Indole-based phosphorus ligands in asymmetric catalysis
Wassenaar, J.

Citation for published version (APA):
Wassenaar, J. (2010). Indole-based phosphorus ligands in asymmetric catalysis

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
IndolPhos: Novel hybrid phosphine-phosphoramidite ligands for asymmetric hydrogenation and hydroformylation†

Abstract: A new class of hybrid bidentate phosphine-phosphoramidite ligands based on the indole backbone is presented. Their coordination mode to Rh is controlled by the steric properties of the ligand, which has shown to play a major role in the asymmetric hydrogenation and hydroformylation leading to high enantioselectivities (up to 98% ee).

† Part of this chapter has been published: Wassenaar, J.; Reek, J. N. H. *Dalton Trans.* 2007, 3750–3753.
2.1 Introduction

Enantioselective transition metal catalysis has emerged as a unique tool for the introduction of chirality in pharmaceuticals and fine chemical intermediates. Asymmetric catalytic hydrogenation has become particularly important as many different building blocks with a variety of functional groups become accessible.\(^1\) Traditionally, chiral bidentate phosphine ligands\(^2\) have dominated this field until more recently Feringa and De Vries,\(^3\) Reetz,\(^4\) and Pringle\(^5\) introduced the use of monodentate phosphites and phosphoramidites. Due to their more simple structure, their synthesis is generally much less elaborate, enabling the preparation of large ligand libraries that are essential to rapidly find new catalysts that enable asymmetric conversion of new substrates. Although these monodentate–based catalysts have been successful for many reactions, bidentate ligands, and heterobidentates in particular, will always be required to achieve high activity, selectivity and stability for a number of transformations. Therefore there is a need to develop novel bidentate ligands, preferentially with straightforward synthetic procedures. A recent advancement in this area is the use of supramolecular bidentate ligands which form by assembly of functionalized simple monodentate building blocks.\(^6,7\) Alternatively, one could devise simple modular synthetic strategies that should lead to easy access to bidentate ligands. Here we present a series of hybrid bidentate phosphine–phosphoramidite ligands 2a–d that are accessible by a two-step synthetic sequence from cheap commercially available building blocks.\(^8\) The new ligands display unusual coordination properties and are highly active and selective in the rhodium catalyzed hydrogenation and hydroformylation.

2.2 Ligand design & synthesis

Browning and co-workers have introduced indolylphosphines 1, which are appealing to us as they are easily prepared in one step from cheap starting materials and offer further phosphorus functionalization through the indolyl nitrogen.\(^9\) The novel bidentate phosphine-phosphoramidite ligand (IndolPhos) contains a two-atom bridge leading to the formation of five-membered coordination cycles as opposed to the frequently reported six–membered cycles.\(^10\) In addition, molecular modelling indicates that the backbone is completely sp\(^2\) hybridized, thereby enforcing a high degree of rigidity (Figure 2.1). The rigidity is expressed by large phosphine–phosphoramidite couplings in the \(^{31}\)P NMR spectra of ligands 2a–d (up to 250 Hz, see experimental section), which is also observed for other rigid small bite angle ligands.\(^8c,11\) Therefore, IndolPhos can be considered as a hybrid analogue of the privileged DuPHOS in terms of bite-angle and rigidity, but variation of substituents is far more facile in the current ligand, enabling the synthesis of large and diverse ligand libraries.
IndolPhos: Novel hybrid phosphine-phosphoramidite ligands for asymmetric hydrogenation and hydroformylation

Figure 2.1 Calculated (DFT, B3LYP, 6-31G*) structure of IndolPhos 2b (green = C, white = H, blue = N, red = O, yellow = P).

We have optimized the synthesis of 3-methyl-2-indolylphosphines by using CO₂ as a protecting and directing group, resulting in a one-pot protocol. Deprotonation of the indolyl NH by n-BuLi is followed by carboxylation to yield the protected 1-carboxyl-3-methylindole in situ. Addition of t-BuLi results in selective deprotonation at the ortho-position of the carboxyl group to yield the 2-lithiated intermediate, which is reacted with the corresponding chlorophosphine. The carboxyl protecting group is removed by mild acidic workup to give indolylphosphines 1 in good yield. Initial condensation attempts of 1 with bisnaphthol phosphorochloridites in the presence of weak bases such as triethylamine failed, probably due to the low nucleophilicity of the indolyl NH. Deprotonation using a strong base such as n-BuLi proved to be effective and IndolPhos ligands 2a–d are obtained in high yield (Scheme 2.1).

Scheme 2.1 Synthesis of IndolPhos ligands.

2.3 Coordination chemistry

The coordination properties of ligands 2a–d to cationic rhodium were investigated by ¹H and ³¹P NMR spectroscopy. Mixing ligand 2a with one equivalent of [Rh(nbd)]BF₄ in CDCl₃ led to the formation of a 1 : 4 mixture of the expected [Rh(2a)(nbd)]BF₄ and a second species exhibiting a complicated AA’XX’ multiplet in
the $^{31}$P NMR spectrum (Figures 2.2 and 2.4). The second species could be identified as $[\text{Rh}(\text{2a})_2]\text{BF}_4$ where phosphines and phosphoramidites of the two ligands are in mutual $cis$ position as indicated by the large $J_{\text{PN,PC}}$ of 389 Hz (Figure 2.3). To our knowledge this is the second report of such a bis-ligated species for hybrid bidentate phosphorus ligands. Importantly, when changing the steric properties of the ligand to more bulky substituents on either the phosphine (2b) or bisnaphthol (2c), only mono-ligated species $[\text{Rh}(\text{2b})(\text{nbd})]\text{BF}_4$ and $[\text{Rh}(\text{2c})(\text{nbd})]\text{BF}_4$ were formed (Figures 2.5 – 2.7). Additional factors disfavouring bis-ligated species in the case of 2b and 2d are the lack of $\pi$-stacking interactions and the stronger $trans$-effect of alkyl phosphines.

