

Lloret-Fillol Research Group



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Abstract

Nature inspire us, we would like to mimic the transformations that sustain life. However, although these are fundamental processes, they have a huge technological potential that remains unharnessed. We aim to transfer concepts from artificial photosynthesis to the organic synthesis, to carry out endergonic transformations using sun-light as a driving force. These studies will trigger the development of new and greener and sustainable methodologies for the synthesis of fuels and transformation of organic molecules. To this end, we are currently investigating transformations catalysed by the reactivity of first

row transition metals (1RTM) Such as i) multi-proton/-electron reactions such as water oxidation, water and CO₂ reduction and reductions of organic compounds as well as ii) electro- and photocatalytic C-X (X = H, F, Cl or Br) activations mediated by biomimetic complexes based on earth abundant elements. Special emphasis is done on unravel the operative mechanisms by combination physical inorganic and organic chemistry, and theoretical methods. We are also rationally designing catalytic systems, with the aid of high-throughput screening techniques (HST), for the development of synthetic applications of interest.

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Single and multi-electron redox transformations are pivotal in metabolic routes that sustain life, and metalloenzymes usually responsible to execute them. Nature found highly efficient active sites bearing one or more redox active metals such as Mn, Fe, Ni, Co and Cu, which can carry out a myriad transformations with great technological potential. Examples of such transformations are the light-driven water oxidation (CaMn_4O_4) and the final storage of sunlight into chemical bonds *via* CO_2 reduction, the H_2 oxidation and proton reduction by hydrogenase enzymes (Fe and Ni), the methane hydroxylation by the soluble methane monooxygenase (sMMO) using O_2 as the oxidant (Fe and Cu), the biological activity of the vitamin B_{12} (Co), the C-H oxidation by heme and non-heme enzymes (Fe) and the dinitrogen fixation to ammonia (Fe, V, Mo). However, our knowledge about the role of the metal center, the biological mechanisms and our capacity of mimicking their reactivity and selectivity is limited. The preparation and study of model systems to emulate this fascinating reactivity is linked to the bases of the chemical fundamentals.

To emulate them with synthetic model systems that perform efficient and selective transformations, we need to consider all aspects present in the metallozymes that enhance the reactivity towards the desired transformations. For instance we need to manage single electron-proton events in all its versions of proton-couple-electron-transfer (PCET). Likewise, we need to control the metal ion oxidation states, understand the relationship between oxidation states, electron density, spin-state and reactivity, as well as how the electronic and geometric modifications of the first coordination sphere and interactions of the second coordination sphere impact in the reactivity and selectivity. In order to understand some of these questions we are development water oxidation, water reduction and CO_2 reduction reactions by bio-inspired catalysts and the expansion to new organic transformations.

Water Oxidation and high oxidation states

Water is the most appealing global-scale source of electrons that can be used to store energy into chemical bonds. However, the oxidation of the water molecule is an energetically uphill multi-proton-electron process identified as one of the bottlenecks for the development of artificial photosynthesis. Water oxidation needs to be catalysed in order to proceed at low energy barriers and practical reaction rates.

Intermediates involved in water oxidation are highly unstable and their characterization is very challenging.

Among the most challenging are the intermediates located after the O-O bond formation event, which is irreversible and usually the rate determining step. For this reason there is not clear experimental information of the reactivity nor of the intermediates after the O-O bond formation event. Fortunately, we have obtained a full characterization and reactivity of an intermediate located after the O-O bond formation.

The missing link characterized is better described as a **Ru^{IV} -peroxo** species (Figure 1) by means of spectroscopic (L-edge XAS) and spectrometric studies in combination with theoretical calculations. Those results will be disclosed in the due course.

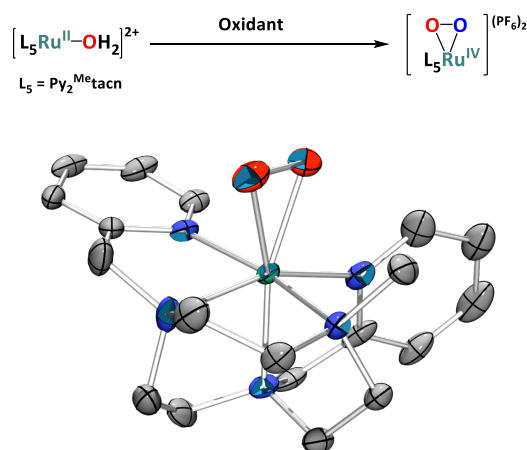


Figure 1. **Ru^{IV} -peroxo** intermediate relevant for water oxidation.

