34
Enantioselective Hydrogenation of C=N Functions and Enamines

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34.1
Introduction

Chiral amines were always considered important targets for synthetic chemists, and attempts to prepare such compounds enantioselectively date back to quite early times. Selected milestones for the development of enantioselective catalysts for the reduction of C=N functions are listed in Table 34.1. At first, only heterogeneous hydrogenation catalysts such as Pt black, Pd/C or Raney nickel were applied. These were modified with chiral auxiliaries in the hope that some induction – that is, transfer of chirality from the auxiliary to the reactant – might occur. These efforts were undertaken on a purely empirical basis, without any understanding of what might influence the desired selectivity. Only very few substrate types were studied and, not surprisingly, enantioselectivities were

Table 34.1 Selected milestones for the enantioselective hydrogenation of C=N functions.

Year	Substrate	Catalyst	Chiral auxiliary [a)]	ee [%]	Comment	Reference
1941	oxime	Pt black	Menthoxyacetic acid	3	First reported experiment	1
1958	dioxime	Pd	Silk fibroin	15	Chiral support	2
1975	oxime	Ru complex	diop	15	Homogeneous Ru catalyst	3
1975	imine	Rh complex	diop	22	Homogeneous Rh catalyst	4
1984	C=N–Alk	Rh complex	bdpp	72	First useful ee	5
1989	C=N–Alk	Rh complex	$bdpp_{sulf}$	94	First very high ee	6
1990	C=N–Ar	Ir complex	bdpp	84	Homogeneous Ir catalyst	7
1992	cycl. imine	Ti complex	ebthi	99	Homogeneous Ti catalyst	8
1992	C=N–X	Rh complex	duphos	96	Acyl hydrazone	9
1996	C=N–X	Ru complex	N′N ligand	97	Transfer hydrogenation	10
1996	MEA imine	Ir complex	josiphos	80	First industrial application	11

a) For structures of ligands, see Figs. 34.1 and 34.3.

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low and could not always be reproduced. The first reports on homogeneous Ru and Rh catalysts appeared in 1975, but useful enantioselectivities were only reported in 1984 by the Marko group. Remarkable progress has been made during the 1990s, however, and today several very selective catalysts are available for different types of C=N functions, with the first industrial process being announced in 1996.

Despite this significant progress, the enantioselective hydrogenation of prochiral C=N groups (imines, oximes, hydrazones, etc.) and enamines to obtain the corresponding chiral amines still represents a major challenge. Whereas many highly enantioselective chiral catalysts have been developed for the asymmetric hydrogenation of alkenes and ketones bearing various functional groups, much fewer catalysts are effective for the hydrogenation of substrates with a C=N function (for pertinent recent reviews, see [12–17]). There are several reasons that might explain this situation. On the one hand, the enantioselective hydrogenation of enamides and other C=C groups (and later also of C=O compounds) was so successful that most attention was directed to these substrates [12]. On the other hand, C=N compounds have some chemical peculiarities that make their stereoselective reduction more complex than that of C=O and C=C compounds. Even though the preparation starting from the corresponding amine derivative and carbonyl compound is relatively simple, complete conversion is not always possible and formation of trimers or oligomers can occur. Both the starting amine (e.g., [6a]) and the oligomers can be catalyst poisons. In addition, the resulting C=N compounds are often sensitive to hydrolysis and the presence of *syn*/*anti* as well as enamine isomers can be a problem for selective hydrogenation.

Generally, the imine substrates are prepared from the corresponding ketone and amine and are hydrogenated as isolated (and purified) compounds. However, reductive amination where the C=N function is prepared *in situ* is attractive from an industrial point of view, and indeed there are some successful examples reported below [18, 19]. It is reasonably certain that most catalysts described in this chapter catalyze the addition of H_2 directly to the C=N bond and not to the tautomeric enamine C=C bond, even though enamines can also be hydrogenated enantioselectively.

The nature of the substituent directly attached to the N-atom influences the properties (basicity, reduction potential, etc.) of the C=N function more than the substituents at the carbon atom. For example, it was found that Ir-diphosphine catalysts that are very active for N-aryl imines are deactivated rapidly when applied for aliphatic imines [7], or that titanocene-based catalysts are active only for *N*-alkyl imines but not for *N*-aryl imines [8, 20, 21]. Oximes and other C=N–X compounds show even more pronounced differences in reactivity.

The following sections provide an overview on the state of the art for the enantioselective hydrogenation (including transfer hydrogenation) of various classes of C=N groups, together with a short, critical assessment of the presently known catalytic systems. Only selective (ee >80%) or otherwise interesting catalysts are included and, furthermore, other reduction methods for C=N functions (hydride reduction, hydrosilylation) are only covered summarily.

34.2
Chiral Ligands

The catalytic properties of an enantioselective homogeneous catalyst are determined by the choice of the metal, the chiral ligand, and the anion. Since the choice of metals is limited – only Ir, Rh, Ru and Ti have proved to be effective – and the anion is usually either coordinating or non-coordinating (leading to cationic catalysts), the chiral ligand is the most important parameter controlling catalyst performance. For the reduction of the various C=N functions, several ligand types have been shown to give satisfactory to very good catalytic properties

