Synthesis of Electronically Deficient Atropisomeric Bisphosphine Ligands and Their Application in Asymmetric Hydrogenation of Quinolines

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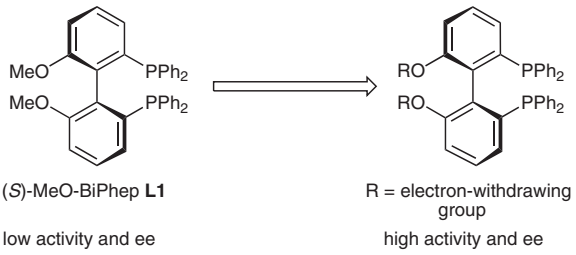
Abstract: A series of electronically deficient atropisomeric bisphosphine ligands have been synthesized from (*S*)-MeO-BiPhep. The introduction of electron-withdrawing groups in the ligands had a dramatic influence on both the enantioselectivity and the activity of catalyst. The iridium complex of the MeO-BiPhep-based ligand bearing a trifluoromethanesulfonyl group was successfully applied in the asymmetric hydrogenation of quinolines with ee values of up to 95% and turnover numbers (TON) of up to 14,600.

Key words: iridium, asymmetric hydrogenation, electron-deficient ligands, quinolines

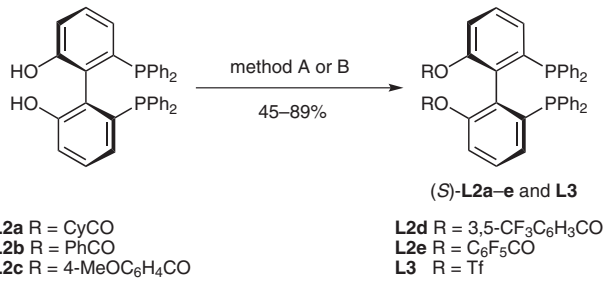
The direct asymmetric hydrogenation of quinoline derivatives provides a convenient route to chiral tetrahydroquinolines, which are useful intermediates and building blocks for the construction of a variety of alkaloids and biologically active compounds.[1] Since our group's pioneering work on the asymmetric hydrogenation of quinolines using the iridium/bisphosphine/iodine catalyst system with high enantioselectivities and yields,[2] exciting advances have been achieved in this field.[3–7] Most effort has focused on developing effective ligands for higher enantioselectivity and catalytic activity, especially the latter. Thus far, several bisphosphine ligands with high catalytic activity have been developed with the iridium-catalyzed system. Fan and co-workers employed BINAP-cored dendrimers as ligands in iridium-catalyzed asymmetric hydrogenation of quinolines with turnover numbers (TON) up to 43,000.[8] The authors proposed that the formation of inactive species was reduced by the encapsulation of the iridium complex into a dendrimer framework and, thus, the activity of the catalyst was enhanced. Very recently, our group also found that the introduction of bulky groups on the coordination phosphorous atoms of P,P- and P,N-ligands could improve the catalytic activity with a substrate-to-catalyst (S/C) ratio of up to 25,000 and ee values up to 93%.[9] For the above work, the steric hindrance of the matrix ligands were modified to improve their activities. Furthermore, the electronic properties of the ligands were also investigated. In 2007, Lemaire and co-workers synthesized several electronically enriched chiral BINAP derivatives and applied them in the iridium-catalyzed asymmetric hydrogenation of quinolines, however, the enantioselectivity and activity were unsatisfactory.[10] Recently, Xu et al. found that air-stable, electronically deficient P-Phos and DifluorPhos showed high activity in the hydrogenation of quinolines with TON up to 43,000.[11]

Encouraged by the above results, we envisioned that the catalytic activity might be improved by introducing electron-withdrawing substituents to the backbone of atropisomeric bisphosphine ligands. Commercially available MeO-BiPhep (**L1**) was thought to be a suitable candidate because of its readily modifiable substituents at the 6- and 6′-positions of the biaryl backbone. Hence, this compound was chosen as the starting material to synthesize electronically deficient atropisomeric bisphosphine ligands (Scheme 1).



Scheme 1 Design of electronically deficient bisphosphine ligands

These ligands were easily obtained through condensation of (*S*)-OH-BiPhep with the corresponding acyl chloride or $PhNTf_2$ (Scheme 2) with 45–89% yields.[12]



Scheme 2 Synthesis of bisphosphine ligands. *Reagents and conditions*: Method A (for **L2a–e**): acyl chloride, *t*-BuOK, CH_2Cl_2; Method B (for **L3**): NaH, $PhNTf_2$, THF.

