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BIFUNCTIONAL HOMOGENEOUS CATALYSTS BASED ON RUTHENIUM, RHODIUM AND IRIDIUM IN ASYMMETRIC HYDROGENATION

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List of Abbreviations	3
I. Introduction.....	4
II. Asymmetric transfer hydrogenations using bifunctional catalysts	7
A. Ruthenium catalysed transfer hydrogenations	7
1. Noyori-type catalysts.	7
2. Shvo-type catalysts.	20
B. Rhodium catalysed transfer hydrogenations	22
1. Diamine tethered η^5 -cyclopentadienyl rhodium complexes with active NH functions.	22
2. Aminoacid derived amides and thioamides with active NH functions.	23
C. Iridium catalysed transfer hydrogenations	26
1. Amino and amido iridium(III) catalysts.	26
2. Octahedral chiral-at-metal iridium(III) catalysts with π -stacking and H-bonding ligands.	28
D. Osmium catalysed transfer hydrogenations	30
III. Asymmetric hydrogenations using bifunctional catalysts.....	31
A. Ruthenium catalysed hydrogenations	31
1. Shvo-type catalysts.	31
2. Noyori-type catalysts.	32
B. Rhodium catalysed hydrogenations	42
1. Catalysts implying hydrogen bondings between ligands and either substrates or halide counteranions	42
2. Catalysts implying ion pairs as non-covalent interactions between ligand and substrates.	50
C. Iridium catalysed hydrogenations	53
1. Iridium catalysts involving active NH functions and related cases.	53
2. Catalysts implying ion pair or hydrogen bonding interactions.	56
3. Iridium phosphates or triflylphosphoramides as bifunctional catalysts.	59
IV. Conclusion	62
V. Acknowledgements	62
VI. References.....	63

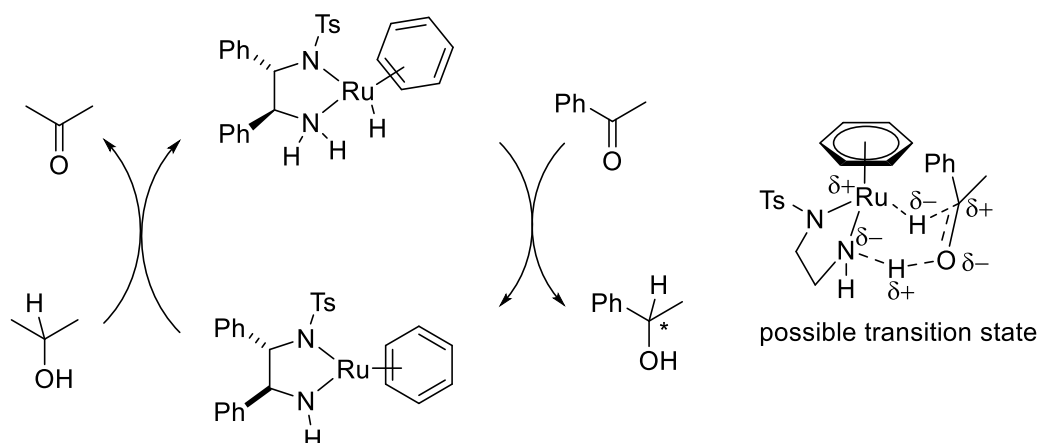
List of Abbreviations

AH:	asymmetric hydrogenation
ATH:	asymmetric transfer hydrogenation
BArF₂₄:	tetrakis[(3,5-trifluoromethyl)phenyl]borate
BINAP:	1,1'-Binaphthalene-2,2'-diylbis(diphenylphosphine)
BINOL:	1,1'-Binaphthalene-2,2'-diol
cat:	catalyst
CBA:	chiral Brønsted acid
COD:	cyclooctadiene
conv:	conversion
Cp:	Cyclopentadienyl
Cp*:	Pentamethylcyclopentadienyl
de:	diastereomeric excess
DENEB:	<i>N</i> -[1,2-Diphenyl-2-(2-(4-methylbenzyloxy)ethylamino)-ethyl]-(chloro)ruthenium(II)
DKR:	dynamic kinetic resolution
DMSO:	dimethylsulfoxide
DPEN:	diphenylethylenediamine
dr:	diastereomeric ratio
ee:	enantiomeric excess
HFIP:	hexafluoroisopropanol
Ms:	methanesulfonyl
NBD:	norbornadiene
NHC:	<i>N</i> -heterocyclic carbene
NMR:	Nuclear Magnetic Resonance
S/C:	Substrate-to-Catalyst ratio
SPO:	secondary phosphine oxide
TBDPS:	<i>tert</i> -butyldiphenylsilyl
TIPP:	2,4,6-triisopropylphenyl
THF:	tetrahydrofuran
TOF:	turnover frequency
TON:	turnover number
TRIP:	3,3'-bis(2,4,6-triisopropylphenyl)-1,1'-binaphthyl-2,2'-diyl hydrogenphosphate
Ts:	<i>p</i> -toluenesulfonyl

I. Introduction

Asymmetric hydrogenation is a fundamental and mature synthetic methodology providing high degree of stereocontrol for the preparation of optically pure fine chemicals like pharmaceuticals, agrochemicals, flavours and fragrances. Asymmetric hydrogenations (AH) of functionalized olefins and ketones have been realized using chiral homogeneous organometallic catalysts in the presence of hydrogen gas and several were applied to single enantiomer syntheses for advanced intermediates at industrial scales.¹⁻¹³ Most of the early methods employed catalysts based on rhodium(I) and required functional groups on the substrates to enable hydrogenation of the unsaturated bonds in highly efficient and selective manner.¹⁴ In addition, such enantioselective hydrogenation catalysts remained almost inert toward simple ketones.¹⁵

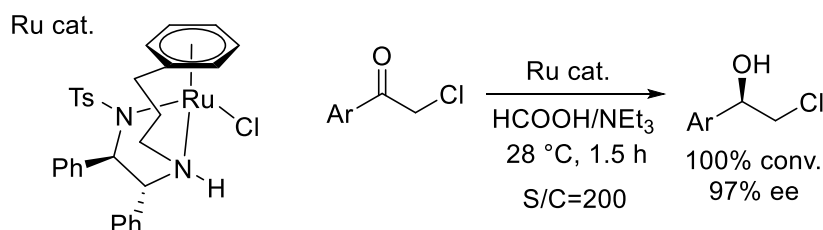
In 1995, a catalyst based on the combination of a ruthenium precursor, BINAP, a chiral diamine and KOH was reported by Noyori and co-workers to be able to hydrogenate simple aromatic ketones with high enantioselectivity in the presence of a hydrogen donor such as isopropanol.¹⁶⁻¹⁷ Subsequently, the same authors had a major breakthrough by introducing η^6 -arene ruthenium catalysts with *N*-sulfonylated 1,2-diamines or amino-alcohol as chiral ligands, for the highly efficient asymmetric transfer hydrogenation (ATH) of ketones.¹⁸⁻²⁰ For both the AH^{15,21} and ATH²²⁻²³ of ketones using these ligands, a metal-ligand bifunctional mechanism was established^{21,24} by means of kinetic studies and isotopic labelling,^{22,25-26} as well as via computational analyses.²⁶⁻²⁸ It was demonstrated that the reaction goes through a six-membered pericyclic transition state involving a ruthenium hydride and one of the NH functions of the diamino (or amino alcohol) ligand (Scheme 1).



Scheme 1. Postulated mechanism for the asymmetric transfer hydrogenation of acetophenone in the presence of 2-propanol.²³

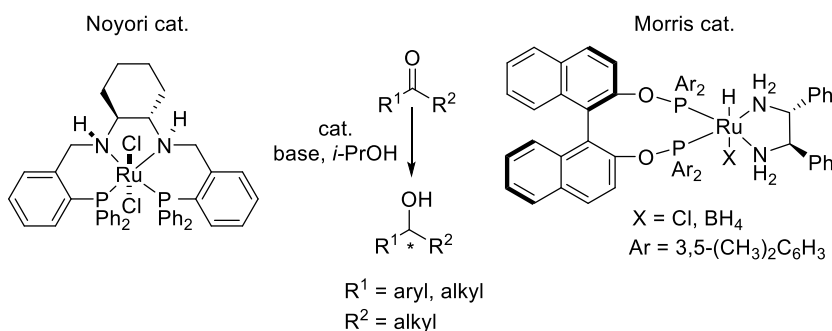
The N-H function of the ligand operates in a cooperative manner with the metal centre during the hydrogenation reaction, which typifies a bifunctional transition metal-based molecular catalyst.^{5,29-30} Since then, the concept of cooperative catalysis has been further applied in C-H, C-C, C-N, and CO formation.³¹⁻³⁸ In transfer hydrogenations, 2-propanol or formic acid are commonly used, i.e. two cheap, non-toxic and environmentally safe hydrogen sources which do not require any specific equipment. A drawback of the use of 2-propanol is the thermodynamic reversibility of the transfer hydrogenation reaction leading to a limited conversion and to a gradual decrease of the enantiomeric purity of the targeted chiral alcohol. This can be overcome by the use of formic acid, since the CO₂ released can be removed to favor full conversions. Overall, the Noyori half-sandwich bifunctional catalysts in Scheme 1 are very effective for ATH using either 2-propanol or an azeotropic mixture of formic acid as hydrogen sources and offer a great potential in enantioselective synthesis.

These ruthenium-based bifunctional catalysts raised a huge interest among the chemistry community and, therefore, the initial studies were followed by numerous other reports focusing on the development of new catalysts based on late-transition metals and, more recently, on first row transition metals. In order to develop more robust catalysts for AH or ATH, half-sandwich η^6 -arene-Ru complexes were modified notably by means of covalent tethers between the arene and the chiral diamine ligands. First introduced by Wills and co-workers, this new family of catalysts exhibited enhanced catalytic performances and stability (Scheme 2).³⁹⁻⁴²



Scheme 2. ATH of α -chloroketones with a diamine tethered arene ruthenium catalyst.³⁹⁻⁴²

Furthermore, the Noyori's ruthenium/diamine/diphosphine catalysts initially applied in AH have inspired the design of tetradentate analogues (Scheme 3, left) for the ATH of aryl-alkyl ketones,⁴³ as well as many other variants such as the phosphinite complexes reported by Morris (Scheme 3, right).⁴⁴⁻⁴⁵



Scheme 3. Ruthenium/P2N2 ATH catalysts developed by Noyori and co-workers (left) and Morris and co-workers (right).⁴³⁻⁴⁵

Since the 90's and to date, bifunctional catalysts for ATH and AH have aroused high interest. This long-term interest for innovative catalyses is due to a lack of general solutions for the catalytic asymmetric hydrogenations and has led to the development of a number of metal catalysts exhibiting new functionalities.⁴⁶ These new generations of catalysts, based on both hydrogen bonding, CH- π stacking and ion-pair interactions, have enabled bifunctional hydrogen transfer as in the Noyori's prototypical examples,⁴⁷ but also activation of organic substrates through secondary interactions (cooperative catalysis)⁴⁸ or heterolytic activation of dihydrogen itself. Interestingly, the significant contributions of weak non-covalent attractive interactions between the substrate and the chiral ligand to enantioselection in hydrogenation reactions have been enlightened by many recent theoretical studies.⁴⁹⁻⁵¹

For clarity's sake, the readers will find below three definitions of the term 'bifunctional catalyst':

- 1) According T. Ikariya:⁵² "*bifunctional catalysts have two functionalities cooperating in substrate activation and transformation*";
- 2) According D. B. Grotjahn:⁵³ "*...organometallic catalysts resulting from including ligands capable of proton transfer or hydrogen bonding*";
- 3) According S. J. Miller:⁵⁴ "*Bifunctional catalysts usually possess a nucleophilic moiety appended to Lewis basic or Brønsted acidic moieties capable of hydrogen bonding or charge stabilization. Coupling of these*

functionalities typically results in cooperative activation of substrates and stabilization of transition states leading to heightened reactivity and higher levels of enantiocontrol in various transformations.”

This book chapter will illustrate the different classes of bifunctional (cooperative) catalysts and the role of non-covalent interactions, by considering ruthenium, rhodium and iridium homogeneous asymmetric hydrogenation catalysts. It will present selected examples of metal complexes developed over the last ten years, i.e. along the 2010 - mid 2020 period, with a special focus on the understanding of their reaction mechanisms. Therefore, new applications of known catalysts in organic syntheses will not be reviewed. Furthermore, neither supported and immobilized catalysts,⁵⁵⁻⁵⁹ nor methods for the asymmetric hydrogenations in water⁶⁰ will be considered herein. Asymmetric transfer hydrogenations and asymmetric hydrogenations will be presented successively in Sections II and III respectively.

II. Asymmetric Transfer Hydrogenations using Bifunctional Catalysts.

A. Ruthenium Catalysed Transfer Hydrogenations.

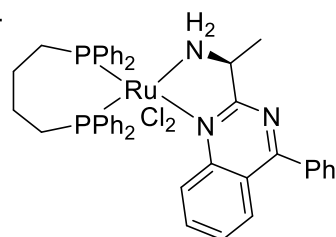
1. Noyori-type Catalysts.

On the basis of the pioneering research of Noyori and co-workers on ruthenium catalysts for the asymmetric transfer hydrogenation (ATH), over the years many efforts have been devoted to the development of new catalysts for the reduction of C=O and C=N double bonds that operate through concerted H-transfer from both the metal and the functional ligand (see Scheme 1). Since ligands with amino alcohols, diamines, natural products-based amines and other chiral structural units had been set by Noyori and co-workers, research has continued following the same directions during the last decade. Thus, diamines and, to a lesser extent, β -amino alcohols have been further investigated in the ATH of ketones and imines by using either η^6 -arene-Ru or diphosphine-Ru complexes.

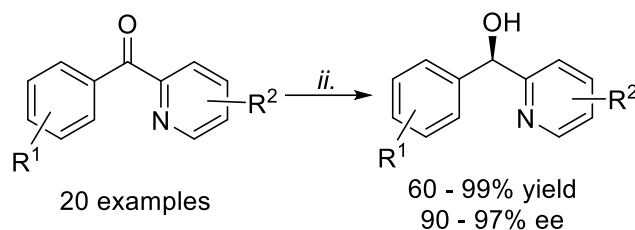
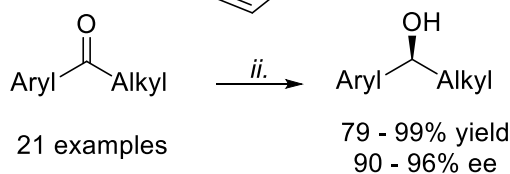
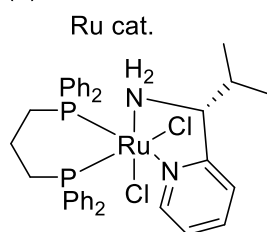
Diphosphine-diamine ruthenium catalysts.

The Ru^{II}(diphosphane)(diamine) complexes in which the ruthenium centre is coordinated by a non-chiral diphosphine and a chiral diamine drew special attention because of the easy variation of their chiral ligands.⁴³⁻⁴⁵ In 2015, Karabuga and co-workers reported on ruthenium complexes that combine quinazoline based chiral diamines (Scheme 4a) and dppb (diphenylphosphinobutane). These complexes catalysed the ATH of aryl methyl ketones with good conversions and variable enantioselectivities (9-91% ee).⁶¹ Moreover, Xing and co-workers disclosed recently Ru(diphosphane)(diamine) ATH catalysts that feature a single stereogenic element, by combining a simple and readily available amino-pyridine ligand (1-(pyridin-2-yl)methanamine) with an achiral diphosphine, 1,3-diphenylphosphinopropane.⁶² The design of this inspiring catalytic system relied on the hypothesis that this combination would replicate the stereo induction of the recognized Noyori's catalyst. Indeed, the catalytic system allowed the practical and highly enantioselective ATH of a wide range of ketones including aryl, alkyl- and aryl,*N*-heteroaryl ketones (Scheme 4b).

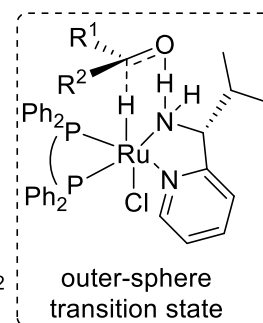
(a) Karabuga (2015) Ru cat.



(b)



ii. Ru cat. (0.1 mol%), KOt-Bu (15 mol%)
i-PrOH/CH₂Cl₂ (2:1)

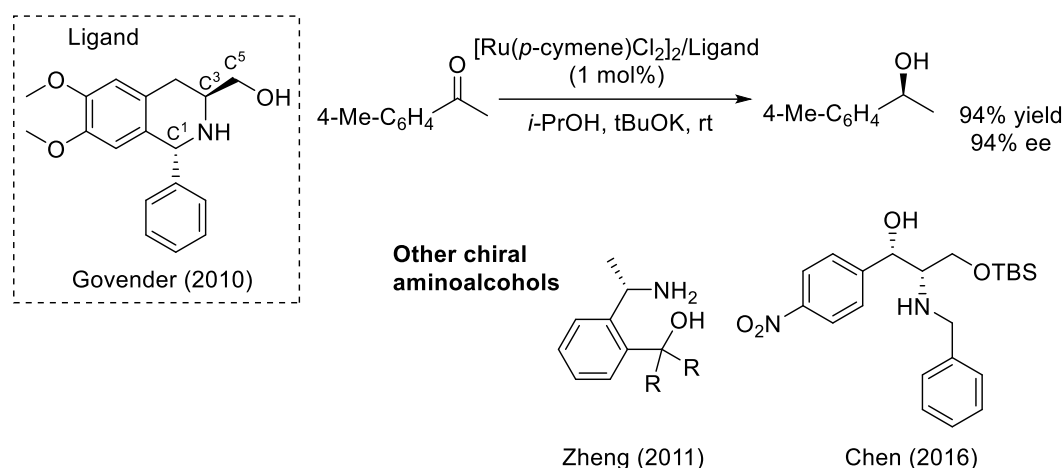


Scheme 4. Ruthenium(diphosphine)(diamine) catalysts with minimal stereogenicity for the ATH of aryl ketones.^{61,62}

Aminoalcohol, diamine and diamide derived η^6 -arene-ruthenium catalysts.

Aminoalcohol derived η^6 -arene-ruthenium catalysts.

As a complement to amino alcohols applied earlier in ATH, such as ephedrine,⁶³ 2-azanorbonyl-methanol derivatives⁶⁴ and 1-aminoindane-2-ol,⁶⁵ Govender, Kruger and co-workers reported in 2010 a series of C¹-substituted tetrahydroisoquinoline derivatives that were applied in the ATH of aromatic ketones. η^6 -Arene ruthenium complexes were generated *in situ* from [(*p*-cymene)RuCl₂]₂ and the chiral aminoalcohol. The ATH reactions were carried out in the presence of KOt-Bu/*i*-PrOH and provided up to 94% ee in the hydrogenation of 4-methylacetophenone (Scheme 5).⁶⁶ The *trans* relative orientation of the C¹ and C³ substituents of the ligand proved essential for high activity and enantioselectivity, while substitutions on C⁵ resulted in a decreased reactivity. The same ligands were also applied in rhodium catalysed ATH.



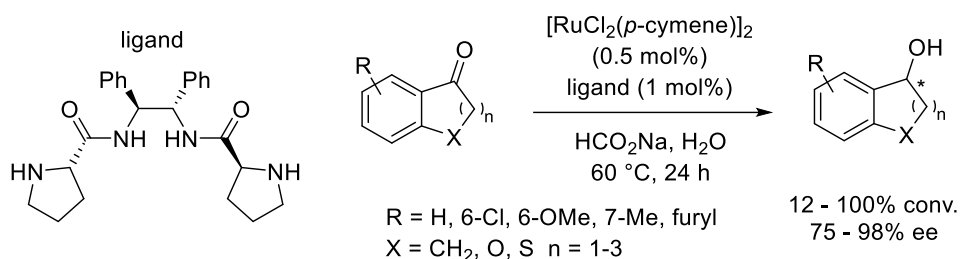
Scheme 5. Examples of recently developed amino alcohol and diamine ligands for ATH.⁶⁶⁻⁶⁸

In 2011, Zheng and co-workers reported another series of amino alcohol ligands derived from 1-phenylethylamine (Scheme 5).⁶⁷ The less sterically demanding ligand of the series (R = H), associated to $[\text{RuCl}_2(p\text{-cymene})]_2$ (0.5 mol%) in the presence of KOH (10 mol%) and *i*-PrOH allowed the reduction of aryl-alkyl ketones in good yields (67-95%) and enantioselectivities (67–95% ee) at -10 °C.

Along the same lines, Chen and co-workers developed the novel chloramphenicol based ligands in Scheme 5 for the ruthenium catalysed ATH of a *N*-Boc α -amino- β -ketoester. Under dynamic kinetic resolution conditions (DKR) in water, the reduced product was obtained in 85% yield, 92% de and 87% ee (conditions: $[\text{RuCl}_2(p\text{-cymene})]_2$, chiral ligand 3 mol%, HCOONa/Tween 20, H₂O, 25 °C).⁶⁸

Aminoamide and diamine derived η^6 -arene-ruthenium catalysts.

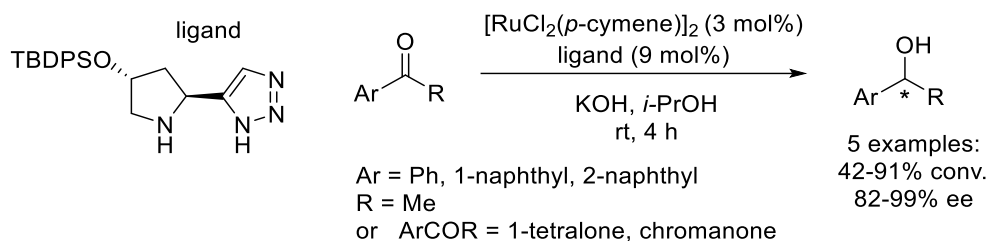
Beside amino alcohols, both diamines and amino amides have been applied as ligands in the ATH of ketones. In 2011, following their continuous efforts to develop asymmetric catalysts for ATH, Wills and co-workers synthesized new ligands containing (*R,R*)- or (*S,S*)-DPEN and one or two proteinogenic (*S*)-proline groups.⁶⁹ The TsDPEN mono-proline ligands led to variable results in ruthenium, iridium and rhodium promoted ATH of ketones in water, with sodium formate as hydrogen donor. On the other hand, the DPEN/bis-proline ligands led to effective ruthenium catalysts in the ATH of cyclic ketones (Scheme 6). The ligand combining (*S,S*)-DPEN and (*S*)-proline units provided the more enantioselective catalyst. Though the ligand bearing two proline groups could coordinate up to two ruthenium atoms, control experiments showed that the active complex contains only one ruthenium per ligand, as well as that the selectivity is most probably controlled by steric factors.



Scheme 6. DPEN/bis-proline ligands applied in ATH of cyclic ketones, by Wills and co-workers.⁶⁹

Pericàs and co-workers prepared diamine ligands that display proline and triazole units, the latter being easily obtained through click chemistry.⁷⁰ It appeared that the compounds with an O-protected 4-

hydroxyproline moiety was an efficient chiral ligand for the ruthenium catalysed ATH of acetophenones and cyclic ketones, while non-substituted proline gave much lower ee (Scheme 7).

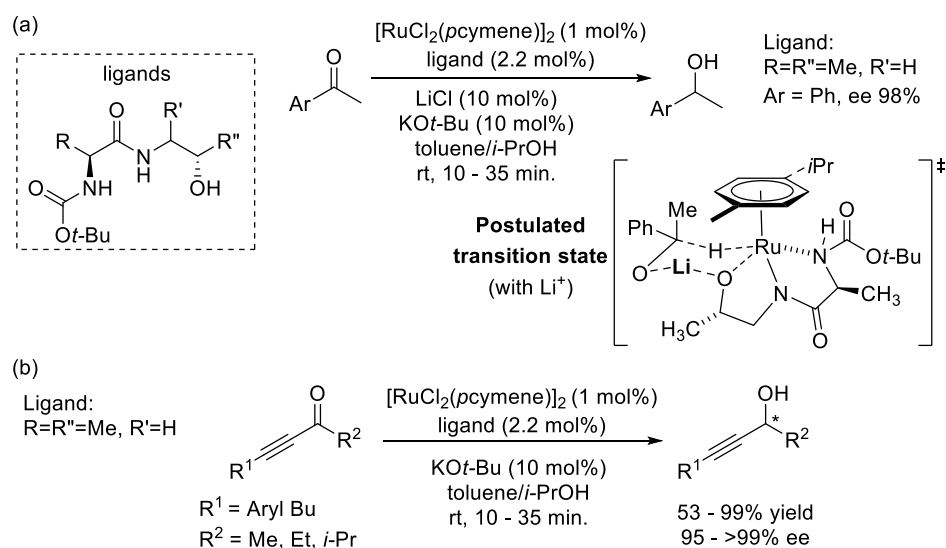


Scheme 7. Hydroxyproline/triazole ligands applied in the ATH of cyclic and acyclic ketones, by Pericas and co-workers.⁷⁰

Amidoalcohol derived η^6 -arene-ruthenium catalysts.

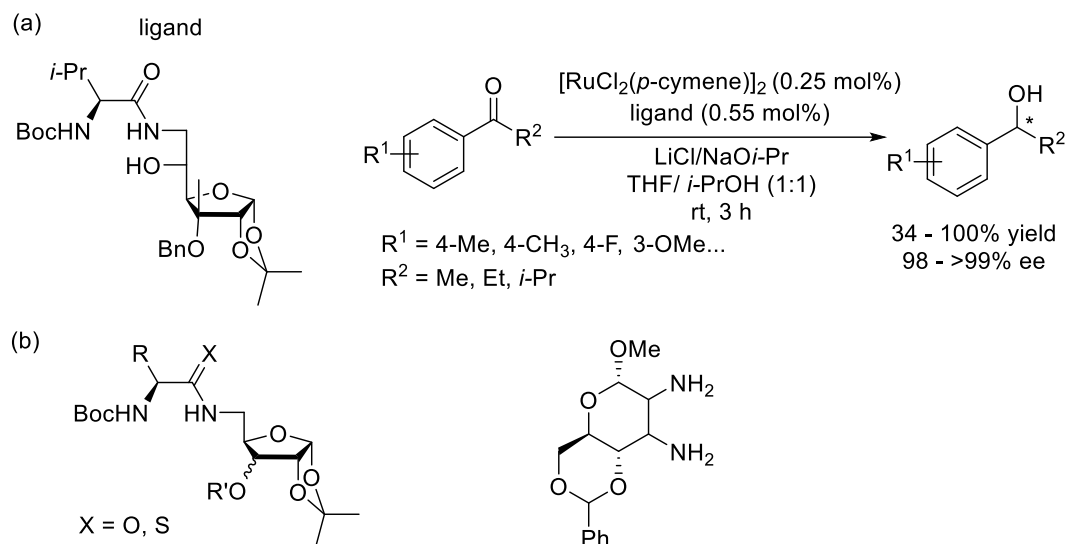
The easy availability and modular nature of α -amino acids makes them very attractive building blocks for the synthesis of chiral ligands. Thus, Adolfsen and co-workers have considered ruthenium and rhodium catalysts bearing pseudo-dipeptide based ligands. The new ligands are *N*-Boc protected α -aminoamides with β -amino alcohol functions. They were applied to ruthenium catalyzed ATH of aryl, alkyl-ketones with excellent results, a variety of acetophenones could be hydrogenated with ee >80% (18 examples, Scheme 8a).⁷¹⁻⁷³ For such catalytic systems, the addition of LiCl was generally beneficial both in terms of enantioselectivity and conversion rate.⁷⁴ Thus, it was suggested that the reaction might involve the transfer of an hydride and lithium ion to the substrate and proceeds via the six-membered transition state shown in Scheme 8a. Interestingly, these pseudo-dipeptide ligands were also applied in the ruthenium catalysed ATH of propargylic ketones (Scheme 8b).⁷⁵ In this case, the addition of LiCl did not change the reaction outcome.

Afterwards, the authors applied further these ruthenium catalysts in the tandem alkylation/ATH of acetophenones with primary alcohols,⁷⁶ in the tandem-isomerization/ATH of allylic alcohols,⁷⁷ while ruthenium and rhodium complexes of this series were also widely tested in high throughput screening experiments.⁷⁸



Scheme 8. Pseudo-dipeptide/ruthenium catalysed ATH of acetophenones and propargylic ketones, by Adolfsen and co-workers.⁷¹⁻⁷⁵

Similarly, Diéguez, Adolfsson and co-workers developed a library of 10 pseudo-dipeptide ligands in which the β -aminoalcohol moiety was obtained from readily available carbohydrates. The corresponding ruthenium catalysts were highly efficient in ATH of aryl,alkyl-ketones (Scheme 9a).⁷⁹

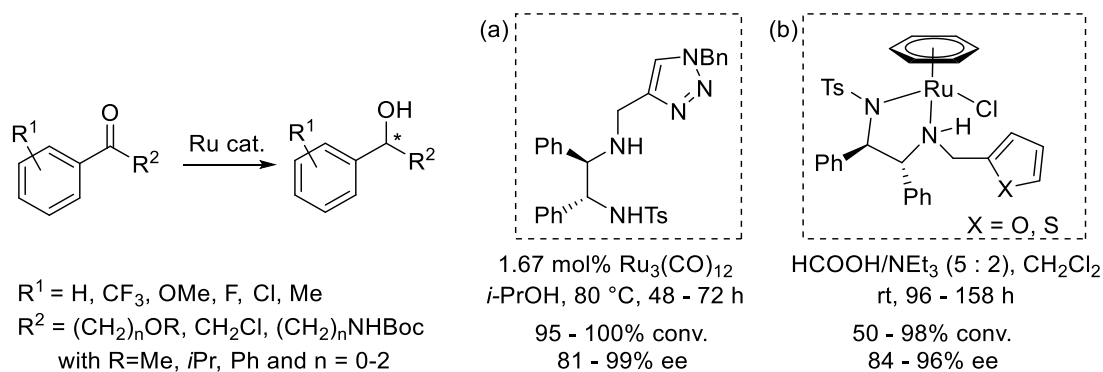


Scheme 9. Carbohydrate derived pseudodipeptides for the ruthenium catalysed ATH of aryl,alkyl-ketones.⁷⁸⁻⁸¹

Furthermore, this approach was extended to other libraries of carbohydrate-based pseudo-dipeptides and thioamides, devoid of the CHOH function (Scheme 9b, left), that were used in ruthenium and rhodium catalysed ATH of aryl,alkyl-ketones (ees up to > 99%). The new ligands were readily prepared from inexpensive D-glucose and D-xylose. They proved to be highly tunable, as far as the substituents of the amide (or thioamide) moiety, substituents at the C⁵ and C³ positions of the sugar and the configuration of C³ are easily adjustable.⁸⁰ In addition, hexapyranoside derived diamines (Scheme 9b, right) were also used in the ATH of acetophenone, associated to ruthenium, rhodium, and iridium catalysts with variable results, the highest ee of 68% being obtained with a ruthenium catalyst.⁸¹

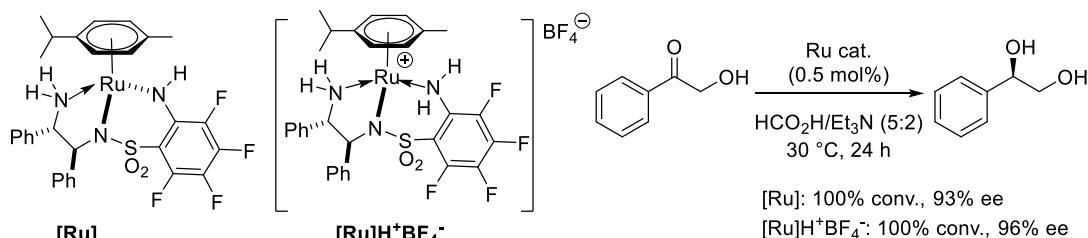
Diamines derived η^6 -arene-ruthenium catalysts.

Despite the development of other diamines, TsDPENs remain ligands of high interest because of their highly enantiodiscriminating properties, possibly tuned by the substituents on the primary amine bound to ruthenium(II).⁸²⁻⁸³ If generally no loss of activity was observed by changing the amine substituent, in some instances beneficial effects were highlighted, such as higher activity in C=N reduction reactions⁸⁴⁻⁸⁷ or increased water solubility.⁸⁸⁻⁹⁰ Wills and co-workers reported a quite versatile series of TsDPENs in which the amine nitrogen atom was functionalized by heterocyclic residues.⁹¹⁻⁹³ These ligands were able to coordinate in either a bidentate or a tridentate mode, depending on the nature of the heterocycle. Good donors, such as pyrazoles, provided tridentate ligands and generated active catalysts from $\text{Ru}_3(\text{CO})_{12}$ (Scheme 10a). Weak donors, such as furan or thiophene, provided bidentate ligands as typified by the (diamine)(benzene)RuCl complexes in Scheme 10b. The two families of complexes were good catalysts for the ATH of a large range of functionalized ketones. In addition, this approach highlighted the subtle effects brought by changes of the nearby donor group, the two catalysts with appended thiophene and furan units being complementary in terms of substrate scope.



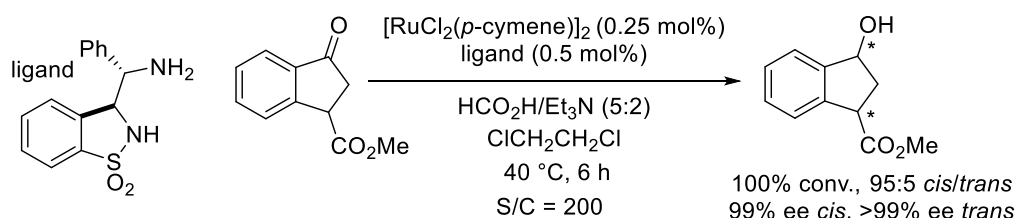
Scheme 10. ATH of ketones with ruthenium catalysts based on TsDPEN ligands bearing additional donor groups.⁹¹⁻⁹³

While investigating ammonia NH cleavage by metal-ligand cooperative catalysis, Kayaki, Dub and co-workers⁹⁴ serendipitously discovered a conceptually novel DPEN-based Noyori-Ikariya type precatalyst that displays a 2-amino-tetrafluorobenzenesulfonamide unit (Scheme 11). The authors underlined the proton-responsive nature of the aryl-amino group of the ligand. Indeed, the neutral Ru-complex ($[\text{Ru}]$ in Scheme 11) could be protonated by various acids to give chiral cationic 18 electron complexes with tunable organic or inorganic counteranions (e.g. $[\text{Ru}]^+\text{BF}_4^-$ in Scheme 11). Beside a full account detailing synthesis, characterization and reactivity studies, the authors showed that both the ionic and non-ionic ruthenium catalysts were efficient in the ATH of acetophenones and α -hydroxyacetophenone. The ionic complex $[\text{Ru}]^+\text{BF}_4^-$ obtained by protonation with the strong acid HBF_4 and the non-ionic complex led to similar results in the ATH of three different substrates.



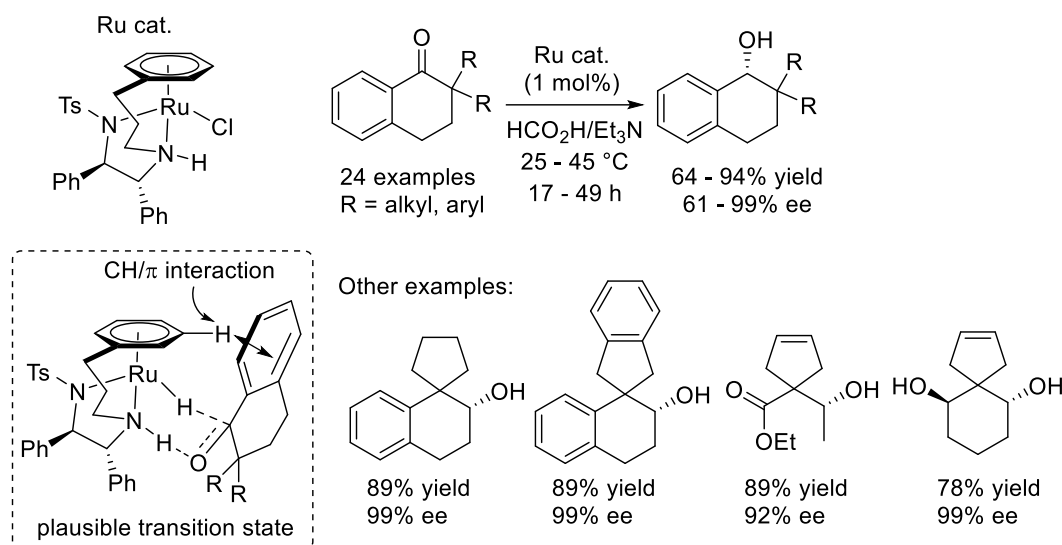
Scheme 11. Ruthenium catalysts developed by Kayaki, Dub and co-workers.⁹⁴

Mohar and co-workers prepared γ -sultam-cored *N,N*-ligands. The in-situ generated ruthenium catalysts were very efficient in ATH in particular for benzo-fused cyclic ketones. The DKR/ATH of a 1-indanone with a γ -carboxylic ester function provided the corresponding alcohol with an excellent stereoselectivity (Scheme 12).⁹⁵



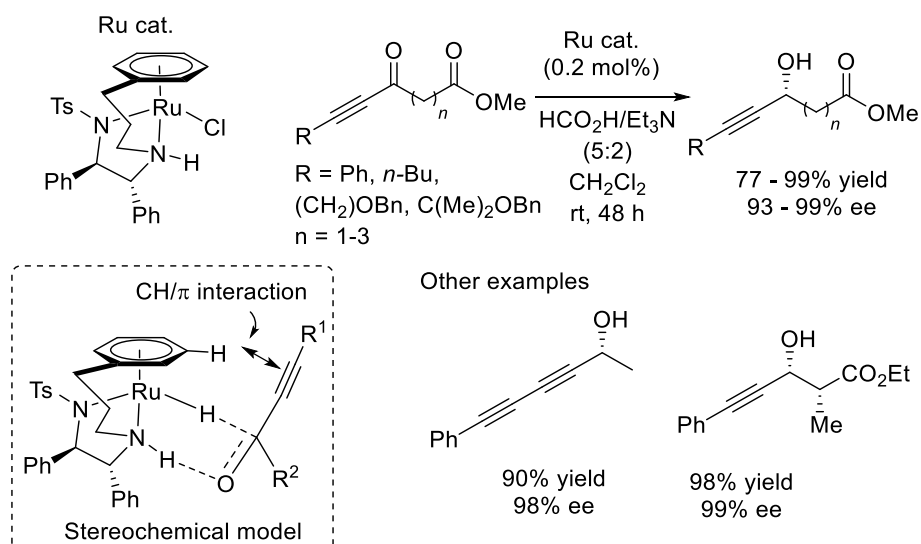
Scheme 12. DKR/ATH of a 1-indanone derivative by Mohar and co-workers.⁹⁵

Ruthenium(II) NNN type complexes containing a chiral pyrazolyl-pyridyl-oxazolynyl ligand were applied in the ATH of a series of aryl,alkyl-ketones (Scheme 13).⁹⁶ The best catalyst of the series



Scheme 15. ATH of hindered α - and β -tetralones and other functionalized ketones and plausible transition state.
104

The tethered catalysts were also valuable for the preparation of propargylic alcohols from functionalized ynones¹⁰⁵ or conjugated diynones¹⁰⁶ in excellent ees. Thus, alkynyl-substituted β , γ and δ -keto esters were reduced with high stereocontrol (Scheme 16). As in the case of ketones and tetralones seen above, the control of enantioselectivity takes place during the transfer of the two hydrogen atoms to the substrate. It was proposed that, at this step, the CH/ π interactions between the alkyne and the catalyst have a major effect on stereocontrol (Scheme 16). In further studies, dynamic kinetic resolution could also be achieved on α -substituted β -ketoesters by using the same catalysts as reported by Ayad, Ratovelomanana-Vidal and co-workers.¹⁰⁷

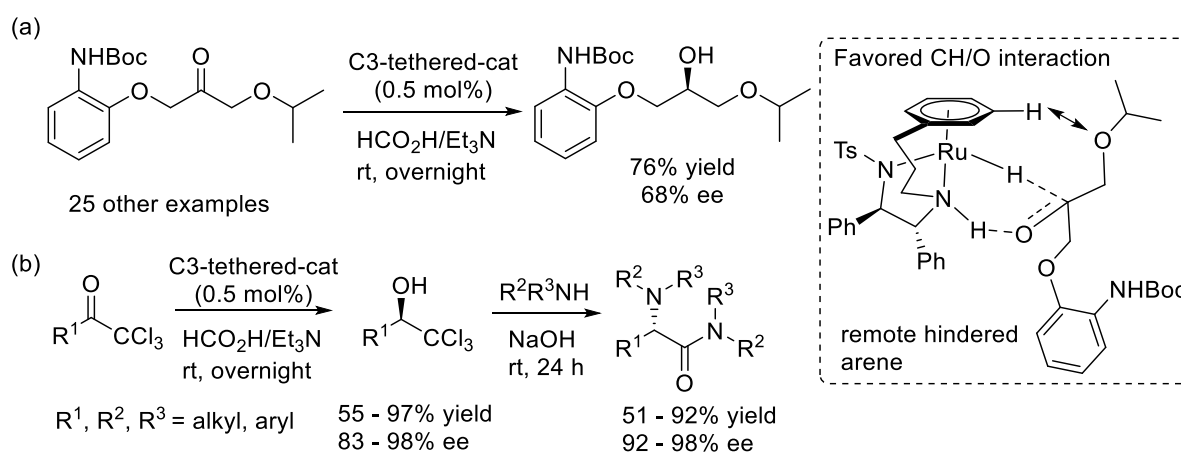


Scheme 16. ATH of acetylenic ketoesters and diynones and proposed stereochemical model, by Wills and co-workers.¹⁰⁵⁻¹⁰⁶

Afterwards, Wills and co-workers applied the same strategy to successfully reduce aryl, acetylenic ketones in the presence of C3-tethered catalysts displaying either a benzene or an anisole moiety

coordinated to the ruthenium centre.¹⁰⁸ Worthy of note, the systematic screening of substrates with highly diverse substituents allowed to rationalize steric and electronic effects and consequently to define the best substrate/catalyst match.

