Amino acid modified phosphine ligands for the development of artificial transition metalloenzymes

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Citation for published version (APA):

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Chapter 2

Amino Acid-functionalized Diphosphine Ligands for Asymmetric Catalysis

Abstract

A series of chiral amino acid-functionalized diphosphine ligands has been synthesized. The *meta* or *para* position of the diphenylphosphino groups of Xantphos and DPEphos were functionalized with relatively small peptide fragments in order to create sterically demanding ligand systems that allow non-covalent secondary interactions between functionalized substrates and the ligand. NMR studies showed that the new xanthene-based ligands display metal coordination behaviour typical of Xantphos-type ligands and no direct influence of the amino acid residues was observed on complex formation. The ligands were tested in the rhodium-catalyzed asymmetric hydroformylation of vinyl acetate. The peptide fragments influenced the stereo- and enantioselective outcome of the reaction. In terms of enantioselectivity, the rigid xanthene-based ligands gave better results than the ligand with the flexible diphenyl ether backbone. In addition, the use of dipeptide-containing Xantphos derivatives had a more pronounced effect on the enantioselectivity than its shorter monopeptide-functionalized analogues, and enantiomeric excesses up to 13 % were achieved. Almost no enantioselective induction was observed in the hydroformylation of the substrate styrene, which contains no heteroatoms. In the Rh-catalyzed hydrogenation of dimethyl itaconate enantioselectivities up to 7 % were obtained with the dipeptide-functionalized ligands.
Chapter 2

Introduction

During the last decades a large number of optically active diphosphine ligands has been synthesized which have shown excellent properties in many catalytic reactions. Most of these chiral ligands, such as BINAP and DIOP (Figure 1), are bis(diphenylphosphino)-derivatives. In these ligands the chiral information is transferred to the catalytically active metal center via the arrangement of the phenyl rings of the diphenylphosphino groups. An alternative approach to design enantioselective transition metal catalysts is by making use of non-covalent secondary interactions between the ligand and the substrate, thereby aiming at enzyme-like behavior.\(^1\) Secondary interactions comprise a variety of ligand-substrate interactions such as hydrogen bonding, electrostatic interactions, van der Waals forces, π-stacking and Lewis acid-base interactions, and these interactions are responsible for the high selectivity in enzymatic reactions. The use of amino acids (or peptides) as chiral supports in homogeneous catalytic systems offers a unique opportunity to develop such bioinspired transition metal catalysts.\(^2\) Peptides are easily prepared, consist of readily available chiral building blocks and can interact with functionalized substrates. Furthermore, catalyst optimization can be achieved both by adjusting the structure of the phosphine ligand part and by modifying the oligopeptide sequence, thereby introducing changes in the tertiary structure and interaction with the substrate.

Notable are the pioneering works of Gilbertson\(^3\) and Hoveyda\(^4\) which constitute important examples of secondary peptide structural elements as a chiral microenvironment for transition metal catalysis. In the majority of the known peptide-based phosphine ligands, the peptide backbone is merely used to enforce a specific orientation of the diarylphosphino groups and not for secondary interactions between substrate and ligand. For example, Gilbertson showed that the selectivity of his β-turn ligands is due to the preformed β-turn secondary structure and not to the chirality of the individual amino acids.\(^5\)

![Figure 1. Structure of well known chelating (chiral) diphosphine ligands.](image)

In this Chapter we present the synthesis of facile ligand systems based on rigid, strongly coordinating diphosphines modified with relatively small peptide fragments, in which the amino acid-fragments are located at the substrate side of the transition metal complex in order to create a chiral second coordination sphere around the metal
Amino Acid-functionalized Diphosphine Ligands

center, reminiscent of enzymes. The new ligand systems will be evaluated in several transition metal catalyzed reactions and the influence of the peptide fragments on the regio- and enantioselective outcome of these reactions will be examined.

A mild method for the synthesis of amino acid-functionalized phosphine ligands is the Schiff-base formation between a phosphino-benzaldehyde derivative and N-amino acids. For the use of this method precursors containing carbonyl groups are required to connect the chiral functionalities. We decided to functionalize the phenyl rings of the well-known ligands Xantphos and DPEphos with formyl groups in meta or para position to obtain sterically demanding ligands systems. The rigid xanthene backbone in Xantphos generates wide bite angle ligands and it has been shown that these ligands bring the substituents close to the metal center. On the other hand, the more flexible diphenyl ether backbone in DPEphos can transfer the chiral information of the amino acids more easily to the transition metal center.

Results and Discussion

The synthetic route to formyl functionalized Xantphos is displayed in Scheme 1. The starting material chosen is the commercially available 4,5-dibromo-2,7-di-tert-butyl-9,9-dimethylxanthene (1). Lithiation of the xanthene backbone and subsequent reaction with ClP(OEt)2 gave diphosphonite 2. This compound was made to react with the lithiated analogue of 2-(3-bromophenyl)-1,3-dioxolane (3) to yield diphosphine 4. Acidic hydrolysis of the four acetal groups of compound 4 gave tetrabenzaldehyde 5 as a white, air-stable powder in 50 % overall yield starting from xanthene 1. The formyl groups formed could be clearly identified by their NMR resonances (1H NMR: δ = 9.84 ppm, 13C {1H} NMR: δ = 192.2 ppm), and their infrared absorptions at 2721 and 1700 cm–1. Tetrabenzaldehyde 8, with the formyl groups on the para-position of the phenyl rings, was synthesized in a similar fashion.

![Scheme 1](image)

Scheme 1. Reagents and conditions: i. a) n-BuLi, THF, –78 °C, b) ClP(OEt)2, –78 °C, 80 %; ii. n-BuLi, 3 or 6, THF, –78 °C, 4: 66 %, 7: 44 %; iii. p-TSOH-H2O, THF, reflux, 5: 94 %, 8: 96 %.
Formyl functionalized DPEphos was synthesized starting from commercially available 4,4'-dimethyldiphenyl ether 9 (Scheme 2). Ortho-lithiation of tolylether 9 and subsequent reaction with \( \text{ClP(NEt}_2\text{)}_2 \) gave diethylamino phosphane 10, which upon treatment with HCl-gas afforded 11. Similar to the synthesis of the xanthene-based ligands, compound 11 was reacted with the lithiated analogue of arylbromide 3, followed by acidic hydrolysis of the acetal groups to give tetrabenzaldehyde 13.

![Scheme 2. Reagents and conditions: i. a) n-BuLi, TMEDA, hexanes, \(-30\) °C, b) ClP(NEt\(_2\))\(_2\), \(-78\) °C, 61 \%; ii. HCl (g), hexanes, 0 °C, 80 \%; iii. n-BuLi, 3, THF, \(-78\) °C, 48 \%; iv. p-TSOH-H\(_2\)O, THF, reflux, 95 \%.]

The condensation of tetraaldehyde 5 with commercially available optically active L-valine methyl ester yielded Schiff-base 14. The reaction was carried out under reflux conditions in dry methylene chloride using molecular sieves as dehydration agent. Starting from tetraaldehydes 5, 8 and 13, eight amino acid-containing ligands were obtained by Schiff-base condensation (Scheme 3). In the IR spectra the strong carbonyl peaks at 1700 cm\(^{-1}\) of the aldehyde precursors disappeared and the characteristic C=N peak of the imine ligands was found at 1640-1643 cm\(^{-1}\). The \(^{31}\)P \{\(^1\)H\} NMR spectra showed sharp singlets for all imine ligands. In the \(^1\)H NMR spectra of the chiral ligands, all the signals deriving from the phenyl and amino acid protons appeared doubled in contrast to the backbone protons (Figure 2). The integration of the doubled signals showed in all cases a 1:1 ratio. The splitting of these proton signals could arise from a diastereotopy – the stereochemical non-equivalence of atoms or groups within a single molecule – of the two phenyl substituents bound to the same phosphorus atom induced by the chiral imine substituents. This behavior was also observed by Brunner and coworkers with their optically active expanded ligand system. It is well known that carbon atoms with four different substituents are chiral, and that the enantiomeric forms can be interconverted by reflection in any mirror plane. However, if two of the substituents are themselves chiral moieties, two isomeric forms result which are meso and cannot be interconverted by reflection in a mirror plane. Such a pair of stereoisomers have been termed a pseudoasymmetric or pseudochiral pair. This phenomenon also holds for phosphorus atoms; pseudochirality of the phosphorus atom has been observed in compounds in which the
phosphorus carries two identical chiral substituents. The P-atoms in compound 14 are pseudochiral, and the two aryl substituents are therefore diastereotopic. In the 1H NMR spectrum of achiral ligand 16 these doubled signals are absent which is in agreement with this explanation (Figure 2).

Scheme 3. Ligands 14 – 21.

In order to investigate the possible influence of the amino acid fragments on the coordination behaviour of these ligands, [(17)PtCl₂], [(14)Rh(H)(CO)(PPh₃)] and [(15)PdCl₂] complexes were synthesized. When [(MeCN)₂PtCl₂] was mixed with one equivalent of diphosphine 17 in acetonitrile, the resulting 3¹P {¹H} NMR spectrum displayed one sharp signal at δ = 4.40 ppm with a ¹J(Pt,P) coupling constant of 3677 Hz. The large coupling constant is typical of a square planar Pt-complex with cis coordinated diphosphine ligands. The previously reported complex [(Xantphos)PtCl₂] showed one signal at δ = 6.6 ppm with ¹J(Pt,P) = 3695 Hz in 3¹P NMR spectroscopy.

