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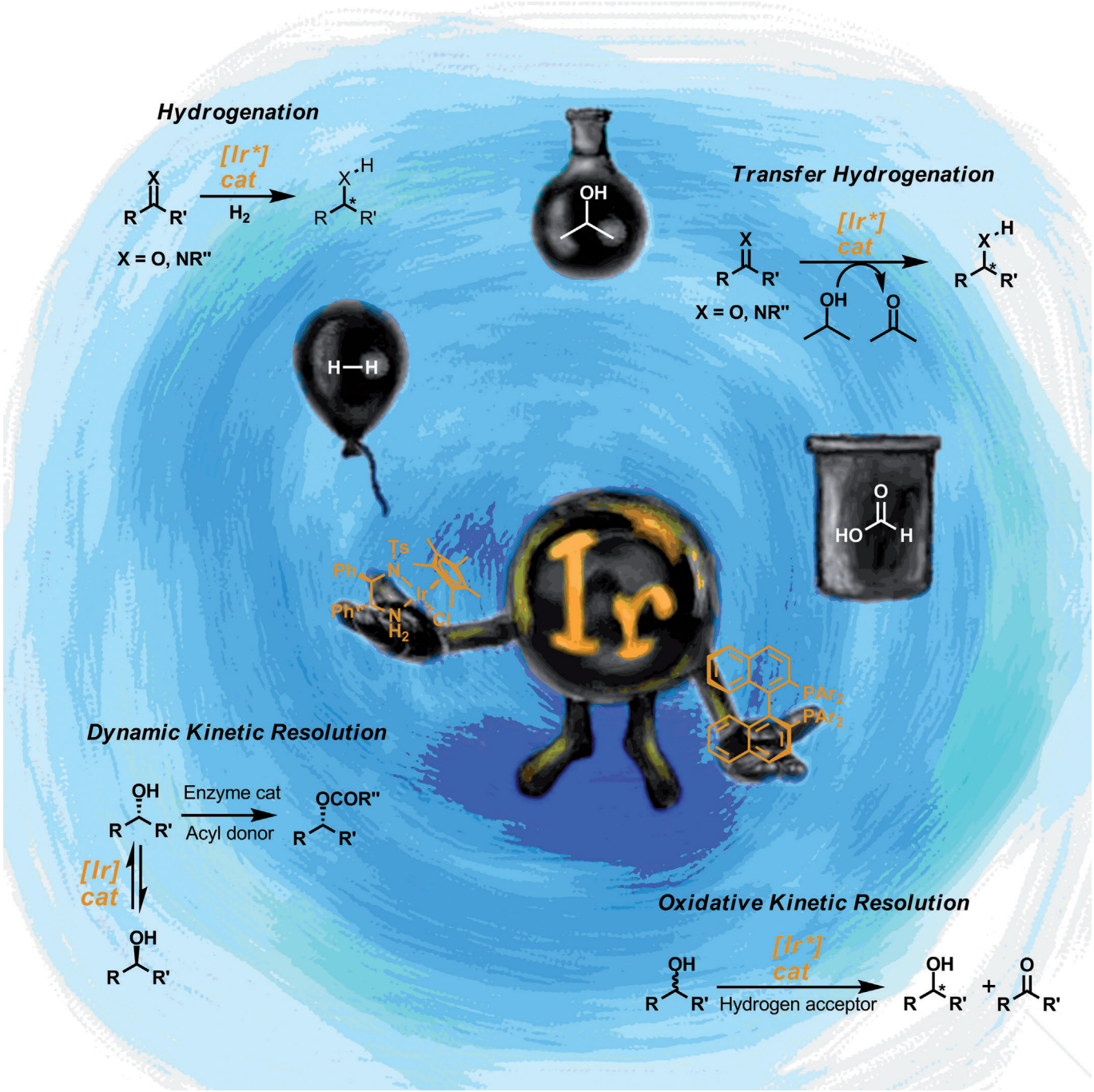
Enantioselective Synthesis of Alcohols and Amines by Iridium-Catalyzed Hydrogenation, Transfer Hydrogenation, and Related Processes

Agnieszka Bartoszewicz,[a, b] Nanna Ahlsten,[a, b] and Belén Martín-Matute*[a, b]

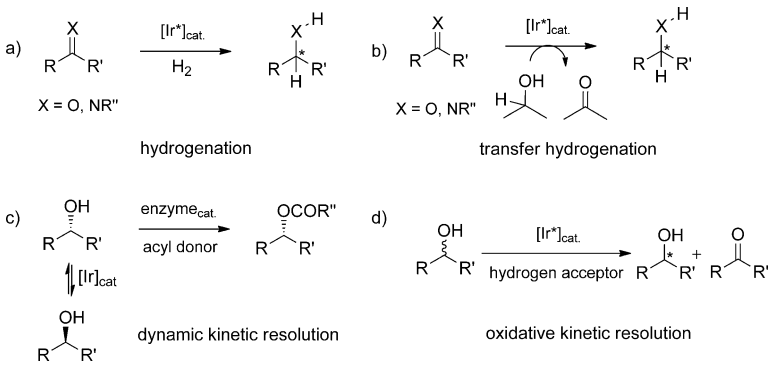


Abstract: The preparation of chiral alcohols and amines by using iridium catalysis is reviewed. The methods presented include the reduction of ketones or imines by using hydrogen (hydrogenations), isopropanol, formic acid, or formate (transfer hydrogenations). Also dynamic and oxidative kinetic resolutions leading to chiral alcohols and amines are included. Selected literature reports from early contributions to December 2012 are discussed.

Keywords: asymmetric catalysis · hydrogenation · iridium · oxidation · transfer hydrogenation

Introduction

Enantiopure alcohols and amines are very important building blocks used in the pharmaceutical, flavors, and fragrances industry. In this review we focus on selected topics in the synthesis of these compounds by using iridium catalysis. The first two chapters describe the synthesis of enantioenriched alcohols and amines by reduction of carbonyls (C=O) and imines (C=N). The reduction is achieved either by direct hydrogenation under hydrogen pressures (Scheme 1a) or under transfer hydrogenation conditions using hydrogen donors, such as *i*PrOH and HCO_2Na (Scheme 1b). Enantioselective hydrogenation of enamines and reductive amination are not included in this review. The last part of this review is devoted to miscellaneous methods in which redox reactions are also involved, such as iridium- and enzyme-catalyzed dynamic kinetic resolutions (DKRs, Scheme 1c), oxidative kinetic resolutions (Scheme 1d), and others. Our intention is to give the reader an overview of the results obtained in the area, and to highlight successful examples for which iridium complexes have been used in asymmetric reductions of carbonyls and imines, and in related processes.[1–4] We have chosen pioneering reports and the most outstanding examples in terms of high enantioselectiviy, high turnover number (TON), and frequency (TOF), mild conditions (i.e., reactivity at low hydrogen pressures), and hydrogenation of challenging substrates. The review examines literature up to December 2012, with the aim of complementing some of the existing excellent reviews reported on this matter.[1,2]



Scheme 1. Selected iridium-catalyzed processes to produce enantioenriched amines or alcohols.

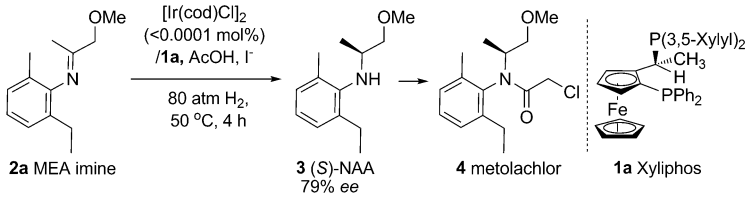
Iridium-Catalyzed Asymmetric Hydrogenation and Transfer Hydrogenation of Imines

The vast majority of examples of asymmetric hydrogenation (AH) of imines reported in the literature involve the use of iridium catalysts. In addition there exist some highly successful industrial applications, the most outstanding example being the Ir–Xyliphos-catalyzed reduction of MEA imine (**2a**; Scheme 2). This is a key step in the production of (*S*)-metolachlor (**4**), a herbicide that is manufactured in >10000 tons per year.[5] Ir–Xyliphos (Ir–**1a**) is also the most active catalyst for imine hydrogenation known to date, reaching TONs higher than $1{\cdot}10^6$ and high reaction rates (initial TOF $>1.8{\cdot}10^6\ h^{-1}$).

Although asymmetric hydrogenation of imines has been extensively developed in the past 20 years, the efficiency achieved in the reaction is, in general, still lower than that of asymmetric hydrogenations of olefins or ketones. The major difficulties encountered are high hydrogen pressures, high catalyst loadings, and low catalyst stability, instability of certain imines, and poor enantiocontrol due to imine–enamine tautomerisation and *E*/*Z* imine interconversion. Nevertheless, several of these drawbacks have been overcome by using excellent iridium catalytic systems, as described below. Several catalytic systems using other transition metals, such as Ti,[6] Zr,[7] Rh,[8] Pd,[9] Ru,[10] and Au,[11] have also been shown to have excellent activity.

[a] Dr. A. Bartoszewicz, Dr. N. Ahlsten, Prof. Dr. B. Martín-Matute
Department of Organic Chemistry, Arrhenius Laboratory
Stockholm University, 106 91 Stockholm (Sweden)
Fax: (+46) 8-15-49-08
E-mail: belen@organ.su.se

[b] Dr. A. Bartoszewicz, Dr. N. Ahlsten, Prof. Dr. B. Martín-Matute
A. Bartoszewicz, N. Ahlsten, B. Martín-Matute
Berzelii Centre EXSELENT on Porous Materials
Stockholm University, 106 91 Stockholm (Sweden)



Scheme 2.

In contrast to iridium-catalyzed asymmetric hydrogenation, very few examples on iridium-catalyzed asymmetric transfer hydrogenation (ATH) exist. The ATH field is much more developed with other metal complexes,[2] containing Ru,[12] Rh,[13] and Fe.[14]

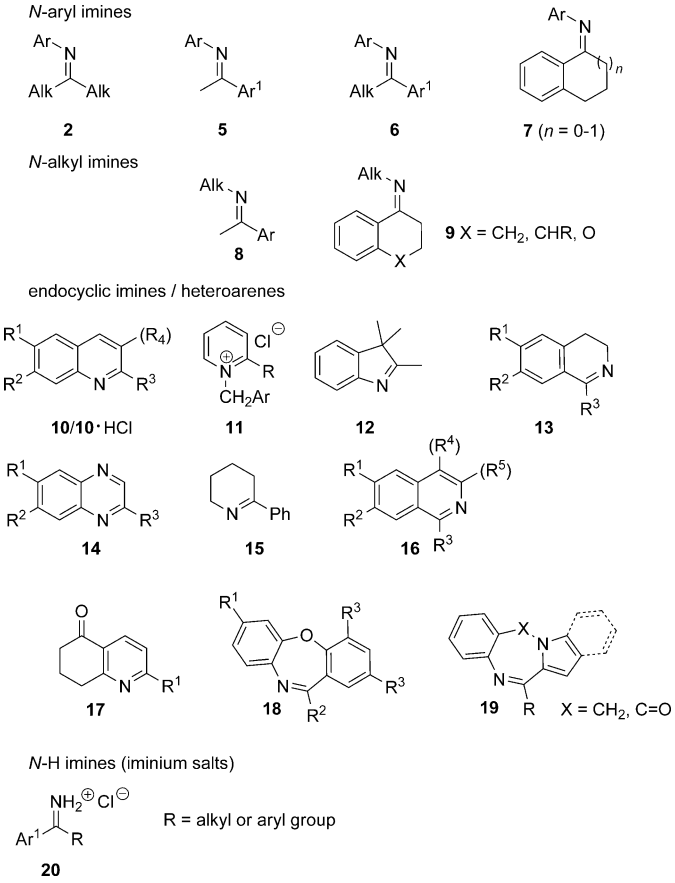
Asymmetric imine hydrogenation: The most commonly used catalyst precursors are the neutral dimer $[IrCl(cod)]_2$ (cod = cyclooctadiene) and cationic complexes $[Ir(cod)_2]X$ ($X = BAr^F = [B(3,5\text{-}(CF_3)_2C_6H_3)_4]^-$, BF_4^-, or PF_6^-). A vast number of chiral ligands have been successfully used, and the majority of them are diphosphines or phosphorus–nitrogen ligands. Imine hydrogenation may occur through a variety of different mechanisms.[15] The type of mechanism may vary for different substrates and it is dependent on the iridium precursor as well as the additives used. In general, the formation of coordinatively unsaturated active catalysts by, for example, hydrogenation of an unsaturated ligand (i.e., cod) is the first step. This is followed by coordination of the chiral ligand to the iridium center. Catalyst oxidation (that is, from Ir^I to Ir^{III}) occurs by oxidative addition of H_2 or it is mediated by the additive (halides such as I_2 are frequently used additives[16]). Common substrates are shown in Scheme 3 and classified as *N*-aryl imines (**2**, **5**–**7**), *N*-alkyl-imines (**8**–**9**), endocyclic imines and *N*-heteroarenes (**10**–**19**), and *N*-H imines (**20**). The development of a general catalytic system for imine hydrogenation is difficult since the substrate selectivity and reactivity are highly dependent on the substituents on the nitrogen atom. Typically, 10–50 atm of hydrogen gas are needed for the reaction. Often, higher pressures accelerate the reactions, but decrease enantioselectivities. A few highly reactive systems can work at pressures as low as 1 atm.

P,P-ligands: Historically, the first examples of asymmetric hydrogenation of imines were attempted with Rh complexes in the 1970s and 80s.[17,18] The first account of Ir-catalyzed asymmetric hydrogenation of imines was reported in 1990 when Osborn, Spindler, and co-workers published their work using Ir–hydride and Ir–chloride complexes bearing bidentate phosphine ligands (Scheme 4).[19] The phosphines used were DIOP (**22a**) and BDPP (**23a**), which afforded moderate to good enantioselectivities (up to 84% *ee* (*ee* = enantiomeric excess) with imine **2b** and up to 80% *ee* with imine **12**). It was observed that the addition of iodide had a positive effect on both activity and selectivity,[19] and that the active coordinatively unsaturated monomers $[Ir(H)I_2(\widehat{PP})]$ ($\widehat{PP}$ = diphosphorus ligand) formed were in equilibrium with dimeric structures $[Ir(H)I_2(\widehat{PP})]_2$.[19a] The group of Osborn also reported that analogous monomeric complexes containing carboxylate anions instead of iodide showed improved enantioselectivity.[20] Among these, the most efficient catalyst was $[Ir(CF_3CO_2)_3(\mathbf{23a})]$, which afforded up to 90% *ee* in the reduction of imine **2b**. Later, an improved catalytic system containing the bulkier phosphines MOD-DIOP (**22c**) and MOD-BDPP (**23b**) was reported (e.g., substrate **12** was reduced with an

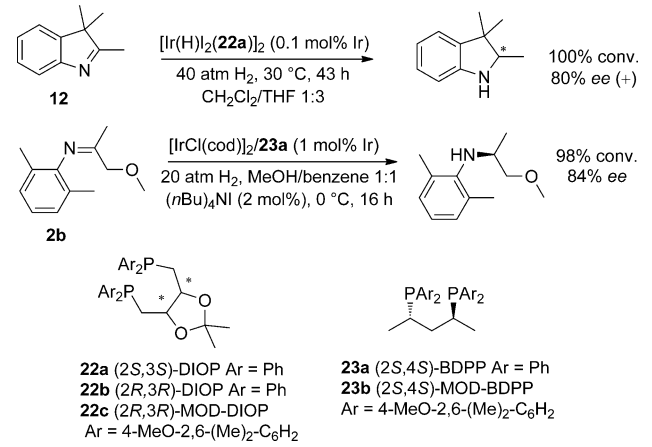
Agnieszka Bartoszewicz was born in Skarzysko-Kamienna (Poland) and received her M.Sc. degree from Warsaw University in 2006. She did her PhD with Assoc. Prof. Belén Martín-Matute at Stockholm University, and graduated in November 2012.

Nanna Ahlsten was born in Gotland (Sweden) and obtained her M. Sc. from Lund University in 2008. In the same year, she joined the research group of Assoc. Prof. Belén Martín-Matute at the Department of Organic Chemistry at Stockholm University and graduated in February 2013.

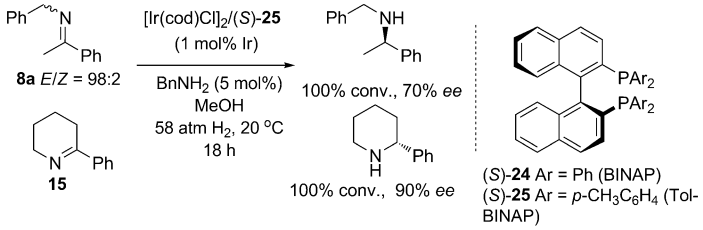
Belén Martín-Matute was born in Madrid and obtained her Ph.D at the Universidad Autónoma de Madrid (UAM 2002) with Prof. A. M. Echavarren. After a postdoctoral stay at Stockholm University with Prof. J.-E. Bäckvall, she joined the UAM as an Assistant Professor (2005–2007) and worked with Prof. J. C. Carretero. She returned to Stockholm in 2007, where in 2011 became Docent and in 2012 Associate Professor. She received the Sigma–Aldrich Young Chemist Award from the Spanish Royal Society of Chemistry in 2007, and the Lindbomska award from the Royal Swedish Academy of Sciences in 2013.



