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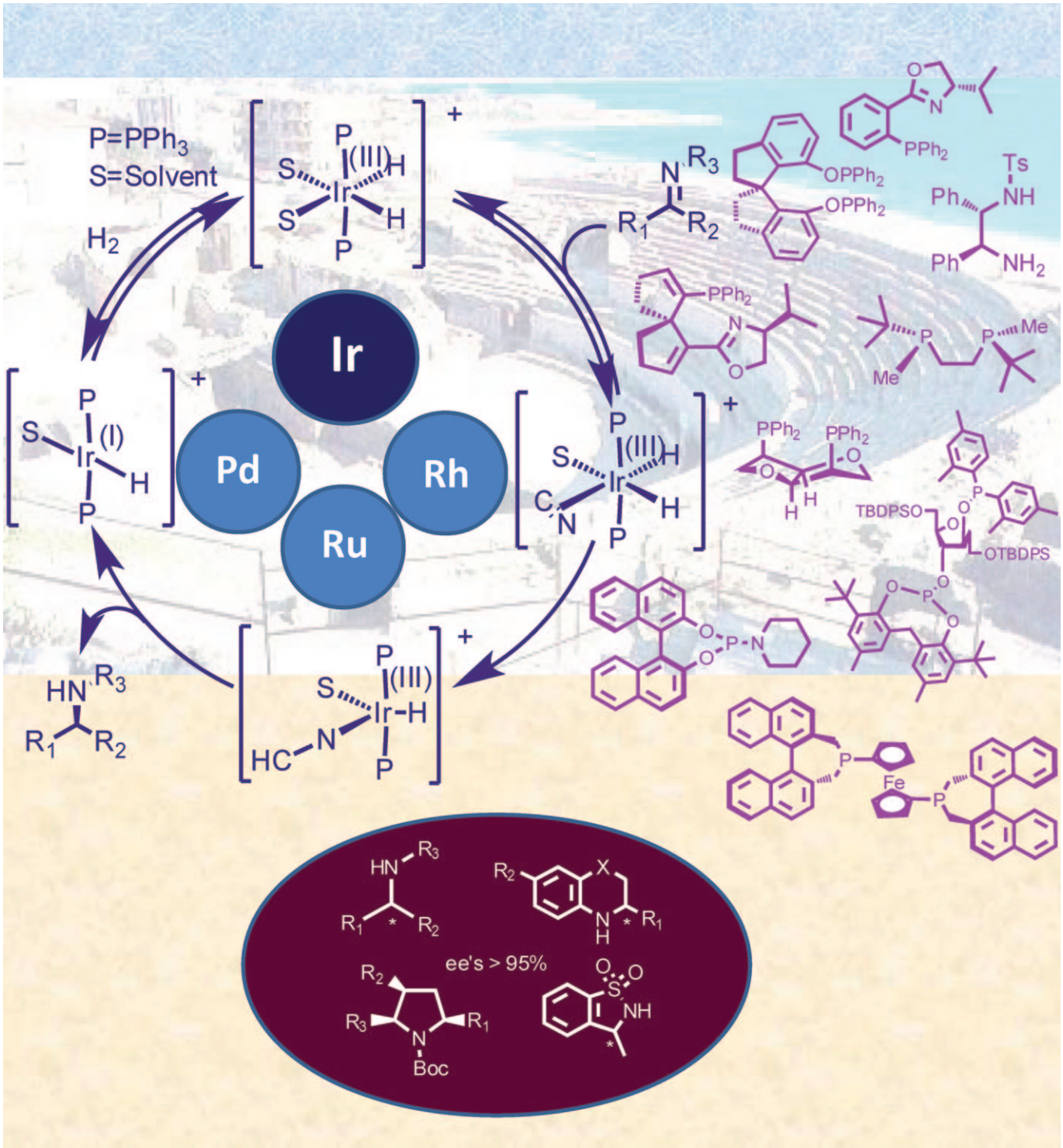
Highlights of Transition Metal-Catalyzed Asymmetric Hydrogenation of Imines

Nicolas Fleury-Brégeot,[a] Verónica de la Fuente,[a] Sergio Castillón,*[b] and Carmen Claver*[a]



This Review deals with the asymmetric hydrogenation and asymmetric transfer hydrogenation of imines and some nitrogen-containing heteroaromatic compounds to afford amines. Hydrogenation and transfer hydrogenation are covered in separate sections. Particular attention is devoted to the substrates, since this reaction is highly substrate dependent. In this way the general structural trends in imine hydrogenation are presented, highlighting the more challenging substrates. Since hydrogenation of acyclic and cyclic (including heteroaromatic) imines have some different features they are also presented separately. The catalytic systems are classified according to the metal, and focus on the most successful catalytic systems and metal–ligand combinations. The catalytic cycles for these hydrogenation processes are also proposed.

Introduction

Chiral amines are important synthetic intermediates due to their application in the pharmaceutical, agrochemical and fine chemical industries. One of the most useful methods for their preparation is the asymmetric hydrogenation of C=N double bonds using chiral transition metal complexes as catalysts.

However, the asymmetric hydrogenation of imines has several important drawbacks, such as the coordination of substrates, which can take place through both the nitrogen donor atom and the double bond, the *E*/*Z* isomeric mixture present in acyclic imines, and the poisoning effect of the resultant amines on the catalyst. In spite of these problems, recent progress in the field of asymmetric hydrogenation of imines has led to the discovery of new catalytic systems able to provide high activities and enantioselectivities (in some cases up to 99%).[1] A relevant example is the iridium–ferrocenyl diphosphine complexes, which, in the presence of both acetic acid and iodine, constitute stable and highly active catalytic systems for imine hydrogenation. This is one of the most important homogeneous processes, being the key step in the industrial production of the chiral herbicide (*S*)-Metolachlor, which is produced in quantities of more than 10000 tonnes per year with 79% enantioselectivity.[1d]

The interest of both academic and industrial research groups in asymmetric hydrogenation of imines has increased in recent years, with a focus on the discovery of catalytic systems that are active under low hydrogen pressures and provide high to excellent enantioselectivities. In parallel, the scope of this reaction has been extended, and more challenging C=N-containing substrates have been transformed using this asymmetric process.[1a]

In this context, we describe herein the recent advances in the asymmetric hydrogenation of different substrates containing imine functions. Imine substrates are classified according to their acyclic or cyclic structures. Asymmetric transfer hydrogenation of both types of substrates is also briefly described. The most relevant catalytic systems and strategies used in these cases are presented.

1. Asymmetric Hydrogenation of Acyclic Imines

This section presents the different strategies and catalyst improvements recently developed for the hydrogenation of acyclic imines. The most relevant contributions are classified according to the metal and the different ligands involved in the catalytic system. The general structures of acyclic imines used as substrates to be hydrogenated are collected in Figure 1.

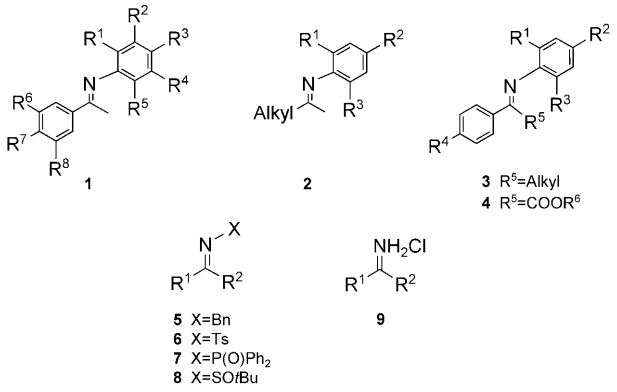


Figure 1. Acyclic imines studied in asymmetric hydrogenation.

1.1. Iridium catalysts

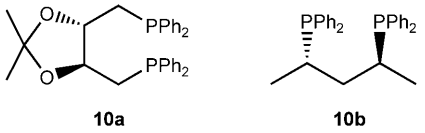
The iridium-catalyzed hydrogenation of imines is one of the most efficient methods for the formation of chiral amines with high to excellent enantioselectivities under mild conditions.[1b] Two different types of iridium precursors are commonly used: a) cationic complexes of the type $[Ir(cod)(L{-}L)]^+X^-$ containing a chelating chiral ligand (L–L), 1,5-cyclooctadiene (cod), and a counter anion, which can have a remarkable effect on the catalysis; b) neutral complexes formed in situ by the reaction of dinuclear complexes, such as $[\{Ir(\mu\text{-}Cl)(cod)\}_2]$ alongside a stoichiometric amount of the corresponding chiral ligand.[1]

Diphosphine ligands

The first catalysts reported for the asymmetric hydrogenation of acyclic imines using Ir complexes bore DIOP (**10b**; Figure 2)

[a] *Dr. N. Fleury-Brégeot, V. de la Fuente, Prof. Dr. C. Claver*
Departament de Química Física i Inorgànica
Universitat Rovira i Virgili, C/Marcel·lí Domingo s/n
43007 Tarragona (Spain)
E-mail: carmen.claver@urv.cat

[b] *Prof. Dr. S. Castillón*
Departament de Química Analítica i Orgànica
Universitat Rovira i Virgili, C/Marcel lí Domingo s/n
43007 Tarragona (Spain)
E-mail: sergio.castillon@urv.cat



10a 10b

Figure 2. First chiral ligands used in the hydrogenation of substrate **5a**.

as chiral diphosphine ligand, and afforded moderate enantioselectivities.[2] The complex [Ir(cod)(**10b**)]PF_6 (Figure 2) was used in the hydrogenation of *N*-(α-methyl-*p*-methoxybenzylidene)benzylamine (**5a**) under mild reaction conditions (0.5 MPa, 40 °C); however, the catalytic system did not afford any enantioselectivity.[3a] In contrast, the corresponding catalyst immobilized in montmorillonite K-10 (MK-10) provided *ee* values up to 59%.[3b] In 2001, Zhang et al. reported a highly enantioselective system for the hydrogenation of *N*-arylimines (**1a–g** and **2a–c**) with a chiral ferrocenyl phosphine ligand, (*R,R*)-f-binaphane **11a**, achieving enantioselectivities up to 99%. The addition of iodine as additive had a beneficial effect on the enantioselectivity (Table 1).[4] To achieve excellent enantioselectivities R^2 and R^3 must be both different than hydrogen and R^4 an aromatic ring. However, this catalytic system failed in the hydrogenation of dialkyl imines **2a–c**.

Other Ir–diphosphine catalytic systems also provided good enantioselectivities in the hydrogenation of acyclic imines. For instance, using 3,6-bis(diphenylphosphino) hexahydrofuro[3,2-b]furan) **14** as chiral ligand, the imines **1a**,**b**,**h**,**j** were hydrogenated to the corresponding chiral amines in quantitative yields with enantioselectivities from 80 to 94% (Table 2). Replacement of the phenyl group attached to the nitrogen (R^1) by a benzyl group produced a dramatic drop in the enantioselectivity.

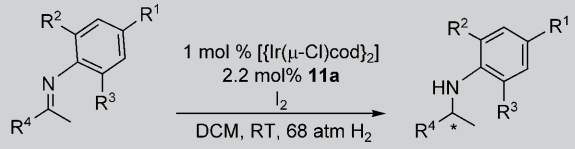
Nicolas Fleury-Brégeot was born in Argenteuil (France) in 1982. He received a chemical engineering degree from Ecole Supérieure de Chimie Organique et Minérale (ESCOM) as well as a M.Sc. Degree from the University of Cergy-Pontoise in 2005. Then he joined the "Institut de Chimie des Substances Naturelles" (ICSN, Gif-sur-Yvette) where he worked on the development of enantioselective reactions organocatalyzed by phosphines under the supervision of Dr. Angela Marinetti. He was awarded his Ph.D. degree in December 2008. He joined the group of Professor Carmen Claver in 2009 where he worked on the synthesis and use of chiral phosphine-imidazoline ligands in metal-catalyzed asymmetric reactions. Since January 2010, he is a postdoctoral fellow at the University of Pennsylvania in the group of Professor Gary Molander.

Sergio Castillón obtained his PhD from the University of Zaragoza in 1982 under the supervision of Prof. J. Vilarrasa. After two years of postdoctoral research in the ICSN, Gif-sur-Yvette (France), in G. Lukacs's group, he moved in 1984 to the Faculty of Chemistry of Tarragona (University of Barcelona) as Associate Professor. In 1995 he became full professor in Organic Chemistry at the same Faculty, now University Rovira i Virgili. He was made Director of the Department of Chemistry and Distinguished Professor of the URV in 2006. His research interests include the development of new synthetic methods, stereoselective synthesis of natural products, and asymmetric catalysis.

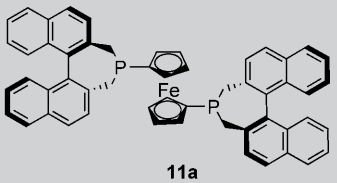
Verónica de la Fuente was born in La Selva del Camp (Spain) in 1984. She completed her undergraduate studies in 2006 at the Universitat Rovira i Virgili. Her Masters degree was developed in collaboration with an industrial company and the Universitat Rovira i Virgili in 2007. She is currently completing her PhD under the supervision of Prof. Carmen Claver and Prof. Sergio Castillón and her work focuses on the synthesis of new ligands, their application in enantioselective catalysis, and the study of reaction mechanisms using NMR spectroscopy..

Carmen Claver is Professor of Inorganic Chemistry at the University Rovira i Virgili in Tarragona (Spain), a position she has held since 1991. She received her PhD in 1978 from the University of Zaragoza (Spain) working in the field of organometallic chemistry and homogeneous catalysis. Her research is aimed at the development of new catalysts, covering the synthesis of ligands and complexes and the characterization of intermediates, focusing mainly in enantioselective catalysis. In recent years her research has been extended to the field of nanocatalysis. She has co-authored scientific contributions in this field and has participated in the editing and publication of several books. She has received several scientific awards, being recognized in 2003 as a distinguished researcher for the Catalan Government and "Chaire Pierre de Fermat" in France in 2009.

Table 1. Enantioselective hydrogenation of substrates **1a–g** and **2a–c** with [Ir]/**11a**.



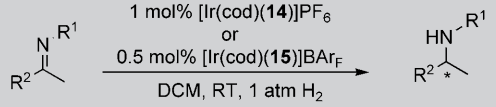
1a-g, **2a-c** **12a-g**, **13a-c**



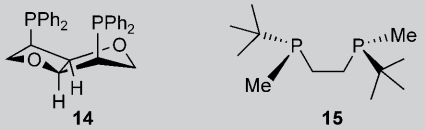
11a

Substrate	R^1	R^2	R^3	R^4	*ee* [%][a]
1a	H	H	H	Ph	84
1b	MeO	H	H	Ph	77
1c	H	MeO	H	Ph	81
1d	H	CH_3	CH_3	Ph	>99
1e	H	CH_3	CH_3	4-$MeOC_6H_4$	98
1f	H	CH_3	CH_3	4-$CF_3C_6H_4$	99
1g	H	MeO	CH_3	1-naph	98
2a	H	CH_3	CH_3	*t*Bu	8
2b	H	CH_3	CH_3	*i*Pr	23
2c	H	CH_3	CH_3	Cy	31

Table 2. Enantioselective hydrogenation of substrates **1a–b**, **1h–o**, and **5b** with [Ir]/**14** or [Ir]/**15** as catalytic system.



1a-b, 1h-o, 5b **12a, 12h-o, 16b**



14 **15**

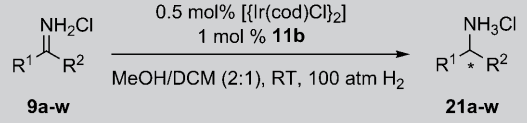
Substrate	R^1	R^2	*ee* [%]	
			14	**15**
1a	Ph	Ph	84	86
1b	4-$MeOC_6H_4$	Ph	94	86
1h	Ph	4-$MeOC_6H_4$	81	69
1i	Ph	4-ClC_6H_4	80	–
1j	Ph	4-FC_6H_4	–	84
1k	4-ClC_6H_4	Ph	–	83
1l	4-FC_6H_4	Ph	–	84
1m	4-$CF_3C_6H_4$	Ph	–	99
1n	3,5-$(CF_3)_2C_6H_3$	Ph	–	90
1o	4-$MeOC_6H_4$	4-$MeOC_6H_4$	–	83
5b	Bn	Ph	5	–

The increase of hydrogen pressure usually has a detrimental effect on the activity of the catalytic system, and the use of coordinating solvents such as THF leads to the deactivation of the catalytic system. The counter anion also has a strong influence on the activity, since noncoordinating anions, such as BF_4^- or PF_6^-, provided active systems, whereas the presence of coordinating chloride ions deactivated the catalyst. The deactivation of the catalytic system is due to the formation of inactive dimeric and trimeric Ir^{III} polyhydride complexes by reaction of the iridium precursor [Ir(cod)(**14**)]PF_6 with hydrogen.[5]

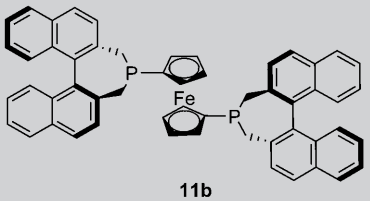
Imamoto and co-workers reported that an iridium(I) complex bearing (*S,S*)-1,2-bis(*tert*-butylmethylphosphino)ethane **15** as a ligand and tetrakis(3,5-bis(trifluoromethyl)phenyl)borate (BAr_F) as a counter anion was an efficient catalytic system for the hydrogenation of acyclic aromatic *N*-arylketimines **1a**,**b**,**h**,**j–o** under atmospheric hydrogen pressure at room temperature. The corresponding chiral amines were obtained with enantioselectivities up to 99% (Table 2).[6] In all cases, the nitrogen atom was bound to a phenyl group. It is interesting to note the strong increase of the enantioselectivity when $R^1 = p$-CF_3Ph.

