Mechanisms of the H₂- and Transfer Hydrogenation of Polar Bonds Catalyzed by Iron Group Hydrides

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This perspective reviews our efforts to use a mechanism-based approach to develop catalysts for the asymmetric hydrogenation of prochiral ketones and imines. A goal is to discover catalysts based on the abundant 3d transition metals, particularly iron.

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Prof. Robert H. Morris was born in Ottawa in 1952. He received his Ph.D. from the University British Columbia in 1978 and held postdoctoral positions at the AFRC Unit of Nitrogen Fixation, Sussex, U.K., and at the Pennsylvania State University before starting at the University of Toronto in 1980 as Assistant Professor. He is now Professor of Chemistry, a Fellow of the Royal Society of Canada and of the Chemical Institute of Canada. He was Acting Chair and then Chair of the Chemistry Department from 2008 to 2013. He received the Rutherford Medal from the RS (Canada), the Alcan Lecture Award from the CIC and the Award for Pure or Applied Inorganic Chemistry from the CSC, the 2017 Inorganic Mechanisms award from the RSC, and 2017 Canadian Green Chemistry and Engineering Network Award and a Killam Research Fellowship from the Canadian Council for the Arts. He is an author of 240 journal articles, 11 book chapters and holds several patents. His research interests include organometallic chemistry and catalysis, particularly involving the iron group elements.

This perspective is based on the RSC Inorganic Mechanism Award lecture presented at the Dalton Conference at the University of Warwick in April 2018.
Introduction

The process of the hydrogenation of polar bonds is academically interesting and industrially important. Fragrance companies selectively hydrogenate the aldehyde C=O bond while leaving the non-polar C=C bond untouched in order to produce fragrant alcohols (e.g. Figure 1, a). Homogeneous Noyori catalysts based on ruthenium show this selectivity and operate by a bifunctional metal hydride amine N-H attack on the aldehyde as shown. Pharmaceutical companies install stereogenic centres enantioselectively by the use of carefully crafted homogeneous catalysts (e.g. Figure 1, b). Alcohols produced by the selective hydrogenation of the C=O bond of esters in bio-derived oils are used in personal care products such as soaps and shampoos. Currently chromium-based heterogeneous catalysts are used to carry out this hydrogenation at elevated temperatures and pressures but recently iron-based catalysts have been reported to do this (e.g. Figure 1, c). Ruthenium- and iron-based homogenous catalysts have been reported for the hydrogenation of the C=O bonds of carbon dioxide to give formic acid or methanol, important renewable energy carriers. New iron catalysts with inexpensive ligands could have a great impact here. The largest industrial asymmetric hydrogenation process is the Metolachlor process for making a bioactive amine for use as a herbicide. It is prepared by the hydrogenation of the C=N bond of a sterically hindered imine (Figure 1 d). A homogeneous iridium catalyst with an enantiopure Josiphos ligand is an exceptional catalyst for this process and may transfer its hydride to the C=N bond in the inner or outer coordination sphere. As well, the hydrogenation of the carbon nitrogen triple bonds of dinitriles to make diamines is important for the polyamide industry and recently active homogeneous catalysts based on cobalt and iron have been reported to do this.

Figure 1. The transfer of hydride and proton equivalents to polar bonds in the outer coordination sphere of a homogeneous transition metal hydride catalyst.

Noyori’s asymmetric hydrogenation catalysts

Particularly well crafted precatalysts are the complexes trans-RuCl₂(R-binap)(R-daipen) developed in the Noyori lab (Figure 2). When activated by a strong base (KOH, KO’Pr or KO’Bu) in 2-PrOH (PrOH will be used in this article), catalysts are generated that are highly active (turnover frequency TOF > 50 s⁻¹) and productive (turnover number TON > 10⁶) when used under 45 atm H₂. These can be used to make enantiopure aryl alcohols that are used for the preparation of antidepressants, antipsychotics and antihistamines, for example.
Dichloride to dihydride mechanism

Our interest in the synthesis and characterization of dihydrogen and hydride complexes of the iron group elements led us to investigate the hydrides present in the Noyori system. We suspected that dihydrides of the type RuH$_2$(diamine)(diphosphine) were formed on the basis of previous studies of ruthenium chemistry. Indeed Abdur-Rashid et al. found that cis-RuH$_2$((R,R)-dach)(PPh$_3$)$_2$, dach = 1,2-trans-diaminocyclohexane was an active catalysts for ketone hydrogenation.\textsuperscript{14} We later found that the starting cis-dihydride isomer is a precatalyst and that it is the trans-dihydride isomer that is the active catalyst.\textsuperscript{15} Noyori’s group also suspected that the active catalysts were hydrides RuH(X)(PR$_3$)$_2$(diamine), either of the type with X = H or OR.\textsuperscript{2}

Previous studies of the formation of dihydrogen complexes by our group in the 1980s showed that trans dihydrides readily form from dichloride precursors in THF solvent by the successive deprotonation of intermediate dihydrogen complexes (Scheme 1).\textsuperscript{16} The removal of the chloride ligands by sodium or potassium cations is important to allow dihydrogen to coordinate and become acidic. In fact a potassium effect was noted in the activation of a Noyori dichloride catalyst system.\textsuperscript{17} The kinetically-formed trans-dihydride appears after two successive dihydrogen intermediates are deprotonated. As shown a trans-dihydride is often in dynamic equilibrium with its cis isomer.\textsuperscript{18}
Scheme 1. The proposed mechanism for the conversion of complex MCl$_2$(diphosphine)$_2$ to MH$_2$(diphosphine)$_2$, M = Fe, Ru, Os, diphosphine = PR$_2$CH$_2$CHPR$_2$, R = Ph, Et (also meso-tetraphos complexes).

For the Noyori catalyst systems, we were able to generate and identify the trans-dihydride complexes trans-RuH$_2$(R-binap)(R,R-diamine), diamine = dpen (NH$_2$CHPhCHPhNH$_2$), daipen (see Figure 2) and tmen (NH$_2$CMe$_2$CMe$_2$NH$_2$) in solution by starting from the new complexes trans-RuHCl(R-binap)(R,R-diamine). Using the tmen ligand which is stable with respect to hydride elimination, we were able to crystallize the dihydride complex trans-RuH$_2$(R-binap)(tmen) and the amidohydride complex RuH(PPh$_3$)$_2$(NHCMe$_2$CMe$_2$) which are stable with respect to dihydrogen elimination or hydride elimination from the diamine or amide ligands.

