DOI: 10.1002/chem.200903418

Iridium-Catalyzed Asymmetric Hydrogenation of Imines

Alejandro Baeza and Andreas Pfaltz*[a]

Abstract: We have evaluated a wide range of iridium complexes derived from chiral oxazoline-based N,P ligands for the asymmetric hydrogenation of imines and identified three efficient catalysts. These catalysts are readily synthesized by straightforward convenient routes and are air and moisture stable. In the reduction of acetophenone N-arylimines and related acyclic substrates, excellent enantioselectivities (up to 96% *ee*) were obtained by using 0.1–0.5 mol% of catalyst at −20°C and 5–50 bar hydrogen pressure.

Keywords: asymmetric catalysis · asymmetric hydrogenation · imines · iridium · N,P ligands

Introduction

Chiral amines occur as structural elements in many biologically active natural and unnatural products. They are also of importance as chiral auxiliaries, catalysts, and resolving agents. Consequently, the asymmetric hydrogenation of imines has found much attention as a direct, atom-economical route to optically active amines. During the last two decades, various highly enantioselective chiral catalysts have been reported for this transformation, many of them based on iridium (see Scheme 1).[1–19] The potential for industrial application is demonstrated by the well-known process for the multiton-scale production of the herbicide (*S*)-metolachlor from an imine precursor.[12] The catalyst used in this process, an iridium–Josiphos complex (Scheme 1, structure **IX)**, stands out for its extremely high activity and efficiency with a turnover number exceeding one million. However, most other catalysts are much less active and require relatively high loadings compared with the standards reached in asymmetric hydrogenations of olefins and ketones. An additional problem is the generally narrow application range. Therefore, the search for new catalysts for the asymmetric hydrogenation of imines remains an important area of research.

In 1997 we reported that cationic iridium–PHOX complexes (Scheme 1, structure **I**) are efficient catalysts for the asymmetric hydrogenation of N-arylimines.[4] In the reduction of acetophenone *N*-phenylimine, up to 89% ee was achieved by using 0.1 mol% catalyst at 5°C. Subsequently, many different iridium catalysts with chiral N,P ligands were developed in other laboratories (see Scheme 1).[5–15] The success we had with modified PHOX and related oxazoline-based N,P ligands in the asymmetric hydrogenation of olefins,[20] including enamines,[21] prompted us to reinvestigate imine hydrogenations with a wide range of Ir–N,P ligand complexes that have been developed in our group during the last 10 years. Herein we report the results of this study, in which we identified several readily accessible, highly efficient catalysts for the asymmetric reduction of acyclic N-arylimines.

Results and Discussion

Initial experiments were performed on the imine **1a**, which results from the condensation of aniline and acetophenone. The reaction was carried out under 5 bar hydrogen pressure for 4 h, with 1 mol% iridium–N,P ligand catalyst in a range of solvents. The catalysts chosen were Ir–PHOX complex **3a** and Ir–ThrePHOX complex **4a**; the latter is commercially available (Table 1).[22] The best enantioselectivities were obtained with the Ir–PHOX complex **3a**. Among the solvents tested, CH_2Cl_2 and toluene (Table 1, entries 1–4) gave the best results. Although both solvents worked equally well, dichloromethane was selected as the solvent of choice because the catalysts were more soluble in this medium. *tert*-Butyl methyl ether (TBME)[7] gave lower enantioselectivities (Table 1, entries 5 and 6), and MeOH or MeOH/toluene mixtures, which gave excellent results for this reaction with other iridium complexes,[8] led to a dramatic drop in both

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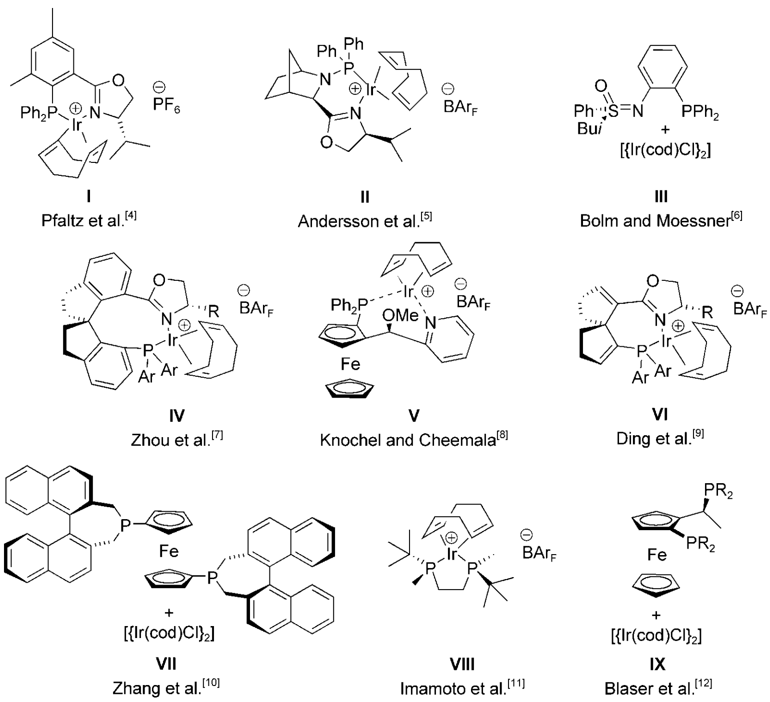
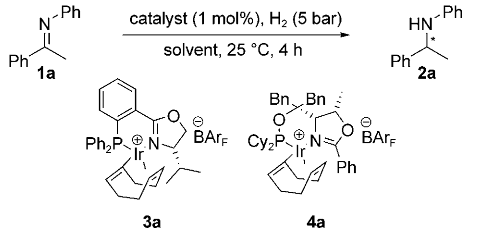
[a] Dr. A. Baeza, Prof. A. Pfaltz
Department of Chemistry, University of Basel
St. Johanns Ring 19, 4056 Basel (Switzerland)
Fax: (+41) 61-267-1103
E-mail: andreas.pfaltz@unibas.ch



Scheme 1. Selected examples of catalysts successfully applied in the asymmetric hydrogenation of imines. COD = 1,5-cyclooctadiene, BAr_F = tetrakis[3,5-bis(trifluoromethyl)phenyl]borate.

Table 1. Solvent influence in the catalytic hydrogenation of imines.