Scheme 3. Substrates used in the hydrogenation of imines.



Scheme 4.

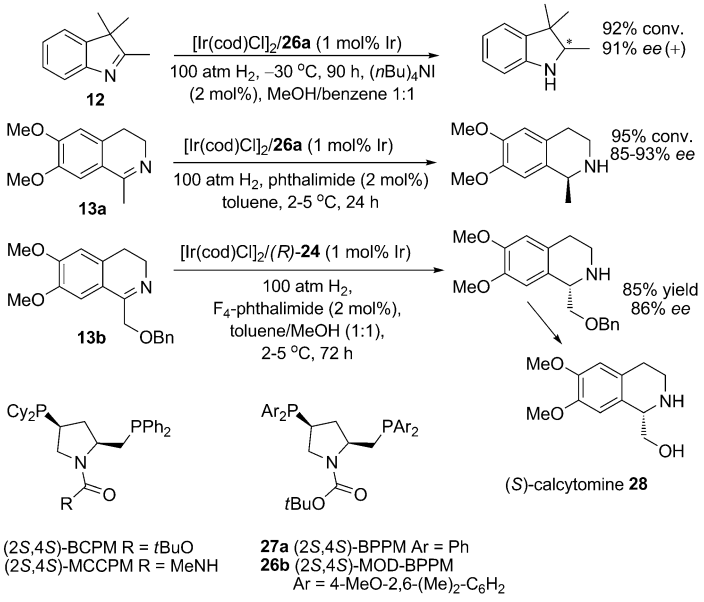


Scheme 5.

ee of 66.2% with **22b** vs. 81.4% *ee* with **22c**).[21] Substrate scope with early catalytic systems suggested that a hindered rotation around the N-aryl bond in the substrate was necessary to obtain good enantioselectivities.

In 1995, Tani and co-workers reported the use of BINAP (**24**) and Tol-BINAP (**25**) in combination with $[IrCl(cod)]_2$ (Scheme 5).[22] In contrast to the results obtained by the group of Osborn, this iridium catalyst did not require iodide as an additive, but addition of small amounts of protic amines, such as benzylamine, were needed.[23] $[IrCl(cod)]_2$/(*S*)-**25** was the most effective, giving 70% *ee* in the reduction of imine **8a** and 90% *ee* with cyclic substrate **15**.

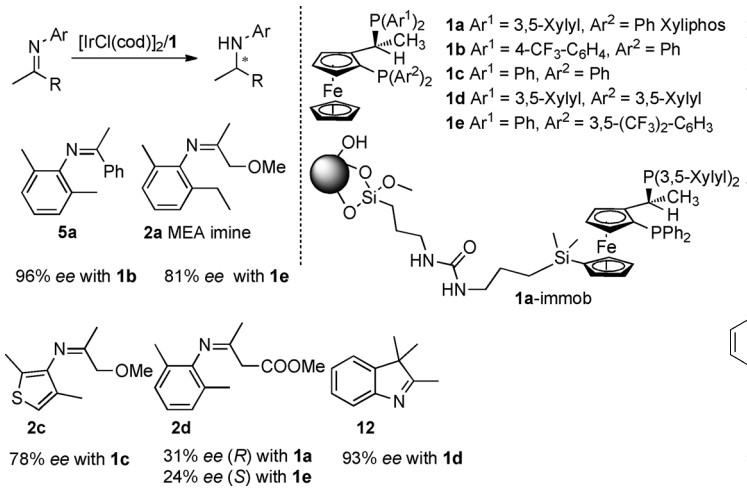
Morimoto and co-workers found that $[IrCl(cod)]_2$ and a pyrrolidine diphosphine ligand (BCPM, **26a**, or its analogue MCCPM, **26b**) were efficient catalysts in the presence of bismuth iodide (Scheme 6).[24] The best result obtained was 91% *ee* for substrate **12**. However, although all reactions proceeded to high conversions, enantioselectivities for other substrates were poor. Interestingly, the use of phthalimide as co-catalyst significantly im-



Scheme 6.

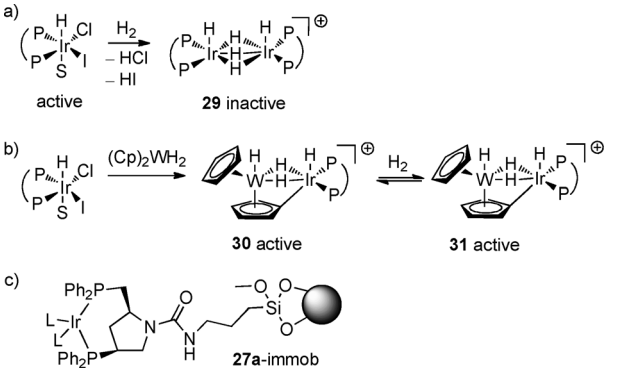
proved the results and imine **13a** could be reduced with an *ee* of up to 93%.[25] Likewise, the use of 3,4,5,6-tetrafluorophthalimide as an additive in combination with Ir–(*R*)-BINAP ((*R*)-**24**) had a positive influence on activity and selectivity (Scheme 6).[26] This system was used in the synthesis of alkaloid (*S*)-calyctomine (**28**), in which the key step, hydrogenation of imine **13b**, was achieved in 85% yield with an *ee* of 86%.

In 1994, Novartis initiated their investigations into the use of stable ferrocenyl diphosphine ligands (**1**), first synthetized by Togni, Spindler, and co-workers.[27] In 1995, the pilot production of (*S*)-metolachlor by using $[IrCl(cod)]_2$/Xyliphos (**1a**) was started, and plant production was launched already in November 1996. Later, Blaser, Spindler, and co-workers reported a full survey of tunable ferrocenyl diphosphine ligands for enantioselective hydrogenation of *N*-aryl imines. Although similar levels of enantioselectivity were obtained, none of the new ligands gave comparable activity to that obtained with the Xyliphos (**1a**) system in the reduction of the industrial target MEA imine (**2a**).[28] The screening showed that ferrocenyl diphosphine ligands are substrate specific, and to obtain high *ee* values the optimal ligand (**1a**–**e**) and reaction conditions had to be varied for each substrate (Scheme 7). Subsequently, the same group prepared an immobilized version of Ir–Xyliphos.[29] Different solid supports and linkers were tested and the best results were obtained with catalyst **1a**-immob (covalently bound to a silica gel, Scheme 7). The enantioselectivities obtained with this system were similar to those with the homogenous analogue. Although the TONs and TOFs (>100000 and 20000 h^{-1}, respectively) were among the highest ever reported using heterogeneous catalysts, the homogeneous complex was substantially more reactive.



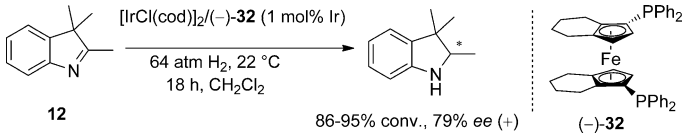
Scheme 7.

A few years later, the Blaser group reported studies on deactivation pathways of their early systems (Ir–**22a**, Ir–**23a**, and Ir–**27a**).[30] They hypothesized that catalyst deactivation took place by irreversible formation of an inactive dimeric species (**29**) (Scheme 8a), similar to the dimers observed by Crabtree during the hydrogenation of alkenes.[31] They proposed two solutions to suppress the formation of the inactive species. The first one was to stabilize the active monomeric species in the form of heterobimetallic complexes that could bind hydrogen reversibly (i.e., **30** and **31**, Scheme 8b). Although this approach led to better results with imine **8a** in terms of TONs, the enantioselectivities obtained were very low. The second approach tested was a low-density immobilization of the catalysts (Ir–**27a**-immob, Scheme 8c) on silica gel. TONs of 10000 and improved *ee* values in the hydrogenation of **2b** were obtained.



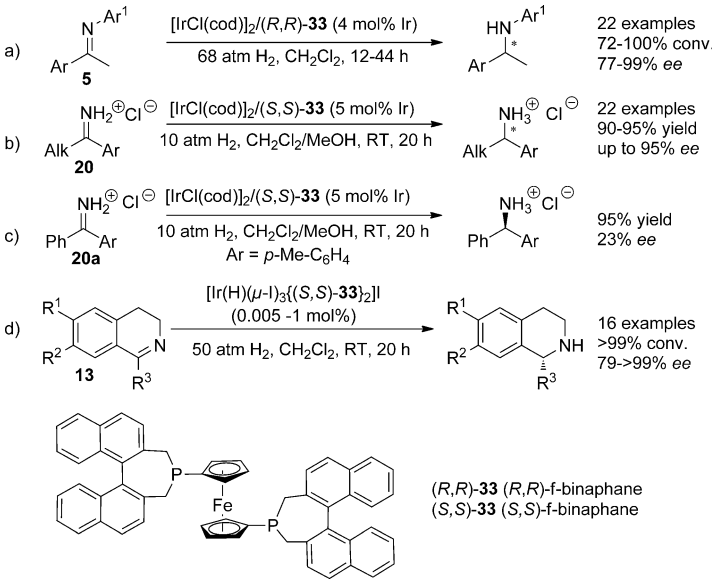
Scheme 8.

A ferrocenyl-based ligand containing only planar chirality ((−)-**32**) was used by Reetz and co-workers, affording *ee* values of up to 79% in the hydrogenation of cyclic imine **12** (Scheme 9).[32]



Scheme 9.

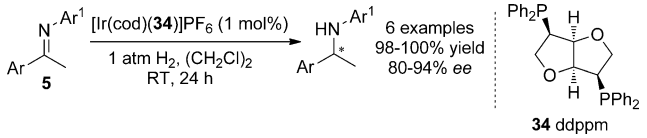
In 2001 Zhang and co-workers reported that Ir–(*R*,*R*)-f-binaphane (Ir–(*R*,*R*)-**33**)[33] is a good catalyst for the hydrogenation of several aromatic imines **5**, affording the corresponding amines with *ee* values of up to 99% (Scheme 10a). In some cases, addition of I_2 had a positive influence on conversion and enantioselectivity, whereas other additives such as phthalimide, tetrabutylamonium iodide, or benzyl amine had no effect. Similarly to the Osborn system,[19a] a mechanism via Ir^{III} intermediates, formed from oxidative addition of iodine to Ir^{I}–(*R*,*R*)-**33**, was proposed. In 2009, Zhang and co-workers reported the first example of iminium salt reduction (**20**) by using Ir–(*S*,*S*)-f-binaphane ((*S*,*S*)-**33**) (Scheme 10b). Enantioselectivities were high in the reduction of aryl/alkyl imminium salts **20**, varying from 80 to 95% *ee*. On



Scheme 10.

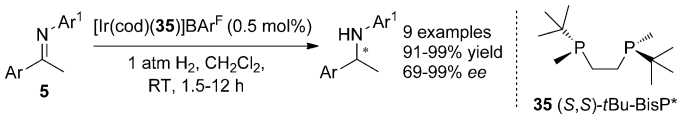
the other hand, diaryl iminium salt **20a** ($Ar^1 = 4\text{-}CH_3C_6H_4$, $Ar^2 = Ph$, Scheme 10c) gave full conversion but low *ee* (23%). Experiments using D_2 suggested a mechanism via enamine intermediates, which is not viable for substrate **20a**. The same ligand ((*S*,*S*)-**33**) was used in Ir-catalyzed hydrogenation of 3,4-dihydroisoquinolines (**13**, Scheme 10d).[34] A premade iodine bridged complex with the formula [Ir(H)-(μ-I)$_3${(*S*,*S*)-**33**}$_2$]I was more effective than the same catalyst prepared in situ, and Ir loadings as low as 0.005 mol% could be used.[35,36]

Dervisi and co-workers used cationic [Ir(cod)(**34**)]X (X = BF_4, PF_6) complexes bearing ddppm (**34**), which were active under atmospheric H_2 pressure (Scheme 11).[37] High enan-



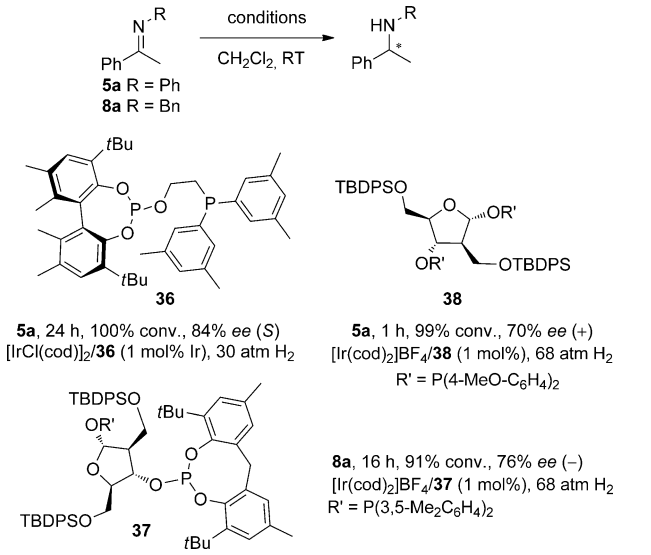
Scheme 11.

tioselectivities were obtained with imines of type **5**. Hydrogen pressures above 1 atm led to deactivation of the catalyst due to formation of inactive dimeric and trimeric Ir^{III}–hydride clusters. The best results were obtained with complexes containing non-coordinating counter anions (BF_4^- and PF_6^-) and in non-coordinating solvents, without additional additives. Atmospheric hydrogen pressure could also be applied with cationic Ir complexes bearing (*S*,*S*)-*t*Bu-BisP* (**35**), which was reported by Imamoto and co-workers (Scheme 12).[38] Dramatic rate accelerations were observed with [Ir(cod)(**35**)]X when BAr^F was used as the counterion. Several aromatic acyclic imines (**5**) could be reduced under mild reaction conditions with *ee* values of up to 99%.



Scheme 12.

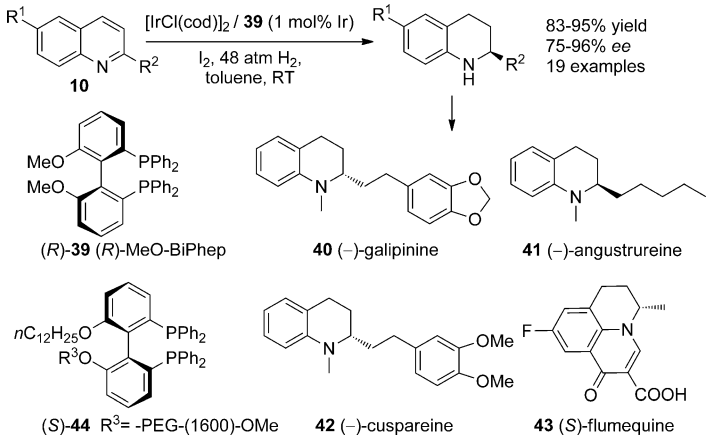
Although asymmetric hydrogenation of acyclic imines by using diphosphine ligands is well documented, other P,P-ligands such as phosphine–phosphite, diphosphinites, or phosphinite–phosphite ligands have rarely been used. In 2005, the group of Pizzano screened a number of phosphine–phosphite ligands, and the best result (84% *ee*) was obtained with ligand **36** and substrate **5a** (Scheme 13).[39] In 2006, Claver, Castillón and co-workers reported an Ir-catalyzed asymmetric reduction of imines with glucosamine derived ligands **37** and **38** (Scheme 13).[40] The enantiomeric ratio ob-



Scheme 13.

tained was 76% in the hydrogenation of **8a** by [Ir-(cod)$_2$]BF_4/**37** and 70% in the hydrogenation of **5a** by [Ir-(cod)$_2$]BF_4/**38**. These results were significantly better than those obtained with ligands derived from xylose, reported earlier by the same group.[41]

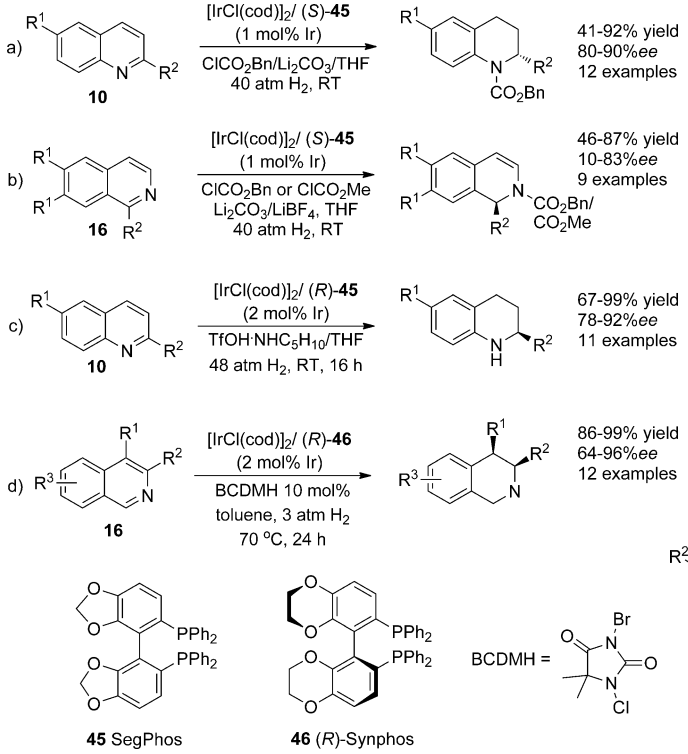
Enantioselective hydrogenation of N-heteroarenes has been mostly studied with iridium and bidentate phosphorus ligands. Zhou and co-workers reported the first highly enantioselective iridium-catalyzed hydrogenation of quinolines **10** (Scheme 14).[42] The optimal reaction conditions found were [IrCl(cod)]$_2$ together with a ligand possessing axial chirality, (*R*)-MeO-BiPhep (**39**), and iodine as the additive. A number of tetrahydroquinolines were prepared with excellent *ee* values (up to 96%). Four products were further transformed into natural alkaloids: galipinine (**40**), angustureine (**41**), cuspareine (**42**), and the antibacterial agent flumequine (**43**). The catalyst was successfully immobilized on a soluble PEG polymer support by replacing one of the OMe



