Catalytic asymmetric hydrogenation of α-ketoesters and quinoline using electronically enriched BINAP

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Abstract—Electronically enriched chiral BINAP derivatives were synthesized incorporating electron-donating substituents at the para-phenyl position and evaluated for the Ru-catalyzed homogeneous asymmetric hydrogenation of α-ketoesters with up to 92% ee. These diphosphines were also excellent ligands for the iridium-catalyzed asymmetric hydrogenation of quinolines.

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1. Introduction

The continually increasing need for enantiomerically pure chemicals has driven numerous major advances in the area of homogeneous asymmetric catalysis.1 The search for easily accessible and versatile chiral ligands for transition metals, showing high enantioselection ability in homogeneous catalysis, is still an ongoing challenge in chemical research, especially in the asymmetric hydrogenation of α-ketoesters and nitrogen-containing heteroaromatic compounds.

The reduction of α-ketoesters and α-ketoamides has attracted considerable attention over the last few years, because optically active α-hydroxy esters represent an important class of building blocks for the synthesis of natural products.2 Amongst the many methods available for the reduction of α-ketoesters, homogeneous hydrogenation with Ru-catalysts is one of the more technically feasible catalytic methods, which allow the preparation of the corresponding hydroxy ester derivatives with enantioselectivities up to 90%.3 Amongst the best catalysts, Chan’s PQ-Phos ligands are very effective for hydrogenation of α and β-ketoesters with ee’s of 96–98%.3i Another notable example is the asymmetric hydrogenation of methyl benzoylformate BICHEP–Ru complexes with an ee of 99%.3i Recently, an optically active atropoisomer diphosphine ligand, Synphos, was studied in ruthenium-catalyzed asymmetric hydrogenation of α and β-ketoesters. This ligand was compared with other atropoisomer diphosphines (BINAP and MeO–BIPHEP) with respect to their calculated dihedral angle.4 However, less is known regarding the asymmetric catalytic hydrogenation of α-ketoesters with chiral ruthenium(II)-modified BINAP catalysts.5

Asymmetric hydrogenation of nitrogen-containing heteroaromatic compounds also provides an attractive and convenient approach to enantiomerically pure heterocycloalkanes as structural units of a number of alkaloids.6 However, a variety of chiral Rh, Ru and Ir complexes, which have been demonstrated to be highly efficient and enantioselective in the hydrogenation of prochiral olefins, ketones and imines, often failed to give good results in this particular case.7 So far only limited examples of the homogeneous asymmetric hydrogenation of heteroaromatic compounds have been reported.3i,7–9 Zhou et al. found that the iridium complex generated in situ from [Ir(COD)Cl]2 and (R)-MeO–BIPHEP, (R)-BINAP or ferrocenyloxazoline-derived P,N ligands worked efficiently in the enantioselective hydrogenation of quinoline derivatives at room temperature, providing optically active tetrahydroquinolines bearing a stereogenic carbon at the 2-position with high enantioselectivities and yields.9a,c More recently, Fan and Chan proposed the use of chiral diphosphinite ligand derived from (R)-1,1’-spiro-biindane-7,7’-dial as a highly effective ligand in the Ir-catalyzed asymmetric hydrogenation of quinolines with high enantioselectivity up to 94%.9c

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Knowing that the electronic tuning of a ligand such as BINAP could be connected to the enantioselectivity, we herein report a comparative study of the asymmetric hydrogenation of α-ketoesters and 2-methylquinoline with commercially available BINAP and electronically enriched BINAP derivatives containing MeO- or HO-phenyl substituted.

2. Results and discussion

2.1. Synthesis of BINAP derivatives

The di-p-anisylphosphine–borane 1 was obtained in 39% yield via the preparation of the bis(4-methoxyphenyl)phosphine oxide intermediate as reported in the literature. The preparation of enantiopure BINAP derivatives involved a coupling reaction of the di-p-anisylphosphine–borane 1 with (R)-2,2'-dinitrofluoromethanesulfonate, 1,1'-binaphthyl in the presence of DABCO and NiCl₂dppe in DMF (Scheme 1). Tetramethoxy-BINAP (R)-2 was obtained in 66% yield. This synthetic method was proven to be more efficient than those previously described by Takaya et al. The tetrahydroxy (R)-3 was obtained by a deprotection of hydroxyl substituents of (R)-2 with BBr₃ in quantitative yield.

