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Asymmetric Hydrogenation of *N*-Alkyl Ketimines with Phosphine-Free, Chiral, Cationic Ru-MsDPEN Catalysts**

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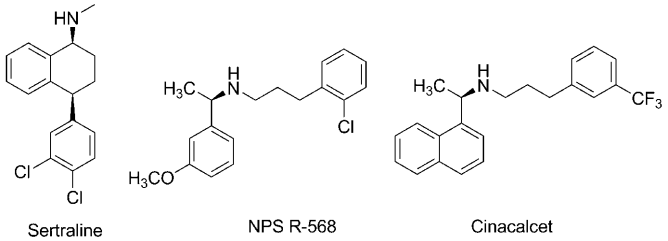
Optically pure amines are an important type of building block for the synthesis of many pharmaceutical and agrochemical substances,[1] examples include Sertraline,[2] NPS R-568,[3] and Cinacalcet.[4] Among the various methods of



Sertraline NPS R-568 Cinacalcet

synthesizing chiral amines, which include metal- and organocatalyzed transfer hydrogenation[5,6] and hydrosilylation,[7] asymmetric hydrogenation of the corresponding prochiral imines represents one of the most direct, efficient, and "green" approaches for attaining optically active amines.[8] Although considerable progress has been made in the last few decades, the asymmetric hydrogenation of imines, particularly acyclic imines, remains a major challenge, in contrast to the advancements achieved in the asymmetric hydrogenation of olefins or ketones.[9] This is probably due to the formation of an *E*/*Z* isomeric mixture of imine substrates and the poisoning effect of the resulting amines on the catalyst.[8a]

In recent years, a variety of chiral metal catalysts, including Ti, Zr, Rh, Ru, Ir, and Pd complexes,[10–15] have been successfully employed in the asymmetric hydrogenation of imines. For example, the chiral titanocene catalysts developed by Buchwald et al. were found to be particularly effective in the hydrogenation of cyclic imines.[10a] Recently, a variety of iridium complexes with chiral P,P[13] or P,N ligands[14] have proven to be exceptionally efficient in the hydrogenation of ketimines. However, most of these catalysts are only effective for *N*-aryl ketimines. Successful examples in the hydrogenation of *N*-alkyl ketimines, particularly with Ru-catalysts[12] are rare.[8d] In 1975, Scorrano et al. first reported the Rh–diphosphine complex catalyzed asymmetric hydrogenation of the *N*-benzylimine of acetophenone in 22% *ee*.[11a] Since then, a variety of rhodium complexes of chiral phosphorous ligands have been investigated in this reaction.[11a–f] Among them, the best result (94% *ee*) was obtained in the hydrogenation of the *N*-benzylimine of acetophenone by using a Rh complex of sulfonated bis(diphenylphosphino)pentane (BDPP) in a two-phase system, as reported by de Vries et al.[11c] However, this catalytic system still suffers from low catalytic activity and very limited substrate scope. Most recently, some iridium complexes were found to be effective catalysts in the hydrogenation of *N*-alkyl ketimines.[13j,k,14d,j] One of the most notable examples was reported by Ding et al. in the hydrogenation of a variety of acyclic *N*-alkyl ketimines, in >90% *ee*, by using a P,N-ligand-modified Ir complex.[14j]

In comparison with chiral phosphorus ligands, chiral diamine ligands are more readily available and air stable.[16] Their Ru complexes, such as Ru^{II}–TsDPEN (TsDPEN = *N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine), have proven to be powerful catalysts for the asymmetric transfer hydrogenation of aromatic ketones and imines.[5] Most recently, Noyori et al. reported that a chiral η^6-arene/TsDPEN–Ru^{II} complex (**1b**) can be used for the asymmetric

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[**] MsDPEN = *N*-(methanesulfonyl)-1,2-diphenylethylenediamine.

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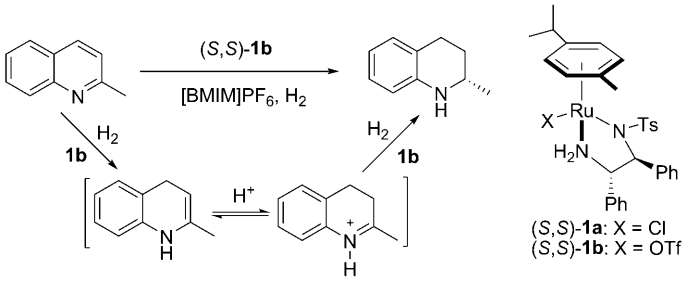
hydrogenation of ketones under slightly acidic conditions.[17,18] Later, we found that this Ru catalyst catalyzes the asymmetric hydrogenation of quinolines in ionic liquids with excellent enantioselectivity and reactivity.[19] Based on our proposed mechanism (Scheme 1),[19,20] we envision that this



