ROYAL SOCIETY OF CHEMISTRY

Journal Name

ARTICLE

Iridacycles for Hydrogenation and Dehydrogenation Reactions

Chao Wang[a] and Jianliang Xiao*[b]

Iridacycles are a group of cyclometalated metal complexes, which have recently been shown to be versatile catalysts in a range of reactions. This Feature Article provides an account of the work carried out in our groups. We start with an introduction to the variety of iridacycles and how they entered into catalysis. The following sections provide an overview of the discovery and applications in catalysis of the iridacycles originated from our labs, including transfer hydrogenation with formic acid, hydrogenation with H_2, dehydrogenation and borrowing-hydrogen reactions. Where possible, mechanistic insight is also presented. A notable advantage of these iridacycles is their ease of preparation, stability to air and water and high modularity. With only one coordination site available for substrate activation, the iridacycles differ from most homogeneous catalysts structure-wise.

1. Introduction

Cyclometalated metal complexes have been well studied in organometallic chemistry, catalysis and material science.[1] These complexes were initially reported sporadically in the 1960's.[2] Since then, a wide variety of cyclometalated complexes has been synthesised by cyclometalation. Among them, the half-sandwich cyclometalated complexes based on Rh and Ir, represented by [Cp*M(C^X)Cl] (M = Rh, Ir; X = C, N, O, P), have received a great deal of attention in the past one

decade or so.[1c, 1d, 1f-i, 3] The interest in these rhodacycles and iridacycles is not least driven by their easy availability through the base-promoted C-H activation of a H-C^X molecule by [Cp*MCl2]2 (Scheme 1). In particular, Beck,[4] Davies[5] and co-workers have shown that the cyclometalation can be readily effected with sodium acetate under mild conditions. Further investigations by the Davies[5b, 5c] and Jones[6] groups have led to deep insight into the mechanism of the reaction, e.g. the role of sodium acetate during the C-H activation and the
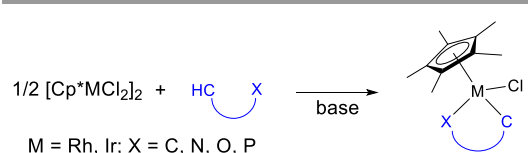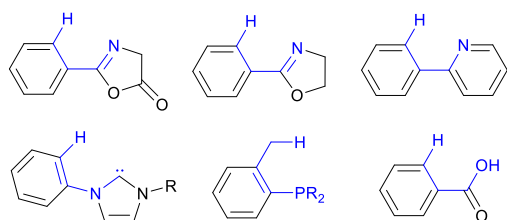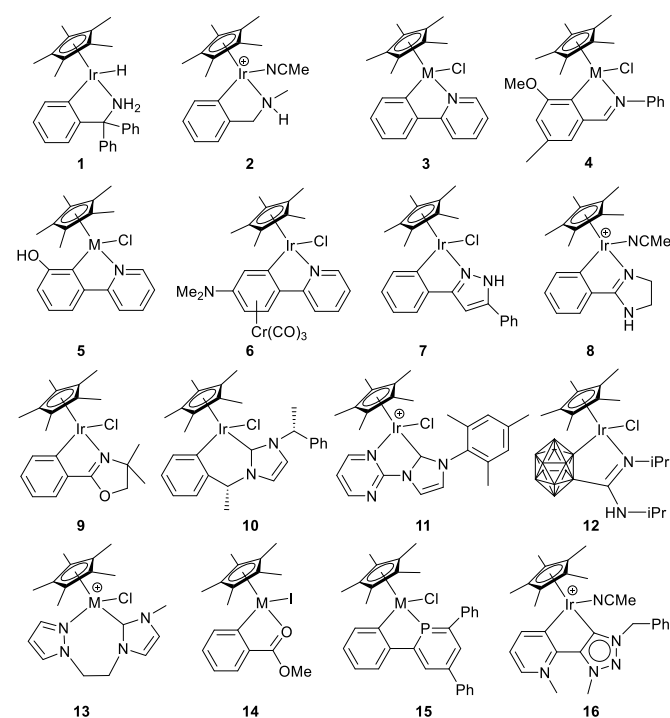

Scheme 1. Base-promoted formation of rhodacycles and iridacycles.

a. Key Laboratory of Applied Surface and Colloid Chemistry, Ministry of Education, and School of Chemistry and Chemical Engineering, Shaanxi Normal University, Xi'an, 710062, P. R. China.
b. Department of Chemistry, University of Liverpool, Oxford Street, L69 7ZD, UK. Email: j.xiao@liv.ac.uk.

Scheme 2. Selected examples of rhodacycles and iridacycles (M = Rh, Ir).

regioselectivity and kinetics of the cyclometalation.[7] These pioneering studies have advanced significantly the synthesis of rhodacycles and iridacycles, making them readily accessible. Selected examples are found in Scheme 2.[5a, 5d, 6, 8]

The rhodacycle and iridacycle complexes have revealed a wealth of interesting chemistry. Apart from illuminating the pathway of C-H activation,[1g, 1h] they show activities towards many small molecules, such as H_2, O_2, CO, CO_2, H_2O and alkenes,[8h, 9] and they may be bio and photo-active.[10] Due to their relative stability, cyclometalated metal complexes have also been explored as building blocks for supramolecular architectures as demonstrated by Jin and co-workers.[1h]

Whilst many rhodacycles and iridacycles have been reported, their application in catalysis has blossomed only in the past several years, with iridacycles being more outstanding. In 2008, Ikariya and co-workers reported that complex **1** (Scheme 2) catalyses aerobic oxidation of alcohols and when the metalacycle was made chiral with a simple chiral amine, oxidative kinetic resolution of racemic alcohols became possible.[8e, 9a] In the same year, Pfeffer, Janssen, Feringa, de Vries et al found that complex **2** with a simple amine ligand is a good catalyst for racemisation of alcohols.[11] Later, Crabtree and co-workers disclosed complex **3** with 2-phenylpyridine as ligand for water oxidation.[8h] The following years have witnessed the flourishing applications of half-sandwich cyclometalated iridium complexes in catalysis, including hydrogenation, reductive amination, dehydrogenation, oxidation, alkylation, racemisation, hydrosilylation, hydroamination, polymerisation and related reactions.[1h, 1i, 12] The chiral version of some of these reactions has also been demonstrated. The interested reader is referred to the reviews published recently.[1h, 1i]

In our search for more effective catalysts for asymmetric reduction of imino bonds, we discovered that ketimines readily undergo C-H activation with [Cp*IrCl₂]₂, affording various half-sandwich iridacycles usually in high yields (Scheme 3).[13] The structures of several of these complexes have been determined by X-ray diffraction.[14] Interestingly, the protons of the *N*-aryl rings in the complexes, e.g. **18**-**21**, often appear as broad peaks in the ¹H NMR spectra at room temperature and resolve into well separated resonances only at low temperature. This broadening is believed to result from the *N*-aryl ring undergoing a rocking motion. No such NMR pattern was observed for complexes prepared from aldimines, however.

Advantages of these iridium complexes include their high modularity permitting easy structure modification, the ease of synthesis and the stability to air (Scheme 3). Also worth noting is that they are coordinatively saturated; thus the chloride must dissociate first to create an active site for any catalysis to occur. In addition, since the ligand generally bears no adjacent functionality for metal-ligand cooperation,[15] the catalysis is brought about only by a single iridium centre. This feature sets the iridacycles apart from most catalysts used in homogeneous catalysis.
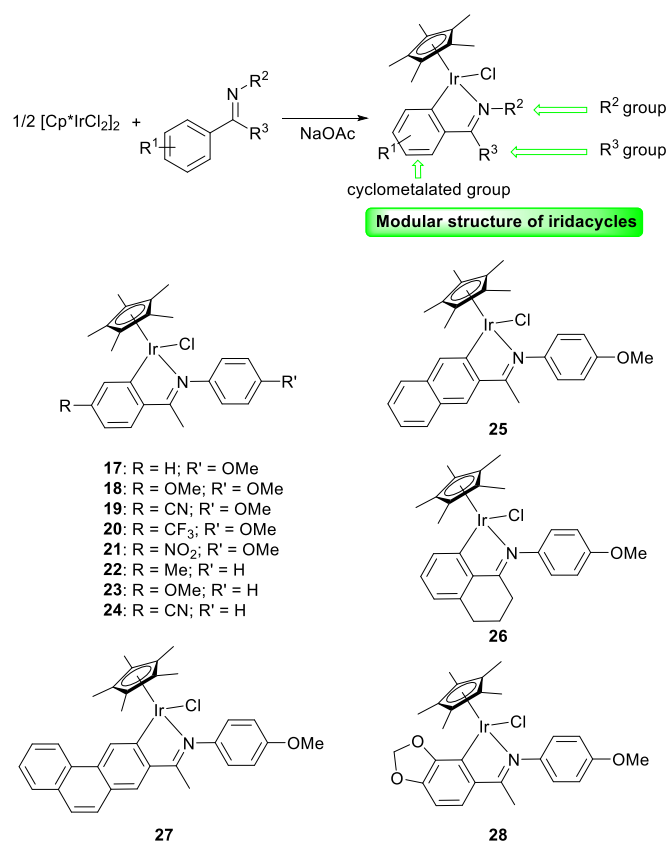
**Scheme 3.** Formation of imino-ligated iridacycles from ketimines.

Since the discovery in 2010, these iridacycles have been found to catalyse a wide range of reactions.[1i, 3b, 16] In this article, we summarise the progress we have made in applying these iridacycles in catalysis. Where appropriate, related work from other groups is also highlighted.

2. Transfer hydrogenation with iridacycles

2.1. Transfer hydrogenation of imines and reductive amination

Our interest in cyclometalated iridium complexes arose from our study of transfer hydrogenation (TH) of imines. Back in 1996, Hashiguchi, Ikariya, Noyori and their co-workers reported that Ru-TsDPEN (TsDPEN = *N*-(p-toluenesulfonyl)-1,2-diphenylethylenediamine) could catalyse asymmetric transfer hydrogenation (ATH) of cyclic imines with outstanding enantioselectivities.[17] However, catalysts able to promote the ATH of acyclic imines were rare. Attempting to develop an ATH system effective for acyclic imines, we discovered an interesting cyclometalated iridium complex **17** (Scheme 3) in the TH of 4-methoxy-N-(1-phenylethylidene)aniline, which resulted from the in situ reaction of [Cp*IrCl₂]₂ with the imine substrate.[13] A variety of such iridacycles have since been synthesized (Scheme 3) and proven to be highly efficient catalyst in a range of reactions.

