2016 Annual Scientific Report



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 characterize different processes in homogeneous catalysis, in most cases in collaboration with experimental groups. Studies in 2016 focused on oxidative coupling, enantioselective organocatalysis and carbon dioxide activation.

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Oxidative coupling

As a natural continuation to our previous extensive work on the mechanism of crosscoupling, we have shifted our interest to dehydrogenative and oxidative coupling. These processes overcome some of the limitations of cross-coupling and are increasingly applied by the homogeneous catalysis community.

The mechanism of one of the leading examples of oxidative coupling, the reaction between benzoic acid and methylphenylacetylene to produce isocoumarin catalyzed by CpRh(OAc)₂ in the presence of a Cu(OAc)₂(H₂O) oxidant, was characterized through DFT calculations with the B97D functional. The conventional mechanism, with separate reductive elimination and reoxidation steps was found to yield a naphtalene derivative as major product via carbon dioxide extrusion, contrarily to the experimental observation.



Fig. 1 - Key transition state in the rhodiumcatalyzed coupling of alkyne and benzoic acid.

The experimental result is reproduced by a lower barrier alternative mechanism where the copper acetate oxidant plays a key role in the reductive elimination step, which takes place through a transition state structure containing rhodium and copper centers (see Fig. 1). This cooperative reductive elimination step would not be accessible with a generic oxidant, which, again, is in agreement with available experimental data.

The Ir-catalyzed C-H borylation of methyl benzoate has been studied with DFT methodology in order to understand the experimentally ligand-induced observed regioselectivity and activity when different [(ligand)lr(Bpin)₃] catalysts are employed. While bidentate ligands such as 4,4'-di-^tBu-2,2'bipyridine (dtbpy) completely inhibit the orthoborylation, the use of selected triphenylphosphine derivatives enables the reaction on that position, avoiding the meta- and para-regioisomers (see Fig. 2). The analysis of the catalytic cycles for the borylation reactions with dtbpy, PPh₃, P(p-CF₃C₆H₄)₃ and P(m,m-(CF₃)₂C₆H₃)₃ allows the interpretation of the observed ligand effects. The different reactivity observed for the different monodentate phosphine ligands can be also rationalized in terms of catalyst stability.



Fig. 2 - Ligand-dependent selectivity in the Ircatalyzed C-H borylation of methyl benzoate.

A project on oxidative amination was carried out in collaboration with the experimental group of Muñiz (ICIQ). The computational study of the mechanism for the iodine(III) mediated oxidative amination of alkenes explained the experimentally observed substrate dependence on product distribution. Calculations with the M06 functional were carried out on the reaction between PhI(N(SO₂Me)₂)₂ and three different representative substrates: styrene, αmethylstyrene and (E)-methylstilbene. All reactions start with the electrophilic attack by a cationic $PhI(N(SO_2Me)_2)^+$ unit on the double bond, and formation of an intermediate with a single C-I bond and a planar sp² carbocationic center. The major path, leading to 1,2diamination, proceeds through a mechanism where the bissulfonimide initially adds to the alkene through an oxygen atom of one sulfonyl group. This behavior was corroborated by



experimental evidence. An alternative path, leading to an allylic amination product, takes pace through deprotonation at an allylic C-H position in the common intermediate. The regioselectivity of this amination depends on the availability of resonant structures of an ulterior carbocationic intermediate. Only in cases where a high electronic delocalization is possible, as in (E)-methylstilbene, the allylic amination takes place without migration of the double bond.

Enantioselective organocatalysis

The mechanism of the organocatalyzed [4+2] cycloaddition of o-hydroxybenzaldimines and 2,3-dihydro-2H-furan (DHF) to form furanobenzopyrans has been computationally investigated. Experiments had shown the reaction produces different products (trans-fused or cis-fused) when different variations of phosphoric acid derivatives were applied. The reaction is shown to proceed through a mechanism in which the imine is re-arranged to an amine, which reacts then with DHF with the mediation of the catalyst.



Fig. 3 - Key transition states controlling enantioselectivity in the organocatalyzed

enantioselective cycloaddition for one of the systems under study

The rate limiting step of the process is the formation of the two new bonds and it is the key step for the selectivity. Selectivity is controlled by the balance between non-covalent interactions between catalvsts and substrates. The discriminating factor between the two catalysts is the presence of a triflyl substituent in one of them that constraints the relative orientation of the substrates. The key transition states involved in the selectivity are shown in Fig. 3. The difference between the structures is highlighted with the help of an NCI analysis, which places green color in the graphic on the regions when there are attractive non covalent interactions.

Carbon dioxide chemistry

Significant progress has been observed in recent years in the synthesis of allylic amines which are important building blocks in synthetic chemistry. Most of these processes are effective towards the preparation of allylic amines with limited potential to introduce three or four different substituents on the olefinic unit in a stereo-controlled fashion. Therefore. the discovery of a mild and operationally simple protocol allowing such challenging stereoselective synthesis of multi-substituted allylic amines remains an inspiring target. We were able, in collaboration with the experimental group of Kleij (ICIQ), to report the first general and practical methodology for the stereoselective synthesis of tri-and tetra-substituted allylic amines based on Pd-catalyzed conversion of allyl surrogates readily obtained from cyclic vinyl carbonates.



Fig. 4 - Key transition state leading to the palladacylic intermediate in the synthesis of allylic amines. Key distances in Å

These unprecedented conversions are characterized by excellent stereo-selectivity, operational simplicity, mild reaction conditions



and wide scope in reaction partners. DFT studies were performed to rationalize the stereocontrol in these allylic amine formation reactions, and evidence is provided that the formation a six-membered palladacyclic intermediate (see Fig. 4) is crucial towards the formation of (Z)-configured allylic amine products..

Articles

"Cooperative Reductive Elimination: The Missing Piece in the Oxidative-Coupling Mechanistic Puzzle"

Angew. Chem. Int. Ed. (**2016**) 55, 2764 – 2767 I. Funes-Ardoiz, F. Maseras

"DFT Rationalization of the Different Outcomes of the Iodine(III)-Mediated Oxidation of Alkenes" *Chem. Eur. J.* (**2016**) *22*, 7545 – 7553

I. Funes-Ardoiz, W. M. C. Sameera, R. M. Romero, C. Martínez, J. A. Souto, D. Sampedro, K. Muñiz, F. Maseras

"Computational Characterization of the Origin of Selectivity in Cycloaddition Reactions Catalyzed by Phosphoric Acid Derivatives" *Chem. Asian J.* (**2016**) *11*, 411–416 C. Liu, M. Besora, F. Maseras

"Stereoselective and Versatile Preparation of Triand Tetrasubstituted Allylic Amine Scaffolds under Mild Conditions"

J. Am. Chem. Soc. (**2016**) *138*, 11970 –11978 W. Guo, L. Martínez-Rodríguez, R. Kuniyil, E. Martin, E. C. Escudero-Adán, F. Maseras, A. W. Kleij

"Mechanistic Investigation of Iridium-Catalyzed C-H Borylation of Methyl Benzoate: Ligand Effects in Regioselectivity and Activity" *Organometallics*. (2016) 35, 3221–3226 J. Jover, F. Maseras

"QM/MM Calculations on Selectivity in Homogeneous Catalysis" *Struct. Bond.* (**2016**) *16*7, 59-79 J. Jover, F. Maseras