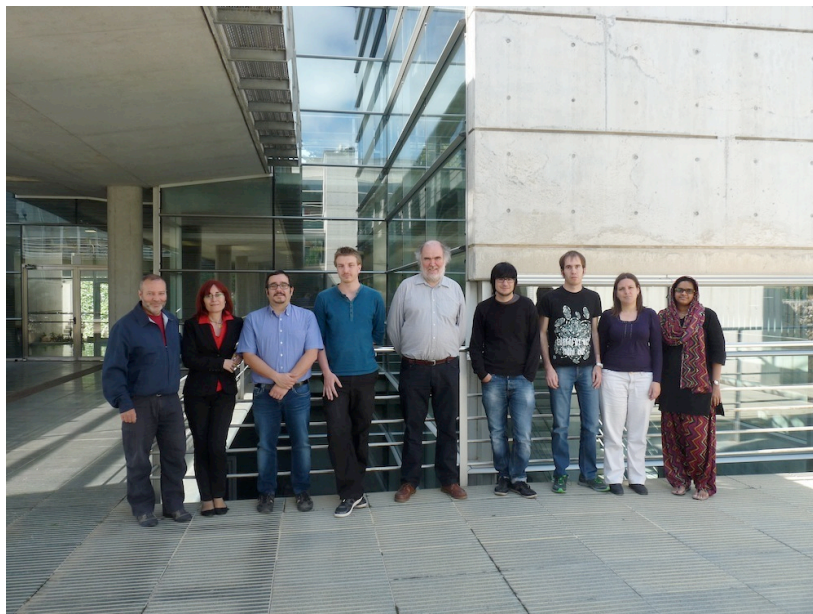


Maseras Research Group



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Abstract

Computational chemistry is applied to the study of different chemical processes of practical interest. DFT and DFT/MM methods are used to different processes in homogeneous catalysis, in

most cases in collaboration with experimental groups. Studies in 2013 focused on cross-coupling processes and the reactivity of metal-stabilized fragments.

Cross-coupling and related processes

Palladium-catalyzed C-C cross-coupling reactions (Suzuki-Miyaura, Negishi, Stille, Sonogashira, etc.) are among the most useful reactions in modern organic synthesis because of their wide scope and selectivity under mild conditions. The many steps involved and the availability of competing pathways with similar energy barriers cause the mechanism to be quite complicated. In addition, the short-lived intermediates are difficult to detect, making it challenging to fully characterize the mechanism of these reactions using purely experimental techniques. Therefore, computational chemistry has proven crucial for elucidating the mechanism and shaping our current understanding of these processes. This mechanistic elucidation provides an opportunity to further expand these reactions to new substrates and to refine the selectivity of these reactions.

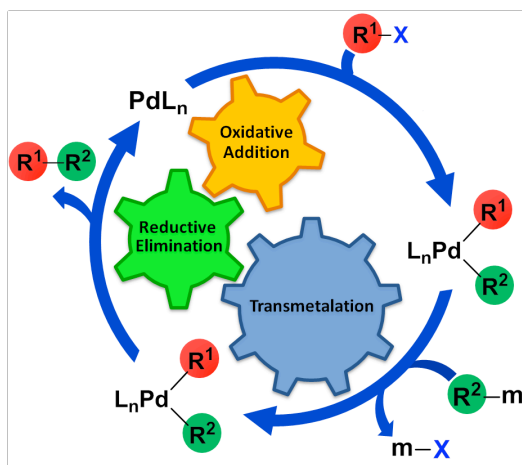


Fig. 1 - Palladium-catalyzed C-C cross-coupling is a complex process where all the gears must work together in order to achieve efficiency.

During the past decade, we have applied computational chemistry, mostly using density functional theory (DFT), to the study of the mechanism of C-C cross-coupling reactions. In this year 2013, we published a review article in collaboration with the group of Prof. Lledós (UAB) summarizing the results of our work (see Fig 1). Apart from a few studies on the general features of the catalytic cycles that have highlighted the existence of manifold competing pathways, most studies have focused on a specific reaction step, leading to the analysis of the oxidative addition, transmetalation, and reductive elimination steps of these processes. In oxidative addition, computational studies have

clarified the connection between coordination number and selectivity. For transmetalation, computation has increased the understanding of different issues for the various named reactions: the role of the base in the Suzuki-Miyaura cross-coupling, the factors distinguishing the cyclic and open mechanisms in the Stille reaction, the identity of the active intermediates in the Negishi cross-coupling, and the different mechanistic alternatives in the Sonogashira reaction. We have also studied the closely related direct arylation process and highlighted the role of an external base as proton abstractor. Finally, we have also rationalized the effect of ligand substitution on the reductive elimination process.

