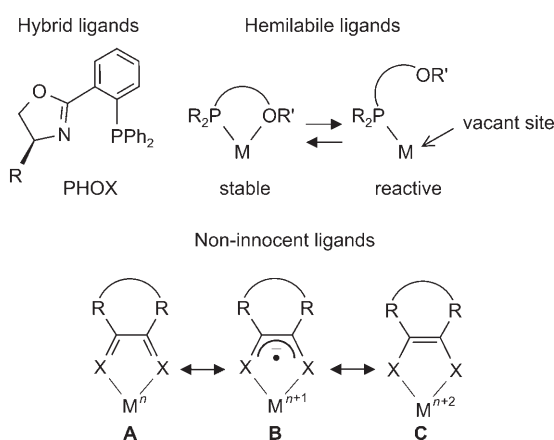


Cooperating Ligands in Catalysis

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cooperative effects · coordination chemistry ·
dehydrogenation · homogeneous catalysis

The properties of a metal complex as a whole are the result of the interaction of the metal center and its surrounding ligands. However, in some cases, a classification of ligands in categories such as hybrid ligands, hemilabile ligands, or non-innocent ligands may be practical (Scheme 1).



Scheme 1. Examples of hybrid ligands (P,N ligands, such as PHOX), hemilabile ligands (P,O ligands, such as phosphanyl ether or ester), and non-innocent ligands, such as 1,4-heterodienes (X = NR, O, S) or quinone derivatives.

Well-known hybrid ligands are P,N-oxazolines, short PHOX, introduced by the groups of Pfaltz and Helmchen^[1] about 15 years ago, which bind by a soft (phosphorus) and hard (nitrogen) donor to the metal center. The distinct *trans* effects of both donor groups control by electronic effects, for example, the selectivity in metal-catalyzed allylations. Hemilabile ligands—a special form of hybrid ligands—consist of one strongly bound donor group and one which binds weakly and reversibly to the metal center. Phosphanyl ether, R₂P-(CR₂)_nOR', or ester R₂P(CR₂)_nCOOR', or phosphanyl amines, R₂P(CR₂)_nNR'₂, are established hemilabile ligands. These may mask a coordination site which is liberated during

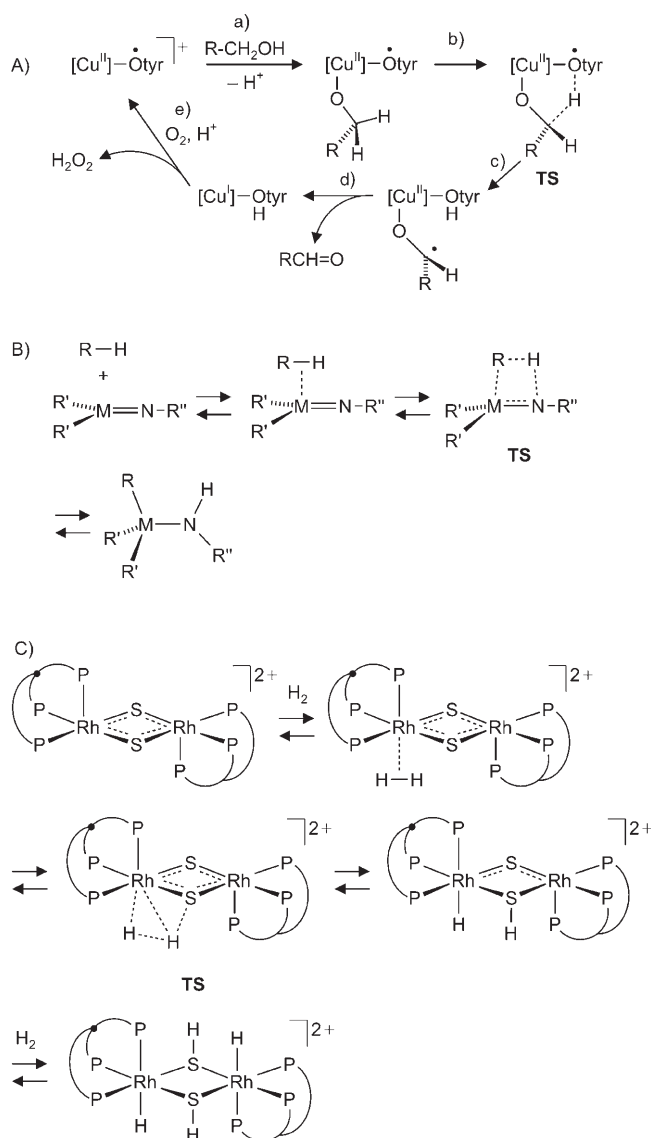
the reaction and thus stabilize a reactive intermediate, which is of advantage for a number of homogeneous metal-catalyzed transformations.^[2] The term innocent ligand was coined 40 years ago by Jørgensen.^[3] An innocent ligand allows the unambiguous determination of the oxidation state of the metal center. Conversely, for a non-innocent ligand, usually with a delocalized π system, simple electron counting rules cannot be applied. Modern theory and spectroscopy, however, can substitute the intuitive and often misleading weighing of the resonance forms **A** ↔ **B** ↔ **C** (Scheme 1) and reveals the true electronic structure of metal complexes with non-innocent ligands.^[4]

