Indole-based phosphorus ligands in asymmetric catalysis
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Chapter 3

Asymmetric synthesis of the Roche Ester and its derivatives by Rh-IndolPhos catalyzed hydrogenation†

Abstract: (S)-3-hydroxy-2-methylpropionate, known as the Roche ester, and several of its derivatives are successfully synthesized through asymmetric rhodium catalyzed hydrogenation, using IndolPhos (diisopropyl{1-[(S)-3,5-dioxa-4-phospha-cyclohepta(2,1-a;3,4-a’)dinaphtalen-4-yl]-3-methyl-2-indoly]phosphine) as the chiral ligand, in excellent yield and very high ee (TOF over 5500 h\(^{-1}\) at 25 °C; up to 98% ee at -40 °C).

3.1 Introduction

Transition metal catalyzed asymmetric hydrogenation has evolved in recent years as a practical and economical strategy in the preparation of fine chemical intermediates for the pharmaceutical industry.¹ In this course, a broad range of chiral hydrogenation catalysts have been developed, most of which rely on chiral mono- or bidentate phosphorus ligands.² The continuous development of new ligands has been shown to be vital in order to discover good catalysts. Two successful strategies in catalyst development have been reported that aim at catalysts for a broad substrate scope; the privileged ligand approach and combinatorial ligand approach. Privileged ligands, as defined by Jacobsen, usually consist of a rigid chiral backbone and give high selectivities for a broad range of substrates requiring only minor or no changes in the ligand structure.³ In ultimate examples the ligands provide selective catalysts for several transition metal catalyzed conversions. Alternatively, the combinatorial ligand approach utilizes facile preparation of ligands enabling the construction of large and diverse ligand libraries that allow, in conjunction with automated screening methods, the identification the optimum catalyst for each individual substrate.⁴ Our group has contributed to this field by developing both combinatorial⁵ as well as privileged ligands.⁶ To illustrate the potential of these ligands though, it is essential to employ them in the synthesis of relevant and challenging chiral targets.⁵f

![Figure 3.1 Structure of the Roche ester 1a and its derivatives.](image)

In the past decade, a few reports appeared on the asymmetric synthesis of methyl 3-hydroxy-2-methylpropionate 1a, known as the Roche ester, by means of enantioselective hydrogenation (Figure 3.1).⁶,⁷,⁸ The Roche ester is a very important chiral starting material for the total synthesis of pharmaceutical compounds, e.g. in the synthesis of anti-tumor agents tedanolide and discodermolide.⁹ Importantly, as the Roche ester is a liquid the optical purity can not be increased by crystallization and therefore asymmetric synthesis of this building block is only interesting if the ee of the product is very high (more than 95 %). Genêt et al. reported a highly enantioselective synthesis of Roche Ester derivatives with bulky ester groups using a Ru-SYNPHOS catalyst.⁸a-b However, the parent Roche ester containing a methyl ester (1a) was obtained in only 88% ee. Saito and co-workers reported 90% ee using a Rh-DuPHOS catalyst.⁸d Until the results in this chapter were published, these examples represented the leads in the asymmetric synthesis of 1a by enantioselective hydrogenation, and routes that provided over 90 % enantiomeric purity remained a challenge. Afterwards, the groups of Börner,¹⁰ Zheng,¹¹ and our own laboratory reported ee’s for this substrate up to 99 %.¹²
Recently, we reported the synthesis of a new hybrid bidentate phosphine-phosphoramidite ligand IndolPhos (4) and its application in asymmetric rhodium catalyzed hydrogenation and hydroformylation (chapter 2). In terms of bite angle and rigidity, the ligand shows similarities with DuPHOS, one of the most successful ligands for the preparation of 1a, which therefore prompted our interest in applying IndolPhos in the synthesis of Roche ester derivatives. We here report the asymmetric synthesis of the Roche ester and its derivatives through rhodium-IndolPhos catalyzed hydrogenation.

3.2 Ligand synthesis

IndolPhos ligands 4a-f are prepared in one step from the corresponding indolylphosphines 3a-d by condensation with a Bisnaphtol phosphorochloridite (Scheme 3.1). It was observed in chapter 2 that bulky phosphines were important in order to achieve high selectivity in asymmetric hydrogenation. Therefore, we expanded the IndolPhos library with a cyclohexylphosphine (4c) and o-tolylphosphine (4d) donor group.

