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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 diphophosphines were also excellent ligands for the iridium-catalyzed asymmetric hydrogenation of quinolines.

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%.[3j] 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.[3j,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 ferrocenyloxazolinc-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′-diol as a highly effective ligand in the Ir-catalyzed asymmetric hydrogenation of quinolines with high enantioselectivity up to 94%.[9e]

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Knowing that the electronic tuning of a ligand such as BINAP could be connected to the enantioselectivity,[10–14] 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.

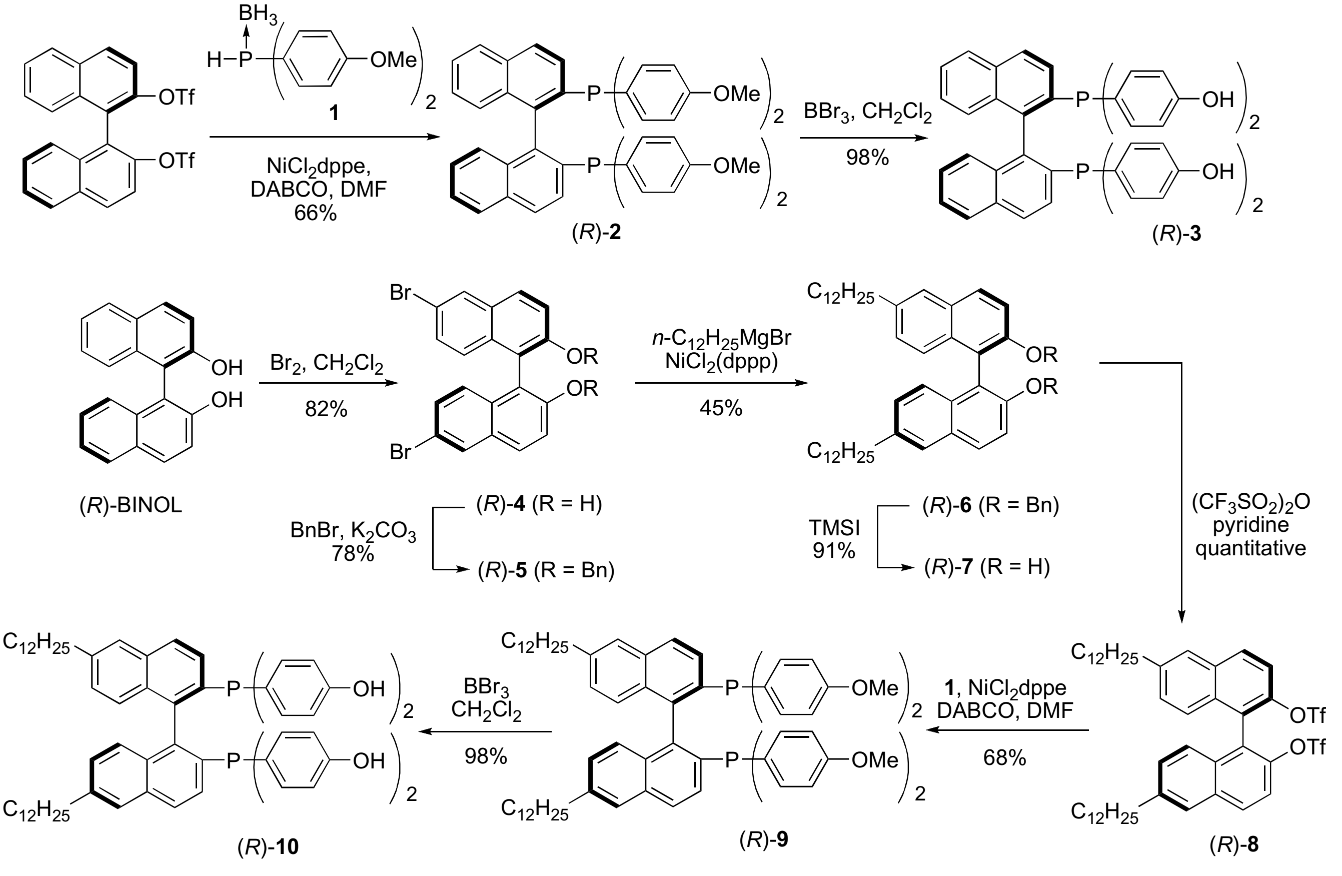
2. Results and discussion

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.[15]