As reported for Xantphos type ligands, the ¹H NMR spectrum of [(14)Rh(CO)(H)(PPh₃)] shows an inequivalence of the two methyl groups of the backbone. This inequivalence finds its origin in the absence of a mirror plane since the complex has C₁ symmetry. In combination with the above mentioned diastereotopy induced by the chiral imine substituents, coordination of diphosphine 14 to [Rh(CO)(H)(PPh₃)] results in an inequivalence of all four phenyl rings. As a
consequence, the $^1$H NMR and $^{13}$C {$^1$H} NMR spectra are complex. Figure 3 shows parts of the $^1$H NMR spectrum of $[(14)\text{Rh(CO)(H)(PPh}_3\text{)}]$ in which, for example, the four inequivalent methylester-signals are clearly visible.

![Figure 2](image)

**Figure 2.** Parts of the $^1$H NMR (500 MHz, CD$_2$Cl$_2$) spectra of ligand 14 (top) and ligand 16 (bottom), (♦: xanthene backbone protons).

The reaction of ligand 15 with $[\text{Pd(cod)Cl}_2]$ (cod = 1,5-cyclooctadiene) in methylene chloride at room temperature gave $[(15)\text{PdCl}_2]$. A $^{31}$P {$^1$H} NMR spectrum of this complex showed one sharp signal at $\delta = 23.5$ ppm, whereas $[(\text{Xantphos})\text{PdCl}_2]$ gave a signal at $\delta = 22.7$ ppm.$^{[16]}$ Summarizing, the ligands display typical coordination behaviour for xanthene-based ligands and no direct influence of the amino acid residues on the metal center was observed.

We explored the behaviour of the new ligands in various catalytic reactions. Recently, Šmejkal and Breit reported the use acylguanidine-functionalized phosphines as ligands in the rhodium-catalyzed hydroformylation of unsaturated carboxylic acids. Unusual regioselectivities were observed which was ascribed to secondary interactions between the guanidinium group of the ligands and the carboxylate of the substrates.$^{[18]}$ Inspired by these results, the amino acid-functionalized bidentate ligands were first studied in the rhodium-catalyzed hydroformylation of vinyl acetate (A) under 10 bar of syngas (CO/H$_2$ = 1:1) at various temperatures (Table 1). The major product was in all cases branched aldehyde B (2-acetoxypropanal). Minor amounts of 3-acetoxypropanal (C) were also produced, but this partly decomposed under the conditions of the reaction to give acetic acid and acrolein which was hydrogenated to give propanal.$^{[19]}$
Hydroformylation of vinyl acetate is selective for the branched product with most phosphine-based rhodium catalysts giving branched to linear ratios between 4 and 20:1. Vinyl acetate possesses a donor group three bonds from the ethylene group and is thought to chelate to the rhodium catalyst. It is proposed that insertion of the alkene into Rh-hydride at the branched carbon atom is stabilized by a five-membered ring (compared to the less stable six-membered ring that would be formed on insertion at the unsubstituted end of the double bond). Matsumato and Tamira have observed the latter complex by low-temperature $^1$H NMR spectroscopy.

Whereas the rhodium complexes based on *meta*-substituted xanthene ligands 14-19 generated lower branched to linear ratios compared to Xantphos, *para*-substituted ligand 20 gave a branched to linear ratio of 5.6 (Entry 8). The amino acid fragments on the *meta* position might impose too large steric bulk for the branched aldehyde to be formed. The high regioselectivity observed with ligand 20 was more pronounced at lower temperatures. Performing the reaction at 40 °C with ligand 20, a branched to linear ratio of 12 was obtained (Entry 13). In the catalytic cycle for a branched selective hydroformylation reaction, the branched Rh-alkyl species forms faster than the linear isomer. The formation of the branched rhodium-alkyl species is reversible through β-hydrogen elimination, whereas the formation of linear rhodium-alkyl species is considered irreversible and can only form linear aldehyde. The β-hydrogen elimination decreases upon lowering the temperature, forming less alkene starting material and more branched aldehyde and thus higher branched to linear ratios are obtained.

The activities of the amino acid-functionalized catalysts with the xanthene backbone were comparable with those from Xantphos. Rhodium complexes based on chiral ligands 14 and 15 influenced the enantiomeric outcome of the reaction to a small extent.
extent and ee’s up to 3% were obtained (Entries 1 and 2). Interestingly, when the dipeptide-containing chiral ligands 17 and 18 were employed, the enantiomeric excess increased slightly to 8 and 7% respectively (Entries 5 and 6). An increase in enantioselectivity was observed on lowering the reaction temperature. The enantiomeric excess of the branched aldehyde increased to 13% using ligand 17 upon decreasing the reaction temperature to 40 °C (Entry 12).

Table 1. Asymmetric hydroformylation of vinyl acetate.[a]

<table>
<thead>
<tr>
<th>entry</th>
<th>ligand</th>
<th>T (°C)</th>
<th>t (h)</th>
<th>conv. (%) [b]</th>
<th>b/l [c]</th>
<th>ee (%) [d]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Xantphos</td>
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<td>20</td>
<td>94</td>
<td>3.3</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>14</td>
<td>60</td>
<td>20</td>
<td>92</td>
<td>3.1</td>
<td>3 (S)</td>
</tr>
<tr>
<td>3</td>
<td>15</td>
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<td>98</td>
<td>2.4</td>
<td>3 (S)</td>
</tr>
<tr>
<td>4</td>
<td>16</td>
<td>60</td>
<td>20</td>
<td>90</td>
<td>2.1</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>17</td>
<td>60</td>
<td>20</td>
<td>91</td>
<td>1.6</td>
<td>8 (S)</td>
</tr>
<tr>
<td>6</td>
<td>18</td>
<td>60</td>
<td>20</td>
<td>97</td>
<td>2.3</td>
<td>7 (S)</td>
</tr>
<tr>
<td>7</td>
<td>19</td>
<td>60</td>
<td>20</td>
<td>88</td>
<td>1.6</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>20</td>
<td>60</td>
<td>20</td>
<td>92</td>
<td>5.6</td>
<td>&lt;1 (S)</td>
</tr>
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<td>60</td>
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<td>87</td>
<td>1.9</td>
<td>2 (S)</td>
</tr>
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<td>55</td>
<td>3.5</td>
<td>-</td>
</tr>
<tr>
<td>11</td>
<td>14</td>
<td>40</td>
<td>44</td>
<td>60</td>
<td>4.1</td>
<td>3 (S)</td>
</tr>
<tr>
<td>12</td>
<td>17</td>
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<td>44</td>
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<td>3.0</td>
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<td>20</td>
<td>40</td>
<td>44</td>
<td>54</td>
<td>12</td>
<td>&lt;1 (S)</td>
</tr>
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</table>

[a] Conditions: [Rh(acac)(CO)₂], [Rh] = 1.0 mM, ligand/Rh = 4, substrate/Rh = 250, p = 10 bar CO/H₂ (1:1), 2.0 mL toluene. [b] Percentage conversion of vinyl acetate, determined by GC. [c] Branched to linear aldehyde ratio, determined by GC from the ratio of branched product B to linear product C plus acetic acid. [d] Enantiomeric excess of branched aldehyde, determined by chiral GC (absolute configuration drawn in parenthesis).

The lower enantioselectivity displayed by para-substituted ligand 20 demonstrates the importance of the positioning of the amino acid-fragments on the enantiomeric outcome of the hydroformylation reaction. In addition, the lower enantiomeric excess obtained with ligand 21, with the more flexible diphenyl ether backbone, compared to its xanthene-based analogue 17 suggests that a well-defined ligand system with a certain rigidity is required for effective substrate-ligand interactions.
In the previous hydroformylation reactions (Table 1) we demonstrated that the chiral iminophosphine ligands influenced the enantiomeric outcome of the reaction. In particular the use of dipeptide-containing ligands 17 and 18 had a beneficial effect on the enantioselectivity in the hydroformylation of vinyl acetate. A second substrate that displays branched regioselectivity in hydroformylation is styrene (D).

Table 2. Asymmetric hydroformylation of styrene.[a]

<table>
<thead>
<tr>
<th>entry</th>
<th>ligand</th>
<th>t (h)</th>
<th>conv. (%) [b]</th>
<th>b/l [c]</th>
<th>ee (%) [d]</th>
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<tr>
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<td>83</td>
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<td>85</td>
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<td>88</td>
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<td>86</td>
<td>2.6</td>
<td>3</td>
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<td>5</td>
<td>20</td>
<td>20</td>
<td>99</td>
<td>6.1</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

[a] Reaction conditions: [Rh(acac)(CO)₂], [Rh] = 1.0 mM, ligand/Rh = 4, substrate/Rh = 1000, p = 20 bar CO/H₂ (1:1); T = 60 °C, 2 mL toluene. [b] Percentage conversion of styrene, determined by GC. [c] Ratio branched (E) to linear (F) aldehyde, determined by GC. [d] Enantiomeric excess of branched aldehyde, determined by chiral GC.

It has been suggested that the origin of the regioselectivity is the formation of an η³-benzyl complex that stabilizes the branched rhodium-alkyl intermediate.[22] We were interested if the new amino acid-functionalized ligands could induce enantioselectivity in the hydroformylation of styrene. Since styrene is lacking donor groups, less interaction between the ligand and the substrate is expected. Hydroformylation of styrene was carried out in toluene at a pressure of 20 bar of syngas (CO/H₂ = 1) and the results are summerized in Table 2. The branched aldehyde 2-phenylpropanal (E) was in all cases the predominant product. The para-substituted ligand 20 gave a higher branched to linear ratio compared to its meta-substituted analogue 17, as was also observed in the hydroformylation of vinyl acetate. With the new chiral ligands very low enantiomeric excesses, if any, were obtained in the hydroformylation of styrene. This can be attributed to the fact that the secondary interactions between the non-functionalized substrate and the amino acid-containing ligands are too weak.

