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Iridium-Catalyzed Asymmetric Hydrogenation of 3-Substituted 2*H*-1,4-Benzoxazines

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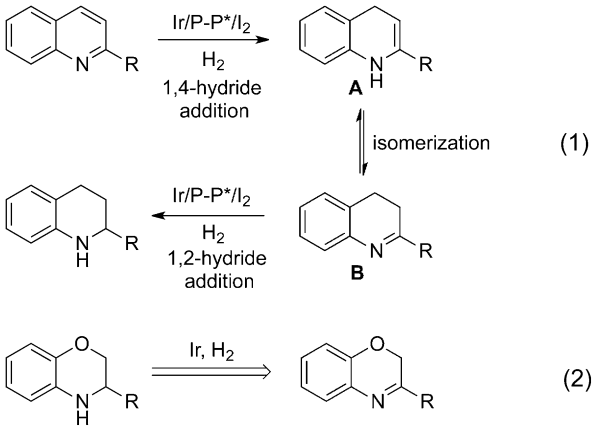
Abstract: The highly enantioselective hydrogenation of 3-aryl-2*H*-1,4-benzoxazines was achieved using the (cyclooctadiene)iridium chloride dimer/(*S*)-SegPhos/iodine {$[Ir(COD)Cl]_2$/(*S*)-SegPhos/I_2} system as catalyst with up to 92% *ee*. The 3-styryl-2*H*-1,4-benzoxazine derivatives were also hydrogenated by the iridium catalyst and Pd/C in two consecutive steps whereby 93–95% *ee* values were obtained.

Keywords: asymmetric hydrogenation; benzoxazines; chiral amines; cyclic imines; iridium

Introduction

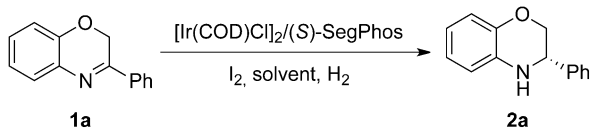
The synthesis of chiral amines is very important both in academic and pharmaceutical research and industry.[1] Although great progress has been made in the transition metal-catalyzed asymmetric hydrogenation of imines,[2–5] the continuing demand for chiral amines is urgent. 3-Substituted-3,4-dihydro-2*H*-1,4-benzoxazines represent the structural motifs of many chiral drugs, and are also employed as building blocks for the synthesis of some natural products,[6,7] therefore, their synthesis has attracted much attention in recent years. Examples including the Ru-BINAP-catalyzed hydrogenation of acetol as key intermediate for the synthesis of levofloxacin,[8a] as well as the Rh/MeDuphos-catalyzed asymmetric hydrogenation of exocyclic enamides have been reported by our group.[9] In 2006, Rueping and co-workers developed a highly enantioselective reduction of 3-aryl-2*H*-1,4-benzoxazines catalyzed by chiral Brønsted acids using a Hantzsch dihydropyridine as hydrogen source.[10a] However, few reports have been concerned with the direct asymmetric hydrogenation of cyclic imines to obtain these important compounds.[11b]

In 2009, our group disclosed the mechanism of the Ir-catalyzed asymmetric hydrogenation of quinolines in the presence of I_2, which was a cascade reaction involving 1,4-hydride addition to form enamine intermediate **A**, then isomerization to cyclic imine **B**, and finally 1,2-hydride addition to obtain the tetrahydroquinoline product [Scheme 1, Eq. (1)].[12h,13h,i] Due to the similarity in the structures of benzoxazine and the imine intermediate **B**, we envisioned that the direct asymmetric hydrogenation of benzoxazines would be an appropriate access to the chiral cyclic amines by using the Ir/diphosphine/I_2 catalyst system developed by us [Scheme 1, Eq. (2)]. Herein, we present our findings on the Ir-catalyzed enantioselective hydrogenation of 3-substituted 2*H*-1,4-benzoxazines.



Scheme 1. Mechanism for the iridium-catalyzed asymmetric hydrogenation of quinolines.

Table 1. Asymmetric hydrogenation of 3-phenyl-2*H*-1,4-benzoxazine (**1a**).[a]



1a **2a**

Entry	Solvent	Conversion [%][b]	*ee* [%][c,d]
1	CH_2Cl_2	>95	80 (*S*)
2	$CHCl_3$	>95	79 (*S*)
3	EtOAc	>95	77 (*S*)
4	MeOH	>95	60 (*S*)
5	THF	>95	75 (*S*)
6	1,4-dioxane	>95	80 (*S*)
7	toluene	>95	85 (*S*)
8	benzene	>95	87 (*S*)

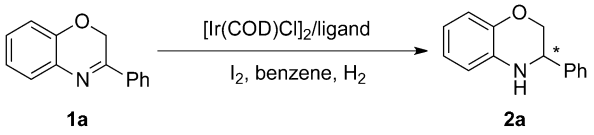
[a] *Reaction conditions*: $[Ir(COD)Cl]_2$ (1 mol%), (*S*)-SegPhos (2.2 mol%), I_2 (10 mol%), 3 mL solvent, H_2 (600 psi), room temperature, 15 h.
[b] Conversions were determined by ^1H NMR analysis of the crude products.
[c] Determined by HPLC analysis with chiral OD-H column.
[d] The absolute configuration of **2a** was assigned by comparison of the observed optical rotation with reported data.

