Catalytic Cycle for the Asymmetric Hydrogenation of Prochiral Ketones to Chiral Alcohols: Direct Hydride and Proton Transfer from Chiral Catalysts *trans*-Ru(H)$_2$(diphosphine)(diamine) to Ketones and Direct Addition of Dihydrogen to the Resulting Hydridoamido Complexes

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The enantioselective hydrogenation of prochiral ketones is a valuable method of producing a range of chiral alcohols. Noyori and co-workers have developed excellent ruthenium catalyst systems in terms of efficiency, enantioselectivity, and flexibility.[1] Catalyst precursors are of the form Ru(Cl)$_2$(diphosphine)-(diamine), where the diphosphine is *R*- or *S*-binap or a derivative of this ligand, and a chiral diamine of correct chirality such as *R,R*-$NH_2CHPhCHPhNH_2$ (dpen) or *R*-$NH_2CH^iPrC(C_6H_4OMe)_2NH_2$ (daipen). An active catalyst mixture consists of the dichloride complex with alkoxide base, dihydrogen, and ketone in 2-propanol. Noyori and Ohkuma postulated that an unidentified complex with *fac* hydride and diamine was responsible for the hydrogen-transfer reaction.[1] Our research showed that the monohydride complexes *trans*-RuH(Cl)(diphosphine)(diamine) are also precursors to the active hydride catalytic species by reaction with alkoxide base and dihydrogen in neat ketones so that prochiral ketones could be hydrogenated to chiral alcohols under mild conditions (20 °C, 1−3 atm H_2).[2]

With active catalyst preparations we have observed NMR resonances consistent with dihydrides *trans*-RuH_2(diphosphine)-(diamine)[3] that form from the chloride precursors by heterolytic H_2 splitting at ruthenium promoted by the alkoxide base.[4] The dihydrides are likely to be the hydrogenation catalysts by analogy to the extremely active ketone hydrogenation catalyst RuH_2-$(PPh_3)_2$(cydn) (cydn = cyclohexyldiamine) that some of us previously identified.[5] However, they are very reactive and tend, in the absence of H_2, to undergo dehydrogenation of the diamine as will be described elsewhere.

Here we use the diamine $NH_2CMe_2CMe_2NH_2$ (tmen)[6] that lacks hydrogens α to the amino groups to solve this problem and provide evidence for the catalytic cycle shown in Scheme 1. This cycle demonstrates the importance of the *trans*-dihydride **1** with the bifunctional motif *cis*-Ru−H···H−N to provide nascent, polarized dihydrogen ($H^{\delta-}\cdots H^{\delta+}$) for the catalytic ionic or heterolytic hydrogenation of polar bonds[7] and of an unprecedented hydridoamido complex **2** for the rapid heterolytic splitting of H_2. It also reveals the origin of the enantioselectivity of the Noyori catalysts. Cycles related to Scheme 1 have been proposed[1,5] and identified for a monohydride areneruthenium catalyst that transfers hydrogen to ketones, not from dihydrogen but from 2-propanol.[8]

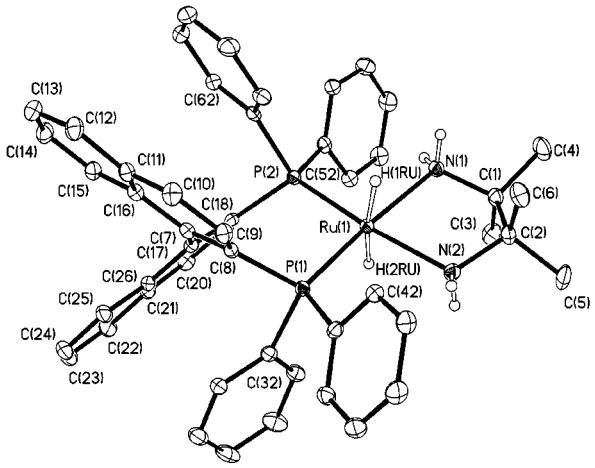
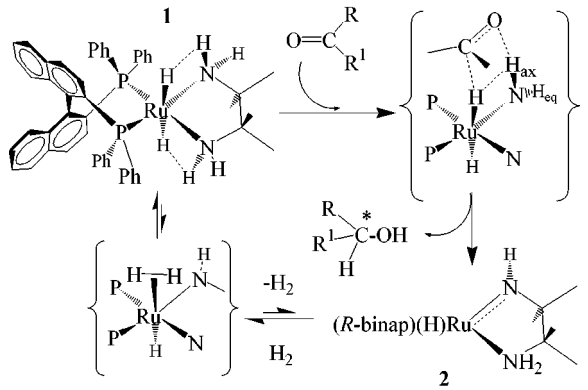


