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FEATURE ARTICLE

Hydrogenation of imino bonds with half-sandwich metal catalysts

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Imines can be reduced to afford synthetically important amines *via* a number of means, of which half-sandwich metal complex-effected reduction has gained particular prominence in the past one decade or so. This Feature Article aims to summarise the progress made with such metal catalysts, placing emphasis on our own work. The article covers transfer hydrogenation and hydrogenation, and finishes with a brief account of catalyst immobilisation and mechanistic understanding.

1. Introduction

Amines, in particular α-chiral amines, are highly valuable products and intermediates of great importance in chemical synthesis. They exist in a vast number of bioactive compounds, displaying activities of relevance to agrochemical and pharmaceutical industries,[1] and are widely used as chiral ligands,[2] auxiliaries[3] or catalysts[4] in asymmetric reactions (Fig. 1). For instance, (*S*)-Metolachlor is a herbicide, which is produced industrially by iridium catalysed asymmetric hydrogenation (AH) of imines,[5] and Tamsulosin, the active ingredient in the blockbuster drug Flomax, improves symptoms in patients with chronic prostatitis.[6] Examples are also seen in chiral cyclic amines, which frequently appear in natural products and biologically important molecules, such as Tubulosine which exhibits high antitumor activity.[7]

Amines can be directly produced by reduction of an imino bond, and a number of methods have been developed for doing this (Scheme 1). Producing no waste, hydrogenation with H_2 is the most desired reduction, both economically and environmentally. It is most effectively catalysed by complexes of Ru, Rh and Ir.[1b,8] However, there are significantly fewer catalysts that are effective for imines than for olefins and ketones. Imines can also be reduced with other hydrogen donors. In transfer hydrogenation (TH), isopropanol and formic acid are most frequently used. Requiring no pressure vessels and with ready availability of hydrogen sources, TH is simple, versatile and less hazardous, supplementing hydrogenation. Similar but often not the same Ru, Rh and Ir complexes are usually the catalysts of choice.[9] Hydroboration with borohydrides provides another means, so does hydrosilylation with silanes. While many borohydrides such as $NaBH_3(CN)$ and $NaBH(OAc)_3$ require no catalyst for reduction

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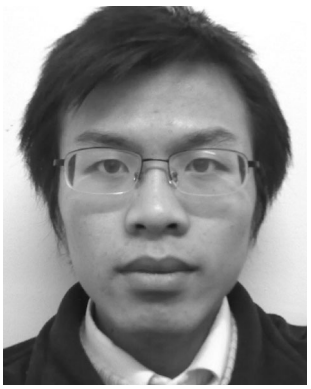


Chao Wang

Chao Wang was born in Hunan, China in 1981. He received his BSc in Chemistry from Hunan Normal University in 2004. He then moved on for a MSc in Organic Chemistry with Prof. Yi Jiang at the Chengdu Institute of Organic Chemistry, Chinese Academy of Sciences. He pursued his PhD study at the University of Liverpool in the group of Prof. Jianliang Xiao. In 2011, he joins Shaanxi Normal University as an Associate Professor. His current research interests lie in the field of catalysis, organometallic chemistry and green chemistry.

Barbara Villa-Marcos

Barbara Villa Marcos was born in Oviedo, Spain in 1984. After obtaining her MSc in Organic Chemistry from the University of Oviedo in 2007, she entered the University of Liverpool as a PhD student. Currently, she is studying for her PhD degree under the guidance of Professor Jianliang Xiao. Her thesis work focuses on the design of new methodologies for the synthesis of chiral amines.

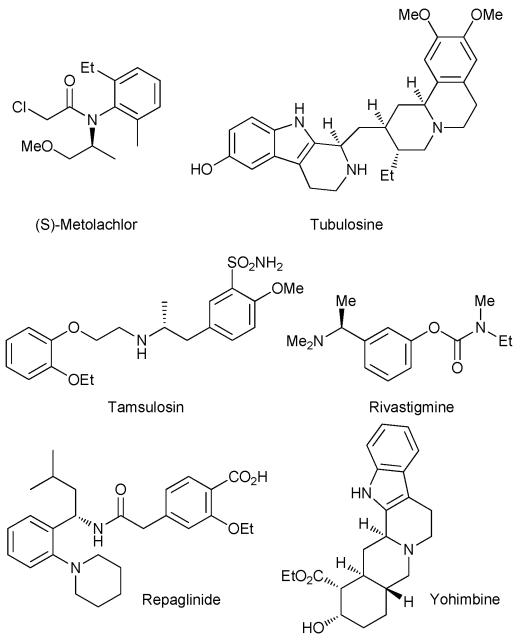
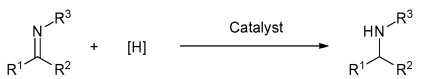


Fig. 1 Examples of chiral amines used in agrochemical and pharmaceutical industries.



[H] = H_2, ROH, HCOOH, HBR_3^-, $HSiR_3$, Hantzsch ester, etc.

Scheme 1 Reduction of imino bond with various hydrogen sources.

to proceed,[10] silanes generally do, and a variety of catalysts are known to promote the reduction.[11] NADH analogues, such as the Hantzsch ester, can also deliver hydrogen by virtue of Brønsted acid catalysis.[12]

Among the various lines of development, homogeneous transition metal-catalysed reduction dominates the scene, and several reviews have been published recently, summarising the progress made thus far.[13] In this Feature Article, we focus on a unique class of metal catalysts, half-sandwich complexes, highlighting their success in imino reduction *via* hydrogenation by drawing various examples, with emphasis on our own work.

Sandwich metal complexes have played a significant role in the history of organometallic chemistry. The elucidation of the sandwich structure of ferrocene by Wilkinson, Woodward, and Fisher led to the 1973 Noble Prize in chemistry and the blossom of organometallic chemistry (Fig. 2). However, it is the half-sandwich complexes that have found most applications as active species in catalysis, where vacant sites are normally required.[14] The arene ligands, particularly the cyclopentadienyl variants, can bind to a metal centre strongly, usually acting as spectator ligands. The electronic, steric, as well as physical properties of the metal complexes may be finely tuned by these ligands, resulting in unique reactivity patterns.

A common problem faced in catalytic imine reduction is deactivation of catalysts by substrates or products. Apart from easy isomerisation, the relatively high LUMO energy of the C=N double bond also renders its reduction more difficult than a C=O bond. However, many half-sandwich complexes have proven to be good catalysts for imine reduction, as attested by examples to follow. Their success may be traced to the strongly-binding arene ligands, which can inhibit catalyst deactivation by simultaneously occupying three vacant sites, and to the hydrogenation pathway they take, which generally appears to be ionic in nature (*vide infra*). Under ionic hydrogenation, the imine is protonated, becoming activated *and* non-coordinative. The robustness of half-sandwich metal complexes also allows the generation of metal hydrides which can tolerate various acidic conditions, accommodating imines of diverse pK_b's. These features will be seen in the examples to be described. We will first present those arising from TH; this is followed by hydrogenation with H_2. A brief account of catalyst immobilization and mechanistic understanding is given towards the end of the Article.

2. TH of imino bonds with half-sandwich complexes

The first TH of imine appears to be reported by Grigg and co-workers. The Wilkinson catalyst, $[RhCl(PPh_3)_3]$, was used to catalyse the reduction of aldimines by isopropanol in the presence of sodium carbonate.[15] A number of catalytic systems, including chiral variants, have since been developed. Among them, the most studied and most successful ones are those employing half-sandwich complexes as catalysts.

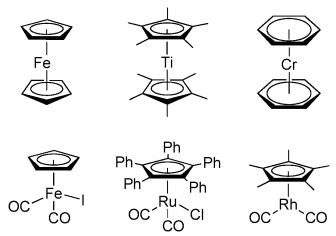


Fig. 2 Examples of sandwich and half-sandwich metal complexes.