The isolation of these well-defined hydrides that start catalysis without an induction period allowed us to do a simple kinetic investigation of the hydrogenation of acetophenone. The only variables were the concentrations of the substrate, hydrogen, catalyst and product alcohol in benzene (Scheme 2). 

\[
\text{acetophenone} \xrightarrow{\text{[Ru]} \text{H}_2 (8-23 \text{ atm}) \text{ benzene, } 28 \degree C} \text{phenylmethanol}
\]

Scheme 2. The hydrogenation of acetophenone in benzene catalyzed by the complexes trans-RuH₂(R-binap)(NH₂CMe₂CMe₂NH₂) or RuH(PPh₃)₃(NHCMelCMe₂NH₂).

The kinetic isotope effect was measured using pressures of D₂ gas. The reactions were done in a pressure reactor, at first with a method to remove samples by syringe, and later, with a dip tube as shown in Figure 4. The samples were analyzed by gas chromatography on a chiral column to separate the enantiomers of the alcohol in the case of the R-binap complex.

Figure 4. The thermostated pressure reactor used for our kinetic studies (the bath around the reactor has been removed). Reproduced with permission from the supporting material of M. Zimmer-De Iuliis and R. H. Morris, J. Am. Chem. Soc., 2009, 131, 11263-11269; https://pubs.acs.org/doi/abs/10.1021/ja9043104. Copyright (2009) American Chemical Society.
Proposed mechanism for ketone hydrogenation by the model catalyst\(\text{trans-RuH}_2(\text{binap})(\text{NH}_2\text{CMe}_2\text{CMe}_2\text{NH}_2)\) in benzene

The proposed catalytic cycle for the hydrogenation of ketones by this complex in benzene is shown in Figure 5a. Dihydrogen is split heterolytically across the ruthenium-amide bond of the 5-coordinate amidohydride complex and then a hydride and proton are transferred to the ketone in the outer coordination sphere to give the product and regenerate the amidohydride complex. There is much evidence for this mechanism. As mentioned the dihydride and amidohydride complexes have been synthesized and characterized by single crystal X-ray diffraction, NMR and IR spectroscopy. The ketone reacts with the dihydride complex and dihydrogen with the amidohydride complex as expected. RuHCl(binap)(tmen) does not react with ketones and is not a catalyst without base added; the high trans influence of hydride in the dihydride complex is important to make the hydride nucleophilic. Similarly \(\text{trans-RuH(OR)(PPh}_3)_2(\text{tmen})\) is also inactive.\(^\text{22}\) The hydrogenation of acetophenone in benzene with no additives consistently produces 1-phenylethanol in 65% ee (\(S\)). Catalysis using deuterium gas gave a kinetic isotope effect (KIE) \(k_{\text{H}_2}/k_{\text{D}_2} = 2.0 \pm 0.1.\(^\text{21}\)

The rate law of the reaction at the concentrations of substrate and catalyst employed was found to be expressed by eq 1.

\[
\text{rate} = k[\text{H}_2][\text{Ru}] \quad (1)
\]

This suggests that heterolytic splitting of dihydrogen is turnover limiting since the rate law is independent of ketone or product alcohol concentration over the concentrations that were investigated. This was supported by Density Functional Theory (DFT) calculations done on simplified structures.\(^\text{20}\) The highest energy transition state was found to be the splitting of dihydrogen while the hydride transfer and proton transfer steps were lower in energy and thought to be concerted.\(^\text{19,20}\) The KIE for the dihydrogen splitting step was calculated using DFT to be 2.1 when all of the NH groups and the hydride in a model of the amido complex are deuterated.\(^\text{21}\) More recently the hydride transfer step has been analyzed by DFT methods using all of the atoms of the catalyst system and found to occur without NH cleavage (not concerted) and the dihydrogen splitting to occur between the metal and an outersphere alkoxide.\(^\text{23}\)
Figure 5. A simplified proposed mechanism of the hydrogenation of ketones catalyzed by ruthenium hydride diamine complexes. (a) the ground state and transition state species; (b) the corresponding results from a DFT calculation showing the geometry of the intermediate dihydride and amidohydride complexes and the two transition states along with their free energies relative to that of the amidohydride complex.

The proposed mechanism is simplified because it was recognized in NMR studies that the amido complex reacts with acidic CH bonds in the enolizable ketone (to form an enolate complex) and the dihydride and the amido complexes can be protonated by the product alcohol to give alkoxide complexes. However these reactions were observed under much higher concentrations of ruthenium than exist in the catalyst solution and so these equilibria may not be significant in benzene. In iPrOH reactions with alcohol are significant and a base such as KOtBu has to be added to restore catalytic activity. This is understandable considering that the concentration of [Ru(H₂)(binap)(dpen)]⁺ in neutral iPrOH is approx. 10⁻¹⁰⁻²⁴ high enough to protonate trans-RuH₂(binap)(dpen), considering that the pKₐ of [Ru(H₂)H(binap)(dpen)]⁺ in iPrOH can be estimated to be 13 (see below). We attributed the beneficial effect of potassium salts reported by Hartmann and Chen on the rate of the Noyori system in iPrOH to the need to activate the catalyst by the formation of KCl (see above). Hartmann and Chen found that potassium alkoxides gave the best rate and proposed that the potassium was involved in both dihydrogen splitting and hydride transfer steps (see below).

The crystal structure of the dihydride complex (Figure 3 above) provided a clue to the origin of the enantioselectivity of the Noyori catalysts towards ketone reduction where the R-binap complex produces the S alcohol. When incoming acetophenone forms a hydrogen bond to the axial NH of the dihydride catalyst, the large aryl group will preferentially position itself away from the stereogenic aryl
groups in yellow on the catalyst (Figure 6). This will result in attack by the hydride on \( Si \) face of the ketone.

![Figure 6. Model of the attack by \( trans-RuH_2(R\text{-}binap)(R,R\text{-}dpen) \) on the \( Si \) face of acetophenone](image)


**Noyori’s mechanistic investigation: hydrogenation of acetophenone using \( RuH(BH_4)(tol\text{-}binap)(dpen) \) in \(^3\text{PrOH} \) with base**