The iridacycles were first testd for TH of imines with formic acid as hydrogen source and shown to be highly active.[13] An example is seen in Scheme 4. In the TH of the imine with
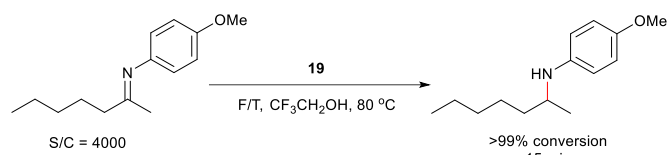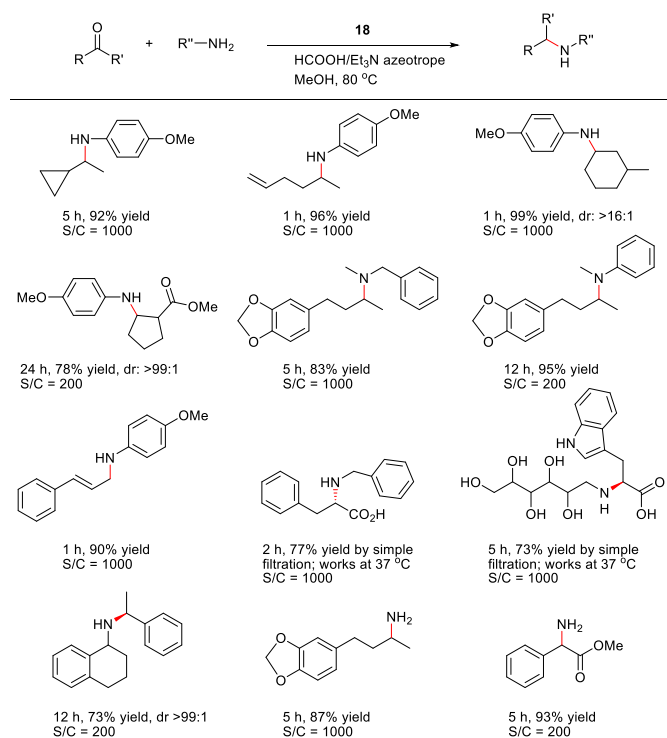
Scheme 4. An example of TH of imine with **19** (S/C: substrate/catalyst ratio).
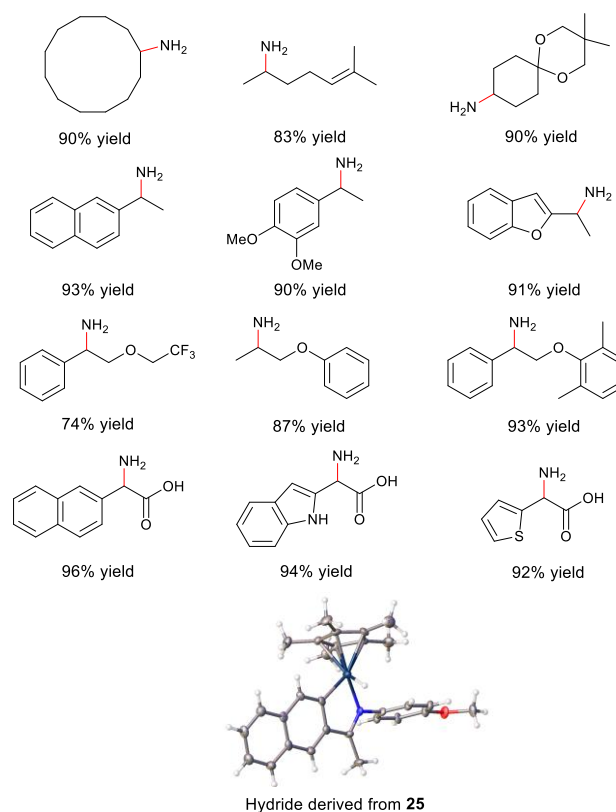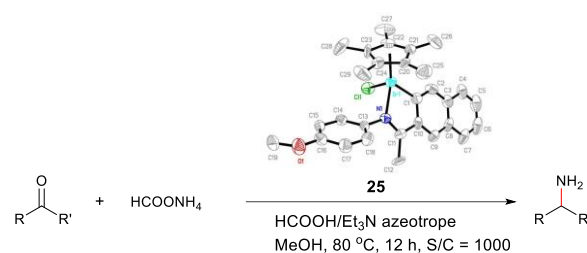
iridacycle **19** at a substrate/catalyst (S/C) ratio of 4000, the reduction was complete in 15 min, giving an initial turnover frequency (TOF) of 1.9×10^4. It is worth noting that the related amino-ligated complex was much less active, so were the diphosphine and diamine complexes.

The catalytic system was subsequently extended to reductive amination (RA) reactions and showed a very broad substrate scope in methanol at 80 °C. Selected examples made possible with **18** are seen in Scheme 5. Notably, C=C double bonds are tolerated, and complex molecules, such as amino acids and glucose, can be used as substrate at mild reaction conditions. Excellent diastereoselectivity was obtained with chiral amines. In addition, ammonium could also be used, allowing for the direct synthesis of primary amines.

Because of the importance of primary amines and scarcity of RA reactions that can be used to access such amines, we undertook further studies and identified a more active iridacycle catalyst **25** for such amines, with $HCOONH_4$ as amine source and $HCOOH/Et_3N$ azeotrope as reductant.[18] Using only 0.1 mol% **25**, various ketones, including both aromatic and aliphatic ketones, β-keto ethers and β-keto acids, could be transformed into primary amines, allowing for the easy access to synthetically and biologically important amines, such as β-amino ethers and non-natural amino acids (Scheme 6). This

Scheme 6. Synthesis of primary amines via **25**-catalysed RA.
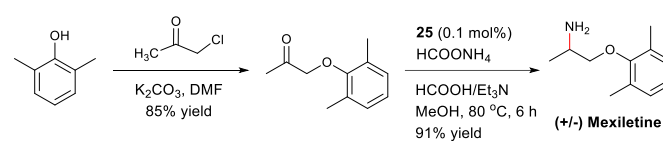

Scheme 7. Synthesis of Mexiletine via **25**-catalysed RA.

protocol was successfully applied to the synthesis of mexiletine, a class Ib antiarrhythmic agent that interferes with the sodium channel (Scheme 7).

The structure of **25** was confirmed by X-ray diffraction. Monitoring the RA reaction by *in situ* ^{1}H-NMR at room temperature showed that a hydride species was formed instantaneously from **25**. However, no other new species were observed, indicating that hydride transfer or imine generation may be more difficult than the hydride formation in the overall RA reaction at this temperature. The structure of the hydride was also confirmed by X-ray analysis (Scheme 6).

Scheme 5. Selected examples of **18**-catalysed RA.

The reactions above were carried out in organic solvents. In continuing our interest in green chemistry and particularly in catalysis in water,[16b, 16c, 19] we wondered whether the alcohol solvents could be replaced with water. Aqueous-phase RA reactions are scarce in the literature. This is not surprising, as water is generally thought to be adverse for the formation of imines, key intermediates in the RA. In fact, drying agents are sometimes used to remove water generated from the imine formation step.[20] It is known that imine formation from the ketone and amine and the subsequent imine reduction benefit from acidic conditions. Thus, we first examined the effect of the pH value of the solution on the model reaction of acetophenone (acp) with *p*-anisidine, with **18** as catalyst and using HCOOH and HCOONa to adjust the solution pH.[21] It was found that both the catalytic activity and selectivity were influenced dramatically by the pH of the solution. At pH 4.8, the best selectivity was observed without sacrificing too much of the activity. Further studies revealed that complex **25** offered the best activity. Under the optimal conditions, 95% isolated yield was obtained for the reaction of acp with *p*-anisidine in 2 h (S/C = 1000) (Scheme 8). This RA system turned out to be very general for a wide range of carbonyl compounds and amines, including those of poor water-solubility.
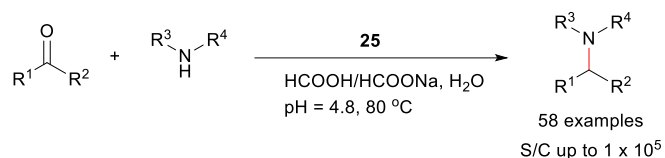
**Scheme 8.** pH-regulated aqueous RA reactions with **25** as catalyst.

It was observed that aliphatic ketones (S/C = 1000) are more active than aromatic ones (S/C = 200), and aldehydes (S/C = 2000) are more active than ketones in general. Thus, the reaction of benzaldehyde with *p*-anisidine with a S/C of 1×10^5 (250 mmol scale) afforded 95% yield in 48 h at pH 4.6, the highest S/C ratio ever reported for RA reactions.

The aqueous RA system has been extended to the transformation of a biomass platform molecule, levulinic acid, into pyrrolidinones (LA).[22] This reaction upgrades LA to value added heterocycles with formic acid, which is a by-product during the production of LA via acidic dehydration of carbohydrates. Thus, using HCOONa to adjust the solution pH to 3.5, LA could react with amines catalysed by **18** at an S/C of 2000, affording various pyrrolidinones as shown in Scheme 9. It was noted that electron-rich amines generally gave higher yields than electron-poor ones. The catalysis could also be applied to the RA of 5-oxohexanoic, affording 2-piperidone derivatives.

Alkynes could also be used as substrate in aqueous RA. As is known, alkynes can be converted to ketones in pure formic acid at 100 °C.[23] This reaction would allow the alkynes to be aminated under suitable reaction conditions. Indeed, following the full conversion of an alkyne to ketone with HCOOH and then increasing the solution pH to 4.8 with NaOH, introduction
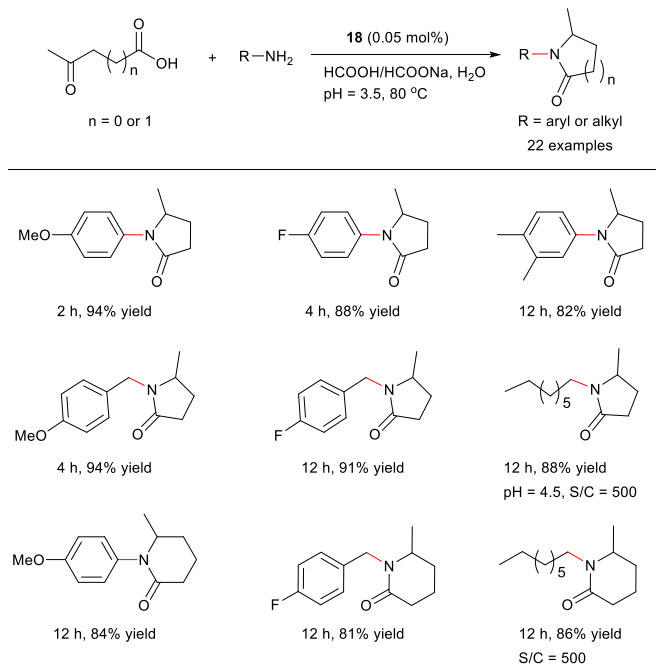
Scheme 9. RA of levulinic acid and 5-oxohexanoic acid with **18**.
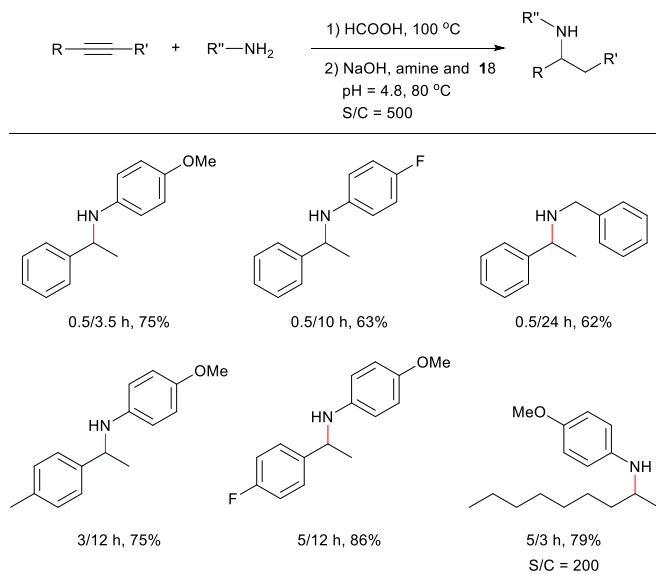
Scheme 10. Application of the aqueous RA reaction to the one-pot transformation of alkynes to amines.

of an amine substrate and the iridacycle **18** started the aqueous RA, leading to the generation of a new amine.[24] Selected examples are shown in Scheme 10. When a chiral reduction catalyst is used, the alkynes can be converted into chiral alcohols. This one-pot alkyne-to-amine protocol differs from the commonly reported reductive hydroamination process, in that it proceeds via a hydration/RA process rather than a hydroamination/reduction pathway.
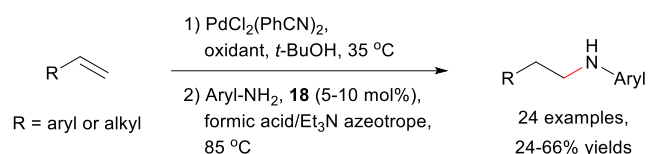
Scheme 11. Application of **18**-catalysed RA to formal anti-Markovnikov hydroamination of alkenes.