Asymmetric reduction of α-ketoesters and hydrogenation of 2-methylquinoline was performed in appropriate solvents, respectively, EtOH or MeOH and toluene. Unfortunately, the low solubility of tetrahydroxy-BINAP (R)-3 in aprotic apolar solvents prevented us to evaluate the efficiency of the ligand for the hydrogenation of the 2-methylquinoline. In order to improve the solubility, we focused our effort on the synthesis of the lipophilic analogue 6,6'-didodecyl tetrahydroxy-BINAP (R)-9, which was prepared in a seven step strategy starting from enantiomerically pure BINOL. As depicted in Scheme 1, the 6,6'-positions were brominated with Br₂ in 75% yield according to Cram et al. Benzylation of the (R)-6,6'-dibromo-1,1'-bis-2-naphthyl (R)-4 afforded (R)-5 in 78% yield. The protected BINOL was cross coupled with commercially available dodecylmagnesium bromide (89%). Deprotection of the resulting (R)-6 using TMSI gave the bis-dodecylbinol (R)-7 in quantitative yield. The (R)-6,6'-didodecyl-2,2'-dinitrofluoromethanesulfonate, 1,1'-binaphthyl (R)-8 was then obtained by trifluoromethanesulfonic anhydride and pyridine. The preparation of the enantiopure 6,6'-didodecyl-tetrahydroxy-BINAP (R)-9 involved a coupling reaction between the di-p-anisylphosphine–borane 1 and (R)-8 in the presence of DABCO and NiCl₂dppe in DMF. 6,6'-Didodecyl-tetrahydroxy-BINAP (R)-9 was obtained in 68% yield. 6,6'-Didodecyl-tetrahydroxy-BINAP (R)-10 was finally obtained by deprotection of the hydroxyl substituents with BBr₃ in 95% yield.

Scheme 1. Synthesis of ligands (R)-2, (R)-3 and (R)-10.
2.2. Hydrogenation of \(\alpha\)-ketoesters

The hydrogenation of various \(\alpha\)-ketoesters was carried out with catalyst, ligands \((R)-2, (R)-3\) and \((R)-10\) and compared with the \((R)\)-BINAP in order to evaluate the effect of the methoxy groups at the para-position of the phenyl of the BINAP. Ru(I)-catalysts 11a-d were prepared in situ by stirring a solution of \([Ru(C_{6}H_{6})Cl_{2}]_{2}\) precursor and the diphosphine ligands (Scheme 2) prior to the introduction of the \(\alpha\)-ketoesters and being pressurized under \(H_{2}\).

The asymmetric hydrogenation reaction was carried out under hydrogen pressure (40 bar) at 50 °C in the presence of the chiral catalyst.

The catalytic hydrogenation of substrates 12a–c using BINAP and BINAP derivatives \((R)-2\) and \((R)-3\) as the ligand was also performed. Whatever the substrate, a total conversion was observed with moderate to good enantioselective excesses (Table 1).

With ees of 87% and 79% (Table 1, entries 3 and 6), the electron enriched tetrahydroxy-BINAP \((R)-3\) was slightly more efficient for the reduction of the methyl and ethyl pyruvate than tetramethoxy-BINAP \((R)-2\) with ees of 84% and 75%, respectively, (Table 1, entries 2 and 5). These results compare favourably to those obtained in the reduction of the methyl pyruvate 12a and ethyl pyruvate 12b using BINAP as ligand in the same solvent (78% and 65% ee) (Table 1, entries 1 and 4). Moreover this phenomenon is particularly observed with methyl benzoylformate 14c, which is hydrogenated with a higher enantioselectivity (92% ee) with the electronically enriched BINAP tetramethoxy-BINAP \((R)-2\) or tetrahydroxy-BINAP \((R)-3\), whereas it is reduced with only 77% ee with the \((R)\)-BINAP. Finally, when 11d was used as catalyst for the hydrogenation of 12c, an ee of 91% was obtained, similar to the ee obtained with 11, demonstrating that the efficiency of the catalyst was not influenced by the alkyl chain grafted on the naphthyl moiety of \((R)-10\).