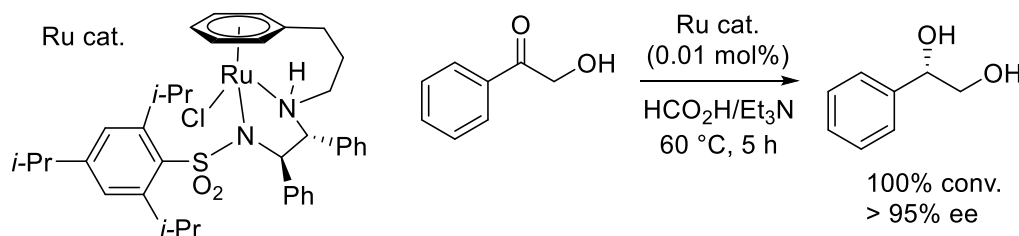
In order to identify more precisely the discriminating factors which underlie the high selectivity of tethered ruthenium catalysts, Wills and co-workers investigated the ATH of challenging 1,3-dialkoxy/aryloxy 2-propanones presenting little difference between the two sides of the C=O functionality (Scheme 17a). They demonstrated that the C3-tethered ruthenium catalyst led to significant ees when both electronic and steric factors differentiate the substituents of the ketone, while tuning of electronic factors only (e.g. using substituted aryloxy substituents) did not allow to improve the enantiomeric excesses.¹⁰⁹



Scheme 17. ATH of a dissymmetric propanone and trichloromethyl ketones.¹⁰⁹⁻¹¹⁰

The C3-tethered catalyst could also reduce efficiently trichloromethyl ketones, as reported by Fox and co-workers (7 substrates, up to 98% ee).¹¹⁰ The corresponding optically enriched alcohols were converted into amino-amides via stereospecific Jocic-type reactions (Scheme 17b).

In the series of alkyl tethered ruthenium complexes, the variation of the size and electron-donor ability of the sulfonyl groups on the DPEN unit was also investigated. Thus, the ruthenium catalysts were optimized by tuning both the tether length and the nature of the sulfonyl group. For example, the reduction of α -hydroxyacetophenone could be performed in high yields and enantioselectivities at low catalyst loading with the C3-tethered catalyst displaying a 2,4,6-triisopropylbenzenesulfonyl function (Scheme 18).¹¹¹

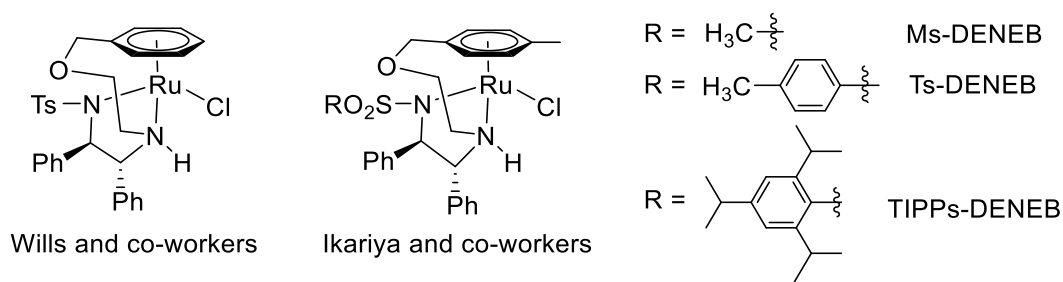


Scheme 18. ATH of α -hydroxyacetophenone catalysed by a C3-tethered catalyst, by Wills and co-workers.¹¹¹

The family of C3-tethered ruthenium catalysts was also applied in the synthesis of various chiral intermediates of interest, notably through ATH of imines,¹¹²⁻¹¹³ β -azidocyclopropane carboxylates¹¹⁴ and α -azidoacrylates.¹¹⁵

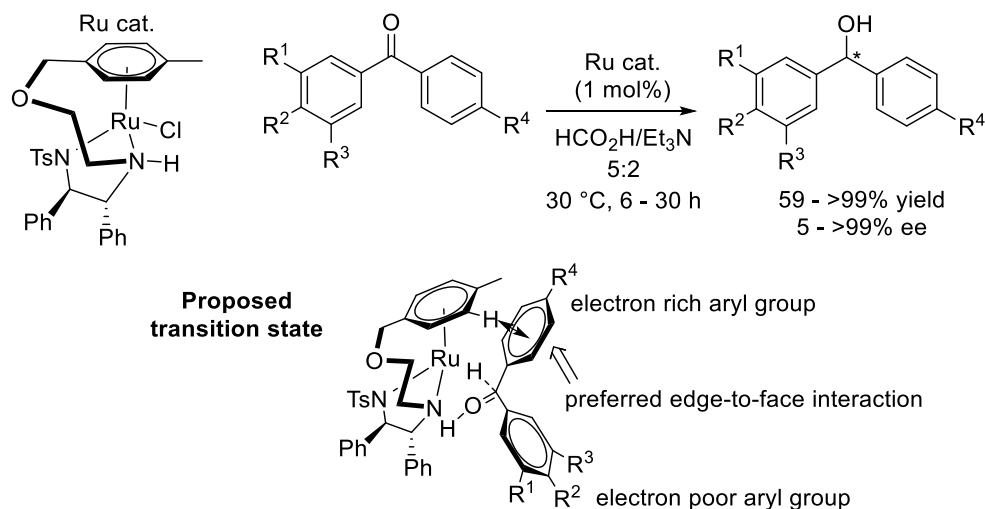
In parallel, Wills and co-workers developed ruthenium catalysts containing a benzyl-type tether (see Scheme 14) that provided high enantioselectivity in the ATH of simple acetophenones and tetralones.^{116,117} The first ligand of this series was also active when associated to rhodium in the ATH of 2-substituted quinolines (up to 94% ee).¹⁰¹

The introduction of an oxygen atom in the catalyst tethering chain was realized independently by Ikariya¹¹⁸ and by Wills¹¹⁹ and co-workers (Scheme 19). Thanks to the optimisation of synthetic routes, the oxo-tethered catalyst Ts-DENE^B® has been prepared on large scale by Takasago Int. Corp. and, like the C3-tethered Wills catalyst, it is commercially available. Compared to other tethered ruthenium catalysts described above, these complexes exhibited either close or complementary catalytic properties in the ATH of aryl-alkyl ketones. Nevertheless, the Ikariya's oxo-tethered catalyst was remarkable as far as it retained excellent catalytic performances under mild reaction conditions, with a substrate/catalyst ratio of 5000¹¹⁸



Scheme 19. Ether-tethered ruthenium catalysts developed by Wills and co-workers¹¹⁹ and Ikariya and co-workers.¹¹⁸

Ikariya, Kayaki and co-workers applied the oxo-tethered catalyst to the ATH of benzophenones, in collaboration with Touge from the Takasago Int. Corp.¹²⁰ The reductions proceeded smoothly at 30 °C in a mixture of formic acid and triethylamine. For substrates possessing an *ortho*-substituted aryl group, the enantiodiscrimination was effective providing high enantiomeric excesses. Noteworthy, with non-*ortho*-substituted benzophenones, the electronic density of the phenyl rings of the substrate could be differentiated by the catalyst, thus maintaining high levels of stereoselectivity (> 99% ee) (Scheme 20). A plausible transition state implying an edge-to-face interaction between the catalyst and the more electron-rich aryl group of the substrate was proposed.

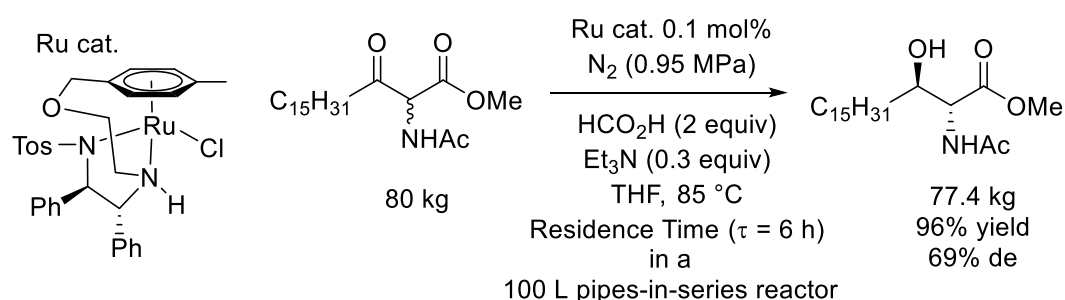


Scheme 20. ATH of benzophenones using an oxo-tethered catalyst and proposed transition state, by Ikariya, Kayaki and co-workers.¹²⁰

Within these studies, Kayaki and co-workers also reported on a concise synthesis of half-sandwich η^6 -arene-Ru-diamine complexes bearing a perfluorinated phenylsulfonyl group in their tethering chains, i.e. displaying N -SO₂-(C₆F₄)-*o*-O(CH₂)_n (n = 1 or 2) tethers (see Scheme 14).¹²¹

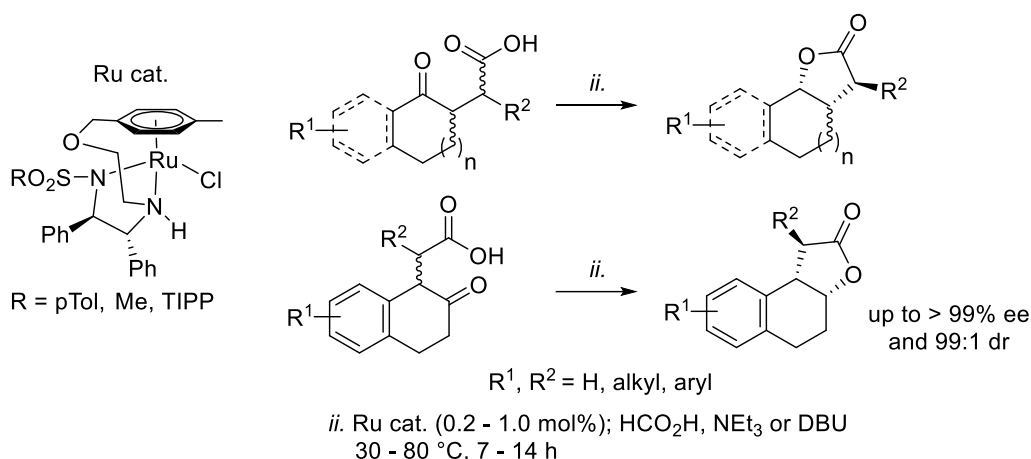
In parallel, Zhou and co-workers applied with success O-tethered ruthenium catalysts in the synthesis of optically enriched aryl *N*-heteroaryl methanols which are pharmaceutical intermediates of interest.¹²² Aryl groups with opposite electronic and steric characters could be discriminated efficiently, which led to highly enantioselective ATH reactions. In this case also, the more electron-rich aryl fragments of the substrates approach preferentially the η^6 -arene ligand.

Yuki, Ikariya, and co-workers, applied with success the O-tethered ruthenium catalysts in the ATH of α -functionalized ketones displaying halide, methoxy, nitro, dimethylamino and ester groups. For example, reductions performed with HCO₂H and HCO₂K in a EtOAc/H₂O solvent system allowed a highly selective access to halohydrins of high synthetic potential. The conditions above suppressed the undesired formylation and other side-reactions often encountered under the classical reaction conditions using an azeotropic mixture of HCO₂H and Et₃N. The excellent activity and selectivity were preserved even with a substrate/catalyst ratio of 5000.¹²³ Interestingly, while optimizing an industrial flow process, Touge and co-workers applied this method to the asymmetric transfer hydrogenation/dynamic kinetic resolution of an α -amido β -keto ester, as a suitable alternative to the previously used asymmetric hydrogenation/hydroxyl inversion on the same substrate (Scheme 21). By using the oxo-tethered catalyst, they accessed the *anti* diastereomer of a key intermediate in the synthesis of the D-erythro-CER[NDS] ceramide at an 80 kg production scale (96% yield, 69% de, 97% ee).¹²⁴ It is worth to note that the robust catalytic process was developed in a pipes-in-series flow reactor. After crystallization, the enantiopure product was obtained at a >50 Kg scale.



Scheme 21. Industrial DKR/ATH of an α -acetamido β -ketoester, by Touge and co-workers (Takasago Int. Corp.).¹²⁴

The synthetic methodology above combining ATH and DKR and using O-tethered catalysts was recently applied by Kayaki, Touge and co-workers in a one step cascade synthesis of γ - and δ -lactones from racemic keto acids, leading to the control of multiple contiguous stereocenters (Scheme 22).¹²⁵ Wine lactone, a natural flavour and fragrance agent, was prepared with unprecedented level of diastereo- and enantioselectivity (95% yield, > 99:1 dr, 92% ee).



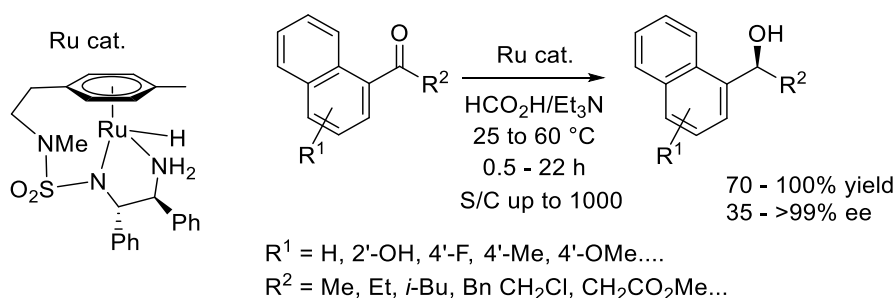
Scheme 22. DKR/ATH of racemic keto acids, by Kayaki, Touge and co-workers.¹²⁵

Another industrial application of the O-tethered ruthenium/DENEb catalyst was reported by Komiyama and co-workers at Teijin Pharma Limited who described the scalable synthesis of the key intermediate of a commercially available β 2-adrenergic receptor agonist.¹²⁶ In this process, an α -NHCBz-acetophenone was reduced into the corresponding alcohol in 71% isolated yield and 99% ee on about 7 kg scale with a S/C ratio of 1000.

In parallel, Chung and co-workers at Merck reported on the development of an efficient process for the multikilogram scale synthesis of omarigliptin, a drug for the treatment of type 2 diabetes, applicable to a manufacturing plant.¹²⁷ The DKR/ATH of an α -NHBoc ketone provided the *anti* amino alcohol with 93% isolated yield, 24:1 dr and >99% ee (0.365 mol of substrate, HCO₂H/DABCO, S/C close to 1000, 35 °C, 20 h). Sparging with N₂ was critical to remove CO₂ and allow an efficient process.

By following a similar approach, Wang and co-workers reported on the application of DKR/ATH for the gram scale production of *syn*- β -hydroxy α -dibenzylamino esters intermediate in the synthesis of Doxidopa.¹²⁸

Other tethered ruthenium catalysts were developed by Mohar and co-workers on the basis of an enantiopure N,C-(*N*-ethylene-*N*-methyl-sulfamoyl)-tethered DPEN-toluene hybrid ligand.¹²⁹ This new catalyst was rather efficient for the ATH of challenging 1-naphthyl ketones, a large array of substrates being reduced in the presence of HCO₂H/NEt₃ (Scheme 23). Similar to other tethered complexes, the high selectivity induced by this catalyst stemmed from dual synergistic stereoelectronic matches between the substrate and the catalyst.

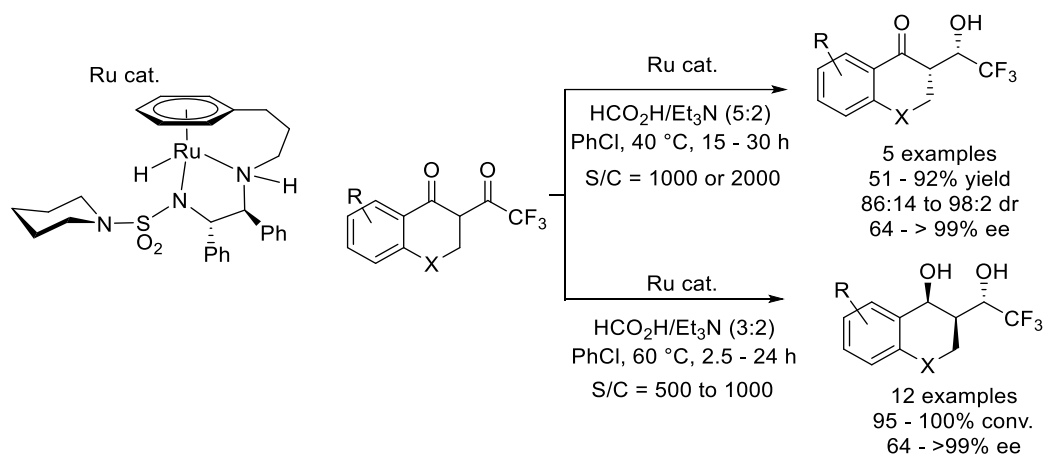


Scheme 23. ATH of 1-naphthyl ketones, by Mohar and co-workers.¹²⁹

Afterwards, Mohar and co-workers explored the modulation of the same complexes by varying the length of the carbon tether (from 1 to 3 CH₂ units) and the *para* substituent (H, CH₃, *i*Pr, OMe) of the η^6 -aryl. The corresponding ruthenium complexes catalysed the ATH of a broad scope of aryl, alkyl-ketones and α or β -diketones, in HCO₂H/Et₃N, under mild conditions, with excellent selectivities (39 substrates, 94 to > 99% ee).¹³⁰ Further modifications of the tethered ruthenium complexes led to new

catalysts bearing $R_2NSO_2DPEN-(CH_2)_n(\eta^6\text{-aryl})$ type ligands¹³¹ that performed well in the ATH of various classes of (hetero)aryl ketones using a mixture of formic acid and triethylamine. Benzo-fused cyclic ketones were hydrogenated with 98 to >99% ee using a low catalyst loading of 0.003 mol%.

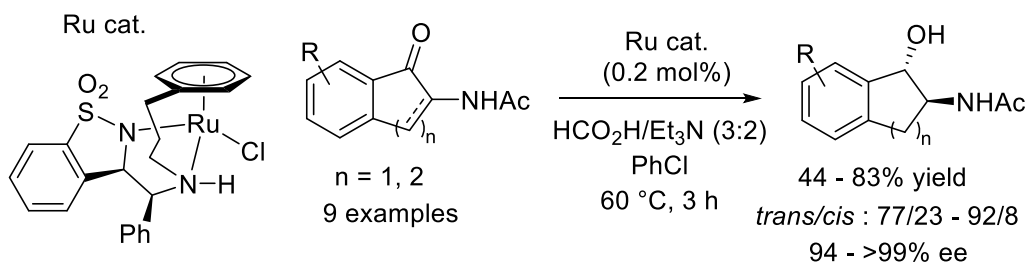
Through further modification of the catalysts based on chiral DPEN tethered aryls, Mohar and co-workers achieved the selective single or double ATH of $CF_3C(O)$ -substituted benzo-fused cyclic ketones, under DKR conditions (Scheme 24).¹³² Synthetic intermediates of interest like CF_3 -substituted 1,3-diols were obtained in excellent enantiopurities and yields applying this efficient and practical methodology. To rationalise the selectivity, it was proposed that the stereocontrol was enforced by either CH/π or CH/F attractive electrostatic interactions. In the first hydrogenation step, the CH/F interaction overcomes the CH/π interaction, thus leading to the the trifluoromethyl carbinol of (*S*) configuration as the singly reduced product, on the way to the fully hydrogenated *anti* diol product.



Scheme 24. ATH of benzo-fused β -diketones leading to either β -keto-alcohols or diols, by Mohar and co-workers.¹³²

Similar tethered ruthenium catalysts were applied to the preparation of hydroxy benzo sultams ($S/C = 10\,000$, HCO_2H/Et_3N , up to >99.9% ee)¹³³ and 2,3-disubstituted-1-indanols through DKR and ATH.¹³⁴

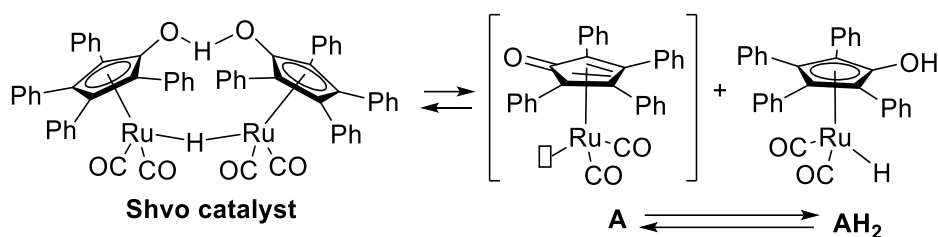
Recently, Mohar and co-workers reported another ruthenium tethered catalyst bearing a diamine ligand comprising a cyclic sulfonamide moiety. This catalyst was efficient in the DKR/ATH of α -acetamido benzo-fused cyclic ketones (Scheme 25).¹³⁵ Calculations were carried out in order to rationalize the high *trans* selectivity of the transformation. Two attractive stabilizing effects which were identified, the first being a “classical” CH/π interaction between the coordinated phenyl ring and the π system of the benzocyclic part of the substrate. The second interaction relied on a hydrogen bond between the SO_2 moiety of the catalyst and the acetamido group of the substrate.



Scheme 25. ATH/DKR of α -acetamido benzocyclic ketones, by Mohar and co-workers.¹³⁵

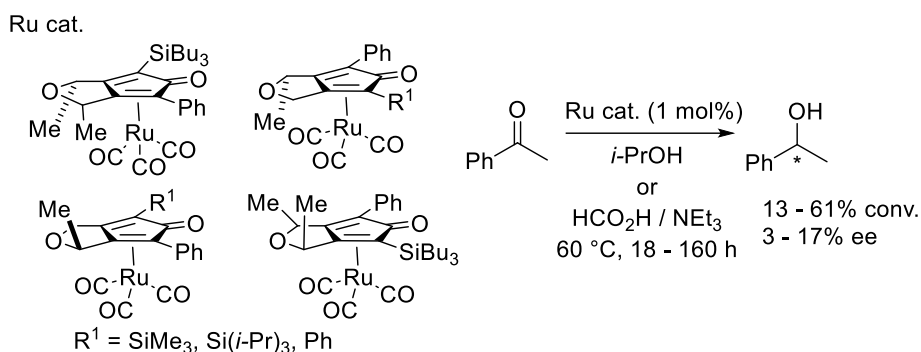
2. Shvo type catalysts.

The Shvo catalyst is a cyclopentadienone-ligated dimeric ruthenium complex that was found to be one of the most active catalysts for the transfer hydrogenation of ketones and imines,¹³⁶⁻¹³⁸ as well as for the chemoenzymatic dynamic kinetic resolution of secondary alcohols and amines (Scheme 26).¹³⁹ While in solution, this binuclear complex is in equilibrium with the coordinatively unsaturated intermediate **A** and the catalytically active ruthenium hydride complex **AH₂**, both species interconverting each other through H₂ exchange. The OH function of **AH₂** and hydride participate in the H-transfer process. After hydrogen transfer to the substrate, the **AH₂** species is reformed through reaction with the hydrogen donor (HCO₂H or *i*-PrOH). Recently, chiral variants of these catalysts have been reported, they displayed however rather poor catalytic properties.



Scheme 26. The Shvo catalyst.¹³⁵⁻¹³⁸

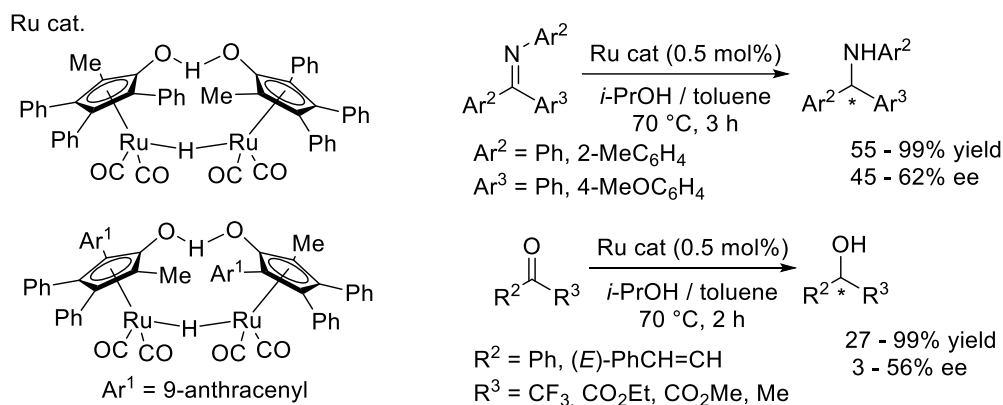
In a detailed study, Wills and co-workers addressed the preparation of a range of diastereopure cyclopentadienone-ruthenium-tricarbonyl complexes, and their application to the ATH of acetophenone (Scheme 27).¹⁴⁰ Though these species did not require any Me₃NO to remove CO and become catalytically active, the corresponding hydrides were formed in situ using NaOH in THF, followed by addition of phosphoric acid, prior to all hydrogenation experiments. Requiring 18 to 160 hours of reaction, the catalyst activities were moderate, leading to low to good conversions (13 to 61%). The modest enantioselectivities of these hydrogenation reactions were regulated by both the stereogenic centres and the planar chirality of the catalysts. The most selective catalysts display a methyl substituent on the ligand, close to the Ru(CO)₃ moiety. Racemization of these catalysts was observed after extended reaction times.



Scheme 27. Ruthenium cyclopentadienone complexes applied to the ATH of acetophenone, by Wills and co-workers.¹⁴⁰

In a novel contribution, Hayashi and Dou prepared planar chiral Shvo catalysts, where the chirality results solely from the non-symmetric substitution patterns of the cyclopentadienone ligands, next to the CO function (Scheme 28).¹⁴¹ The ATH of imines and ketones proceeded using a 0.5 mol% catalyst loading and afforded the corresponding reduction products in average to high yields with low to average

enantioselectivities, with maximum ees of about 60%. Acetophenone was much less reactive than the other activated ketones, it required 20 hours of reaction and led to lower ee.



Scheme 28. Ruthenium-Shvo complexes applied to the ATH of ketones and imines, by Dou and Hayashi.¹⁴¹

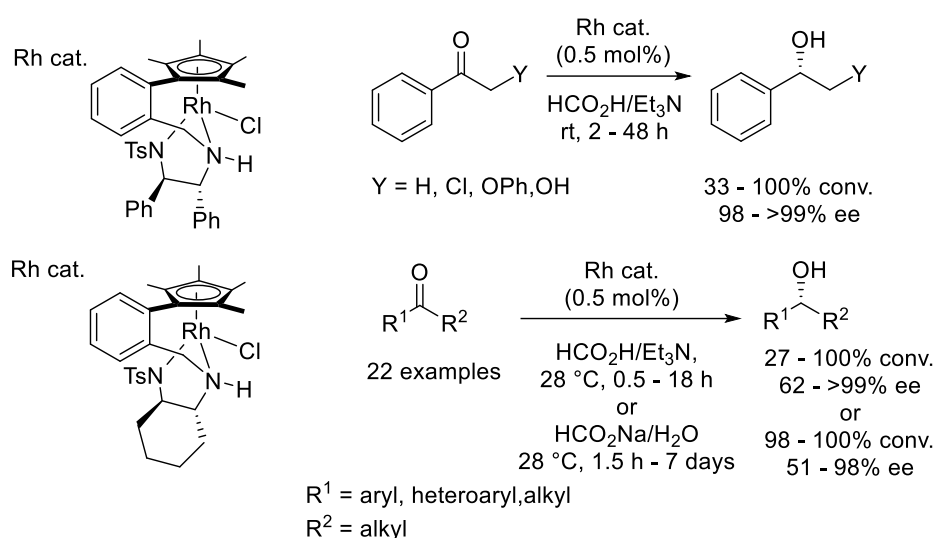
Overall, the known chiral Shvo-type ruthenium catalysts do not meet the current standards for enantioselective AHT reactions, in terms of both catalytic activity and enantioselectivity. Nevertheless, the promising features of the parent achiral catalyst should encourage further efforts toward catalyst design in the future.

B. Rhodium Catalysed Transfer Hydrogenations.

Compared to the Noyori-type ruthenium(II) catalysts, the corresponding isoelectronic bifunctional rhodium(III) complexes, namely $\text{Cp}^*\text{Rh}^{\text{III}}(\text{N-Ts-diamine})$ type complexes,¹⁴² have been less investigated in asymmetric transfer hydrogenations. Notably, the rhodium catalysts exhibited good stability and provided variable conversions and enantioselectivities in the ATH of various ketones.⁸ In the time frame covered by this review, new catalytic applications of the known ligands have been developed and, moreover, two directions have been investigated more intensively: the synthesis of new ligands based on natural building blocks and the development of tethered complexes. Significant advances have been made by using these ligands and complexes in the Rh-promoted hydrogenation of a variety of ketones and functionalised olefins.

1. Diamine tethered η^5 -cyclopentadienyl rhodium complexes with active NH functions

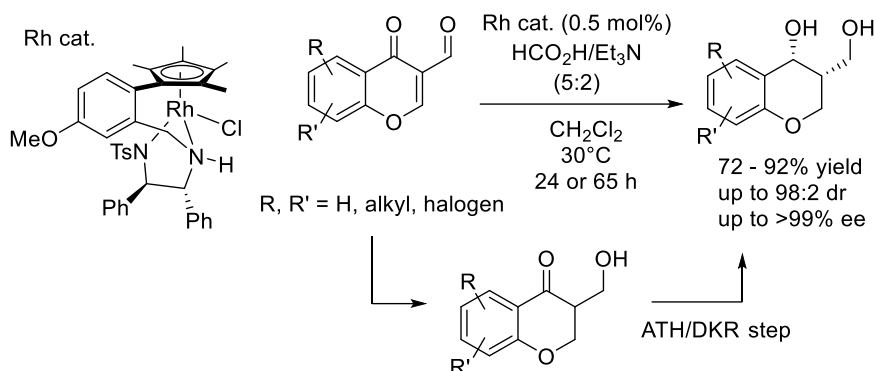
Wills and co-workers^{42,143-144} followed by Ratovelomanana-Vidal, Phansavath and co-workers¹⁴⁵⁻¹⁵² developed rhodium catalysts displaying a benzyl tether between the cyclopentadienyl and TsDPEN units, for applications in the ATH of ketones. The rhodium catalysts developed by Wills and co-workers proved to be very efficient for the reduction of a series of ketones, especially in aqueous solutions (Scheme 29).^{42,143-144}



Scheme 29. ATH of ketones with tethered cyclopentadienyl-diamine rhodium catalysts, by Wills and co-workers.^{42,143-144}

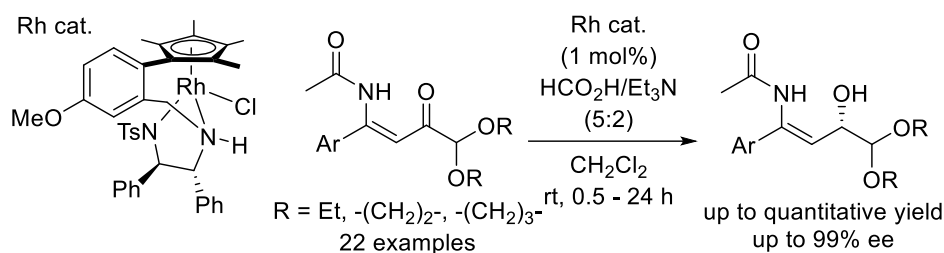
Ratovelomanana-Vidal and co-workers developed the synthesis of a series of new ligands closely related to the Wills ligands, by introducing a substituent on the aromatic unit of the tether (Me, OMe, F, CH_3).¹⁴⁵⁻¹⁵² These ligands provided tethered rhodium(III) catalysts efficient in the ATH of alkyl, aryl-ketones¹⁴⁵⁻¹⁴⁶ and in the DKR/ATH of α -amino- β -ketoesters, leading to functionalized alcohols with high syn/anti ratios and ee.¹⁴⁷ The DKR/ATH of α -methoxy- β -keto esters in water/cetyltrimethylammonium bromide was carried out then by using a tethered rhodium(III) complex that displays a $N\text{-C}_6\text{F}_5\text{SO}_2$ substituted DPEN ligand.¹⁴⁸ In addition, Ratovelomanana-Vidal and co-workers prepared *cis*-3-(hydroxymethyl)chromanol derivatives with excellent diastereo- and enantioselectivity by applying the tethered rhodium(III) catalyst in the DKR/ATH of 3-substituted chromanones, under mild conditions and using $\text{HCO}_2\text{H}/\text{Et}_3\text{N}$ as hydrogen source (Scheme 30).¹⁴⁹ The reaction proceeds via three separate hydrogenation steps. After reduction of the aldehyde and the $\text{C}=\text{C}$ bond, the intermediate hydroxymethyl

chromanone undergoes the highly enantioselective ATH reaction under dynamic kinetic resolution conditions.



Scheme 30. DKR/ATH of 3-formyl chromanones, by Ratovelomanana-Vidal and co-workers.¹⁴⁹

Very recently, the same group described the first highly chemo- and stereoselective ATH of γ -keto- δ -acetal enamides in the presence of a tethered rhodium(III) catalyst (Scheme 31).¹⁵⁰ A high chemoselectivity in favour of the reduction of the carbonyl group over the C=C bond was observed. The reaction tolerated various aromatic substituents and demonstrated better enantioselectivities with substrates bearing a dioxane as the acetal moiety (up to 99% ee).



Scheme 31. Chemoselective ATH of γ -keto- δ -acetal enamides, by Ratovelomanana-Vidal and co-workers.¹⁵⁰

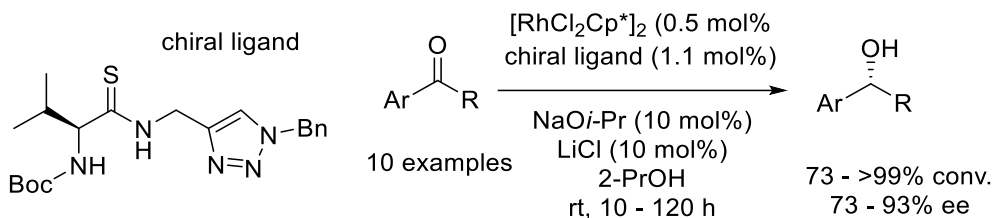
Furthermore, Ratovelomanana-Vidal and co-workers used the same rhodium(III) catalyst to develop the first ATH of 4-quinolone derivatives and obtained 1,2,3,4-tetrahydroquinolin-4-ol derivatives with excellent levels of enantioselectivity.¹⁵¹ In collaboration with Zhang and co-workers the tethered rhodium(III) catalyst has been applied also in the diastereoselective transfer hydrogenation of optically pure α -aminoalkyl- α' -chloromethyl ketones. The method allowed to prepare the key intermediates for the synthesis of HIV protease inhibitors (up to 99% yield, up to 99:1 dr).¹⁵²

Overall, the results above clearly demonstrate that tethering the Cp* and diamine ligands is a suitable strategy for the design of rhodium-based catalysts for enantioselective reactions.