The iridacycle-catalysed RA was exploited by Grubbs and co-workers to realise the formal anti-Markovnikov hydroamination of terminal alkenes.[25] By coupling of the Pd-catalysed Wacker reaction that selectively affords aldehydes with **18**-catalysed RA, terminal alkenes are converted to linear amines, complementing the existing hydroamination reaction characteristic of Markovnikov selectivity (Scheme 11). Both aromatic and aliphatic olefins could react with aryl amines to afford the corresponding linear amines.

The remarkable performance of the iridacycles in reducing imino bonds with formate prompted us to look into the reaction mechanism. Several lines of study were carried out, pointing to the mechanism depicted in Scheme 12 for the TH of a model imine catalysed by the iridacycle **19**.[26] The first step of the reaction is to replace the chloride from **19** with formate to form the formato intermediate **A**. Although a formato iridacycle has not been isolated, closely related formate complexes are known.[27] The next step is hydride formation
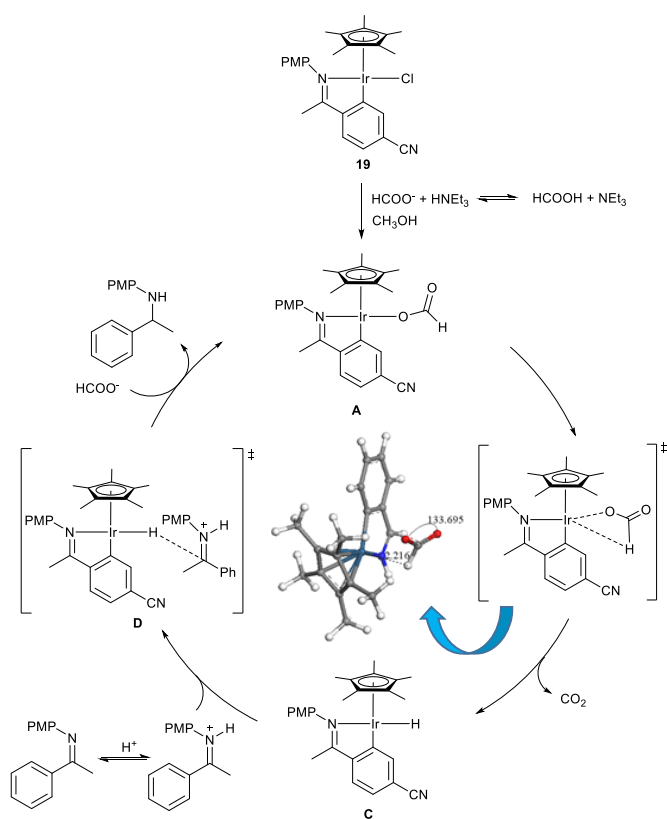
Scheme 12. Proposed mechanism for imine reduction catalysed by **19**. PMP = *para*-methoxybenzene group.
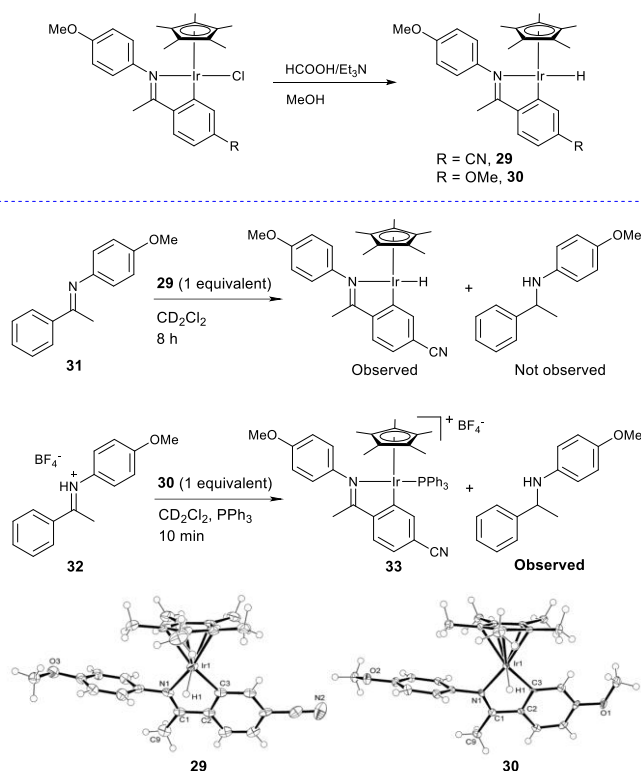
Scheme 13. Formation of iridium hydride complexes and their reactivity towards imine/iminium reduction.

from **A** to give **C** via the transition state **B**. The resulting hydride then transfers to the protonated imine via the transition state **D**, affording the amine product while regenerating **A**. The key intermediate hydride is found to form easily from the HCOOH-NEt$_3$ azeotrope in MeOH. Thus, when complex **19** was treated with the azeotrope (4 equivalents of HCO$_2$H) at room temperature, about 50% of **19** was converted into the hydride **29** in 10 min, the structure of which and its analogue **30** were confirmed by X-ray diffraction (Scheme 13).[14] The hydride reacted with the neutral imine only very slowly; but its reaction with the protonated imine was instant (Scheme 13), showing that in the TH reaction, the hydride transfers to the iminium ion, instead of the imine. Upon hydride transfer, **29** was converted into a cationic species trapped as the phosphine compound **33**.

Kinetic measurements were also carried out for the TH of imine **31** catalysed by **19** with the HCOOH-NEt$_3$ azeotrope in MeOH.[26] The results suggest that the hydrogenation rate is second order in formic acid concentration, first order in catalyst concentration and zero order in the imine substrate. When HCOOH was replaced with DCOOD, a kinetic isotopic effect k_H/k_D of ca 1.9 was estimated. Taken together, these observations support the assertion that the TH is turnover-limited by the hydride formation step. This is not necessarily at odds with the RA reaction mentioned above, in which the imine formation could be more energy-costly (Scheme 6).

The experimental study corroborates well with the DFT modelling of the mechanism illustrated in Scheme 12.[26] The calculations, carried out by the Catlow group in collaboration

with us, revealed the activation energy of the hydride formation step (26–28 kcal/mol) to be much higher than that of the hydride transfer step (7–8 kcal/mol). Interestingly, introducing one explicit methanol molecule into the modelling alters the energy barrier significantly. The activation energies in the hydride formation and transfer steps drop to 18 kcal/mol and 2 kcal/mol, respectively. Thus, the hydrogenation is rate-limited by the hydride formation step and methanol lowers its energy barrier.

The study also led to further insight into the two key steps in the mechanism.[26] In particular, the transition state **B** features breakage of the Ir-O bond but only insignificant lengthening of the formate C-H bond; hence **C** can be treated as an ion pair (Scheme 12). Thus, somewhat counter-intuitively, the energy cost for the rate-limiting step stems mainly from the breaking of the Ir-O bond which is accompanied with charge separation, instead of that of the C-H bond of formate, from which the hydride derives. The transition state **E** involves no coordination of the C=N bond to the metal; thus the hydride transfer step is typical of an outer-sphere mechanism. The DFT investigation further shows that methanol participates in the transition state **B**, hydrogen-bonding to the formate anion and thereby stabilising the ion pair. This finding explains, pleasingly, why the TH reactions with iridacycles necessitate the use of polar protic solvents in general.

2.2. Transfer hydrogenation of aldehydes and ketones

In the RA reactions, the imine intermediate is selectively reduced over carbonyl groups by the iridacycle catalyst. Further studies revealed that carbonyl compounds could also be reduced efficiently in water with the iridacycle complexes, if the solution pH is properly chosen. Thus, catalysed with **24** at pH 2.5, various simple ketones and aromatic aldehydes were reduced with HCOOH/HCOONa at 80 °C (Scheme 14).[28] Interestingly, using **18** as catalyst, the highest reduction rate was observed at a higher pH 3.5. We note that these optimal values are quite different from those observed with the previous Noyori–Ikariya catalysts, which perform best at neutral pH.[16, 19] This difference most likely results from the notation that the reduction with the iridacycles necessitates activation of the ketone by an acidic medium, which provides hydrogen-bonding hydroxonium ions, whereas the Noyori–Ikariya catalyst needs basic conditions to generate an active 16e⁻ catalytic intermediate and is bifunctional, in which the ligand NH proton activates the substrate.[15] However, when the pH becomes too low, the active iridacycle species, iridium hydride, will be protonated. Hence, there exists an optimal pH value to balance the two competing reactions.

