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Bicyclic phosphine-thiazole ligands for the asymmetric hydrogenation of olefins

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Dedicated to Professor Henri Kagan on the occasion of his 80th birthday

ABSTRACT

New bicyclic thiazole-based chiral N,P-chelating ligands were developed. High activities and enantioselectivities were achieved in the iridium-catalyzed asymmetric hydrogenation of olefins with the new ligands.

1. Introduction

Chiral compounds and their preparation play an important role in the production of fine chemicals, pharmaceuticals, and natural products.[1] As a result, various methods for creating stereogenic centers have been developed. Due to its high efficiency, atom economy, and operational simplicity, the asymmetric hydrogenation (the addition of H_2 to a C=X (X = C, N or O) bond) has been widely used in asymmetric synthesis.[2] Early reports were dominated by rhodium- and ruthenium-based catalysts.[3] However the highly stereoselective hydrogenation of olefins by rhodium- and ruthenium-based catalysts usually requires a coordinating group close to the carbon–carbon double bond.[4] By contrast, iridium complexes with chiral N,P-chelating ligands do not need a coordinating group to achieve high enantioselectivity. They have therefore become powerful tools for the hydrogenation of unfunctionalized olefins, and useful complements to rhodium- and ruthenium-based catalysts. [5] Since the success of Pfaltz' PHOX catalysts,[6] which are chiral analogues of Crabtree's catalyst, a number of chiral N,P-chelating ligands have been prepared and tested in the iridium-catalyzed asymmetric hydrogenation of olefins.[5a,b,d,e,7,8] The bicyclic phosphine-oxazoline ligands **1** (Fig. 1) are among the most successful types and give excellent results in the hydrogenation of acyclic aromatic *N*-arylimines[9a,b] and enol phosphinates.[9c,d] Thiazole ligands **2** are also highly enantioselective in the hydrogenation of a wide range of olefins.[8b,d,k,j] Encouraged by the excellent results achieved with ligands **1** and **2**, we developed the bicyclic phosphine-thiazole ligand **3c**, which was effective in the hydrogenation of vinyl boronates.[10] The iridium-catalyzed asymmetric hydrogenation of unfunctionalized olefins is still highly substrate dependent, and the development of new chiral ligands for this reaction remains an important task.[11] In known ligands, heteroaromatic moieties have significantly affected enantioselectivities in the hydrogenation of olefins.[12] Thus we chose to synthesize more members of the set of bicyclic phosphine-thiazole ligands and investigate their performance in the iridium-catalyzed asymmetric hydrogenation.

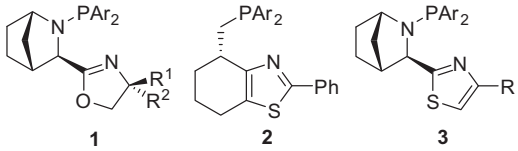

Figure 1. Bicyclic phosphine-oxazoline ligands **1**, thiazole liangds **2**, and bicyclic phosphine-thiazole ligands **3**.

2. Results and discussion

2.1. Synthesis of iridium complex 7

As shown in Scheme 1, *N*-Boc-protected thioamide **4** was cyclized with an α-bromoketone to yield the corresponding N-protected thiazole **5**. The protecting group was readily removed under acidic conditions to afford amine **6**. Ligand **3** was obtained by treating **6** with a diarylphosphine chloride in the presence of di-*iso*-propylethylamine. Iridium complex **7** was prepared by refluxing **3** and $[Ir(COD)Cl]_2$ in CH_2Cl_2 followed by counterion exchange with $NaBAr_F{\cdot}3H_2O$ in a CH_2Cl_2/water mixture. Compound **7** was purified by flash chromatography on silica gel. All complexes were isolated as air stable solids. No decomposition of the complexes was observed by ^1H and ^{31}P NMR after months in air.

2.2. Asymmetric hydrogenation of olefins

Complexes **7a–d** were evaluated in the asymmetric hydrogenations of various olefins (Table 1). Generally, complexes **7c** and **7d** were more stereoselective than **7a** and **7b**. Complex **7b** gave a low conversion for most trisubstituted olefins. This is likely

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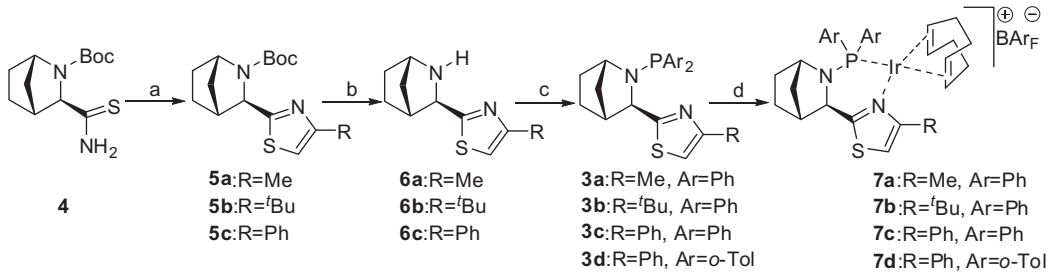


Scheme 1. Synthesis of iridium complexes **7**. Reagents and conditions: (a) MeOH, α-bromo ketone, $CaCO_3$, reflux, 4 h; (b) THF, 12 M HCl, 2 h; (c) Ar_2PCl, $^iPr_2NEt$, THF, 0 °C then 4 °C overnight; (d) $[Ir(COD)Cl]_2$, CH_2Cl_2, reflux 1 h then H_2O, $NaBAr_F{\cdot}3H_2O$, rt, 2 h.

because it bears a bulky *tert*-butyl group on the thiazole ring. When the phosphine moiety was changed from diphenylphosphine to di-*o*-tolylphosphine, enantioselectivities were moderately improved for most substrates (compare **7c** vs **7d**. Table 1, entries 2, 4, 5, 8, and 9). The difference was quite dramatic in the case of α-methyl *trans*-cinnamate **13**.