2. Aminoacid derived amides and thioamides with active NH functions

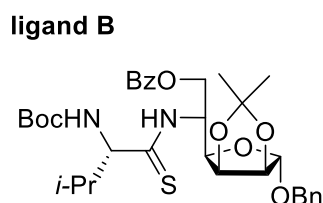
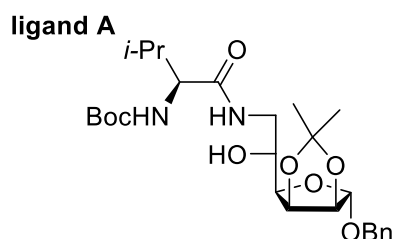
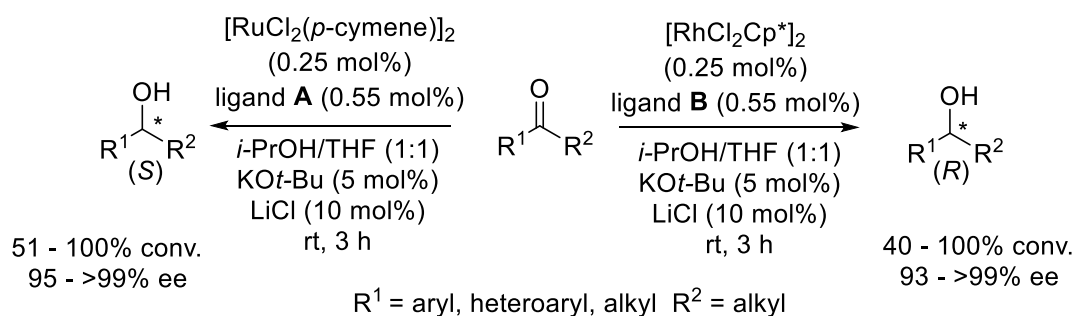
Natural products were also used as chiral motifs for the development of original ligands. Essentially, ligands based on amino acid derivatives and pseudopeptides, possibly combined with sugars, were investigated as already highlighted in Section II.A.1 above. Thus, within their extended studies on the application of amino acids as ligand precursors,¹⁵³⁻¹⁵⁴ Adolfsson and co-workers synthesized a series of 1,2,3-triazole-functionalized amino acid derived thioamide ligands. A ligand of this series, when associated to the dimeric Cp*-rhodium dichloride, provided good catalysts for the ATH of aryl, alkyl-ketones in the

presence of sodium *iso*-propoxide and lithium chloride in 2-propanol (Scheme 32).¹⁵⁵ The corresponding alcohols were obtained with good to high conversion rates, with enantioselectivities up to 93%. Himo, Adolfsson and co-workers carried out then a theoretical study on the ATH of ketones catalysed by these amino acid-derived rhodium complexes.¹⁵⁶ Similarly to the ruthenium complexes described above (see for instance Schemes 1 and 13), the rhodium(III) complexes proved to operate as bifunctional catalysts and CH/ π interactions between the substrate and the Cp* ligand were shown to significantly contribute to the stereoselectivity of the reductions.

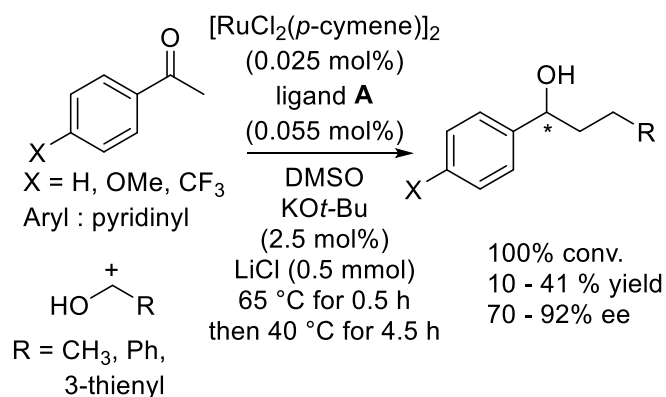


Scheme 32. Triazole containing pseudodipeptides in rhodium catalysed ATH of aryl,alkyl-ketones, by Adolfsson and co-workers.¹⁵⁵

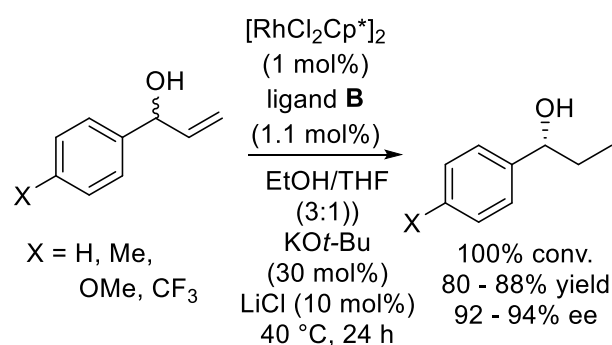
The first generation of pseudodipeptide ligands modified by carbohydrates shown in Scheme 9, was also applied with success in rhodium catalysed ATH reactions.⁷⁹ Later on, 2nd and 3rd generation ligands were prepared by Diéguez, Pàmies and co-workers, as well as by Adolfsson and co-workers for applications in rhodium and ruthenium ATH of ketones. The second generation was composed of thioamides obtained by combining D-glucose derivatives and various α -amino acids which were tuned for optimization. The resulting rhodium catalysts enabled ATH of aryl,alkyl- and heteroaromatic-ketones with excellent enantioselectivity.^{79,157} The third generation of α -amino acid derived amides and thioamides were D-mannose derivatives. The corresponding ruthenium complexes of β -hydroxy-amides and rhodium-complexes of thioamides acted as ATH catalysts for ketones in a complementary way and allowed to access both enantiomers of each alcohol (Scheme 33).¹⁵⁸ These catalysts were highly efficient in the ATH of a broad scope of ketones (41 examples, up to >99% ee), i.e. aryl,alkyl-, alkyl,alkyl-, heteroaryl- and unsaturated ketones, but also in tandem isomerization/ATH reactions (rhodium and ruthenium catalysts, 11 examples, up to 99% ee) and in the tandem alkylation/ATH of acetophenones and acetyl pyridine (ruthenium catalyst, 8 examples, up to 92% ee).



Tandem α -alkylation/ATH



Tandem isomerization/ATH



Scheme 33. Sugar-modified α -amino acid derived hydroxyamide and thioamide ligands applied in the ATH and tandem reactions of ketones by Diéguez, Pàmies and co-workers.¹⁵⁸

These recent developments prove that chiral rhodium catalysts bearing either thetered Cp*/diamine ligands or amino acid as well as pseudopeptide based ligands are suited for asymmetric transfer hydrogenation of various ketones. Even if they were less investigated then their ruthenium congeners, efforts to design new chiral ligands for rhodium catalyzed asymmetric transfer hydrogenation has led to significant achievements.

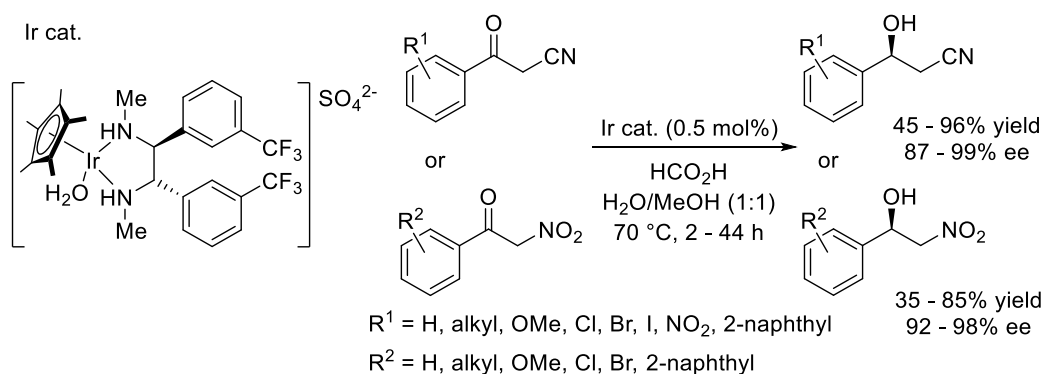
C. Iridium Catalysed Transfer Hydrogenations.

Only a few new bifunctional iridium catalysts have been developed in the last decade for applications in ATH. These catalysts may display either active NH functions, according to the Noyori's model, or remote H-bonding functions that participate in the stereochemical control by interacting with the substrates. Two innovative concepts have been introduced in terms of catalyst design, i.e. the use of iridium-based artificial metallo-enzymes and chiral-at-metal octahedral complexes.

1. Amino- and Amido Iridium(III) Catalysts with Active NH Functions.

Iridium catalysts displaying classical diamines, sulfonylated diamines or tridentate phosphine-diamines as chiral ligands, were often investigated in parallel to ruthenium and rhodium catalysts and proved to be useful for the ATH of ketones and imines.^{11,159} The common feature of these complexes is that an NH function of the ligand participates in the enantiodetermining step via H-transfer to the substrate.

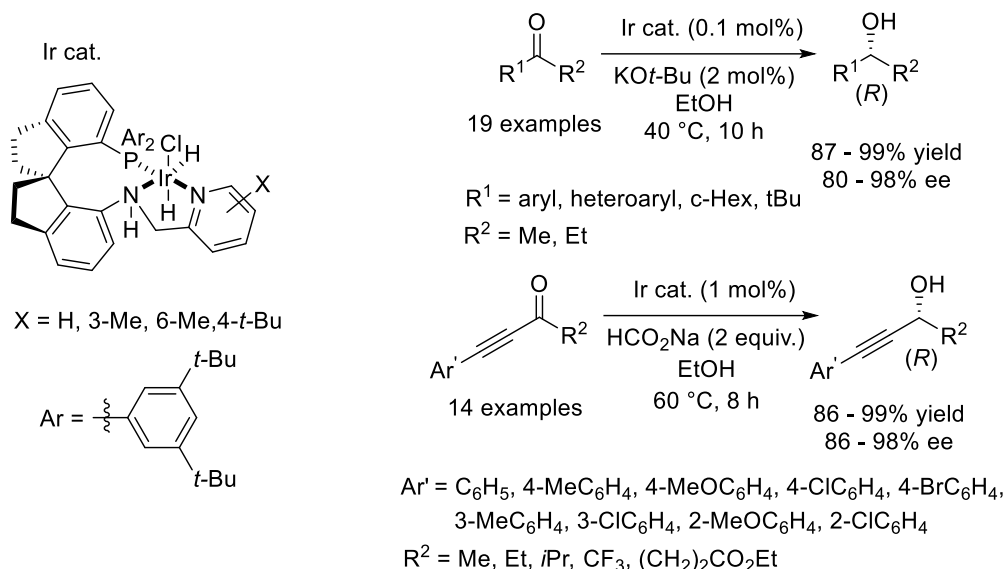
Initially, Wills and co-workers applied proline-functionalized DPEN, already introduced in section II.A.1 as chiral ligands for ruthenium complexes, to rhodium and iridium promoted ATH of ketones.⁶⁹ However, these catalysts were far less efficient than their ruthenium counterparts. Combined with $[\text{RhCl}_2\text{Cp}^*]_2$, these ligands gave 3-68% conversions and up to 85% ee; while with $[\text{IrCl}_2\text{Cp}^*]_2$, they gave 0-33% conversion and 14-47% ee (4 examples). In parallel studies however, Carreira and co-workers designed new aqua iridium(III) catalysts that proved successful for the challenging ATH of α -cyano and α -nitro acetophenones (Scheme 34).¹⁶⁰ Optically active 1,2-diamine ligands appeared as interesting alternatives to the commonly used monosulfonylated diamines. Four stable aqua iridium(III)-diamine complexes were evaluated in the ATH of 2-cyanoacetophenone with sodium formate in water/methanol and led to the corresponding alcohols in 63-90% yields and 47-95% ees. The best catalyst proved to be a DPEN derivative with *m*-CF₃ substituents on the phenyl groups of the diamine. It was highly active for the ATH of α -cyanoketones and little less active for the ATH of α -nitroketones, high enantioselectivities being reached in both cases. In particular, *ortho*-substituted acetophenones ketones were hydrogenated with excellent ees thanks to an “*ortho*-effect”.



Scheme 34. ATH of α -cyano and α -nitro acetophenones with iridium aqua-diamine complexes, by Carreira and co-workers.¹⁶⁰

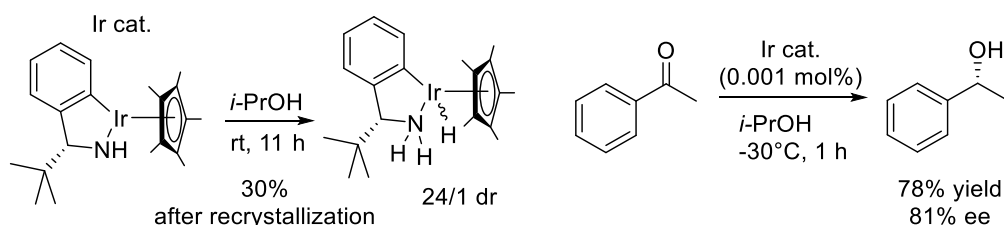
Other catalytic processes were developed by Xie, Zhou and co-workers by applying iridium(III) catalysts based on tridentate pyridine-aminophosphine ligands displaying a spiranic scaffold to the ATH of ketones and alkynyl ketones (Scheme 35).¹⁶¹ The reactions proceeded in ethanol and afforded the corresponding chiral alcohols with excellent conversions and enantioselectivities. Authors demonstrated that ethanol was converted into ethyl acetate, thus providing the hydride required for the hydrogenation

reaction. Zhou and co-workers subsequently studied the ATH of alkynyl ketones using the same family of iridium complexes. Thanks to a combination of sodium formate and ethanol as hydrogen sources, the catalytic system did not require any base to proceed and led to the very efficient ATH of alkynyl ketones (catalyst 0.5–1 mol%, 90 °C, 4–48 h, 86–99% yield and 84–98% ee).¹⁶²



Scheme 35. P,N,N-tridentate ligands for the iridium catalysed ATH of aryl,alkyl-ketones and alkynyl ketones, by Xie, Zhou and co-workers.¹⁶¹⁻¹⁶²

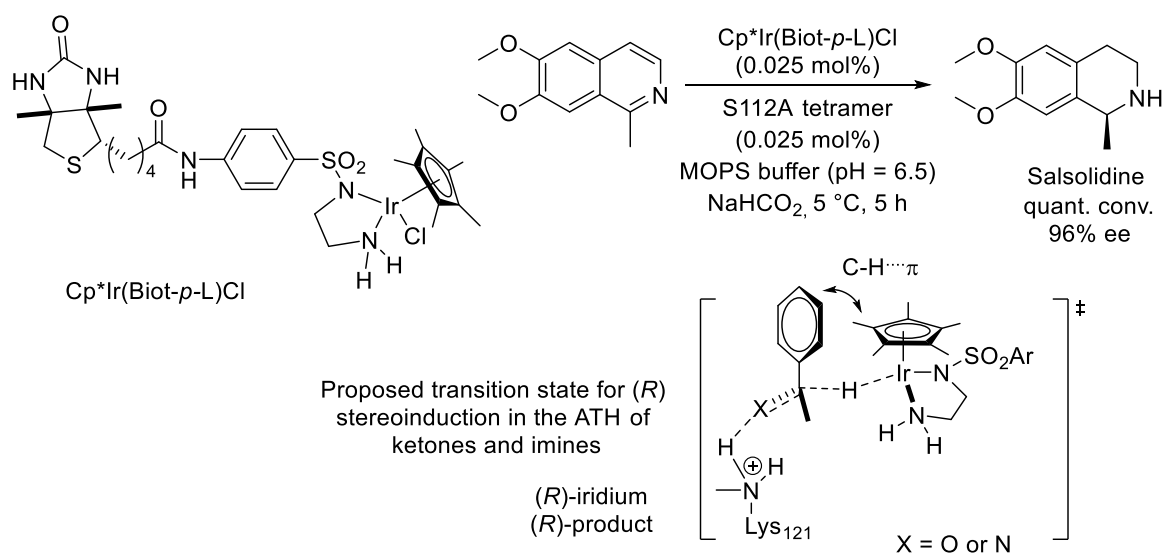
Ikariya, Kayaki and co-workers prepared C,N-chelated amidoiridium metallacycles bearing a stereogenic carbon centre α to the amido moiety.¹⁶³ Monomeric and dimeric iridium complexes were characterized. Monomeric species exhibited outstanding catalytic activity in the ATH of acetophenone in *i*-PrOH, furnishing (*S*)-phenyl ethanol with high ee (*S*/*C* = 1000, 4 h at -30°C, 78% yield, 81% ee). It was demonstrated that the unsaturated amido iridium complex reacts with *i*-PrOH to give the corresponding amino-hydrido complex as a mixture of two diastereoisomers in a 24/1 ratio (Scheme 36). It was proposed that the steric hindrance of the *t*-Bu group directs the addition of *i*-PrOH to the amido complex, leading to the highly selective formation of the $R_C S_I$ isomer of the iridium hydride. In the ATH reaction, this complex induced then hydride and proton transfers to the *Re*-face of the ketone, the reaction being controlled by the attractive CH/ π interactions between the phenyl ring of the substrate and the Cp* ligand.



Scheme 36. Cyclometalated amidoiridium catalyst in the ATH of acetophenone, by Ikariya, Kayaki and co-workers.¹⁶³

A highly innovative approach to enantioselective metal catalysis has been introduced by T. Ward who developed the so-called artificial metalloenzymes, by introducing an organometallic catalyst within a protein environment by means of non-covalent interactions. Among others, in 2008, Ward, Stenkamp and co-workers reported η^6 -arene-ruthenium complexes bearing a biotinylated aminosulfonamide ligand that, combined with suitable proteins, could be used in the ATH of ketones.¹⁶⁴ Later on, in 2011, Ward and co-

workers described the application of analogous iridium complexes to ATH reactions.¹⁶⁵⁻¹⁶⁸ They identified a biotinylated Cp* iridium complex, combined with streptavidin (Sav), as the most promising catalyst for the ATH of imines, while ruthenium and rhodium complexes were superior for the hydrogenation of ketones.¹⁶⁶ Iridium complexes were used notably for the preparation of Salsolidine through ATH of the isoquinoline precursor. After chemical and genetic optimization of the artificial transfer hydrogenase, the synthesis of Salsolidine was efficiently realized with up to 96% ee (Scheme 37). Based on X-Ray structural data, the authors suggested that the reaction could proceed through a non-concerted mechanism, that a CH- π interaction may contribute to the stereochemical control and that the K121 residue of S112A Sav may participate in the protonation step to afford the chiral amine (Scheme 37). This proton transfer from the ammonium group of the supramolecular biotine-Sav ligand to the imine seems essential for the ATH reaction to proceed.^{167,168}

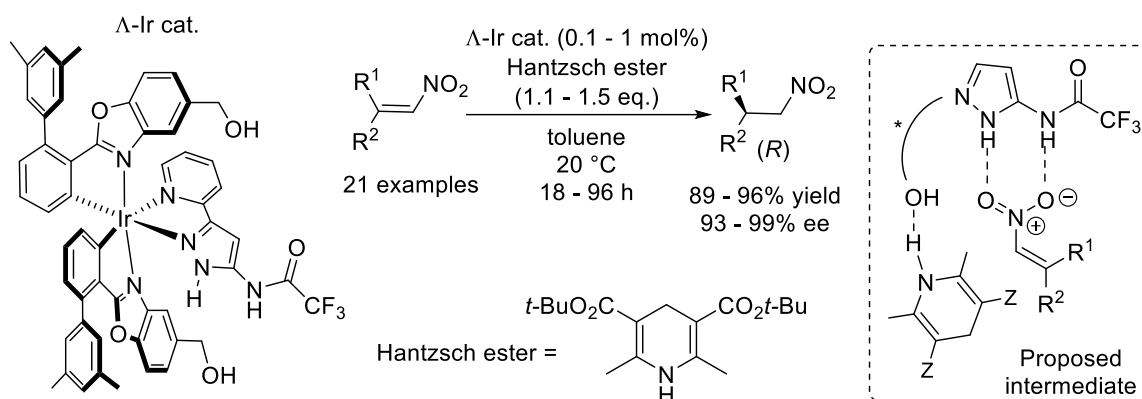


Scheme 37. Salsolidine synthesis by ATH catalyzed by an artificial enzyme and postulated transition state, by Ward and co-workers.¹⁶⁶

Thus, this work on iridium complexes provides new examples of reactions where a supramolecular ligand enables a catalytic process thanks to the involvement of a remote functional group.

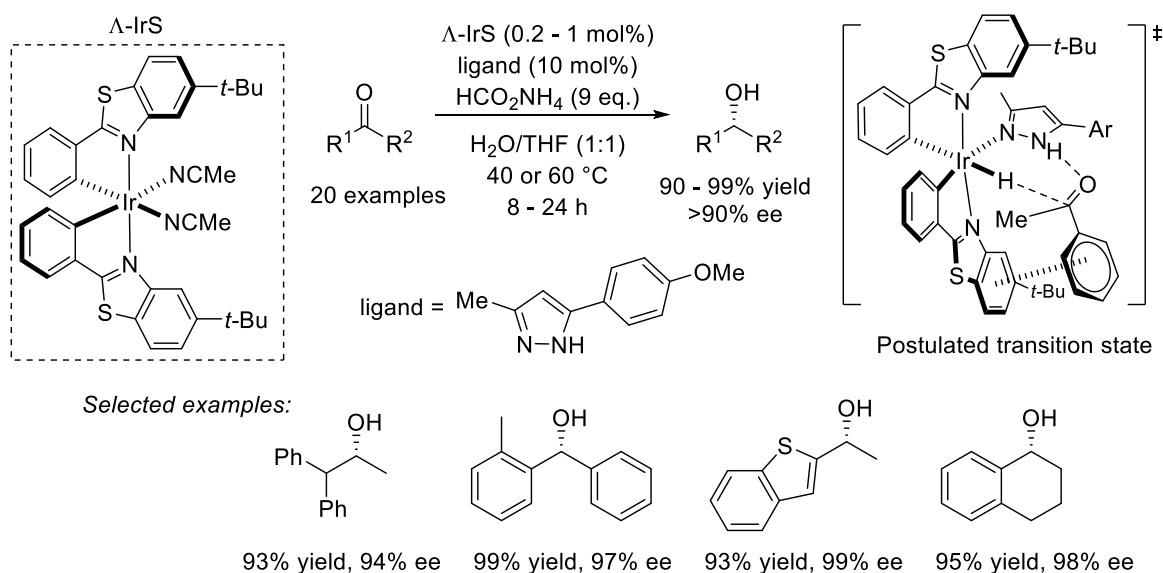
2. Octahedral Chiral-at-Metal Iridium(III) Catalysts with π -Stacking and H-Bonding Ligands.

Within their extended studies on chiral-at-metal complexes, Meggers and co-workers developed bis-cyclometalated octahedral iridium(III) complexes in which the metal is the only stereogenic element.¹⁶⁹ These complexes contain two metallacyclic units made of C,N-bidentate benzoxazole-type ligands positioned in a propeller-type fashion. The chiral iridium centre is also coordinated by a bidentate 5-trifluoroacetamido-3-(2-pyridyl)-1H-pyrazole ligand (Scheme 38). In the ATH of nitroalkenes with Hantzsch esters as hydrogen donors, the trifluoroacetamido-pyrazole unit of the ligand acted as a double hydrogen-bond donor to the substrate. Concurrently, the hydroxymethyl substituent of one of the benzoxazole ligands served as hydrogen-bond acceptor toward the Hantzsch ester. Thanks to the conformational constraints generated by these cooperative interactions between the catalyst and the substrate, the ATH of nitroalkenes proceeded in high yields and enantioselectivities at low catalysts loadings.



Scheme 38. Chiral-at-metal iridium catalysts for ATH of nitroalkenes and proposed reaction intermediate, by Meggers and co-workers.¹⁶⁹

In order to access highly efficient catalysts for the ATH of ketones, Meggers and co-workers modified their catalyst by combining two phenylbenzothiazole-based metallacycles and a monodentate ligand.¹⁷⁰ 3,5-dimethyl-pyrazole appeared to be the best choice to reach efficient and selective iridium catalysts for ATHs using HCO_2NH_4 as hydrogen source in $\text{H}_2\text{O}/\text{THF}$ as solvent mixture (Scheme 39). It was proposed that, after coordination of the pyrazole ligand to the Ir precursor by substitution of acetonitrile, the iridium complex reacts with ammonium formate to generate an active iridium hydride species, with the assistance of the pyrazole ligand. The complex behaves as a bifunctional catalyst, giving concerted transfer of both the hydride and the pyrazole NH proton to the carbonyl, and leads to the chiral alcohol product. Minimal steric hindrance as well as additional π - π stacking between the aromatic ring of the substrate and one of the benzothiazole ligands were suggested to account for the high level of asymmetric induction (Scheme 39).

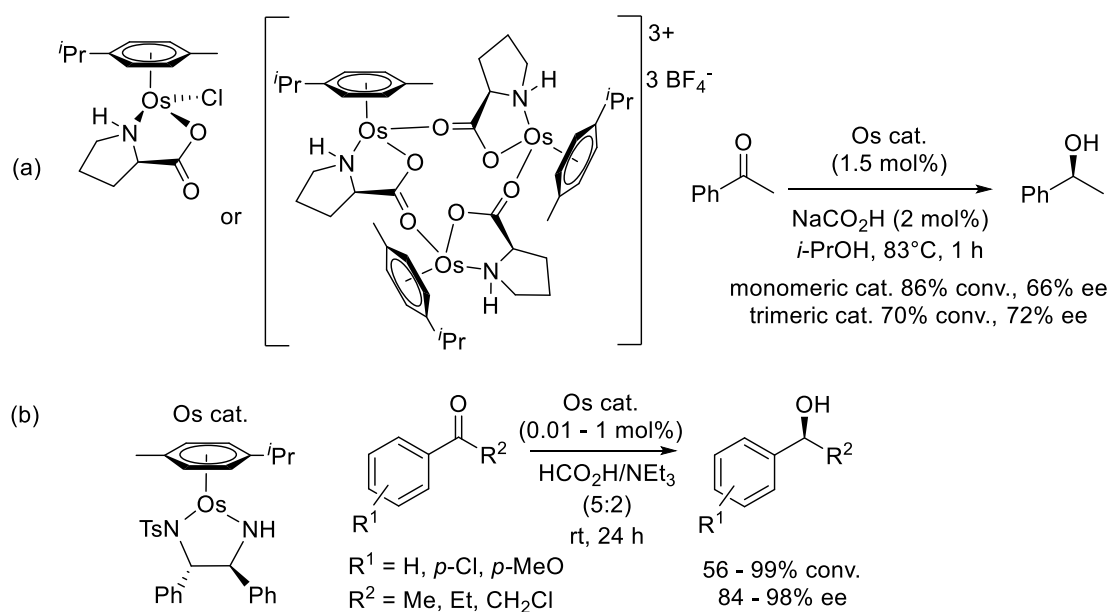


Scheme 39. Chiral-at-metal iridium catalysts for ATH of ketones and proposed transition state, by Meggers and co-workers.¹⁷⁰

Enantiomeric excesses of over 90% were attained in the ATH of a variety of aryl- or heteroaryl-methyl ketones, β -ketoesters, indanone and a diaryl-ketone (20 examples). These excellent results have validated the Meggers's ambitious design of chiral-at-metal catalysts for ATH reactions.

D. Osmium Catalysed Transfer Hydrogenations.

Considering the potential of ruthenium catalysts for application in ATH of ketones, it was not surprising the potential of osmium catalysts was similarly considered. Indeed, piano stool osmium complexes were investigated while being associated essentially with ligands like α -amino acid derivatives¹⁷¹ and TsDPEN.¹⁷² The ATH mechanism of such catalysts was also studied by calculations for the specific case of pyruvic acid reduction.¹⁷³ Carmona and co-workers developed the synthesis of mono and trimeric half-sandwich osmium complexes bearing amino acid derivatives.¹⁷¹ The neutral monomeric and cationic trimeric compounds catalysed ATH of few ketones like acetophenone using *i*-PrOH with up to 72% ee (Scheme 40a). It was assumed that these catalysts proceeded through a Noyori's bifunctional mechanism. Afterwards, Sadler, Wills and co-workers developed robust and effective (*p*-cymene)osmium catalysts containing the original TsDPEN ligand coordinated in monodentate or bidentate modes in ATH of acetophenone derivatives was successfully performed in average to high conversions and high ees (Scheme 40b).¹⁷²



Scheme 40. Monomeric and trimeric arene-osmium catalyst for ATH of ketones by Carmona and co-workers¹⁷¹ (a) and by Sadler, Wills and co-workers (b).¹⁷²

These new osmium-arene catalysts are effective in the ATH of prochiral ketones. They operate most probably following Noyori's bifunctional mechanism. The ease of preparation of the pre-catalysts and their high stability makes them attractive for applications in ATH transformations.

III. Asymmetric Hydrogenations Using Bifunctional Catalysts.

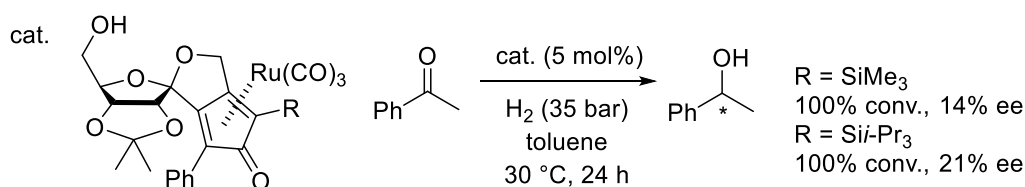
This section relates to the catalytic hydrogenations of ketones, imines and olefins where molecular hydrogen itself is used as the reducing agent, under metal activation. As in the previous section, ruthenium, rhodium and iridium-based catalysts that operate as bifunctional catalysts are considered. In terms of reaction pathways, the most frequent remains the cooperative H-transfer from the metal and from an amino-group of the ligand. In addition, bifunctional catalysts giving H-bonds with the substrates have been reported.

A. Ruthenium Catalysed Hydrogenations.

1. Shvo Type Catalysts.

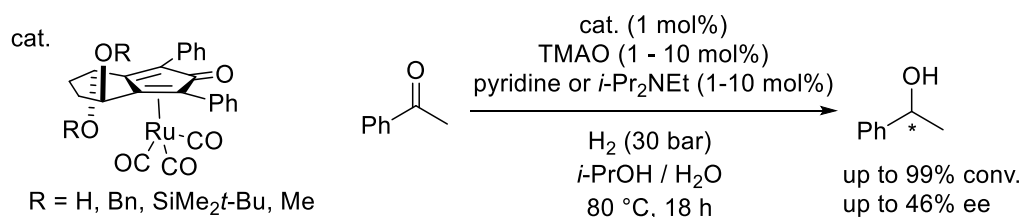
Recently, a few attempts have been made to use chiral analogues of the Shvo catalyst in the asymmetric hydrogenation (AH) of simple ketones. Despite the high catalytic activity, these attempts met with moderate success only, in terms of enantioselectivity levels.

Thus, inspired by the Shvo catalyst (Scheme 26),¹³⁶⁻¹³⁸ Yamamoto and co-workers reported the synthesis of spirocyclic C-ribose derived ruthenium complexes (Scheme 41).¹⁷⁴ In terms of mechanism, the successful application of an ex-situ prepared active hydride ruthenium complex bearing the ribose-derived hydroxycyclopentadienyl ligand allows a close correlation with the bifunctional Shvo catalysts mode of action described in ATH section II.A.2. Such chiral ruthenium catalysts proved to be active for the asymmetric hydrogenation of acetophenone, but the enantiomeric excesses were low.



Scheme 41. AH of acetophenone using a ruthenium cyclopentadienone catalyst, by Yamamoto and co-workers.¹⁷⁴

In 2019, Wills and co-workers reported a series of four enantiomerically-pure ruthenium tricarbonyl cyclopentadienone complexes derived from chiral bicyclic cyclopentenones (Scheme 42).¹⁷⁵ All were active in the model AH of acetophenone but the enantiomeric excesses were low. Interestingly, enantiomeric excesses could be increased up to 46% by combining hydrogenation and transfer hydrogenation, i.e. by running the reaction under hydrogen, in aqueous isopropanol with a catalytic amount of *i*-Pr₂NEt or pyridine.



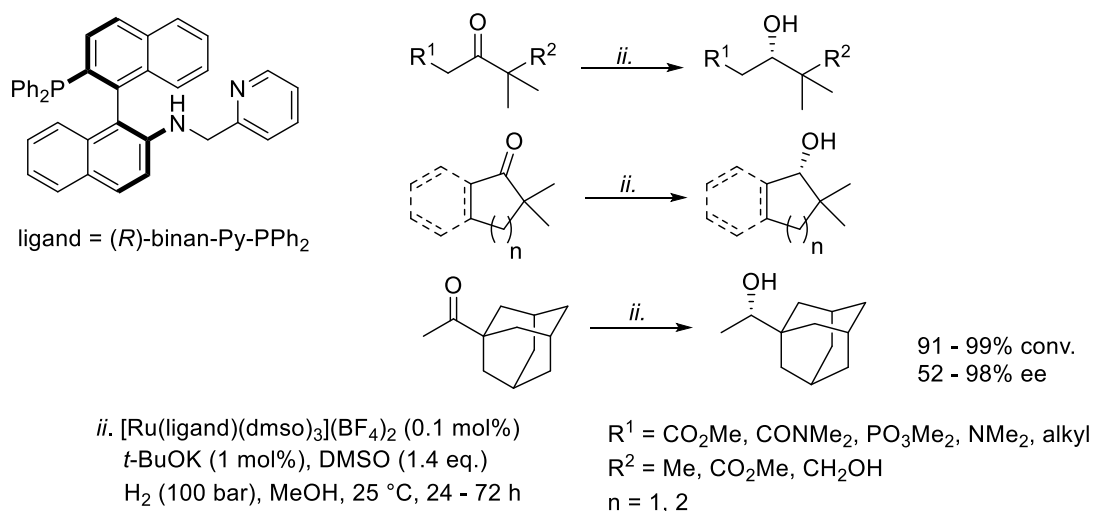
Scheme 42. AH of acetophenone using a ruthenium cyclopentadienone catalyst, by Wills and co-workers.¹⁷⁵

2. Noyori Type Catalysts.

Parallel to the investigation of Noyori type ruthenium catalysts for the asymmetric transfer hydrogenation, research efforts have been directed toward the application of such catalysts also in asymmetric hydrogenation in presence of molecular hydrogen. During the last decade, several classes of chiral ligands such as diaminophosphines (P,N,N) and tetradentate (N₂(NH)₂) have been associated to ruthenium as well as phosphino amine (P,N) and diamines (N,N) to η^6 -arene-ruthenium, and diamines tethered to η^6 -arenes. Selected examples of applications of such ligands are given below.

Tridentate phosphino diamine ruthenium catalyst.

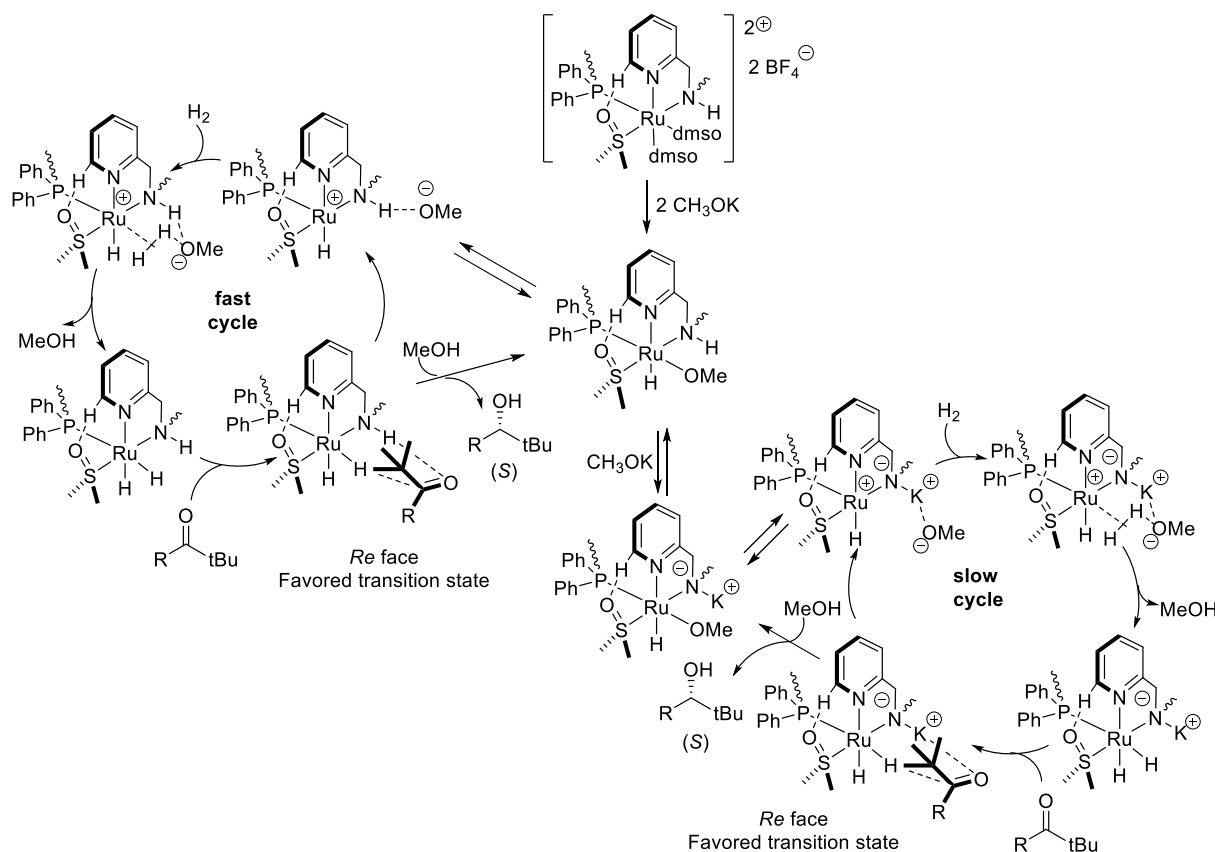
Kitamura and co-workers developed a chiral ruthenium(II) complex based on an axially chiral PN(H)N ligand, called binan-Py-PPh₂, and containing dimethylsulfoxides as additional ligands.¹⁷⁶⁻¹⁷⁷ Once combined with a catalytic amount of base and an excess of dimethylsulfoxide, this complex catalysed effectively the challenging AH of functionalized and unfunctionalized *tert*-alkyl ketones, the resulting alcohols being obtained in high yields, with good to excellent enantioselectivities (Scheme 43).¹⁷⁶⁻¹⁷⁷



Scheme 43. AH of sterically hindered ketones using a PN(H)N ligand-based ruthenium catalyst, by Kitamura and co-workers.¹⁷⁶⁻¹⁷⁷

Kitamura and co-workers investigated the mechanism of these catalysed hydrogenations through structural analyses, NMR experiments including isotope labelings, kinetic and rate law studies as well as control experiments (Scheme 44).¹⁷⁷⁻¹⁷⁸ At first, the linear and flexible tridentate ligand PN(H)N coordinated to ruthenium and formed selectively a *fac*-octahedral complex by reacting with DMSO. Indeed, the *fac*-[Ru(PN(H)N)(dmsO)₃](BF₄)₂ complex results from the coordination of three DMSO ligands through their soft sulfur atom to the soft ruthenium center, in relative *cis*-positions. Afterwards, the reaction of this pre-catalyst with two equivalents of potassium methanolate, generated from *t*-BuOK in a 9:1 CH₃OH–DMSO mixture, led to the catalytically active ruthenium hydride methanolate complex. The hydrogenation of *tert*-alkyl ketones proceeded then via one of the two outer-sphere bifunctional mechanisms displayed in Scheme 44. Indeed, the hydride methanolate complex may be in equilibrium with the cationic complex with a methanolate counterion, or, alternatively, it can be deprotonated by

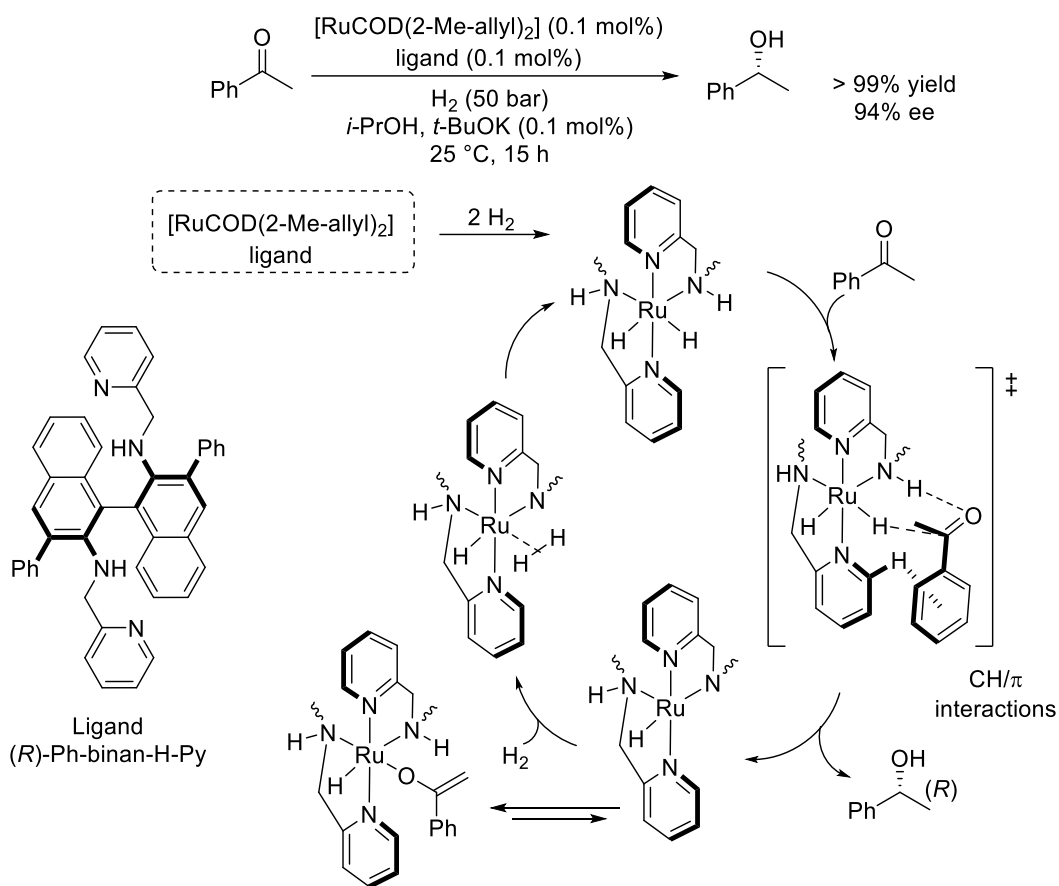
MeOK to give a potassium amide complex. Both complexes proved able to split hydrogen and form active ruthenium dihydride complexes which will transfer then the hydride preferentially to the *Re*-face of the *tert*-alkyl ketone substrates. Finally, the (*S*)-configured alcohols were delivered by reaction with methanol. The catalytic cycle involving the potassium amide complex (Scheme 44, right) is slower and its contribution to the asymmetric hydrogenation was found to depend on the concentration of the base and the pKa of the ketone substrate.