Scheme 14.

groups by MeO-PEG-(1600).[43] The enantioselectivity obtained with the heterogenized catalytic system (*S*)-MeO-Biphep-PEG-(1600) (**44**) was similar to that obtained under homogenous conditions and **44** could be recycled up to five times with no significant drop in conversion and enantioselectivity.[42]

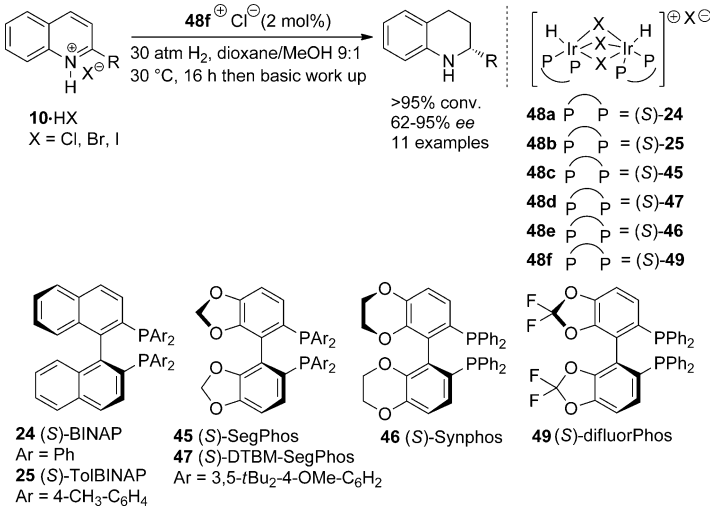
The same group reported that benzyl chloroformate was an excellent imine-activating reagent (Scheme 15a and b).[44] (*S*)-SegPhos ((*S*)-**45**) was the most active among all the ligands tested; several quinolines (**10**) and isoquinolines (**16**) activated with chloroformate could be hydrogenated with *ee* values up to 90%. In a recent hydrogenation protocol using $[IrCl(cod)]_2$/(*R*)-**45**, it was found that certain Brønsted acids



Scheme 15.

(e.g., piperidine·TfOH) used in catalytic amounts were excellent substrate activators for quinolines (**10**) and quinoxalines (**14**) (Scheme 15c).[45] Other catalytic systems using $[IrCl(cod)]_2$/(*R*)-Synphos (**46**) could hydrogenate for the first time 3,4-disubstituted isoquinolines (Scheme 15d) to 3,4-disubstituted tetrahydroisoquinolines with high *ee* and diastereomeric ratio (d.r.) values.[46] The use of 1-bromo-3-chloro-5,5-dimethylhydantoin (BCDMH; Scheme 15) as a halogen source additive together with toluene as the solvent was crucial to obtain high activity and selectivity.

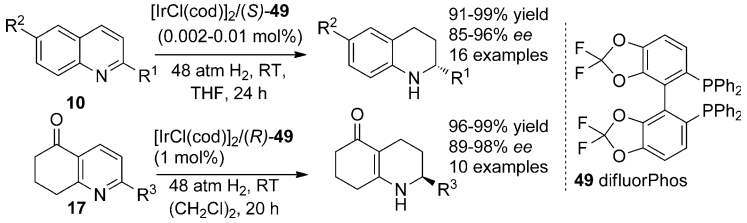
Mashima, Ratovelomanana-Vidal, Ohshima, and co-workers reported that the hydro halide salts (halide = Br, Cl) of quinolines **10** can be efficiently hydrogenated with cationic dinuclear iridium precatalysts **48** (Scheme 16).[47] The enan-



Scheme 16.

tioselectivity is highly dependent on the dihedral angles (θ) of the ligand, and the highest *ee* was obtained with (*S*)-difluorphos (**49**), which has the smallest angle. In contrast to other reports,[34,35] chloro and bromo-bridged complexes **48** were working better than iodo-bridged ones. The Ir-(*S*)-difluorphos **48 f** catalytic system gave similar results (up to 92% *ee*) in the reduction of quinolines (**10**), reported earlier by the same group.[48]

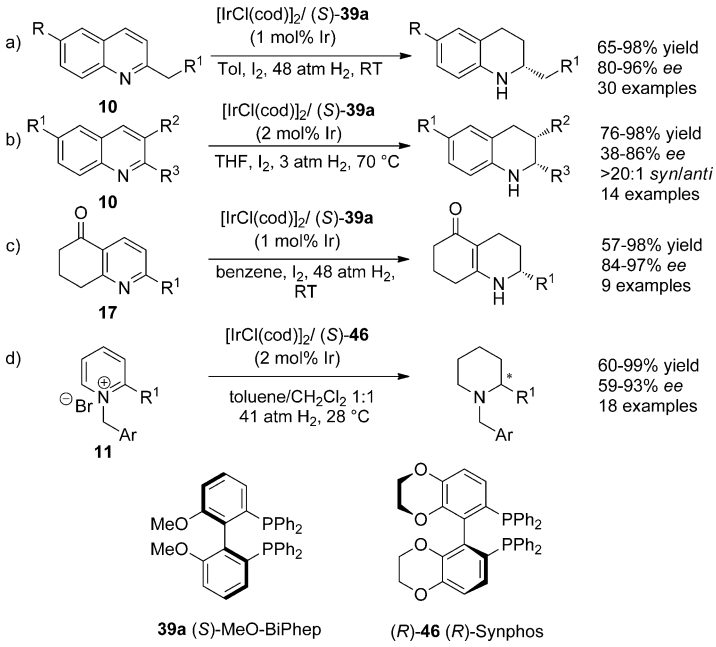
Another $[IrCl(cod)]_2$/(*R*)-difluorphos ((*R*)-**49**)/I_2 system was successfully applied in the hydrogenation of quinolines (**10**) and pyridines (**17**) by the group of Xu (Scheme 17).[49] In the hydrogenation of quinolines, low catalyst loadings



Scheme 17.

(0.05–0.002 mol%) could be used, and enantioselectivities up to 96% together with excellent catalytic activity (TOF up to 3510 h^{-1} and TON up to 43000) was obtained. Pyridines required 1 mol% of catalyst and the enantioselectivities obtained were up to 98%.

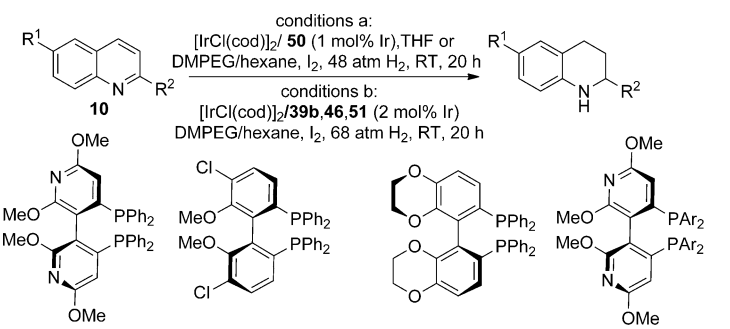
Zhou and co-workers developed a highly enantioselective protocol for the iridium-catalyzed hydrogenation of 2-benzylquinolines (Scheme 18a) and 2,3-disubstituted quinolines



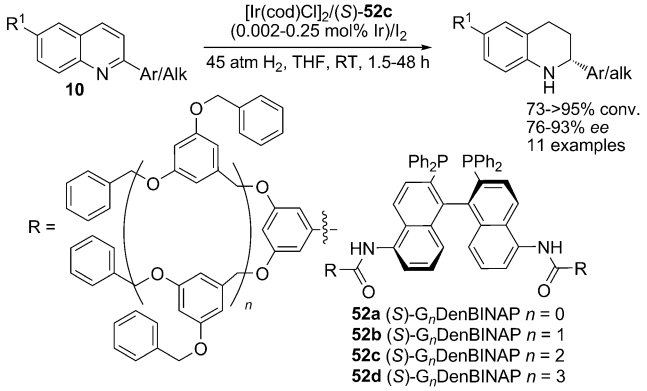
Scheme 18.

(Scheme 18b) by using (*S*)-MeO-BiPhep (**39a**).[50] Tetrahydroquinolines with two stereocenters could be formed in high yields, d.r., and *ee*. The mechanistic experiments supported a mechanism through 1,4-addition, enamine/imine tautomerization, and 1,2-addition. The same catalytic system $[IrCl(cod)]_2$/**39a** could be used for efficient and selective asymmetric hydrogenation of pyridine derivatives **17** (Scheme 18c).[51] In another protocol by the same group, various 2-substituted pyridinium salts (**11**) could be hydrogenated to provide chiral piperidines with high yield and enantioselectivity (Scheme 18d).[52]

Chan, Fan, and co-workers reported a highly air-stable system, $[IrCl(cod)]_2$/(P-Phos)/I_2 (**50**/I_2), for the hydrogenation of quinolines (**10**) (Scheme 19).[53] When the catalyst was immobilized in DMPEG (polyethylene glycol dimethyl ether), it could be recycled by simple phase separation up to eight times without loss of activity or enantioselectivity. DMPEG-immobilized iridium complexes containing similar C_2-symmetrical ligands (Xyl-P-Phos (**51**), Cl-MeO-BiPhep (**39b**), SynPhos (**46**), and DifluorPhos (**49**)) gave comparable results; *ee* values up to 92% and the catalyst could be recycled (Scheme 19).[54] The same authors prepared four generations of {Ir(BINAP)}-cored dendrimers (**52a–d**) that showed excellent enantioselectivities (up to 93%) in the hydrogenation of quinolines (**10**) (Scheme 20).[55] The encapsulation in the dendrimer framework prevented formation of inactive dimers and resulted in a very active system reaching



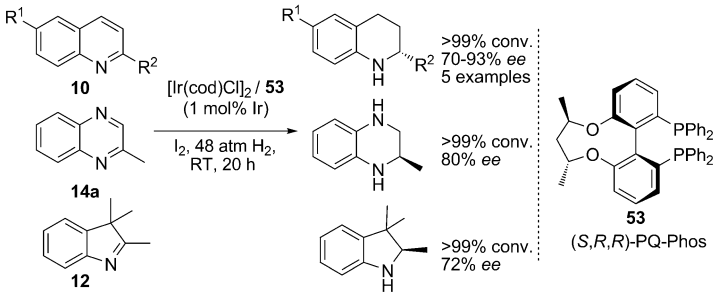
Scheme 19.



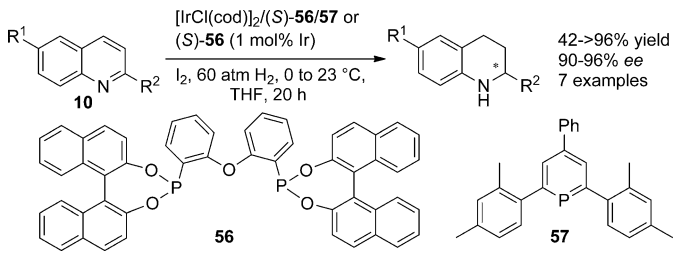
Scheme 20.

TOF's up to 3450 h^{-1} and TON's up to 43000. The third catalyst generation (**52c**, $n=2$) retained activity and selectivity for at least six cycles. The same group tested a family of atropoisomeric PQ-Phos ligands and observed that the enantioselectivities obtained in the hydrogenation of imines were dependent on the dihedral angle of the ligand used.[56] The best results in the reduction of quinolines (**10**), 2-methylquinoxaline (**14a**), and 2,3,3-trimethyllindolenine (**12**) were obtained with the ligand (*S*,*R*,*R*)-PQ-Phos (**53**; Scheme 21).

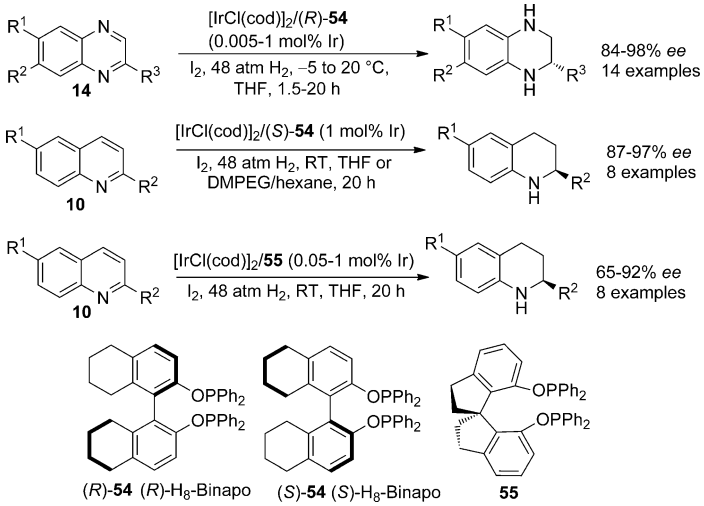
The hydrogenation of quinoxalines (**14**) could be significantly improved to 84-98% *ee* (vs. 80% *ee* with $[IrCl(cod)]_2$/**53**, Scheme 21) when diphosphonite ligand (*R*)-H_8-Binapo ((*R*)-**54**) was used (Scheme 22).[57] This catalyst system had high activity (up to TOF 5620 h^{-1} and TON 18140), affording outstanding results with heteroaromatic substrates. A similar catalytic system with (*S*)-**54** was used for the hydrogenation of quinoline derivatives affording *ee* values in the range of 87–97%.[58] Another ligand, (*R*)-1,1′-spirobiindane-



Scheme 21.



Scheme 23.



Scheme 22.

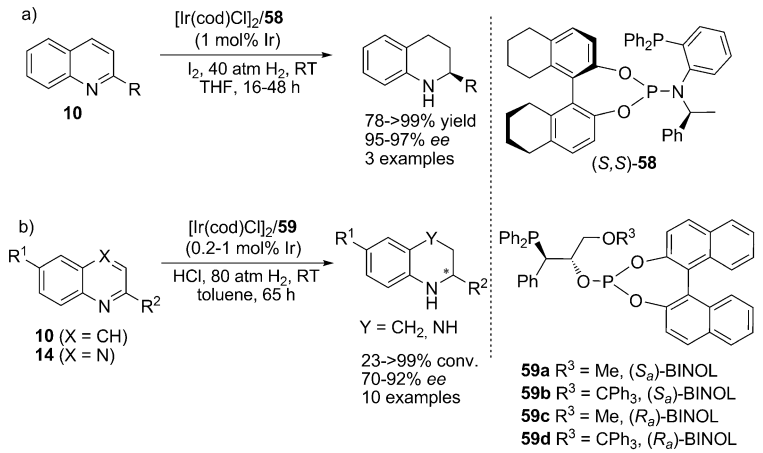
7,7′-diol (**55**), afforded up to 94% *ee*. The amount of catalyst [IrCl(cod)]$_2$/**55** could be lowered to 0.05 mol% maintaining the activity and selectivity (Scheme 22).

Reetz and co-workers reported that chiral diphosphonite ligand **56** derived from (*S*)-BINOL gives up to 96% *ee* in the hydrogenation of quinolines (**10**) (Scheme 23).[59] The use of an achiral phosphine additive (i.e., **57**) slightly improved the enantioselectivity.

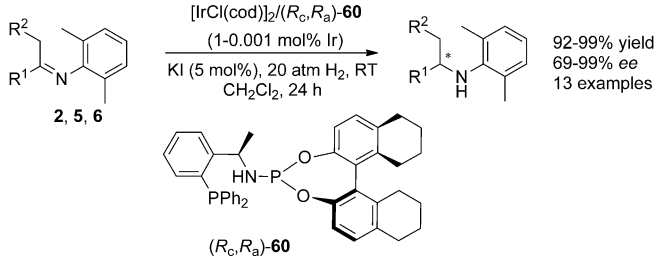
Leitner, Franciò, and co-workers tested phosphine–phosphoramidite ligand **58**[60] and observed a synergistic influence of axial and central chirality in the matched case, ligand ((*S*,*S*)-**58**), which afforded 95–97% *ee* in the reduction of quinolines (**10**) (Scheme 24a). Slightly lower enantioselectivities (71–93%) of quinolines (**10**) were obtained when phosphinite–phosphite ligands **59a–d** were used (Scheme 24b).[61] This system worked without iodine additive; however, catalytic amounts of anhydrous HCl were required. The catalyst loading could be decreased to 0.2 mol%.

Hu and co-workers used iridium complexes containing phosphine–phosphoramidite ligand **60** for hydrogenation of sterically hindered imines **2**, **5**, and **6**.[62] It was suggested that ligands with N–H and H_8-binaphtyl moieties are crucial to obtain high activity and selectivity. Catalyst loading could be decreased to 0.001 mol% and high yields and *ee* values were maintained. A practical application of this catalytic system was demonstrated in the reduction of MEA imine **2a** on a large scale by using 0.001 mol% of catalyst (Scheme 25).