**Scheme 3.1** Synthesis of IndolPhos ligands.

\[
\begin{align*}
3a & \quad R = \text{Ph} \\
3b & \quad R = \text{Pr} \\
3c & \quad R = \text{Cy} \\
3d & \quad R = \text{"Tol} \\
4a & \quad R = \text{Ph; } R' = \text{H} \\
4b & \quad R = \text{Pr; } R' = \text{H} \\
4c & \quad R = \text{Cy; } R' = \text{H} \\
4d & \quad R = \text{"Tol; } R' = \text{H} \\
4e & \quad R = \text{Ph; } R' = \text{SiMe}_3 \\
4f & \quad R = \text{Pr; } R' = \text{Me}
\end{align*}
\]

3.3 Asymmetric hydrogenation

Ligands 4a-f were studied in the rhodium catalyzed hydrogenation of methyl 2-hydroxymethylacrylate 2a, which is available in one step via Baylis-Hillman reaction of methyl acrylate and formaldehyde, giving Roche ester 1a (Scheme 3.2). The catalysts were generated in situ from [Rh(nbd)_2]BF_4 and the corresponding IndolPhos ligand in dichloromethane (Table 3.1). All ligands give rhodium catalysts that display high activity as all reactions are (almost) completed after 20 h at 10 bar H_2 and room temperature, providing 1a as the only product. On the other hand, large variations are observed with regard to the enantioselectivity of the catalysts based on the various ligands. The catalyst generated from parent IndolPhos ligand 4a gives an almost racemic product, whereas the introduction of bulky groups on the Bisnaphtol moiety or the use of bulky phosphines results in moderate to excellent enantioselectivities up to 91 % ee (Table 3.1, entries 1-6).
Scheme 3.2 Synthetic strategy for the Roche Ester synthesis.

The large dependence of the enantioselectivity on the steric properties of the ligand may be rationalized by the formation of bis-ligated species $[\text{Rh}(4\text{a})_2]\text{BF}_4$. In chapter 2 we detected this species by NMR spectroscopy when mixing equimolar amounts of $4\text{a}$ with $[\text{Rh}(\text{nbd})_2]\text{BF}_4$. Importantly, when changing the steric properties of the ligand to more bulky substituents on either the phosphine ($4\text{b-d}$) or Bisnaphthol ($4\text{e}$), only mono-ligated species $[\text{Rh}(4)(\text{nbd})]\text{BF}_4$ were observed. Additional factors disfavoring bis-ligated species in the case of $4\text{b-c}$ and $4\text{f}$ are the lack of \text{π}-stacking interactions and the stronger trans-effect of alkyl phosphines.

Table 3.1 Ligand screening in the rhodium catalyzed asymmetric hydrogenation of methyl 2-hydroxymethylacrylate.$^a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>% conv.</th>
<th>% ee$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4a</td>
<td>100</td>
<td>7</td>
</tr>
<tr>
<td>2</td>
<td>4b</td>
<td>100</td>
<td>91</td>
</tr>
<tr>
<td>3</td>
<td>4c</td>
<td>100</td>
<td>85</td>
</tr>
<tr>
<td>4</td>
<td>4d</td>
<td>100</td>
<td>66</td>
</tr>
<tr>
<td>5</td>
<td>4e</td>
<td>80</td>
<td>62</td>
</tr>
<tr>
<td>6</td>
<td>4f</td>
<td>100</td>
<td>74</td>
</tr>
<tr>
<td>7</td>
<td>($S$)-Monophos$^c$</td>
<td>100</td>
<td>43</td>
</tr>
</tbody>
</table>

$^a$ Reactions were performed in CH$_2$Cl$_2$, Rh/L = 1:1.1, Rh/substrate = 1:100, [Rh] = 1.0 mM, 10 bar of H$_2$, at 20°C for 20 h using $[\text{Rh}(\text{nbd})_2]\text{BF}_4$ as metal precursor. $^b$ The ($S$)-enantiomer was obtained in all cases. $^c$ ($S$)-(+)-(3,5-Dioxa-4-phospha-cyclohepta[2,1-a;3,4-a'] dinaphthalen-4-yl)dimethylamine.

