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Iron group hydrides in Noyori bifunctional catalysis

Robert H.Morris*^[a]

Dedicated to Professor Ryoji Noyori

ABSTRACT: This is an overview of the hydride-containing catalysts prepared in the Morris group for the efficient hydrogenation of simple ketones, imines, nitriles and esters and the asymmetric hydrogenation and transfer hydrogenation of prochiral ketones and imines. The work was inspired by and makes use of Noyori metal-ligand bifunctional concepts involving the hydride-ruthenium amine-hydrogen HRuNH design. It describes the synthesis and some catalytic properties of hydridochloro, dihydride and amide complexes of ruthenium and in one case, osmium, with monodentate, bidentate and tetradentate phosphorus and nitrogen donor ligands. The iron hydride that has been identified in a very effective asymmetric transfer hydrogenation process is also mentioned. The link between the HMNH structure and the sense of enantioinduction is demonstrated by use of simple transition state models.

Keywords: asymmetric synthesis, homogeneous catalysis, hydrogen transfer, ketones, imines, esters, transition metal hydrides

1. Introduction

A true turning point in chemistry was the Noyori group's report in 1995 of the remarkable effect of a primary diamine ligand on the activation of ruthenium homogeneous catalysts for the hydrogenation of simple ketones.^[1] This amine N-H effect could be successfully utilized to vastly improve catalysts for direct hydrogenation^[2-8] or transfer hydrogenation^[9-14] of ketones and imines, particularly the industrially important asymmetric hydrogenation (AH) using H₂ and asymmetric transfer hydrogen (ATH) using 2-propanol or formate as the reductant. The further rapid catalyst development in the Noyori lab of ruthenium catalysts revealed the effectiveness of the (*S,S*)- or (*R,R*)-1,2-diphenyldiaminoethane ((*S,S*) or (*R,R*)-DPEN), its *para*-tolylsulfonate derivative and other related diamines (e.g. DIAPEN) in asymmetric catalysis. They matched the chirality of ligands based on the BINAP design with those of the diamine on ruthenium to achieve spectacular activity and enantioselectivity in prochiral ketone hydrogenation. The mechanism was proposed to involve ruthenium-ligand bifunctional catalysis^[15] where a ruthenium hydride and amine proton smoothly transfer a dihydrogen equivalent to a ketone or imine (Figure 1, M = Ru). This concept has been applied widely in catalysis and extended to several transition metals and the work has been reviewed by our group^[16-19] and others.^[20-27]

Fig. 1. The rapid bifunctional attack of a metal hydride and ligand-amine proton on a prochiral ketone.

The Noyori foundational work in ruthenium-based catalysis offered our group, specializing in the synthesis and characterization of transition metal hydride and dihydrogen complexes, opportunities to explore the properties of the intermediates in these catalytic systems and to develop our own catalyst variants. This is a Record of the hydride species that we encountered and the new catalyst systems we developed along the way.

2. Hydride complexes with triphenylphosphine ligands

The original 1995 report from the Noyori group described how a mixture of ethylene diamine or DPEN with $\text{RuCl}_2(\text{PPh}_3)_3$ in 2-propanol solvent with added KOH resulted in the formation of active catalyst solutions under dihydrogen gas (eq 1).

Interestingly dihydrogen and not 2-propanol was the reductant of the ketones, considering that $\text{RuHCl}(\text{PPh}_3)_3$ was already known to catalyze the transfer hydrogenation of ketones in 2-propanol under nitrogen.^[28] This hydride is prepared in a very similar fashion to that of eq 1 with the difference that a tertiary amine, NEt_3 , is used in its synthesis.^[29, 30] Thus the presence of the primary diamine introduced a different mode of reactivity. We wondered whether $\text{RuH}^{\delta-}-\text{H}^{\delta+}\text{N}$ hydridic protonic interactions were involved in hydride formation since we had previously observed these to promote the heterolytic splitting of dihydrogen in certain iridium^[31] and ruthenium complexes.^[32] Dihydride formation was also possible. $\text{Ru}(\text{L})(\text{H})_2(\text{PPh}_3)_3$, $\text{L} = \text{N}_2, \text{H}_2$ were known to be ketone hydrogenation catalysts^[33] and we had shown that iron group dichloride phosphine complexes are converted to dihydride complexes by the successive dissociation of the chloride, dihydrogen coordination, and then deprotonation of the resulting cationic dihydrogen complex.^[34]

The hydride complex $\text{RuHCl}(\text{PPh}_3)_3$ turned out to be an excellent starting material for the preparation by my group of a wide range of catalytically active hydride compounds containing a HRuNH motif (Scheme 1). The central starting hydride $\text{RuHCl}(\text{PPh}_3)_3$ is drawn with a trigonal bipyramidal structure distorted in the equatorial plane from 120° angles to a Y shape of $\text{ClRu}(\text{P})(\text{H})$ atoms with an angle of 82° between the phosphorus and hydride; this P and H are located across the metal from the π -donor chloride ligand (Figure 2, left). The electronic reason for this distortion has been described.^[35] This type of structure is a recurring theme of the hydride chemistry of Noyori bifunctional catalysis.