Hartmann and Chen showed that the kinetics in isopropanol starting with a Noyori dichloride precursor \( \text{RuCl}_2(R\text{-}binap)(R,R\text{-}dpen) \) are complex because of a slow step in the formation of the active hydride catalysts.\(^{27} \) Sandoval et al used the fast-activating precatalyst, \( trans-RuH(BH_4)(S\text{-}tol\text{-}binap)(S,S\text{-}dpen) \) in \(^3\text{PrOH} \), the optimum solvent for this catalyst. A base was added to activate the catalyst, either potassium tert-butoxide or Schwesinger’s \( P_4^{\text{tBu}} \) base, \( \{(Me_2N)_3PN\}_3PN^{\text{tBu}} \). Both of these bases are leveled in strength to that of \( \text{[PrO]}^- \) in \(^3\text{PrOH} \). The cation that will ion pair with this alkoxide is \( \text{[K(OH}_{3}\text{Pr)}n]}' \) or \( \text{[\{(Me_2N)_3PN\}_3PN^{\text{tBu}}]'}. \) A very interesting base dependence on the effective rate constant was reported (Figure 7) where two regimes were observed: regime 1, where there is a “volcano” shaped region centered on the critical base concentration of 0.01 M (pH approximately 18); regime 2 where a constant, lower rate constant (for KO’Pr), or declining rate constant (for \( P_4^{\text{tBu}} \)) with greater base concentration where the pH is in the range of approximately 19 to 21. The rate constant is up to twice as large for \( P_4^{\text{tBu}} \) and four times as large for KO’Bu in regime 1 than in regime 2. When \( D_2 \) is used, a large kinetic isotope effect (KIE) is observed for regime 1 and a KIE of \( k_{D2}^{102} / k_{D2}^{202} = 2 \) for regime 2. In all cases R-1-phenylethanol is the major enantiomer of the ketone hydrogenation reaction with a constant 82% enantiomeric excess (ee) independent of the conditions. This suggests that the hydride-transferring intermediate, likely \( trans-RuH_2(R\text{-}tol\text{-}binap)(dpen) \), is always the same independent of the conditions. Other hydride transferring species have been suggested that contain potassium\(^{17,29,30} \) but these might be expected to change the enantioselectivity of the hydride transfer reaction and are not relevant when the \( P_4^{\text{tBu}} \) base is used.
Noyori and coworkers proposed the existence of a two cycle mechanism, one for each regime (Scheme 3). At the optimum pH of regime 1 they attributed the greater rate constant to a catalytic cycle involving the deprotonation of the intermediate dihydrogen complex $\text{trans-}[\text{Ru(H$_2$)H(S-tol-binap)(S,S-dpen)}]^+$, presumably by an alkoxide in the outer sphere. They point out the reasonable assumption that the relative acidity of the $\eta^2$-H$_2$ ligand is greater than that of diamine NH groups and that the amido complex RuH(S-tol-binap)(S,S-dpen-amido) would be protonated under these conditions to give a cation that will likely bind dihydrogen. More recently detailed DFT calculations by Dub and Gordon indicate that the hydride transfer to the ketone involves the deprotonation of the intermediate dihydrogen complex $\text{trans-}[\text{Ru(H$_2$)H(S-tol-binap)(S,S-dpen)}]^+$, which can then directly split dihydrogen to generate the dihydride complex, thus bypassing the amido complex. In the higher base concentration regime 2, Noyori and coworkers proposed that the cycle is the same as the one proposed for our RuH$_2$(R-binap)(tmen) system above, involving the amido intermediate RuH(S-tol-binap)(S,S-dpen-amido), that is responsible for the heterolytic splitting of dihydrogen. In fact the KIE of 2 for this regime is the same as the one we measured for the RuH$_2$(R-binap)(tmen) system ($k_{H2}/k_{D2} = 2.0\pm0.1$).

The critical effective pH of regime 1 is reminiscent of the kinetics of enzymes where the $pK_a$ of functional groups are adjusted by the protein to achieve a maximum rate at pH 7.\textsuperscript{31,32}
Scheme 3. Part of the proposed mechanism for the hydrogenation of acetophenone in iPrOH catalyzed by \textit{trans}-RuH(BH₄)(S-tol-binap)(S,S-dpen) with [base] < 10⁻² M (regime 1) and > 10⁻² M (regime 2).²⁸

**The alcohol product can promote autocatalysis**

The Noyori studies found that iPrOH was often the best solvent for hydrogenation catalyzed by amine ruthenium complexes. They proposed for the binap system just discussed that the alcohol serves as a proton shuttle in the splitting of the dihydrogen (Figure 8a). Several groups have noted that the use of alcohol solvents such as iPrOH enhance the rate of the hydrogenation of ketones. These include pentamethylcyclopentadienyl systems shown in Figure 8b and 8c³³,³⁴ and a very active tetradentate PNPN ruthenium hydrogenation catalyst that we studied in collaboration with the Firmenich group (Figure 8d).¹

![Proposals of alcohol-assisted splitting of dihydrogen.](image)

**Figure 8.** Proposals of alcohol-assisted splitting of dihydrogen.

Dub et al.³⁰ have found that when iPrOH solvation is applied, the calculation of the transition state for dihydrogen splitting in the complete \textit{trans}-[Ru(H₂)H(S-binap)(S,S-dpen)][OR] system consists of dihydrogen splitting between Ru(II) and the outer sphere alkoxide without the involvement of the amido complex (Figure 9a). They also calculated that replacement of NH for NK was also feasible and proposed a network of pathways for the catalytic system.
Figure 9 (a) Dihydrogen splitting to outer sphere alkoxide in generic Noyori-type complexes. A transition state calculated for dihydrogen splitting based on a ruthenium hydride model with complete binap and amido/potassium structures with iPrOH solvation (X, Y = H or K). ωB97X-D/6-31G*/SDD on Ru/SMD iPrOH.29 (b) Hydrogen shuttle dihydrogen splitting TS. TS mPW1PW91/6-311++G(d, p)/SDD on Ru.35

The role of alcohol was particularly noticeable in our study of a related ruthenium amido-based catalyst RuH(R-binap)(HNCMe₂py) shown in Figure 10.35

Figure 10. Representations of the single-crystal X-ray structure of RuH(R-binap)(HNCMe₂py).

The progress of the reaction of this complex compared to that of RuH₂(R-binap)(tmen) is shown in Figure 11. The alcohol product is seen to have an autocatalytic effect on the rate of acetophenone hydrogenation catalyzed by the amido complex.
Figure 11. The hydrogenation (5 atm) of acetophenone (0.3 M) in benzene catalyzed by the ruthenium complexes shown (3x10^{-4} M catalyst) with no base added.