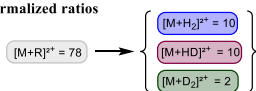
On the other hand, catalysts based on earth-abundant elements are also particularly desirable because of the low cost and availability, being iron among the most attractive candidates. We have shown that iron complexes are highly efficient water oxidation catalysts.

Likewise, the study of high oxidation states at iron complexes can trigger the development of other synthetic useful transformations. In this regard, the photolysis of $[\text{Fe}^{\text{III}}(\text{N}_3)(\text{MePy}_2\text{tacn})](\text{PF}_6)_2$ at 470 nm or 530 nm caused N_2 elimination and generation of a nitride species that on the basis of Mössbauer, magnetic susceptibility, EPR, and X-ray absorption, in conjunction with DFT computational analyses, which is formulated as

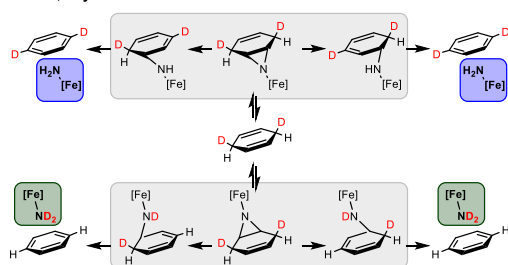
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$[\text{Fe}^{\text{V}}(\text{N})(\text{MePy}_2\text{tacn})]^{2+}$. Results indicate that the later compound is a low-spin ($S = 1/2$) iron(V) species, which exhibits a short Fe-N distance (1.64 Å), as deduced from EXAFS analysis. $[\text{Fe}^{\text{V}}(\text{N})(\text{MePy}_2\text{tacn})]^{2+}$ is only stable at cryogenic (liquid N_2) temperatures, and frozen solutions as well as solid samples decompose rapidly upon warming, producing N_2 . However, the high-valent compound could be generated in the gas phase and its reactivity against olefins, sulphides and substrates with weak C-H bonds studied. $[\text{Fe}^{\text{V}}(\text{N})(\text{MePy}_2\text{tacn})]^{2+}$ proved to be a powerful two-electron oxidant that can add the nitride ligand to olefin and sulphide sites, as well as oxidize cyclohexadiene (Figure 2) substrates to benzene in a formal H_2 transfer process. In summary, $[\text{Fe}^{\text{V}}(\text{N})(\text{MePy}_2\text{tacn})]^{2+}$ constitutes the first case of an octahedral $\text{Fe}^{\text{V}}(\text{N})$ species prepared within a neutral ligand framework, and adds to the few examples of Fe^{V} species that could be spectroscopically and chemically characterized.

Experimental normalized ratios



cis-d6-1,4-cyclohexadiene.



trans-d6-1,4-cyclohexadiene.

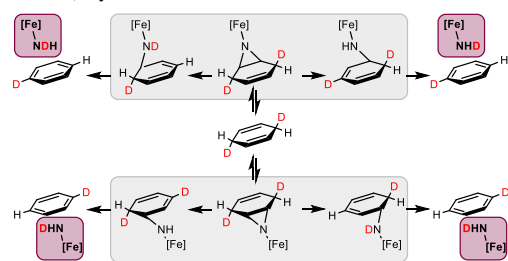


Figure 2. Reactivity of $[\text{Fe}^{\text{V}}(\text{N})(\text{MePy}_2\text{tacn})]^{2+}$ in gas phase against d6-1,6-cyclohexadiene.

Water and CO_2 Reduction

Metal complexes have shown to be very efficient in the catalytic water and CO_2 reduction under electro- and photocatalytic conditions. However, the operating mechanisms are still not fully understood and efficiencies do not meet the

requirements for real world applications yet. Therefore, there is still a need for developing new systems to extract mechanistic information, and exploring new concepts to enhance their reactivity and selectivity. Indeed, selectivity is a key issue in CO_2 reduction that can be controlled by molecular complexes. In addition, new reactivity could be envisioned from intermediates involved in these transformations. For example metal complexes in low oxidation state and transition metal hydride complexes ($\text{M}-\text{H}$) are intermediates in hydrogen evolution catalysis. Therefore, new selectivities of reduction of organic molecules can be envisioned by following reaction pathways via $\text{M}-\text{H}$ heterolytic (H^- transfer) or homolytic (H^\bullet transfer) cleavage.

