol of arylboroxine and 10 µl of n-tridecane (internal standard for GC) were added and the resulting mixture was stirred for 2 min. An initial sample was taken before the addition of 0.1 ml of water after which the mixture was degassed and stirred for 3 hours at the indicated temperature. During the reaction, samples of 0.1 ml were taken from the reaction mixture with a glass pipette and added to 1 ml of a stirred mixture of diethyl ether : saturated aqueous NaHCO$_3$ (1:1). After a few minutes the organic layer was decanted, filtered over Na$_2$SO$_4$, and subjected to GC and HPLC analysis.

p-Tolyloboroxine. According to a modified literature procedure.$^{42}$ In a drying pistol 2.5 g (18 mmol) of p-tolyloboronic acid was heated overnight at 145°C in vacuo to give 1.9 g (5 mmol, 90% yield) of p-tolyloboroxine as a white powder. Spectral data were in accordance with literature.$^{42}$
2-Phenyl-2-(4-methylphenyl)-nitroethane (5.20). See Chapter 4.

4-Phenyl-4-p-tolyl-butan-2-one (5.21). According to general procedure B, 146 mg (1.0 mmol) of 5.15 gave 187 mg (0.8 mmol, 79% yield) of 5.21 as a colorless oil after column chromatography (heptanes:diethyl ether 4:1, Rf 0.4). Spectral data were in accordance with literature.43 Enantiomer separation on a Chiralpak OD column, heptanes/isopropanol 99/1, 210 nm, 12.7 / 14.3 min (HPLC).

3-Phenylcyclohexanone (5.23). According to general procedure B, spectral data were in accordance with literature.44 Enantiomer separation on a Chiraldex A-TA column, 30m x 0.25 mm x 0.12 µm, 120°C isothermic, 58.0 / 60.1 min (GC).

31P-NMR of the Rh(acac)(Lx)(Ly) complexes. In a nitrogen filled NMR sample tube containing 3.22 mg (0.012 mmol, 1 eq) of Rh(acac)(eth)2 and two 0.012 mmol (1 eq each) portions of phosphoramidite was added 0.6 ml of CDCl3. The spectra were acquired with a T1 of 1.2 sec. and a 90° pulse (Table 5.9).

<table>
<thead>
<tr>
<th>Homo-complex (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rh(L3)2</td>
</tr>
<tr>
<td>Rh(L5)2</td>
</tr>
<tr>
<td>Rh(L7)2</td>
</tr>
<tr>
<td>Rh(L9)2</td>
</tr>
<tr>
<td>Rh(L11)2</td>
</tr>
<tr>
<td>Rh(L13)2</td>
</tr>
<tr>
<td>Rh(L15)2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hetero-complex (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rh(L3)(L5)</td>
</tr>
<tr>
<td>Rh(L3)(L9)</td>
</tr>
<tr>
<td>Rh(L5)(L9)</td>
</tr>
</tbody>
</table>
The monodentate ligand combination approach

Rh(L5)(L11) 158.1 (dd, $J_{Rh,P}$= 291, $J_{P,P}$= 90 Hz), 167.6 (dd, $J_{Rh,P}$= 294, $J_{P,P}$= 90 Hz)
Rh(L3)(L13) 122.1 (dd, $J_{Rh,P}$= 323, $J_{P,P}$= 98 Hz), 158.1 (dd, $J_{Rh,P}$= 280, $J_{P,P}$= 98 Hz)
Rh(L5)(L13) 120.0 (dd, $J_{Rh,P}$= 318, $J_{P,P}$= 97 Hz), 158.1 (dd, $J_{Rh,P}$= 284, $J_{P,P}$= 97 Hz)
Rh(L3)(L15) 159.5 (d br, $J_{Rh,P}$= 287 Hz)
Rh(L5)(L15) 158.1 (d br, $J_{Rh,P}$= 286 Hz)
Rh(L7)(L15) 158.3 (d br, $J_{Rh,P}$= 286 Hz)

5.9 References