Scheme 44. Mechanism of the AH of sterically hindered ketones using a ruthenium catalyst based on a PN(H)N ligand, by Kitamura and co-workers.¹⁷⁷⁻¹⁷⁸

Tetradentate $N_2(NH)_2$ ruthenium catalyst.

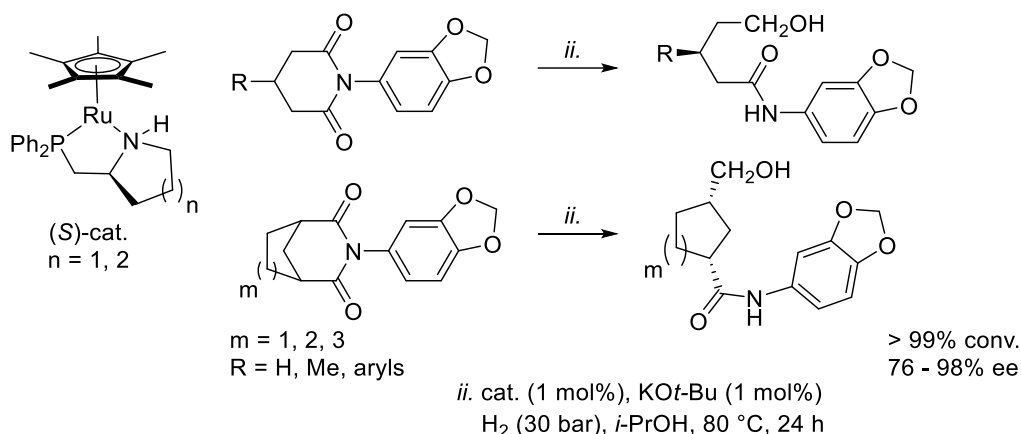
In another work, Kitamura and co-workers focused on a ruthenium(II) catalyst based on a chiral tetradentate amino-pyridine, $N_2(NH)_2$ Goodwin-Lions-type ligand, (*R*)-Ph-binan-H-Py.¹⁷⁹ The AH of acetophenone was effectively performed in high enantiomeric excess and the reaction mechanism was investigated through structural analyses, NMR experiments and kinetic studies (Scheme 45). Authors showed that the reaction between the chiral $N_2(NH)_2$ ligand and the bis(2-methylallyl)cyclooctadiene ruthenium complex, under H_2 pressure, provided the expected *cis* ruthenium dihydride complex in tiny amounts only, the starting materials remaining mostly unreacted. This species proved able to catalyze the hydrogenation of acetophenone through the usual outer sphere H-transfer bifunctional mechanism. The approach of acetophenone to the ruthenium complex through its *Si*-face is efficiently directed by CH/π and hydrogen bonding interactions. This allows a combined hydride and proton transfer affording (*R*)-phenylethanol and a ruthenium amide complex which could be reversibly trapped by acetophenone to give a ruthenium enolate species. Finally, the ruthenium amide complex led to the starting ruthenium dihydride by coordination and split of hydrogen, the hydrogen splitting step being rate-determining.



Scheme 45. Mechanism of the AH of ketones using a ruthenium catalyst based on a $\text{N}_2(\text{NH})_2$ Goodwin-Lions-type ligand, by Kitamura and co-workers.¹⁷⁹

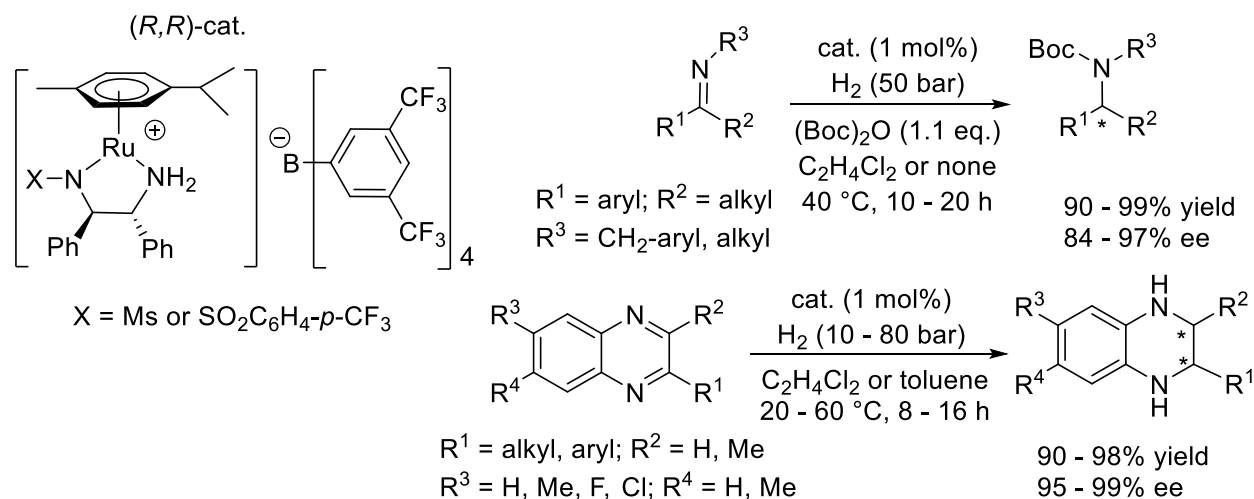
Phosphino amine derived η^6 -arene-ruthenium catalysts.

In 2010, Ikariya and co-workers reported AHs catalysed by piano stool, Cp*-ruthenium(II) complexes comprising simple chiral amino-phosphine ligands, that were initially applied to ATH. For example, ruthenium(II) catalysts based on chiral cyclic PN ligands were applied to the asymmetric hydrogenation/desymetrization of cyclic and bicyclic imides (Scheme 46).¹⁸⁰ These reactions involved cleavage of a C-N bond and led to amides with remote hydroxymethyl groups, with high conversions and good to excellent enantioselectivities. Later on, analogous diamine-based catalysts have been applied to hydrogenative DKR of a lactone.¹⁸¹



Scheme 46. AH of imides using a ruthenium catalyst based on a PN ligand, by Ikariya and co-workers.¹⁸⁰

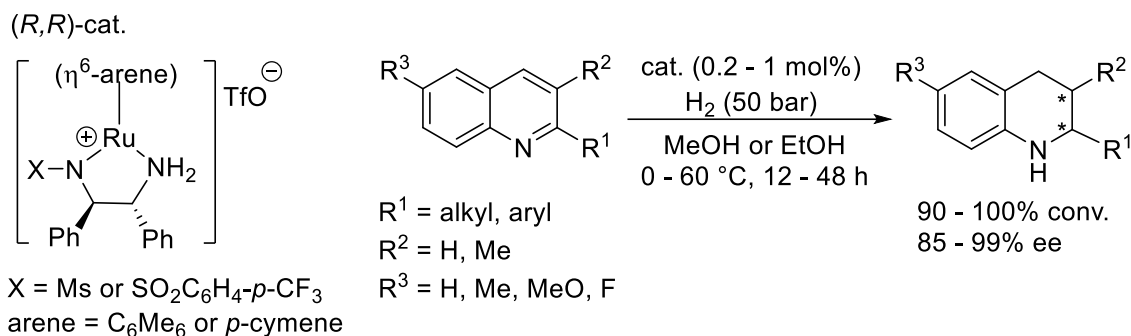
Fan and co-workers studied chiral η^6 -arene-ruthenium(II)-MsDPEN (or other sulfonylated DPEN) catalysts in the AH of a broad range of acyclic and cyclic imines¹⁸²⁻¹⁸³ including quinoxalines (Scheme 47).¹⁸⁴ They demonstrated the use of a cationic catalyst displaying a lipophilic and non-coordinating counterion, i.e. tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (BARF₂₄). This catalyst led to the hydrogenation of these substrates in high yields and enantioselectivities.



Scheme 47. AH of imines and quinoxalines using a cationic ruthenium amido catalyst, by Fan and co-workers.¹⁸²⁻¹⁸⁴

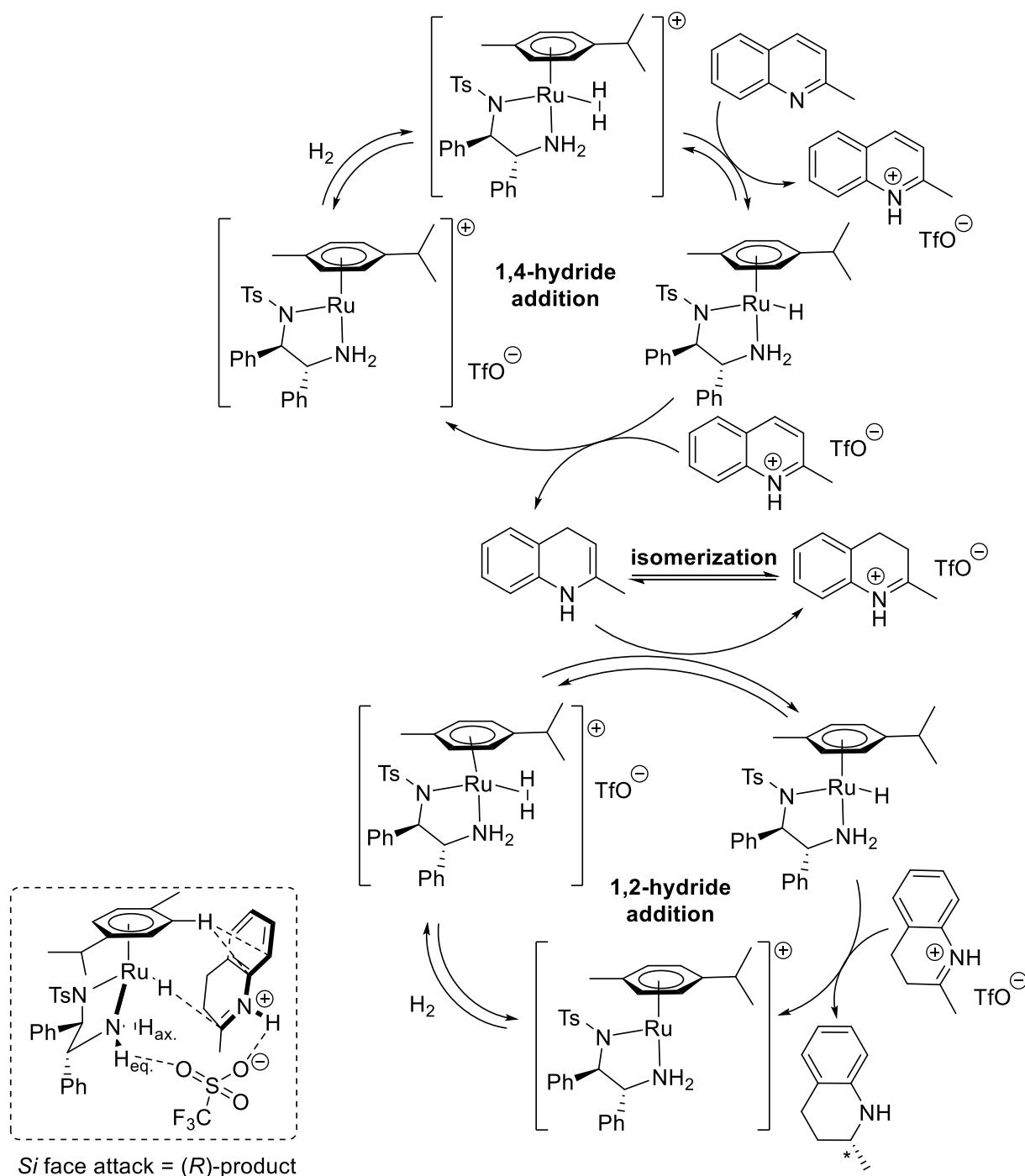
In parallel studies, Chan, Fan and co-workers applied analogous cationic η^6 -arene-ruthenium(II)-MsDPEN or TsDPEN complexes with triflate counterions, to the AH of a broad scope of quinolines

(Scheme 48).¹⁸⁵ The resulting 1,2,3,4-tetrahydroquinolines were obtained with full conversions and high enantioselectivities.



Scheme 48. AH of quinolines using a cationic ruthenium amido catalyst, by Chan and co-workers.¹⁸⁵

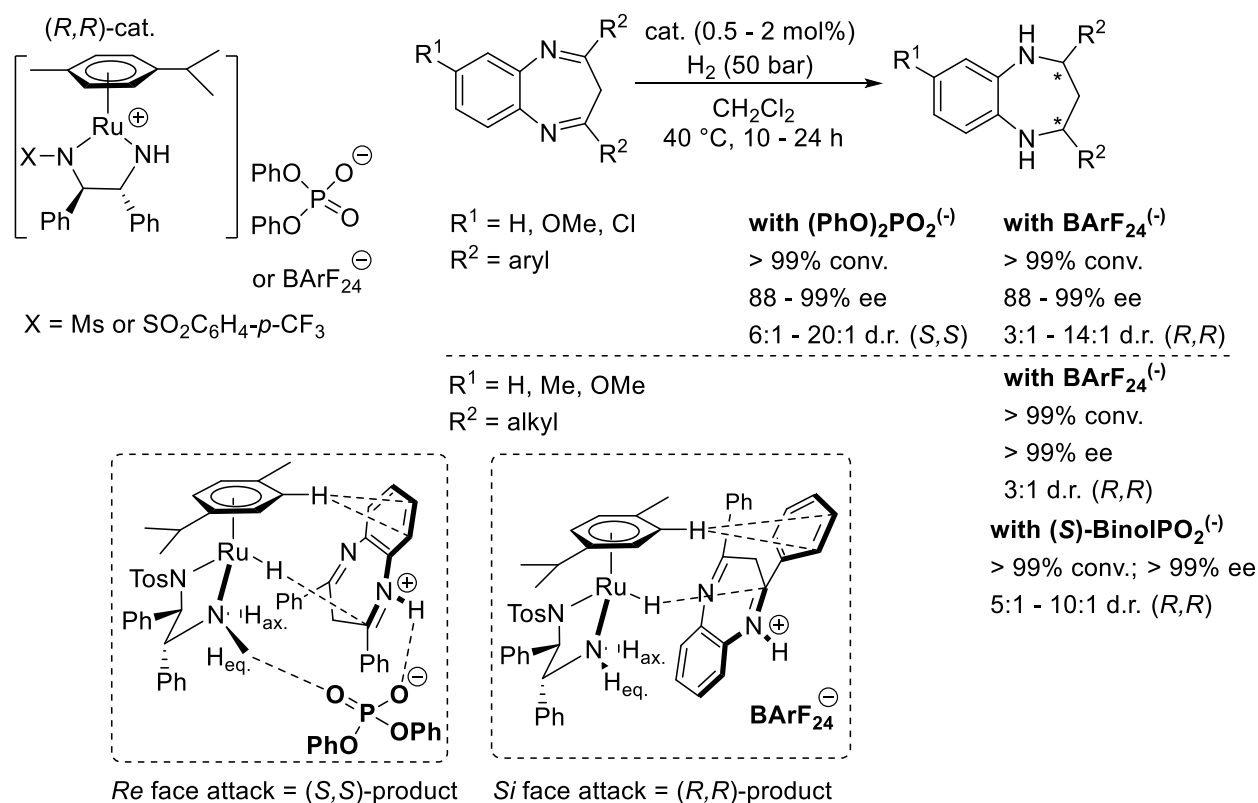
The reaction mechanism was studied through stoichiometric reactions, isolation of intermediates, isotope labelings and theoretical studies. These studies demonstrated a cationic cascade pathway including a 1,4-hydride addition, an isomerization step and a 1,2-hydride addition (Scheme 49). At first, the cationic ruthenium complex coordinates and splits dihydrogen with the assistance of the basic substrate. The resulting ruthenium hydride reacts with the protonated quinoline through a 1,4-hydride transfer to release 1,4-dihydroquinoline and the starting cationic complex. The dihydroquinoline undergoes proton transfer to generate the isomeric 3,4-dihydroquinolinium triflate which serves then as a substrate for the second hydrogenation cycle. The enantiodetermining step consists in an irreversible 1,2-hydride transfer to the iminium salt, assisted by the triflate anion. According to theoretical studies, the transition state would involve CH/ π interactions between the ruthenium arene ligand and the fused phenyl ring of the substrate, as well as hydrogen bonds between the triflate anion and the NH functions of both the substrate and the diamine ligand (Scheme 49). The hydride transfer would proceed on the *Si* face of the dihydroquinolinium and lead to an (*R*)-configured tetrahydroquinoline, as observed experimentally.



Scheme 49. Mechanism of the AH of quinolines using a cationic ruthenium amido catalyst, by Chan and co-workers.¹⁸⁵

Fan and co-workers applied cationic η^6 -arene-ruthenium(II) Ms-DPEN or Tos-DPEN catalysts to the AH of 2,4-disubstituted 1,5-benzodiazepines (Scheme 50).¹⁸⁶ The reduced products were obtained in high yields, enantioselectivities and diastereoselectivities. Upon changing the achiral counteranion from phosphate (PhO)₂PO₂⁽⁻⁾ to BArF₂₄⁽⁻⁾, authors observed a reversal of the enantioselectivity in the hydrogenation of aryl substituted benzodiazepines. Surprisingly, the use of chiral counteranion (*S*-BinolPO₂⁽⁻⁾) did not result in an enantioinversion, perhaps due to its bulkiness. In order to rationalize the enantioinversion, two different transition states were proposed (Scheme 50). The first one would involve

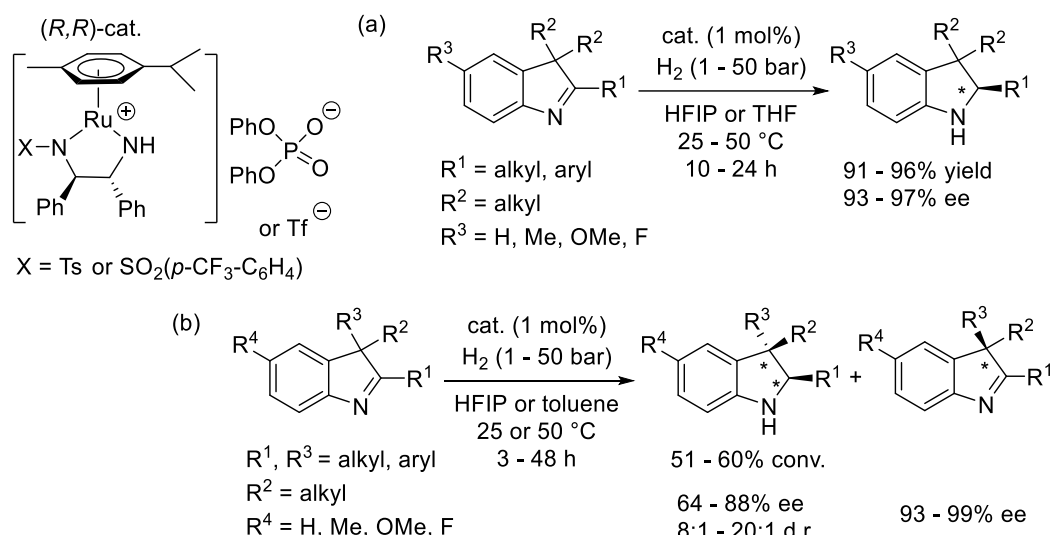
the (*R,R*)-ruthenium catalyst, the phosphate anion and the substrate. CH/ π interactions are established between the η^6 -arene ligand and the fused phenyl ring of the substrate, while hydrogen bonds are formed between the phosphate anion and the NH functions of both the substrate and the diamine ligand. This transition state would allow an hydride transfer to the *Re* face of the substrate and lead to an (*S,S*)-configured product, as observed experimentally. The second possible transition state would involve the (*R,R*)-ruthenium catalyst and the substrate, with CH/ π interactions between the arene ligand and a phenyl substituent of the substrate. The non-coordinating BArF₂₄ anion does not play any role (Scheme 51). This would allow an hydride transfer to the *Si* face of the substrate imine moiety and lead to an (*R,R*)-tetrahydrobenzodiazepine, as observed.



Scheme 50. AH of benzodiazepines using cationic η^6 -arene ruthenium amido catalysts, by Fan and co-workers.¹⁸⁶

Further experimental data confirmed these models. Indeed, the enantioinversion was not observed with alkyl substituted substrates. Moreover, the addition of increasing amounts of methanol, that is expected to suppress hydrogen bonds in the postulated transition state, led to a gradual decrease of the enantioselectivity and even to enantioinversion when the phosphate was the counterion.

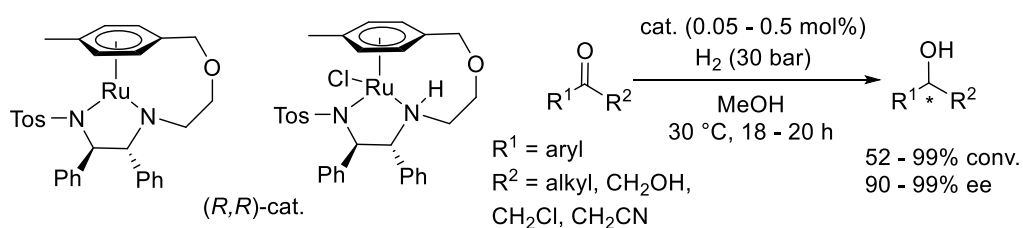
Fan and co-workers applied further the same catalytic system to the AH of imines and indoles (Scheme 51a).¹⁸⁷⁻¹⁸⁸ The reactions proceeded in high yields and enantioselectivities and the kinetic resolution of racemic 3,3-unsymmetrically disubstituted 3H-indoles was also achieved (Scheme 51b).



Scheme 51. AH of indoles using a η^6 -arene amido-ruthenium catalyst, by Fan and co-workers.¹⁸⁷⁻¹⁸⁸

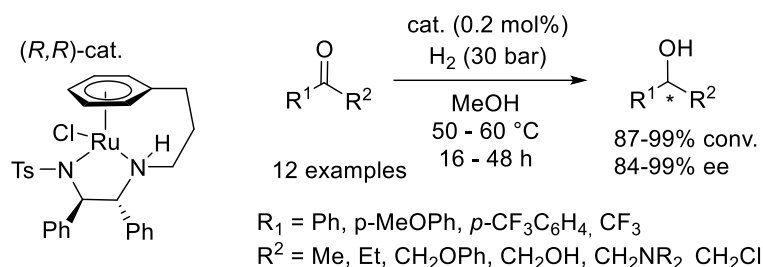
Diamine tethered η^6 -arene-ruthenium catalysts.

Following the successful development by Wills of ruthenium catalysts with η^6 -arenes tethered to diamine ligands, Ikariya and co-workers reported the synthesis and applications of oxo-tethered ruthenium(II) complexes for both ATH (see Scheme 18) and AH reactions (Scheme 52).¹¹⁸ Thus, for instance, the bis-amido-ruthenium complex in Scheme 52 and its HCl adduct could be used in AH reactions. By comparison to non-tethered catalysts, the activity of these species was much higher, ketones being hydrogenated in high yields and enantioselectivities in shorter reaction times, at low catalyst loadings. Results underlined that a fine tuning of the electronic features of the metal and the nitrogen ligands was required in order to optimize the catalyst performances, as well as that the bis-amido complex is usually more active than the ruthenium chloride analogue.



Scheme 52. AH of ketones using oxo-tethered ruthenium catalysts, by Ikariya and co-workers.¹¹⁸

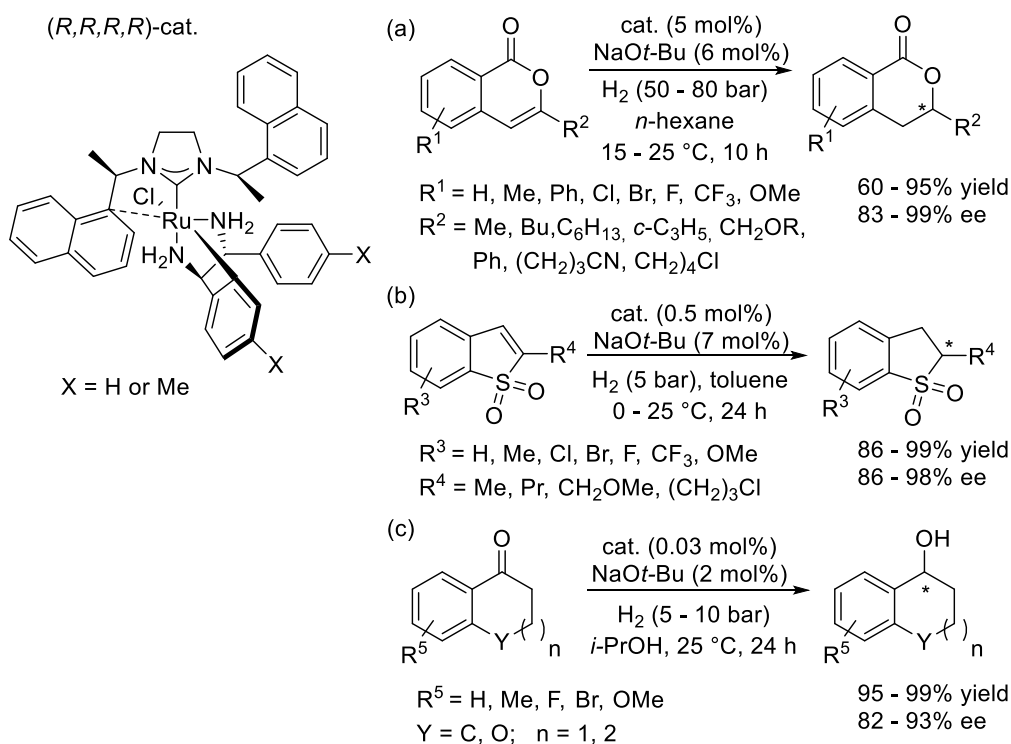
Wills and co-workers studied arene-diamine tethered ruthenium(II) catalysts in the AH of several simple ketones (Scheme 53).¹⁰² At the exception of fluorinated, sterically hindered and α,β -conjugated ketones, all substrates were reduced with high conversions and enantioselectivities using the ruthenium chloride pre-catalysts and without any additional base.



Scheme 53. AH of ketones using a tethered ruthenium amido catalyst, by Wills and co-workers.¹⁰²

Outer sphere hydrogenation catalysts with active NH functions (Noyori's type)

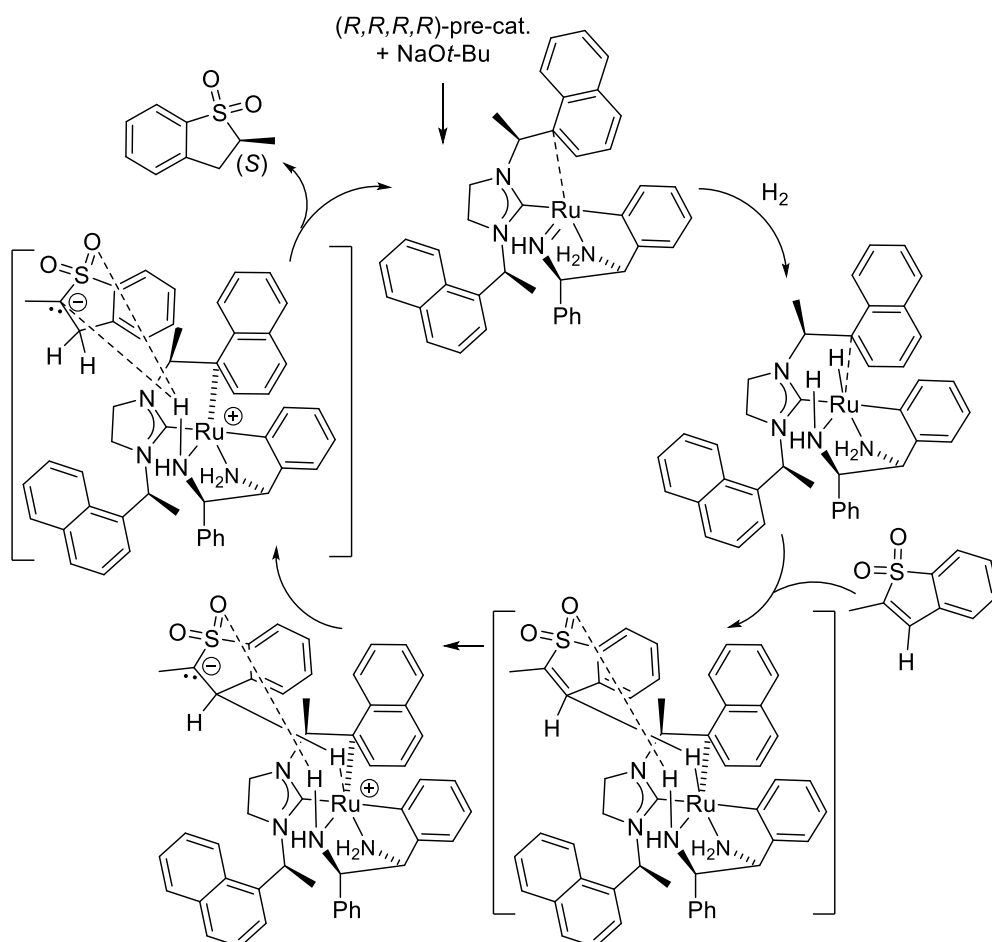
Glorius and co-workers reported the synthesis and applications of some unusual ruthenium(II) complexes displaying chiral *N*-heterocyclic carbenes (NHC) and DPEN type diamine ligands (Scheme 54).¹⁸⁹⁻¹⁹⁰ These complexes feature a C,N-metallacyclic structure involving the phenyl substituent of the DPEN ligand. After activation with *t*BuOK, the complexes catalyse the AH of various isocoumarins in high yields and enantioselectivities, affording key building blocks for the total synthesis of compounds of biological interest like *O*-methylmellein, mellein, and ochratoxin A.¹⁸⁹



Scheme 54. AH of isocoumarins, benzothiophene 1,1-dioxide and cyclic ketones using a ruthenium NHC catalyst, by Glorius and co-workers.¹⁸⁹⁻¹⁹⁰

The catalyst was also effective in the AH of a range of benzothiophene 1,1-dioxides (Scheme 53b), and some cyclic ketones (Scheme 54c).¹⁹⁰ Studies by stoichiometric reactions, NMR experiments and calculations led to a possible reaction mechanism for the hydrogenation of benzothiophene dioxides (Scheme 55). At first, the ruthenium pre-catalyst reacts with the base to give an amido complex which is able to split dihydrogen heterolytically, leading to a ruthenium hydride species. Afterwards, the benzothiophene 1,1-dioxide interacts with the catalyst through hydrogen bonding between the oxygen atom

of the sulfone and the amine NH proton. The hydride and proton transfers proceed in a stepwise manner, as known for other outer-sphere bifunctional hydrogenation processes. First, the nucleophilic ruthenium hydride adds to the β -position of the sulfone to give a stabilized intermediate. Follows a proton transfer from the amine NH to the α -position of the sulfone which takes place preferentially at the *Re* face of the substrate, leading to the (*S*)-configured reduced product. The ruthenium amido complex is released as the catalyst resting state.



Scheme 55. Mechanism of the AH of benzothiophene 1,1-dioxide using a ruthenium NHC-diamine catalyst by Glorius and co-workers.¹⁹⁰

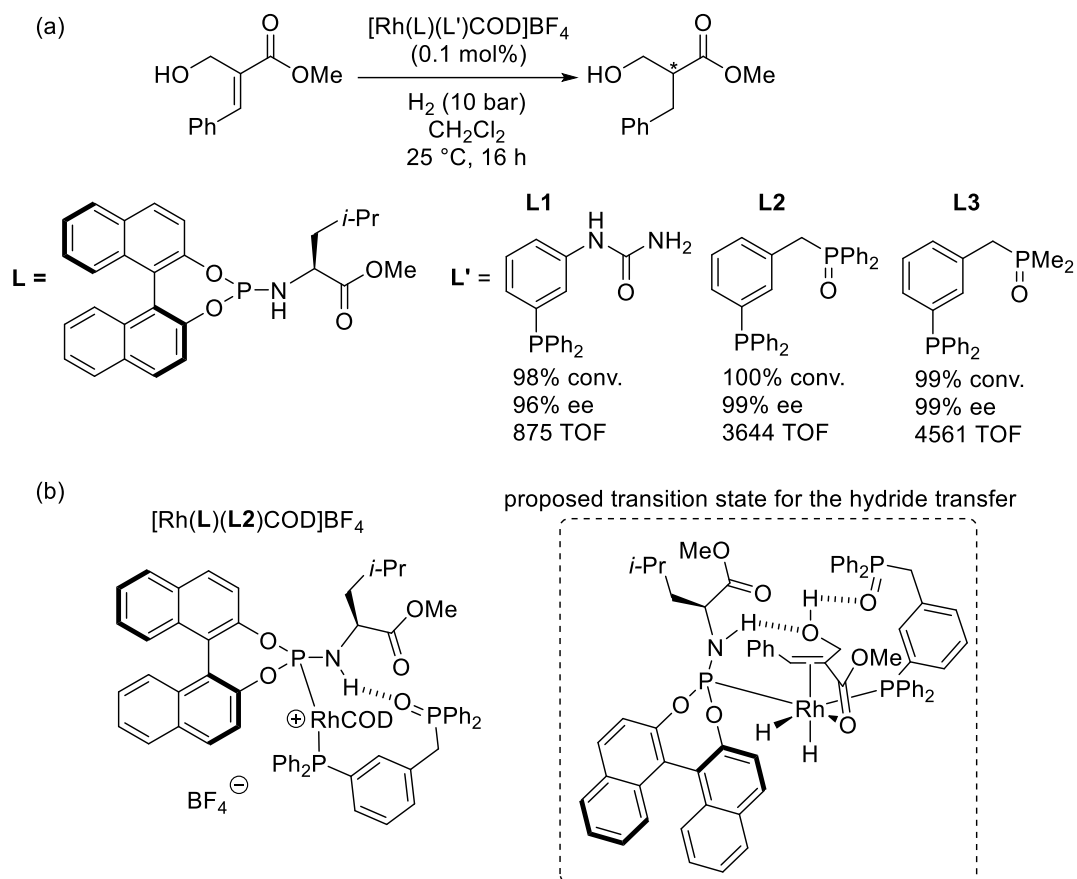
B. Rhodium Catalysed Hydrogenations.

The strategy implying a catalytic rhodium active site combined with a second activation mode has also been investigated in the asymmetric hydrogenation with molecular hydrogen. Hydrogen bonding between ligands and either the substrates or halide counteranions as well as non-covalent interactions through ions pairing between ligands or substrates have been smartly investigated. The selected recent examples given below will highlight the value of such approaches.

1. Catalysts Implying Hydrogen Bondings between Ligands and Either Substrates or Halide Counteranions

Several rhodium-based catalysts for AH reactions have been developed recently by taking advantage of weak, non-covalent interactions between suitably functionalized ligands and substrates to increase the stereochemical control. If classical H-bonding with substrates are still prevailing in this field, the possible role of bondings between H-donors and halide counterions (anion binding catalysis) has been also highlighted and successfully exploited recently. A few examples of these two activation pathways are shown hereafter.

