**Cooperative Effects**

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# Cooperating Ligands in Catalysis

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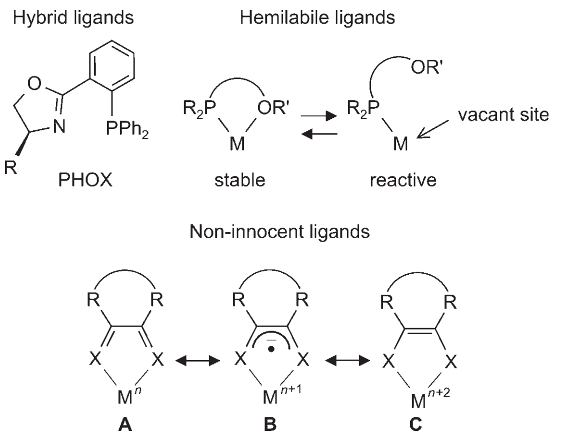
The properties of a metal complex as a whole are the result of the interaction of the metal center and its surrounding ligands. However, in some cases, a classification of ligands in categories such as hybrid ligands, hemilabile ligands, or non-innocent ligands may be practical (Scheme 1).



***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, $R_2P(CR_2)_nOR'$, or ester $R_2P(CR_2)_nCOOR'$, or phosphanyl amines, $R_2P(CR_2)_nNR'_2$, 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$^\bullet$, which is coordinated to a copper(II) center. With impressive activity (turnover frequencies, TOF, of up to $1\times10^6\,h^{-1}$) this enzyme converts chemoselectively primary alcohols into aldehydes (Scheme 2 A).[5] In the key step (b) of the catalytic cycle, the oxygen atom of the tyrosinyl radical abstracts a hydrogen atom from the α-$CH_2$ 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 an 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 2 B).[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 $H_2$ to give [$Cp^*_2$HTi-SH] (Cp* = pentamethylcyclopentadienyl, py = pyridine).[10] The activation of $H_2$ is also

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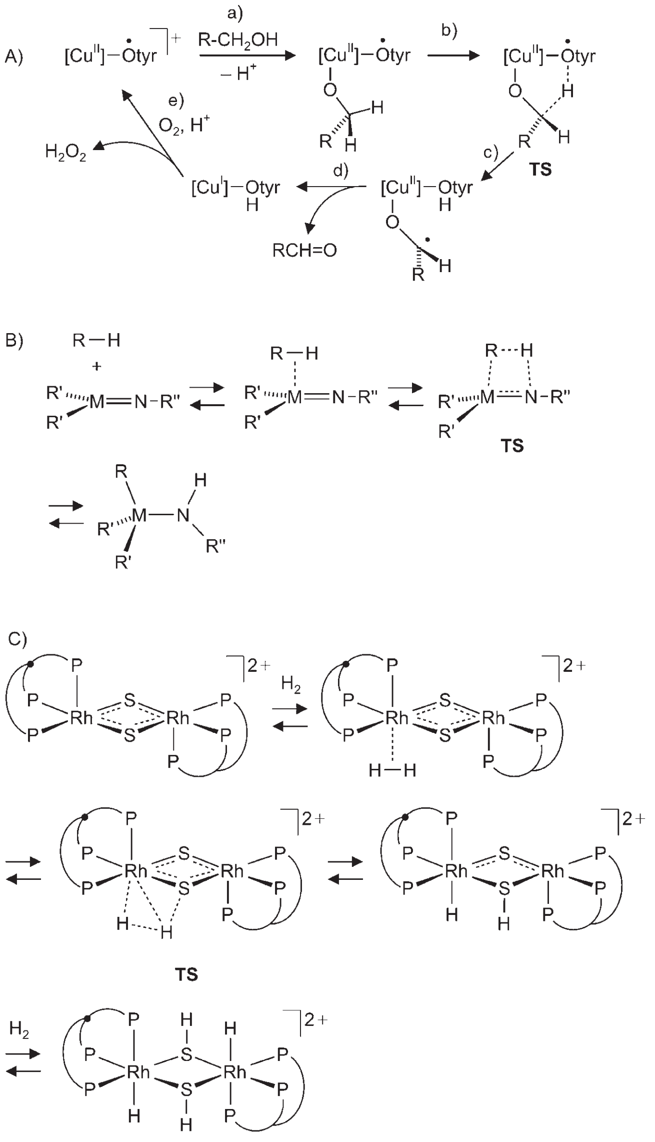
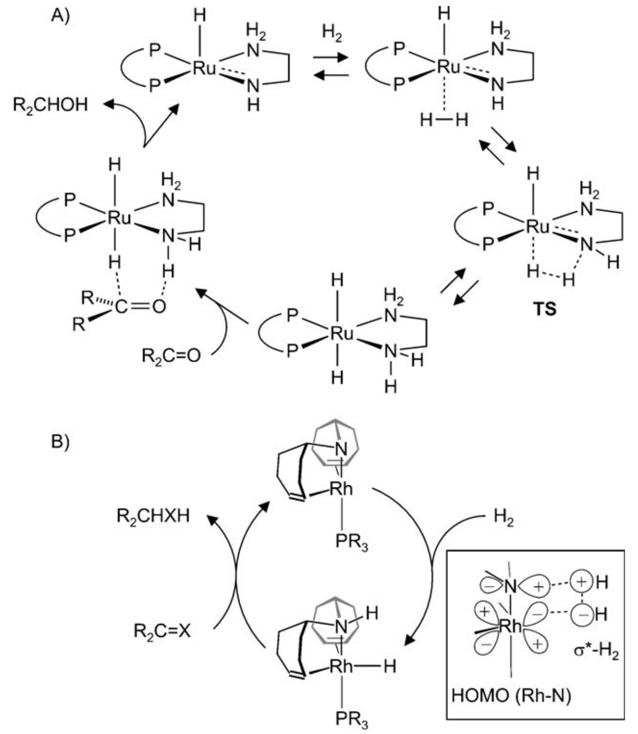