**Figure 2.2** Calculated (top) and measured (bottom) $^{31}$P{${}^1$H} NMR spectra for $[\text{Rh}(\text{2a})_2]\text{BF}_4$. Coupling constants used for the simulated spectrum: $J_{\text{PN,Rh}} = 225$ Hz, $J_{\text{PC,Rh}} = 124$ Hz, $J_{\text{PN,PN}} = 26$ Hz, $J_{\text{PC,PC}} = 17$ Hz, $J_{\text{PN,PC}(\text{cis})} = -62$ Hz, $J_{\text{PN,PC}(\text{trans})} = 389$ Hz. The additional double of doublets in the measured spectrum stems from $[\text{Rh}(\text{2a})(\text{nbd})]\text{BF}_4$.

**Figure 2.3** Structure of $[\text{Rh}(\text{2a})_2]\text{BF}_4$ (left) and assignment of $^{31}$P NMR coupling constants (right).

### 2.4 Asymmetric hydrogenation & hydroformylation

The special coordination properties of ligands 2a–d prompted us to investigate their influence on the catalytic performance in the Rh-catalyzed asymmetric
hydrogenation and hydroformylation. The hydrogenation of benchmark substrates dimethyl itaconate (A) and methyl 2-acetamidoacrylate (B) using ligands 2a–d was studied (Table 2.1). To our surprise it was observed that ligand 2a, although it forms unreactive bis-ligated species, was able to hydrogenate A and B to full conversion, inducing a considerable amount of ee (entries 1 and 5). It is proposed that the minor mono-ligated species performs most of the catalysis along with the achiral Rh-precursor which lowers the ee. Control experiments showed that ligand free [Rh(nbd)₂]BF₄ was able to fully convert A and B within 12 h. The more bulky ligand 2c bearing trimethylsilyl groups in ortho-position on the Bisnaphthol, preventing formation of bis-ligated species, results in similar activities compared to ligand 2a as full conversion is obtained. However, the selectivity obtained with the catalyst based on 2c was rather low (entries 3 and 7). Interestingly, full conversion and high selectivities were obtained when the steric bulk was introduced on the phosphine moiety (2b, up to 98% ee, entries 2 and 6). For MAA (B), the enantioselectivity could be further enhanced by introducing methyl substituents in ortho-position of the Bisnaphthol moiety (2d, up to 97% ee, entries 4 and 8).

**Table 2.1** Rhodium catalyzed asymmetric hydrogenation of dimethyl itaconate and methyl 2-acetamidoacrylate.a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Substrate</th>
<th>% conv.</th>
<th>% ee (config)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2a</td>
<td>A</td>
<td>100</td>
<td>73 (S)</td>
</tr>
<tr>
<td>2</td>
<td>2b</td>
<td>A</td>
<td>100</td>
<td>98 (S)</td>
</tr>
<tr>
<td>3</td>
<td>2c</td>
<td>A</td>
<td>100</td>
<td>12 (S)</td>
</tr>
<tr>
<td>4</td>
<td>2d</td>
<td>A</td>
<td>100</td>
<td>92 (S)</td>
</tr>
<tr>
<td>5</td>
<td>2a</td>
<td>B</td>
<td>100</td>
<td>13 (S)</td>
</tr>
<tr>
<td>6</td>
<td>2b</td>
<td>B</td>
<td>100</td>
<td>86 (R)</td>
</tr>
<tr>
<td>7</td>
<td>2c</td>
<td>B</td>
<td>100</td>
<td>36 (R)</td>
</tr>
<tr>
<td>8</td>
<td>2d</td>
<td>B</td>
<td>100</td>
<td>97 (R)</td>
</tr>
</tbody>
</table>

a Reactions were performed in CH₂Cl₂, Rh/L = 1:1.1, Rh/substrate = 1:100, 10 bar of H₂, at 25°C for 16 h using [Rh(nbd)₂]BF₄ as metal precursor. b [Rh(2c)(cod)]BF₄ was used instead of the in situ generated catalyst.

In all ligands the absolute configuration of the Bisnaphthol, the only source of chirality in the molecule, was identical. It is therefore surprising that 2a gives the opposite enantiomer of the product compared to 2b–d in the hydrogenation of B (entries 5–8). This result suggests that a different mechanism is operating in the case of 2a.¹⁴ Jugé et al. have described a similar effect when changing substituents on their hybrid aminophosphine–phosphinite system.¹⁵ They observed a reversal of enantioselectivity when aryl substituents were replaced by alkyl, which is explained by
steric effects in the intermediate olefin complexes forcing the substrate to coordinate with the other prochiral face. A similar explanation is likely for the origin of the effects we observe, as the change in substituents is comparable.

Table 2.2 Rhodium catalysed asymmetric hydroformylation of styrene.

<table>
<thead>
<tr>
<th>Entry</th>
<th>T (°C)</th>
<th>Ligand</th>
<th>% conv.</th>
<th>b/l</th>
<th>% ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>60</td>
<td>2a</td>
<td>3</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>2'</td>
<td>40</td>
<td>2b</td>
<td>84</td>
<td>17</td>
<td>50</td>
</tr>
<tr>
<td>3</td>
<td>60</td>
<td>2b</td>
<td>55</td>
<td>6</td>
<td>51</td>
</tr>
<tr>
<td>4</td>
<td>60</td>
<td>2c</td>
<td>99</td>
<td>12</td>
<td>9</td>
</tr>
<tr>
<td>5</td>
<td>40</td>
<td>2d</td>
<td>96</td>
<td>10</td>
<td>72</td>
</tr>
<tr>
<td>6</td>
<td>60</td>
<td>2d</td>
<td>97</td>
<td>7</td>
<td>61</td>
</tr>
</tbody>
</table>

\[\text{[Rh(acac)(CO)\textsubscript{2}]} = 1.0 \text{ mmol/l in toluene, [ligand] = 4.0 \text{ mmol/l}, styrene/rhodium = 1000, pressure = 10 \text{ bar (CO/H\textsubscript{2}} = 1/1).} \]

\[\text{Percentage conversion; the reaction was stopped after 19 h.} \]

\[\text{Ratio of branched to linear product.} \]

\[\text{In all cases the R enantiomer of the product was formed.} \]

