Transfer Hydrogenation

Iridicycle-Catalysed Imine Reduction: An Experimental and Computational Study of the Mechanism


Abstract: The mechanism of imine reduction by formic acid with a single-site iridicycle catalyst has been investigated by density functional theory (DFT), NMR spectroscopy, and kinetic measurements. The NMR and kinetic studies suggest that the transfer hydrogenation is turnover-limited by the hydride formation step. The calculations reveal that, amongst a number of possibilities, hydride formation from the iridicycle and formate probably proceeds by an ion-pair mechanism, whereas the hydride transfer to the imino bond occurs in an outer-sphere manner. In the gas phase, in the most favourable pathway, the activation energies in the hydride formation and transfer steps are 26–28 and 7–8 kcal mol⁻¹, respectively. Introducing one explicit methanol molecule into the modelling alters the energy barrier significantly, reducing the energies to around 18 and 2 kcal mol⁻¹ for the two steps, respectively. The DFT investigation further shows that methanol participates in the transition state of the turn-over-limiting hydride formation step by hydrogen-bonding to the formate anion and thereby stabilising the ion pair.

Introduction

Transfer hydrogenation (TH), whereby a non-H₂ hydrogen source is used, has become an established method in the reduction of various polar bonds in the last two decades or so, finding numerous applications in synthetic chemistry.[1] There are two hydrogen sources that have primarily been used in metal-catalysed TH; isopropanol and formic acid. Whereas the mechanism of TH with the former has been studied in depth by the groups of Noyori,[2] Ikariya,[3] Bäckvall,[4] Casey,[1g, 5] and others,[6] reports concerning the mechanism(s) of TH with formic acid have been sporadic.[7] Understanding the mechanism is not only necessary to develop more efficient TH catalysts but the knowledge gained will also impact on research concerning the hydrogenation of CO₂[8] and dehydrogenation of formic acid,[9] an area that has drawn a great deal of attention in the past few years.

Metal-catalysed TH with formic acid or formate involves two main steps, formation of a metal hydride and transfer of the hydride to a substrate. Since the 1970s, several mechanisms concerning formate decarboxylation to form a metal hydride have been put forward.[7b] All the mechanisms involve initial formate coordination to the metal centre, affording a formato complex. They differ in the key step of hydride generation, which can be represented by the three modes shown in Scheme 1. The β-hydrogen elimination pathway, proposed by Darensbourg et al.[10] and earlier researchers,[11] involves a coordinated formate and necessitates a vacant coordination site at the metal centre. In line with this, it has been stated that the formate anion must occupy two coordination sites before the cleavage of its C–H bond.[11] Recent DFT calculations of iron-catalysed dehydrogenation of formic acid[9k] showed that β-hydrogen elimination is similarly involved in the transition state (TS) of hydride formation.[12] In contrast, the ion-pair mechanism suggested by Merrifield and Gladysz[13] and the ligand-as-
sisted decarboxylation reported by Casey et al.\textsuperscript{[14]} do not feature coordinated formate. Instead, in the Gladysz mechanism the hydride is formed by direct hydride transfer to the metal centre in a tight ion pair, whereas in the Casey mechanism deprotonation of a non-coordinated formic acid by the ligand triggers the hydride transfer to the metal. For coordinatively saturated metal formate complexes, it is reasonable to expect that decarboxylation more likely occurs through the latter two mechanisms. However, to our knowledge, the ion-pair mechanism had not been theoretically studied before this work was initiated.\textsuperscript{[15]}

The step of hydride transfer from a metal to a substrate, such as a ketone, is common to all hydrogen sources including H\textsubscript{2}, and has been extensively investigated.\textsuperscript{[3, 4b, 6a–d]} However, in the area of TH of imines, the subject of this work, the mechanistic details are far less clear. For M–H hydride complexes that are coordinatively unsaturated, contain labile ligands or are capable of ring slippage, an inner-sphere mechanism has been suggested, in which the imine, which may be formally neutral or protonated, coordinates to the metal prior to the hydride transfer.\textsuperscript{[4c, e]} An outer-sphere mechanism is also possible, in which the hydride transfers to a protonated imine without direct interaction of the C=N bond with the metal centre.\textsuperscript{[14d, 16]} Scheme 2 illustrates the key aspects of these two mechanisms.

\begin{equation}
\text{Scheme 2. Reduction of C=N bonds by the inner and outer-sphere mechanisms.}
\end{equation}

Recent DFT calculations by Hopmann and Bayer showed that the imine hydrogenation with the iridium phosphinoxazoline (PHOX) catalysts reported by Pfaltz and co-workers can proceed by the outer-sphere pathway.\textsuperscript{[16, 17]}

Concerning coordinatively saturated M–H hydrides, it appears that the hydride can only transfer through the outer-sphere mechanism. This is supported by experimental observations from several groups,\textsuperscript{[4d, 18, 19]} whereby coordinatively saturated [L\textsubscript{2}Ru\textsubscript{II}H\textsuperscript{−}–H] and [L\textsubscript{2}Ir\textsuperscript{III}H\textsuperscript{−}–H] species readily reduce iminium cations, but not the neutral imines as may be expected. Ikariya and co-workers suggested that Ag\textsuperscript{+}-coordinated imines are similarly reduced.\textsuperscript{[20]} In an earlier mechanistic study, Norton proposed that the diphosphine complex [CpRuH(P\textsubscript{2}P)] catalyses the hydrogenation of iminium ions through an inner mechanism, that is, the outer-sphere mechanism.\textsuperscript{[21]} However, as in the case of hydride generation, few theoretical studies are available of the outer-sphere mechanism for coordinatively saturated metal hydrides.\textsuperscript{[14d, 16]}