Recent discoveries make the introduction of a further ligand class meaningful, which could be useful guidance for new developments. Cooperating ligands may be defined as those which participate directly in a bond activation reaction and undergo a reversible chemical transformation. Thus the metal and the ligand cooperate in a synergistic manner and their interplay facilitates a chemical process.

An example of a non-innocent ligand that is also cooperative is found in nature. The enzyme galactose oxidase, GOase, contains a tyrosinyl radical, tyrO[•], which is coordinated to a copper(II) center. With impressive activity (turnover frequencies, TOF, of up to 1 × 10⁶ h⁻¹) this enzyme converts chemoselectively primary alcohols into aldehydes (Scheme 2A).^[5] In the key step (b) of the catalytic cycle, the oxygen atom of the tyrosinyl radical abstracts a hydrogen atom from the α-CH₂ group of the alcohol substrate which is bonded to the Lewis-acidic Cu^{II} center. The resulting tyrosine (c) is subsequently converted back into the tyrosine radical through coupled redox and proton-transfer steps (d,e). Numerous model complexes^[6] have been developed which successfully mimic GOase reactivity, and a wide range of substrates (alcohols, amines) can be oxidized, sometimes even under aerobic conditions.

The imido group acts as a cooperating ligand in early transition metal imido complexes of the form [(M)=NR] (M = metal fragment with Ti, Zr, Ta, W). Remarkably, even unactivated C–H bonds can be reversibly added across the M=N double bond (Scheme 2B).^[7] A recent study investigated the relative kinetic and thermodynamic selectivity for this 1,2-R–H addition.^[8] The H–H bond or the Si–H bond of silanes can also be reversibly cleaved across M=X multiple bonds.^[9] In this case, even a sulfido ligand X=S may act as an cooperating ligand. For example, [Cp*₂(py)Ti=S] cleaves reversibly H₂ to give [Cp*₂HTi-SH] (Cp* = pentamethylcyclopentadienyl, py = pyridine).^[10] The activation of H₂ is also