Figure 1. Molecular structure of **1**.

Scheme 1



Reaction of the precursor RuH(Cl)(R-binap)(tmen) (**3**)[9] in THF with hydride sources including K[HB^{sec}Bu$_3$] or KO^{i}Pr/H_2 produces the yellow dihydride *trans*-Ru$(H)_2$(R-binap)(tmen) (**1**).[10] A single-crystal X-ray diffraction structure determination reveals an approximately C_2-symmetric, octahedral *trans*-dihydride complex (Figure 1).

The tmen ligand is in the δ conformation with two sets of axial groups N−H_{ax} and C−Me_{ax} (C(6) and C(3)) and equatorial groups N−H_{eq} and C−Me_{eq} (C(4) and C(5)). The Ru−H bond lengths are 1.64(3) and 1.70(3) Å. The RuH···H_{ax}N distances of about

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(2) Abdur-Rashid, K.; Lough, A. J.; Morris, R. H. *Organometallics* **2001**, *20*, 1047. The chirality of the product alcohols described in this article is *S*.

(3) *trans*-RuH_2(*R, R*-dpen)(*R*-binap). ^{1}H NMR (C_6D_6) δ: −4.5 (t, $^2J_{HP}$ = 16.6 Hz); ^{31}P{^{1}H}: 89.6 ppm (s). *trans*-Ru$(H^1)(H^2)$(*R*-daipen)(*R*-binap). ^{1}H NMR (C_6D_6) δ: −4.32 (t, $^2J_{HP}$ = 17.4 Hz, RuH^1, $J_{H^1H^2}$ < 7 Hz), −4.66 (t, $^2J_{HP}$ = 16.6 Hz, RuH^2); ^{31}P{^{1}H}: 90.2 ppm (d), 88.6 (d), $^2J_{PP}$ = 47.2 Hz. *trans*-RuH_2(R-binap)(R-cydn) ^{1}H NMR(C_6D_6) δ: −6.1 (t, $^2J_{HP}$ = 20.0 Hz); ^{31}P{^{1}H}: 89.4 ppm (s).

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(9) *trans*-RuH(Cl)(*R*-binap)(tmen) **3** was prepared in a fashion similar to that for related RuH(Cl)(diphosphine)(diamine) complexes[2] and characterized by elemental analysis, NMR, IR, and X-ray crystallography.

(10) *trans*-RuH_2(*R*-binap)(tmen) **1**. KHB^{sec}Bu$_3$ (0.76 g of a 1.0 M solution in THF, 0.83 mmol) was added to **3** (0.76 g, 0.87 mmol), and the mixture was stirred for 30 min under N_2. The resulting mixture was filtered, and hexanes (5 mL) were added, precipitating a bright yellow solid. Yield 0.57 g, 70%. ^{1}H NMR(C_6D_6) δ: −4.81 (t, $^2J_{HP}$ 17.2 Hz, 2H, RuH, T_1^{min} 0.38 s at 20 °C, 500 MHz), 0.21 (s, 6H, Me), 1.06 (s, 6H, Me), 0.95 (d, $^2J_{HH}$ 10.2 Hz, 2H, NH), 3.13 (d, $^2J_{HH}$ 9.9 Hz, 2H, NH), 6.56−8.60 (m, 32H). ^{31}P{^{1}H}: 89.9 (s). IR(Nujol): 1774 (νRuH), 3355, 3344, 3292, 3287 cm^{-1} (νNH). Crystals were obtained by layering a diethyl ether solution of the complex with hexanes under 1 atm H_2.