The brief survey above indicates that the mechanism of TH with formic acid largely remains to be delineated, particularly when a single-site catalyst, that is, catalysts with only one coordination site available, is employed and imines are the substrates. Imine reduction is an area of great importance to fine chemical, pharmaceutical and agrochemical synthesis.\textsuperscript{[22]} In comparison with the situation of alkene and carbonyl compounds, however, catalysts that are active and selective for imine reduction are far fewer in number.\textsuperscript{[23, 24–c]}

One of our groups recently reported a new class of single-site catalysts, cyclometalated [Cp\textsuperscript{″}Ir–imino] complexes, which show only one open coordination site upon chloride dissociation (Scheme 3).\textsuperscript{[19c]} Analogous complexes have been known for over two decades and their chemistry has been widely investigated, particularly by Davies and co-workers.\textsuperscript{[23]} Less known are their applications in catalytic reactions. In the past a few years, we have disclosed that such cyclometalated [Cp\textsuperscript{″}Ir–imino] complexes, that is, iridicycles, are active and selective catalysts for a wide range of reactions.\textsuperscript{[19e, 24]} Representative examples are given in Scheme 3. Some of these iridicycles are particularly active in imine reduction, delivering, for instance, TOFs of up to 19 000 h\textsuperscript{−1} in the transfer hydrogenation of imines with HCOOH.\textsuperscript{[19e]} Remarkably, they also catalyse highly efficient reductive amination in water, allowing substrate/catalyst ratios as high as 1 × 10\textsuperscript{3} to be used.\textsuperscript{[24c]} Closely related complexes bearing cyclometalated C\textsubscript{N} ligands have been reported by the research groups of Ikariya,\textsuperscript{[25]} Crabtree,\textsuperscript{[26]} Pfeffer,\textsuperscript{[27]} Feringa,\textsuperscript{[28]} de Vries\textsuperscript{[29]} and others\textsuperscript{[30]} and have been explored in a wide range of catalytic reactions. In most cases, however, the C\textsubscript{N} ligands reported bear an N–H functionality, which can allow for metal–ligand bifunctional catalysis.\textsuperscript{[14, 22–c]}

The mechanism of the TH of imines with the iridicycle catalysts remains speculative. Circumstantial evidence indicates that the hydrogenation proceeds through an outer-sphere or ionic mechanism, in which an Ir\textsuperscript{III} hydride, resulting from the reaction of an iridicycle with a hydrogen source such as HCOOH, transfers the hydride directly to a protonated imine, thus affording the reduction of the imine (Scheme 4).\textsuperscript{[19d, 24b, 31]} Since the imino ligand in the iridicycle is not capable of interacting with the imine substrate and the iridium hydride is coordinatively saturated, the mechanism appears reasonable. However, the details of the mechanism, concerning particularly how the hydride is formed and transferred, were not known. Given the widely reported TH reactions with formate and the

\begin{equation}
\text{Scheme 3. Examples of iridicycle-catalysed hydrogenation and dehydrogenation reactions.}
\end{equation}
lack of mechanistic understanding, we undertook a kinetic and computational study of a model TH reaction [Eq. (1)], aiming to gain insight into the mechanism and map out the pathways of hydride formation and transfer. Described herein are our findings. The precatalyst 1 was previously shown to be highly active in catalysing the TH of various imines with HCO\textsubscript{2}H in protic solvents, such as methanol and trifluoroethanol.[19a,24b,f,j]

We first describe experimental observations of hydride formation from 1 and HCOOH and the hydride transfer to an iminium cation. This is followed by a detailed computational study of possible pathways in the hydride formation (HF) and hydride transfer (HT) steps, initially without solvent and then with implicit and explicit solvent participation considered.

Results and Discussion

Experimental hydride formation and transfer

The reduction of imines by HCOOH with 1 is likely to start with converting 1 into a hydride. Indeed, the reaction of 1 with the HCOOH–Et\textsubscript{3}N (F/T) azeotrope in MeOH resulted in the formation of the hydride 2, which was isolated and structurally characterised [Eq. (2)].[19b] Monitoring by "H NMR spectroscopy showed that the hydride is readily formed. Thus, when complex 1 was treated with the F/T azeotrope (4 equivalents of HCO\textsubscript{2}H) in CD\textsubscript{3}OD in an NMR tube at room temperature, new peaks attributed to hydride 2 appeared, with about 50% of conversion of 1 into 2 in 10 min. The characteristic hydride peak was found at δ = −16.45 ppm. The hydride compound is stable in the solid state under a N\textsubscript{2} atmosphere and even in air at room temperature. For example, after three weeks of storage in air, the "H NMR spectrum of 2 was identical to that of the freshly prepared hydride compound.

An interesting observation in the NMR study is that when CD\textsubscript{3}Cl\textsubscript{2} was used as the solvent for hydride formation, little hydride could be formed (< 5% yield in 18 h). Speculating that this might be due to the coordination of chloride in 1, stoichiometric AgSbF\textsubscript{6} was added into a CD\textsubscript{3}Cl\textsubscript{2} solution of complex 1. However, there was still no hydride peak in the "H NMR spectrum after a period of several hours. These observations indicate that the MeOH solvent plays an important role in hydride formation, corroborating the fact that hydrogenation reactions catalysed by 1 and its analogues always require a protic solvent.[19a,c,24] Indeed, when the solvent for the catalytic reaction in Eq. (1) was changed from methanol to 1,2-dichloroethane (2 mL), the product was formed in only 5% of NMR yield (1 mol% of 1, 80 °C, 1 h). In stark contrast, introducing trifluoroethanol (1 mL) to the reaction mixture gave rise to a yield of 57% under the same conditions.