Scheme 1. A condensed overview of representative ruthenium hydride complexes prepared starting from RuHCl(PPh₃)₃; more details can be found later in the text. Reaction 1a: D-NH₂ represents a variety of bidentate ligands where D- is an amine^[36-38] or 2-pyridyl^[39] donor with a group linking to the NH₂; X = BH₄, or H⁻ from H₂/base; Reaction 2a: PAr₂-PAr₂ = BINAP^[37, 40-43] or BINOP,^[44, 45] and D-NH₂ represents a variety of bidentate ligands with D = amine, pyridyl or phosphine donor moiety; Reaction 3a: PPh₂-NH₂ represents a variety of β-aminophosphine bidentate ligands (the ligand PNOR is shown);^[42, 43, 46] Reaction 4a: PPh₂-N-N-PPh₂ is a tetradentate ligand with diphenylphosphino and imine or amine donors (the ligand derived from (*R,R*)-diaminocyclohexane is shown).^[47-49]

Fig. 2. The distorted trigonal bipyramidal complexes. Left: hydrido chloro complex $\text{RuHCl}(\text{PPh}_3)_3$ (structure HCPPRU01 of the CCDC)^[50]; middle: amido complex $\text{RuH}(\text{NHCMe}_2\text{CMe}_2\text{NH}_2)(\text{PPh}_3)_2$ (structure UPNAX)^[37]; right: $\text{RuH}(\text{NHCMe}_2\text{py})((S)\text{-BINAP})$ (structure LISMUW).^[51] Only the *ipso* carbons of the phenyl groups on phosphorus and selected hydrogens are shown.

The addition of 1,2-*trans*-diaminocyclohexane (DACH) to $\text{RuHCl}(\text{PPh}_3)_3$ produced the hydrido chloro complex $\text{RuHCl}(\text{DACH})(\text{PPh}_3)_2$ (Scheme 1, reaction 1).^[36] A partial crystal structure is shown in Scheme 2, where the close contact between an amine proton and the chloride ligand is emphasized by a dotted line. The addition of a hydride reagent ($\text{X} = \text{H}$ in reaction 1b) such as $\text{KBH}(\text{secBu})_3$ produces the dihydride complex $\text{RuH}_2(\text{DACH})(\text{PPh}_3)_2$ which rearranges from the initial *trans* dihydride isomer^[30] to the isomer with *cis* hydrides and *trans* PPh_3 groups. The complexes $\text{RuHCl}(\text{DACH})(\text{PPh}_3)_2$ and $\text{RuH}_2(\text{DACH})(\text{PPh}_3)_2$ were tested for ketone hydrogenation but only the dihydride complex was found to catalyze the hydrogenation at 3.5 atm of a variety of neat ketones (or solutions of ketones in benzene) to the alcohols and imines to the amines; $\text{RuHCl}(\text{DACH})(\text{PPh}_3)_2$ was inactive. When NaOH or NaOiPr was added to $\text{RuHCl}(\text{DACH})(\text{PPh}_3)_2$ in neat ketone under H_2 , the reaction was particularly efficient. While a *cis*-dihydride mechanism was proposed in this first study,^[36] later mechanistic studies revealed that a *trans*-dihydride was the active catalyst (Scheme 2).^[30] The (*R,R*)-DACH dihydride complex transfers, in a bifunctional reaction, a hydride from the ruthenium and a proton from the amine nitrogen to the acetophenone to give 1-phenylethanol in 63% e.e. (*S*). This results in the formation of a ruthenium amide complex which reacts with dihydrogen to regenerate the *trans*-dihydride via the 4-membered transition state (TS) for the H_2 heterolytic splitting step (Scheme 2). The $\text{H}\cdots\text{H}$ distance in the TS of 1.0 Å calculated using DFT methods^[37, 52] is elongated relative to that of free H_2 gas (0.74 Å) but falls in the range observed for ruthenium η^2 -dihydrogen complexes, as do the Ru-H distances.^[52-54] The pyramidalized nitrogen can be viewed as the base that is deprotonating a dihydrogen ligand that is acidified by binding to the ruthenium(II) ion.^[55, 56]

Scheme 2. Proposed mechanism for the (asymmetric) hydrogenation of acetophenone catalyzed by $\text{RuH}_2(\text{DACH})(\text{PPh}_3)_2$ ($\text{R}^1\text{-R}^1 = \text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2$, $\text{R}^2 = \text{H}$)^[30] and by $\text{RuH}(\text{NHCM}_2\text{CMe}_2\text{NH}_2)(\text{PPh}_3)_2$ ($\text{R}^1, \text{R}^2 = \text{Me}$)^[37]. The simplified structure of the transition state for dihydrogen splitting calculated by DFT is shown on the top left: $d_{\text{H}\cdots\text{H}}$ 1.01 Å, $d_{\text{H}\cdots\text{N}}$ 1.41 Å, $d_{\text{Ru-N}}$ 2.17 Å, $d_{\text{Ru}\cdots\text{H}}$ 1.80 Å).^[37, 52, 57]

The proposed intermediate in Scheme 2 is the amido complex $\text{RuH}(\text{NHCR}^1\text{R}^2\text{CR}^2\text{R}^1\text{NH}_2)(\text{PPh}_3)_2$ which was detected by NMR for the DACH complex^[30] and crystallized from solution for the complex with the diamine $\text{NH}_2\text{CMe}_2\text{CMe}_2\text{NH}_2$ (TMEN).^[37] The crystal structure of this complex is shown in Figure 2 (middle structure; see above). It is a 16-electron five coordinate Ru(II) complex stabilized by the amido nitrogen π -donor. The amido nitrogen, the hydride and a phosphorus make up the Y-shaped equatorial plane in this case with the amine nitrogen in an axial position on the trigonal bipyramid. The use of methyl groups on the diamine backbone prevents β -hydride elimination and decomposition that is observed if the corresponding DACH amide complex is not kept under H_2 .^[30] The isostructural osmium complex $\text{OsH}(\text{NHCM}_2\text{CMe}_2\text{NH}_2)(\text{PPh}_3)_2$ has also been prepared and found to be an active ketone hydrogenation catalyst.^[58, 59] The rate law for the hydrogenation of acetophenone at 20°C, 1-15 atm H_2 , $[\text{Ru}]$ 10^{-3} to 10^{-4} M, $[\text{ketone}]$ 0.02 M in benzene is shown in eq. 2 where $k = 110 \text{ M}^{-1}\text{s}^{-1}$ for the DACH complex and $k = 8 \text{ M}^{-1}\text{s}^{-1}$ for the more sterically hindered TMEN complex.

