

Maseras Research Group



Group Leader: Feliu Maseras

Postdoctoral Researchers: Maria Besora / Oier Lakuntza

PhD Students: Víctor Fernández / Rositha Kuniyil/ Ignacio Funes / Charles Goehry (until July)

Master Students: Adiran J. De Aguirre

System administrator: Martín Gumbau

Programmer: Moisés Alvarez

Administrative Support: Núria Vendrell

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 2014 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. We have studied in the last decade a variety of these processes by computational means, with particular emphasis on the Suzuki-Miyaura reaction.

Recent experimental reports had called into question the validity of the boronate mechanism (through a $R-B(OH)_3^-$ intermediate) for the transmetalation step in the Suzuki-Miyaura cross-coupling, favoring instead the palladium hydroxo pathway (through a $[L_nPd(R')(OH)]$ intermediate). We reported, in a collaboration with the group of Lledós and Ujaque at Universitat Autònoma de Barcelona, Density Functional Theory (DFT) calculations with the M06 functional carried out on realistic model systems, including a combination of explicit solvent molecules along with a continuum method. DFT calculations account for the role of the hydroxide base in the Suzuki-Miyaura transmetalation step, considering either boronate species or Pd-hydroxo complexes. Theory confirms that both scenarios leading to Pd-boronate species are feasible, although the pathway involving boronate intermediates is favored. Overall, the highest energy transition state corresponds with the Pd-C bond formation process. The mechanistic proposal, summarized in Fig. 1, is shown to be compatible with the available experimental evidence.

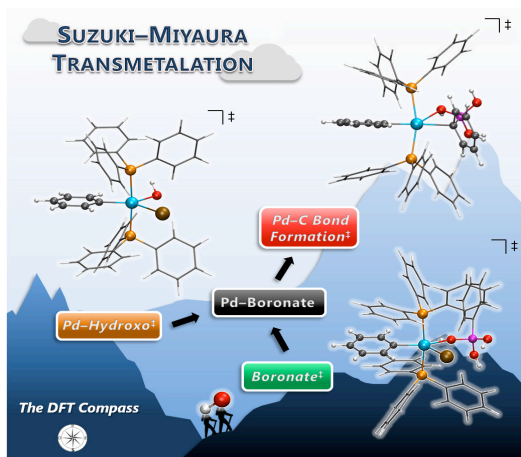


Fig. 1 - Computed free energy landscape for the transmetalation in the Suzuki-Miyaura reaction.

An interesting extension to the conventional cross-coupling, where one organic fragment is bound to an electropositive substituent and the other one is bound to an electronegative one, is provided by oxidative coupling, where both organic fragments to electronegative fragments, which are in principle more abundant. The copper-catalyzed oxidative homocoupling of terminal alkynes was studied with DFT methods. The role of Cu(I) or Cu(II) as initial oxidation state, as well as the effect of changes in the substrate and the base were examined. Oxidants responsible for outer- and inner-sphere electron transfer processes were also investigated. The Cu/O₂ interactions, which arise when dioxygen is employed as oxidant, were treated explicitly to fully describe the 4-electron reduction process, providing a plausible mechanism that could serve as a model for other aerobic oxidative couplings. The obtained results, highlighted in Fig. 2, completely agree with the reported experimental data, the computed free energy barriers are low enough for the reactions to proceed at room temperature, and electron-poor alkynes and stronger bases lead to faster reactions.

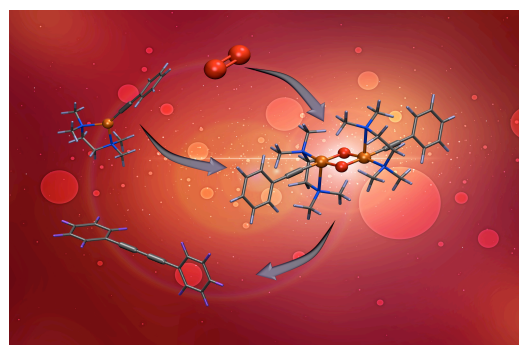


Fig. 2 - Reaction scheme for the oxidative coupling of two terminal alkynes catalyzed by copper complexes using dioxygen as oxidant.

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. One such reactive fragments, nitrene, was found to play a key role in two different studies in collaboration with different experimental groups.

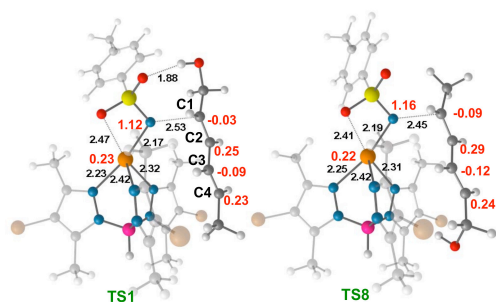


Fig. 3 - The two lowest energy transition states leading to aziridine products of (2*E*,4*E*)-hexa-2,4-dien-1-ol catalyzed by $\text{Tp}^{\text{Br}}\text{Ag}$. Selected distances (Å) in black. Selected spin atomic populations in red.