With the hydride complex in hand, we went on to study the reaction of 2 with a model imine and iminium salt, aiming to shed light on the hydride transfer step (Scheme 5). Upon mixing 2 with the neutral imine (1 equivalent) prepared from acetophenone and p-anisidine in CD\textsubscript{3}Cl\textsubscript{2} in an NMR tube at room temperature, new peaks appeared in the "H NMR spec-
but the disappearance of the hydride signal was very slow. Even after 8 h of mixing, the hydride signal was still observable, and no signal due to the amine product was seen. Notably, no acceleration was observed for this reaction with the addition of the protic solvent trifluoroethanol. In contrast, the reaction of 1 with the corresponding tetrafluoroborate iminium salt was instant, possibly forming an amine-coordinated complex initially.\textsuperscript{[4c]} The hydride signal disappeared in the \( ^1\)H NMR after 10 min together with a solution colour change from red to brown, showing that the transfer of hydride to the iminium salt is much faster than to the imine. Similar observations have been made in related reactions.\textsuperscript{[4d, 18a]} After addition of 1 equivalent of PPh_3 to the reaction mixture, the colour of the solution changed to yellow, as a result of the formation of 3, and the amine product was observed in the \( ^1\)H NMR spectrum.

Further stoichiometric reactions were carried out to confirm the formation of 3. When 1 equivalent of PPh_3 was added to the hydride 2 in CD_2Cl_2, no change was observed in the \( ^1\)H NMR spectrum and the \( ^3\)P NMR only showed the free PPh_3 at \( \delta = -5.6 \) ppm. However, upon addition of 1 equivalent of the iminium salt, the hydride disappeared in a few minutes and the complex 3 appeared at \( \delta = 2.9 \) ppm in the \( ^3\)P NMR spectrum. This complex was also synthesised separately. Thus, treating 1 with 1 equivalent of PPh_3 and AgBF_4 in CH_2Cl_2 at room temperature afforded 3 in 93\% yield (isolated product; Eq. (3)). Similarly, 3 could be prepared in high yield by treating 2 with PPh_3 and HPF_6 (see the Experimental Section).

The results above show that the key intermediate hydride in the TH can be formed easily from the F/T azeotrope in MeOH and that the hydride transfer to the iminium ion, but not to the imine, is facile. However, NMR monitoring of the TH shown in Eq. (1) at ambient temperature revealed no hydride resonance in the \( ^1\)H NMR spectrum while the amine product was formed, indicating that the TH is likely to be controlled in turnover by the hydride formation step. This view also supports the kinetic isotope effect. Thus, when the imine prepared from \textit{para}-methoxylacetophenone and \textit{p}-anisidine was reduced with HCOOH and DCOOD separately, a \( k_H/k_D \) value of approximately 1.9 was measured based on the conversions during the initial 5 min of the TH (60°C, 0.1 mol\% of 1, in TFE), indicative of the involvement of formate C–H bond cleavage in the turnover-limiting step of the TH.\textsuperscript{[31]}

**Kinetic measurements**

To gain further insight into the hydrogenation mechanism, kinetic measurements were carried out for the catalytic reaction shown in Eq. (1). The reaction was carried out in trifluoroethanol at 28°C, with the concentration of one of the components, imine, 1 or HCOOH, varied while holding that of the other two constant. Plotting the ln(initial rate) vs ln[HCOOH], ln[1] and ln[imine] leads to Figure 1. With a slope approaching 2, 1 and 0 when the concentration of HCOOH, 1 and imine was varied, respectively, these profiles suggest that the hydrogenation rate

![Figure 1. Variation of ln(initial rate) with ln(concentration) in the TH shown in Eq. (1) at 28°C (trifluoroethanol as solvent; in MeOH the TH is slower). The rate and concentrations are given in mol L\(^{-1}\) s\(^{-1}\) and mol L\(^{-1}\), respectively. The plots are based on single measurements. For more details, see the Experimental Section.](image-url)
is second order in formic acid concentration, first order in catalyst concentration and zero order in the imine substrate:

\[-\frac{\text{d}[\text{imine}]}{\text{dt}} = k[HCOOH]^2\]  [1].

The independence of rate on the imine concentration points again to the catalytic turnover being limited by the hydride formation step, in line with the NMR observations and kinetic isotopic effects measured. The second-order dependence on the concentration of formic acid is difficult to comprehend, although it may indicate that two HCO\textsubscript{2}H molecules are involved in and/or prior to the hydride formation step. However, caution should be exercised in interpreting this, as the hydrogenation was carried out in the presence of a large amount of NET\textsubscript{4} which is likely to equilibrate with HCOOH (pK\textsubscript{a}=3.75 in water but is expected to be much higher in MeOH and much closer to that of NET\textsubscript{4} in MeOH than in water).\textsuperscript{[12]} It is also noted that it is the formate ion, rather than its conjugate acid, that participates in the hydride formation (see below).