The ligand screening experiments indicate that especially bulky, electron-rich alkylphosphines are required for catalysts that provide the product in ee values over 80%. Comparison with Monophos confirms this necessity and demonstrates the added value of hybrid ligands in this transformation (Table 3.1, entry 7).$^{15}$

After the encouraging screening results, conditions were optimized for the most selective catalyst based on ligand $4\text{b}$. These optimization experiments were carried out in an AMTEC SPR16, consisting of 16 parallel reactors equipped with temperature and pressure sensors and a mass flow controller, allowing the reaction rates to be determined from gas-uptake profiles. The rate measurements revealed turnover...
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frequencies of over 5500 mol\(_{1a}\) mol\(_{Rh}^{-1}\) h\(^{-1}\) (Table 3.2, entry 2). Lowering the hydrogen pressure does not affect the ee but leads to an almost linear decrease of the rate, suggesting a first order dependency on the partial hydrogen pressure (Table 3.2, entries 1-2). When the catalyst loading was reduced to 0.25 - 0.1 mol%, activity dropped and full conversion was no longer reached (Table 2, entry 2-4). The gas uptake profiles (Figure 3.2) for entries 3 and 4 level off at 95% and 46% conversion, respectively, indicating catalyst deactivation at lower catalyst loading, which is most probably caused by small, undetectable, impurities in the substrate. In order to increase the enantioselectivity, we conducted the hydrogenation at -15 °C and -40 °C, which results in a, at the time of publication, unprecedented ee of 98% and full conversion (Table 3.2, entry 5-6). Following these optimized reaction conditions (-40 °C), Roche ester 1a was obtained on a 50 mmol scale in high isolated yield (87 %) and an excellent ee of 98 % (Table 3.2. entry 7).

Table 3.2 Variation of conditions in the rhodium catalyzed asymmetric hydrogenation of methyl 2-hydroxymethylacrylate using ligand 4b.\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>S/C</th>
<th>(P) (bar)</th>
<th>(T) (°C)</th>
<th>% conv.</th>
<th>TOF(^b)</th>
<th>% ee(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>100</td>
<td>5</td>
<td>25</td>
<td>100</td>
<td>3.2 (\times)10(^3)</td>
<td>93</td>
</tr>
<tr>
<td>2</td>
<td>100</td>
<td>10</td>
<td>25</td>
<td>100</td>
<td>5.7 (\times)10(^3)</td>
<td>93</td>
</tr>
<tr>
<td>3</td>
<td>400</td>
<td>10</td>
<td>25</td>
<td>95</td>
<td>1.1 (\times)10(^3)</td>
<td>93</td>
</tr>
<tr>
<td>4</td>
<td>1000</td>
<td>10</td>
<td>-15</td>
<td>46</td>
<td>2.5 (\times)10(^3)</td>
<td>92</td>
</tr>
<tr>
<td>5(^d)</td>
<td>100</td>
<td>10</td>
<td>-15</td>
<td>100</td>
<td>n.d.</td>
<td>95</td>
</tr>
<tr>
<td>6(^d)</td>
<td>100</td>
<td>10</td>
<td>-40</td>
<td>100</td>
<td>n.d.</td>
<td>98</td>
</tr>
<tr>
<td>7(^d,e)</td>
<td>100</td>
<td>20</td>
<td>-40</td>
<td>100 (87)(^f)</td>
<td>n.d.</td>
<td>98</td>
</tr>
</tbody>
</table>

\(^a\) Reactions were performed in CH\(_2\)Cl\(_2\), Rh/L = 1:1.1 for 1.5 h using [Rh(nbd)\(_2\)]BF\(_4\) as metal precursor. \(^b\) Turnover frequency determined at 10% conversion (mol\(_{1a}\) mol\(_{Rh}^{-1}\) h\(^{-1}\)). \(^c\) The (S)-enantiomer was obtained in all cases. \(^d\) 15 h of reaction time. \(^e\) Reaction performed on a 50 mmol scale. \(^f\) Isolated yield after flash chromatography.

The scope of the Rh-IndolPhos catalyzed hydrogenation towards Roche ester derivatives 1b-d was studied to explore the limits of the approach and to identify structural motifs in the substrate governing the stereoselective outcome. First, the methyl ester was replaced with a benzyl ester (2b), and also this substrate was fully converted in high stereoselectivity (Table 3.3, entries 1-2). The substrate that is protected with an acyl group at the primary alcohol functionality (2c) seems less reactive as it is not fully converted under these conditions and the ee of the product reaches only 35%, indicating the importance of the alcohol group in the enantiodiscriminating step (Table 3.3, entries 3-4). Introduction of a phenyl group on the double bond (2d) also reduces the reactivity of the substrate (35 % conversion), and the product formed is racemic (Table 3.3, entries 5-6).