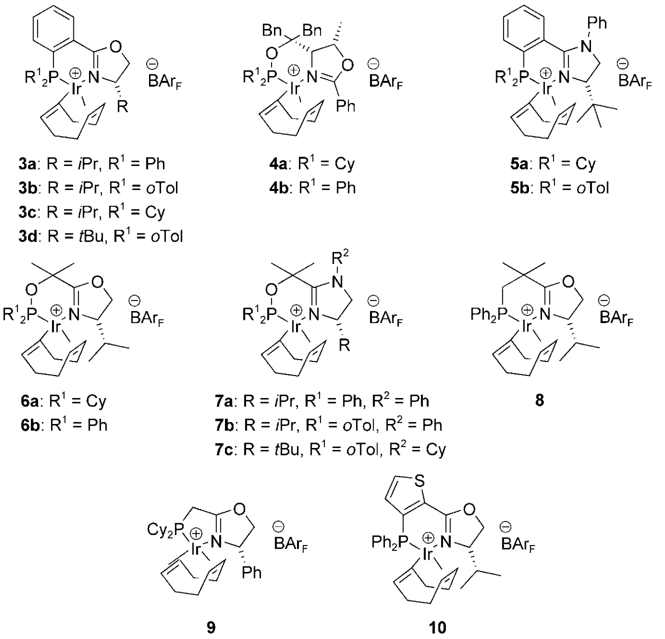
Entry	Catalyst	Solvent	Conv. [%][a]	*ee* [%][b]
1	**3a**	CH_2Cl_2	>99	85
2	**4a**	CH_2Cl_2	>99	67
3	**3a**	$PhCH_3$	>99	85
4	**4a**	$PhCH_3$	>99	67
5	**3a**	TBME[c]	>99	72
6	**4a**	TBME[c]	>99	69
7	**3a**	MeOH	5	44
8	**3a**	$PhCH_3$/MeOH (4/1)	10	30

[a] Determined by GC analysis of the reaction mixture after removal of the catalyst (see the Experimental Section for details). [b] Determined by chiral HPLC analysis using a Daicel Chiralcel OD-H column (see the Experimental Section for details). [c] *tert*-Butyl methyl ether.

conversion and enantioselectivity (Table 1, entries 7 and 8). The use of additives, such as iodine[6,10] or phthalimide,[23] often employed in these reactions, was also tested but gave poor results.

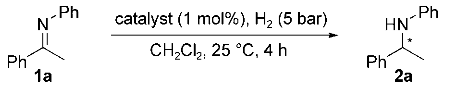
Subsequently, a series of different catalysts was screened under standard conditions in CH_2Cl_2 at 5 bar hydrogen pressure (Scheme 2 and Table 2). In general, we used BAr_F salts in this study rather than hexafluorophosphates, as in our previous work.[4] In the hydrogenation of unfunctionalized olefins, much larger turnover numbers are achieved when BAr_F instead of hexafluorophosphate salts are employed and, consequently, BAr_F salts have become the catalysts of choice.[24] The positive effect of BAr_F is much less pronounced in the hydrogenation of imines. Preliminary tests showed only a slightly higher rate and no difference in *ee* value for the BAr_F salt **3c** relative to the corresponding hexafluorophosphate. However, the BAr_F salts have the advantage that they are more soluble in apolar media. In addition, they are less moisture sensitive and easier to handle and, therefore, were chosen as standard catalysts.

Ir–PHOX complexes **3a–c** all reacted with full conversion and enantioselectivities of 82–85 % *ee* (Table 2, entries 1–3). In contrast, the sterically more demanding catalyst **3d** with a *tert*-butyl group in the oxazoline ring and a bis(*ortho*-tolyl)-substituted P atom (Table 2, entry 4) gave only 90 % conversion and a lower *ee* value. This is in line with previous work, which had shown



Scheme 2. Catalysts employed in the screening of asymmetric hydrogenation of imines.

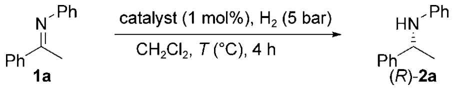
Table 2. Asymmetric hydrogenation of imines: Catalyst screening.



Entry	Catalyst	Conv. [%][a]	*ee* [%][b]
1	**3a**	>99	85
2	**3b**	>99	82
3	**3c**	>99	84
4	**3d**	90	72
5	**4a**	>99	67
6	**4b**	>99	63
7	**5a**	90	79
8	**5b**	5	60
9	**6a**	>99	88
10	**6b**	>99	74
11	**7a**	>99	82
12	**7b**	>99	89
13	**7c**	5	5
14	**8**	>99	85
15	**9**	80	60
16	**10**	>99	83

[a] Determined by GC analysis of the reaction mixture after removal of the catalyst (see the Experimental Section for details). [b] Determined by chiral HPLC analysis using a Daicel Chiralcel OD-H column (see the Experimental Section for details).

Table 3. Asymmetric hydrogenation of imines: Variation of the temperature.



Entry	Catalyst	*T* [°C]	Conv. [%][a]	*ee* [%][b]
1	**3a**	0	>99	90
2	**6a**	0	>99	92
3	**7b**	0	>99	92
4	**8**	0	>99	90
5	**3a**	−20	95	93
6	**6a**	−20	>99	95.5
7	**7b**	−20	80	95.5
8	**8**	−20	>99	94
9	**3a**	−40[c]	10	94
10	**6a**	−40[c]	80	97
11	**3a**	40	>99	84
12	**6a**	40	>99	86

[a] Determined by GC analysis of the reaction mixture after removal of the catalyst (see the Experimental Section for details). [b] Determined by chiral HPLC analysis using a Daicel Chiralcel OD-H column (see the Experimental Section for details). [c] 6 h reaction time.

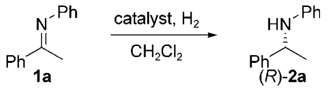
that large substituents at these positions led to lower reactivity and enantioselectivity. As expected, other complexes with a *tert*-butyl group at the stereogenic center, such as the phosphanyl–imidazoline complexes **5a**, **5b**, and **7c**, also gave unsatisfactory results (Table 2, entries 7, 8, 13). Ir–ThrePHOX complexes **4a** and **4b** gave full conversion, but only moderate enantioselectivity (Table 2, entries 5 and 6). Very promising results (full conversion and 88% *ee*) were achieved with the Ir–SimplePHOX complex **6a**, with an electron-rich dicyclohexyl-substituted P atom, whereas the corresponding diphenylphosphanyl derivative **6b** gave only 74% *ee* (Table 2, entries 9 and 10). The imidazoline analogues **7a** and **7b**, the recently developed NeoPHOX complex **8**,[25] and catalyst **10**[26] with a thiophene backbone also performed well, with *ee* values between 82 and 89% (Table 2, entries 11, 12, 14, 16). Complex **9**, on the other hand, which is an excellent catalyst for the hydrogenation of tetrasubstituted olefins,[27] gave poor results.