*Scheme 2.* A) Simplified catalytic cycle of alcohol dehydrogenation promoted by the copper enzyme galactose oxidase (GOase) with the tyrosinyl radical as cooperating ligand. B) C–H activation promoted by imido complexes (M = Ti, Zr; R′ = siloxy or Cp, Cp*) with the imido group as cooperating ligand. C) Dihydrogen activation promoted by a $[(triphos)Rh^{III}(\mu\text{-}S)_2Rh^{III}(triphos)]^{2+}$ 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 $Rh^{III}$–S multiple bond of order 1.5 in the binuclear complex $[(triphos)Rh^{III}(\mu\text{-}S)_2Rh^{III}(triphos)]^{2+}$ (triphos = 1,1,1-tris(diphenylphosphanylmethyl)ethane) with a four-membered $Rh_2S_2$ heterocycle in the core (Scheme 2C).[11] The related $Ir^{II}$ sulfide, $[Ir_2(\mu\text{-}S)_2(PPh_3)_4]$, which contains an butterfly-$Ir_2S_2$ core, reacts with two equivalents of $H_2$ to give $[Ir_2H_2(\mu\text{-}H)(\mu\text{-}S)(\mu\text{-}SH)(PPh_3)_4]$.[12] It is proposed that in the first step, $H_2$ adds oxidatively across the central $Ir^{II}$–$Ir^{II}$ bond, and in the second step, $H_2$ is split heterolytically across an Ir–S bond, probably in an analogous fashion to that discussed above for the rhodium complex $[(triphos)Rh^{III}(\mu\text{-}S)_2Rh^{III}(triphos)]^{2+}$. 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 $[RuCp(H_2)(H_2O)_3(pta)_2]^+$ 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]

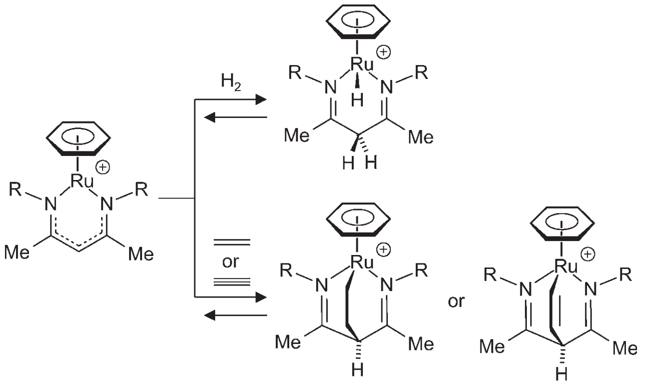
Amido ligands have been recognized as cooperating ligands in the homogeneously catalyzed hydrogenation of unsaturated substrates $RR^1C{=}X$, especially X = O, NR.[14] Noyori's chiral $Ru^{II}$ amido complexes stand out both in activity and enantioselectivity (TOF > 200 000 $h^{-1}$; turnover numbers (TON) > $2\times10^6$; *ee* > 98 %).[15] In the metal–ligand bifunctional mechanism (Scheme 3 A), the $H_2$ molecule is cleaved across the $Ru^{II}$–amide bond to give a $Ru^{II}$ amino hydride complex. The substrate binds to this complex in the second coordination sphere by the $NH^{\delta+}$ and $RuH^{\delta-}$ groups, and is hydrogenated in a more-or-less concerted manner. Frequently, the bond activation process proceeds stepwise. The X–H bond coordinates to a vacant coordination site at an