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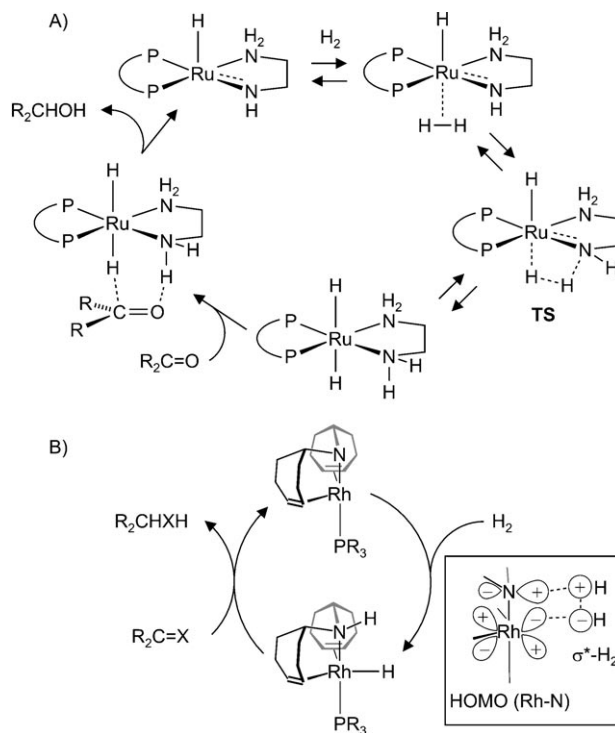


Scheme 2. A) Simplified catalytic cycle of alcohol dehydrogenation promoted by the copper enzyme galactose oxidase (GOase) with the tyrosinyl radical as cooperating ligand. B) C–H activation promoted by imido complexes ($\text{M}=\text{Ti, Zr}$; R' = siloxy or Cp, Cp^*) with the imido group as cooperating ligand. C) Dihydrogen activation promoted by a $[(\text{triphos})\text{Rh}^{\text{III}}(\mu\text{-S})_2\text{Rh}^{\text{III}}(\text{triphos})]^{2+}$ with a sulfido center as cooperating ligand. **TS** = transition state.

promoted by late transition-metal–sulfur bonds. A thorough computational study of this process showed that the H_2 molecule is heterolytically cleaved across a partial $\text{Rh}^{\text{III}}\text{-S}$ multiple bond of order 1.5 in the binuclear complex $[(\text{triphos})\text{Rh}^{\text{III}}(\mu\text{-S})_2\text{Rh}^{\text{III}}(\text{triphos})]^{2+}$ (triphos = 1,1,1-tris(diphenylphosphanyl)methyl)ethane) with a four-membered Rh_2S_2 heterocycle in the core (Scheme 2C).^[11] The related Ir^{II} sulfide, $[\text{Ir}_2(\mu\text{-S})_2(\text{PPh}_3)_4]$, which contains an butterfly- Ir_2S_2 core, reacts with two equivalents of H_2 to give $[\text{Ir}_2\text{H}_2(\mu\text{-H})(\mu\text{-S})(\mu\text{-SH})(\text{PPh}_3)_4]$.^[12] It is proposed that in the first step, H_2 adds oxidatively across the central $\text{Ir}^{\text{II}}\text{-Ir}^{\text{II}}$ bond, and in the second step, H_2 is split heterolytically across an $\text{Ir}\text{-S}$ bond, probably in an analogous fashion to that discussed above for

the rhodium complex $[(\text{triphos})\text{Rh}^{\text{III}}(\mu\text{-S})_2\text{Rh}^{\text{III}}(\text{triphos})]^{2+}$. A possible extension of the concept of cooperating ligands for heterolytic H_2 activation was recently discussed: The role of water molecules as ligands in the second coordination sphere which facilitate the heterolytic cleavage of H_2 in a Ru^{II} complex has been investigated with DFT methods. In the intermediate $[\text{RuCp}(\text{H}_2)(\text{H}_2\text{O})_3(\text{pta})_2]^+$ extensive hydrogen bonding through a chain of three H_2O molecules between the coordinated acidic H_2 molecule, and a remote basic nitrogen center in the pta ligand is proposed to be responsible for the lowering of the activation barrier (pta = 1,3,5-triaza-7-phosphaadamantane).^[13]

Amido ligands have been recognized as cooperating ligands in the homogeneously catalyzed hydrogenation of unsaturated substrates $\text{RR}^1\text{C}=\text{X}$, especially $\text{X}=\text{O, NR}$.^[14] Noyori's chiral Ru^{II} amido complexes stand out both in activity and enantioselectivity (TOF > 200 000 h^{-1} ; turnover numbers (TON) > 2×10^6 ; $ee > 98\%$).^[15] In the metal–ligand bifunctional mechanism (Scheme 3A), the H_2 molecule is