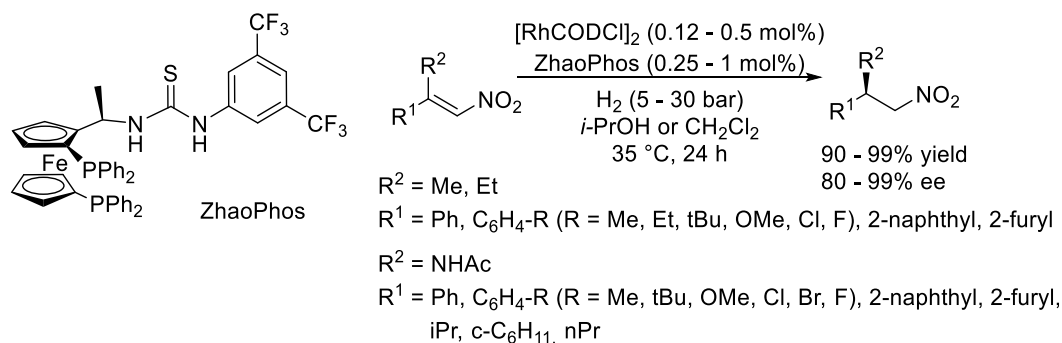
For more than a decade, Reek and co-workers have been working on the application of supramolecular ligands to homogeneous catalysis.¹⁹¹⁻¹⁹² In this context, special attention was paid to ligands able to give H-bondings to other ligands and, therefore, H-bonding phenomena involving ligands and substrates have been often highlighted. A first generation of supramolecular ligands had implied a hydrogen bond between the NH moiety of a phosphoramidite and the carbonyl of a urea-functionalized phosphine.¹⁹¹ A second generation associated phosphoramidites and diphosphine monoxides.¹⁹²⁻¹⁹³ While investigating these second generation catalysts in the rhodium catalysed AH of α,β -unsaturated esters, the authors noticed especially high activities and enantioselectivities for substrates bearing a hydroxyl group (Scheme 56). According to NMR, kinetic and theoretical studies, the catalyst and the α,β -conjugated ester interact through coordination of the C=C and C=O double bonds to rhodium and, additionally, by two hydrogen bonds connecting the hydroxyl group to both the phosphine oxide and the phosphoramidite NH functions. These supramolecular interactions were shown to be strong enough to stabilize the transition state in the rate determining hydride transfer step (see Scheme 56b), thus leading to higher catalytic activities.



Scheme 56. AH of α,β -conjugated ester using supramolecular rhodium catalysts, by Reek and co-workers.¹⁹¹⁻¹⁹³

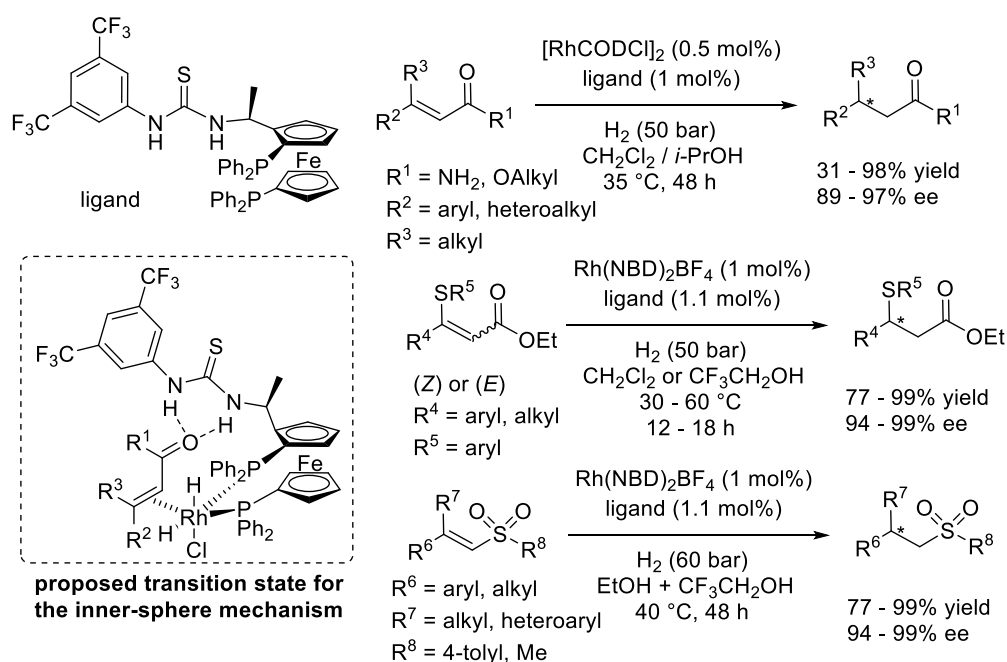
In 2013, Zhang, Wang and co-workers introduced a novel chiral ferrocene-based bisphosphine-thiourea ligand named ZhaoPhos, in order to take advantage from thiourea as an activating and directing group (Scheme 57).¹⁹⁴ This ligand design proved especially successful for applications in rhodium-promoted asymmetric hydrogenations of functionalized, cyclic and acyclic olefins and iminium salts. A few recent examples are shown hereafter.

A rhodium(I)-ZhaoPhos complex was applied to the AH of some challenging β,β -disubstituted nitroalkenes and the hydrogenated products were obtained in high yields and enantioselectivities. According to control experiments and by comparison with other diphosphine ligands, it was demonstrated that the activation of the substrate was effectively directed by the thiourea moiety of the ligand. The catalytic system was further applied to the AH of β -amido nitroolefins, the resulting chiral β -amino nitroalkanes being obtained in high yields and enantioselectivities.¹⁹⁵



Scheme 57. AH of α,β -disubstituted nitroalkenes using a rhodium catalyst based on a bisphosphine-thiourea ligand, by Zhang, Wang, Dong and co-workers.¹⁹⁴⁻¹⁹⁵

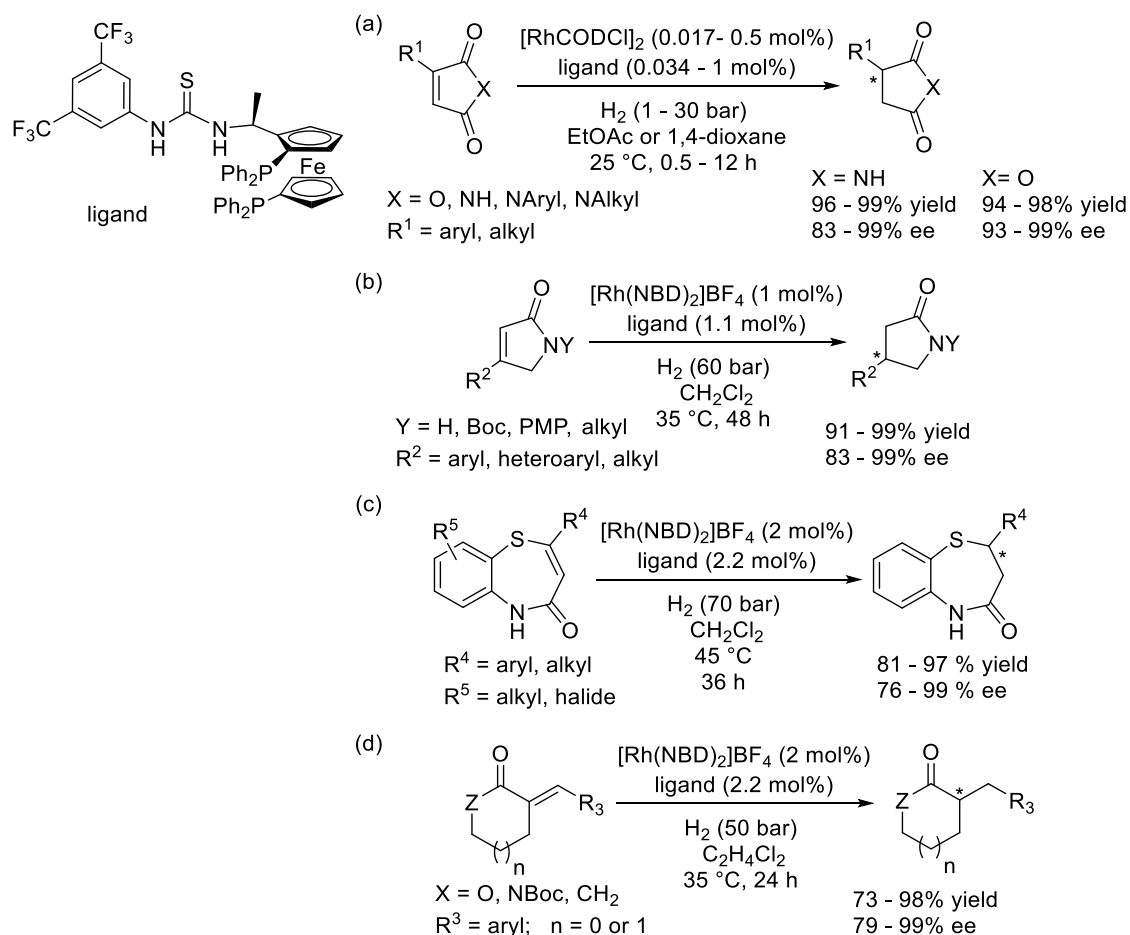
Zhang and co-workers also reported the AH of α,β -unsaturated carbonyl compounds promoted by the rhodium-ZhaoPhos complexes (Scheme 58).¹⁹⁶ At the exception of sterically hindered substrates, the resulting chiral amides and esters were obtained in high yields and enantioselectivities. A reaction under deuterium gas led to an α - and β -deuterated product and therefore indicated an inner-sphere mechanism, like in most common rhodium catalysed hydrogenations. Authors proposed a transition state implying coordination of the C=C double bond to rhodium and H-bonding of the carbonyl with the thiourea moiety. Such catalytic system was then effectively applied to the AH of ethyl (*Z*)- and (*E*)-3-substituted-3-thio-acrylates¹⁹⁷ and α,β -unsaturated sulfones,¹⁹⁸ the latter requiring a specific solvent mixture in order to avoid decomposition of the catalyst (Scheme 58).



Scheme 58. AH of α,β -unsaturated esters and amides, 3-substituted-3-thio-acrylates and α,β -unsaturated sulfones using a ZhaoPhos rhodium catalyst, by Zhang and co-workers.¹⁹⁶⁻¹⁹⁸

The same catalytic system was further applied to the AH of cyclic electron-poor olefins like 3-substituted maleic anhydrides and maleimides (Scheme 59a).¹⁹⁹⁻²⁰⁰ The corresponding 3-substituted succinic anhydrides and succinimides were obtained in high yields and enantioselectivities, using low catalyst loadings. The method was successfully applied to the synthesis of bioactive compounds such as the hypoglycemic drug mitiglinide and a potent α -2-adrenoceptor antagonist.

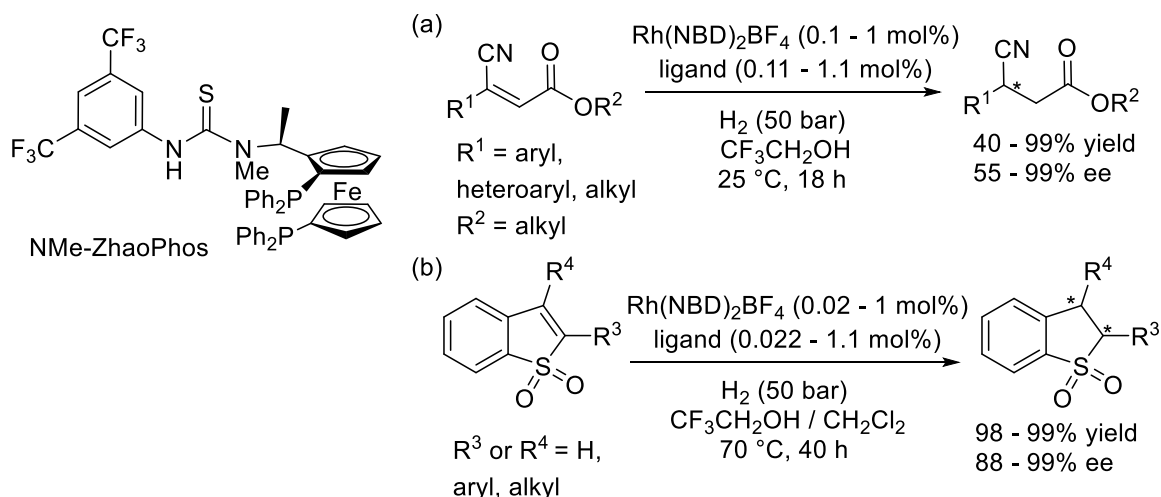
In addition, β -substituted α,β -unsaturated lactams were reduced to the corresponding chiral γ -lactams in high yields and enantioselectivities irrespective of the substituents on the lactam nitrogen (Scheme 59b).²⁰¹ This methodology allowed the synthesis of chiral bioactive compounds such as (*R*)-rolipram, pyrrolidines and γ -amino acids like (*R*)-baclofen, a GABA receptor agonist. 1,5-benzothiazepines were also prepared stereoselectively, without any catalyst inhibition related to the sulfur atom (Scheme 59c). The method allowed a direct access to the antidepressant drug (*R*)-(-)-thiazesim.²⁰² Finally, this catalytic AH could be applied to the reduction of exocyclic double bonds of α,β -unsaturated cyclic carbonyl compounds. The corresponding lactones, lactams and cyclic ketones were obtained in high yields and enantioselectivities (Scheme 59d).²⁰³



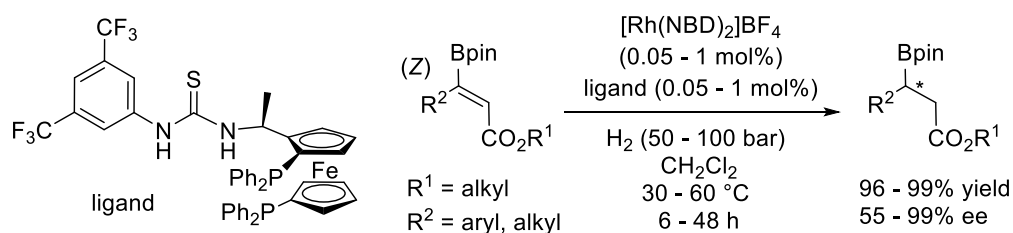
Scheme 59. AH of β -substituted α,β -unsaturated lactams, α,β -unsaturated carbonyl compounds, 3-substituted maleic anhydrides and maleimides using a ZhaoPhos rhodium catalyst, by Zhang, Dong, Yin, Wen, Lv and co-workers.¹⁹⁹⁻²⁰³

While studying the AH of β -cyanocinnamic esters, Zhang and co-workers demonstrated that the simple *N*-methylation of one NH group of the ZhaoPhos ligand improved significantly the enantioselectivity of the hydrogenation reaction, thus enabling an efficient synthesis of chiral γ -aminobutyric acid (GABA) derivatives (Scheme 60a).²⁰⁴ Experiments and calculations were performed to investigate the non-covalent interactions between the substrate and the possible catalytically active species. The results indicated that the *N*-methylated ligand, a single hydrogen bond donor, affords a stronger hydrogen bonding than ZhaoPhos itself that is a potential double hydrogen bond donor. Finally, this catalytic AH was effectively applied to the synthesis of a number of compounds of interest like (*S*)-pregabalin, (*R*)-phenibut, (*R*)-baclofen, chiral δ -amino alcohols, chiral γ -lactam and chiral pyrrolidines.

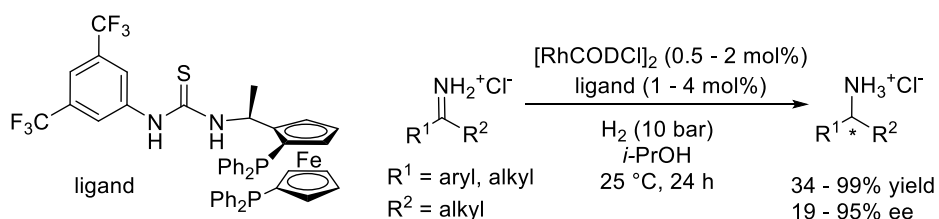
It is worth to note that a series of substituted benzo[*b*]thiophene 1,1-dioxides were also hydrogenated in high yields and enantioselectivities at low catalyst loadings (Scheme 60b).²⁰⁵



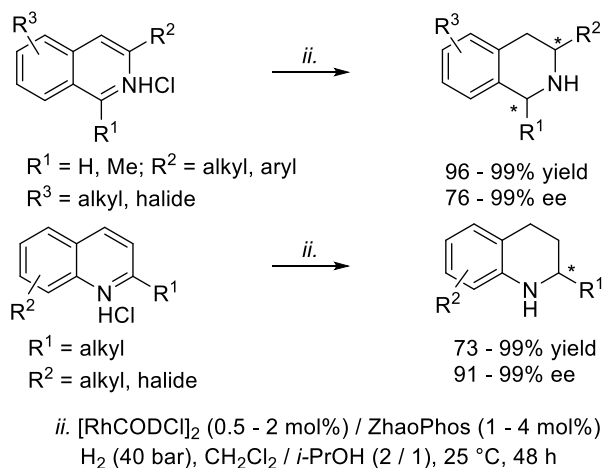
In a recent report, Zhang, Dong and co-workers studied the AH of (*Z*)- β -substituted- β -boryl- α,β -unsaturated esters in the presence of the rhodium-ZhaoPhos catalyst (Scheme 61).²⁰⁶ At the exception of alkyl derivatives (R^2 =alkyl), the β -boryl saturated ester products were obtained in high yields and enantioselectivities, some being subsequently converted to other versatile synthetic intermediates, like methyl (*S*)-3-hydroxy-3-phenylpropanoate and methyl (*S*)-3-(furan-2-yl)-3-phenylpropanoate.



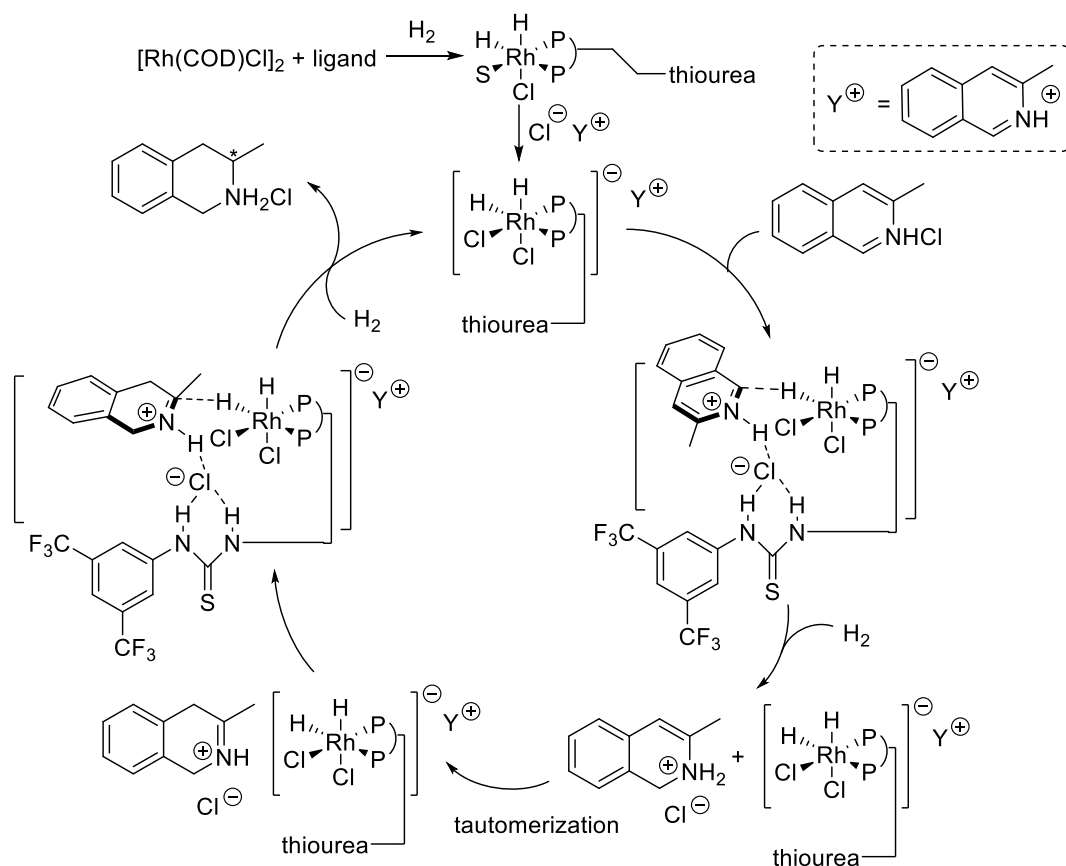
The application of the same bisphosphine-thiourea ligand to hydrogenation processes involving anion-binding type catalysis has been reported. This is typified by the AH of unprotected NH imines shown in Scheme 62. The catalyst was generated in situ from the ligand and $[(\text{COD})\text{RhCl}]_2\text{L}$ and the desired amines were obtained in high yields and enantioselectivities, at the exception of dialkylated substrates.²⁰⁷ While control experiments highlighted that chloride was the best anion for an effective and enantioselective catalytic reaction, a NMR study confirmed that, in the key hydrogenation step, a dual NH-halogen bonding interaction took place between the thiourea unit of the ligand and the chloride counterion, while rhodium was bound to the C=N double bond of the imine substrate.



Zhang, Zhao and co-workers further reported another example of anion binding catalysis by applying the ZhaoPhos ligand to rhodium-catalysed AH of isoquinolines and quinolines activated by HCl (Scheme 63).²⁰⁸ A broad range of substrates was hydrogenated in high yields and enantioselectivities. NMR studies and ligand screening evidenced an anion binding between the thiourea moiety of the ligand and the chloride counterion of the heterocyclic substrate. On the basis of previous reports on the hydrogenation of protonated heterocycles, a σ - or π -bonding between the substrate and the rhodium catalyst, and therefore an inner-sphere reaction mechanism, was unlikely in this case. Hence, a possible outer-sphere reaction mechanism implying a hydride transfer was proposed (Scheme 64). The starting rhodium(I) complex would undergo an oxidative addition of dihydrogen leading to a rhodium(III) dihydride species. The subsequent reaction with isoquinolinium chloride provides an anionic rhodium dichloro dihydride complex. Afterwards, a hydride transfer shall proceed between the equatorial hydride and the isoquinolinium chloride. In this key step, the isoquinolinium chloride is activated by the interaction between the chloride and the thiourea moiety of the ligand. The 1,2-addition process is achieved then by reaction with H₂. The resulting dihydro-isoquinolinium will undergo tautomerization into the corresponding iminium, as confirmed by deuterium labeling experiments. The second hydrogenation step proceeds in a similar way, the enantio-determining hydride transfer being directed by binding of the chloride anion to the thiourea moiety. Finally, reaction with dihydrogen would release the hydrogenated product and the rhodium dichloro dihydride catalyst.

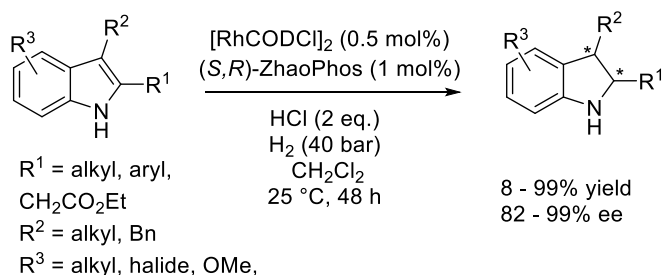


Scheme 63. AH of isoquinolines and quinolines using the ZhaoPhos-rhodium catalyst, by Zhang, Zhao and co-workers.²⁰⁸

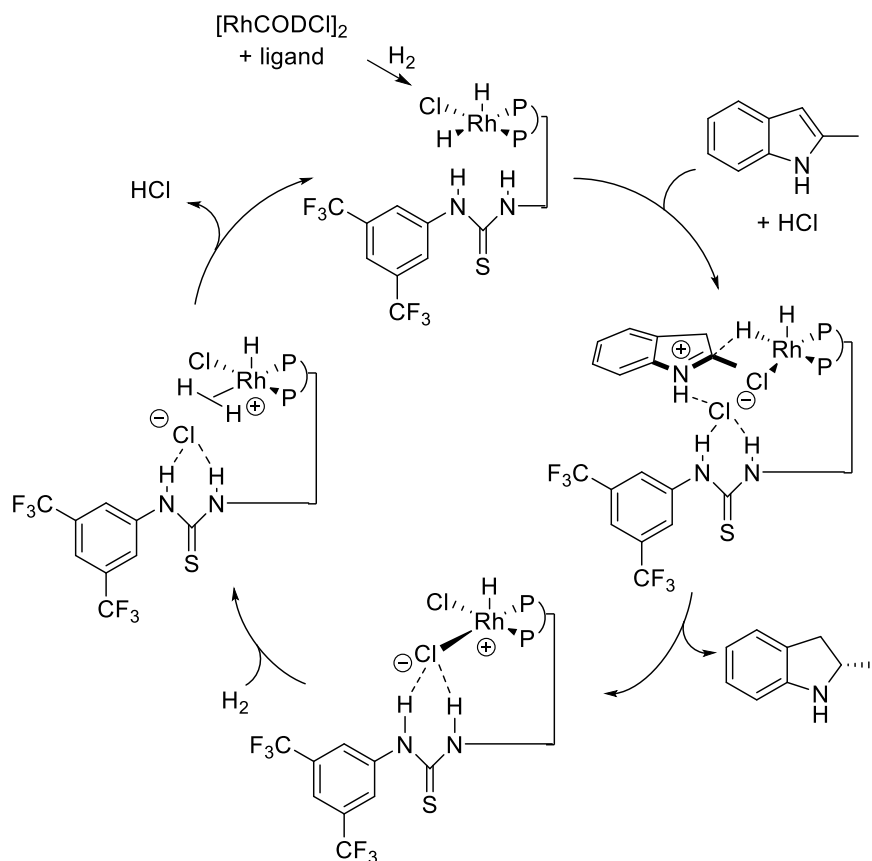


Scheme 64. Mechanism of the AH of isoquinolines using the ZhaoPhos-rhodium catalyst, by Zhang, Zhao and co-workers.²⁰⁸

A similar approach has been used for the rhodium catalysed AH of unprotected indoles in the presence of acids (Scheme 65).²⁰⁹ At the exception of 2-aryl derivatives which were poorly reactive, all substrates led to chiral indolines in high yields and enantioselectivities. Once again NMR and mechanistic studies evidenced an anion binding between the thiourea moiety of the catalyst and the chloride counterion of the heterocyclic substrate. An outer-sphere reaction mechanism was proposed according to deuterium labelling experiments and calculations (Scheme 66), although a mechanism implying an electrostatic interaction between an anionic rhodium complex and the cationic indolinium could not be excluded. At first, the starting rhodium(I) complex undergoes an oxidative addition of hydrogen to generate the active five-coordinated rhodium(III) dihydride species. Further reaction with the indole hydrochloride affords a catalyst-substrate adduct wherein the hydride transfer occurs at the *Re*-face of the protonated indole, in position 2, following an outer-sphere process. The enantioselection is directed by the chloride bridge between the protonated substrate and the thiourea moiety. After release of the indoline, the catalyst is activated by heterolytic cleavage of a hydrogen molecule assisted by the chloride anion. This rate-determining step gives HCl and the active rhodium dihydride species.



Scheme 65. AH of unprotected indoles using a ZhaoPhos-rhodium catalyst, by Zhang, Chung and co-workers.²⁰⁹



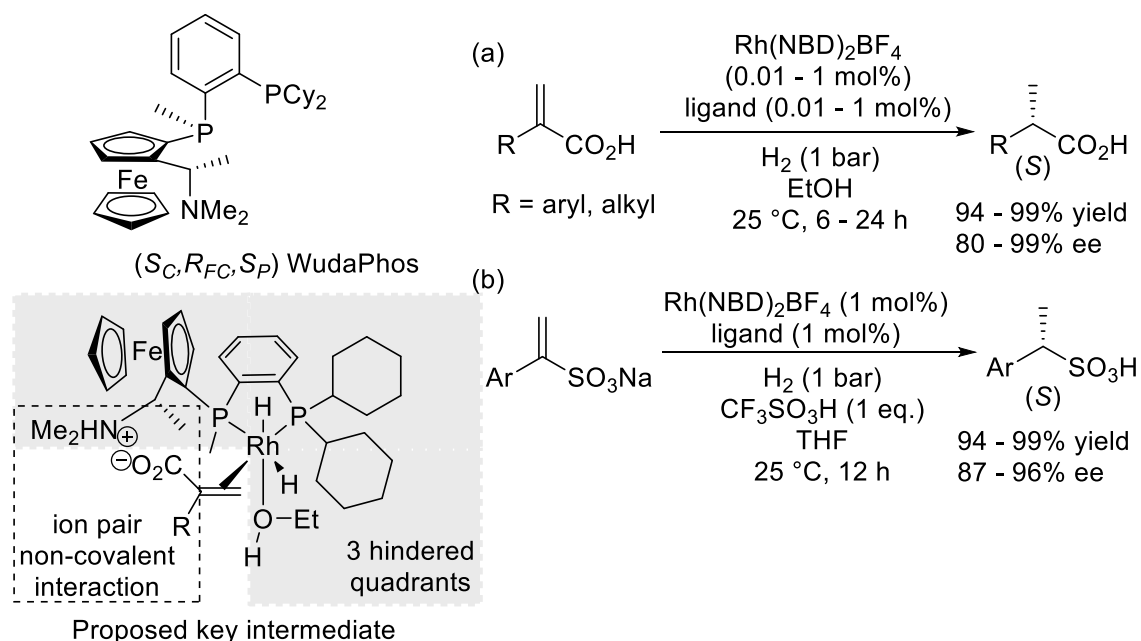
Scheme 66. Mechanism of the hydrogenation of unprotected indoles using a ZhaoPhos rhodium catalyst, by Zhang, Chung and co-workers.²⁰⁹

Overall, the results summarized in schemes 57-66 above demonstrate the exceptional efficiency of the ferrocene-based thiourea diphosphine ZhaoPhos developed by Zhang and Dong, in a variety of asymmetric hydrogenation reactions. This powerful synthetic method combines low catalyst loading, full conversion and excellent enantioselectivity levels. The successful application of the same phosphine in iridium promoted AH reactions will be discussed in section II.C.2 hereafter.

2. Catalysts Implying Ion Pairs as Non-Covalent Interactions between Ligands and Substrates.

This section illustrates the use of chiral ligands displaying amino functions that, after protonation, may give ion pairs with anionic functions of the substrates. These non-covalent interactions alone, or combined with other H-bonding type interactions, enable excellent stereocontrol in the AH of selected olefinic substrates, under rhodium catalysis.

In 2016, Zhang, Dong and co-workers reported rhodium catalysed AH of 2-substituted acrylic acids by applying the concept of ion pairs as non-covalent directing interactions (Scheme 67a).²¹⁰ They used a bidentate ligand comprising a P-stereogenic diphosphine and the planar chiral Ugi amine moiety, called Wudaphos. The AH of various acrylic acids with α -alkyl or aryl substituents proceeded with high conversions and enantioselectivities in base free and mild reaction conditions, with a S/C ratio up to 20 000. Interestingly, the enantioselectivity dropped dramatically for olefins displaying carbon spacers between the C=C bond and the acid function (7% ee for the olefin with a CH₂ spacer). Thus, the attractive ion pair, non-covalent interaction between the carboxylate and the protonated dimethylamine moiety of the ligand was postulated to play a key role in the stereochemical control. This role was further confirmed by control experiments: esters were unreactive and the reaction in presence of a base led to a large drop of enantioselectivity. On the basis of the X-Ray structure of the ligand and previous calculations, authors rationalized the enantioselection by applying the quadrants model (Scheme 67). The acrylic acid could coordinate to the rhodium catalyst in the free quadrant and a favorable ion pair interaction will enable discrimination between the two faces of the substrate, leading to an (*S*)-configured hydrogenation product. Afterwards, the rhodium/Wudaphos combination was also applied to the AH of sodium α -arylethenylsulfonates (Scheme 67b).²¹¹ The reactions proceeded only in the presence of one equivalent of triflic acid and afforded the α -arylethylsulfonic acids in high yields and enantioselectivities.



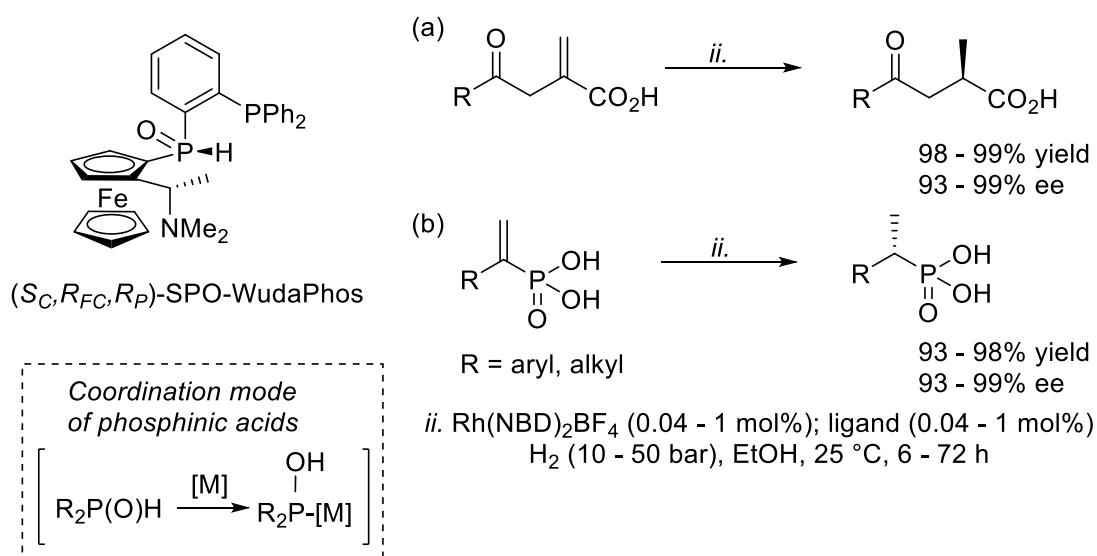
Scheme 67. AH of 2-substituted acrylic acids using a rhodium-WudaPhos catalyst, by Zhang, Dong and co-workers.²¹⁰⁻²¹¹

Zhang, Dong, Chung and co-workers further improved their concept by combining ion pair non-covalent interactions with hydrogen bondings. The WudaPhos ligand was modified by introducing a

secondary phosphine oxide (SPO) moiety instead of the P-stereogenic tertiary phosphine function (Scheme 68).²¹² It was expected indeed that the SPO ligand would coordinate the rhodium center via the P-atom of its phosphinic acid form ($R_2P(OH)$, see Chapter 1.2 of this book). The free hydroxy group on phosphorus will enable then hydrogen bondings with the substrate to hydrogenate. The base-free AH of various α -methylene- γ -keto carboxylic acids afforded the corresponding γ -keto acids in high yields and enantioselectivities (Scheme 68a), the carbonyl group of the substrate behaving here as the H-bonding acceptor. Interestingly, a further AH of the resulting chiral γ -keto acids, in the presence of chiral iridium or ruthenium catalysts and a base, led respectively to the corresponding *syn*- or *anti*-lactones which are interesting building blocks for the synthesis of bioactive compounds. As an example, the potent antimetastatic agent cryptophycin has been prepared.

In these experiments, the use of the SPO-Wudaphos ligand proved to be critical to attain high enantioselection, as demonstrated by comparison with the WudaPhos ligand itself. The role of the dual ion pair and hydrogen bond noncovalent interactions was further confirmed by reactions conducted in the presence of a base, a large drop of activity and enantioselectivity being observed. A similar drop was observed while hydrogenating substrates such as unsaturated carboxylic esters or carboxylic acids devoid of keto-functions.

Theoretical studies confirmed the favorable dual interaction between the catalyst and the substrate, i.e. the strong ion pair between the dimethylamino moiety and the acidic group, combined with H-bonding between the hydroxy group of the SPO ligand and the ketone moiety. Both contributed to an extended interaction between the substrate and the catalyst and led selectively to the (*R*)-hydrogenated product.

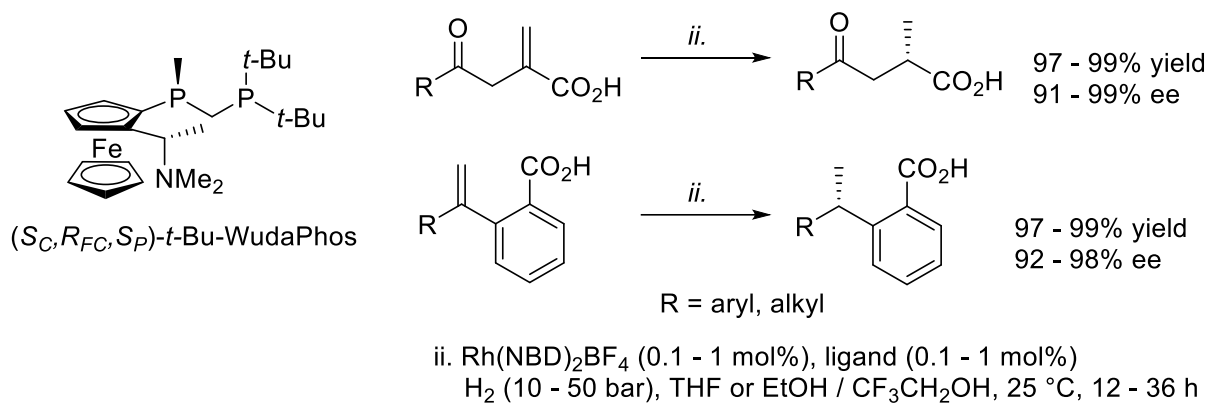


Scheme 68. Base-free AH of α -methylene- γ -keto carboxylic acids and α -substituted ethenylphosphonic acids using the SPO-WudaPhos rhodium catalyst, by Zhang, Dong, Chung and co-workers.²¹²⁻²¹³

The SPO-Wudaphos ligand was further combined with rhodium for the AH of α -substituted ethenylphosphonic acids (Scheme 67b).²¹³ The related phosphoric acids were obtained in high yields and enantioselectivities using low catalyst loading. The role of ion pair and hydrogen bond non-covalent interaction was confirmed by reactions in presence of a base, large drop of enantioselectivity being observed. Similarly, no reaction was observed for 1-phenylethenylphosphonate. In this case the H-bonding of the P-OH group is not mentioned explicitly as a regulating effect.

Pursuing their efforts in the development of catalysts involving ion pair interactions, Zhang, Dong and co-workers reported a modified Wudaphos ligand comprising a bis-tertiobutylphosphine moiety (Scheme

69). The combination of this ligand and rhodium allowed the AH of α -methylene- γ -keto carboxylic acids²¹⁴ as well as of disubstituted terminal olefins displaying a carboxylic acid directing group on an aryl-substituent.²¹⁵ In both cases, the hydrogenated products were obtained in high yields and enantioselectivities. As in the case of the Wudaphos based catalyst in Scheme 67, the quadrants model, combined with the favorable ion pair directing interaction, accounts for the sense of chiral induction and the almost perfect enantioselectivity.