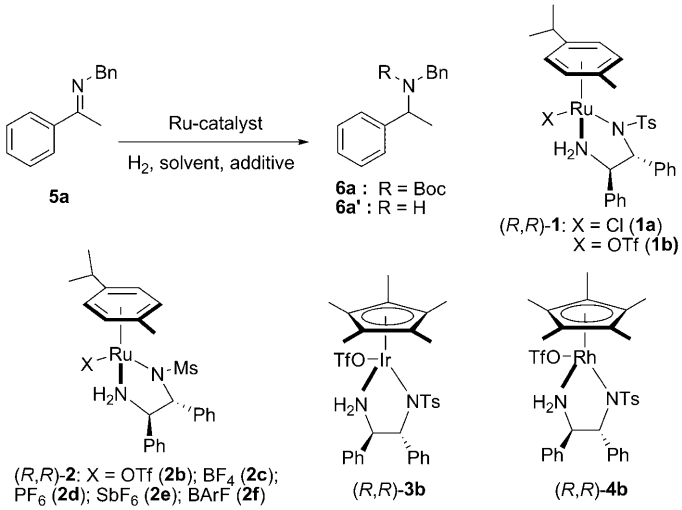
Scheme 1. The asymmetric hydrogenation of 2-methylquinoline catalyzed by chiral TsDPEN–Ru^{II} and the possible intermediate.[19]

catalyst could also be used to enantioselectively hydrogenate imines. At the same time, Xiao et al. demonstrated that a cationic Cp*Rh^{III}–TsDPEN (Cp* = pentamethylcyclopentadienyl) complex is an efficient catalyst for the asymmetric hydrogenation of cyclic imines in the presence of $AgSbF_6$.[21a] Furthermore, they found that a combination of an Ir–diamine complex together with a chiral phosphate anion efficiently hydrogenates a variety of acyclic *N*-aryl imines in excellent enantioselectivities.[21b–c] Most recently, Ikariya et al. reported that a Cp*Ir complex of an *N*-sulfonylated diamine can efficiently catalyze the asymmetric hydrogenation of acyclic ketimines in the presence of silver salts in up to 78% *ee*.[22]

Despite these impressive achievements, *N*-alkyl ketimines remain very challenging substrates in terms of catalytic activity and enantioselectivity. As a continuation of our ongoing endeavor to develop effective catalysts for the asymmetric hydrogenation of heteroaromatic compounds and imines,[19,23] we report, herein, the use of cationic Ru-diamine complexes for the asymmetric hydrogenation of a broad range of often-problematic *N*-alkyl ketimines, even under solvent-free conditions, affording chiral amines in up to 99% *ee*.

First, we examined the asymmetric hydrogenation of the *N*-benzylimine of acetophenone (**5a**) catalyzed by (*R*,*R*)-**1b** (2 mol%) in methanol. To our delight, the reaction proceeded smoothly, affording (*R*)-*N*-benzyl-*N*-(1-phenylethyl)-amine (**6a′**) in quantatitive yield and 63% *ee* (Table 1, entry 1). Higher enantioselectivities were observed in either 1-butyl-3-methylimidazolium hexafluorophosphate ([BMIM]PF_6) or dichloromethane, but the reaction was found to be sluggish in these solvents (Table 1, entries 2 and 3). The addition of $AgSbF_6$ showed no positive effect on the reactivity or enantioselectivity (Table 1, entry 4). After careful examination of the reaction mixture, some of the imine substrate (2–22%) was found to have decomposed into benzylamine, which may have a strong inhibitory effect on the

Table 1. The asymmetric hydrogenation of *N*-benzylimine of acetophenone (**5a**).[a]



Entry	Catalyst	Solvent	*T* [h]	Conversion [%][b]	*ee* [%][c]
1	**1b**	MeOH	15	>99	63
2	**1b**	[BMIM]PF_6	48	34 (2)[d]	77
3	**1b**	CH_2Cl_2	48	30 (8)[d]	79
4	**1a**	CH_2Cl_2	48	53 (22)[d]	78
5	**1b**	CH_2Cl_2	10	>99	86
6	**2b**	CH_2Cl_2	10	>99	89
7	**3b**	CH_2Cl_2	10	>99	68
8	**4b**	CH_2Cl_2	10	>99	27
9	**2c**	CH_2Cl_2	10	>99	89
10	**2d**	CH_2Cl_2	10	>99	93
11	**2e**	CH_2Cl_2	10	>99	92
12	**2f**	CH_2Cl_2	10	>99	95
13	**2f**	$ClCH_2CH_2Cl$	10	>99	96
14	**2f**	toluene	10	>99	96
15[e]	**2f**	CH_2Cl_2	10	25 (13)[d]	49
16[e]	**2f**	solvent free	15	>99	91
17[f]	**2f**	solvent free	48	>99	89