The asymmetric hydrogenation of the structurally related α-methylcinnamic acid 5 results in moderate yield and an enantioselectivity of 78% ee (Table 3.3, entries 7-8).
Considering the structural similarity of 2d and 5, the difference in reactivity and selectivity towards asymmetric hydrogenation is remarkable.

As control experiments we also studied MonoPhos based rhodium catalysts in these hydrogenation reactions. As is clear from the results, in none of the examples this catalyst gave better results than IndolPhos based catalysts (Table 3.1, entry 6, and Table 3.3, entries 2, 4, 6 and 9). This superiority of IndolPhos over MonoPhos in the hydrogenation of Roche ester derivatives shows the importance of chelating ligands in this reaction.

Table 3.3 Scope of the Rh-IndolPhos catalyzed hydrogenation.\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Ligand</th>
<th>% conv.</th>
<th>% ee (config.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4b</td>
<td>(S)-MonoPhos(^b)</td>
<td>100</td>
<td>89 (S)</td>
</tr>
<tr>
<td>2</td>
<td>2b</td>
<td>(S)-MonoPhos(^b)</td>
<td>90</td>
<td>48 (S)</td>
</tr>
<tr>
<td>3</td>
<td>2b</td>
<td>4b</td>
<td>34</td>
<td>35 (S)</td>
</tr>
<tr>
<td>4</td>
<td>(S)-MonoPhos(^b)</td>
<td>50</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>4a</td>
<td>(S)-MonoPhos(^b)</td>
<td>33</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>(S)-MonoPhos(^b)</td>
<td>23</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>4e</td>
<td>4e</td>
<td>45</td>
<td>78 (R)</td>
</tr>
<tr>
<td>8(^c)</td>
<td>4e</td>
<td>4e</td>
<td>46</td>
<td>73 (R)</td>
</tr>
<tr>
<td>9(^d)</td>
<td>4e</td>
<td>(R)-MonoPhos(^b)</td>
<td>43</td>
<td>8 (S)</td>
</tr>
</tbody>
</table>

\(^a\) Reactions were performed in CH\(_2\)Cl\(_2\), Rh/L = 1:1.1, Rh/substrate = 1:100, 10 bar of H\(_2\), at 20°C for 20 h using [Rh(nbd)]BF\(_4\) as metal precursor. Additional catalytic results are available in the experimental section. \(^b\) (S)-(+)-(3,5-Dioxa-4-phospha-cyclohepta[2,1-a;3,4-a']dinaphthalen-4-yl)dimethylamine. \(^c\) 20 bar H\(_2\). \(^d\) Literature value.\(^{16}\)

3.4 Conclusion

In conclusion, Roche ester 1a and some of its derivatives are successfully synthesized through asymmetric rhodium catalyzed hydrogenation using IndolPhos in high yield and, at the time of publication, unprecedented enantioselectivity (up to 98% ee) on a preparative scale. The bidentate character of IndolPhos is of importance as all experiments with monodentate MonoPhos ligands resulted in poor ee of the product. A short study of the substrate scope revealed little sensitivity of the catalyst with regard to the ester group present in the substrate; both methyl as benzyl ester were converted in high selectivity. However, the primary alcohol function seems to have an important function, as the acyl-protected substrate could not be hydrogenated in high selectivity. The tri-substituted substrate with an additional phenyl group at the 3-position is less reactive and forms the product as a racemate. Hydrogenation of the structurally related
α-methylcinnamic acid 5 results in moderate activity and high enantioselectivity up to 78% ee.

3.5 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 benzenophene ketyl; CH₂Cl₂, isopropanol and methanol were distilled from CaH₂ 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, methyl 2-hydroxymethylacrylate (2a), benzyl 2-hydroxymethyl-acrylate (2b), and methyl (2E)-3-phenyl-2-hydroxymethylacrylate (2d). Melting points were recorded on a Gallenkamp melting point apparatus and are uncorrected. NMR spectra (1H, 31P and 13C) 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. Chiral GC separations were conducted on an Interscience Trace GC Ultra (FID detector) with a Chiralsil DEX-CB column (internal diameter 0.1 mm, 5 m column, film thickness 0.1 µm) and an Interscience HR GC Mega 2 apparatus (split/splitless injector, carrier gas 70 kPa He, FID detector) with a Supelco BETA DEX column (0.25 mm x 30 m). Chiral HPLC separations were conducted on a Shimadzu 10A HPLC, equipped with a UV-detector.