Unfunctionalized N–H imines (**9a–w**) constitute an interesting type of substrate that has been much less explored (Table 3). Recently, Zhang and co-workers published the first example of efficient enantioselective hydrogenation of primary imines,[7,8] a fundamental step in the development of an ideal

Table 3. Enantioselective hydrogenation of substrates **9a–w** with [Ir]/**11b** catalytic system.



9a-w **21a-w**



11b

Substrate	R^1	R^2	*ee* [%]
9a	2-$CH_3C_6H_4$	CH_3	95
9b	4-$CH_3C_6H_4$	CH_3	95
9c	Ph	CH_3	93
9d	Ph	Et	86
9e	Ph	*n*Bu	88
9f	Ph	*t*Bu	80
9g	4-$MeOC_6H_4$	CH_3	93
9h	4-FC_6H_4	CH_3	92
9i	4-ClC_6H_4	CH_3	94
9j	4-BrC_6H_4	CH_3	93
9k	4-$CF_3C_6H_4$	CH_3	93
9l	3-$CH_3C_6H_4$	CH_3	92
9m	3-$MeOC_6H_4$	CH_3	94
9n	3-ClC_6H_4	CH_3	92
9o	3-BrC_6H_4	CH_3	91
9p	2-$CH_3C_6H_4$	CH_3	81
9q	2-$MeOC_6H_4$	CH_3	92
9r	2-ClC_6H_4	CH_3	81
9s	1-naphthyl	CH_3	93
9t	2-naphthyl	CH_3	92
9u	*t*Bu	CH_3	17
9v	Cy	CH_3	73
9w	4-$CH_3C_6H_4$	Ph	23

direct asymmetric reductive amination of ketones to give primary amines.

Initially, experiments with Ir complexes containing chiral diphosphines such as TangPhos (**17**), DuanPhos (**18**), binap (**19**) and MeDuPHOS (**20**; Figure 3) led to poor *ee* values. However,

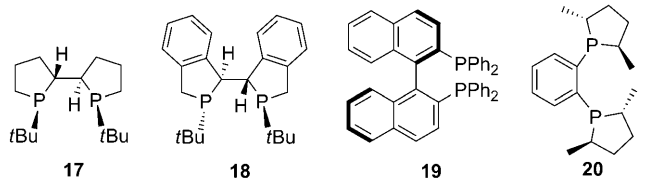


Figure 3. Ligands **17**–**20** used in the enantioselective hydrogenation of **9a**–**w**.

Ir/(*S,S*)-f-binaphane (**11b**) afforded moderate conversion and enantioselectivity in trifluoroethanol (TFE). Using MeOH as solvent led to complete conversion albeit poor enantioselectivity. A 2:1 v/v mixture of MeOH and CH_2Cl_2 proved the best solvent combination, providing complete conversion and enantioselectivities up to 95%.

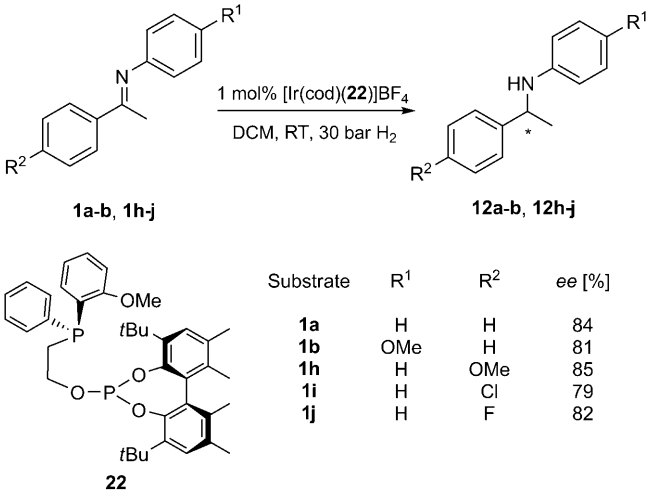
The catalytic system described above is similar to that shown in Table 1, and also required the presence of halides to give good enantioselectivity. A large number of N–H imines were examined under optimized reaction conditions. The presence of groups other than methyl at R^2 decreased the enantioselectivity. Concerning R^1, the presence of electron-donating or withdrawing substituents on the aromatic ring did not affect the enantioselectivity. The [Ir]/**11b** catalytic system showed promising enantioselectivities for dialkyl imine **9v** and diaryl imine **9w** (Table 3).[8]

Phosphine–phosphite ligands

Bidentate ligands that combine a phosphine and a phosphite moiety constitute an interesting family of ligands containing two different phosphorus functionalities, both of which are strongly coordinating, but only one is a good π-acceptor. A family of modular phosphine–phosphite ligands with a 2-phosphinoethanol backbone was tested in the iridium-catalyzed hydrogenation of *N*-aryl imines **1a**,**b**,**h**–**j**.[9] The stereogenic phosphorus was crucial to achieve high enantioselectivity. The best results were obtained using Ir catalysts with 2-(*S*)-[(*o*-anisyl)-phenylphosphino]ethyl (*S*)-(3-3′-di-*tert*-butyl-5,5′,6,6′-tetramethylbiphenyl-2,2′-diyl)phosphite **22** as ligand. Neutral precatalysts provided better results than the cationic ones. Under these conditions, different *N*-aryl imines (**1a**,**b**,**h**–**j**) were hydrogenated with enantioselectivities between 72 and 85% (Scheme 1).[9]

Diphosphite, diphosphinite, and phosphinite–phosphite ligands

Iridium complexes containing xylose diphosphite ligand **23** are active catalysts for the hydrogenation of imines, although high

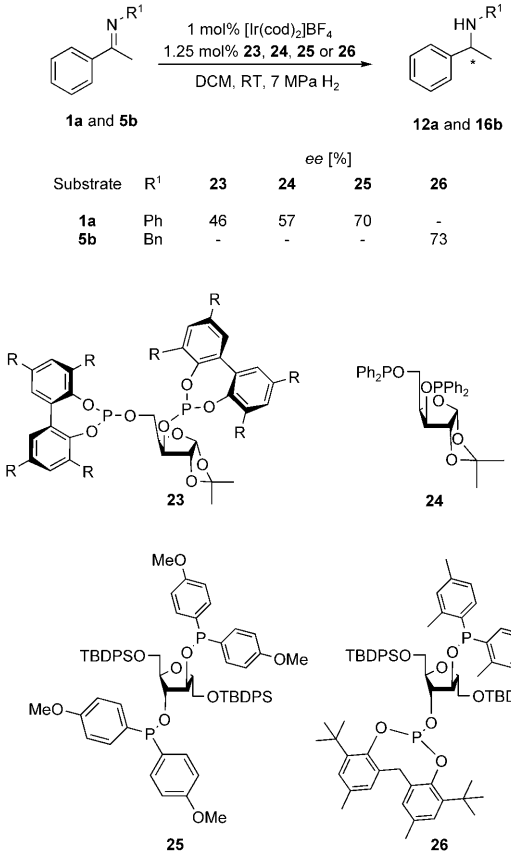


Substrate	R^1	R^2	*ee* [%]
1a	H	H	84
1b	OMe	H	81
1h	H	OMe	85
1i	H	Cl	79
1j	H	F	82

Scheme 1. Enantioselective hydrogenation of substrates **1a**–**b** and **1h**–**j** with [Ir]/**22**.

hydrogen pressure is required and they provide moderate enantioselectivities (Scheme 2).[10] Diphosphinite **24**, which has an identical backbone to diphosphite **23**, provided a slightly better enantioselectivity under similar reaction conditions.

C_2-symmetric diphosphinite ligands **25**, containing various electron-donating or electron-withdrawing groups on the aryls,



Substrate	R^1	*ee* [%] **23**	**24**	**25**	**26**
1a	Ph	46	57	70	-
5b	Bn	-	-	-	73

Scheme 2. Enantioselective hydrogenation of substrate **1a** and **5b** with [Ir]/**23**–**26**.

and C_1-symmetric phosphinite–phosphite **26**, both derived from glucosamine, were tested in the Ir-catalyzed asymmetric hydrogenation of **1a** and **5b**. Cationic complexes such as $[Ir(cod)(L{-}L)]BF_4$ were more active than the corresponding neutral iridium complexes. The use of additives was detrimental for conversion and enantioselectivity. The use of diphosphite **23** as a ligand provided a 70% *ee* in the hydrogenation of **1a** (Scheme 2).[11] Ligand **26** provided a 73% *ee* in the hydrogenation of the benzyl derivative **5b**.

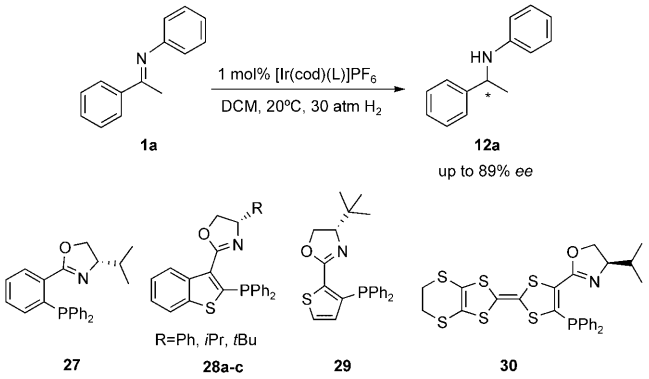
Phosphorus–nitrogen ligands

In 1977, Crabtree and co-workers reported an achiral iridium complex $[Ir(cod)(py)(PCy_3)]PF_6$ that displayed high catalytic activity as a homogeneous hydrogenation catalyst.[12]

Since then, a number of research groups have evaluated chiral analogues of Crabtree's catalyst in asymmetric reductions.[13,14] In 1997, Pfaltz et al. reported that iridium complexes containing chiral phosphine–oxazolines **27** (PHOX), **28**, and **29** were highly efficient in the hydrogenation of imines (*ee* values up to 89% using ligand **27**; Scheme 3).[15] Cationic iridium(I) complexes with ligand **27**, modified with perfluoroalkyl chains on the phenyl groups of the phosphine moiety, were efficient catalysts in supercritical CO_2 ($scCO_2$), giving 89% *ee* and full conversion in the hydrogenation of **1a**. Hydrogenation of imine **5b** gave very low conversions. Both the side chains and the lipophilic anions increased the solubility of the complex in $scCO_2$, but the choice of anion also had a dramatic effect on the enantioselectivity with BAr_F leading to the best results (*ee* values up to 81%).[16]

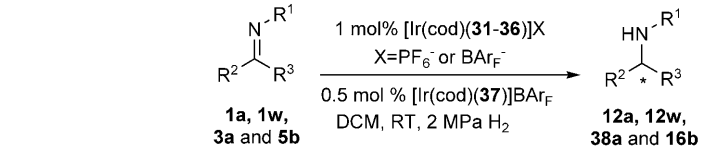
Cationic iridium complexes bearing the enantiomerically pure tetrathiafulvalene–oxazoline ligand **30** were also used in the asymmetric hydrogenation of **1a**, affording complete conversions and enantioselectivities up to 68%. Decreasing the temperature has a detrimental effect on the conversion and enantioselectivity for this catalytic system. When two different counter anions (PF_6^- or BAr_F^-) were used under the same reaction conditions, the best results were achieved with the more hindered noncoordinating anion BAr_F^-[17] (Scheme 3).

Related catalytic systems have been prepared in situ by addition of phosphine–imidazoline **31**[18] or oxazoline–thioether **32**[19] as ligands to the iridium precursor $[Ir(cod)_2]BF_4$. In both cases the enantioselectivities achieved were moderate (up to 50% for **31**). The addition of additives had a negative effect on the enantioselectivity and the use of cationic precursors provided better results than those obtained with the neutral dinuclear complex $[\{Ir(\mu\text{-}Cl)(cod)\}_2]$/L (Scheme 4).



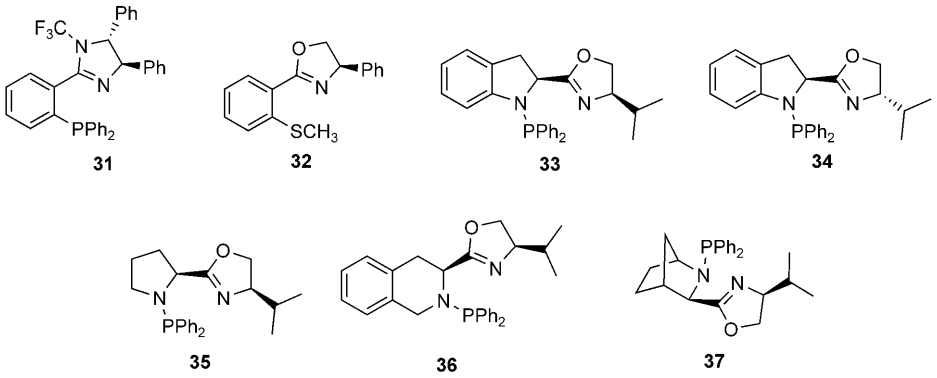
Scheme 3. Enantioselective hydrogenation of substrate **1a** with [Ir]/**27**–**30**.

Related ligands incorporating aminophosphine–oxazoline functionalities **33**–**37**, containing two stereocenters, were also applied in the Ir-catalyzed asymmetric hydrogenation of **1a**, with enantioselectivities of up to 90%. The hydrogenation of the benzyl derivative **5b** was achieved with 82% *ee* (Table 4). The stereogenic center of the oxazoline unit has a considerable impact on the enantioselectivity of the reaction. Thus, the iridium catalyst containing ligand **33**, with (*R*) configuration on the oxazoline ring and (*S*) configuration on the aminophosphine moiety induced a higher enantioselectivity (90% *ee*) than its diastereoisomer containing ligand **34**, which has (*S*) configuration on the oxazoline ring (14% *ee*).[20]



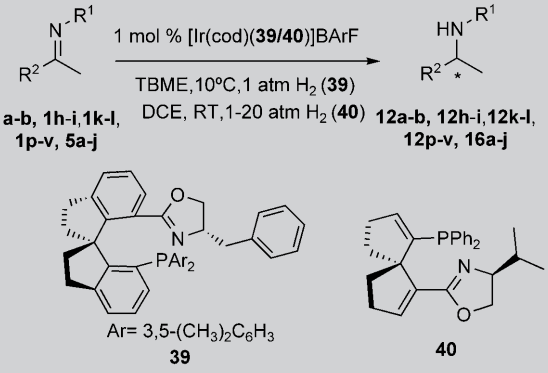
ee [%]

Substrate	R^1	R^2	R^3	**31**	**32**	**33**	**34**	**35**	**36**	**37**
1a	Ph	Ph	CH_3	51	-	90	14	85	68	90
1w	Ph	Cy	CH_3	-	-	-	-	-	-	30
3a	Ph	Ph	Et	-	-	-	-	-	-	78
5b	Bn	Ph	CH_3	11	15	82	-	62	60	-



Scheme 4. Enantioselective hydrogenation of **1a** and **5b** with [Ir]/**31**–**36** and **1a**, **1w**, and **3a** with [Ir]/**37**.

Table 4. Enantioselective hydrogenation of substrates **1a**, **1h–i**, and **1p–v** with [Ir]/**39**, and **1a**, **1b**, **1i**, **1k–l**, **1p–s**, and **5a–h** with [Ir]/**40**.