Overall, complexes with an isopropyl group at the stereogenic center showed the best performance irrespective of the ligand backbone. On the other hand, no clear trends emerged for the substituents on the P atom. Based on these results, the most promising catalysts **3a**, **6a**, **7b**, and **8** were selected for further optimization of the reaction conditions.

We first studied the influence of the reaction temperature (Table 3). At 0 °C (Table 3, entries 1–4), full conversion and a considerable improvement in enantioselectivity was achieved in all cases (*ee* values were around 4–5% higher than at room temperature). When the temperature was decreased to −20 °C, the enantioselectivity increased even further (Table 3, entries 5–8). However, catalysts **3a** and **7b** gave only 95 and 80% conversion, respectively, under these conditions (Table 3, entries 5 and 7). The reaction was also carried out at −40 °C with complexes **3a** and **6a** (Table 3, entries 9 and 10), but in both cases the reaction did not go to completion, even when the reaction time was increased to 6 h, and only a slight improvement in enantioselectivity was observed. However, these results demonstrated that catalyst **6a** is more active than **3a**. At 40 °C, almost the same *ee* values were obtained as those at room temperature (Table 3, entries 11 and 12, compare with Table 2, entries 1 and 9).

We next studied the effects of catalyst loading and hydrogen pressure (Table 4). At 0.5 mol% catalyst loading and 5 bar hydrogen pressure at 0 °C, full conversion and the same *ee* value as with 1 mol% catalyst was achieved by using complex **3a**. By using the same catalyst loading and pressure, the more reactive complex **8** gave 98% conversion

Table 4. Asymmetric hydrogenation of imines: Optimization of reaction conditions.



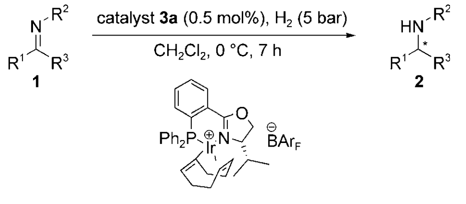
Entry	Catalyst ([mol%])	*T* [°C]	H_2 pressure [bar]	*t* [h]	Conv. [%][a]	*ee* [%][b]
1	**3a** (0.5)	0	5	7	>99	90
2	**6a** (0.5)	−20	5	8	67	95.5
3	**7b** (0.5)	0	5	7	88	92
4	**8** (0.5)	−20	5	8	98	94
5	**3a** (0.5)	−20	10	6	25	93
6	**6a** (0.5)	−20	10	6	>99	95.5
7	**7b** (0.5)	−20	10	6	54	95
8	**6a** (0.1)	−20	50	6	94	96
9	**8** (0.1)	−20	50	6	>99	94

[a] Determined by GC analysis of the reaction mixture after removal of the catalyst (see the Experimental Section for details). [b] Determined by chiral HPLC analysis using a Daicel Chiralcel OD-H column (see the Experimental Section for details).

and 94 % *ee* at −20 °C (Table 4, entry 4). With 0.5 mol % of complex **6a**, the hydrogen pressure had to be increased to 10 bar, to achieve full conversion at −20 °C (Table 4, entry 6). Complex **7b** gave unsatisfactory conversion at −20 and 0 °C and 0.5 mol % catalyst loading (Table 4, entry 7). Excellent enantioselectivities were also obtained when the reaction was performed by using 0.1 mol % of the most active catalysts **6a** and **8** at −20 °C, although 50 bar of hydrogen pressure was needed to reach high conversion (Table 4, entries 8 and 9). In conclusion, the influence of the catalyst loading and hydrogen pressure on the enantioselectivity seems to be negligible. Based on these results, the substrate scope of catalysts **3a**, **6a**, and **8** was evaluated under the optimized conditions.

Hydrogenations with complex **3a** were carried out with 0.5 mol % catalyst loading at 0 °C and 5 bar hydrogen pressure (Table 5). Introduction of a 4-chloro or 4-methoxy substituent in the N-aryl group of the acetophenone imine had no significant influence on the enantioselectivity and conversion (Table 5, entries 1–3). *N*-phenylimines of 4-chloro- and 4-methoxyacetophenone also gave essentially the same *ee* value and conversion as the unsubstituted imine **1a** (Table 5, entries 4 and 5). The *N*-phenylimine of ethyl phenyl ketone, on the other hand, reacted with lower enantioselectivity but full conversion (79 % *ee*, Table 5, entry 7, compared with 90 % *ee* for **1a**; Table 4, entry 1). A possible explanation[2] for the lower *ee* value in this case could be the lower *E*/*Z* ratio of the starting imine (*E*/*Z* 91:9) compared with **1a**, which (according to ^{1}H NMR spectroscopic analysis) exists in solution as pure *E* isomer. Hydrogenation of *N*-benzylimine **1f** proved to be slower, resulting in low conversion and only 74 % *ee* (Table 5, entry 6). The low reactivity of this substrate is likely to be due to the higher basicity of the hydrogenation product **2f**, which is expected to coordinate more strongly to the iridium catalyst than the less basic analogous phenylamine **2a**. It is known that coordinating species deactivate the catalyst.[4]

Table 5. Asymmetric hydrogenation of imines using catalyst PHOX **3a**.



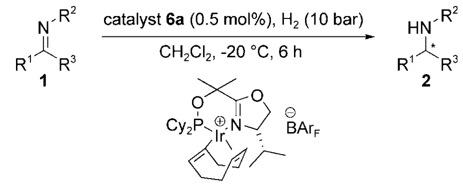
3a

Entry	R^1	R^2	R^3	**2**	Conv. [%][a]	*ee* [%][b]
1	Ph	Ph	Me	**2a**	>99	90
2	Ph	$\text{4-ClC}_6\text{H}_4$	Me	**2b**	>99	88.5
3	Ph	$\text{4-(MeO)C}_6\text{H}_4$	Me	**2c**	99	89
4	$\text{4-ClC}_6\text{H}_4$	Ph	Me	**2d**	>99	90
5	$\text{4-(MeO)C}_6\text{H}_4$	Ph	Me	**2e**	98	88.5
6	Ph	PhCH_2	Me	**2f**[c]	20	74
7	Ph	Ph	Et	**2g**[d]	>99	79

[a] Determined by GC analysis of the reaction mixture after removal of the catalyst (see the Experimental Section for details). [b] Determined by chiral HPLC analysis using a Daicel Chiralcel OD-H column (see Experimental Section for details). [c] The starting imine was isolated as 92:8 *E*/*Z* isomer mixture. [d] The starting imine was isolated as 91:9 *E*/*Z* isomer mixture.

