Indole-based phosphorus ligands in asymmetric catalysis
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Chapter 1

Phosphorus ligands in asymmetric catalysis – a general introduction

Abstract: The development of chiral phosphorus ligands for asymmetric catalysis is reviewed. The important breakthroughs in this evolution are summarized, starting from P-chiral monodentate phosphines and including $C_2$ symmetric diphosphine, P-N and P-S, hybrid phosphine-phosphite and phosphine-phosphoramidite, Binol-derived monodentate, and supramolecular bidentate ligands.
1.1 The ligand as molecular steering wheel

The pursuit of creating new matter with desirable properties is a long-standing motivation for chemists throughout the centuries. Already the alchemists in medieval days sought after a transformation of cheap common metals into gold and a synthesis of the “elixir of life”. After Antoine Lavoisier revolutionized our conception of chemical reactions in 1764 by thinking in terms of molecules, synthetic (organic) chemistry has taken a leap and soon after many new compounds and materials were created through controlled stoichiometric reactions. However, it was not until roughly 150 years ago that the Swedish chemist Berzelius coined the term catalysis for the changes that were observed in substances, which were exposed to certain species called “ferments”. In 1895, a more general definition was introduced by Ostwald that is still used today: A catalyst is a substance, which increases the rate at which a chemical reaction approaches equilibrium without becoming itself permanently involved.¹

Nowadays, four types of catalysis can be discerned: homogeneous catalysis, heterogeneous catalysis, biocatalysis, and organocatalysis. This thesis exclusively deals with homogeneous catalysts, in particular transition metal catalysts where the catalytic reaction takes place at the metal center by a sequence of elementary steps, as opposed to e.g. Lewis acid catalysts. The thus defined organometallic catalysts are composed of a metal ion and a ligand, which binds to the metal ion by coordinating atoms such as carbon, nitrogen, phosphorus, arsenic, sulfur, etc. The ligand is the key element for optimizing catalyst performance such as activity and selectivity. Especially when enantioselectivity is desired, the ligand bears the chiral information, which is transferred to the products via the transition metal. In other words, the ligand ‘steers’ the reaction exclusively towards the desired product.

In this chapter, the development of phosphorus ligands for asymmetric catalysis is reviewed with a focus on hybrid phosphine-phosphoramidite ligands. Naturally, this review summarizes only the most important breakthroughs and is by no means comprehensive. The aim is to introduce the reader to the field of asymmetric catalysis using chiral phosphorus ligands, in order to put the subsequent chapters about the development of novel ligands into perspective. At the end, an attempt is made to differentiate privileged ligands from combinatorial ligand libraries and ultimately the scope and outline of this thesis are introduced.

1.2 Monodentate P-chirogenic phosphines

The evolution of chiral phosphorus ligands is strongly coupled to the development of asymmetric hydrogenation. In fact, it was only after the discovery of chiral phosphorus ligands that efficient asymmetric hydrogenations became feasible. In 1968, the first ligands that were found to induce enantioselectivity in asymmetric hydrogenations were optically active tertiary phosphines, introduced by Horner² and
The neutral rhodium catalysts based on \((R)\)-methyl-\(n\)-propylphenylphosphine gave low ee values up to 28 % in the hydrogenation of \(\alpha\)-acylaminoacrylic acid derivatives (Scheme 1.1).\(^4\) These selectivities were improved to up to 52 % ee soon afterward by the group of Morrison and co-workers using a monodentate phosphine derived from \((-\)\)-menthol (NMDPP), which contains the chiral information on carbon instead of phosphorus.\(^5\) Incorporation of \(o\)-anisyl and cyclohexyl substituents in PAMP and CAMP on the \(P\)-chiral ligand of Knowles resulted in enantioselectivities up to 88 % ee.\(^6\) In addition, cationic rather than neutral Rh-complexes were used that gave more active and selective catalysts. The potential of the, in that time, novel asymmetric hydrogenation reaction was demonstrated in the industrial synthesis of \(\text{L-DOPA}\) using the complex \([\text{Rh(CAMP)}_2(\text{cod})]\text{BF}_4.\(^7\) However, the initial successes of these monodentate phosphines were soon overshadowed by their bidentate analogues and it took almost thirty years until chiral monodentate phosphorus ligands were rediscovered (see section 1.5).