$$d[\text{alcohol}]/dt = k[\text{Ru}][\text{H}_2] \quad (2)$$

This rate law is typical for Noyori-like hydrogenation catalysts^[60] where the rate increases with the hydrogen pressure but is (usually) independent of the ketone concentration (when the catalyst is saturated in a high ketone concentration regime). In this way we found that the turn-over limiting step is the splitting of dihydrogen across the ruthenium-amide bond, a conclusion supported by DFT

calculations.^[37] Evidence for the important role that the primary amine group plays in the mechanism was provided by the Noyori group, noting that the use of the complex N,N,N',N'-tetramethylethylenediamine resulting in an inactive catalyst.^[8] Similarly we found that the complexes $\text{RuH}_2(\text{bipyridine})(\text{PPh}_3)_2$ and $\text{RuH}_2(\text{phenanthroline})(\text{PPh}_3)_2$ that do not contain NH groups were inactive while $\text{RuH}_2(\text{AMPY})(\text{PPh}_3)_2$, AMPY = 2-methylaminopyridine, was even more active than the DACH system.^[39] The flat backbone of the AMPY ligand appears to be responsible for the high activity of other catalysts with this ligand that are effective, for example, in the AH of hindered *tert*-butyl ketones^[61] and the transfer hydrogenation of ketones.^[24]

The activity of catalysts with other X groups trans to hydride in $\text{RuHX}(\text{TMEN})(\text{PPh}_3)_2$ was also explored.^[38] The complexes with X = OPh, 4- $\text{SC}_6\text{H}_4\text{OMe}$, OPPh_2 , $\text{OP}(\text{OEt})_2$, CCPh were synthesized as in reaction 1b of Scheme 1. Only the last complex in the list, $\text{RuH}(\text{CCPh})(\text{TMEN})(\text{PPh}_3)_2$ had activity for ketone hydrogenation; however there was evidence that in fact it served as a precatalyst to $\text{RuH}_2(\text{TMEN})(\text{PPh}_3)_2$ by hydrogenolysis of the alkynyl group.

3. Hydride complexes with bidentate ligands

The availability of the TMEN diamine offered us the possibility to isolate hydride complexes with structures related to those generated in the important $\text{RuCl}_2(\text{diamine})(\text{BINAP})$ AH systems of the Noyori group. The reaction of $\text{RuHCl}(\text{PPh}_3)_3$ with (*R*)-BINAP produces the useful five coordinate complex $\text{RuHCl}((R)\text{-BINAP})(\text{PPh}_3)$.^[41] This complex was reacted with TMEN to produce $\text{RuHCl}(\text{TMEN})((R)\text{-BINAP})$ (reaction 2a, Scheme 1) and then with a strong base KHBsecBu_3 or KOtBu under hydrogen to give the *trans*-dihydride complex $\text{RuH}_2(\text{TMEN})((R)\text{-BINAP})$. The Ru-H and an axial NH group are perfectly aligned on each side of the C_2 symmetrical complex in the crystal structure (Figure 3. Left). The rigid, asymmetric nature of the BINAP ligand is evident from the stacking of the aryl rings as indicated by the dotted lines. The dihydride has characteristic hydride resonances in the proton NMR spectrum at -4.8 ppm as a triplet.

Fig. 3. (Left) The structure of $\text{RuH}_2(\text{TMEN})((R)\text{-BINAP})$ (RAMGER)^[40] showing only a few of the key hydrogens including the parallel RuH and NH units and the 2.4 Å H...H hydridic protonic contacts. The stacking of the phenyl rings of the PPh_2 against the naphthyl groups in the BINAP ligand are indicated by dotted lines. (right) The structure of $\text{RuHCl}((R,R)\text{-DPEN})((R)\text{-BINAP})$ (XIDGAS).^[41]

$\text{RuH}_2(\text{TMEN})((R)\text{-BINAP})$ is active in benzene for the hydrogenation of acetophenone to (*S*)-1-phenylethanol in 63% e.e., $[\text{ketone}] = 0.5 \text{ M}$, $[\text{Ru}] = 1 \times 10^{-4} \text{ M}$, TON 5000.^[37] As in the case of the triphenylphosphine system, the amido complex $\text{RuH}(\text{NHCMe}_2\text{CMe}_2\text{NH}_2)((R)\text{-BINAP})$ could be characterized by NMR. This system has particularly simple kinetics with $k = 3 \text{ M}^{-1}\text{s}^{-1}$ for eq. 2, again consistent with dihydrogen activation being the turn-over limiting step with a mechanism similar to that of Scheme 2. The kinetic isotope effect on the rate of dihydrogen/dideuterium splitting was measured as 2.0 ± 0.1 and calculated by DFT as 2.1.^[52] This compares well with the KIE of 2 reported by the Noyori group for the hydrogenation of acetophenone catalyzed by $\text{RuH}(\text{BH}_4)(\text{xylylBINAP})(\text{DPEN})$ in 2-propanol with excess strong base present.^[60]