After the promising results obtained in the asymmetric hydrogenation, we investigated the catalytic properties of ligands 2a–d in the more challenging hydroformylation of styrene (Table 2.2). We were encouraged by the results of Zhang and co-workers who obtained complete enantioselection in the hydroformylation of styrene using a hybrid phosphine-phosphoramidite ligand derived from NOBIN. Initial results were disappointing as the application of parent ligand 2a gave rise to low conversion (entry 1). Since the hydroformylation reaction is carried out in the presence of excess ligand with respect to rhodium, this low activity can be explained by the formation of inactive complexes with two ligands 2a coordinated to rhodium, as was also observed in the NMR experiments \textit{(vide supra)}, and for TangPhos ligands. Indeed, introduction of sterically more demanding groups suppresses the formation of such species. Instead active catalysts are formed that provide the product with moderate to good ee’s with a maximum of 72% ee (ligand 2d entry 5). A high selectivity for the branched product with a b/l ratio of 17 was obtained using ligand 2b (entry 2). We expect that further optimization of this ligand will lead to a catalyst that will give both high regio- and enantioselectivity, as will be discussed in chapter 6.

2.5 Conclusion

In summary, we have developed a new set of hybrid bidentate phosphine-phosphoramidite ligands based on the indole backbone. Their coordination mode to Rh is controlled by the steric properties of the ligand, which has been shown to play a major role in the asymmetric hydrogenation and hydroformylation. High enantioselectivities (up to 98% ee) are obtained with ligands 2b and 2d in the
asymmetric hydrogenation of benchmark substrates A and B. A high selectivity for the branched aldehyde along with good ee (up to 72%) is reached in the hydroformylation of styrene. The modular synthetic sequence allows for easy derivatization of the ligand enabling high-throughput screening of a IndolPhos library to convert more challenging substrates, which is treated in chapters 3 and 4. In chapter 5, the mechanism of enantioselection is investigated in more detail by kinetic studies, high-pressure NMR spectroscopy, and DFT calculations. In chapter 6, the substrate scope and mechanism of the IndolPhos-Rh catalyzed asymmetric hydroformylation is investigated in detail.

2.6 Experimental section

**General procedures.** All reactions were carried out under an atmosphere of argon using standard Schlenk techniques. THF, pentane, hexane and diethyl ether were distilled from sodium benzophenone ketyl; CH$_2$Cl$_2$, isopropanol and methanol were distilled from CaH$_2$ and toluene was distilled from sodium under nitrogen. With exception of the compounds given below, all reagents were purchased from commercial suppliers and used without further purification. The following compounds were synthesized according to published procedures: phosphorochloridite of (S)-(−)-2,2′-bisnaphthol,\textsuperscript{17} phosphorochloridite of (S)-(−)-3,3′-bis(trimethylsilyl)-2,2′-bisnaphthol,\textsuperscript{17} phosphorochloridite of (S)-(−)-3,3′-dimethyl-2,2′-bisnaphthol.\textsuperscript{18} NMR spectra (\textsuperscript{1}H, \textsuperscript{31}P and \textsuperscript{13}C) were measured on a Varian INOVA 500 MHz. Optical rotations were determined on a Perkin-Elmer 241 polarimeter. High resolution mass spectra were recorded on a JEOL JMS SX/SX102A four sector mass spectrometer; for FAB-MS 3-nitrobenzyl alcohol was used as matrix. Gas chromatographic analyses were run on a Shimadzu GC-17A apparatus (split/splitless, equipped with a FID detector and a BPX35 column, internal diameter of 0.22 mm, film thickness 0.25 µm, carrier gas 70 kPa He). Chiral GC separations were conducted on an Interscience Trace GC Ultra (FID detector) with a ph Megadex column (internal diameter 0.1 mm, 5 m column, film thickness 0.1 µm) and an Interscience Focus GC (FID detector) with a Supelco BETA DEX column (0.25 mm x 30 m).

**Synthesis of diphenyl(3-methyl-2-indolyl)phosphine (1a).\textsuperscript{9}** To a solution of 3-methylindole (2.46 g, 18.8 mmol) in THF (50 mL) was added dropwise 7.9 mL of n-BuLi (2.5 M in hexanes) at -78 °C. The resulting suspension was stirred at -78 °C for 20 min. Carbon dioxide was bubbled through the suspension for 30 min allowing the mixture to warm to room temperature, after which the solvent was removed in vacuo. The resulting white residue was dissolved in THF (50 mL) to give a clear yellow solution, which was cooled to -78 °C. To this solution 11.6 mL of t-BuLi (1.7 M in pentanes) was added and the resulting orange solution was stirred at -78 °C for 1 h. Chlorodiphenylphosphine (3.37 mL, 18.8 mmol) was added dropwise and the reaction mixture was stirred for 16 h allowing to warm to room temperature. The resulting yellow solution was washed with 50 mL degassed sat. aq. NH$_4$Cl. The organic layer was dried over MgSO$_4$, filtered and the solvent was removed in vacuo. The crude pale yellow residue was recrystallised from MeOH to yield the product as a white powder. Yield: 4.01 g (68 %). \textsuperscript{1}H NMR (CDCl$_3$, 500 MHz, 298 K): δ (ppm) 7.63 (d, $J = 8.0$ Hz, 1H), 7.48 (bs, 1H), 7.38-7.33 (m, 10H), 7.24 (d, $J = 8.0$ Hz, 1H), 7.21 (dt, $J = 7.0$ Hz, 1.0 Hz, 1H), 7.13 (dt, $J = 7.0$ Hz, 1.0 Hz, 1H), 2.49 (s, 3H). \textsuperscript{13}C NMR (CDCl$_3$, 125.5 MHz, 298 K): δ (ppm) 138.3, 136.43,
136.36, 133.32, 133.2, 129.52, 129.47, 129.07, 129.05, 129.01, 127.4, 127.3, 123.3, 122.5, 122.3, 119.6, 119.4, 111.2, 10.1. $^{31}\text{P}^1(\text{H})$ NMR (CDCl$_3$, 202.3 MHz, 298 K): $\delta$ (ppm) -32.08 (s). HRMS (FAB) calcd for [M + H]$^+$ C$_{21}$H$_{29}$NP, 316.1255; found, 316.1242.