When 0.04 M rac-1-phenylethanol was added so that it was present at the beginning of the reaction, the reaction proceeded at the maximum rate in a linear fashion from the start. DFT calculations on a simplified catalyst system ((PH$_3$)$_2$ replacing R-Binap) without a solvation model supported the idea that the added alcohol was acting as a proton shuttle. A transition state for the proton transferring from dihydrogen to the alcohol oxygen as the alcohol hydrogen transferred to the nitrogen was located for both iPrOH and 1-phenylethanol (Figure 9b). The hydride transfer to the ketone was found to occur before the proton transfer (not concerted) if explicit alcohol solvation was introduced.$^{35}$

Reactions of dihydrogen complexes

The question of the mechanism of the heterolytic splitting of dihydrogen has been posed since the beginning of homogeneous hydrogenation catalysis.$^{36, 37}$ Our discovery of group 8 η²-dihydrogen complexes in the 1980s after Kubas’ report of group 6 complexes$^{38}$ and the reactions of dihydrogen complexes (Scheme 4) naturally led to the same questions concerning the mechanism and thermodynamics of dihydrogen deprotonation. The mechanisms were classified as intermolecular or intramolecular$^{39}$ where the latter were divided into direct proton transfer to a ligand lone pair (e.g. Figure 5) or external base catalyzed proton transfer (e.g. Figure 9a).
Scheme 4. The modes of dihydrogen activation at a metal centre.

A striking example of a proposed intramolecular dihydrogen splitting was provided by the iridium system of Figure 12. The hydride and NH protons undergo H/D exchange when a CD$_2$Cl$_2$ solution is exposed to D$_2$ gas. It was discovered by use of T$_1$ measurements that there are short proton-hydride contacts of approx. 1.8 Å (now referred to as a dihydrogen bond) in the cation. However this exchange is “switched off” in a solution in THF presumably because the oxygen of THF is a better hydrogen bond acceptor than the hydride ligands. More recently the catalytic photochemical formation of dihydrogen from aqueous solution using a nickel mercaptopyridine system was proposed to proceed via such a dihydrogen-bonded intermediate. Finding the balance between a dihydrogen ligand in a thiolate complex and hydride in a thiol complex is relevant to the action of hydrogenase enzymes and potentially to hydrodesulfurization catalysis.

The strategy of using a “pendant base” to catalyze dihydrogen oxidation or evolution can rely on finding the balance point between an acidic dihydrogen complex and the protonated base, a strategy that nature exploits in hydrogenase enzymes.

Figure 12. The splitting of dihydrogen at an iridium mercaptopyridine complex (L = PCy$_3$).

Prediction of the pK$_a$ of dihydrogen and hydride complexes

Can one predict the structures of complexes that efficiently split dihydrogen intramolecularly? One parameter of significance is the pK$_a$ of the dihydrogen complex and it appears that these can be estimated for diamagnetic complexes from chromium to gold. Dihydrogen in solution is not acidic (pK$_{a\,\text{aq}} \approx 25$, pK$_{a\,\text{MeCN}}$ approx. 50). However when it binds to a cationic metal complex it can become very acidic. Our group has measured the pK$_a$ of a range of dihydrogen and hydride complexes, predominantly of the group 8 elements. When these values are combined with those measured in other solvents after adjusting for the different solvent scales with their different references an interesting trend emerges. For example Figure 13 shows that monocationic hydride or dihydrogen complexes with the same set of neutral ligands, but with different metals and numbers of hydrogens bonded to the metal, have a narrow range of pK$_a$ values (within about 5 units). Thus the complexes [MH$_x$(Cp*)$_2$]$^+$, specifically [Mo(H$_2$)H(Cp*)(Cp*)]$^+$, [RuH(Cp*)(Cp*)]$^+$ and [OsH(Cp*)(Cp*)]$^+$ (Cp* = η$^5$-C$_5$Me$_5$), have similar acidities (pK$_{a\,\text{THF}}$ approx. 8) as do the complexes [MH$_x$(PR$_3$)$_2$]$^+$, including [ReH$_x$(PMe$_3$)$_2$]$^+$, [Fe(H$_2$)H$_2$(PMe$_3$)$_2$]$^+$, [Ru(H$_2$)H$_2$(PMe$_3$)$_2$]$^+$ and [OsH$_x$(PMe$_3$)$_2$]$^+$ (pK$_{a\,\text{THF}}$ approx. 27). Such observations led to the proposal of a simple LAC equation (LAC is ligand acidity constant) to estimate pK$_a$ with the assumption that similar classes of ligands have similar additive contributions.
and can be used to estimate the pKₜ in various non-aqueous solvents.

\[
\begin{align*}
[MH_x(Cp)(PPh_3)_2]^+ \\
[MH_x(Cp)(PPh_3)]^+ \\
[MH_x(Cp)]^+ \\
[MH_x(CO)_3(PMe_2Ph)_2]^+ \\
[MH_x(CO)_3(PMePh_2)_2]^+ \\
[Ru(H_2)(PPh_3)(CO)(HBPz_3)]^+ \\
\text{CH}_3\text{CN} & \quad 0 \quad 5 \quad 10 \quad 15 \quad 20 \quad 25 \quad 30 \quad 35 \quad 40 \quad 45 \\
\text{THF, DCM} & \quad 0 \quad 5 \quad 10 \quad 15 \quad 20 \quad 25 \quad 30 \quad 35 \quad 40 \quad 45 \\
\text{DMSO} & \quad 0 \quad 5 \quad 10 \quad 15 \quad 20 \quad 25 \quad 30 \quad 35 \quad 40 \quad 45 \\
\end{align*}
\]

![Diagram](image)


The LAC equation refers to the reaction of eq 2.

\[
K_{LAC}^{\text{ML}} \xrightleftharpoons[+H^+]{\Sigma A_L} [ML_x]^{x+1} 
\]

(2)

The pKₜ LAC for a hydride or dihydrogen complex is calculated according to eq 3.

\[
pK_{LAC} = \Sigma A_L + C_{\text{charge}} + C_{\text{nd}} + C_{\text{d6}} 
\]

(3)

In eq 3, acidity constant values (Aₐ, Table 1) for each of the four to eight ligands around the metal in the conjugate base complex are added. When the ligand binds to the metal at more than one coordination site (i.e. it is bi- or polydentate), the Aₐ value represents the contribution to each coordination site.
Table 1. Ligand acidity constants $A_L$ of eq 3. $^a$