Both the thiazole complex **7d** and the analogous oxazoline complex **8** gave excellent enantioselectivities in the asymmetric hydrogenation of substrates **9** and **10** (Table 1, entries 1 and 2). Complex **7d** out-performed **8** in the reduction of substrates **11**, **12**, **15**, **16**, and **17** (entries 3, 4, 7, 8, and 9). Complex **7d** also gave high yield and excellent enantioselectivity in the hydrogenation of allylic alcohol **14**, toward which **8** was inactive (entry 6). In general, the new complexes provided good to excellent enantioselectivities for the hydrogenation of trisubstituted olefins (entries 1–6), but low enantioselectivities for 1,1-disubstituted olefins (entries 7, 8, and 9).

3. Conclusion

We have developed a set of bicyclic thiazole-phosphine ligands that were synthesized from readily available α-bromoketones. Iridium complexes made from the new ligands were highly active and enantioselective in the asymmetric hydrogenation of several olefins. The best of these new iridium complexes, **7d**, often gave better results than its oxazoline analogue **8**.

4. Experimental procedures

4.1. General

α-Bromoacetophenone, *trans*-α-methylstilbene **10**, and *trans*-2-methyl-3-phenyl-2-propen-1-ol **14** were purchased from Sigma–Aldrich Co. and used as received. Methanol was distilled from Mg. Tetrahydrofuran was dried over and distilled from Na/benzophenone ketyl under N_2. CH_2Cl_2 and di-*iso*-propylethylamine were distilled from CaH_2. Flash chromatography was performed using silica gel (Merck kieselgel 60 H 37–70 μm). Reactions were monitored using TLC (Merck kieselgel 60 0.20 mm layer, UV_{254}), and the plates were visualized with UV light at 254 nm or stained with ethanolic ninhydrin and then heated.

The ^1H NMR, ^{13}C NMR, and ^{31}P NMR spectra were acquired in $CDCl_3$ or C_6D_6 on 400 or 300 MHz spectrometer. ^1H NMR and ^{13}C NMR spectra were referenced to residual $CHCl_3$ (7.26 ppm ^1H; 77.16 ppm ^{13}C) or C_6H_6 (7.16 ppm ^1H; 128.62 ppm ^{13}C). ^{31}P NMR spectra were referenced to external H_3PO_4. Chemical shifts are reported in parts per million (ppm) and coupling constants, *J*, are reported in hertz. Mass spectra were measured at 70 eV (EI). High resolution mass spectrometric (HRMS) data were obtained using a Bruker microTOF-Q II instrument operating at ambient temperatures, using a sample concentration of approximately 1 ppm. Infrared (IR) spectra were recorded on a Perkin–Elmer 100 FT/IR spectrometer. Optical rotations were measured on a thermostated polarimeter using a 1.0 dm cell and are reported as follows: concentration (c = g/dL) and solvent. Melting points were recorded as their uncorrected values.

Enantiomeric excesses (ees) were determined by chiral HPLC or GC. HPLC was performed with a DAD detector using Daicel Chiralpak OJ, OB-H, and AS-H columns. GC analysis was performed using a Chiraldex β-DM column. Absolute configurations were determined by comparing the retention times to those previously reported.[7g,8h]

4.2. Literature preparations

Substrates **1**,[13] **9**,[8b] **11**,[8b] **12**,[8b] **13**,[8b] **15**,[7g] **16**,[7g] **17**,[7g] α-bromoacetone,[14] and α-bromopinacolone[15] were prepared according to the literature procedures.

4.3. General procedure for the preparation of N-protected thiazoles 5a–c

The *N*-Boc-protected thioamide **4** (5 mmol), α-bromo ketone (5 mmol), and $CaCO_3$ (25 mmol) were mixed in dry methanol (25 mL). The reaction mixture was heated at reflux for 4 h. Once TLC analysis indicated that the reaction was complete, the mixture was filtered through a pad of Celite to remove $CaCO_3$. The crude filtrate was purified by flash chromatography in EtOAc/pentane (9:100) to afford **5** as white solids.

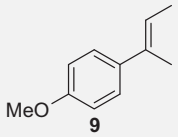
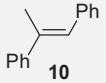
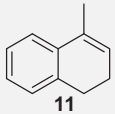
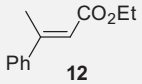
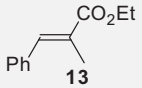
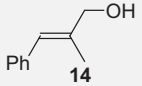
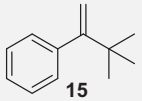
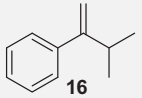
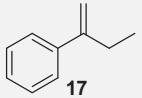
4.3.1. (1*S*,3*R*,4*R*)-*tert*-Butyl 3-(4-methylthiazol-2-yl)-2-azabicyclo[2.2.1]heptane-2-carboxylate 5a