Jianliang Xiao

Jianliang Xiao received a B.Eng at Northwest University in 1982. This was followed by a MEng with Profs. Chi Wu and Junyu Wang at the Research Institute of Petroleum Processing and a PhD in chemistry with Prof. Marty Cowie at Alberta. After a postdoctoral appointment with Prof. Puddephatt, he joined the ERATO Molecular Catalysis Project directed by Prof. Noyori. In 1996 he took up a Principal Scientist position at the University of Liverpool, becoming a lecturer in the Chemistry Department in 1999. He was promoted to professor in 2005 and awarded the UK Prize for Process Chemistry Research 2008.

2.1 Achiral TH of imines

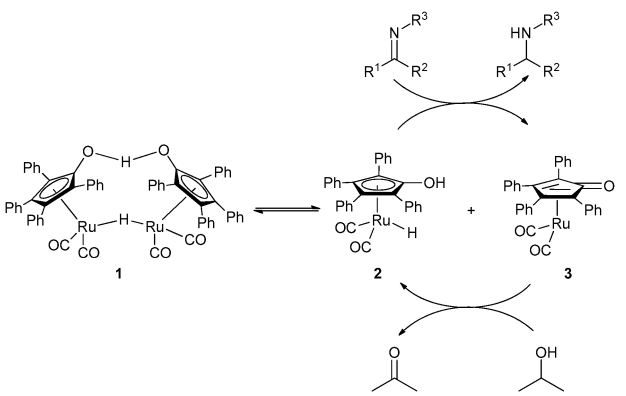
Casey and co-workers reported in 2001 the stoichiometric transfer of hydride generated from the Shvo's catalyst **1** to imine substrates.[16] Catalytic reduction of imines with **1** was subsequently realised by Bäckvall and co-workers, using isopropanol as hydrogen source. In solution, the dimeric Shvo's catalyst dissociates into interchangeable species **2** and **3**; **2** effects the hydrogenation, turning into **3** which dehydrogenates isopropanol to regenerate **2** (Scheme 2). The catalytic system works for a range of *N*-aryl imines, with TOFs up to 700 h^{-1}.[17]

The simpler, more easily accessible $[Cp^*RhCl_2]_2$ is shown by Kitamura and co-workers to be effective for the amination of ketones with ammonium formate as both the amine source and hydrogen source (Scheme 3). In this reductive amination reaction, the imino bond is *in situ* formed from the condensation of ketone and ammonia. The catalyst is also effective for α-keto acids, affording amino acids.[18]

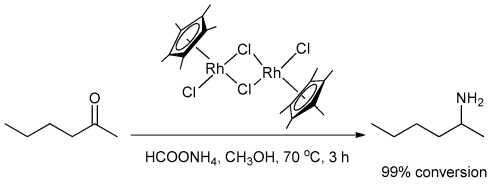
In 2004, Ogo and co-workers reported a water-soluble iridium catalyst **4**, which enables reductive amination of α-keto acids to produce amino acids in aqueous solution (Scheme 4).[19] The solution pH is crucial for obtaining high selectivity as well as high activity, with pH 5 being the optimal. An electron-rich variant of this catalyst, **5**, has been used to modify proteins *via* reductive alkylation of the amino groups on proteins with aldehydes (Scheme 4). Proteins possessing various polar functional groups were alkylated with aldehydes of diverse properties.[20] **4** led to lower yields, however.

The iridium carbene complex **6** was reported to catalyse the reduction of imine by isopropanol at room temperature (Scheme 5).[21] It works under base free conditions, even for aldehydes and ketones; however a silver salt was necessary. Substrate to catalyst ratio (S/C) of 1000 can be used for the imine tested. However, only one example of imine reduction was described.

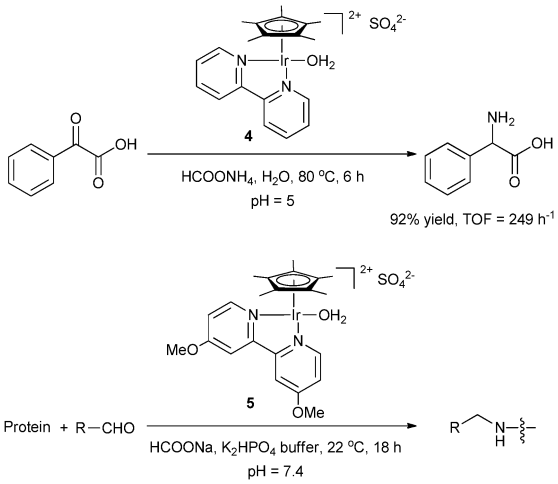
In continuing study into asymmetric reduction with half-sandwich complexes,[22] we recently disclosed a class of cyclometalated iridium complexes that are excellent catalysts for both imine reduction and reductive amination using formic acid as hydrogen source.[23] This finding resulted from an attempt to develop a catalytic system for reductive amination *via* TH. We initially examined reaction conditions for the TH of a model imine prepared from acetophenone and *p*-anisidine.



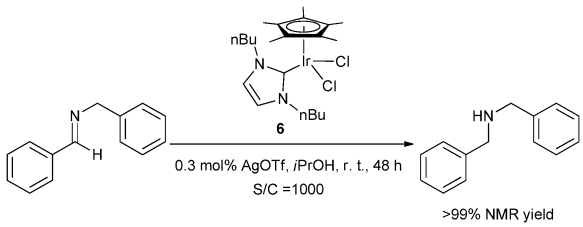
Scheme 2 Reduction of imines with Shvo's catalyst.



Scheme 3 Reductive amination with $HCOONH_4$ catalysed by a Rh complex.

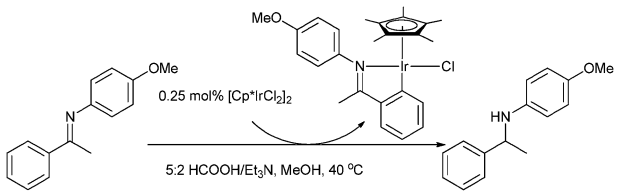


Scheme 4 Reductive amination catalysed by iridium bipyridine complexes.



Scheme 5 Imine reduction catalysed by an iridium carbene catalyst.

Using a pre-prepared Ir-TsDPEN [TsDPEN = (1*R*,2*R*)-*N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine] catalyst (0.5 mol%),[24] [Cp*IrCl(TsDEPN-H)], a 30% conversion to the corresponding amine in 13% ee was observed by using the azeotropic mixture of formic acid/triethylamine in MeOH at 40 °C in 3 h. Surprisingly, when the catalyst was *in situ* prepared by reacting $[Cp^*IrCl_2]_2$ with TsDPEN, the conversion rose to 95% but the resulting amine was racemic. Still interestingly, using $[Cp^*IrCl_2]_2$ (0.25 mol%) without any added ligand, the reaction proceeded to afford the same result as that obtained with the *in situ* catalyst. These results suggest that the chiral ligand is not involved in the reduction. Indeed, we quickly learned that the ketimine substrate reacts with the iridium, resulting in the formation of a cyclometalated imino iridium complex *via* C–H activation (Scheme 6).[25] Delightfully, the cyclometalated iridium complexes were shown to catalyse fast reduction of various imines, affording TOF as high as 1.9×10^4 h^{-1}, the highest value ever reported for TH of imino bonds. In contrast, amine and phosphine ligands were much less efficient.



Scheme 6 Reduction of imine by an *in situ* generated cyclometalated iridium complex.