**Computational study**

To gain further insight into the mechanism of imine hydrogenation with 1, we undertook a computational (DFT) study of the reaction using a simplified imine and catalyst. On the basis of the above results, a tentative catalytic cycle is proposed using these model compounds (Scheme 6). The first step of the reaction is to replace the chloride from complex A with formate to form B. Although a formato iridicycle complex has not been isolated, closely related formato complexes are known.\textsuperscript{[8p, 10, 33]} The next step is hydride formation from B to give D via the TS C, the structure of which is yet to be determined and for which three possibilities will be considered. Following the hydride formation, the next step is hydride transfer. Five possible pathways will be scrutinised. We will also compute the effect of solvent molecules, with implicit and explicit MeOH being considered. As indicated above, the cationic iminium, expected to be formed by protonation with HCOOH, instead of the neutral imine, is the species that is reduced (Scheme 4), and the hydride formation step is likely to be turnover-limiting in the overall reaction.

The cyclometalated Ir–Cl complex 1 [Eq. (1)] was used to select the optimal exchange-correlation functional, basis set and pseudopotential. By comparing with the X-ray structure of 1,\textsuperscript{[19b]} PBE and PBE0/SDD (6-31G**) were selected to optimise the geometry and search for the TSs (see the Experimental Section and Table S1 in the Supporting Information for details).

**Suggested pathways for hydride formation**

The mechanism of formation of hydrides from a cyclometalated iridium formato complex has not been reported to date. In this study, we have suggested three possible reaction mechanisms for the hydride formation (HF) step, each of which starts from the coordinatively saturated, 18 e\textsuperscript{−} complex B to form complex D and one CO\textsubscript{2} molecule (see Scheme 7 and details below). The possibility of the imino ligand being reduced to amino in the TH reaction is not considered, as the latter is much less effective than the former in the iridicycle-catalysed TH of imines.\textsuperscript{[19a]}

HF-I (ion-pair mechanism): In this mechanism, the hydride D is formed via a TS in which the formato in B dissociates from the Ir\textsuperscript{III} centre, giving rise to an ion pair between the dissociated formato and the cationic 16e\textsuperscript{−} Ir\textsuperscript{III} complex. C–H bond cleavage affords the hydride D and CO\textsubscript{2}. The Cp\textsuperscript{*} ligand is assumed to be η\textsuperscript{5}-coordinated to Ir\textsuperscript{III} throughout.

HF-II (ring-slippage mechanism): HF-II features a change in the hapticity of the Cp\textsuperscript{*} group from η\textsuperscript{5} to η\textsuperscript{3} by ring slippage when approaching the TS. No dissociation of the formato is envisioned; rather, the interaction of its hydridic hydrogen with Ir\textsuperscript{III} is assumed to account for the formation of D and CO\textsubscript{2}.

HF-III (ligand-dissociation mechanism): The possibility of the imino ligand dissociation from the Ir\textsuperscript{III} centre is featured in HF-III. The breakage of the Ir–N bond offers a coordination site for the hydridic hydrogen of the formato to interact with Ir\textsuperscript{III}, from which D and CO\textsubscript{2} result.

Scheme 6. A tentative catalytic cycle for the TH of a model imine with a model iridicycle catalyst.
Computational study of hydride formation

HF-I: The structures of the complexes B, TS C, and iridium hydride D plus CO₂ were determined at the PBE0 level of theory using the SDD effective core potential for iridium in combination with the 6-31G (d,p) polarised double-zeta basis set for all the other atoms. Complex B features a η¹ coordinated formato ligand, with the Ir–O bond length being 2.086 Å, which is similar to the values of 2.062 Å and 2.155 Å in Ir–formato complexes determined with X-ray crystallography (Figure 2). It also compares well with the Rh–O distances of approximately 2.1 Å in a related [Cp*Rh III/formato] complex. The Ir–H distance is 2.884 Å in B, showing that there is little interaction between the hydridic hydrogen of the formate and the Ir III centre. On going from B to the transition state C, the Ir–H distance changes from 2.884 to 2.216 Å, which is much longer than the Ir–H bond lengths in D (ca. 1.6 Å) and the sum of the atomic radius of iridium and hydrogen (1.55 Å), showing that a covalent Ir–H bond has not been formed in the TS of hydride formation. In line with this, the formate C–H bond length increases by only 5 %, from 1.119 Å in B to 1.176 Å in C. This insignificant lengthening lends support to the kinetic isotope effect mentioned above, which is significantly smaller than the values observed in C–H bond homolysis in formic acid. The Ir–H distance of 2.216 Å is, however, consistent with a hydrogen bonding interaction between the cationic Ir III and the hydridic hydrogen of the formate. Significantly, on going to C, the Ir–O bond is broken and the O–C–O angle changes from 125° in B to 134° in C, with the Ir–O distances being 2.720 and 3.568 Å. The charge of the hydridic hydrogen in B, C and D is —1.2, —0.9 and —1, respectively, based on electrostatic potential (ESP) analysis, revealing that the hydridic ligand in D is indeed hydridic.

In the TS C, the formate bears a charge of —0.331. Together with the long Ir–O distances and the almost intact C–H bond, this indicates that C can be treated as an ion pair. Decomposition of C leads to the hydride D and free CO₂ (the O–C–O bond angle being 178°; Figure 2). The activation energy $E_a$ on going from B to C is 28.4 kcal mol⁻¹ and the product (D + CO₂) is 12.2 kcal mol⁻¹ thermodynamically more stable than the species B, at the PBE0 level of theory. Notably, breaking the C–H bond of formate is not the main energy cost in forming the hydride along HF-I. Rather it is the breaking of the Ir–O bond accompanied with the charge separation that may primarily account for the cost.