Substrate	R^1	R^2	*ee* [%]	
			39	**40**
1a	Ph	Ph	93	91
1b	4-$MeOC_6H_4$	Ph	–	90
1h	Ph	4-$MeOC_6H_4$	94	–
1i	Ph	4-ClC_6H_4	90	92
1k	4-ClC_6H_4	Ph	–	91
1l	4-BrC_6H_4	Ph	–	89
1p	Ph	4-BrC_6H_4	91	91
1q	Ph	3,4-$(CH_3)_2C_6H_3$	94	95
1r	Ph	3-ClC_6H_4	93	93
1s	Ph	3-BrC_6H_4	92	93
1t	4-ClC_6H_4	Ph	97	–
1u	4-BrC_6H_4	Ph	96	–
1v	3-BrC_6H_4	Ph	94	–
5a	Bn	4-$MeOC_6H_4$	–	90
5b	Bn	Ph	–	91
5c	Bn	4-$CH_3C_6H_4$	–	89
5d	Bn	4-ClC_6H_4	–	91
5e	Bn	4-FC_6H_4	–	88
5f	Bn	4-BrC_6H_4	–	89
5g	Bn	1-naphthyl	–	92
5h	Bn	4-MeO-naphthyl	–	93

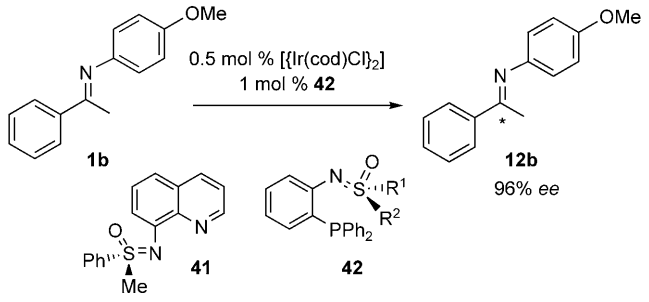
Andersson et al. reported a new class of aminophosphine–oxazoline ligands **37** with a 2-azanorbornane backbone that provided high *ee* values in the iridium-catalyzed hydrogenation of acyclic *N*-arylimines. The *N*-(1-phenylethylidene)aniline **1a** was hydrogenated with 98% conversion and 90% *ee*. The introduction of substituents on the aromatic ring attached to the phosphorus atom had a very moderate effect on the resulting enantioselectivity. However, the structure of the substrate had a strong effect. The best results were obtained when $R^1 = R^2 = Ph$; replacement of R^2 by cyclohexyl or *tert*-butyl groups or of R^3 by groups other than methyl had a detrimental effect on the enantioselectivity (Scheme 4).[21]

Phosphine–oxazoline ligands containing a spiranic backbone provided the best enantioselectivity of this family of ligands. Thus, spirobiindane-based (SIPHOX) ligand **39** was used in the asymmetric hydrogenation of **1a**, **h**, **i**, **p–v** at ambient hydrogen pressure with enantioselectivities up to 97%. The enantioselectivity increased when the reaction was carried out in weakly polar solvents such as CH_2Cl_2, toluene, ether, or *tert*-butyl methyl ether. The presence of 3,5-dimethyl groups on the *P*-phenyl ring had a positive effect on the conversion but the enantioselectivity was not affected. The introduction of electron-donating or electron-withdrawing groups on the α-phenyl ring of the ketimine slightly increased the enantioselectivity. Furthermore, iridium complexes bearing SIPHOX ligand **39** were resistant to the formation of inactive trimers under hydrogenation conditions (Table 4).[22]

Zhang, Ding, and co-workers recently reported a related phosphine–oxazoline ligand **40** with a spiro[4,4]-1,6-nonadiene backbone (SpinPHOX; Table 4). The [Ir]/**40** catalytic system was successfully used in the asymmetric hydrogenation of challenging *N*-alkyl ketimine substrates, such as **5a–h**, with up to 93% *ee*.

The chirality on the spiro backbone in ligands **39** and **40** has a significant impact on the asymmetric induction. The matched combination is obtained with an (*R*) configuration on the spiro backbone and (*S*) configuration on the oxazoline moiety. The *i*Pr group appears to be the substituent of choice (Scheme 4).[23]

Chiral sulfoximines such as **41**[24a] and **42**[24b,c] are versatile ligands for asymmetric catalysis, and constitute an interesting new type of P,N ligands, where the chirality lies in the sulfur atom (Scheme 5). The catalyst generated in situ by mixing

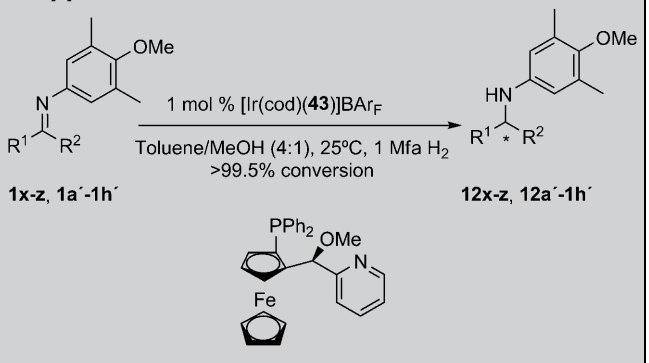


Scheme 5. Enantioselective hydrogenation of **1b** with [Ir]/**42**.

[{Ir(μ-Cl)(cod)}$_2$] with phosphinosulfoximine ligand (**42**, $R^1 = Ph$, $R^2 = CH_3$) and iodine as additive, was used in the hydrogenation of (*p*-MeO)PhN=CMe(Ph) (**1h**) and provided an enantiomeric excess of 79%. In general, the introduction of bulkier alkyl groups on the sulfoximine moiety produced lower conversions and enantioselectivities. However, the combination of $R^1 = Ph$ and $R^2 = i$Pr resulted particularly suitable, and imine **1b** was hydrogenated with enantioselectivity of 96% (Scheme 5).

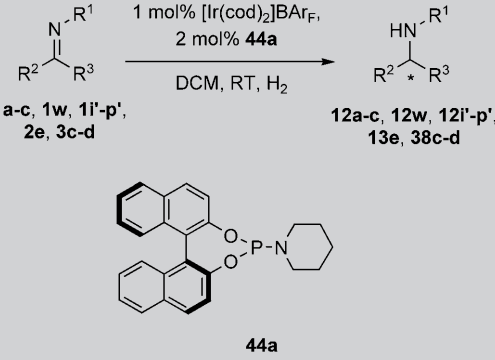
The Ir-catalyzed enantioselective hydrogenation of a range of *N*-(3,5-dimethyl-4-methoxy)phenylimines (**1x–z** and **1a′–h′**) was performed under mild conditions (1 MPa) in the presence of the isolated P,N-ferrocenyl iridium complex [Ir(cod)(**43**)]BAr_F, producing chiral amines in high yields and up to 99% enantioselectivities (Table 5). The solvent has a strong effect on the catalysis. The use of toluene afforded excellent conversion but poor enantioselectivity (11%). In contrast, when the reaction was carried out in methanol, poor conversions and moderate enantioselectivities were achieved. The optimized solvent mixture, 4:1 toluene/MeOH, gave full conversion and up to 84% enantioselectivity.

Table 5. Enantioselective hydrogenation of substrates **1x–z** and **1a′–h′** with [Ir]/**43**.



Substrate	R^1	R^2	*ee* [%]
1x	3-$CH_3C_6H_4$	CH_3	93
1y	4-PhC_6H_4	CH_3	92
1z	4-$CF_3C_6H_4$	CH_3	89
1a′	4-ClC_6H_4	CH_3	92
1b′	4-$CH_3CO_2C_6H_4$	CH_3	94
1c′	3-FC_6H_4	CH_3	93
1d′	2-$CH_3C_6H_4$	CH_3	94
1e′	2-naphthyl	CH_3	93
1f′	Ph	Et	94
1g′	Ph	pentyl	95
1h′	Ph	$PhCO(CH_2)_3$	99

Table 6. Enantioselective hydrogenation of substrates **1a–c**, **1w**, **1i′–p′**, **2e**, and **3c–d** with [Ir]/**44**.



Substrate	R^1	R^2	R^3	*ee* [%]
1a	Ph	Ph	CH_3	87
1b	4-$MeOC_6H_4$	Ph	CH_3	71
1c	2-$MeOC_6H_4$	Ph	CH_3	97
1w	3,5-$(CH_3)_2C_6H_3$	4-FC_6H_4	CH_3	97
1i′	3,5-$(CH_3)_2C_6H_3$	Ph	CH_3	99
1j′	2-$MeOC_6H_4$	Ph	CH_3	99
1k′	2-$MeOC_6H_4$	4-$CH_3C_6H_4$	CH_3	99
1l′	2-$MeOC_6H_4$	4-ClC_6H_4	CH_3	97
1m′	2-$MeOC_6H_4$	4-$CF_3C_6H_4$	CH_3	97
1n′	2-$MeOC_6H_4$	3-$CH_3C_6H_4$	CH_3	93
1o′	2-$MeOC_6H_4$	4-$NO_2C_6H_4$	CH_3	61
1p′	2-$MeOC_6H_4$	2-naphthyl	CH_3	99
2e	2-$MeOC_6H_4$	*n*Bu	CH_3	16
3d	2-$MeOC_6H_4$	Ph	Et	94
3c	2-$MeOC_6H_4$	Ph	Pr	97

Deprotection of the 3,5-dimethyl-4-methoxyphenyl moiety of amines was performed under mild conditions with cerium ammonium nitrate[25] in a 6:1 MeOH/H_2O mixture, providing the corresponding primary amines in good yield. The authors also carried out the asymmetric synthesis of chiral γ- and δ-lactams[26–27] in 92–97% *ee*.[28] The highest *ee* values were obtained with substrates bearing a remote carbonyl group (**1h′**).

Monodentate phosphorus ligands

Bidentate ligands have been considered superior over monodentate ones in metal-catalyzed asymmetric hydrogenation reaction for more than 30 years because of the rigidity provided by their chelating nature.[1,29,30] Monodentate ligands, however, have afforded excellent results in terms of conversion and enantioselectivity in several catalytic processes, including hydrogenation reactions. In particular, monodentate phosphoramidite ligands present the advantage of being readily accessible, highly modular, air stable, and inexpensive compared to most bidentate ligands.[31] Feringa et al. reported the highly enantioselective asymmetric hydrogenation of acyclic *N*-arylimines (**1a**,**d**–**f**,**h**–**j**,**p**, and **2a**) using (*S*)-PipPhos **44**, a monodentate 1,1′-bi-2-naphthol (binol)-derived phosphoramidite, with excellent conversions and *ee* values up to 99% (Table 6).

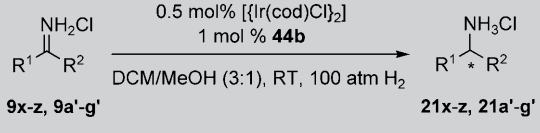
As previously indicated, the presence of a substituted phenyl ring as R^1 is required to achieve high enantioselectivities and the best results were obtained with 3,5-dimethylphenyl and 2-methoxyphenyl groups. When both R^2 and R^3 were alkyl groups, the enantioselectivity dropped. The catalytic systems were prepared in situ by mixing $[Ir(cod)_2]BAr_F$ and the monodentate PipPhos ligand **44a**. The reaction was strongly solvent dependent, dichloromethane being the most effective, whereas the use of protic solvents, such as methanol, did not provide any reactivity. The hydrogenation reactions were all carried out under mild conditions (0.1–05 MPa).[29]

Recently, Zhang and co-workers reported the asymmetric hydrogenation of very challenging benzophenone N–H imines (**9x**–**z**,**a′**–**g′**) with ortho substituents in at least one of the phenyl rings, using the monodentate phosphoramidite ligand **44b**, and achieved excellent enantioselectivities and conversions (Table 7).[32] A key point in the strategy was the presence of *ortho* substituents in the phenyl ring. The reaction worked at very high H_2 pressures (see also Scheme 3).

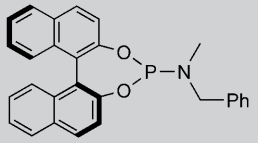
Monotosylated diamine ligands

As mentioned above, most of the transition metal catalysts used in the asymmetric hydrogenation of imines contain phosphorus ligands, and it is believed that the reduction proceeds through imine nitrogen coordination to the metal center.[1] However, Norton and co-workers reported that imines can also be reduced through an ionic pathway, whereby a $\{Ru^{II}–H_2\}$ complex is deprotonated by an imine and the resulting $\{Ru^{II}–H\}$ reduces the preformed iminium salts.[33] In the field of organocatalysis[34a] a highly enantioselective transfer hydrogenation reaction of imines with Hantzsch ester using a chiral phosphoric acid was recently reported.[34b–d] The acid protonated the

Table 7. Enantioselective hydrogenation of substrates **9x–z** and **9a′–g′** with [Ir]/**44b**.



9x-z, 9a'-g' **21x-z, 21a'-g'**

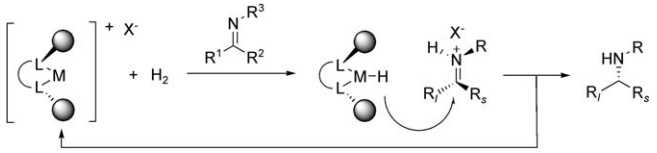


44b

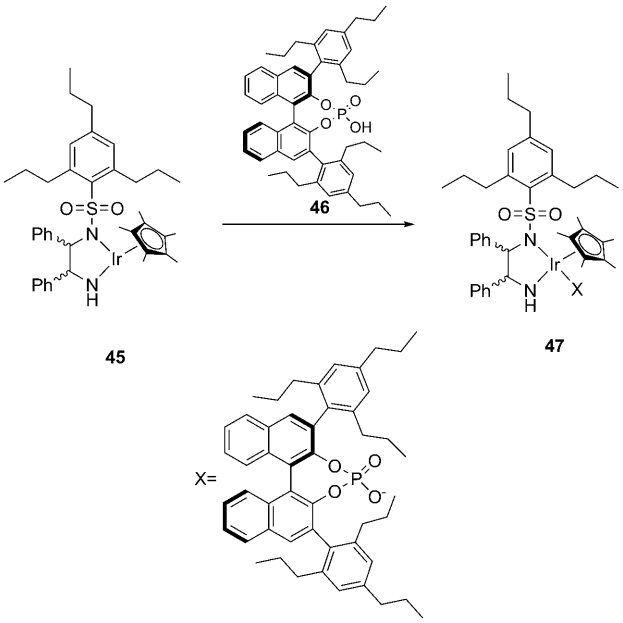
Substrate	R^1	R^2	*ee* [%]
9x	2-ClC_6H_4	Ph	87
9y	2-BrC_6H_4	Ph	91
9z	2-$CH_3C_6H_4$	Ph	82
9a′	2-$MeOC_6H_4$	Ph	76
9b′	2-FC_6H_4	Ph	36
9c′	2-$CF_3C_6H_4$	Ph	98
9d′	2-ClC_6H_4	Ph	92
9e′	2-ClC_6H_4	Ph	93
9f′	2-$CH_3C_6H_4$	4-$CH_3C_6H_4$	91
9g′	2-$CH_3C_6H_4$	2-$MeOC_6H_4$	94

imine and the anion directed the facial attack of the hydride. Based on this system, Xiao and co-workers reported Ir^{III} catalysts containing a coordinated diamine, which behaved as heterolytically hydrogen-activating catalysts. A chiral phosphate anion (X^-) influenced the enantiodiscrimination of the chiral ligand by ion-pairing with the resulting iminium cation (Scheme 6).[34e]

The best results were obtained by combining the 16 electron {Cp*Ir^{III}} complex **45** with a bulky phosphoric acid **46** used as a promoter to form the complex **47** (Scheme 7). This catalytic system was applied in the asymmetric hydrogenation of a wide range of imines affording excellent yields and enantioselectivities (88–96% and 92–98%, respectively). Only for substrate **1q′** were *ee* values lower than 90%.The reactions involving ion-pairing intermediates are solvent sensitive. In solvents more polar than toluene, such as THF or MeCN, which limit the ion pair formation, lower enantioselectivities were obtained, indicating that the enantioselectivity is the result of a cooperative effect between the chiral metal catalyst and its chiral counteranion (Table 8).[35] For all substrates under study, R^1 was a phenyl ring mainly with electron-donating substituents at the 4-position. Interestingly, high enantioselectivities were also obtained when both R^2 and R^3 were alkyl groups.

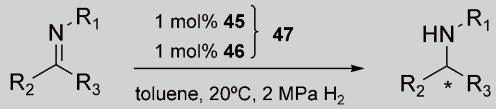


Scheme 6. Enantiodiscrimination of the chiral ligand by ion pairing with the resulting iminium cation.



Scheme 7. Formation of the complex **47**.

Table 8. Enantioselective hydrogenation of substrates related to **1a–b**, **1h**, **1n–o**, **1q′–y′**, and **3e–h** with complex **47**.