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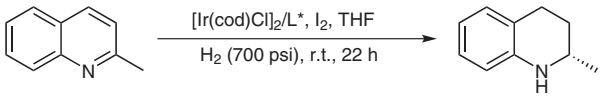
With these electronically deficient ligands in hand, iridium-catalyzed asymmetric hydrogenation of quinolines was investigated. Initially, 2-methylquinoline was chosen as a model substrate and the catalysts were prepared in situ from $[Ir(cod)Cl]_2$ and the ligands in tetrahydrofuran. The hydrogenation reaction was run on a S/C molar ratio of 1000, with molecular iodine (0.5 mol%) as additive; the results are summarized in Table 1. After 22 hours, full conversions were obtained for all ligands. The lowest ee value was obtained (entry 1; 78%) for the matrix ligand MeO-BiPhep (**L1**), which was also lower than that obtained with a catalyst loading of 100 (78 vs 94% ee).[2] Gratifyingly, the enantioselectivity was enhanced dramatically with the introduction of electron-withdrawing ester groups on the ligand (entries 2–7). For the commercially available ligand **L2a**, with a cyclohexanecarbonyl instead of a methyl group, 86% ee was obtained (entry 2). When more electron-withdrawing aroyl groups were introduced, the enantioselectivities were further increased (entries 3–6; 89–91% ee). It is noteworthy that the highest enantioselectivity was achieved for **L3**, with an electron-withdrawing trifluoromethanesulfonyl group (entry 7; 95% ee), which was consistent with our initial expectation. Based on the above results, it was clear that the ligands with electronically deficient substituents showed excellent performance in iridium-catalyzed asymmetric hydrogenation of 2-methylquinoline, with high enantioselectivity and activity being achieved.

Table 1 Asymmetric Hydrogenation of 2-Methylquinoline[a]



1a 2a

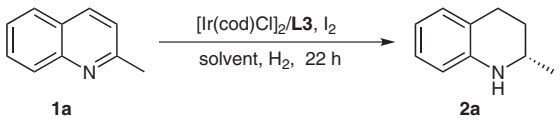
Entry	Ligand	Yield (%)[b]	ee (%)[c]
1	**L1**	98	78 (*S*)
2	**L2a**	98	86 (*S*)
3	**L2b**	99	90 (*S*)
4	**L2c**	98	91 (*S*)
5	**L2d**	98	89 (*S*)
6	**L2e**	98	91 (*S*)
7	**L3**	99	95 (*S*)

[a] Reaction conditions: **1a** (1 mmol), $[Ir(cod)Cl]_2$ (0.0005 mmol), ligand (0.0011 mmol), I_2 (0.0050 mmol), THF (2 mL), r.t., 22 h.
[b] Isolated yield.
[c] Determined by HPLC analysis.

With these promising results in hand, the effect of solvent, amount of iodine, hydrogen pressure, and temperature on the activity and enantioselectivity was further studied using iridium complexes of **L3** as the catalyst; the results are summarized in Table 2. Solvent screening trials indicated that the reaction was strongly solvent-dependent. The use of toluene and benzene gave similar enantioselectivities to those achieved with tetrahydrofuran, but gave lower yields (entries 2 and 3). The use of dichloromethane and 2-propanol resulted in much lower yields and enantioselectivities (entries 4 and 5). Slightly lower yield and enantioselectivity were obtained in ethyl acetate (entry 6). Ethereal solvents were more effective than other solvents (entries 1 and 7), and the highest enantioselectivity was obtained in tetrahydrofuran (entry 1; 95%). Thus, tetrahydrofuran was the best choice in terms of both yield and enantioselectivity.

It was noticed that the catalytic performance was also related to the amount of additive iodine. In the absence of iodine, very low yield and enantioselectivity were observed (entry 11). Increasing the amount of iodine to 1 mol%, or decreasing the amount to 0.25 mol% had no obvious effect on either the yield or enantioselectivity (entries 8 and 9), but the ee value decreased significantly with 0.125 mol% iodine (entry 10). Either reducing the pressure or increasing the temperature gave full conversions but slightly lower enantioselectivities (entries 12 and 13). Thus, the optimized reaction conditions were: $[Ir(cod)Cl]_2$, **L3**, and iodine (0.5 mol%) in tetrahydrofuran under a hydrogen atmosphere (700 psi) at room temperature.