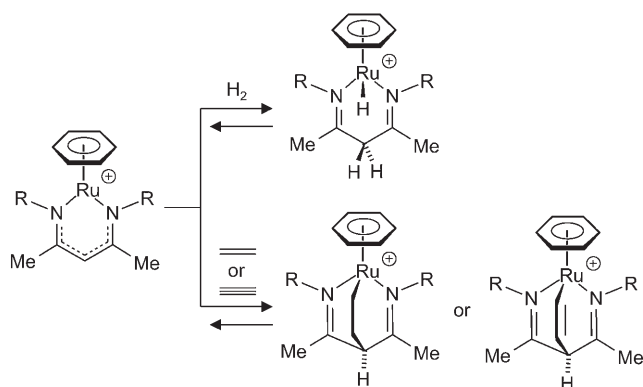


Scheme 3. A) Selected steps in the catalytic cycle of the Noyori–Morris mechanism, highlighting the role of the cooperating amido ligand in the heterolytic cleavage of the H_2 molecule promoted by $[\text{Ru}^{\text{II}}(\text{H})(\text{P}\text{P})\text{-}(\text{HN}\text{NH}_2)]$ complexes (PP = chelating diphosphane; HNNH_2 = ethylenediamine derivative). B) Dihydrogen activation and simplified catalytic cycle promoted by a Rh^{I} amido complex. **TS** = transition state.

cleaved across the $\text{Ru}^{\text{II}}\text{-amide}$ bond to give a Ru^{II} amino hydride complex. The substrate binds to this complex in the second coordination sphere by the $\text{NH}^{\delta+}$ and $\text{RuH}^{\delta-}$ groups, and is hydrogenated in a more-or-less concerted manner. Frequently, the bond activation process proceeds stepwise. The $\text{X}\text{-H}$ bond coordinates to a vacant coordination site at an

electrophilic metal center to form a $M(X-H)-\sigma$ -complex (valence electron configurations d^0-d^6) prior to the heterolytic cleavage across the $M-X$ bond, which has at least partial multiple-bond character. Experimental and theoretical studies indicate that the heterolytic cleavage reaction is generally the rate-determining step, with computed activation energies, E_a^{calc} , in the range of 8–10 kcal mol⁻¹.^[7,11,16] An exception is seen with a rhodium(I) amido complex with a sawhorse-type structure. The heterolytic cleavage of H_2 across the Rh^I amide single bond is exothermic and proceeds in a single step via a transition state at 14.5 kcal mol⁻¹ (Scheme 3B).^[17] This example also illustrates the performance of metal–ligand cooperation: The classical (metal monofunctional) oxidative addition of H_2 to the tetracoordinated Rh^I center leading to a Rh^{III} dihydride species has a higher activation barrier and is furthermore endothermic. The efficiency of the heterolytic cleavage is due to the fact that the HOMO of the Rh^I amide corresponds to the energetically high-lying anti-bonding combination of the lone pair at the nitrogen atom and the filled d_{xz} orbital at the Rh^I center which interacts favorably with the σ^* orbital of the H_2 molecule.

Unsaturated metallacycles can also show the characteristics of metal–ligand cooperativity in substrate binding (Scheme 4). The cationic Ru^{II} β -diketiminato complex adds



Scheme 4. Reversible binding of H_2 , ethylene, and acetylene to an unsaturated Ru^{II} β -diketiminato complex. $R = 2,6-(CH_3)_2C_6H_3$.

H_2 , ethylene, or acetylene across the ruthenium center and the central carbon atom of the β -diketiminato ligand, that is not directly bonded to the metal.^[18] Remarkably, these additions are fully reversible. Upon standing at room temperature in solution, complete recovery of the starting materials is achieved. In how far these equilibria play a role in the hydrogenation of unsaturated molecules remains to be investigated, but in the presence of the Ru^{II} β -diketiminato, catalytic hydrogenation of styrene is observed with modest activity.