Since the first report on water reduction with aminopyridine complexes the family of compounds has notably grown. These cobalt systems have several advantages i) are water soluble, ii) are based on abundant metals in the earth crust and iii) their electronic and steric properties are easily tuneable. Moreover, the high basicity of the ligands favours the heterolytic water reduction mechanism, which is highly desirable for the immobilization of the catalysts onto an electrode or a semiconductor, since the homolytic mechanism follows a bimetallic coupling pathway. Altogether suggests that they are very appealing catalysts to study the water reduction mechanism.

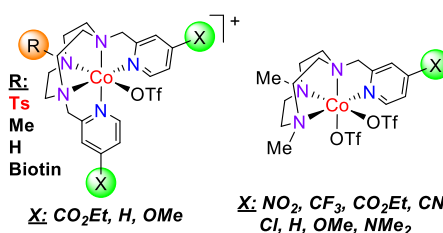


Figure 3. Cobalt aminopyridine complexes active in electro- and photocatalytic proton and CO_2 reduction.

In 2014, we reported an new family of very efficient electro- and photochemical water reduction catalysts (WRC) $[\text{Co}(\text{Py}_2^{\text{Ts}}\text{tacn})(\text{OTf})](\text{OTf})$ (Figure 3), even in pure water which is still very difficult to achieve. The system based 1,3,5-triazacyclononane (tacn), a very basic moiety, which confer unique properties among WRC. In this line we have expanded the family of cobalt catalysts $[\text{Co}^{\text{II}}(\text{OTf})_2(\text{Y}^{\text{X}}\text{PyMetacn})]$ to the readily available family of tetradentate ligands 1,4-dimethyl-7-[2'-(4 β ,6 γ -pyridyl)methyl]-1,4,7-triazanonane (Figure 3). The modification of

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electronic properties of the ligand is done by introducing a range of substituents at the pyridine ring. The catalysts obtained show high activity in both electrochemical (overpotentials 150-500 mV) and photochemical reduction of water to H₂. Up to TON >8500, TOF >14 s⁻¹ were obtained in CH₃CN:H₂O:Et₃N (6:4:0.2 mL) at 25 °C. Moreover, we provided evidences of the key intermediates in the photocatalytic water reduction and identified the protonation of the cobalt as the rate-determining step by combination of stoichiometric, kinetics, deuterium labelling and computational modelling. Moreover, we provided a unified scheme to rationalize the electronic effects. This information will be of value for the design of more active water reduction catalysis.

The easy functionalization of the catalysts allows us to obtain metalloenzymes based on the biotin-streptavidin adduct. Interestingly, the cobalt complex is more active as photo- and electrocatalyst for water reduction inside of the protein cavity. We rationalized this effect with the help of computational dynamics due to the proximity of protonated aminoacids of the cavity and the metal center (Figure 4).

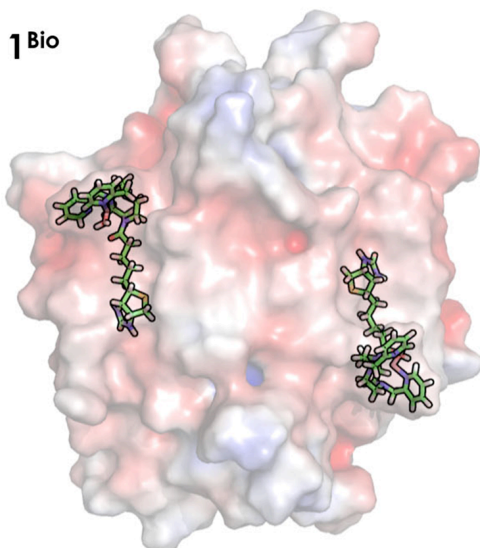


Figure 4. The most populated structure out of 3 independent MD simulation. The cobalt complexes has the general formula [Co(^XPy₂^Rtacn)(OTf)](OTf).

Our results also show that both families of complexes are active as catalysts for both photo- and electro CO₂ reduction to CO with an exquisite selectivity.