Table 2 Optimization of Reaction Conditions[a]



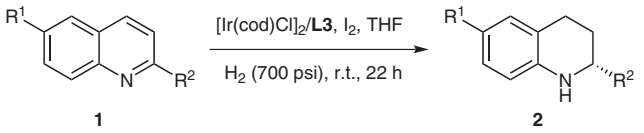
1a 2a

Entry	Solvent	I_2 (mol%)	Yield (%)[b]	ee (%)[c]
1	THF	0.5	99	95 (*S*)
2	toluene	0.5	19	94 (*S*)
3	benzene	0.5	46	93 (*S*)
4	CH_2Cl_2	0.5	10	71 (*S*)
5	*i*-PrOH	0.5	15	41 (*S*)
6	EtOAc	0.5	91	90 (*S*)
7	dioxane	0.5	98	94 (*S*)
8	THF	1.0	98	95 (*S*)
9	THF	0.25	98	94 (*S*)
10	THF	0.125	97	91 (*S*)
11	THF	–	19	6 (*S*)
12[d]	THF	0.5	99	94 (*S*)
13[e]	THF	0.5	99	93 (*S*)

[a] Reaction conditions: **1a** (1 mmol), $[Ir(cod)Cl]_2$ (0.0005 mmol), **L3** (0.0011 mmol), H_2 (700 psi), solvent (2 mL), r.t., 22 h.
[b] Isolated yield.
[c] Determined by HPLC analysis.
[d] H_2 (300 psi), r.t.
[e] H_2 (700 psi), 50 °C.

Having established the optimal conditions, a variety of 2-substituted quinoline derivatives were tested to explore the scope of the reaction. As summarized in Table 3, several 2-alkyl substituted quinolines were hydrogenated with high yields and excellent enantioselectivities, regardless of the length of side chain (entries 1–5; >93% ee). Remarkably, the carbon–carbon double bond in the side chain of the substrate was also hydrogenated (entry 4). Slightly lower enantioselectivity was obtained with hydroxyl groups on the side chain (entry 6). It was noted that excellent yields and good enantioselectivities were also observed for 2-arylethyl substituted quinolines (entries 7 and 8). For substrates possessing a substituent on the 6-position, the yields were also excellent, but slightly lower enantioselectivities were observed (entries 9 and 10). Moreover, it was found that the presence of an electron-withdrawing group at the 6-position of the substrate gave better results than those with an electron-donating substituent (92 versus 87% ee). The yield was also excellent with 2-aryl-substituted quinoline, but the enantioselectivity was only moderate (entry 11).

Table 3 Asymmetric Hydrogenation of Quinoline Derivatives[a]



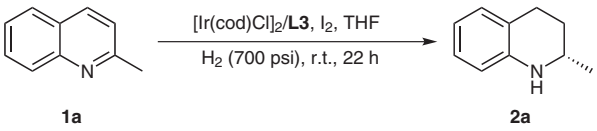
1 2

Entry	R^1	R^2	Product	Yield (%)[b]	ee (%)[c]
1	H	Me	**2a**	99	95 (*S*)
2	H	Et	**2b**	93	95 (*S*)
3	H	*n*-Pr	**2c**	97	94 (*S*)
4	H	3-butenyl	**2d**	95	94 (*S*)
5	H	*n*-pentyl	**2e**	98	94 (*S*)
6	H	$Me_2C(OH)CH_2$-	**2f**	99	87 (*R*)
7	H	3,4-$(MeO)_2C_6H_3(CH_2)_2$-	**2g**	99	93 (*S*)
8	H	3-BnO-4-$MeOC_6H_3(CH_2)_2$-	**2h**	96	93 (*S*)
9	Me	Me	**2i**	96	87 (*S*)
10	F	Me	**2j**	97	92 (*S*)
11	H	Ph	**2k**	95	60 (*R*)

[a] Reaction conditions: **1** (1 mmol), $[Ir(cod)Cl]_2$ (0.0005 mmol), **L3** (0.0011 mmol), I_2 (0.0050 mmol), H_2 (700 psi), THF (2 mL), r.t., 22 h.
[b] Isolated yield.
[c] Determined by HPLC analysis.

To further evaluate the catalytic efficiency of the $[Ir(cod)Cl]_2$, **L3**, and iodine system in asymmetric hydrogenation, the effect of the S/C molar ratio on the conversion and enantioselectivity of this reaction was investigated. 2-Methylquinoline was selected as substrate and the results are shown in Table 4.

Table 4 Effect of S/C Ratio on the Conversion and Enantioselectivity[a]



1a 2a

S/C	1000	5000[d]	10000[d,e]	20000[d,e]
Conv. (%)[b]	>95	>95	>95	73
Ee (%)[c]	95	95	95	95

[a] Reaction conditions: **1a** (1 mmol), $[Ir(cod)Cl]_2$/**L3** (0.5/1.1), I_2 (0.0050 mmol), H_2 (700 psi), THF (2 mL), r.t., 22 h.
[b] Determined by ^1H NMR analysis.
[c] Determined by HPLC analysis.
[d] I_2 (0.0100 mmol) was used.
[e] Reaction time: 36 h.

It was notable that the enantioselectivity remained unchanged (95% ee) when the S/C ratio was increased. When the S/C ratio was raised to 5000:1, the reaction proceeded smoothly with complete conversion. When the S/C ratio was increased to 10000:1, prolonging the reaction time could facilitate the reaction to full conversion. However, when the S/C ratio was increased to 20000:1, the conversion decreased to 73%.