Scheme 69. AH of α -methylene- γ -keto carboxylic acids and disubstituted terminal olefins using a tBu-WudaPhos rhodium catalyst, by Zhang, Dong and co-workers.^{214,215}

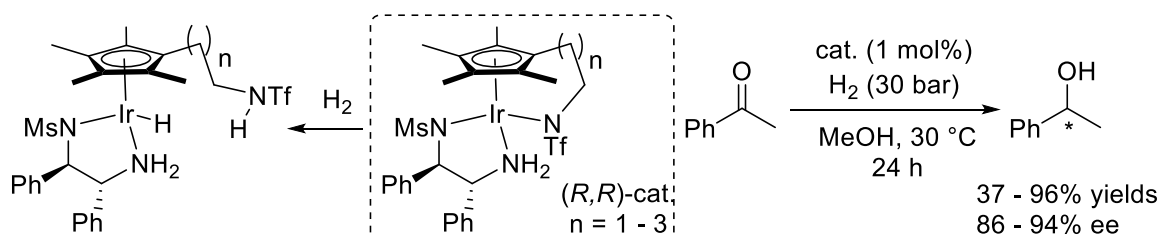
Overall, the few examples recalled in this section demonstrate the high potential of ion pairing effects as tools for the stereochemical control in rhodium promoted asymmetric hydrogenations. Remarkably, in the examples above, ion pairing effects increase significantly the discriminating ability of structurally simple and easily available chiral phosphorus ligands.

C. Iridium Catalysed Hydrogenations.

This section deals first with iridium complexes of bidentate ligands that operate through monohydrido intermediates and outer sphere H-transfer to the substrate from both the metal and a coordinated NH moiety. In the second part of this section, examples of catalysts implying ion pair or hydrogen bonding interactions will be presented.

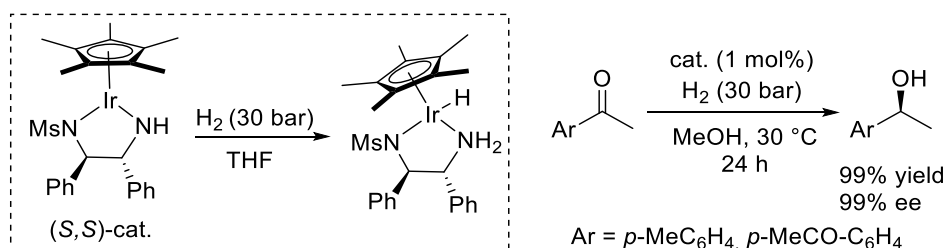
1. Iridium catalysts involving active NH functions and related cases.

In line with their work on η^6 -arene-ruthenium(II) catalysts with tethered amine-amido ligands (see Scheme 19 and following), Ikariya and co-workers developed η^5 -cyclopentadienyl-iridium(III) complexes displaying a triflylamido ligand tethered to the cyclopentadienyl, and a chiral N-mesylated 1,2-diphenylethyldiamine (Scheme 70).²¹⁶ Such complexes were able to activate hydrogen and effectively catalysed the AH of acetophenone. However, the length of the tethering carbon chain had a significant effect on the catalyst activity and stereoselectivity, complexes with 2- and 3-carbon chains leading to inferior performances compared to the complex with a C4-chain. According to the authors, the tether effect could result from a hydrogen bond between the NH_2 group of the diamine ligand and one of the triflylamide oxygens.



Scheme 70. AH of acetophenone using an iridium triflylamide tethered catalyst by Ikariya and co-workers.²¹⁶

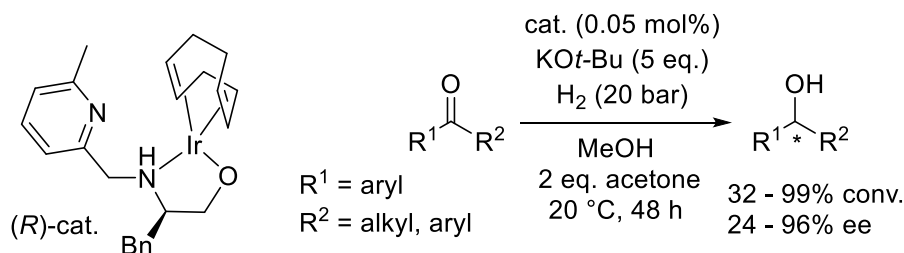
Ikariya and co-workers demonstrated that a diamido iridium(III)-Cp* complex derived from a chiral 1,2-diphenylethyldiamine, was able to activate hydrogen by forming a monohydrido-amine complex that catalysed the AH of acetophenone in high yield and enantioselectivity (Scheme 71).²¹⁷ Deuterium labelling showed that, for reactions carried out in methanol, the hydrogenation reaction competes with hydrogen transfer from the solvent and increases the enantioselectivity by preventing the reversible hydrogen transfer reaction to take place.



Scheme 71. Hydrogenation of acetophenone using an iridium amido pre-catalyst by Ikariya and co-workers.²¹⁷

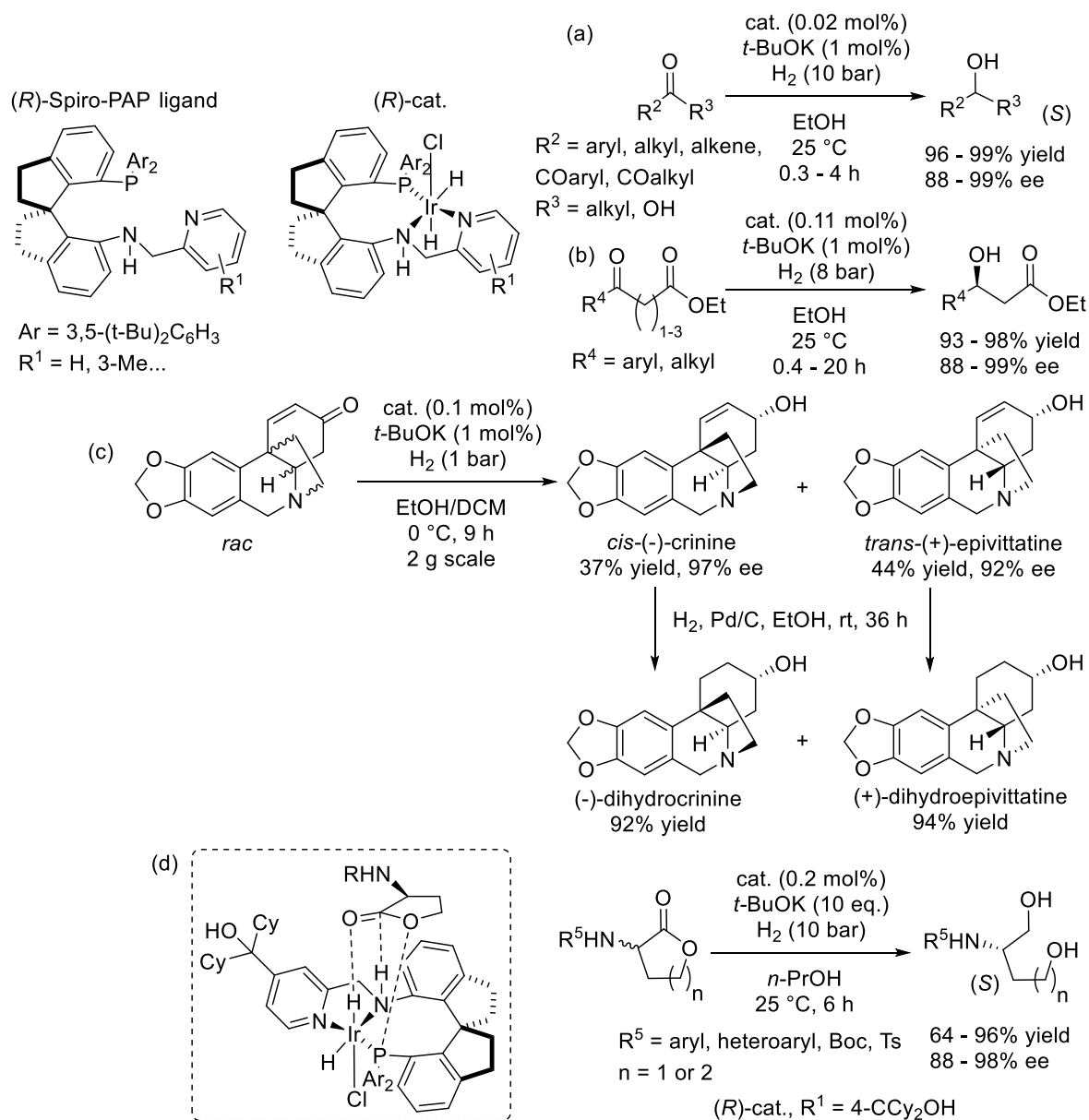
Kempe and co-workers observed also such advantage of combining hydrogenation and transfer hydrogenation.²¹⁸ They applied an iridium(I) complex based on an aminopyridinato ligand for AH of various ketones (Scheme 71). The reaction led to conversions and enantioselectivities from low to high.

Better activities and enantioselectivities were observed at low catalyst loading upon addition of large amounts of base and 2 equivalents of acetone.



Scheme 71. Hydrogenation of ketones using an iridium catalyst based on a aminopyridinato ligand by Kempe and co-workers.²¹⁸

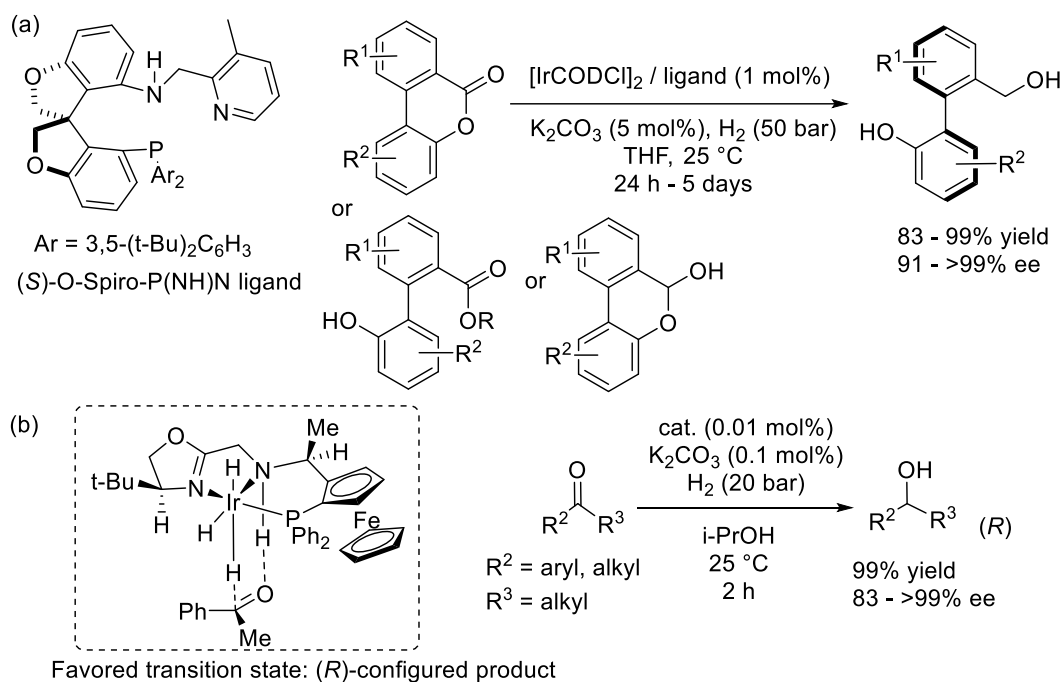
In 2011, Zhou, Xie and co-workers developed iridium(III) dihydride catalysts based on a P(NH)N tridentate ligand, called Spiro-PAP. The ligands display a spiranic backbone with phosphino and secondary amino functions and an appended pyridyl fragment (Scheme 72).²¹⁹ Such catalysts proved to be highly effective and enantioselective for the AH of an impressive variety of ketones, enones, β -ketolactams, α -keto acids (Scheme 72a), β - or δ -ketoesters (Scheme 72b) and others.²²⁰⁻²²⁴ Moreover, this type of iridium(III) catalyst was involved in several DKR processes and enabled the asymmetric total synthesis of compounds of biological interest like crinine-type alkaloids (Scheme 72c), gracilamine alkaloids, (-)-goniomitine, mulinane diterpenoids, (-)-hamigeran B, (-)-mesembrine and others.²²⁵⁻²³² A recent application to the AH/Dynamic kinetic resolution of racemic α -arylamino- γ -lactones and α -arylamino- δ -lactones led to the corresponding chiral 2-amino diols with high yields and enantioselectivities (Scheme 72d).²³³⁻²³⁴ According to theoretical studies, the hydride and proton transfer step proceeds via a cyclic 6-membered transition state. The calculated transition state of lowest energy leads to the (*S*)-2-amino-diol, as observed experimentally.



Scheme 72. AH of ketones, lactones and β -ketoesters using an iridium catalyst based on a P(NH)N spiro ligand by Zhou, Xie and co-workers.²¹⁹⁻²³⁴

This method provides one of the most impressive recent applications of Ir-bifunctional catalysts in asymmetric hydrogenation, in terms of both catalytic efficiency, enantioselectivity, substrate scope and synthetic potential.

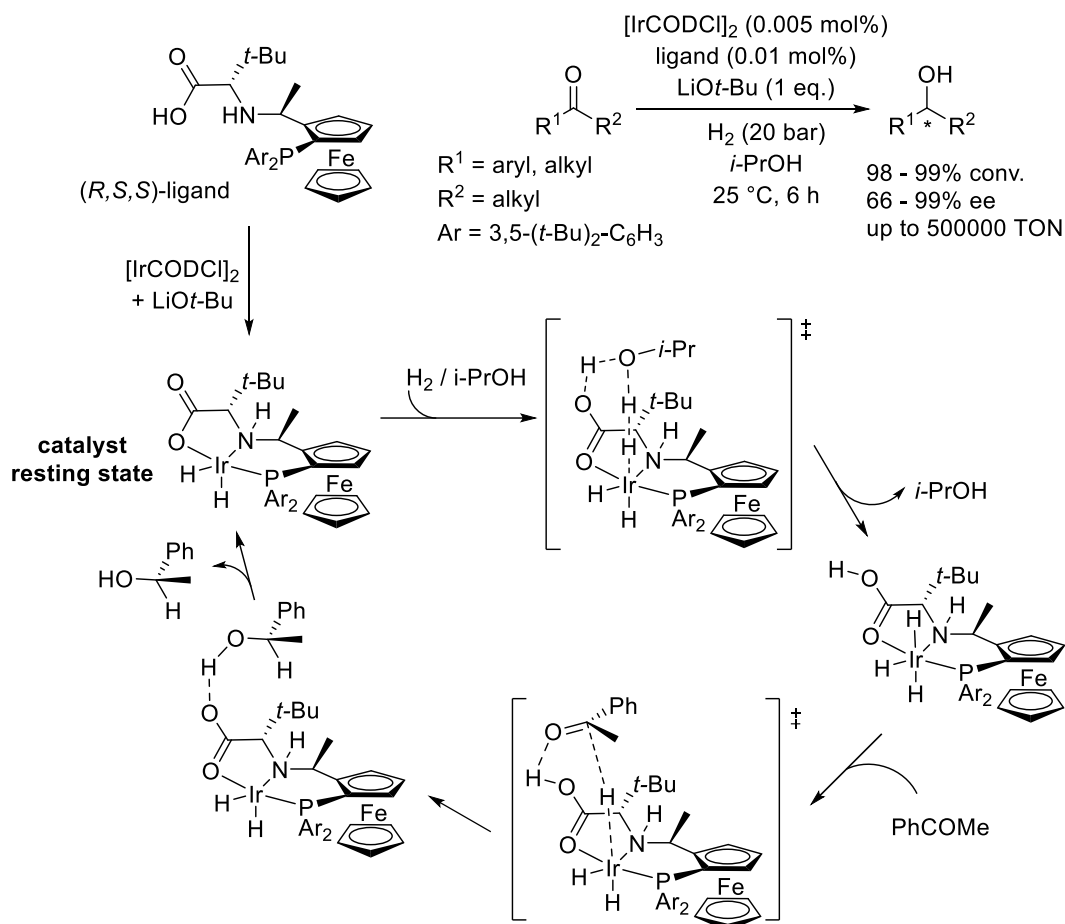
It is worth to note that Zhang, Yin and co-workers reported in parallel the synthesis of rather similar oxaspirocyclic chiral ligands and applied them to iridium-catalyzed direct asymmetric hydrogenation of Bringmann's lactones (Scheme 73a).²³⁵ Moreover, in another report, Zhang, Dong, Lan and co-workers developed another type of P(NH)N tridentate ligand based on a ferrocene aminophosphoxazoline which led to an effective iridium catalyst for the hydrogenation of ketones with very high enantioselectivities and catalytic activities (TON and TOF) (Scheme 73b).²³⁶ A theoretical study highlighted the hydrogenation mechanism and the origins of enantioselectivity, underlying the key bifunctional role of the active amidohydriridium(III) species in the activation of hydrogen.



Scheme 73. AH of Bringmann's lactones and ketones using iridium catalysts based on P(NH)N tridentate ligands by Zhang and co-workers.^{235,236}

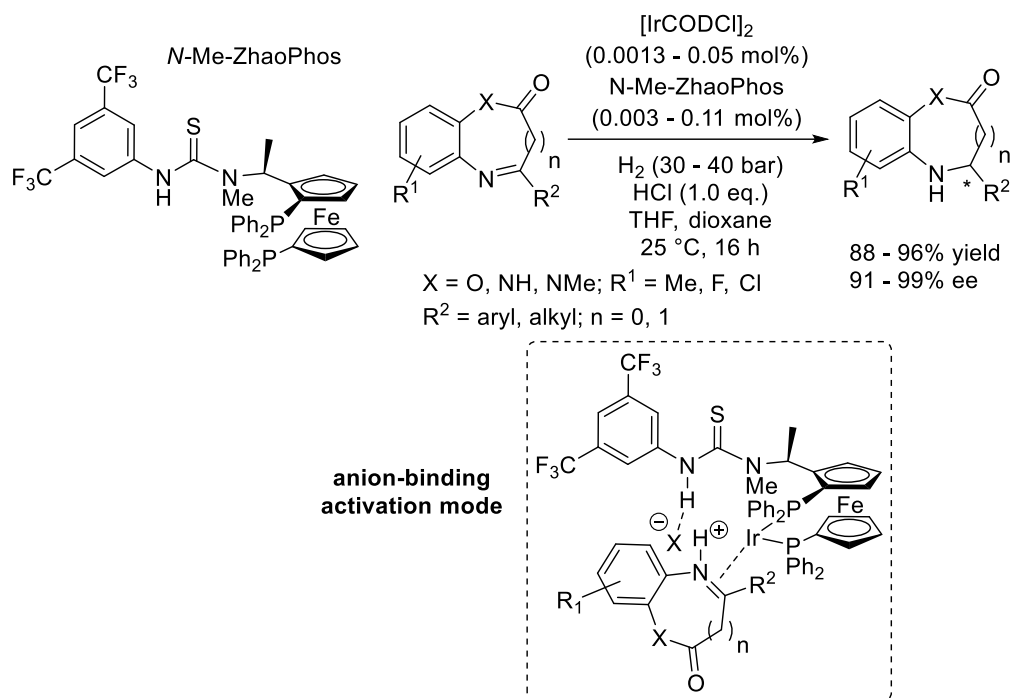
2. Catalysts Implying Ion Pair or Hydrogen Bonding Interactions.

In 2017, Zhang, Dong, Chung and co-workers reported the synthesis of chiral tridentate ferrocene ligands (f-Ampha) comprising an amino-phosphine and a carboxylic acid function (Scheme 74).²³⁷ The combination of such ligands with [Ir(COD)Cl]₂ and a base catalysed the AH of various aryl,alkyl-ketones with high yields and enantioselectivities. The catalytic activity was excellent, catalyst loadings being as low as 0.0002 mol%. Theoretical studies have suggested a catalytic cycle implying an iridium(III) dihydride complex in which the ligand behaves as a tridentate PNO species, as catalyst resting state (Scheme 74). This complex results from the reaction of the chiral ligand with [Ir(COD)Cl]₂ in the presence of a base, followed by oxydative addition of dihydrogen and cyclooctadiene decoordination. The iridium(III) dihydride complex reacts first with hydrogen which undergoes heterolytic splitting assisted by both the 2-propanol used as solvent and the carboxylate moiety of the ligand. The resulting iridium(III) trihydride is then involved in the hydride transfer to the carbonyl-type substrate, that represents the rate and enantiodetermining step. In this key step, the substrate is activated by hydrogen-bonding to the carboxylic acid moiety of the ligand which finally behaves as the proton source. Overall, the stepwise transfer of an hydride from the metal and a proton from the ligand takes place through an outer-sphere mechanism, while steric repulsions between the substrate and the catalyst favour the (*R*) enantiomer. The final release of the alcohol product generates the iridium(III) dihydride complex as the catalyst resting species.



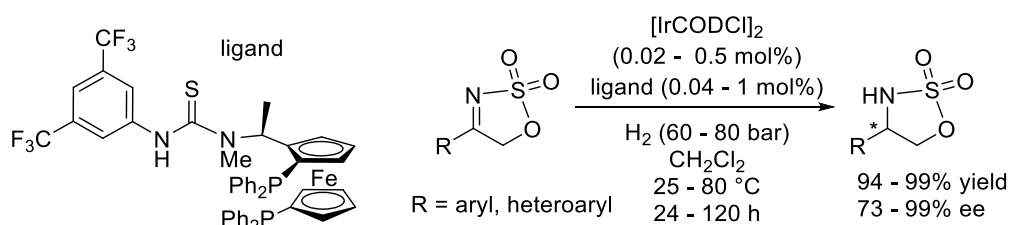
Scheme 74. AH of ketones using an iridium catalyst based on an amino-phosphine acid ligand (f-Ampha) by Zhang, Dong, Chung and co-workers.²³⁷

Zhang, Dong and co-workers applied a chiral ferrocene based bisphosphine-thiourea ligand of the ZhaoPhos series (see Scheme 56 and following) to the iridium-catalysed AH of benzoxazinones and quinoxalinones (Scheme 75).²³⁸ The reactions proceeded at low catalyst loadings and afforded the reduced products in high yields and enantioselectivities, by combining the *N*-methylated ligand with $[\text{Ir}(\text{COD})\text{Cl}]_2$, hydrogen and HCl. By considering the strong effect of the acid on the catalytic activity and stereoselectivity, authors suggested that, after complexation, the imine function of the substrate might be protonated by HCl to give the iminium chloride and that a hydrogen-bonding might be established between the chloride and the thiourea moiety of the ligand. No non-linear effects were observed along these AH. This methodology was successfully applied in the synthesis of a potential IgE/IgG receptor modulator.



Scheme 75. AH of benzoxazinones and analogues using the *N*-Me-ZhaoPhos iridium catalyst by Zhang, Dong and co-workers.²³⁸

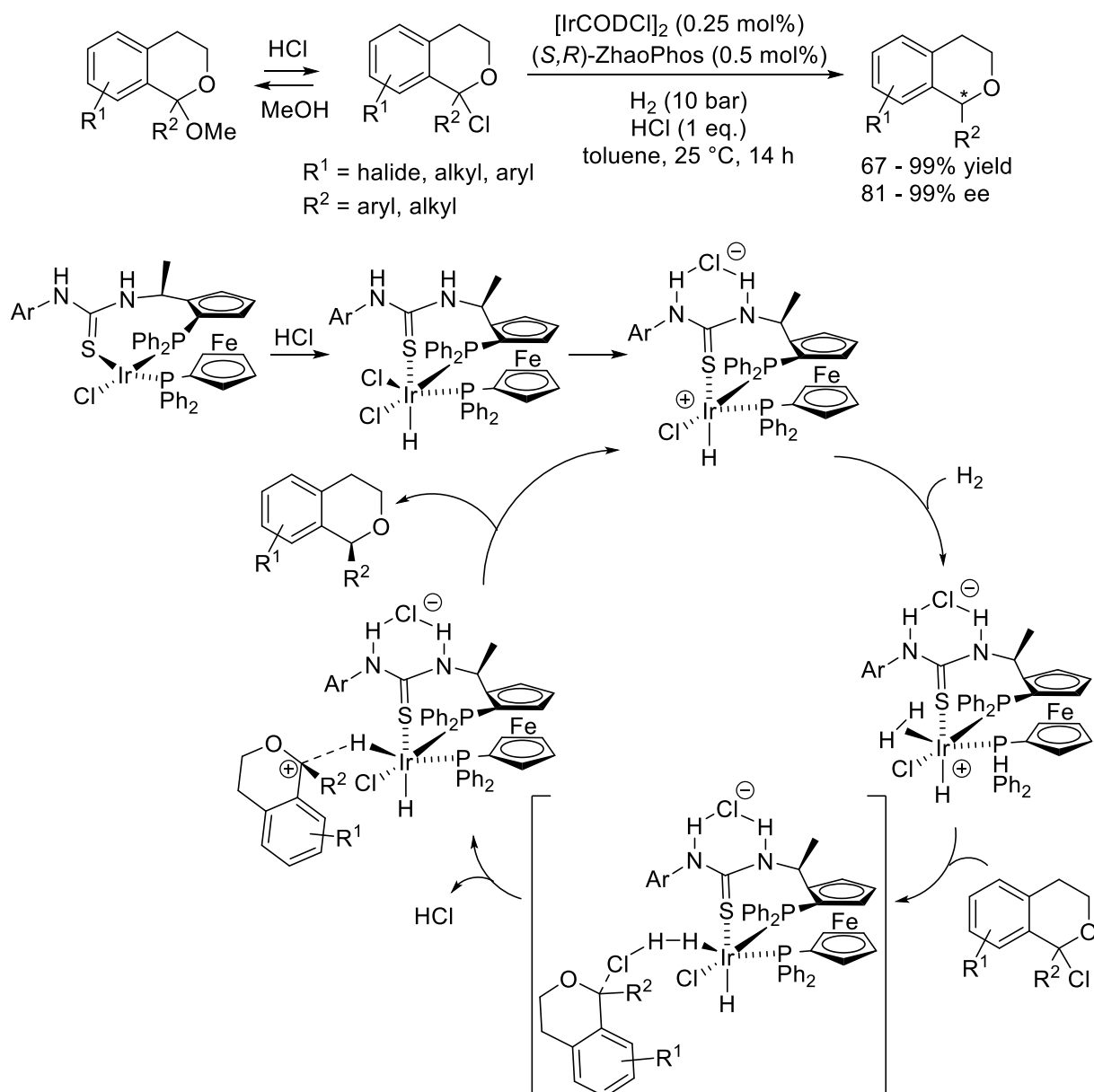
Zhang, Dong and co-workers also reported the application of the methylated ZhaoPhos ligand to the iridium catalysed AH of cyclic sulfamidate imines (Scheme 76).²³⁹ Compared to some of the privileged ligands like (*S*)-BINAP, (*S*)-SegPhos and (*R,S*)-DuanPhos, the bisphosphine-thiourea produced the cyclic sulfamidates in higher yields and enantioselectivities even at a gram scale, with rather low catalyst loadings.



Scheme 76. AH of cyclic sulfamidate imines using *N*-Me-ZhaoPhos-iridium catalysts by Zhang, Dong and co-workers.²³⁹

In a recent work, Zhang, Wen, Lin and co-workers applied the ZhaoPhos-iridium catalyst in the AH of isochroman acetals (Scheme 77).²⁴⁰ The reactions were carried out in the presence of one equivalent of HCl and the corresponding isochromans were recovered in high yields, chemo- and enantioselectivities. In the presence of HCl, isochroman acetals are known to be in equilibrium with the corresponding α -chloroisochromans, from which chloride dissociation will generate reactive oxocarbeniums. Such oxocarbeniums ions are postulated to be key intermediates in the iridium-promoted hydrogenations. The reaction mechanism was studied through experiments and calculations. While kinetics suggested a first-order dependence on the substrate and a half-order dependence on the catalyst, a positive non-linear effect was observed and therefore dimerization of the dichloro pre-catalyst was suggested. According to calculations, the starting iridium(I) complex reacts with HCl through oxidative addition to lead to a dichloro-hydrido-iridium(III) complex (Scheme 77). A subsequent isomerization generates a cationic iridium(III) hydride where the thiourea fragment of the ligand binds the chloride counterion. This species is considered to be the catalyst resting state. After coordination of H_2 , the heterolytic hydrogen split

proceeds concomitantly with the cleavage of the C-Cl bond of the substrate, resulting in the release of HCl and formation of the reactive oxocarbenium ion (Ionic hydrogenation pathway). The carbenium binds to the iridium dihydride-ZhaoPhos complex through both ionic and Van der Waals interactions. In the enantiodetermining step, it undergoes hydride transfer to lead to the preferred (*S*)-isochroman product.



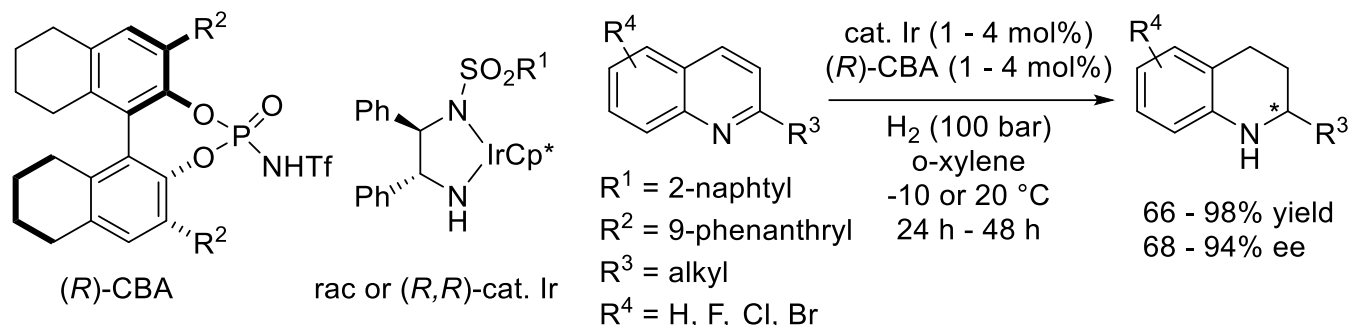
Scheme 77. AH of iso-chroman acetals using a ZhaoPhos-iridium catalyst by Zhang, Wen, Lin and co-workers.²⁴⁰

3. Iridium Phosphates or Triflylphosphoramides as Bifunctional Catalysts

The last examples hereafter deal with another class of bifunctional catalysts, i.e. cationic amido iridium complexes whose counteranion participates in the catalytic process via non-covalent interactions. In this field, initial disclosures from Rueping and Koenigs have been extended and enlightened later by Xiao and co-workers.

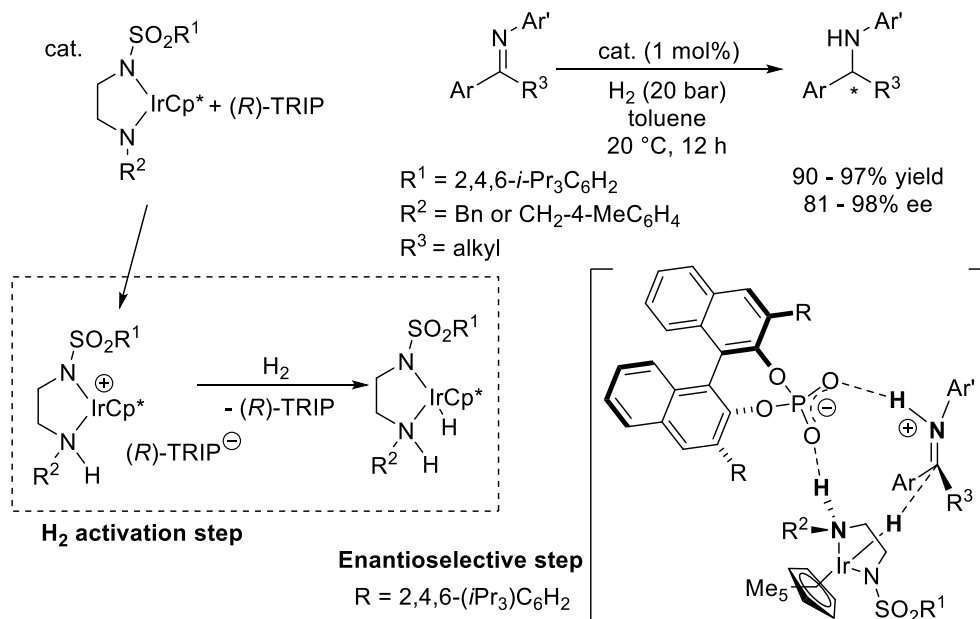
Rueping and Koenigs reported that chiral *N*-triflylphosphoramidate Brønsted acids, combined with *N*-sufonylated DPEN-iridium(III) complexes provide active and effective catalysts for the AH of quinolines (Scheme 78).²⁴¹ Both racemic and optically pure DPEN-Ir catalysts gave highly enantioenriched

hydrogenation products, however the (*R,R*)-DPEN-iridium catalyst afforded tetrahydroquinolines with higher enantioselectivities than the racemic complex. These results demonstrated the key role of positive match effects and suggested the implication of chiral metal-phosphoramidite ion pairs in these hydrogenation reactions.



Scheme 78. AH of quinolines using a combination of *N*-triflylphosphoramidite Brønsted acids and DPEN-derived iridium catalysts by Rueping and co-workers.²⁴¹

An analogous behaviour has been highlighted and investigated in more depth, in the case of iridium-promoted hydrogenation of imines in the presence of BINOL-derived phosphoric acids. Xiao and co-workers have demonstrated the combined use of (*R*)-TRIP phosphoric acid and an achiral pentamethylcyclopentadienyl iridium complex with a sulfonated 1,2-ethylenediamine ligand, in the AH of ketimines (Scheme 79).^{242,243} High yields and enantioselectivities were obtained despite the rather long reaction times due to the steric hindrance imposed by the chiral phosphoric acid. Combined NMR and theoretical studies have shown that the reaction of the Ir complex with the phosphoric acid gives several isomeric cationic iridium hydrides, all bearing secondary amine ligands and phosphate counterions. In the catalytic cycle, the phosphate counterion participates first in the heterolytic split of H₂ leading to an Ir-hydride intermediate by acting as a proton relay for the protonation of the imine substrate. Furthermore, the enantioselective hydride transfer step is likely to proceed via a supramolecular ternary complex involving the iridium hydride complex, the chiral phosphate anion and the protonated imine. Hydrogen bonding and CH/π interactions may contribute to the stereochemical control of this key step.



Scheme 79. AH of imines using combined phosphoric acid and iridium-amido catalysts by Xiao and co-workers.²⁴²

243

Afterwards, Zhao and co-workers developed a highly selective ATH of ketimines using a similar catalytic system comprising a *meso* diol as hydrogen donor and a combination of TRIP chiral phosphoric acid and an iridium(III) complex based on a chiral sulfonylated diphenylethylene diamine ligand.²⁴⁴ The nature of the alcohol hydrogen donor had a strong influence on the efficiency and selectivity of the hydrogenation, *meso* diols leading to good to high yields and enantioselectivities. Experimental and theoretical studies supported a reaction pathway involving an iridium alkoxide as the reducing species and proceeding through a concerted proton and hydride transfer. The reaction enantioselectivity was apparently controlled by the chiral iridium(III) complex and the chiral Brønsted acid, non-covalent interactions being observed between the acid, the *meso* diol and the substrate.

IV. Conclusion

We have seen that the application of bifunctional catalysts to asymmetric hydrogenations is blooming. New examples of bifunctional catalysts implying ruthenium, rhodium and iridium appeared thanks to ligand modifications. Beyond the classical bifunctional catalysts that rely on H-transfer from the ligand itself (Noyori approach), the development of cooperative approaches allowed specific non-covalent interactions between the substrates and the ligands or counterions of specifically designed metal complexes. These non-covalent interactions operate as both activating tools (increased catalytic activity) and stereocontrol devices (increased enantioselectivity levels). Major advances in this field have been achieved thanks to a better knowledge of the catalysts features by combining the development of synthetic methods with structural and kinetic studies as well as with theoretical studies.

Nowadays, asymmetric hydrogenation (AH) and asymmetric transfer hydrogenation (ATH) are catalysed by well-known series of privileged organometallic species which have complementary activities and stereo-, chemo- and regioselectivities. Though these catalysts hydrogenate with high selectivities a great diversity of organic substrates with carbonyl, imine or olefin functions,⁴⁶ other substrates like alkyl ketones and imines,²⁴⁵ carbocyclic arenes,^{246,247} some nitrogen based heterocycles²⁴⁸ and tri-/tetrasubstituted alkenes^{249,250} are still challenging and the development of chemoselective catalytic processes is also highly desirable.²⁵¹

While new effective hydrogenation catalysts are searched out,⁴⁶ there's a growing interest in hydrogenation catalysts based on abundant metals due to economic, environmental and societal issues.²⁵¹⁻²⁵³ Several examples of bifunctional catalysts have already been reported in this field and others will surely appear in the future. Finally, the development of highly active catalysts, i.e. high turnover number catalysts, as well as applications in flow chemistry,^{124,254-256} shall certainly be privileged when considering industrial perspectives.^{257,258}

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VI. References

1. Noyori, R. In *Asymmetric Catalysis In Organic Synthesis*, Wiley, New York, **1994**, chapter 2.
2. Ohkuma, T.; Kitamura, M.; Noyori, R. In *Catalytic Asymmetric Synthesis 2nd Edition*; Ojima, I., Ed.; Wiley-VCH, **2000**, p 1.
3. Blaser, H.-U.; Federsel, H.-J.; Eds. In *Asymmetric Catalysis on Industrial Scale*; Wiley-VCH, **2010**.
4. Knowles, W. S.; Asymmetric Hydrogenations (Nobel Lecture). *Angew. Chem. Int. Ed.* **2002**, *41*, 1998–2007.
5. Noyori, R. Asymmetric Catalysis: Science and Opportunities (Nobel Lecture) *Angew. Chem. Int. Ed.* **2002**, *41*, 2008–2022.
6. Noyori, R. Asymmetric Catalysis: Science and Opportunities (Nobel Lecture 2001). *Adv. Synth. Catal.* **2003**, *345*, 15–32.
7. Blaser, H. U.; Pugin, B.; Spindler, F.; Saudan L. A.; Hydrogenation. In *Applied Homogeneous Catalysis with Organometallic Compounds 3rd Edition*, Cornils, B.; Herrmann, W. A.; Beller, M.; Paciello, R., Eds; Wiley-VCH, **2018**, *2*, p 621–690.
8. Foubelo, F.; Najera, C.; Yus, M. Catalytic asymmetric transfer hydrogenation of ketones: recent advances. *Tetrahedron: Asymmetry* **2015**, *26*, 769–790.
9. Nedden, H. G.; Zanotti-Gerosa, A.; Wills, M. The Development of Phosphine-Free "Tethered" Ruthenium(II) Catalysts for the Asymmetric Reduction of Ketones and Imines. *Chem. Record* **2016**, *16*, 2619–2639.
10. Stefane, B.; Pozgan, F. Metal-Catalysed Transfer Hydrogenation of Ketones. *Topics in Current Chem.* **2016**, *374*, 1–67.
11. Wang, D.; Astruc, D. The Golden Age of Transfer Hydrogenation. *Chem. Rev.* **2015**, *115*, 6621–6686.
12. Matsunami, A.; Kayaki, Y. Upgrading and Expanding the Scope of Homogeneous Transfer Hydrogenation. *Tetrahedron Lett.* **2018**, *59*, 504–513.
13. Baráth, E. Hydrogen Transfer Reactions of Carbonyls, Alkynes, and Alkenes with Noble Metals in the Presence of Alcohols/Ethers and Amines as Hydrogen Donors. *Catalysts* **2018**, *8*, 671–696.
14. Etayo, P.; Vidal-Ferran, A. Rhodium-Catalyzed Asymmetric Hydrogenation as a Valuable Synthetic Tool for the Preparation of Chiral Drugs. *Chem. Soc. Rev.* **2013**, *42*, 728–754.
15. Ohkuma, T.; Noyori, R.; Asymmetric Catalysis by Architectural and Functional Molecular Engineering: Practical Chemo- and Stereoselective Hydrogenation of Ketones. *Angew. Chem. Int. Ed.* **2001**, *40*, 40–73.
16. Ohkuma, T.; Ooka, H.; Hashiguchi, S.; Ikariya, T.; Noyori, R.; Practical Enantioselective Hydrogenation of Aromatic Ketones. *J. Am. Chem. Soc.* **1995**, *117*, 2675–2676.
17. Noyori, R.; Hashiguchi, S.; Asymmetric Transfer Hydrogenation Catalyzed by Chiral Ruthenium Complexes. *Acc. Chem. Res.* **1997**, *30*, 97–102.