Results and Discussion

Based on our previous work,[12] the hydrogenation of 3-phenyl-2*H*-1,4-benzoxazine (**1a**) was initially performed in CH_2Cl_2 under 600 psi of H_2 at room temperature in the presence of 1 mol% iridium catalyst generated *in situ* from $[Ir(COD)Cl]_2$, (*S*)-SegPhos and additive I_2. To our delight, the reaction ran smoothly and with moderate enantioselectivity (80% *ee*, Table 1, entry 1). Encouraged by this result, the effect of solvents was investigated as shown in Table 1. Full conversions were achieved for all solvents (Table 1, entries 2–8), and benzene was the best choice in terms of conversion and enantioselectivity (87% *ee*, Table 1, entry 8).

Subsequently, some commercially available chiral ligands were screened (Figure 1, Table 2). The reaction with WalPhos ligand gave full conversion, but moderate *ee* was obtained (Table 2, entry 2). Me-DuPhos and PHOX ligands gave both low reactivity and poor enantioselectivity (Table 2, entries 3 and 4). SynPhos and its analogues such as C4-TunPhos and MeO-BiPhep exhibited good enantioselectivities

Table 2. Screening of ligands for the hydrogenation of 3-phenyl-2*H*-1,4-benzoxazine (**1a**).[a]



1a **2a**

Entry	Ligand	Conversion [%][b]	*ee* [%][c]
1	(*S*)-SegPhos	>95	87 (*S*)
2	(R,R_p)-WalPhos	>95	56 (*S*)
3	(*R*,*R*)-Me-DuPhos	45	4 (*S*)
4	(*S*)-*i*Pr-PHOX	32	38 (*R*)
5	(*R*)-SynPhos	>95	85 (*R*)
6	(*R*)-C4-TunePhos	>95	77 (*R*)
7	(*R*)-MeO-BiPhep	>95	81 (*R*)
8	(*S*)-BINAP	>95	16 (*S*)
9	(*R*)-DTBM-SegPhos	>95	31 (*R*)
10	(*S*)-MeO-MOP	70	6 (*S*)
11[d]	(*S*)-SegPhos	>95	88 (*S*)

[a] *Reaction conditions*: $[Ir(COD)Cl]_2$ (1 mol%), ligand (2.2 mol%), I_2 (10 mol%), 3 mL benzene, H_2 (600 psi), room temperature, 15 h.
[b] Conversions were determined by ^1H NMR analysis of the crude products.
[c] Determined by HPLC analysis with a chiral OD-H column.
[d] Run under 400 psi of H_2.

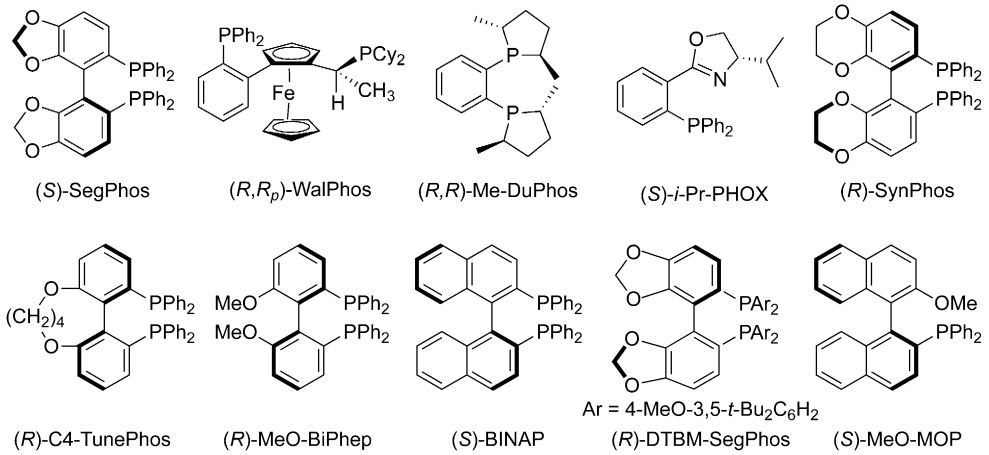
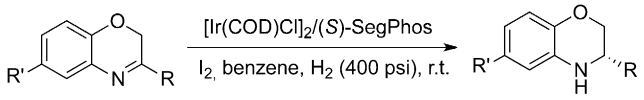


Figure 1. Structures of the examined chiral phosphine ligands.