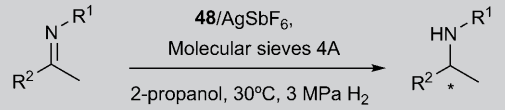


1a-b, 1h, 1n-o, 1q'-y', 3e-h **12a-b, 12h, 12n-o, 12q'-y', 38e-h**

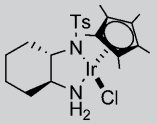
Substrate	R^1	R^2	R^3	*ee* [%]
1a	Ph	Ph	CH_3	95
1b	4-$MeOC_6H_4$	Ph	CH_3	97
1h	Ph	4-$MeOC_6H_4$	CH_3	97
1n	4-BrC_6H_4	Ph	CH_3	98
1o	4-$MeOC_6H_4$	4-$MeOC_6H_4$	CH_3	97
1q′	4-$MeOC_6H_4$	3-$NO_2C_6H_4$	CH_3	84
1r′	4-$MeOC_6H_4$	4-$CH_3C_6H_4$	CH_3	97
1s′	4-$MeOC_6H_4$	3-$CH_3C_6H_4$	CH_3	96
1t′	4-$MeOC_6H_4$	4-$C_4H_8C_6H_4$	CH_3	98
1u′	4-$MeOC_6H_4$	4-BrC_6H_4	CH_3	97
1v′	4-$MeOC_6H_4$	4-ClC_6H_4	CH_3	96
1w′	4-$MeOC_6H_4$	3,4-$(CH_3)_2C_6H_3$	CH_3	97
1x′	4-$MeOC_6H_4$	4-CNC_6H_4	CH_3	93
1y′	4-$MeOC_6H_4$	4-$NO_2C_6H_4$	CH_3	92
3e	4-$MeOC_6H_4$	Ph	Et	90
3f	4-$MeOC_6H_4$	4-$CH_3C_6H_4$	Et	91
3g	4-$MeOC_6H_4$	C_4H_7	CH_3	95
3h	4-$MeOC_6H_4$	C_5H_{11}	CH_3	94

Noyori, Ikariya and co-workers discovered a conceptually new chiral Ru catalyst bearing *N*-sulfonylated 1,2-diamines that is highly efficient in asymmetric hydrogen transfer of imines.[36] Based on that system, Ikariya et al. recently reported the iridium chiral complex, [Cp*IrCl{(*S*,*S*)-Tscydn}] **48** ((*S*,*S*)-Tscydn = (*S*,*S*)-(+)-*N*-*p*-tosyl-1,2-cyclohexanediamine) efficient for the asymmetric hydrogenation of acyclic imines. The addition of

Table 9. Enantioselective hydrogenation of substrates **1a**, **5b**, and **5i–n** with complex **48**.



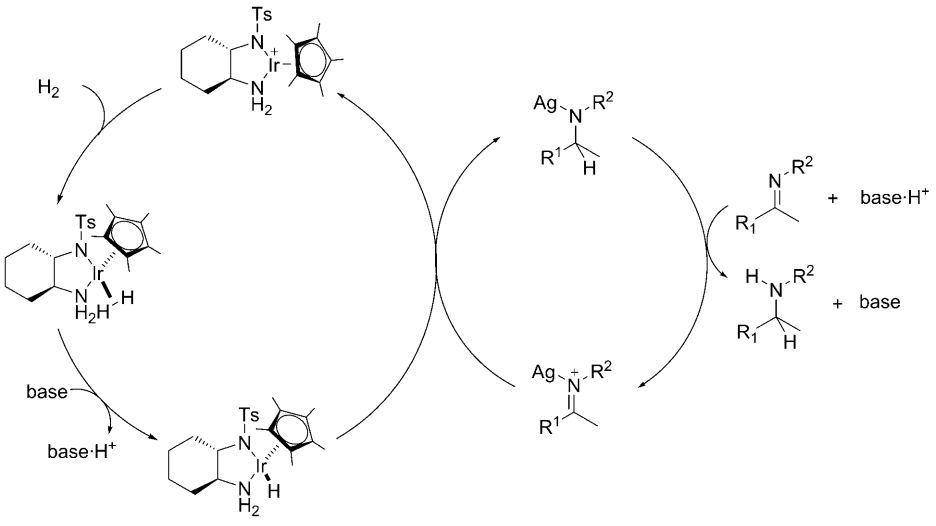
1a, **5b** and **5i-n** — **12a, 16b, 16j-n**



48

Substrate	R^1	R^2	*ee* [%]
1a	Ph	Ph	93
5b	Bn	Ph	92
5i	Bn	4-$CF_3C_6H_4$	89
5j	4-$CF_3C_6H_4CH_2$	Ph	92
5k	4-$ClC_6H_4CH_2$	Ph	94
5l	4-$CH_3C_6H_4CH_2$	Ph	93
5m	2-$CF_3C_6H_4CH_2$	Ph	94
5n	4-$MeOC_6H_4CH_2$	Ph	93

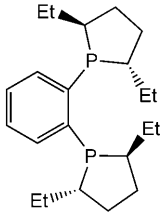
silver salts such as $AgSbF_6$ caused an improvement in conversion and enantioselectivity in the asymmetric hydrogenation of *N*-(1-*p*henylethylidene)benzylamine (**5b**; Table 9). Although the origin of the enantiofacial discrimination remains unknown, it is thought that the formation of the N–Ag bond facilitates the hydride attack to the *Re* face of the imine, providing better enantioselectivities (Scheme 8).[37]



Scheme 8. Hydrogenation mechanism for the Ir–Tscydn System.

1.2. Ruthenium catalysts

Noyori's catalysts, ruthenium(II) dichloride(diphosphine)-(diamine) complexes, were successfully used in the asymmetric hydrogenation of imines.[38] The effect of different steric and electronic substituents has been studied for a large library of different diphosphine and diamine ligands. The best enantioselectivity reported (92%) was achieved with the combination of (*R,R*)-EtDuPHOS **49** and (*R,R*)-DACH **50** (DACH = 1,2-diaminocyclohexane; Figure 4).[39] *N*-tosylimines (**6a–p**) are hydrogenated



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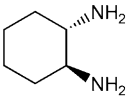


50

Figure 4. (*R,R*)-EtDuPhos **49** and (*R,R*)-diaminocyclohexane **50**.

with Ru-binap catalyst (binap = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl) with enantioselectivities up to 84%.[40] Despite these results, the asymmetric hydrogenation of imines with Ru catalysts and molecular hydrogen as a source of protons has received less attention. There have been no reports of these conditions since 2006. However, in recent years, Ru catalysts have been shown to efficiently catalyze asymmetric transfer hydrogenation (ATH).

1.3. Rhodium catalysts

Although they are used less often than Ir catalysts, Rh^I catalysts with dialkyl- and diarylphosphine and diphosphinite ligands are known to be active in the asymmetric hydrogenation of imines. The reactivity of the such diphosphine catalysts increases upon addition of *p*-toluenesulfonic acid.[41] The Rh system bearing diphosphinite **51** provided 71% *ee* in the hydrogenation of **1a**.[41] No additives were required.

Hydrogenation of several *N*-tosylimines (**6**) was performed by mixing the rhodium precursor $[Rh(cod)_2]BF_4$ with chiral diphosphines such as (*S,S,R,R*)-TangPhos (**17**), (R_P,S_C)-DuanPhos (**18**), S_P-binapine (**52**) and (*S*)-C_3-TunePhos (**53**; Figures 3 and 5), giving enantioselectivities of 80–94%. Rhodium catalysts bearing the ligands (*R,R*)-EtDuPHOS (**49**) or (*R,R*)-MeDuPHOS (**20**) showed high conversions, although enantioselectivities were moderate (63 and 67%).[42] [Rh]/EtDuPHOS (**49**) catalytic systems were more successful in the hydrogenation of *N*-acylhydrazones, giving up to 88% *ee*.[43]

A highly enantioselective synthesis of chiral 2-arylglycine derivatives **54a–o** was achieved through rhodium-catalyzed

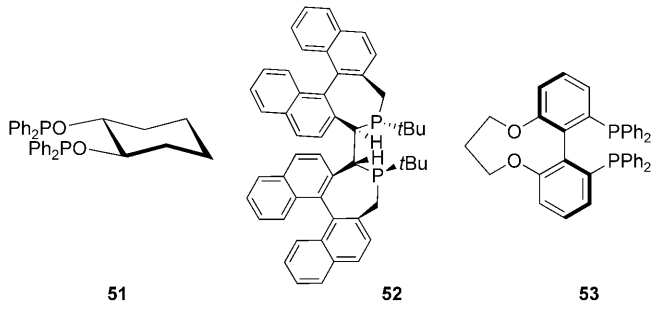
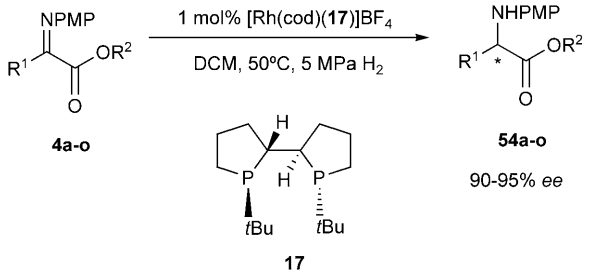


Figure 5. Ligands **51**–**53**.

asymmetric hydrogenation of α-arylimino esters **4a**–**o** with a Rh complex of TangPhos **17**. The electron-rich character, rigid conformation and well-defined geometry resulted in a catalyst that provided high activities and up to 95% enantioselectivities. When R^2 was an ethyl group (**4n**), enantioselectivity was lower than 90%. The electronic properties of the substituents of the substrate had no apparent effect on the yield of the reaction (Scheme 9).[43]

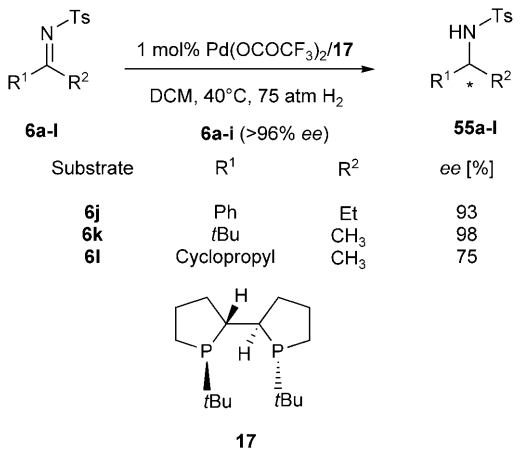


Scheme 9. Enantioselective hydrogenation of substrates **4a–o** with [Rh]/**17**.

1.4. Palladium catalysts

In 2006, Zhang and co-workers reported the first example of Pd-catalyzed asymmetric hydrogenation of imines using a series of diphosphine ligands such as TangPhos, DuanPhos, binap, and C_n-TunePhos (Figures 3 and 4). The best results were achieved in the hydrogenation of *N*-tosylimines, with complete conversion and enantioselectivities up to 99%, using the Pd-TangPhos catalyst. The presence of weakly coordinating ions such as $CF_3CO_2^-$ is required to achieve high conversion with the palladium precursors. The nature of the solvent affected neither the activity nor the enantioselectivity of the reaction. The hydrogenation of doubly alkyl-substituted *N*-tosylimines was carried out with high to excellent enantioselectivities (up to 98%). However, this catalytic system has significant limitations because high hydrogen pressure is required[43] (Scheme 10).

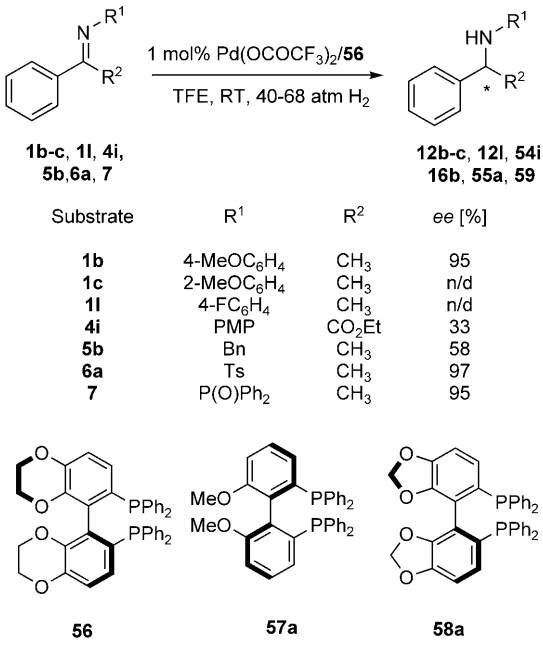
Atropoisomeric diphosphine ligands **56**–**58** were used in Pd-catalyzed asymmetric imine hydrogenation. The catalytic system Pd(CF_3CO_2)/(*S*)-SynPhos **56** gave enantioselectivities of 95% and 97% in the hydrogenation of *N*-diphenylphosphinyl ketimine **7** and chiral *N*-sulfonylamines, respectively. Similar results were obtained when ligand SegPhos **58** was used. Imine



Scheme 10. Enantioselective hydrogenation of substrates **6a–l** with [Pd]/**17**.

1b bearing a 4-methoxy-phenyl group linked to nitrogen was hydrogenated with excellent *ee* values. Both ligands provided low enantioselectivities in the hydrogenation of the benzylimine derivative **5b**. The presence of electron-withdrawing groups, such as tosyl or diphenylphosphinyl, reduced the inhibiting effect on the catalyst induced by the coordination of substrate and product. Furthermore, in these cases imines existed exclusively as the *E* isomer, which led to better conversions and enantioselectivities. The reaction is strongly solvent dependent, trifluoroethanol being the only efficient solvent. Various palladium precursors were tested. $PdCl_2$ was inactive under the catalytic reaction conditions[44] (Scheme 11).

From the results presented above, it appears that Ir remains the most used metal for asymmetric imine hydrogenation catalysis. However, other metals have emerged and offer interest-



Scheme 11. Enantioselective hydrogenation of substrates **1b–c**, **1l**, **4i**, **5b**, **6a**, and **7** with [Pd]/**56**–**58**.

ing alternatives. Very diverse ligands have been developed in terms of structures and functionalities. Among these ligands, atropoisomeric and ferrocenyl diphosphines, and phosphine–oxazoline are some of the most represented class of ligands. However, recent results suggest that monodentate ligands such as phosphoramidites are extremely promising. The substrate structures are also evolving. The most recent catalytic systems are now able to hydrogenate imine substrates that bear no chelating group to orientate the reduction. An important breakthrough has been achieved with the hydrogenation of unfunctionalized NH imines, giving easily access to chiral secondary amines.

2. Asymmetric Hydrogenation of Cyclic Imines

The symmetric hydrogenation of cyclic imines, and particularly heteroaromatic compounds, although less explored than their acyclic analogue, was reviewed in 2007.[45] Indeed, beside the fact that, as aromatic compounds are more stable, their hydrogenation requires harsher reaction conditions, it suffers from easy deactivation of the catalysts through poisoning. Additionally, the presence of functional groups coordinating the metal catalyst is usually necessary to achieve high enantioselectivities. Nevertheless, hydrogenation of cyclic imines has been studied over the last years and important breakthroughs were made. The range of cyclic imines and heteroaromatic compounds used as substrates in asymmetric hydrogenation are depicted in Figure 6. The indoles **64** and **65** and pyrrole **66** are also included since their hydrogenation is usually studied in parallel to the other cyclic or heterocyclic imines discussed below.

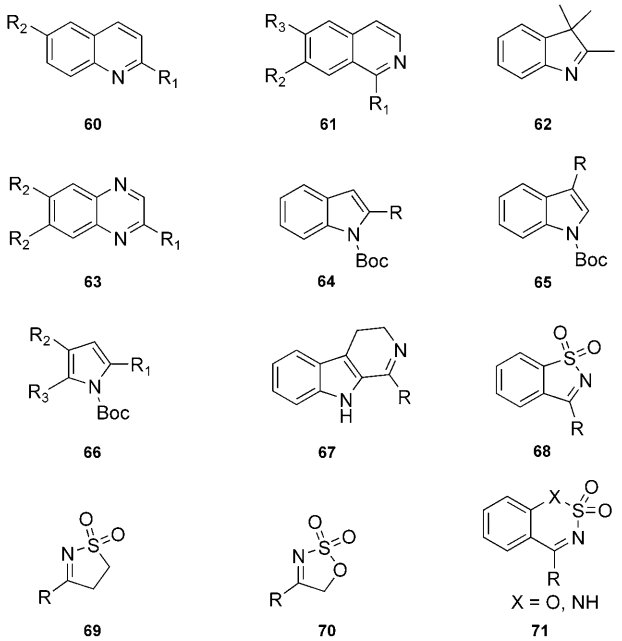


Figure 6. Cyclic imines and heteroaromatic compounds studied in asymmetric hydrogenation.

2.1. Iridium catalysts

As previously described for acyclic imines, iridium is the most efficient and studied metal in asymmetric hydrogenation of cyclic imines. The catalytic system is often formed in situ by addition of chiral ligands to an Ir precursor. Bidentate phosphorus ligands are still the most studied and provide excellent results.