18. Hashiguchi, S.; Fujii, A.; Takehara, J.; Ikariya, T.; Noyori, R.; Asymmetric Transfer Hydrogenation of Aromatic Ketones Catalysed by Chiral Ruthenium(II) Complexes. *J. Am. Chem. Soc.* **1995**, *117*, 7562–7563
19. Doucet, H.; Ohkuma, T.; Murata, K.; Yokozawa, T.; Kozawa, M.; Katayama, E.; England, A. F.; Ikariya, T.; Noyori, R.; trans-[RuCl₂(phosphane)₂(1,2-diamine)] and Chiral trans-[RuCl₂(diphosphane)(1,2-diamine): Shelf-Stable Precatalysts for the Rapid, Productive, and Stereoselective Hydrogenation of Ketones. *Angew. Chem., Int. Ed.*, **1998**, *37*, 1703–1707.
20. Ohkuma, T.; Koizumi, M.; Muñiz, K.; Hilt, G.; Kabuto, C.; Noyori, R. Trans-RuH(η -BH₄)(binap)(1,2-diamine): A Catalyst for Asymmetric Hydrogenation of Simple Ketones under Base-Free Conditions. *J. Am. Chem. Soc.* **2002**, *124*, 6508–6509.
21. Sandoval, C. A.; Ohkuma, T.; Muñiz, K.; Noyori, R.; Mechanism of Asymmetric Hydrogenation of Ketones Catalyzed by BINAP/1,2-Diamine-Ruthenium(II) Complexes. *J. Am. Chem. Soc.* **2003**, *125*, 13490–13503
22. Haack, K.-J.; Hashiguchi, S.; Fujii, A.; Ikariya, T.; Noyori, R.; The Catalyst Precursor, Catalyst, and Intermediate in the Ru^{II}-Promoted Asymmetric Hydrogen Transfer between Alcohols and Ketones. *Angew. Chem. Int. Ed.* **1997**, *36*, 285–288
23. Palmer, M. J.; Wills, M.; Asymmetric Transfer Hydrogenation of C=O and C=N Bonds. *Tetrahedron: Asymmetry* **1999**, *10*, 2045–2061
24. Clamham, S.; Hadzovic, A.; Morris, R. H.; Mechanisms of the H₂-Hydrogenation and Transfer Hydrogenation of Polar Bonds Catalyzed by Ruthenium Hydride Complexes. *Coord. Chem. Rev.* **2004**, *248*, 2201–2237
25. Casey, C. P.; Johnson, J. B.; Kinetic Isotope Effect Evidence for a Concerted Hydrogen Transfer Mechanism in Transfer Hydrogenations Catalyzed by [*p*-(Me₂CH)C₆H₄Me]Ru-(NHCHPhCHPhNSO₂C₆H₄-*p*-CH₃). *J. Org. Chem.* **2003**, *68*, 1998–2001
26. Alonso, D. A.; Brandt, P.; Nordin, S. J. M.; Andersson, P. G.; Ru(arene)(amino alcohol)-Catalyzed Transfer Hydrogenation of Ketones: Mechanism and Origin of Enantioselectivity. *J. Am. Chem. Soc.* **1999**, *121*, 41, 9580–9588.
27. Yamakawa, M.; Ito, H.; Noyori, R.; The Metal-Ligand Bifunctional Catalysis: A Theoretical Study on the Ruthenium(II)-Catalyzed Hydrogen Transfer Between Alcohols and Carbonyl Compounds. *J. Am. Chem. Soc.* **2000**, *122*, 1466–1478.
28. Joseph, S. M.; Samec, J. S.; Bäckvall, J.-E.; Andersson, P. G.; Brandt, P. Mechanistic Aspects of Transition Metal-Catalyzed Hydrogen Transfer Reactions. *Chem. Soc. Rev.* **2006**, *35*, 237–248.
29. Ikariya, T.; Murata, K.; Noyori, R.; Bifunctional Transition Metal-Based Molecular Catalysts for Asymmetric Syntheses. *Org. Biomol. Chem.* **2006**, *4*, 393–406.
30. Ikariya, T.; Blacker, A. J. Asymmetric Transfer Hydrogenation of Ketones with Bifunctional Transition Metal-Based Molecular Catalysts. *Acc. Chem. Res.* **2007**, *40*, 1300–1308.
31. Sawamura, M.; Ito, Y.; Catalytic Asymmetric Synthesis by Means of Secondary Interaction between Chiral Ligands and Substrates. *Chem. Rev.* **1992**, *92*, 857–871.
32. Steinhagen, H.; Helmchen, G.; Asymmetric Two-Center Catalysis - Learning from Nature. *Angew. Chem. Int. Ed.* **1996**, *35*, 2339–2342.
33. Shibasaki, M.; Sasai, H.; Arai, T.; Asymmetric Catalysis with Heterobimetallic Compounds. *Angew. Chem. Int. Ed.* **1997**, *36*, 1236–1256.

34. Van den Beuken, E. K.; Feringa, B. L.; Bimetallic Catalysis by Late Transition Metal Complexes *Tetrahedron* **1998**, *54*, 12985–13011.
35. Rowlands, G. J.; Ambifunctional Cooperative Catalysts. *Tetrahedron* **2001**, *57*, 1865–1882.
36. H. Gröger, The Development of New Monometallic Bifunctional Catalysts with Lewis acid and Lewis Base Properties, and their Application in Asymmetric Cyanation Reactions *Chem.–Eur. J.* **2001**, *7*, 5246–5251.
37. Shibasaki, M.; Yoshikawa, N.; Lanthanide Complexes in Multifunctional Asymmetric Catalysis. *Chem. Rev.* **2002**, *102*, 2187–2209.
38. Ma, J.-A.; Cahard, D.; Towards Perfect Catalytic Asymmetric Synthesis: Dual Activation of the Electrophile and the Nucleophile. *Angew. Chem. Int. Ed.* **2004**, *43*, 4566–4583.
39. Hannedouche, J.; Clarkson, G. J.; Wills, M.; A New Class of “Tethered” Ruthenium(II) Catalyst for Asymmetric Transfer Hydrogenation Reactions. *J. Am. Chem. Soc.* **2004**, *126*, 986–987.
40. Hayes, A. M.; Morris, D. J.; Clarkson, G. J.; Wills, M.; A Class of Ruthenium(II) Catalyst for Asymmetric Transfer Hydrogenations of Ketones. *J. Am. Chem. Soc.* **2005**, *127*, 7318–7319.
41. Morris, D. J.; Hayes, A. M.; Wills, M.; The “Reverse-Tethered” Ruthenium(II) Catalyst for Asymmetric Transfer Hydrogenation: Further Applications. *J. Org. Chem.* **2006**, *71*, 7035–7044.
42. Matharu, D. S.; Morris, D. J.; Kawamoto, A. M.; Clarkson, G. J.; Wills, M.; A Stereochemically Well-Defined Rhodium(III) Catalyst for Asymmetric Transfer Hydrogenation of Ketones. *Org. Lett.* **2005**, *7*, 5489–5491.
43. Gao, J.- X.; Ikariya, T.; Noyori, R.; A Ruthenium(II) Complex with a C_2 -Symmetric Diphosphine/Diamine Tetradentate Ligand for Asymmetric Transfer Hydrogenation of Aromatic Ketones. *Organometallics* **1996**, *15*, 1087–1089.
44. Guo, R.; Elpelt, C.; Chen, X.; Song, D.; Morris, R. H.; A Modular Design of Ruthenium Catalysts with Diamine and BINOL-Derived Phosphinite Ligands that are Enantiomerically-Matched for the Effective Asymmetric Transfer Hydrogenation of Simple Ketones. *Chem. Commun.* **2005**, 3050–3052.
45. Guo, R.; Chen, X.; Elpelt, C.; Song, D.; Morris, R. H.; Applications of Ruthenium Hydride Borohydride Complexes Containing Phosphinite and Diamine Ligands to Asymmetric Catalytic Reactions. *Org. Lett.* **2005**, *7*, 1757–1759.
46. Seo, C. S. G.; Morris, R. H. Catalytic Homogeneous Asymmetric Hydrogenation: Successes and Opportunities. *Organometallics* **2019**, *38*, 47–65.
47. Ikariya, T.; Kayaki, Y. Hydrogenation of Carboxylic Acid Derivatives with Bifunctional Ruthenium Catalysts. *Pure and Applied Chem.* **2014**, *86*, 933–943.
48. Dong, X.-Q.; Zhao, Q.; Li, P.; Chen, C.; Zhang, X.; Metalorganocatalysis: Cooperating Transition Metal Catalysis and Organocatalysis Through a Covalent Bond. *Org. Chem. Front.* **2015**, *2*, 1425–1431.
49. Gridnev, I. V. Attraction versus Repulsion in Rhodium-Catalyzed Asymmetric Hydrogenation. *ChemCatChem* **2016**, *8*, 3463–3465.
50. Zhang, J.; Jia, J.; Zeng, X.; Wang, Y.; Zhang, Z.; Gridnev, I. D.; Zhang, W. Chemo- and Enantioselective Hydrogenation of α -Formyl Enamides: An Efficient Access to Chiral α -Amido Aldehydes. *Angew. Chem. Int. Ed.* **2019**, *58*, 11505–11512.

51. Chen, J.; Gridnev, I. D. Size is Important: Artificial Catalyst Mimics Behavior of Natural Enzymes. *iScience* **2020**, *23*, 100960–100972.
52. Kuwata, S.; Ikariya, T. Quest for Metal/NH Bifunctional Bioinspired Catalysis in a Dinuclear Platform. *Dalton Trans.* **2010**, *39*, 2984–2992.
53. Grotjahn, D. B. Heteroatoms Moving Protons: Synthetic and Mechanistic Studies of Bifunctional Organometallic Catalysis. *Pure Applied Chem.* **2010**, *82*, 635–647.
54. Mbofana, C. T.; Miller, S. J. Bifunctional Catalysis with Lewis Base and X-H Sites That Facilitate Proton Transfer or Hydrogen Bonding ($n \rightarrow \pi^*$) in *Lewis Base Catalysis in Organic Synthesis*; Vedejs, E.; Denmark, S. E. Ed.; Wiley-VCH, Weinheim, 2016, p 1259–1288.
55. Barath, E. Selective Reduction of Carbonyl Compounds via (Asymmetric) Transfer Hydrogenation on Heterogeneous Catalysts. *Synthesis* **2020**, *52*, 504–520.
56. Cheng, T.; Zhao, Q.; Zhang, D.; Liu, G. Transition-Metal-Functionalized Ordered Mesoporous Silicas: An Overview of Sustainable Chiral Catalysts for Enantioselective Transformations. *Green Chem.* **2015**, *17*, 2100–2122.
57. Wang, Q.; Astruc, D. State of the Art and Prospects in Metal–Organic Framework (MOF)-Based and MOF-Derived Nanocatalysis. *Chem. Rev.* **2020**, *120*, 1438–1511.
58. Altava, B.; Burguete, M. I.; García-Verdugo, E.; Luis, S. V. Chiral Catalysts Immobilized on Achiral Polymers: Effect of the Polymer Support on the Performance of the Catalyst. *Chem. Soc. Rev.* **2018**, *47*, 2722–2771.
59. Baig, R. B. N.; Nadagouda, M. N.; Varma, R. S. Magnetically Retrievable Catalysts for Asymmetric Synthesis. *Coord. Chem. Rev.* **2015**, *287*, 137–156.
60. Wei, Y.; Wu, X.; Wang, C.; Xiao, J. Transfer Hydrogenation in Aqueous Media. *Catal. Today* **2015**, *247*, 104–116.
61. Kucukturkmen, C.; Agac, A.; Eren, A.; Karakaya, I.; Aslantas, M.; Celik, O.; Ulukanli, S.; Karabuga, S. Asymmetric Transfer Hydrogenation of Ketones by *N,N*-Containing Quinazoline-Based Ruthenium(II) Complexes. *Catal. Commun.* **2016**, *74*, 122–125.
62. Chen, F.; He, D.; Chen, L.; Chang, X.; Wang, D. Z.; Xu, C.; Xing, X. Chirality-Economy Catalysis: Asymmetric Transfer Hydrogenation of Ketones by Ru-Catalysts of Minimal Stereogenicity. *ACS Catal.* **2019**, *9*, 5562–5566.
63. Takehara, J.; Hashiguchi, S.; Fujii, A.; Inoue, S.; Ikariya, T.; Noyori, R. Amino Alcohol Effects on the Ruthenium(II)-Catalysed Asymmetric Transfer Hydrogenation of Ketones in Propan-2-ol. *J. Chem. Soc., Chem. Commun.* **1996**, 233–234.
64. Alonso, D. A.; Guijarro, D.; Pinho, P.; Temme, O.; Andersson, P. G. (1*S*,3*R*,4*R*)-2-Azanorbornylmethanol, an Efficient Ligand for Ruthenium-Catalyzed Asymmetric Transfer Hydrogenation of Ketones. *J. Org. Chem.* **1998**, *63*, 2749–2751.
65. Palmer, M.; Walsgrove, T.; Wills, M. (1*R*,2*S*)-(+)-*cis*-1-Amino-2-indanol: An Effective Ligand for Asymmetric Catalysis of Transfer Hydrogenations of Ketones. *J. Org. Chem.* **1997**, *62*, 5226–5228.
66. Chakka, S. K.; Andersson, P. G.; Maguire, G. E. M.; Kruger, H. G.; Govender, T. Synthesis and Screening of C¹-Substituted Tetrahydroisoquinoline Derivatives or Asymmetric Transfer Hydrogenation Reactions. *Eur. J. Org. Chem.* **2010**, 972–980.

67. Han, M.-L.; Hu, X.-P.; Huang, J.-D.; Chen, L.-G.; Zheng, Z. New Chiral Amino Alcohol Ligands Derived from 1-Phenylethylamine for Efficient Ru-Catalyzed Asymmetric Transfer Hydrogenation. *Tetrahedron: Asymmetry* **2011**, *22*, 222–225.
68. Wang, X.; Xu, L.; Yan, L.; Wang, H.; Han, S.; Wu, Y.; Chen, F. Catalytic Asymmetric Transfer Hydrogenation/Dynamic Kinetic Resolution: an Efficient Synthesis of Florfenicol. *Tetrahedron* **2016**, *72*, 1787–1793.
69. Manville, C. V.; Docherty, G.; Padda, R.; Wills, M. Application of Proline-Functionalized 1,2-Diphenylethane-1,2-diamine (DPEN) in Asymmetric Transfer Hydrogenation of Ketones. *Eur. J. Org. Chem.* **2011**, 6893–9901.
70. Cambeiro, X. C.; Pericàs, M. A. Proline-Derived Aminotriazole Ligands: Preparation and Use in the Ruthenium-Catalyzed Asymmetric Transfer Hydrogenation. *Adv. Synth. Catal.* **2011**, *353*, 113–124.
71. Pastor, I. M.; Västilä, P.; Adolfsson, H. Novel Simple and Highly Modular Ligands for Efficient Asymmetric Transfer-Hydrogenation of Ketones. *Chem. Commun.* **2002**, *39*, 2046–2047.
72. Pastor, I. M.; Västilä, P.; Adolfsson, H. Employing the Structural Diversity of Nature: Development of Modular Dipeptide-Analogue Ligands for Ruthenium-Catalyzed Enantioselective Transfer Hydrogenation of Ketones. *Chem. Eur. J.* **2003**, *9*, 4031–4045.
73. Lundberg, H.; Hans Adolfsson, H. Ruthenium-Catalyzed Asymmetric Transfer Hydrogenation of Ketones in Ethanol. *Tetrahedron Lett.* **2011**, *52*, 2754–2758.
74. Shatskiy, A.; Kivijärvi, T.; Lundberg, H.; Tinnis, F.; Adolfsson, H. Ruthenium-Catalyzed Asymmetric Transfer Hydrogenation of Propargylic Ketones. *ChemCatChem* **2015**, *7*, 3818–3821.
75. Västilä, P.; Zaitsev, A. B.; Wettergren, J.; Privalov, T.; Adolfsson, H. The Importance of Alkali Cations in the [$\text{RuCl}_2(p\text{-cymene})_2$]-Pseudodipeptide-Catalyzed Enantioselective Transfer Hydrogenation of Ketones. *Chem. Eur. J.* **2006**, *12*, 3218–3225.
76. Kovalenko, O. O.; Lundberg, H.; Hübner, D.; Adolfsson, H. Tandem α -Alkylation/Asymmetric Transfer Hydrogenation of Acetophenones with Primary Alcohols. *Eur. J. Org. Chem.* **2014**, 6639–6642.
77. Slagbrand, T.; Lundberg, H.; Adolfsson, H. Ruthenium-Catalyzed Tandem-Isomerization/Asymmetric Transfer Hydrogenation of Allylic Alcohols. *Chem. Eur. J.* **2014**, *20*, 16102–16106.
78. Buitrago, E.; Lundberg, H.; Andersson, H.; Ryberg, P.; Adolfsson, H. High Throughput Screening of a Catalyst Library for the Asymmetric Transfer Hydrogenation of Heteroaromatic Ketones: Formal Syntheses of (*R*)-Fluoxetine and (*S*)-Duloxetine. *ChemCatChem* **2012**, *4*, 2082–2089.
79. Coll, M.; Pàmies, O.; Adolfsson, H.; Diéguez, M. Carbohydrate-Based Pseudo-Dipeptides: New Ligands for the Highly Enantioselective Ru-Catalyzed Transfer Hydrogenation Reaction. *Chem. Commun.* **2011**, *47*, 12188–12190.
80. Coll, M.; Ahlford, K.; Pàmies, O.; Adolfsson, H.; Diéguez, M. Modular Furanoside Pseudodipeptides and Thioamides, Readily Available Ligand Libraries for Metal-Catalyzed Transfer Hydrogenation Reactions: Scope and Limitations. *Adv. Synth. Catal.* **2012**, *354*, 415–427.
81. Boege, M.; Heck, J. Catalytic Sugar-Assisted Transfer Hydrogenation with Ru(II), Rh(III) and Ir(III) Half-Sandwich Complexes. *J. Mol. Catal. A: Chem* **2015**, *408*, 107–122.

82. Soni, R.; Cheung, F. K.; Clarkson, G. C.; Martins, J. E. D.; Graham, M. A.; Wills, M. The Importance of the N-H Bond in Ru/TsDPEN Complexes for Asymmetric Transfer Hydrogenation of Ketones and Imines. *Org. Biomol. Chem.* **2011**, *9*, 3290–3294.
83. Barrios-Rivera, J.; Xu, Y.; Wills, M. Applications of N'-monofunctionalised TsDPEN Derivatives in Asymmetric Catalysis. *Org. Biomol. Chem.* **2019**, *17*, 1301–1321.
84. Martins, J. E. D.; Clarkson, G. J.; Wills, M. Ru(II) Complexes of N-Alkylated TsDPEN Ligands in Asymmetric Transfer Hydrogenation of Ketones and Imines. *Org. Lett.* **2009**, *11*, 847–850.
85. Martins, J. E. D.; Contreras Redondo, M. A.; Wills, M.; Applications of N'-Alkylated Derivatives of TsDPEN in the Asymmetric Transfer Hydrogenation of C=O and C=N Bonds. *Tetrahedron: Asymmetry* **2010**, *21*, 2258–2264.
86. Soni, R.; Hall, T. H.; Morris, D. J.; Clarkson, G. J.; Owen, M. R.; Wills, M. N-Functionalised TsDPEN Catalysts for Asymmetric Transfer Hydrogenation; Synthesis and Applications. *Tetrahedron Lett.* **2015**, *56*, 6397–6401.
87. Ma, W.; Zhang, J.; Xu, C.; Chen, F.; He, Y.-M.; Fan, Q.-H. Highly Enantioselective Direct Synthesis of Endocyclic Vicinal Diamines through Chiral Ru(diamine)-Catalyzed Hydrogenation of 2,2'-Bisquinoline Derivatives. *Angew. Chem. Int. Ed.* **2016**, *55*, 12891–12894.
88. Shan, W.; Meng, F.; Wu, Y.; Mao, F.; Li, X. J. The Synthesis of a New Nitrogen Joined N-PEG-TsDPEN Ligand and its Application in Asymmetric Transfer Hydrogenation of Ketones in Neat Water. *J. Organomet. Chem.* **2011**, *696*, 1687–1690.
89. Zimbron, J. M.; Dauphinais, M.; Charette, A. B. Noyori–Ikariya Catalyst Supported on Tetraaryolphosphonium salt for Asymmetric Transfer Hydrogenation in Water. *Green Chem.* **2015**, *17*, 3255–3259.
90. Wang, R.; Wan, J.; Ma, X.; Xu X.; Liu L. Anchored [RuCl₂(p-cymene)]₂ in Hybrid Zirconium Phosphate–Phosphonate Coated and Pillared with Double-stranded Hydrophobic Linear Polystyrene as Heterogeneous Catalyst Suitable for Aqueous Asymmetric Transfer Hydrogenation. *Dalton Trans.* **2013**, *42*, 6513–6522.
91. Johnson, T. C.; Totty, W. G.; Wills, M. Application of Ruthenium Complexes of Triazole-Containing Tridentate Ligands to Asymmetric Transfer Hydrogenation of Ketones. *Org. Lett.* **2012**, *14*, 5230–5233.
92. Darwish, M. O.; Wallace, A.; Clarkson, G. J.; Wills, M. Use of Tridentate TsDPEN/Pyridine Ligands in Ruthenium-Catalysed Asymmetric Reduction of Ketones. *Tetrahedron Lett.* **2013**, *54*, 4250–4253.
93. Barrios-Rivera, J.; Xu, Y.; Wills, M. Probing the Effects of Heterocyclic Functionality in [(Benzene)Ru(TsDPENR)Cl] Catalysts for Asymmetric Transfer Hydrogenation. *Org. Lett.* **2019**, *21*, 7223–7227.
94. Dub, P. A.; Matsunami, A.; Kuwata, S.; Kayaki, Y. Cleavage of N–H Bond of Ammonia via Metal–Ligand Cooperation Enables Rational Design of a Conceptually New Noyori–Ikariya Catalyst. *J. Am. Chem. Soc.* **2019**, *141*, 2661–2677.
95. Rast, S.; Modéc, B.; Stephan, M.; Mohar, B. γ -Sultam-Cored N,N-Ligands in the Ruthenium(II)-Catalyzed Asymmetric Transfer Hydrogenation of Aryl Ketones. *Org. Biomol. Chem.* **2016**, *14*, 2112–2120.
96. Ye, W.; Zhao, M.; Yu, Z. Ruthenium(II) Pyrazolyl–Pyridyl–Oxazolanyl Complex Catalysts for the Asymmetric Transfer Hydrogenation of Ketones. *Chem. Eur. J.* **2012**, *18*, 10843–10846.

97. Nedden, H. G.; Zanotti-Gerosa, A.; Wills, M. The Development of Phosphine-Free Tethered Ruthenium(II) Catalysts for the Asymmetric Reduction of Ketones and Imines. *Chem. Rec.* **2016**, *16*, 2623–2643.
98. Cheung, F. K.; Lin, C.; Minissi, F.; Crivillé, A. L.; Graham, M. A.; Fox, D. J.; Wills, W. An Investigation into the Tether Length and Substitution Pattern of Arene-Substituted Complexes for Asymmetric Transfer Hydrogenation of Ketones. *Org. Lett.* **2007**, *9*, 4659–4662.
99. Martins, J. E. D.; Morris, D. J.; Tripathi, B.; Wills, M. Further ‘Tethered’ Ru(II) Catalysts for Asymmetric Transfer Hydrogenation (ATH) of Ketones; The Use of a Benzylic Linker and a Cyclohexyldiamine Ligand. *J. Organomet. Chem.* **2008**, *693*, 3527–3532.
100. Cheung, F. K.; Clarke, A. J.; Clarkson, G. J.; Fox, D. J.; Graham, M. A.; Lin, C.; Criville, A. L.; Wills, M. Kinetic and Structural Studies on ‘Tethered’ Ru(II) arene Ketone Reduction Catalysts. *Dalton trans.* **2010**, *39*, 1395–1402.
101. Parekh, V.; Ramsden, J. A.; Wills, M. Asymmetric Transfer Hydrogenation of Quinolines Using Tethered Ru(II) Catalysts. *Tetrahedron Asym.* **2010**, *21*, 1549–1556.
102. Jolley, K. E.; Zanotti-Gerosa, A.; Hancock, F.; Dyke, A.; Grainger, D. M.; Medlock, J. A.; Nedden, H. G.; Le Paih, J. J. M.; Roseblade, S. J.; Seger, A.; Sivakumar, V.; Prokes, I.; Morris, D. J.; Wills, M. Application of Tethered Ruthenium Catalysts to Asymmetric Hydrogenation of Ketones, and the Selective Hydrogenation of Aldehydes. *Adv. Synth. Catal.* **2012**, *354*, 2545–2555.
103. Soni, R.; Jolley, K. E.; Clarkson, G. J.; Wills, M. Direct Formation of Tethered Ru(II) Catalysts Using Arene Exchange. *Org. Lett.* **2013**, *15*, 5110–5113.
104. Soni, R.; Collinson, J.-M.; Clarkson, G. C.; Wills, M. An Unexpected Directing Effect in the Asymmetric Transfer Hydrogenation of α,α -Disubstituted Ketones. *Org. Lett.* **2011**, *13*, 4304–4307.
105. Fang, Z.; Wills, M. Asymmetric Transfer Hydrogenation of Functionalized Acetylenic Ketones. *J. Org. Chem.* **2013**, *78*, 8594–8605.
106. Fang Z, Wills M. Asymmetric Reduction of Diynones and the Total Synthesis of (*S*)-Panaxjapyne A. *Org Lett.* **2014**, *16*, 374–377.
107. Monnereau, L.; Cartigny, D.; Scalone, M.; Ayad, T.; Ratovelomanana-Vidal, V. Efficient Synthesis of Differentiated syn-1,2-Diol Derivatives by Asymmetric Transfer Hydrogenation–Dynamic Kinetic Resolution of α -Alkoxy-Substituted β -Ketoesters. *Chem. Eur. J.* **2015**, *21*, 11799–11806.
108. Vyas, V. K.; Knighton, R. C.; Bhanage, B. M.; Wills, M. Combining Electronic and Steric Effects To Generate Hindered Propargylic Alcohols in High Enantiomeric Excess. *Org. Lett.* **2018**, *20*, 975–978.
109. Forshaw, S.; Matthews, A. J.; Brown, T. J.; Diorazio, L. J.; Williams, L. Wills, M. Asymmetric Transfer Hydrogenation of 1,3-Alkoxy/Aryloxy Propanones Using Tethered Arene/Ru(II)/TsDPEN Complexes. *Org. Lett.* **2017**, *19*, 2789–2792.
110. Perryman, M. S.; Harris, M. E.; Foster, J. L.; Joshi, A.; Clarkson, G. J.; Fox, D. J. Trichloromethyl Ketones: Asymmetric Transfer Hydrogenation and Subsequent Jocic-Type Reactions with Amines. *Chem. Commun.* **2013**, *49*, 10022–10024.
111. Hodgkinson, R.; Jurčík, V.; Zanotti-Gerosa, A.; Nedden, H. G.; Blackaby, A.; Clarkson, G. J.; Wills, M. Synthesis and Catalytic Applications of an Extended Range of Tethered Ruthenium(II)/ η^6 -Arene/Diamine Complexes. *Organometallics* **2014**, *33*, 5517–5524.

112. Vyas, V. K.; Bhanage, B. M. Kinetic Resolution Driven Diastereo- and Enantioselective Synthesis of cis- β -Heteroaryl Amino Cycloalkanols by Ruthenium-Catalyzed Asymmetric Transfer Hydrogenation. *Org. Lett.* **2016**, *18*, 6436–6439.
113. Mangion, I. K.; Chen, C.-y.; Li, H.; Maligres, P.; Chen, Y.; Christensen, M.; Cohen, R.; Jeon, I.; Klapars, A.; Krska, S.; Nguyen, H.; Reamer, R. A.; Sherry, B. D.; Zavialov, I. Enantioselective Synthesis of an HCV NS5a Antagonist. *Org. Lett.* **2014**, *16*, 2310–2313.
114. Su, Y.; Tu, Y.-Q.; Gu, P. Preparation of Enantioenriched γ -Substituted Lactones via Asymmetric Transfer Hydrogenation of β -Azidocyclopropane Carboxylates Using the Ru-TsDPEN Complex. *Org. Lett.* **2014**, *16*, 4204–4207.
115. Ji, Y.; Xue, P.; Ma, D. D.; Li, X. Q.; Gu, P.; Li, R. Asymmetric Transfer Hydrogenation of Alpha-Azido Acrylates. *Tetrahedron Lett.* **2015**, *56*, 192–194.
116. Soni, R.; Jolley, K. E.; Gosiewska, S.; Clarkson, G. J.; Fang, Z.; Hall, T. H.; Treloar, B. N.; Knighton, R. C.; Wills, M. Synthesis of Enantiomerically Pure and Racemic Benzyl-Tethered Ru(II)/TsDPEN Complexes by Direct Arene Substitution: Further Complexes and Applications. *Organometallics* **2018**, *37*, 48–64.
117. Knighton, R. C.; Vyas, V. K.; Mailey, L. H.; Bhanage, B. M.; Wills, M.; Asymmetric Transfer Hydrogenation of Acetophenone Derivatives using 2-Benzyl-Tethered Ruthenium(II)/TsDPEN Complexes Bearing η^6 -(p-OR) (R = H, iPr, Bn, Ph) Ligands. *J. Organomet. Chem.* **2018**, *875*, 72–79.
118. Touge, T.; Hakamata, T.; Nara, H.; Kobayashi, T.; Sayo, N.; Saito, T.; Kayaki, Y.; Ikariya, T. Oxo-Tethered Ruthenium(II) Complex as a Bifunctional Catalyst for Asymmetric Transfer Hydrogenation and H₂ Hydrogenation. *J. Am. Chem. Soc.* **2011**, *133*, 14960–14963.
119. Parekh, V.; Ramsden, J. A.; Wills, M. Ether-Tethered Ru(II)/TsDPEN Complexes. Synthesis and Applications to Asymmetric Transfer Hydrogenation. *Catal. Sci. Technol.* **2012**, *2*, 406–414.
120. Touge, T.; Nara, H.; Fujiwhara, M.; Kayaki, Y.; Ikariya, T. Efficient Access to Chiral Benzhydrols via Asymmetric Transfer Hydrogenation of Unsymmetrical Benzophenones with Bifunctional Oxo-Tethered Ruthenium Catalysts. *J. Am. Chem. Soc.* **2016**, *138*, 10084–10087.
121. Matsunami, A.; Ikeda, M.; Nakamura, H.; Yoshida, M.; Kuwata, S. Kayaki, Y. Accessible Bifunctional Oxy-Tethered Ruthenium(II) Catalysts for Asymmetric Transfer Hydrogenation. *Org. Lett.* **2018**, *20*, 5213–5218.
122. Wang, B.; Zhou, H.; Lu, G.; Liu, Q.; Jiang, X. Bifunctional Oxo-Tethered Ruthenium Complex Catalyzed Asymmetric Transfer Hydrogenation of Aryl N-Heteroaryl Ketones. *Org. Lett.* **2017**, *19*, 2094–2097.
123. Yuki, Y.; Touge, T.; Nara, H.; Matsumura, K.; Fujiwhara, M.; Kayaki, Y.; Ikariya, T. Selective Asymmetric Transfer Hydrogenation of α -Substituted Acetophenones with Bifunctional Oxo-Tethered Ruthenium(II) Catalysts. *Adv. Synth. Catal.* **2018**, *360*, 568–574.
124. Touge, T.; Kuwana, M.; Komatsuki, K.; Tanaka, S.; Matsumu, K.; Sayo, N.; Kashibuchi, Y.; Saito, T. Development of Asymmetric Transfer Hydrogenation with a Bifunctional Oxo-Tethered Ruthenium Catalyst in Flow for the Synthesis of a Ceramide (D-erythro-CER[NDS]). *Org. Process Res. Dev.* **2019**, *23*, 452–461.
125. Touge, T.; Sakaguchi, K.; Tamaki, N.; Hideki Nara, Yokozawa, T.; Matsumura, K.; Kayaki, Y. Multiple Absolute Stereocontrol in Cascade Lactone Formation via Dynamic Kinetic Resolution Driven by the Asymmetric Transfer Hydrogenation of Keto Acids with Oxo-Tethered Ruthenium Catalysts. *J. Am. Chem. Soc.* **2019**, *141*, 16354–16361.

126. Komiyama, M.; Itoh, T.; Takeyasu, T. Scalable Ruthenium-Catalyzed Asymmetric Synthesis of a Key Intermediate for the β 2-Adrenergic Receptor Agonist. *Org. Process Res. Dev.* **2015**, *19*, 315–319.
127. Chung, J. Y. L.; Scott, J. P.; Andersson, C.; Bishop, B.; Bremeyer, N.; Cao, Y.; Chen, Q.; Dunn, R.; Kassim, A.; Lieberman, D.; Moment, A. J.; Sheen, F. Zacuto, M. Evolution of a Manufacturing Route to Omarigliptin, A Long-Acting DPP-4 Inhibitor for the Treatment of Type 2 Diabetes. *Org. Process Res. Dev.* **2015**, *19*, 1760–1768.
128. Sun, G.; Zhou, Z.; Luo, Z.; Wang, H.; Chen, L.; Xu, Y.; Li, S.; Jian, W.; Zeng, J.; Hu, B.; Han, X.; Lin, Y.; Wang, Z. Highly Enantioselective Synthesis of Syn- β -Hydroxy α -Dibenzylamino Esters via DKR Asymmetric Transfer Hydrogenation and Gram-Scale Preparation of Droxidopa. *Org. Lett.* **2017**, *19*, 4339–4342.
129. Kistic, A.; Stephan, M.; Mohar, B. Asymmetric Transfer Hydrogenation of 1-Naphthyl Ketones by an Ansa-Ru(II) Complex of a DPENSO₂N(Me)-(CH₂)₂(η^6 -p-Tol) Combined Ligand. *Org. Lett.* **2013**, *15*, 1614–1617.
130. Kistic, A.; Stephan, M.; Mohar, B. Ansa-Ruthenium(II) Complexes of DPEN-SO₂N(Me)(CH₂)_n(η^6 -aryl) Conjugate Ligands for Asymmetric Transfer Hydrogenation of Aryl Ketones. *Adv. Synth. Catal.* **2014**, *356*, 3193–3198.
131. Kistic, A.; Stephan, M.; Mohar, B. Ansa-Ruthenium(II) Complexes of R₂NSO₂DPEN-(CH₂)_n(η^6 -Aryl) Conjugate Ligands for Asymmetric Transfer Hydrogenation of Aryl Ketones. *Adv. Synth. Catal.* **2015**, *357*, 2540–2546.
132. Cotman, A. E.; Cahard, D.; Mohar, B. Stereoarrayed CF₃-Substituted 1,3-Diols by Dynamic Kinetic Resolution: Ruthenium(II)-Catalyzed Asymmetric Transfer Hydrogenation. *Angew. Chem. Int. Ed.* **2016**, *55*, 5294–5298.
133. Jeran, M.; Cotman, A. E.; Stephan, M.; Mohar, B. Stereopure Functionalized Benzosultams via Ruthenium(II)-Catalyzed Dynamic Kinetic Resolution- Asymmetric Transfer Hydrogenation. *Org. Lett.* **2017**, *19*, 2042–2045.
134. Cotman, A. E.; Modéc, B.; Mohar, B. Stereoarrayed 2,3-Disubstituted 1-Indanols via Ruthenium(II)-Catalyzed Dynamic Kinetic Resolution-Asymmetric Transfer Hydrogenation. *Org. Lett.* **2018**, *20*, 2921–2924.
135. Cotman, A. E.; Lozinsek, M.; Wang, B.; Stephan, M.; Mohar, B. Trans-Diastereoselective Ru(II)-Catalyzed Asymmetric Transfer Hydrogenation of α -Acetamido Benzocyclic Ketones via Dynamic Kinetic Resolution. *Org. Lett.* **2019**, *21*, 3644–3648.
136. Shvo, Y.; Czarkie, D.; Rahamim, Y. A New Group of Ruthenium Complexes: Structure and Catalysis. *J. Am. Chem. Soc.* **1986**, *108*, 7400–7402.
137. Conley, B. L.; Pennington-Boggio, M. K.; Boz, E.; Williams, T. J. Discovery, Applications, and Catalytic Mechanisms of Shvo's Catalyst. *Chem. Rev.* **2010**, *110*, 2294–2312.
138. Warner, M. C.; Casey, C. P.; Bäckvall, J.-E. Shvo's Catalyst in Hydrogen Transfer Reactions. *Top. Organomet. Chem.* **2011**, *37*, 85–125.
139. Verho, O.; Bäckvall, J.-E. Chemoenzymatic Dynamic Kinetic Resolution: A Powerful Tool for the Preparation of Enantiomerically Pure Alcohols and Amines. *J. Am. Chem. Soc.* **2015**, *137*, 3996–4009.