In conclusion, a series of electronically deficient atropisomeric bisphosphine ligands were conveniently synthesized and successfully applied in the asymmetric hydrogenation of quinoline derivatives; up to 95% ee was obtained and TON reached 14,600. More importantly, we have shown that the introduction of electron-withdrawing groups to (*S*)-MeO-BiPhep had a dramatic effect on the enantioselectivity and the activity of catalyst. Our future work will focus on designing other ligands and extending the catalytic system to other hydrogenation reactions.

All reactions were performed under N_2 in dried flasks using Schlenk techniques. Commercially available reagents were used without further purification. Solvents were dried and distilled under N_2 before use. ^1H, ^{13}C and ^{31}P NMR spectra were recorded at r.t. in $CDCl_3$ with a 400 MHz Bruker DRX-400 spectrometer. Enantiomeric excesses were determined by HPLC analysis with an Agilent 1100 instrument fitted with a chiral column as described below. Optical rotations were measured with a JASCO P-1010 polarimeter. All reactions were monitored by TLC analysis. Flash column chromatography was performed on either silica gel (particle size 200–300 mesh) or Al_2O_3 gel (particle size 200–300 mesh).

Bisphosphine Ligands (*S*)-L2a–e; General Procedure A[12a]

Under an N_2 atmosphere, to a solution of (*S*)-OH-BiPhep[4f] (1.0 equiv) in anhydrous CH_2Cl_2 (10 mL), was added *t*-BuOK (2.4 equiv) and the mixture was stirred at r.t. for 30 min. Acyl chloride **a–e** (2.4 equiv) was added and the solution was stirred at r.t. for an additional 2 h. Degassed H_2O (10 mL) was added, the organic layer separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by either recrystallization or column chromatography.

(*S*)-6,6′-Bis(diphenylphosphino)-1,1′-biphenyl-2,2′-diylbis(cyclohexanecarboxylate) (L2a)[13]

Obtained following General Procedure A, with (*S*)-OH-BiPhep (83 mg, 0.15 mmol), *t*-BuOK (40 mg, 0.36 mmol), and cyclohexanecarbonyl chloride **a** (53 mg, 0.36 mmol). The crude product was purified by column chromatography on silica gel (PE–EtOAc, 30:1→25:1) to give compound **L2a**.

Yield: 67 mg (58%); white solid; mp 234–235 °C; R_f = 0.82 (PE–EtOAc, 5:1); $[\alpha]_D^{23}$ –92.2 (*c* 0.67, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.23 (m, 12 H), 7.15–7.23 (m, 6 H), 7.03–7.14 (m, 8 H), 1.77–1.94 (m, 2 H), 1.18–1.69 (m, 10 H), 0.93–1.18 (m, 9 H), 0.74–0.93 (m, 1 H).

(*S*)-6,6′-Bis(diphenylphosphino)-1,1′-biphenyl-2,2′-diylbis(benzenecarboxylate) (L2b)

Obtained following General Procedure A, with (*S*)-OH-BiPhep (110 mg, 0.20 mmol), *t*-BuOK (54 mg, 0.48 mmol), and benzoyl chloride **b** (68 mg, 0.48 mmol). The crude product was purified by recrystallization (CH_2Cl_2–*n*-hexane) to give compound **L2b**.

Yield: 97 mg (64%); white solid; mp 195–196 °C; R_f = 0.64 (PE–EtOAc, 5:1); $[\alpha]_D^{23}$ –38.6 (*c* 0.70, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.53 (m, 6 H), 7.33–7.40 (m, 4 H), 7.10–7.30 (m, 22 H), 7.03 (t, *J* = 7.3 Hz, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.9, 149.4, 149.3, 140.4, 138.4, 138.3, 136.2, 136.1, 134.8, 134.7, 134.6, 133.3, 133.2, 133.1, 131.7, 130.3, 129.6, 129.0, 128.9, 128.5, 128.4, 128.2, 128.1, 123.0.

^{31}P NMR (162 MHz, $CDCl_3$): δ = –15.28 (s).

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{50}H_{36}O_4P_2Na$: 785.1987; found: 785.1988.

(*S*)-6,6′-Bis(diphenylphosphino)-1,1′-biphenyl-2,2′-diylbis(4-methoxybenzenecarboxylate) (L2c)

Obtained following General Procedure A, with (*S*)-OH-BiPhep (110 mg, 0.20 mmol) and *t*-BuOK (54 mg, 0.48 mmol), and 4-methoxybenzoyl chloride **c** (82 mg, 0.48 mmol). The crude product was purified by column chromatography on Al_2O_3 gel (PE–EtOAc, 10:1→5:1) to give **L2c**.