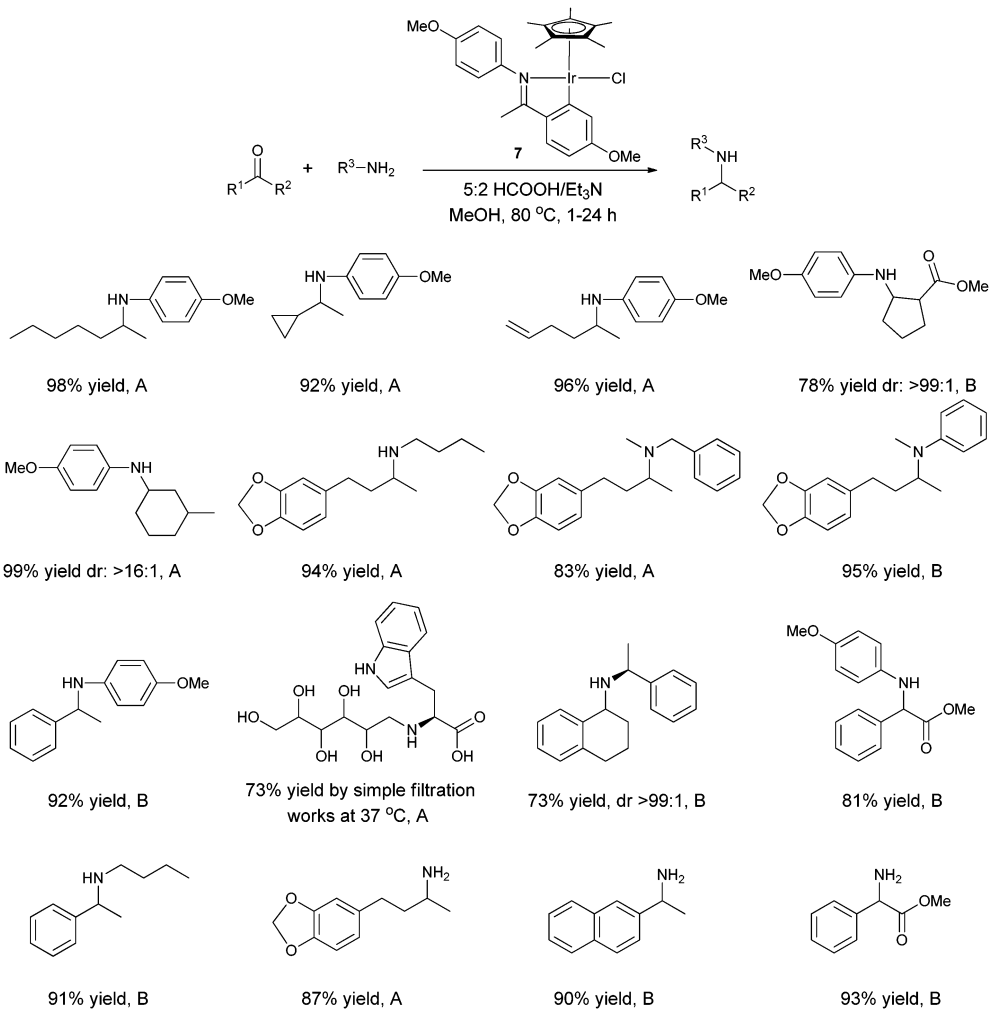
The cyclometalated iridium complexes also enable efficient reductive amination using the formic acid/triethylamine azeotrope in MeOH. In particular, complex **7** catalyses the amination of a wide range of carbonyl compounds with various amines, such as aliphatic and aromatic ketones and primary and secondary amines (Scheme 7). Even glucose and amino acids can be used as substrates without any protection. Moreover, ammonia or ammonium formate can be used as the amine source, allowing for the production of unprotected amines directly. Although achiral, this is probably the first catalytic system that rivals boron hydrides in chemoselectivity, activity and substrate scope in reductive amination. Further advantages include the modular nature of ligands and easy preparation of catalysts.

2.2 Asymmetric transfer hydrogenation of imines

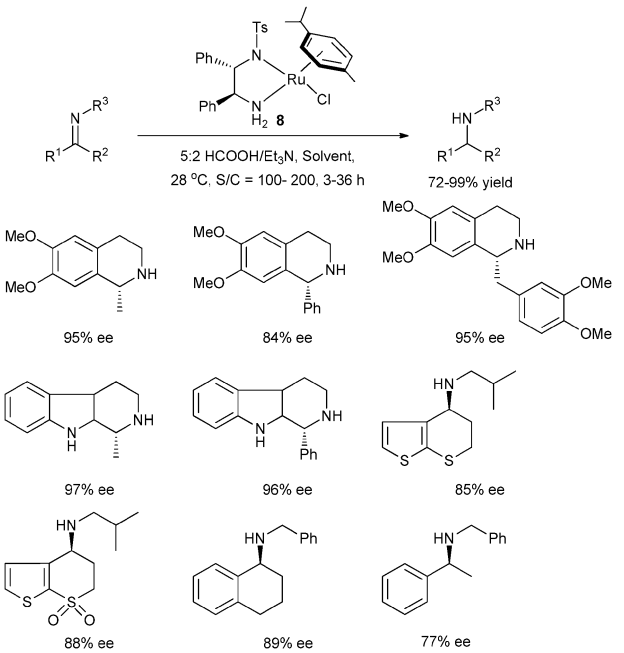
The first asymmetric transfer hydrogenation (ATH) of imines was reported by Noyori and co-workers in 1996, using the half-sandwich Ru-TsDPEN complex **8** as catalyst.[26] As shown in Scheme 8, various imines can be reduced with high yield and enantioselectivity in the formic acid/triethylamine azeotrope. Under the acidic conditions used, C=N bond is preferentially reduced over C=O bond, which would otherwise be expected to be more reactive under relatively neutral conditions. However, acyclic imines led to lower enantioselectivity.

This seminal discovery has since brought about a great deal of excitement in developing methods for asymmetric imino reduction. Soon after its discovery, the Noyori catalytic system was applied to the synthesis of substituted isoquinolines by Vedejs.[27] Wills and co-workers reported a one-pot reductive amination (Scheme 9).[28] Whilst good enantioselectivity was obtained, the catalyst only worked for intramolecular reductive amination.

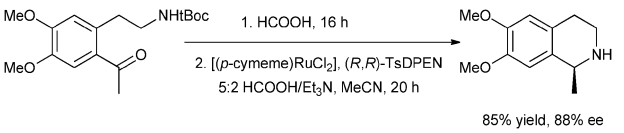
Another interesting application of the Noyori system is seen in the dynamic kinetic resolution (DKR) of α-branched ketimines.[29] Excellent diastereoselectivities and good to excellent enantioselectivities were obtained for a range of substrates with the Ru-TsDPEN catalyst or an analogous



Scheme 7 Cyclometalated iridium catalysed reductive amination. A: S/C = 1000; B: S/C = 200.



Scheme 8 ATH of imines with the Noyori–Ikariya catalyst **8**.

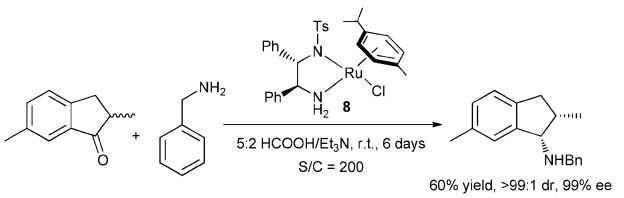


Scheme 9 Asymmetric intramolecular reductive amination *via* TH.

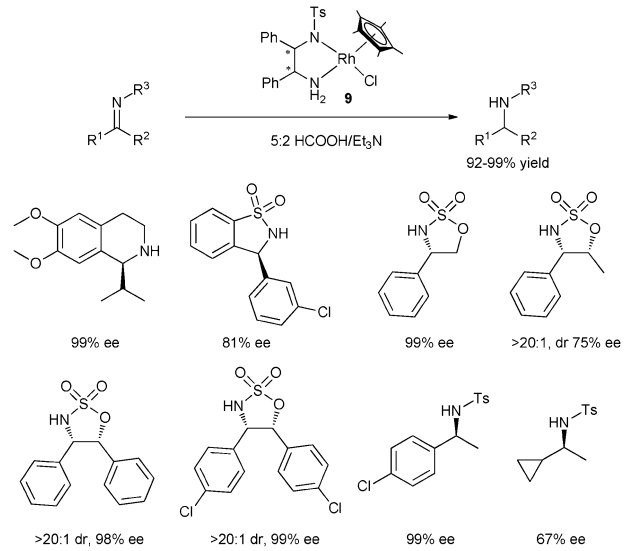
iridium catalyst. One-pot reductive amination of α-branched ketones *via* DKR could also be achieved, albeit requiring a long reaction time (Scheme 10)