Table 3. Asymmetric hydrogenation of 3-aryl-2*H*-1,4-benzoxazines **1**.[a]



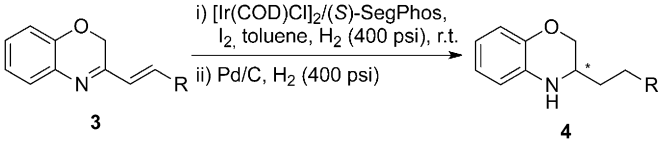
Entry	R′/R	Yield [%][b]	*ee* [%][c,d]
1	H/Ph (**1a**)	91 (**2a**)	88 (*S*)
2	H/3-Me-C_6H_4 (**1b**)	95 (**2b**)	85 (*S*)
3	H/3-MeO-C_6H_4 (**1c**)	97 (**2c**)	87 (*S*)
4	H/4-Me-C_6H_4 (**1d**)	91 (**2d**)	86 (*S*)
5	H/4-C_6H_5-C_6H_4 (**1e**)	98 (**2e**)	85 (*S*)
6	H/2-F-C_6H_4 (**1f**)	93 (**2f**)	84 (*S*)
7	H/3-F-C_6H_4 (**1g**)	95 (**2g**)	85 (*S*)
8	H/4-F-C_6H_4 (**1h**)	96 (**2h**)	88 (*S*)
9	H/3-Cl-C_6H_4 (**1i**)	98 (**2i**)	88 (*S*)
10	H/4-Cl-C_6H_4 (**1j**)	97 (**2j**)	90 (*S*)
11	H/3-Br-C_6H_4 (**1k**)	96 (**2k**)	88 (*S*)
12	H/4-Br-C_6H_4 (**1l**)	96 (**2l**)	89 (*S*)
13	H/4-CF_3-C_6H_4 (**1m**)	98 (**2m**)	89 (*S*)
14	H/3,4-Cl_2-C_6H_3 (**1n**)	97 (**2n**)	92 (*S*)
15	*t*-Bu/Ph (**1o**)	93 (**2o**)	79 (*S*)

[a] *Reaction conditions*: $[Ir(COD)Cl]_2$ (1 mol%), (*S*)-SegPhos (2.2 mol%), I_2 (10 mol%), 3 mL benzene, H_2 (400 psi), room temperature, 15 h.
[b] Isolated yields.
[c] Determined by HPLC analysis with chiral column.
[d] The absolute configuration of **2a** was assigned by comparison of the observed optical rotation with the reported data. The absolute configurations of the other products were deduced by analogy to **2a**.

(Table 2, entries 5–7), while, BINAP showed lower *ee* (Table 2, entry 8). Although the sterically demanding DTBM-SegPhos provided high *ee*s in the asymmetric hydrogenation of quinolines,[14] low enantiocontrol was observed for benzoxazines (Table 2, entry 9). The monodentate ligand MeO-MOP was also tested and yielded poor results (Table 2, entry 10). Eventually, (*S*)-SegPhos gave the highest *ee* (87% *ee*, Table 2, entry 1). On lowering the hydrogen pressure, the enantioselectivity increased slightly (88% *ee*, Table 2, entry 11). Thus, the optimal conditions were established as: $[Ir(COD)Cl]_2$/(*S*)-SegPhos/I_2/benzene/H_2 (400 psi).

With the optimized conditions in hand, a variety of benzoxazines was evaluated to examine the substrate scope. As shown in Table 3, all the 3-aryl substituted benzoxazines were completely converted to the corresponding amines with high enantioselectivities regardless of the position and electronic effects of substituents R on the benzene ring (84–92% *ee*s, Table 3, entries 1–14). The substrate with a *tert*-butyl group at the 6-position revealed a negative effect the on enantioselectivity which may be ascribed to steric effects (Table 3, entry 15).

Table 4. Hydrogenation of 3-styryl-2*H*-1,4-benzoxazine derivatives **3**.[a]



Entry	R	Yield [%][b]	*ee* [%][c]
1	Ph (**3a**)	80 (**4a**)	94 (–)
2	4-Me-C_6H_4 (**3b**)	73 (**4b**)	93 (–)
3	4-F-C_6H_4 (**3c**)	77 (**4c**)	94 (–)
4	4-Cl-C_6H_4 (**3d**)	71 (**4d**)	95 (–)
5	4-CF_3- C_6H_4 (**3e**)	66 (**4e**)	95 (–)

[a] *Reaction conditions*: i) $[Ir(COD)Cl]_2$ (1 mol%), (*S*)-SegPhos (2.2 mol%), I_2 (2 mol%), 3 mL toluene, H_2 (400 psi), room temperature, 15 h; ii) Pd/C, H_2 (400 psi), THF, room temperature.
[b] Isolated yields.
[c] Determined by HPLC analysis with a chiral column.