**Scheme 1.1** Rh-catalyzed asymmetric hydrogenation of cinnamic acid derivatives with chiral monodentate phosphines

\[
\begin{align*}
\text{H}_2 & \quad \text{cat. [Rh] + L*} \\
\begin{array}{c}
\text{R} = \text{NHAc, Me} \\
\end{array}
\end{align*}
\]

1.3 Bidentate phosphines

Kagan made an important breakthrough in 1971 with the development of a chiral bidentate phosphine based on tartaric acid, DIOP (Figure 1.1).\(^8\) Catalysts based on this ligand achieved up to 72 % ee for the hydrogenation of acylaminocinnamic acids, which he ascribed to two factors. Firstly, rigidity and stronger binding is enforced by bidentate coordination, minimizing conformational ambiguity. Secondly, a \(C_2\)-symmetric catalyst reduces the number of possible catalyst-substrate complexes by a factor two.\(^9\)

Knowles took advantage of bidentate coordination and chirality at phosphorus, resulting in the synthesis of DIPAMP.\(^10\) This ligand achieved for the first time enantioselectivities above 90 % ee and quickly replaced CAMP in the synthesis of \(\text{L-DOPA}\) giving the optically active drug in up to 95 % ee, an achievement for which Knowles was awarded the Nobel prize in chemistry in 2001.\(^7\) The next breakthrough in the field was realized by Noyori (who shared in the 2001 Nobel prize) and Takaya...
Figure 1.1 Privileged bidentate phosphorus ligands

with the development of BINAP.\textsuperscript{11} By virtue of the axial chirality of the binaphthyl moiety, the conformation of the phenyl rings on the phosphorus donor atoms is locked and the chirality is efficiently transmitted to the metal. Its rhodium complexes catalyze the enantioselective reduction of α-acylaminoacrylic acids in up to 99.9 % ee. In addition, this ligand proved to be extremely versatile and is used nowadays as a benchmark ligand in almost every asymmetric transition metal catalyzed reaction.\textsuperscript{12} One more example worth mentioning in this context is the DuPHOS ligand class, developed by Burk and co-workers at Dupont.\textsuperscript{13} The chiral information in these ligands is contained in the phospholane rings positioned in close proximity to the metal when coordinated. Together with the rigid backbone, this leads to a catalyst that can handle a broad substrate scope requiring only minor variations on the R-substituents. Many more chiral diphosphate ligands have been reported up to now that are discussed in detail in a large number of reviews.\textsuperscript{14}

The ligands displayed in Figure 1.1 all feature $C_2$ symmetry and a high degree of rigidity. Jacobsen\textsuperscript{15} and Pfaltz\textsuperscript{16} identified these structures as privileged ligands for asymmetric catalysis. Even though they were designed for asymmetric hydrogenation reactions, these ligands, or analogues thereof, provide excellent enantioselectivities in many reactions such as asymmetric hydroformylation, allylic substitution, hydroamination, hydrosilylation, conjugate additions, etc. In section 1.6 we will compare these privileged examples to recent combinatorial approaches in ligand development.

1.4 Hybrid bidentate phosphorus ligands

The use of two inequivalent donor atoms in a chiral bidentate ligand introduces a second handle to control the steric and electronic properties of the coordination sphere around the metal. This may be beneficial when regioselectivity is required and it can potentially lead to higher enantioselectivities due to specific binding of the substrate. Hybrid ligands can be composed of a phosphorus atom and a second metal binding heteroatom such as sulfur or nitrogen (P-S, P-N), or composed of two phosphorus atoms that are inequivalent e.g. phosphine-phosphite or phosphine-phosphoramidite. Here we will briefly discuss P-X type ligands and focus on the hybrid ligands with two inequivalent phosphorus donors.
**P-N and P-S ligands.** Chiral P-N ligands were initially designed for asymmetric allylic alkylation reactions and subsequently used as chiral bidentate analogues of Crabtree’s catalyst [Ir(cod)(Pyridine)PCy$_3$]PF$_6$ for the asymmetric hydrogenation of unfunctionalized alkenes.$^{17}$ Pfaltz reported the first successful example of enantioselective hydrogenation of non-heteroatom containing alkenes using the so-called PHOX ligand, which is based on a phosphine-functionalized chiral oxazoline.$^{18}$ It was also independently synthesized by Helmchen et al. (Scheme 1.2).$^{19}$ Many derivatives of the PHOX ligand have been reported by Pfaltz’s group based on the same design concept.$^{20}$ Examples by other groups include JM-Phos developed by Burgess, which contains the chiral information in the backbone rather than in the side-arm of the ligand.$^{21}$ Andersson and co-workers reported chiral P-N ligands based on a bicyclic backbone and an oxazole (1) or thiazole moiety.$^{22}$ Later they also reported 2-azanorbornane derivative 2,$^{23}$ which also proved effective in the hydrogenation of fluorinated olefins and enol phosphinates.$^{24}$ For more examples the reader is referred to the comprehensive review by Cui and Burgess.$^{25}$

Scheme 1.2 Chiral P,N ligands in the Ir-catalyzed asymmetric hydrogenation of α-methylstilbene.