Yield = 86%. Mp = 70.0–70.9 °C. (NMR spectra are reported for a mixture of two rotamers.) ^1H NMR (400 MHz, $CDCl_3$): δ 6.70–6.64 (m, 1H), 4.63–4.40 (m, 1H), 4.32–4.08 (m, 1H), 2.78–2.60 (m, 1H), 2.38–2.22 (m, 3H), 1.92–1.30 (m, 6H), 1.28–1.12 (m, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.3, 172.7, 155.0, 154.2, 152.5, 152.3, 112.7, 112.5, 79.8, 65.3, 64.9, 57.9, 56.8, 44.7, 43.9, 34.9, 34.1, 30.2, 29.6, 28.3, 28.1, 27.2, 27.0, 17.0. IR (neat, cm^{-1}): 1694, 1379, 1166, 1123, 1096. MS (EI) *m*/*z* (rel. intensity): 295 (M^++1, 100%). HRMS (ESI) *m*/*z* = 295.1480, calcd for $C_{15}H_{23}N_2O_2S$ $[M+H]^+$: 259.1480.

4.3.2. (1*S*,3*R*,4*R*)-*tert*-Butyl 3-(4-*tert*-butylthiazol-2-yl)-2-azabicyclo[2.2.1]heptane-2-carboxylate 5b

Yield = 89%. Mp = 117.1–180.0 °C. (NMR spectra are reported for a mixture of two rotamers.) ^1H NMR (300 MHz, $CDCl_3$): δ 6.74–6.66 (m, 1H), 4.64–4.51 (m, 1H), 4.34–4.16 (m, 1H), 2.81–2.64 (m, 1H), 1.98–1.40 (m, 6H), 1.32–1.28 (m, 9H), 1.28–1.20 (m, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.0, 172.4, 166.7, 166.3, 155.2, 154.2, 109.4, 109.3, 79.7, 65.2, 64.9, 58.0, 56.6, 44.6, 43.9, 34.9, 34.6, 34.2, 30.2, 29.9, 29.7, 28.4, 28.1, 27.4, 27.0. IR (neat, cm^{-1}): 1703, 1362, 1156, 1128, 1094. MS (EI) *m*/*z* (rel. intensity): 337 (M^++1, 100%). HRMS (ESI) *m*/*z* = 337.1944, calcd for $C_{18}H_{29}N_2O_2S$ $[M+H]^+$: 337.1950.

Table 1
Asymmetric hydrogenations catalyzed by the iridium complexes **7a–d** and **8**[a]

Entry	Substrate	**7a**		**7b**		**7c**		**7d**		**8**	
		Conv.[b] (%)	ee[c] (%)	Conv.[b] (%)	ee[c] (%)	Conv.[b] (%)	ee[c] (%)	Conv.[b] (%)	ee[c] (%)	Conv.[b] (%)	ee[c] (%)
1	 **9**	99	82 (*R*)	99	22 (*R*)	99	97 (*R*)	99	97 (*R*)	99	99 (*R*)
2	 **10**	83	97 (*R*)	0		45	97 (*R*)	99	99 (*R*)	99	98 (*R*)
3	 **11**	99	32 (*S*)	28	47 (*S*)	97	83 (*S*)	99	76 (*S*)	36	38 (*S*)
4	 **12**	98	85 (*R*)	0		66	92 (*R*)	99	98 (*R*)	99	69 (*R*)
5	 **13**	58	54 (*R*)	0		82	15 (*R*)	99	84 (*R*)	99	90 (*R*)
6	 **14**	99	45 (*R*)	0		99	93 (*R*)	95	93 (*R*)	0	
7	 **15**	99	49 (*S*)	96	20 (*R*)	99	86 (*S*)	99	83 (*S*)	99	81 (*S*)
8	 **16**	99	15 (*S*)	99	3 (*S*)	99	44 (*S*)	99	50 (*S*)	99	28 (*S*)
9	 **17**	99	2 (*S*)	99	3 (*S*)	99	2 (*S*)	99	17 (*S*)	99	3 (*S*)

[a] Conditions: 0.25 M substrate in CH_2Cl_2, 0.5 mol % catalyst, 50 bar H_2, rt, overnight.
[b] Determined by ^1H NMR spectroscopy.
[c] Determined by chiral GC or HPLC compared to the literature.[7g,8h]

4.3.3. (1*S*,3*R*,4*R*)-*tert*-Butyl 3-(4-phenylthiazol-2-yl)-2-azabicyclo[2.2.1]heptane-2-carboxylate 5c

Yield = 80%. Mp = 170.9–171.3 °C. (NMR spectra are reported for a mixture of two rotamers.) ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92–7.83 (m, 2H), 7.46–7.28 (m, 4H), 4.78–4.60 (m, 1H), 4.42–4.21 (m, 1H), 2.97–2.83 (m, 1H), 2.02–1.62 (m, 5H), 1.56–1.26 (m, 9H), 0.93–0.77 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.0, 173.4, 155.5, 155.2, 154.3, 134.8, 134.5, 128.6, 128.5, 127.8, 127.7, 126.2, 126.1, 112.4, 112.1, 80.0, 79.9, 65.3, 64.9, 58.0, 56.9, 44.7, 43.8, 35.0, 34.2, 30.2, 29.6, 28.3, 28.1, 27.2, 26.9. IR (neat, cm^{-1}): 1683, 1384, 1155, 1122, 1103. MS (EI) *m*/*z* (rel. intensity): 357 (M^++1, 45%), 300 (100), 227 (92). HRMS (ESI) *m*/*z* = 357.1620, calcd for $C_{20}H_{25}N_2O_2S$ $[M+H]^+$: 357.1637.