The isoelectronic Rh-TsDPEN catalyst **9** appears to be more active in imine reduction.[30] However, the enantioselectivities obtained are lower than those observed with Ru-TsDPEN and acyclic imines afford almost racemic products. The rhodium catalyst **9** has recently been applied to the reduction of cyclic sulfamidates[31] and *N*-sulfonyl ketimines (Scheme 11).[32] Interestingly, in the case of sulfamidates, DKR of disubstituted cyclic imines took place, affording up to 99% yield, $>$ 20 : 1 dr and 99% ee.[31b]

Wills and co-workers introduced elegant modifications to the M-TsDPEN catalysts. In particular, installing a tether group between the diamine and the Cp* ligand gives rise to a very active and selective Rh(III) catalyst for the reduction of ketones and to some degree imines.[33] *N*-Alkylated Ts-DPEN ligands were also used for Ru catalysed reduction of imines, offering insight into the mechanism of the reaction.[34]



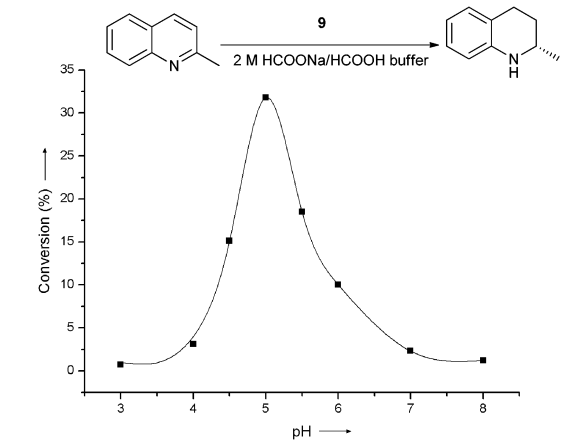
Scheme 10 DKR *via* transfer hydrogenative reductive amination.



Scheme 11 Rh-TsDPEN catalysed imino bond reduction.

Our group had previously shown that without any modification, the water-insoluble M-TsDPEN (M = Ru, Rh, Ir) catalysts allow for highly efficient reduction of ketones in neat water using sodium formate as hydrogen source, providing fast reduction rate and high enantioselectivity.[22] An important observation was that the solution pH plays a vital role in obtaining high activity and ee, with neutral pH being optimal. Prompted by the "green" feature of this aqueous reduction, we investigated the ATH of quinolines using (*S*,*S*)-**9** as catalyst in water. Tetrahydroquinolines, product of quinoline reduction, are commonly present in alkaloids and are required in pharmaceutical and agrochemical synthesis; but quinolines are relatively more difficult to reduce than normal imines, due to the destruction of aromaticity. We set out to examine the reduction of a model substrate 2-methylquinoline with HCOONa in water. Disappointingly, a conversion of only 17% was obtained at 40 °C and a S/C ratio of 100 in 12 h. The enantioselectivity was excellent, however, at 96% ee. Bearing in mind the finding from ketone reduction, we studied the effect of solution pH on the ATH rate. As shown in Scheme 12, the reduction was indeed strongly affected by the solution pH, with the maximum conversion observed at pH 5; the enantioselectivity did not vary though. This volcano curve is consistent with quinoline being reduced in its protonated rather neutral form. The pK_a of protonated 2-methylquinoline is 5.4. At high pH ($>$5.4), the concentration of protonated quinoline becomes low, whilst at low pH ($<$3.6) the concentration of reductant, formate, diminishes (pK_a of HCOOH is 3.6). Thus, a high concentration of protonated 2-methylquinoline and formate is expected in between pH 3.6–5.4. This would benefit the catalysis if the turnover is limited by the step of hydrogen transfer.

However, when conducted at the best pH 5, the reduction, though fast initially, could not complete even after a prolonged reaction time. Accompanied with this change in reaction rate was the solution pH, which quickly rose to 8 and hardly changed thereafter. This observation led us to speculate if the rise in solution pH was responsible for the



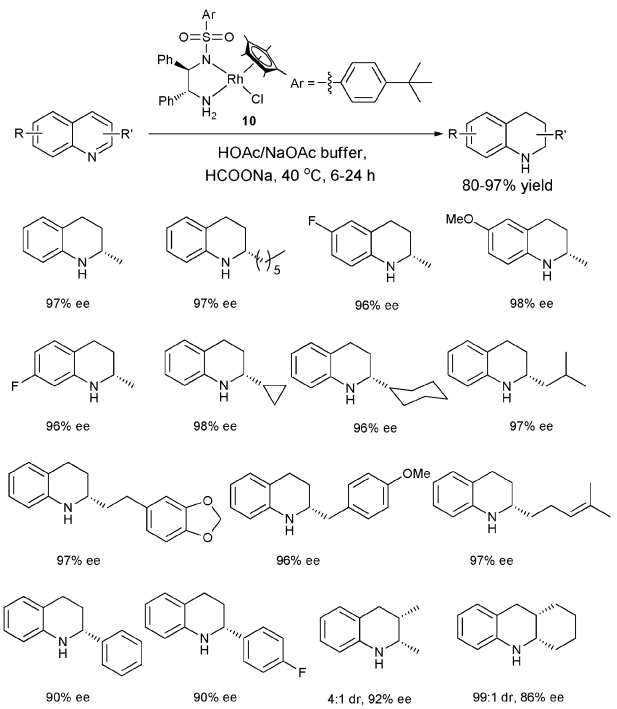
Scheme 12 Effect of solution pH on quinoline reduction in water.

slowing down in the reduction rate with time. Indeed, we found that the reduction was no longer stagnant when the pH was controlled. Thus, when a 2 M HOAc/NaOAc buffer solution was used instead of neat water, the ATH led to a 95% conversion in 3 h, with the enantioselectivity being identical to that observed in the aqueous formate.

With complex **10** as the catalyst, a broad range of quinoline substrates were then reduced under the buffered conditions, affording excellent yields and enantioselectivities (Scheme 13). This is the first organometallic ATH system for heterocyclic compounds, and it provides the widest substrate scope for quinolines.[35]

3. Hydrogenation of imino bonds with half-sandwich complexes

AH of imino bonds with H_2 and half-sandwich metal complexes was reported by Norton and co-workers in 2001.[36]



Scheme 13 pH-regulated ATH of quinolines.

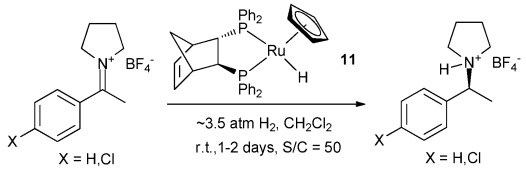
Using a CpRu-diphosphine complex **11** as catalyst, they were able to reduce *N*,*N*-dialkyl iminium cations, obtaining up to 60% ee (Scheme 14). This is the first study, which shows that C=N double bonds can be hydrogenated in an ionic mechanism (*vide infra*). Involving no imine coordination to the metal complex, this mechanism is characterised with hydride transfer to a protonated imine, thereby resulting in the reduction of the imino bond.[37]

Highly enantioselective hydrogenation has recently been demonstrated with the M-TsDPEN type catalysts. Fan and co-workers reported the hydrogenation of quinolines using **12**, an analogue of **8**, in the ionic liquid [BMIM][PF_6] [BMIM = 1-*n*-butyl-3-methylimidazolium] (Scheme 15).[38] The catalyst **12** was previously shown by Noyori and co-workers to be viable for asymmetric ketone hydrogenation.[39] Although the catalyst performed well in methanol,[40] ionic liquid led to a higher ee and dramatically enhanced catalyst stability. A further advantage is that the ionic liquid permits recycle of catalyst without sacrificing reactivity or enantioselectivity. Interestingly, their more recent study has revealed that the reaction proceeds efficiently even under solvent-free conditions, at a lower catalyst loading of 0.02%, but crucially in the presence of 0.1% TfOH.[41] Excellent yields and enantioselectivities of up to 97% were obtained for a range of 2,6-substituted quinolines.

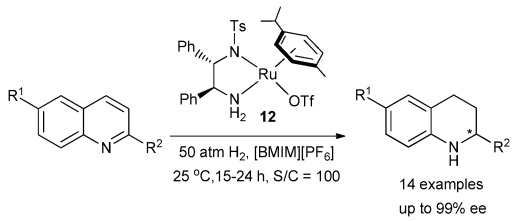
The Fan group also reported AH of cyclic *N*-sulfonylimines.[42] A Ru-MsDPEN [MsDPEN = *N*-(methanesulfonyl)-1,2-diphenylethylenediamine] catalyst afforded the best results, with enantioselectivity up to 93% ee (Fig. 3). However, the substrate scope appears limited, and the iridium and rhodium analogues showed lower enantioselectivities under the same conditions.