The preparation of enantiopure BINAP derivatives involved a coupling reaction of the di-*p*-anisylphosphine–borane **1** with (*R*)-2,2′-ditrifluoromethanesulfonate-1,1′-binaphthyl[16] in the presence of DABCO and $NiCl_2$dppe in DMF (Scheme 1). Tetramethoxy-BINAP (*R*)-**2** was obtained in 66% yield.[14,17] This synthetic method was proved to be more efficient than those previously described by Takaya et al.[18] The tetrahydroxy (*R*)-**3** was obtained by a deprotection of hydroxyl substituents of (*R*)-**2** with BBr_3 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 Br_2 in 75% yield according to Cram et al.[19] Benzylation of the (*R*)-6,6′-dibromo-1,1′-bis-2-naphtol (*R*)-**4** afforded (*R*)-**5** in 78% yield.[20] The protected BINOL was cross coupled[21] with commercially available dodecylmagnesium bromide (89%). Deprotection of the resulting (*R*)-**6** using TMSI[22] gave the bis-dodecylbinol (*R*)-**7** in 91% yield. The (*R*)-6,6′-didodecyl-2,2′-ditrifluoromethanesulfonate-1,1′-binaphthyl (*R*)-**8** was then obtained using trifluoromethanesulfonic anhydride and pyridine.[23] The preparation of the enantiopure 6,6′-didodecyl-tetramethoxy-BINAP (*R*)-**9** involved a coupling reaction between the di-*p*-anisylphosphine–borane **1** and (*R*)-**8** in the presence of DABCO and $NiCl_2$dppe in DMF. 6,6′-Didodecyl-tetramethoxy-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 BBr_3 in 95% yield.



Scheme 1. Synthesis of ligands (*R*)-**2**, (*R*)-**3** and (*R*)-**10**.

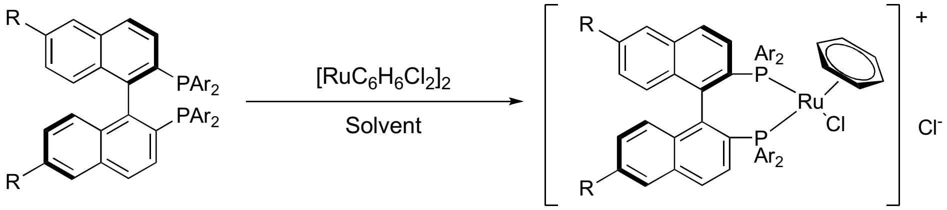
2.2. Hydrogenation of α-ketoesters

The hydrogenation of various α-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 $[Ru(C_6H_6)Cl_2]_2$ precursor and the diphosphine ligands (Scheme 2) prior to the introduction of the α-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 enantiomeric 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**.

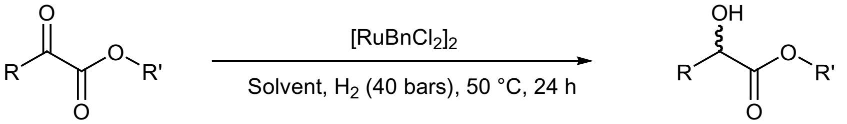


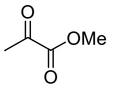
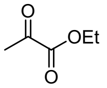
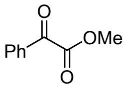
(*R*)-BINAP: R = H; Ar = Ph
(*R*)-**2**: R = H; Ar = *p*-$MeOC_6H_4$
(*R*)-**3**: R = H; Ar = *p*-HOC_6H_4
(*R*)-**10**: R = $C_{12}H_{25}$; Ar = p-HOC_6H_4

11a-d

Scheme 2. General procedure for BINAP complex synthesis.

Table 1. Ruthenium-catalyzed reduction of ketoesters with (*R*)-BINAP, tetramethoxy-BINAP (*R*)-**2** and tetrahydroxy-BINAP (*R*)-**3**

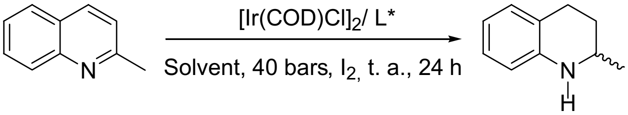


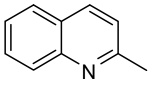
Substrate[a]	Entry	Ligand	Solvent	Conv.[b] (%)	ee[b] (%)
 **12a**	1	(*R*)-BINAP	MeOH	100	78 (*R*)
	2	(*R*)-2	MeOH	100	84 (*R*)
	3	(*R*)-3	MeOH	97	87 (*R*)
 **12b**	4	(*R*)-BINAP	EtOH	100	65 (*R*)
	5	(*R*)-2	EtOH	100	75 (*R*)
	6	(*R*)-3	EtOH	95	79 (*R*)
 **12c**	7	(*R*)-BINAP	MeOH	100	77 (*R*)
	8	(*R*)-2	MeOH	100	91 (*R*)
	9	(*R*)-3	MeOH	100	92 (*R*)
	10	(*R*)-10	MeOH	100	91 (*R*)

[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* + 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.