![Scheme 2. General procedure for BINAP complex synthesis.](image)

![Table 1. Ruthenium-catalyzed reduction of ketoesters with \((R)\)-BINAP, tetramethoxy-BINAP \((R)-2\) and tetrahydroxy-BINAP \((R)-3\)](image)

<table>
<thead>
<tr>
<th>Substrate(^{a})</th>
<th>Entry</th>
<th>Ligand</th>
<th>Solvent</th>
<th>Conv.(^{b}) (%)</th>
<th>ee(^{b}) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12a OMe</td>
<td>1</td>
<td>((R))-BINAP</td>
<td>MeOH</td>
<td>100</td>
<td>78 ((R))</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>((R)-2)</td>
<td>MeOH</td>
<td>100</td>
<td>84 ((R))</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>((R)-3)</td>
<td>MeOH</td>
<td>97</td>
<td>87 ((R))</td>
</tr>
<tr>
<td>12b OEt</td>
<td>4</td>
<td>((R))-BINAP</td>
<td>EtOH</td>
<td>100</td>
<td>65 ((R))</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>((R)-2)</td>
<td>EtOH</td>
<td>100</td>
<td>75 ((R))</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>((R)-3)</td>
<td>EtOH</td>
<td>95</td>
<td>79 ((R))</td>
</tr>
<tr>
<td>12c PhOMe</td>
<td>7</td>
<td>((R))-BINAP</td>
<td>MeOH</td>
<td>100</td>
<td>77 ((R))</td>
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<td>8</td>
<td>((R)-2)</td>
<td>MeOH</td>
<td>100</td>
<td>91 ((R))</td>
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<td></td>
<td>9</td>
<td>((R)-3)</td>
<td>MeOH</td>
<td>100</td>
<td>92 ((R))</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>((R)-10)</td>
<td>MeOH</td>
<td>100</td>
<td>91 ((R))</td>
</tr>
</tbody>
</table>

\(^{a}\)Hydrogenation was performed in homogeneous conditions, \([S]\) = 0.8 M; \(L/M = 1\); \(S/metal = 100\); 40 bars \(H_{2}\); 50 °C; 24 h; \([M] + L^{*} + \text{solvent, stirring 16 h at rt + substrate.}\)

\(^{b}\)Conversion and enantioselectivity were determined by GC on a lipodex A (25 m × 0.25 mm) column.
With a higher Hammett $\sigma$-coefficient for the $p$-OH-BINAP derivative ($-0.38$) than that of $p$-OMe–BINAP derivative ($-0.28$), enantioselectivities of the hydrogenation of $\alpha$-ketoesters appeared to be better with the $p$-OH–BINAP (Table 1, entries 8 and 9).

2.3. Hydrogenation of 2-methylquinoline

2-Methylquinoline 13 was reduced in toluene to compare (R)-BINAP with tetramethoxy–BINAP (R)-2 and 6,6′-didodecyl tetrahydroxy–BINAP (R)-10, which was more soluble in the solvent than the nonalkylated tetrahydroxy–BINAP (R)-3. The asymmetric hydrogenation reaction was carried out under hydrogen pressure (40 bar) at room temperature, in the presence of the chiral catalyst prepared in situ. The catalysts were obtained by the addition of the chiral ligand to the metal precursor in toluene. Iodine and the 2-methylquinoline were added successively to the reaction mixture before setting under hydrogen pressure. The results obtained are shown in Table 2.