Beyond Artificial Photosynthesis

Mimicking Natural photosynthesis has the potential to provide greener and light-driven methodologies for sustainable fuel production but also synthetic products. In both cases endergonic reactions must be carried out. Nevertheless, added value chemicals have less scaling and economic restrictions than the production of energy carriers. Therefore, the use of concepts derived from Natural and artificial photosynthesis to perform selective transformations can provide the development of greener chemical transformations.

Currently, we are expanding this concept by employing our designed cobalt complexes, based on aminopyridine ligands and initially developed for water reduction to hydrogen, in combination with a photoredox catalyst to reduce organic molecules (Figure 5).

Mechanistic investigations suggested that molecular cobalt-hydride intermediates are involved in the H₂ formation when using aminopyridine-based cobalt complexes. Based on these findings, we envisioned that the photochemically-obtained [Co]-H species could be a potential catalytic intermediate for the reduction of organic functionalities using the combination of light, H₂O and an electron donor as formal hydrogen source.

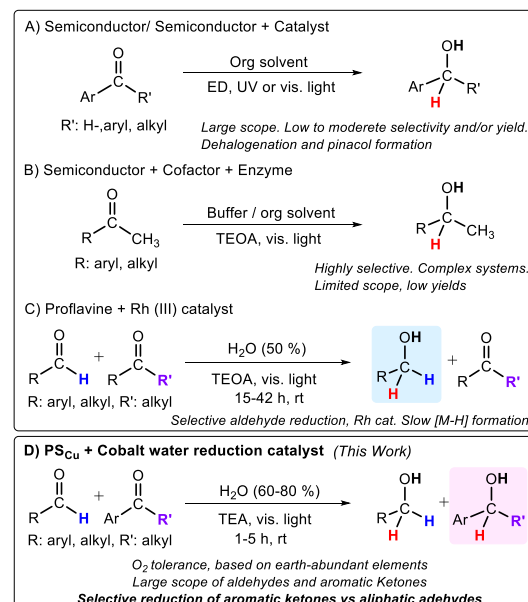


Figure 5. Methodologies for the light-driven reduction of carbonyl compounds. Abbreviations: ED: Electron Donor, TEOA: Triethanolamine, TEA: triethylamine.

We have developed a methodology for the light-driven reduction of ketones, aldehydes and olefins. We have also obtained the

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homocoupling of olefins. The reduction of those organic substrates in aqueous media is very remarkable since the putative cobalt-hydride intermediates are highly reactive towards protons (Figure 6).

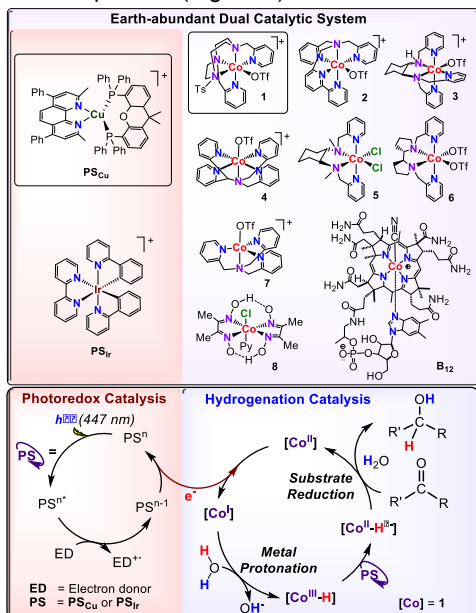


Figure 6. Earth-abundant Dual Catalytic System for the photoreduction of aromatic ketones and aldehydes.

Our mechanistic investigations suggest that the reduction mechanism is substrate dependent, being both active the hydride transference and the hydrogen atom transfer.