In a similar fashion according to Reaction 2 of Scheme 1, the complexes $\text{RuHCl}((R,R)\text{-DPEN})((R)\text{-BINAP})$, $\text{RuHCl}((R,R)\text{-DACH})((R)\text{-BINAP})$ and $\text{RuHCl}((R,R)\text{-DAIPEN})((R)\text{-BINAP})$, $\text{DAIPEN} = \text{NH}_2\text{CAr}_2\text{CH}/\text{PrNH}_2$, $\text{Ar} = p\text{-MeOC}_6\text{H}_4$, can be synthesized and converted in solution to their corresponding *trans*-dihydrides with ^1H NMR chemical shifts of the hydrides similar to that of $\text{RuH}_2(\text{TMEN})((R)\text{-BINAP})$.^[40] As expected the DAIPEN complex of C_1 symmetry has magnetically inequivalent hydrides. The complex $\text{RuHCl}((R,R)\text{-DPEN})((R)\text{-BINAP})$ was characterized by single crystal X-ray diffraction (Figure 3, right), with stacked aryl rings on BINAP and equatorial phenyl groups on the diamine.^[41] This conformation of the five membered ring that the DPEN makes with ruthenium causes an N-H group on each side of the molecule to be perfectly axial, an important structural feature for asymmetric catalysts that utilize the HM-NH bifunctional mechanism.^[37] With this data in hand we proposed a mechanism that explained the main features of the catalytic hydrogenation of prochiral ketones catalyzed by $\text{RuX}_2(\text{BINAP})(\text{diamine})$ systems (Scheme 3).^[37, 40] Hydrogen reacts with the amido complex in a slow step and the resulting dihydride with the bifunctional HRuNH structure attacks the prochiral ketone so that the NH group hydrogen bonds with the oxygen while the hydride transfers to the carbon on the side of the double bond that positions the large R^{large} group (usually an aryl group) away from the aryl groups of the BINAP ligand.^[40, 46] In this way the (*R*)(*R,R*) catalyst produces the alcohol predominantly in the (*S*) configuration.

Scheme 3. Proposed mechanism for the hydrogenation of prochiral ketones catalyzed by Noyori-type $\text{RuX}_2((R,R)\text{-diamine})((R)\text{-BINAP})$ complexes.

The crystal structure of the hydrogenation catalyst $\text{RuH}(\text{BH}_4)((R,R)\text{-DPEN})((R)\text{-xylylBINAP})$ reported by Noyori and coworkers^[62] also has the DPEN in this conformation although the position of the NH groups are turned so that they can both participate in dihydrogen bonding with the BH_4^- group (Figure 4). This complex is a highly productive and active ketone hydrogenation catalyst, reducing 3 M solutions of acetophenone in 2-propanol to (*S*)-1-phenylethanol in 99% e.e. with 3×10^{-5} M catalyst, TON 100,000, at 8 atm H_2 , 25 °C. The kinetics of the catalysis are complex, with a rate constant that depends on the amount of MOtBu , $\text{M} = \text{Na}, \text{K}$, or phosphazene P_4 base added, going through a maximum at a base concentration in 2-propanol of about 10^{-2} M.^[60] Traces of a more reactive dihydride, deprotonated at a nitrogen,^[63, 64] might explain this enhancement in rate although there is no direct experimental evidence for this in 2-propanol solvent.

Fig. 4. The $\text{RuH}(\text{BH}_4)((R,R)\text{-DPEN})((R)\text{-xylylBINAP})$ structure.^[62]

Alcohols are the preferred solvents for hydrogenation reactions using the $\text{RuX}_2(\text{diamine})(\text{BINAP})$ catalyst systems because the rates are generally higher. There is general agreement that alcohols can lower the energy of the highest transition state in the catalytic cycle, usually the heterolytic splitting of H_2 step as shown in Scheme 2, by providing an alternate proton transfer pathway in a hydrogen-bonded six-membered transition state structure.^[60, 65, 66] We encountered this phenomenon when studying the kinetics of hydrogenation of acetophenone in benzene catalyzed by the amido complex $\text{RuH}(\text{NHCMe}_2\text{py})((S)\text{-BINAP})$.^[51] This amido complex was prepared from the two chloro diastereomers of $\text{RuHCl}(\text{NH}_2\text{CMe}_2\text{py})((S)\text{-BINAP})$ (Scheme 4) and characterized by X-ray crystallography (Figure 2, right side). It has the typical distorted trigonal bipyramidal geometry with a Y-shaped equatorial plane (H-Ru-P 83.6°) as discussed above and is the best model so far of the $\text{RuH}(\text{amido-amine})(\text{BINAP})$ intermediate of the hydrogenation mechanism shown in Scheme 3. As a side note, the corresponding ligand AMPY without *gem*-dimethyl substituents on the backbone undergoes a β -hydride elimination reaction making the amido complex unstable.^[39]

Scheme 4. Preparation of $\text{RuH}(\text{NHCMe}_2\text{py})((S)\text{-BINAP})$.

When the progress of reaction of the hydrogenation of acetophenone in benzene is plotted for this amido catalyst $\text{RuH}(\text{NHCMe}_2\text{py})((S)\text{-BINAP})$ and compared to that of the $\text{RuH}_2(\text{TMEN})(\text{BINAP})$ catalyst under identical conditions, the plots shown in Figure 5. are obtained.

Fig. 5. Progress of the hydrogenation of acetophenone catalyzed by two catalysts under the same conditions ($[\text{Ru}] = 3 \times 10^{-4} \text{ M}$, $[\text{ketone}] = 0.12 \text{ M}$, 5 atm H_2 , 20 °C in C_6H_6).

While the latter catalyst produces alcohol in a linear fashion from the beginning, the former starts slowly and speeds up over time, exceeding the TOF of the dihydride catalyst. If 0.04 M 1-phenylethanol or 2-propanol is present initially in the benzene solution, then the reaction starts in a linear fashion at a greater TOF. The fastest conversion and TOF is obtained if the reaction is conducted in 2-propanol. DFT calculations support the finding that the S-shaped curve results from an autocatalytic production of the alcohol which progressively changes the transition state of the turn-over limiting step, the heterolytic splitting of dihydrogen from the slow path A to the rapid path B in Scheme 5. The alcohol serves to create a hydrogen bonded network which allows rapid proton shifts to occur.