After establishing the successful asymmetric hydrogenation of 3-aryl-substituted benzoxazines, we applied this catalyst system to hydrogenate the interesting 3-styryl-2*H*-1,4-benzoxazine derivatives (Table 4). The reaction gave full conversions, but with mixtures of partially and completely hydrogenated products. For example, for the hydrogenation of 3-styryl-2*H*-1,4-benzoxazine (**3a**), the ratio of the corresponding products was 1:4 (determined by NMR). Next, we tried to optimize the ratio of hydrogenation products by varying the solvents, hydrogen pressure and reaction time, however, the results were unsatisfactory. Therefore, Pd/C was added after the completion of the iridium hydrogenation to reduce the remaining C=C bond of the partially hydrogenated product. Fortunately, high yields (66–80%) and excellent *ee* values (93–95%) were achieved for the hydrogenation of 3-styryl-2*H*-1,4-benzoxazine derivatives. Substrates with both electron-donating and electron-withdrawing substituents on the phenyl group can be tolerated (Table 4).

Conclusions

In summary, the asymmetric hydrogenation of 3-aryl-2*H*-1,4-benzoxazines utilizing the $[Ir(COD)Cl]_2$/(*S*)-SegPhos/I_2 catalyst system was achieved with up to 92% *ee*. Furthermore, the intriguing 3-styryl-2*H*-1,4-benzoxazine derivatives were also hydrogenated by iridium catalyst and Pd/C in two consecutive steps whereby 93–95% *ee* values were obtained. This method provides an atom economical access to pharmaceutically relevant chiral amines. Further work will be directed to the asymmetric hydrogenation of other heterocyclic compounds.

Experimental Section

General Remarks

All reactions were carried out under an atmosphere of nitrogen using standard Schlenk techniques, unless otherwise noted. ^{1}H NMR and ^{13}C NMR spectra were recorded at room temperature in $CDCl_3$ on a 400 MHz instrument with tetramethylsilane (TMS) as internal standard. Enantiomeric excesses were determined by HPLC analysis. Optical rotations were measured by a polarimeter. Flash column chromatography was performed on silica gel (200–300 mesh). All reactions were monitored by TLC analysis. 3-Substituted 2*H*-1,4-benzoxazines were synthesized according to the literature procedure.[15]

General Procedure for the Synthesis of 3-Substituted 2*H*-1,4-Benzoxazines

To a round-bottom flask were added the appropriate 2-aminophenol (3 mmol) and CH_2Cl_2 (20 mL), then 20% aqueous K_2CO_3 solution (20 mL) and $(n\text{-Bu})_4NHSO_4$ (1 mg) was added. The substituted 2-bromoacetophenone or (*E*)-1-bromo-4-phenylbut-3-en-2-one (3 mmol) was dissolved in 5 mL CH_2Cl_2 and added dropwise to the reaction mixture which was then stirred at room temperature and monitored by TLC. After the consumption of the starting materials, the organic layer was washed with water (30 mL) and brine (20 mL), then dried by anhydrous Na_2SO_4. The solvent was removed under vacuum and the crude product was purified by column chromatography using petroleum ether and EtOAc as eluent to obtain the corresponding benzoxazines.

3-(3-Methylphenyl)-2*H*-1,4-benzoxazine (1b): yield: 86%; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.42$ (s, 3H), 5.04 (s, 2H), 6.90 (d, $J = 8.0$ Hz, 1H), 7.01 (t, $J = 7.5$ Hz, 1H), 7.13 (t, $J = 7.6$ Hz, 1H), 7.38–7.26 (m, 2H), 7.43 (d, $J = 7.7$ Hz, 1H), 7.65 (d, $J = 7.6$ Hz, 1H), 7.77 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 21.7$, 63.2, 115.7, 122.5, 123.8, 127.2, 128.0, 128.7, 128.8, 132.2, 135.6, 138.7, 146.6, 159.1; HR-MS: $m/z =$ 224.1081, calculated for $C_{15}H_{14}NO$ $[M+H]^+$: 224.1075.

General Procedure for Asymmetric Hydrogenation of 1

In a nitrogen-filled glovebox, a mixture of $[Ir(COD)Cl]_2$ (1.7 mg, 0.0025 mmol) and (*S*)-SegPhos (3.4 mg, 0.0055 mmol) was stirred in benzene (1 mL) at room temperature for 5 min, then I_2 (6.4 mg, 0.025 mmol) was added. The mixture stirred for another 5 min and then the imine substrate (0.25 mmol) together with 2 mL benzene were added. The resulting solution was transferred from the glovebox to an autoclave. Then the autoclave was charged with 400 psi of H_2. The hydrogenation was performed at room temperature for 15 h. After carefully releasing the hydrogen gas, the reaction mixture was concentrated to afford the crude product which was purified by silica gel column with petroleum ether and EtOAc as eluent to furnish the corresponding hydrogenation product. The enantiomeric excesses were determined by chiral HPLC with chiral columns (OD-H or AD-H).