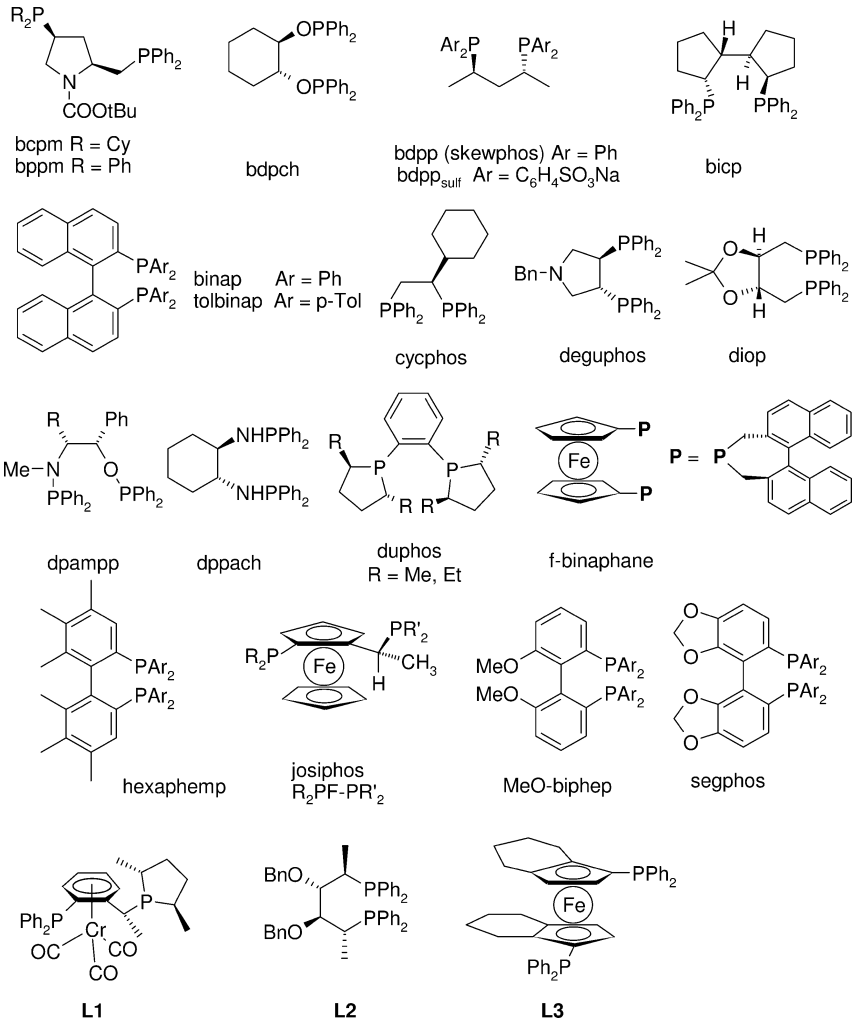


Fig. 34.1 Structures and abbreviations/numbers for diphosphine ligands.

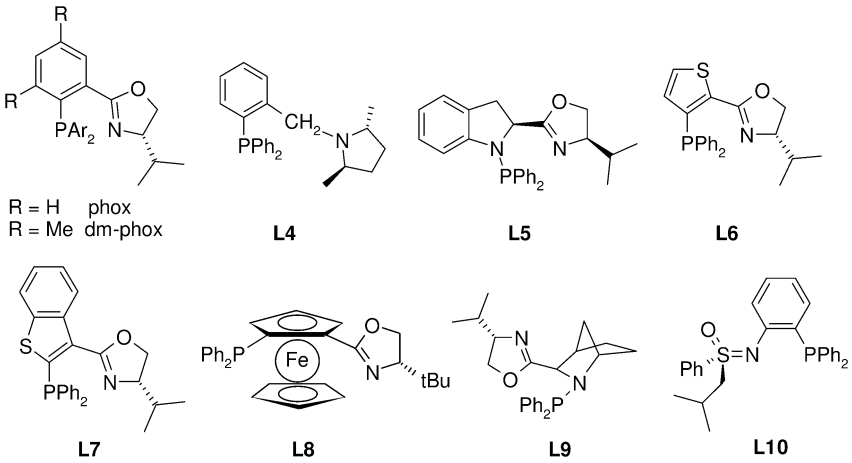


Fig. 34.2 Structures and abbreviations/numbers for PN ligands.

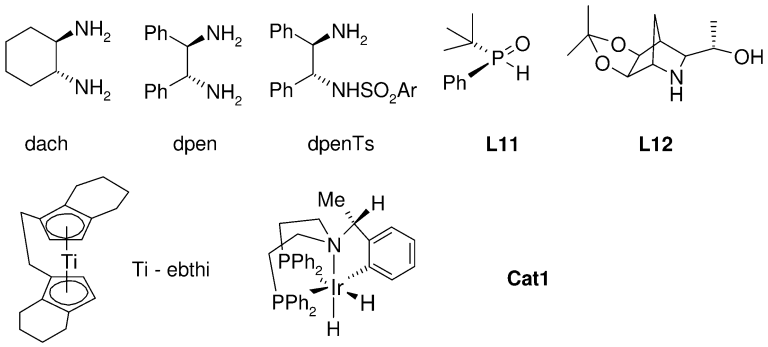


Fig. 34.3 Structures and abbreviations/numbers for miscellaneous ligands and catalysts.

– that is, enantioselectivity (ee, %), productivity (turnover number; TON) or substrate:catalyst ratio (SCR) and activity (turnover frequency; TOF; h^{-1}). We have depicted the most important ligands in Figs. 34.1 to 34.3, arranged either alphabetically for those with a name, or numbered as **Lx**. A cursory investigation of the depicted ligands shows a bewildering diversity of structural elements. Most ligands have actually been prepared not with the reduction of C=N compounds in mind, but have first been tested on C=C or C=O groups and later shown also to be viable for C=N functions. Most ligands are not (yet) available commercially, which diminishes their attractiveness for synthetic applications.

34.3
N-Aryl Imines

With the exception of the (*S*)-metolachlor process, no C=N hydrogenation has been commercialized and most investigations described in this chapter have been carried out with a few model substrates. Much effort has been devoted in identifying catalysts which are able to hydrogenate substrates of the type **1** (see Fig. 34.4), since *N*-alkyl-2,6-disubstituted anilines with a stereogenic C-atom in the *α*-position are intermediates for a number of important acylanilide pesticides, the most important example being the herbicide Metolachlor® (Fig. 34.5) [11, 22]. Since not all stereoisomers are biologically active, the stereoselective synthesis of the most effective ones is of industrial interest. Hence, the enantioselective hydrogenation of the imine **1a** will be discussed in somewhat more detail.

Hydrogenation of the imines **1a** and **1b** was investigated extensively by several research groups [28]. Whilst, initially, useful results were obtained with chiral Rh diphosphine catalysts [29], an important step towards a technically feasible catalyst was made with newly developed Ir diphosphine complexes [7]. Despite a significant tendency for deactivation, SCR values of ≥10 000 and reasonable reaction rates were achieved for the hydrogenation of MEA-imine with an Ir–diop complex in the presence of iodide ions (Table 34.2; entry 2.1). The hydrogenation of other *N*-aryl imines with similar structural elements showed that both the 2,6-alkyl substituents of the *N*-phenyl group as well as the methoxy-substituent contribute to the high enantioselectivity. Replacing the methoxy group of the DMA-imine **1b** by an ethyl group led to a decrease in ee from 69% to 52%, while further replacement of the 2,6-dimethyl phenyl by a phenyl group reduced the ee to 18% [7]. Despite these good results, both catalyst activity as well as productivity were insufficient for a technical application for a high-volume product.

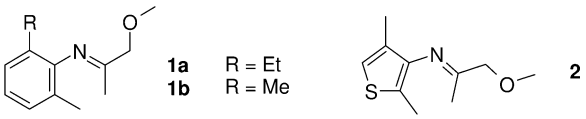


Fig. 34.4 Structures of *N*-aryl imines.

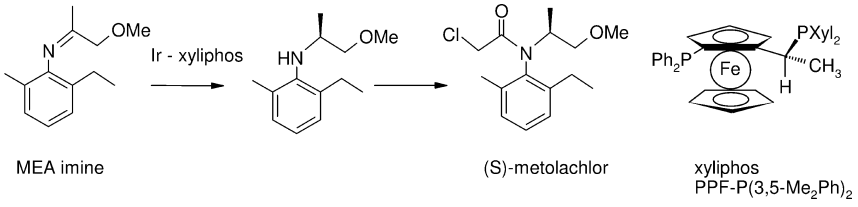


Fig. 34.5 Synthesis of *S*-metolachlor.