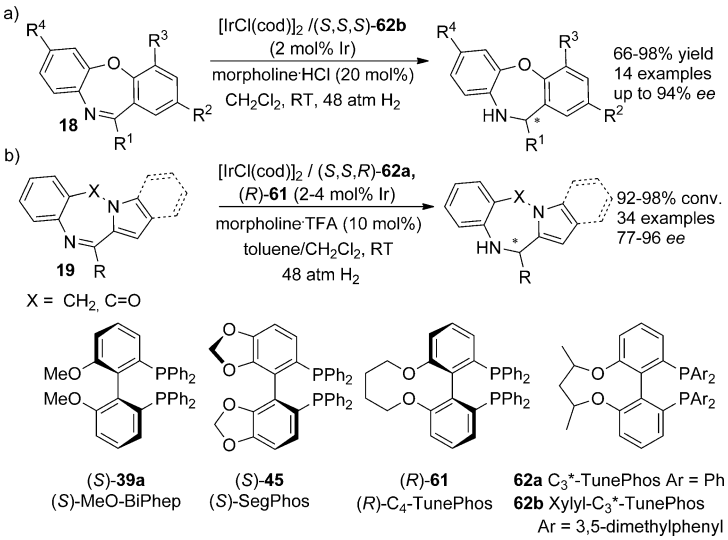
In 2011, the groups of Zhou and Zhang reported a highly enantioselective hydrogenation of seven-membered cyclic imines dibenzo[*b*,*f*][1,4]oxazepines (**18**), which are important biologically active compounds (Scheme 26a).[63] Among the ligands tested, MeO-BiPhep (**39a**), (*S*)-SegPhos (**45**), (*R*)-C_4-TunePhos (**61**), (*S*,*S*,*S*)-C_3*-TunePhos (**62a**), and (*S*,*S*,*S*)-Xylyl-C_3*-TunePhos (**62b**) gave the highest enantioselectivities. The best results, up to 94% *ee*, were obtained with Ir–**62b** and morpholine as the additive. The same group also reported the hydrogenation of other types of seven-membered cyclic imines, such as benzodiazepinones and benzo-



Scheme 24.



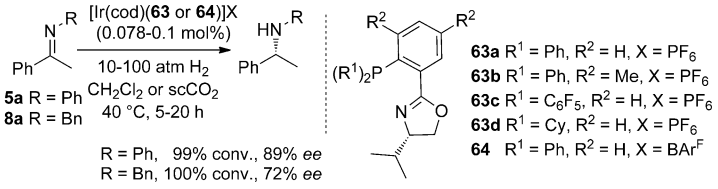
Scheme 25.



Scheme 26.

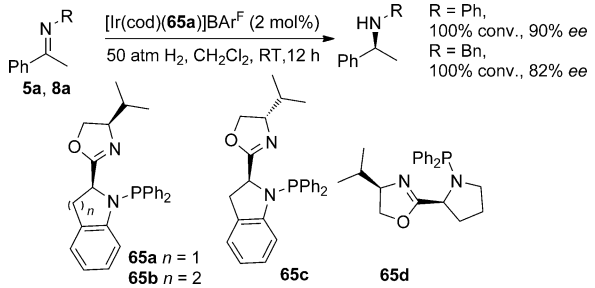
diazepines, with $[IrCl(cod)]_2$ and (*S*,*S*,*R*)-C_3*-TunePhos (**62a**) and (*R*)-C_4-TunePhos (**61**) (Scheme 26b).[64]

P,N-ligands: Pfaltz reported the first example using P,N-ligands in the Ir-catalyzed asymmetric hydrogenation of imines (1997).[65] Inspired by the good results obtained with the achiral complex $[Ir(cod)(py)(PCy_3)]PF_6$ (py = pyridine, PCy3 = tricyclohexylphosphine), developed for hydrogenation reactions by Crabtree,[31,66] the Pfaltz group prepared a family of analogous chiral iridium–PHOX (**63**) complexes (Scheme 27). The best results were obtained with ligand **63b** in combination with low iridium loadings (0.1 mol%). Interestingly, the enatioselectivity increased when the catalyst loadings and concentrations were decreased. Although a good 89% *ee* and high TON (5000) could be achieved only with one substrate (**5a**), the high potential of such phosphine–oxazoline ligands was envisioned. With the similar ligand **64**, catalyst loadings could be further decreased to 0.078 mol% when supercritical carbon dioxide was used as the solvent and the catalyst system could be recycled.[67] The use of



Scheme 27.

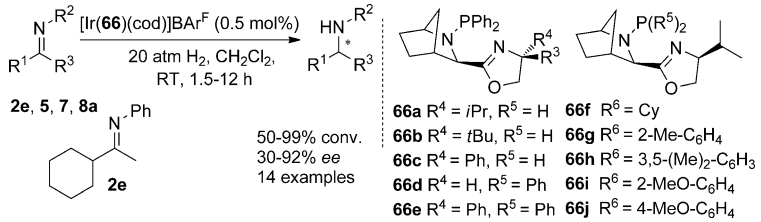
BAr^F suppressed catalyst deactivation through formation of hydride-bridged trimers, and also resulted in better moisture and air stability, and higher turnover numbers than those previously obtained with **63**.[68] By following the pioneering Pfaltz report,[66] several catalysts containing a phosphine–oxazoline skeleton were prepared. Niedercorn and co-workers used related phosphine–oxazolines and found that ligand **65a**, which is more flexible than other PHOX ligands (e.g., **63** and **64**), afforded up to 90% *ee* in the reduction of imines **5a** and **8a** (Scheme 28).[69] Ligand **65a**, with an *R*-



Scheme 28.

configured oxazoline ring and an *S*-configured aminophosphine, induced a much higher enantioselectivity than the corresponding (*S*,*S*)-configured diastereomeric ligand **65c** (which gave only a 14% *ee* in the reduction of **5a**).

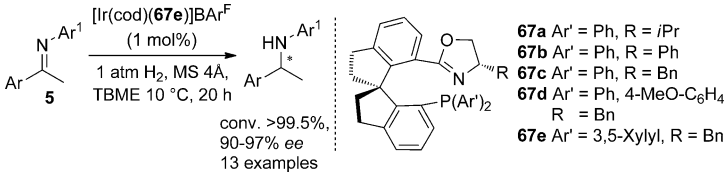
Andersson and co-workers have prepared a large family of ligands **66** with the 2-azanorborane skeleton introduced into the phosphine–oxazoline structures (Scheme 29).[70,71] The substituents on the oxazoline ring have an important influence on the enantioselection, whereas those on phosphorus do not affect it to a great extent. This system was tested in the reduction of a wide variety of aromatic and nonaromatic imines. The best results were obtained with ligands **66g** and **66h**. In general, imines of type **5** could be reduced



Scheme 29.

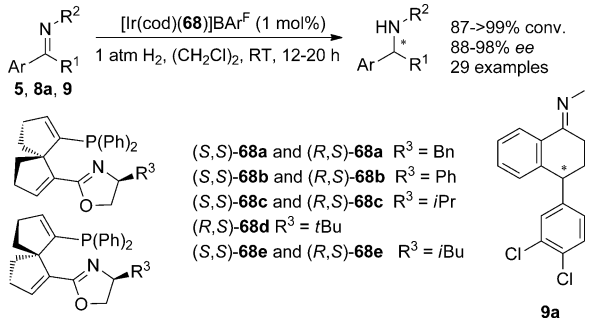
with an *ee* of up to 92%, whereas imine **2e** was reduced with poor enantioselectivity (30% *ee*).

Another group of phosphine–oxazoline ligands, the SIPHOX family **67**, was prepared by Zhou and co-workers (Scheme 30).[72] Catalyst [Ir(cod)(**67**)]BAr^F could be used



Scheme 30.

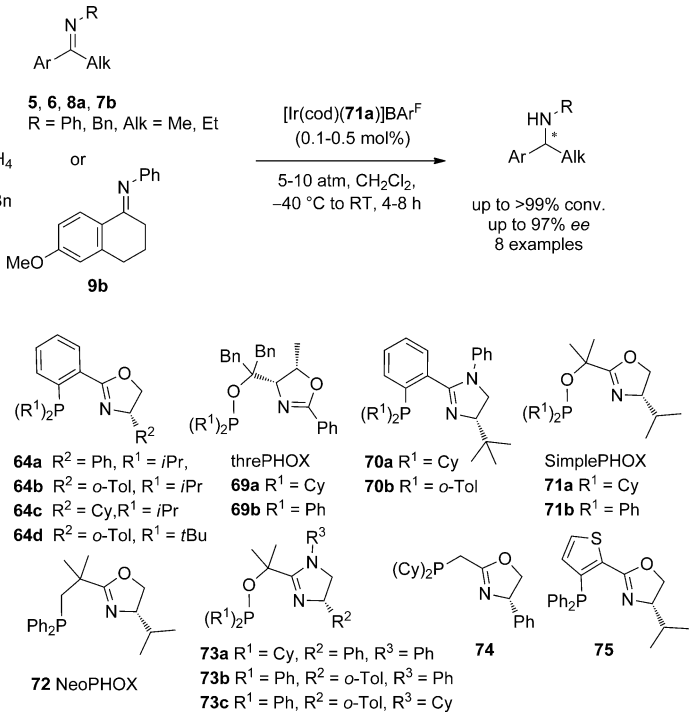
under atmospheric pressure and at low temperatures and gave excellent enantioselectivities (up to 97% *ee*) in the reduction of various N-aryl aromatic imines. The highly rigid and bulky ligand scaffold prevented deactivation of the catalyst by inhibiting the formation of inactive hydride-bridged trimers, which were produced with Ir and Rh systems in combination with PHOX ligands.[68] The *S*-configured oxazoline ring together with *S*-configured spirobindane backbone was found to be the matched case. Further studies revealed that benzyl-substituted oxazoline **67c** gave the best *ee*. Although the nature of the aryl groups on the phosphine did not influence the enantioselectivity, the reaction rate increased with electron-rich aromatics, as in ligand **67e**. Nonpolar solvents, such as *tert*-butyl methyl ether (TBME), afforded fast reaction rates and high *ee* values. Ding and coworkers obtained excellent results by using iridium complexes with the related SpinPHOX ligands (**68**) (Scheme 31).[73] The substrate scope included *N*-aryl aromat-



Scheme 31.

ic imines (**5**), *N*-benzyl imines (**8**), and tetralon-derived imines (**9**). High enantioselectivities (88–98%) were obtained with all substrates tested under mild reaction conditions (room temperature and atmospheric hydrogen pressures). The methodology was applied in the reduction of imine **9a** leading to Sertraline, an antidepressant drug, with >99% *ee* and >99% d.r. (Scheme 31).

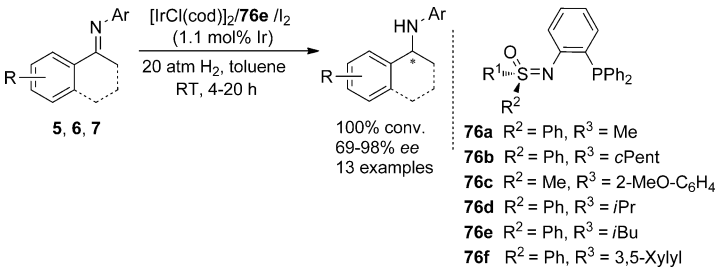
Pfaltz and co-workers have evaluated a variety of chiral phosphineoxazoline-based P,N-ligands, developed earlier in the group for the hydrogenation of olefins and enamines (Scheme 32).[74,75] Among all the catalysts screened, **64a**, **71a**, **72**, and **73b** showed the best performance; the isoprop-



Scheme 32.

yl substituent on the oxazoline ring plays an important role and most ligands containing this group afforded good results. The catalyst **71a** worked well with imines of the type **5**, **6**, **8a**, and **9b**, which were reduced with *ee* values of 92, 97, 81, and 82% *ee*, respectively.

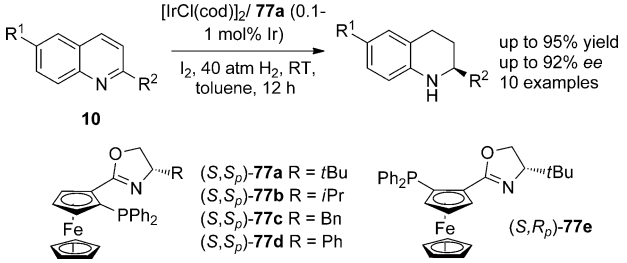
Bolm and co-workers applied another type of P,N-ligand, phosphine-substituted sulfoximines **76** (Scheme 33).[76] Addition of iodine was necessary to generate the active catalys-



Scheme 33.

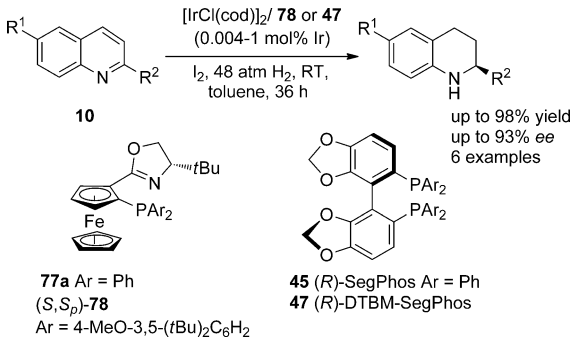
t.[19a] Acetophenone (**5**), propiophenone (**6a**), and tetralon (**7**)-derived imines, protected with the easily removable *N*-(4-*m*ethoxy)phenyl group, could be reduced with *ee* values up to 98% in short reaction times with [IrCl(cod)]$_2$/**76e**.

Zhou and co-workers used chiral ferrocenyl-derived P,N-ligands **77** in the Ir-catalyzed asymmetric hydrogenation of quinolines (**10**) with up to 92% *ee* (Scheme 34).[77] The cata-



Scheme 34.

lyst loading could be lowered to 0.1 mol% without a significant drop in conversion or enantioselectivity. The central chirality of the oxazoline ring was shown to have a higher influence on the product configuration than the planar chirality of the ferrocenyl group. The catalyst efficiency could be increased significantly by replacing the phenyl groups on the phosphorus with more bulky 4-MeO-3,5-$tBu_2C_6H_2$ (DTBM) groups (**78**), which prevented dimerization of the active catalyst (Scheme 35).[78] A catalyst loading of

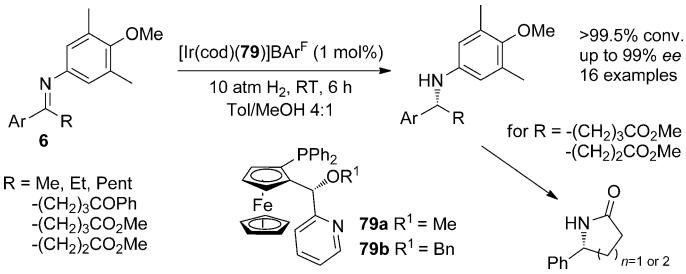


Scheme 35.

0.02 mol% afforded *ee* values up to 93%. Similarly, replacement of the phenyl groups on phosphorus in (*R*)-SegPhos (**45**) with DTBM groups led to a more efficient catalyst (**47**) that could be used with catalyst loadings as low as 0.004 mol%.

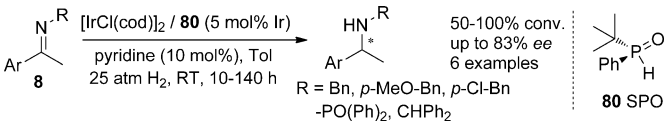
Knochel, Cheemala, and co-workers used chiral P,N-ferrocenyl ligands **79** in the Ir-catalyzed reduction of *N*-(3,5-dimethyl-4-methoxy)phenylalkylimines, which worked under mild reaction conditions and afforded excellent enantioselectivities (Scheme 36).[79] The 3,5-dimethyl-4-methoxyphenyl protecting group could be easily removed with $Ce(NH_4)_2(NO_3)_6$. This method was used to prepare γ- and δ-lactams in quantitative yields with *ee* values of 92–97%.

Modondentate P ligands: The Ir-catalyzed hydrogenation of imines with mododentate secondary phosphine oxide ligands



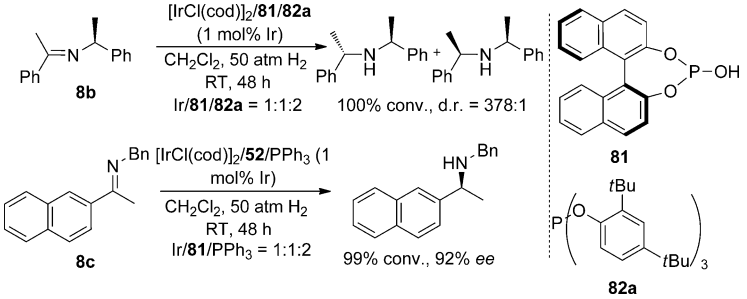
Scheme 36.

(SPO's) was first reported by De Vries, Feringa, and co-workers (Scheme 37).[80] SPO's are highly modular, air-stable and can be easily prepared in a two-step one-pot procedure from $RPCl_2$ and Grignard reagents. Among the several ligands prepared only **80** showed good activity. Addition of pyridine to the reaction improved the enantioselectivity and allowed a decrease in the ligand to iridium ratio from 2:1 to 1:1.