4.4. General procedure for preparation of thiazoles 6a–c

N-Protected thiazole **5** (3 mmol) was dissolved in THF (15 mL). Then 12 M HCl (15 mL) was added slowly and the reaction mixture was stirred at rt for 2 h. THF was then removed under vacuum. The reaction mixture was slowly poured into aqueous saturated $NaHCO_3$ solution and the mixture was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layer was dried over $MgSO_4$. After concentration under vacuum, the residue was purified by flash chromatography on silica gel (deactivated with 5% Et_3N) with Et_3N/EtOAc/pentane (5:8:100) as the eluent to afford **6** as white solids.

4.4.1. 2-((1*S*,3*R*,4*R*)-2-Azabicyclo[2.2.1]heptan-3-yl)-4-methylthiazole 6a

Yield = 87%. $[\alpha]_D^{23} = +48.5$ (*c* 1, $CHCl_3$). Mp = 81.3–81.9 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.73 (s, 1H), 4.10–4.08 (m, 1H), 3.60–3.58 (m, 1H), 2.69–2.66 (m, 1H), 2.35 (s, 3H), 1.95 (br s, 1H), 1.75–1.54 (m, 4H), 1.47–1.41 (m, 1H), 1.19–1.15 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.8, 153.1, 113.3, 62.4, 56.0, 44.3, 33.8, 33.2, 28.4, 17.2. IR (neat, cm^{-1}): 3298, 2957, 1526 1194, 727. MS (EI) *m*/*z* (rel. intensity): 195 (M^++1, 100%), 194 (34), 165 (46). HRMS (ESI) *m*/*z* = 195.0959, calcd for $C_{10}H_{15}N_2S$ $[M+H]^+$: 195.0956.

4.4.2. 2-((1*S*,3*R*,4*R*)-2-Azabicyclo[2.2.1]heptan-3-yl)-4-*tert*-butylthiazole 6b

Yield = 87%. $[\alpha]_D^{23} = +42.2$ (*c* 1, $CHCl_3$). Mp = 102.9–103.4 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.76 (s, 1H), 4.13–4.11 (m, 1H), 3.61–3.58 (m, 1H), 2.67–2.64 (m, 1H), 2.03 (br s, 1H), 1.75–1.57 (m, 4H), 1.49–1.42 (m, 1H), 1.32 (s, 9H), 1.20–1.15 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.8, 167.0, 109.9, 62.5, 56.0, 44.4, 34.8, 33.9, 33.0, 30.1, 28.4. IR (neat, cm^{-1}): 3330, 2965, 1513, 1199, 754. MS (EI) *m*/*z* (rel. intensity): 237 (M^++1, 100%), 236 (27), 207 (70). HRMS (ESI) *m*/*z* = 237.1421, calcd for $C_{13}H_{21}N_2S$ $[M+H]^+$: 237.1425.

4.4.3. 2-((1*S*,3*R*,4*R*)-2-Azabicyclo[2.2.1]heptan-3-yl)-4-phenylthiazole 6c

Yield = 97%. $[\alpha]_D^{23} = +58.6$ (*c* 1, $CHCl_3$). Mp = 100.2–100.6 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96–7.82 (m, 2H), 7.43–7.40 (m, 2H), 7.35 (s, 1H), 7.34–7.26 (m, 1H), 4.20–4.14 (m, 1H), 3.64–3.59 (m, 1H), 2.81–2.77 (m, 1H), 2.01 (br s, 1H), 1.78–1.67 (m, 3H), 1.66–1.57 (m, 1H), 1.51–1.41 (m, 1H), 1.23–1.16 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.7, 156.0, 135.1, 128.6, 127.7, 126.2, 112.9, 62.4, 56.0, 44.3, 33.8, 33.3, 28.3. IR (neat, cm^{-1}): 3312, 2947, 1492, 1177, 743. MS (EI) *m*/*z* (rel. intensity): 257 (M^++1, 100%), 256 (62), 227 (90). HRMS (ESI) *m*/*z* = 257.1108, calcd for $C_{15}H_{17}N_2S$ $[M+H]^+$: 257.1112.

4.5. General procedure for preparation of ligands 3a–d

Compound **6** (1 mmol) was co-evaporated with dry toluene (3 × 20 mL) and dissolved in dry THF (6 mL) under N_2. Freshly distilled di-*iso*-propylethylamine (3 mmol) was added and the solution was cooled to 0 °C in an ice-bath. Freshly distilled Ar_2PCl (1.2 mmol) was added dropwise and the reaction mixture was kept in fridge (4 °C) overnight. The solution was allowed to warm to rt and was then washed with saturated $NaHCO_3$ (20 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL) and the combined organic layers were dried over Na_2SO_4. The crude product was purified by flash chromatography on silica gel (deactivated with 5% Et_3N) with Et_3N/CH_2Cl_2/pentane (0.5:20:80) as the eluent to afford **3** as white foams.