![Scheme 1.2](image)

P-N ligands show a great diversity in structure and are easy to derivatize as they are synthesized in a small number of steps. However, the successful examples all contain a six-membered coordination cycle and a bulky substituent close to the metal. Even though developed mainly for the hydrogenation of unfunctionalized substrates, the P-N ligand based Ir-catalysts prove to be efficient for a range of alkenes, including α,β-unsaturated esters, furans, imines and pyridines. In addition, many have shown to be also active in other reactions such as allylic substitution, in which the difference in trans-influence of the two inequivalent donor atoms aids to obtain high enantio- and regioselectivities.$^{17}$ More examples and other types of P-N ligands containing amino and imino donor groups are reviewed elsewhere.$^{26}$

Compared to P-N ligands, their sulfur analogues remain a rarity in asymmetric catalysis. However, a particularly interesting and efficient C$_1$ symmetric P-S ligand
family has been reported by the laboratory of David Evans (Scheme 1.3). Ligands 3 and 4 have been used for highly enantioselective Pd-catalyzed allylic substitution and Rh-catalyzed hydrogenation. It was shown that the Rh-complex of 4 is able to bind the substrate selectively at only one enantiotopic face. The thus formed major substrate-catalyst complex leads to the product after oxidative addition of molecular hydrogen, migratory insertion of the olefin into the Rh-H bond, and reductive elimination. This mode of enantioselection is very different from the anti-lock-and-key mechanism observed for \(C_2\) symmetric diphosphines in which the minor substrate-catalyst complex leads to the product (see chapter 5).

**Scheme 1.3** Asymmetric allylic alkylation and hydrogenation using chiral P-S ligands 3 and 4 (\(\alpha\)-Nap = \(\alpha\)-naphtyl).

**Phosphine-phosph(on)ite ligands.** The discovery of Binaphos and its excellent enantioselectivities in Rh-catalyzed asymmetric hydroformylation by Nozaki and Takaya was a major breakthrough, and stimulated the development of this hybrid ligand class. The controlled spatial arrangement of two chiral Bisnaphthol backbones in conjunction with the difference in electronic properties of phosphine and phosphite, result in a well-defined hydroformylation catalyst giving more than 90 % ee using styrene as a substrate (Figure 1.2, Scheme 1.4). However, the lengthy synthesis and low b/l (branched aldehyde / linear aldehyde) ratio’s motivated further research in this area. Van Leeuwen and co-workers reported ligand 5 that is based on a \(tropos\) biphenyl backbone connected to a P-chiral phosphine by a flexible linker. The configuration of the biphenyl group is controlled by the adjacent stereocenter. Enantioselectivities up to 63 % were achieved in the asymmetric hydroformylation of styrene, significantly lower than with Binaphos. Ruiz and Claver introduced sugar backbones, as linker unit between phosphine and phosphite, but this additional chirality did not prove beneficial for hydroformylation reactions as moderate.
ee’s up to 38 % were achieved with ligand 6.\textsuperscript{30}

The groups of Pizzano and Schmalz took advantage of a more rigid phenyl scaffold to link the inequivalent donor atoms in ligands 7 and 8. Ligand 7 was initially developed for asymmetric hydrogenation of dehydroamino acid esters and enol ester phosphonates, giving selectivities up to 95 % ee.\textsuperscript{31} The ee’s in hydroformylation reactions did not exceed 71 % for styrene.\textsuperscript{32} Higher selectivities, up to 85 % ee, were obtained using the Taddol functionalized ligand 8,\textsuperscript{33} which was initially used for hydroboration reactions.\textsuperscript{34} The ortho-substituent next to the phosphite moiety proved to be pivotal in order to obtain high ee’s. Only with t-Bu and Ph substituents, ee’s over 80 % were achieved, again indicating the importance of rigidity and control over the coordination sphere. Our group took advantage of these concepts in the design of Xantphos derivative 9. The rigid xanthene backbone was equipped with a diphenylphosphine and a bulky octahydrobinol derived phosphonite. High enantioselectivities (up to 91 % ee) were obtained for dihydrofuran substrates.\textsuperscript{35}