Table 2. Iridium-catalyzed reduction of 2-methylquinoline with (*R*)-BINAP, tétraméthoxy-BINAP (*R*)-**2** and 6,6′-didodecyl tetrahydroxy-BINAP (*R*)-**10**



Substrate[a]	Entry	Ligand	Solvent	Conv.[b] (%)	ee[b] (%)
 **13**	1	(*R*)-BINAP	Toluene	30–70	33–55 (*R*)
	2	(*R*)-2	Toluene	70–75	63 (*R*)
	3	(*R*)-3	Toluene	10	—
	4	(*R*)-10	Toluene	89	70 (*R*)

[a] Hydrogenation was performed in homogeneous conditions, [S] = 0.2 M; L/M = 1.1; S/M = 100; 40 bars H_2; I_2/M = 5; 24 h at rt.

[b] Conversion and enantioselectivity were determined by HPLC: Chiralcel OJ-H column.

With a higher Hammett σ-coefficient for the *p*-OH-BINAP derivative (−0.38) than that of *p*-OMe–BINAP derivative (−0.28), enantioselectivities of the hydrogenation of α-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.[9a] for this reduction, in the presence of the BINAP, is 87% while working in a gloves box. On the other hand, in the presence of tetramethoxy-BINAP (*R*)-**2**, the reduction is reproducible (63% ee, 75% yield). Very low conversion was observed in the presence of tetrahydroxy-BINAP (*R*)-**3** probably due to the poor solubility of this ligand in toluene (Table 2, entry 3). Conversely, when we used the more soluble 6,6′-didodecyl tetrahydroxy-BINAP (*R*)-**10**, an increase in enantiomeric excess was observed (70% ee, 89% yield) (Table 2, entry 4).

3. Conclusion

In conclusion we have devised an effective approach to the synthesis and tested new BINAP derivatives for the Ru-catalyzed homogeneous asymmetric hydrogenation of α-ketoesters and quinoline. We have shown that in both cases, electronically enriched BINAP derivatives lead to higher ees than (*R*)-BINAP the best ligand being tetrahydroxy-BINAP (*R*)-**3** and (*R*)-6,6′-didodecyl-tetrahydroxy-BINAP (*R*)-**10**.

The nature of the groups at the *para*-phenyl position clearly influences 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 concentrated 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; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.71 (s, 6H, OCH_3), 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); ^{13}C NMR (300 MHz, $CDCl_3$): 55.8, 114.7 (d, $J = 20$), 123.5 (d, $J = 110$), 133.0 (d, $J = 20$), 163.2 (d, $J = 10$); ^{31}P{^{1}H} NMR (81 MHz, $CDCl_3$): 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 THF (35 mL) was stirred under Ar at room temperature (25 °C) for 30 min. Sodium borohydride (1.8 g, 47.28 mmol) was added and the mixture stirred at room temperature for 1 h. Next bis(4-methoxyphenyl)phosphine oxide (4 g, 15.25 mmol) and lithium aluminium hydride (0.7 g, 18.3 mmol) were added successively at 5 °C and the mixture stirred at room temperature for 3 h. 3 M-NaOH (50 mL) was added at 3 °C, followed by ethyl acetate (50 mL), water (20 mL) and filtered on Celite. The mixture was stirred at room temperature for 30 min and then filtered. The filtrate was partitioned, and the aqueous layer was extracted three times with ethyl acetate (90 mL). The combined organic layers were washed with water (2×100 mL), brine (100 mL), dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (eluent *n*-hexane/ethyl acetate 5:1→2:1) to give **1** (2.4 g, white crystals, 60%). ^{1}H NMR (300 MHz, $CDCl_3$): 0.43–1.57 (m, 3H, BH_3): δ 3.82 (s, 6H, OCH_3), 6.24 (dq, $J = 377.9$, 6.78 Hz, 1H, HP), 6.95 (dd, $J = 8.71$, 1.72 Hz, 4H, $H_{arom.}$), 7.53–7.60 (m, 4H, $H_{arom.}$); ^{31}P{^{1}H} NMR (81 MHz, $CDCl_3$): δ −4.53 to −2.73 (m), −1.26 to 0.40 (m), −4.15 (m).