Diphosphine, phosphine, and phosphoramidite ligands

Atropoisomeric diphosphines were shown to be highly efficient in the Ir-catalyzed hydrogenation of cyclic imines (Figure 7).[45–57] Zhou et al. developed a catalytic system that

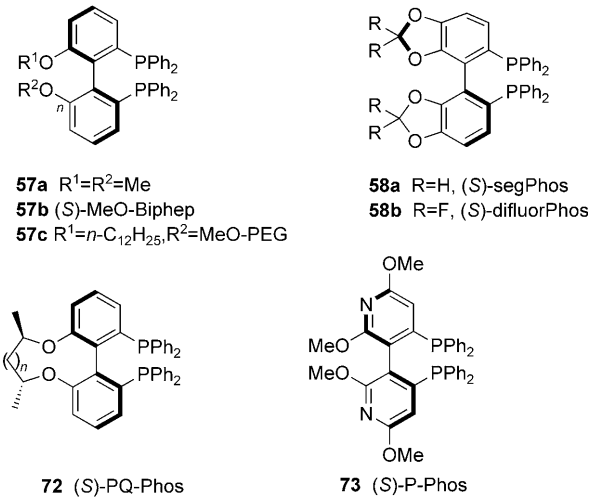
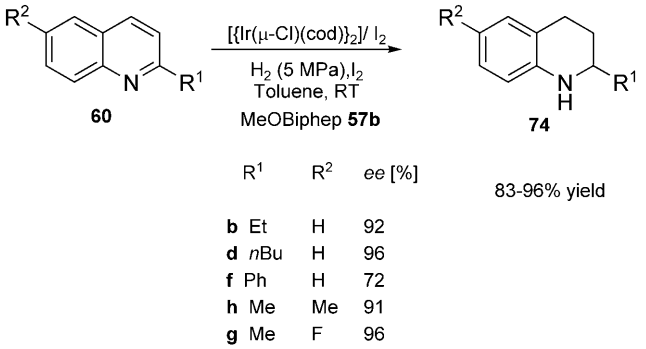


Figure 7. Atropoisomeric diphosphines **57**–**58**, **72**–**73** used as highly efficient ligands in the hydrogenation of cyclic imines.

consists of [{Ir(μ-Cl)(cod)}$_2$] as precursor, MeOBiphep **57** as ligand, and iodine as additive. This system provided excellent results with full conversion and *ee* values up to 96% under 5 MPa of pressure for the hydrogenation of quinolines **60** (Scheme 12).[46]

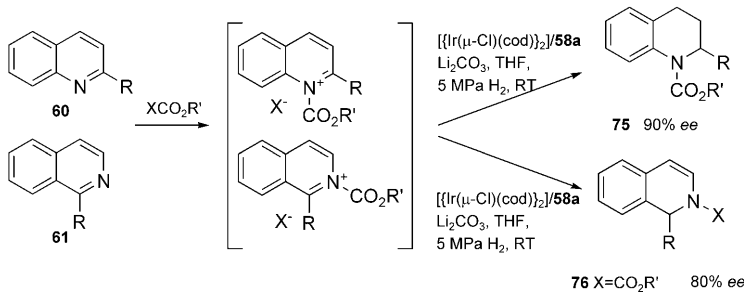
This catalyst was modified by the introduction of a MeO-PEG side chain, which allowed efficient recycling by precipitation



Scheme 12. Enantioselective hydrogenantion of substrate **60** using ligand **57b**.

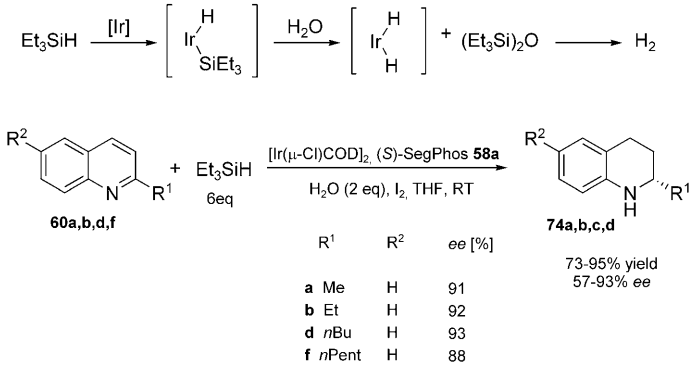
and filtration of the catalyst.[47] The substrate scope was extended to diversely substituted quinolines **60**, isoquinolines **61** (only monohydrogenation), and their derivatives.[48]

The use of chloroformates as activating agents, instead of iodine and in combination with Li_2CO_3 as base, was investigated with some success. Under these conditions, SegPhos **58a** provided the best results (Scheme 13).[49]



Scheme 13. Use of chloroformates as activating agents in the iridium-catalyzed asymmetric hydrogenation of substrates **60** and **61**.

Recently, the hydrogenation of quinolines **60** using [{Ir(μ-Cl)(cod)}$_2$]/(*S*)-SegPhos **58a**, and iodine, with a mixture of water and silane as the hydrogen source, was reported. The combination of silane and iridium led to a metal silyl compound that reacted with water to produce an {Ir–H} complex (Scheme 14).[50] This complex was applied as catalyst for the



Scheme 14. Hydrogenation of quinolines **60** using water and silane as the source of hydrogen.

reduction of various quinolines up to 93% *ee* under mild conditions.

Some other chiral-bridged atropoisomeric diphosphines, based on a MeOBiphep skeleton, were synthesized by Chan et al. and tested in the hydrogenation of various substrates, including *N*-heteroaromatic compounds.[51,52]

P-Phos **73** was applied in the hydrogenation of 2-substituted quinolines **60** and provides *ee* values of up to 90%. The use of poly(ethylene glycol) dimethyl ether (DMPEG)/hexane as a reaction medium allowed effective product separation and recycling.[53] This reaction medium was later used for other ligands as well.[54]

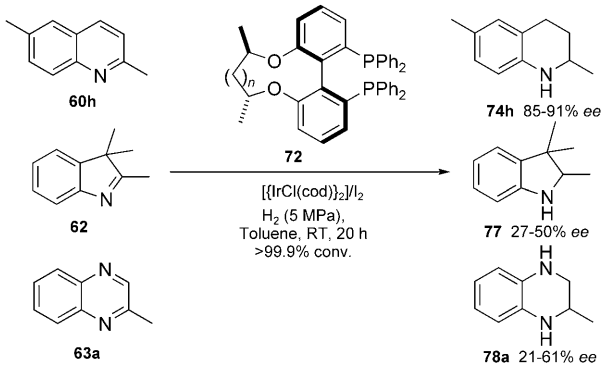
PQ-Phos **72** is a family of versatile atropoisomeric diphosphines, analogues of the TunaPhos ligands.[55] The synthetic pathway starts from commercial chiral diols and includes a very elegant diastereoselective Ullman coupling step.[52] This cross-coupling reaction is highly diastereospecific and, in order to access other diastereoisomers, the synthetic pathway had to be modified. The length of the carbon chain of the diol can be easily varied, thus changing the dihedral angle of the corresponding ligand.

The *N*-heterocycles **60h**, **62**, and **63a** were subsequently hydrogenated. Some of the results are summarized in Scheme 15. A previous successful asymmetric reduction of 2-methylquinoxaline **63a** was reported in 1998 by Bianchini et al. (90% *ee*).[56]

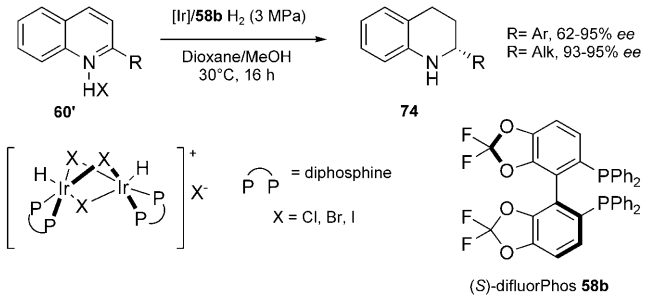
Recent progress towards the hydrogenation of 2-arylquinolinium salts **60′** has been made using the DifluorPhos ligand **58b** (Scheme 16).[53,56] Cationic dinuclear triply halogen-bridged iridium(III) complex-containing diphosphines provided good results under milder reaction conditions[57,58]

Almost all of the aforementioned catalytic systems suffer from a low activity due to some catalyst deactivation along the catalytic cycle, resulting in the use of low substrate/catalyst ratios (around 100). Fan et al. demonstrated that deactivation could be avoided by using {Ir–binap}-cored dendrimers **79**. This catalytic system was applied in the hydrogenation of 2-substituted quinolines **60**, and hydrogenation was still effective with a substrate/catalyst ratio of up to 50000. The dendrimer structure conferred a very high stability to the catalyst and recycling experiments were carried out with up to six runs without any important loss of activity or enantioselectivity (Scheme 17).[59]

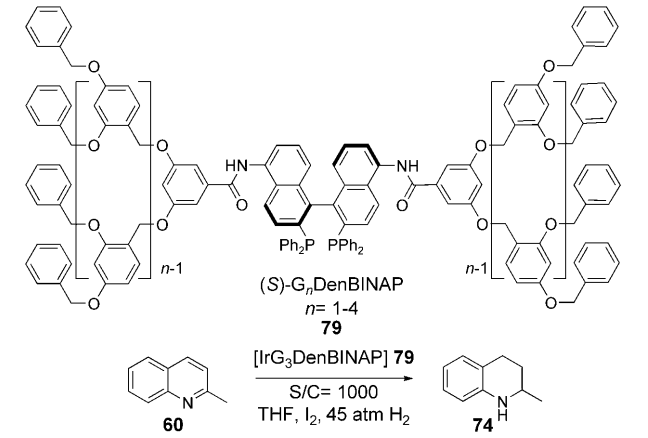
Recently, a new class of phosphine–phosphoramidite ligands **80**, combining central and axial chirality, was reported by Leitner et al.[60] The synthesis relied on a Pd-catalyzed Buchwald–Hartwig amination and an alkylation step with phosphochloridites derived from (*R*)- or (*S*)-binol (Figure 8). They were tested in



Scheme 15. Enantioselective hydrogenation of substrates **60h**, **62**, and **63a** using [Ir]PQ-Phos (**72**).



Scheme 16. Use of Ir^{III} bridged complex bearing ligand **58b** for the hydrogenation of substrate **60′**.



Scheme 17. Binap-cored dendrimers **79** and their application in the Ir-catalyzed hydrogenation of quinoline **60**.

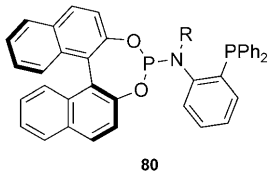


Figure 8. Phosphine–phosphoroamidite ligand **80**.

the iridium-catalyzed hydrogenation of **60a** and **j**, providing enantioselectivities of 97% and 95%, respectively.

Diphosphinite ligands

Although much less represented than diphosphines in the field of cyclic imine hydrogenation, diphosphinite ligands possess several advantages, such as the ease of preparation and derivatization. Some diphosphinites have been successfully tested in the Ir catalyzed hydrogenation of quinolines. (Figure 9).[61–62]

For instance, the spiro (*R*)-sdpo (sdpo = spirobiindanediphosphinite) ligand **82** obtained from (*R*)-1,1′-spirobiindane-7,7′-diol provided enantioselectivities up to 95% in the hydrogenation of 2-alkyl quinolines **60**, with high substrate/catalyst ratios (up to 5000).[62] These results were improved by up to 97% by

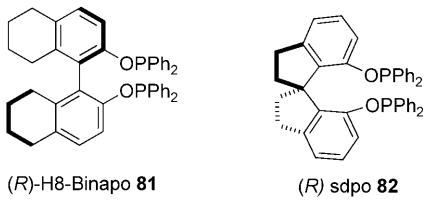
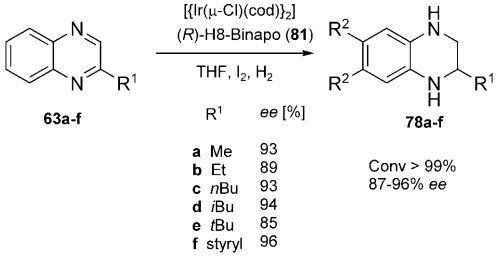


Figure 9. Diphosphinite ligands **81** and **82**.

using the H8-binapo ligand **81**.[61] The latter was also recently used in the asymmetric hydrogenation of quinoxalines with excellent results (Scheme 18).[63]



Scheme 18. [Ir]/**81** catalytic system in hydrogenation of quinoxalines **63**.

Diphosphonite ligands

There is only one recent report dealing with the use of diphosphonites in the metal-catalyzed asymmetric hydrogenation of cyclic imines.[64] These ligands, easily available from chiral binols, were developed by Reetz et al. for the Rh-catalyzed hydrogenation of olefins (Figure 10).[65]

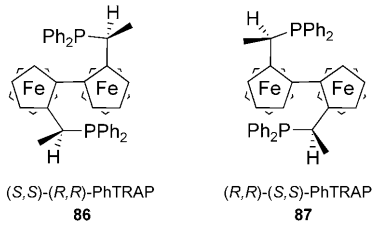
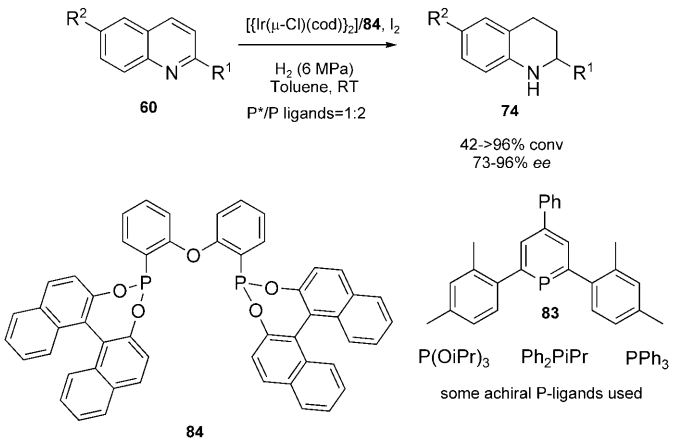


Figure 10. Ferrocenyl diphosphines **86** and **87**.

Interestingly, the mixture of binol-based phosphonite ligand **84** in combination with achiral P ligands **83** and other (1:2 ratio) improved the catalytic activity without loss of enantioselectivity (Scheme 19).

Phosphorus-nitrogen ligands

Bolm and co-workers reported a series of naphthalene-bridged phosphinosulfoximine ligands that provided 92% *ee* in the iridium-catalyzed hydrogenation of quinoline **60a**. Other alkyl substituted quinolines were hydrogenated with lower enantioselectivities.[66]



Scheme 19. Hydrogenation of quinolines **60** with [Ir]/**84**.

Monodentate phosphorus ligands

As described above, the successful application of phosphites, phosphonites, and particularly that of phosphoramidites has increased the attention on this family of ligands[31] Recently, it was reported that (*S*)-PipPhos **44** (Table 6), a binol-based phosphoramidite, provides excellent results in hydrogenation of quinoline derivatives, with *ee* values up to 89%. The addition of an achiral phosphine such as tri-*o*-tolylphosphine and piperidine hydrochloride as another additive improved both the conversion and the enantioselectivity (Figure 11).[67] The crucial role of these additives has not yet been determined.

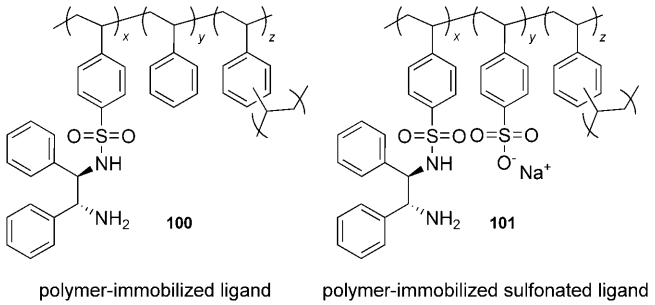
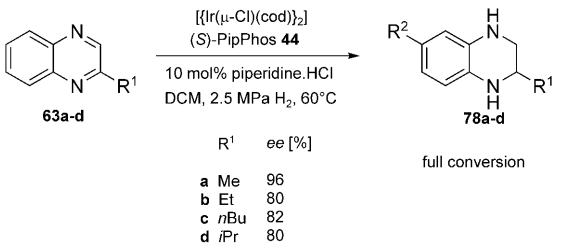


Figure 11. Examples of polymer-immobilized diamine ligands.

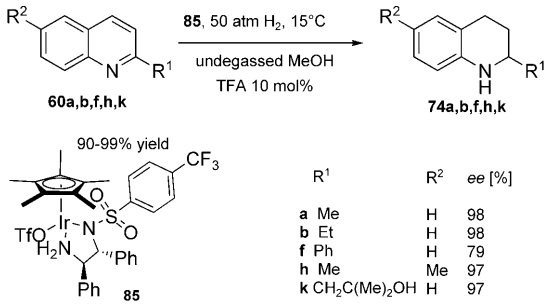
The catalytic system [{Ir(μ-Cl)(cod)}$_2$]/**44**/tri-*o*-tolylphosphine/piperidine·HCl has also been applied to the hydrogenation of quinoxalines **63**, although for these substrates the effect of tri-*o*-tolylphosphine was found to be negligible (Scheme 20).[68]

Monotosylated diamine ligands

Efficient hydrogenation of cyclic imines with diamine based iridium complexes using H_2 pressure is quite rare. For instance, the sole recent reported example is the use of [IrCp*(OTf)(CF_3TsDPEN)] complex **85** (CF_3TsDPEN = *N*-(*p*-trifluoromethylbenzenesulfonyl)-1,2-diphenylethylenediamine)



Scheme 20. [Ir]/**44** catalytic system for the hydrogenation of quinoxalines **63**.



Scheme 21. Example of diamine-based Ir complex **85** applied in the hydrogenation of susbtrates **60**.

as an air-stable, highly enantioselective catalyst for hydrogenation of quinolines **60** (Scheme 21).[69]

Since the synthesis in 1999 of metal complexes of the type [MCp*Cl{Ts(diamine)}],[70] they had been used in transfer hydrogenation of various ketones and imines but they had never been employed in the hydrogenation of cyclic imines. In addition of giving very good results (*ee* up to 99%), this robust catalytic system allows the reaction to be carried out in presence of air. The development of such complexes opens new perspectives in the field of hydrogenation.