Very recently, the group extended the application of Ru-MsDPEN. Catalyst **13** was used for the AH of *N*-alkylketimines in dichloroethane or under solvent-free conditions, furnishing excellent enantioselectivities (Scheme 16).[43] The presence of $(Boc)_2O$ proves to be essential for the performance of the catalyst. If the imine decomposes, the resulting benzylamine may inhibit the catalysis by coordination to the Ru(II). $(Boc)_2O$ prevents this inhibition by protection of the benzylamine.

Our interest in AH of imino bonds arises from a study of carbonyl reduction, where we showed that a tosylated Ir-TsEN (EN = ethylene diamine) catalyst is capable of fast TH as well as hydrogenation of ketones and aldehydes in water.[22b,44] While that research was underway, Noyori and co-workers published the hydrogenation of ketones with catalysts of the type **12**.[39,45] We therefore attempted the hydrogenation of imines with the iridium catalyst, initially focusing on 3,4-dihydroisoquinolines; however, the Ir-TsEN



Scheme 14 AH of iminium salts by a ruthenium hydride.



Scheme 15 Ru-catalysed AH of quinolines.

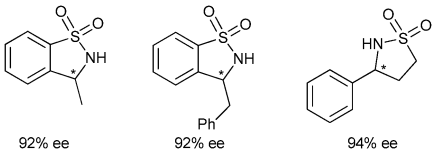
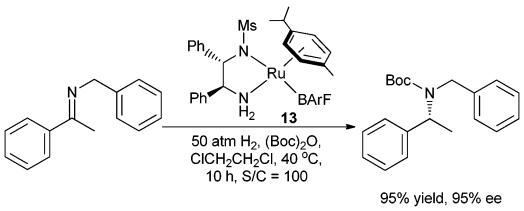


Fig. 3 Examples of sultams synthesised by AH.

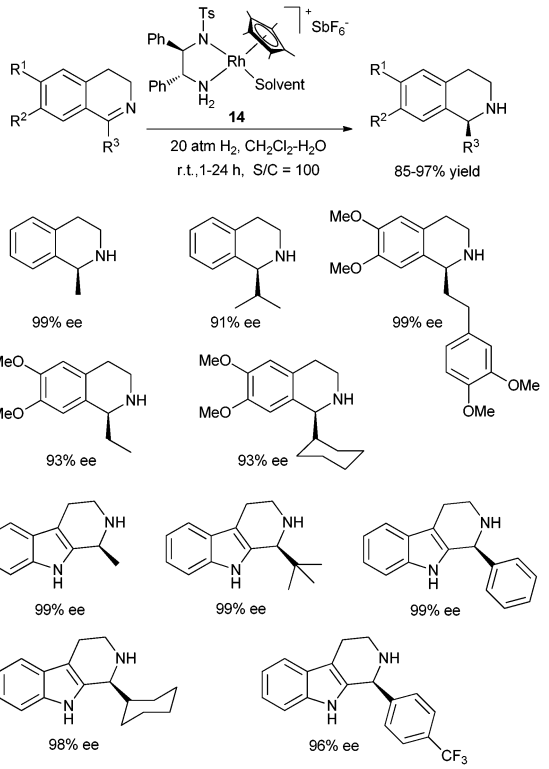


Scheme 16 AH of *N*-alkyl ketimine by Ru-MsDPEN.

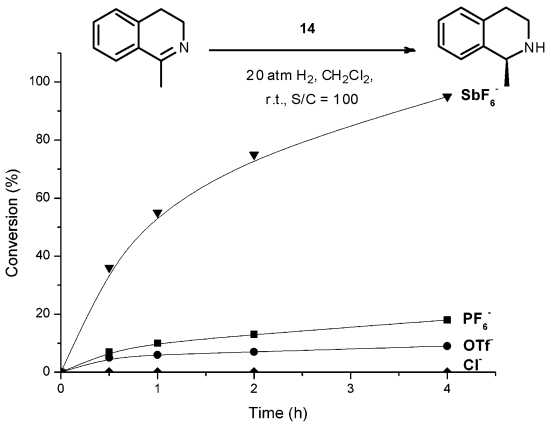
catalyst was inefficient. On screening a variety of potential catalysts with focus on non-coordinating counterions to encourage H_2 coordination, the rhodium complex **14**, generated *in situ* from the corresponding chloride complex, emerged to be very effective, catalysing the hydrogenation of a series of dihydroisoquinolines and dihydro-β-carbolines with excellent yields and enantioselectivities at 20 atm H_2 and 20 °C (Scheme 17).[46]

The key to the success of **14** lies in its bulky counteranion, SbF_6^-. Scheme 18 compares the effect of anions on the hydrogenation of 1-methyl-3,4-dihydroisoquinoline. Clearly, the smaller and coordinating anions exert a dramatically inhibiting effect on the catalysis. Whilst the low activity of the chloride and triflate complexes is likely to be a result of unfavoured anion dissociation from the Rh(III) which retards H_2 coordination, the inability of the PF_6^- salt is less clear, though it may be due to dimerisation of active rhodium species.[47] The effect of counterions has also been studied by Ikariya and co-workers in the AH of acyclic imines with catalyst **15** (Scheme 19).[48] The addition of silver salt enhances both activity and enantioselectivity, with more coordinating counterions leading to lower enantioselectivities. The Ag^+ ion is Lewis acidic and may bind to the imine, activating it towards hydride addition. This is supported by NMR experiments, where a downfield shift in the imine carbon is observed in the presence of the silver salt.

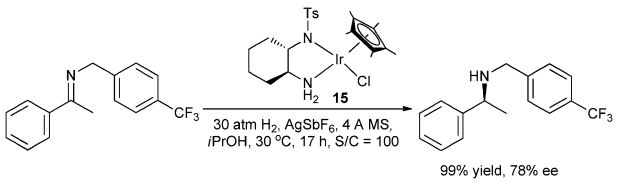
Further work in our group exploited the effect of metal-counteranion cooperative catalysis. Having succeeded in AH of isoquinoline derivatives, we tested the rhodium catalyst **14** for the more challenging acyclic imines, disappointingly observing almost racemic product. Better enantioselectivities were obtained with an analogous Ir(III) catalyst, however.



Scheme 17 AH of isoquinolines and dihydro-β-carbolines with a cationic Rh-diamine complex.

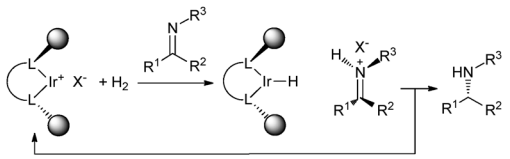


Scheme 18 Effect of counterion on the rate of hydrogenation of 1-methyl-3,4-dihydroisoquinoline.



Scheme 19 Ir-TsCYDN catalysed AH of an acyclic imine.

Inspired by studies in organocatalytic imino reduction with Hantzsch esters,[49] we envisioned that replacing the achiral counteranion with a chiral phosphate might improve the

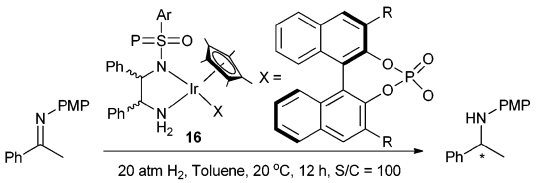


Scheme 20 Schematic illustration of imine hydrogenation *via* cooperative catalysis.

enantioselectivity, since the phosphate could be expected to ion-pair with the iminium cation resulting from deprotonation of the Ir–H_2 intermediate and thereby affect the facial selectivity of the Ir–H hydride (Scheme 20).[50] Delightfully, this mere change in anion boosted the enantioselectivity from 22% to 97% ee for the reaction shown in Scheme 21. This synergistic effect necessitates a match in chirality between the metal cation and its counteranion, however. Thus, changing the configuration in the diamine ligand from *S*,*S* to *R*,*R* leads to a change in the product ee from 97% (*S*) to 38% (*R*) (entry 1 *vs* 2, Scheme 21). The substituents on the 3 and 3′ position of the phosphoric acid also exert a remarkable effect on the enantioselectivity. Without substitution or with a simple phenyl ring at the 3 and 3′ positions, the enantiodifferentiation is poor. Surprisingly, increasing the bulkiness of the substituent affords a product of not only higher ee but also opposite configuration (entries 3 and 4 *vs* 1, 5 and 6, Scheme 21). These results suggest that the metal cation and its counteranion are both involved in the *enantio*-determining step.