**Synthesis of diisopropyl(3-methyl-2-indolyl)phosphine (1b).** To a solution of 3-methylindole (3.55 g, 27.1 mmol) in THF (70 mL) was added dropwise 11.4 mL of n-BuLi (2.5 M in hexanes) at -78 °C. The resulting suspension was stirred at -78 °C for 20 min. Carbon dioxide was bubbled through the suspension for 30 min allowing the mixture to warm to room temperature, after which the solvent was removed in vacuo. The resulting white residue was dissolved in THF (70 mL) to give a clear yellow solution, which was cooled to -78 °C. To this solution 18.9 mL of t-BuLi (1.5 M in pentanes) was added and the resulting orange solution was stirred at -78 °C for 1 h. Chlorodisopropylphosphine (4.31 mL, 27.1 mmol) was added dropwise and the reaction mixture was stirred for 16 h allowing to warm to room temperature. The resulting yellow solution was washed with 50 mL degassed sat. aq. NH$_4$Cl. The organic layer was dried over MgSO$_4$, filtered and the solvent was removed in vacuo. The crude pale yellow residue was dissolved in 60% EtOAc/Hexanes and filtered through a pad of SiO$_2$ to obtain the product as an off white powder. Yield: 5.23 g (78%). $^1$H NMR (CDCl$_3$, 500 MHz, 298 K): $\delta$ (ppm) 7.91 (br s, 1H), 7.60 (d, $J$ = 8.0 Hz, 1H), 7.36 (d, $J$ = 7.5 Hz, 1H), 7.23 (t, $J$ = 7.5 Hz, 1H), 7.13 (t, $J$ = 7.5 Hz, 1H), 2.48 (s, 3H), 2.18 (septet, $J$ = 7.0 Hz, 2H), 1.16 (dd, $J_{HH}$ = 7.0 Hz, $J_{PH}$ = 16.0 Hz, 6H), 1.01 (dd, $J_{Hh}$ = 7.0 Hz, $J_{PH}$ = 11.0 Hz, 6H). $^{13}$C NMR (CDCl$_3$, 125.5 MHz, 298 K): $\delta$ (ppm) 138.0, 129.2, 129.1, 127.9, 127.7, 123.5, 123.4, 123.0, 119.24, 119.22, 110.7, 23.9, 23.8, 20.6, 20.5, 19.9, 19.8, 10.4, 10.3. $^{31}\text{P}^1(\text{H})$ NMR (CDCl$_3$, 202.3 MHz, 298 K): $\delta$ (ppm) -17.70 (s). HRMS (FAB) calcd for [M + H]$^+$ C$_{13}$H$_{23}$NP, 248.1568; found, 248.1561.

**Synthesis of diphenyl[1-[(S)-3,5-dioxo-4-phospha-cyclohepta(2,1-α;3,4-α')] dinaphtalen-4-yl]-3-methyl-2-indolyl]phosphine (2a).** To a solution of 1a (1.05 g, 3.3 mmol) in THF (15 mL) was added dropwise 1.33 mL of n-BuLi (2.5 M in hexanes) at -78 °C. The resulting yellow-orange solution was stirred for 0.5 h at -78 °C and allowed to warm to room temperature. This solution was added dropwise to a solution of (S)-(−)-2,2'-bisnaphtol phosphorochloridite (1.17 g, 3.3 mmol) in THF (10 mL) at -78 °C. The reaction mixture was stirred for 15 h allowing to warm to room temperature. The resulting pale yellow solution was filtered through a pad of SiO$_2$, which was rinsed twice with THF (2 x 10 mL). The solvent was removed in vacuo. Co-evaporation with pentanes gave the product as a white powder. Yield: 2.08 g (99 %). $[\alpha]^{22}_D$ = +238.2 (c = 2.9, CHCl$_3$). $^1$H NMR (CDCl$_3$, 500 MHz, 298 K): $\delta$ (ppm) 7.97 (d, $J$ = 9.0 Hz, 1H), 7.94 (d, $J$ = 8.5 Hz, 1H), 7.83 (d, $J$ = 8.0 Hz, 1H), 7.56-7.31 (m, 18H), 7.28 (m, 1H), 6.89 (t, $J$ = 7.3 Hz, 1H), 6.75 (d, $J$ = 8.5 Hz, 1H), 6.53 (d, $J$ = 8.5 Hz, 1H), 6.24 (t, $J$ = 7.8 Hz, 1H), 2.04 (s, 3H). $^{13}$C NMR (CDCl$_3$, 125.5 MHz, 298 K): $\delta$ (ppm) 150.4, 148.7, 140.6, 135.7, 135.1, 133.2, 132.9, 132.8, 132.2, 132.0, 131.5, 130.9, 130.6, 128.9, 128.81, 128.76, 128.68, 128.64, 128.62, 128.58, 128.47, 128.1, 127.3, 126.9, 126.62, 126.55, 125.5, 125.1, 124.7, 123.8, 123.0, 121.9, 121.5, 121.2, 118.6, 116.3, 10.8. $^{31}\text{P}^1(\text{H})$ NMR (CDCl$_3$, 202.3 MHz, 298 K): $\delta$ (ppm) 143.43 (d, $J_{PP}$ = 165.7 Hz), -27.95 (d, $J_{PP}$ = 165.7 Hz). HRMS (FAB) calcd for [M + H]$^+$ C$_{41}$H$_{58}$NO$_2$P$_2$, 630.1752; found, 630.1743.