<table>
<thead>
<tr>
<th>Type of ligand</th>
<th>$A_L$</th>
<th>Type of ligand</th>
<th>$A_L$</th>
</tr>
</thead>
<tbody>
<tr>
<td>SiCl$_3^-$</td>
<td>-12±5</td>
<td>PX$_3$ (P(OR)$_3$)</td>
<td>1.6±0.5</td>
</tr>
<tr>
<td>CN$^-$</td>
<td>-8±5</td>
<td>PA$_3$ (PPh$_3$, binap)</td>
<td>2.7±0.5</td>
</tr>
<tr>
<td>Cl$^-$</td>
<td>-4±5</td>
<td>PA$_2$R (PPh$_3$Me; dppe, dppm; dppp)</td>
<td>3.0±0.5</td>
</tr>
<tr>
<td>CO (also PF$_3$)</td>
<td>-4.1±0.5</td>
<td>PA$_2$R$_2$ (PPhMe$_2$; EtXantphos)</td>
<td>4.0±0.5</td>
</tr>
<tr>
<td>Olefin (C$_2$H$_4$, COD)</td>
<td>-2 (x 1 or x 2)</td>
<td>Nitrogen donors (MeCN; py)</td>
<td>4±0.5</td>
</tr>
<tr>
<td>Hydridotris(pyrazolyl)borate, Tp$^-$</td>
<td>0</td>
<td>NHC</td>
<td>5±1</td>
</tr>
<tr>
<td>Hydride, H$^-$</td>
<td>0</td>
<td>PR$_3$ (PCy$_3$; P$i$Pr$_3$; PMe$_3$; 0.5 dmpm)</td>
<td>4.9±0.5</td>
</tr>
<tr>
<td>$\eta^5$-Cyclopentadienide, Cp$^-$</td>
<td>0.6 (x 3)$^b$</td>
<td>H$_2$O</td>
<td>6±1</td>
</tr>
<tr>
<td>$\eta^5$-Pentamethylcyclopentadienide, Cp*</td>
<td>0.9 (x 3)$^b$</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$^a$ Abbreviations: COD = 1,5 cyclooctadiene; dtpe = (4-CF$_3$C$_6$H$_4$)$_2$CH$_2$CH$_2$(4-CF$_3$C$_6$H$_4$)$_2$; dppv = PPh$_2$CH=CHPPh$_2$; dppe = PPh$_2$CH$_2$CH$_2$PPh$_2$; dppm = PPh$_2$CH$_2$PPh$_2$; dppp = PPh$_2$CH$_2$CH$_2$CH$_2$PPh$_2$; EtXantphos = 9, 9-diethyl-4,5-bis(diphenylphosphino)xanthene; py = pyridine; dach = trans-diaminocyclohexane, NHC = N-heterocyclic carbene.

$^b$ Assumed to occupy 3 coordination sites: 3$A_L$(Tp) = 0, 3$A_L$(Cp) = 1.8, 3$A_L$(Cp*) = 2.7.


The value of $C_{\text{charge}}$ in eq 3 depends on the charge $x$ of the conjugate base, $[\text{ML}_x]^-$, of eq 2 (}
Table 2).
Table 2 The constant \( C_{\text{charge}} \) of eq 3.

<table>
<thead>
<tr>
<th>( x )</th>
<th>( C_{\text{charge}} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>+1</td>
<td>-15</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>-1</td>
<td>30</td>
</tr>
</tbody>
</table>

The constant \( C_{\text{nd}} \) accounts for the fact that the stronger M-H bonds of the 5d metals will result in weaker acids. \( C_{\text{nd}} = 0 \) for 3d and 4d metals or \( C_{\text{nd}} = 2 \) for 5d metals.

The \( C_{d6} \) constant accounts for the high stability of hydride complexes of metals with a \( d^6 \) octahedral coordination due to the high ligand field stabilization energy. \( C_{d6} = 6 \) when the metal ion of the acidic hydride complex loses the \( d^6 \) octahedral configuration on going to the lower coordinate conjugate base form; otherwise \( C_{d6} = 0 \).

The \( pK_a^{\text{LAC}} \) match known \( pK_a^{\text{THF}} \) or \( pK_a^{\text{DCM}} \) values for hydrides, usually within 3 \( pK_a \) units. The LAC method is still a crude method of prediction since there are many ligand substituent effects and specific solvation effects that are not accounted for. Nevertheless we find that useful trends in the literature emerge when the reactions of transition metal hydrides are analyzed in the light of these predicted values.

DFT calculations supporting additivity (\( pK_a^{\text{LAC}} \sim pK_a^{\text{THF}} \))

Density Functional Theory calculations also support the additive acid constant approach. The successive replacement of carbonyls (\( A_L \sim 4.1 \)) with trialkylphosphines (\( A_L \sim 4.9 \)) in \([\text{FeHL}_5]^+\) complexes should result in steps of 9 \( pK_a \) units in the \( pK_a \) of the complexes according to the LAC equation 3.\(^{51}\) Figure 14 shows that indeed there is a linear increase of \( pK_a \), but with steps of 11 units. The discrepancy in the size of the steps is not clear at this time. Another finding of this study is that the \( pK_a \) of the complexes are linearly proportional to the energy of the HOMO electrons of the conjugate base complex. The HOMO is the pair of non-bonding \( d \) electrons that are protonated in the oxidative addition to form the hydride complex. Therefore, as is often the case, the strength of the acid is dominated by the energetics of its conjugate base.
Figure 14. The correlation between the $pK_a^{\text{LAC}}$ from eq 3 and the $pK_a^{\text{DFT}}$ calculated by use of DFT methods with THF solvation. Adapted with permission from M. M. H. Sung and R. H. Morris, Inorg. Chem., 2016, 55, 9596−9600; https://pubs.acs.org/doi/abs/10.1021/acs.inorgchem.6b01274. Copyright (2016) American Chemical Society.

New $A_L$ for anionic ligands from DFT for MHXL$_4 \rightleftharpoons MXL^- + H^+$; Fe, Ru, Os

The ligand acidity constant equation was also probed by calculating, using DFT methods, the relative $pK_a$ of complexes MHXL$_4$ where $M = \text{Fe}, \text{Ru}, \text{Os}, L = \text{CO}$ or $L_2 = \text{dmpe}$, $X$ specified in Tables 3 and 4.$^{52}$ The $X$ ligands were chosen to provide new parameters to be used for the prediction of acidity of catalytically important hydrides. These $L$ ligand sets were chosen to test the extremes of the expected $pK_a$ of the complexes, with the tetracarbonyl set the most acidic and the (PMe$_3$)$_4$ set the most basic. This required the geometry optimization of both the cis and trans isomers as well as that of the possible square pyramidal and trigonal bipyramidal conjugate base forms. While only a few of the $pK_a$ have been measured experimentally, a large number of relative $pK_a$ values were determined for these complexes. This study revealed limitations of the LAC equation.$^{52}$ While some $A_L$ for the ligands $X$ (Table 3) had a relatively constant values when applied to the complexes MHXL$_4$, others (Table 4) had values that varied by up to $\pm 5$ between complexes with the $(\text{CO})_4$ and $(\text{PMe}_3)_4$ ligand sets or between Fe, Ru and Os. Nevertheless the SiCl$_3^-$ ligand with $A_L$ -12 was found to be extremely acidifying, as noted previously.$^{25}$ The finding that fluoride is less acidifying than iodide might seem counterintuitive on the basis of electronegativity values. It is explained by the greater destabilization of the conjugate base.
anion \([MXL_3]^-\) by fluoride. In general, the more polarizable anions make a more negative contribution to the \(pK_a\) of the complex \(MHXL_4\).