Next, the amino acid-functionalized ligands were studied in the rhodium-catalyzed asymmetric hydrogenation of dimethyl itaconate (G) and methyl α-acetamidoacrylate (H). The reactions were carried out in a stainless steel autoclave at a hydrogen pressure of 5 bar, using [Rh(cod)₂]BF₄ as pre-catalyst. The results are summarized in Table 3.
Chapter 2

Table 3. Results of asymmetric hydrogenation

<table>
<thead>
<tr>
<th>entry</th>
<th>ligand</th>
<th>substrate</th>
<th>solvent</th>
<th>conv. (%) [b]</th>
<th>ee (%) [c]</th>
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<tbody>
<tr>
<td>1</td>
<td>15</td>
<td>G</td>
<td>CH₂Cl₂</td>
<td>&gt; 99</td>
<td>3.4 (R)</td>
</tr>
<tr>
<td>2</td>
<td>18</td>
<td>G</td>
<td>CH₂Cl₂</td>
<td>&gt; 99</td>
<td>7.3 (R)</td>
</tr>
<tr>
<td>3</td>
<td>18</td>
<td>G</td>
<td>MeOH</td>
<td>&gt; 99</td>
<td>3.6 (R)</td>
</tr>
<tr>
<td>4</td>
<td>20</td>
<td>G</td>
<td>CH₂Cl₂</td>
<td>&gt; 99</td>
<td>4.3 (R)</td>
</tr>
<tr>
<td>5</td>
<td>20</td>
<td>G</td>
<td>MeOH</td>
<td>&gt; 99</td>
<td>2.3 (R)</td>
</tr>
<tr>
<td>6</td>
<td>21</td>
<td>G</td>
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<tr>
<td>7</td>
<td>15</td>
<td>H</td>
<td>CH₂Cl₂</td>
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<td>n.d.</td>
</tr>
<tr>
<td>8</td>
<td>18</td>
<td>H</td>
<td>CH₂Cl₂</td>
<td>5</td>
<td>n.d.</td>
</tr>
</tbody>
</table>

[a] Reaction conditions: [Rh(cod)₂]BF₄, [Rh] = 1.0 mM, ligand/Rh = 1.1, substrate/Rh = 100, p(H₂) = 5 bar, T = 25 °C, t = 16 h, 0.5 mL solvent. [b] Percentage conversion of substrate, determined by GC. [c] Enantiomeric excess of product, determined by chiral GC (absolute configuration drawn in parenthesis). n.d. = not determined

The catalytic systems obtained with the tested diphosphines 15, 18, 20 and 21 were active in the hydrogenation of dimethyl itaconate (G) providing dimethyl-methylsuccinate with complete conversion (Entries 1-6). Although the enantioselectivity was low in all cases, it is noteworthy that the enantiomeric excess of the hydrogenated product was twice as high when dipeptide-containing ligand 18 was employed compared to its smaller analogue 15 (Entries 1 and 2). Performing the reaction in methanol, a common solvent for the rhodium-catalyzed asymmetric hydrogenation reaction, resulted in lower enantioselectivities.

Interestingly, in the hydrogenation of methyl α-acetamidoacrylate (H), the alanine derivative was obtained in very low yield, even after prolonged reaction times (Entries 7 and 8). Presumably due to substrate-inhibition only low conversions are observed in the hydrogenation of H. The hydrogenation results show again that the presence of amino acid-fragments located at the substrate side of the transition metal complex has an influence on the activity and selectivity in the catalytic reaction.

Conclusions

In conclusion, we synthesized ligands based on rigid strongly coordinating phosphines modified with relatively small peptide fragments. The meta or para position of the diphenylphosphino groups of Xantphos and DPEphos were functionalized with amino
Amino Acid-functionalized Diphosphine Ligands

acid-fragments in order to create sterically demanding ligand systems that allow non-covalent secondary interactions between functionalized substrates and the ligand. NMR studies showed the new xanthene-based ligands display typical metal coordination behaviour for Xantphos-type ligands and no direct influence of the amino acid residues was observed, apart from diastereotopic effects in the NMR spectra of the chiral ligands as a result of the pseudochirality of the phosphorus atoms.

The ligands were tested in the asymmetric hydroformylation of vinyl acetate resulting in low enantioselectivities. Nevertheless, in terms of enantioselectivity, the rigid xanthene-based ligands gave higher ee’s than the ligand with the flexible diphenyl ether backbone. In addition, the dipeptide-containing Xantphos derivatives generated higher enantiomeric excesses than the shorter monopeptide-functionalized analogues. In the hydroformylation of styrene low enantioselectivities were obtained presumably due to insufficient substrate-ligand secondary interactions. The new chiral ligands were active in the hydrogenation of dimethyl itaconate and enantiomeric excesses up to 7% were obtained. In the hydrogenation of methyl α-acetamidoacrylate only low conversions were reached even after prolonged reaction times. Thus, the results reported in this Chapter illustrate that it is possible to influence the enantiomeric outcome of asymmetric catalytic reactions by making use of non-covalent secondary interactions between amino acid-functionalized ligands and prochiral substrates, although the ee values obtained so far are disappointing. In order to fully exploit these interactions, other better defined ligand systems need to be developed.

Experimental Section

General remarks. Unless stated otherwise, reactions were carried out under an atmosphere of argon using standard Schlenk techniques. THF, diethyl ether and hexanes were distilled from sodium/benzophenone. Tertiary amines, CH₂Cl₂ and methanol were distilled from CaH₂ and toluene was distilled from sodium. Deuterated solvents were distilled from the appropriate drying agents. Unless stated otherwise, all chemicals were obtained from commercial suppliers and used as received. Bis(diethylamino)chlorophosphine[23] was synthesized according to a reported procedure. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. NMR spectra were recorded on a Varian Mercury 300, a Varian Inova 500 or a Bruker Avance DRX-300 spectrometer. Chemical shifts are reported in ppm and are given relative to tetramethylsilane (¹H, ¹³C) and 85% H₃PO₄ (³¹P). Standard infrared spectra were recorded on a Nicolet Nexus 670 FT-IR spectrophotometer. High Resolution Mass Spectra were recorded at the Department of Mass Spectrometry at the University of Amsterdam using Fast Atom Bombardment (FAB) ionization on a JOEL JMS SX/SX102A four-sector mass spectrometer, coupled to a JEOL MS-MP9021D/UPD system program. Elemental analyses were carried out by H. Kolbe Mikroanalytisches Laboratorium, Mülheim an der Ruhr (Germany).
2,7-Di-tert-butyl-4,5-bis(diethoxyphosphino)-9,9-dimethyl-xanthene (2): This compound was prepared according to a literature procedure. To a solution of 2,7-di-tert-butyl-4,5-dibromo-9,9-dimethylxanthene (5.00 g, 10.4 mmol) in THF (80 mL) was added n-BuLi (8.3 mL, 2.5 M in hexanes, 20.8 mmol) at −78 °C. The mixture was stirred for 2 h at this temperature. Then, a solution of diethyl chlorophosphite (3.25 g, 20.8 mmol) in THF (20 mL) was added dropwise. The mixture was allowed to stir at room temperature for 16 h. The solvent was removed under reduced pressure. The residue was taken up in methylene chloride (100 mL) and washed with water (50 mL). The organic phase was dried over MgSO₄ and concentrated under reduced pressure to give 2 in 80 % yield (4.67 g) as a pale yellow oil. ¹H NMR (300 MHz, CDCl₃): δ = 7.60 (s, 2H, H-arom), 7.42 (s, 2H, H-arom), 4.04-3.87 (m, 8H, OCH₂), 1.62 (s, 6H, CH₃), 1.33 (s, 18H, C(CH₃)₃), 1.28 (t, J = 7.0 Hz, 12H, OCH₂CH₃); ³¹P {¹H} NMR (121 MHz, CDCl₃): δ = 153.20.

2-(3-Bromophenyl)-1,3-dioxolane (3): To a solution of 4-bromobenzaldehyde (79.0 g, 427 mmol) in toluene (600 mL) was added p-toluenesulfonic acid monohydrate (0.30 g, 1.7 mmol) and ethylene glycol (39.8 g, 640 mmol). The reaction mixture was refluxed in a Dean-Stark apparatus for 24 h. After cooling to room temperature, the reaction mixture was washed with saturated aqueous NaHCO₃ (200 mL) and brine (200 mL). The organic phase was dried over MgSO₄, filtered and concentrated in vacuo. The residual oil was purified by distillation (110 °C, 0.2 mbar) to give 3 (84.5 g, 86 %) as a colourless oil which became solid on cooling to room temperature. ¹H NMR (300 MHz, CDCl₃): δ = 7.65 (s, 1H, H-arom), 7.47 (d, J = 7.2 Hz, 1H, H-arom), 7.38 (d, J = 7.8 Hz, 1H, H-arom), 7.20 (t, J = 7.7 Hz, 1H, H-arom), 5.73 (s, 1H, OCHO), 4.02-3.93 (m, 4H, H-dioxolan); ¹³C NMR (75 MHz, CDCl₃): δ = 140.7 (C), 132.4 (CH), 130.3 (CH), 129.8 (CH), 125.6 (CH), 122.7 (CBr), 102.9 (CH), 65.5 (CH₂).[24]