**Synthesis of diisopropyl[1-[(S)-3,5-dioxo-4-phospha-cyclohepta(2,1-α;3,4-α')] dinaphtalen-4-yl]-3-methyl-2-indolyl]phosphine (2b).** To a solution of 1b (298 mg, 1.2 mmol) in THF (10 mL) was added dropwise 0.48 mL of n-BuLi (2.5 M in hexanes) at -78°C. The resulting pale yellow solution was stirred for 1 h at -78 °C and allowed to warm to room
temperature. This solution was added dropwise to a solution of (S)-(−)-2,2′-bisnaphtol phosphorochloridite (422 mg, 1.2 mmol) in THF (5 mL) at -78 °C. The reaction mixture was stirred for 1 h at -78 °C and then allowed to warm to room temperature. The resulting pale yellow solution was filtered through a pad of SiO₂, which was rinsed twice with THF (2 x 10 mL). The solvent was removed in vacuo. The crude off-white solid was purified by SiO₂ column chromatography (5 % EtOAc/Hexanes) to obtain the product as a white powder. Yield: 598 mg (89 %). [α]₂²₅D = +366.1 (c = 2.1, CHCl₃). ¹H NMR (CDCl₃, 500 MHz, 298 K): δ (ppm) 8.06 (d, J = 9.0 Hz, 1H), 7.99 (d, J = 8.5 Hz, 1H), 7.84 (d, J = 8.0 Hz, 1H), 7.60 (d, J = 9.0 Hz, 1H), 7.55 (d, J = 8.5 Hz, 1H), 7.51-7.45 (m, 4H), 7.40 (d, J = 7.5 Hz, 1H), 7.37-7.31 (m, 2H), 6.87 (t, J = 7.5 Hz, 1H), 6.79 (d, J = 9.0 Hz, 1H), 6.52 (br d, J = 6.5 Hz, 1H), 6.18 (t, J = 8.5 Hz, 1H), 2.75 (br m, 1H), 2.67 (m, 1H), 2.50 (s, 3H), 1.33-1.27 (m, 6H), 1.18-0.99 (m, 6H). ¹³C NMR (CDCl₃, 125.5 MHz, 298 K): δ (ppm) 150.6, 148.9, 140.4, 133.2, 132.9, 132.0, 131.5, 131.0, 130.7, 128.7, 128.6, 127.4, 127.0. 126.7, 126.59, 125.57, 125.2, 124.9, 123.4, 122.97, 122.94, 121.9, 121.6, 119.2, 118.6, 116.4, 110.7, 26.2, 25.6, 23.9, 23.8, 22.4, 22.1, 21.61, 21.54, 21.45, 20.6, 20.5, 19.89, 19.83, 11.5, 11.4. ³¹P{¹H} NMR (CDCl₃, 202.3 MHz, 223 K): δ (ppm) 143.61 (d, Jpp = 249.2 Hz, 0.5P), 142.17 (s, 0.5P), -10.39 (d, Jpp = 247.8 Hz, 0.5P), -11.52 (s, 0.5P). HRMS (FAB) calcld for [M + H]⁺ C₃₈H₃₄NO₃P₂: 562.2065; found, 562.2070.

Synthesis of diphényl[1-[(S)-2,6-bis(trimethylsilyl)-3,5-dioxa-4-phospha-cyclohepta(2,1-a;3,4-a′)dinaphtalen-4-yl]-3-methyl-2-indolyl]phosphine (2c). To a solution of 1a (218 mg, 0.69 mmol) in THF (5 mL) was added dropwise 0.276 mL of n-BuLi (2.5 M in hexanes) at -78 °C. The resulting yellow-orange solution was stirred for 0.5 h at -78 °C and allowed to warm to room temperature. This solution was added dropwise to a solution of (S)-(−)-3,3′-bis(trimethylsilyl)-2,2′-bisnaphtol phosphorochloridite (343 mg, 0.69 mmol) in THF (5 mL) at -78 °C. The reaction mixture was stirred for 1 h at -78 °C and then allowed to warm to room temperature. The resulting red solution was filtered through a pad of SiO₂, which was rinsed twice with THF (3 x 5 mL). The solvent was removed in vacuo. Co-evaporation with CH₂Cl₂ gave the product as an off white powder. Yield: 493 mg (92 %). ¹H NMR (CDCl₃, 500 MHz, 298 K): δ (ppm) 8.05 (s, 1H), 7.92 (d, J = 7.5 Hz, 1H), 7.89 (s, 2H), 7.52-7.22 (m, 17H), 6.90 (t, J = 7.5 Hz, 1H), 6.42 (d, J = 8.5 Hz, 1H), 6.28 (t, J = 7.75 Hz, 1H), 1.70 (s, 3H), 0.05 (s, 9H), 0.01 (s, 9H). ¹³C NMR (CDCl₃, 125.5 MHz, 298 K): δ (ppm) 154.9, 153.0, 139.7, 137.9, 137.5, 134.21, 134.15, 134.03, 133.99, 132.9, 132.8, 132.6, 132.0, 131.5, 130.9, 129.2, 129.13, 129.08, 128.71, 128.66, 128.59, 128.47, 128.38, 127.2, 127.1, 126.78, 126.72, 125.3, 124.9, 123.9, 123.6, 121.9, 121.2, 118.2, 116.5, 10.6, -0.1, -0.3. ³¹P{¹H} NMR (CDCl₃, 202.3 MHz, 298 K): δ (ppm) 133.73 (d, Jpp = 250.4 Hz), -25.82 (d, Jpp = 253.3 Hz). HRMS (FAB) calcld for [M + H]⁺ C₃₈H₃₂NO₃P₂Si₂: 774.2542; found, 774.2532.