Table 34.2 Selected results for the enantioselective hydrogenation of *N*-aryl imines **1** and **2** (for structures, see Fig. 34.4): Catalytic system, reaction conditions, enantioselectivity, productivity and activity.

Entry	Substrate	Catalyst	p [bar]	ee [%]	SCR	TOF [h^{-1}]	Reference
2.1	**1a**	Ir–diop/I^-	100	62	10 000	200	7
2.2	**1a**	Ir–PPF-PXyl_2/I^-/H^+	80	78	1 000 000	350 000	23
2.3	**1a**	Ir–PPF-PAr_2 [a]/I^-/H^+	80	87	5 000	31	23
2.4	**2**	Ir–PPF-Pxyl_2/ I^-/H^+	60	80	100	200	23
2.5	**1b**	[Ir(diop)$(OCOCF_3)_3$]	40	90	500	3	24
2.6	**1a** [b]	Ir–PPF-PXyl_2/I^-/H^+	80	78	10 000	>600	25
2.7	**1a**	Ir–PPF-PXyl_2 [c]/I^-/H^+	80	78	120 000	12 000	26
2.8	**1a**	Ir–**L1**	80	82	100	~6	27

Reactions carried out between r.t. and 50 °C, unless otherwise noted.

a) Ar = 3,5-Me_2-4-NPr_2-Ph.

b) Formed *in situ* from 2-methyl-6-ethyl-aniline + methoxyacetone.

c) Immobilized on SiO_2.

SCR: Substrate:catalyst ratio.

The final breakthrough on the way to a production process for the metolachlor herbicide came in 1993. A new class of Ir–ferrocenyl diphosphine complexes turned out to be stable and, in the presence of both acetic acid and iodide, provided extraordinarily active and productive catalysts which also did not deactivate [30]. An extensive ligand optimization led to the choice of [Ir(cod)Cl]$_2$-PPF-PXyl_2 (xyliphos) as the optimal catalyst. At a hydrogen pressure of 80 bar, a temperature of 50 °C, and using an SCR of >10 000, complete conversion could be reached within 3–4 h with an enantiomeric excess of around 80% (Table 34.2; entry 2.2). The best enantioselectivities of 87% were obtained with N-substituted xyliphos ligands, albeit with much lower activity (e.g., see entry 2.3). It is noteworthy, that the 2,6-disubstituted phenyl group in **1** could be replaced by a 2,4-disubstituted thien-3-yl group (imine **2**) without loss in catalyst activity (entry 2.4). Scale-up presented no major problems, and the production plant was opened officially in November 1996. At present, there is no convincing explanation for the remarkable effect of iodide and acid and, interestingly, Osborn and Sablong reported that completely halogen-free catalysts can also give very good enantioselectivities (e.g., 90% ee with imine **1b**) (entry 2.5). The Ir-xyliphos catalyst was also tested for the reductive amination where the MEA imine is prepared *in situ* [25], as well in an immobilized version [26]. However, while for both variants the ee-values were satisfactory, catalyst productivity was not sufficient for a commercial application (Table 34.2; entries 2.6 and 2.7). Even though the scope of this new catalytic system has not yet been fully determined, it was successfully applied to the hydrogenation of imines **2** (entry 2.4), **3a** and **9** (see below). Recently, Salzer reported very good ee-values

with an interesting josiphos analogue **L1** based on an arene chromium tricarbonyl scaffold, but the TON and TOF were both very low (entry 2.8).

As can be seen from the data in Table 34.3, there are today a number of catalysts achieving medium to very high ee-values for the model substrates of the type **3**. Most of the successful catalyst systems are Ir-diphosphines, inspired by the catalysts described above for the metolachlor production and Ir-phosphinooxazoline complexes originally developed by Pfaltz [31].

Ir–josiphos and the Ir–f-binaphane catalyst developed by Zhang and coworkers achieved ee-values of 94 to >99% with several imines of the type **3** (Table 34.3; entries 3.1, 3.2, 3.8) and in presence of 1.5 equiv. Ti(*Oi*Pr)$_4$. Ir–f-binaphane was also able to catalyze the reductive amination of aromatic ketones with a variety of substituted anilines with high ee-values but relatively low catalyst activity (entry 3.9). Claver and coworkers achieved ee-values of up to 57% for the Ir-catalyzed hydrogenation of **3b** using sugar-derived bisphosphinite and bisphosphite ligands [39], while Vargas et al. [40] reported 84% ee with an Ir-phosphine-phosphite catalyst.

Several new PN ligands were developed and tested using model substrates **3**. The Ir-phox catalyst originally developed by Pfaltz achieved ee-values of up to 89% with reasonable TONs which could be increased up to 6800 in supercritical CO_2 ($scCO_2$), albeit with some loss in enantioselectivity (Table 34.3; entries 3.3, 3.4). Ir catalysts with similar P-N ligands also achieved respectable catalyst performances (see entries 3.5, 3.6, 3.10). It was also shown that various Ir-phosphinooxazoline catalysts work well in $scCO_2$-ionic liquid systems, allowing easy separation and recycling of the catalyst with similar catalyst performance [31b]. Very recently, Moessner and Bolm [41] reported phosphinosulfoximines such as **L10** as a new, very efficient ligand class for the Ir-catalyzed hydrogenation of selected *N*-aryl imines. The best enantioselectivities (90–98% ee) were obtained for imines with an *N*-(*p*-MeO)-phenyl group, with TONs up to 1000 (e.g., see entry 3.11). The addition of iodine is required in order to produce an active catalyst.

Ru–diphosphine–diamine complexes developed originally by Noyori for the hydrogenation of aryl ketones are also suitable for the hydrogenation of imines. The best results are obtained for *N*-aryl imines where a Ru–duphos–diamine complex achieved up to 94% ee, albeit with relatively low activity and productivity (entry 3.7) (for data relating to cyclic imines, see Table 34.5).

Besides these results, we registered with interest the first example of a Pd–binap-catalyzed hydrogenation of a fluorinated α-imino ester in the presence of trifluoroacetic acid in fluorinated alcohols (with ee-values up to 91%, but very low TON and TOF) [42].

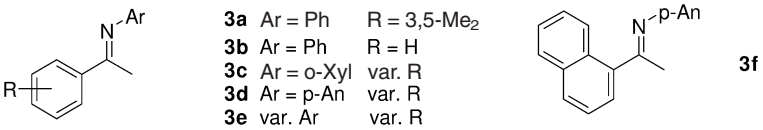


Fig. 34.6 Structure of *N*-aryl imines.