[a] Reaction conditions: **5a** (0.2 mmol) in solvent (1 mL) or **5a** (2.5 mmol) under solvent-free conditions, catalyst (2 mol%), H_2 (50 atm), stirred at 40°C for the specified period of time. $(Boc)_2O$ (1.1 equiv) was added as an additive except for entries 1–3, which did not have an additive, and entry 4, which used $AgSbF_6$ (0.08 equiv) as the additive. [b] The conversions were determined by ^1H NMR spectroscopy of the crude reaction mixture. [c] The enantiomeric excesses were determined by HPLC with a chiral AD-H column. [d] Data in parentheses are the percentage of decomposed imine, as determined by ^1H NMR spectroscopy. [e] With catalyst (0.1 mol%). [f] With catalyst (0.05 mol%).

catalyst (Table S1, entry 2 in the Supporting Information).[24] Thus, $(Boc)_2O$ ($(Boc)_2O$ = di-*tert*-butyl dicarbonate) was utilized to eliminate inhibition by this byproduct through in situ protection of the resulting primary amine.[24] As expected, full conversion and high enantioselectivity were observed in the presence of $(Boc)_2O$ (0.2–1.1 equiv; Table 1, entry 5 and Table S1 in Supporting Information).

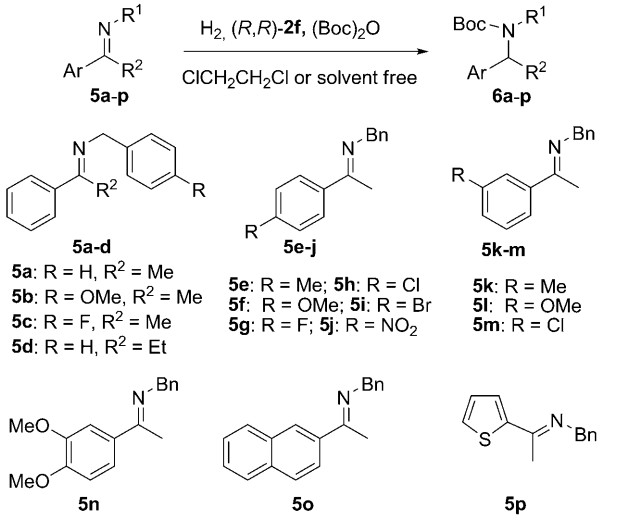
Subsequently, encouraged by this exciting result obtained for the hydrogenation of **5a** with (*R*,*R*)-**1b** in the presence of $(Boc)_2O$ (1.1 equiv), we investigated the effect of different catalysts and other reaction conditions on this reaction (Table 1 and Tables S1–4 in the Supporting Information).

After a survey of a variety of catalysts for the hydrogenation of **5a** (Table S2 in the Supporting Information), catalyst **2b** was found to be the optimal catalyst in terms of both reactivity and enantioselectivity (Table 1, entry 6). Notably, both of the Ir- and Rh-catalysts showed much lower enantioselectivities under otherwise identical reaction conditions (Table 1, entries 7 and 8). Furthermore, it was found that weakly coordinating counterions influenced the enantioselectivity, and a higher enantioselectivity was obtained with $BArF^-$ as the counterion (Table 1, entries 6 and 9–12).[25] In addition, the solvent effect was studied and the results are sumarized in Table S3 in the Supporting Information. It was found that weakly polar solvents, such as CH_2Cl_2, $ClCH_2CH_2Cl$, and toluene, are suitable for to obtain high enantioselectivities (Table 1, entries 12–14). Interestingly, the reaction can be carried out under solvent-free conditions.[26,27] Remarkably, in comparison with the reaction in CH_2Cl_2, significantly higher reactivity and enantioselectivity were observed if the hydrogenation was carried out at a substrate/catalyst ratio of 1000:1, under solvent-free conditions (Table 1, entry 15 vs. entry 16). Even if the catalyst loading was reduced to 0.05 mol%, the reaction still gave the product in full conversion and 89% *ee* after prolonged reaction time (Table 1, entry 17). To the best of our knowledge, this is the highest turnover number for an asymmetric hydrogenation of *N*-alkyl ketimines.

Under the optimized reaction conditions, a variety of acyclic *N*-benzyl ketimines were efficiently hydrogenated in the presence of (*R*,*R*)-**2f** (1.0 mol%) to afford the corresponding chiral Boc-protected *N*-benzylamines with unprecedented high enantioselectivities (86–97% *ee*, Table 2, entries 1–16). It was found that the introduction of an electron-donating or electron-withdrawing group on the *N*-benzyl ring had no apparent effect on the enantioselectivity (Table 2, entries 1–3). However, an electron-withdrawing substituent on the α-phenyl ring of the ketimines decreased both the reactivity and the enantioselectivity (Table 2, entries 7 and 10). Notably, the hydrogenation of the ketimine of propiophenone (**5d**), which had an *E*/*Z* ratio of 2:1, afforded the corresponding Boc-protected amine in 91% *ee* (Table 2, entry 4). The highest enantioselectivity (97% *ee*) was achieved in the hydrogenation of 2-thiophene ketone imine (**5p**; Table 2, entry 16). Notably, most of these substrates can be efficiently hydrogenated in the presence of 0.2 mol% catalyst, under solvent-free conditions, in excellent enantioselectivities that are only slightly lower than those obtained in 1,2-dichloroethane.