Synthesis of diisopropyl[1-[(S)-2,6-dimethyl-3,5-dioxa-4-phospha-cyclohepta(2,1-a;3,4-a′)di-naphtalen-4-yl]-3-methyl-2-indolyl]phosphine (2d). To a solution of 1b (314 mg, 1.3 mmol) in THF (8 mL) was added dropwise 1.07 mL of sec-BuLi (1.3 M in cyclohexane/hexanes) at -78°C. The resulting pale yellow solution was stirred for 1 h at -78 °C and allowed to warm to room temperature. This solution was added dropwise to a solution of (S)-(−)-3,3′-dimethyl-2,2′-bisnaphtol phosphorochloridite (481 mg, 1.3 mmol) in THF (5 mL) at -78 °C. The reaction mixture was stirred for 1 h at -78 °C and then allowed to warm to room temperature. The solvent was removed in vacuo and the reddish-brown residue was redissolved in a 20:80 mixture of EtOAc/Hexanes (20 mL). The resulting suspension was filtered through a
pad of SiO₂, which was rinsed with a 20:80 mixture of EtOAc/Hexanes (20 mL). The solvent was removed in vacuo to obtain the product as a white powder. Yield: 695 mg (93 %). [α]D²² = +401.3 (c = 3.5, CHCl₃). ¹H NMR (CDCl₃, 500 MHz, 298 K): δ (ppm) 7.90 (m, 2H), 7.80 (d, J = 8.0 Hz, 1H), 7.47–7.39 (m, 6H), 7.29–7.23 (m, 2H), 6.93 (t, J = 7.5 Hz, 1H), 6.51 (d, J = 8.5 Hz, 1H), 6.24 (t, J = 7.5 Hz, 1H), 2.75 (m, 2H), 2.62 (s, 3H), 2.54 (s, 3H), 1.69 (s, 3H), 1.33–1.27 (m, 6H), 1.17–1.07 (m, 3H), 1.05–1.00 (m, 3H). ¹³C NMR (CDCl₃, 125.5 MHz, 298 K): δ (ppm) 150.8, 148.1, 140.2, 132.2, 132.0, 131.9, 131.6, 131.5, 130.6, 130.41, 130.35, 130.25, 127.84, 127.76, 127.3, 127.2, 127.1, 125.7, 125.6, 125.34, 125.29, 125.1, 123.4, 123.0, 122.6, 121.4, 119.2, 118.6, 116.5, 30.3, 30.2, 26.9, 26.8, 26.66, 23.9, 23.8, 22.1, 22.0, 21.4, 20.6, 20.5, 19.9, 19.8, 17.4, 17.2, 11.6, 11.4. ³¹P{¹H} NMR (CDCl₃, 202.3 MHz, 223 K): δ (ppm) 137.65 (d, JPP = 239.7 Hz, 0.25P), 136.34 (s, 0.75P), -9.80 (d, JPP = 239.7 Hz, 0.25P), -11.25 (s, 0.75P). HRMS (FAB) calcld for [M + H]⁺ C₃₇H₂₇NO₂P₂Si₂Rh, 590.2378; found, 590.2356.

**Synthesis of [Rh(2c)(cod)]BF₄.** A suspension of [Rh(cod)Cl]₂ (56 mg, 0.11 mmol) and AgBF₄ (44 mg, 0.23 mmol) in THF (4 mL) was stirred for 45 minutes protected from light. The resulting yellow mixture was filtered over a short pad of Celite, which was rinsed with THF (4 mL). To this solution, 2c (176 mg, 0.23 mmol) in THF (8 mL) was added dropwise and the resulting orange solution was stirred for 1 h, filtered, and the solution was concentrated in vacuo to ca. 0.5 mL. Pentane (20 mL) was added to precipitate an orange solid, which was washed with pentanes (20 mL) and dried in vacuo. Yield: 203 mg (83 %). ¹H NMR (CDCl₃, 500 MHz, 298 K): δ (ppm) 8.21 (s, 1H), 8.04 (d, J = 8.5 Hz, 1H), 7.99 (m, 3H), 7.67–7.54 (m, 8H), 7.44 (m, 4H), 7.36 (m, 2H), 7.23 (d, J = 8.5 Hz, 1H), 7.08 (t, J = 7.5 Hz, 2H), 6.50 (t, J = 8.0 Hz, 1H), 6.02 (d, J = 8.5 Hz, 1H), 5.76 (br s, 1H), 5.44 (br s, 2H), 4.08 (br s, 1H), 2.48–2.05 (m, 8H), 1.94 (s, 3H), 0.29 (s, 9H), 0.12 (s, 9H). ¹³C NMR (CDCl₃, 125.5 MHz, 298 K): δ (ppm) 153.8, 153.7, 139.1, 138.4, 137.7, 137.4, 134.1, 133.8, 133.7, 133.6, 132.9, 132.4, 131.68, 131.64, 131.55, 131.45, 130.7, 130.44, 130.36, 130.0, 129.9, 129.1, 128.81, 128.77, 128.3, 128.2, 127.9, 127.1, 126.94, 126.85, 126.83, 126.5, 126.4, 126.1, 126.0, 123.6, 122.0, 120.6, 120.5, 115.5, 111.6, 108.9, 97.1, 31.3, 30.2, 30.0, 29.0, 10.4, 1.0, -0.9. ³¹P{¹H} NMR (CDCl₃, 202.3 MHz, 298 K): δ (ppm) 137.83 (dd, JDRh = 257.3 Hz, JPP = 45.9 Hz), 24.94 (dd, JDRh = 140.2 Hz JPP = 45.9 Hz). HRMS (FAB) calcld for [M – BF₄]⁺ C₃₅H₂₃NO₂P₂Si₂Rh, 984.2458; found, 984.2459.