Scheme 5. The autocatalytic role of the product alcohol in the hydrogenation of acetophenone catalyzed by $\text{RuH}(\text{NHCMe}_2\text{py})((S)\text{-BINAP})$.

We reported that complexes of the type $\text{RuHCl}(\text{diamine})(\text{diphosphine})$ are excellent catalysts when activated with base under H_2 for the hydrogenation of simple imines to amines and the AH of prochiral ketimines to enantiomerically enriched amines.^[41] For example the imine MePhC=NPh is hydrogenated under 3 atm H_2 in benzene at 20 °C to the amine MePhHC-NHPh in 71% e.e. in 36 h using $\text{RuHCl}((R,R)\text{-DACH})(R)\text{-BINAP})/\text{KO}i\text{Pr}$ with $[\text{imine}]:[\text{Ru}]=500:1$. Cobley and Henschke later found that $\text{RuCl}_2((R,R)\text{-DACH})((R,R)\text{-EtDUPHOS})$ can be used to hydrogenate this imine in 92% e.e. (*S*).^[67] These turn out to be some of the most active AH systems known for this type of imine.^[68]

It was discovered early on that complexes of the type $\text{RuXY}(\text{PPh}_2\text{CH}_2\text{CH}_2\text{NH}_2)_2$ $X, Y = \text{Cl}$ or $X = \text{H}, Y = \text{Cl}$, with the phosphorus donors and primary amine donors connected together as β -aminophosphine ligands were precursors to very active ketone hydrogenation,^[42, 69] imine hydrogenation,^[42] and more recently, ester hydrogenation catalysts.^[70] A large variety of these β -aminophosphine ligands are now available.^[71] We prepared, by following reaction 3 of Scheme 1, the complexes (*S,S*)- $\text{RuHCl}(\text{PPh}_2\text{CH}_2\text{CHMeNH}_2)_2$ and (*S,S*)- $\text{RuHCl}(\text{PPh}_2\text{proline})_2$ after making the ligands from the amino acids alanine and proline. They produced alcohols in very low e.e. in ketone hydrogenation reactions. More promising was the ligand (*R,R*)- $\text{PPh}_2\text{CHPhCHMeNH}_2$ (PNOR) which was prepared from the amino alcohol (*S,R*)-norephedrine.^[46] The complex $\text{RuHCl}(\text{PNOR})_2$ (Figure 6, left) was prepared as in reaction 3 of Scheme 1. When it was activated with $\text{NaO}i\text{Pr}$ under H_2 in order to produce the active dihydride, it reduced acetophenone at 5 °C, 3 atm H_2 , to the alcohol in 47% e.e. (*R*). The model at the right of Figure

6 indicates the stereogenic regions coloured in yellow of the metal complex and the preferred pro-*R* orientation of acetophenone when hydrogen-bonded to the axial NH of the dihydride catalyst $\text{RuH}_2(\text{PNOR})_2$.

Fig. 6. Left: The structure of $\text{RuHCl}(\text{PNOR})_2$ (BIKWIC of the CCDC). Right: a proposed transition state for the reaction of $\text{RuH}_2(\text{PNOR})_2$ with acetophenone to give 1-phenylethanol in the (*R*)-configuration (47% e.e.).

The complexes $\text{RuHCl}(\text{PNOR})(\text{BINAP})$ with (*R*)- and (*S*)-BINAP were also prepared according to reaction 2 of Scheme 1. The use of the compound $\text{RuHCl}((R,R)\text{-PNOR})((S)\text{-BINAP})$ (Figure 7) had the correct chirality match of ligands to produce the e.e. of 71% (*S*) in the product 1-phenylethanol (ketone:KOtBu:Ru = 2000:30:1, 5 °C, 3 h, 2-PrOH), higher than the e.e. of 61% (*S*) when the (*R*)-BINAP compound was used. The proposed transition state structure that leads to this (*S*) alcohol is shown next to the crystal structure in Figure 7. This model structure was derived by simply replacing the chloride in the crystal structure with a hydride. The dotted line between this chloride ligand and the axial NH of the PNOR ligand demonstrates that the resulting hydride complex will have a HRuNH unit that is suitably aligned for the bifunctional transfer of H^+ and H^- to the ketone. The aryl groups of the BINAP ligand are stacked against each other and one is stacked against the phenyl on the PNOR ligand to make a cavity to receive the ketone in the pro-*S* configuration.

Fig. 7. Left: The structure of $\text{RuHCl(PNOR)((S)-BINAP)}$ ((BIKWUO) of the CCDC); Right: a proposed transition state for the reaction of $\text{RuH}_2\text{(PNOR)((S)-BINAP)}$ with acetophenone to give 1-phenylethanol in the (*S*)-configuration (71% e.e.).

Replacement of the hydride ligand in $\text{RuHCl}((R,R)\text{-PNOR})((S)\text{-BINAP})$ with a borohydride ligand gives $\text{RuH(BH}_4\text{)}((R,R)\text{-PNOR})((S)\text{-BINAP})$ (reaction 2c of Scheme 1). This complex turned out to be a catalyst with dual reactivity to carry out first an excellent asymmetric Michael reaction (96% e.e. (*S*)) followed by an AH of the resulting ketone (Scheme 6) to install two stereogenic centers in a one pot reaction.^[43]

Scheme 6. Successive asymmetric Michael addition followed by AH catalyzed by $\text{RuH(BH}_4\text{)}((R,R)\text{-PNOR})((S)\text{-BINAP})$ (1% catalyst loading).