![Phosphine-phosph(on)ite ligands for Rh-catalyzed asymmetric hydroformylation.](image)

In addition to the examples discussed above, other chiral phosphine-phosphite ligands were reported based on the Binaphos platform by Zhang et al.,\textsuperscript{36} and ferrocene derivatives by Chan et al.\textsuperscript{37} Phosphine-phosphite ligands made most impact on the field of asymmetric hydroformylation, however, they have also been successfully employed in allylic alkylation,\textsuperscript{38} conjugate addition,\textsuperscript{39} hydroboration, and hydrogenation.\textsuperscript{40} Again, the difference in trans-influence between the donor atoms facilitates regioselective reactions and specific binding of prochiral substrates. From the examples reported up to now, it seems that rigidity is a key element in this ligand class. Furthermore, combinatorial synthesis of some of these ligands allows for fine-
tuning,\textsuperscript{34,38b} which is necessary as subtle changes in the ligand structure can have dramatic effects on the efficiency of enantioselection.\textsuperscript{33}

**Phosphine-phosphoramidite ligands.** Notwithstanding the fact that phosphoramidite ligands are electronically very similar to phosphites, the steric properties show some marked differences. The nitrogen atom in a phosphoramidite is trivalent versus a bivalent oxygen in a phosphite. This makes phosphoramidites slightly more congested and also offers additional opportunities for derivatization for a more precise control over the positioning of the steric bulk. Moreover, it also enables the incorporation of the nitrogen in a cyclic framework, leading to a higher degree of rigidity. Introduction of an additional phosphate-coordinating group further increases the rigidity. The class of phosphine-phosphoramidite ligands will be treated in detail as the IndolPhos ligands discussed in this thesis belong to this class.

In the review of Crévisy, phosphine-phosphoramidites are divided into four classes based on their amine building blocks: cyclic amines, ferrocene, benzyl/aryl-amines, and chiral-pool diphenylphosphinoamines.\textsuperscript{41} In order to reduce ambiguity, we would like to introduce an alternative classification based on the linker unit between phosphine and phosphoramidite. The linker can be a rigid cyclic amine (1), rigid (bi)cyclic moiety (2), or a flexible chain containing at least one non-cyclic sp\textsuperscript{3}-hybridized carbon atom (3). We believe that this classification is able to cover all examples reported up to now and differentiates clearly in the degree of rigidity, which is a key element in the ligand design.

![Figure 1.3 Cyclic amine containing phosphine-phosphoramidites Quinaphos and IndolPhos.](image)

**Class 1.** In 2000, Leitner reported the first example of a phosphine-phosphoramidite ligand, Quinaphos, which was used for highly enantioselective Rh-catalyzed hydrogenation of dimethyl itaconate and methyl 2-acetamidoacrylate (hereafter dmi and maa, Figure 1.3 and Table 1.1).\textsuperscript{42} A pronounced matched/mismatched effect was observed for the configuration of the two stereocenters. Moreover, this versatile class of ligands was also used successfully in Ru-catalyzed hydrogenation of ketones with ee’s up to 94 %.\textsuperscript{43} Quinaphos ligands are synthesized from 8-bromoquinoline in two consecutive lithiation steps, followed by separation of the two diastereomers formed. This separation results in a low yield for the desired diastereomer giving high ee in catalysis. The second example in this class is the IndolPhos ligand, which will be discussed in detail in the following chapters.
Class 2. Xumu Zhang and co-workers replaced the oxygen linker in Binaphos for an ethylamino group to obtain its phosphoramidite analogue YanPhos (Figure 1.4). The added rigidity and slight change in the ligand’s conformation imposed by using nitrogen instead of oxygen was beneficial for the application of the ligand in asymmetric hydroformylation of styrene, vinyl acetate and allyl cyanide giving ee’s of 99, 98, and 96 %, respectively. These enantioselectivities even surpass Binaphos but the b/l selectivity was moderate. The synthesis of the ligand is, as in the case of Binaphos, long, laborious, and low yielding (> 10 steps). Triphosphorus phosphine-phosphoramidite ligand 10, also developed by Zhang et al., coordinates to Rh and Pd in a bidentate fashion leaving one PPh2 group uncoordinated. The ligand is obtained in four steps from commercially available Binol in good overall yield. It gives rise to highly enantioselective hydrogenation of aryl enamides, dehydroamino acid esters, and itaconic acid derivatives (up to 99 % ee). A remarkable solvent effect was observed in the hydrogenation of these itaconates, switching the absolute configuration of the product when the reaction was performed in ketonic solvents. The reason for this enantioreversal remains unclear.