**General procedure for the asymmetric hydrogenation.** The hydrogenation experiments were carried out in a stainless steel autoclave (150 mL) charged with an insert suitable for 5 reaction vessels (including Teflon mini stirring bars) for conducting parallel reactions. In a typical experiment, the reaction vessels were charged with 2.5 µmol of [Rh(nbd)₂]BF₄, 2.75 µmol of ligand and 0.25 mmol of alkene substrate in 2.5 mL of CH₂Cl₂. In case of ligand 2c the corresponding rhodium complex [Rh(2c)(cod)]BF₄ was used instead of the in situ generated catalyst because the free ligand 2c proved to be very unstable towards hydrolysis by moisture. Before starting the catalytic reactions, the charged autoclave was purged three times with 15 bar of dihydrogen and then pressurised at 10 bar H₂. The reaction mixtures were stirred at 25 °C for the appropriate reaction time. After catalysis the pressure was reduced to 1.0 bar and the conversion and enantiomeric purity was determined by chiral GC (dimethyl itaconate: Supelco BETA DEX, isothermal at 68 °C, tr (R) = 43.1 min. and tr (S) = 43.7 min.; methyl 2-acetamidoacrylate: ph Megadex column, initial temperature = 70 °C and ΔT = 7 °C min⁻¹; tr (S) = 3.32 min. and tr (R) = 4.05 min.).
General procedure for the asymmetric hydroformylation of styrene. The reactions were performed in a stainless steel autoclave containing a 15 mL glass beaker equipped with a Teflon stirring bar. The substrate styrene was filtered freshly over basic alumina to remove possible peroxide impurities. The autoclave was charged with 3.0 µmol of [Rh(acac)(CO)$_2$], 12.0 µmol of ligand, 344 µl of styrene and 193 µl of decane in 3.0 ml of toluene. Before starting the catalytic reactions, the charged autoclave was purged three times with 15 bar of syngas (CO/H$_2$=1/1) and then pressurized at 10 bar (CO/H$_2$ = 1/1). The reaction mixtures were stirred at 40 °C or 60 °C for the appropriate reaction time. After catalysis the pressure was reduced to 1.0 bar and the conversion was checked by GC. The enantiomeric purity was determined by chiral GC (ph Megadex column; initial temperature = 40 °C and ΔT = 25 °C min$^{-1}$; $t_R$ (R) = 4.51 min. and $t_R$ (S) = 4.64 min.).

NMR spectroscopy study of [Rh(2a)$_2$]BF$_4$ and [Rh(2a)(nbd)]BF$_4$. [Rh(nbd)$_2$]BF$_4$ (6.44 mg, 17.2 µmol) and 2a (10.76 mg, 17.1 µmol) were dissolved in CDCl$_3$ (1 mL) and stirred for 3 h to allow complex formation. A 4:1 mixture of [Rh(2a)$_2$]BF$_4$ and [Rh(2a)(nbd)]BF$_4$ was obtained (Figure 2.4). [Rh(2a)$_2$]BF$_4$: $^1$H NMR (CDCl$_3$, 500 MHz, 298 K): δ (ppm) 7.93-7.14 (m, 42 H), 7.01 (d, $J$ = 8.5 Hz, 1H), 6.93 (t, $J$ = 7.5 Hz, 1H), 6.85 (m, 2H), 6.75 (t, $J$ = 7.3 Hz, 1H), 6.61 (t, $J$ = 8.3 Hz, 2H), 6.17 (t, $J$ = 8.0 Hz, 1H), 5.80 (d, $J$ = 9.0 Hz, 1H), 5.46 (d, $J$ = 9.0 Hz, 1H), 1.80 (s, 3H), 1.29 (s, 3H). $^{31}$P{$^1$H} NMR (CDCl$_3$, 202.3 MHz, 298 K): δ (ppm) 157.05 (m, $J_{PN,Rh}$ = 225.2 Hz, $J_{PN,PC}$trans = 388.7 Hz, $J_{PN,PC}$cis = -61.8 Hz, $J_{PN,PN'}$ = 25.7 Hz), 24.83 (m, $J_{PC,Rh}$ = 124.0 Hz, $J_{PC,PN}$trans = 388.7 Hz, $J_{PC,PN}$cis = -61.8 Hz, $J_{PC,PC'}$ = 16.9 Hz). [Rh(2a)(nbd)]BF$_4$: $^{31}$P{$^1$H} NMR (CDCl$_3$, 202.3 MHz, 298 K): δ (ppm) 147.06 (dd, $J_{PN,Rh}$ = 270.9 Hz, $J_{PN,PC}$ = 56.6 Hz), 26.51 (dd, $J_{PC,Rh}$ = 144.2, $J_{PC,PN}$ = 55.2 Hz).