3-Phenyl-3,4-dihydro-2*H*-1,4-benzoxazine (2a): known compound;[10a] yield: 91%; 88% *ee*; $[\alpha]_D^{r.t.}$: +102.0 (*c* 1.08, $CHCl_3$), {Lit. $[\alpha]_D^{r.t.}$: −118.1 (*c* 1.0, $CHCl_3$) for 98% *ee* of (*R*)-enantiomer};[10a] ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.98$–4.03 (m, 2H), 4.27–4.31 (m, 1H), 4.52 (dd, $J = 8.5$, 3.0 Hz, 1H), 6.67–6.73 (m, 2H), 6.80–6.87 (m, 2H), 7.33–7.43 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 54.4$, 71.2, 115.6, 116.8, 119.1, 121.7, 127.4, 128.5, 129.0, 134.1, 139.3, 143.7; HPLC (OD-H, eluent: hexanes/*i*-PrOH = 70/30, detector: 254 nm, flow rate: 0.7 mL min^{-1}): $t_1 = 10.6$ min (minor), $t_2 = 13.9$ min (major).

General Procedure for Hydrogenation of 3

In a nitrogen-filled glovebox, a mixture of $[Ir(COD)Cl]_2$ (1.7 mg, 0.0025 mmol) and (*S*)-SegPhos (3.4 mg, 0.0055 mmol) was stirred in toluene (1 mL) at room temperature for 5 min, then I_2 (1.3 mg, 0.005 mmol) was added. The mixture was stirred for another 5 min and then imine substrate (0.25 mmol) together with 2 mL toluene were added. The resulting solution was transferred from the glovebox to an autoclave. Then the autoclave was charged with 400 psi of H_2. The hydrogenation was performed at room temperature for 15 h. After carefully releasing the hydrogen gas, the solvent was removed under vacuum, then the Pd/C reduction was conducted in THF to hydrogenate the remaining C=C bond of the partially hydrogenated product. After that, the reaction mixture was concentrated and the residue was purified by column chromatography to furnish the corresponding hydrogenation product, which was then analyzed by chiral HPLC on a column (OJ-H) to determine the enantiomeric excess.

3-Phenethyl-3,4-dihydro-2*H*-1,4-benzoxazine (4a): yield: 80%; 94% *ee*; $[\alpha]_D^{r.t.}$: −18.8 (*c* 1.20, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.82$–1.88 (m, 2H), 2.78 (dd, $J = 8.7$, 1.9 Hz, 2H), 3.41–3.44 (m, 1H), 3.71 (br, 1H), 3.92 (dd, $J = 10.5$, 7.3 Hz, 1H), 4.23 (dd, $J = 10.5$, 2.7 Hz, 1H), 6.58 (dd, $J = 7.7$, 1.4 Hz, 1H), 6.67 (td, $J = 7.7$, 1.5 Hz, 1H), 6.79–6.82 (m, 2H), 7.24 (t, $J = 7.1$ Hz, 3H), 7.31–7.35 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 32.1$, 34.0, 49.4, 69.4, 115.7, 116.7, 118.9, 121.6, 126.4, 128.5, 128.8, 133.4, 141.3, 144.0; HPLC (OJ-H, eluent: hexanes/*i*-PrOH = 60/40, detector: 254 nm, flow rate: 0.8 mL min^{-1}), $t_1 = 18.5$ min (major), $t_2 =$ 21.1 min (minor); HR-MS: $m/z = 262.1206$, calculated for $C_{16}H_{17}NONa$ $[M+Na]^+$: 262.1208.

Acknowledgements

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References

[1] a) D.-W. Wang, Y.-G. Zhou, Q.-A. Chen, D.-S. Wang, in: *Chiral Amine Synthesis: Methods, Developments and Applications*, 1st edn., (Ed.: T. C. Nugent), Wiley-VCH, Weinheim, **2010**, pp 299–339; b) T. Ohkuma, M. Kitamura, R. Noyori, in: *Catalytical Asymmetric Synthesis*, 2nd edn., (Ed.: I. Ojima), Wiley, New York, **2000**, pp 410–421; c) H.-U. Blaser, C. Malan, B. Pugin, F. Spindler, H. Steiner, M. Studer, *Adv. Synth. Catal.*

2003, *345*, 1031; d) S. Kobayashi, H. Ishitani, *Chem. Rev.* **1999**, *99*, 1069.

[2] For reviews, see: a) W. Tang, X. Zhang, *Chem. Rev.* **2003**, *103*, 3029; b) N. Fleury-Brégeot, V. de La Fuente, S. Castillón, C. Claver, *ChemCatChem* **2010**, *2*, 1346; c) J.-H. Xie, S.-F. Zhu, Q.-L. Zhou, *Chem. Rev.* **2011**, *111*, 1713.