4.2.3. (*R*)-2,2′-Bis[bis(4-methoxyphenyl)phosphino]-1,1′-binaphthyl (*R*)-2. Under an argon atmosphere, to a solution (5 mL) of [1,2-bis(diphenylphosphino)-ethane]dichloronickel (53 mg, 0.1 equiv), (*R*)-2,2′-bis(trifluoromethanesulfonyloxy)-1,1′binaphtyl (500 mg, 0.91 mmol) and 1,4-diazabicyclo[2,2,2]octane (613 mg, 6.0 equiv) in DMF was added at room temperature bis(4-methoxyphenyl)phosphine-borane complex **1** (543 mg, 2.3 equiv) 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 give the title compound (*R*)-**2** (444 mg, white crystals, 66%). $[\alpha]_D^{25} = +107.6$ (*c* 0.4, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.73 (s, 12H, CH_3), 6.64 (d, $J = 8.35$ Hz, 4H, $H_{arom.}$), 6.69 (d, $J = 8.19$ Hz, 4H, $H_{arom.}$), 6.80 (d, $J = 8.49$ Hz, 2H, $H_{arom.}$), 6.92–7.03 (m, 10H, $H_{arom.}$), 7.30–7.38 (m, 2H, $H_{arom.}$), 7.40–7.45 (m, 2H, $H_{arom.}$), 7.82 (d, $J = 8.13$ Hz, 2H, $H_{arom.}$), 7.87 (d, $J = 8.52$ Hz, 2H, $H_{arom.}$); ^{31}P{^{1}H} NMR (81 MHz, $CDCl_3$): δ −16.86 (s).

4.2.4. (*R*)-2,2′-Bis[bis(4-hydroxyphenyl)phosphino]-1,1′-binaphthyl (*R*)-3. A solution of (*R*)-2,2′-bis[bis(4-methoxyphenyl)phosphino]-1,1′-binaphthyl (433 mg, 0.56 mmol) in dry CH_2Cl_2 (20 mL) was cooled at 0 °C. A 1 M solution of BBr_3 in CH_2Cl_2 (5.6 mL, 5.6 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 CH_3OH (10 mL) was carefully added. After removal of the organic solvents, the residue was recrystallized from hot CH_3OH (10 mL) by adding cold water (5 mL) to give (*R*)-**3** (392 mg, 98%). White solid; mp >220 °C; $[\alpha]_D^{25} = +29$ (*c* 0.9, MeOH); ^{1}H NMR (300 MHz, DMSO-d_6): 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); ^{31}P {^{1}H}NMR (81 MHz, DMSO-d_6): −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′-dinaphthyl [(*R*)-BINOL] was dissolved in CH_2Cl_2 (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 Br_2 was destroyed by the addition of 50 mL of 10% aqueous solution of sodium bisulfite. The layers were separated, and the organic layer was washed with brine, dried over $MgSO_4$, 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. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.69 (s, 2H, OH), 6.90 (d, $J = 8.8$ Hz, 2H, $H_{arom.}$), 7.30 (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; $[\alpha]_D^{25} = -129$ (*c* 1, CH_2Cl_2).

4.2.6. (*R*)-6,6′-Dibromo-2,2′-dibenzoxy-1,1′-binaphthyl (*R*)-5. (*R*)-6,6′-Dibromo-1,1′-bis-2-naphtol (*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 $MgSO_4$, 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.

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.0 (s, 4H, $2OCH_2$), 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, $H_{arom.}$); $[\alpha]_D^{25} = +188$ (*c* 1, CH_2Cl_2).