It should be noted that Ru complex **2f** was also an effective catalyst for the hydrogenation of exocyclic *N*-alkyl ketimines. As shown in Table 3, the *N*-benzyl ketimine derived from indanone (**7a**) was hydrogenated in the presence of (*R*,*R*)-**2f** (2 or 1 mol%) at 40°C to afford the corresponding Boc-protected amine in up to 98% *ee* (Table 3, entry 1). Similarly, hydrogenation of *N*-alkyl ketimines derived from tetralone analogues gave the corresponding *N*-benzyl-, *N*-isobutyl-, or *N*-methyl-1,2,3,4-tetrahydronaphthalen-1-amine derivatives in 92–97% *ee* (Table 3, entries 2–5).

Table 2. The asymmetric hydrogenation of acyclic *N*-benzyl ketimines with **2f** in 1,2-dichloroethane or under solvent-free conditions.[a]

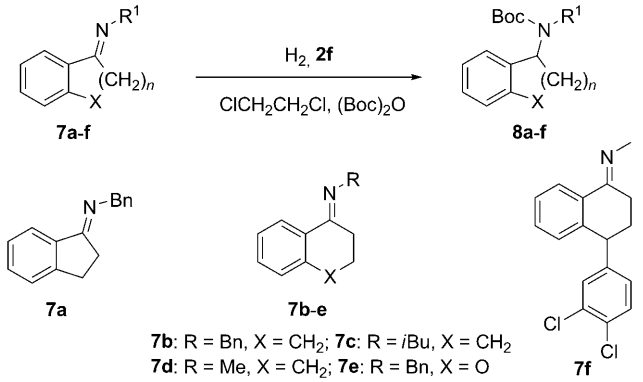


Entry	Imine (*E*/*Z* ratio)	Yield [%][b]	*ee* [%][c,d]
1	**5a** (12:1)	95 (99)	95 (93)
2	**5b** (11:1)	93 (96)	94 (90)
3	**5c** (12:1)	92 (98)	95 (91)
4	**5d** (2:1)	93 (97)	91 (90)
5	**5e** (12:1)	93 (98)	96 (91)
6	**5f** (20:1)	93 (97)	94 (91)
7	**5g** (25:1)	90	90
8	**5h** (22:1)	92 (97)	93 (91)
9	**5i** (40:1)	93 (97)	96 (90)
10	**5j** (35:1)	90 (95)	86 (84)
11	**5k** (11:1)	92 (96)	92 (92)
12	**5l** (28:1)	91 (97)	94 (89)
13	**5m** (22:1)	92	91
14	**5n** (16:1)	92 (95)	95 (89)
15	**5o** (16:1)	96	96
16	**5p** (>100)	96 (98)	97 (95)

[a] Reaction conditions: substrate (**5a**–**p**; 0.2 mmol) in 1,2-dichloroethane (1 mL) or under solvent-free conditions (2.5 mmol), catalyst ((*R*,*R*)-**2f**; 1 mol%), H_2 (50 atm), $(Boc)_2O$ (1.1 equiv), stirred at 40°C for 10 h, except for entries 7 and 10, which were stirred for 20 h. [b] Isolated yields in 1,2-dichloroethane. Data in parentheses correspond to the reactions conducted under solvent-free conditions. [c] The enantiomeric excesses were determined by HPLC with a chiral AD-H column. [d] Data in parentheses were obtained with catalyst (0.2 mol%) after 20 h under solvent-free conditions.

These remarkable results prompted us to apply our new protocol to the synthesis of (+)-*cis*-(1*S*,4*S*)-1-methylamino-4-(3,4-dichlorophenyl)tetralin (Sertraline), a chiral antidepressant drug,[2] as an example of the *N*-alkyl amine class of biologically important compounds. To our delight, the asymmetric hydrogenation of racemic imine precursor **7f** in the presence of catalyst (*R*,*R*)-**2f** (1 mol%) afforded the chiral amine isomers *cis*-**8f** and *trans*-**8f** in 62 and 98% *ee* and a ratio of approximately 3:2 (Table 3, entry 6). Encouraged by these results, we then employed enantiopure imine (*S*)-**7f** as the substrate for the hydrogenation. It was found that catalyst (*R*,*R*)-**2f** showed *trans* diastereoselectivity (80:20 d.r.), affording each isomer in >99% *ee* (Table 3, entry 8). Significantly, catalyst (*S*,*S*)-**2f** exhibited extremely