2.2. Ruthenium catalyst

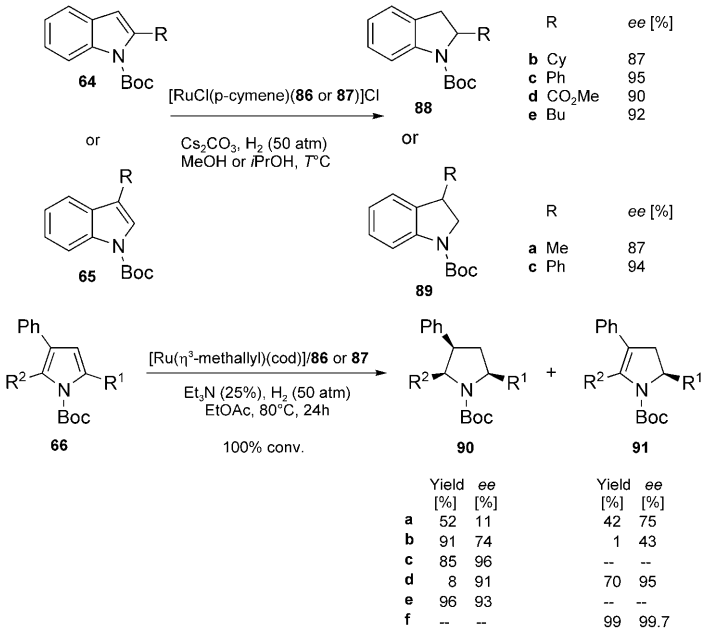
Metals other than iridium were also tested in the asymmetric hydrogenation of cyclic imines and other substrates. Among them, ruthenium is the second most studied. It has provided modest results in hydrogenation using molecular hydrogen, which explains the fewer articles published in the recent years. However, it is commonly used and provides excellent results in asymmetric transfer hydrogenation (see Section 3).

Diphosphine ligands

Kuwano et al. reported the use of biferrocenyl-derived diphosphines **86** and **87** in the ruthenium-catalyzed hydrogenation of heterocycles such as pyrroles **64** and indoles **65**.[71,72] The same ligand had previously been reported by this group for hydrogenation of indoles using Rh based catalysts (Figure 10).[73,74]

Diphosphines **86** and **87**,[75,76] combined with a ruthenium source such as [{$RuCl_2$(*p*-cymene)}$_2$] or [Ru(η^3-methallyl)(cod)] provided enantioselectivities up to 99.7%. The activity was

enhanced by addition of catalytic amounts of base, such as Cs_2CO_3 or triethylamine. First applied to *N*-Boc-protected indole derivatives,[71] the scope of this catalytic system was successfully extended to 2,3,5-trisubstituted pyrroles[72] (Scheme 22).



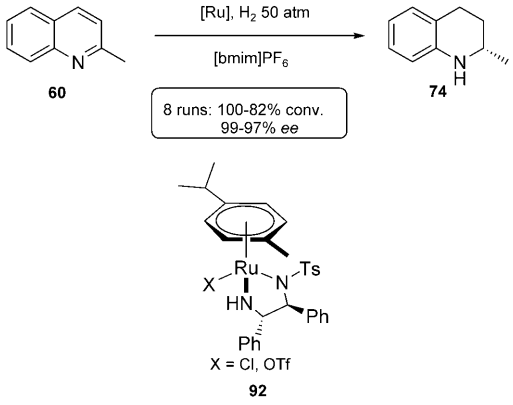
Scheme 22. Application of ligands **86** and **87** in the Ru-catalyzed hydrogenation of substrates **64**, **65**, and **66**.

The hydrogenation of 2,3,5-trisubtituted pyrroles **66** gave a mixture of dihydro- and tetrahydropyrroles in various ratios, although some clear trends can be established as a function of the substituents in the pyrrole ring. Thus, hydrogenation of triaryl derivatives resulted in the exclusive formation of dihydropyrroles (see, for instance, **91 f**), with excellent yields and enantioselectivities. It should be noted that no traces of regioisomers of dihydropyrroles were detected, thus suggesting that the hydrogenation proceeds stepwise via successive 1,2-additions of hydrogen to the two C=C double bonds. However, when dialkyl or trialkyl substituents were present, pyrrolidines were mainly obtained (**90 a**–**e** versus **91 a**–**e**; Scheme 22).

The obtained pyrrolidines **90** had *cis* configuration in all cases, which indicates that the stereoselectivity of the second hydrogenation was controlled by the configuration of the asymmetric center resulting from the first double-bond reduction (Scheme 22).

Monotosylated diamine ligands

It has recently been demonstrated that Ru^{II} complexes bearing diamine ligands **92** (Scheme 23), widely used in asymmetric transfer hydrogenation,[77] could be highly efficient in asymmetric hydrogenation of ketones using molecular H_2.[78] This discovery has been transferred to the hydrogenation of quinolines in ionic liquids, thus affording a recyclable phosphine-free catalytic system.[79] The same system was also used under solvent-free or highly concentrated conditions with excellent results (Scheme 23).[80]



Scheme 23. Diamine-based Ru complex **92** in the hydrogenation of quinoline **60** in Ionic Liquids.

2.3. Rhodium catalysts

If some catalytic systems can be transposed from hydrogenation to transfer hydrogenation,[81] the opposite is also possible (see Section 2.2 on Ru/monotosylated diamine ligands). In the same manner, an ionic {Cp^*Rh^{III}} catalyst has been successfully utilized in the hydrogenation of imines (Scheme 24).[82]

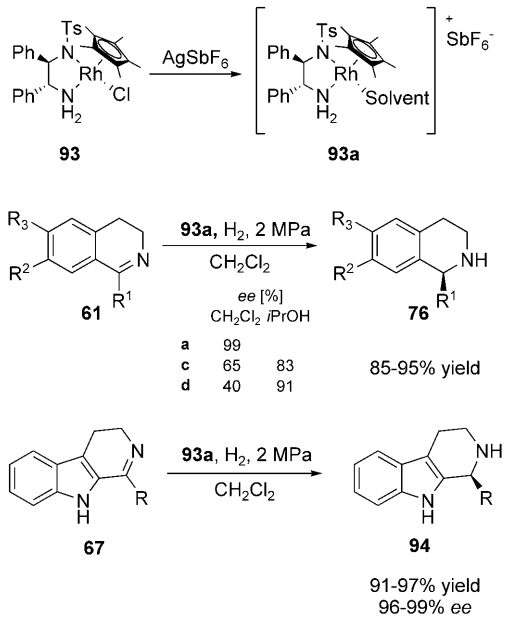
The active species **93 a** was generated in situ by the action of silver salts on the precatalyst (**93**). Several salts were tested. Pretreatment with $AgSbF_6$ in the presence of traces of water led to a dramatic improvement in conversions.

In the case of the catalytic system [Rh]/**93 a**, the results depend on the solvent as well as the presence of bulky
substituents at R^1 and R^2 in the substrate (**61 a** versus **61 c**, **d**). The best enantioselectivities were obtained in isopropanol.

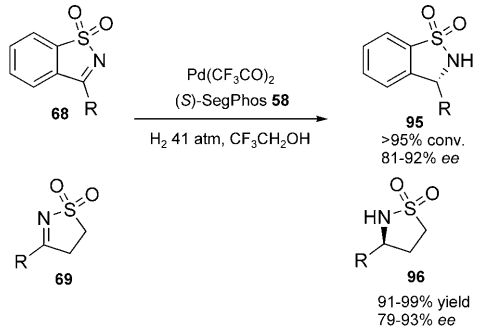
2.4. Palladium catalysts

Little attention has been paid to the use of Pd complexes in asymmetric hydrogenation of cyclic imines. Nevertheless, there have been a few successful recent examples.[44,83–84] Zhou et al. used the catalytic system defined by Amii et al. for the Pd-catalyzed asymmetric hydrogenation of α-fluorinated iminoesters in trifluoroethanol,[85] with different chiral diphosphines in the asymmetric hydrogenation of various imines.[44] They obtained good results with (*S*)-SegPhos **58** for the hydrogenation of cyclic *N*-sulfonylimines **68** and **69** with up to 92% *ee* (Scheme 25).

The same group later reported the use of (*S,S*)-f-binaphane **11 b** in the hydrogenation of cyclic *N*-sulfonylimines **70** using



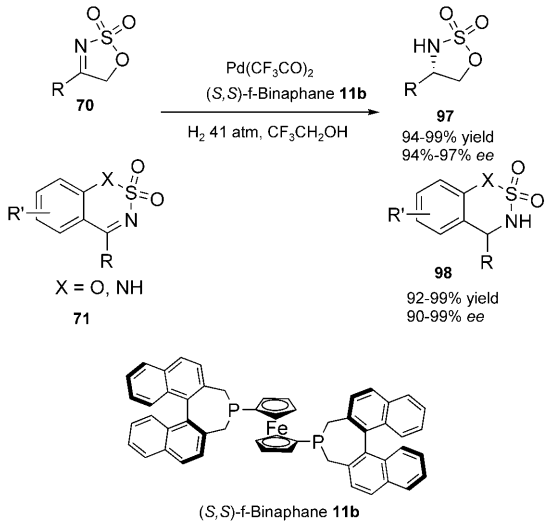
Scheme 24. Hydrogenation of substrates **61** and **67** by Rh diamine-based catalytic system **93a**.



Scheme 25. Hydrogenation of substrates **68** and **69** using [Pd]/**58**.

the same Pd catalyst and obtained excellent conversions and enantioselectivities (Scheme 26).[84] The use of ferrocene-based diphosphine improved the enantioselectivities up to 99% in the case of the cyclic *N*-sulfonylimines **71** (Scheme 26).

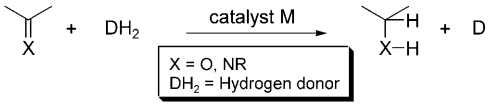
These substrates were long considered too difficult to hydrogenate, although recent progress in the design of catalytic systems has made the reduction of heteroaromatic imines feasible and successful. For such transformations, atropoisomeric diphosphines and Ir seem to have provided the best results to date. However, other metals can also be used as alternatives and catalytic systems adapted from ATH have proven very efficient. Although most of the systems require high pressures of hydrogen, an interesting system, based on the in situ generation of H_2 from water and silane, was recently proposed. More and more efforts are ongoing to develop recyclable and sustainable catalytic systems. The next step in this field would be the design of catalytic systems that allow the presence of other functionalities on the substrates and that provide chemoselectivity.



Scheme 26. Hydrogenation of substrates **70** and **71** using [Pd]/**11b**.

3. Asymmetric Transfer Hydrogenation

ATH is a very efficient strategy to reduce ketones or imines using hydrogen sources other than hydrogen gas (Scheme 27).[77,86,87] This reaction can be promoted by homoge-



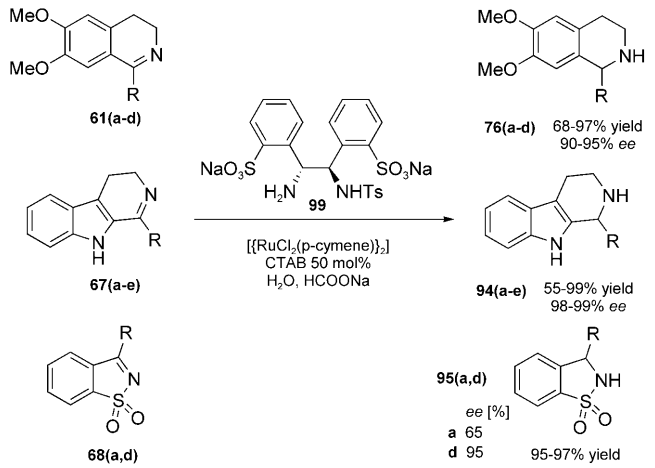
Scheme 27. Principle of the ATH.

neous transition metal catalysts and offers considerable potential. Since the discovery by Noyori et al. of Ru^{II} catalysts bearing monotosylated 1,2-diamines or amino alcohols affording enantioselectivities up to 98%,[36a] many efforts have been devoted in the last decade towards the development of catalytic systems for the asymmetric transfer hydrogenation of ketones and imines.[88]

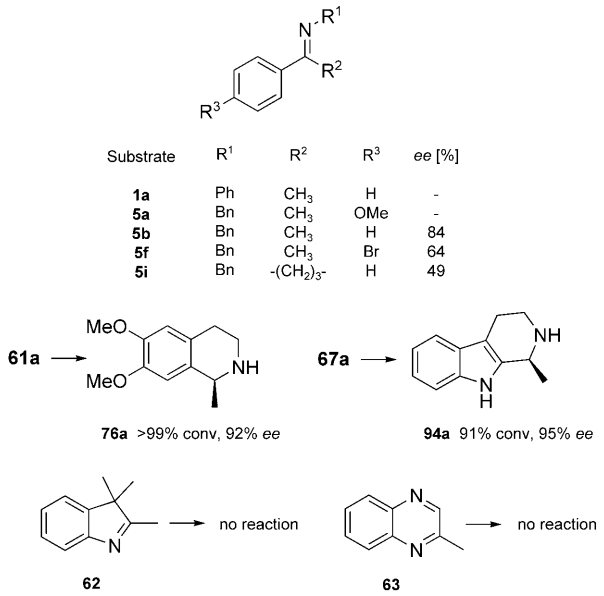
The main catalytic systems encountered for the hydrogenation of cyclic imines are based on an arene or Cp-metal complex with a chiral bidentate ligand (a monotosylated 1,2-diamine or aminoalcohols) and an halide ligand. The most popular hydrogen donors are alcohols (*i*PrOH) and the azeotrope mixture of formic acid and triethylamine. Ruthenium is the most studied metal, but other metals can also be used.

3.1. Ruthenium catalysts

Recent developments mainly focus on a more environmentally friendly use of Ru-TsDPEN (TsDPEN = *N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine) derivatives **99** for the reduction of cyclic imines.[89–92] In 2006, Deng et al. reported the asymmetric transfer hydrogenation of imines and iminiums in water using this soluble ligand (Scheme 28).[89]



Scheme 28. Asymmetric transfer hydrogenation of substrates **61**, **67**, and **68** with [Ru]/**99**.



Scheme 29. Asymmetric transfer hydrogenation using [Ru]/**100**–**101**.

All the attempts at transfer hydrogenation of acyclic imines such as **5a** and **6a** in water resulted either in no reaction, as for **5a**, or complete decomposition, as for **6a**. However, high yields and enantioselectivities were obtained in the asymmetric transfer hydrogenation of cyclic imines **61**, **67**, and **68** in water using sodium formate as the hydrogen source and CTAB (cetyltrimethylammonium bromide) as a surfactant in combination with *o*,*o*′-disulfonated *N*-tosyl-1,2-diphenylethylene diamine **99** in the presence of [{$RuCl_2$(*p*-cymene)}$_2$] as metal source (Scheme 28).

Complexes of the type [{Cp*MCl_2}$_2$]/**99** (M = Rh, Ir) also provided *ee* values higher than 90% under similar reaction conditions. Curiously, acyclic imines, such as **1e**′, were not hydrogenated under similar conditions using this ruthenium catalyst.

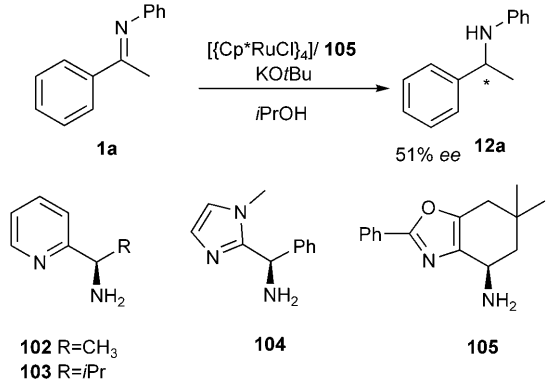
Imine **61d** was not hydrogenated using the previous catalyst and conditions. However, the complete conversion and 94% *ee* were attained when the reaction was carried out with the corresponding benzyliminium salt. Hydrogenation of **68** afforded different results depending on the R substituent (Scheme 29). The catalyst could be recovered and recycled at least three times without loss of enantioselectivity.

The diamine ligand was immobilized by radical polymerization between the enantiopure 1,2-diamine monosulfonamide monomer styrene derivative and divinylbenzene (Figure 11).[91]

The polymer-immobilized ligand **100** was tested in the transfer hydrogenation of various imines in CH_2Cl_2. The acyclic substrates **5b**, **f**, and **i**, were hydrogenated with enantioselectivities of 84, 64, and 49%, respectively. However, the transfer hydrogenation of **5a** resulted in the decomposition of the substrate and for imine **1a** no reaction was observed. Cyclic imines **61a** and **67a** were hydrogenated with high enantioselectivities (92 and 95% *ee*, respectively) but no reaction was observed for imines **62** and **63** (see Scheme 28).

The sulfonated polymer-immobilized ligand **101** was used for the ruthenium-catalyzed transfer hydrogenation in water of the quinoline substrate with conversions and enantioselectivities up to 95%. Acyclic imines hydrolyze under these reactions conditions. Rhodium and iridium complexes were also found to be effective metal precursors in the asymmetric transfer hydrogenation of **61a** in water.