Figure 2 also shows the frontier orbitals of the species involved in HF-I. As may be expected, the HOMO in C is primarily located on the carboxylate unit of the formate ligand. In complex D, the Ir–O bond contributes significantly to the HOMO, indicating the hydride to be nucleophilic, and not surprisingly, there is no orbital overlap between the Ir III and CO₂. The orbital of the hydride D in the LUMO diagram is more localised than that in the HOMO diagram.

HF-II: This pathway features the ring slippage of the Cp* ligand from η⁵ to η³ coordination on going from B to the TS of hydride formation. The TS was found and verified, as shown in Figure 3. In comparison with the species C in HF-I, the most notable feature here is that in the TS, the Ir–O bond remains intact (bond length of 2.187 Å in HF-II vs 2.720 Å in HF-I), while
the Ir–H bond has formed to a significant degree, with a bond length of 1.818 Å. Figure 3 also displays the reaction coordinate diagram, revealing the activation energy to be 32 kcal mol\(^{-1}\) at PBE level of theory. This value is 8 kcal mol\(^{-1}\) higher than that computed for the ion-pair mechanism (pathway HF-I, 24.2 kcal mol\(^{-1}\) at PBE; see the Supporting Information, Table S1), suggesting that the pathway HF-II is less favourable than HF-I in hydride formation.

HF-III: To investigate the viability of this mechanism, we attempted to find a stable intermediate, in which the nitrogen is dissociated from iridium. However, this structure always reverts to the original complex B. We therefore concluded that this pathway is unfeasible. Thus, of the three HF pathways examined herein (HF-I–III), the ion-pair mechanism HF-I is the most favourable.

Suggested pathways for hydride transfer

In this section we consider the second half of the catalytic cycle, that is, the hydride transfer (HT) step, for the reduction of imines to amines catalysed by iridicyles. We have proposed five possible reaction pathways, each starting with the hydride D (Scheme 8). The reaction mechanism along each pathway is outlined first and then discussed in detail in the next section.

HT-I: The iminium substrate is stabilised with the formate through hydrogen bonding. However, the Cp* ligand remains \(\eta^5\)-coordinated to Ir\(^{III}\). Thus, there is no vacant site for the iridium to bond to the oxygen atom of the formate. Therefore, no interaction between the iridium and formate is expected in the TS of HT-I.

HT-II: The iminium substrate is stabilised with the formate through hydrogen bonding, as in HT-I. In the TS, \(\eta^1\) to \(\eta^3\) ring slippage occurs, which would permit the coordination of the formate to Ir\(^{III}\). The formation of the Ir–O bond would be accompanied with the weakening of the Ir–H bond and the formation of the new H–C bond, leading eventually to the product amine and the iridium formato complex B.

HT-III: Pathway HT-III assumes no involvement of the formate ion prior to and at the TS of hydride transfer. The iminium is reduced through direct transfer of the hydride to the iminium carbon atom. Two possible products are considered. In one of them, the resulting amine is free (PRO1), whereas in the other the amine coordinates to Ir\(^{III}\) (PRO2). The formate then reacts with the cationic iridium complexes, forming complex B.

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Figure 2. Structural properties and molecular orbitals of species B, C and D along the pathway HF-I (selected bond lengths and angle are given). Grey: C; white: H; red: O; blue: N; turquoise: Ir.

Figure 3. Reaction coordinate diagram for hydride formation along the pathway HF-II. The initial and final structures were fully optimised. Those constrained structures in between were optimised by NEB method.
HT-IV: This pathway assumes that the imine, not the iminium, interacts with D. Following the hydride transfer to the carbon of the imine, an amido intermediate is formed. Protonation of the intermediate by formic acid releases the amine and affords B.

HT-V: This pathway again starts with the imine; but in the TS, a change in the hapticity of the Cp* group from $\eta^5$ to $\eta^3$ by ring slippage occurs, permitting the imine coordination to the Ir$^{III}$ during the hydride transfer. The same amido intermediate product as that in HT-IV is formed.

Computational study of hydride transfer

HT-I: In this pathway, the iminium cation is assumed to be stabilised by the formate anion. First of all, the most stable configurations of the starting compounds, intermediate (D + iminium + formate, denoted as INT) and the products (B + amine, denoted as PRO) were searched. Four possible configurations for INT and PRO were computed, and their energies and structures are reported in Figure S2. The most stable configurations were selected to search for the TS, which was identified with an energy barrier of 13.0 kcal mol$^{-1}$. The configurations and relative energies of INT, TS and PRO are all shown in Figure 4. With the Cp* ligand being $\eta^3$-coordinated, the Ir–H and Ir–O bond lengths in the TS are 1.843 and 3.984–4.404 Å, respectively, showing that the formate is not bound to Ir$^{III}$ in the hydride transfer step.