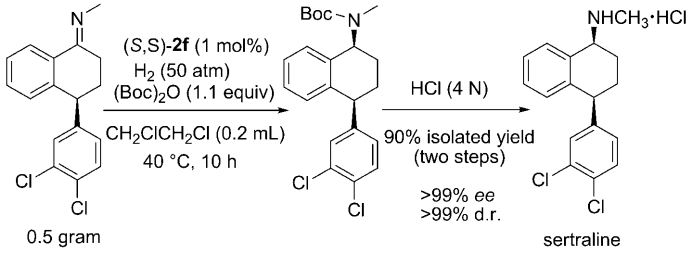
Table 3. The enantioselective hydrogenation of exocyclic *N*-alkyl ketimines catalyzed by ruthenium complex **2f**.[a]



Entry	Imine[b]	Yield [%][c]	*ee* [%][d,e]
1	**7a**	96	98 (94)
2	**7b**	95	96 (95)
3	**7c**	96	93 (91)
4	**7d**	95	92 (87)
5	**7e**	96	97 (96)
6	(±)-**7f**	98 (60:40)	62 (1*R*,4*R*); 98 (1*R*,4*S*)
7	(±)-**7f**	98 (60:40)	68 (1*S*,4*S*); 98 (1*S*,4*R*)
8	(*S*)-**7f**	98 (20:80)	>99 (1*S*,4*S*); >99 (1*R*,4*S*)
9	(*S*)-**7f**	98 (>99:1)	>99 (1*S*, 4*S*); >99 (1*R*,4*S*)

[a] Reaction conditions: substrates (0.2 mmol) in 1,2-dichloroethane (1 mL), (*R*,*R*)-**2f** (2 mol%) for entries 1–5, (*R*,*R*)-**2f** (1 mol%) for entries 6 and 8, and (*S*,*S*)-**2f** (1 mol%) for entries 7 and 9, H_2 (50 atm), $(Boc)_2O$ (1.1 equiv), stirred at 40°C for 10 h. [b] The *E*/*Z* ratios of imines **7a**–**f** were >100:1. [c] Isolated yields. The *cis*/*trans* ratios of **8f** (in parentheses) were determined by ^1H NMR spectroscopy of the crude reaction mixture. [d] The enantiomeric excesses were determined by HPLC with a chiral AD-H column. [e] Data in parentheses were obtained at a substrate/catalyst ratio of 100:1.

high *cis* selectivity (>99:1 d.r.) and afforded Boc-protected Sertraline [(1*S*,4*S*)-**8f**] in enantiopure form in nearly quantitative yield (Table 3, entry 9). In addition, the reaction proceeded smoothly in the presence of **2f** (1 mol%) on a 0.5 g scale at high concentration (8.25 M). After cleavage of the Boc protecting group by HCl under very mild conditions, optically pure Sertraline hydrochloride was obtained in 90% overall yield, >99% *ee*, and >99% d.r. (Scheme 2).



Scheme 2. The synthesis of Sertraline hydrochloride.

In summary, we have shown that a phosphine-free, chiral, cationic Ru–MsDPEN (**2f**; MsDPEN = *N*-(methanesulfonyl)-1,2-diphenylethylenediamine) complex is a highly efficient catalyst for the enantioselective hydrogenation of a broad range of often-problematic *N*-alkyl ketimines (up to 99% *ee*). *N*-Benzyl ketimines can be efficiently hydrogenated under more environmentally friendly solvent-free conditions at low catalyst loadings (as low as 0.05 mol%). This new method provides a more practical and greener synthetic approach to the preparation of optically active amines, particularly *N*-alkyl amines, such as Sertraline. An investigation into the underlying mechanistic aspects that account for the high enantioselective control is in progress.

Experimental Section

Typical procedure: A glass-lined stainless-steel reactor (50 mL) equipped with a magnetic stir bar was charged with Ru catalyst **2f** (2.8 mg, 0.002 mmol), the corresponding imine (0.2 mmol), and $(Boc)_2O$ (1.1 equiv) in 1,2-dichloroethane (1 mL), under a nitrogen atmosphere, in a glovebox. The autoclave was closed and, after purging with hydrogen gas several times, the final pressure of hydrogen gas was adjusted to 50 atm. The reaction mixture was stirred at 40°C for the specified period of time. Then, the hydrogen gas was carefully released and the conversion was determined by ^1H NMR spectroscopy. The reaction mixture was filtered through a short pad of silica and eluted with a mixture of dichloromethane and petroleum (1:1, v/v) to give the pure products. The *ee* of the product was determined by HPLC through a chiral AD-H column.