Table 34.3 Selected results for the enantioselective hydrogenation of the model *N*-aryl imines **3** (for structures, see Fig. 34.6): Catalytic system, reaction conditions, enantioselectivity, productivity and activity.

Entry	Substrate	Catalyst	p [bar]	ee [%]	SCR	TOF [h^{-1}]	Reference(s)
3.1	**3a**	Ir–PPF-P(4-CF_3Ph)$_2$/I^-/H^+	80	96	200	n.a.	23
3.2	**3a**	Ir–f-binaphane	~70	>99	100	2–4	32
3.3	**3b**	Ir–dm-phox	100	89 [a]	1000	~100	31a
3.4	**3b**	Ir–phox (scCO_2)	30	74	6800	2800	33
3.5	**3b**	Ir–**L5**	20	90	50	4	34a
3.6	**3b**	Ir–**L6** or **L7**	50	83–86	1000	250	34b
3.7	**3b**	Ru–Et-duphos–diamine [b]/ *t*BuOK	15	92–94	100	≤5	35, 36
3.8	**3c**	Ir–f-binaphane/I_2	~70	94–95	100	2–4	32
3.9	**3d** [c]	Ir–f-binaphane/I_2/Ti(*O*i Pr)$_4$	~70	90–96	100	10	37
3.10	**3e**	Ir–**L9**	20	80–90	200	~100	38
3.11	**3f**	Ir–**L10**/I_2	20	98	200 [d]	50	41

Reactions carried out between r.t. and 50 °C, unless otherwise noted.

a) At 5 °C.

b) dach or dpen.

c) Formed *in situ* from the corresponding acetophenones and anilines.

d) At SCR 1000, a pressure of 50 bar is required for full conversion.

n.a.: data not available.

34.4 *N*-Alkyl Imines

Until now, few acyclic *N*-alkyl imines or the corresponding amines have been found to be of practical industrial importance. Most studies reported herein were carried out with model substrates, especially with the *N*-benzyl imine of acetophenone **5a** and some analogues thereof (Fig. 34.7). One reason for this choice could be the easy preparation of a pure crystalline starting material, and another reason might be that the chiral primary amines can be obtained by hydrogenolysis of the benzyl group. As can be seen in Table 34.4, there are several catalyst systems with fair to good ee-values and activities.

Enantioselectivities >90% were reported for a Ti–ebthi catalyst (Table 34.4; entry 4.1) and for some Rh–diphosphine complexes (entries 4.2–4.4). Interestingly, the highest ee-values were obtained using sulfonated diphosphines (bdpp$_{sulf}$) in an aqueous biphasic medium (entry 4.3). The degree of sulfonation strongly affected the enantioselectivity: the Rh–mono-sulfonated bdpp gave 94% ee, compared to 65% ee with Rh–bdpp in MeOH, and almost racemic product with bis- or tris-sulfonated ligands. In addition, the activity of the mono-sulfonated cata-

Table 34.4 Selected results for the enantioselective hydrogenation of *N*-alkyl imines and enamines (for structures, see Fig. 34.7): Catalytic system, reaction conditions, enantioselectivity, productivity and activity.

Entry	Substrate	Catalyst	p [bar]	ee [%]	SCR	TOF [h^{-1}]	Reference
4.1	**4**	Ti–ebthi	5	92	20	4	21
4.2	**5a**	Rh–cycphos	100	91	100	0.7	43
4.3	**5a**	Rh–$bdpp_{sulf}$	70	96	100	16	6b
4.4	**5b**	Rh–bdpp/AOT micelles	70	92	100	4.6	44
4.5	**5a**	Ir–**L4**	100	46	100	>36000	45
4.6	**5a**	Ir–**L5**	50	82	50	4	34
4.7	**5a**	Ru–dppach–dach	3	92	1500	23	47
4.8	**5**	Ir–**L11**/pyridine	25	80–83	20	<1	46
4.9	a)	Rh–deguphos	60	98	200	~60	48

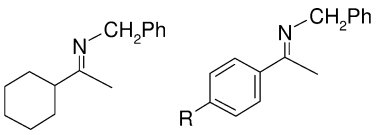
Reactions carried out between r.t. and 50 °C, unless otherwise noted.

a) Reductive amination of PhCOCOOH or $PhCH_2COCOOH$ with $BnNH_2$.

lyst was higher by a factor of 5 compared to bdpp [6b]. A similar positive effect for the presence of a sulfo group was described by Buriak and Osborn (entry 4.4). *N*-Alkyl imines of cyclic ketones can be reduced with moderate to good enantioselectivities using a Ru–diamine complex and formate as transfer reducing agent, but the catalytic activities and productivities for all of these catalysts ranged from very low to modest [10].

Ir–PN catalysts which are quite effective for *N*-aryl imines also show some promise for *N*-alkyl derivatives. Of special interest were the high TOF claimed for the Ir–**L4** system, but unfortunately the ee is very low (entry 4.5). Several other Ir–PN were described with moderate to good ee-values, but again the TON and TOF were modest, as shown (Table 34.4; entry 4.6 (see also [49]).

Imine **5a** is also hydrogenated with good ee and TON using a Ru–diphosphine–diamine complex originally developed by Noyori (entry 4.7). An unusual



4 **5a** R = H
5b R = OMe

Fig. 34.7 Structures of *N*-alkyl imines.

catalyst was developed by Feringa and de Vries, who applied secondary phosphine oxides of the type **L11** for the Ir-catalyzed hydrogenation of various benzyl imines **5**. While the enantioselectivities were surprisingly good, activity and productivity were very low (e.g., see entry 4.8).

Recently, Börner and coworkers described an efficient Rh–deguphos catalyst for the reductive amination of α-keto acids with benzyl amine. *E.e.*-values up to 98% were obtained for the reaction of phenyl pyruvic acid and $PhCH_2COCOOH$ (entry 4.9), albeit with often incomplete conversion and low TOFs. Similar results were also obtained for several other α-keto acids, and also with ligands such as norphos and chiraphos. An interesting variant for the preparation of α-amino acid derivatives is the one-pot preparation of aromatic α-(*N*-cyclohexylamino) amides from the corresponding aryl iodide, cyclohexylamine under a H_2/CO atmosphere catalyzed by Pd–duphos or Pd–Trost ligands [50]. Yields and ee-values were in the order of 30–50% and 90>99%, respectively, and a catalyst loading of around 4% was necessary.

Besides these results, we registered with interest the claim by Magee and Norton [51] that (Cp)W–diphosphine complexes are able to hydrogenate imines via a novel ionic mechanism, albeit with low ee and TOF.