The phosphate catalyst **16** [R = 2,4,6-(2-C_3H_7)$_3C_6H_2$] was applied to a wide range of imines, affording excellent yields (88–96%) and up to 98% ee (Scheme 22). A variety of functional groups were tolerated either on the ketone or the aniline ring, and the catalyst was selective to C=N bond over other reducible groups, such as alkenyl, nitrile and cyclopropyl. Furthermore, it also allows the reduction of dialkyl *N*-aryl imines.

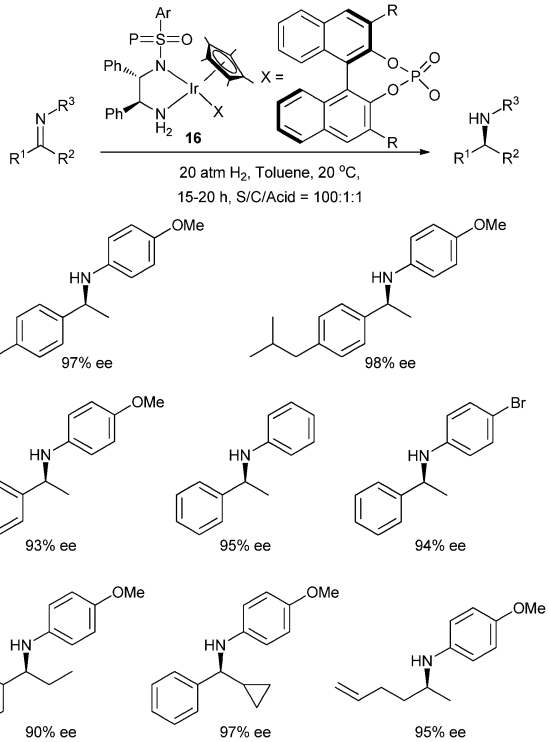
One-pot reductive amination is a more eco-friendly way for accessing chiral amines, as tedious isolation of often unstable imines is not required. The Ir(III)-phosphate cooperative catalyst is shown to be viable for this transformation, under



Entry[a]	Conf.[b]	R	Conv. (%)	ee (%)
1	*(S,S)*	R_1[c]	60	97 *(S)*
2	*(R,R)*	R_1[c]	47	38 *(R)*
3	*(S,S)*	H	53	17 *(R)*
4	*(S,S)*	Ph	57	26 *(R)*
5	*(S,S)*	R_2[d]	40	20 *(S)*
6	*(S,S)*	R_3[e]	43	38 *(S)*

[a]PMP: *p*-CH_3O-C_6H_4; Ar: 2,4,6-(2-C_3H_7)$_3C_6H_2$. [b]Configuration of diamine ligand in **16**. [c]R_1: 2,4,6-(2-C_3H_7)$_3C_6H_2$. [d]R_2: 3,5-$(CF_3)_2C_6H_3$. [e]R_3: 1-naphthyl.

Scheme 21 Match/mismatch effect on the cooperative catalysis.



Scheme 22 Examples of amines accessed by imine hydrogenation *via* cooperative catalysis.

mild conditions, *i.e.* a low pressure of 5 atm H_2 and 35 °C.[50b,c] Once again, a wide substrate scope is demonstrated (Fig. 4). In particular, a number of aliphatic ketones were aminated with excellent enantioselectivities. Historically, these substrates have proven to be problematic, giving poor yields and enantioselectivities.[13b] As Fig. 4 attests, this cooperative catalysis is triple-selective, reducing imine over ketone and imine over other reducible groups, and being enantioselective.

The asymmetric cooperative catalysis can also be brought about by combining a chiral counteranion with an *achiral* metal partner or *vice versa*, making the catalysis more economic.[51] We demonstrated that replacing the chiral diamine in **16** with the TsEN type achiral ligands still afforded asymmetric hydrogenation of the imine (Scheme 21), giving up to 70% ee.[51a] More recently, Rueping and co-workers have shown that the chiral *N*-trifylphosphoramide **19** can induce chirality in the metal complex **17**, although a low enantioselectivity was observed for the hydrogenation of quinolines (Scheme 23).[51b] More successful was the combination of the chiral complex **18** with **19**. And interestingly, **19** recognises **18**, with **19**-(*R*,*R*)-**18** being more active and selective.

4. Immobilised and water-soluble half-sandwich catalysts

As with most other organometallic catalysts, the half-sandwich catalysts described above are not easy to separate from products and be reused. Both economically and environmentally, they should be. Effort has been made to immobilise these catalysts on solid surface or in water.[12c,52] Deng, Tu and co-workers reported the immobilisation of the

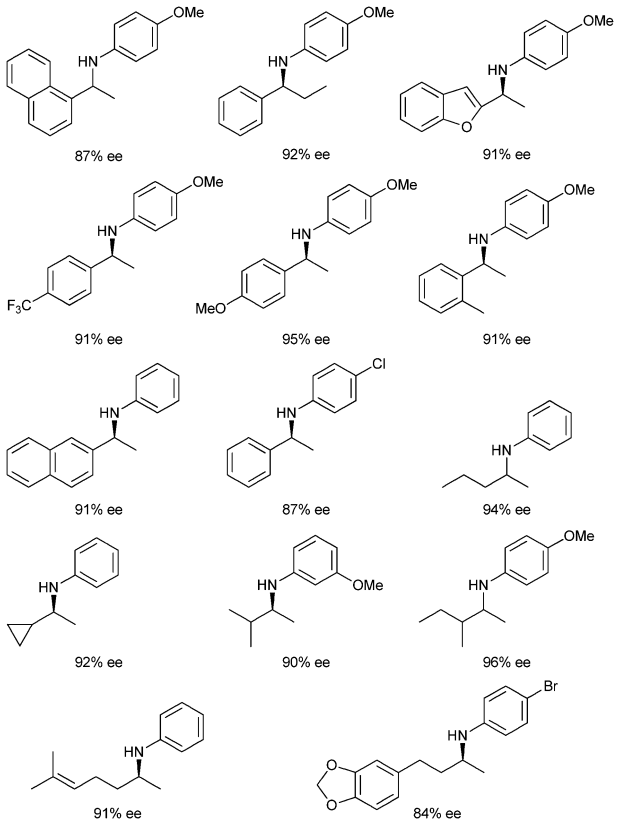
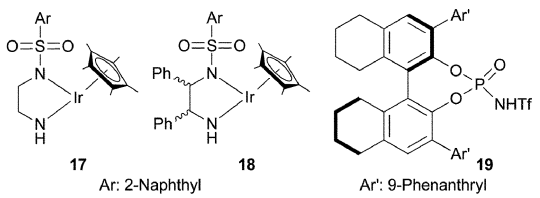


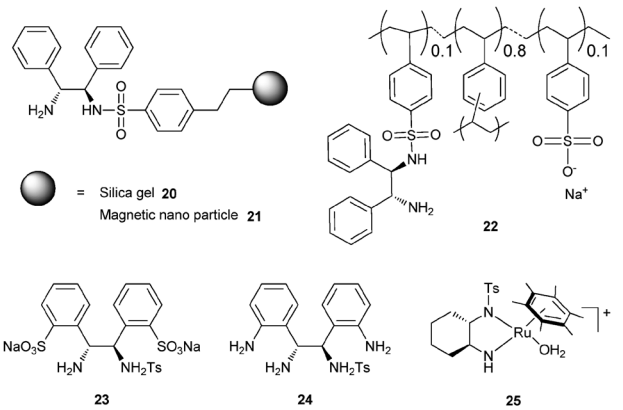
Fig. 4 Examples of chiral amines accessed *via* asymmetric reductive amination using catalyst **16**.