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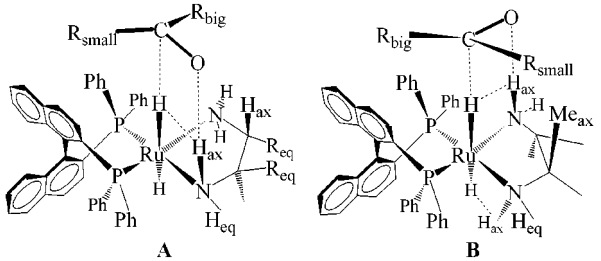
2.4 Å are at the outer limit of protonic−hydridic or dihydrogen bonding.[11] A characteristically low wavenumber Ru−H vibration at 1774 cm^{-1} due to the high trans influence of hydride also provides evidence for the uncommon trans stereochemistry in the solid state.[12] This weakening of the Ru−H bond helps explain the reactivity of this hydridic hydride toward ketones. The Ru(1)−N(1) and Ru(1)−N(2) bond lengths of 2.202(2) and 2.193(2) Å are shorter than those reported for *cis*-$RuH_2(PPh_3)_2$-(cydn) but are comparable to those of *trans*-RuHCl(*R*-binap)-(dpen)[2] and *trans*-RuHCl(*R*-binap)(tmen).[9] The temperature-independent dihydride triplet at −4.8 ppm in the ^1H NMR and singlet or triplet at 89.9 ppm in the $^{31}P\{^1H\}$ or ^{31}P NMR spectra, respectively, of **1** in solution are unambiguous for a trans structure. The rigid stereochemistry of the ligands dictates that there are two axial (H_{ax}) and two equatorial (H_{eq}) N−H hydrogens. Their chemical shifts are 3.13 and 0.95 ppm, respectively according to nOe and T_1 experiments. The T_1 of H_{ax} is about 20% lower that that of H_{eq} over the temperature range 215−313 K. These data along with T_1^{min}(RuH) [10] indicate the presence of a RuH···H_{ax} interaction with an H···H_{ax} distance of 2.2 Å. The complex RuH-(tsdpen)(cymene) has a 2.2 Å RuH···HN bond.[8a]

Complex **1** is yellow under H_2 but under Ar, N_2 or vacuum slowly loses H_2 in the solid state to produce a dark-red ruthenium hydridoamido complex, Ru(H)($NHCMe_2CMe_2NH_2$)(R-binap) (**2**). This process is accelerated by refluxing a THF solution of **1** under Ar to produce a pure sample of the very air-sensitive complex **2**.[13] Complex **2** can also be produced by the reaction of **3** with a strong base such as KO^{i}Pr under Ar. The complex is fluxional in solution and produces a broad hydride triplet in the ^1H NMR spectrum at −19.2 ppm at room temperature. The related amido complex [Ru(bipy)($NHCMe_2CMe_2NH_2$)$_2$]($ZnBr_4$) has been reported.[6]