In the presence of BINAP, the reduction of 2-methylquinoline is difficult to reproduce under our conditions. Indeed, under identical conditions, the conversion rate varied between 30% and 70%. As for enantiomeric excess, it varies between 33% and 53%. It should be noted that the enantiomeric excess reported by Zhou et al. for this reduction, in a mini-autoclave of stainless steel of 15 mL from Amtec (www.amtec-chemnitz.de), could have a direct influence on the enantiomeric excess. More importantly, we have shown that the introduction of electron-donating groups on the $para$-phenyl position of the BINAP could have a direct influence on the enantiomeric excess and on the activity of catalyst (under identical operating conditions).

4. Experimental

4.1. General methods

All organic and organometallic reagents used were pure commercial products. $^1$H, $^{13}$C and $^{31}$P NMR spectra were recorded with a Bruker AM300 ($^1$H, $300$ MHz, $^{13}$C, $75$ MHz) in CDCl$_3$ as solvent. Polarimetric measurements were performed on a Perkin–Elmer 241 apparatus, at ambient temperature. Conversions and enantiomeric excesses were determined by GC analysis on a chiral CHIRASIL-VAL column. Hydrogenation experiments were performed in a mini-autoclave of stainless steel of 15 mL from Amtec (www.amtec-chemnitz.de).

(R)-BINAP was purchased from Stem Chemicals. All yields are isolated yields.

4.2. Synthesis of ligands

4.2.1. Bis(4-methoxyphenyl)phosphine oxide. A solution of magnesium (4.125 g, 0.171 mol) in THF (10 mL) was stirred under Ar at room temperature for 1 h. A solution of 4-bromoanisole (19.53 mL, 0.156 mol) in THF (30 mL) was slowly added at 45 °C and the mixture was stirred at 5 °C for 1 h. Next, diethyl phosphite (10 mL, 0.78 mol) was added and the mixture was stirred at 45 °C for 2 h. After cooling (0 °C), water (50 mL), ethyl acetate (100 mL) and HCl 10% (50 mL) were added successively. The mixture was stirred at room temperature for 30 min. The reaction mixture was portioned, and the aqueous layer extracted three times with ethyl acetate (60 mL). The combined organic layers were washed with HCl 2% (200 mL) and brine (100 mL), and dried over anhydrous magnesium sulfate. The solution was then filtered and the filtrate con-
centrated under reduced pressure. The residue obtained was purified by column chromatography on silica gel using ethyl acetate as the eluent to give the product (13.2 g, white crystal, 65%). Mp = 124–125 °C; 1H NMR (300 MHz, CDCl3): δ 3.71 (s, 6H, OCH3), 6.92 (d, J = 7 Hz, 4H, H arom.), 7.55 (dd, J = 14.2, 7 Hz, 4H, H arom.), 7.94 (d, J = 480 Hz, 1H, HP); 13C NMR (300 MHz, CDCl3): 55.8, 114.7 (d, J = 20), 123.5 (d, J = 110), 133.0 (d, J = 20), 163.2 (d, J = 10); 31P{1H} NMR (81 MHz, CDCl3): δ 20.9 (s).

4.2.2. Bis(4-methoxyphenyl)phosphine–borane complex 1. A solution of cerium chloride (11.27 g, 45.75 mmol) in dry CH2Cl2 (20 mL) was cooled at 0 °C, and a 1 M solution of BBr3 in CH2Cl2 (5.6 mL, 5.6 mmol) was added, and the reaction mixture was stirred at room temperature for 1 h, and then at room temperature for 24 h. The solution was cooled to 5 °C and CH2OH (10 mL) was carefully added. After removal of the organic solvents, the residue was recrystallized from hot CH2OH (10 mL) by adding cold water (5 mL) to give (R)-3 (392 mg, 98%). White solid; mp >220 °C; [α]D = +29 (c 0.9, MeOH); 1H NMR (300 MHz, DMSO-d6): δ 6.55 (d, J = 8.6 Hz, 2H, H arom.), 6.65–6.69 (m, 6H, H arom.), 6.82 (br t, J = 7.5 Hz, 2H, H arom.), 7.13 (dd, J = 11.5, 8.6 Hz, 4H, H arom.), 7.31 (dd, J = 11.5, 8.6 Hz, 2H, H arom.), 7.38 (br t, J = 7.5 Hz, 2H, H arom.), 7.44 (dd, J = 11.5, 8.6 Hz, 2H, H arom.), 7.86–7.92 (m, 4H, H arom.), 9.95 (s, 4H, OH); 31P{1H} NMR (81 MHz, DMSO-d6): −18.42 (s).