4.2.7. (*R*)-6,6′-Didodecyl-2,2′-dibenzoxy-1,1′-binaphthyl (*R*)-6. [1,3-Bis(diphenylphosphino)propane]$NiCl_2$ (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 $MgSO_4$ filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel using (heptane/diethyl ether 98.5:1.5) as the eluent to afford (*R*)-(*R*)-**6** (3.39 g, 89%) as a colourless viscous oil. ^1H NMR (300 MHz, $CDCl_3$): δ 0.85–0.95 (t, $J = 6.8$ Hz, 6H, $2 \times CH_3$), 1.22–1.41 (m, 36H, 2 $(CH_2)_9CH_3$), 1.65–1.72 (m, 4H, 2 $ArCH_2CH_2$) 2.73 (t, $J = 7.7$ Hz, 4H, 2 $ArCH_2$), 5.04 (s, 4H, $2OCH_2$), 6.96–6.98 (m, 4H, $H_{arom.}$), 7.08–7.18 (m, 10H, $H_{arom.}$), 7.39 (d, $J = 9$ Hz, 2H, $H_{arom.}$), 7.66 (br s, 2H, $H_{arom.}$), 7.87 (d, $J = 9$ Hz, 2H, $H_{arom.}$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 20.4, 22.7, 22.4, 29.5, 29.6, 29.7, 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, 137.7, 138.2, 153.5; MS (ESI): *m*/*z*: 803.5 $[M+H]^+$; Elemental Anal. Calcd for $C_{58}H_{74}O_2$(803.24): C, 86.73; H, 9.29. Found: C, 86.60; H, 9.30; $R_f = 0.63$ (light petroleum/diethyl ether, 2:1); $[\alpha]_D^{25} = +205.7$ (*c* 1, $CHCl_3$).

4.2.8. (*R*)-6,6′-Didodecyl-2,2′-dihydroxy-1,1′-binaphthyl (*R*)-7. NaI (2.13 g, 14.21 mmol) and TMSCl (1.80 mL, 14.21 mmol) were added to a stirred solution of didodecylbisether (*R*)-**6** (1.14 g, 1.42 mmol) in toluene (20 mL) and acetonitrile (40 mL). The reaction mixture was heated at 40 °C for 2 h. After cooling to room temperature, water (40 mL) was added, the aqueous phase was then separated and extracted with diethyl ether (3 × 40 mL). The combined organic components were washed with a 1 M aqueous $Na_2S_2O_3$ solution (60 mL) and brine (60 mL), dried over $MgSO_4$, filtered and concentrated under a reduced pressure. The crude product was purified by flash chromatography on silica gel using (heptane/diethyl ether 10:1) as the eluent to afford (*R*)-**7** (0.82 g, 91%) as a colourless oil; ^1H NMR (300 MHz, $CDCl_3$): δ 0.84–0.95 (t, $J = 6.8$ Hz, 6H, $2CH_3$), 1.22–1.41 (m, 36H, $2(CH_2)_9CH_3$), 1.64–1.71 (m, 4H, $2ArCH_2CH_2$), 2.73 (t, $J = 7.7$ Hz, 4H, 2 $ArCH_2$), 5.00 (s, 2H, 2OH), 7.10 (d, $J = 8.6$ Hz, 2H, $H_{arom.}$), 7.17 (dd, $J = 8.6$, 1.5 Hz, 2H, $H_{arom.}$), 7.35 (d, $J = 8.9$ Hz, 2H, $H_{arom.}$), 7.67 (br s, 2H, $H_{arom.}$), 7.91 (d, $J = 8.6$ Hz, 2H, $H_{arom.}$); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ 14.1, 22.7, 29.2, 29.3, 29.4, 29.6, 29.7, 29.8, 31.4, 31.9, 35.8, 110.8, 117.6, 124.1, 126.8, 129.0, 129.5, 130.8, 131.7, 138.6, 152.0; MS (ESI): *m*/*z*: 623.5 $[M+H]^+$; Elemental Anal. Calcd for $C_{44}H_{62}O_2$ (622.98): C, 84.83; H, 10.03. Found: C, 84.60; H, 10.27; $R_f = 0.16$ (light petroleum/diethyl ether, 3:1); $[\alpha]_D^{25} = -51.4$ (*c* 1, $CHCl_3$).