Hydrogenations with the more reactive catalyst **6a** were carried out at −20 °C (Table 6). With all substrates tested, the enantioselectivities were consistently higher than with catalyst **3a**, exceeding 90 % *ee*, except for the *N*-benzylimine **1f** (Table 6, entry 6), which gave **2f** with 81 % *ee* but this time full conversion. With 0.5 mol % catalyst and 10 bar hydrogen pressure, the reaction went to completion in all cases with the exception of the 4-methoxyphenyl imine **1c** (Table 6, entry 3), which gave only 85 % conversion even at longer reaction times. At 50 bar hydrogen pressure, high conversion and excellent enantioselectivities were achieved in the hydrogenation of the acetophenone and 4-chloroacetophenone imines **1a** and **1d**, (Table 6, entries 1 and 4), even at catalyst loadings of 0.1 mol %, making this catalyst attractive for applications on a larger scale. The less reactive 4-methoxyphenyl imine **1c** gave only moderate conversion under these conditions.

Table 6. Asymmetric hydrogenation of imines using catalyst **6a**.



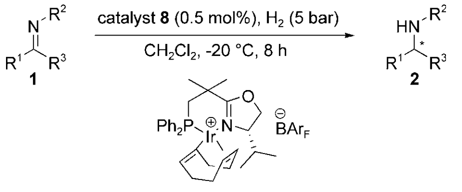
6a

Entry	R^1	R^2	R^3	**2**	Conv. [%][a]	*ee* [%][b]
1	Ph	Ph	Me	**2a**	>99	95.5
2	Ph	$\text{4-ClC}_6\text{H}_4$	Me	**2b**	>99	93.5
3	Ph	$\text{4-(MeO)C}_6\text{H}_4$	Me	**2c**	85	95
4	$\text{4-ClC}_6\text{H}_4$	Ph	Me	**2d**	>99	95.5
5	$\text{4-(MeO)C}_6\text{H}_4$	Ph	Me	**2e**	99	94
6	Ph	PhCH_2	Me	**2f**[c]	>99	81
7	Ph	Ph	Et	**2g**[d]	>99	91.5
8[e]	Ph	Ph	Me	**2a**	94	96
9[e]	Ph	$\text{4-(MeO)C}_6\text{H}_4$	Me	**2c**	56	95.5
10[e]	$\text{4-ClC}_6\text{H}_4$	Ph	Me	**2d**	>99	95.5

[a] Determined by GC analysis of the reaction mixture after removal of the catalyst (see the Experimental Section for details). [b] Determined by chiral HPLC analysis using a Daicel Chiralcel OD-H column (see the Experimental Section for details). [c] The starting imine was isolated as 92:8 *E*/*Z* isomer mixture. [d] The starting imine was isolated as 91:9 *E*/*Z* isomer mixture. [e] The reaction was carried out using 0.1 mol % of catalyst under 50 bar of H_2 pressure.

The Ir–NeoPHOX complex **8** gave similar results to those recorded for the SimplePHOX complex **6a** (Table 7). Essentially full conversions were obtained for all substrates with the exception of the less reactive 4-methoxyphenyl imine **1c** (Table 7, entries 3 and 9). In general, the enantioselectivities were only slightly lower than with catalyst **6a**; only the imine derived from phenylethyl ketone **2g** gave a significantly lower *ee* value (82 % *ee*, Table 7, entry 7, compared with 91.5 % *ee* with catalyst **6a**, Table 6, entry 7). With 0.1 mol % catalyst at 50 bar hydrogen pressure, higher con-

Table 7. Asymmetric hydrogenation of imines by using catalyst **8**.



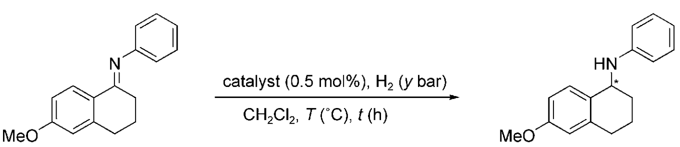
8

Entry	R^1	R^2	R^3	**2**	Conv. [%][a]	*ee* [%][b]
1	Ph	Ph	Me	**2a**	98	94
2	Ph	4-ClC_6H_4	Me	**2b**	>99	92
3	Ph	4-$(MeO)C_6H_4$	Me	**2c**	85	94
4	4-ClC_6H_4	Ph	Me	**2d**	>99	95
5	4-$(MeO)C_6H_4$	Ph	Me	**2e**	98	90
6	Ph	$PhCH_2$	Me	**2f**[c]	>99	77
7	Ph	Ph	Et	**2g**[d]	>99	82
8[e]	Ph	Ph	Me	**2a**	>99	94
9[e]	Ph	4-$(MeO)C_6H_4$	Me	**2c**	85	93.5
10[e]	4-ClC_6H_4	Ph	Me	**2d**	>99	95

[a] Determined by GC analysis of the reaction mixture after removal of the catalyst (see the Experimental Section for details). [b] Determined by chiral HPLC analysis using a Daicel Chiralcel OD-H column (see the Experimental Section for details). [c] The starting imine was isolated as 92:8 *E*/*Z* isomer mixture. [d] The starting imine was isolated as 91:9 *E*/*Z* isomer mixture. [e] The reaction was carried out using 0.1 mol% of catalyst under 50 bar of H_2 pressure for 6 h.

versions and almost the same enantioselectivities were achieved compared with the reactions with catalyst **6a** (Table 7, entries 8–10).

The cyclic imine **11** gave high conversion with catalysts **3a**, **6a**, and **8**, but the enantioselectivities were lower than with analogous acyclic imines (Scheme 3). The most selective catalyst in this case was complex **6a**, which gave amine **12** with 82% *ee* under standard conditions. Imines derived from dialkylketones gave only low conversion and enantioselectivity, whereas cyclic imines with a C=N bond in a five- or six-membered ring showed no reactivity.