[3] a) C. A. Willoughby, S. L. Buchwald, *J. Am. Chem. Soc.* **1994**, *116*, 8952; b) J. Campora, S. L. Buchwald, E. Gutierrez-Puebla, A. Monge, *Organometallics* **1995**, *14*, 2039; c) M. Ringwald, R. Sturmer, H. H. Brintzinger, *J. Am. Chem. Soc.* **1999**, *121*, 1524; d) H. B. Kagan, N. Langlois, T. P. Dang, *J. Organomet. Chem.* **1975**, *90*, 353; e) M. J. Burk, J. E. Feaster, *J. Am. Chem. Soc.* **1992**, *114*, 6266; f) V. I. Tararov, R. Kadyrov, T. H. Riermeier, C. Fischer, A. Börner, *Adv. Synth. Catal.* **2004**, *346*, 561; g) G. Shang, Q. Yang, X. Zhang, *Angew. Chem.* **2006**, *118*, 6508; *Angew. Chem. Int. Ed.* **2006**, *45*, 6360; h) C. Q. Li, J. L. Xiao, *J. Am. Chem. Soc.* **2008**, *130*, 13208; i) C. Botteghi, M. Bianchi, E. Benedetti, U. Matteoli, *Chimia* **1975**, *29*, 256; j) W. Oppolzer, M. Wills, C. Starkemann, G. Bernardinelli, *Tetrahedron Lett.* **1990**, *31*, 4117; k) J. C. Cobley, J. P. Henschke, *Adv. Synth. Catal.* **2003**, *345*, 195; l) J. C. Cobley, E. Foucher, J.-P. Lecouve, I. C. Lennon, J. A. Ramsden, G. Thominot, *Tetrahedron: Asymmetry* **2003**, *14*, 3431; m) P. Cheruku, T. L. Church, P. G. Andersson, *Chem. Asian J.* **2008**, *3*, 1390; n) F. Chen, T. Wang, Y. He, Z. Ding, Z. Li, L. Xu, Q.-H. Fan, *Chem. Eur. J.* **2011**, *17*, 1109; o) F. Chen, Z. Ding, J. Qin, T. Wang, Y. He, Q.-H. Fan, *Org. Lett.* **2011**, *13*, 4348.

[4] a) Y.-Q. Wang, Y.-G. Zhou, *Synlett* **2006**, 1189; b) Q. Yang, G. Shang, W. Gao, J. Deng, X. Zhang, *Angew. Chem.* **2006**, *118*, 3916; *Angew. Chem. Int. Ed.* **2006**, *45*, 3832; c) Y.-Q. Wang, S.-M. Lu, Y.-G. Zhou, *J. Org. Chem.* **2007**, *72*, 3729; d) C.-B. Yu, D.-W. Wang, Y.-G. Zhou, *J. Org. Chem.* **2009**, *74*, 5633; e) M.-W. Chen, Y. Duan, Q.-A. Chen, D.-S. Wang, C.-B. Yu, Y.-G. Zhou, *Org. Lett.* **2010**, *12*, 507; f) C.-B. Yu, K. Gao, D.-S. Wang, L. Shi, Y.-G. Zhou, *Chem. Commun.* **2011**, *47*, 5052.

[5] Selected examples for Ir-catalyzed asymmetric hydrogenation of imines, see: a) Y. N. C. Chan, J. A. Osborn, *J. Am. Chem. Soc.* **1990**, *112*, 9400; b) P. Schbider, G. Koch, R. Prétôt, G. Wang, F. M. Bohnen, C. Krüger, A. Pfaltz, *Chem. Eur. J.* **1997**, *3*, 887; c) D. Xiao, X. Zhang, *Angew. Chem.* **2001**, *113*, 3533; *Angew. Chem. Int. Ed.* **2001**, *40*, 3425; d) B. Pugin, H. Landert, F. Spindler, H.-U. Blaser, *Adv. Synth. Catal.* **2002**, *344*, 974; e) C. Moessner, C. Bolm, *Angew. Chem.* **2005**, *117*, 7736; *Angew. Chem. Int. Ed.* **2005**, *44*, 7564; f) A. Trifonova, J. S. Diesen, P. G. Andersson, *Chem. Eur. J.* **2006**, *12*, 2318; g) S.-F. Zhu, J.-B. Xie, Y.-Z. Zhang, S. Li, Q.-L. Zhou, *J. Am. Chem. Soc.* **2006**, *128*, 12886; h) T. Imamoto, N. Iwadate, K. Yoshida, *Org. Lett.* **2006**, *8*, 2289; i) M. N. Cheemala, P. Knochel, *Org. Lett.* **2007**, *9*, 3089; j) M. T. Reetz, O. Bondarev, *Angew. Chem.* **2007**, *119*, 4607; *Angew. Chem. Int. Ed.* **2007**, *46*, 4523; k) C. Li, C. Wang, B. Villa-Marcos, J. Xiao, *J. Am. Chem. Soc.* **2008**, *130*, 14450; l) Z. Han, Z. Wang, X. Zhang, K. Ding, *Angew. Chem.* **2009**, *121*, 5449; *Angew. Chem. Int. Ed.* **2009**, *48*, 5345; m) N. Mršić, A. J. Minnaard, B. L. Feringa, J. G. de Vries, *J. Am. Chem. Soc.* **2009**, *131*, 8358; n) M. Chang, W. Li, G. Hou, X. Zhang, *Adv. Synth. Catal.* **2010**, *352*, 3121; o) K. Kutlescha, T. Irrgang, R. Kempe, *Adv. Synth. Catal.* **2010**, *352*, 3126; p) K. Gao, C.-B. Yu, W. Li, Y.-G. Zhou, X. Zhang, *Chem. Commun.* **2011**, *47*, 7845.