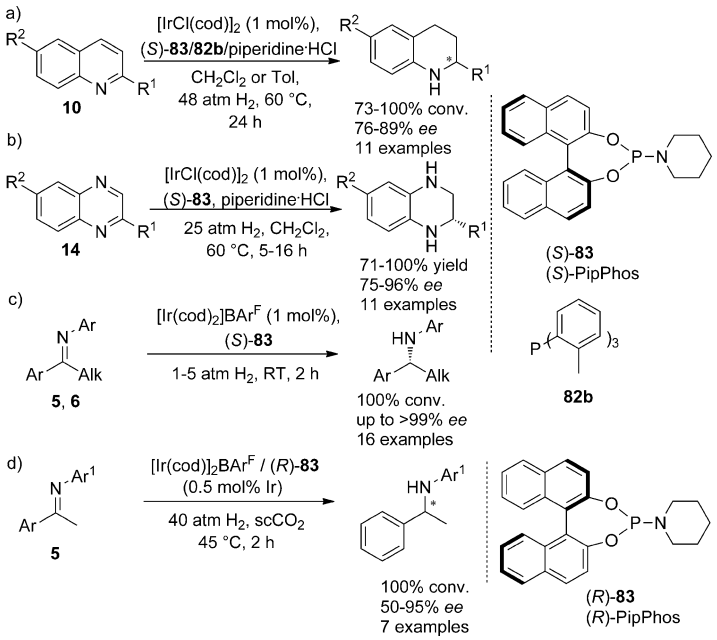
Scheme 37.

Reetz and Bondarev used a mixture of chiral phosphorous acid diesters and achiral phosphine ligands in the Ir catalyzed enantio- and diastereoselective hydrogenation of ketimines **8b** and **8c**.[81] The idea of using a mixture of two different monodentate ligands came from the observation that in the Rh-catalyzed hydrogenation of olefins, two monodentate ligands are bound to the metal in the most active species.[82] It was envisioned that catalysts of the type ML_aL_b could be much more efficient than ML_aL_a or ML_bL_b.[83] Extensive screening combining BINOL-derived phosphorous acid diester **81** with BINOL-derived phosphites, phosphonites, and several achiral P ligands (i.e., **82a**) led to excellent catalytic systems. Unfortunately, a unique combination of ligands was needed for each substrate (Scheme 38).



Scheme 38.

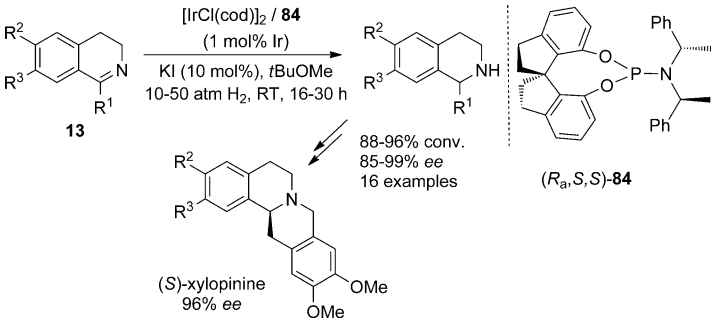
The same authors reported the asymmetric hydrogenation of quinolines **10**,[84] quinoxalines **14**,[85] and *N*-aryl imines **5**[86] with iridium complexes containing monodentate BINOL-derived phosphoramidites ligands, such as (*S*)-PipPhos ((*S*)-**83**) (Scheme 39). In the reduction of 2,6-substituted quinolines **10**, piperidine hydrochloride together with achiral tri(*o*-tolyl)phosphine (**82b**) additives were found to be important,[84] and the cationic iridium complex [Ir(cod)$_2$]BAr^F was the best catalyst precursor (Scheme 39a). A similar system without addition of **82b** was used in the reduction of quinoxalines (Scheme 39b).[85] Hydrogenation of aryl imines **5** and **6** with a similar system (without achiral phosphine additive) gave excellent *ee* values (up to >99%; Scheme 39c).[86] Amine products containing a 2-amethoxyphenyl protecting group could be easily transformed to primary amines after treatment with trichloroisocyanuric acid. It was also found that the expensive BAr^F anion could be replaced by methylaluminoxane (MAO), which showed similar reactivity.[87]



Scheme 39.

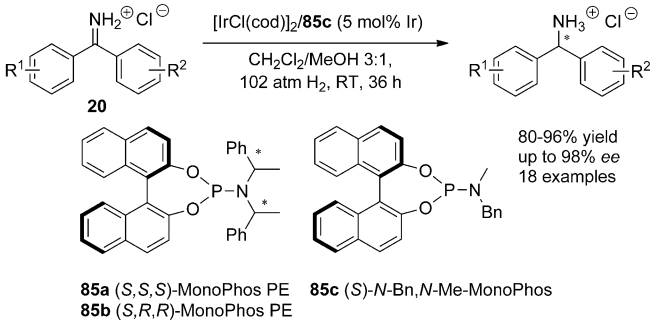
Recently Lyubimov et al. reported another example of Ir-catalyzed asymmetric hydrogenation of imines with (*R*)-PipPhos ((*R*)-**83**) and [Ir(cod)]$_2$BAr^F as the catalyst precursor in supercritical CO_2 (Scheme 39c).[88] Several aromatic imines were reduced in good to high enantioselectivities in short reaction times.

The group of Zhou reported asymmetric hydrogenation of 3,4-dihydroisoquinolines (**13**) catalyzed by [IrCl(cod)]$_2$ with chiral spiro phosphoramidite ligand **84** (Scheme 40). The utility of the reaction was demonstrated by synthesizing alkaloid (*S*)-xylopinine in high yield and enantioselectivity.[89]



Scheme 40.

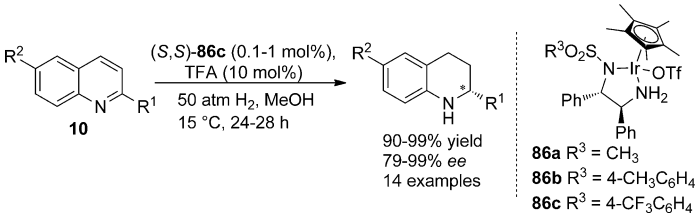
Zhang, Gosselin, and co-workers developed an iridium-catalyzed asymmetric hydrogenation of imines of type **20** with different mododentate phosphoramidite ligands **84**–**85** and [IrCl(cod)]$_2$ (Scheme 41).[90] The reaction could be performed at room temperature, although high hydrogen pressures (200 atm) were required. Several diarylmethylamines **20**, including those with substituents at the *ortho* position, were obtained with excellent *ee* and yield.



Scheme 41.

N,N-ligands: N,N-ligands are commonly used in combination with the {Ir^{III}(Cp*)} (Cp* = 1,2,3,4,5-pentamethylcyclopentadienyl) core, such as, for example, in complexes **86**, **87**, **88**, and **90**. The nitrogenated ligands do not only provide an asymmetric environment, but are also involved in protonation/deprotonation steps. This metal–ligand cooperation is called bifunctional catalysis.[91]

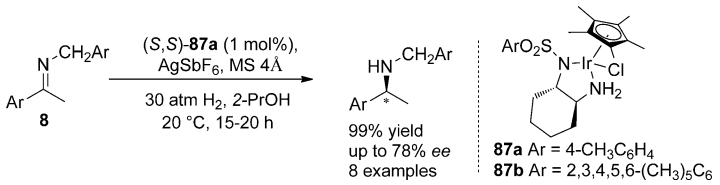
Xu, Fan, and co-workers used diamine-based catalyst **86** in the asymmetric hydrogenation of quinolines with up to 99% *ee* (Scheme 42).[92] The catalyst is highly air-stable, and the reactions were performed in nondegassed methanol.



Scheme 42.

Catalytic amounts of trifluoroacetic acid (TFA) are necessary to obtain high activity.

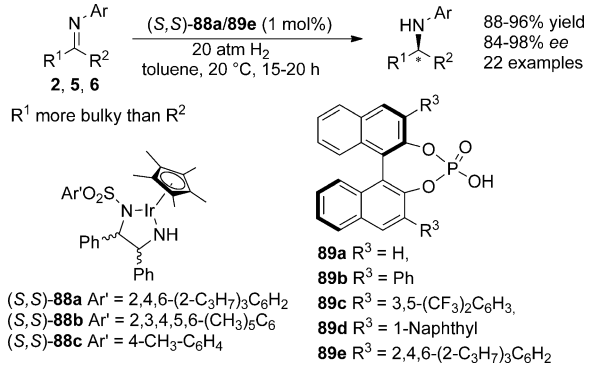
In 2009, Ikariya and co-workers reported the hydrogenation of imines **8** with metal–ligand-bifunctional[91] Ir catalysts **87a**–**b**, bearing *N*-toluenesulfonyl-(1*S*,2*S*)-1,2-diaminocyclohexane (TsCYDN) ligands (Scheme 43).[93] Up to 78% *ee*



Scheme 43.

could be obtained with (*S*,*S*)-TsCYDN (**87a**). Addition of $AgSbF_6$ significantly enhanced the catalytic activity and selectivity. The silver additives were thought to have a dual role, catalyst activators and Lewis acids.

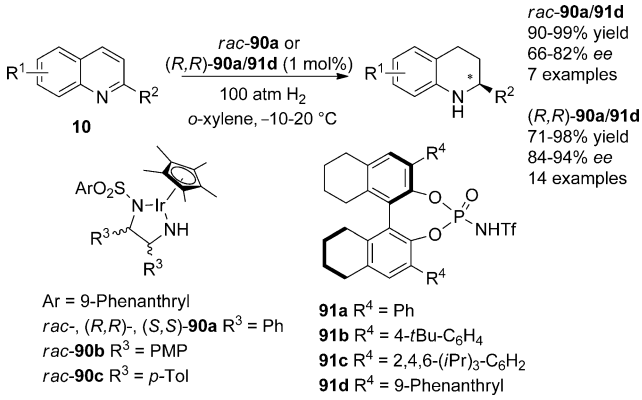
Xiao reported the use of a chiral {Ir^{III}(Cp*)} catalyst precursor (**88**) in combination with chiral phosphate anions **89** (Scheme 44).[94] The role of the chiral anion was to form an



Scheme 44.

iminium salt and thus direct the enantiodiscrimination in the facial attack of the Ir hydride. The active catalyst was generated in situ from the 16e-Ir precursor **88** and the corresponding phosphoric acid **89**. It was shown that the chirality of the counter ion had to match the chirality of the catalyst precursor. Only Ir catalysts bearing a (*S*,*S*)-diamine ligand combined with **89** gave excellent enantioselectivities (up to 99% *ee* when the reactions are performed at 10°C). This protocol allowed the hydrogenation of *N*-aryl ketimines **6** with *ee* values of 90–98%. These imines are considered to be very difficult substrates, hardly ever giving more than 80% *ee*.

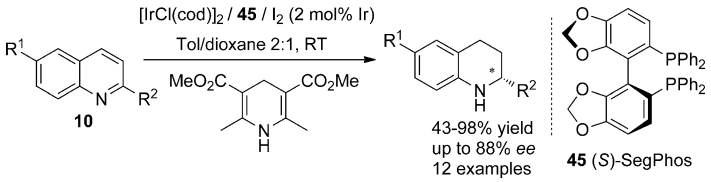
Rueping and Koenigs applied a similar methodology in the reduction of quinolines (**10**; Scheme 45).[95] Combination of racemic diamine-derived Ir^{III} complexes (**90**) with chiral *N*-trifrylphosphoramides (**91**) afforded enantioselectivities



Scheme 45.

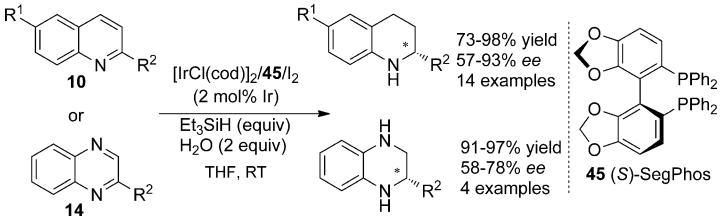
up to 82%. When the enantiopure ligand was used, the enantioselectivities obtained in the matched case, (*R*,*R*)-**90** with *N*-triflylphosphoramide (**91d**), were higher (up to 94% *ee*).

Asymmetric imine transfer hydrogenation: Iridium-catalyzed asymmetric transfer hydrogenation of imines is still a highly underdeveloped area of research compared to the large amount of existing reports using ruthenium-based catalytic systems. In 2007, the group of Zhou reported the ATH of quinolines with the $[IrCl(cod)]_2$/SegPhos(**45**)/I_2 system and the Hantzsch ester as a hydrogen source (Scheme 46).[96] The system worked under mild conditions and good enentioselectivities (up to 88% *ee*) were obtained.



Scheme 46.

Water/silane was applied as the hydride source using $[IrCl(cod)]_2$/SegPhos(**45**)/I_2 as the catalyst system to hydrogenate quinolines and quinoxalines (Scheme 47).[97] High enantioselectivities (up to 93% *ee*) were obtained for most substrates. Similar to previous protocols,[42] the methodology could be applied in the synthesis of alkaloids and certain chiral drugs.

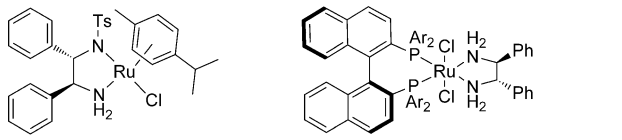


Scheme 47.

Iridium-Catalyzed Asymmetric Hydrogenation and Transfer Hydrogenation of Ketones

Transition-metal-catalyzed ATH and AH of ketones have been the subject of intense research in the last two decades and a vast number of catalytic systems that are able to produce chiral alcohols with high enantiomeric excess have been reported.[3] Much effort has been devoted to the design and synthesis of ligands and the catalytic efficiency has been evaluated, in particular, with Ru, Rh, Ir, and recently also Fe complexes.[98]

In 1995, Noyori, Ikariya, and co-workers reported the first example of what has become the most notable type of catalysts used in the ATH of ketones: Ruthenium complexes with monotosylated diamines, such as [Ru(Cl)(*p*-cymene)TsDPEN] (TsDPEN = *N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine, Figure 1, left) were able to reduce



[RuCl(*p*-cymene){(*S,S*)-TsDPEN}] [RuCl$_2$){(*S*)-BINAP}{(*S,S*)-dpen}] Ar = Ph

Figure 1. Ruthenium complexes with diamines ligands.

simple ketones into chiral alcohols with exceptional efficiency.[99] This result triggered deep mechanistic investigations into what has become known as "metal–ligand bifunctional catalysis".[3g,91] With these systems, the substrate is reduced by the concerted delivery of a hydridic H from the metal and a protic H from the amino functionality of the ligand. The high enantioselectivity obtained spurred the development of numerous related catalysts containing a N–H functionality, including the iridium-based complexes that will be discussed in this chapter.

The first highly selective and useful examples of AH of carbonyl compounds were the ruthenium–BINAP catalysts reported by Noyori and co-workers in the 1980s.[3d,e,100] In particular, the discovery of ruthenium(II)-BINAP/1,2-diamine complexes (Figure 1, right) as homogenous catalysts in the enantioselective reduction of simple aromatic ketones in 1995 represented a major breakthrough.[101] The high levels of enantioselectivity, chemoselectivity, and high TOF's and TON's observed with this and related complexes may arise from an efficient metal–ligand bifunctional mechanism as well as synergistic effects between the chiral diphosphine and diamine ligands.[3b,d,e,102] These types of catalysts have found applications in industrial processes as a result of the outstanding performance for a great variety of substrates.[103] The importance of this transformation was recognized in 2001 when Noyori was awarded the Nobel Prize for Chemistry, shared with Knowles and Sharpless.[104]

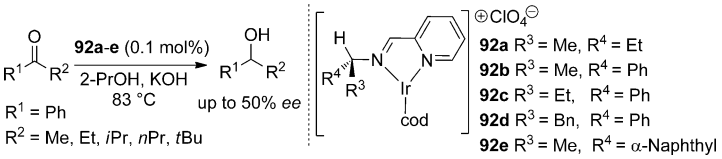
While ruthenium complexes have been undisputedly popular catalysts in ATH[105] and in AH[106] of ketones, iridium-based systems have received more attention in the asymmetric hydrogenation of imines[1] (vide supra) as well as in asymmetric hydrogenations of (unfunctionalized) olefins.[4] Nonetheless, recent developments have demonstrated the great potential of chiral iridium complexes also as catalysts for ketone reductions.[3] As expected, many of the catalytic systems based on iridium have drawn inspiration from ruthenium and rhodium analogues. An array of chiral ligands have been combined with Ir^{I} and Ir^{III} precursors to provide efficient catalysts for both ATH and AH of ketones.

The first part of the chapter focuses on Ir-catalyzed ATH. Early reports mainly described Ir^{I} complexes with diphosphines or amine/imine ligands and afforded poor to moderate selectivities. From the mid 1990s, 1,2-diamine ligands have been extensively used and, in particular, their combination with [Ir^{III}(Cp*)L_n] complexes has been successful. Hydrogen donors are either 2-PrOH, formate salts, or formic acid; however, the formic acid/triethylamine azeotrope has rarely been efficient with Ir catalysts. In general, most systems require the addition of catalytic amounts of base, although there exist a few examples in which base is not needed.