At still a higher pH 4.5 with **25** as catalyst, various α-substituted ketones could be reduced to afford a series of synthetically important β-functionalised alcohols.[29] Compared with acetophenone derivatives, α-halo-, hydroxyl- and nitrile-substituted ketones are more challenging to reduce, due to the ease of dissociation/decomposition of these α-functional groups under the reaction conditions. The iridacycle appears to tolerate these functionalities well. As illustrated in Scheme
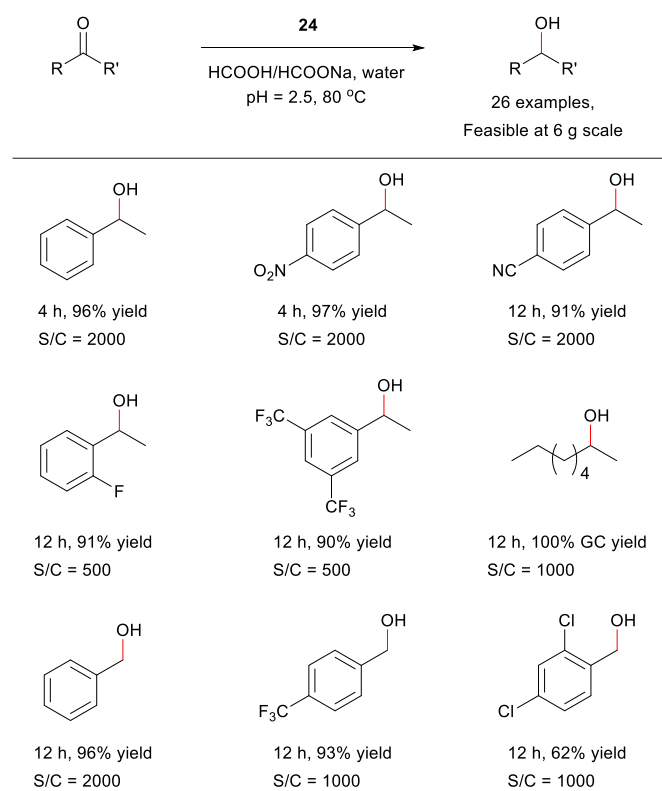
Scheme 14. Aqueous phase TH of ketones and aldehydes with **24**.
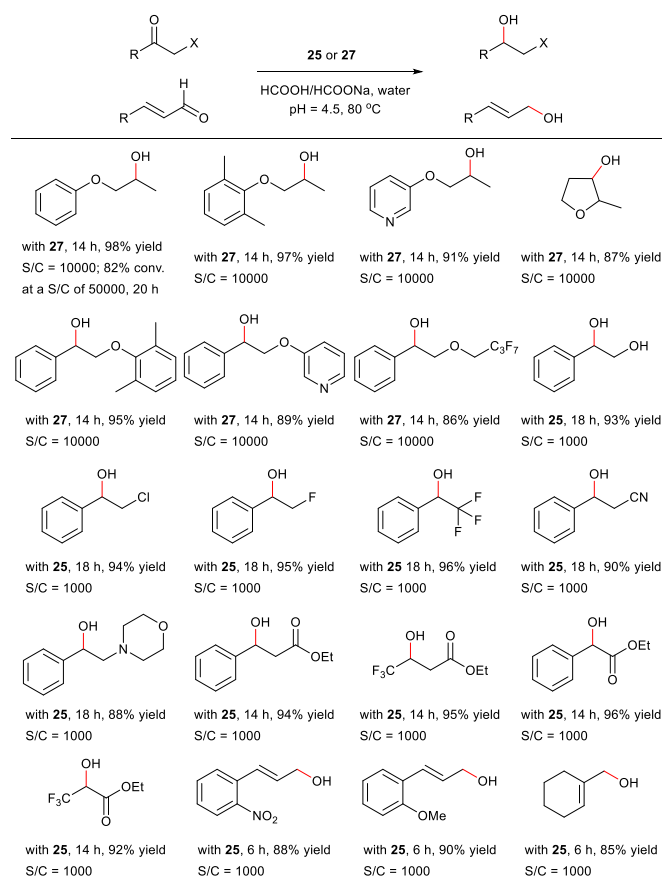
**Scheme 15.** Aqueous phase TH of α- or β-functionalised carbonyl compounds.

15, the desired products were obtained with high yields for these problematic ketones.

The much less studied β-keto ethers were also effectively and chemoselectively reduced to the desired β-hydroxyethers with iridacycle **27** (Scheme 15).[29] Controlling the solution pH is critical, with pH 4.5 being optimal. Under these conditions, keto ethers featuring either aromatic or aliphatic units and aromatic, aliphatic, heterocyclic and fluorinated ethers were all viable and gave excellent yields at a S/C ratio of 10000 on a 2.5 mmol substrate scale without dissociation of any ether groups.

In addition, the reduction of keto esters with the iridacycle catalysts was also shown to be feasible.[29] Thus, catalysed by iridacycle **25**, both α- and β-keto esters, including those aromatic and aliphatic ones, were reduced to the corresponding alcohols with excellent yields (Scheme 15).

2.3. Transfer hydrogenation of N-heterocycles

The reduction of N-heterocycles is more challenging due to the aromaticity of the heterocycles. Indeed, in comparison with the situation of ketone reduction, TH of such compounds has been much less reported.[30] The iridacycles have again been shown to be viable. Thus, using complex **25** as catalyst in water, various quinolines and indoles could be reduced to tetrahydroquinolines and indolines, respectively, at 30 °C with formate, using as low as 0.01 mo% catalyst (Scheme 16).[31] The solution pH again is critical for the catalytic activity, with pH 4.5 giving the best yield. Large-scale reduction was shown to be feasible as well. Thus, quinoline (35.8 g, 250 mmol) was reduced with 0.01 mol% catalyst at 30 °C in 24 h, affording
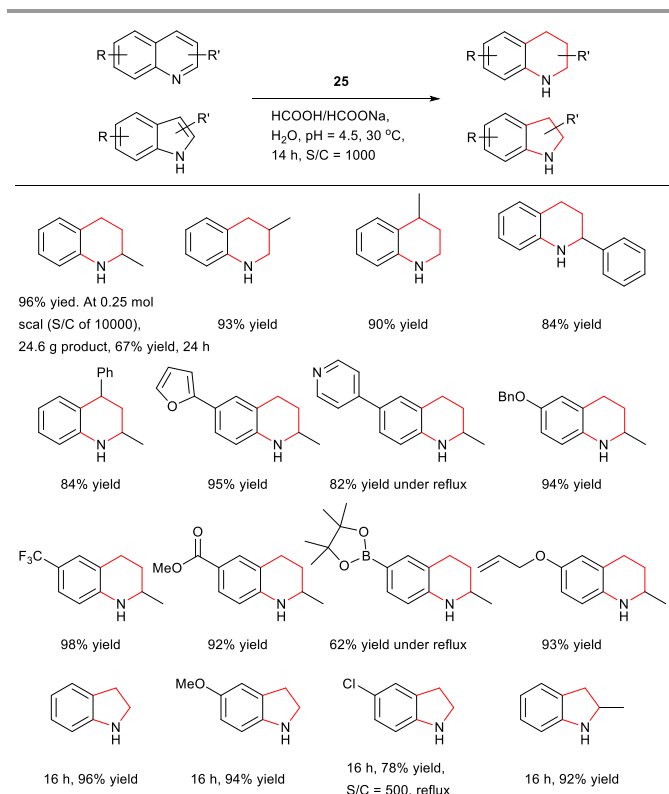
Scheme 16. Aqueous phase TH of quinolines and indoles with **25**.
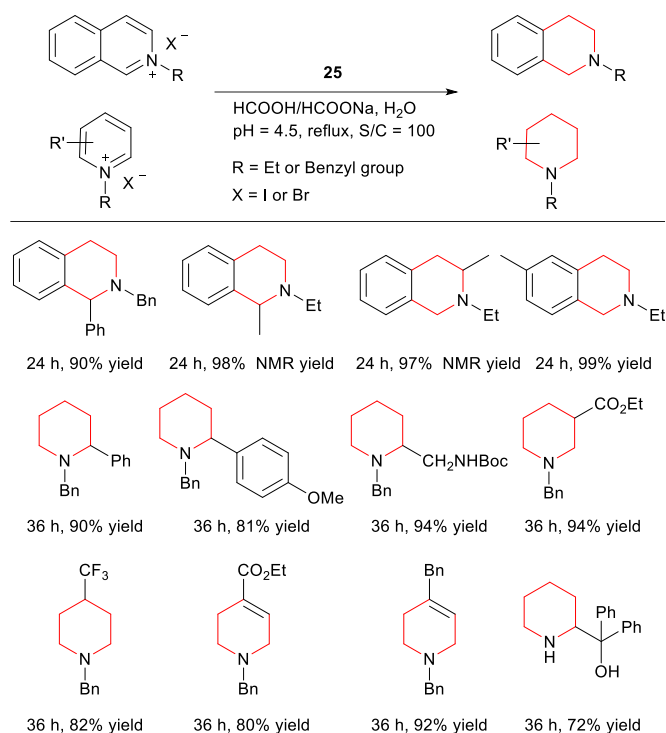
**Scheme 17.** Aqueous phase TH of isoquinolinium and pyridinium salts with **25**.

67% yield of product. The product was separated from the reaction mixture by a simple phase separation and purified by fractional distillation. No special equipment was required for this reaction, nor was an inert atmosphere necessary. In addition, no organic solvent was used for the entire operation.

The more challenging substrates, isoquinolines and pyridines, could be reduced after quaternisation with 1 mol% of **25** under refluxing conditions, affording synthetically significant heterocyclic compounds.[31] Examples of these reactions are given in Scheme 17. The versatility of these cyclometalated iridium catalysts have been further demonstrated by the efficient TH of other heterocycles and imines, including deuteriation with DCOOD.

3. Hydrogenation with iridacycles

Although the iridacycle catalysts were initially used for TH reactions with formic acid as hydrogen source, further studies have demonstrated that they can also split H₂, allowing for the hydrogenation of imino bonds. Thus, with **26** as catalyst, various ketimines derived from aromatic ketones and aromatic amines were hydrogenated to amines at an S/C of 10000 or higher under 20 bar H₂ at 85 °C in trifluoroethanol (TFE) (Scheme 18).[32] Similarly, complex **21** is highly efficient for the hydrogenation of various imines derived from aromatic and aliphatic ketones. The reaction could also take place at a lower temperature of 25 °C.[33]

Whilst the common iridacycles such as **17**-**19** were ineffective in promoting the hydrogenation of *N*-heterocycles, the methylenedioxy-substituted **28** was shown to be highly effective under remarkably mild conditions in TFE.[34] The
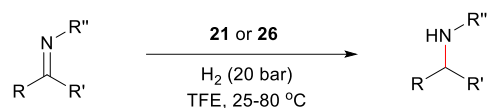
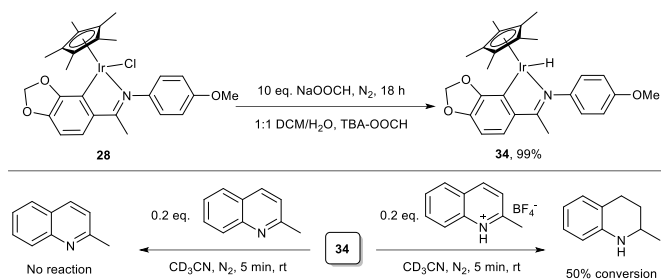**Scheme 18.** Hydrogenation of imines with iridacycles.

molecular structure of **28** was confirmed by X-ray diffraction; there appears to be a significant *ortho*-directing effect from the oxygen atoms in its formation. As illustrated in Scheme 19, various nitrogen heterocycles, including quinolines, quinoxalines, indoles and cyclic imines, were hydrogenated at room temperature with a balloon pressure of hydrogen gas with 1 mol% of **28**. The iridacycle thus provides a highly effective alternative to the heterogeneous metal catalysts and borohydrides commonly used for these reactions, while offering greatly increased reactivity and selectivity.