34.5
Cyclic Imines and Heteraromatic Substrates

Cyclic imines do not have the problem of *syn*/*anti* isomerism and therefore, in principle, higher enantioselectivities can be expected (Fig. 34.8). Several cyclic model substrates **6** were hydrogenated using the Ti–ebthi catalyst, with ee-values up to 99% (Table 34.5; entry 5.1), whereas enantioselectivities for acyclic imines were ≤90% [20, 21]. Unfortunately, these very selective catalysts operate at low SCRs and exhibit TOFs $< 3\ h^{-1}$. In this respect, iridium–diphosphine catalysts, in the presence of various additives, seem more promising because they show higher activities. With several different ligands such as josiphos, bicp, bi-

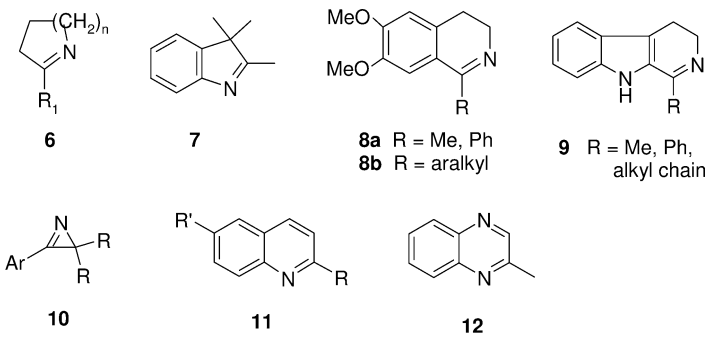


Fig. 34.8 Structures of cyclic imines and heteroaromatic substrates.

Table 34.5 Selected results for the enantioselective hydrogenation of cyclic imines (for structures, see Fig. 34.8): Catalytic system, reaction conditions, enantioselectivity, productivity and activity.

Entry	Substrate	Catalyst	p [bar]	ee [%]	SCR	TOF [h^{-1}]	Reference
5.1	**6**	Ti–ebthi	5	99	100	up to 2	8
5.2	**7**	Ir–bicp/phthalimide	70	95	200	2	52
5.3	**7**	Ir–Xyl_2PF-PXyl_2/I^-/H^+	40	93	250	56	23
5.4	**7**	Ir–Tol-binap/$PhCH_2NH_2$	60	90	100	6	53
5.5	**7**	Ir–**L2**/I_2	~70	82–85	100	~4	54
5.6	**7**	Ir–**L3**	65	79	100	~5	55
5.7	**8a**	Ti–ebthi	5	96	20	<1	8
5.8	**8a**	Ru–dpenTs	F[a]	84	200	6–30	10
5.9	**8b**	Ir–bcpm or binap/F_4-phthalimide	100	86–88	100	5	56
5.10	**8b**	Ru–dpenTs	F[a]	92–95	200	15–30	10
5.11	**9**	Ru–dpenTs	F[a]	96–97	1000	35–83	10
5.12	**9**	Ru–dpenTs	F[a]	>98	~2000	~800	57
5.13	**10**	Ru–**L12**/*i*PrOH	IP[a]	44–78	100	up to 3000	58
5.14	**11**	Ir–**L7**/I_2	~40	90–92	1000	~80	59
5.15	**11**[b]	Ir–MeO-biphep/I_2	50	90–96	100	~6	60
5.16	**11**[b]	Ir–P-phos	50	88–92	100	~6	61
5.17	**12**	**Cat1** (see Fig. 34.3)	5[c]	90	100	~4	62

Reactions carried out between r.t. and 50 °C, unless otherwise noted.

a) Reducing agent ammonium formate (F) or *i*PrOH (IP).

b) With a wide variety of R and R' substituents.

c) At 100 °C, yield 54%.

nap or the diop analogue **L2**, model compound **7** was reduced with ee-values of 79–94% Only moderate TONs and, with the exception of Ir–josiphos, also very low TOFs were observed (entries 5.2–5.6). Interestingly, the best enantioselectivities were achieved in the presence of a variety of additives with unknown function. Recently, Giernoth demonstrated that the reaction with an Ir–josiphos catalyst could also be carried out in ionic liquids, with slightly lower enantioselectivities but similar catalyst activities [63].

Cyclic imines **8** and **9** are intermediates or models of biologically active compounds and can be reduced with ee-values of 88 to 96% using Ti–ebthi, Ir–bcpm or Ir–binap in the presence of additives (entries 5.7, 5.9), as well as with the transfer hydrogenation catalyst Ru–dpenTs (entries 5.8, 5.10–5.12). As pointed out earlier, Ru–diphosphine–diamine complexes are also effective for imines, and the best results for **7** and **8a** were 88% and 79% ee, respectively [36]. Azirines **10** are unusual substrates which could be transfer-hydrogenated with a catalyst prepared *in situ* from $[RuCl_2(p\text{-cymene})]_2$ and amino alcohol **L12**, with ee-values of 44 to 78% and respectable TOFs of up to 3000 (entry 5.13).

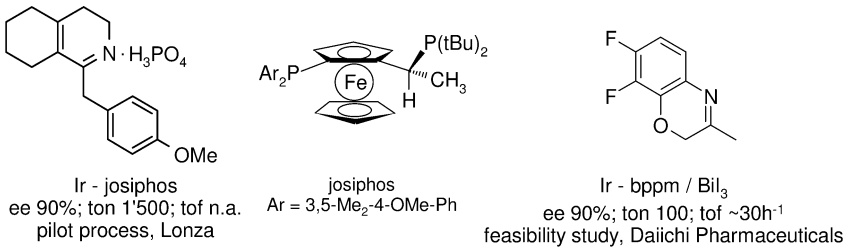


Fig. 34.9 Hydrogenation of a dextromethorphan and levofloxacin intermediate.

The hydrogenation of substituted heteroaromatic substrates such as pyridines, pyrazines or quinolines also allows access to a variety of cyclic amines. Until now, the results with pyridines have been disappointing (ee-values < 30% [64]) except for a report claiming the hydrogenation of *N*-iminium pyridine ylides using Ir–phox catalysts with ee-values up to 90% (TON 50, TOF ~6 h^{-1}) [65]. A patent described the Ir–josiphos-catalyzed hydrogenation of a pyrazine amide with ee-values up to 77% but very low catalyst activity (TON ~20, TOF 1 h^{-1}) [66]. Better results were obtained for the Ir-catalyzed hydrogenation of quinoline derivatives **11** (various R and R′ substituents) using ferrocene-based PN ligand **L7** (entry 5.14), MeO-biphep (entry 5.15) and P-phos (entry 5.16). In the best cases, ee-values of 90–96% were obtained with SCRs up to 1000, leading to full conversion after 12 h. Similarly, quinoxaline **12** was hydrogenated with **Cat1** containing a tridentate PNN ligand (entry 5.17). Quinoxaline **12** serves a model substrate for the diastereoselective reduction of folic acid for which high selectivity was claimed for an Ir–bppm complex adsorbed onto silica, a claim which later had to be retracted [67]. At present, the best stereoselectivities for folic acid derivatives are about 50% diastereomeric excess (d.e.) using water-soluble Rh–josiphos or Rh–biphep catalysts [68, 69].