The last part of the chapter reviews Ir-catalyzed AH with molecular hydrogen. Similar to ATH, most catalysts are based on neutral or cationic Ir^{I} precursors, or Ir^{III} complexes containing the Cp* ligand. Diphosphines, diamines, and mixed bidentate ligands are commonly used. Hydrogen pressures between 4–6 atmospheres are reported, although most systems require significantly higher pressures to obtain high activities. Selected examples from early contributions to the latest achievements are discussed.[3]

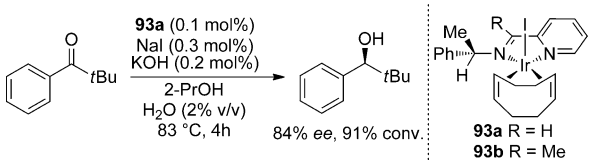
Iridium-catalyzed asymmetric transfer hydrogenation of ketones

Early reports: The first example of iridium-catalyzed TH (transfer hydrogenation) was reported already in 1967 by Henbest.[107] It took several more years for the first ATH reports using iridium catalysis to appear. An early example was reported by Zassinovich, Mestroni, and co-workers, who described the ATH of aryl alkyl ketones with cationic Ir^{I} perchlorate complexes with chelating pyridinimines (**92a–e**) in 2-PrOH/KOH (Scheme 48).[108,109] Overall, the catalytic activities were good; conversions over 90% were reached within 1–5 h when using 0.1 mol% of Ir. However, enantioselectivities were quite modest; optical yields of up to 41.5% for propiophenone and 50% for *tert*-butyl phenyl ketone were obtained. The enantioselectivity was improved a few years later when the corresponding penta-coordinated iridium iodide complexes **93a–b** were used instead



Scheme 48.

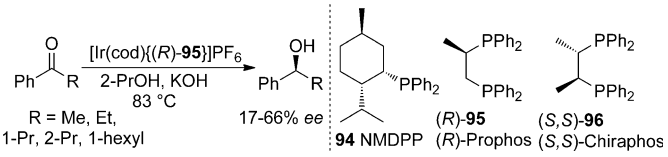
(Scheme 49).[110] The highest enantioselectivities were reached in the presence of water (1% v/v) and NaI ([NaI]/**93a** = 3), which minimized the formation of undesired spe-



Scheme 49.

cies by dissociation of iodide from **93a**. With this method, *tert*-butyl phenyl ketone was reduced to the corresponding alcohol with an *ee* of 84 and 91% conversion (Scheme 49). Sterically less hindered aryl alkyl ketones were reduced with significantly lower selectivities (e.g., 36% *ee* for acetophenone).

Graziani and co-workers used Ir^I complexes with phosphine ligands, such as neomenthyl diphenylphosphine (NMDPP, **94**), (*R*)-Prophos ((*R*)-**95**), and (*S*,*S*)-Chiraphos ((*S*,*S*)-**96**).[111,112] Among the complexes tested, the best results were obtained with [Ir(cod)(Prophos)]PF_6, which afforded optical yields of up to 66% in the ATH of propiophenone in 2-PrOH/KOH (aq) (Scheme 50). The enantiose-

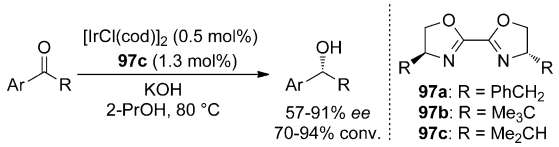


Scheme 50.

lectivities were strongly influenced by the conditions used for catalyst activation; for example, variation of the time allowed for the active catalyst to form from [Ir{(*S*,*S*)-Chiraphos}(cod)]PF_6/KOH could even alter the absolute configuration of the product from (*S*)- to (*R*)-phenyl ethanol (albeit in low *ee*).

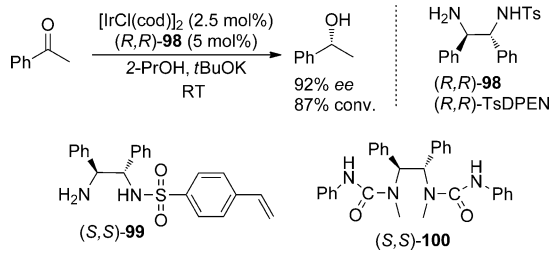
Other early reports (prior to 1990) in which bidentate ligands have been used with Ir afforded moderate to low enantioselectivities. For instance, in the reduction of acetophenone, Ir^I–phosphinite complexes formed in situ from (2*R*,4*R*)-2,4-bis(diphenylphosphinoxy)pentane, $[IrCl_2(cod)]_2$, and NaOMe afforded up to 18% *ee* at 85% conversion,[113] and NMDPP (**94**) with [Ir(acac)(cod)] (acac = acetylacetone) a maximum of 42% *ee* at 87% conversion in refluxing 2-PrOH with NaOH.[114]

N,N-ligands: Bi(2-oxazoline) and amine–oxazoline ligands have been employed in iridium-catalyzed ATH with moderate to good success.[115,116] Notably, in 1991 Pfaltz reported the first highly successful example of Ir-catalyzed ATH; C_2-symmetrical Ir^I–bi(2-oxazoline) complexes prepared in situ from $[IrCl_2(cod)]_2$ and ligands **97a–c** yielded alkyl aryl alcohols in up to 91% *ee* (Scheme 51).[115]



Scheme 51.

The introduction of the bifunctional Ru–TsDPEN[99] catalyst in 1995 marked a significant breakthrough in ATH. In response, numerous related [Ir(Cp*)$(L)_n$] complexes have been reported and various ethylenediamine ligands have been combined with other Ir^I and Ir^{III} sources. For instance, Lemaire used a catalyst formed in situ from TsDPEN (**98**) and $[IrCl(cod)]_2$ in 2-PrOH/*t*BuOK to reduce acetophenone with an *ee* of 92% (87% conv.) after one day at room temperature (Scheme 52).[117] The analogous heterogenized ver-

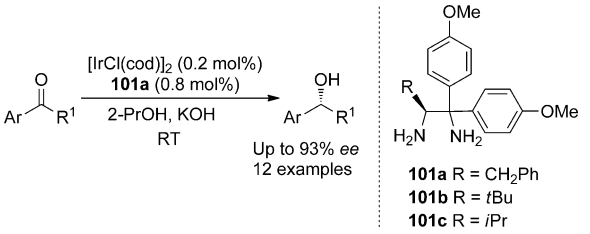


Scheme 52.

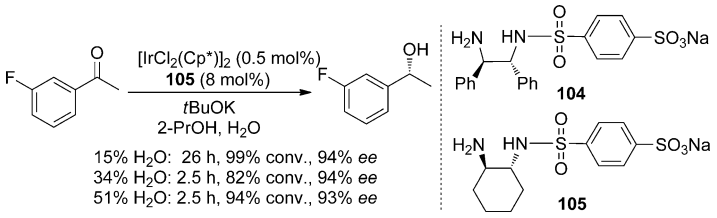
sion, in which (1*S*,2*S*)-*N*-(styrene-*p*-sulfonyl)-1,2-diphenylethylenediamine ((*S*,*S*)-**99**) was incorporated in a polymeric matrix, afforded similar enantioselectivity (94% *ee*), but the reactions were slower (96% conv. after three days) and recycling was unsuccessful.[118] The same group used the diurea ligand (*S*,*S*)-**100** with $[MCl(cod)]_2$ (M = Rh, Ir). Although, *ee* values up to 80% were obtained with rhodium, and even higher (95% *ee*) in the case of a heterogeneous polyurea–rhodium catalyst, the maximum *ee* obtained with iridium in the reduction of acetophenone was 57% (Scheme 52).[119,120] Also heterogenized dialdimines afforded modest results and poor recyclability.[121]

Inoue and co-workers found that Ir^I complexes prepared in situ from $[IrCl(cod)]_2$ and 1,1-di(*p*-anisyl)ethylenediamine derivatives **101a–c** are efficient catalysts for ATH of alkyl aryl ketones at room temperature in 2-PrOH/NaOH (Scheme 53).[122] The benzyl derivative **101a** afforded the best results; several substrates were reduced with overall high enantioselectivities and yields (71–93% *ee*, 79–97% yield). Exceptions were 4-methoxyacetophenone and 3-nitroacetophenone, which afforded low yield or enantioselectivity, respectively.

Ikariya and co-workers prepared the [IrCl(Cp*)(diamine)] complexes **102–103** (diamine = TsDPEN, TsCYDN) and

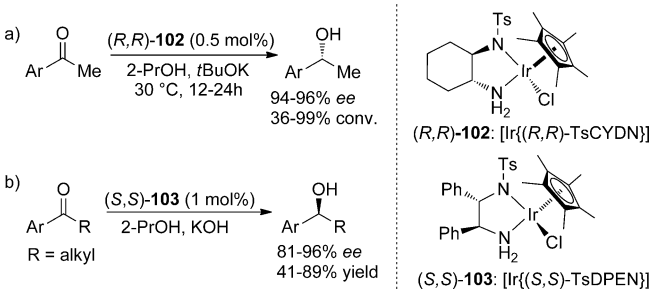


Scheme 53.



Scheme 55.

evaluated their use as catalysts in ATH in 2-PrOH/*t*BuOK (Scheme 54a).[123] Ir–(*R*,*R*)-TsCYDN ((*R*,*R*)-**102**) performed better than Ir–(*R*,*R*)-TsDPEN ((*R*,*R*)-**103**), reducing aceto-

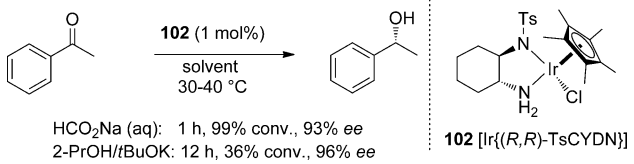


Scheme 54.

phenone with an enantiomeric excess of 96% (36% conv.) and 3-(trifluoromethylphenyl)acetophenone with an *ee* of 94% (99% conv.). Overall, the catalytic performance of (*R*,*R*)-**102** and (*R*,*R*)-**103** were slightly inferior to that of their rhodium analogues. Simultaneously, Mashima, Tani, and co-workers reported the preparation of Ir–(*S*,*S*)-TsDPEN ((*S*,*S*)-**103**).[124,125] Aryl alkyl ketones were reduced with high enantioselectivity (88–96% *ee*, 41–89% yield) in 2-PrOH/KOH (aq). Similar to the findings of Ikariya, the highest enantioselectivities were obtained with the corresponding rhodium catalysts (Scheme 54b).

Several groups have studied ATH in water or aqueous mixtures, and in some instances in the presence of surfactants. Both hydrophilic ligands (e.g., sulphonated ligands) and nonmodified ligands and complexes have been used. In some examples, using water as a solvent or co-solvent has led to a noticeable increase of reaction rates. Williams and co-workers used complexes formed in situ from $[IrCl_2(Cp^*)]_2$ and water-soluble *para*-sulfonated analogues of TsDPEN (**104**) and TsCYDN (**105**) with *t*BuOK in 2-PrOH/H_2O (Scheme 55).[126] The amount of water in the solvent mixture affected both the transfer hydrogenation rate (26 h with 15% v/v of water vs. 2.5 h with 51% v/v, Scheme 55) and in the case of ligand **104**, a higher water concentration had a positive influence on the enantioselectivities. The overall best enantioselectivities were obtained with **105**, which afforded 94–97% *ee* in the ATH of various aryl alkyl ketones, although electron-rich ketones required long reaction times (>100 h) even with the highest water content.

Xiao and co-workers also observed significantly higher reaction rates with [IrCl(Cp*){(*R*,*R*)-TsCYDN}] (**102**) in aqueous HCO_2Na relative to when isopropanol or azeotropic HCO_2H/NEt_3 mixtures were used (Scheme 56).[127] The cata-



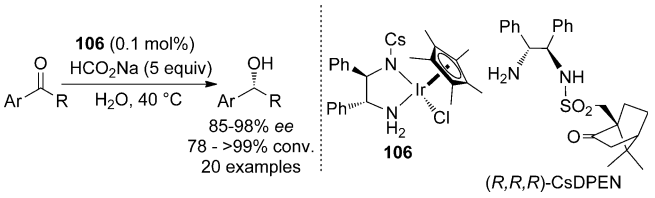
Scheme 56.

lyst was completely tolerant to aerobic conditions, and afforded (*R*)-1-phenylethanol with an *ee* of 93% and with 99% conversion within 1 h. In terms of activity and enantioselectivity, **102** was better than [Ru(Cl)(*p*-cymene)-(TsCYDN)] (c.f. 85% *ee*, 2 h), but it was less active than the analogous Rh-based complex (c.f. 95% *ee*, 15 min).

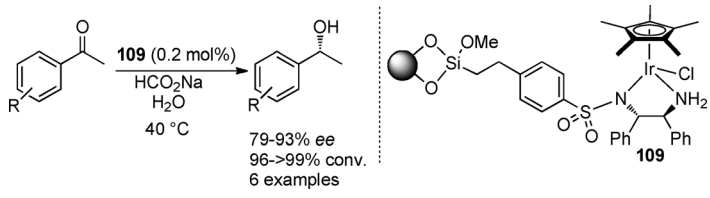
Likewise, higher reaction rates and improved enantioselectivities were found when [IrCl(Cp*){(*R*,*R*)-TsDPEN}] (**103**) was used in aqueous HCO_2Na (93% *ee*, 99% conv. in 3 h for acetophenone) rather than in 2-PrOH/KOH (87% *ee*, 48% conv. in 24 h).[128] Moreover, and in contrast to the related [RuCl(*p*-cymene)(TsDPEN)], the activity of the iridium catalyst was completely inhibited in the HCO_2H/NEt_3 azeotrope. The rate of reduction was strongly pH dependent, with the highest TOF's achieved within a 2-unit window around pH 7.5. Deng, Zhu, and co-workers used [IrCl(Cp*)(TsDPEN)] (**103**) together with surfactants SDS (sodium dodecyl sulfate) and CTAB (cetrimonium bromide) in water to achieve reduction of α-bromoacetophenone with up to 97% *ee*.[129]

The camphor sulfonyl 1,2-diphenylethylendiamine ligand (CsDPEN) has been used for ATH of aromatic ketones in water. With [IrCl(Cp*){(*R*,*R*,*R*)-CsDPEN}] (**106**) and HCO_2Na, aromatic ketones were reduced with high enantiomeric excess and conversions (85–97% *ee*, 78–99% conv.; Scheme 57).[130] The iridium-based catalyst was not sensitive to air, and displayed considerably higher activity than either Rh or Ru analogues.

Carreira and co-workers have employed a number of [Ir^{III}(aqua)(Cp*)] complexes in the ATH of α-cyano and α-nitro ketones. In particular, it was found that the use of electron-poor ligands enhanced the enantioselectivity and the catalytic activity; with complex **107** bearing a perfluorinated

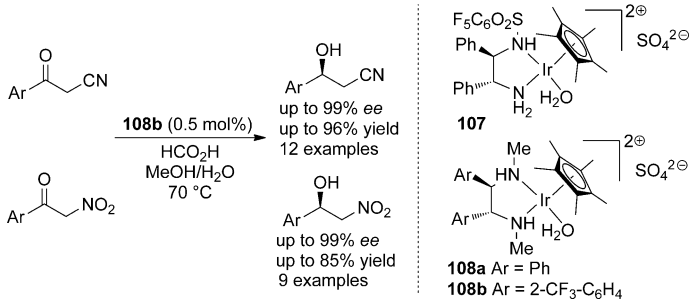


Scheme 57.



Scheme 59.

sulphonylamide, 2-cyanoacetophenone was reduced with an *ee* of 94% (c.f. with TsDPEN 84% *ee*; Scheme 58).[131] Moreover, iridium–aqua complexes with nonsulfonylated

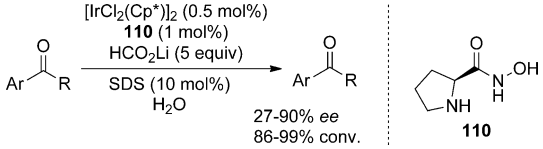


Scheme 58.

electron-poor diamines were excellent catalysts: with Ir–(*R*,*R*)-Me-CF_3-DPEN **108b**, a range of α-cyano and α-nitro acetophenones were reduced in overall very high yields and enantioselectivities (up to >99% *ee* and 96% yield; Scheme 58).[132] Especially, high *ee* values (99%) were observed with *o*-substituted substrates. The high stability of the Ir complexes towards air and moisture enabled the reactions to be run in water/methanol mixtures (1:1) under air at 70°C. The highest activity (and maintained enantioselectivity) was observed in acidic media (pH 2) when using HCO_2H rather than HCO_2Na as the hydride source.

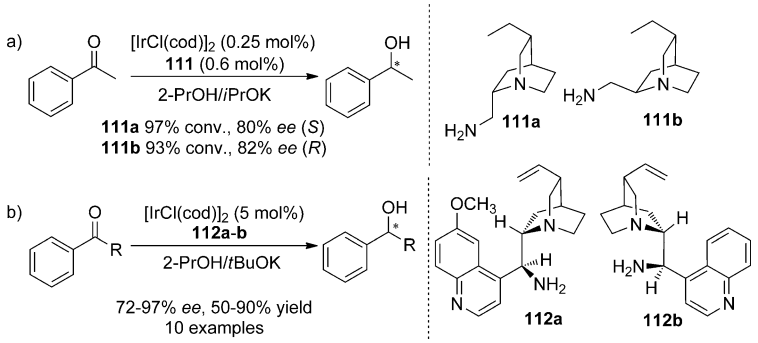
Liu, Li, and co-workers used a [IrCl(Cp*)(TsDPEN)] derivative immobilized onto silica-coated magnetic Fe_3O_4 nanoparticles (**109**).[133] The catalyst was employed in aqueous ATH of acetophenones with HCO_2Na (Scheme 59). Electron-rich and electron poor substrates were reduced with high selectivity (79–93% *ee*, 96–99% conv.). After the reaction, the recovered particles (with a magnet) catalyzed the reaction with minor decreases in enantioselectivity and activity after ten runs.