Yield: 74 mg (45%); white solid; mp 161–162 °C; R_f = 0.36 (PE–EtOAc, 5:1); $[\alpha]_D^{23}$ –8.0 (*c* 0.67, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41 (d, *J* = 8.8 Hz, 4 H), 7.35 (d, *J* = 4.4 Hz, 4 H), 7.15–7.31 (m, 16 H), 7.09–7.15 (m, 2 H), 7.05 (t, *J* = 7.4 Hz, 4 H), 6.73 (d, *J* = 8.9 Hz, 4 H), 3.81 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.6, 149.4, 134.8, 134.7, 134.6, 133.3, 133.2, 133.1, 132.4, 131.5, 128.9, 128.4, 128.1, 123.0, 122.1, 113.5, 55.6.

^{31}P NMR (162 MHz, $CDCl_3$): δ = –15.23 (s).

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{52}H_{40}O_6P_2Na$: 845.2198; found: 845.2175.

(*S*)-6,6′-Bis(diphenylphosphino)-1,1′-biphenyl-2,2′-diylbis(3,5-bistrifluoromethylbenzenecarboxylate) (L2d)

Obtained following General Procedure A, with (*S*)-OH-BiPhep (110 mg, 0.20 mmol), *t*-BuOK (54 mg, 0.48 mmol), and 3,5-bis(trifluoromethyl)benzoyl chloride **d** (133 mg, 0.48 mmol). The crude product was purified by column chromatography on silica gel (PE–EtOAc, 50:1→30:1) to give **L2d**.

Yield: 185 mg (89%); white solid; mp 76–77 °C; R_f = 0.82 (PE–EtOAc, 5:1); $[\alpha]_D^{23}$ –11.8 (*c* 0.70, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 (s, 2 H), 7.76 (s, 4 H), 7.37–7.53 (m, 4 H), 7.24–7.34 (m, 12 H), 7.16–7.23 (m, 4 H), 7.08 (t, *J* = 7.4 Hz, 2 H), 6.97 (t, *J* = 7.5 Hz, 4 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 161.2, 148.8, 148.7, 141.4, 141.3, 137.9, 137.8, 137.7, 135.2, 135.1, 135.0, 133.9, 133.7, 133.5, 133.0, 132.9, 132.8, 132.5, 132.2, 132.1, 131.8, 131.6, 131.5, 130.3, 129.5, 129.4, 128.6, 128.5, 128.4, 126.7, 126.6, 124.3, 122.4, 121.6.

^{31}P NMR (162 MHz, $CDCl_3$): δ = –15.00 (s).

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{54}H_{32}F_{12}O_4P_2Na$: 1057.1482; found: 1057.1479.

(*S*)-6,6′-Bis(diphenylphosphino)-1,1′-biphenyl-2,2′-diylbis(2,3,4,5,6-pentafluorobenzenecarboxylate) (L2e)

Obtained following General Procedure A, with (*S*)-OH-BiPhep (110 mg, 0.20 mmol), *t*-BuOK (54 mg, 0.48 mmol), and 2,3,4,5,6-pentafluorobenzoyl chloride **e** (111 mg, 0.48 mmol). The crude product was purified by column chromatography on silica gel (PE–EtOAc, 50:1→30:1) to give **L2e**.

Yield: 157 mg (83%); white solid; mp 68–69 °C; R_f = 0.76 (PE–EtOAc, 5:1); $[\alpha]_D^{23}$ –86.4 (*c* 0.73, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44 (t, *J* = 7.9 Hz, 2 H), 7.19–7.31 (m, 14 H), 7.12–7.19 (m, 6 H), 7.09 (t, *J* = 7.4 Hz, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.7, 148.7, 148.6, 146.8, 146.7, 146.6, 144.9, 144.8, 144.7, 144.3, 144.2, 144.0, 142.4, 142.2, 142.0, 141.3, 141.2, 139.0, 138.8, 138.7, 137.7, 137.6, 136.5, 136.3, 136.2, 136.0, 135.9, 135.2, 135.0, 134.9, 134.8, 134.6, 134.3, 134.1, 133.9, 133.2, 133.1, 133.0, 132.8, 129.5, 128.9, 128.5, 128.3, 128.1, 128.0, 122.8.

^{31}P NMR (162 MHz, $CDCl_3$): δ = –14.84 (s).

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{50}H_{26}F_{10}O_4P_2$: 943.1225; found: 943.1248.

(*S*)-6,6′-Bis(diphenylphosphino)-1,1′-biphenyl-2,2′-diylbis(trifluoromethylsulfonate) (L3)[12b]

To a suspension of NaH (60% in mineral oil, 10 mg, 0.24 mmol) in THF (7 mL) under argon, was carefully added a solution of (*S*)-OH-BiPhep (55 mg, 0.10 mmol) in THF (8 mL) at 0 °C, and the resulting mixture was stirred at r.t. for 30 min. After cooling to 0 °C, $PhNTf_2$ (86 mg, 0.24 mmol) was added and the mixture was stirred at r.t. for an additional 2 h. The mixture was cooled to 0 °C and degassed H_2O (10 mL) was added. The resulting mixture was diluted with CH_2Cl_2 (40 mL) and the organic layer was washed with degassed H_2O (10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (PE–EtOAc, 20:1→10:1) to give **L3**.