2,7-Di-tert-butyl-4,5-bis[d(3-(1,3-dioxolan)phenyl)phosphino]-9,9-dimethylxanthene (4): n-BuLi (12.4 mL, 2.5 M in hexanes, 31.0 mmol) was added dropwise to a solution of 2-(3-bromophenyl)-1,3-dioxolane 3 (7.10 g, 31.0 mmol) in THF (100 mL) at −78 °C. The mixture was stirred at this temperature for 30 min, after which a solution of phosphonite 2 (3.50 g, 6.20 mmol) in THF (20 mL) was added. The mixture was allowed to warm to room temperature gradually. After stirring for 16 h, the reaction mixture was concentrated in vacuo. The resulting oil was taken up in methylene chloride (100 mL) and washed with water (100 mL), and then the organic layer was dried over MgSO₄, filtered and concentrated under reduced pressure. Crystallization from methylene chloride/methanol gave 4 (4.02 g, 66 %) as a white solid. ¹H NMR (500 MHz, CDCl₃): δ = 7.36 (m, 10H, H-arom, H-1, H-8), 7.21 (t, J = 7.5 Hz, 4H, H-arom), 7.13 (m, 4H, H-arom), 6.52 (d, J = 1.8 Hz, 2H, H-3, H-6), 5.73 (s, 4H, OCHO), 3.95-3.93 (m, 16H, H-dioxolan), 1.64 (s, 6H, CH₃), 1.08 (s, 18H, C(CH₃)₃); ¹³C {¹H} NMR (125 MHz, CDCl₃): 150.6 (t, J = 19.4 Hz, CO), 145.6 (C-2, C-7), 137.9 (m, PC, Cq), 134.9 (t, J = 18.2 Hz, CH), 132.5 (t, J = 24.3 Hz, CH), 129.4 (C-3, C-6), 129.2 (C-9), 128.4 (CH), 126.6 (CH), 124.6 (t, J = 18.2 Hz, C-4, C-5), 123.2 (C-1, C-8), 103.9 (CH), 65.3 (CH₂), 35.1 (C-9), 34.7 (C(CH₃)₃), 32.2 (CH₃), 31.5 (C(CH₃)₃); ³¹P {¹H} NMR (121 MHz, CDCl₃): δ = -15.39; IR (KBr, cm⁻¹): 3056 (w), 2962 (m), 2883 (w), 1720 (s), 1476 (m), 1426 (s), 1266 (s), 1088 (s), 968 (m), 944 (m), 794 (s), 751 (m), 700 (w).
2,7-Di-tert-butyl-4,5-bis[di(3-formylphenyl)phosphino]-9,9-dimethyl-xanthene (5): Compound 4 (3.00 g, 3.06 mmol) was dissolved in a mixture of water and tetrahydrofuran (40 mL, 1:1). After the addition of a catalytic amount of p-toluenesulfonic acid monohydrate (0.18 g, 0.94 mmol), the reaction mixture was stirred for 4 h at reflux temperature. After cooling to room temperature, the mixture was extracted with methylene chloride (40 mL). The organic phase was dried over MgSO₄ and concentrated in vacuo. Crystallization from methylene chloride/methanol gave 5 (2.26 g, 94 %) as a white solid. 1H NMR (500 MHz, CDCl₃): δ = 9.84 (s, 4H, CHO), 7.75 (t, J = 8.1 Hz, 4H, H-arom), 7.64 (m, 4H, H-arom), 7.45 (d, J = 2.1 Hz, 2H, H-1, H-8), 7.38 (m, 8H, H-arom), 6.39 (d, J = 2.4 Hz, 2H, H-3, H-6), 1.70 (s, 6H, CH₃), 1.06 (s, 18H, C(CH₃)₃); 13C {1H} NMR (125 MHz, CDCl₃): δ = 192.2 (CHO), 150.8 (t, J = 19.0 Hz, CO), 146.6 (C-2, C-7), 139.7 (t, J = 18.9 Hz, CH), 136.6 (t, J = 15.5 Hz, PC), 135.6 (Cq), 135.6 (t, J = 21.9 Hz, CH), 130.0 (C-3, C-6), 129.9 (CC-9), 129.2 (CH), 128.9 (CH), 124.1 (C-1, C-8), 122.4 (t, J = 17.1 Hz, C-4, C-5), 35.1 (C-9), 34.8 (C(CH₃)₃), 34.8 (CH₃), 31.5 (C(CH₃)₃); 31P {1H} NMR (121 MHz, CDCl₃): δ = –14.60; IR (KBr, cm –1): 3056 (w), 2962 (m), 2721 (w), 1700 (w), 1035 (s), 894 (m), 863 (m), 794 (s), 688 (s), 647 (s); HRMS (FAB+): m/z calcd. for C₅₉H₇₆O₉P₂ (M+H⁺): 979.4104; found: 979.4111; anal. calcd. for C₅₉H₇₆O₉P₂: C 72.38, H 6.59; found: C 72.47, H 6.67.

2-(4-Bromophenyl)-1,3-dioxolane (6): Starting from 4-bromobenzaldehyde (99.1 g, 0.535 mol), compound 6 was obtained as a colourless liquid using the same procedure as described for compound 3. Yield: 90 % (110.3 g). 1H NMR (300 MHz, CDCl₃): δ = 7.45 (d, J = 8.7 Hz, 2H, H-arom), 7.29 (d, J = 8.4 Hz, 1H, H-arom), 5.67 (s, 1H, OCHO), 3.97-3.88 (m, 4H, H-dioxolan); 13C NMR (75 MHz, CDCl₃): δ = 137.4 (C), 131.7 (CH), 128.6 (CH), 124.4 (t, J = 17.1 Hz, C-4, C-5), 103.1 (CH), 65.5 (CH₂).

2,7-Di-tert-butyl-4,5-bis[di(4-(1,3-dioxolan)phenyl)phosphino]-9,9-dimethyl-xanthene (7): From 2-(4-bromophenyl)-1,3-dioxolane 6 (8.02 g, 35.0 mmol) and phosphonite 2 (3.94 g, 7.0 mmol), compound 7 was obtained as a white solid using the same procedure as described for compound 4. Yield 44 % (3.03 g). 1H NMR (500 MHz, CDCl₃): δ = 7.36 (d, J = 2.0 Hz, 2H, H-1, H-8), 7.32 (d, J = 8.0 Hz, 8H, H-arom), 7.20 (m, 8H, H-arom), 6.58 (d, J = 2.0 Hz, 2H, H-3, H-6), 5.80 (s, 4H, OCHO), 4.11-4.02 (m, 16H, H-dioxolan), 1.65 (s, 6H, CH₃), 1.09 (s, 18H, C(CH₃)₃); 13C {1H} NMR (125 MHz, CDCl₃): δ = 137.4 (C), 132.9 (CH), 128.6 (CH), 124.4 (C-4, C-5), 130.9 (CH), 65.5 (CH₂), 35.1 (C-9), 34.8 (C(CH₃)₃), 32.5 (CH₃), 31.6 (C(CH₃)₃); 31P {1H} NMR (121 MHz, CDCl₃): δ = –16.94; IR (KBr, cm –1): 3043 (w), 2962 (m), 2882 (w), 1720 (w), 1602 (w), 1571 (w), 1475 (m), 1380 (w), 1265 (s), 1075 (s), 972 (m), 942 (s), 808 (s); HRMS (FAB+): m/z calcd. for C₅₉H₇₆O₉P₂ (M+H⁺): 979.4104; found: 979.4111; anal. calcd. for C₅₉H₇₆O₉P₂: C 72.38, H 6.59; found: C 72.30, H 6.60.
2,7-Di-tert-butyl-4,5-bis[d(4-(formylphenyl)phosphino)]-9,9-dimethyl-xanthene (8): Starting from bisphosphine 7 (1.52 g, 1.55 mmol), compound 8 was obtained as a white solid using the same procedure as described for compound 5. Yield 96 % (1.20 g). 1H NMR (500 MHz, CDCl3): δ = 9.92 (s, 4H, CHO), 7.67 (d, J = 8.1 Hz, 8H, H-arom), 7.46 (d, J = 2.1 Hz, 2H, H-1, H-8), 7.27 (m, 8H, H-arom), 6.44 (d, J = 2.1 Hz, 2H, H-3, H-6), 1.71 (s, 6H, CH3), 1.07 (s, 18H, C(CH3)3); 13C {1H} NMR (125 MHz, CDCl3): δ = 192.2 (CHO), 150.6 (t, J = 19.4 Hz, CO), 146.6 (C-2, C-7), 145.1 (t, J = 17.3 Hz, PC), 136.4 (CH), 134.3 (t, J = 20.6 Hz, CH), 129.7 (C-3, C-6), 129.4 (m, CC-9, CH), 124.5 (C-1, C-8), 121.8 (t, J = 15.7 Hz, C-4, C-5), 35.2 (C-9), 34.9 (C(CH3)3), 32.3 (CH3), 31.4 (C(CH3)3); 31P {1H} NMR (121 MHz, CDCl3): δ = –13.08; IR (KBr, cm⁻¹): 3060 (w), 2961 (m), 2734 (w), 1702 (s), 1593 (m), 1562 (m), 1476 (m), 1426 (s), 1264 (s), 1248 (s), 1206 (s), 837 (m), 816 (m), 692 (s); HRMS (FAB+): m/z calcd. for C51H49O5P2 (M+H⁺): 803.3055; found: 803.3048; anal. calcd. for C51H48O5P2: C 76.29, H 6.03; found: C 76.20, H 6.08.

2,2′-Bis[bis(diethylamino)phosphino]-4,4′-dimethyl-diphenylether (10): This compound was prepared according to a literature procedure.[11] To a solution of di-p-tolylether (5.0 g, 25.2 mmol) and TMEDA (8.4 mL, 55.5 mmol) in hexanes (20 mL) was added n-butyllithium (2.5 M in hexanes, 22.2 mL, 55.5 mmol) at –30 °C. The reaction mixture was allowed to stir at room temperature for 16 h. The dilithio-diphenylether was collected by filtration, washed with hexanes and dried in vacuo. The dilithiated p-tolylether was dissolved in diethyl ether (40 mL) and added to a solution of bis(diethylamino)chlorophosphine (11.1 mL, 53.0 mmol) in hexanes (40 mL) at –78 °C. The reaction mixture was allowed to warm to room temperature overnight with stirring. The reaction mixture was filtered and the solvents were evaporated. The residue was purified by flash column chromatography over basic alumina (5 % ethyl acetate in light petroleum) to give 10 in 61 % yield (8.4 g) as a colourless oil. 1H NMR (300 MHz, C6D6): δ = 7.51 (m, 2H, H-arom), 6.90 (m, 4H, H-arom), 3.22-2.96 (m, 16H, C6H2CH3), 2.23 (s, 6H, CH3), 1.10 (t, J = 7.0 Hz, 24H, CH2C6H3); 31P {1H} NMR (121 MHz, C6D6): δ = 93.40.