In collaboration with the experimental groups of Pérez (Huelva) and Castellón (URV), we studied the control of regio and enantioselectivity in a silver-catalyzed aziridination. Silver complexes bearing trispyrazolylborate ligands (Tp^{x}) catalyze the aziridination of 2,4-diene-1-ols in a chemo-regio- and stereoselective manner to give vinylaziridines in high yields by means of the metal-mediated transfer of NTs (Ts = *p*-toluensulfonyl) units from $\text{PhI}=\text{NTs}$. The preferential aziridination occurs at the double bond neighboring to the hydroxyl end in ca 9:1 ratios that assessed a very high degree of regioselectivity. The reaction with the silver-based catalysts proceeds in a stereospecific manner, *i. e.*, the initial configuration of the C=C bond is maintained in the aziridine product (*cis* or *trans*). The degree of regioselectivity was explained with the aid of DFT studies, where the directing effect of the OH of group of 2,4-diene-1-ols play a key role (see key transition state in Fig. 3). Effective strategies for ring-opening of the new aziridines, deprotection of the Ts group and subsequent formation of β -amino alcohols were also developed.

In collaboration with the groups of Pérez (Huelva) and Pericàs (ICIQ) we characterized the mechanism of a copper-catalyzed synthesis of oxazoles. Well-defined copper(I) complexes of composition $[\text{Tpm}^{\text{Br}}\text{Cu}(\text{NCMe})]\text{BF}_4$ (Tpm^{Br} = tris(3,5-dimethyl-4-bromo-pyrazolyl)methane) or $[\text{Tpa}^{\text{x}}\text{Cu}]\text{PF}_6$ (Tpa^{x} = tris(3,5-dimethyl-pyrazolylmethyl)amine) catalyze the formation of 2,5-disubstituted oxazoles from carbonyl azides and terminal alkynes in a direct manner. This process represents a novel procedure for the synthesis of this valuable heterocycle from

readily available starting materials, leading exclusively to the 2,5-isomer, assessing a completely regioselective transformation. Experimental evidences and computational studies (see key transition states in Fig. 4) allowed the proposal of a reaction mechanism based on the initial formation of a copper-acyl nitrene species, in contrast with the well-known mechanism for the copper-catalyzed alkyne and azide cycloaddition reactions (CuAAC) that is triggered by the formation of a copper-acetylide complex.

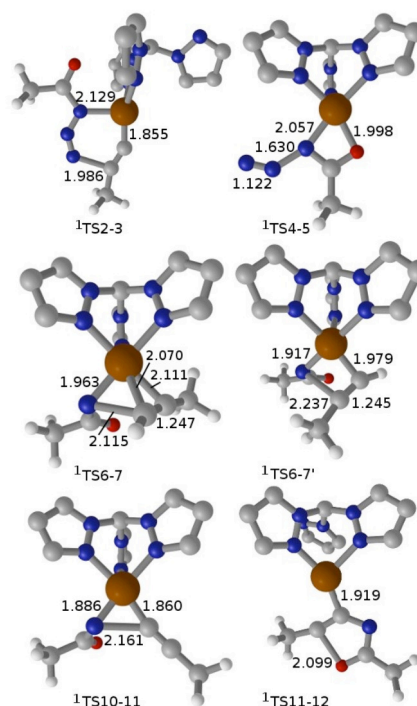


Fig. 4 - Key transition states in the copper-catalyzed synthesis of oxazoles. Key distances given in Å.

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 2014 we examined two such processes, dicarbonylation and carbon dioxide fixation.

The mechanism for the phosphine free palladium catalyzed carbonylation of aryl iodides with amines using DBU as a base that had been reported by the group of Claver (URV) was investigated at the DFT level in collaboration with the group of Carbó (URV). Paths were

identified for both mono- and dicarbonylation, and the computed selectivity for three different substrates was shown to be in agreement with experiment. In the double carbonylation, yielding α -ketoamides, the second carbon-carbon bond formation occurs via reductive elimination in the Pd-acyl-amide intermediate after the DBU base-assisted nucleophilic attack of an amine at a terminal CO. This path operates to yield the major product with iodobenzene, and the almost exclusive product with (*p*-methoxy)iodobenzene. There are two different possible pathways yielding the monocarbonylated amide product. In one of them, operating to obtain the minor product for iodobenzene, the base-assisted nucleophilic attack of the amine takes place on the Pd-acyl ligand. For substrates with electron donor substituents, like (*p*-cyano)iodobenzene, the aryl migration to the CO ligand is disfavoured, allowing the base-assisted amine attack to a terminal CO early in the catalytic cycle. From the resulting Pd-amide-aryl complex, the subsequent reductive elimination occurs easily and the monocarbonylation becomes favored.

We were finally able to examine the structure of a complex that is related to carbon dioxide fixation, in collaboration with the experimental group of Hazari (Yale) and the computational group of Eisenstein (Montpellier). This compound presented an unusual example of

hypervalent silicon center. Pd and Ni dimers supported by a PSiP ligand, in which two hypervalent five coordinate Si atoms bridge the two metal centers, are reported. Crystallographic characterization reveals an extremely rare square pyramidal geometry at Si. The structures were further analyzed by DFT and NBO analysis and the computational studies indicate that an asymmetric four-center two-electron (4c-2e) bond stabilizes the hypervalent Si atoms. To the best of our knowledge, our PSiP “pincer” ligand bridged Pd and Ni complexes represent the only examples of 4c-2e bonding stabilizing hypervalent Si atoms.