The group of Zhuo Zheng reported the synthesis of tetrahydronaphthalene- and naphthalene-bridged phosphine-phosphoramidites THNAPhos and HY-Phos, respectively. The phosphine was introduced by directed lithiation of (R)-1,2,3,4-tetrahydro-1-naphtylamine or 1-aminonaphtalene followed by condensation with a bisnaphthol phosphorochloridite. Even though the synthesis is short, the yields for the directed lithiation are moderate (30 – 52 %). Both ligands proved to be highly efficient for Rh-catalyzed hydrogenation. Over 95 % ee was obtained for a variety of prochiral olefins, including α-enol phosphonates, dehydroamino acids, aryl enamides,
hydroxymethylacrylates, and α-dehydroamino acid esters.\textsuperscript{49}

Kostas and Börner described the synthesis of Me-AnilaPhos that is obtained in a single step from 2-diphenylphosphino-\(N\)-methylaniline. It can be considered as the phosphoramidite analogue of ligand 7, which gave rise to the formation of good hydrogenation catalysts. Indeed, the Rh-complex of Me-AnilaPhos is highly active for the hydrogenation of methyl 2-acetamidocinnamate (mac) and dmi giving selectivities of 98 and 96 % ee, respectively.\textsuperscript{50} Derivatives of this ligand containing chiral substituents on the phosphoramidite (11), were successfully applied in the asymmetric hydrogenation of olefins, β-ketoesters, and quinolines.\textsuperscript{51}

Class 3. Ferrocenylphosphine derived ligands 12 were independently reported by the groups of Chan and Zheng (Figure 1.5).\textsuperscript{37,52} They are prepared in a four-step synthesis from commercially available Ugi’s amine, \(N,N\)-dimethyl-1-ferrocenylethylamine, in moderate overall yield. Application of ligand 12 in asymmetric hydrogenation reactions leads to highly active and selective catalysts. Excellent enantioselectivity up to 99.9 % ee was obtained for a broad range of substrates, including β-dehydro amino acid esters.\textsuperscript{53} Moreover, the catalyst loading could be lowered to 0.01 mol% while full conversion was obtained within 30 minutes. The outstanding performance of these catalysts may be seen as the result of combining two privileged chiral scaffolds, \textit{i.e.} the bisnaphthol and chiral ferrocene fragment of the very successful ligands BINAP and Josiphos,\textsuperscript{54} respectively. Similar results were obtained using the H\(_8\)-Binol derivative.\textsuperscript{55}

![Figure 1.5](image-url) Hybrid phosphine-phosphoramidites based on a more flexible linker.

Phenylethylamine-based ligands, PEAPhos reported by Zheng \textit{et al.},\textsuperscript{56} feature a similar linking unit as ferrocenyl-based ligands 12. Replacing the ferrocene moiety with a benzene unit significantly shortens the synthesis, starting from commercially available phenylethylamine. The ligands were evaluated in the Rh-catalyzed asymmetric hydrogenation of α-dehydroamino acid esters, arylenamides and dimethyl itaconate, generating up to 99.9 % ee. Crévisy and co-workers reported the similar
ligand 13,\(^4\) which does not contain a chiral center in the linker. This ligand is obtained from \(\alpha\)-diphenylphosphinobenzaldehyde that is converted to the aminophosphine by reductive amination. Subsequent treatment with \(\text{PCl}_3\) and \((S)\)-Binol furnishes the hybrid phosphine-phosphoramidite. Unfortunately, no application of this ligand in catalysis has been reported, which would give valuable information on the importance of the chiral center in the linker. Ligand 14, containing a short fully aliphatic linker, was prepared in five steps from Boc-protected phenylalaninol. Up to now, this ligand was only evaluated in Cu-catalyzed conjugate additions, resulting in poor \(ee\) values not exceeding 5 %.\(^5\)