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Keywords: asymmetric catalysis · diamine ligands · hydrogenation · ketimines · ruthenium

[1] For a review, see: *Chiral Amine Synthesis: Methods Developments and Applications* (Ed.: T. C. Nugent), Wiley-VCH, Weinheim, **2010**.
[2] W. M. Welch, A. R. Kraska, R. Sarges, B. K. Koe, *J. Med. Chem.* **1984**, *27*, 1508–1515.
[3] A. Kessler, H. Faure, C. Petrel, D. Rognan, M. Césario, M. Ruat, P. Dauban, R. H. Dodd, *J. Med. Chem.* **2006**, *49*, 5119–5128.
[4] O. R. Thiel, C. Bernard, W. Tormos, A. Brewin, S. Hirotani, K. Murakami, K. Saito, R. D. Larsen, M. J. Martinelli, P. J. Reider, *Tetrahedron Lett.* **2008**, *49*, 13–15.
[5] For selected reviews on metal-catalyzed asymmetric transfer hydrogenation, see: a) R. Noyori, S. Hashiguchi, *Acc. Chem. Res.* **1997**, *30*, 97–102; b) S. Gladiali, E. Alberico, *Chem. Soc. Rev.* **2006**, *35*, 226–236. For a pioneering contribution, see: c) N. Uematsu, A. Fujii, S. Hashiguchi, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.* **1996**, *118*, 4916–4917.
[6] For selected examples of the organocatalytic asymmetric transfer hydrogenation of imines, 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.

[7] For selected examples of the hydrosilylation of imines, see: a) X. Verdaguer, U. E. W. Lange, M. T. Reding, S. L. Buchwald, *J. Am. Chem. Soc.* **1996**, *118*, 6784–6785; b) C. Wang, X. Wu, L. Zhou, J. Sun, *Chem. Eur. J.* **2008**, *14*, 8789–8792.

[8] For selected reviews on the asymmetric hydrogenation of imines, see: a) F. Spindler, H.-U. Blaser in *Handbook of Homogeneous Hydrogenation* (Eds.: J. G. de Vries, C. J. Elsevier), Wiley-VCH, Weinheim, **2007**, p. 1193; b) T. L. Church, P. G. Andersson in *Chiral Amine Synthesis: Methods Developments and Applications* (Ed.: T. C. Nugent), Wiley-VCH, Weinheim, **2010**, p. 179; c) W. Tang, X. Zhang, *Chem. Rev.* **2003**, *103*, 3029–3069; d) T. C. Nugent, M. El-Shazly, *Adv. Synth. Catal.* **2010**, *352*, 753–819.

[9] For selected reviews, see: a) R. Noyori, *Asymmetric Catalysis in Organic Synthesis*, Wiley, New York, **1994**; b) *Comprehensive Asymmetric Catalysis, Vols. I–III* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**.

[10] For examples of Ti and Zr catalysis, see: a) C. A. Willoughby, S. L. Buchwald, *J. Am. Chem. Soc.* **1994**, *116*, 8952–8965; b) J. Cámpora, S. L. Buchwald, E. Gutiérrez-Puebla, A. Monge, *Organometallics* **1995**, *14*, 2039–2046; c) M. Ringwald, R. Stürmer, H. H. Brintzinger, *J. Am. Chem. Soc.* **1999**, *121*, 1524–1527.

[11] For examples of Rh catalysis, see: a) A. Levi, G. Modena, G. Scorrano, *J. Chem. Soc. Chem. Commun.* **1975**, 6–7; b) G. J. Kang, W. R. Cullen, M. D. Fryzuk, B. R. James, J. P. Kutney, *J. Chem. Soc. Chem. Commun.* **1988**, 1466–1467; c) C. Lensink, E. Rijnberg, J. G. de Vries, *J. Mol. Catal. A* **1997**, *116*, 199–207; d) A. G. Becalski, W. R. Cullen, M. D. Fryzuk, B. R. James, G. J. Kang, S. Rettig, *Inorg. Chem.* **1991**, *30*, 5002–5008; e) J. M. Buriak, J. A. Osborn, *Organometallics* **1996**, *15*, 3161–3169; f) V. I. Tararov, R. Kadyrov, T. H. Riermeier, J. Holz, A. Börner, *Tetrahedron: Asymmetry* **1999**, *10*, 4009–4015; g) F. Spindler, H. U. Blaser, *Adv. Synth. Catal.* **2001**, *343*, 68–70; h) G. Shang, Q. Yang, X. Zhang, *Angew. Chem.* **2006**, *118*, 6508–6510; *Angew. Chem. Int. Ed.* **2006**, *45*, 6360–6362; i) M. J. Burk, J. E. Feaster, *J. Am. Chem. Soc.* **1992**, *114*, 6266–6267.