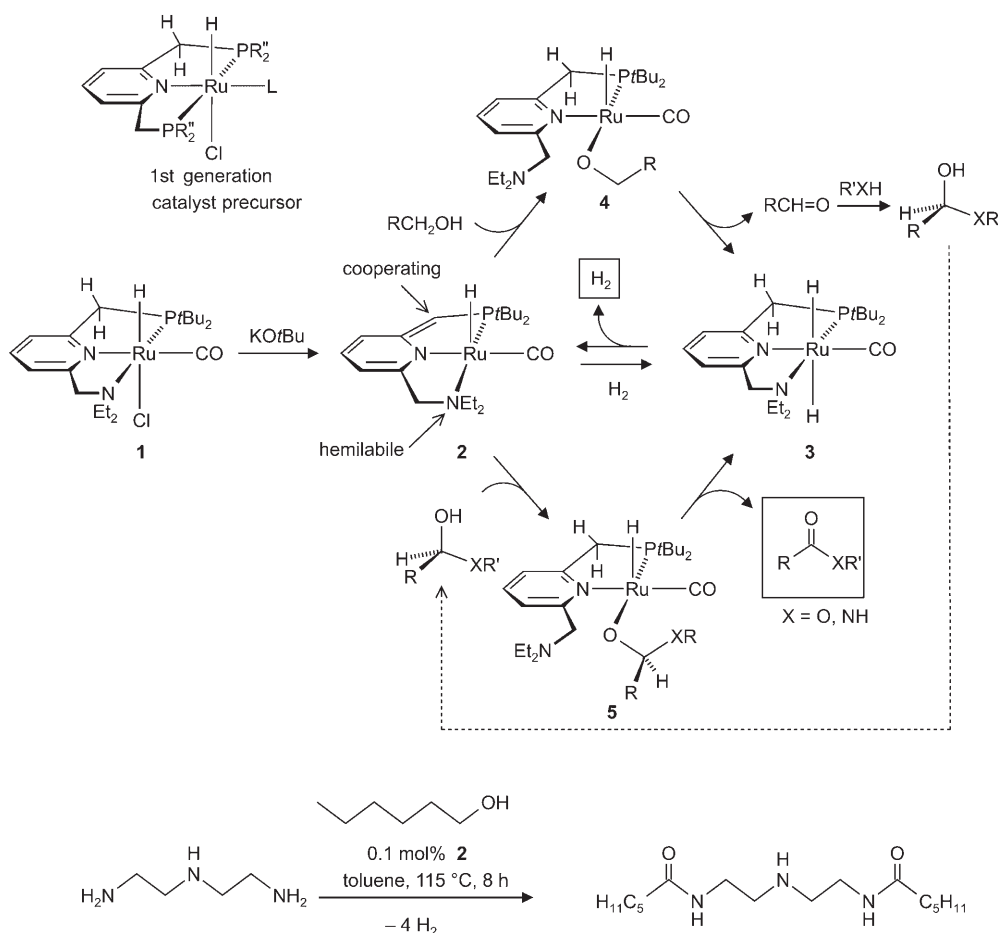
A few years ago, Milstein and co-workers started to investigate the ability of Ru^{II} complexes with the “pincer” bis(di(*tert*-butyl)phosphinomethyl)pyridine ligand (*t*Bu-PNP) to promote the acceptorless and acid-free dehydrogenation of alcohols to carbonyl compounds. With the complex $[Ru^{II}Cl(N_2)H(tBu-PNP)]$ (Scheme 5) with this first-generation catalyst precursor, secondary alcohols are converted into