Figure 2.4 $^{31}$P{$^1$H} NMR spectrum of complex study with ligand 2a. ♠ [Rh(2a)$_2$]BF$_4$, ♥ [Rh(2a)(nbd)]BF$_4$. 29
NMR spectroscopy study of [Rh(2b)(nbd)]BF₄. [Rh(nbd)₂]BF₄ (5.26 mg, 14.0 µmol) and 2b (7.15 mg, 12.7 µmol) were dissolved in CDCl₃ (1 mL) and stirred for 1 h to allow complex formation (Figure 2.5). ¹H NMR (CDCl₃, 500 MHz, 298 K): δ (ppm) 8.23 (d, J = 8.5 Hz, 1H), 8.07 (d, J = 8.5 Hz, 1H), 7.90 (d, J = 8.5 Hz, 1H), 7.81 (d, J = 9.0 Hz, 1H), 7.66 (d, J = 8.5 Hz, 1H), 7.60-7.53 (m, 2H), 7.45-7.35 (m, 5H), 6.99 (t, J = 7.5 Hz, 1H), 6.83 (d, J = 9.0 Hz, 1H), 6.62 (br s, 1H), 6.48 (br s, 1H), 6.26 (t, J = 7.8 Hz, 1H), 5.98 (d, J = 8.5 Hz, 1H), 5.48 (br s, 2H), 4.39 (br s, 1H), 4.13 (br s, 1H), 3.01 (m, 2H), 2.47 (s, 3H), 1.72 (br s, 2H), 1.54-1.34 (m, 12H). ³¹P{¹H} NMR (CDCl₃, 202.3 MHz, 298 K): δ (ppm) 146.05 (dd, Jₚₖₐ,Rh = 272.1 Hz, Jₚₖₐ,PC = 51.2 Hz), 53.23 (dd, Jₚₖₐ,Rh = 142.8 Hz, Jₚₖₐ,PN = 52.6 Hz).

Figure 2.5 ³¹P{¹H} NMR spectrum of complex study with ligand 2b.

NMR spectroscopy study of [Rh(2c)(nbd)]BF₄. [Rh(nbd)₂]BF₄ (4.97 mg, 13.3 µmol) and 2c (10.22 mg, 13.2 µmol) were dissolved in CDCl₃ (1 mL) and stirred for 0.5 h to allow complex formation (Figure 2.6). ¹H NMR (CDCl₃, 500 MHz, 298 K): δ (ppm) 8.26 (s, 1H), 8.06 (d, J = 8.5 Hz, 1H), 7.99 (d, J = 8.5 Hz, 1H), 7.98 (s, 1H), 7.89 (d, J = 6.5 Hz, 1H), 7.86 (d, J = 7.0 Hz, 1H), 7.63 (m, 6H), 7.57 (m, 2H), 7.47 (d, J = 8.0 Hz, 1H), 7.36 (t, J = 8.0 Hz, 2H), 7.30 (m, 2H), 7.20 (d, J = 9.0 Hz, 1H), 7.15 (d, J = 8.5 Hz, 1H), 7.10 (t, J = 7.0 Hz, 1H), 6.52 (t, J = 8.0 Hz, 1H), 5.97 (d, J = 8.0 Hz, 1H), 5.82 (br s, 1H), 5.76 (br s, 1H), 5.69 (br s, 1H), 4.17 (br s, 1H), 4.09 (br s, 1H), 4.04 (br s, 1H), 3.92 (s, 3H), 1.80 (d, J = 9.5 Hz, 1H), 1.60 (d, J = 9.0 Hz, 1H), 0.31 (s, 9H), -0.07 (s, 9H). ³¹P{¹H} NMR (CDCl₃, 202.3 MHz, 298 K): δ (ppm) 139.58 (dd, Jₚₖₐ,Rh = 268.0 Hz, Jₚₖₐ,PC = 53.8 Hz), 25.04 (dd, Jₚₖₐ,Rh = 145.5 Hz, Jₚₖₐ,PN = 53.8 Hz).
IndolPhos: Novel hybrid phosphine-phosphoramidite ligands for asymmetric hydrogenation and hydroformylation

**Figure 2.6** $^{31}$P{$^1$H} NMR spectrum of complex study with ligand 2c.

**Figure 2.7** $^{31}$P{$^1$H} NMR spectrum of complex study with ligand 2d.
NMR spectroscopy study of \([\text{Rh}(2d)\{\text{nbd}\}]\text{BF}_4\). \([\text{Rh}(\text{nbd})_3]\text{BF}_4\) (4.27 mg, 11.4 μmol) and \(2d\) (7.50 mg, 12.7 μmol) were dissolved in CDCl₃ (1 mL) and stirred for 1h to allow complex formation (Figure 2.7). \(^1\)H NMR (CDCl₃, 500 MHz, 298 K): \(\delta\) (ppm) 8.04 (s, 1H), 7.98 (d, \(J = 8.0\) Hz, 1H), 7.86 (d, \(J = 8.0\) Hz, 1H), 7.60 (s, 1H), 7.56-7.50 (m, 2H), 7.47 (d, \(J = 7.5\) Hz, 1H), 7.35-7.28 (m, 3H), 7.22 (d, \(J = 8.5\) Hz, 1H), 7.05 (t, \(J = 7.5\) Hz, 1H), 6.72 (br s, 1H), 6.56 (br s, 1H), 6.36 (t, \(J = 8.0\) Hz, 1H), 5.85 (d, \(J = 8.5\) Hz, 1H), 5.60 (br s, 1H), 4.75 (br s, 1H), 4.30 (br s, 1H), 4.17 (br s, 1H), 3.08 (m, 1H), 2.96 (m, 1H), 2.80 (s, 3H), 2.49 (s, 3H), 1.90 (br d, \(J = 6.0\) Hz, 1H), 1.82 (s, 3H), 1.66 (br d, \(J = 7.5\) Hz, 1H), 1.53-1.44 (m, 6H), 1.36 (dd, \(J = 19.0, 7.0\) Hz, 3H), 1.14 (dd, \(J = 22.0, 6.5\) Hz, 3H). \(^3\)P\(^{1}\)H NMR (CDCl₃, 202.3 MHz, 298 K): \(\delta\) (ppm) 141.67 (dd, \(J_{\text{PN,Rh}} = 272.1\) Hz, \(J_{\text{PN,PC}} = 52.4\) Hz), 55.36 (dd, \(J_{\text{PC,Rh}} = 142.8\) Hz, \(J_{\text{PC,PN}} = 52.6\) Hz).

### 2.7 References

19. Not all $^1$H NMR shifts could be identified because many are obscured by signals stemming from [Rh(2a):BF$_4$].