4.2.5. (R)-6,6'-Dibromo-2,2'-dihydroxy-1,1'-binaphthyl (R)-4. (2.10 g, 7.34 mmol) of enantiomerically pure (R)-2,2'-dihydroxy-1,1'-binaphthyl [(R)-BINOL] was dissolved in CH2Cl2 (40 mL), and the system was cooled to −75 °C. Bromine (1 mL, 19.6 mmol) was added dropwise over 20–30 min with constant stirring at −75 °C. After stirring an additional 2.5 h while warming to 25 °C, the reaction mixture was stirred further for 30 min and the excess Br2 was destroyed by the addition of 50 mL of 10% aqueous solution of sodium bisulphite. The layers were separated, and the organic layer was washed with brine, dried over MgSO4, filtered and concentrated under reduced pressure to give 3.6 g of solid, which was recrystallized from toluene–cyclohexane to afford (R)-4 (2.73 g, 84%) as a white solid. 1H NMR (300 MHz, CDCl3): δ 4.69 (s, 2H, OH), 6.90 (d, J = 8.8 Hz, 2H, H arom.), 7.20 (d, J = 9.2 Hz, 2H, H arom.), 7.31 (dd, J = 8.8, 2.2 Hz, 2H, H arom.), 7.80 (d, J = 8.8 Hz, 2H, H arom.), 7.98 (d, J = 2.2 Hz, 2H, H arom.); mp 210 °C; [α]D = −129 (c 1, CH2Cl2).

4.2.6. (R)-6,6'-Dibromo-2,2'-dibenzyloxy-1,1'-binaphthyl (R)-5. (R)-6,6'-Dibromo-1,1'-bis-2-naphthol (R)-4 (0.50 g, 1.13 mmol), benzyl bromide (0.40 mL, 3.38 mmol) and potassium carbonate (0.78 g, 5.65 mol) were stirred in refluxing acetone (10 mL) under an argon atmosphere for 18 h. After cooling to room temperature, the reaction mixture was poured into dichloromethane (25 mL) and water (25 mL). The layers were separated and the aqueous layer extracted with dichloromethane (2 × 25 mL). The combined organic layers were dried over MgSO4, filtered and solvents removed in vacuo. The residue was purified by trituration with hexane to afford (R)-5 (0.55 g, 78%) as a white solid.

1H NMR (300 MHz, CDCl3): δ 5.0 (s, 4H, 2OCH3), 6.88 (m, 4H, H arom.), 7.05 (m, 6H, H arom.), 7.25–7.29 (m, 4H, H arom.), 7.34 (d, J = 9.03 Hz, 2H, H arom.), 7.75 (d, J = 9.03 Hz, 2H, H arom.), 7.95 (d, J = 3.18 Hz, 2H, H arom.); [α]D = +188 (c 1, CDCl3).

4.2.7. (R)-6,6'-Didodecyl-2,2'-dibenzyloxy-1,1'-binaphthyl (R)-6. [1,3-Bis(diphenylphosphino)propane]NiCl2 (65 mg, 0.12 mmol) and n-dodecyl magnesium bromide (14.4 mL of a 1.0 M solution in diethyl ether, 0.48 mmol, Acros) were added to a stirred solution of (R)-2,2'-dibenzyloxy-6,6'-dibromo-1,1'-binaphthyl (R)-5 (3 g, 4.8 mmol) in diethyl ether (150 mL). After heating at reflux for 16 h, the solution was