2,2′-Bis[dichlorophosphino]-4,4′-dimethyl-diphenylether (11): This compound was prepared according to a literature procedure.[11] Compound 10 (4.24 g, 7.75 mmol) was dissolved in hexanes (500 mL) and cooled to 0 °C. HCl-gas was bubbled through the stirred reaction mixture for 1.5 h. The salts were filtered off and washed with diethyl ether (100 mL). Evaporation of the solvents resulted in a white solid residue. Recrystallization from hexanes (30 mL) at −20 °C yielded 11 as a white powder (80 %, 4.94 g). 1H NMR (300 MHz, C6D6): δ = 7.74 (d, J = 1.5 Hz, 2H, H-arom), 6.75 (dd, J = 8.1 Hz, J = 2.1 Hz, 2H, H-arom), 6.44 (dt, J = 8.4 Hz, J = 2.9 Hz, 2H, H-arom), 1.94 (s, 6H, CH3); 31P {1H} NMR (121 MHz, C6D6): δ = 158.99.

2,2′-Bis[d(3-(1,3-dioxolan)phenyl)phosphino]-4,4′-dimethyl-diphenylether (12): n-BuLi (12.8 mL, 2.5 M in hexanes, 32.0 mmol) was added dropwise to a solution of 2-(4-bromophenyl)-1,3-dioxolane 3 (7.33 g, 32.0 mmol) in THF (80 mL) at −78 °C. The mixture was stirred at this temperature for 1 h, after which a solution of 11 (2.48 g, 6.2 mmol) in THF (20 mL) was added. The mixture was allowed to
to warm to room temperature. After stirring for 16 h, the reaction mixture was concentrated in vacuo. The resulting oil was taken up in toluene (100 mL) and washed with water (100 mL), and then the organic layer was dried over MgSO₄, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (70 % EtOAc in light petroleum) to afford 12 in 48 % yield (2.55 g) as a white solid. ¹H NMR (500 MHz, CDCl₃): δ = 7.39 (m, 8H, H-arom), 7.26 (t, J = 7.5 Hz, 4H, H-arom), 7.17 (t, J = 6.5 Hz, 4H, H-arom), 6.96 (d, J = 8.0 Hz, 2H, H-arom), 6.59 (d, J = 2.0 Hz, 2H, H-arom), 6.53 (dd, J = 8.0 Hz, J = 4.5 Hz, 2H, H-arom), 5.74 (s, 4H, OCHO), 4.05-3.94 (m, 16H, H-dioxolan), 2.13 (s, 6H, CH₃); ¹³C {¹H} NMR (125 MHz, CDCl₃): 157.2 (d, J = 17.7 Hz, Cq), 137.6 (m, Cq), 136.7 (d, J = 12.7 Hz, Cq), 134.5 (d, J = 17.3 Hz, CH), 134.1 (CH), 132.6 (Cq), 132.1 (d, J = 24.9 Hz, CH), 130.8 (CH), 128.2 (t, J = 5.5 Hz, CH), 126.4 (CH), 117.7 (CH), 103.5 (CH), 65.0 (CH₂), 20.7 (CH₃); ³¹P {¹H} NMR (121 MHz, CDCl₃): δ = –14.50; HRMS (FAB+): m/z calcd. for C₅₀H₄₉O₉P₂ (M+H⁺): 855.2852; found: 855.2855.

2,2’-Bis[di(3-formylphenyl)phosphino]-4,4’-dimethyl-diphenylether (13): Compound 12 (2.0 g, 2.34 mmol) was dissolved in a mixture of water and tetrahydrofuran (50 mL, 1:1). After the addition of a catalytic amount of p-toluenesulfonic acid monohydrate (0.017 g, 0.09 mmol), the reaction mixture was stirred for 4 h at reflux temperature. After cooling to room temperature, the mixture was extracted with methylene chloride (70 mL). The organic phase was dried over MgSO₄ and concentrated in vacuo. Crystallization from methylene chloride/methanol gave 13 (1.51 g, 95 %) as a white solid. ¹H NMR (500 MHz, CDCl₃): δ = 9.89 (s, 4H, CHO), 7.78 (d, J = 7.5 Hz, 4H, H-arom), 7.67 (d, J = 7.5 Hz, 4H, H-arom), 7.40 (m, 8H, H-arom), 7.07 (dd, J = 8.0 Hz, J = 2.0 Hz, 2H, H-arom), 6.65 (dd, J = 8.5 Hz, J = 4.5 Hz, 2H, H-arom), 6.49 (d, J = 3.5 Hz, 2H, H-arom), 2.15 (s, 6H, CH₃); ¹³C {¹H} NMR (125 MHz, CDCl₃): δ = 192.0 (CHO), 156.9 (d, J = 16.5 Hz, Cq), 139.4 (d, J = 19.5 Hz, CH), 137.7 (d, J = 14.8 Hz, Cq), 136.3 (t, J = 6.6 Hz, Cq), 135.1 (d, J = 22.0 Hz, CH), 134.1 (CH), 133.7 (Cq), 131.8 (CH), 129.7 (CH), 129.1 (t, J = 6.4 Hz, CH), 125.9 (d, J = 14.8 Hz, CH), 118.0 (CH), 20.8 (CH₃); ³¹P {¹H} NMR (121 MHz, CDCl₃): δ = –13.94; HRMS (FAB+): m/z calcd. for C₄₂H₃₃O₅P₂ (M+H⁺): 679.1803; found: 679.1804; anal. calcd. for C₄₂H₃₂O₅P₂: C 74.33, H 4.75; found: C 74.55, H 4.90.

H-L-Val-L-Val-OMe·HCl (I): N-Boc-L-valine (10.0 g, 46.0 mmol) was dissolved in CH₂Cl₂ (200 mL) and cooled in an ice bath. L-Valine methyl ester hydrochloride (8.5 g, 50.6 mmol) was added followed by EDC (8.8 g, 46.0 mmol) and DIPEA (21 mL, 126.6 mmol). After stirring for 16 h at room temperature the reaction mixture was concentrated under reduced pressure. The residu was taken up in ethyl acetate (200 mL) and washed with saturated aqueous NH₄Cl (200 mL) and brine (200 mL). After stirring for 16 h at room temperature the reaction mixture was concentrated under reduced pressure. The residu was dried over MgSO₄ and concentrated under reduced pressure. Precipitation from light petroleum gave N-Boc-Val-Val-OMe (10.03 g) in 66 % yield as a white solid. ¹H NMR (300 MHz, CDCl₃): δ = 6.39 (d, J = 7.2 Hz, 1H, NH), 5.06 (d, J = 8.4 Hz, 1H, NH), 4.54 (m, 1H, Ha), 3.91 (m, 1H, Ha), 3.73 (m, 3H, OCHO), 2.16 (m, 2H, Hβ), 1.43 (m, 9H, C(CH₃)₃), 0.93 (m, 12H, 4 × CH₃). Next, N-Boc-Val-Val-OMe (6.09 g, 18.4 mmol) was stirred in a mixture of TFA/CH₂Cl₂ (40 mL, 1:1) for 30 min at room temperature. All volatiles were removed under reduced pressure. Traces of TFA were removed by co-evaporation with CH₂Cl₂ (3 × 20 mL). The residu was treated with HCl (g) in
ethyl acetate for 30 min. All volatiles were removed under reduced pressure and traces of HCl were removed by co-evaporation with EtOAc (3 × 20 mL). Precipitation from diethyl ether yielded I (4.67 g) in 95 % as a white solid. ¹H NMR (300 MHz, MeOH-d₄): δ = 8.58 (d, J = 7.2 Hz, 1H, NH), 4.34 (m, 1H, Hα), 3.83 (m, 1H, Hα), 3.71 (s, 3H, OCH₃), 2.21 (m, 2H, Hβ), 1.01 (m, 12H, CH₃) [26]

H-L-Phe-L-Phe-OMe·HCl (II): Following the procedure as described for dipeptide I, first N-Boc-L-phenylalanine (2.27 g, 8.58 mmol) was reacted with L-phenylalanine methyl ester hydrochloride (1.85 g, 8.58 mmol) to give, after purification by silica gel column chromatography (EtOAc/light petroleum, 1/1), N-Boc-Phe-Phe-OMe (2.78 g, 76 %) as a white solid. ¹H NMR (300 MHz, CDCl₃): δ = 7.30-7.16 (m, 8H, H-arom), 6.96 (m, 2H, H-arom), 6.27 (d, J = 6.6 Hz, 1H, NH), 4.93 (bs, 1H, NH), 4.78 (m, 1H, Hα), 4.32 (m, 1H, Hα), 3.66 (s, 3H, OCH₃), 3.03 (m, 4H, Hβ), 1.38 (s, 9H, C(CH₃)₃). Next N-Boc-Phe-Phe-OMe (2.56 g, 6.0 mmol) was deprotected as described above to yield II (2.05 g, 94 %) as a white solid. ¹H NMR (300 MHz, CDCl₃): δ = 9.03 (d, J = 7.5 Hz, 1H, NH), 8.16 (bs, 3H, NH₃), 7.31-7.19 (m, 10H, H-arom), 4.55 (m, 1H, Hα), 4.03 (m, 1H, Hα), 3.59 (s, 3H, OCH₃) [27]

H-Gly-Gly-OMe·HCl (III): Thionyl chloride (0.6 mL, 8.3 mmol) was added to a suspension of glycylglycine (1.0 g, 7.6 mmol) in methanol (5 mL) at 0 °C. Next, the mixture was stirred at reflux temperature for 2 h. After cooling to room temperature, methanol and excess thionyl chloride were removed under reduced pressure. Precipitation from methanol/diethyl ether gave glycylglycine methyl ester hydrochloride III (1.25 g) in 90 % yield as a white solid. ¹H NMR (300 MHz, D₂O): δ = 4.07 (s, 2H, CH₂), 3.88 (s, 2H, CH₂), 3.74 (s, 3H, OCH₃).