Yield: 71 mg (87%); white solid; mp 159–160 °C; R_f = 0.70 (PE–EtOAc, 5:1); $[\alpha]_D^{23}$ +12.2 (*c* 0.97, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44 (t, *J* = 8.0 Hz, 2 H), 7.25–7.36 (m, 8 H), 7.14–7.25 (m, 12 H), 6.98–7.07 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.7, 148.6, 142.5, 142.4, 136.7, 136.6, 136.5, 135.2, 135.1, 134.7, 134.5, 134.4, 134.3, 134.1, 133.7, 133.5, 133.4, 133.3, 133.1, 132.9, 130.7, 129.4, 128.8, 128.6, 120.6, 119.9, 116.7.

^{31}P NMR (162 MHz, $CDCl_3$): δ = –14.47 (s).

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{38}H_{26}F_6O_6P_2S_2Na$: 841.0448; found: 841.0454.

Iridium-Catalyzed Asymmetric Hydrogenation of Quinoline Derivatives: General Procedure B

A mixture of $[Ir(cod)Cl]_2$ (1.0 mg, 0.0015 mmol) and **L3** (2.7 mg, 0.0033 mmol) in THF (3.0 mL) was stirred at r.t. for 10 min in a glovebox. I_2 (1.3 mg, 0.0050 mmol) and substrate (1.0 mmol) in THF (1.0 mL) were placed in a stainless steel autoclave and the catalyst solution (1.0 mL) was added by using a syringe. The hydrogenation was performed at r.t. under H_2 (700 psi) for 22 h. After

carefully releasing the hydrogen, the reaction mixture was concentrated to afford the crude product. Purification was performed by silica gel column chromatography (PE–EtOAc) to give the pure product. The enantiomeric excesses were determined by chiral HPLC with chiral columns (OJ-H, OD-H, or AS-H).

(*S*)-2-Methyl-1,2,3,4-tetrahydroquinoline (2a)[2]
Yield: 99%; yellow oil; 95% ee; $[\alpha]_D^{22}$ –82.8 (*c* 0.87, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.95–7.04 (m, 2 H), 6.59–6.70 (m, 1 H), 6.45–6.56 (m, 1 H), 3.68 (br, 1 H), 3.29–3.51 (m, 1 H), 2.82–2.94 (m, 1 H), 2.70–2.84 (m, 1 H), 1.91–2.01 (t, *J* = 12.3 Hz, 1 H), 1.54–1.69 (t, *J* = 21.4 Hz, 1 H), 1.24 (dd, *J* = 6.2, 3.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.0, 129.4, 126.9, 121.3, 117.1, 114.2, 47.3, 30.3, 26.8, 22.8.

HPLC (OJ-H; *n*-hexane–*i*-PrOH, 95:5; 254 nm; 0.8 mL/min): t_R = 13.8 [(*S*) major], 15.4 [(*R*) minor] min.

(*S*)-2-Ethyl-1,2,3,4-tetrahydroquinoline (2b)[2]
Yield: 93%; yellow oil; 95% ee; $[\alpha]_D^{23}$ –83.1 (*c* 1.00, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.00 (t, *J* = 7.2 Hz, 2 H), 6.63 (t, *J* = 7.3 Hz, 1 H), 6.51 (d, *J* = 8.0 Hz, 1 H), 3.80 (br, 1 H), 3.13–3.26 (m, 1 H), 2.66–2.96 (m, 2 H), 1.90–2.13 (m, 1 H), 1.47–1.76 (m, 3 H), 1.03 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.9, 129.4, 126.9, 121.6, 117.0, 114.2, 53.2, 29.6, 27.8, 26.6, 10.2.

HPLC (OJ-H; *n*-hexane–*i*-PrOH, 90:10; 254 nm; 0.8 mL/min): t_R = 9.8 [(*S*) major], 10.8 [(*R*) minor] min.

(*S*)-2-Propyl-1,2,3,4-tetrahydroquinoline (2c)[2]
Yield: 97%; yellow oil; 94% ee; $[\alpha]_D^{23}$ –72.6 (*c* 0.70, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.00 (t, *J* = 7.2 Hz, 2 H), 6.63 (t, *J* = 7.3 Hz, 1 H), 6.50 (d, *J* = 8.4 Hz, 1 H), 3.78 (br, 1 H), 3.23–3.33 (m, 1 H), 2.58–2.99 (m, 2 H), 1.94–2.04 (m, 1 H), 1.57–1.70 (m, 1 H), 1.38–1.56 (m, 4 H), 0.89–1.12 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.9, 129.4, 126.9, 121.5, 117.0, 114.2, 51.5, 39.1, 28.3, 26.6, 19.1, 14.4.