Table 3. Relatively constant \(A_L\) values (±2 \(pK_a\) units):

<table>
<thead>
<tr>
<th>(X)</th>
<th>(\text{Me}^+)</th>
<th>(\text{OH}^-)</th>
<th>(\text{B(OCH}_2\text{CH}_2\text{O)}^-)</th>
<th>(\text{OMe}^-)</th>
<th>(\text{SH}^-)</th>
<th>(\text{SMe}^-)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(A_L)</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>-1</td>
<td>-2</td>
<td>-3</td>
</tr>
</tbody>
</table>

Table 4. Not as constant \(A_L\) values (±3 to ±5 \(pK_a\) units):

<table>
<thead>
<tr>
<th>(X)</th>
<th>(\text{NH}_2^-)</th>
<th>(F^-)</th>
<th>(\text{Cl}^-)</th>
<th>(\text{Br}^-)</th>
<th>(\text{I}^-)</th>
<th>(\text{SiCl}_3^-)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(A_L)</td>
<td>1</td>
<td>-1</td>
<td>-2</td>
<td>-4</td>
<td>-5</td>
<td>-12</td>
</tr>
</tbody>
</table>

Predicting hydride or dihydrogen acidity in catalysis (\(pK_a^{\text{THF}}\))

The LAC equation is useful in understanding the acid-base chemistry of several catalytic cycles.\textsuperscript{10} For example the dihydrogen complex \([\text{Re(H}_2\text{(CO)}_3\text{PMel}_3)_2]^+\) (\(pK_a^{\text{LAC}} = 2 + 0 + 3 \times -4 + 2 \times 5 = 0\) using eq 3) is an imine hydrogenation catalyst (Scheme 5) while \([\text{Re(H}_2\text{(CO)}\text{PMel}_3)_4]^+\) (\(pK_a^{\text{LAC}} = 2 + 0 - 4 + 4 \times 5 = 18\) is not.\textsuperscript{53}

![Scheme 5: The ionic hydrogenation of imines catalyzed by acidic rhenium dihydrogen complexes.](image)

The proposed mechanism is a proton-first, hydride-second mechanism (Scheme 6)\textsuperscript{54} also known as an ionic hydrogenation mechanism.\textsuperscript{55} In this mechanism an acidic dihydrogen or dihydride complex forms which then protonates the imine (\(pK_a^{\text{LAC}} 5\) to 10) and then transfers the hydride to produce the amine. Complex \([\text{Re(H}_2\text{(CO)}\text{PMel}_3)_3]^+\) is acidic enough to protonate the imine while complex \([\text{Re(H}_2\text{(CO)}\text{PMel}_3)_4]^+\) is not.

![Scheme 6: The proton first, hydride second hydrogenation of imines catalyzed by cationic transition metal complexes.](image)
Classifying hydride attack mechanisms

One way to classify the mechanisms of hydride transfer is using the labels provided in a review on the mechanisms of hydrogenation of polar bonds catalyzed by ruthenium hydride complexes.\textsuperscript{56} Figure 15 illustrates some more recent examples of these classifications. A transition state has been located using DFT for the hydride transfer step in an inner sphere hydrogenation (HI) of acetophenone catalyzed by a ruthenium(II) arene complex containing an N-heterocyclic carbene complex with a pendant amine which does not participate in the reaction.\textsuperscript{57} On the other hand mechanisms have been proposed that involve the outer sphere hydrogenation (HO) of imines (Scheme 6 above and Figure 15 \textsuperscript{58}). In many cases the ligand can assist in the hydride transfer. Figure 15 illustrates the proposed inner sphere ligand-assisted hydride transfer (HIL) to a ketone\textsuperscript{2} and a transition state calculated for the outer sphere ligand-assisted hydride transfer (HOL) to an ester.\textsuperscript{59}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure15.png}
\caption{The classification of hydrogenation mechanisms: HI: hydride transfer to the substrate in the inner sphere; HO: hydride transfer to the substrate in the outer sphere; HIL: hydride transfer in the inner sphere with ligand assistance; HOL: hydride transfer to the substrate in the outer sphere with ligand assistance.\textsuperscript{59}}
\end{figure}

While the catalysts discussed to this point utilize platinum metal ions, there is a current push to develop ones that use more sustainable and benign metals. We have focused on the possible use of iron in place of ruthenium for polar bond hydrogenation. Iron is much more abundant and is essential to life. While traces of ruthenium must be removed from pharmaceutical intermediates before the next step in the synthesis of a drug, iron as an impurity is not as critical.

Transfer hydrogenation of polar bonds using iron catalysts

Our first effective iron catalysts utilized the process of asymmetric transfer hydrogenation (ATH) for the reduction of ketones and imines. The structure of our best catalyst (FeATHer-III) along with an outline
of the ATH mechanism and a valuable, enantiopure amine that can be produced using this catalyst are shown in Figure 16.  

![Diagram of the ATH mechanism](image)

**Figure 16.** The transfer of a hydride-proton equivalent from iPrOH (the solvent) to a coordinatively unsaturated amido complex (abbreviated M-N) to give a hydride amine complex (HM-NH) followed by the transfer of this hydride-proton equivalent to an imine to produce an amine.  

The developments that led up to the discovery of the FeATHer-III catalyst shown in Figure 16 have been widely reviewed by our group and others. In this review I will concentrate on evidence for the proposed mechanisms. Our first iron catalysts that were reported in 2008 were based on P-N-N-P tetradentate ligands that formed two six and one five membered chelate rings with the iron(II). They were found to promote reduction to iron nanoparticles which, surprisingly, catalyzed the ATH of ketones, but with less activity than our later homogeneous iron catalysts. Key evidence was based on the observation of: (1) a variable induction period before catalysis commenced; (2) poisoning of catalysis by addition of substoichiometric PMe$_3$; (3) 2 nm, highly oxygen sensitive Fe(0) nanoparticles by use of electron microscopy.

The second generation iron catalysts that were discovered in 2009 were much more active (Scheme 7). The aryl substituted phosphine complexes were the most active with Ar = p-tolyl achieving a maximum turnover frequency of 8 s$^{-1}$ and a turn over number of 5000 in the ATH of acetophenone in iPrOH.  