4.5.1. Ligand 3a

Yield = quant. $[\alpha]_D^{23} = -2.9$ (*c* 1, C_6D_6). ^{1}H NMR (300 MHz, C_6D_6): δ 7.66–7.58 (m, 2H), 7.56–7.48 (m, 2H), 7.28–7.21 (m, 2H), 7.18–7.01 (m, 5H), 6.25 (q, *J* = 1.1 Hz, 1H), 4.58 (d, *J* = 7.1 Hz, 1H), 3.80 (s, 1H), 2.66 (m, 1H), 2.28 (d, *J* = 1.0 Hz, 3H), 2.10 (dp, *J* = 9.6, 2.0, 1H), 1.04–1.24 (m, 2H), 0.93 (m, 1H), 0.83 (m, 1H), 0.69 (m, 1H). ^{13}C NMR (75 MHz, C_6D_6): δ 176.0, 153.5, 140.7, 140.4, 140.3, 140.3, 134.5 (d, *J* = 24.1), 131.7 (d, *J* = 16.8), 129.6, 128.6, 128.5, 128.3, 127.8, 113.2, 69.1 (d, *J* = 30.2), 58.8 (d, *J* = 7.5), 46.8 (d, *J* = 6.1), 36.8, 29.7, 28.3, 17.4. ^{31}P NMR (121 MHz, C_6D_6): δ 40.68. IR (neat, cm^{-1}): 2965, 2871, 1478, 1430, 729, 699. MS (EI) *m*/*z* (rel. intensity): 378 (M^+, 8%), 301 (9), 166 (15), 162 (10), 136 (13), 84 (100). HRMS (ESI) *m*/*z* = 379.1387, calcd for $C_{22}H_{24}N_2PS$ $[M+H]^+$: 379.1398.

4.5.2. Ligand 3b

Yield = quant. $[\alpha]_D^{23} = -5.0$ (*c* 1, C_6D_6) ^{1}H NMR (300 MHz, C_6D_6): δ 7.71–7.63 (m, 2H), 7.57–7.48 (m, 2H), 7.32–7.24 (m, 2H), 7.22–7.15 (m, 2H), 7.14–7.03 (m, 2H), 6.43 (s, 1H), 4.58 (d, *J* = 7.4 Hz, 1H), 4.30 (s, 1H), 3.83 (s, 1H), 2.64 (m, 1H), 2.18 (dp, *J* = 9.6, 2.0, 1H), 1.39 (s, 9H), 1.28–1.05 (m, 2H), 0.97 (m, 1H), 0.89 (m, 1H), 0.77 (m, 1H). ^{13}C NMR (75 MHz, C_6D_6): δ 175.7, 167.1, 140.8, 140.5, 140.4, 140.3, 134.3 (d, *J* = 23.6), 131.8 (d, *J* = 17.7), 129.5, 128.6, 128.5, 128.3, 127.8, 110.1, 69.0 (d, *J* = 29.6), 58.9 (d, *J* = 6.6), 46.9 (d, *J* = 6.4), 36.9, 35.1, 30.3, 29.9, 28.4. ^{31}P NMR (121 MHz, C_6D_6): δ 40.83. IR (neat, cm^{-1}): 2958, 2867, 1586, 1511, 1479, 1458, 1433, 1058, 740, 695. MS (EI) *m*/*z* (rel. intensity): 421 (M^+, 41%), 420 (100), 391 (17), 343 (29), 325 (35), 266 (70), 253 (37), 235 (29), 220 (23), 185 (31), 183 (69), 84 (24). HRMS (ESI) *m*/*z* = 421.1860, calcd for $C_{25}H_{30}N_2PS$ $[M+H]^+$: 421.1867.

4.5.3. Ligand 3c

Yield = quant. $[\alpha]_D^{23} = +3.1$ (*c* 1, C_6D_6). ^{1}H NMR (300 MHz, C_6D_6): δ 8.03–7.98 (m, 2H), 7.67–7.61 (m, 2H), 7.58–7.50 (m, 2H), 7.31–7.20 (m, 4H), 7.19–7.02 (m, 5H), 6.87 (s, 1H), 4.62 (d, *J* = 7.6, 1H), 3.83 (s, 1H), 2.67 (s, 1H), 2.09 (m, 1H), 1.27–1.07 (m, 2H), 0.95 (m, 1H), 0.86 (m, 1H), 0.73 (m, 1H). ^{13}C NMR (75 MHz, C_6D_6): δ 176.8, 156.3, 140.6, 140.3, 140.2, 140.2, 135.6, 134.5 (d, *J* = 23.6), 131.7 (d, *J* = 17.7), 129.7, 128.9, 128.7, 128.6, 127.9, 126.8, 112.7, 69.1 (d, *J* = 28.4), 58.9 (d, *J* = 7.9), 46.9 (d, *J* = 6.4), 36.8, 29.8, 28.4. ^{31}P NMR (121 MHz, C_6D_6): δ 40.84. IR (neat, cm^{-1}): 2971, 2868, 1479, 1432, 1050, 735, 692. MS (EI) *m*/*z* (rel. intensity): 441 (M, 6%), 440 (11), 363 (10), 266 (14), 166 (24), 136 (11), 129 (19), 114 (11), 84 (100). HRMS (ESI) *m*/*z* = 441.1547, calcd for $C_{27}H_{26}N_2PS$ $[M+H]^+$: 441.1554.