A variety of $\text{RuHX}((R)\text{-BINOP})(\text{DPEN})$ complexes, $\text{X} = \text{Cl}$ or BH_4 , are prepared using (*R,R*)- (Figure 8) or (*S,S*)-DPEN according to Scheme 1, Reaction 2. The complex $\text{RuHX}((R,R)\text{-DPEN})((R)\text{-BINOP})$, $\text{Ar} = \text{Ph}$, has the correct matching of diphosphinite and diamine ligands for the enantioselective tandem reaction shown in Scheme 6, however producing the intermediate Michael adduct in the opposite configuration, 90% e.e. (*R*) and then the (*R,R*)-alcohol product in $\text{dr} = (R,R)/(R,S) = 10/1$ in 90% e.e.^[45] The complex with $\text{Ar} = \text{xylyl}$, $\text{X} = \text{BH}_4$ is an effective catalyst in 2-propanol for the base-free ATH of aryl ketones to the (*R*) alcohols in greater than 90% e.e.^[45] while the complex with $\text{X} = \text{Cl}$ is equally effective if 10 equiv. of KOtBu are added.^[44]

Fig. 8. The structure of $\text{RuHX}((R,R)\text{-DPEN})(R)\text{-BINOP}$, $\text{X} = \text{Cl}, \text{BH}_4$, $\text{Ar} = \text{Ph}, 3,5\text{-Me}_2\text{C}_6\text{H}_3$ (Left) and the X-ray structure of the BH_4 complex with only the *ipso* carbons of the xylyl groups on phosphorus shown (structure WANQUY of CCDC).

In view of the effectiveness of β -aminophosphine ligands in hydrogenation reactions we wondered whether equivalent ligands with N-heterocyclic carbenes in place of the phosphine could be prepared. The challenge is that primary amines are acidic and free carbenes are strongly basic, making the free ligand unstable. To overcome this problem we prepared the ligand on nickel(II) by a sodium borohydride reduction of a nitrile-substituted imidazolium salt (Scheme 7). The ligand can then be transferred directly from nickel to other metal ions including Ru(II) ,^[72-77] Ir(I) ^[78] and Ir(III) .^[79]

Scheme 7. Preparation of an amino-NHC ligand on nickel(II) followed by transmetalation to ruthenium.

Scheme 7 shows the preparation of the ruthenium(II) NHC complex which has the most interesting catalytic reactivity of the complexes synthesized so far. With 0.07% catalyst loading with 8 equiv. KOtBu in THF under 9 atm H_2 at 25 °C, it catalyzes the efficient hydrogenation of arylketones such as acetophenone ($\text{TOF } 10,000 \text{ h}^{-1}$) including bulky ketones like $t\text{BuCOPh}$ ($\text{TOF } 10,000 \text{ h}^{-1}$),^[73] a ketimine, PhMeC=NPh ($\text{TOF } 250 \text{ h}^{-1}$), to the amine^[73] and esters to the alcohols.^[77] Spectroscopic and kinetics studies and DFT calculations provide evidence for a ruthenium-amide/ruthenium hydride – amine bifunctional mechanism. The one proposed for ester hydrogenation is shown in Scheme 8.^[77] NMR spectroscopy provides evidence that the hydride complex $\text{RuH}(\text{Cp}^*)(\text{NHC-NH}_2)$ forms by reaction with dihydrogen and the added base. It has the required Noyori-like HRuNH bifunctional motif to attack the ester's carbonyl group in the outer coordination sphere with a transition state barrier calculated to be $\Delta G^\ddagger = 22 \text{ kcal/mol}$. This produces a hemiacetal which coordinates to the metal and splits into an alcohol

and an aldehyde which is rapidly hydrogenated catalytically to the alcohol. This leaves a ruthenium amido complex which activates dihydrogen in the usual fashion ($\Delta G^\ddagger = 18$ kcal/mol) to regenerate the HRuNH hydride complex. This hydrogenation catalyst system turns out to be one of the most active known to date. Efforts are underway in our lab to make asymmetric NHC-NH₂ ligands for asymmetric catalysis.

Scheme 8. Mechanism of the hydrogenation of esters catalyzed by $[\text{Ru}(\text{py})(\text{Cp}^*)(\text{NHC-NH}_2)]\text{PF}_6$ (0.07%) with 8 equiv. KOtBu in THF at 50 °C under 26 atm H_2 .

4. Hydride complexes with tetradentate ligands

Inspiration for this work was provided by the report of Gao, Ikariya and Noyori^[10] on the ATH of ketones catalyzed the complex $\text{RuCl}_2(\text{PPh}_2\text{-NH-NH-PPh}_2)$ with the P-NH-NH-P ligand ($\text{DACH}(\text{NH})_2\text{P}_2$) prepared using the DACH diamine shown in Scheme 1. This complex was shown to be an ATH catalyst when activated with base in 2-PrOH. Again we were interested in the hydride complexes in such systems and so we prepared, via the route shown in Scheme 1, reaction 4a, a variety of hydride complexes $\text{RuHX}\{\text{P-NH-NH-P}\}$, with ligands such as $\text{DACH}(\text{NH})_2\text{P}_2$ and $\text{TMEN}(\text{NH})_2\text{P}_2$ (Figure 9). The complexes $\text{RuXY}\{\text{DACH}(\text{NH})_2\text{P}_2\}$, X= H or Cl, Y = Cl were found to be not only ATH catalysts when activated by KOtBu but also very active ketone and imine hydrogenation catalysts, although the enantioenrichment of the products from the hydrogenation of prochiral substrates was low.^[47, 80] For example a 2 M solution of acetophenone was hydrogenated to 1-phenylethanol (20% e.e.(*R*)) in 3 h, 46 atm H_2 , 60 °C, when catalyzed by $\text{RuCl}_2\{\text{DACH}(\text{NH})_2\text{P}_2\}/\text{KOtBu}$ in 2-PrOH with TON 10^5 , TOF $3 \times 10^4 \text{ h}^{-1}$.

Fig. 9. Tetradentate ligands for ruthenium(II).