A technical process was developed by Lonza for the Ir-catalyzed hydrogenation of an intermediate of dextromethorphan (Fig. 34.9) which was carried out on a >100-kg scale [70]. Important success factors were ligand fine tuning and the use of a biphasic system; chemoselectivity with respect to C=C hydrogenation was high, but catalyst productivity rather low for an economical technical application. Satoh et al. reported up to 90% ee for the hydrogenation of an intermediate of the antibiotic levofloxacin using Ir–diphosphine complexes. Best results were obtained with bppm and a modified diop in the presence of bismuth iodide at low temperature [71].

34.6 Miscellaneous C=N–X Systems

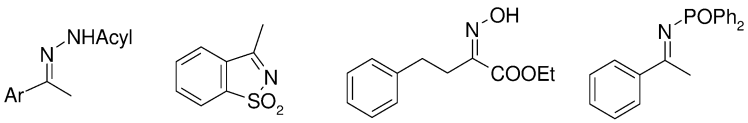
Less-common types of C=N derivatives can also be reduced enantioselectively. An interesting example is the hydrogenation of the aromatic *N*-acyl hydrazones **13** with the Rh–duphos catalyst (Table 34.6; entry 6.1). This reaction was devel-

Table 34.6 Selected results for the enantioselective hydrogenation of miscellaneous C=N–X compounds (for structures, see Fig. 34.10): Catalytic system, reaction conditions, enantioselectivity, productivity and activity.

Entry	Substrate	Catalyst	p [bar]	ee [%]	SCR	TOF [h^{-1}]	Reference
6.1	**13**	Rh–duphos	4	88–96	500	14–42	9
6.2	**14**	Ru–binap	4	99	90	6	72
6.3	**15**	Ir–dpampp/I^-	48	93	100 [a]	0.5	73
6.4	**16**	Rh–josiphos, Cy_2PF-PCy_2	70	99	500	500	74

Reactions carried out between r.t. and 50 °C, unless otherwise noted.

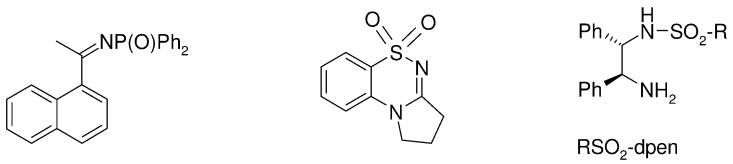
a) Conversion 22%.



13 **14** **15** **16**

Fig. 34.10 Structures of miscellaneous C=N–X substrates.

oped by Burk et al. [9] in analogy to the well-known hydrogenation of enamides. The results confirm that the presence of a second group in the substrate molecule that is able to bind to the metal is beneficial for achieving high enantioselectivity. The resulting *N*-acyl hydrazines can be reduced to the primary amine using SmI_2, but an effective technical solution for cleavage of the N–N bond to obtain the primary amine without racemization is still lacking. A cyclic *N*-sulfonyl-imine **14** can be hydrogenated with Ru–binap with good to very good enantioselectives (entry 6.2), whereas acyclic analogues are reduced with lower ee-values [75]. Oximes can be hydrogenated with very good enantioselectivity (but low activity) with the novel Ir–dpampp complex (entry 6.3), while Ru–binap [76a] or Rh–binap [76b] were also active but with modest ee-values. Phosphinyl imines



Me_5cpRh - RSO_2dpen
ee 99%; ton ~1'000; tof 1000h^{-1}
pilot process?, Avecia

Ru - binap - dpen
ee 87%; ton 2'500; tof ~400h-1
bench scale, Dow Chirotech

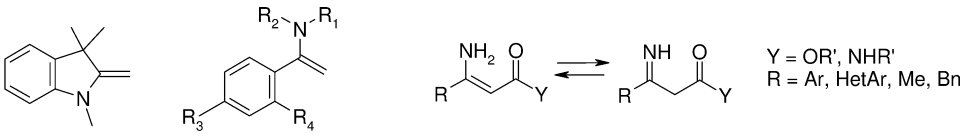
Fig. 34.11 Industrial processes with C=N–X substrates.

16 are highly suitable substrates for Rh–josiphos catalysts, with ee-values up to 99% (entry 6.4) (Fig. 34.10).

Two technical applications of C=N–X substrates have been reported. Noyori's Ru–PP–NN catalyst system was successfully applied in a feasibility study by Dow Chirotech for the hydrogenation of a sulfonyl amidine [77], while Avecia showed the commercial viability of its CATHy catalyst based on a pentamethyl cyclopentadienyl Rh complex for the reduction of phosphinyl imines [78] (Fig. 34.11).

34.7 Enamines

Until recently, the hydrogenation of enamines has scarcely been investigated. Results have been reported for model substrates **17** and **18**, indicating that such transformations are possible in principle (Fig. 34.12). Substrate **17** was hydrogenated with Ir–diop with ee-values of 60–64% and with Rh–bdpch with 72% ee



17 **18** **19**

Fig. 34.12 Structures of enamines.

Table 34.7 Selected results for the enantioselective hydrogenation of enamines (for structures, see Fig. 34.12): Catalytic system, reaction conditions, enantioselectivity, productivity and activity.

Entry	Substrate	Catalyst	p [bar]	ee [%]	SCR	TOF [h^{-1}]	Reference
7.1	**17**	Ir–diop/iodide	20	60–64	50	n.a.	79
7.2	**17**	Rh–bdpch	20	60–72	50	n.a.	80
7.3	**18**	Ti–ebthi	1–5	89–98	20	<1	81
7.4	**19**	Rh–josiphos	~6	93–97	330	20–30	82
7.5	**19** [a)]	Ru–tol-binap or segphos	30	94–97	100 [b)]	1–5	83a
7.6	**20**	Rh–josiphos, (4-CF_3Ph)$_2$PF-P*t*Bu$_2$	~6	94	350	50	84

Reactions carried out between r.t. and 50 °C, unless otherwise noted.

a) Y=RO.

b) In some cases SCR 1000, conversions 10–85%.

n.a.: data not available.

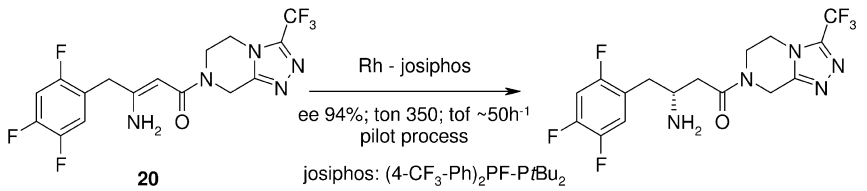


Fig. 34.13 Hydrogenation of the *β*-dehydro amino acid amide intermediate for MK-0431.