the corresponding ketones with liberation of dihydrogen. However, the activity was low even at elevated temperatures (100 °C). A Ru^{II} dihydride as intermediate and classical organometallic steps were proposed for the catalytic cycle.^[19] Primary alcohols are not converted unless the steric hindrance of the metal complex is diminished by substituting the phosphorus-bonded *tert*-butyl groups for *i*Pr. With $[Ru^{II}Cl(CO)H(iPr-PNP)]$, 1-hexanol could be converted into the corresponding ester hexyl hexanoate and H_2 ; however, the activity was still low (68% conversion at 157 °C in 24 h with a substrate/catalyst (S/C) ratio of 1000:1).^[20] A significant improvement was achieved when a ligand was constructed which combines hemilability and cooperativity. Replacing one R''_2PCH_2 arm in the tridentate PNP ligand with an aminomethyl group leads to a PNN pincer ligand and introduces hemilability by the less strongly bound amino function (Scheme 5).

Reaction between precursor complex **1** and one equivalent of $KOtBu$ resulted in the deprotonation at the benzylic position of the R''_2PCH_2 arm and gave complex **2**. This red-brown complex contains an *exo*-methylene-substituted pyridine ring and a basic site in a β position to the metal. Remarkably, complex **2** reacts reversibly with H_2 to give the *trans*-dihydride **3**. Rearomatization of the pyridine ring is likely to be responsible for the cooperative effect of the ligand in this heterolytic cleavage reaction. Complex **2** is the most active catalyst for the acceptorless dehydrogenative esterification of alcohols known to date. A $TOF_{50} > 300 h^{-1}$ at 50% conversion and $TON > 900$ can be obtained in relatively short times (4–6 h) at temperatures slightly above 100 °C.

Milstein et al. report now the unique dehydrogenative coupling of primary amines and alcohols which directly leads to amides under liberation of H_2 ; this is a new reaction.^[21] With a loading of 0.1 mol% catalyst, >95% conversion is reached within a couple of hours at 115 °C. The catalyst in this reaction is again the Ru^{II} hydride complex **2** with the “dearomatized” PNN ligand. Key features that make this reaction successful are:

- 1) The ligand is hemilabile, and possesses a cooperative basic site in a β position to the metal (the deprotonated benzylic carbon of the *t*Bu₂PCH₂ substituent) which facilitates binding of the alcohol substrate to give intermediate **4**.
- 2) A β elimination process generates the dihydride **3** and an aldehyde. The latter reacts either with a second equivalent of alcohol to give a hemiacetal, or with an amine to give a hemiaminal, in a nonmetal-assisted reaction.
- 3) The dihydride **3** liberates a H_2 molecule to regenerate the catalyst **2**. Because H_2 escapes from the reaction mixture into the gas phase at elevated temperatures, the overall endothermic dehydrogenation reaction is driven to the product side. This elimination process is only possible because of the cooperative effect of the ligand (H_2 is formed from the $H^{\delta+}$ of the CH_2 group in the ligand and the $RuH^{\delta-}$ in a *cis* position). *Trans*-dihydrides are usually reluctant to eliminate H_2 .
- 4) In a second cycle, **2** may react with the hemiacetal or hemiaminal $RCH(OH)(XR')$ ($X = O, NH$) to form the product $RCO(XR')$ and a second equivalent of H_2 via intermediate **5**.



Scheme 5. Dehydrogenation of ROH to esters RCO(OR), or ROH and R'NH₂ to amides RCO(NHR') (R ≠ R') with Milstein's catalyst **2**. R'' = *i*Pr, *t*Bu; L = N₂, CO.

This process is highly selective, and in substrates with secondary and primary amine functions, only the latter are converted into amide groups. Thus, diethylenetriamine is converted in about 90% yield with two equivalents of 1-hexanol to the corresponding bis(amide) without any protecting group methodology (see Scheme 5, bottom).

The selected findings highlighted herein define ways for the rational design of new ligands. Further developments in catalysts in which metal and ligand cooperate in the sense defined above may eventually lead to more active species than classical transition metal catalysts in which the binding of the substrates and bond activation occurs only at a metal center. Even new catalytic reactions can be found, as the results of Milstein and co-workers impressively show. The future of homogeneous catalysts gained an even deeper shade of green.^[22]

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