[12] For examples of Ru catalysis, see: a) K. Abdur-Rashid, A. J. Lough, R. H. Morris, *Organometallics* **2001**, *20*, 1047–1049; b) C. J. Cobley, J. P. Henschke, *Adv. Synth. Catal.* **2003**, *345*, 195–201; c) M. Jackson, I. C. Lennon, *Tetrahedron Lett.* **2007**, *48*, 1831–1834; d) W. Oppolzer, M. Wills, C. Starkemann, G. Bernardinelli, *Tetrahedron Lett.* **1990**, *31*, 4117–4120; e) A. Charette, A. Giroux, *Tetrahedron Lett.* **1996**, *37*, 6669–6672; f) H. Guan, M. Iimura, M. P. Magee, J. R. Norton, G. Zhu, *J. Am. Chem. Soc.* **2005**, *127*, 7805–7814.

[13] For examples of Ir catalysis with P,P ligands, see: a) Y. N. C. Chan, J. A. Osborn, *J. Am. Chem. Soc.* **1990**, *112*, 9400–9401; b) F. Spindler, B. Pugin, H. U. Blaser, *Angew. Chem.* **1990**, *102*, 561–562; *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 558–559; c) B. Pugin, H. Landert, F. Spindler, H.-U. Blaser, *Adv. Synth. Catal.* **2002**, *344*, 974–979; d) D. Xiao, X. Zhang, *Angew. Chem.* **2001**, *113*, 3533–3536; *Angew. Chem. Int. Ed.* **2001**, *40*, 3425–3428; e) E. Guiu, B. Muñoz, S. Castillón, C. Claver, *Adv. Synth. Catal.* **2003**, *345*, 169–171; f) A. Dervisi, C. Carcedo, L. Ool, *Adv. Synth. Catal.* **2006**, *348*, 175–183; g) T. Imamoto, N. Iwadate, K. Yoshida, *Org. Lett.* **2006**, *8*, 2289–2292; h) W. Li, G. Hou, M. Chang, X. Zhang, *Adv. Synth. Catal.* **2009**, *351*, 3123–3127; i) 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; j) X. B. Jiang, A. J. Minnaard, B. Hessen, B. L. Feringa, A. L. L. Duchateau, J. G. O. Andrien, J. A. F. Boogers, J. G. de Vries, *Org. Lett.* **2003**, *5*, 1503–1506; k) M. T. Reetz, O. Bondarev, *Angew. Chem.* **2007**, *119*, 4607–4610; *Angew. Chem. Int. Ed.* **2007**, *46*, 4523–4526; l) N. Mršić, A. J. Minnaard, B. L. Feringa, J. G. de Vries, *J. Am. Chem. Soc.* **2009**, *131*, 8358–8359; m) G. Hou, R. Tao, Y. Sun, X. Zhang, F. Gosselin, *J. Am. Chem. Soc.* **2010**, *132*, 2124–2125.

[14] For examples of Ir catalysis with P,N ligands, see: a) P. Schnider, G. Koch, R. Prétôt, G. Wang, F. M. Bohnen, C. Krüger, A. Pfaltz, *Chem. Eur. J.* **1997**, *3*, 887–892; b) S. Kainz, A. Brinkmann, W. Leitner, A. Pfaltz, *J. Am. Chem. Soc.* **1999**, *121*, 6421–6429; c) M. Solinas, A. Pfaltz, P. G. Cozzi, W. Leitner, *J. Am. Chem. Soc.* **2004**, *126*, 16142–16147; d) A. Baeza, A. Pfaltz, *Chem. Eur. J.* **2010**, *16*, 4003–4009; e) A. Trifonova, J. S. Diesen, C. J. Chapman, P. G. Andersson, *Org. Lett.* **2004**, *6*, 3825–3827; f) A. Trifonova, J. S. Diesen, P. G. Andersson, *Chem. Eur. J.* **2006**, *12*, 2318–2328; g) M. N. Cheemala, P. Knochel, *Org. Lett.* **2007**, *9*, 3089–3092; h) C. Moessner, C. Bolm, *Angew. Chem.* **2005**, *117*, 7736–7739; *Angew. Chem. Int. Ed.* **2005**, *44*, 7564–7567; i) S. F. Zhu, J. B. Xie, Y. Z. Zhang, S. Li, Q. L. Zhou, *J. Am. Chem. Soc.* **2006**, *128*, 12886–12891; j) Z. Han, Z. Wang, X. Zhang, K. Ding, *Angew. Chem.* **2009**, *121*, 5449–5453; *Angew. Chem. Int. Ed.* **2009**, *48*, 5345–5349.