(Table 34.7; entries 7.1 and 7.2). Enamines of the type **18** were reduced in presence of Ti–ebthi with high enantioselectivities of 89–98% (entry 7.3), while Rh–diop achieved only 39% ee [80]. In both cases, catalyst activities and productivities are too low for practical purposes.

This has changed recently with the development of the hydrogenation of primary enamines/imines **19** leading to *β*-amino acid derivatives, a reaction with considerable synthetic and industrial potential. While the hydrogenation of analogous acylated derivatives is a well-known transformation, it was quite unexpected that the unprotected substrate is amenable to enantioselective hydrogenation. Indeed, two catalysts, Rh–josiphos and Ru–binap (and analogues) were found by Merck [82] and Takasago [83], respectively, at almost the same time. With both catalysts, very good ee-values are achieved for several different derivatives of **19** (Table 34.7; entries 7.4 and 7.5), but for both activity is an issue. While the Rh–josiphos gives high conversion at an SCR of 330 after 6 to 20 h, the Ru–binap catalysts at an SCR of 100 (in some cases 1000) do not give full conversion even after 15 to 88 h. Interestingly, deuteration experiments performed by Merck indicate that it is not the enamine C=C bond which is reduced, but the tautomeric primary imine.

Merck has developed a pilot process for the hydrogenation of an intermediate **20** for MK-0431 (Fig. 34.13) and carried out the reduction on a >50-kg scale with ee-values up to 98%, albeit with low to medium TONs and TOFs [84]. Takasago has developed a reductive amination version where the corresponding *β*-keto ester is hydrogenated in the presence of amines, giving directly the corresponding *β*-amino ester, though as yet no details are available of this process [83].

34.8 Mechanistic Aspects

Only a few detailed studies of the reaction mechanism of the homogeneous hydrogenation of imines have been published until now. A generalization seems to be very difficult for two reasons. First, rather different catalyst types are effective and probably act by different mechanisms. Second, the effect of certain additives (especially iodide or iodine and acid/base) is often decisive for ee and rate, but a promoter in one case can be a deactivator in another case.

For Rh and Ir diphosphine-based catalysts there exist some indications on reactive species and also on hydrogen activation. James and coworkers [43, 85] investigated the Rh-catalyzed DMA-imine hydrogenation and concluded that the imine is η^1-coordinated to the Rh center via the nitrogen lone pair, and not via the π-system of the C=N bond. They also suggested that the hydrogen activation occurs after the imine is coordinated.

Osborn and Chan [86] isolated and characterized Ir^{III} complexes of the type: $[Ir(diphosphine)I_4]^-$, $[Ir(diphosphine)I_2]_2$ and $[Ir(diphosphine)I_3]_2$. All three Ir complexes were found to be catalytically active for the hydrogenation of DMA imine **1b**, suggesting the formation of the same active monomeric Ir species as for the *in-situ*-formed catalyst by splitting of the iodo-bridge. Based on these results, the catalytic cycle depicted in Figure 34.14 can be postulated: The starting species is an Ir^{III}–H species that coordinates the imine via the lone pair in a η^1-manner (as proposed for the Rh-catalyzed reaction). A η^1,η^2-migration leads to two diastereomeric adducts with a π-coordinated imine that then inserts into the Ir–H bond to give the corresponding Ir amide complexes. The last step is a simultaneous hydrogenolysis of the Ir–N and the formation of an Ir–H bond, presumably via heterolytic splitting of the dihydrogen bond. In contrast to the Rh diphosphine-catalyzed hydrogenation of C=C bonds that most likely occurs via Rh^I and Rh^{III} species, the cycle in Figure 34.14 consists exclusively of Ir^{III} species. It is clear, that this basic catalytic cycles neither explains the mode of enantioselection nor the sometimes dramatic effects of additives – for example, the strong rate enhancement by acids observed for the Ir–xyliphos-catalyzed MEA imine hydrogenation.

A similar mechanism was postulated for the Ti-catalyzed reactions by Buchwald [21, 87]. The active catalyst was proposed to be the monohydride species ebthi-Ti-H, produced by reacting ebthi-TiR_2 with *n*-BuLi followed by phenylsi-

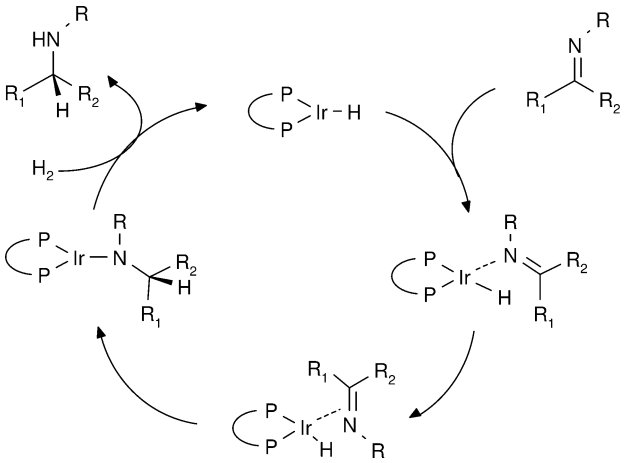


Fig. 34.14 Schematic catalytic cycle postulated for the Ir diphosphine-catalyzed hydrogenation of *N*-aryl imines. For clarity, the halide ligands are not shown.

lane. Kinetic and deuterium-labeling studies are in agreement with the following reaction sequence: Ebthi-Ti-H reacts with the imine via 1,2 insertion reaction to form two diastereomeric Ti amide complexes which react via σ bond metathesis with dihydrogen to regenerate the titanium hydride and to form the two product enantiomers. The reaction of the titanium amide complex with molecular hydrogen is proposed to be the rate-determining step. The discrimination of the catalyst is due only to the size difference of the imine substituents, thereby explaining the potential detrimental effect of the presence of *syn* and *anti* isomers. The absolute configuration of the major enantiomer can be predicted by simple steric arguments, assuming that the 1,2-insertion is the product-determining step.

34.9 Alternative Reduction Systems

Hydride reductions of C=N groups are well known in organic chemistry. It was therefore obvious to try to use chiral auxiliaries in order to render the reducing agent enantioselective [88]. The chiral catalyst is prepared by addition of a chiral diol or amino alcohol, and the active species is formed by reaction of OH or NH groups of the chiral auxiliary with the metal hydride. A major drawback of most hydride reduction methods is the fact that stoichiometric or higher amounts of chiral material are needed and that the hydrolyzed borates and aluminates must be disposed of, which leads to increased costs for the reduction step.