General procedure for the synthesis of Indolylphosphines 3a-d. To a solution of 3-methylindole (1.78 g, 13.6 mmol) in THF (40 mL) was added dropwise 5.7 mL of t-BuLi (2.5 M in hexanes) at -70 °C. The resulting suspension was stirred at -78 °C for 20 min. Carbon dioxide was bubbled through the suspension for 10 min to give a clear pale yellow solution which was allowed to warm to room temperature after which the solvent was removed in vacuo. The resulting white residue was dissolved in THF (40 mL) to give a clear pale yellow solution, which was cooled to -78 °C. To this solution, 8.4 mL of benzyltriphenylphosphine (1.7 M in pentanes) was added and the resulting orange solution was stirred at -70 °C for 1 h. The appropriate chlorophosphine (13.6 mmol) was added and the reaction mixture was stirred for 16 h allowing to warm to room temperature. The resulting yellow solution was washed with 40 mL degassed sat. aq. NH₄Cl. The organic layer was dried over MgSO₄, filtered and the solvent was removed in vacuo. The crude, pale yellow solid was recrystallized from hot MeOH to yield the product as colourless crystals.

Dicyclohexyl(3-methyl-2-indolyl)phosphine (3c). Yield: 2.84 g (64 %). Mp = 118 °C. 1H NMR (CDCl₃, 499.8 MHz, 298 K): δ (ppm) 7.89 (br s, 1H), 7.59 (d, J = 8.0 Hz, 1H), 7.36 (d, J = 8.0 Hz, 1H), 7.22 (t, J = 8.0 Hz, 1H), 7.12 (t, J = 7.5 Hz, 1H), 2.45 (s, 3H), 1.99-1.89 (m, 4H), 1.81-1.78 (m, 2H), 1.70-1.62 (m, 6H), 1.38-1.08 (m, 10H). 13C NMR (CDCl₃, 125.7 MHz, 298 K): δ (ppm) 137.9 (C₅), 129.2 (d, JCP = 5.9 Hz, C₃), 127.8 (d, JCP = 27.9 Hz, C₄), 123.5 (d, JCP = 24.9 Hz, C₆), 122.9, 119.3, 119.2, 110.8, 33.4 (d, JCP = 9.3 Hz), 30.9 (d, JCP = 17.7 Hz, CH₃), 29.9 (d, JCP = 6.3 Hz, CH₃), 27.4 (d, JCP = 16.5 Hz, CH₂), 27.3 (d, JCP = 10.6 Hz, CH₂), 26.5 (CH₃), 10.4 (d, JCP = 12.7 Hz, CH₃). 31P{1H} NMR (CDCl₃, 202.3 MHz, 298 K): δ (ppm) -26.95 (s). HRMS (FAB) calcd for [M + H]+ C₂₃H₃₁NP, 328.2194; found, 328.2193.
Di-(o-Tolyl)-(3-methyl-2-indoly)phosphine (3d). Yield: 3.88 g (83 %). Mp = 194 °C. 1H NMR (CDCl3, 499.8 MHz, 298 K): δ (ppm) 7.64 (d, J = 7.5 Hz, 1H), 7.36 (br s, 1H), 7.29 (t, J = 7.5 Hz, 2H), 7.26-7.18 (m, 4H), 7.15-7.10 (m, 3H), 6.86 (m, 2H), 2.48 (s, 3H), 2.38 (s, 6H). 13C NMR (CDCl3, 125.7 MHz, 298 K): δ (ppm) 142.4 (d, JCP = 25.8 Hz, Cq), 138.4 (Cq), 134.3 (d, JCP = 9.3 Hz, Cq), 132.5, 130.7 (d, JCP = 4.7 Hz), 129.5 (d, JCP = 6.4 Hz, Cq), 129.2, 126.6, 125.9 (d, JCP = 17.2 Hz, Cq), 123.1, 122.5 (d, JCP = 28.3 Hz, Cq), 119.5, 119.4, 111.1, 21.2 (d, JCP = 20.6 Hz, CH3), 9.9 (d, JCP = 11.3 Hz, CH3). 31P{1H} NMR (CDCl3, 202.3 MHz, 298 K): δ (ppm) -46.53 (s). HRMS (FAB) calcd for [M + H]+ C23H25NP, 344.1568; found, 344.1571.