4.5.4. Ligand 3d

Yield = 67%. $[\alpha]_D^{23} = -81.1$ (*c* 1, C_6D_6). ^{1}H NMR (300 MHz, C_6D_6): δ 8.07 (m, 1H), 7.96 (m, 1H), 7.46 (m, 1H), 7.27–7.06 (m, 5H), 7.04–6.94 (m, 2H), 6.82 (m, 1H), 6.76 (s, 1H), 4.76 (d, *J* = 6.1, 1H), 3.86 (s, 1H), 2.72 (s, 1H), 2.65 (s, 3H), 2.30 (s, 1H), 2.11 (d, *J* = 9.9), 1.98 (d, *J* = 1.8, 3H), 1.31–1.24 (m, 2H), 0.88–0.67 (m, 2H). ^{13}C NMR (75 MHz, C_6D_6): δ 177.2, 156.2, 143.1, 142.7, 140.1, 139.8, 139.1, 139.0, 137.8, 137.6, 135.6, 132.5, 131.8, 130.9, 130.4, 130.3, 129.5, 128.9, 126.8, 126.4, 125.8, 112.8, 70.4 (d, *J* = 34.2), 59.2 (d,

J = 9.5), 47.2 (d, J = 7.1), 36.6, 29.8, 28.7, 21.9 (d, J = 24.0), 20.8 (d, J = 20.3). ^{31}P NMR (121 MHz, C_6D_6): δ 23.35. IR (neat, cm^{-1}): 2971, 2869, 1488, 1466, 1445, 1052, 748, 691. MS (EI) m/z (rel. intensity): 469 (M, 31%), 468 (64), 453 (18), 377 (17), 370 (15), 257 (20), 256 (30), 255 (100), 179 (21), 165 (21), 84 (19). HRMS (ESI) m/z = 469.1859, calcd for $C_{29}H_{30}N_2PS$ $[M+H]^+$: 469.1867.

4.6. General procedure for the preparation of iridium complexes 7a–d

Compound **3** (0.5 mmol) was dissolved in CH_2Cl_2 (20 mL) and $[Ir(COD)Cl]_2$ (0.25 mmol) was added. The atmosphere in the flask was evacuated and replenished with N_2 three times. The mixture was heated at reflux for 1 h. After the solution was cooled to rt, distilled H_2O was added. Under vigorous stirring, $NaBAr_F{\cdot}3H_2O$ was added to the biphasic solution in one portion. The mixture was stirred vigorously for 1 h and extracted with CH_2Cl_2 (3 × 10 mL). Combined organic phase was dried over Na_2SO_4. After concentration in vacuum, the residue was purified on silica gel with CH_2Cl_2/pentane (1:1) as the eluent to afford **7** as an orange solid.

4.6.1. Complex 7a

Yield = 84%. $[\alpha]_D^{23} = -35.5$ (c 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.76–7.68 (m, 9H), 7.55–7.27 (m, 13H), 6.87 (s, 1H), 5.00–4.93 (m, 1H), 4.92–4.88 (m, 1H), 4.55–4.44 (m, 1H), 3.95–3.87 (m, 2H), 3.17–3.06 (m, 1H), 3.04–2.98 (m, 1H), 2.52 (s, 3H), 2.49–2.28 (m, 4H), 2.10–1.75 (m, 5H), 1.71–1.46 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.8 (d, J = 10.6), 161.7 (q, J = 49.6), 152.6, 134.8–134.5 (m), 133.8, 132.2–131.9 (m), 132.1, 130.0, 129.6–128.3 (m), 126.9, 126.3, 126.0, 122.8, 119.1, 117.5 (m), 116.8, 96.7 (d, J = 10.9), 87.8 (d, J = 15.0), 67.5 (d, J = 8.4), 66.1, 65.7, 60.5 (d, J = 6.1), 42.3 (d, J = 5.2), 37.5, 36.7, 33.9, 32.3, 28.3, 27.4, 25.6, 18.3. ^{31}P NMR (121 MHz, $CDCl_3$): δ 57.7. IR (neat, cm^{-1}): 1353, 1272, 1166, 1123, 1103. HRMS (ESI) m/z = 679.1899, calcd for $C_{30}H_{35}IrN_2PS$ $[M-BAr_F]^+$: 679.1888.

4.6.2. Complex 7b

Yield = 69%. $[\alpha]_D^{23} = +54.3$ (c 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78–7.68 (m, 10H), 7.63–7.36 (m, 10H), 7.11 (s, 1H), 7.04–6.93 (m, 2H), 5.05–5.00 (m, 1H), 4.69–4.62 (m, 1H), 4.61–4.53 (m, 1H), 3.75–3.66 (m, 2H), 3.54–3.43 (m, 1H), 3.08–3.02 (m, 1H), 2.51–2.28 (m, 2H), 2.22–1.66 (m, 5H), 1.60–1.27 (m, 7H), 1.21 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.7 (d, J = 172.6), 162.1 (q, J = 47.9), 134.8 (m), 133.2, 132.6–132.4 (m), 132.1, 130.9, 130.0, 129.9–128.4 (m), 127.2, 126.4, 122.8, 119.1, 117.9 (m), 116.4, 89.8 (d, J = 6.4), 75.6 (d, J = 20.2), 70.2, 68.6 (d, J = 11.7), 67.8, 59.5 (d, J = 5.0), 42.8 (d, J = 6.1), 38.0, 37.9, 36.4, 35.1, 32.6, 30.5, 27.7, 27.5, 24.3. ^{31}P NMR (121 MHz, $CDCl_3$): δ 50.8. IR (neat, cm^{-1}): 1352, 1274, 1165, 1125, 1079. HRMS (ESI) m/z = 721.2349, calcd for $C_{33}H_{41}IrN_2PS$ $[M-BAr_F]^+$: 721.2357.