Adolfsson and co-workers have prepared a large library of amino acid derived ligands for ATH. For instance, the proline-based hydroxamic acid **110** and $[IrCl_2(Cp^*)]_2$ afforded up to 90% *ee* and 99% conversion in the reduction of acetophenones with HCO_2Li as the hydrogen source (Scheme 60).[134]



Scheme 60.

A number of cinchona alkaloid derived ligands have been tested and good to excellent enantioselectivities were obtained. Arvidsson and co-workers used ligands **111a–b** with $[IrCl(cod)]_2$ in 2-PrOH/2-PrOK to reduce aromatic ketones in 75–95% *ee* and with opposite enantioselectivity (Scheme 61a).[135]

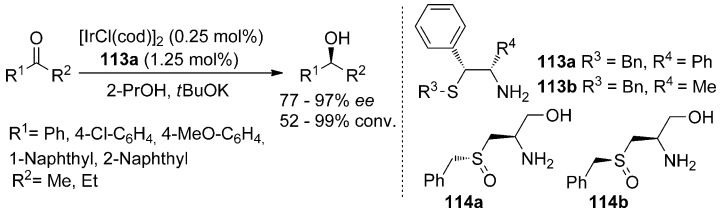


Scheme 61.

Quinine and cinchonine-derived ligands **112a** and **112b** in combination with $[IrCl(cod)]_2$ afforded chiral alcohols with opposite configuration and with good to excellent enantioselectivities (72–97% *ee*) in 2-PrOH/KOH (Scheme 61b).[136,137] Slightly better results were obtained with $[IrCl(cod)]_2$ than with $[RhCl(cod)]_2$. High catalyst loadings were required, but the catalyst could be recovered by acidic extraction through formation of its hydrochloric adduct, and recycled up to five times without loss in enantioselectivity (94–95% *ee*).

N,S-, N,O-, P,N-, and tetradentate ligands: Van Leeuwen and co-workers have synthesized a series of N,S-chelating amino-

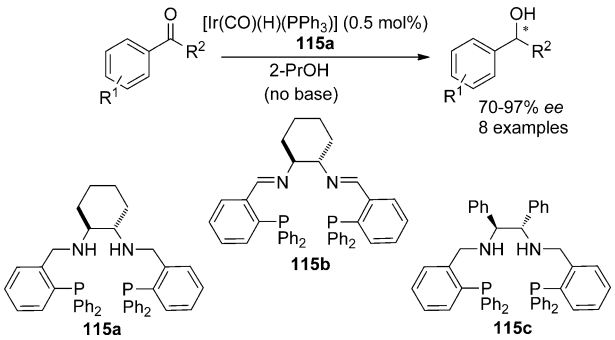
sulfide (**113**) and aminosulfoxide ligands (**114**) (Scheme 62).[138,139] Variation of the substituents in **113** strongly affected the catalytic performance, and after signifi-



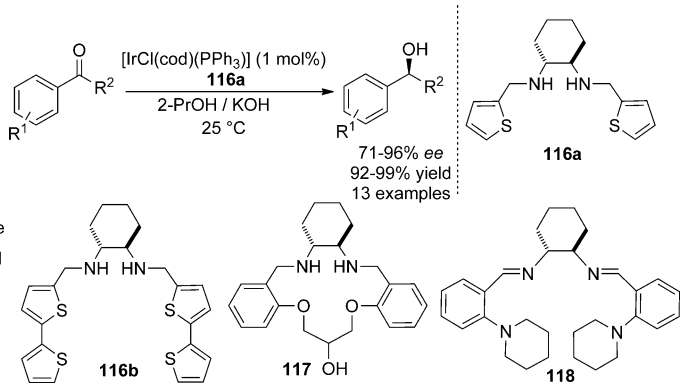
Scheme 62.

cant screening, **113a**/$[IrCl(cod)]_2$ was found to give the highest enantioselectivities (up to 97%) in 2-PrOH. When used in HCO_2H/NEt_3 azeotrope, the opposite enantiomer was obtained (56% *ee*), but only in 2% yield. In contrast, **113b** afforded better results in HCO_2H/NEt_3 (up to 79% *ee*, >99% conv.) The diastereomeric aminosulfoxides **114a** and **114b** afforded 66% *ee* of the (*S*)- (99% conv., 0.5 h) and 27% *ee* of the (*R*)-enantiomer (56% conv., 1 h), respectively, in the ATH of acetophenone in HCO_2H/NEt_3 azeotrope.

Gao and co-workers have used a series of tetradentate XNNX (X=P, N, O, or S) mixed donor ligands in Ir-catalyzed ATH. The best results were obtained with PNNP ligands **115a–c** together with $[IrCl(cod)]_2$, $[Ir(CO)(H)(PPh_3)]$, or $[IrCl_2(cod)(H)]_2$ (Scheme 63).[140–142] For example, with **115a**/$[IrCl_2(cod)(H)]_2$, 1,1-diphenylacetone was reduced in 2-PrOH under base-free conditions with an *ee* of 99% using a S/C ratio as high as 10000.[141] The use of a phase-transfer catalyst, or introduction of sodium sulfonate groups in the ligands, enabled the system to operate in H_2O/2-PrOH mixtures.[143,144] With the diamino[bis(thiophene)] ligand **116a**/$[IrCl(cod)(PPh_3)]$, a range of aryl alkyl ketones were reduced with 71–95% *ee* at room temperature, in 2-PrOH, and under an air atmosphere (Scheme 64).[145] Iridium complexes of related diamino[bis(bithiophene)]-substituted ligand **116b**,[146] macrocyclic ligand **117**,[147] and tetraaza ligand **118**[148] afforded good enantioselectivities (up to 90–91% *ee*). In all cases, ligands **116–118** performed worse with Rh or Ru catalyst precursors than with Ir.

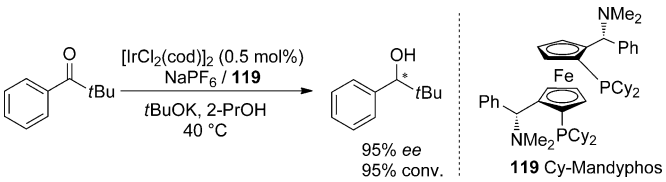


Scheme 63.



Scheme 64.

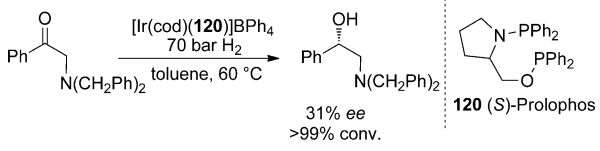
Cationic iridium complexes formed from $[IrCl(cod)]_2$, $NaPF_6$, and Cy-Mandyphos (**119**) were found to be selective, particularly for the reduction of sterically hindered ketones (Scheme 65).[149] The highest enantioselectivity was obtained in the reduction of *tert*-butyl phenyl ketone (95% *ee*, 95% conv.).



Scheme 65.

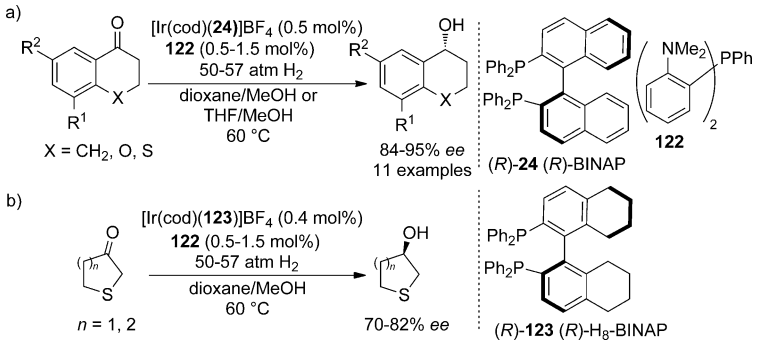
Asymmetric ketone hydrogenation

P,P-, P,N-, and P,S-ligands: In 1989, Graziani and co-workers reported that cationic Ir complexes with chelating diphosphines, such as Prolophos ((*S*)-**120**) were active in the enantioselective reduction of benzylideneacetone and α-aminoketones. Enantioselectivities were low (up to 31% *ee*) and the reactions were run at high H_2 pressure (70 bar; Scheme 66).[150,151]



Scheme 66.

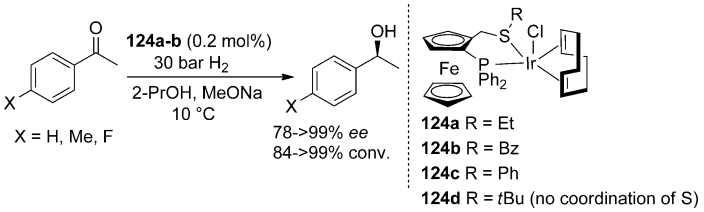
A few years later, Takaya and co-workers found that the reduction of five- and six-membered 1,2-benzocycloalkanones proceeded with 84–95% *ee* when [Ir{(*R*)-binap}(cod)]BF_4 was used together with the achiral tertiary P,N-donor ligand (bis(*o*-(*N*,*N*-dimethylamino)phenyl)phenylphosphine) **122** (Scheme 67a).[152] The same Ir source selectively reduced β-thiacycloalkanones to the corresponding al-



Scheme 67.

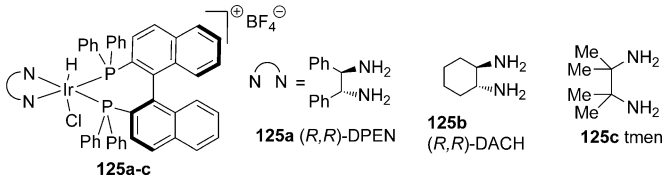
cohols with up to 82% *ee* when (*R*)-H_8-BINAP ((*R*)-**123**) was used (Scheme 67b).

A series of Ir complexes **124a–d** with planar chiral P,S-ferrocenyl ligands were prepared by Peruzzini, Manoury, and co-workers and used in the ATH of acetophenones with up to >99% *ee* in 2-PrOH/MeONa (Scheme 68).[153] Hydrogenation originating from H_2 (rather than a transfer hydrogenation pathway) was supported by high conversions also when toluene was used as the solvent (in the absence of 2-PrOH), and lower conversions at reduced H_2 pressure.



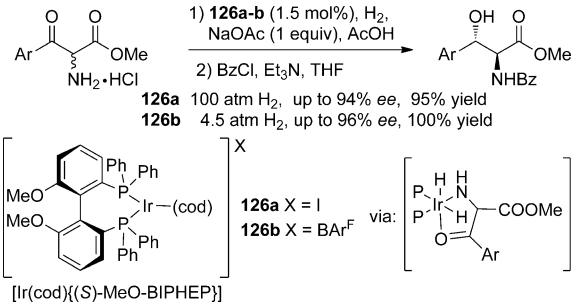
Scheme 68.

Dalenburgh and co-workers have prepared a large number of iridium complexes bearing N,N- and P,P-ligands (**125a–c**, Scheme 69).[154,155] The best enantioselectivity was obtained with the Ir chloro hydride **125a** (N,N = (*R*,*R*)-DPEN and P,P = (*R*)-BINAP), either preformed or generated in situ, which afforded (*S*)-phenylethanol with *ee* values of 82–84% at low catalyst loadings (0.2 mol%) under 20 bars of H_2 in methanol. Also in this case, the authors were able to exclude a catalytic cycle through transfer hydrogenation conditions by using D_2 instead of H_2. Only minor loss of enantioselectivity was observed on substitution of (*R*,*R*)-DPEN for (*rac*)-DPEN, which indicated that (*R*)-BINAP is the ligand with a larger influence on the induced enantioselectivity.



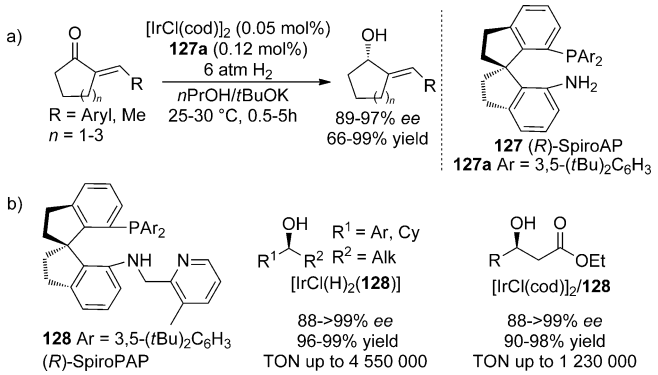
Scheme 69.

The Ir-(*S*)-MeO-BIPHEP iodide complex **126a** has been used by Hamada and co-workers in a highly *anti*-selective and asymmetric hydrogenation of aromatic α-amino-β-keto ester hydrochlorides through DKR (Scheme 70).[156] Base and iodide additives strongly affected both the enantioselectivity and the reactivity, and the best system was obtained with a catalyst prepared from $[IrCl(cod)]_2$, MeO-BIPHEP, NaOAc, and NaI. Aromatic substrates were reduced with 75–95% *ee*, and in most cases with a diastereomeric ratio of >99:1 in AcOH under high H_2 pressure (100 atm). A second generation catalyst **126b** with BAr^F as the counterion turned out to be significantly more active at low H_2 pressure (4.5 atm), and yielded better results also in terms of enantioselectivity.[157,158] Mechanistic studies indicated the reduction of the substrate took place through the keto tautomer coordinated to iridium in a five-membered cyclic intermediate.



Scheme 70.

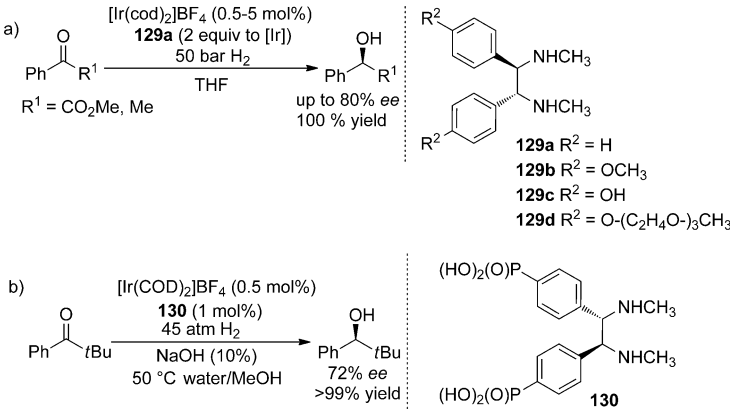
Recently, the group of Zhou reported the use of highly active complexes formed in situ from $[IrCl(cod)]_2$ and spiro aminophosphine ligand **127** (SpiroAP) in a very selective hydrogenation of exocyclic aliphatic α,β-unsaturated ketones and aromatic ketones.[159–161] (*E*)-α-Arylmethylene cycloalkanones were reduced to the corresponding allylic alcohols under 6 atm of H_2 in 1-PrOH with overall excellent enantioselectivities and yields (i.e., 89–97% *ee*, 95–99% yield; Scheme 71a). Excellent reactivity was also observed with aromatic ketones (up to 97% *ee* and >99% yield) at catalyst loadings down to 0.01 mol%.[160] Catalyst deactivation pathways were attributed to the formation of an inactive Ir dihydride species containing two coordinated SpiroAP ligands. An improved catalytic system, in which the generation of such species is suppressed, was obtained through modification of the catalyst into a tridentate spiro P,N,N-ligand with a pendant pyridine group (SpiroPAP, **128**; Scheme 71b). With this new ligand, an exceptionally active



Scheme 71.

and more enantioselective system formed, which afforded 1-phenylethanol in a quantitative yield at room temperature in 30 h with an *ee* of 98% under 50–20 atm of H_2 by using a S/C = 1000000. The lowest catalyst loading (S/C = 5000000) produced the same enantioselectivity at 91% conversion in 15 days under 100–60 atm of H_2. In addition to aromatic ketones, also β-aryl-β-ketoesters were reduced with very high TON's and with 95 to >99% *ee*.[162]

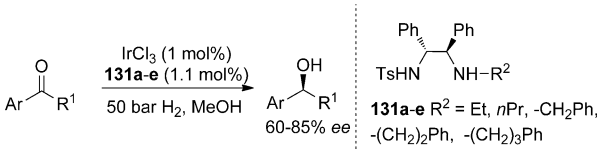
N,N-ligands: Lemaire and co-workers have combined several C_2-symmetrical diamines **129a–d** with Ir^I precursors in asymmetric hydrogenation. $[Ir(cod)_2]BF_4$/**129a** afforded moderate enantioselectivities in the reduction of methylbenzoylformate (up to 80% *ee*) and acetophenone (up to 63% *ee*; Scheme 72a).[163,164] With hydrophilic diamines



Scheme 72.