HT-II: Several estimated TS models were constructed, based on the TS of HT-I, using the STQN method without and with polarisable continuum model (PCM) and dispersion corrections. All
of the results show that in the estimated TS, when the oxygen atom of formate is close to Ir(III), at $d$(Ir–O)\(\approx\) 2.28 and $d$(Ir–H)\(\approx\) 1.85 Å, the formate preferably bonds to the iminium and moves away from Ir(III). The resulting structure resembles either the INT or TS of HT-I in Figure 4. We therefore concluded that the HT-II mechanism is unfavourable. Bäckvall and co-workers suggested that, in imine hydrogenation with the Shvo catalyst, ring slippage of the Cp ring is possible, with an energy barrier of 15 kcal mol\(^{-1}\).[4c] although further studies have shown an outer-sphere mechanism involving no coordination of the imine to Ru to be more favourable.[6e]

**HT-III**: The configurations and relative energies for the starting compounds (D, iminium, INT), TS of hydride transfer, and the products (PRO1 and PRO2) are shown in Figure 5. Interestingly, the PRO1 immediately after the TS is a relatively stable cationic Ir(III) species, being –0.53 kcal mol\(^{-1}\) more stable than the INT. To some degree, this is because the Ir–H bond has not broken completely, as evidenced by the Ir···H distance of 1.983 Å. The identification of this species is interesting, as it indicates that the dehydrogenation of amines catalysed by iridicyles[24e] could proceed through direct hydride transfer. Soon after the hydride transfer to the iminium, the resulting amine coordinates to the Ir(III) centre, forming a stable product, PRO2, which is 13.7 kcal mol\(^{-1}\) more stable than the INT. Thus, PRO1 is a transient intermediate in the formation of PRO2.

The TS of the hydride transfer is verified. It occurs when the Ir–H bond length changes from 1.615 Å to 1.646 Å and the H–C distance approaches 1.853 Å. This small change in the Ir–H bond length and the long C–H separation indicate that the TS identified is early and hence may be expected to be of a low barrier. Indeed, the $E_a$ along this hydride transfer pathway is only 7.7 kcal mol\(^{-1}\), which is 20.7 kcal mol\(^{-1}\) lower than the $E_a$ in the hydride formation step. No Cp* ring slippage or C=–N bond interaction with Ir(III) is involved. However, the phenyl ring of the iminium substrate is 3.2–3.6 Å away from the imino unit of the Ir(III) complex, indicating weak interactions between these two fragments. Considering that the hydride ligand in D bears a charge of –1, the electrostatic interaction between D and the iminium cation presumably play a key role in facilitating the formation of the TS.

**HT-IV and HT-V**: Various orientations of the amine product interacting with the Ir complex were considered. However, the resulting amido product was found to be 10.3 kcal mol\(^{-1}\) less stable than the reactant (species D, imine). Thus, the energy barrier of this endergonic reaction is expected to be higher than the energy barrier in HT-III, which is 7.7 kcal mol\(^{-1}\). The trend remains unchanged even with consideration of PCM and

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dispersion corrections. As a result, we conclude that pathways HT-IV and HT-V are less favourable than HT-III.

Taken together, the calculations suggest that the hydride transfer is most favourable along the pathway HT-III amongst the five possibilities considered herein.

**Solvent effects on the hydride formation and transfer**

Protic solvents have been shown to affect the mechanism and rate of TH of ketones with the Noyori–Ikariya bifunctional catalysts. For the current mono-functional iridicycle catalyst, the alcohol solvent used in the reaction is known to impact on the TH of imines (see above) and so could enter into specific interactions with the catalyst, affecting the TH mechanism or the energy barriers. In this section we present calculations aimed at addressing these issues. The solvent effect was modelled firstly by treating the solvent implicitly according to the PCM and then explicitly by introducing one single MeOH molecule. In both cases, only the most favoured pathways HF-I and HT-III were considered.

**Effect of implicit methanol**

Table S3 (see the Supporting Information) reports the effect of the solvent on the activation energies along pathways HF-I and HT-III, PCM being used to simulate the methanol environment. The results show that the activation energies $E_a$ differ by 7.0 and 0.3 kcal mol$^{-1}$ for the hydride formation and hydride transfer, respectively, compared to those in the gas phase. Thus, the changes in activation energy computed according to PCM indicate that solvent treated at this level has significant influence on the rate-limiting hydride formation step in the imine reduction with the iridicycle catalyst. This may not be surprising, given the charge separation in the TS of HF-I, which is expected to be stabilised by a polar medium.

**Effect of explicit methanol**

We next introduced an explicit MeOH molecule in the vicinity of the starting compounds, transition states and products in both the hydride formation and transfer steps. Following geometry optimisation, several initial configurations were examined. The most stable $B + MeOH$ (INT), the product $D + CO_2 + MeOH$ (PRO), and the corresponding TS along the hydride formation pathway HF-I are depicted in Figure 6. As can be seen, the methanol molecule forms hydrogen bonds to the formate oxygen in $B$ and the $CO_2$ in the product. Most interestingly, a strong hydrogen bond, with an $O$--$H$ distance of 1.663 Å, is formed in the TS, driven clearly by the negative charge developed at the formate. Not surprisingly, it is found that the $E_a$ drops by 10.6 kcal mol$^{-1}$, from 28.4 kcal mol$^{-1}$ without considering methanol to 17.8 kcal mol$^{-1}$ with one explicit methanol introduced in the hydride formation step at PBE0. It is also interesting to note that the presence of MeOH does not alter significantly the trend of formate $C$--$H$ bond length change on going from the INT to TS (1.113 to 1.156 Å with MeOH vs 1.119 to 1.176 Å without it). This lowered activation energy compares well with the Gibbs free energy barrier of 16.5 kcal mol$^{-1}$ found in the intramolecular decarboxylation of formate by a Rh$^{IV}$ complex. Recently, Lewis acids have been suggested to play a similar role in promoting the hydride formation from an iron-formato species. Earlier, water was shown to accelerate the reverse process, that is, hydrogenation of $CO_2$ through hydrogen bonding. We note that the TS of the hydride formation under investigation features the separation of the formate from the Ir$^{III}$ centre, rather than breaking of the formate $C$--$H$ bond, with or without solvent involvement.