Complex **2** in toluene-d_8 reacts instantaneously with 1 atm H_2 at 293 K and reacts even at 213 K, to produce **1**. Complex **1** in C_6D_6 reacts with D_2 to produce H_2 and HD gas and isotopomers deuterated at the Ru−D and N−D_{ax} and N−D_{eq} positions as expected if dihydrogen loss and addition is reversible as shown in Scheme 1. The reversible intramolecular heterolytic splitting of dihydrogen is rare and may proceed by an η^2-dihydrogen[14] intermediate. Attempts are underway to try and detect such an intermediate. The irreversible reaction of the related 16-electron, silyl-stabilized amido complex Ru(Cl){N($SiMe_2CH_2PPh_2$)$_2$}(PPh_3) with dihydrogen gives an amino hydride complex,[15] possibly via a dihydrogen complex.[14b] The ^1H NMR resonance of the RuH(D) isotopomer appears at −4.75 ppm, showing a downfield isotope shift of 0.06 ppm that is also observed for other *trans*-RuH_2(diamine)(diphosphine) species.[3] The NHD resonances at 1.45 and 3.55 ppm experience even larger downfield shifts of about 0.5 ppm from the NH_2 chemical shifts and large increases in T_1 values.

Chart 1



When one equivalent of acetophenone is added to **1** in C_6D_6, the yellow color immediately changes to deep red, and ^1H resonances associated with the complex **2** appear. When this solution is placed under H_2, **1** is regenerated along with phenylethanol. Complex **1** in acetophenone under H_2 catalytically produces *S*-phenylethanol in about 14% ee. In contrast the RuH_2-(*R*,*R*-dpen)(*R*-binap) and RuH_2(*R*-daipen)(*R*-binap) systems are more active and produce alcohols in the *S* configuration in very high ee as observed also starting from dichloride or hydridochloride precursors.[1,2] These observations are nicely explained by the structures in Chart 1.

The prochiral ketone with a big substitutent (R_{big}, e.g., Ph) and small substituent (R_{small}, e.g., Me) is shown approaching the *trans*-dihydride so that the oxygen forms a hydrogen bond with an axial NH and the carbon starts accepting the hydride. To complexes with the diamine locked into the λ configuration with equatorial aryl groups and axial hydrogens C−H_{ax} such as *R*,*R*-dpen or *R*-daipen (Chart 1, **A**), the ketone will approach with R_{big} away from the binap backbone and axial phenyl. Direct transfer of polarized dihydrogen to the polar C=O bond provides the observed *S*-alcohol. In C_2-symmetric dihydrides, the asymmetric induction will be identical for dihydrogen transfer from the $HRuNH_{ax}$ unit on either face of the complex. It is clear that a change in substitution of C−H_{ax} in **A** with C−Me_{ax} in **B** and a flipping of the five-membered ring into the δ configuration as observed for the tmen ligand will result in more steric interference of the H_2 transfer process and result in a less active and enantioselective catalyst. This is observed experimentally for **1**.

In conclusion the use of a diamine without α-hydrogens allows the isolation of a *trans*-dihydride and the amido complex with which it is in equilibrium by loss of H_2. Such species are proposed to form in the Noyori mixture used for the enantioselective hydrogenation of ketones by the reaction of the precursor chloro complexes with dihydrogen and alkoxide base. A model of $H^{\delta+}$···$H^{\delta-}$ transfer from such a *trans*-dihydridediamine complex to a prochiral ketone is proposed that explains, and allows the prediction of, the stereochemistry of the chiral alcohols produced in these reactions.

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Supporting Information Available: Preparation and properties of the complexes **1**, **2**, and **3** (PDF). The X-ray structure data for complexes **1** and **3** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) RuH(*R*-binap)($NHCMe_2CMe_2NH_2$) **2.** ^1H NMR(C_6D_6) δ: −19.23 (t, $^2J_{HP}$ = 33 Hz, 1H RuH), 0.86−0.94 (m, br, 12H, CH_3), 1.22 (s, br, 1H, NH), 2.80 (s, br, 1H, NH), 3.39 (s, br, 1H, NH), 6.53−8.65 (m, 32H). $^{31}P\{^1H\}$: 79.2 ppm (br) 78.7 (br). IR (Nujol): 2000, 1953 cm^{-1} (νRuH), 3332, 3276 cm^{-1} (νNH).

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