As in the case of TH, it is the protonated imino bond that is saturated, instead of the neutral substrate, in these reactions with H$_2$.[34] Thus, treatment of the iridium hydride **34**, derived from **28**, with 2-methylquinoline did not lead to the formation of tetahydroquinoline; however, rapid hydride transfer occurred when 2-methyl quinolinium tetrafluoroborate was used (Scheme 20).
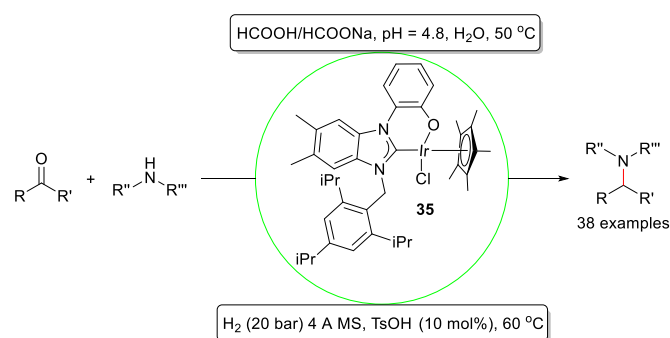
For these hydrogenation reactions, TFE appears to be essential for good catalytic activity. No or only slow hydrogenation was observed in aprotic solvents or protic
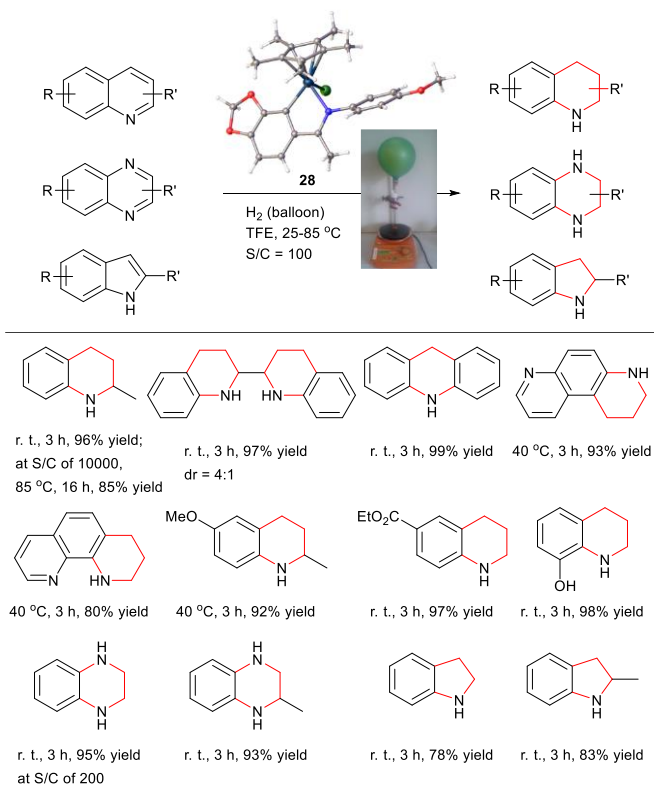
Scheme 20. Mechanistic probing of the reduction of quinolines with iridacycle catalyst.


Scheme 21. Hydrogenative and transfer hydrogenative RA with a phenoxide-chelated iridacycle catalyst.

solvents of lower acidity such as DCM, TFH or MeOH. TFE is known to solvate chloride ions much more strongly than MeOH, and so may enhance the dissociation of chloride from the coordinatively saturated 18e$^-$ iridacycle, such as **21** and **28**, creating a vacant, active site on Ir(III) for H$_2$ coordination. In addition, the acidic TFE (pKa 12.4) (cf MeOH, pKa 15.5) may hydrogen-bond to the product, preventing it from competing with H$_2$ for the single vacant site on Ir(III).

More recently we reported a new type iridacycle catalyst. Complex **35** contains a chelating N-heterocyclic carbene-phenoxide ligand (Scheme 21).[35] This complex is found to catalyse successfully both transfer hydrogenative and hydrogenative RA of various ketones and aldehydes with aniline derivatives (Scheme 21). The transfer hydrogenative RA was effected with formate in water. As with the iridacycles above, controlling of the solution pH is important, with pH 4.8 being optimal. In contrast with the previous iridacycles, e.g. **25**, deviating from the pH 4.8 did not lead to ketone reduction, however. The hydrogenative RA with H$_2$ proceeds in MeOH, necessitating the use of p-toluenesulfonic acid (10 mol%) and 4 Å molecular sieves. It is interesting to note that the hydrogenative RA is considerably faster. Complex **35** is one of the few catalysts that enable efficiently both transfer hydrogenative and hydrogenative RA of various ketones and aldehydes.

Preliminary mechanistic studies into the iridacycle-catalysed hydrogenation of imino bonds with H$_2$ suggest a mechanism similar to that of TH.[35] As depicted in Scheme 22, the hydrogenation catalysed by the iridacycle **21** proceeds through an ionic pathway, in which the imine is protonated

Scheme 19. Hydrogenation of *N*-heterocycles with iridacycle **28**.
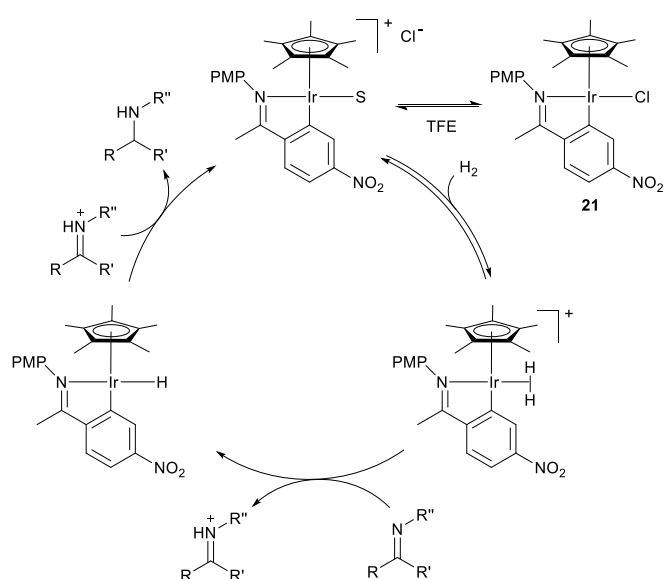
Scheme 22. Proposed mechanism for the hydrogenation of imines with iridacycle (S denotes an amine or solvent molecule).

and the resulting iminum ion is hydrogenated with no coordination to the iridium centre. The reaction appears to be rate-limited by the hydride formation step involving heterolytic cleavage of H_2. Mechanistic studies on the ionic pathway and the hydrogenation of imines have been reported previously.[36]
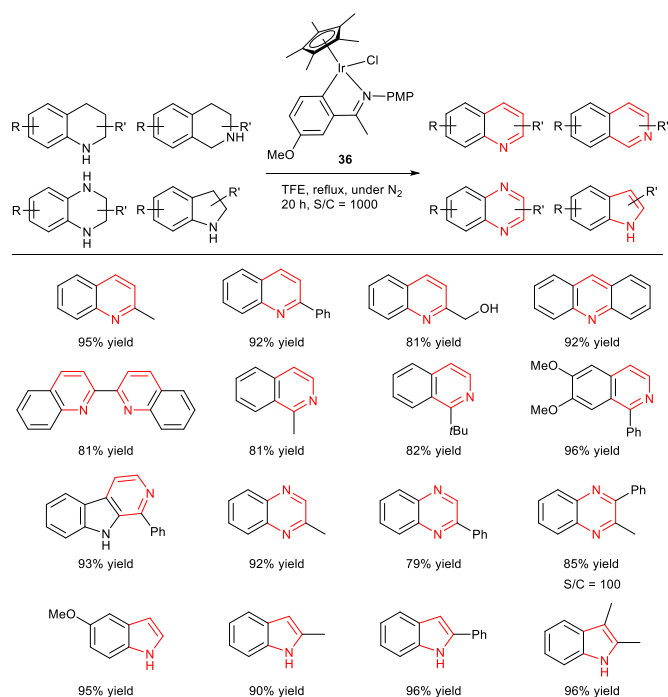
4. Dehydrogenation with iridacycles
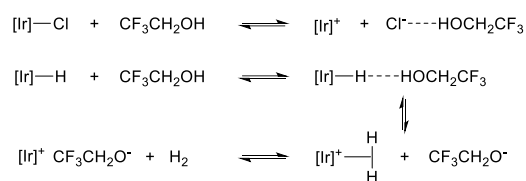
4.1. Dehydrogenation of N-heterocycles

Catalytic dehydrogenation (CDH) is one of the most important reactions in the manufacturing of commodity chemicals. However, it has been much less used in the synthesis of fine chemicals, pharmaceuticals, and agrochemicals, although it offers considerable benefits with respect to atom economy and environmental impact because of the avoidance of stoichiometric oxidants.[37] Following Fujita and Yamaguchi's report on the homogeneous dehydrogenation of tetrahydroquinolines using a [Cp*Ir(2-hydroxypyridine)] catalyst,[38] we showed that iridacycles, in particular **36**, catalyse acceptorless dehydrogenation of various benzofused *N*-heterocycles under much milder conditions.[39] Selected examples are found in Scheme 23.

TFE was again shown to be important for the reaction to proceed.[39] Apart from promoting halide dissociation from **36**, it may protonate the iridium hydride intermediate formed during the dehydrogenation, facilitating the release of H_2 (Scheme 24). In fact, the CDH appears to be turnover-limited by the step of dihydrogen formation, as strong reflux was necessary for higher conversions. Remarkably, when nitrogen was bubbled through the solution, the CDH could occur even at room temperature.
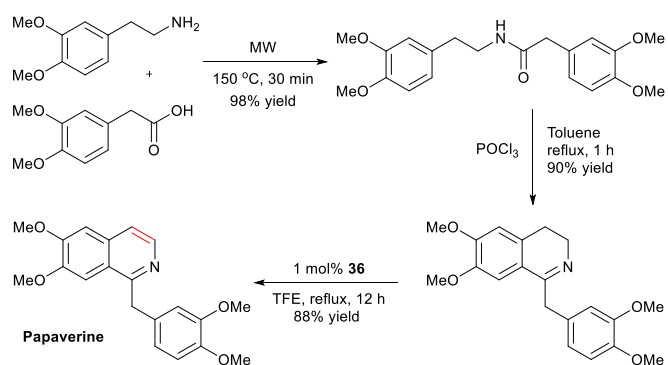
The synthetic utility of the CDH is demonstrated in the synthesis of well-known alkaloids.[39] An example is seen in papaverine, an opium alkaloid antispasmodic drug (Scheme

Scheme 23. Dehydrogenation of heterocycles with iridacycle **36**.

Scheme 24. Suggested role of TFE in dehydrogenation of heterocycles.

Scheme 25. Synthesis of Papaverine via iridacycle-catalysed dehydrogenation.

25). The synthesis started with the condensation of homoveratric acid and homoveratrylamine under microwave-assisted, neat conditions. The last step was accomplished by **36**-catalyzed CDH of the 3,4-dihydroisoquinoline. This three-step synthesis, employing commercially available materials with an overall yield of 78%, appears to offer a most efficient and economically sound method for this significant alkaloid.