General procedure for the synthesis of IndolPhos ligands 4a-f. To a solution of the corresponding indolylphosphine 3 (1.46 mmol) in THF (5 mL) was added dropwise 0.58 mL of n-BuLi (2.5 M in hexanes) at -78°C. The resulting pale yellow solution was stirred for 0.5 h at -78 °C. To this solution, a solution of (S)-(−)-2,2′-bisnaphtil phosphorochloridite (0.51 g, 1.46 mmol) in THF (4 mL) was added 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 concentrated in vacuo. Toluene (5 mL) was added and the suspension was filtered over Celite after which the solvent was removed in vacuo to obtain a white powder. In selected cases the crude product was further purified by SiO2 chromatography.

Dicyclohexyl[1-[S]-3,5-dioxa-4-phospha-cyclohepta(2,1-a;3,4-a′)-diphenyl-4-yl]3-methyl-2-indoly)phosphine (4c). Yield: 553 mg (59 %). Mp = 255 °C. [α]20D = +286.6 (c = 1.2, CHCl3). 1H NMR (CDCl3, 500 MHz, 298 K): δ (ppm) 8.06 (d, J = 8.5 Hz, 1H), 7.99 (d, J = 8.0 Hz, 1H), 7.85 (br d, J = 7.5 Hz, 1H), 7.59 (br d, J = 7.0 Hz, 1H), 7.55 (d, J = 8.5 Hz, 1H), 7.51-7.46 (m, 4H), 7.39 (d, J = 8.0 Hz, 1H), 7.36-7.32 (m, 2H), 6.87 (t, J = 7.5 Hz, 1H), 6.83 (br s, 1H), 6.42 (br s, 1H), 6.20 (t, J = 8.0 Hz, 1H), 2.61 (br s, 2H), 2.48 (s, 3H), 2.00 (m, 2H), 1.86-1.55 (m, 8H), 1.43-1.20 (m, 10H). 13C NMR (CDCl3, 125.5 MHz, 298 K): δ (ppm) 150.7 (Cq), 148.9 (Cq), 140.3 (Cq), 133.1 (d, JCP = 33.8 Hz, Cq), 132.0 (Cq), 131.8 (d, JCP = 67.1 Hz, Cq), 131.1, 128.7 (d, JCP = 10.1 Hz), 127.4, 127.0, 126.7 (d, JCP = 20.0 Hz). 125.6, 125.2, 124.9 (d, JCP = 5.9 Hz, Cq), 122.9 (Cq), 121.8, 121.6, 121.1, 32.6 (d, JCP = 21.1 Hz), 31.1 (CH3), 30.9 (d, JCP = 9.3 Hz, CH2), 27.4 (d, JCP = 7.5 Hz, CH2), 27.0 (d, JCP = 14.7 Hz, CH3), 26.5 (d, JCP = 7.7 Hz, CH3), 11.5 (d, JCP = 17.3 Hz, CH3). 31P{1H} NMR (CDCl3, 202.3 MHz, 233 K): δ (ppm) 144.24 (d, JPP = 249.2 Hz, 0.3P), 141.50 (s, 0.7P), −19.91 (d, JPP = 251.9 Hz, 0.3P), −22.17 (s, 0.7P). HRMS (FAB) calcd for [M + H]+ C41H32NO2P2, 642.2691; found, 642.2697.

Di-(o-Tolyl)-(1-[S]-3,5-dioxa-4-phospha-cyclohepta(2,1-a;3,4-a′)-diphenyl-4-yl]3-methyl-2-indoly)phosphine (4d). Yield: 749 mg (78 %). Mp = 175 °C. [α]20D = +207.2 (c = 1.1, CHCl3). 1H NMR (CDCl3, 500 MHz, 298 K): δ (ppm) 7.98 (d, J = 8.5 Hz, 1H), 7.95 (d, J = 8.0 Hz, 1H), 7.83 (d, J = 8.0 Hz, 1H), 7.56 (d, J = 9.0 Hz, 1H), 7.50-7.42 (m, 5H), 7.38-7.21 (m, 8H), 7.19-7.12 (m, 3H), 6.88 (t, J = 7.5 Hz, 1H), 6.75 (d, J = 9.0 Hz, 1H), 6.56 (d, J = 8.5 Hz, 1H), 6.24 (t, J = 7.8 Hz, 1H), 2.48 (s, 3H), 2.44 (s, 3H), 1.78 (s, 3H). 13C NMR (CDCl3, 125.5 MHz, 298 K): δ (ppm) 150.3 (d, JCP = 5.5 Hz, Cq), 148.8 (Cq), 142.5 (d, JCP = 26.5 Hz, Cq), 142.2 (d, JCP = 26.1 Hz, Cq), 140.5 (d, JCP = 5.5 Hz, Cq), 133.6, 133.1 (Cq), 133.0 (Cq), 132.5, 132.2 (Cq), 132.0 (Cq), 131.5 (Cq), 130.8, 130.6, 130.5 (d, JCP = 4.5 Hz), 130.1 (d, JCP = 6.3 Hz, Cq), 129.9 (d, JCP = 6.8 Hz, Cq), 129.2, 129.0, 128.6, 128.5, 127.5 (Cq), 126.9, 126.6, 126.5 (d, JCP = 4.7), 126.4, 126.1, 125.8, 125.1, 124.8 (d, JCP = 5.9 Hz, Cq), 123.6, 123.2 (Cq), 123.0, 122.0, 121.6, 121.1, 119.4 (d, JCP = 8.9 Hz), 118.3, 116.1, 111.1, 21.7 (d, JCP = 19.9 Hz, CH3), 21.5 (d, JCP = 19.4 Hz, CH3), 9.9 (d, JCP = 3.4 Hz, CH3). 31P{1H} NMR (CDCl3, 202.3
Asymmetric synthesis of the Roche Ester and its derivatives by Rh-IndolPhos catalyzed hydrogenation