4.2.9. (*R*)-6,6′-Didodecyl-2,2′-ditrifluoromethanesulfonate-1,1′-binaphthyl (*R*)-8. To a solution of (*R*)-6,6′-didodecyl-2,2′-dihydroxy-1,1′-binaphthyl (*R*)-**7** (6.23 g, 10.2 mmol) in dichloromethane (15 mL) was added pyridine (2.5 mL, 30.6 mmol) at room temperature. Trifluoromethanesulfonic anhydride (4 mL, 23.8 mmol) was added at 5 °C and the mixture was stirred at 5–10 °C for 8 h. Hexane (15 mL) was then added and the mixture stirred at room temperature for 30 min. The reaction mixture was filtered and purified on silica gel using (dichloromethane/hexane 1:1) as the eluent and the filtrate was concentrated under reduced pressure to afford (*R*)-**8** (8.96 g, 99%) as a grey oil. ^1H NMR (300 MHz, $CDCl_3$): δ 0.85–0.95 (t, $J = 6.8$ Hz, 6H, $2CH_3$), 1.22–1.41 (m, 36H, $2(CH_2)_9CH_3$), 1.58–1.71 (m, 4H, $2ArCH_2CH_2$) 2.78 (t, $J = 7.7$ Hz, 4H, 2 $ArCH_2$), 7.15 (d, $J = 8.7$ Hz, 2H, $H_{arom.}$), 7.20 (d, $J = 8.25$ Hz, 2H, $H_{arom.}$), 7.35 (d, $J = 8.6$ Hz, 2H, $H_{arom.}$), 7.75 (s, 2H, $H_{arom.}$), 8.03 (d, $J = 9.03$ Hz, 2H, $H_{arom.}$); ^{19}F NMR (122 MHz, $CDCl_3$): δ −75.2 (s).

4.2.10. (*R*)-6,6′-Didodecyl-2,2′-bis[bis(4-methoxyphenyl)-phosphino]-1,1′-binaphthyl (*R*)-9. To a solution of [1,2-bis(diphenylphosphino)-ethane]dichloronickel (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, $CDCl_3$): δ 0.80 (t, $J = 6.55$ Hz, 6H, $2CH_3$), 1.20–1.30 (m, 36H, $2(CH_2)_9CH_3$), 1.47–1.58 (m, 4H, $2ArCH_2CH_2$), 2.60–2.70 (m, 4H, 2 $ArCH_2$), 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, $H_{arom.}$), ^{31}P NMR (81 MHz, $CDCl_3$): δ −17.5 (s); Elemental Anal. Calcd for $C_{72}H_{88}O_4P_2$ (1078.41): C, 80.11; H, 8.22; P, 5.74. Found: C, 80.39; H, 8.37; P, 5.69; $[\alpha]_D^{25} = -25.65$ (*c* 0.635, $CHCl_3$).

4.2.11. (*R*)-6,6′-Didodecyl-2-2′-bis[bis(4-hydroxyphenyl)-phosphino]-binaphthyl (*R*)-10. A solution of (*R*)-6,6′-didodecyl-2,2′-bis[bis(4-methoxyphenyl)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 BBr_3 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, $CDCl_3$): δ 0.87 (t, $J = 6.50$ Hz, 6H, $2CH_3$), 1.20–1.35 (m, 36H, 2 $(CH_2)_9CH_3$), 1.40–1.60 (m, 4H, $2ArCH_2CH_2$), 2.65–2.78 (m, 4H, $2ArCH_2$), 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) ^{31}P NMR (81 MHz, $CDCl_3$): δ −17.2 (s); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): 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 $C_{68}H_{80}O_4P_2$ (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; $R_f = 0.32$ (cyclohexane/ethylacetate 95:5); $[\alpha]_D^{25} = +42.0$ (*c* 0.83, CH_2Cl_2).

4.2.12. General procedure for hydrogenation of α-ketoesters 12a–c with the system $[Ru(C_6H_6)Cl_2]_2$/chiral ligand. In a Schlenk tube, $[Ru(C_6H_6)Cl_2]_2$ (2 mg, 8 μmol) and ligand (8 μmol) 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-steal 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.

GC conditions

Substrate	Conditions	Retention time
Methyl pyruvate **12a**	Lipodex A 50 °C (1 min)–1 °C/min–70 °C (1 min)	Starting material: 3.30 min Enantiomers: 3.75; 4.62 min
Ethyl pyruvate **12b**	Lipodex A 40 °C (15 min)–1 °C/min–60 °C (5 min)	Starting material: 4.42 min Enantiomers: 8.01; 9.45 min
Methyl benzoylformate **12c**	Lipodex A 80 °C (1 min)–1 °C/min–150 °C (1 min)	Starting material: 23.31 min Enantiomers: 25.98; 27.24 min

4.2.13. Procedure for Ir-catalyzed asymmetric hydrogenation of 2-methylquinoline 13. A mixture of $[Ir(COD)Cl]_2$ (3.4 mg, 5 μmol) and the desired ligand (11 μmol) 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 I_2 (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.

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