[6] a) K. S. Brown, C. Djerassi, *J. Am. Chem. Soc.* **1964**, *86*, 2451; b) S. D. McAllister, G. Rizvi, S. Anavi-Goffer, D. P. Hurst, J. Barnett-Norris, D. L. Lynch, P. H. Reggio, M. E. Abood, *J. Med. Chem.* **2003**, *46*, 5139; c) J. IIas, P. S. Anderluh, M. S. Dolene, D. Kikelj, *Tetrahedron* **2005**, *61*, 7325; d) A. Belattar, J. E. Saxton, *J. Chem. Soc. Perkin Trans. 1* **1992**, 679; e) J. Y. Shim, E. R. Collantes, W. J. Welsh, *J. Med. Chem.* **1998**, *41*, 4521; f) S. Daiichi, *Drugs Future* **1992**, *17*, 559.

[7] a) V. P. Krasnov, G. L. Levit, I. M. Bukrina, I. N. Andreeva, L. S. Sadretdinova, M. A. Korolyova, M. I. Kodess, V. N. Charushin, O. N. Chupakhin, *Tetrahedron*: *Asymmetry* **2003**, *14*, 1985; b) V. N. Charushin, V. P. Krasnov, G. L. Levit, M. A. Korolyova, M. I. Kodess, O. N. Chupakhin, M. H. Kim, H. S. Lee, Y. J. Park, K. C. Kim, *Tetrahedron*: *Asymmetry* **1999**, *10*, 2691; c) V. P. Krasnov, G. L. Levit, M. I. Kodess, V. N. Charushin, O. N. Chupakhin, *Tetrahedron*: *Asymmetry* **2004**, *15*, 859; d) V. A. Potemkin, V. P. Krasnov, G. L. Levit, E. V. Bartashevich, I. N. Andreeva, M. B. Kuzminsky, N. A. Anikin, V. N. Charushin, O. N. Chupakhin, *Mendeleev Commun.* **2004**, *14*, 69.

[8] a) R. Noyori, *Acta Chem. Scand.* **1996**, *50*, 380; b) A. Miyadera, A. Imura, *Tetrahedron*: *Asymmetry* **1999**, *10*, 119; c) K. Sakano, S. Yokohama, I. Hayakawa, S. Atarashi, S. Kadoya, *Agric. Biol. Chem.* **1987**, *51*, 1265; d) M. Imamura, I. Hayakawa, *Chem. Pharm. Bull.* **1987**, *35*, 1896; e) R. Noyori, T. Ohkuma, *Angew. Chem.* **2001**, *113*, 40; *Angew. Chem. Int. Ed.* **2001**, *40*, 40.

[9] Y.-G. Zhou, P.-Y. Yang, X.-W. Han, *J. Org. Chem.* **2005**, *70*, 1679–1683.

[10] a) M. Rueping, A. P. Antonchick, T. Theissmann, *Angew. Chem.* **2006**, *118*, 6903; *Angew. Chem. Int. Ed.* **2006**, *45*, 6751; b) R. I. Storer, D. E. Carrera, Y. Ni, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2006**, *128*, 84; c) M. Rueping, F. Tato, F. R. Schoepke, *Chem. Eur. J.* **2010**, *16*, 2688; d) M. Rueping, E. Sugiono, F. R. Schoepke, *Synlett* **2010**, 852; e) M. Rueping, E. Sugiono, A. Steck, T. Theissmann, *Adv. Synth. Catal.* **2010**, *352*, 281; f) M. Rueping, E. Merino, R. M. Koenigs, *Adv. Synth. Catal.* 2010, **352**, 2629; g) A. V. Malkov, K. Vranková, S. Stončius, P. Kočovský, *J. Org. Chem.* **2009**, *74*, 5839; h) M. Rueping, M. Stoeckel, E. Sugiono, T. Theissmann, *Tetrahedron* **2010**, *66*, 6565; i) Z.-Y. Xue, Y. Jiang, X.-Z. Peng, W.-C. Yuan, X.-M. Zhang, *Adv. Synth. Catal.* **2010**, *352*, 2132; j) M. Rueping, C. Brinkmann, A. P. Antonchick, L. Atodiresei, *Org. Lett.* **2010**, *12*, 4604; k) Z.-Y. Xue, Y. Jiang, W.-C. Yuan, X.-M. Zhang, *Eur. J. Org. Chem.* **2010**, 616.