HPLC (OJ-H; *n*-hexane–*i*-PrOH, 90:10; 254 nm; 0.8 mL/min): t_R = 9.1 [(*S*) major], 11.2 [(*R*) minor] min.

(*S*)-2-Butyl-1,2,3,4-tetrahydroquinoline (2d)[2]
Yield: 95%; yellow oil; 94% ee; $[\alpha]_D^{22}$ –82.8 (*c* 1.07, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.97 (t, *J* = 7.3 Hz, 2 H), 6.61 (t, *J* = 7.3 Hz, 1 H), 6.49 (d, *J* = 8.2 Hz, 1 H), 3.78 (br, 1 H), 3.12–3.43 (m, 1 H), 2.61–2.99 (m, 2 H), 1.88–2.12 (m, 1 H), 1.56–1.68 (m, 1 H), 1.46–1.55 (m, 2 H), 1.26–1.45 (m, 4 H), 0.92–0.99 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.9, 129.4, 126.9, 121.6, 117.1, 114.2, 51.8, 36.6, 28.3, 28.1, 26.6, 23.0, 14.3.

HPLC (OJ-H; *n*-hexane–*i*-PrOH, 90:10; 254 nm; 0.8 mL/min): t_R = 8.1 [(*S*) major], 9.3 [(*R*) minor] min.

(*S*)-2-Pentyl-1,2,3,4-tetrahydroquinoline (2e)[2]
Yield: 98%; yellow oil; 94% ee; $[\alpha]_D^{23}$ –75.1 (*c* 0.73, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.00 (t, *J* = 7.5 Hz, 2 H), 6.65 (t, *J* = 7.4 Hz, 1 H), 6.57 (d, *J* = 7.8 Hz, 1 H), 4.26 (br, 1 H), 3.23–3.33 (m, 1 H), 2.71–2.89 (m, 2 H), 1.90–2.05 (m, 1 H), 1.24–1.72 (m, 9 H), 0.94 (t, *J* = 6.7 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.2, 129.5, 126.9, 122.0, 117.7, 114.7, 52.0, 36.6, 32.1, 28.1, 26.5, 25.6, 22.8, 14.3.

HPLC (OJ-H; *n*-hexane–*i*-PrOH, 90:10; 254 nm; 0.8 mL/min): t_R = 7.4 [(*S*) major], 8.0 [(*R*) minor] min.

(*R*)-2-Methyl-1-(1,2,3,4-tetrahydroquinolin-2-yl)propan-2-ol (2f)[2]
Yield: 99%; white solid; 87% ee; $[\alpha]_D^{23}$ –52.0 (*c* 0.70, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.96 (t, *J* = 7.7 Hz, 2 H), 6.59 (t, *J* = 7.3 Hz, 1 H), 6.49 (d, *J* = 7.9 Hz, 1 H), 3.51–3.63 (m, 1 H), 2.82–2.95 (m, 1 H), 2.67–2.79 (m, 1 H), 1.80–1.90 (m, 1 H), 1.55–1.77 (m, 3 H), 1.32 (d, *J* = 5.2 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.8, 129.4, 126.9, 121.1, 116.9, 114.6, 72.2, 49.0, 48.6, 33.0, 30.0, 28.0, 26.8.

HPLC (OD-H; *n*-hexane–*i*-PrOH, 90:10; 254 nm; 0.8 mL/min): t_R = 8.1 [(*S*) minor], 9.4 [(*R*) major] min.

(*S*)-2-(3′,4′-Dimethoxyphenethyl)-1,2,3,4-tetrahydroquinoline (2g)[2]
Yield: 99%; yellow oil; 93% ee; $[\alpha]_D^{23}$ –75.3 (*c* 0.73, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.93–7.02 (m, 2 H), 6.80–6.84 (m, 1 H), 6.73–6.79 (m, 2 H), 6.62 (t, *J* = 7.3 Hz, 1 H), 6.46 (d, *J* = 8.1 Hz, 1 H), 3.89 (s, 3 H), 3.88 (s, 3 H), 3.79 (br, 1 H), 3.29–3.35 (m, 1 H), 2.74–2.89 (m, 2 H), 2.66–2.74 (m, 2 H), 1.95–2.06 (m, 1 H), 1.77–1.88 (m, 2 H), 1.61–1.76 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.1, 147.4, 144.7, 134.6, 129.4, 126.9, 121.5, 120.3, 117.2, 114.3, 111.8, 111.4, 56.1, 56.0, 51.4, 38.6, 32.0, 28.2, 26.4.