11 **12**

Catalyst **3a**: 5 bar, 0 °C, 7h — 98% conv., 65% *ee*
Catalyst **6a**: 10 bar, -20 °C, 6h — >99% conv., 82% *ee*
Catalyst **8**: 5 bar, -20 °C, 8h — >99% conv., 56% *ee*

Scheme 3. Asymmetric hydrogenation of exocyclic imine **11**.

Conclusion

By screening various iridium complexes derived from chiral oxazoline-based N,P ligands that were developed in our laboratory, we have identified three efficient catalysts for the asymmetric hydrogenation of imines derived from arylalkyl ketones. These catalysts are readily accessible by a short, convenient synthesis and are air and moisture stable. In terms of enantioselectivity, catalytic activity, and turnover numbers, they rival the best catalysts reported to date. Due to their high activity, reactions proceed smoothly even at low catalyst loading, low temperature, and moderate hydrogen pressure.

Experimental Section

General: All reactions involving air- or moisture-sensitive reagents were performed under argon by using standard Schlenk techniques or under purified N_2 gas in an MBraun glove box. All solvents and reagents were obtained from Fluka, Aldrich, or Alfa Aesar and were used without further purification. Iridium complexes were prepared according to literature procedures.[28] ^1H and ^{13}C NMR spectra were recorded at 25 °C on a 400 MHz Bruker Avance spectrometer, using $CDCl_3$ as solvent and TMS as internal standard; chemical shifts are given in ppm, unless otherwise stated. Mass spectra (EI) were recorded on a VG70-250 machine. Chiral HPLC analyses were performed on a Shimadzu Class-VP Version 5.0 instrument equipped with a chiral Daicel Chiralcel OD-H column; the retention time of the major isomer is highlighted in bold. Optical rotations were measured on a Perkin–Elmer 341 polarimeter. Imine conversions were determined by GC analysis on a Carlo Erba Instrument GC 8000 Top using a Macherey–Nagel Optima 5-Amin column (30 m x 0.25 mm x 0.5 μm). IR spectra were recorded on a Perkin–Elmer FTIR RX1 instrument and only the most structurally relevant peaks are listed. Melting points were measured with a Büchi 535 melting point apparatus and are not corrected. Elemental analyses were carried out by the Micro-Analytical laboratory of the Department of Chemistry of the University of Basel. Analytical TLC was performed on Macherey–Nagel Polygram Sil G/UV_{254} plates and Merck silica gel 60 (0.0040–0.0063 mm) was employed for flash chromatography.

General procedure for the preparation of imines 1: Imines **1** were prepared following literature procedures (for example, see reference [4]). The analytical data given below is for the only imine (**11**) not described in the literature, and may be taken as representative.

(*E*)-*N*-(6-methoxy-3,4-dihydronaphthalen-1-(2H)-ylidene)benzylamine (11): Slightly yellow solid. M.p.94–95 °C; $R_f = 0.72$ (hexane/ethyl acetate 5/1); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.90$ (q, $J = 6.1$ Hz, 2H; CH_2), 2.48 and 2.86 (2×t, $J = 6.1$ Hz, 2×2H; 2×CH_2), 3.85 (s, 3H; OCH_3), 6.68 (d, $J = 2.5$ Hz, 1H; ArH), 6.79 (d, $J = 7.3$ Hz, 2H; ArH), 6.84 (dd, $J = 2.6$, 8.7 Hz, 1H; ArH), 7.05 (t, $J = 7.6$ Hz, 1H; ArH), 7.32 (t, $J = 7.6$ Hz, 2H; ArH), 8.26 ppm (d, $J = 8.6$ Hz, 1H; ArH); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 23.2$, 29.9, 30.5 (CH_2), 55.5 (CH_3), 112.8, 113.2, 119.9, 122.9, 127.2, 128.5, 129.0, 143.4, 161.6, 165.2 (ArC), 152.0 ppm (C=N); IR (KCl): $\nu =$ 1591, 1496, 1248 cm^{-1}; MS (EI): *m*/*z* (%): 251 (100) $[M]^+$, 223 (58), 208 (13), 180 (32), 77 (35); elemental analysis calcd (%) for $C_{17}H_{17}NO$: C 81.24, H 6.82, N 5.57; found: C 81.38, H 6.79, N 5.44.

General procedure for the iridium-catalyzed asymmetric hydrogenation of imines: A solution of imine (0.2 mmol) and iridium complex (1–0.1 mol%) in dry dichloromethane (1 mL) under inert atmosphere was placed in an autoclave, which was sealed and placed in a bath for 1 h at the appropriate temperature. After this time, the autoclave was purged with hydrogen gas, pressurized to the desired hydrogen pressure and stirred at the corresponding temperature for the indicated time. After this time, the solvent was evaporated and the catalyst was removed by filtration through a short silica gel column (3×1 cm) with a mixture of pentane and diethyl ether (1:1) as eluent to give the amine product as a pure compound after evaporation of the solvent. For the amine **10c**, which was not obtained as a pure product after workup, flash chromatography (15×3 cm) was needed, using a mixture of pentane and ethyl acetate (97:3) as eluent.

For catalyst screening, reactions were performed on a 0.1 mmol scale.

The absolute configuration of the resulting amines **2a**, **2c**, **2f**, and **2g** was found to be *R* and was assigned by comparison with known literature values,[4,5,11] for optical rotation and HPLC retention times.

Analytical data are given below. For known products, only $[\alpha]_D$, ^1H, ^{13}C NMR, and HPLC data are listed.

(*R*)-*N*-Phenyl-1-phenylethylamine (2a):[4] $[\alpha]_D^{20}=-27.8$ ($c=1$ in CH_2Cl_2); 95.5 % ee from HPLC Daicel Chiralcel OD-H ($\lambda=225$, 254 nm, 20 °C, *n*-heptane/2-propanol 99/1, 0.5 mL min^{-1}; $t_r=24.4$ and 32.7 min); ^1H NMR (400 MHz, $CDCl_3$): $\delta=1.51$ (d, $J=6.6$ Hz, 3H; CH_3), 4.03 (brs, 1H; NH), 4.48 (q, $J=6.6$ Hz, 1H; CH), 6.49–6.52 (m, 2H; ArH), 6.62–6.66 (m, 1H; ArH), 7.07–7.11 (m, 2H; ArH), 7.21–7.38 ppm (m, 5H; ArH); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta=25.0$ (CH_3), 53.4 (CH), 113.2, 117.2, 125.8, 126.8, 128.6, 129.1, 145.2, 147.2 ppm (ArC).