[11] a) S. Atarashi, H. Tsurumi, T. Fujiwara, I. Hayakawa, *J. Heterocycl. Chem.* **1991**, *28*, 329; b) K. Satoh, M. Inenaga, K. Kanai, *Tetrahedron: Asymmetry* **1998**, *9*, 2657; c) L. Xie, *J. Chin. Chem. Lett.* **1995**, *6*, 857; d) J. Adrio, J. C. Carretero, J. L. G. Ruano, A. Pallarés, M. Vicioso, *Heterocycles* **1999**, *51*, 1563.

[12] For our group's work on the asymmetric reduction of quinolines, see: a) W.-B. Wang, S.-M. Lu, P.-Y. Yang, X.-W. Han, Y.-G. Zhou, *J. Am. Chem. Soc.* **2003**, *125*, 10536; b) S.-M. Lu, X.-W. Han, Y.-G. Zhou, *Adv. Synth. Catal.* **2004**, *346*, 909; c) Y.-J. Zhao, Y.-Q. Wang, Y.-G. Zhou, *Chin. J. Catal.* **2005**, *26*, 737; d) S.-M. Lu, Y.-Q. Wang, X.-W. Han, Y.-G. Zhou, *Angew. Chem.* **2006**, *118*, 2318; *Angew. Chem. Int. Ed.* **2006**, *45*, 2260; e) D.-W. Wang, W. Zeng, Y.-G. Zhou, *Tetrahedron: Asymmetry* **2007**, *18*, 1103; f) Y.-G. Zhou, *Acc. Chem. Res.* **2007**, *40*, 1357; g) X.-B. Wang, Y.-G. Zhou, *J. Org. Chem.* **2008**, *73*, 5640; h) D.-W. Wang, X.-B. Wang, D.-S. Wang, S.-M. Lu, Y.-G. Zhou, Y.-X. Li, *J. Org. Chem.* **2009**, *74*, 2780; i) D.-W. Wang, D.-S. Wang, Q.-A. Chen, Y.-G. Zhou, *Chem. Eur. J.* **2010**, *16*, 1133; j) D.-S. Wang, Y.-G. Zhou, *Tetrahedron Lett.* **2010**, *51*, 3014.

[13] Recent examples on asymmetric hydrogenation of quinolines by other groups, see: a) H. Zhou, Z. Li, Z. Wang, T. Wang, L. Xu, Y. He, Q.-H. Fan, J. Pan, L. Gu, A. S. C. Chan, *Angew. Chem.* **2008**, *120*, 8592; *Angew. Chem. Int. Ed.* **2008**, *47*, 8464; b) N. Mršić, L. Lefort, J. A. F. Boogers, A. J. Minnaard, B. L. Feringa, J. G. de Vries, *Adv. Synth. Catal.* **2008**, *350*, 1081; c) H. Tadaoka, D. Cartigny, T. Nagano, T. Gosavi, T. Ayad, J.-P. Genêt, T. Oshima, V. Ratovelomanana-Vidal, K. Mashima, *Chem. Eur. J.* **2009**, *15*, 9990; d) S.-M. Lu, C. Bolm, *Adv. Synth. Catal.* **2008**, *350*, 1101; e) Z. Li, T. Wang, Y. He, Z. Wang, Q.-H. Fan, J. Pan, L.-J. Xu, *Org. Lett.* **2008**, *10*, 5265; f) M. T. Reetz, X. Li, *Chem. Commun.* **2006**, *42*, 2159; g) J. L. Núñez-Rico, H. Fernández-Pérez, J. Benet-Buchholz, A. Vidal-Ferran, *Organometallics* **2010**, *29*, 6627; h) G. E. Dobereiner, A. Nova, N. D. Schley, N. Hazari, S. J. Miller, O. Eisenstein, R. H. Crabtree, *J. Am. Chem. Soc.* **2011**, *133*, 7547; i) T. Wang, L.-G. Zhuo, Z. Li, F. Chen, Z. Ding, Y. He, Q.-H. Fan, J. Xiang, Z.-X. Yu, A. S. C. Chan, *J. Am. Chem. Soc.* **2011**, *133*, 9878.

[14] D.-S. Wang, J. Zhou, D.-W. Wang, Y.-L. Guo, Y.-G. Zhou, *Tetrahedron Lett.* **2010**, *51*, 525.

[15] a) G. Sabitha, A. V. S. Rao, *Synth. Commun.* **1987**, *17*, 341; b) M. Ju Young, J. H. Ahn, H. M. Kim, N. M. Yoon, K. W. Kim, J. H. Kang, S. J. Lee, *J. Heterocycl. Chem.* **2002**, *39*, 1065; c) Y. Ma, Y. Zhang, *J. Chem. Res.* **2000**, 388; d) C. Banzatti, F. Heidempergher, P. Melloni, *J. Heterocycl. Chem.* **1983**, *20*, 259.