General procedure for the preparation of imines 14-21.
A Schlenk vessel was charged with tetraaldehyde 5, 8 or 13 (0.40 mmol), L-amino acid methyl ester hydrochloride or a dipeptide analogue (1.76 mmol), 3 Å molecular sieves (2 g) and methylene chloride (5 mL). To the suspension was added triethylamine (1.76 mmol) and the reaction mixture was stirred for 48 h at reflux temperature. The solution was filtered, washed with water (2 mL) and the organic layer was dried over Na₂SO₄ and concentrated under reduced pressure. The imines were recrystallized from light petroleum.

2,7-Di-tert-butyl-4,5-bis[di(3-((S)-(1-methoxy-3-methyl-1-oxobutan-2-ylimino)methyl)phenylphosphino]-9,9-dimethylxanthene (14): Compound 14 was prepared according to the general procedure starting from L-valine methyl ester hydrochloride (0.28 g, 1.64 mmol) and tetraaldehyde 5 (0.30 g, 0.37 mmol) in 80 % yield (0.37 g) as a white solid. [α]D²⁰ = –91.8 ° (c 1.0, CHCl₃); ¹H NMR (500 MHz, CD₂Cl₂): δ = 8.13 (s, 2H, CH=N), 8.12 (s, 2H, CH=N), 7.76 (d, J = 7.5 Hz, 2H, H-arom), 7.72 (d, J = 7.5 Hz, 2H, H-arom), 7.57 (m, 4H, H-arom), 7.45 (d, J = 2.0 Hz, 2H, H-1, H-8), 7.31 (t, J = 7.5 Hz, 2H, H-arom), 7.30 (t, J = 7.5 Hz, 2H, H-arom), 7.22 (m, 4H, H-arom), 6.53 (d, J = 2.5 Hz, 2H, H-3, H-6), 3.68 (s, 6H, OCH₃), 3.65 (s, 6H, OCH₃), 3.61 (d, J = 2.5 Hz, 2H, Ha), 3.60 (d, J = 3.0 Hz, 2H, Ha), 2.27 (m, 4H, Hβ), 1.69 (s, 6H, CH₃), 1.09 (s, 18H, C(CH₃)₃), 0.89 (dd, J = 7.0 Hz, J = 3.0 Hz, 12H, CH₃), 0.84 (dd, J = 8.5 Hz, J = 7.0 Hz, 12H, CH₃); ¹3C [¹H] NMR (125 MHz, CD₂Cl₂): δ = 172.7 (C=O),
2,7-Di-tert-butyl-4,5-bis[di(3-((S)-(1-methoxy-1-oxo-3-phenylpropan-2-ylimino)methyl)phenyl)phosphino]-9,9-dimethylxanthene (15): Compound 15 was prepared according to the general procedure starting from L-phenylalanine methyl ester hydrochloride (0.95 g, 4.4 mmol) and tetraaldehyde 5 (0.80 g, 1.0 mmol) in 86% yield (1.25 g) as a white solid. 

$[^1]H$ NMR (300 MHz, CDCl$_3$): $\delta = 7.69-7.61$ (m, 8H, CH=N, H-arom), 7.39-7.35 (m, 6H, H-arom), 7.17-7.01 (m, 26H, H-arom), 6.38 (d, $J = 2.4$ Hz, 2H, H-3, H-6), 4.08 (m, 4H, H$\alpha$), 3.70 (s, 6H, OCH$_3$), 3.69 (s, 6H, OCH$_3$), 3.32 (dd, $J = 13.5$ Hz, $J = 9.0$ Hz, 4H, H$\beta$), 3.08 (dd, $J = 13.5$ Hz, $J = 9.0$ Hz, 4H, H$\beta$) 1.69 (s, 6H, CH$_3$), 1.07 (s, 18H, C(CH$_3$)$_3$); $^{13}$C $[^1]H$ NMR (125 MHz, CD$_2$Cl$_2$): $\delta = 172.3$ (C=O), 164.0 (C=N), 163.9 (C=N), 150.9 (t, $J = 21.3$ Hz, CO), 146.4 (C-2, C-7), 138.2 (Cq), 137.0 (m, CH), 136.0 (Cq), 131.4 (Cq), 130.2 (CH), 129.5 (C-3, C-6), 129.5 (CH), 128.8 (CH), 128.7 (CH), 127.4 (CH), 121.6 (C-1, C-8), 121.4 (C-1, C-8), 123.7 (m, C-4, C-5), 75.3 (CH), 52.5 (OCH$_3$), 40.2 (CH$_2$), 35.5 (C-9), 35.0 (C(CH$_3$)$_3$), 32.4 (CH$_3$), 31.6 (C(CH$_3$)$_3$); $^{31}$P $[^1]H$ NMR (121 MHz, CDCl$_3$): $\delta = -14.47$; IR (KBr, cm$^{-1}$): 3052 (w), 2954 (m), 2876 (w), 1740 (s), 1640 (s), 1424 (s), 1263 (s), 1202 (s), 1165 (s), 1084 (s), 1030 (m), 795 (s), 750 (s), 698 (s); HRMS (FAB+): m/z calcld. for C$_91$H$_93$N$_4$O$_9$P$_2$ (M+H$^+$): 1447.6418; found: 1447.6451.

2,7-Di-tert-butyl-4,5-bis[di(3-((2-methoxy-2-oxoethylimino)methyl)phenyl)phosphino]-9,9-dimethylxanthene (16): Compound 16 was prepared according to the general procedure starting from glycine methyl ester hydrochloride (0.21 g, 1.64 mmol) and tetraaldehyde 5 (0.30 g, 0.37 mmol) in 82% yield (0.33 g) as a yellowish solid. $[^1]H$ NMR (500 MHz, CD$_2$Cl$_2$): $\delta = 8.14$ (s, 4H, CH=N), 7.74 (d, $J = 7.5$ Hz, 4H, H-arom), 7.53 (m, 4H, H-arom), 7.47 (d, $J = 2.5$ Hz, 2H, H-1, H-8), 7.31 (t, $J = 7.5$ Hz, 4H, H-arom), 7.23 (m, 4H, H-arom), 6.54 (d, $J = 2.0$ Hz, 2H, H-3, H-6), 4.33 (s, 8H, CH$_2$), 3.71 (s, 12H, OCH$_3$), 1.70 (s, 6H, CH$_3$), 1.10 (s, 18H, C(CH$_3$)$_3$); $^{13}$C $[^1]H$ NMR (125 MHz, CD$_2$Cl$_2$): $\delta = 171.0$ (C=O), 165.6 (C=N), 151.1 (t, $J = 19.4$ Hz, CO), 146.5 (C-2, C-7), 138.6 (t, $J = 14.3$ Hz, PC), 137.0 (t, $J = 17.7$ Hz, CH), 136.2 (t, $J = 7.2$ Hz, Cq), 135.1 (t, $J = 24.4$ Hz, CH), 130.1 (CC-9), 129.5 (C-3, C-6), 129.1 (CH), 128.4 (CH), 121.6 (C-1, C-8), 123.7 (t, $J = 17.7$ Hz, C-4, C-5), 62.4 (CH$_2$), 52.4 (OCH$_3$), 35.5 (C-9), 35.0 (C(CH$_3$)$_3$), 32.0 (CH$_3$), 31.6 (C(CH$_3$)$_3$); $^{31}$P $[^1]H$ NMR (121 MHz, CD$_2$Cl$_2$): $\delta = -14.42$; IR (KBr, cm$^{-1}$): 3052 (w), 2954 (m), 2876 (w), 1740 (s), 1640 (s), 1424 (s), 1263 (s), 1201 (s), 1109 (s), 795 (m), 691 (s); HRMS (FAB+): m/z calcld. for C$_{91}$H$_{93}$N$_4$O$_9$P$_2$ (M+H$^+$): 1087.4540; found: 1087.4576.
2,7-Di-tert-butyl-4,5-bis[di(3-(((S)-1-((S)-1-methoxy-3-methyl-1-oxobutan-2-ylamino)-3-methyl-1-oxobutan-2-ylamino)methyl)phenyl)phosphino]-9,9-dimethylxanthene (17): Compound 17 was prepared according to the general procedure starting from valylvaline methyl ester I (0.18 g, 0.66 mmol) and tetraaldehyde 5 (0.12 g, 0.15 mmol) in 73 % yield (0.18 g) as a white solid. $\left[\alpha\right]_{D}^{20} = +62.3 ^\circ$ (c 1.0, CHCl$_3$); $^1$H NMR (500 MHz, CD$_2$Cl$_2$): $\delta = 8.04$ (s, 2H, CH=N), 8.03 (s, 2H, CH=N), 7.84 (d, $J = 8.0$ Hz, 2H, H-arom), 7.75 (d, $J = 7.5$ Hz, 2H, H-arom), 7.61 (m, 4H, H-arom), 7.45 (d, $J = 2.0$ Hz, 2H, H-1, H-8), 7.25 (m, 12H, NH, H-arom), 6.52 (d, $J = 2.5$ Hz, 2H, H-3, H-6), 4.46 (m, 4H, Ha), 3.61 (s, 6H, OCH$_3$), 3.56 (s, 6H, OCH$_3$), 3.55 (m, 4H, H$_\alpha$), 2.19 (m, 8H, H$_\beta$), 1.68 (s, 6H, CH$_3$), 1.08 (s, 18H, C(CH$_3$)$_3$), 0.91 (m, 48H, CH$_3$); $^{13}$C $\{^1$H$\}$ NMR (125 MHz, CD$_2$Cl$_2$): $\delta = 172.6-172.5$ (C=O), 163.0 (C=N), 151.0 (t, $J = 19.0$ Hz, CO), 146.6 (C-2, C-7), 138.6 (m, PC), 137.0 (m, CH), 136.2 (m, Cq), 135.6 (m, CH), 135.6 (m, CH), 130.1 (CC-9), 129.6 (C-3, C-6), 129.3 (m, CH), 128.6 (C-1, C-8), 124.2 (C-1, C-8), 123.7 (m, C-4, C-5), 80.0 (CH), 79.8 (CH), 57.4 (CH), 52.3 (OCH$_3$), 35.5 (C-9), 35.0 (C(CH$_3$)$_3$), 33.5 (CH), 32.2 (CH$_3$), 31.8 (CH), 31.5 (C(CH$_3$)$_3$), 19.8, 19.5, 18.4, 18.3, 18.1, 18.0 (CH$_3$); $^{31}$P $\{^1$H$\}$ NMR (121 MHz, CD$_2$Cl$_2$): $\delta = –14.81$; IR (KBr, cm$^{-1}$): 3388 (m), 3043 (w), 2963 (m), 2872 (w), 1744 (s), 1683 (s), 1507 (s), 1424 (s), 1370 (m), 1263 (s), 1207 (s), 1101 (m), 796 (s), 693 (s); HRMS (FAB+): m/z calcd. for C$_{95}$H$_{129}$N$_8$O$_{13}$P$_2$ ($M^{+}$H$^+$): 1651.9154; found: 1651.9113.