Figure 7 shows the configurations and relative energies of the starting compounds (INT), TS, and the product (PRO2) in the presence of one MeOH molecule in the hydride transfer step along the pathway HT-III. As may be expected, the methanol molecule hydrogen-bonds to the $N$--$H$ proton in each case. As a result, the activation energy drops by 5.5 kcal mol$^{-1}$, from 7.7 kcal mol$^{-1}$ without considering methanol to 2.2 kcal mol$^{-1}$.
with one explicit methanol considered. In comparison, the effect of MeOH on the stability of PRO2 is insignificant.

The energy profiles for hydride formation (HF) and hydride transfer (HT) without and with one explicit methanol molecule included are summarised in Figure 8. Without the involvement of methanol, the reaction requires 28.4 kcal mol\(^{-1}\) to form the iridium hydride D and one CO\(_2\) molecule, relative to the formate-coordinated species B. In complex D, there still exist weak interactions between the catalyst and CO\(_2\) as judged by the distances of 2.463–3.408 Å between (N–H···O–(CO)) and (Ir–H···O–(CO)) (Figure 2). As a result, an energy of 2.5 kcal mol\(^{-1}\) is needed to separate D and CO\(_2\).

When the iminium ion is brought to interact with the hydride D, the energy drops by 20.7 kcal mol\(^{-1}\), probably due to stabilisation of the cation by the hydride in vacuum. After overcoming a barrier of 7.7 kcal mol\(^{-1}\) in transferring the hydride to the iminium ion, an amine-coordinated iridium cationic complex is formed. This energy barrier is computed with respect to D plus one iminium ion. Due to the different charge states, 0 for the HF and +1 for the HT, we have not compared the HF and HT by using the same energetic references. The amine-coordinated product PRO2 is found to be 13.7 kcal mol\(^{-1}\) more stable than the reactants. This is at least partly due to the amine coordination, which stabilises the resulting cationic Ir\(^{3+}\). Additionally, PRO2 is stabilised by the π–CH\(_3\) interaction between the phenyl group of the amine and the methyl group of Cp*.

When the solvent molecule is incorporated, the values of \(E_a\) in the hydride formation step and hydride transfer step are lowered to 17.8 and 2.2 kcal mol\(^{-1}\), respectively. Thus, the presence of the solvent methanol significantly lowers the energy barriers of both the hydride formation and hydride transfer steps. However, the effect on the hydride formation is more significant to the overall reaction, and it remains the rate-determining step of the catalytic cycle, with or without the methanol.

**Conclusion**

For the first time, the iridicycle-catalysed TH of imines with formic acid has been studied mechanistically in a systematic way. Our NMR and kinetic studies suggest that the TH is turnover-limited by the hydride formation step. This corroborates well with the findings made from DFT calculations. The calculations revealed that, amongst a number of possibilities, hydride formation from the single-site iridicycle proceeds probably by
an ion-pair mechanism, whereas the hydride transfers to the imino bond by an outer-sphere mechanism involving no coordination of the C=N bond to the metal. In the gas phase, in the most favourable pathway, the activation energies in the hydride formation and transfer steps are calculated to be 26–28 kcal mol$^{-1}$ and 7–8 kcal mol$^{-1}$, respectively. 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 approximately 18 kcal mol$^{-1}$ and 2 kcal mol$^{-1}$, respectively. Thus, the TH in question is rate-limited by the hydride formation step and methanol lowers the activation energy. However, somewhat counterintuitively, only insignificant formate C=H bond cleavage is featured in this step. The DFT investigation further shows that methanol participates in the transition state of the hydride formation, hydrogen-bonding to the formate anion and thereby stabilising the ion pair. This finding is important, as it explains why TH reactions with the iridacycle catalysts necessitate the use of polar protic solvents.

**Experimental Section**

**Synthesis of 3**

An oven-dried Radley tube was cooled to room temperature under $N_2$, charged with iridium hydride complex 2 (30 mg, 0.052 mmol) and PPh$_3$ (13.5 mg, 0.052 mmol) and degassed with $N_2$. Upon introducing fresh distilled CH$_2$Cl$_2$ (10 mL), the mixture turned into a purple-red solution. Subsequently, a HPr$_x$ solution (7.7 µL, 0.052 mmol) in CH$_2$Cl$_2$ was added to the reaction mixture, the colour of which changed to dark red in several seconds. The reaction mixture was stirred at room temperature under $N_2$, with the colour changing into light yellow in half hour. After stirring for another half hour, the mixture was washed with a 10% NaOH aqueous solution and dried over anhydrous Na$_2$SO$_4$. Complex 3 was obtained as yellow powder (42 mg, 96% yield). $^1$H NMR (300 MHz, CDCl$_3$): δ = 1.34 (s, 15H), 2.21 (s, 3H), 3.86 (s, 3H), 6.47 (brs, 1H), 6.84–6.90 (m, 3H), 6.99 (brs, 2H), 7.16–7.26 (m, 4H), 7.31 (d, J = 8 Hz, 5H), 7.47–7.63 (m, 6H), 7.73 ppm (brs, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ = 7.84, 18.1, 28.7, 54.8, 96.5, 113.1, 117.7, 123.9, 125.5, 128.3, 129.4, 130.6, 132.2, 136.5, 141.0, 151.5, 158.2, 184.7 ppm; $^3$P NMR (121 MHz, CDCl$_3$): δ = 3.0 ppm; HRMS (ESI): m/z calc for C$_{44}$H$_{43}$IrN$_2$OP: 839.2742; found: 839.2686.