129b–d and $[Ir(cod)_2]BF_4$, (*S*)-phenyl ethanol was obtained with an *ee* of 68%, and the catalyst could be recycled from MeOH/water mixtures if methoxytriethylene glycol was used as an additive for catalyst recovery. Bujoli and co-workers used the related water-soluble PO_3H_2-functionalized diamine **130** under similar conditions and obtained up to 72% *ee* in the reduction of *tert*-butylphenyl ketone (Scheme 72b).[165]

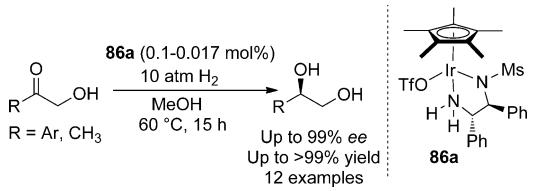
With the aim of using simple metal salts as catalyst precursors, Wills and co-workers screened a large number of 1,2-diphenyl-ethylene diamines with $IrCl_3$. The best results were obtained with N-alkylated Ts-DPEN ligands **131a–e**, which reduced aryl alkyl ketones into the corresponding alcohols with moderate to good enantioselectivities (Scheme 73).[166,167] Interestingly, $IrCl_3$ was fully selective for



Scheme 73.

ketone reduction, whereas the use of the corresponding Ru^{III} or Rh^{III} chlorides resulted in concomitant arene reduction to some extent.

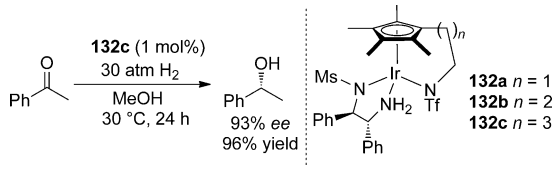
Iridium complexes ([Ir(Cp*)(L)]) with diamine ligands have been used not only in ATH, but also in AH. Thus, complexes with labile counter ions (e.g., OTf) have been used under non-basic conditions in alcoholic solvents, to alter the catalytic activity from transfer hydrogenation to hydrogenation.[106l,168] Ohkuma and co-workers used the iridium triflate complex [Ir(Cp*){(*S*,*S*)-MsDPEN}(OTf)] (**86a**) in a highly enantioselective hydrogenation of α-hydroxy aromatic ketones at catalyst loadings down to 0.017 mol% (S/C = 6000) under 10 atm H_2 (Scheme 74).[169] In addition to



Scheme 74.

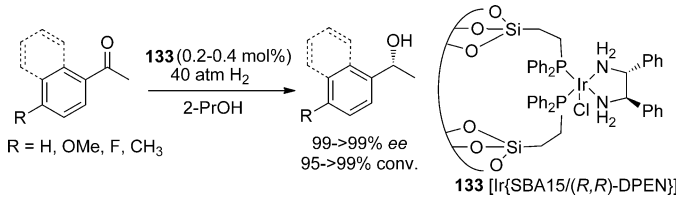
aromatic ketones, reduction of aliphatic 1-hydroxy-2-propanone afforded (*R*)-1,2-propanediol with an *ee* of 80% in 97% yield. The mesityl substituent in **86a** is important for the catalyst performance; hence, substitution of (*S*,*S*)-MsDPEN for (*S*,*S*)-TsDPEN resulted in decreased conversions, together with lower *ee* values.

Trifylamide-tethered $[Ir^{III}(Cp^*)(MsDPEN)]$ complexes **132a–c** were synthesized by Ikariya and co-workers and studied for the hydrogenation of acetophenone (Scheme 75).[170] The effect of the (NTf)-tether was to switch the catalytic activity from transfer hydrogenation to hydrogenation, by suppressing alcohol dehydrogenation and instead promote heterolytic cleavage of hydrogen, as previously observed for the corresponding [Ru(arene)(TsDPEN)] analogues.[106j] Complex **132c** with four carbon atoms in the tether displayed the overall best reactivity (93% *ee*, 96% yield).



Scheme 75.

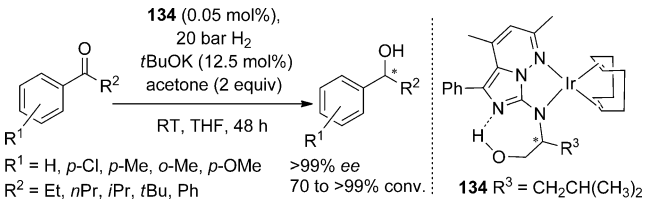
Liu, Li, and co-workers prepared a highly enantioselective silica-supported catalyst. The Ir–(*R*,*R*)-DPEN catalyst **133** was grafted onto mesopourous SBA-15 silica via silanol-linked phosphines (Scheme 76).[171] Excellent *ee* values and conversions were obtained at low catalyst loadings, and the catalyst could be recovered and reused without a significant decrease of *ee*.



Scheme 76.

The [Ir(Cp*)(TsDPEN)] catalyst has been heterogenized onto mesopourous silica and afforded good enantioselectivities (93% *ee* for acetophenone) at 10 atm of H_2.[172] A heterogenous Ir/SiO_2 catalyst prepared from SiO_2, H_2IrCl_6, and PPh_3 and modified with cinchona alkaloid 9-amino-(9-deoxy)epicinchonine has also been used to reduce aromatic ketones in up to 96% *ee*.[173]

Kempe and co-workers recently reported that iridium amido complex **134** is a highly efficient catalyst for the AH of aromatic ketones (Scheme 77).[174] Catalytic activity was



Scheme 77.

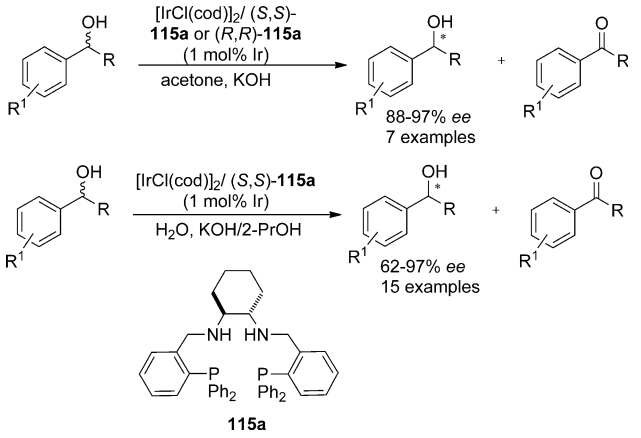
promoted by activation of **134** with *t*BuOK, upon which a catalytically active heterobimetallic potassium–iridium–amido–alkoxy complex formed. Substituted acetophenones, including 2-methylbenzophenone, were hydrogenated with excellent enantioselectivity (>99% *ee*) by using 0.05 mol% Ir at room temperature under 20 bar of H_2. Addition of acetone as a sacrificial nonprochiral ketone was essential to obtain excellent *ee* values, and was rationalized by in situ formation of a more enantioselective catalyst.

Miscellaneous Methods to Prepare Enantioenriched Alcohols and Amines by Iridium-Catalyzed (Temporary) Alcohol Oxidation

In the next section, other methods to prepare enantiopure amines and alcohols that involve transfer hydrogenation are described.[175,176] In some cases, a chiral iridium catalyst is used, whereas in other examples an achiral iridium catalyst is used in combination with a biocatalyst (enzyme).

Iridium-catalyzed oxidative kinetic resolutions of *sec*-alcohols and oxidative desymmetrization of meso diols: Oxidation (dehydrogenation) of *sec*-alcohols can be mediated by transition-metal complexes. In some instances, a hydrogen acceptor, such as acetone is employed. The oxidant may also be molecular oxygen, resulting in the production of water as the sole byproduct. When a chiral transition-metal complex catalyzes the reaction, oxidation of one of the two enantiomers of the racemate may occur preferentially. In the ideal case, this oxidative kinetic resolution process would allow the recovery of 50% of enantiopure remaining *sec*-alcohol.[177–178]

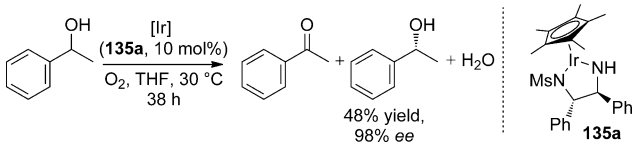
Gao and co-workers used chiral diaminodiphosphine–Ir^I complexes **115a** in the enantioselective oxidation of *sec*-benzylic alcohols in acetone as the solvent and obtained up to 98% *ee* (Scheme 78).[178f] The same Ir catalyst could be applied in the oxidative kinetic resolution of various racemic secondary alcohols in water with up to 97% *ee*.[181]



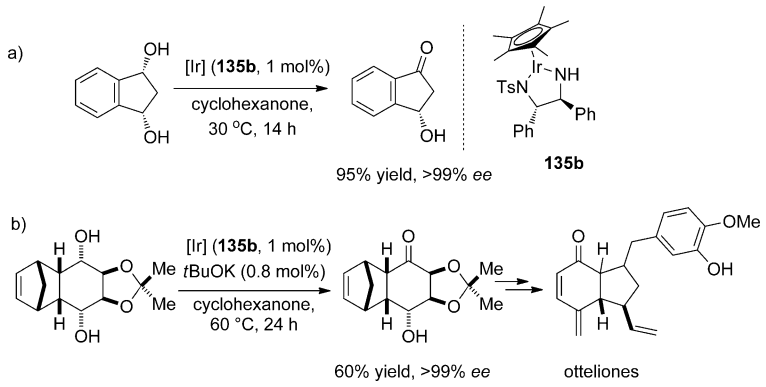
Scheme 78.

Ikariya reported a similar process in which an iridium-catalyzed oxidative kinetic resolution of *sec*-alcohols was achieved by using molecular oxygen and a bifunctional iridium catalyst (**135a**, Scheme 79).[180]

A related process is the oxidative desymmetrization of *meso*-diols.[181] In this case, in the presence of a chiral catalyst, ketoalcohols in up to 100% yield with excellent enantiocontrol can be obtained. An example by the group of Suzuki and co-workers is shown in Scheme 80a, in which desymmetrization of a *meso*-diol is achieved with chiral iridi-

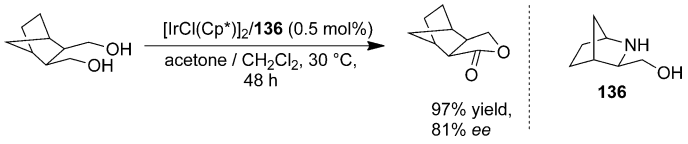


Scheme 79.



Scheme 80. Iridium-catalyzed desymmetrization of *meso*-diols.

um complex **135b** in the presence of cyclohexanone as the hydrogen acceptor.[182a–b] The methodology was used to synthesize a key intermediate in the preparation of otteliones A and B (Scheme 80b).[182b] In some instances, a lactonization occurs after the selective oxidation. For example, oxidative lactonization was achieved when a primary *meso*-diol was treated with an iridium complex formed in situ from $[IrCl(Cp^*)]_2$ and chiral amino alcohol **136**, affording the corresponding lactone with an *ee* of 81% (Scheme 81) in 97% yield.[182c]

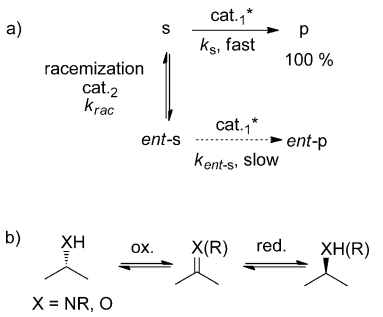


Scheme 81. Iridium-catalyzed oxidative lactonization.

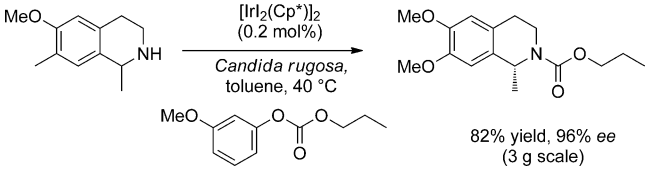
Iridium-catalyzed dynamic kinetic resolution: Kinetic resolution of racemic mixtures is one of the most important methods for the preparation of enantiomerically pure compounds.[183] When biocatalysts (i.e., enzymes) are used, excellent enantioselectivities are generally obtained. An important disadvantage of kinetic resolutions is that a maximum yield of 50% can be obtained. However, this can be overcome by combining the kinetic resolution with a racemization process, in which the enantiomers are interconverted into one another as the kinetic resolution occurs. In this DKR process, a 100% theoretical yield of one enantiomer can be obtained (Scheme 82a).[184] When *sec*-alcohols or amines are used, the racemization occurs by reversible oxidation of these substrates with concomitant formation of transition-metal hydrides (Scheme 82b).

There exist several examples of efficient DKRs for which enzymes and transition-metal catalysts work simultaneously, such as in the synthesis of acetylated secondary alcohols and amines catalyzed by lipases and metal complexes. Ruthenium complexes are to date the most efficient catalysts for this transformation.[185] Iridium complexes, although to a less extent, have also been used as racemization catalysts in enzymatic DKR. Page and co-workers used an Ir^{III} catalyst in combination with *Candida rugosa* in the DKR of cyclic secondary amines (Scheme 83).[186,187]

Saunders, Marr, and co-workers have used *Candida antarctica* lipase B (CALB) and an iridium(III) complex **137** bearing a carbene ligand, in the DKR of *sec*-alcohols. The reaction was performed at 70°C, and the corresponding alcohol



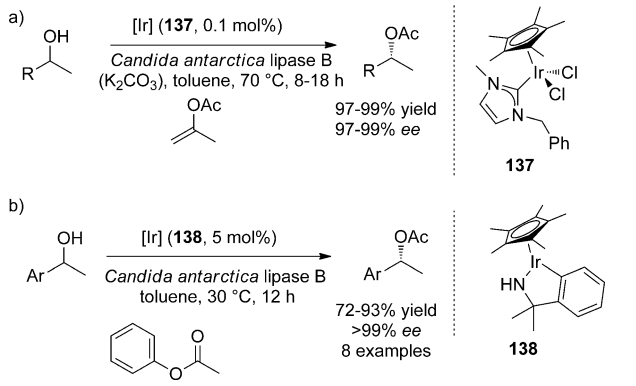
Scheme 82. a) DKR of racemates (s: substrate; p: product; cat.*: chiral catalyst). b) Amine and alcohol racemization mechanism.



Scheme 83. DKR of amines by using an Ir racemization catalyst.

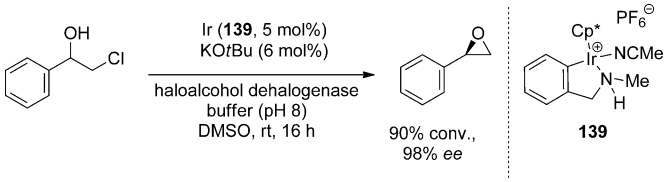
derivatives (acetates) were obtained in quantitative yields with excellent enantioselectivities (>97% *ee*) (Scheme 84a).[188] Recently Ikariya and co-workers reported another system for DKR of secondary alcohols by using bifunctional complex **138** in combination with CALB (Scheme 84b).[189] Unsaturated amido complex **138** could efficiently racemize alcohols under mild and base-free conditions.

Although resulting in the synthesis of chiral epoxides, a similar process combining iridium with enzyme catalysis was reported in 2008 by de Vries, Feringa, and co-workers. The DKR of β-haloalcohols catalyzed by an iridacyle (**139**) and a haloalcohol dehalogenase afforded chiral epoxides in good



Scheme 84. DKR of alcohols by using and Ir racemization catalyst.

yields and enantioselectivities (Scheme 85).[190,191] This process occurs by racemization of the *sec*-alcohol by the achiral Ir complex.



Scheme 85. Combination of an achiral iridium complex (racemization catalyst) with an enzyme (enantioselective epoxidation catalyst).

Summary

The use of iridium complexes in hydrogenations and hydrogen-transfer reactions has emerged as a powerful synthetic tool for the enantioselective preparation of amines and alcohols. Notably, in the asymmetric hydrogenation of imines, iridium complexes have been used ahead of those of other transition metals due to their excellent selectivity and reactivity (mild reaction conditions and hydrogen pressures as low as 1 atm). Thus, the iridium–Xyliphos family reported by Blaser and Spindler, the iridium–PHOX system reported by Pfaltz, and the iridium–f-binaphane system reported by Zhang are among the most successful imine-hydrogenation systems. On the other hand, the majority of transfer hydrogenations of imines use ruthenium catalysts, and only a handful of iridium-catalyzed examples have been reported.

Asymmetric hydrogenation and asymmetric transfer hydrogenation of ketones has historically been dominated by ruthenium and rhodium catalysts. Exceptional high reactivity, broad substrate scope, and excellent selectivity have been achieved with the Noyori family of bifunctional ruthenium complexes in hydrogenations, and with the ruthenium Noyori–Ikariya binfunctional catalysts in transfer hydrogenations. These systems have served as an inspiration in the design of complexes of other transition metals. Nevertheless, significant research on iridium catalysis during the last decade, including the design of new ligands, has resulted in remarkable advances. Thus, *ee* values of >99% can be reached, and high TOF's and TON's are achieved for several systems (particularly in the asymmetric hydrogenation of ketones). Future efforts may focus on using iridium catalysts for the reduction of carbonyls in highly functionalized molecules.

Iridium catalysts (chiral complexes or achiral complexes in combination with other chiral catalysts) have also been successfully used in other miscellaneous processes to synthesize alcohols or amines enantioselectively. These transformations involve a temporary oxidation of the substrates by transferring hydrogen to a transition-metal complex. Examples using iridium catalysts have been scarcer than those using ruthenium or rhodium complexes. There are, however, some unique cases in which the use of iridium catalysis has been essential for efficient transformations. For example, the ability of certain iridium complexes to catalyze alcohol racemizations in aqueous solvents has been pivotal in DKRs with enzymes requiring aqueous reaction media.

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