HPLC (AS-H; *n*-hexane–*i*-PrOH, 95:5; 254 nm; 0.8 mL/min): t_R = 14.5 [(*R*) minor], 15.4 [(*S*) major] min.

(*S*)-2-(3′-Benzyloxy-4′-methoxyphenethyl)-1,2,3,4-tetrahydroquinoline (2h)[4b]
Yield: 96%; yellow oil; 93% ee; $[\alpha]_D^{23}$ –49.2 (*c* 0.80, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.47 (m, 2 H), 7.33–7.39 (m, 2 H), 7.27–7.32 (m, 1 H), 6.92–7.00 (m, 2 H), 6.83 (d, *J* = 8.5 Hz, 1 H), 6.73–6.79 (m, 2 H), 6.60 (t, *J* = 7.2 Hz, 1 H), 6.44 (d, *J* = 7.8 Hz, 1 H), 5.15 (s, 2 H), 3.88 (s, 3 H), 3.71 (br, 1 H), 3.14–3.28 (m, 1 H), 2.67–2.84 (m, 2 H), 2.60–2.67 (m, 2 H), 1.89–2.00 (m, 1 H), 1.71–1.80 (m, 2 H), 1.53–1.70 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.2, 148.1, 144.6, 137.3, 134.4, 129.3, 128.6, 127.9, 127.4, 126.8, 121.3, 121.0, 117.1, 114.7, 114.2, 112.1, 71.1, 56.2, 51.0, 38.3, 31.7, 28.0, 26.3.

HPLC (AS-H; *n*-hexane–*i*-PrOH, 97:3; 254 nm; 0.5 mL/min): t_R = 30.1 [(*R*) minor], 32.2 [(*S*) major] min.

(*S*)-2,6-Dimethyl-1,2,3,4-tetrahydroquinoline (2i)[2]
Yield: 96%; yellow solid; 87% ee; $[\alpha]_D^{22}$ –68.1 (*c* 0.73, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.79–6.81 (m, 2 H), 6.43 (d, *J* = 7.9 Hz, 1 H), 3.58 (br, 1 H), 3.32–3.43 (m, 1 H), 2.78–2.90 (m, 1 H), 2.66–2.76 (m, 1 H), 2.23 (s, 3 H), 1.88–1.98 (m, 1 H), 1.53–1.66 (m, 1 H), 1.22 (d, *J* = 6.3 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.6, 130.0, 127.4, 126.4, 121.4, 114.4, 47.5, 30.5, 26.8, 22.8, 20.6.

HPLC (OJ-H; *n*-hexane–*i*-PrOH, 90:10; 254 nm; 0.8 mL/min): t_R = 13.5 [(*S*) major], 16.7 [(*R*) minor] min.

(*S*)-6-Fluoro-2-methyl-1,2,3,4-tetrahydroquinoline (2j)[2]
Yield: 97%; yellow solid; 92% ee; $[\alpha]_D^{23}$ –80.7 (*c* 0.73, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.65–6.72 (m, 2 H), 6.36–6.44 (m, 1 H), 3.57 (br, 1 H), 3.30–3.40 (m, 1 H), 2.77–2.90 (m, 1 H), 2.66–2.75 (m, 1 H), 1.89–1.97 (m, 1 H), 1.51–1.63 (m, 1 H), 1.21 (d, *J* = 6.3 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.8, 154.5, 141.2, 122.7, 122.6, 115.7, 115.5, 114.9, 114.8, 113.4, 113.2, 47.5, 30.1, 26.9, 22.7.

HPLC (OD-H; *n*-hexane–*i*-PrOH, 95:5; 254 nm; 0.8 mL/min): t_R = 6.8 [(*R*) minor], 8.1 [(*S*) major] min.

(*R*)-2-Phenyl-1,2,3,4-tetrahydroquinoline (2k)[6a]
Yield: 95%; yellow solid; 60% ee; $[\alpha]_D^{23}$ +19.1 (*c* 1.00, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28–7.49 (m, 5 H), 6.97–7.10 (m, 2 H), 6.69 (t, *J* = 7.3 Hz, 1 H), 6.57 (d, *J* = 7.9 Hz, 1 H), 4.47 (dd, *J* = 9.3, 2.9 Hz, 1 H), 4.06 (br, 1 H), 2.89–3.02 (m, 1 H), 2.71–2.84 (m, 1 H), 2.10–2.22 (m, 1 H), 1.96–2.09 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.0, 144.9, 129.5, 128.8, 127.6, 127.1, 126.7, 121.0, 117.3, 114.1, 56.4, 31.2, 26.6.

HPLC (AS-H; *n*-hexane–*i*-PrOH, 95:5; 254 nm; 0.8 mL/min): t_R = 7.1 [(*R*) major], 21.5 [(*S*) minor] min.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals /toc/synthesis.

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