It was at first surprising that the RuXY{DACH(NH)₂P₂} d⁶ octahedral, coordinatively saturated ruthenium complexes were active catalysts when activated with base under H₂. However mechanistic investigations explained the reason – a d⁶ octahedral dihydride RuH₂{DACH(NH)₂P₂} with HRuNH groups is produced by reaction of the chloro precursor complexes with H₂ and base and this dihydride efficiently transfers H⁻/H⁺ equivalents to polar C=O or C=N bonds. Kinetic measurements and more recent information provided the evidence for the mechanism shown in Scheme 9.^[47] The rate constant k₃ for the slow step in the mechanism was found to be much larger (1.23x10³ M⁻¹ s⁻¹) when 2-PrOH was used as the solvent than when benzene was used (130 M⁻¹ s⁻¹). These rate constant are comparable to that of RuH₂(DACH)(PPh₃)₂ (110 M⁻¹ s⁻¹ in benzene) and much greater than that of RuH₂(TMEN)(BINAP) (3 M⁻¹ s⁻¹) cited above. Higher concentrations of ketone resulted in a diminution of the rate, possibly due to the formation of an enolate complex as shown.

Scheme 9. Proposed mechanism for the hydrogenation of acetophenone catalyzed by $\text{RuHCl}\{\text{DACH}(\text{NH})_2\text{P}_2\}/\text{KOtBu}$ in 2-PrOH at 25 °C, 7-13 atm H_2 , . rate = $k_3[\text{Ru}^{\text{tot}}][\text{H}_2]/(1+K_2[\text{acetophenone}])$, $k_3 = 1.23 \times 10^3 \text{ M}^{-1} \text{ s}^{-1}$, $K_2 = 1.20 \text{ M}^{-1}$.

Further evidence for the mechanism was provided by the structural characterization of the dihydride $\text{RuH}_2\{\text{TMEN}(\text{NH})_2\text{P}_2\}$ and hydridoamido $\text{RuH}\{\text{TMEN}(\text{NH})(\text{N})\text{P}_2\}$ complexes (Figure 10).^[48] The dihydride structure is drawn to emphasize the parallel RuH and NH groups. The amido structure has structural features similar to the complexes of Figure 2. The Y shaped equatorial plane of the distorted trigonal bipyramid has a small P-Ru-H angle of 76.6° . The $\text{RuH}_2\{\text{TMEN}(\text{NH})_2\text{P}_2\}$ catalyst is 140 times less active than the $\text{RuHCl}\{\text{DACH}(\text{NH})_2\text{P}_2\}/\text{KOtBu}$ system in benzene for the hydrogenation of 0.17 M acetophenone at 20 °C. The low activity of the TMEN-substituted catalysts is attributed to steric blocking of the axial RuH and NH groups by the axial CMe groups on the backbone of the diamine. However the $\text{RuH}_2\{\text{TMEN}(\text{NH})_2\text{P}_2\}$ catalyst is also active for the hydration of benzonitrile to benzamide.^[49]

Fig. 10. Left: structure of $\text{RuH}_2\{\text{TMEN}(\text{NH})_2\text{P}_2\}$ (FAMGAC); Right: structure of $\text{RuH}\{\text{TMEN}(\text{NH})(\text{N})\text{P}_2\}$ (FAMFUV). Only selected hydrogens are shown.

The complex $\text{RuHCl}\{\text{EN}(\text{NH})_2\text{P}_2\}$ with the ligand prepared from 1,2-diaminoethane is a catalyst for the hydrogenation of benzonitrile to benzylamine. ^[49] DFT calculations provided the first evidence for the outersphere hydrogenation of the CN triple bond by the metal-hydride amine-proton bifunctional attack (Scheme 10). Ruthenium(II) and iron(II) pincer systems have more recently been found to catalyze the hydrogenation of a range of nitriles and the mechanism proposed is similar. ^[81-83]

Scheme 10. The successive outersphere hydrogenation of benzonitrile (left side) and then benzylideneimine (right side) by the dihydride $\text{RuH}_2(\text{EN}(\text{NH})_2\text{P}_2)$.

The high activity of the $\text{RuHX}(\text{P-NH-NH-P})$ systems for hydrogenation catalysis encouraged us to search for equivalent iron catalysts. The search for these iron catalysts has been described extensively

elsewhere.^[17-19, 84, 85] After several years of research we learned that only certain tetradentate ligands were suitable to stabilize iron hydrides with respect to reduction to iron nanoparticles under AH and ATH conditions.^[86] In addition one carbonyl ligand appears to be important to keep the iron(II) low spin.^[19] Only one important iron hydride complex that we discovered is discussed here.

The most active catalyst system known for the ATH of ketones at room temperature is the mixture of the complex (S,S) -[FeCl(CO)(PPh₂CH₂CH=NCHPhCHPhNHCH₂CH₂PPh₂)]BF₄ ("FeATHER") with 8 equiv. KOH or KO^tBu in 2-PrOH (Scheme 11).^[85] This catalyst reduces a wide range of aryl ketones by hydrogen transfer from 2-PrOH with TON of 5000 and TOF ranging from 4 to 200 s⁻¹ depending on the structure, with electronegative substituents such as CF₃, Cl on the ketone and pyridyl ketones giving the highest rates of reduction.^[85, 87] While the e.e. of the alcohols produced often starts at over 90% at low conversions, by the time equilibrium is reached the e.e. tend to fall to between 70 and 90% e.e. (*R*). The e.e. can be increased for some ketone substrates to over 90% by using two Pxylyl₂ groups^[85, 87] or one PCy₂ and one PPh₂ group^[88] in the ligand structure. The e.e. is greater than 99% (*R*) for the reduction of the diphenylphosphinoyl-functionalized imines PhMeC=NPOPh₂ and ThMeC=NPOPh₂, Th = 2-thiophene.^[85]

Scheme 11. The proposed mechanism for the ATH of ketones catalyzed by the FeATHER complex in basic 2-PrOH.