Several stoichiometric chiral reducing agents starting from BH_3, $LiAlH_4$ or $NaBH_4$ and relatively cheap amino alcohols or diols have been developed for the reduction of imines and oxime derivatives [89, 90]. The ee-values are medium to very high. The most effective chiral auxiliaries can be prepared in one or two steps from rather cheap starting materials such as amino acids, tartaric acid or sugars, and they can probably be recycled. As an overall assessment, chiral hydrides are at present useful on a laboratory scale, but their potential for technical applications is medium to low.

The situation for the hydrosilylation of C=N functions with regard to ecology and economy is somewhat similar as for the hydride reduction, except that fewer effective catalytic systems have been developed [91]. Despite some recent progress with highly selective Ti-based [92] and Cu-based [93] catalysts using cheap polymethylhydrosiloxane as reducing agent, hydrosilylation will see its major applications in small-scale laboratory synthesis.

Chiral amines can also be produced using aminotransferases, either by kinetic resolution of the racemic amine or by asymmetric synthesis from the corresponding prochiral ketone. The reaction involves the transfer of an amino group, a proton and two electrons from a primary amine to a ketone, and proceeds via an intermediate imine adduct. A variety of chiral amines can be obtained with high to very high ee-values. Several transformations have been developed and can be carried out on a 100-kg scale [94].

34.10
Assessment of Catalysts and Conclusions

Different criteria are important for assessing the applicability of a catalyst, either for preparative purposes or for the technical manufacture of chiral fine and specialty chemicals [95]. In both cases, enantioselectivity is of course the decisive prerequisite. For preparative use, easy availability and handling of the catalyst will probably play a major role. For technical applications, catalyst activity (TOF), productivity (TON), availability on a large scale and of course cost, also play important roles. In general, ee's should be >90%, unless a further enrichment is straightforward. The minimal activity and productivity required is less predictable. Consider an example of this situation. For an SCR of 1000 and a TOF of 10 h^{-1}, the reaction will take 100 h for completion – certainly not an acceptable reaction time for a large-volume chemical. However, for preparative small-scale applications, the SCR could be lowered to 100 and the reaction time would be an acceptable 10 h. A summary of the range of reaction conditions, ee-values, SCRs and TOF for important chiral catalysts and substrates is provided in Table 34.8. An overall assessment for the different systems takes into consideration not only the catalytic properties of a catalyst for a given transformation but also its ecological and economical aspects.

34.10.1
Iridium Complexes

Among the various catalyst types investigated in recent years for the hydrogenation of imines, Ir–diphosphine complexes have proved to be most versatile catalysts. The first catalyst of this type generated *in situ* from $[Ir(cod)Cl]_2$, a chiral diphosphine and iodide was developed by the Ciba-Geigy catalysis group in 1985. Ir ferrocenyl diphosphines (josiphos) complexes in presence of iodide and acid

Table 34.8 Typical ranges of reaction conditions, optical yields, turnover frequencies (TOF) and substrate:catalyst ratios (SCR) for the hydrogenation of C=N functions using various chiral catalytic systems.

Catalyst	Substrate type	p [bar]	T [°C]	ee [%]	SCR	TOF [h^{-1}]
Ir–PP	N-aryl imines	20–80	0–30	70–99	100–>1 000 000	2–>350 000
	Cyclic imines	40–70	20–30	80–97	100–1000	5–50
Ir–PN	Imines	100	r.t.	75–90	25–>1000	4–250
Rh–PP	Imines	60–100	<0–30	80–96	40–1000	0.1–50
	N-acyl hydrazones	4	<0–20	70–96	500–1000	10–1000
	Phosphinylimines	70	60	90–99	100–500	100–500
Ru–PP–NN	Acyclic imines	3–20	30	60–94	500–1500	20–50
Ru–NN	Imines	Formate	30	85–97	100–1000	6–83
Ti–ebthi	Cyclic imines	5–33	45–65	98–99	20–100	0.4–2.4

are the most active and productive enantioselective catalysts for the hydrogenation of the *N*-aryl-imines. The josiphos ligands are quite stable, easy to tune to the special needs of the imine structure, and a large variety is commercially available in technical quantities. Most other Ir complexes have not been studied in great detail, and many require the presence of additives such as iodine or phthalimide for good performance. Ligands such as f-binaphane, bicp or the tolbinap are patent-protected but are available commercially. The Ir–phox catalysts developed by Pfaltz and related Ir–PN complexes have some potential for C=N hydrogenation but, curiously, it seems that there is a limit to their enantioselectivity at ca. 90% ee.

34.10.2
Rhodium Complexes

Rhodium diphosphine catalysts can be easily prepared from $[Rh(nbd)Cl]_2$ and a chiral diphosphine, and are suitable for the hydrogenation of imines and *N*-acyl hydrazones. However, with most imine substrates they exhibit lower activities than the analogous Ir catalysts. The most selective diphosphine ligand is $bdpp_{sulf}$, which is not easily available. Rh–duphos is very selective for the hydrogenation of *N*-acyl hydrazones and with TOFs up to 1000 h^{-1} would be active enough for a technical application. Rh–josiphos complexes are the catalysts of choice for the hydrogenation of phosphinyl imines. Recently developed (pentamethylcyclopentyl)Rh–tosylated diamine or amino alcohol complexes are active for the transfer hydrogenation for a variety of C=N functions, and can be an attractive alternative for specific applications.

34.10.3
Ruthenium Complexes

In contrast to the wide scope of Ru–binap for the hydrogenation of substituted alkenes and ketones, their use in the hydrogenation C=N groups is limited due to the tendency to deactivate in presence of bases. Of more interest, though not yet fully explored, are Ru complexes containing both a diphosphine and a diamine. (Arene)Ru complexes in the presence of tosylated diamines are also able to reduce imines under transfer hydrogenation conditions with high activities and high to very high enantioselectivities.

34.10.4
Titanium Complexes

Despite the remarkable enantioselectivities observed with the Ti–ebthi catalyst for the imine and enamine hydrogenation, we consider its technical potential rather low. The ligand is difficult to prepare, the activation of the catalyst precursor is tricky, for the moment the catalytic activity is far too low for preparative purposes, and last – but not least – its tolerance for other functional groups is low.

A summary of the present state of the art for the enantioselective hydrogenation organized according to catalyst type is provided in Table 34.8. While an increasing number of catalysts with high ee-values are reported, progress concerning activity and productivity is much slower. Compared to the situation for the analogous C=C and C=O hydrogenation, there are still many areas where minimal systematic information is available. The most visible success stories such as the (*S*)-metolachlor case are rather "anecdotal" in nature. Nevertheless, they are proof that it is possible to hydrogenate C=N functions with not only adequate enantioselectivity but also high activity and productivity.

Abbreviations

d.e.	diastereomeric excess
ee	enantiomeric excess
SCR	substrate:catalyst ratio
TOF	turnover frequency
TON	turnover number

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