The CDH of 2-methyl-1,2,3,4-tetrahydroquinoline by **36** is proposed to proceed via the mechanism shown in Scheme 26.[39] Evidence in support of the mechanism includes the
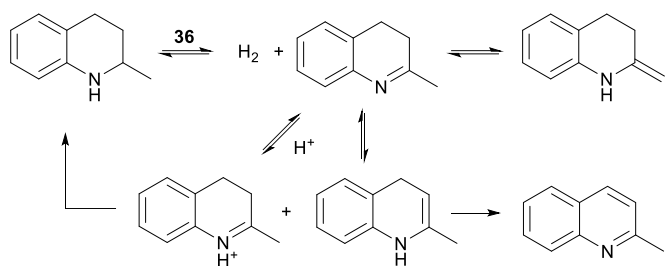
Scheme 26. Proposed mechanism for dehydrogenation of 2-methylquinoline.
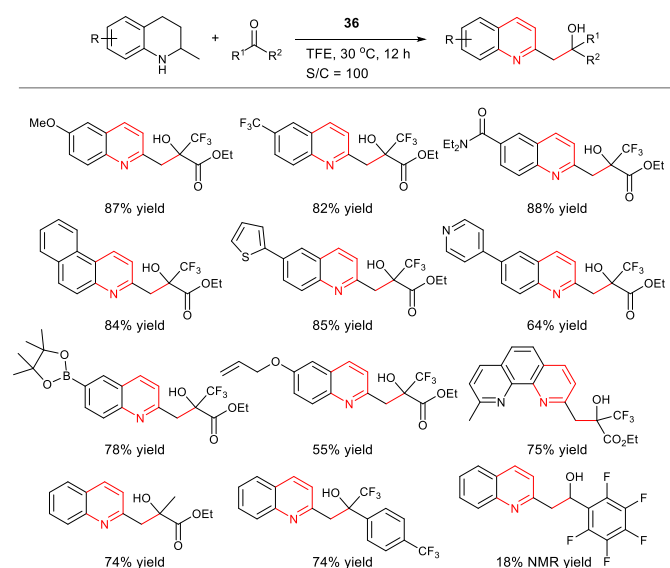
Scheme 27. Dehydrogenative coupling of quinolines with carbonyls catalysed by **36**.

Scheme 28. One-pot sequential Friedel-Crafts dehydrogenative coupling of 2-methylquinoline.

observation that when performed in a deuterated solvent, the reaction led to extensive H-D exchange at the methyl unit. We envisioned that the nucleophilic enamine might be intercepted by a carbon-based electrophile, thus affording C-C bond formation at the α-methyl substituent. This would lead to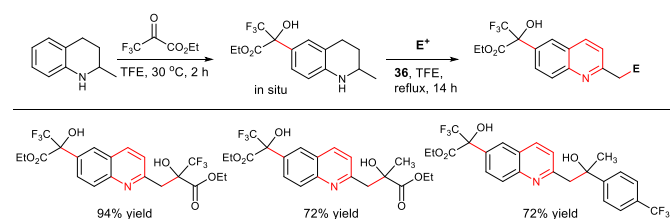 a new method, i.e. acceptorless dehydrogenative coupling (ADC), for the functionalization of 2-methyl azaarenes. Indeed, using the iridacycle **36**, tetrahydroquinolines, hydrophenanthroline and indolines could be dehydrogenated and in situ coupled with electron-deficient carbonyl compounds under mild conditions. Selected examples are found in Scheme 27.

It is known that tetrahydroquinolines can undergo Friedel–Crafts reactions at the 6-position.[40] This reaction could be cascaded with the ADC in question. As shown in Scheme 28, 2-methyl tetrahydroquinoline was first alkylated at the 6

position with a carbonyl electrophile in TFE; ADC then occurred at the methyl position by introducing more electrophile and raising the temperature.[41] Two different electrophiles can be introduced into the nucleophile in this one-pot protocol (Scheme 28).
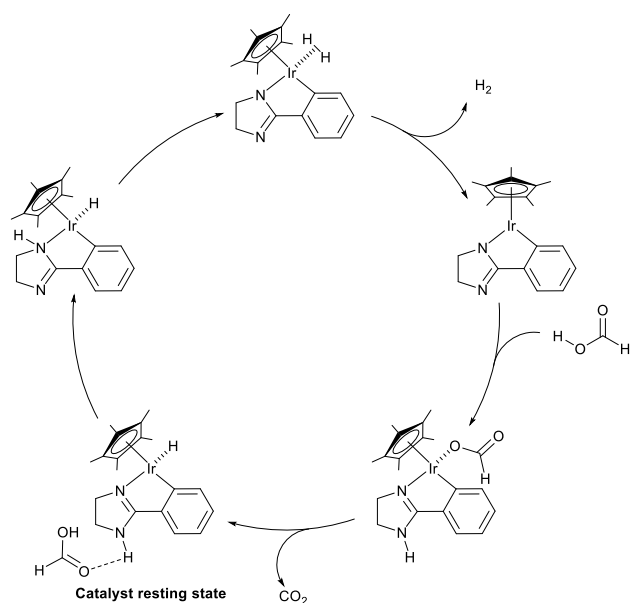
4.2. Dehydrogenation of formic acid

Formic acid is used as a reducing reagent in the reactions above. Containing 4.4 wt% of H_2, it is also an attractive H_2 storage medium.[42] Formic acid may be decomposed to give H_2 and CO_2 via a variety of methods, including transition metal catalysed dehydrogenation.[43] In the TH reactions with formic acid, the iridacycle first reacts with formate to form a metal hydride intermediate (Scheme 12), which then transfers the hydride to unsaturated substrates. With ligand of suitable electronic property, the metal hydride could also be protonated to form H_2. In fact, during our studies we often noted varying degrees of gas evolution, which might result from the decomposition of formic acid into CO_2 and H_2 and is one of the reasons, as aforementioned, why the solution pH needs to be controlled during TH reactions. Prompted by these observations, the need for highly active catalysts for formic acid dehydrogenation and the high modularity of the iridacycle complexes, we systematically studied the effect of the structure of iridacycle catalysts on the dehydrogenation rate of formic acid, arriving at an informing structure–activity relationship.[44] Thus, bulky imidazolinyl ligands were found to give the highest TON than imino or other N-heterocyclic donors, and installing an electron donor group on the cyclometalated aryl ring enhances the catalytic activity (Scheme 3). Varying the aryl ring revealed a ρ value of -1.8 in the Hammett plot, suggesting that positive charge is developed in the transition state of the rate-determining step of the dehydrogenation reaction. Most importantly, we found the presence of the remote γ-NH unit in the imidazoline ligand to be essential for catalytic activity, without which no reaction occurs.

Bearing the structure–activity relationship in mind, a new iridacycle **37** was synthesised, the structure of which was confirmed by X-ray diffraction.[44] Delightfully, **37** demonstrated the highest catalytic activity, affording an initial TOF of 2570 h^{-1} at 25 °C and a TOF up to 147000 h^{-1} at 40 °C (Scheme 29).

Mechanistic studies suggest that the dehydrogenation proceeds via a pathway shown in Scheme 30.[44] The key feature of the mechanism is that the catalytic turnover is rate-

$$HCOOH \xrightarrow[\text{Et}_3\text{N, 40 °C}]{} CO_2 + H_2$$

TON up to 147000 h^{-1}
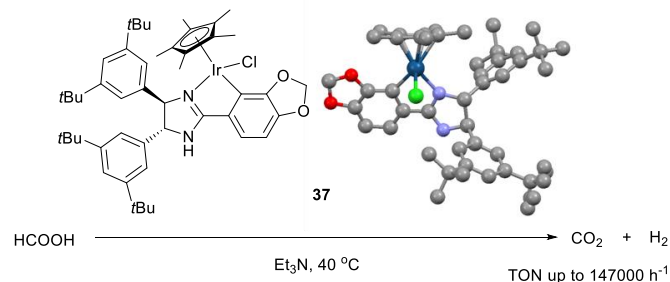
Scheme 29. Dehydrogenation of formic acid with iridacycle **37**.

Scheme 30. Proposed mechanism for the dehydrogenation of formic acid with iridacycle.

limited by the protonation of the Ir–H hydride, which is the resting state of the catalyst, and that its protonation involves participation of both formic acid and the distal NH functionality, which is critical for catalysis to proceed. Most likely, the protonation proceeds via formic acid-assisted proton hopping from the distal to the proximal nitrogen, whereupon protonation takes place, forming the dihydrogen complex and eventually H_2.

5. Borrowing hydrogen reactions with iridacycles

Iridacycles are capable of both hydrogenation and dehydrogenation reactions. Thus, it would be natural to envision that they could catalyse "borrowing hydrogen" or "hydrogen autotransfer" reactions.[45] Indeed, iridacycle **18** was found to be an efficient catalyst for the alkylation of amines by alcohols via this borrowing hydrogen strategy (Scheme 31).[46] With 1 mol% of **18**, benzylic as well as aliphatic primary alcohols could react with various aromatic amines to afford new amine products in TFE at 100 °C in the presence 5 mol% of K_2CO_3. Of note is that the cheap, readily available methanol can be used as the alkylating reagent, affording N-methylated products. Still interestingly, by varying the ratio of substrates, both mono- and bis-alkylated amines could be obtained with good selectivity.

The catalyst also promotes the alkylation of amines with other amines, providing a mild protocol for the cross coupling of amine substrates (Scheme 31).[46] This is notable, as most of the catalysts reported only work for alkylation with alcohols or amines, but not with both.

The use of TFE as solvent is critical for the reaction to proceed;[46] no reaction was observed with other solvents tested. Again, the beneficial effect of TFE may stem from its strong hydrogen-bond-donating ability, which could promote

the dissociation of the chloride anion from **18** to form the active catalyst and/or activate the imine toward hydride transfer, as indicated above.

A novel application of the iridacycles in borrowing hydrogen reactions is seen in a more recent example of dehydrogenative coupling of indolines with alcohols.[47] Functionalization of indoles via alkylation with alcohol is appealing, water being the only by-product. However, the control of the N-[48] or C3-[49] alkylation selectivity is not easy, with most catalytic systems preferring C3-alkylation. Catalysed by the iridacycle **18**, indolines can now be alkylated with alcohols, affording either N- or C3-alkylated indoles by a simple change in the reaction procedure.