**Table 1.1** Rh-catalyzed asymmetric hydrogenation of dimethyl itaconate (dmi), methyl 2-acetamidoacrylate (maa) and methyl 2-acetamidocinnamate (mac) using phosphine-phosphoramidite ligands.\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand (config Binol)</th>
<th>Substrate</th>
<th>Solvent</th>
<th>(H_2) Press. (bar)</th>
<th>% Conv.</th>
<th>% (ee) (config)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Quinaphos (R)</td>
<td>dmi</td>
<td>CH(_2)Cl(_2)</td>
<td>30</td>
<td>&gt; 99</td>
<td>99 (R)</td>
</tr>
<tr>
<td>2</td>
<td>IndolPhos (S)</td>
<td>dmi</td>
<td>CH(_2)Cl(_2)</td>
<td>10</td>
<td>&gt; 99</td>
<td>98 (S)</td>
</tr>
<tr>
<td>3</td>
<td>10 (R)</td>
<td>dmi</td>
<td>TFE</td>
<td>1</td>
<td>&gt; 99</td>
<td>99 (R)</td>
</tr>
<tr>
<td>4</td>
<td>THNAPhos (R)</td>
<td>dmi</td>
<td>CH(_2)Cl(_2)</td>
<td>10</td>
<td>&gt; 99</td>
<td>99 (R)</td>
</tr>
<tr>
<td>5</td>
<td>Me-AnilaPhos (R)</td>
<td>dmi</td>
<td>CH(_2)Cl(_2)</td>
<td>1</td>
<td>&gt; 99</td>
<td>96 (R)</td>
</tr>
<tr>
<td>6</td>
<td>11 (S)</td>
<td>dmi</td>
<td>CH(_2)Cl(_2)</td>
<td>10</td>
<td>&gt; 99</td>
<td>99 (S)</td>
</tr>
<tr>
<td>7</td>
<td>12 (S)</td>
<td>dmi</td>
<td>CH(_2)Cl(_2)</td>
<td>10</td>
<td>&gt; 99</td>
<td>99 (S)</td>
</tr>
<tr>
<td>8</td>
<td>PEAPhos (S)</td>
<td>dmi</td>
<td>CH(_2)Cl(_2)</td>
<td>10</td>
<td>&gt; 99</td>
<td>99 (nd)</td>
</tr>
<tr>
<td>9</td>
<td>Quinaphos (S)</td>
<td>maa</td>
<td>CH(_2)Cl(_2)</td>
<td>30</td>
<td>&gt; 99</td>
<td>98 (S)</td>
</tr>
<tr>
<td>10</td>
<td>IndolPhos (S)</td>
<td>maa</td>
<td>CH(_2)Cl(_2)</td>
<td>10</td>
<td>&gt; 99</td>
<td>98 (R)</td>
</tr>
<tr>
<td>11</td>
<td>10 (R)</td>
<td>maa</td>
<td>acetone</td>
<td>1</td>
<td>&gt; 99</td>
<td>99 (R)</td>
</tr>
<tr>
<td>12</td>
<td>THNAPhos (R)</td>
<td>mac</td>
<td>CH(_2)Cl(_2)</td>
<td>10</td>
<td>&gt; 99</td>
<td>99 (S)</td>
</tr>
<tr>
<td>13</td>
<td>HY-Phos (S)</td>
<td>mac</td>
<td>CH(_2)Cl(_2)</td>
<td>10</td>
<td>&gt; 99</td>
<td>98 (R)</td>
</tr>
<tr>
<td>14</td>
<td>Me-AnilaPhos (R)</td>
<td>mac</td>
<td>CH(_2)Cl(_2)</td>
<td>1</td>
<td>&gt; 99</td>
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<tr>
<td>15</td>
<td>11 (S)</td>
<td>maa</td>
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<td>10</td>
<td>&gt; 99</td>
<td>99 (R)</td>
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<tr>
<td>16</td>
<td>12 (S)</td>
<td>maa</td>
<td>CH(_2)Cl(_2)</td>
<td>10</td>
<td>&gt; 99</td>
<td>99 (R)</td>
</tr>
<tr>
<td>17</td>
<td>PEAPhos (S)</td>
<td>mac</td>
<td>CH(_2)Cl(_2)</td>
<td>10</td>
<td>&gt; 99</td>
<td>99 (R)</td>
</tr>
</tbody>
</table>

\(^a\) Reactions were performed at Rh/L \(\leq 1:1.1\), Rh/substrate \(\leq 1:100\), at 25 °C for \(\leq 24\) h using \([\text{Rh(nbd)}_2]\)BF\(_4\) or \([\text{Rh(cod)}_2]\)BF\(_4\) as metal precursor. (TFE = trifluoroethanol)