2,7-Di-tert-butyl-4,5-bis[di(3-((2-(2-methoxy-2-oxoethylamino)-2-oxoethylimino)methyl)pheny)]phosphino]-9,9-dimethylxanthene (18): Compound 18 was prepared according to the general procedure starting from phenylalanyl-phenylalanine methyl ester II (0.24 g, 0.66 mmol) and tetraaldehyde 5 (0.12 g, 0.15 mmol) in 86 % yield (0.26 g) as a white solid. $\left[\alpha\right]_{D}^{20} = –122.1 ^\circ$ (c 1.0, CHCl$_3$); $^1$H NMR (500 MHz, CD$_2$Cl$_2$): $\delta = 7.57-7.53$ (m, 4H, CH=N), 7.46 (m, 4H, H-arom), 7.36 (m, 4H, H-arom), 7.16-6.93 (m, 54H, NH, H-arom), 6.44 (d, $J = 2.0$ Hz, 2H, H-3, H-6), 4.72 (m, 4H, H$_\alpha$), 3.90 (m, 4H, H$_\alpha$), 3.59 (s, 6H, OCH$_3$), 3.52 (s, 6H, OCH$_3$), 3.08 (m, 4H, H$_\beta$), 3.00 (m, 8H, H$_\beta$), 1.70 (s, 6H, CH$_3$), 1.09 (s, 18H, C(CH$_3$)$_3$); $^{13}$C $\{^1$H$\}$ NMR (125 MHz, CD$_2$Cl$_2$): $\delta = 172.2-172.0$ (C=O), 163.2 (C=N), 151.0 (t, $J = 21.3$ Hz, CO), 146.5 (C-2, C-7), 138.4 (m, Cq), 137.9 (Cq), 136.7 (Cq), 135.8 (m, Cq), 135.1 (m, CH), 130.5 (CH), 129.9 (CH), 129.2 (CH), 129.1 (CH), 128.1 (CH), 127.9 (CH), 127.7 (CH), 127.6 (CH), 127.0 (CH), 124.3 (C-1, C-8), 123.6 (t, $J = 17.5$ Hz, C-4, C-5), 75.2 (CH), 75.0 (CH), 53.3 (CH), 53.2 (CH), 52.7 (OCH$_3$), 52.6 (OCH$_3$), 41.7 (CH$_2$), 38.5 (CH$_2$), 35.4 (C-9), 35.0 (C(CH$_3$)$_3$), 32.6 (CH$_3$), 31.6 (C(CH$_3$)$_3$); $^{31}$P $\{^1$H$\}$ NMR (121 MHz, CD$_2$Cl$_2$): $\delta = –15.19$; IR (KBr, cm$^{-1}$): 3378 (m), 3061 (w), 2982 (w), 2928 (w), 2853 (w), 1744 (s), 1679 (s), 1497 (s), 1424 (s), 1362 (m), 1212 (s), 1112 (m), 1081 (m), 1030 (m), 795 (s), 747 (s), 670 (s); HRMS (FAB+): m/z calcd. for C$_{127}$H$_{129}$N$_8$O$_{13}$P$_2$ ($M^{+}$H$^+$): 2035.9154; found: 2035.9182.

2,7-Di-tert-butyl-4,5-bis[di(3-(((2-(2-methoxy-2-oxoethylamino)-2-oxoethylimino)methyl)phenyl)phosphino]-9,9-dimethylxanthene (19): Compound 19 was prepared according to the general procedure starting from glycylglycine methyl ester III (0.30 g, 1.64 mmol) and tetraaldehyde 5 (0.30 g, 0.37 mmol) in 84 % yield (0.41 g) as a slightly yellow solid. $\left[\alpha\right]_{D}^{20} = 8.18 ^\circ$ (c 4H, CH=–N), 7.77 (d, $J = 7.7$ Hz, 4H, H-arom), 7.61 (m, 4H, H-arom), 7.48 (d, $J = 2.1$ Hz, 2H, H-1, H-8), 7.39-7.26 (m, 12H, NH, H-arom), 6.56 (d, $J = 2.0$ Hz, 2H, H-3, H-6), 4.23 (s, 8H, CH$_2$), 4.02 (s, 8H, H-arom).
2,7-Di-tert-butyl-4,5-bis[(S)-1-((S)-1-methoxy-3-methyl-1-oxobutan-2-ylamino)-3-methyl-1-oxobutan-2-ylimino)methyl]phenyl]phosphino]-9,9-dimethylxanthene (20): Compound 20 was prepared according to the general procedure starting from valylvaline methyl ester I (0.12 g, 0.44 mmol) and tetraaldehyde 8 (0.08 g, 0.1 mmol) in 86% yield (0.14 g) as a white solid. \[\delta_{\text{H}}^{1H} = +70.9^\circ\] (c 1.0, CHCl₃); 1H NMR (500 MHz, CD₂Cl₂): δ = 8.13 (s, 2H, CH=N), 8.11 (s, 2H, CH=N), 7.70 (m, 8H, H-arom), 7.49 (d, 2H, J = 2.0 Hz, H-1, H-8), 7.29 (m, 12H, N, H-arom), 6.58 (d, 2H, J = 2.5 Hz, H-3, H-6), 4.52 (m, 4H, Hα), 3.72 (s, 6H, OCH₃), 3.63 (s, 6H, OCH₃), 3.62 (m, 4H, Hα), 2.25 (m, 8H, Hβ), 1.73 (s, 6H, CH₃), 1.12 (s, 18H, C(CH₃)₃), 0.92 (m, 48H, CH₃); 13C {1H} NMR (125 MHz, CD₂Cl₂): δ = 172.7-172.6 (C=O), 162.8 (C=N), 150.6 (t, J = 19.0 Hz, CO), 146.6 (C-2, C-7), 136.4 (Cq), 136.2 (Cq), 134.8 (m, CH), 134.4 (m, CH), 132.3 (Cq), 131.4 (m, CH), 129.8 (CH), 129.7 (C-3, C-6), 129.3 (CH), 128.6 (CH), 124.5 (C-1, C-8), 123.5 (m, C-4, C-5), 79.7 (CH), 79.6 (CH), 57.4 (CH), 52.4 (OCH₃), 52.3 (OCH₃), 52.3 (OCH₃), 35.4 (C-9), 35.0 (C(CH₃)₃), 20.0, 19.9, 19.5, 18.2, 18.1, 18.0 (CH₃); 31P {1H} NMR (121 MHz, CD₂Cl₂): δ = –14.81; IR (KBr, cm⁻¹): 3386 (m), 3068 (w), 2964 (s), 2873 (w), 1743 (s), 1680 (s), 1507 (s), 1426 (s), 1262 (s), 1153 (m), 1110 (m), 1017 (m), 820 (s), 803 (s), 699 (s); HRMS (FAB+): m/z calcd. for C₈₉H₁₁₂N₄O₆P₂ (M+H⁺): 1651.9154; found: 1651.9111.