[15] For examples of Pd catalysis, see: a) H. Abe, H. Amii, K. Uneyama, *Org. Lett.* **2001**, *3*, 313–315; b) Q. Yang, G. Shang, W. Gao, J. Deng, X. Zhang, *Angew. Chem.* **2006**, *118*, 3916–3919; *Angew. Chem. Int. Ed.* **2006**, *45*, 3832–3835; c) Y. Q. Wang, S. M. Lu, Y. G. Zhou, *J. Org. Chem.* **2007**, *72*, 3729–3734; d) Y. Q. Wang, C. B. Yu, D. W. Wang, X. B. Wang, Y. G. Zhou, *Org. Lett.* **2008**, *10*, 2071–2074; e) C. B. Yu, D. W. Wang, Y. G. Zhou, *J. Org. Chem.* **2009**, *74*, 5633–5635.

[16] F. Fache, E. Schulz, M. L. Tommasino, M. Lemaire, *Chem. Rev.* **2000**, *100*, 2159–2232.

[17] a) T. Ohkuma, N. Utsumi, K. Tsutsumi, K. Murata, C. A. Sandoval, R. Noyori, *J. Am. Chem. Soc.* **2006**, *128*, 8724–8725; b) C. A. Sandoval, T. Ohkuma, N. Utsumi, K. Tsutsumi, K. Murata, R. Noyori, *Chem. Asian J.* **2006**, *1*, 102–110; c) T. Ohkuma, K. Tsutsumi, N. Utsumi, N. Arai, R. Noyori, K. Murata, *Org. Lett.* **2007**, *9*, 255–257.

[18] For examples of Ru complexes of diamines for the asymmetric hydrogenation of ketones, see: a) M. Ito, M. Hirakawa, K. Murata, T. Ikariya, *Organometallics* **2001**, *20*, 379–381; b) C. Hedberg, K. Källström, P. I. Arvidsson, P. Brandt, P. G. Andersson, *J. Am. Chem. Soc.* **2005**, *127*, 15083–15090; c) A. Paptchikhine, K. Källström, P. G. Andersson, *C. R. Chim.* **2007**, *10*, 213–219; d) P. Cheruku, T. L. Church, P. G. Andersson, *Chem. Asian J.* **2008**, *3*, 1390–1394; e) M. Ito, Y. Endo, T. Ikariya, *Organometallics* **2008**, *27*, 6053–6055.

[19] 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*, 8592–8595; *Angew. Chem. Int. Ed.* **2008**, *47*, 8464–8467.

[20] For mechanistic investigations into the reduction of imines, see: a) J. B. Åberg, J. S. M. Samec, J. E. Bäckvall, *Chem. Commun.* **2006**, 2771–2773; b) J. E. D. Martins, G. J. Clarkson, M. Wills, *Org. Lett.* **2009**, *11*, 847–850.

[21] a) C. Li, J. Xiao, *J. Am. Chem. Soc.* **2008**, *130*, 13208–13209; b) C. Li, C. Wang, B. Villa-Marcos, J. Xiao, *J. Am. Chem. Soc.* **2008**, *130*, 14450–14451; c) C. Li, B. Villa-Marcos, J. Xiao, *J. Am. Chem. Soc.* **2009**, *131*, 6967–6969.

[22] S. Shirai, H. Nara, Y. Kayaki, T. Ikariya, *Organometallics* **2009**, *28*, 802–809.

[23] a) Y. M. He, Q. H. Fan, *Org. Biomol. Chem.* **2010**, *8*, 2497–2504; b) Z. W. Li, T. L. Wang, Y. M. He, Z. J. Wang, Q. H. Fan, J. Pan, L. J. Xu, *Org. Lett.* **2008**, *10*, 5265–5268; c) Z. J. Wang, G. J. Deng, Y. Li, Y. M. He, W. J. Tang, Q. H. Fan, *Org. Lett.* **2007**, *9*, 1243–1246; d) W. Tang, L. Xu, Q. H. Fan, J. Wang, B. Fan, Z. Zhou, K. H. Lam, A. S. C. Chan, *Angew. Chem.* **2009**, *121*, 9299–9302; *Angew. Chem. Int. Ed.* **2009**, *48*, 9135–9138.

[24] K. B. Hansen, T. Rosner, M. Kubryk, P. G. Dormer, J. D. Armstrong, *Org. Lett.* **2005**, *7*, 4935–4938.

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

[26] For a comprehensive review, see: P. J. Walsh, H. Li, C. A. de Parrodi, *Chem. Rev.* **2007**, *107*, 2503–2545.

[27] To date, only three examples of transition-metal-catalyzed asymmetric hydrogenation under solvent-free conditions have been reported, see Ref. [12a] and: a) X. Wan, Y. Sun, Y. Luo, D. Li, Z. Zhang, *J. Org. Chem.* **2005**, *70*, 1070–1072; b) Z. J. Wang, H. F. Zhou, T. L. Wang, Y. M. He, Q. H. Fan, *Green Chem.* **2009**, *11*, 767–769.

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