Entry	[Ir]	Time (h)	Conv. (%)	ee (%)
1	**17**	60	40	32
2	*rac*-**18**	24	>95	82
3	(*S*,*S*)-**18**	40	75	-68
4	(*R*,*R*)-**18**	24	>95	88

Scheme 23 Effect of the metal part on the AH of quinoline in cooperative catalysis.

TsDPEN ligand on silica.[53] The immobilised ligand **20** (Scheme 24), when ligated to $[RuCl_2(p\text{-cymene})]_2$, is effective for both ketone and imine reduction using $HCOOH/Et_3N$ azeotrope as both the solvent and hydrogen source. The catalyst can be recycled up to 7 times for the reduction of cyclic imines. A similar system was reported by Ying and co-workers.[54] More recently, Li and co-workers immobilised the Noyori–Ikariya catalyst onto mesoporous magnetic silica.[55]



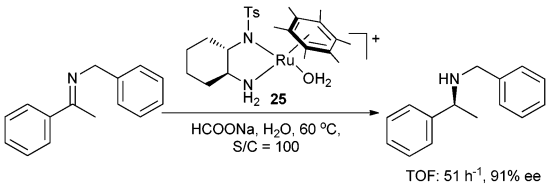
Scheme 24 Immobilised and water-soluble ligands/catalysts.

The catalyst prepared from the ligand **21** and $[RuCl_2(p\text{-cymene})]_2$ afforded comparable enantioselectivity to the homogeneous catalyst **8** in dichloromethane. Being easily separated from the reaction mixture with an external magnet, the catalyst can be reused for up to 9 times without notable decrease of ee. Polymer supported TsDPEN type ligand **22** was also prepared.[56] When combined with ruthenium, it afforded improved enantioselectivity for some acyclic imines in organic solvent using the $HCOOH/Et_3N$ azeotrope as hydrogen source; and for cyclic imines, the reaction can be performed in water using sodium formate as hydrogen source.

Although it may appear counter-intuitive given imines are generally water-sensitive, attempts have been made to reduce imines with water-soluble catalysts in water. Deng and co-workers were the first to develop water soluble Noyori–Ikariya catalyst using ligand **23** and applied the catalyst for aqueous reduction of imines.[57] Using sodium formate as hydrogen source in the presence of a surfactant, a series of cyclic imines were reduced in high yields and enantioselectivities. It is worth noting that alkylated iminium salts of cyclic imines were reduced equally well, indicating a mechanism different from the metal ligand bifunctional mechanism for ketone reduction.[58] However, acyclic imines were not viable, being probably decomposed under the aqueous conditions. When combined with $[Cp^*RhCl_2]_2$, ligand **24** also catalyses the reduction of cyclic imines in water, with sodium formate as hydrogen source.[59] Suss-Fink and co-workers reported a series of cationic aqua ruthenium complexes, which are water soluble.[60] These complexes catalyse the reduction of both acyclic and cyclic imines by sodium formate in water. Impressively, with the catalyst **25** acyclic imines can be reduced in up to 91% ee in aqueous conditions (Scheme 25).

5. Mechanistic insight

As it is clear now, imines can be reduced by either hydrogenation with H_2 or TH, using similar half-sandwich catalysts. Mechanistic understanding of the reduction has been less developed, however, compared with the case of carbonyl groups.[16,61] There are two critical steps in both hydrogenation and TH, *i.e.* hydride formation and hydride transfer, either of which may control the turnover rate. These are illustrated in



Scheme 25 ATH of an acyclic imine in water.

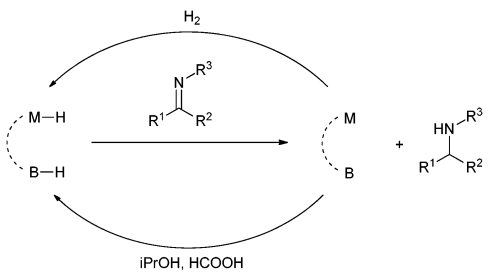
the "hydrogenation/transfer hydrogenation network"[39] shown in Scheme 26, where B represents a Brønsted basic group, which may or may not link to the metal and could be an amine or imine in the reaction system. As can be seen, it is the hydride formation step that differentiates hydrogenation with H_2 from TH with other hydrogen sources.

In probably all the half-sandwich complexes described above, the hydride is generated from a $16e^-$ intermediate, *i.e.* the M-B species in Scheme 26. Scheme 27 illustrates how the hydride is formed from the three widely used hydrogen sources, isopropanol, formic acid and hydrogen.

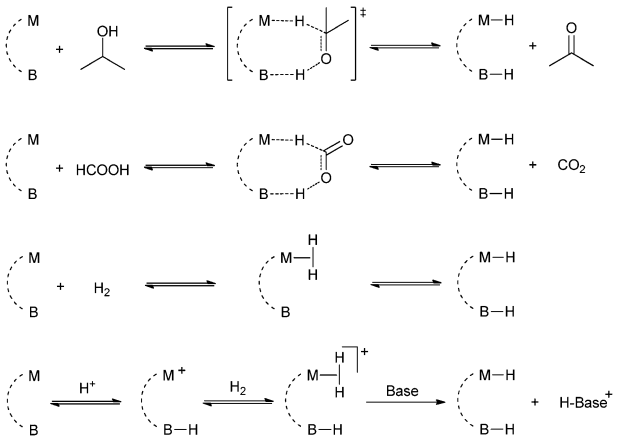
Whilst dehydrogenation of isopropanol to give the M–H hydride *via* the pericyclic six-membered transition state is well understood,[16,61] hydride formation from formic acid or formate is less clear. Ikariya and co-workers showed that the $16e^-$ Ru(II) complex generated from **8** is readily protonated by HCOOH at the amide nitrogen, forming an ion pair, which then collapses to give the formate complex (Scheme 28). Decarboxylation took place at −15 °C, affording the hydride.[62] Interestingly, the reverse reaction, CO_2 insertion to reform the formate species, proceeded rapidly even at −78 °C. The NH moiety is critical for CO_2 insertion, hydrogen-bonding to the carbonyl oxygen, and it must also be the case for the decarboxylation according to the principle of microscopic reversibility. The activation parameters obtained are in line with an organised transition state.

The presence of the NH moiety is not always necessary for hydride formation, however. For instance, our recently developed cyclometalated iridium catalyst **7** has shown fast decarboxylation rate to form the hydride. The complex $[(\eta^6\text{-}C_6Me_6)Ru(bpy)(H_2O)]^{2+}$ reacts with formate in water, affording structurally characterised formate and hydride complexes.[63] Notable is that the formation of these species is solution-pH dependent.

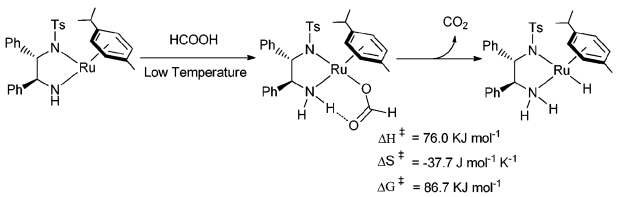
Hydrogenation of neutral half-sandwich $16e^-$ complexes with H_2 to generate the hydride is sluggish under neutral or basic conditions, as shown by the work of Noyori, Ikariya and Rauchfuss.[61a,64] Presumably this stems from bonding of the lone pair on B (Scheme 27) with the metal. In fact, complexes



Scheme 26 The hydrogenation/TH network for imine reduction.



Scheme 27 Formation of hydrides from bifunctional metal-base pair.