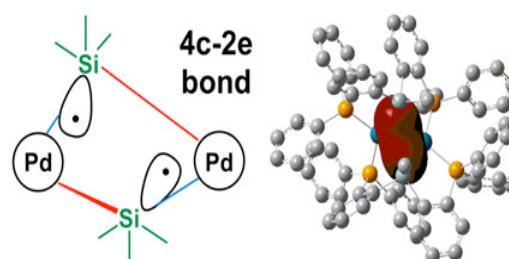


Fig. 5 - The 4 center-2 electron bonding interaction in $[(\text{PhPSiP})_2\text{Pd}_2]$, together with the corresponding NLMO orbital.

Articles

“An Unusual Example of Hypervalent Silicon: A Five-Coordinate Silyl Group Bridging Two Palladium or Nickel Centers through a Nonsymmetrical Four-Center Two-Electron Bond”

Angew. Chem. Int. Ed. (2014) 53, 1103–1108
A. Nova, H-W. Suh, T.J. Schmeier, L. M. Guard, O. Eisenstein, N. Hazari, F. Maseras

“Rationale for the sluggish oxidative addition of aryl halides to Au(I)”

Chem. Commun. (2014) 50, 1533–1536
M. Livendahl, C. Goehry, F. Maseras, A. M. Echavarren

“Reaction of Alkynes and Azides: Not Triazoles Through Copper–Acetylides but Oxazoles Through Copper–Nitrene Intermediates”

Chem. Eur. J. (2014) 20, 3463–3474
E. Haldón, M. Besora, I. Cano, X. C. Cambeiro, M. A. Pericàs, F. Maseras, M. C. Nicasio, P. J. Pérez

“Chemo-, regio-, and stereoselective silver-catalyzed aziridination of dienes: scope, mechanistic studies, and ring-opening reactions”

J. Am. Chem. Soc. (2014) 136, 5342–5350
J. Llaveria, A. Beltrán, W. M. C. Sameera, A. Locati, M. M. Díaz-Requejo, M. I. Matheu, S. Castillón, F. Maseras, P. J. Pérez

“Silver-Catalyzed Functionalization of Esters by Carbene Transfer: The Role of Ylide Zwitterionic Intermediates”

ChemCatChem (2014) 6, 2206–2210
R. Gava, M. Á. Fuentes, M. Besora, T. R. Belderrain, K. Jacob, F. Maseras, M. Etienne, A. Caballero, P. J. Pérez

“Toward a mechanistic understanding of oxidative homocoupling: the Glaser–Hay reaction”

Catal. Sci. Technol. (2014) 4, 4200
J. Jover, P. Spuhler, L. Zhao, C. McArdle, F. Maseras

2014 Annual Scientific Report

"The Transmetalation Process in Suzuki-Miyaura Reactions: Calculations Indicate Lower Barrier via Boronate Intermediate"

ChemCatChem. (2014) 6, 3132–3138

M. A. Ortuño, A. Lledós, F. Maseras, G. Ujaque

"On the Feasibility of Ni-catalyzed Triuoromethylation of Aryl Halides"

Organometallics (2014) 33, 6531–6543

J. Jover, F. M. Miloserdov, J. Benet-Buchholz, V. V. Grushin, F. Maseras

"Computational characterization of the mechanism for coinage metal-catalyzed carboxylation of terminal alkynes"

J. Org. Chem. (2014) 79, 11981–11987

J. Jover, F. Maseras

" β -H Abstraction / 1,3-CH bond addition: a generalized mechanism for the activation of CH bonds at early transition metal centers"

Organometallics (2014) 33, 7270–7278

Y. Hu, N. Romero, C. Dinoi, L. Vendier, S. Mallet-Ladeira, J. E. McGrady, A. Locati, F. Maseras, M. Etienne

"Catalytic copper-mediated ring opening and functionalization of benzoxazoles"

ACS Catalysis (2014) 4, 4215–4222

M. Corro, M. Besora, C. Maya, E. Álvarez, J. Urbano, M. Fructos, F. Maseras, P. J. Pérez

"Pd-Catalyzed Double and Monocarbonylation of Aryl Iodides. Insights into the Mechanism and the Selectivity"

Chem. Eur. J., (2014) 20, 10982–10989

V. M. Fernández-Álvarez, V. de la Fuente, C. Godard, S. Castellón, C. Claver, F. Maseras, J. J. Carbó

"Chiral Transition-Metal Complexes as Brønsted-Acid Catalysts for the Asymmetric Friedel-Crafts Hydroxyalkylation of Indole"

Dalton Trans., (2014) 43, 11260–11268

D. Carmona, M. P. Lamata, A. Sánchez, F. Viguri, R. Rodríguez, L. A. Oro, C. Liu, S. Díez-González, F. Maseras