As shown in Scheme 32, dehydrogenative N-alkylation of indolines took place when the indolines were treated with an alcohol in the presence of a base K_2CO_3, affording various N-alkylated indoles.[47] In contrast, when the same reaction was conducted with the base introduced a few hours after, C3-alkylated product was formed exclusively (Scheme 32). Mechanistic studies suggest that a tandem borrowing hydrogen/dehydrogenation process and a tandem dehydrogenation/borrowing hydrogen process are responsible for the N-alkylation and C3-alkylation reactions, respectively.
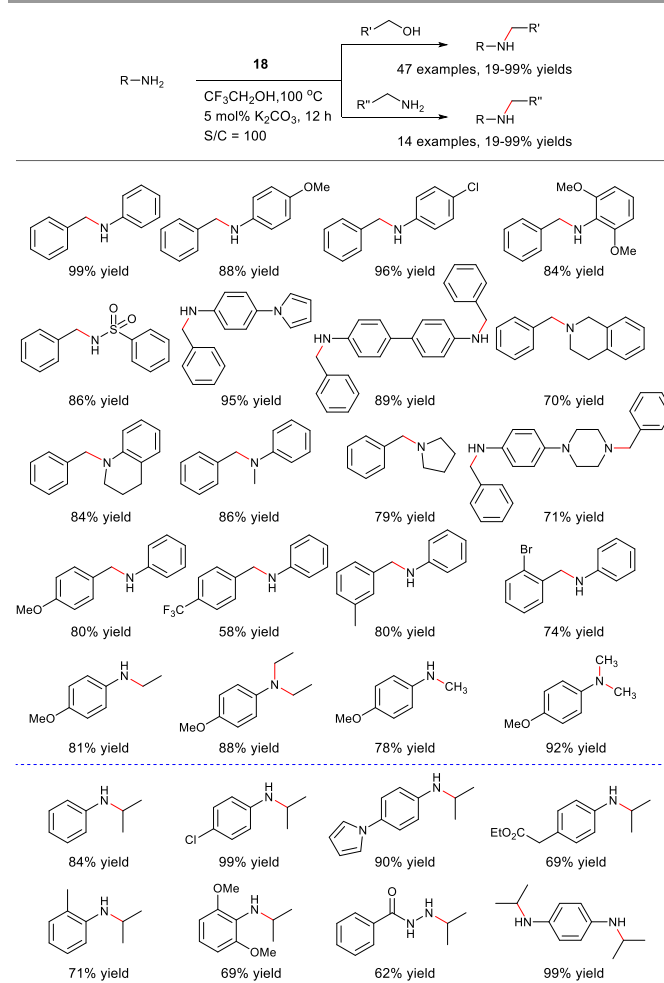
Scheme 31. Alkylation of amines with alcohols and cross coupling of amines catalysed by **18**.
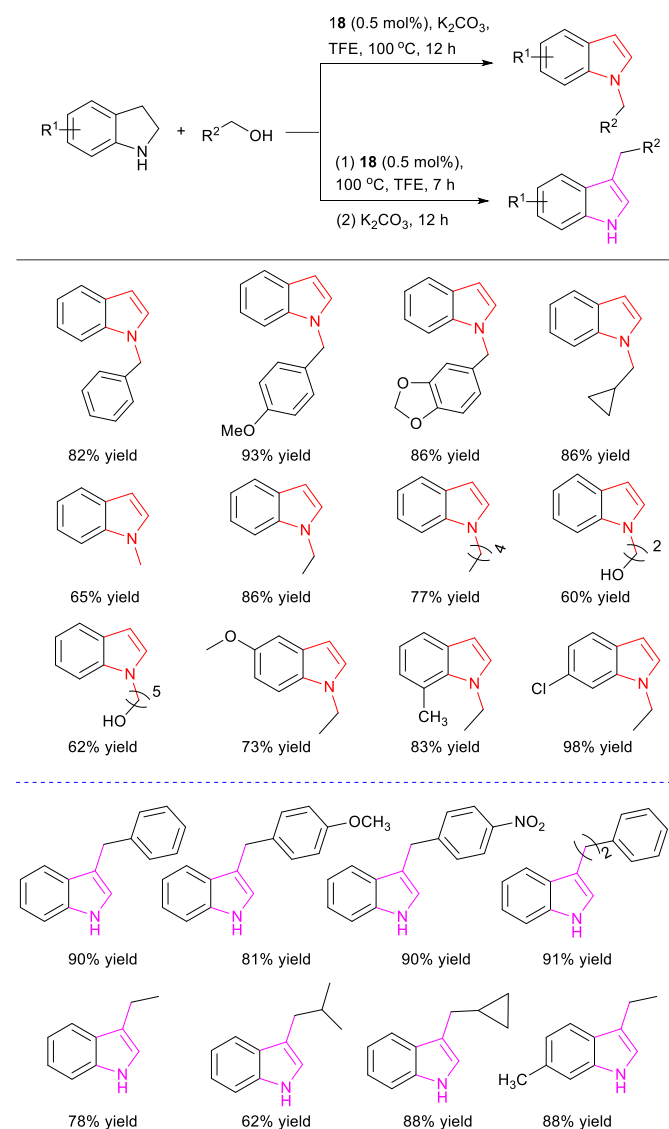
Scheme 32. Divergent alkylation of indoles via dehydrogenative coupling of indolines with alcohols.

6. Summary

Our interest in the iridacycles arose from a serendipitous discovery of their easy formation when attempting to reduce a ketimine in 2010. Since then, a variety of such complexes have been synthesized and as the foregoing text attests, they are capable of catalysing efficiently a wide range of reactions. They are highly modular, meaning their steric and electronic properties can be readily tuned to enable a reaction. Having only one coordination site available for reactions, these complexes are generally resistant to air and water, and they may be referred to as a true molecular single-site catalyst. Mechanistically, this single-site feature implies that for reactions involving multiple substrates, the catalysis is more likely to proceed in an outer-sphere fashion compared with catalysts having two or more coordination sites. Whether or not this is advantageous or disadvantageous would depend on the reaction one is dealing with. Looking forward, a chiral version would certainly add a lot more value to these catalytically versatile complexes.

Acknowledgments

Notes and references

1   (a) M. E. van der Boom and D. Milstein, *Chem. Rev.*, 2003, **103**, 1759-1792; (b) M. Albrecht, *Chem. Rev.*, 2010, **110**, 576-623; (c) D. A. Colby, R. G. Bergman and J. A. Ellman, *Chem. Rev.*, 2010, **110**, 624-655; (d) T. Satoh and M. Miura, *Chem. Eur. J.*, 2010, **16**, 11212-11222; (e) L. Ackermann, *Chem. Rev.*, 2011, **111**, 1315-1345; (f) D. A. Colby, A. S. Tsai, R. G. Bergman and J. A. Ellman, *Acc. Chem. Res.*, 2012, **45**, 814-825; (g)   G. Song, F. Wang and X. Li, *Chem. Soc. Rev.*, 2012, **41**, 3651-3678; (h)Y.-F. Han and G.-X. Jin, *Chem. Soc. Rev.*, 2014, **43**, 2799-2823; (i)   C. Michon, K. MacIntyre, Y. Corre and F. Agbossou-Niedercorn, *Chemcatchem*, 2016, **8**, 1755-1762.

2   (a) J. P. Kleiman and M. Dubeck, *J. Am. Chem. Soc.*, 1963, **85**, 1544-1545; (b)M. I. Bruce, *Angew. Chem. Int. Ed.*, 1977, **16**, 73-86.

3   (a) J. Liu, X. Wu, J. A. Iggo and J. Xiao, *Coord. Chem. Rev.*, 2008, **252**, 782-809; (b) C. Wang, B. Villa-Marcos and J. Xiao, *Chem. Commun.*, 2011, **47**, 9773-9785.

4   W. Bauer, M. Prem, K. Polborn, K. Sünkel, W. Steglich and W. Beck, *Eur J Inorg Chem*, 1998, **1998**, 485-493.

5   (a) D. L. Davies, O. Al-Duaij, J. Fawcett, M. Giardiello, S. T. Hilton and D. R. Russell, *Dalton Trans.*, 2003, 4132-4138; (b) D. L. Davies, S. M. A. Donald, O. Al-Duaij, S. A. Macgregor and M. Pölleth, *J. Am. Chem. Soc.*, 2006, **128**, 4210-4211; (c) Y. Boutadla, O. Al-Duaij, D. L. Davies, G. A. Griffith and K. Singh, *Organometallics*, 2009, **28**, 433-440; (d) Y. Boutadla, D. L. Davies, R. C. Jones and K. Singh, *Chem. Eur. J.*, 2011, **17**, 3438-3448; (e)D. L. Davies, M. P. Lowe, K. S. Ryder, K. Singh and S. Singh, *Dalton Trans.*, 2011, **40**, 1028-1030.

6   L. Li, W. W. Brennessel and W. D. Jones, *Organometallics*, 2009, **28**, 3492-3500.

7   J. Li, W. Hu, Y. Peng, Y. Zhang, J. Li and W. Zheng, *Organometallics*, 2014, **33**, 2150-2159.

8   (a) J. M. Kisenyi, J. A. Cabeza, A. J. Smith, H. Adams, G. J. Sunley, N. J. S. Salt and P. M. Maitlis, *J. Chem. Soc., Chem. Commun.*, 1985, 770-771; (b) R. Corberán, V. Lillo, J. A. Mata, E. Fernandez and E. Peris, *Organometallics*, 2007, **26**, 4350-4353; (c) C. Scheeren, F. Maasarani, A. Hijazi, J.-P. Djukic, M. Pfeffer, S. D. Zarić, X.-F. Le Goff and L. Ricard,

Organometallics, 2007, **26**, 3336-3345; (d) J.-B. Sortais, N. Pannetier, A. Holuigue, L. Barloy, C. Sirlin, M. Pfeffer and N. Kyritsakas, *Organometallics*, 2007, **26**, 1856-1867; (e) S. Arita, T. Koike, Y. Kayaki and T. Ikariya, *Angew. Chem. Int. Ed.*, 2008, **47**, 2447-2449; (f) J.-P. Djukic, C. Boulho, D. Sredojevic, C. Scheeren, S. Zaric, L. Ricard and M. Pfeffer, *Chem. Eur. J.*, 2009, **15**, 10830-10842; (g) D. Gnanamgari, E. L. O. Sauer, N. D. Schley, C. Butler, C. D. Incarvito and R. H. Crabtree, *Organometallics*, 2009, **28**, 321-325; (h) J. F. Hull, D. Balcells, J. D. Blakemore, C. D. Incarvito, O. Eisenstein, G. W. Brudvig and R. H. Crabtree, *J. Am. Chem. Soc.*, 2009, **131**, 8730-8731; (i) Y. Kashiwame, S. Kuwata and T. Ikariya, *Chem. Eur. J.*, 2010, **16**, 766-770; (j) R. Lalrempuia, N. D. McDaniel, H. Müller-Bunz, S. Bernhard and M. Albrecht, *Angew. Chem. Int. Ed.*, 2010, **49**, 9765-9768; (k) L. Barloy, J.-T. Issenhuth, M. G. Weaver, N. Pannetier, C. Sirlin and M. Pfeffer, *Organometallics*, 2011, **30**, 1168-1174; (l) T. P. Brewster, J. D. Blakemore, N. D. Schley, C. D. Incarvito, N. Hazari, G. W. Brudvig and R. H. Crabtree, *Organometallics*, 2011, **30**, 965-973; (m) L. E. E. Broeckx, M. Lutz, D. Vogt and C. Muller, *Chem. Commun.*, 2011, **47**, 2003-2005; (n) J.-P. Djukic, W. Iali, M. Pfeffer and X.-F. L. Goff, *Chem. Commun.*, 2011, **47**, 3631-3633; (o) K.-i. Fujita, T. Yoshida, Y. Imori and R. Yamaguchi, *Org. Lett.*, 2011, **13**, 2278-2281; (p) Z.-J. Yao, G. Su and G.-X. Jin, *Chem. Eur. J.*, 2011, **17**, 13298-13307; (q) J.-P. Djukic, W. Iali, M. Pfeffer and X.-F. Le Goff, *Chem. Eur. J.*, 2012, **18**, 6063-6078; (r) K. Gray, M. J. Page, J. Wagler and B. A. Messerle, *Organometallics*, 2012, **31**, 6270-6277; (s) J. J. M. Weemers, W. N. P. van der Graaff, E. A. Pidko, M. Lutz and C. Müller, *Chem. Eur. J.*, 2013, **19**, 8991-9004.