MHz, 298 K): δ (ppm) 144.11 (d, J_{PP} = 210.2 Hz), −40.08 (d, J_{PP} = 211.6 Hz). HRMS (FAB) calcd for [M + H]^+ C_{43}H_{33}NO_2P_2, 658.2065; found, 658.2063.

General procedure for hydrogenation catalyst screening experiments. The hydrogenation experiments were carried out in a stainless steel autoclave (150 mL) charged with an insert suitable for 8 reaction vessels (including Teflon mini stirring bars) for conducting parallel reactions. In a typical experiment, the reaction vessels were charged with 1.0 µmol of [Rh(nbd)_2]BF_4, 1.1 µmol of ligand and 0.10 mmol of alkene substrate in 1.0 mL of CH_2Cl_2. Before starting the catalytic reactions, the charged autoclave was purged three times with 15 bar of dihydrogen and then pressurized at 10 bar H_2. The reaction mixtures were stirred at 20 °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 or HPLC.

Preparative scale asymmetric hydrogenation of methyl 2-hydroxymethylacrylate (2a). IndolPhos ligand 4b (309 mg, 0.55 mmol) and [Rh(nbd)_2]BF_4 (187 mg, 0.50 mmol) were dissolved in dry DCM (50 mL). Methyl 2-hydroxymethylacrylate 2a (5.8 g, 50 mmol) was added and the mixture was transferred to a 150 mL stainless steel autoclave equipped with a glass insert and a mechanical stirrer. The autoclave was cooled to -40 °C and subsequently purged three times with 15 bar of dihydrogen and pressurized at 20 bar H_2. The reaction mixture was stirred for 15 h at -40 °C after which it was allowed to warm to room temperature. The pressure was reduced to 1.0 bar and the solvent was removed under reduced pressure. Et_2O (50 mL) was added to the residue and the resulting yellow suspension was filtered through a plug of SiO_2 which was rinsed twice with Et_2O (2 x 50 mL). Removal of the solvent under reduced pressure gave a colourless oil. Yield: 5.16 g (87 %). 98 % ee (chiral GC). [α]_20^D = +15.4 (c = 3.1, CHCl_3).

1H NMR (CDCl_3, 500 MHz, 298 K): δ (ppm) 3.72 (m, 5H), 2.68 (m, 1H), 2.10 (br s, 1H), 1.18 (d, J = 7.5 Hz, 3H).

13C NMR (CDCl_3, 125.5 MHz, 298 K): δ (ppm) 176.1 (C_q), 64.6 (CH_2), 51.8 (CH_3), 41.6 (CH), 13.4 (CH_3).

AMTEC experimental details. The experiments were carried out in a AMTEC SPR16 consisting of 16 parallel reactors equipped with temperature and pressure sensors, and a mass flow controller. The apparatus is suited for monitoring gas uptake profiles during the catalytic reactions. Four autoclaves were heated to 110 °C and flushed with argon (22 bar) five times. Next the reactors were cooled to 25 °C and flushed again with argon (22 bar) five times. The autoclaves were charged with the appropriate amount of [Rh(nbd)_2(BF_4)] and methyl2-hydroxymethylacrylate in 8.00 ml of CH_2Cl_2 under argon. The reactors were pressurized with 5 (reactor 1) or 10 (reactors 2-4) bar H_2 and the pressure was kept constant during the whole reaction. The reaction mixtures were stirred at 25 °C for 1.5 h and the hydrogen uptake was monitored and recorded for every reactor. After catalysis the pressure was reduced to 2.0 bar and samples (0.2 ml) were taken. The results are summarized in Table 3.4.