4.6.3. Complex 7c

Yield = 60%. $[\alpha]_D^{23} = +8.5$ (c 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82–7.71 (m, 8H), 7.70–7.62 (m, 2H), 7.60–7.40 (m, 12H), 7.35–7.21 (m, 4H), 7.12–7.08 (m, 2H), 5.06–4.98 (m, 1H), 4.75–4.61 (m, 1H), 4.20–4.07 (m, 1H), 3.84–3.73 (m, 1H), 3.55–3.43 (m, 1H), 3.21–3.05 (m, 2H), 2.41–2.26 (m, 1H), 2.22–2.00 (m, 5H), 1.97–1.85 (m, 2H), 1.84–1.73 (m, 1H), 1.68–1.59 (m, 1H), 1.44–1.08 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.9 (d, J = 2.5), 116.7 (q, J = 50.2), 157.9, 134.8, 132.8, 132.5, 132.4, 123.2, 132.1, 130.4, 130.0–129.4 (m), 129.3–128.5 (m), 128.4–128.2 (m), 127.7, 126.4, 126.2, 125.3, 122.8, 119.1, 117.5, 116.5, 95.3 (d, J = 11.0), 89.0 (d, J = 15.3), 68.1 (d, J = 12.6), 66.1, 64.9, 59.8, 42.6 (d, J = 5.46), 38.3, 36.5, 33.9, 30.6, 28.1, 27.5, 25.0. ^{31}P NMR (121 MHz, $CDCl_3$): δ 50.3. IR (neat, cm^{-1}): 1353, 1274, 1158, 1119, 1067. HRMS (ESI) m/z = 741.2042, calcd for $C_{35}H_{37}IrN_2PS$ $[M-BAr_F]^+$: 741.2044.

4.6.4. Complex 7d

Yield = 75%. $[\alpha]_D^{23} = +14.5$ (c 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86–7.70 (m, 9H), 7.62–6.89 (m, 16H), 6.70 (s, 1H), 5.11–5.01 (m, 1H), 4.85–4.78 (m, 1H), 4.77–4.68 (m, 1H), 3.75–3.57 (m, 2H), 3.30 (s, 3H), 3.22–3.10 (m, 1H), 2.87–2.75 (m, 1H), 2.38–2.14 (m, 5H), 2.10–2.05 (m, 1H), 1.99–1.88 (m, 1H), 1.82–1.62 (m, 5H), 1.52–0.98 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.8 (d, J = 2.8), 161.8 (q, J = 51.4), 157.8, 141.8 (d, J = 14.4), 139.5 (q, J = 16.0), 134.8 (m), 132.9, 132.6–132.3 (m), 132.0, 131.2, 130.2, 130.0–128.3 (m), 127.4 (d, J = 7.2), 126.9, 126.5, 126.4, 125.3, 124.5, 122.8, 119.2, 117.5, 116.4, 89.9 (d, J = 6.9), 77.9, 75.6, 67.0 (d, J = 20.9), 64.9, 60.0, 42.4, 38.8, 36.3, 34.6, 29.8, 29.0, 27.8, 24.4 (d, J = 6.5), 24.1, 21.6 (d, J = 7.1). ^{31}P NMR (121 MHz, $CDCl_3$): δ 50.5. IR (neat, cm^{-1}): 1353, 1273, 1161, 1121, 1095. HRMS (ESI) m/z = 769.2343, calcd for $C_{37}H_{41}IrN_2PS$ $[M-BAr_F]^+$: 769.2357.

4.7. General procedure for iridium-catalyzed asymmetric hydro genation of olefins

A vial was charged with substrate (0.25 mmol) and an Ir complex (0.5 mol %). Dry CH_2Cl_2 was added and the vial was placed in a high-pressure hydrogenation apparatus, which was then purged with H_2 three times before H_2 pressure was adjusted to 50 bar. The mixture was stirred at rt overnight. After the pressure was released, solvent was removed under vacuum. Conversion was determined by ^{1}H NMR of the crude product. The residue was filtered through a short plug of silica gel with pentane/diethyl ether (1:1) as the eluent. After the solvent was removed under vacuum, enantiomeric excesses were determined by chiral HPLC or GC.