![Scheme 7](image)

**Scheme 7.** The ATH of acetophenone catalyzed by the FeATHer-II with base activation.

In 2011 the concentration dependencies of the rate of ATH of acetophenone were investigated for the (S,S)-FeATHer-II catalyst in order to probe the mechanism of catalyst activation and turnover. Samples
were withdrawn as the reaction progresses from a thermostated vial inside an argon glovebox. The initial concentrations ranged from $1 \times 10^{-4}$ to $2 \times 10^{-5}$ M for the catalyst concentration, 0.26 to 0.66 M acetophenone, 0 to 0.2 M acetone, $1.4 \times 10^{-3}$ to $4.1 \times 10^{-4}$ M KOTBu in iPrOH. Typical reaction profiles with the fitted kinetic scheme of Figure 17 are shown in Figure 18.\textsuperscript{75}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure17.png}
\caption{Proposed mechanism for the ATH of acetophenone catalyzed by FeATHer-II and FeATHer-III (green).}
\end{figure}

The reaction progress is slow at the start, a feature also observed for the nanoparticles. However in this case the addition of one equivalent of PMe\textsubscript{3} causes only a minor reduction in the reaction rate which suggests the presence of a sterically hindered reaction site on a homogeneous catalyst instead of nanoparticles. The temperature dependence was also examined from 19 to 41 °C. This work along with a Density Functional Theory computational study\textsuperscript{76} provided evidence for the proposed scheme (Figure 17). Under the reaction conditions the FeATHer-II precatalyst is deprotonated twice to rapidly give a bis-eneamido intermediate. Then a slow step ($k_{\text{act}} 4.5 \text{ M}^{-1}\text{s}^{-1}$) results in the reduction of one side of the unsaturated ligand backbone to produce an amido-eneamido ligand scaffold in $\text{Fe}_a$. The turn-over limiting step within the catalytic cycle ($k_1 11 \text{ M}^{-1}\text{s}^{-1}$, $k_1 450 \text{ M}^{-1}\text{s}^{-1}$) is the reversible, stepwise transfer of a proton and a hydride to this amido group to give the amino hydride iron complex $\text{Fe}_a\text{H}$. The hydride then transfers a hydride/proton equivalent to the acetophenone to give 1-phenylethanol (in 78% ee $R$).
The kinetic modelling showed that the precatalyst was slowly being activated throughout the progress of the reduction of the ketone. It became obvious that in order to avoid this induction period, the amino-enzyme ligand structure of Fe₃H in Figure 17 was required. This was achieved by starting with an enantiopure (S,S)-P-NH-NH₂ component (Scheme 8). In this way several variants of the FeATHer-III structure were prepared.⁶⁰

Scheme 8. The synthesis of FeATHer-III catalysts.

The FeATHer-III catalyst (R’ = Ar = Ph) is particularly enantioselective in the reduction of N-diphenylphosphinyl-substituted imines to the amines (>99% conversion, 99% ee R) (Figure 16 above).⁶⁰ The complex with 3,5-xylyl groups on the phosphorus atoms is superior for use in the ATH of the electron deficient ketone 3,5-(CF₃)₂C₆H₄COMe (>99% conversion, >98% ee R).⁶⁰ The complex with (R’ = Cy, Ar = Ph) actually exists in the solid state at a mixture of cis-beta-diastereomers but is highly enantioselective in the reduction of a variety of aryl ketones (ee > 94%, conversion > 70%).⁷⁷,⁷⁸
FeATHer-III catalysts: kinetics fit to a simple model

The FeATHer-III catalyst was found to be activated by base rapidly without an induction period as shown in green in Figure 17 (above) and the reaction profile of Figure 19. Figure 19 dramatically shows the exceptional initial velocity of this reaction (turnover frequency 235 s\(^{-1}\)) and the fact that 0.3 M product is obtained after 100 s despite the low catalyst loading of 0.01 mol % with respect to ketone. The catalyst should be killed by exposure to air at 100 s to obtain the best ee (79% \textit{R}) since the ee degrades after this point. A simple kinetic model initially proposed by Hintermann\textsuperscript{79} can be used to fit the concentration and ee data for the reaction progress of the ATH of acetophenone (AP) in \textit{i}PrOH (Figure 19). The experiment and model show the continuous decline of ee of the 1-phenylethanol (PE) product after the equilibrium with acetophenone and acetone is reached. Only three parameters are needed to fit the data: (1) the rate constant \(k_R\) for the conversion of acetophenone to the \textit{R} alcohol (2) \(k_S\) to the \textit{S} alcohol; (3) the equilibrium constant for the reaction \(K_{rac}\) where \textit{rac} refers to the racemate of the product alcohol. In this case the ratio of \(k_R\) to \(k_S\) is 12 and \(K_{rac} = 12\). The size of \(K_{rac}\) determines the ratios \(2k_R/k_S\) and \(2k_S/k_S\). Therefore the larger the \(K_{rac}\), the less rapid is the back reaction and the loss in ee after the equilibrium is reached.
Figure 19. The ATH of acetophenone (0.4 M) in iPrOH catalyzed by FeATHer-III (0.01 mol%) and KO'Bu (0.08 mol%) at 28 °C. The solid lines represent a fit to the kinetic model. AP is acetophenone, PE is 1-phenylethanol. Reproduced with permission from S. A. M. Smith, D. E. Prokopchuk, A. J. Lough and R. H.
The mechanism shown in Figure 17 above was also supported by the observation of the hydride structure by use of NMR where a close contact between the NH and FeH groups was detected by use of a $^1$H,$^1$H NOESY experiment.  The transition state for the enantiodetermining hydride transfer from this hydride to acetophenone in the outer coordination sphere to give (R)-1-phenylethanol was also located by use of DFT methods (Figure 20). This was shown to be 1.5 kcal/mol lower in energy than the pro S transfer.

![Figure 20](image)

Figure 20. The pro-R enantiodetermining hydride transfer transition state. The oxygen of the acetophenone is hydrogen-bonded to the FeATHer-III NH group and the hydride on iron is found halfway between the iron and the carbonyl carbon. The methyl group sits in a narrow “valley” between phenyl groups on phosphorus while the phenyl group of the ketone lies over the flat enamido moiety (M06L/TZVP/TZVPFit with iPrOH solvation model).

A larger equilibrium constant for the ATH reaction is preferable for good conversion and the conservation of the ee of the alcohol product. This is demonstrated for the equilibrium shown in Scheme 9 which has a $K_{rac} > 100$ because of the higher reduction potential caused by the electronegative substituents on the ketone. The reaction profile (Figure 21) is fit with $S = k_R/k_S = 19$ and $K_{rac} = 2 K_R = 2 K_S > 100.0$ and the same ee of 90% is maintained throughout the reaction. In order to achieve a higher ee (98% R) the catalyst with P(3,5-xylyl)$_2$ groups (Scheme 8 above, $R' = Ar = 3,5$-xylyl) is used.

$$\text{O} \quad \text{H} \quad \text{F}_3\text{C} \quad \text{O} \quad \text{C} \quad \text{C} \quad \text{CF}_3 \quad \text{[Fe]}\text{KOH}_{\text{Bu}} \quad \xrightarrow{} \quad \text{F}_3\text{C} \quad \text{O} \quad \text{H} \quad \text{C} \quad \text{C} \quad \text{CF}_3 \quad \text{CF}_3$$
The FeATHer-III catalyst with R’ = Cy, Ar = Ph (Scheme 8 above) has a very high selectivity factor $S$ of 510 for the reduction of acetophenone. In this case the ee of the product alcohol remains at 98% (R) despite the $K_{rac}$ of 12.  