Comparison of the catalytic properties of the phosphine-phosphoramidites discussed above may give valuable insight into the structure-reactivity/selectivity relationship within this class of ligands. Unfortunately, not all ligands have been applied in the same reaction, prohibiting direct comparison of all ligands. However, results in asymmetric hydrogenation have been reported for most examples and are summarized in Table 1.1 for dmi and maa. When results for maa were unavailable,
results obtained with mac, a structurally similar substrate, are included. For these substrates, all ligands give full conversion and enantioselectivities range between 96 and 99 %. In nearly all cases, the absolute configuration of the bisnaphthol backbone determines the absolute configuration of the product. This indicates a similar mechanism of enantioselection for the whole class of phosphine-phosphoramidites, except for ligand 10. This exception can be understood as in this case the Bisnaphthol moiety is the linking unit, whereas in all other cases it is not involved in connecting the phosphine and phosphoramidite. For some examples, the activity was studied more carefully.\textsuperscript{42,52} It was found that phosphine-phosphoramidite give unusually active hydrogenation catalysts, which may be explained by a perfect synergy between the electron-donating properties of the phosphine and $\pi$-acidic character of the phosphoramidite. Summarizing, the excellent activities and enantioselectivities obtained in asymmetric hydrogenation reactions illustrate the practical potential of phosphine-phosphoramidites. Especially ligands that are synthesized in only two or three synthetic steps are promising candidates to be applied in fine-chemical synthesis on an industrial scale.

1.5 Next generation chiral monodentate and supramolecular phosphorus ligands

In 2000, the groups of Reetz, Feringa and de Vries, and Pringle independently reported the use of Binol-based phosphites (15),\textsuperscript{58} phosphoramidites (16),\textsuperscript{59} and phosphonites (17),\textsuperscript{60} respectively, as ligands in Rh-catalyzed asymmetric hydrogenation reactions (Figure 1.6).\textsuperscript{61} These ligands are attractive as they induce high enantioselectivities up to 99 % ee and for their ease of preparation; just one or two steps from cheap commercially available starting materials. The active Rh-species is found to be coordinated by two monodentate ligands.\textsuperscript{62} This opens up the possibility of mixing monodentate ligands in order to increase the number of successful catalyst.\textsuperscript{63} This combinatorial approach has significantly contributed to the success of this class of ligands enabling asymmetric hydrogenation of a broad range of substrates and application in many other reactions such as Cu-catalyzed conjugate additions.\textsuperscript{64}

![Figure 1.6 Next generation monodentate Binol-based phosphites, phosphoramidites and phosphonites](image-url)
Application of mixtures of monodentate ligands is an attractive strategy to generate large ligand libraries but also has the inherent drawback that the homocombinations, which are likely present, have a detrimental effect on the enantioselectivity. By tuning the ratio’s between the two different ligands, this problem can be circumvented, however, at the expense of inefficient use of rhodium as part is captured in an inactive complex. Alternatively, a supramolecular recognition group can be build into the monodentate building blocks, forming an attractive interaction that generates a supramolecular bidentate ligand upon self-assembly.

Supramolecular phosphorus ligands enable the construction of a combinatorial library of bidentate ligands. Early examples based on metal-ligand interactions were reported by our group and Takacs et al. Even though excellent catalytic results were obtained with these ligands, their lengthy synthesis and high molecular weight hampers commercial applications. More recently, hydrogen-bonding interactions are being used to obtain supramolecular bidentate ligands, which are prepared in a few synthetic steps only and do not exceed molecular weights of classic bidentate ligands. Breit and co-workers took advantage of nature’s hydrogen-bonding pattern in DNA in the supramolecular bidentate ligand composed of 19a and 19b (Figure 1.7). The power of this binding motif is that the aminopyridine and isoquinoline building blocks bind cooperatively. Even though they are self-complementary in the absence of a metal, coordination of the phosphines preorganizes the binding motifs, which leads to exclusive formation of supramolecular heterobidentate ligands. Achiral versions of these catalysts have been shown to generate high l/b ratio’s in the hydroformylation of linear olefins, which are normally only achieved with wide bite-angle diphosphine ligands, thus indicating the bidentate character of these supramolecular ligands.

Heterobidentate ligands containing a chiral Binol derived phosphonite, were shown to give high enantioselectivities up to 99 % ee for the asymmetric hydrogenation of dmi and maa.