**Kinetic measurements**

The initial rates were calculated by extrapolating the conversion of the imine to the starting point of a TH reaction. The conversions were measured periodically when the concentration of one of these components was varied, HCOOH, imine and 1. Variation of [HCOOH] was achieved by varying the azeotropic [F/T]: An oven-dried TH reaction mixture and hydride transfer steps are calculated to be 26–28 kcal mol$^{-1}$ and 7–8 kcal mol$^{-1}$, respectively. 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 approximately 18 kcal mol$^{-1}$ and 2 kcal mol$^{-1}$, respectively. Thus, the TH in question is rate-limited by the hydride formation step and methanol lowers the activation energy. However, somewhat counterintuitively, only insignificant formate C=H bond cleavage is featured in this step. The DFT investigation further shows that methanol participates in the transition state of the hydride formation, hydrogen-bonding to the formate anion and thereby stabilising the ion pair. This finding is important, as it explains why TH reactions with the iridacycle catalysts necessitate the use of polar protic solvents.

**Computation**

Since imine reduction catalysed by the cyclopentadienyl iridium imido complexes had not been theoretically investigated before, it was essential to determine the appropriate computational methodology in advance. Density functional theory (DFT) calculations were carried out by using the DMol$^3$, Gaussian, and CP2K codes. In DMol$^3$, the wave function is expanded in a localised atom-centred basis set with each basis function defined numerically, on a dense radial grid. In this study, we employed the double-numerically-polarised (DNP) basis set. Each basis function was restricted to within a cutoff radius of 4.7 Å. The electron density was approximated by using a multipolar expansion up to octupolar. For total energies and geometry optimisation, the gradient corrected PBE exchange-correlation functional was employed. The inner core-electrons for iridium were represented by the Density Functional Semi-core Pseudo Potentials (DSPP), which was generated by fitting all-electron relativistic DFT results, and specifically developed to improve the accuracy of DMol$^3$ calculations. In the optimisation procedure, the geometry was considered to be converged when the energy change was less than 10$^{-5}$ Hartree and the gradient was less than 2×10$^{-5}$ HartreeÅ$^{-1}$. In Gaussian, the PBE0, B3LYP and MPW1PW91 hybrid exchange-correlation functionals were employed. We also compared different basis sets - 6–31G(d,p), 6–311G(d,p), 6–31+G(d,p), 6–311+G(d,p) - for hydrogen, carbon, nitrogen and oxygen; for iridium, we used the SDD and LANLDZ2D basis set coupled with the SDD and LANLDZ2P pseudopotentials respectively. In CP2K, the PBE exchange-correlation functional was employed, together with the TZV2P-MOLOPT-GTH basis set for the hydrogen, carbon, nitrogen and oxygen, and the DZVP-MOLOPT-SR-GTH basis set together with the GTH pseudopotential for the heavier iridium.

With regard to computing activation energies, there is no nominally best level of theory, as it depends on the systems. In the beginning, the constrained optimisation by fixing the guessed reaction coordinate was conducted. Nevertheless, this approach failed in searching for the two transition states (TS) in the hydride formation and hydride transfer reactions. Therefore we turned to the Synchronous Transit-Guided Quasi-Newton (STQN) method using Gaussian. In some cases (HF-II), we also employed the Nudged
Elastic Band (NEB) [20] method using CP2K to verify the TS found by STQ method. The NEB method was mainly used to locate the TS in the H-Fll pathway. To compare the energy barriers, The NEB approach was also applied in the HF-II pathway.

The implicit solvent effects were examined by using the polarisable continuum model (PCM) [21], which provides a simple but useful estimate of solvation energies, and by introducing one methanol molecule into the model compounds. Those structures were all fully optimised in PCM.

Counterpoise correction, London-dispersion corrections, DFT-D3 and DFT-D3 (BJ), considering Becke-Johnson damping, have been examined in some cases. The results reveal that the dispersion correction slightly shortens the unbound bond lengths of the minima (INT and PRO) within about 3 Å. However, in general, the dispersion effect does not have a significant influence on the activation energies.

Regarding the structures, similar configurations remain with shorter or longer bond lengths in both hydride formation and hydride transfer (for details, see the Supporting Information, Table S3 and Figure S1).

Zero-point energies, enthalpies and Gibbs free energies were examined for several pathways (see the Supporting Information, Table S4). Gibbs free energies have a more evident influence on the energy barrier in the hydride transfer step, where two fragments interact with each other, indicating that the vibrational contributions are more pronounced in the HT step. However, in general, the results show that the determination of preferred mechanism is not affected by computing either only electronic energies or with consideration of zero-point energy correction, enthalpies and Gibbs free energies (at 298.15 K and 1 atm) in this system. Based on the thermodynamic data, we consider the electronic energies reported in this manuscript reliable.

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Workin’ on an imine: Transfer hydrogenation of imines by formic acid with a single-site iridicycle catalyst has been investigated by density functional theory (DFT), NMR spectroscopy, and kinetic measurements. The mechanism is shown to be turnover-limited by the hydride formation step, the barrier of which is significantly lowered by a protic solvent.

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Transfer Hydrogenation

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