Andersson et al. reported the ability of [Cp*Ru(diamine)] complexes to catalyze the hydrogenation of imine **1a**. The chiral diamines used (**102**–**105**) are shown in Scheme 30. The



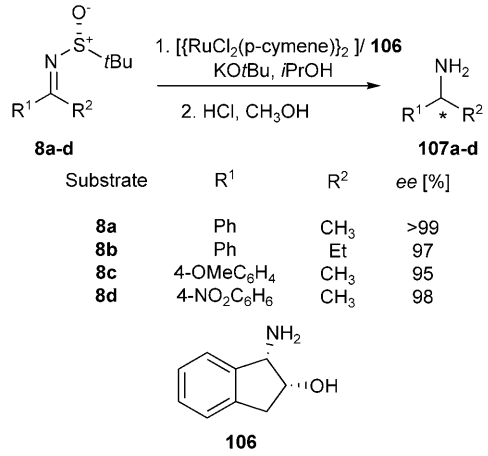
Scheme 30. Results of hydrogenation of **1a** using [Ru]/**102**–**105**.

catalytic systems bearing ligands **102** and **103** afforded excellent conversions but did not induce any enantioselectivity. The catalytic system [Ru]/**105** gave 51% *ee* (Scheme 30).[93]

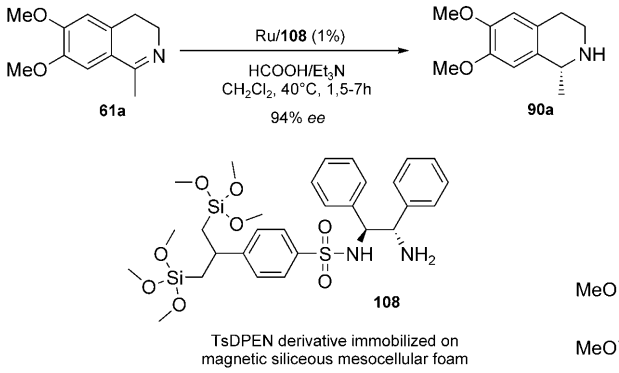
The ruthenium complex prepared from [{$RuCl_2$(*p*-cymene)}$_2$] and (1*S*,2*R*)-1-amino-2-indanol (**106**) is a very efficient catalyst for the asymmetric transfer hydrogenation of (*R*)-*N*-(*tert*-butanesulfinyl)ketimines **8a**–**d** in isopropanol. Chiral primary amines were obtained with excellent enantioselectivities (up to >99% *ee*) by the diastereoselective reduction of imines followed by removal of the sulfinyl group under mild acidic conditions. The methodology is equally efficient for the reduction of phenone-derived imines bearing either electron-

withdrawing or electron-donating groups on the aromatic ring (Scheme 31).[94]

Li et al. immobilized a Ru–TsDPEN-derived catalyst in a magnetic siliceous mesocellular foam material (Scheme 32).[90] The resulting heterogeneous hybrid catalyst was then successfully



Scheme 31. Asymmetric transfer hydrogenation of substrates **8a–d** with [Ru]/**106**.



Scheme 32. Asymmetric transfer hydrogenation of imine **61a** using the immobilized Ru–TsDPEN (**108**) catalytic system.

employed in the asymmetric transfer hydrogenation of **61a** and showed high stability and impressive recycling abilities by filtration with an external magnet up to nine times without loss of enantioselectivity.

3.2. Iridium and Rhodium catalysts

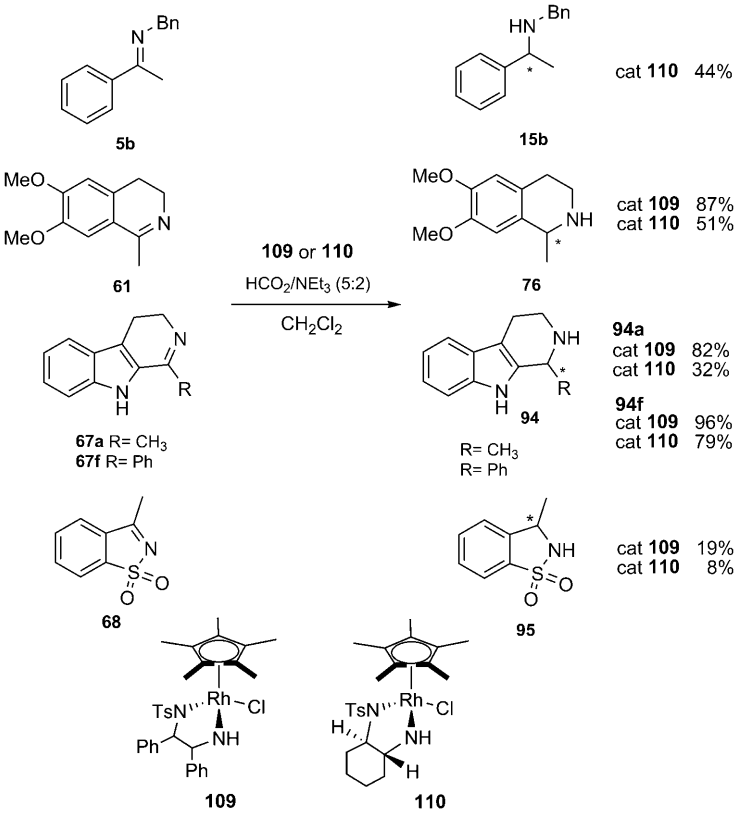
Wills and co-workers reported a Rh^{III} catalyst containing a tetramethylcyclopentadienyl group and a monotosyl diamine ligand which was a very efficient system in the asymmetric transfer hydrogenation (ATH) of ketones. The catalytic systems **109** and **110** both afforded high enantioselectivities and activities at low catalyst loadings. The introduction of a methoxy group on the tethering aryl ring did not influence the performance of the catalyst, thus opening up a route to supported derivatives (Scheme 33).[95]

The catalytic system developed by Zhou et al. ([Ir]/SegPhos **58** and iodine) for hydrogenation of heterocycles under hydrogen pressure was successfully used in transfer hydrogenation using Hantzsch esters as the hydrogen source (Scheme 34). The ester groups of the hydrogen donor strongly influence the enantioselectivity of the reaction.[81]

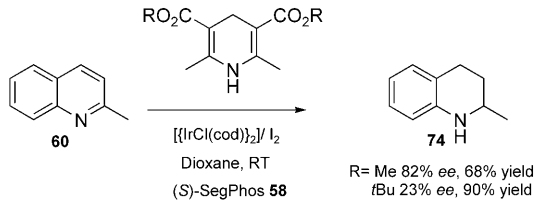
Other catalytic systems[70] originally designed for transfer hydrogenation including Ir or Rh were applied in the reduction of cyclic imines.[89,96,97] The Rh catalysts provided the best results. For instance, in the novel generation of water-soluble chiral diamine designed by Deng et al., conversions and enantioselectivities were improved by using [{Cp*$RhCl_2$}$_2$] (Scheme 35).[96]

It appears that the pH is a very important factor for the reaction rate in water.[98] Thus, Xiao et al. recently achieved the transfer hydrogenation of quinolines by using a HOAc/NaOAc pH 5 buffer solution.[99]

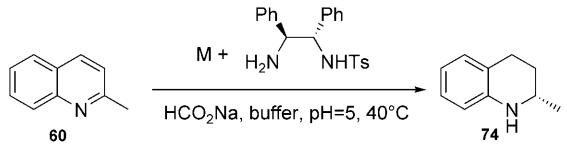
In recent years, ATH has proven to be a very powerful method to perform the reduction of either C=O and C=N bonds providing high enantioselectivity. The absence of hydrogen gas makes this reaction easy to handle. In the future, apart from on the Ru-based catalysts more ATH catalytic systems will certainly be developed and the scope will broaden to more challenging substrates.



Scheme 33. Asymmetric transfer hydrogenation of substrates **5b**, **61**, **67a**, **67f**, and **68** with **109** and **110**.



Scheme 34. Hydrogenation of methylquinoline **60** using [Ir]/**58** and Hantzsch esters as the hydrogen source.



Entry	M	Conv [%]	*ee* [%]
1	[{$RuCl_2$(*p*-cymene)}$_2$]	32	90
2	[{Cp*$IrCl_2$}$_2$]	88	11
3	[{Cp*$RhCl_2$}$_2$]	95	96

Scheme 35. Comparison of some results of hydrogenation of quinolines by ATH using various metal sources.

4. Mechanistic Insights

4.1. Acyclic imines

Several mechanisms have been proposed for the hydrogenation of imines because slight modifications of the substrate, addition of additives, solvent used, or acidity of the medium produce remarkable effects on the catalytic activity.

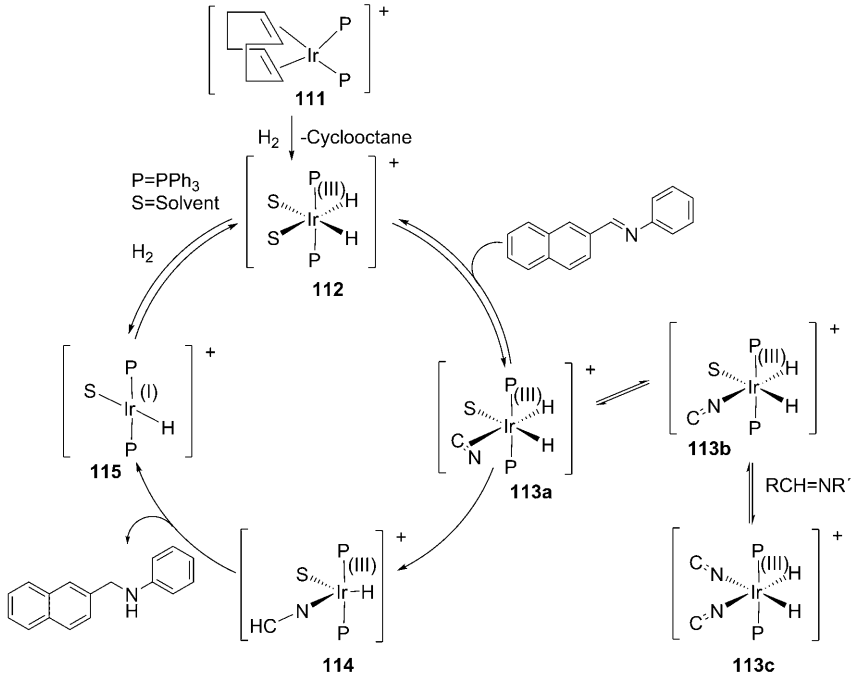
One of the first mechanisms proposed was based on a kinetic study of the hydrogenation of *N*-(β-naphthylmethylene)aniline using the cationic iridium complex [Ir(cod)(PPh_3)$_2$]PF_6 **111** as catalytic precursor, in which reductive elimination was the rate determining step.[100] The catalytic cycle shown in Scheme 36 was proposed. The catalytic precursor reacts with hydrogen to afford complex **112**, which is the initial complex entering the catalytic cycle. Next, the coordination of the substrate occurs through the nitrogen atom (η^1) or the C=N (η^2) to form the species **113a**–**c**. Then, hydride transfer to the imine in **113a** generates the iridium–alkylaminium intermediate **114**, which undergoes reductive elimination to afford the desired amine and the intermediate **115**, from which the starting species **112** can be regenerated.

James et al. reported that the use of methanol as solvent or co-solvent was necessary to obtain high conversion in the hydrogenation of imines catalyzed by Rh/diphosphine complexes.[101] It was proposed that the role of methanol is to favor the coordination of the imine through the C=N double bond rather than the nitrogen atom. The catalytic cycle proposed for Rh/diphosphine systems was based on a hydride pathway whereby the imine had to be η^2-coordinated before the hydrogen transfer (Scheme 37). However, further mechanistic studies showed that the η^2-coordination of the imines was easier than hydride formation.[101]

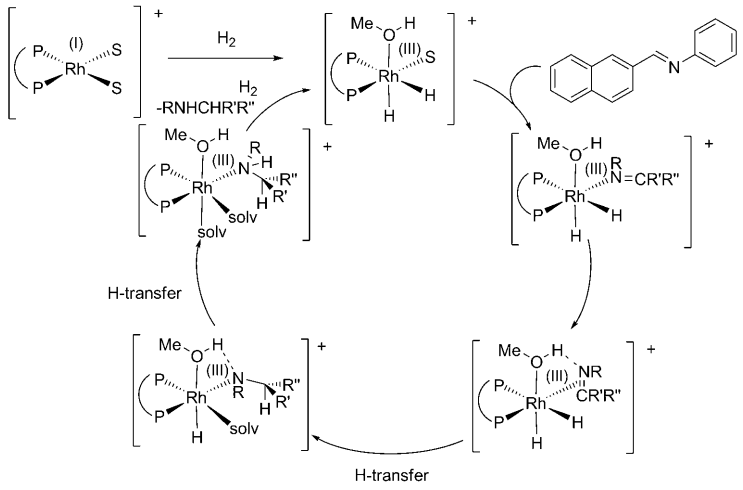
One of the main disadvantages of this reaction is the deactivation of the catalyst due to the formation of hydride-bridged structures analogous to those proposed by Crabtree.[102] To prevent the deactivation of the catalyst, various additives, particularly iodine or iodides, were tested. However, the deactivation of the catalysts could also be due to the strong donor character of the NH group of the product.[103]

Osborn and co-workers synthesized Ir^{III} complexes such as [Ir(P–P)I_4]$^-$, [{$IrHI_2$(P–P)}$_2$], and [{IrI_3(P–P)}$_2$], and demonstrated that these catalytic systems avoided the formation of inactive species.[104] In this case, the catalyst consisted of Ir^{III} species, and a catalytic cycle, in which an initial dissociation of a dimeric complex yields unsaturated monomeric Ir^{III} complex [$IrHI_2$(P–P)] **116** (Scheme 38, path a), was proposed. Substrate coordination, hydride transfer from the metal to the sp^2 carbon, and hydrogenolysis of the Ir–N bond produce the imine and regenerate the hydride **116**, thus completing the cycle.

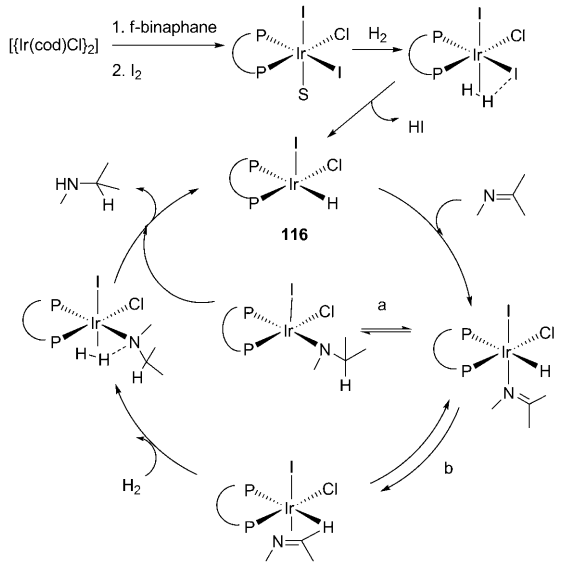
Zhang et al. reported a highly enantioselective catalytic system for the hydrogenation of hindered imines based on an Ir–fer-



Scheme 36. Catalytic cycle proposed for the hydrogenation of *N*-(β-naphthylmethylene)aniline.



Scheme 37. Catalytic cycle proposed for the hydrogenation of imines in the presence of methanol catalyzed by Rh–diphosphine systems.



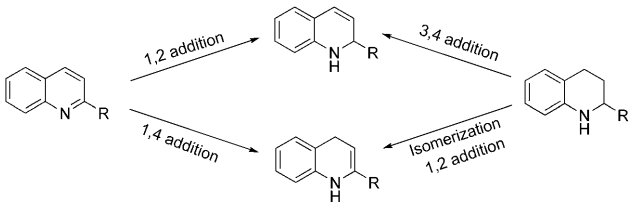
Scheme 38. Catalytic cycle proposed for the hydrogenation of imines catalyzed by Ir^{III}/I_2 complexes.

rocene binaphane complex (Table 1).[105] The activity and enantioselectivity of the reaction were increased in the presence of I_2. The oxidative addition of iodine to the initial Ir^{I} complex to give an Ir^{III}/f-binaphane/I_2 system was proposed (Scheme 38, path b). Then, after hydrogen coordination, the heterolytic cleavage of hydrogen favors the formation of {Ir^{III}—H} intermediates related to those reported by Osborn, as well as the other intermediates in the catalytic cycle.

Oro, Sola, and co-workers recently reported a mechanistic study of imine hydrogenation using cationic and dinuclear iridium complexes.[106]

The hydrogenation of 2 alkyl-quinoline derivatives was reported in 2009 by Zhou, Li, and co-workers,[48] who proposed two possible hydrogenation pathways depending on the initial 1,2-or 1,4-hydrogen addition (Scheme 39).