9   (a) S. Arita, T. Koike, Y. Kayaki and T. Ikariya, *Organometallics*, 2008, **27**, 2795-2802; (b) L. Li, W. W. Brennessel and W. D. Jones, *J. Am. Chem. Soc.*, 2008, **130**, 12414-12419; (c) D. L. Davies, O. Al-Duaij, J. Fawcett and K. Singh, *Organometallics*, 2010, **29**, 1413-1420; (d) L. Li, Y. Jiao, W. W. Brennessel and W. D. Jones, *Organometallics*, 2010, **29**, 4593-4605; (e) Y. Du, T. K. Hyster and T. Rovis, *Chem. Commun.*, 2011, **47**, 12074-12076; (f) Y.-F. Han, H. Li, P. Hu and G.-X. Jin, *Organometallics*, 2011, **30**, 905-911; (g) S. Shibata, T. Suenobu and S. Fukuzumi, *Angew. Chem. Int. Ed.*, 2013, **52**, 12327-12331.

10 (a) Z. Liu and P. J. Sadler, *Acc. Chem. Res.*, 2014, **47**, 1174-1185; (b) I. Omae, *Coord. Chem. Rev.*, 2014, **280**, 84-95; (c) J. W. Beatty and C. R. J. Stephenson, *Acc. Chem. Res.*, 2015, **48**, 1474-1484; (d) C.-H. Leung, S. Lin, H.-J. Zhong and D.-L. Ma, *Chem Sci.*, 2015, **6**, 871-884; (e) S. Medici, M. Peana, V. M. Nurchi, J. I. Lachowicz, G. Crisponi and M. A. Zoroddu, *Coord. Chem. Rev.*, 2015, **284**, 329-350.

11 (a) R. M. Haak, F. Berthiol, T. Jerphagnon, A. J. A. Gayet, C. Tarabiono, C. P. Postema, V. Ritleng, M. Pfeffer, D. B. Janssen, A. J. Minnaard, B. L. Feringa and J. G. de Vries, *J. Am. Chem. Soc.*, 2008, **130**, 13508-13509; (b) T. Jerphagnon, A. J. A. Gayet, F. Berthiol, V. Ritleng, N. Mršić, A. Meetsma, M. Pfeffer, A. J. Minnaard, B. L. Feringa and J. G. de Vries, *Chem. Eur. J.*, 2009, **15**, 12780-12790.

12 (a) H. Kim and S. Chang, *ACS Catal.*, 2015, **5**, 6665-6669; (b) R. A. Arthurs, M. Ismail, C. C. Prior, V. S. Oganesyan, P. N.

Horton, S. J. Coles and C. J. Richards, *Chem. Eur. J.*, 2016, **22**, 3065-3072; (c) R. A. Arthurs, P. N. Horton, S. J. Coles and C. J. Richards, *Eur. J. Inorg. Chem.*, 2017, **2017**, 229-232.

13 C. Wang, A. Pettman, J. Bacsa and J. Xiao, *Angew. Chem. Int. Ed.*, 2010, **49**, 7548-7552.

14 C. Wang, H.-Y. T. Chen, J. Bacsa, C. R. A. Catlow and J. Xiao, *Dalton Trans.*, 2013, **42**, 935-940.

15 (a) R. Noyori and S. Hashiguchi, *Acc. Chem. Res.*, 1997, **30**, 97-102; (b) T. Ikariya, K. Murata and R. Noyori, *Org. Biomol. Chem.*, 2006, **4**, 393-406; (c) T. Ikariya and A. J. Blacker, *Acc. Chem. Res.*, 2007, **40**, 1300-1308.

16 (a) Y.-M. He and Q.-H. Fan, *Chemcatchem*, 2015, **7**, 398-400; (b) Y. Wei, X. Wu, C. Wang and J. Xiao, *Catal Today*, 2015, **247**, 104-116; (c) X. Wu, C. Wang and J. Xiao, *Chem. Rec.*, 2016, **16**, 2768-2782.

17 N. Uematsu, A. Fujii, S. Hashiguchi, T. Ikariya and R. Noyori, *J. Am. Chem. Soc.*, 1996, **118**, 4916-4917.

18 D. Talwar, N. P. Salguero, C. M. Robertson and J. Xiao, *Chem. Eur. J.*, 2014, **20**, 245-252.

19 (a) X. Wu and J. Xiao, *Chem. Commun.*, 2007, 2449-2466; (b) C. Wang, X. Wu and J. Xiao, *Chem. Asian J.*, 2008, **3**, 1750-1770; (c) B. X. Wu, C. Wang and J. Xiao, *Platin. Met. Rev.*, 2010, **54**, 3-19.

20 (a) S. Hoffmann, M. Nicoletti and B. List, *J. Am. Chem. Soc.*, 2006, **128**, 13074-13075; (b) R. I. Storer, D. E. Carrera, Y. Ni and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2006, **128**, 84-86.

21 Q. Lei, Y. Wei, D. Talwar, C. Wang, D. Xue and J. Xiao, *Chem. Eur. J.*, 2013, **19**, 4021-4029.

22 Y. Wei, C. Wang, X. Jiang, D. Xue, J. Li and J. Xiao, *Chem. Commun.*, 2013, **49**, 5408-5410.

23 (a) N. Menashe, D. Reshef and Y. Shvo, *J. Org. Chem.*, 1991, **56**, 2912-2914; (b) N. Menashe and Y. Shvo, *J. Org. Chem.y*, 1993, **58**, 7434-7439; (c) Z. Wan, C. D. Jones, D. Mitchell, J. Y. Pu and T. Y. Zhang, *J. Org. Chem.*, 2006, **71**, 826-828.

24 J. Li, C. Wang, D. Xue, Y. Wei and J. Xiao, *Green Chem.*, 2013, **15**, 2685-2689.

25 S. M. Bronner and R. H. Grubbs, *Chem Sci.*, 2014, **5**, 101-106.

26 H.-Y. T. Chen, C. Wang, X. Wu, X. Jiang, C. R. A. Catlow and J. Xiao, *Chem. Eur. J.*, 2015, **21**, 16564-16577.

27 (a) D. J. Darensbourg, M. B. Fischer, R. E. Schmidt and B. J. Baldwin, *J. Am. Chem. Soc.*, 1981, **103**, 1297-1298; (b) N. Kanematsu, M. Ebihara and T. Kawamura, *Inorg. Chim. Acta*, 2001, **323**, 96-104; (c) T. J. Schmeier, G. E. Dobereiner, R. H. Crabtree and N. Hazari, *J. Am. Chem. Soc.*, 2011, **133**, 9274-9277.

28 Y. Wei, D. Xue, Q. Lei, C. Wang and J. Xiao, *Green Chem.*, 2013, **15**, 629-634.

29 D. Talwar, X. Wu, O. Saidi, N. P. Salguero and J. Xiao, *Chem. Eur. J.*, 2014, **20**, 12835-12842.

30 D.-S. Wang, Q.-A. Chen, S.-M. Lu and Y.-G. Zhou, *Chem. Rev.*, 2012, **112**, 2557-2590.

31 D. Talwar, H. Y. Li, E. Durham and J. Xiao, *Chem. Eur. J.*, 2015, **21**, 5370-5379.

32 W. Tang, C. Lau, X. Wu and J. Xiao, *Synlett*, 2014, **25**, 81-84.

33 B. Villa-Marcos, W. Tang, X. Wu and J. Xiao, *Org. Biomol. Chem.*, 2013, **11**, 6934-6939.

34 J. Wu, J. H. Barnard, Y. Zhang, D. Talwar, C. M. Robertson and J. Xiao, *Chem. Commun.*, 2013, **49**, 7052-7054.

35 D. Gülcemal, S. Gülcemal, C. M. Robertson and J. Xiao, *Organometallics*, 2015, **34**, 4394-4400.

36 (a) M. P. Magee and J. R. Norton, *J. Am. Chem. Soc.*, 2001, **123**, 1778-1779; (b) S. E. Clapham, A. Hadzovic and R. H. Morris, *Coord. Chem. Rev.*, 2004, **248**, 2201-2237.

37 (a) G. E. Dobereiner and R. H. Crabtree, *Chem. Rev.*, 2010, **110**, 681-703; (b) J. Choi, A. H. R. MacArthur, M. Brookhart and A. S. Goldman, *Chem. Rev.*, 2011, **111**, 1761-1779.

38 K.-i. Fujita, Y. Tanaka, M. Kobayashi and R. Yamaguchi, *J. Am. Chem. Soc.*, 2014, **136**, 4829-4832.

39 J. Wu, D. Talwar, S. Johnston, M. Yan and J. Xiao, *Angew. Chem. Int. Ed.*, 2013, **52**, 6983-6987.

40 T. B. Poulsen and K. A. Jørgensen, *Chem. Rev.*, 2008, **108**, 2903-2915.

41 D. Talwar, A. Gonzalez-de-Castro, H. Y. Li and J. Xiao, *Angew. Chem. Int. Ed.*, 2015, **54**, 5223-5227.

42 (a) T. C. Johnson, D. J. Morris and M. Wills, *Chem. Soc. Rev.*, 2010, **39**, 81-88; (b) B. Loges, A. Boddien, F. Gärtner, H. Junge and M. Beller, *Top. Catal.*, 2010, **53**, 902-914; (c) M. Grasemann and G. Laurenczy, *Energ. Environ. Sci.*, 2012, **5**, 8171-8181.

43 Q.-L. Zhu and Q. Xu, *Energ. Environ. Sci.*, 2015, **8**, 478-512.

44 J. H. Barnard, C. Wang, N. G. Berry and J. Xiao, *Chem Sci.*, 2013, **4**, 1234-1244.

45 (a) M. H. S. A. Hamid, P. A. Slatford and J. M. J. Williams, *Adv. Synth. Catal.*, 2007, **349**, 1555-1575; (b) G. Guillena, D. J. Ramón and M. Yus, *Chem. Rev.*, 2009, **110**, 1611-1641; (c) A. J. A. Watson and J. M. J. Williams, *Science*, 2010, **329**, 635-636; (d) C. Gunanathan and D. Milstein, *Science*, 2013, **341**, 1229712; (e) Y. Obora, *ACS Catal.*, 2014, **4**, 3972-3981; (f) Q. Yang, Q. Wang and Z. Yu, *Chem. Soc. Rev.*, 2015, **44**, 2305-2329.

46 Q. Zou, C. Wang, J. Smith, D. Xue and J. Xiao, *Chem. Eur. J.*, 2015, **21**, 9656-9661.

47 X. Jiang, W. Tang, D. Xue, J. Xiao and C. Wang, *ACS Catal.*, 2017, **7**, 1831-1835.

48 (a) S. M. A. H. Siddiki, K. Kon and K.-i. Shimizu, *Green Chem.*, 2015, **17**, 173-177; (b) S. Bähn, S. Imm, K. Mevius, L. Neubert, A. Tillack, J. M. J. Williams and M. Beller, *Chem. Eur. J.*, 2010, **16**, 3590-3593.

49 (a) S. Whitney, R. Grigg, A. Derrick and A. Keep, *Org. Lett.*, 2007, **9**, 3299-3302; (b) S. Imm, S. Bähn, A. Tillack, K. Mevius, L. Neubert and M. Beller, *Chem. Eur. J.*, 2010, **16**, 2705-2709; (c) R. Cano, M. Yus and D. J. Ramón, *Tetrahedron Lett.*, 2013, **54**, 3394-3397; (d) S. Bartolucci, M. Mari, A. Bedini, G. Piersanti and G. Spadoni, *J. Org. Chem.*, 2015, **80**, 3217-3222; (e) M. Weiss and R. Peters, *ACS Catal.*, 2015, **5**, 310-316.