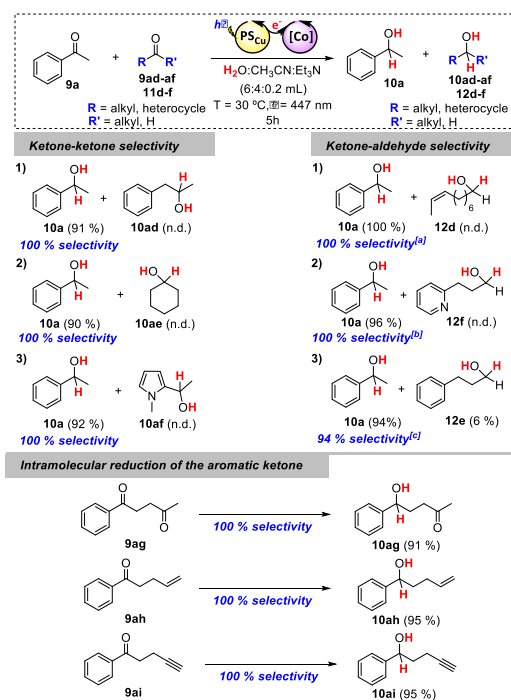


Figure 7. Competitive photoreductions. Conditions: 1 (1 mol%), PSCu (1.5 mol%), Substrate A + B (16.5 mM, 1:1), in H₂O:CH₃CN:Et₃N (6:4:0.2 mL) irradiated (447 nm) for 5 h at 30 °C under N₂. ^[a]35, ^[b]50 and ^[c]30 min reaction, respectively. The isolated products were identified and characterized by NMR.

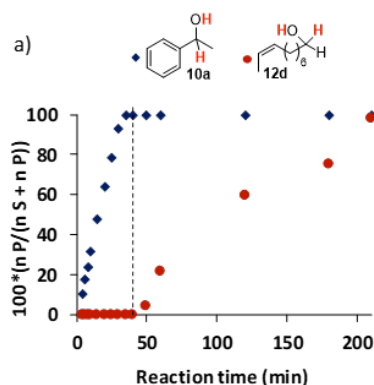


Figure 8. Competitive photoreductions. The black dotted line indicates where the aldehyde start reacting.

More interestingly, the system presents an exquisite selectivity for the reduction of acetophenone versus aliphatic aldehydes. Indeed, this selectivity is unprecedented for previous metal catalyzed transformations. The present system benefits from avoiding the use of protecting-deprotecting steps and the use of stoichiometric amounts of lanthanides, which are required in other reduction methods of ketones and aldehydes (Figure 7 and 8).

High-throughput experimental techniques

In order to accelerate the development of light-driven methodologies we have developed parallel screening platforms of 24 and 48 reactions under temperature (-80 to 120 °C) and light intensity control. A new design provides an anaerobic environment, which allows for low temperature studies. The irradiation is homogeneous in all reaction positions with a standard deviation lower than 2.5 %.



Figure 9. New design of the photoreactor with Bluetooth interphase.

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We have developed a system to calibrate the light-intensity. With the calibration, the High-throughput screening photoreactors (HTSP)

designed are a convenient toolkit to precisely control all different variables that affect the reactions.

Articles

"Making and Breaking of the O-O Bond at Iron Complexes" *Coord. Chem. Rev.* **2017**, *334*, 2-24. Ilaria Gamba, Zoel Codolà, Julio Lloret-Fillol,* Miquel Costas*

"Generation, spectroscopic and chemical characterization of an octahedral iron (V) – nitrido species with a neutral TACN-based pentadentate ligand platform" *J. Am. Chem. Soc.*, **2017**, *139*, 9168–9177. Gerard Sabenya, Laura Lázaro, Ilaria Gamba, Vlad Martin-Diaconescu,* Erik Andris, Thomas Weyhermüller, Frank Neese,* Jana Roithova,* Eckhard Bill,* Julio Lloret-Fillol,* Miquel Costas.*

"Cobalt-Copper Dual Light-Driven Catalytic Reduction of Aldehydes and Aromatic Ketones in Aqueous Media" *Chem. Sci.*, **2017**, *8*, 4739-4749. Arnau Call, Carla Casadevall, Ferran Acuña-Parés, Alicia Casitas, and Julio Lloret-Fillol* *Cover picture and Highlighted in Chemistry World from RSC and ChemistryViews from wiley.*

Patents

Lloret-Fillol, J.; Casadevall, C.; León, J.; Call, A.; Casitas, A.; Pla, J. J.; Hernández, P. J.; Caldentey, X. F.: Photoreactor. Submitted as: European Patent. Fundació privada Institut Català d'Investigació Química (Application No 17382313.9-1370, application date 31.05.2017)

Lloret-Fillol, J.; Casitas, A.; Call, A.; Casadevall, C. Un procedimiento de reducción fotocatalítico y una composición catalizadora utilizada en el procedimiento. Submitted as: PCT. Fundació privada Institut Català d'Investigació Química (Application No PCT/ES2017/070314, application date 10.05.2017)