Apart from that, we examined in this year 2013 one of the fundamental steps of the catalytic cycle, oxidative addition, in collaboration with the experimental group of Prof McIndoe (Victoria, Canada) (see Fig. 2). Palladium(0) complexes facilitate many catalytic transformations that begin with the oxidative addition of a halobenzene. The ligation state of the palladium during this reaction is a vexing issue, owing to the inherent difficulty of isolating reactive, coordinatively unsaturated metal complexes. By isolating them in the gas phase in an ion-trap mass spectrometer, the reactivity of mono- and bisligated palladium complexes can be directly compared, and the former proved to be several orders of magnitude more reactive towards halobenzenes. Calculations of barrier heights for the oxidative addition led to additional experiments, which demonstrated that although the reaction proceeded to completion for iodobenzene, the reaction was slower for bromobenzene and progressed only as far as an ion-molecule adduct for chloro- and fluorobenzene.

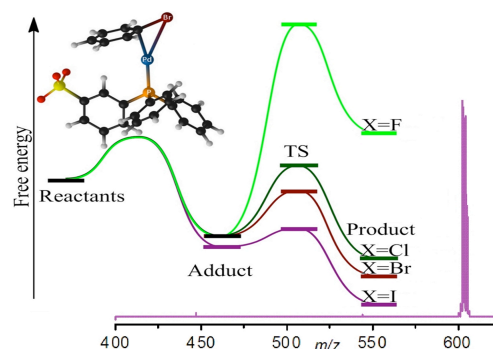


Fig. 2 - Computed free energy profile for the oxidative addition of halobenzenes to PdL complexes, together with the mass spectrometry result from the experiment with iodobenzene.

Metal-stabilized reactive fragments

There is an important family of processes where a chemical bond that is usually inert is activated by a high-energy intermediate where a reactive fragment is stabilized by its association to a transition metal center. Two such reactive fragments, carbene and nitrene, were considered in two different collaborations with the group of Prof. Pérez (Huelva).

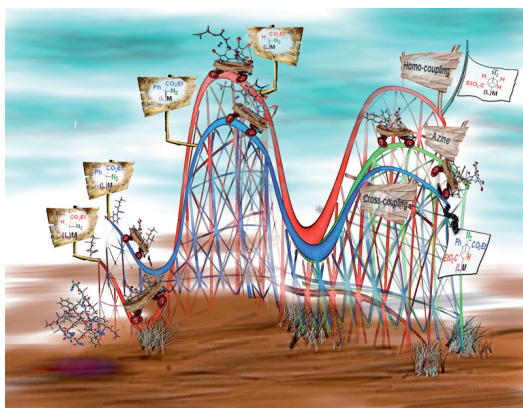


Fig. 3 - The reaction of diazocompounds with copper and silver complexes leads to a rollercoaster of reaction pathways leading to up to three different products.

Concerning carbene reactivity, we examined the ability of Tp^xM (Tp^x = hydrotris(pyrazolyl)borate ligand; $\text{M} = \text{Cu}$ and Ag) and IPrMCl ($\text{IPr} = 1,3$ -bis(diisopropylphenyl)imidazol-2-ylidene; $\text{M} = \text{Cu}, \text{Ag}, \text{Au}$) complexes as catalyst precursors for the coupling of diazo compounds. Experimental data showed that the metal centre can be tuned with the appropriate selection of the ligand to yield either the homo- or hetero-coupling (cross-coupling) products. A computational study of the reaction mechanism allowed the rationalization of the experimental reactivity patterns (see Fig. 3), and the identification of the key reaction step controlling the selectivity: the initial reaction between the metallocarbene intermediate and one of the diazo compounds.