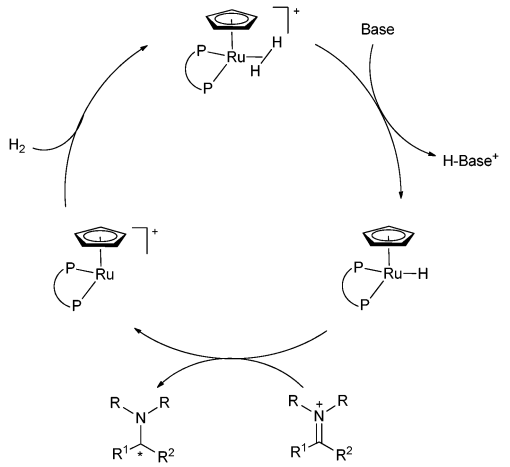


Scheme 28 Hydride formation *via* decarboxylation of HCOOH.

of the type **18** do not react with PPh_3 or MeCN. However, formation of the hydride takes place readily in acidic conditions, under which the basic group B is protonated. The resulting metal cation reacts readily with H_2 to give the hydride, probably *via* a dihydrogen intermediate, which is deprotonated by a base (Scheme 27). The enhanced Lewis acidity, which would encourage H_2 coordination and the subsequent deprotonation, is most likely to be responsible for the much higher activity of the metal complex towards H_2.

Turning attention to the hydride transfer step, various lines of evidence appear to favour an ionic mechanism,[37,65] where the M–H hydride transfers to a protonated and hence activated imine, involving no coordination of the imine to the metal centre during the transfer. This is in contrast to the well-established metal–ligand bifunctional pathway for ketone reductions.[61a,c,d] A clear illustration of the ionic mechanism is seen in Norton's work on the AH of *N*,*N*-dialkyl iminium cations with the CpRu-diphosphine complex **11** (Scheme 14).[36,66] Kinetic studies reveal that the hydrogenation proceeds *via* the mechanism shown in Scheme 29, consisting of coordination of the H_2 molecule to the cationic metal centre, followed by heterolytic cleavage of H_2 into H^+ and H^-; hydride transfer to the iminium cation completes the catalytic cycle, with the turnover limited by the hydride transfer step. Deprotonation of the coordinated dihydrogen, the pK_a of which is *ca.* 7, may be by the action of the product or even the substrate.

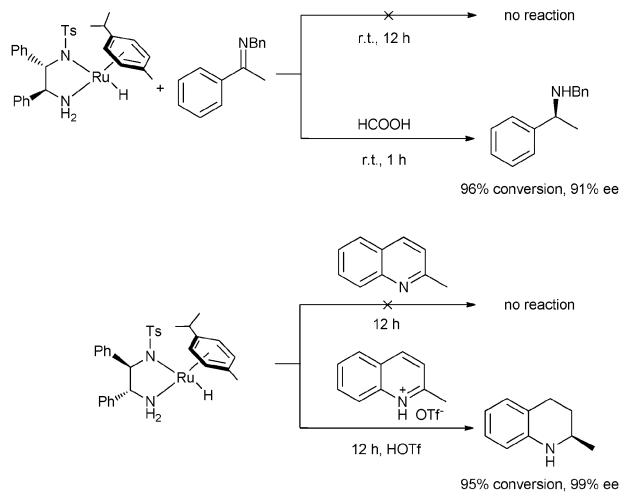
Stoichiometric reduction also supports the ionic pathway. Thus, the isolated Ru–H derived from **8** does not reduce free imines; however, the reaction takes place quite rapidly in the presence of acid additives (Scheme 30).[67] Similarly, Fan reported no reduction of 2-methylquinoline even in the



Scheme 29 Imine hydrogenation through an ionic mechanism.

presence of excess of the hydride; but the protonated species reacts smoothly to give the tetrahydroquinoline product (Scheme 30).[38] These observations are inconsistent with a neutral imine being the species undergoing reduction, but are in line with the ionic mechanism.[68] Still interesting is that the hydrogenation rate in Scheme 29 agrees with that measured in stoichiometric reduction using isolated Ru–H hydride, lending support to the ionic hydrogenation pathway.[36,66] Further evidence for the ionic pathway is found in the TH of quinolines, where acidic conditions are required.[35] The cyclometalated iridium catalysts developed by our group are also likely to proceed *via* the ionic mechanism, where no free NH is available for metal–ligand bifunctional action.[23]

The ionic mechanism also appears to be applicable to the reduction catalysed by Shvo's catalyst. In the so called outer-sphere mechanism proposed by Casey and co-workers,[16,69] the hydride and the proton from the hydroxyl group of the Cp ligand transfer simultaneously to an imino bond (Scheme 31). Cp ring slippage does not take place, which would otherwise allow imine coordination. Interestingly, DFT calculations revealed that the proton and hydride transfer is *asynchronous*,



Scheme 30 Stoichiometric reduction with isolated Ru–H hydride.

with the former being more transferred than the latter at the transition state, thus resembling protonation of the substrate and hence the ionic mechanism.[70]

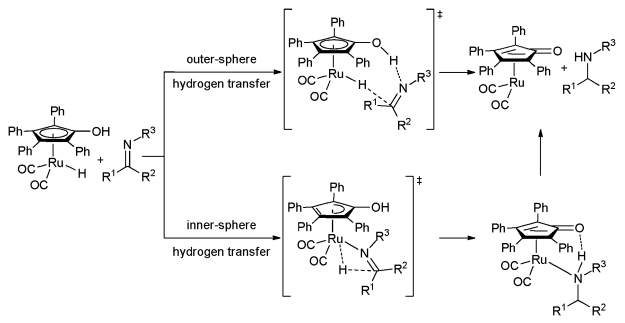
Bäckvall and co-workers has suggested an inner-sphere mechanism, the key step of which involves ring slippage of the Cp ring (Scheme 31).[71] Imine coordination is then followed by hydride transfer. Whilst calculations showed a reasonable energy barrier of 15 kcal mol^{-1} for the ring slippage and imine coordination step, with the rest of the steps displaying similar but lower energies,[71] further studies have shown that the outer-sphere, asynchronous hydrogen transfer is favoured by more than 10 kcal mol^{-1}.[70]

6. Concluding remarks

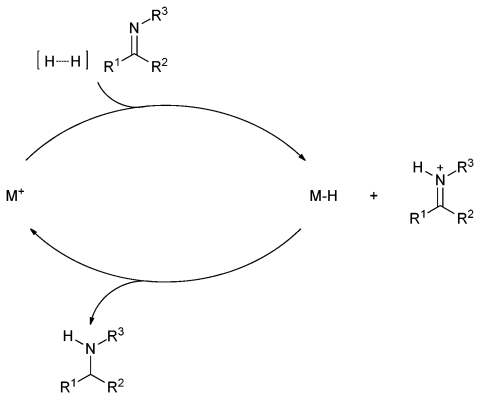
Half-sandwich metal complexes have shown to be excellent catalysts for both TH and hydrogenation. A variety of imines, either pre- or *in situ*-formed, can be reduced, affording excellent chemo- and *enantio*-selectivities in a number of cases. Most likely, the reduction reactions proceed *via* an ionic mechanism, in which the catalyst delivers a hydride to an imine protonated by a dihydrogen complex or a proton. Scheme 32 illustrates the essential aspect of this mechanism.

This ionic mode of reduction is particularly suited for the half-sandwich catalysts, since incorporating a bidentate ligand will leave only one open site for H_2 coordination and hydride formation. Unless ring slippage takes place with a low energy barrier, imine will not be able to coordinate. However, for arene rings substituted with non-conjugating groups, which is the case for most of the catalysts described in this Article, this slippage may not be easy.[72] and as recent theoretical studies have shown, hydrogen bonding of the Cp hydroxyl with the imine can substantially lower the hydride transfer barrier (Scheme 31).[71] Protonated imines are expected and have been shown to be much more reactive than imines, supporting the ionic pathway.

The ionic reduction mimics what nature does in enzymatic catalysis, where the NADH or NADPH cofactors serve as the hydride donor. The man-made version could be more advantageous, however, given the diversity of the hydrogen sources and the tunability of the catalysts. More enabling catalysts are expected to emerge, with which we will be able to tackle more challenging substrates with more desirable selectivity, productivity and eco-compatibility.



Scheme 31 Outer-sphere *vs* inner-sphere mechanism for imine reduction with Shvo's catalyst.



Scheme 32 General representation of the ionic mechanism for imino bond reduction.

Acknowledgements

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