Our group contributed to self-assembled hydrogen-bonded bidentate ligands with UREAPhos, which has shown excellent efficiencies in asymmetric hydrogenation reactions of industrially relevant substrates. Initially, these ligands were applied

Figure 1.7 Supramolecular approaches towards chiral bidentate ligands based on hydrogen-bonding interactions.
as supramolecular homobidentate ligands, but more recently they have been
successfully used as supramolecular heterobidentates by combining with
ureaphosphines (22).\textsuperscript{72} We also reported the use of sulfonamido-functionalized
phosphines, METAMORPhos, to form supramolecular bidentate ligands (Figure
1.7).\textsuperscript{73} The adaptive character of the ligand allows the formation of purely
heterobidentate complexes that show excellent activity and selectivity (up to 99 \% ee)
in the hydrogenation of maa. In the presence of cationic Rh-precursors the
Bisnaphthol-based METAMORPhos ligands give rise to the formation of dinuclear
species that show unprecedented selectivities up to 99 \% ee for tetrasubstituted
prochiral olefins.\textsuperscript{74}

A second recent example of hydrogen-bonded supramolecular phosphorus ligands,
LEUPhos, is based on the complementary interaction of an amino acid derived
phosphoramidite (21) with an ureaphosphine (22).\textsuperscript{75} The self-assembled catalyst was
shown to be highly active for the synthesis of Roche ester derivatives by means of
asymmetric hydrogenation. By now, many more examples of supramolecular ligands
have been reported based on metal-ligand interactions, hydrogen bonding, and ion
pairing,\textsuperscript{76} which are reviewed elsewhere.\textsuperscript{67b,68,77}

1.6 Privileged vs. combinatorial ligands

Since the introduction of the term ‘privileged ligand’, this classification is found
widespread in the literature concerning ligand design. However, the meaning is not
always the same and therefore a stricter definition in this context is used here: A
privileged ligand is a single chiral structure that provides highly active and
enantioselective catalysts for a broad range of substrates and reactions. Privileged
ligands exhibit a high degree of generality, which opposes the specificity found in
enzymes and recent developments in combinatorial approaches towards ligand design.
In the last approach, for each substrate in a particular reaction a tailor made ligand is
provided. In this section, we will try to identify advantages and disadvantages of both
strategies and highlight their complementarities.

Comparing different ligands without a specific reaction or substrate is not very
informative; therefore we will illustrate differences based on two different cases. In the
case of a new asymmetric reaction that is not yet mechanistically fully understood,
such as asymmetric hydroamination with Rh or Pd,\textsuperscript{78} privileged ligands are often the
first choice. Their rigidity and bidentate coordination result in well-defined complexes,
which is often advantageous when not all reaction parameters are optimized. Good
ee’s are obtained for a small number of model substrates. However, when an
asymmetric reaction is to be applied for real-life substrates of which the products are
to be used as \textit{e.g.} pharmaceutical intermediates, the privileged ligand approach is often
insufficient (asymmetric hydrogenation). Fine-tuning of the catalyst is required in
those cases, which can be achieved through modular ligand synthesis (hybrid ligands)
or combinatorial approaches (monodentate and supramolecular ligands).
Privileged and combinatorial ligands are therefore complementary strategies for catalyst optimization. Whereas privileged ligands will be valuable in the early stages of reaction discovery, optimization and application for real-life substrates necessitates fine-tuning provided by combinatorial approaches. Hybrid ligands can be considered as an intermediate option between these two extremes, as they offer possibilities for fine-tuning but still display a high degree of generality.

In conclusion, it is in our opinion impossible to ever find one ligand that will be suitable for all substrates in a specific reaction, let alone multiple reactions. New ligands for new applications will therefore always be required. It is important, however, that these new ligands are able to also transform real-life, non-benchmark substrates. We therefore would like to encourage all researchers in this field to evaluate their new ligands for challenging substrates next to some benchmark substrates, as it is hard to judge the potential of a new ligand solely on the results obtained for benchmark substrates.

1.7 Outline of the thesis

Based on the work on chiral phosphorus ligands discussed in this chapter, hybrid ligands clearly have a great potential to play a major role in applications of asymmetric catalysis in industry. However, the cost effectiveness of these ligands is not ideal in many cases and short and robust synthetic sequences are desirable. In this thesis we describe the development of a new hybrid ligand, IndolPhos, which is able to address this question and shows applicability for a broad range of substrates and reactions (Chapters 2-7). Apart from their facile preparation, the ligands exhibit interesting metal-coordination properties and unusual reaction mechanisms. In addition, the newly developed synthetic methodology has also been applied in the synthesis of tetraphosphine ligands and their corresponding Rh-complexes, which give rise to the formation of stable metalloradicals that enable oxidative activation of dihydrogen (Chapter 9).

An important aspect of contemporary combinatorial ligand synthesis is the evaluation of the large number of catalysts generated. Catalyst selection tools offer a rapid alternative to individual testing. In chapter 8, we introduce a screening protocol based on the stability of catalytic intermediates determined by mass spectrometry. We demonstrated the concept successfully in the Pd-catalyzed allylic alkylation using diphosphine and IndolPhos ligands.

1.8 References

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