Their mechanistic studies indicated that hydrogenation of quinolines followed a "1,4-hydride addition–isomerization–1,2-hydride addition" pathway. It was also proposed that the role of iodine was to oxidize the Ir^{I} catalyst precursor to an Ir^{III} complex, which in the presence of hydrogen affords to a highly active {Ir^{III}—H} catalytic species (Scheme 39). Subsequently, after quinoline coordination, 1,4-hydride transfer takes place to form an amino–iridium intermediate. Heterolytic cleavage of H_2 then regenerates the active Ir^{III} species and the product of 1,4 addition. This product undergoes an HI-mediated isomerization, and coordination of the resulting enamine to the Ir^{III} active species, followed by insertion and σ-bond metathesis yield the 1,2,3,4-tetrahydroquinoline (Scheme 40).



Scheme 39. Possible pathways for the hydrogenation of quinolines.

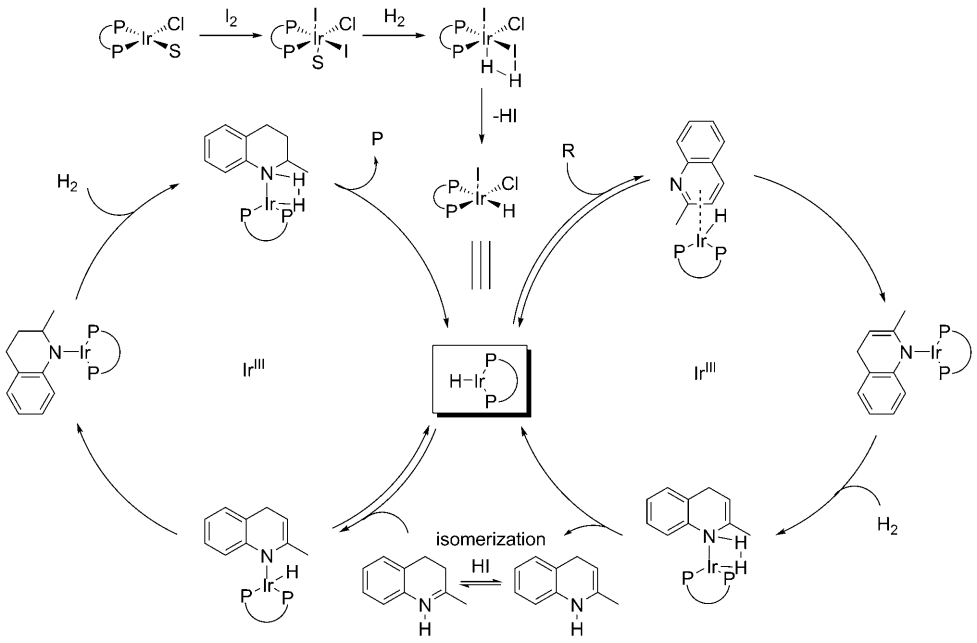
In the case of 2,3-disubstituted quinolines, the enantiodetermining step is the isomerization of the enamine to the imine and subsequent hydrogenation of the C=N bond. This step corresponds to a dynamic kinetic resolution process (Scheme 41). Thus, to obtain high enantioselectivities, it is necessary to adapt the reaction conditions to favor the isomerization process; that is to increase the temperature and to decrease the hydrogen pressure to slow down the hydrogenation.

Apart from the case of iodine, the specific role of the additives and the reaction conditions is very rarely fully understood. Further efforts to understand the mechanism of this transformation will undoubtedly lead to important discoveries in the future.

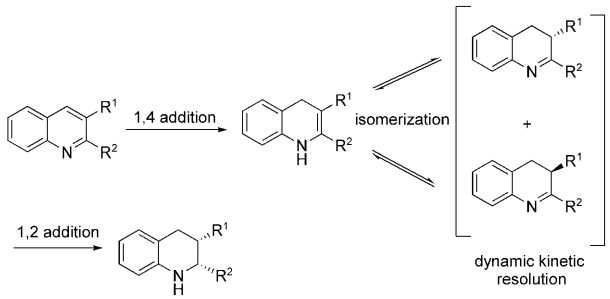
4.2. Asymmetric transfer hydrogenation

Although the mechanism for transition metal-catalyzed transfer hydrogenation of ketones has been extensively studied and is now relatively well established, it is much less clear in the case of imines.[77,87,107,108] The reduction of ketones using bifunctional catalysts is proposed to go through a concerted transfer of proton and hydride to the substrate in a six-membered transition state without prior coordination of the substrate to the metal (ATH outer-sphere mechanism[57]). This mechanism, first proposed by Noyori,[77] is supported by mechanistic and computational studies.[36a,77,109,110]

In view of the work of Bäckvall et al.,[111] it is clear that the concerted mechanism is not operative for the reduction of imines. The isolated active species for the reduction of ketones

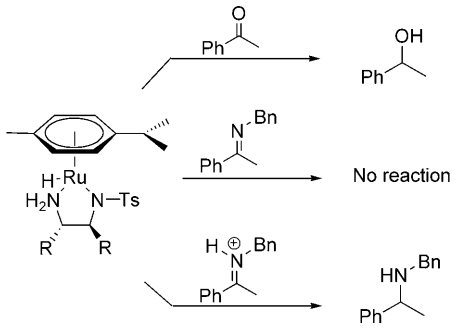


Scheme 40. Postulated mechanism for the hydrogenation of quinolines.



Scheme 41. Description of the enantiodetermining step in the mechanism of hydrogenation of 2,3-disubstituted quinolines.

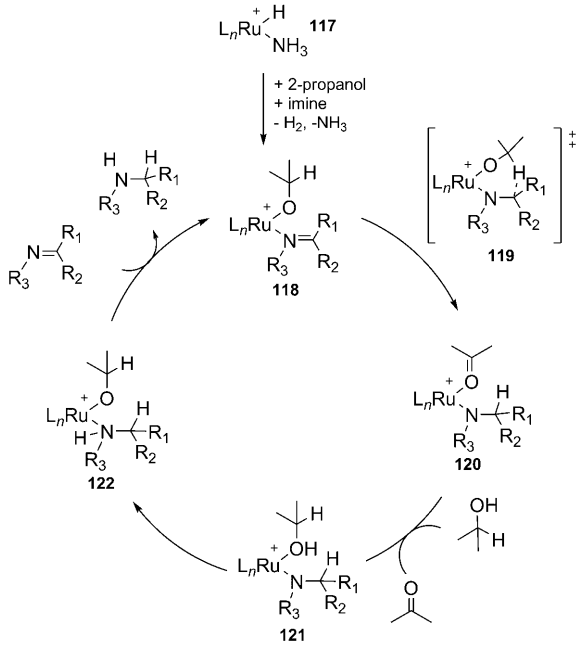
(or aldehydes) in the presence of imines did not lead to the formation of the expected amine. Indeed, the addition of acid was required to bring about fast and effective reduction. These findings suggest that the reaction with imines proceeds through an ionic pathway (Scheme 42).[34a,b]



Scheme 42. Experiments proving that a concerted mechanism is not operative in the reduction of imines by ATH.

A kinetic study by Blackmond et al. showed that the reaction conditions, the acid–base equilibria between HCOOH and the triethylamine, imine, and amine in the mixture, are essential in the kinetic study.[112] A slow addition of formic acid during the reaction improves significantly the productivity. In contrast with the observations of Bäckvall et al., their results are in favor of an unprotonated imine as the true substrate.

Yamamoto et al. proposed a catalytic cycle for the transfer hydrogenation of imines catalyzed by the cationic monohydride complex **117**, based on deuterium-labeling experiments (Scheme 43). The catalytic cycle



Scheme 43. Mechanism of transfer hydrogenation of imines.

starts with the formation of the imine-coordinated isopropoxide complex **118** by the reaction of the cationic ruthenium hydride **117** with 2-propanol in the presence of imine. Hydrogen transfer from the isopropoxide to the coordinated imine carbon through cyclic transition state **119** gives the acetone-coordinated amido complex **120**. Substitution of the coordinated acetone by 2-propanol gives the intermediate **122**. A second proton transfer from 2-propanol to the nitrogen generates **123**. Replacement of the amine with the incoming imine

liberates the hydrogenation product, regenerating **118** (Scheme 43).[113]

A recent study by Wills et al., based on computational and experimental results, indicated that the reaction should proceed through an ionic pathway involving the following transition state (Figure 12).[114]

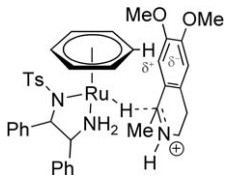


Figure 12. Proposed transition state for the reduction of imines.

Although there is some evidence to support the ionic mechanism, with the isolation of intermediates of modified catalysts,[115] the pathway of the transfer hydrogenation of imines is not yet completely understood and the possibility of a substrate-specific mechanism cannot be completely ruled out.

5. Conclusions

The results described herein include some recent advances in the transition metal-catalyzed asymmetric hydrogenation of imines. Despite the existence of several significant drawbacks, the discovery of efficient catalysts based on transition metals combined with the appropriate chiral ligands has afforded high activities and enantioselectivities for imine hydrogenation.

5.1. Catalyst scope

It is not easy to extract general trends from the presented results, due to the variety of substrates, catalysts, and reaction mechanisms involved. As usual, the efficiency of a catalytic system is specific for a particular substrate.

In the case of imine hydrogenation, this fact is particularly relevant since hydrogenation of acyclic substrates, which exist as *Z/E* mixtures, and cyclic imines, where only a configuration imposed by the cycle exists, present quite different problems. Thus, catalytic systems used in the hydrogenation of cyclic or heteroaromatic imines are usually distinct from those used in acyclic imines.

Concerning the hydrogenation of acyclic imines, excellent results were described using several catalysts based on Ir, Rh, Ru, and Pd, although Ir complexes are still the most widely studied catalysts and comparison of the different parameters influencing the catalytic results are easier to make in this case. In general, two types of iridium precursors are used—cationic $[Ir(cod)_2]X$ or neutral $[\{Ir(\mu\text{-}Cl)(cod)\}_2]$—in the presence of bidentate phosphorus ligands (diphosphine, diphosphinite, diphosphite, phosphine–phosphite) as well as monodentate P ligands (phosphoroamidite, phosphine) and P,N ligands, in particular phosphine–oxazoline derivatives. Cationic complexes are more common and BAr_F is the counter anion of choice. The use of additives, such as I_2, yields Ir^{III} species, thus modifying the catalytic cycle.

There are only a few examples of the use of ruthenium complexes of the type [Ru(diamine)(diphosphine)]. Rhodium complexes $[Rh(diphosphine)(cod)]^+X^-$ of similar structure to those of iridium were used. In the case of palladium, $Pd(OCOCF_3)_2$ in the presence of diphosphines provided the best enantioselectivities. Reported acyclic and cyclic substrates hydrogenated with palladium complexes bear a sulfonyl group bound to nitrogen.

A singular case is the use of amine/tosylamine ligands in Ir^{III} complexes such as $[Cp^*Ir(NH_2\text{–}NHTs)]^+X^-$.These complexes were used in transfer hydrogenation, and provided excellent enantioselectivities when the counter anion was chiral.

Transfer hydrogenation gives generally poor results in the hydrogenation of acyclic imines. The only exception concerns substrates bearing a sulfoxide group bound to the imine nitrogen.

The hydrogenation of cyclic imines with Ir catalysts is mainly carried out using neutral precursors in the presence of iodine as additive. However, catalytic systems based on Pd were similar to those used in hydrogenation of acyclic imines. Catalytic systems based on ruthenium [RuCl(*p*-cymene)]Cl/bisferrocenyl diphosphine were particularly successful.

Catalytic systems with monotosylated diamine ligands, such as $[Cp^*Ir(TfO)(NH_2\text{—}NHTs)]$, $[Cp^*Ir(TfO)(NH_2\text{—}NHTs)(solvent)]^+X^-$ and $[RuCl(p\text{-cymene})(NH_2\text{—}NHTs)]^+X^-$ also provided very good enantioselectivities. Related complexes were very successful in transfer hydrogenation, even performing the reaction in water and with supported ligands. Ru and Rh complexes are currently the most efficient choices for this process.

5.2. Substrate scope

Traditionally, the research in asymmetric imine hydrogenation has been oriented to develop new catalysts able to provide good conversions and enantioselectivities. Benchmark substrates have been widely studied. However, in recent years, an increase in the range of substrates studied has enlarged the scope of this reaction (Figure 13).

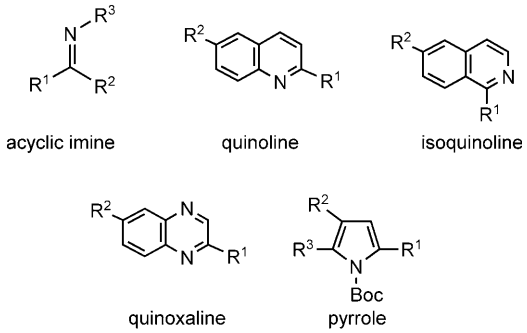


Figure 13. Substrate scope.

5.3. Acyclic imines

Concerning acyclic imines, much research has been oriented to the preparation of primary amines, that is, the group linked to the nitrogen atom was considered as a protecting group, and consequently could be easily removed. For this reason benzyl derivatives were initially explored. It is now established that these imines are particularly challenging, and there are only a few catalytic systems able to provide high enantioselectivities, such as [Ir]/spiranic phosphine–oxazoline, with these substrates.

In the hydrogenation of acyclic imines, the following trends can be observed:

a) The substituent R^3 is crucial to obtain excellent enantioselectivities. The most successful groups at R^3 were 4-methoxyphenyl, 3,5-dimethyl-4-methoxyphenyl, 4-trifluoromethylphenyl, 2,6-dimethylphenyl, 2-methoxyphenyl, tosyl, and diphenylphosphinyl. There are synthetic procedures to remove all of them to afford primary amines. The presence of substituents at the 2-, 3-, 4-, and 6-positions of the phenyl ring (R^3 = Ph) increases the bulk at the nitrogen atom, which can also influence the enantioselectivity by shifting the *Z*/*E* equilibrium. The electronic effects from substituents at the 4-position are more difficult to rationalize, since electron-donor and withdrawing groups and sometimes halides are the groups of choice. The electronic properties of the ligands could be related with this fact.

b) A relevant example is constituted by substrates where R^3 = H, for which no further deprotection is required. Since the real substrate is a chlorhydrate salt, and, consequently, there is an excess of chloride in the medium, [Ir(μ-Cl)(diphosphine)] was used as precursor.

c) Groups R^1 and R^2 are also crucial to achieve high *ee* values. Most of the successful examples mentioned above are imines in which R^1 = aryl and R^2 = Me. The asymmetric hydrogenation of imines in which R^2 is distinct from methyl or both groups are alkyl is particularly challenging. Catalytic systems such as [Ir]/phosphine–oxazoline or [Ir]/phosphoramidite, together with some [Rh]/diphosphine systems, present the best results and the widest scope in this sense.

5.4. Cyclic Imines

The scope of the C=N asymmetric hydrogenation reaction has been extended in recent years. Cyclic imines, quinolines, and unfunctionalized N–H imines have been successfully transformed in enantiomerically enriched amines. The asymmetric hydrogenation of heteroaromatic compounds, in particular cyclic imines, requires in general harsher reaction conditions, because of the high stability of the aromatic ring and the facile poisoning of the catalyst. Relevant results have been however obtained in the hydrogenation and particularly in transfer hydrogenation of cyclic and heteroaromatic imines.

The following trends related with the influence of the structure of the cyclic imines in the efficiency of their hydrogenation, can be established:

a) Hydrogenation of quinolines, isoquinolines, and quinoxalines is very dependent on the nature of the substituent R^1. The best *ee* values were obtained when R_1 was methyl, although good results were also obtained when other alkyl groups were present. When R^1 was aryl, the enantioselectivity dropped significantly.

b) A particular case is that of the pyrrole derivatives, where the existence of a carboxylate methyl group at R^1 was required to give excellent enantioselectivities, independently of substituents R^2 and R^3.

c) The formation of iminium cations by reaction with methyl chloroformate increased yields and selectivities.

The development of efficient catalysts, the broadening of the substrate scope, and the knowledge of the reaction mechanism allow to envision asymmetric imine hydrogenation as a useful synthetic tool in organic synthesis.

5.5. Outlook

The advances described herein show the potential of asymmetric hydrogenation of imines and the extension of the scope of both catalysts and substrates, which can result in interesting applications.

During the last few years, research in asymmetric imine hydrogenation has led to the discovery of new and efficient catalytic systems, in both hydrogenation and transfer hydrogenation, and the number of substrates studied has enlarged exponentially. Unsubstituted imines, which directly provide primary amines by hydrogenation, are particularly interesting, and open a new route for the synthesis of these compounds. Asymmetric imine hydrogenation has now reached a level of development that should make this reaction a useful tool in organic synthesis in the near future. However, despite this progress, there are still some challenges that need to be solved. Robust and supportable catalytic systems efficient for a wide range of substrates are still necessary. In this sense, the results obtained with amine–tosylamine ligands are extremely promising, but other related catalytic systems should be explored. Concerning substrates, the discovery of catalysts providing high enantioselectivities in the hydrogenation of dialkyl imines or phenyl substituted quinolines are challenges to be tackled.

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