(−)-*N*-(4-Chlorophenyl)-1-phenylethylamine (2b):[10] $[\alpha]_D^{20}=-5.1$ ($c=1$ in CH_2Cl_2); 93.5 % *ee* from HPLC Daicel Chiralcel OD-H ($\lambda=225$, 254 nm, 20 °C, *n*-heptane/2-propanol 98/2, 0.5 mL min^{-1}; $t_r=19.3$ and 27.2 min); ^1H NMR (400 MHz, $CDCl_3$): $\delta=1.50$ (d, $J=6.6$ Hz, 3H; CH_3), 4.05 (brs, 1H; NH), 4.43 (q, $J=6.6$ Hz, 1H; CH), 6.41 (dd, $J=2.1$, 6.7 Hz, 2H; ArH), 7.01 (dd, $J=2.1$, 6.7 Hz, 2H; ArH), 7.20–7.24 (m, 1H; ArH), 7.29–7.34 ppm (m, 4H; ArH); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta=25.0$ (CH_3), 53.6 (CH), 114.3, 121.8, 125.7, 127.0, 128.7, 128.9, 144.7, 145.7 ppm (ArC).

(*R*)-*N*-(4-Methoxyphenyl)-1-phenylethylamine (2c):[5] $[\alpha]_D^{20}=-21.3$ ($c=1$ in CH_2Cl_2), $[\alpha]_D^{20}=+1.9$ ($c=1$ in $CHCl_3$); 95 % *ee* from HPLC Daicel Chiralcel OD-H ($\lambda=225$, 254 nm, 20 °C, *n*-heptane/2-propanol 99/1, 0.5 mL min^{-1}; $t_r=31.2$ and 35.3 min); ^1H NMR (400 MHz, $CDCl_3$): $\delta=1.49$ (d, $J=6.8$ Hz, 3H; CH_3), 3.69 (s, 3H; OCH_3), 3.74 (brs, 1H; NH), 4.40 (q, $J=6.8$ Hz, 1H; CH), 6.46 (dd, $J=2.1$, 6.7 Hz, 2H; ArH), 6.68 (dd, $J=2.1$, 6.7 Hz, 2H; ArH), 7.20–7.25 (m, 1H; ArH), 7.29–7.37 ppm (m, 4H; ArH); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta=25.1$ (CH_3), 54.2 (CH), 55.7 (OCH_3), 114.5, 114.7, 125.9, 126.8, 128.6, 141.5, 145.4, 151.9 ppm (ArC).

(−)-*N*-Phenyl-1-(4-chlorophenyl)-ethylamine (2d):[7] $[\alpha]_D^{20}=-15.3$ ($c=1$ in CH_2Cl_2), $[\alpha]_D^{20}=+3.2$ ($c=1$ in $CHCl_3$); 95.5 % *ee* from HPLC Daicel Chiralcel OD-H ($\lambda=225$, 254 nm, 20 °C, *n*-heptane/2-propanol 98/2, 0.5 mL min^{-1}; $t_r=26.7$ and 35.9 min); ^1H NMR (400 MHz, $CDCl_3$): $\delta=1.48$ (d, $J=6.8$ Hz, 3H; CH_3), 4.00 (brs, 1H; NH), 4.44 (q, $J=6.8$ Hz, 1H; CH), 6.47 (d, $J=7.6$ Hz, 2H; ArH), 6.65 (t, $J=7.4$ Hz, 1H; ArH), 7.08 (m, 2H; ArH), 7.25–7.31 ppm (m, 4H; ArH); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta=25.1$ (CH_3), 53.0 (CH), 113.3, 117.5, 127.2, 128.8, 129.1, 132.4, 143.8, 146.9 ppm (ArC).

(−)-*N*-Phenyl-1-(4-methoxyphenyl)-ethylamine (2e):[11] $[\alpha]_D^{20}=-15.5$ ($c=1$ in CH_2Cl_2); 94 % ee from HPLC Daicel Chiralcel OD-H ($\lambda=225$, 254 nm, 20 °C, *n*-heptane/2-propanol 99/1, 0.5 mL min^{-1}; $t_r=32.4$ and 37.4 min); ^1H NMR (400 MHz, $CDCl_3$): $\delta=1.49$ (d, $J=6.6$ Hz, 3H; CH_3), 3.78 (s, 3H; OCH_3), 4.01 (brs, 1H; NH), 4.44 (q, $J=6.8$ Hz, 1H; CH), 6.51 (dd, $J=1.0$, 8.6 Hz, 2H; ArH), 6.64 (t, $J=7.3$ Hz, 1H; ArH), 6.85 (dd, $J=2.0$, 6.6 Hz, 2H; ArH), 7.07–7.11 (m, 2H; ArH), 7.25–7.29 ppm (m, 2H; ArH); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta=25.0$ (CH_3), 52.8 (CH), 55.2 (OCH_3), 113.3, 114.0, 117.1, 126.9, 129.1, 137.2, 147.3, 158.4 ppm (ArC).

(*R*)-*N*-Benzyl-1-phenylethylamine (2f):[4] $[\alpha]_D^{20}=+29.5$ ($c=1$ in $CHCl_3$); 81 % ee from HPLC Daicel Chiralcel OD-H ($\lambda=225$, 254 nm, 20 °C, *n*-heptane/2-propanol 99/1, 0.5 mL min^{-1}; $t_r=12.3$ and 14.4 min); ^1H NMR (400 MHz, $CDCl_3$): $\delta=1.37$ (d, $J=6.7$ Hz, 3H; CH_3), 1.61 (s, 1H; NH), 3.59 and 3.66 (2×d, $J=13.2$ Hz, 2×1H; CH_2Ph), 3.81 (q, $J=6.6$ Hz, 1H; CH), 7.24–7.36 ppm (m, 10H; ArH); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta=24.5$ (CH_3), 51.6 (CH_2), 57.5 (CH), 127.7, 127.8, 127.9, 128.1, 128.3, 128.4, 140.8, 145.5 ppm (ArC).