140. Hopewell, J. P.; Martins, J. E. D.; Johnson, T. C.; Godfrey, J.; Wills, M. Developing Asymmetric Iron and Ruthenium-Based Cyclone Complexes; Complex Factors Influence the Asymmetric Induction in the Transfer Hydrogenation of Ketones. *Org. Biomol. Chem.* **2012**, *10*, 134–145.
141. Dou, X.; Hayashi, T. Synthesis of Planar Chiral Shvo Catalysts for Asymmetric Transfer Hydrogenation. *Adv. Synth. Catal.* **2016**, *358*, 1054–1058.
142. Nova, A.; Taylor, D. J.; Blacker, A. J.; Duckett, S. B.; Perutz, R. N.; Eisenstein, O. Computational Studies Explain the Importance of Two Different Substituents on the Chelating Bis(amido) Ligand for Transfer Hydrogenation by Bifunctional Cp*Rh(III) Catalysts. *Organometallics* **2014**, *33*, 3433–3442.
143. Matharu, D. S.; Morris, D.J.; Clarkson, G. J.; Wills, M.; An Outstanding Catalyst for Asymmetric Transfer Hydrogenation in Aqueous Solution and Formic Acid/Triethylamine. *Chem Commun.* **2006**, *52*, 3232–3234.
144. Matharu, D. S.; Martins, J. E. D.; Wills, M.; Asymmetric Transfer Hydrogenation of C=O and C=N Bonds by Tethered Rh^{III} Catalysts. *Chem. Asian J.* **2008**, *3*, 1374–1383.
145. Echeverria, P.-G.; Ferard, C.; Phansavath, P.; Ratovelomanana-Vidal, V. Synthesis, Characterization and Use of a New Tethered Rh(III) Complex in Asymmetric Transfer Hydrogenation of Ketones. *Catal. Commun.* **2015**, *62*, 95–99.
146. Zheng, L.-S.; Llopis, Q.; Echeverria, P.-G.; Ferard, C.; Guillamot, G.; Phansavath, P.; Ratovelomanana-Vidal, V. Asymmetric Transfer Hydrogenation of (Hetero)arylketones with Tethered Rh(III)-*N*-(*p*-Tolylsulfonyl)-1,2-diphenylethylene-1,2-diamine Complexes: Scope and Limitations. *J. Org. Chem.* **2017**, *82*, 5607–5615.
147. Llopis, Q.; Ferard, C.; Guillamot, G.; Phansavath, P.; Ratovelomanana-Vidal, V. Rhodium-Catalyzed anti and syn Enantio- and Diastereoselective Transfer Hydrogenation of α -Amino β -Keto Ester Hydrochlorides through Dynamic Kinetic Resolution. *Synthesis* **2016**, *48*, 3357–3363.
148. He, B.; Zheng, L.-S.; Phansavath, P.; Ratovelomanana-Vidal, V. Rh^{III}-Catalyzed Asymmetric Transfer Hydrogenation of α -Methoxy β -Ketoesters through DKR in Water: Toward a Greener Procedure. *ChemSusChem* **2019**, *12*, 3032–3036.
149. He, B.; Phansavath, P.; Ratovelomanana-Vidal, V. Rh-Mediated Asymmetric-Transfer Hydrogenation of 3-Substituted Chromones: A Route to Enantioenriched cis-3-(Hydroxymethyl)chroman-4-ol Derivatives through Dynamic Kinetic Resolution. *Org. Lett.* **2019**, *21*, 3276–3280.
150. Westermeyer, A.; Guillamot, G.; Phansavath, P.; Ratovelomanana-Vidal, V. Synthesis of Enantioenriched β -Hydroxy- γ -acetal Enamides by Rhodium-Catalyzed Asymmetric Transfer Hydrogenation. *Org. Lett.* **2020**, *22*, 3911–3914.
151. He, B.; Phansavath, P.; Ratovelomanana-Vidal, V. Rhodium-Catalyzed Asymmetric Transfer Hydrogenation of 4-quinolone derivatives. *Org. Chem. Front.* **2020**, *7*, 975–979.
152. Wang, F.; Zheng, L.-S.; Lang, Q.-W.; Yin, C.; Wu, T.; Phansavath, P.; Chen, G.-Q.; Ratovelomanana-Vidal, V. Zhang, X. Rh(III)-Catalyzed Diastereoselective Transfer Hydrogenation: an Efficient Entry to Key Intermediates of HIV Protease Inhibitors. *Chem. Commun.* **2020**, *56*, 3119–3122.
153. Ahlford, K.; Adolfsson, H. Amino Acid Derived Amides and Hydroxamic Acids as Ligands for Asymmetric Transfer Hydrogenation in Aqueous Media. *Catal. Commun.* **2011**, *12*, 1118–1121.

154. Ahlford, K.; Ekström, J.; Zaitsev, A. B.; Ryberg, P.; Eriksson, L.; Adolfsson, H. Asymmetric Transfer Hydrogenation of Ketones Catalyzed by Amino Acid Derived Rhodium Complexes: On the Origin of Enantioselectivity and Enantioswitchability. *Chem. Eur. J.* **2009**, *15*, 11197–11209.
155. Tinnis, F.; Adolfsson, H. Asymmetric Transfer Hydrogenation of Ketones Catalyzed by Rhodium Complexes Containing Amino Acid Triazole Ligands. *Org. Biomol. Chem.* **2010**, *8*, 4536–4539.
156. Nordin, M.; Liao, R.-Z.; Ahlford, K.; Adolfsson, H.; Himo, F. Theoretical Study of Asymmetric Transfer Hydrogenation of Ketones Catalyzed by Amino Acid-Derived Rhodium Complexes. *ChemCatChem* **2012**, *48*, 1095–1104.
157. Coll, M. Pàmies, O.; Adolfsson, H.; Diéguez, M. Second-Generation Amino Acid Furanoside Based Ligands from D-glucose for the Asymmetric Transfer Hydrogenation of Ketones. *ChemCatChem* **2013**, *5*, 3821–3828.
158. Margalef, J.; Slagbrand, T.; Tinnis, F.; Adolfsson, H.; Diéguez, M.; Pàmies, O. Third-Generation Amino Acid Furanoside-Based Ligands from D-Mannose for the Asymmetric Transfer Hydrogenation of Ketones: Catalysts with an Exceptionally Wide Substrate Scope. *Adv. Synth. Catal.* **2016**, *358*, 4006–4018.
159. Bartoszewicz, A.; Ahlsten, N.; Martín-Matute, B. Enantioselective Synthesis of Alcohols and Amines by Iridium-Catalyzed Hydrogenation, Transfer Hydrogenation, and Related Processes. *Chem. Eur. J.* **2013**, *19*, 7274–7302.
160. Vázquez-Villa, H.; Reber, S.; Ariger, M. A.; Carreira, E. M. Iridium Diamine Catalyst for the Asymmetric Transfer Hydrogenation of Ketones. *Angew. Chem. Int. Ed.* **2011**, *50*, 8979–8981.
161. Liu, W.-P.; Yuan, M.-L.; Yang, X.-H.; Li, K.; Xie, J.-H.; Zhou, Q.-L. Efficient Asymmetric Transfer Hydrogenation of Ketones in Ethanol with Chiral Iridium Complexes of SpiroPAP Ligands as Catalysts. *Chem. Commun.* **2015**, *51*, 6123–6125.
162. Zhang, Y.-M.; Yuan, M.-L.; Liu, W.-P.; Xie, J.-H.; Zhou, Q.-L. Iridium-Catalyzed Asymmetric Transfer Hydrogenation of Alkynyl Ketones Using Sodium Formate and Ethanol as Hydrogen Sources. *Org. Lett.* **2018**, *20*, 4486–4489.
163. Sato, Y.; Kayaki, Y.; Ikariya, T.; Comparative Study of Bifunctional Mononuclear and Dinuclear Amidoiridium Complexes with Chiral C-N Chelating Ligands for the Asymmetric Transfer Hydrogenation of Ketones. *Chem. Asian J.* **2016**, *11*, 2924–2931.
164. Creus, M.; Pordea, A.; Rossel, T.; Sardo, A.; Letondor, C.; Ivanova, A.; LeTrong, I.; Stenkamp, R. E.; Ward, T. R. X-Ray Structure and Designed Evolution of an Artificial Transfer Hydrogenase. *Angew. Chem. Int. Ed.* **2008**, *47*, 1400–1404.
165. Dürrenberger, M.; Heinisch, T.; Wilson, Y. M.; Rossel, T.; Nogueira, E.; Knörr, L.; Mutschler, A.; Kersten, K.; Zimbron, Malcolm, M.; Pierron, J.; Schnirmer, T.; Ward, T. R. Artificial Transfer Hydrogenases for the Enantioselective Reduction of Cyclic Imines. *Angew. Chem. Int. Ed.* **2011**, *50*, 3026–3029.
166. Letondor, C.; Pordea, A.; Humbert, N.; Ivanova, A.; Mazurek, S.; Novic, M.; Ward, T. R. Artificial Transfer Hydrogenases Based on the Biotin-(Strept)avidin Technology: Fine Tuning the Selectivity by Saturation Mutagenesis of the Host Protein. *J. Am. Chem. Soc.* **2006**, *128*, 8320–8328.
167. Blackmond, D. G.; Ropic, M.; Stefinovic, M. Kinetic Studies of the Asymmetric Transfer Hydrogenation of Imines with Formic Acid Catalyzed by Rh-Diamine Catalysts. *Org. Process Res. Dev.* **2006**, *10*, 457–463.

168. Åberg, J. B.; Samec, J. S. M.; Bäckvall, J.-E. Mechanistic Investigation on the Hydrogenation of Imines by $[p\text{-(Me}_2\text{CH)C}_6\text{H}_4\text{Me}]\text{RuH}(\text{NH}_2\text{CHPhCHPhNSO}_2\text{C}_6\text{H}_4\text{-}p\text{-CH}_3)$. Experimental Support for an Ionic Pathway. *Chem. Commun.* **2006**, 2771–2773.
169. Chen, L.-A.; Xu, W.; Huang, B.; Ma, J.; Wang, L.; Xi, J.; Harms, K.; Gong, L.; Meggers, E. Asymmetric Catalysis with an Inert Chiral-at-Metal Iridium Complex. *J. Am. Chem. Soc.* **2013**, *135*, 10598–10601.
170. Tian, C.; Gong, L.; Meggers, E. Chiral-at-Metal Iridium Complex for Efficient Enantioselective Transfer Hydrogenation of Ketones. *Chem. Commun.* **2016**, 4207–4210.
171. Carmona, D.; Lahoz, F. J.; García-Orduña, P.; Oro, L. A.; Lamata, M. P.; Viguri, F. Half-Sandwich Complexes of Osmium(II) with L- α -Amino Carboxylate Ligands as Asymmetric Transfer Hydrogenation Catalysts. On the Origin of the Enantioselectivity. *Organometallics* **2012**, *31*, 3333–3345.
172. Coverdale, J. P. C.; Sanchez-Cano, C.; Clarkson, G. J.; Soni, R.; Wills, M.; Sadler, P. J. Easy To Synthesize, Robust Organo-osmium Asymmetric Transfer Hydrogenation Catalysts. *Chem. Eur. J.* **2015**, *21*, 8043–8046.
173. Wang, W.; Xinzhen Yang, X. Mechanistic Insights into Asymmetric Transfer Hydrogenation of Pyruvic Acid Catalysed by Chiral Osmium Complexes with Formic Acid Assisted Proton Transfer. *Chem. Commun.* **2019**, *55*, 9633–9636.
174. Yamamoto, Y.; Yamashita, K.; Nakamura, M. Synthesis of Organometallic Analogues Spirocyclic C-Arylribosides. *Organometallics* **2010**, *29*, 1472–1478.
175. Del Grosso, A.; Clarkson, G. J.; Wills, M. Asymmetric Ruthenium Tricarbonyl Cyclopentadienone Complexes; Synthesis and Application to Asymmetric Hydrogenation of Ketones. *Inorg. Chim. Acta* **2019**, *496*, 119043–119049.
176. Yamamura, T.; Nakatsuka, H.; Tanaka, S.; Kitamura, M. Asymmetric Hydrogenation of Tert-Alkyl Ketones: DMSO Effect in Unification of Stereoisomeric Ruthenium Complexes. *Angew. Chem. Int. Ed.* **2013**, *52*, 9313–9315.
177. Yamamura, T.; Nakane, S.; Nomura, Y.; Tanaka, S.; Kitamura, M. Development of an Axially Chiral $\text{sp}_3\text{P}/\text{sp}_3\text{NH}/\text{sp}_2\text{N}$ -Combined Linear Tridentate Ligand-fac-Selective Formation of Ru(II) Complexes and Application to Ketone Hydrogenation. *Tetrahedron* **2016**, *72*, 3781–3789.
178. Nakane, S.; Yamamura, T.; M., Sudipta K.; Tanaka, S.; Kitamura, M. Mechanistic Study of the Ru-Catalyzed Asymmetric Hydrogenation of Nonchelatable and Chelatable tert-Alkyl Ketones Using the Linear Tridentate $\text{sp}_3\text{P}/\text{sp}_3\text{NH}/\text{sp}_2\text{N}$ -Combined Ligand PN(H)N: RuNH- and RuNK-Involved Dual Catalytic Cycle. *ACS Catal.* **2018**, *8*, 11059–11075.
179. Nakatsuka H.; Yamamura T.; Shuto Y.; Tanaka S.; Kitamura M.; Yoshimura M. Mechanism of Asymmetric Hydrogenation of Aromatic Ketones Catalyzed by a Combined System of Ru($\pi\text{-CH}_2\text{C}(\text{CH}_3)\text{CH}_2$)₂(cod) and the Chiral sp(2)N/sp(3)NH Hybrid Linear N4 Ligand Ph-BINAN-H-Py. *J. Am. Chem. Soc.* **2015**, *137*, 8138–8149.
180. Ito, M.; Kobayashi, C.; Himizu, A.; Ikariya, T. Highly Enantioselective Hydrogenative Desymmetrization of Bicyclic Imides Leading to Multiply Functionalized Chiral Cyclic Compounds. *J. Am. Chem. Soc.* **2010**, *132*, 11414–11415.
181. Ito, M.; Ootsuka, T.; Watari, R.; Shiibashi, A.; Himizu, A.; Ikariya, T. Catalytic Hydrogenation of Carboxamides and Esters by Well-Defined Cp*Ru Complexes Bearing a Protic Amine Ligand. *J. Am. Chem. Soc.* **2011**, *133*, 4240–4242.

182. Chen, F.; Wang, T.; He, Y.; Ding, Z.; Li, Z.; Xu, L.; Fan, Q.-H. Asymmetric Hydrogenation of *N*-Alkyl Ketimines with Phosphine-Free, Chiral, Cationic Ru-MsDPEN Catalysts. *Chem. Eur. J.* **2011**, *17*, 1109–1113.
183. Chen, F.; Ding, Z.; Qin, J.; Wang, T.; He, Y.; Fan, Q.-H. Highly Effective Asymmetric Hydrogenation of Cyclic *N*-Alkyl Imines with Chiral Cationic Ru-MsDPEN Catalysts. *Org. Lett.* **2011**, *13*, 4348–4351.
184. Qin, J.; Chen, F.; Ding, Z.; He, Y.-M.; Xu, L.; Fan, Q.-H. Asymmetric Hydrogenation of 2- and 2,3-Substituted Quinoxalines with Chiral Cationic Ruthenium Diamine Catalysts. *Org. Lett.* **2011**, *13*, 6568–6571.
185. Wang, T.; Zhuo, L.-G.; Li, Z.; Chen, F.; Ding, Z.; He, Yanmei; Fan, Q.-H.; Xiang, J.; Yu, Z.-X.; Chan, A. S. C. Highly Enantioselective Hydrogenation of Quinolines Using Phosphine-Free Chiral Cationic Ruthenium Catalysts: Scope, Mechanism and Origin of Enantioselectivity. *J. Am. Chem. Soc.* **2011**, *133*, 9878–9891.
186. Ding, Z.-Y.; Chen, F.; Qin, J.; He, Y.-M.; Fan, Q.-H. Asymmetric Hydrogenation of 2,4-Disubstituted 1,5-Benzodiazepines Using Cationic Ruthenium Diamine Catalysts: An Unusual Achiral Counteranion Induced Reversal of Enantioselectivity. *Angew. Chem. Int. Ed.* **2012**, *51*, 5706–5710.
187. Chen, F.; Ding, Z.; He, Y.; Qin, J.; Wang, T.; Fan, Q.-H. Asymmetric hydrogenation of *N*-alkyl and *N*-Aryl Ketimines using Chiral Cationic Ru(Diamine) Complexes as Catalysts: the Counteranion and Solvent Effects and Substrate Scope. *Tetrahedron* **2012**, *68*, 5248–5257.
188. Yang, Z.; Chen, F.; He, Y.; Yang, N.; Fan, Q.-H. Highly Enantioselective Synthesis of Indolines: Asymmetric Hydrogenation at Ambient Temperature and Pressure with Cationic Ruthenium Diamine Catalysts. *Angew. Chem. Int. Ed.* **2016**, *55*, 13863–13866.
189. Li, W.; Wiesenfeldt, M. P.; Glorius, F. Ruthenium–NHC–Diamine Catalyzed Enantioselective Hydrogenation of Isocoumarins. *J. Am. Chem. Soc.* **2017**, *139*, 2585–2588.
190. Li, W.; Wagener, T.; Hellmann, L.; Daniliuc, C. G.; Mück-Lichtenfeld, C.; Neugebauer, J.; Glorius, F. Design of Ru(II)-NHC-Diamine Precatalysts Directed by Ligand Cooperation: Applications and Mechanistic Investigations for Asymmetric Hydrogenation. *J. Am. Chem. Soc.* **2020**, *142*, 7100–7107.
191. Breuil, P.-A. R.; Patureau, F. W.; Reek, J. N. H. Singly Hydrogen Bonded Supramolecular Ligands for Highly Selective Rhodium-Catalyzed Hydrogenation Reactions. *Angew. Chem., Int. Ed.* **2009**, *48*, 2162–2165.
192. Daubignard, J.; Detz, R. J.; Jans, A. C. H.; de Bruin, B.; Reek, J. N. H. Rational Optimization of Supramolecular Catalysts for the Rhodium-Catalyzed Asymmetric Hydrogenation Reaction. *Angew. Chem. Int. Ed.* **2017**, *56*, 13056–13060.
193. Daubignard, J.; Detz, R. J.; de Bruin, B.; Reek, J. N. H. Phosphine Oxide Based Supramolecular Ligands in the Rhodium-Catalyzed Asymmetric Hydrogenation. *Organometallics* **2019**, *38*, 3961–3969.
194. Zhao, Q.; Li, S.; Huang, K.; Wang, R.; Zhang, X. A Novel Chiral Bisphosphine-Thiourea Ligand for Asymmetric Hydrogenation of α,α -Disubstituted Nitroalkenes. *Org. Lett.* **2013**, *15*, 4014–4017.
195. Li, P.; Zhou, M.; Zhao, Q.; Wu, W.; Hu, X.; Dong, X.-Q. Zhang, X. Synthesis of Chiral β -Amino Nitroalkanes via Rhodium-Catalyzed Asymmetric Hydrogenation. *Org. Lett.* **2016**, *18*, 40–43.

196. Wen, J.; Jiang, J.; Zhang, X. Rhodium-Catalyzed Asymmetric Hydrogenation of α,β -Unsaturated Carbonyl Compounds via Thiourea Hydrogen Bonding. *Org. Lett.* **2016**, *18*, 4451–4453.
197. Liu, G.; Han, Z.; Dong, X.-Q.; Zhang, X. Rh-Catalyzed Asymmetric Hydrogenation of β -Substituted- β -thio- α,β -Unsaturated Esters: Expeditious Access to Chiral Organic Sulfides. *Org. Lett.* **2018**, *20*, 5636–5639.
198. Sun, Y.; Jiang, J.; Guo, X.; Wen, J.; Zhang, X. Asymmetric Hydrogenation of α,β -Unsaturated Sulfones by a Rhodium/Thiourea–Bisphosphine Complex. *Org. Chem. Front.* **2019**, *6*, 1438–1441.
199. Han, Z.; Li, P.; Zhang, Z.; Chen, C.; Wang, Q.; Dong, X.-Q.; Zhang, X. Highly Enantioselective Synthesis of Chiral Succinimides via Rh/Bisphosphine-Thiourea-Catalyzed Asymmetric Hydrogenation. *ACS Catal.* **2016**, *6*, 6214–6218.
200. Han, Z.; Wang, R.; Gu, G.; Dong, X.-Q.; Zhang, X. Asymmetric Hydrogenation of Maleic Anhydrides Catalyzed by Rh/Bisphosphine-Thiourea: Efficient Construction of Chiral Succinic Anhydrides. *Chem. Commun.* **2017**, *53*, 4226–4229.
201. Lang, Q.; Gu, G.; Cheng, Y.; Yin, Q.; Zhang, X. Highly Enantioselective Synthesis of Chiral γ -Lactams by Rh-Catalyzed Asymmetric Hydrogenation. *ACS Catal.* **2018**, *8*, 4824–4828.
202. Yin, C.; Yang, T.; Pan, Y.; Wen, J.; Zhang, X. Rh-Catalyzed Asymmetric Hydrogenation of Unsaturated Medium-Ring NH Lactams: Highly Enantioselective Synthesis of *N*-Unprotected 2,3-Dihydro-1,5-benzothiazepinones. *Org. Lett.* **2020**, *22*, 920–923.
203. Yang, J.; Li, X.; You, C.; Li, S.; Guan, Y.-Q.; Lv, H.; Zhang, X. Rhodium-Catalyzed Asymmetric Hydrogenation of Exocyclic α,β -Unsaturated Carbonyl Compounds. *Org. Biomol. Chem.* **2020**, *18*, 856–859.
204. Li, X.; You, C.; Yang, Y.; Yang, Y.; Li, P.; Gu, G.; Chung, L. W.; Lv, H.; Zhang, X. Rhodium-Catalyzed Asymmetric Hydrogenation of β -Cyanocinnamic Esters with the Assistance of a Single Hydrogen Bond in a Precise Position. *Chem. Sci.* **2018**, *9*, 1919–1924.
205. Liu, G.; Zhang, H.; Huang, Y.; Han, Z.; Liu, G.; Liu, Y.; Dong, X.-Q.; Zhang, X. Efficient Synthesis of Chiral 2,3-Dihydro-Benzo[b]thiophene 1,1-Dioxides via Rh-Catalyzed Hydrogenation. *Chem. Sci.* **2019**, *10*, 2507–2512.
206. Liu, G.; Li, A.; Qin, X.; Han, Z.; Dong, X.-Q.; Zhang, X. Efficient Access to Chiral β -Borylated Carboxylic Esters via Rh-Catalyzed Hydrogenation. *Adv. Synth. Catal.* **2019**, *361*, 2844–2848.
207. Zhao, Q.; Wen, J.; Tan, R.; Huang, K.; Metola, P.; Wang, R.; Anslyn, E. V.; Zhang, X. Rhodium-Catalyzed Asymmetric Hydrogenation of Unprotected NH Imines Assisted by a Thiourea. *Angew. Chem. Int. Ed.* **2014**, *53*, 8467–8470.
208. Wen, J.; Tan, R.; Liu, S.; Zhao, Q.; Zhang, X. Strong Brønsted Acid Promoted Asymmetric Hydrogenation of Isoquinolines and Quinolines Catalyzed by a Rh–Thiourea Chiral Phosphine Complex via Anion Binding. *Chem. Sci.* **2016**, *7*, 3047–3051.
209. Wen, J.; Fan, X.; Tan, R.; Chien, H.-C.; Zhou, Q.; Chung, L.W.; Zhang, X. Brønsted-Acid-Promoted Rh-Catalyzed Asymmetric Hydrogenation of *N*-Unprotected Indoles: A Cocatalysis of Transition Metal and Anion Binding. *Org. Lett.* **2018**, *20*, 2143–2147.
210. Chen, C.; Wang, H.; Zhang, Z.; Jin, S.; Wen, S.; Ji, J.; Chung, L. W.; Dong, X.-Q.; Zhang, X. Ferrocenyl Chiral Bisphosphorus Ligands for Highly Enantioselective Asymmetric Hydrogenation via Noncovalent Ion Pair Interaction. *Chem. Sci.* **2016**, *7*, 6669–6673.

211. Yin, X.; Chen, C.; Dong, X.-Q.; Zhang, X. Rh/Wudaphos-Catalyzed Asymmetric Hydrogenation of Sodium α -Arylethenylsulfonates: A Method To Access Chiral α -Arylethylsulfonic Acids. *Org. Lett.* **2017**, *19*, 2678–2681.
212. Chen, C.; Zhang, Z.; Jin, S.; Fan, X.; Geng, M.; Zhou, Y.; Wen, S.; Wang, X.; Chung, L. W.; Dong, X.-Q.; Zhang, X. Enzyme-Inspired Chiral Secondary-Phosphine-Oxide Ligand with Dual Noncovalent Interactions for Asymmetric Hydrogenation. *Angew. Chem. Int. Ed.* **2017**, *56*, 6808–6812.
213. Rh/SPO-WudaPhos-Catalyzed Asymmetric Hydrogenation of α -Substituted Ethenylphosphonic Acids via Noncovalent Ion-Pair Interaction. Yin, X.; Chen, C.; Li, X.; Dong, X.-Q.; Zhang, X. *Org. Lett.* **2017**, *19*, 4375–4378.
214. Chen, C.; Wen, S.; Geng, M.; Jin, S.; Zhang, Z.; Dong, X.-Q.; Zhang, X. A New Ferrocenyl Bisphosphorus Ligand for the Asymmetric Hydrogenation of α -Methylene- γ -Keto-Carboxylic Acids. *Chem. Commun.* **2017**, *53*, 9785–9788.
215. Wen, S.; Chen, C.; Du, S.; Zhang, Z.; Huang, Y.; Han, Z.; Dong, X.-Q.; Zhang, X. Highly Enantioselective Asymmetric Hydrogenation of Carboxy-Directed α,α -Disubstituted Terminal Olefins via the Ion Pair Noncovalent Interaction. *Org. Lett.* **2017**, *19*, 6474–6477.
216. Ito, M.; Endo, Y.; Tejima, N.; Ikariya, T. Bifunctional Triflylamide-Tethered Cp'Rh and Cp'Ir Complexes: A New Entry for Asymmetric Hydrogenation Catalysts. *Organometallics* **2010**, *29*, 2397–2399.
217. Moritani, J.; Kayaki, Y.; Ikariya, T. Advantageous Asymmetric Ketone Reduction with a Competitive Hydrogenation/Transfer Hydrogenation System Using Chiral Bifunctional Iridium Catalysts. *RSC Adv.* **2014**, *4*, 61001–61004.
218. Kumar, P.; Irrgang, T.; Kostakis, G. E.; Kempe, R. Phosphine-Free Chiral Iridium Catalysts for Asymmetric Catalytic Hydrogenation of Simple Ketones. *RSC Adv.* **2016**, *6*, 39335–39342.
219. Xie, J.-H.; Liu, X.-Y.; Xie, J.-B.; Wang, L.-X.; Zhou, Q.-L. An Additional Coordination Group Leads to Extremely Efficient Chiral Iridium Catalysts for Asymmetric Hydrogenation of Ketones. *Angew. Chem., Int. Ed.* **2011**, *50*, 7329–7332.
220. Xie, J.-H.; Liu, X.-Y.; Yang, X.-H.; Xie, J.-B.; Wang, L.-X.; Zhou, Q.-L. Chiral Iridium Catalysts Bearing Spiro Pyridine-Aminophosphine Ligands Enable Highly Efficient Asymmetric Hydrogenation of β -Aryl β -Ketoesters. *Angew. Chem. Int. Ed.* **2012**, *51*, 201–203.
221. Bao, D.-H.; Wu, H.-L.; Liu, C.-L.; Xie, J.-H.; Zhou, Q.-L. Development of Chiral Spiro P-N-S Ligands for Iridium-Catalyzed Asymmetric Hydrogenation of β -Alkyl- β -Ketoesters. *Angew. Chem. Int. Ed.* **2015**, *54*, 8791–8794.
222. Zhang, Q.-Q.; Xie, J.-H.; Yang, X.-H.; Xie, J.-B.; Zhou, Q.-L. Iridium-Catalyzed Asymmetric Hydrogenation of α -Substituted α,β -Unsaturated Acyclic Ketones: Enantioselective Total Synthesis of (-)-Mesembrine. *Org. Lett.* **2012**, *14*, 6158–6161.
223. Yang, X.-H.; Xie, J.-H.; Liu, W.-P.; Zhou, Q.-L. Catalytic Asymmetric Hydrogenation of δ -Ketoesters: Highly Efficient Approach to Chiral 1,5-Diols. *Angew. Chem. Int. Ed.* **2013**, *52*, 7833–7836.
224. Yan, P.-C.; Xie, J.-H.; Zhang, X.-D.; Chen, K.; Li, Y.-Q.; Zhou, Q.-L.; Che, D.-Q. Direct Asymmetric Hydrogenation of α -Keto Acids by Using the Highly Efficient Chiral Spiro Iridium Catalysts. *Chem. Commun.* **2014**, *50*, 15987–15990.

225. Yang, X.-H.; Wang, K.; Zhu, S.-F.; Xie, J.-H.; Zhou, Q.-L. Remote Ester Group Leads to Efficient Kinetic Resolution of Racemic Aliphatic Alcohols via Asymmetric Hydrogenation. *J. Am. Chem. Soc.* **2014**, *136*, 17426–17429.
226. Lin, H.; Xiao, L.-J.; Zhou, M.-J.; Yu, H.-M.; Xie, J.-H.; Zhou, Q.-L. Enantioselective Approach to (-)-Hamigeran B and (-)-4-Bromohamigeran B via Catalytic Asymmetric Hydrogenation of Racemic Ketone To Assemble the Chiral Core Framework. *Org. Lett.* **2016**, *18*, 1434–1437.
227. Bao, D.-H.; Gu, X.-S.; Xie, J.-H.; Zhou, Q.-L. Iridium-Catalyzed Asymmetric Hydrogenation of Racemic β -Keto Lactams via Dynamic Kinetic Resolution. *Org. Lett.* **2017**, *19*, 118–121.
228. Liu, Y.-T.; Chen, J.-Q.; Li, L.-P.; Shao, X.-Y.; Xie, J.-H.; Zhou, Q.-L. Asymmetric Hydrogenation of Tetrasubstituted Cyclic Enones to Chiral Cycloalkanols with Three Contiguous Stereocenters. *Org. Lett.* **2017**, *19*, 3231–3234.
229. Zuo, X.-D.; Guo, S.-M.; Yang, R.; Xie, J.-H.; Zhou, Q.-L. Bioinspired Enantioselective Synthesis of Crinine-Type Alkaloids via Iridium-Catalyzed Asymmetric Hydrogenation of Enones. *Chem. Sci.* **2017**, *8*, 6202–6206.
230. Liu, Y.-T.; Li, L.-P.; Xie, J.-H.; Zhou, Q.-L. Divergent Asymmetric Total Synthesis of Mulinane Diterpenoids. *Angew. Chem. Int. Ed.* **2017**, *56*, 12708–12711.
231. Zuo, X.-D.; Guo, S.-M.; Yang, R.; Xie, J.-H.; Zhou, Q.-L. Asymmetric Total Synthesis of Gracilamine and Determination of Its Absolute Configuration. *Org. Lett.* **2017**, *19*, 5240–5243.
232. Bin, H.-Y.; Wang, K.; Yang, D.; Yang, X.-H.; Xie, J.-H.; Zhou, Q.-L. Scalable Enantioselective Total Synthesis of (-)-Goniomitine. *Angew. Chem. Int. Ed.* **2019**, *58*, 1174–1177.
233. Gu, X.-S.; Yu, N.; Yang, X.-H.; Zhu, A.-T.; Xie, J.-H.; Zhou, Q. L. Enantioselective Hydrogenation of Racemic α -Arylamino Lactones to Chiral Amino Diols with Site-Specifically Modified Chiral Spiro Iridium Catalysts. *Org. Lett.* **2019**, *21*, 4111–4115.
234. Hua, Y.-Y.; Bin, H.-Y.; Wei, T.; Cheng, H.-A.; Lin, Z.-P.; Fu, X.-F.; Li, Y.-Q.; Xie, J.-H.; Yan, P.-C.; Zhou, Q.-L. Iridium-Catalyzed Asymmetric Hydrogenation of γ - and δ -Ketoacids for Enantioselective Synthesis of γ - and δ -Lactones. *Org. Lett.* **2020**, *22*, 818–822.
235. Chen, G.-Q.; Lin, B.-J.; Huang, J.-M.; Zhao, L.-Y.; Chen, Q.-S.; Jia, S.-P.; Yin, Q.; Zhang, X. Design and Synthesis of Chiral oxa-Spirocyclic Ligands for Ir-Catalyzed Direct Asymmetric Reduction of Bringmann's Lactones with Molecular H₂. *J. Am. Chem. Soc.* **2018**, *140*, 8064–8068.
236. Wu, W.; Liu, S.; Duan, M.; Tan, X.; Chen, C.; Xie, Y.; Lan, Y.; Dong, X.-Q.; Zhang, X. Iridium Catalysts with f-Amphox Ligands: Asymmetric Hydrogenation of Simple Ketones. *Org. Lett.* **2016**, *18*, 2938–2941.
237. Yu, J.; Long, J.; Yang, Y.; Wu, W.; Xue, P.; Chung, L. W.; Dong, X.-Q.; Zhang, X. Iridium-Catalyzed Asymmetric Hydrogenation of Ketones with Accessible and Modular Ferrocene-Based Amino-phosphine Acid (f-Ampha) Ligands. *Org. Lett.* **2017**, *19*, 690–693.
238. Han, Z.; Liu, G.; Wang, R.; Dong, X.-Q.; Zhang, X. Highly Efficient Ir-Catalyzed Asymmetric Hydrogenation of Benzoxazinones and Derivatives with a Brønsted Acid Cocatalyst. *Chem. Sci.* **2019**, *10*, 4328–4333.
239. Liu, Y.; Huang, Y.; Yi, Z.; Liu, G.; Dong, X.-Q.; Zhang, X. Enantioselective Access to Chiral Cyclic Sulfamidates Through Iridium-Catalyzed Asymmetric Hydrogenation. *Adv. Synth. Catal.* **2019**, *361*, 1582–1586.

240. Yang, T.; Sun, Y.; Wang, H.; Lin, Z.; Wen, J.; Zhang, X. Iridium-Catalyzed Enantioselective Hydrogenation of Oxocarbenium Ions: A Case of Ionic Hydrogenation. *Angew. Chem. Int. Ed.* **2020**, *59*, 6108–6114.
241. Rueping, M.; Koenigs, R. M. Brønsted Acid Differentiated Metal Catalysis by Kinetic Discrimination. *Chem. Commun.* **2011**, *47*, 304–306.
242. Tang, W.; Johnston, S.; Iggo, J. A.; Berry, N. G.; Phelan, M.; Lian, L.; Bacsa, J.; Xiao, J. Cooperative Catalysis through Noncovalent Interactions. *Angew. Chem. Int. Ed.* **2013**, *52*, 1668–1672.
243. Tang, W.; Johnston, S.; Li, C.; Iggo, J. A.; Bacsa, J.; Xiao, J. Cooperative Catalysis: Combining an Achiral Metal Catalyst with a Chiral Bronsted Acid Enables Highly Enantioselective Hydrogenation of Imines. *Chem. Eur. J.* **2013**, *19*, 14187–14193.
244. Pan, H.-J.; Zhang, Y.; Shan, C.; Yu, Z.; Lan, Y.; Zhao, Y. Asymmetric Transfer Hydrogenation of Imines using Alcohol: Efficiency and Selectivity are Influenced by the Hydrogen Donor. *Angew. Chem. Int. Ed.* **2016**, *55*, 9615–9619.
245. Ohkuma, T.; Sandoval, C. A.; Srinivasan, R.; Lin, Q.; Wei, Y.; Muniz, K.; Noyori, R. Asymmetric Hydrogenation of Tert-Alkyl Ketones. *J. Am. Chem. Soc.* **2005**, *127*, 8288–8289.
246. Kuwano, R.; Morioka, R.; Kashiwabara, M.; Kameyama, N. Catalytic Asymmetric Hydrogenation of Naphthalenes. *Angew. Chem. Int. Ed.* **2012**, *51*, 4136–4139.
247. Wang, D.-S.; Chen, Q.-A.; Lu, S.-M.; Zhou, Y.-G. Asymmetric Hydrogenation of Heteroarenes and Arenes. *Chem. Rev.* **2012**, *112*, 2557–2590.
248. Margarita, C.; Andersson, P. G. Evolution and Prospects of the Asymmetric Hydrogenation of Unfunctionalized Olefins. *J. Am. Chem. Soc.* **2017**, *139*, 1346–1356.
249. Kraft, S.; Ryan, K.; Kargbo, R. B. Recent Advances in Asymmetric Hydrogenation of Tetrasubstituted Olefins. *J. Am. Chem. Soc.* **2017**, *139*, 11630–11641.
250. Gensch, T.; Teders, M.; Glorius, F. Approach to Comparing the Functional Group Tolerance of Reactions. *J. Org. Chem.* **2017**, *82*, 9154–9159.
251. Bullock, R. M. Abundant Metals Give Precious Hydrogenation Performance. *Science* **2013**, *342*, 1054–1055.
252. Ludwig, J. R.; Schindler, C. S. Catalyst: Sustainable Catalysis. *Chem* **2017**, *2*, 313–316.
253. Agbossou-Niedercorn, F.; Michon, C. Bifunctional catalysts based on first row transition metals for asymmetric hydrogenation. *Coord. Chem. Rev.* **2020**, *425*, 213523–213559.
254. Duque, R.; Pogorzelec, P. J.; Cole-Hamilton, D. J. A Single Enantiomer (99%) Directly from Continuous-Flow Asymmetric Hydrogenation. *Angew. Chem., Int. Ed.* **2013**, *52*, 9805–9807.
255. O'Neal, E. J.; Lee, C. H.; Brathwaite, J.; Jensen, K. F. Continuous Nanofiltration and Recycle of an Asymmetric Ketone Hydrogenation Catalyst. *ACS Catalysis* **2015**, *5*, 2615–2622.
256. Geier, D.; Schmitz, P.; Walkowiak, J.; Leitner, W.; Francio, G. Continuous Flow Asymmetric Hydrogenation with Supported Ionic Liquid Phase Catalysts Using Modified CO₂ as the Mobile Phase: from Model Substrate to an Active Pharmaceutical Ingredient. *ACS Catalysis* **2018**, *8*, 3297–3303.
257. Gladysz, J. A. Recoverable Catalysts. Ultimate Goals, Criteria of Evaluation, and the Green Chemistry Interface. *Pure Appl. Chem.* **2001**, *73*, 1319–1324.

258. Hübner, S.; de Vries, J. G.; Farina, V. Why Does Industry Not Use Immobilized Transition Metal Complexes as Catalysts? *Adv. Synth. Catal.* **2016**, *358*, 3–25.