Table 3.4 Hydrogenation of methyl 2-hydroxymethylacrylate (2a) under various conditions in AMTEC parallel reactor.

<table>
<thead>
<tr>
<th>reactor</th>
<th>ligand</th>
<th>Rh^a (µmol)</th>
<th>2a (µmol)</th>
<th>PH_2 (bar)</th>
<th>t (h)</th>
<th>conv (%)</th>
<th>ee (%)</th>
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<td>800</td>
<td>5</td>
<td>1.6</td>
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<td>93</td>
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<td>4b</td>
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<td>800</td>
<td>10</td>
<td>1.5</td>
<td>100</td>
<td>93</td>
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<td>4</td>
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<td>320</td>
<td>10</td>
<td>1.4</td>
<td>95</td>
<td>93</td>
</tr>
</tbody>
</table>

a [Rh(nbd)_2BF_4]
and the gas-uptake profiles are depicted in Figure 3.2.

**Chiral GC and HPLC separation data for hydrogenation products.**

**Methyl 3-hydroxy-2-methylpropionate (1a):** The conversion and ee were determined by chiral GC analysis (Chiralsil DEX-CB, isothermal at 75 °C for 2.0 min., 5 °C/min to 90 °C, 50 °C/min to 220 °C; t<sub>R</sub> (R) = 5.42 min., t<sub>R</sub> (S) = 5.52 min., and t<sub>R</sub> (substrate) = 5.62 min.).

**Benzyl 3-hydroxy-2-methylpropionate (1b):** Conversion was determined by GC analysis (Chiralsil DEX-CB, isothermal at 110 °C for 30.0 min., 2 °C/min to 140 °C; t<sub>R</sub> (substrate) = 20.94 min., t<sub>R</sub> (S) = 41.16 min., and t<sub>R</sub> (R) = 41.38 min.). The ee was determined by chiral HPLC analysis (Chiralcel OJ-H, flow rate: 1.0 mL/min, eluent: hexane/isopropanol (90/10), detection at 254 nm; t<sub>R</sub> (S) = 12.01 min., and t<sub>R</sub> (R) = 12.87 min.).

**Methyl 3-acetoxy-2-methylpropionate (1c):** The conversion and ee were determined by chiral GC analysis (Supelco BETA DEX, isothermal at 70 °C for 30.0 min., 25 °C/min to 220 °C; t<sub>R</sub> (R) = 28.19 min., t<sub>R</sub> (S) = 28.78 min., and t<sub>R</sub> (substrate) = 32.27 min.).

**Methyl 3-hydroxy-2-benzylpropionate (1d):** The conversion and ee were determined by chiral GC analysis (Chiralsil DEX-CB, isothermal at 115 °C for 30.0 min., 2 °C/min to 150 °C; t<sub>R</sub> (enantiomer 1) = 44.13 min., t<sub>R</sub> (enantiomer 2) = 44.61 min., and t<sub>R</sub> (substrate) = 46.36 min.).

**2-methyl-3-phenylpropanoic acid:** Prior to analysis, the product from the hydrogenation of α-methylcinnamic acid (5) was converted to the methyl ester using trimethylsilyldiazomethane in MeOH. The conversion and ee were determined by chiral HPLC analysis (Chiralcel OD-H, flow-rate: 1.0 mL/min, eluent: hexane/isopropanol (99.5/0.5), detection at 210 nm, t<sub>R</sub> (R) = 9.1 min., t<sub>R</sub> (S) = 10.7 min., and t<sub>R</sub> (substrate) = 15.0 min.).

### 3.6 Acknowledgements

Dr. M. Kuil is kindly acknowledged for assistance with the AMTEC experiments.
3.7 References


7. The name Roche ester, which is nowadays frequently used for (S)-3-hydroxy-2-methylpropionate, should not be confused with the Roche company. The name is derived from the university of Rochester (New York, USA) where its synthesis has been described for the first time by Herrman and Schlessinger. See: Herrman, J. L.; Schlessinger, R. H. *Tetrahedron Lett. 1973*, 14, 2429-2432.