(*R*)-*N*-Phenyl-1-phenylpropylamine (2g):[5] $[\alpha]_D^{20}=+20.5$ ($c=1$ in $CHCl_3$); 91.5 % ee from HPLC Daicel Chiralcel OD-H ($\lambda=225$, 254 nm, 20 °C, *n*-heptane/2-propanol 98/2, 0.5 mL min^{-1}; $t_r=14.2$ and 17.2 min); ^1H NMR (400 MHz, $CDCl_3$): $\delta=0.95$ (t, $J=7.3$ Hz, 3H; CH_3), 1.61 (m, 2H; CH_2), 4.06 (brs, 1H; NH), 4.22 (t, $J=6.6$ Hz, 1H; CHPh), 6.51 (m, 2H; ArH), 6.62 (t, $J=7.3$ Hz, 1H; ArH), 7.08 (t, $J=7.4$ Hz, 2H; ArH), 7.20–7.35 ppm (m, 5H; ArH); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta=10.8$ (CH_3), 31.6 (CH_2), 59.7 (CH), 113.2, 117.1, 126.4, 126.8, 128.5, 129.0, 143.9, 147.5 ppm (ArC).

(+)-*N*-Phenyl-(6-methoxy)-1,2,3,4-tetrahydronaphthalen-1-amine (12): White solid. M.p. 72–73 °C; $R_f=0.70$ (hexane/ethyl acetate 4/1); $[\alpha]_D^{20}=+12.8$ ($c=1$ in $CHCl_3$); 82 % ee from HPLC Daicel Chiralcel OD-H ($\lambda=225$, 254 nm, 20 °C, *n*-heptane/2-propanol 99/1, 0.5 mL min^{-1}; $t_r=27.7$ and 39.6 min); ^1H NMR (400 MHz, $CDCl_3$): $\delta=1.75$–2.03 (m, 4H; 2× CH_2), 2.72–2.84 (m, 2H; CH_2), 3.80 (s, 3H; OCH_3), 3.84 (s, 1H; NH), 4.60 (t, $J=4.5$ Hz, 1H; CH), 6.65–6.76 (m, 5H; ArH), 7.18–7.23 (m, 2H; ArH), 7.31 ppm (d, $J=8.6$ Hz, 1H; ArH); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta=19.2$, 28.7, 29.7 (CH_2), 50.4 (CH), 55.2 (CH_3), 112.5, 112.8, 113.2, 116.9, 129.3, 130.4, 130.5, 138.9, 147.4, 158.5 ppm (ArC); IR (KCl): $\nu=$ 3399, 2932, 1601, 1499, 1249 cm^{-1}; MS (EI): *m*/*z* (%): 253 (14) $[M]^+$, 162 (14), 161 (100); elemental analysis calcd (%) for $C_{17}H_{19}NO$: C 80.60, H 7.56, N 5.53; found: C 80.78, H 7.64, N 5.39.

Acknowledgements

A.B would like to thank the Spanish Ministerio de Educación, Ciencia y Deporte (MECD) and Fundación Española para la Ciencia y la Tecnología (FECYT) for a postdoctoral fellowship. Support of this work by the Swiss National Science Foundationand the Federal Commission for Technology and Innovation (KTI) is gratefully acknowledged.

[1] For reviews, see: a) H. U. Blaser, F. Spindler in *Comprehensive Asymmetric Catalysis, Vol. 1* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**, pp. 247–265; b) R. L. Halterman in *Comprehensive Asymmetric Catalysis, Vol. 1* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**, pp. 183–195; c) S. Kobayashi, H. Ishitani, *Chem. Rev.* **1999**, *99*, 1069–1094; d) W. Tang, X. Zhang, *Chem. Rev.* **2003**, *103*, 3029–3069; e) H. U. Blaser, C. Malan, B. Pugin, F. Spinder, H. Steiner, M. Studer, *Adv. Synth. Catal.* **2003**, *345*, 103–151; f) T. Ohkuma, R. Noyori in *Comprehensive Asymmetric Catalysis* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **2004**, pp. 43–53; g) H. U. Blaser, F. Spindler in *Handbook of Homogeneous Hydrogenation, Vol. 3* (Eds.: J. G. de Vries, C. J. Elsevier), Wiley-VCH, Weinheim, **2007**, pp. 1193–1214.

[2] Titanocene catalysts: a) C. A. Willoughby, S. L. Buchwald, *J. Am. Chem. Soc.* **1992**, *114*, 7562–7564; b) C. A. Willoughby, S. L. Buchwald, *J. Org. Chem.* **1993**, *58*, 7627–7629; c) C. A. Willoughby, S. L. Buchwald, *J. Am. Chem. Soc.* **1994**, *116*, 8952–8965; d) A. Viso, N. L Lee, S. L. Buchwald, *J. Am. Chem. Soc.* **1994**, *116*, 9373–9374; e) C. A. Willoughby, S. L. Buchwald, *J. Am. Chem. Soc.* **1994**, *116*, 11703–11714.

[3] Ruthenium catalysts: a) W. Oppolzer, M. Willis, M. Starkemann, G. Bernardinelli, *Tetrahedron Lett.* **1990**, *31*, 4117–4120; b) N. Uematsu, A. Fujii, S. Hashiguchi, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.* **1996**, *118*, 4916–4917; c) A. B. Charette, A. Giroux, *Tetrahedron Lett.* **1996**, *37*, 6669–6672; d) C. J. Cobley, J. P. Henschke, *Adv. Synth. Catal.* **2003**, *345*, 195–201; rhodium catalysts: e) A. G. Becalski, W. R. Cullen, M. D. Fryzuk, B. R. James, G.-J. Kang, S. R. Rettig, *Inorg. Chem.* **1991**, *30*, 5002–5008; f) J. Bakos, A. Orosz, B. Heil, M. Laghmari, P. Lhoste, D. Sinou, *J. Chem. Soc. Chem. Commun.* **1991**, 1684–1685; g) M. J. Burk, J. E. Feaster, *J. Am. Chem. Soc.* **1992**, *114*, 6266; h) J. Mao, D. C. Baker, *Org. Lett.* **1999**, *1*, 841–843; i) F. Spinder, H. U. Blaser, *Adv. Synth. Catal.* **2001**, *343*, 68–70.

[4] P. Schnider, G. Koch, R. Prétôt, G. Wang, F. M. Bohnen, C. Krüger, A. Pfaltz, *Chem. Eur. J.* **1997**, *3*, 887–892.

[5] a) A. Trifonova, J. S. Diesen, C. J. Chapman, P. G. Andersson, *Org. Lett.* **2004**, *6*, 3825–3827; b) A. Trifonova, J. S. Diesen, P. G. Andersson, *Chem. Eur. J.* **2006**, *12*, 2318–2328.

[6] C. Moessner, C. Bolm, *Angew. Chem.* **2005**, *117*, 7736–7739; *Angew. Chem. Int. Ed.* **2005**, *44*, 7564–7567.