At least two equivalents of base are required to activate the FeATHER complex. One equivalent removes a proton from the CH₂ group next to the imine while the second removes HCl from the ClFeNH unit to generate the iron amido complex (Scheme 11). The resulting amido complex reacts with isopropanol to generate the iron hydride complex of interest. This highly reactive and oxygen sensitive yellow diamagnetic Fe(II) complex has only been characterized in solution^[85] and by DFT calculations.^[89] The ¹H NMR spectrum has a doublet of doublet pattern at -2.2 ppm. A NOESY experiment demonstrated that the hydride is in close contact with the N-H amine proton as shown in Scheme 11. The actual structure of the hydride complex can be surmised by replacing the chloride in the X-ray-diffraction-derived structure of the complex (S,S) -FeCl(CO)(Ptol₂CH=CHNCHPhCHPhNHCH₂CH₂Ph₂)^[89] (Figure 11) with a hydride ligand. The structure of the hydride as determined by DFT calculations is

shown on the right. Thus again we see the important HMNH motif for efficient outersphere polar bond reduction and indeed when acetophenone is added to this hydride complex it reacts rapidly to give the 1-phenylethanol product.^[85]

Fig. 11. Left: Structure of $(S,S)\text{-FeCl(CO)(Ptol}_2\text{CH=CHNCHPhCHPhNHCH}_2\text{CH}_2\text{Ph}_2)$ as determined by single crystal X-ray diffraction. Only the *ipso* carbons on the tol and Ph groups on the phosphorus atoms are shown. Right: Structure of $(S,S)\text{-FeH(CO)(Ptol}_2\text{CH=CHNCHPhCHPhNHCH}_2\text{CH}_2\text{Ph}_2)$ by DFT calculation.

DFT calculations have also been used to explain why the (S,S) -FeAther catalyst hydrogenates acetophenone to produce the 1-phenylethanol enriched to about 88% e.e. in the (R) configuration. It is clear from the transition state structures shown in Figure 12 that the acetophenone fits better over the HFeNH motif when the small Me on the ketone is against the “phenyl wall” from PPh_2 groups while the phenyl on the ketone lies flat over the ene-amido part. This is calculated to be 2 kcal/mol lower in energy than the alternative transition state that leads to the (S) product where the large phenyl group on the ketone is pushing against the phenyl wall.^[89]

Fig. 12. The structure of the transition states leading to the favored (R) -1-phenylethanol and disfavored (S) -alcohol on the right. The acetophenone is shown in wireframe with yellow dots on the atoms while

the sterically interacting phenyl groups on the FeATHer hydride catalyst are space-filled, the rest in ball and stick.

The same FeATHer system does catalyze the hydrogenation of ketones using pressures of hydrogen (20 atm) at 50 °C in benzene but there is little enantioselectivity. The same iron hydride of Figure 11 and Scheme 11 has been detected to form using dihydrogen gas but under the conditions of catalysis decomposition of the catalyst leads to poor performance. A possible explanation is that the dihydrogen ligand upon reaction with the iron amido complex is not acidic enough to quickly protonate the amido.^[56] In fact DFT calculations show that the heterolytically splitting of dihydrogen has the highest barrier in the catalytic cycle.^[89] This is an unusual example of a catalyst system that catalyzes both hydrogenation and ATH.

5. Conclusions

Our quest to understand the hydride and dihydrogen chemistry involved in the catalytic hydrogenation of simple ketones, imines, nitriles and esters has led to further applications of Noyori's HM-NH metal-ligand bifunctional motif shown in Figure 1, M = Fe, Ru, Os. Useful hydridochloro ruthenium(II) complexes with monodentate, bidentate and tetradentate phosphorus donor ligands or phosphorus and nitrogen donor ligands were shown to be efficient precatalysts to the active distorted trigonal bipyramidal amide catalysts. These react with dihydrogen to produce *trans*-dihydride amine ruthenium catalysts with parallel Ru-H and N-H bonds in the HM-NH structure. The enantioselectivity of the H⁻/H⁺ transfer to the substrate from the HMNH catalyst can be explained by simple models based on the structure of the *trans*-dihydride or more elaborate transition state structures calculated using DFT methods. Initial work with phosphorus-free catalysts based on a ligand with an N-heterocyclic carbene donor and a primary amine donor demonstrates promising activity in ketone and ester hydrogenation. More recently we have described an extension of the metal ligand bifunctional concept to the use of iron carbonyl hydride complexes with the correct tetradentate ligands in the asymmetric transfer hydrogenation of ketones and certain imines. There is great interest in the use of catalysts based on earth-abundant, non-toxic transition metals such as iron in the pharmaceutical industry as well as in large scale hydrogenation processes. This will ensure that the Noyori catalysis legacy will continue to have a huge impact on the design of future chemical processes.

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Biographical Sketch of Robert H. Morris

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 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 and a 2015 Killam Research Fellow. He was Acting Chair and then Chair of the Chemistry Department from 2008 to 2013. He received the Rutherford Medal from the RSC, the Alcan Lecture Award from the CIC and the Award for Pure or Applied Inorganic Chemistry from the CSC. He is an author of 220 journal articles, 10 book chapters and holds four patents. His research interests include organometallic chemistry and catalysis, particularly involving the iron group elements.

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Graphical Table of Contents

This is an overview of hydride-containing catalysts prepared in the Morris group for the efficient hydrogenation of simple ketones, imines, nitriles and esters and the asymmetric hydrogenation and transfer hydrogenation of prochiral ketones and imines. The work was inspired by and makes use of the Noyori metal-ligand bifunctional concepts involving the hydride-ruthenium amine-hydrogen HRuNH design.