cooled to room temperature. Water (100 mL) was carefully added followed by HCl (2 M, 100 mL). The aqueous phase was then separated and extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with brine (2 × 50 mL), dried over MgSO4 filtered and purified on silica gel using (dichloromethane/ethyl acetate (3:1) as a colourless viscous oil. 1H NMR (300 MHz, CDCl3): δ 8.05–0.95 (t, J = 6.8 Hz, 6H, 2ArCH3), 1.22–1.41 (m, 36H, 2(C138H27O2)2), 1.65–1.72 (m, 4H, 2 ArCH2CH3), 2.73 (t, J = 7.7 Hz, 4H, 2 ArCH2), 5.04 (s, 4H, 2OCH2), 6.96–9.8 (m, 4H, 2H, H arom.), 7.08–7.18 (m, 10H, H arom.); 13C NMR (75 MHz, CDCl3): δ 14.1, 20.4, 22.7, 22.4, 29.5, 29.6, 29.7, 29.78, 31.4, 31.9, 35.9, 71.3, 116.2, 120.9, 125.5, 126.2, 126.8, 127.2, 127.9, 128.1, 128.6, 129.6, 132.6, 135.7, 138.2, 153.5; MS (ESI): m/z: 803.5 [M+H]+; Elemental Anal. Calcd for C58H74O2(803.24): C, 86.73; H, 9.29. Found: C, 86.60; H, 9.30; F = 0.63 (light petroleum/diethyl ether, 95:5); 19F NMR (122 MHz, CDCl3): δ −75.2 (s).

4.2.10. (R)-6,6'-Didodecyl-2,2'-bis[(4-methoxyphenyl)-phosphino]-1,1'-binaphthyl (R)-9. To a solution of [1,2-bis(diphenylphosphino)-ethane]dichlororonic (30 mg, 0.05 mmol), (R)-2,2'-bis(trifluoromethanesulfonyloxy)-1,1'binaphthyl (R)-8 (450 mg, 0.5 mmol) and 1,4-diazabicyclo[2,2,2]octane (340 mg, 3 mmol) in anhydrous DMF (5 mL) under an argon atmosphere was added at room temperature bis(4-methoxyphenyl)phosphine–borane complex 1 (330 mg, 1.2 mmol) and the mixture stirred at room temperature for 30 min and then at 110 °C for 48 h. DMF was evaporated under reduced pressure and methanol was added to the residue to afford (R)-9 (380 mg, 68%) as a white solid.

1H NMR (300 MHz, CDCl3): δ 8.08 (t, J = 6.55 Hz, 6H, 2ArCH3), 1.20–1.30 (m, 36H, 2(C138H27O2)2), 1.47–1.58 (m, 4H, 2 ArCH2CH3), 2.60–2.70 (m, 4H, 2 ArCH2), 6.40 (d, J = 8.67 Hz, 6H, H arom.), 6.75 (m, 6H, H arom.), 6.80 (dd, J = 9.63, 1.5, 2H, H arom.), 7.09 (t, J = 6.78 Hz, 2H, H arom.), 7.26 (m, 6H, H arom.), 7.56 (m, 3H, H arom.), 7.76 (d, J = 8.85 Hz, 1H, H arom.), 13P NMR (81 MHz, CDCl3): δ −17.5 (s); Elemental Anal. Calcd for C72H88O2P2 (1078.41): C, 80.11; H, 8.22; P, 5.74. Found: C, 80.39; H, 8.37; P, 5.69; [R]25 = −25.65 (c 0.635, CHCl3).