[7] S.-F. Zhu, J.-B. Xie, Y.-Z. Zhang, S. Li, Q.-L. Zhou, *J. Am. Chem. Soc.* **2006**, *128*, 12886–12891.

[8] M. N. Cheemala, P. Knochel, *Org. Lett.* **2007**, *9*, 3089–3092.

[9] Z. Han, Z. Wang, X. Zhang, K. Ding, *Angew. Chem.* **2009**, *121*, 5449–5453; *Angew. Chem. Int. Ed.* **2009**, *48*, 5345–5349.

[10] a) D. Xiao, X. Zhang, *Angew. Chem.* **2001**, *113*, 3533–3536; *Angew. Chem. Int. Ed.* **2001**, *40*, 3425–3428; b) G. Hou, F. Gosselin, W. Li, J. C. McWilliams, Y. Sun, M. Weisel, P. D. O'Shea, C. Y. Chen, I. W. Davies, X. Zhang, *J. Am. Chem. Soc.* **2009**, *131*, 9882–9883.

[11] T. Imamoto, N. Iwadate, K. Yoshida, *Org. Lett.* **2006**, *8*, 2289–2292.

[12] a) H.-U. Blaser, *Adv. Synth. Catal.* **2002**, *344*, 17–31; b) H. U. Blaser, R. Hanreich, H. D. Schneider, F. Spindler, B. Steinacher in *Asymmetric Catalysis on Industrial Scale* (Eds.: H. U. Blaser, E. Schmidt), Wiley-VCH, Weinheim, **2004**, pp. 55–70; c) H. U. Blaser, B. Pugin, F. Spindler, M. Thommen, *Acc. Chem. Res.* **2007**, *40*, 1240–1250, and references therein.

[13] M. T. Reetz, O. Bondarev, *Angew. Chem.* **2007**, *119*, 4607–4610; *Angew. Chem. Int. Ed.* **2007**, *46*, 4523–4526.

[14] N. Mršić, A. J. Minnaard, B. L. Feringa, J. G. de Vries, *J. Am. Chem. Soc.* **2009**, *131*, 8358–8359.

[15] C. Li, C. Wang, B. Villa-Marcos, J. Xiao, *J. Am. Chem. Soc.* **2008**, *130*, 14450–14451.

[16] For transition metal-catalyzed asymmetric hydrosilylations of imines, see: a) H. Nishiyama in *Comprehensive Asymmetric Catalysis, Vol. 1* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**, pp. 247–265; b) O. Riant, N. Mostefaï, J. Courmarcel, *Synthesis* **2004**, 2943–2958, and references therein.

[17] For reviews of organocatalytic C=N reduction, see: a) S. G. Quellet, A. M. Walji, D. W. C. MacMillan, *Acc. Chem. Res.* **2007**, *40*, 1327–1339; b) S. L. You, *Chem. Asian J.* **2007**, *2*, 820–827.

[18] For organocatalytic asymmetric C=N reduction with Hantzsch esters, see: a) M. Rueping, E. Sugiono, C. Azap, T. Theissmann, M. Bolte, *Org. Lett.* **2005**, *7*, 3781–3783; b) S. Hoffmann, A. M. Seayad, B. List, *Angew. Chem.* **2005**, *117*, 7590–7593; *Angew. Chem. Int. Ed.* **2005**, *44*, 7424–7427; c) R. I. Storer, D. E. Carrera, Y. Ni, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2006**, *128*, 84–86; d) M. Rueping, A. P. Antonchick, T. Theissmann, *Angew. Chem.* **2006**, *118*, 6903–6907; *Angew. Chem. Int. Ed.* **2006**, *45*, 6751–6755; e) M. Rueping, T. Theissmann, S. Raja, J. W. Bats, *Adv. Synth. Catal.* **2008**, *350*, 1001–1006, and references therein.

[19] For examples of organocatalytic asymmetric hydrosilylations of imines, see: a) O. Onomura, Y. Kouchi, F. Iwasaki, Y. Matsumura, *Tetrahedron Lett.* **2006**, *47*, 3751–3754; b) A. V. Malkov, M. Figlus, S. Stoncius, P. Kocovsky, *Angew. Chem.* **2007**, *119*, 3796–3798; *Angew. Chem. Int. Ed.* **2007**, *46*, 3722–3724; c) C. Baudequin, D. Chaturvedi, S. B. Tsogoeva, *Eur. J. Org. Chem.* **2007**, 2623–2629; d) C. Wang, X. Wu, L. Zhou, J. Sun, *Chem. Eur. J.* **2008**, *14*, 8789–8792; e) S. Guizzetti, M. Benaglia, S. Rossi, *Org. Lett.* **2009**, *11*, 2928–2931, and references therein.

[20] S. Roseblade, A. Pfaltz, *Acc. Chem. Res.* **2007**, *40*, 1402–1411.

[21] A. Baeza, A. Pfaltz, *Chem. Eur. J.* **2009**, *15*, 2266–2269.

[22] Two Ir–ThrePHOX complexes are commercially available from Strem (catalog no. 77-5009, 77-5019).

[23] T. Morimoto, K. Achiwa, *Tetrahedron: Asymmetry* **1995**, *6*, 2661–2664.

[24] S. P. Smidt, N. Zimmermann, M. Studer, A. Pflatz, *Chem. Eur. J.* **2004**, *10*, 4685–4693.

[25] M. G. Schrems, A. Pfaltz, *Chem. Commun.* **2009**, 6210–6212.

[26] P. G. Cozzi, F. Menges, S. Kaiser, *Synlett* **2003**, 0833–0836.

[27] M. G. Schrems, E. Neumann, A. Pfaltz, *Angew. Chem.* ***2007**, 119*, 8422–8424; *Angew. Chem. Int. Ed.* **2007**, *46*, 8274–8276.

[28] For example, see: a) A. Pfaltz, J. Blankestein, R. Hilgraf, E. Hörmann, S. McIntyre, F. Menges, M. Schönleber, S. P. Smidt, B. Wüstenberg, N. Zimmermann, *Adv. Synth. Catal.* **2002**, *344*, 33–44; b) A. Pfaltz, S. Bell in *Handbook of Homogeneous Hydrogenation, Vol. 2* (Eds.: J. G. de Vries, C. J. Elsevier), Wiley-VCH, Weinheim, **2007**, 1029–1048, and references therein.

Received: December 14, 2009