### Synthesis of iron asymmetric hydrogenation catalysts

The use of hydrogen gas in direct asymmetric hydrogenation (AH) gets around the problems associated with the equilibrium involved in ATH and is completely atom economical. It is the method of choice in large scale industrial processes such as the Metolachlor process (Figure 1). Our group as well as several others were inspired to make Fe(P-N-P)(CO)(H)X, X = halide, BH$_4$, hydride complexes after the report by Milstein and coworkers. These authors described the direct hydrogenation of ketones catalyzed by the complex Fe(P-N-P)(CO)(H)Br with a tridentate (achiral) $2,6-(P^3 {Pr}_2CH_2)_2C_6H_3N$ ligand using mild pressures and temperatures. Our group focused on asymmetric hydrogenation and developed new unsymmetrical, enantiopure ligands by reduction of an imine ligand on the iron or by the preferred reductive amination protocol shown in Scheme 11.  

We focused on the complexes with alkyl groups R
= Cy, tPr on PR₂ because earlier work showed that similar complexes with R = Ph were not active hydrogenation catalysts.⁸¹, ⁸²

Scheme 11. The synthesis of unsymmetrical enantiopure P-NH-P’ ligands.

This ligand synthesis provides great flexibility to the sterics and electronics of the system. As long as R¹ is phenyl or isopropyl, the monohydride complexes FeH(CO)Cl(P-NH-P’) can be prepared as described in Scheme 12.⁸³ The structure of the complex with R¹ = Ph and R² = H is shown in Figure 22. The Fe-H and N-H bonds are aligned in a favourable orientation for hydride-proton transfer; however this complex does not react until it is converted to a trans-dihydride complex by reaction with dihydrogen and base. The complex with R¹ = tPr was prepared as a complex mixture of isomers and was not studied further.

Scheme 12. The synthesis of monohydride iron(II) complexes FeH(CO)Cl(P-NH-P’).

These monohydride complexes are active catalysts for the hydrogenation of aryl ketones (Figure 23). The enantioselectivity for the AH of acetophenone increases as $R^2$ in Scheme 12 is changed from H to Ph and is highest for $R^1 = R^2 = \text{Ph}$. This substitution locks the five-membered Fe-PPh$_2$-CHPh-CHPh-NH- ring and hinders the rotation of the phenyls on the phosphorus.

![Catalyst structure](image)

Figure 23. The effect of the catalyst structure on the time to completion and the ee in the AH of acetophenone. The result from the second entry was taken from reference 81.

Other ketones were reduced by this system to ee >89% (S) including the aryl alkyl ketones shown in Figure 24. When the ketone becomes too bulky (e.g. the cyclohexyl compound), the conversion and ee suffer. Thus the iron active site is somewhat crowded. Methylisopropyl ketone was converted to the alcohol but only in 45% ee (R). Finding selective catalysts for alkylketones remains a challenge.
The mechanism of the FeH(CO)X(P-NH-P)-catalyzed hydrogenation of ketones, imines and nitriles has been proposed by others to involve an amido complex FeH(CO)(P-N-P) to heterolytically split dihydrogen and a trans-dihydrogen complex trans-FeH₂(CO)(P-NH-P) to transfer the hydride to the ketone (c.f. the ruthenium reaction above in Figure 5). We have characterized the trans-dihydride complex trans-(S,S)-FeH₂(CO)(PPr₂CH₂CH₂NHCHMeCHPhPPh₂) by NMR and proposed a similar mechanism. The favoured pro-S transition state for the hydride transfer which we have calculated by use of DFT methods has similar features to the one for the P-N-NH-P system above (Figure 20) with the ketone oxygen hydrogen-bonded to the NH, the methyl fitting between the phenyl groups of the PPh₂ group and the carbonyl carbon being attacked by the hydride (Figure 25). In addition there is a similarity to the proposed transition state for the Noyori ruthenium systems (Figure 5) which also have hydride trans to hydride. One additional factor favouring higher enantioselectivity which is visible in the structure (Figure 25) is the CH₃...aryl centroid interaction between an isopropyl group on the ligand and the ketone aryl group. The pro-R transition state was calculated to have an energy about 2 kcal/mol higher than the one shown, consistent with the > 90% ee (S) observed for acetophenone reduction. Other iron systems have been reported for the AH of ketones and imines.
Figure 25. The transition state for the hydride transfer from the catalyst trans-\(\text{S,S}\)-Fe\(\text{H}_2\text{(CO)(PPh}_2\text{CHPhCHPhNHCH}_2\text{CH}_2\text{PPr}_2}\) to the Si face of acetophenone calculated using DFT with G09/M11L/6-31G* except SDD for Fe/PCM THF. The free energy of activation was calculated to be 31.5 kcal/mol at 50 deg.\(^8^3\)

**Conclusions**

Both asymmetric hydrogenation and asymmetric transfer hydrogenation catalysts based on iron have now been discovered that begin to rival the activity and productivity of Noyori-type ruthenium catalysts. The progress was aided by a mechanistic understanding of the outer sphere hydride transfer mechanism along with mechanistic evidence obtained by synthesis, spectroscopy, kinetic measurements and computational chemistry. The FeATHer-III catalysts show excellent enantioselectivity for the transfer hydrogenation of selected ketones and imines. The best results for ketone reduction are obtained when there are electronegative groups on the ketone to push the equilibrium of the ATH to products in order to maximize conversion and minimize the loss of ee over time. Evidence was provided for a mechanism involving the outer sphere attack of well-defined metal hydrides on the ketone carbonyl in the enantiodetermining step. The activation of dihydrogen is proposed to involve its heterolytic splitting across the metal-amido bond of a distorted five-coordinate metal complex in aprotic solvents such as benzene or THF or from a cationic dihydrogen complex to an outer sphere alkoxide when alcohol is
present to stabilize the alkoxide. A simple Ligand Acidity Constant (LAC) equation 3 is proposed to allow the prediction of the $pK_a$ and hence the reactivity of transition metal dihydrogen and hydride complexes.

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