2,2'-Bis[di(3-((S)-1-((S)-1-methoxy-3-methyl-1-oxobutan-2-ylamino)-3-methyl-1-oxobutan-2-ylimino)methyl]phenyl]phosphino]-4,4'-dimethyl-diphenylether (21): Compound 21 was prepared according to the general procedure starting from valylvaline methyl ester I (0.26 g, 0.97 mmol) and tetraaldehyde 13 (0.15 g, 0.22 mmol) in 89% yield (0.30 g) as an off-white solid. \[\delta_{\text{H}}^{1H} = +42.0^\circ\] (c 1.0, CHCl₃); 1H NMR (500 MHz, CD₂Cl₂): δ = 8.11 (s, 2H, CH=N), 8.10 (s, 2H, CH=N), 7.86 (d, J = 8.0 Hz, 2H, H-arom), 7.82 (d, J = 7.5 Hz, 2H, H-arom), 7.62 (t, J = 7.7 Hz, 2H, H-arom), 7.36 (m, 4H, NH, H-arom), 7.27 (d, J = 5.5 Hz, 4H, NH), 7.17 (m, 4H, H-arom), 7.03 (d, J = 6.5 Hz, 2H, H-arom), 6.64 (d, J = 2.5 Hz, 2H, H-arom), 6.60 (dd, J = 8.5 Hz, J = 4.5 Hz, 2H, H-arom), 4.46 (m, 4H, Ha), 3.61 (s, 6H, OCH₃), 3.60 (m, 4H, Ha), 3.59 (s, 6H, OCH₃), 2.20 (m, 8H, Hβ), 2.14 (s, 6H, CH₃), 0.92 (m, 48H, CH₃); 13C {1H} NMR (125 MHz, CD₂Cl₂): δ = 172.6-172.5 (C=O), 162.8 (C=N), 157.7 (d, J = 17.7 Hz, Cq), 137.8 (m, Cq), 137.0 (m, CH), 136.3 (m, Cq), 135.0 (d, J = 24.1 Hz, CH), 135.1 (d, J = 23.8 Hz, CH), 134.7 (CH), 133.9 (Cq), 131.8 (CH), 129.4 (CH), 128.3 (d, J = 12.2 Hz, CH), 127.8 (m, Cq), 118.3 (CH), 79.8 (CH), 57.4 (CH), 52.4 (OCH₃), 52.3 (OCH₃), 33.6 (CH), 31.8 (CH), 20.0 (CH₃), 19.8, 19.5, 18.3, 18.2, 18.1, 18.0 (CH₃); 31P {1H} NMR (121 MHz, CD₂Cl₂): δ = –14.76; IR (KBr, cm⁻¹): 3386 (m),
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3071 (w), 2963 (s), 2873 (w), 1743 (s), 1680 (s), 1510 (s), 1467 (s), 1370 (m), 1264 (s), 1211 (s), 1153 (s), 798 (s), 693 (s); HRMS (FAB+): m/z calcd. for C₉₆H₁₁₅N₈O₁₃P₂(M+H⁺): 1527.7902; found: 1527.7880.

[(17)PtCl₂]: Ligand 17 (22.3 mg, 13.5 μmol) and [(MeCN)₂PtCl₂] (4.7 mg, 13.5 μmol) were placed in a Schlenk flask. Acetonitrile (2 mL) was added and the reaction mixture was stirred overnight at room temperature. The solvent was removed under reduced pressure. The resulting white solid was washed with hexanes and dried in vacuo. ³¹P {¹H} NMR (121 MHz, CDCl₃): δ = 4.40 (1 JPt,P = 3677 Hz); HRMS (FAB+): m/z calcd. for C₉₅H₁₂₉ClN₈O₁₃P₂Pt(M–Cl⁻): 1881.8430; found: 1881.8442.

[(15)PdCl₂]: Ligand 15 (72.4 mg, 50 μmol) and [Pd(cod)Cl₂] (19.2 mg, 50 μmol) were placed in a Schlenk flask. THF (4 mL) was added and the reaction mixture was stirred overnight at room temperature. The solvent was removed under reduced pressure. The resulting yellow powder was washed with diethyl ether and dried in vacuo. ³¹P {¹H} NMR (121 MHz, CDCl₃): δ = 23.45; HRMS (FAB+): m/z calcd. for C₉₁H₉₂ClN₄O₉P₂Pd(M–Cl⁻): 1589.5089; found: 1589.5065.

[(14)Rh(H)(CO)(PPh₃)]: A solution of ligand 14 (16.9 mg, 13.5 μmol) and [(PPh₃)₃Rh(H)(CO)] (12.4 mg, 13.5 μmol) in CH₂Cl₂ (2 mL) was stirred for 4 h. The solvent was removed in vacuo and the residue was analyzed by NMR spectroscopy. ¹H NMR (300 MHz, C₆D₆): δ = 7.80-7.71 (m, 12H, H-arom), 7.68 (m, 10H, H-arom), 7.05-6.96 (m, 22H, H-arom), 3.55 (d, J = 6.9 Hz, 2H, Ha), 3.49 (dd, J = 6.9 Hz, J = 3.6 Hz, 2H, Ha), 3.36 (s, 3H, OCH₃), 3.33 (s, 3H, OCH₃), 3.31 (s, 3H, OCH₃), 3.29 (s, 3H, OCH₃), 2.46 (m, 4H, Hβ), 1.81 (s, 3H, CH₃), 1.68 (s, 3H, CH₃), 1.12 (s, 18H, C(CH₃)₃), 0.91 (m, 24H, CH₃), –9.60 (dt, JRh,P = 18.7 Hz, Jₚ,P = 12.4 Hz, 1H, RhH); ³¹P {¹H} NMR (121 MHz, C₆D₆): δ = 41.63 (dt, JRh,P = 170 Hz, Jₚ,P = 132 Hz, PPh₃), 22.01 (dd, JRh,P = 148 Hz, Jₚ,P = 132 Hz, P).

General procedure for the asymmetric hydroformylation of vinyl acetate.
The hydroformylation experiments were performed in a stainless steel autoclave with a glass inner beaker (15 mL) and a substrate inlet vessel. In a typical experiment, [Rh(acac)(CO)₂] (2 μmol) and phosphorus ligand (4 eq.) were dissolved in toluene (1.5 mL). The catalyst solution was introduced into the autoclave via a syringe. The autoclave was flushed three times with 7.0 bar of CO/H₂, then pressurized to 7.0 bar CO/H₂ and heated to 60 °C. The solution was stirred for 1 h at this temperature. A mixture of vinyl acetate (0.5 mmol) and heptane as an internal standard (0.25 mmol) in toluene (0.5 mL) was introduced, and the pressure was raised to 10.0 bar of CO/H₂. After the appropriate reaction time, the magnetic stirrer was stopped and the reactor cooled rapidly. The pressure was reduced to 1.0 bar and the conversion was determined by GC using a DB-1 (J&W) column (40 °C for 20 min, then ΔT = 20 °C min⁻¹, retention times: 5.6 min for vinyl acetate, 6.5 min for acetic acid, 14.2 min for heptane, 22.5 min for 2-acetoxy-propanal and 25.5 min for 3-acetoxy-propanal. The enantiomeric purity of the branched aldehyde was determined by chiral GC using a Chiralsil DEX-CB column (50 °C for 5 min, then ΔT = 6 °C min⁻¹, tr (R) = 7.2 min, tr (S) = 7.6 min).
General procedure for the asymmetric hydroformylation of styrene.
The hydroformylation experiments were performed in a stainless steel autoclave with a glass inner beaker (15 mL) and a substrate inlet vessel. Styrene was filtered over basic alumina to remove possible peroxide impurities. In a typical experiment, \([\text{Rh(acac})(\text{CO})_2]\) (2 μmol) and phosphorus ligand (4 eq.) were dissolved in toluene (1.5 mL). The catalyst solution was introduced into the autoclave via a syringe. The autoclave was flushed three times with 15.0 bar of CO/H\textsubscript{2}, then pressurized to 15.0 bar CO/H\textsubscript{2} and heated to 60 °C. The solution was stirred for 1 h at this temperature. A mixture of styrene (0.5 mmol) and decane as internal standard (0.25 mmol) in toluene (0.5 mL) was introduced, and the pressure was raised to 20.0 bar of CO/H\textsubscript{2}. After the appropriate reaction time, the magnetic stirrer was stopped and the reactor cooled rapidly. The pressure was reduced to 1.0 bar and a few drops of tri-\textit{n}-butylphosphite were added to prevent any further reaction. The conversion was determined by GC using a DB-1 (J&W) column (70 °C for 1 min, then \(\Delta T_1 = 7 \text{ °C min}^{-1}\) to 120 °C and \(\Delta T_2 = 13 \text{ °C min}^{-1}\) to 250 °C; retention times: 9.0 min for styrene, 11.3 min for decane, 12.9 min for 2-phenylpropanal and 13.8 min for 3-phenylpropanal. The enantiomeric purity was determined by chiral GC using a Supelco β-DEX 225 column (T = 100 °C for 5 min, then \(\Delta T = 4 \text{ °C min}^{-1}\), \(t_R\) (branced \(R\)) = 11.8 min, \(t_R\) (branced \(S\)) = 12.1 min, \(t_R\) (linear) = 15.6 min).

General procedure for asymmetric hydrogenation experiments.
The hydrogenation experiments were carried out in a stainless steel autoclave (total volume is 150 mL) charged with an insert suitable for 8 or 14 reaction vessels including Teflon mini stirring bars for conducting parallel reactions. In a typical experiment, a reaction vessel was charged with \([\text{Rh(cod)}_2]\)BF\(_4\) (0.50 μmol), bidentate ligand (0.55 μmol), substrate (50 μmol) and decane (25 μmol) in 0.5 mL of solvent. Before starting the catalytic reactions, the charged autoclave was purged three times with 5 bar of dihydrogen and then pressurized to 5 bar H\textsubscript{2}. The reaction mixtures were stirred at 25 °C for 20 h. Next, the autoclave was depressurized and the reaction mixtures were filtered over a plug of silica. The conversion was determined by GC measurement and the enantiomeric excess was measured by chiral GC using the following columns and conditions: for G: ChiralSIL DEX-CB column (T = 70 °C for 1 min, then \(\Delta T = 7 \text{ °C min}^{-1}\), \(t_R\) (G) = 6.4 min, \(t_R\) (S) = 7.2 min, \(t_R\) (R) = 7.4 min); and for H: Supelco β-DEX 225 column (T = 70 °C for 50 min, then \(\Delta T = 25 \text{ °C min}^{-1}\), \(t_R\) (S) = 51.7 min, \(t_R\) (R) = 52.3 min, \(t_R\) (H) = 53.5 min).

References and Notes


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[7] Ligand abbreviations: Xantphos = 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene, DPEphos = bis(2-diphenylphosphinophenyl)ether.


[15]
Xantphos has $\text{C}_2$-symmetry even though the xanthene plane is rapidly flipping. As a result of the backbone flip, Xantphos $\text{X}_1$ changes to conformer $\text{X}_2$ which, followed by rotation around the P-C bonds, results in $\text{X}_3$. Since substituent $a$ is identical to substituent $b$, conformers $\text{X}_1$ and $\text{X}_3$ are the same. This behaviour of the xanthene backbone is therefore not responsible for the observed diastereotopy.