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References

1. Noyori, R. *Asymmetric Catalysis in Organic synthesis*; Wiley: New York, 1994; (b)*Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vols. 1–3, (c)*Principles and Applications of Asymmetric Synthesis*; Lin, G.-Q., Li, Y.-M., Chan, A. S. C., Eds.; Wiley-Interscience: John Wiley & Sons, 2001.
2. Diesen, J. S.; Andersson, P. G. In *Modern Reduction Methods*; Andersson, P. G., Munslow, I. J., Eds.; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2008; pp 39–86; (b) Noyori, R. *Angew. Chem., Int. Ed.* **2002**, *41*, 2008–2022.
3. (a) Kagan, H. B.; Dang, T. P. *J. Am. Chem. Soc.* **1972**, *94*, 6429–6433; (b) Ikariya, T.; Ishii, Y.; Kawano, H.; Arai, T.; Saburi, M.; Yoshikawa, S.; Akutagawa, S. *J. Chem. Soc., Chem. Commun.* **1985**, 922–924.
4. (a) Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029–3070; (b) Zhang, W.; Chi, Y.; Zhang, X. *Acc. Chem. Res.* **2007**, *40*, 1278–1290.
5. (a) Pfaltz, A.; Blankenstein, J.; Hilgraf, R.; Hörmann, E.; McIntyre, S.; Menges, F.; Schönleber, M.; Smidt, S. P.; Wüstenberg, B.; Zimmermann, N. *Adv. Synth. Catal.* **2003**, *345*, 33–43; (b) Cui, X.; Burgess, K. *Chem. Rev.* **2005**, *105*, 3272–3296; (c) Källström, K.; Munsow, I.; Andersson, P. G. *Chem. Eur. J.* **2006**, *12*, 3194–3200; (d) Roseblade, S. J.; Pfaltz, A. *Acc. Chem. Res.* **2007**, *40*, 1402–1441; (e) Church, T. L.; Andersson, P. G. *Coord. Chem. Rev.* **2008**, *252*, 513–531; (f) Brandt, P.; Hedberg, C.; Andersson, P. G. *Chem. Eur. J.* **2003**, *9*, 339–347.
6. Lightfoot, A.; Pfaltz, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 2897–2899.
7. (a) Blankenstein, J.; Pfaltz, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4445–4447; (b) Bunlaksananurson, T.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 3941–3943; (c) Drury, W. J., III; Zimmermann, N.; Keenan, M.; Hayashi, M.; Kaiser, S.; Goddard, R.; Pfaltz, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 70–74; (d) Cheemala, M. N.; Knochel, P. *Org. Lett.* **2007**, *9*, 3089–3092; (e) Diéguez, M.; Mazuela, J.; Pàmies, O.; Verendel, J. J.; Andersson, P. G. *Chem. Commun.* **2008**, 3888–3890; (f) Diéguez, M.; Mazuela, J.; Pàmies, O.; Verendel, J. J.; Andersson, P. G. *J. Am. Chem. Soc.* **2008**, *130*, 7208–7209; (g) Mazuela, J.; Verendel, J. J.; Coll, M.; Schäffner, B.; Börner, A.; Andersson, P. G.; Pàmies, O.; Diéguez, M. *J. Am. Chem. Soc.* **2009**, *131*, 12344–12353.

8. (a) Källström, K.; Hedberg, C.; Brandt, P.; Bayer, A.; Andersson, P. G. *J. Am. Chem. Soc.* **2004**, *126*, 14308–14309; (b) Hedberg, C.; Källström, K.; Brandt, P.; Hansen, L. K.; Andersson, P. G. *J. Am. Chem. Soc.* **2006**, *128*, 2995–3001; (c) Källström, K.; Andersson, P. G. *Tetrahedron Lett.* **2006**, *47*, 7477–7480; (d) Källström, K.; Munslow, I. J.; Hedberg, C.; Andersson, P. G. *Adv. Synth. Catal.* **2006**, *348*, 2575–2578; (e) Engman, M.; Diesen, J. S.; Paptchikhine, A.; Andersson, P. G. *J. Am. Chem. Soc.* **2007**, *129*, 4536–4537; (f) Verendel, J. J.; Andersson, P. G. *Dalton Trans.* **2007**, 5603–5610; (g) Cheruku, P.; Paptchikhine, A.; Ali, M.; Neudörfl, J.-M.; Andersson, P. G. *Org. Biomol. Chem.* **2008**, *6*, 366–373; (h) Kaukoranta, P.; Engman, M.; Hedberg, C.; Bergquist, J.; Andersson, P. G. *Adv. Synth. Catal.* **2008**, *350*, 1168–1176; (i) Cheruku, P.; Church, T. L.; Trifonova, A.; Wartmann, T.; Andersson, P. G. *Tetrahedron Lett.* **2008**, *49*, 7290–7293; (j) Engman, M.; Cheruku, P.; Tolstoy, P.; Bergquist, J.; Volker, S. F.; Andersson, P. G. *Adv. Synth. Catal.* **2009**, *351*, 375–378; (k) Cheruku, P.; Paptchikhine, A.; Church, T. L.; Andersson, P. G. *J. Am. Chem. Soc.* **2009**, *131*, 8285–8289; (l) Tolstoy, P.; Engman, M.; Paptchikhine, A.; Bergquist, J.; Church, T. L.; Leung, A. W.-M.; Andersson, P. G. *J. Am. Chem. Soc.* **2009**, *131*, 8855–8860.
9. (a) Trifonova, A.; Diesen, J. S.; Chapman, C. J.; Andersson, P. G. *Org. Lett.* **2004**, *6*, 3825–3827; (b) Trifonova, A.; Diesen, J. S.; Andersson, P. G. *Chem. Eur. J.* **2006**, *12*, 2318–2328; (c) Cheruku, P.; Gohil, S.; Andersson, P. G. *Org. Lett.* **2007**, *9*, 1659–1661; (d) Cheruku, P.; Diesen, J.; Andersson, P. G. *J. Am. Chem. Soc.* **2008**, *130*, 5595–5599.
10. Paptchikhine, A.; Cheruku, P.; Engman, M.; Andersson, P. G. *Chem. Commun.* **2009**, 5996–5998.
11. (a) Zhou, Y.-Q. *Acc. Chem. Res.* **2007**, *40*, 1357–1366; (b) Xie, J.-H.; Zhou, Q.-L. *Acc. Chem. Res.* **2008**, *41*, 581–593.
12. Roseblade, S. J.; Pfaltz, A. *C. R. Chimie* **2007**, *10*, 178–187.
13. Brandt, P.; Andersson, P. G. *Synlett* **2000**, 1092–1106.
14. Levene, P. A. *Org. Synth.* **1930**, *10*, 10–11.
15. Ohkuma, T.; Sandoval, C. A.; Srinivasan, R.; Lin, Q.; Wei, Y.; Muniz, K.; Noyori, R. *J. Am. Chem. Soc.* **2005**, *127*, 8288–8289.