*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 $[Ru^{II}(H)(\widehat{P\,P})(H\widehat{N\,N}H_2)]$ complexes ($\widehat{P\,P}$ = chelating diphosphane; $H\widehat{N\,N}H_2$ = ethylenediamine derivative). B) Dihydrogen activation and simplified catalytic cycle promoted by a $Rh^I$ amido complex. **TS** = transition state.

electrophilic metal center to form a M(X−H)-σ-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-diketiminate complex adds $H_2$, ethylene, or acetylene across the ruthenium center and the central carbon atom of the β-diketiminate 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-diketiminate, catalytic hydrogenation of styrene is observed with modest activity.



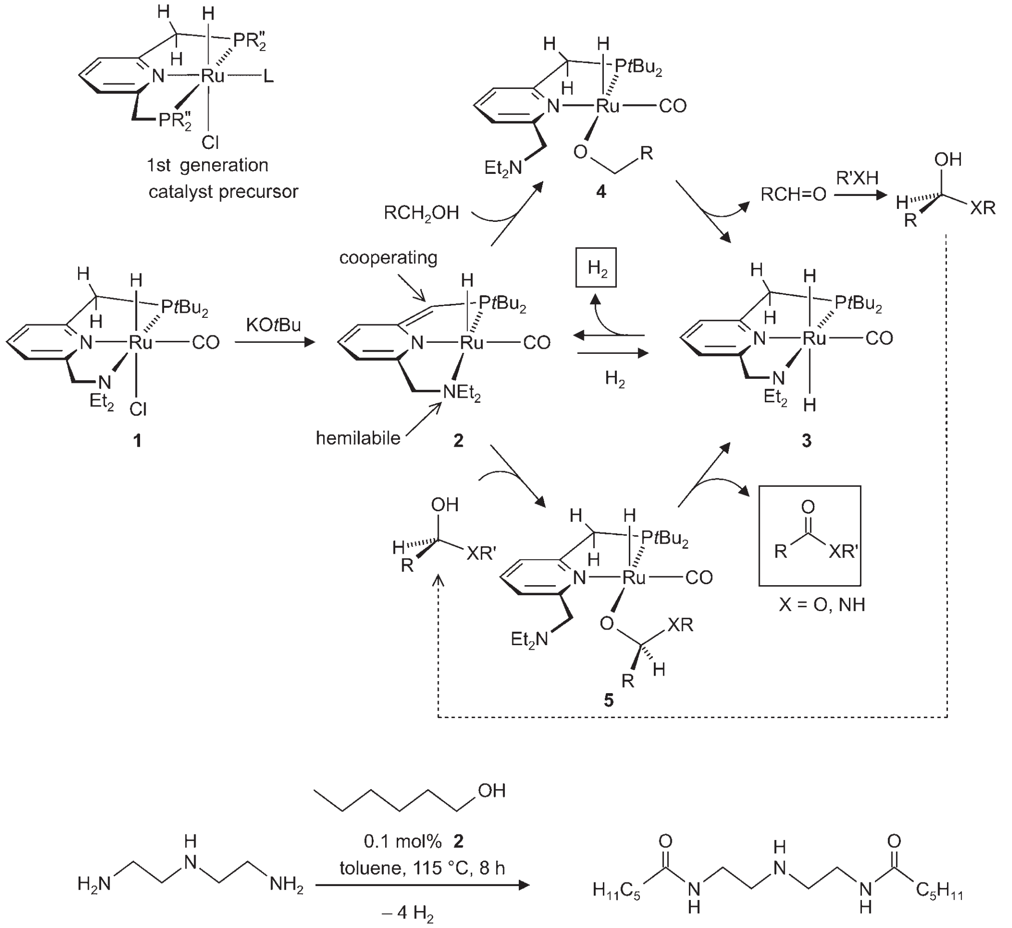
***Scheme 4.*** Reversible binding of $H_2$, ethylene, and acetylene to an unsaturated $Ru^{II}$ β-diketiminate complex. R = 2,6-$(CH_3)_2C_6H_3$.

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 $[Ru^{II}Cl(N_2)H(t\text{Bu-PNP})]$ (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 $[Ru^{II}Cl(CO)H(i\text{Pr-PNP})]$, 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 tridenate 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 KO*t*Bu 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 $tBu_2PCH_2$ 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 $R'NH_2$ to amides RCO(NHR′) (R ≠ R′) with Milstein's catalyst **2**. R″ = *i*Pr, *t*Bu; L = $N_2$, 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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