Concerning the reactivity of nitrenes, we examined the mechanism of olefin aziridination processes. The olefin aziridination reactions catalyzed by copper and silver complexes bearing hydrotris(pyrazolyl)borate (Tp^x) ligands have been investigated from a mechanistic

point of view. Several mechanistic probe reactions were carried out, specifically competition experiments with *p*-substituted styrenes, stereospecificity of olefins, effects of the radical inhibitors, and use of a radical clock. Data from these experiments seem to be contradictory, as they do not fully support the previously reported concerted or stepwise mechanisms. But theoretical calculations have provided the reaction profiles for both the silver and copper systems with different olefins to satisfy all experimental data. The key happens to be in the spin states (see Fig. 4). A mechanistic proposal has been made on the basis of the information that we collected from experimental and theoretical studies. In all cases, the reaction starts with the formation of a metal–nitrene species that holds some radical character, and therefore the aziridination reaction proceeds through the radical mechanism. The silver-based systems however hold a minimum energy crossing point (MECP) between the triplet and closed-shell singlet surfaces, which induce the direct formation of the aziridines, and stereochemistry of the olefin is retained. In the case of copper, a radical intermediate is formed, and this intermediate constitutes the starting point for competition steps involving ring-closure (through a MECP between the open-shell singlet and triplet surfaces) or carbon–carbon bond rotation, and explains the loss of stereochemistry with a given substrate. Overall, all the initially contradictory experimental data fit in a mechanistic proposal that involves both the singlet and the triplet pathways.

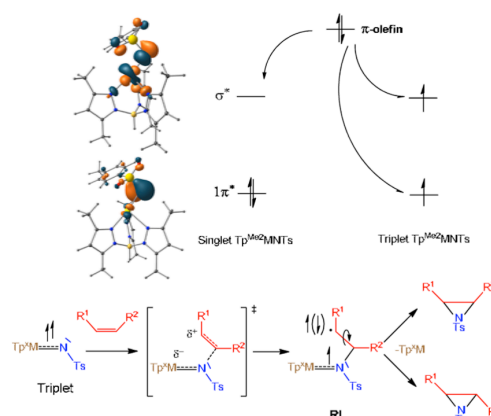


Fig. 4 - Molecular orbitals involved in the singlet-triplet conversion during the olefin aziridination process.

Other catalytic processes

Apart from the main lines of research outlined above, we make also an effort to study promising new processes where mechanistic understanding is still lacking. During this year 2013 we examined a process that combines two increasingly appealing reactions such as oxidative coupling and trifluoromethylation (see Fig. 5).

The reaction mechanism for the copper(I)-catalyzed oxidative aerobic trifluoromethylation of terminal alkynes has been determined by DFT calculations. The transmetalation of CF_3^- to copper appears to be a ligand replacement process independent of the metal. The dioxygen activation follows the sequence η^1 -

superoxocopper (II), μ - η^2 : η^2 -peroxodicopper (II) and bis(μ -oxo)-dicopper (III).

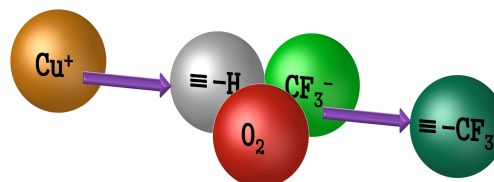


Fig. 5 - A single catalytic process is able to replace the terminal hydrogen of an alkyne by trifluoromethyl.

Articles

“A General Mechanism for the Copper- and Silver-Catalyzed Olefin Aziridination Reactions: Concomitant Involvement of the Singlet and Triplet Pathways”

J. Am. Chem. Soc. (2013) 135, 1338 – 1348

L. Maestre, W. M. C. Sameera, M. M. Díaz-Requejo, F. Maseras, P. J. Pérez

“Oxidative Additions of Aryl Halides to Palladium Proceed through the Monoligated Complex”

K. Vikse, T. Naka, J. S. McIndoe, M. Besora, F. Maseras

ChemCatChem (2013) 5, 3604 – 3609

“Catalytic cross-coupling of diazo compounds with coinage metal-based catalysts: an experimental and theoretical study”

Dalton Trans. (2013) 42, 4132 – 4138

I. Rivilla, W. M. C. Sameera, E. Alvarez, M. M. Díaz-Requejo, F. Maseras, P. J. Pérez

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“Computational perspective on Pd-catalyzed C-C cross-coupling reaction mechanisms”

Acc. Chem. Res. (2013) 46, 2626 – 2634

M. García-Melchor, A.A.C. Braga, A.Lledós, G. Ujaque, F. Maseras