4.2.11. (R)-6,6'-Didodecyl-2,2'-bis[(4-hydroxyphenyl)-phosphino]-binaphthyl (R)-10. A solution of (R)-6,6'-didodecyl-2,2'-bis[(4-hydroxyphenyl)phosphino]-1,1'-binaphthyl (R)-9 (1.055 g, 1 mmol) in dry dichloromethane (20 mL) was cooled at 0 °C. A 1 M solution of BBr3 in dichloromethane (10 mL, 10 mmol) was added and the reaction mixture was stirred at 0 °C for 1 h, and then at room temperature for 24 h. The solution was cooled to 5 °C and methanol (20 mL) was added carefully. After removal of the organic solvents, the crude product was recrystallized from hot methanol (20 mL) by adding cold water (10 mL) to afford hydroxyphosphine (R)-10 (970 mg, 95%) as a white solid. 1H NMR (300 MHz, CDCl3): 6 0.87 (t, J = 6.50 Hz, 6H, 2CH3), 1.20–1.35 (m, 36H, 2(C138H27O2)2), 1.40–1.40 (m, 4H, 2 ArCH2CH2), 2.65–2.78 (m, 4H, 2 ArCH2), 6.58 (br t, J = 8.88 Hz, 8H, H arom.), 6.73 (d, J = 8.67 Hz, 2H, H arom.), 6.75 (dd, J = 9.60, 1.49 Hz, 2H, H arom.), 6.81–6.89 (m, 8H, H arom.), 7.35 (dd, J = 8.20, 2.41 Hz, 2H, H arom.), 7.60 (s, 2H, H arom.), 7.80 (d, J = 8.50 Hz, 2H, H arom.), 9.95 (s, 4H, 4 OH); 13C NMR (75 MHz, CDCl3): δ −17.2 (s); 31P NMR (81 MHz, CDCl3): δ −17.2 (s); 1H NMR (300 MHz, CDCl3): δ 14.6, 21.5, 23.1, 27.3, 29.8, 29.9, 30.0, 30.1, 30.2, 31.8, 32.3, 36.5, 115.8, 128.0, 128.1, 128.5, 131.4, 131.9, 132.3, 133.9, 134.4, 134.9, 135.6, 135.9, 141.8, 156.4, 172.5; Elemental Anal. Calcd for C68H50O2P2 (1022.55): C, 79.81; H, 7.88; P, 6.05. Found: C, 79.59; H, 7.67; P, 6.02; mp 127–129 °C; [R]25 = −0.32 (cyclohexane/ethylacetate 95:5); [R]25 = +42.0 (c 0.83, CH2Cl2).
4.2.12. General procedure for hydrogenation of \( \alpha \)-ketoesters 12a–c with the system [Ru(\( C_5 H_5 \))Cl\(_2 \)]/chiral ligand. In a Schlenk tube, [Ru(\( C_5 H_5 \))Cl\(_2 \)] (2 mg, 8 \( \mu \)mol) and ligand (8 \( \mu \)mol) were mixed in 1 mL of solvent. After 16 h of stirring at room temperature under an argon atmosphere, the substrate (0.8 mmol) was introduced and the resulting solution was stirred under a hydrogen pressure (40 bars) in a stainless-steel reactor (previously degased three times with argon and twice with hydrogen) for 24 h, at 50 °C. The reaction mixture was filtered on Celite and analyzed by chiral GC (Lipodex A, 25 m) to determine both conversion and enantiomeric excess.

4.2.13. Procedure for Ir-catalyzed asymmetric hydrogenation of 2-methylquinoline 13. A mixture of [Ir(COD)Cl\(_2 \)] (3.4 mg, 5 \( \mu \)mol) and the desired ligand (11 \( \mu \)mol) in dry toluene (5 mL) was stirred at room temperature for 30 min under an argon atmosphere at room temperature. The mixture was transferred by syringe to a stainless steel autoclave, in which \( \lambda_1 \) (12.7 mg, 0.05 mmol) and 2-methylquinoline 15 (1.0 mmol) were placed beforehand. The hydrogenation was performed at room temperature under hydrogen (40 bars) for 12–15 h. The conversion and enantiomeric excess were determined by chiral HPLC with chiral columns (OJ-H).

4.2.14. HPLC conditions for the 2-methylquinoline. Chiralcel® OJ-H column, heptane/isopropanol (90:10), 0.5 mL/min, starting material 12.12 min, enantiomers 17.49 and 19.40 min, wavelength: 260 nm.

### References


