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Max García Melchor

# A Theoretical Study of Pd-Catalyzed C–C Cross-Coupling Reactions

Doctoral Thesis accepted by
the Autonomous University of Barcelona, Spain

Springer

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2) **M. García-Melchor**, G. Ujaque, F. Maseras, A. Lledós. In "Phosphorus Compounds: Advanced Tools in Catalysis and Material Sciences". Series: Catalysis by Metal Complexes (CMCO), M. Peruzzini, L. Gonsalvi, Eds., Springer-Verlag (Berlin): **2011**, Vol. *37*, Chapter 3, pp 57–84.

3) **M. García-Melchor**, B. Fuentes, A. Lledós, J. A. Casares, G. Ujaque, P. Espinet. "Cationic intermediates in the Pd-Catalyzed Negishi Coupling. Kinetic and DFT Study of Alternative Transmetalation pathways in the Me-Me Coupling of $ZnMe_2$ and *trans*-[PdMeCl($PMePh_2$)$_2$]". *J. Am. Chem. Soc.* **2011**, *133*, 13519–13526.

4) **M. García-Melchor**, M. C. Pacheco, C. Nájera, G. Ujaque, A. Lledós. "Mechanistic Exploration of the Pd-Catalyzed Copper-Free Sonogashira Reaction". *ACS Catal.* **2012**, *2*, 135–144.

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*Dedicated to Rosa, Emma*
*and the rest of my family*

# Supervisors' Foreword

Pd-catalyzed C–C cross-coupling reactions have become one of the most useful tools for organic synthesis. Their development was recognized with the Nobel Prize in Chemistry in 2010 awarded to Profs. R. F. Heck, E. Negishi, and A. Suzuki. Applications of these reactions are found in several fields of social interest as agrochemicals, pharmaceuticals, etc. These reactions can be classified depending on the metal or semi-metal present in the nucleophile. For instance, Stille reaction is tin-mediated, Negishi zinc-mediated, etc. The reaction mechanism is generally described in three steps: oxidative addition, transmetalation, and reductive elimination. A deeper understanding of reaction mechanisms is mandatory to control and improve chemical processes. In the present Ph.D. dissertation theoretical calculations have been used to determine, elucidate, and propose mechanisms for Pd-catalyzed C–C cross-coupling reactions. Reaction intermediates and transition states involved in the Negishi, the copper-free Sonogashira, and the asymmetric version of the Suzuki coupling have been characterized, providing a detailed picture of their reaction mechanisms. These results can guide further experimental investigations.

Cerdanyola del Vallès, May 2013

Prof. Agustí Lledós
Prof. Gregori Ujaque

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*No man succeeds without a good woman behind him.*
*Wife or mother, if it is both, he is twice blessed indeed.*

Harold MacMillan

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# Contents

# Abbreviations

| | |
|---|---|
| Ar | Any aromatic group |
| B3LYP | Becke's three-parameter, Lee-Yang-Parr exchange-correlation functional |
| $^{t}$Bu | *tert*-butyl |
| dba | dibenzylideneacetone |
| DCM | Dichloromethane |
| DMF | N,N-Dimethylformamide |
| DFT | Density Functional Theory |
| DMSO | Dimethyl sulfoxide |
| ee | Enantiomeric excess |
| EDG | Electron Donating Group |
| EWG | Electron Withdrawing Group |
| GGA | Generalized Gradient Approximation |
| HF | Hartree-Fock |
| IUPAC | International Union of Pure and Applied Chemistry |
| KS | Kohn-Sham |
| LDA | Local Density Approximation |
| LSDA | Local Spin Density Approximation |
| MA | Maleic Anhydride |
| Me | Methyl |
| MeCN | Acetonitrile |
| MM | Molecular Mechanics |
| MP2 | Møller-Plesset perturbation theory to second order |
| NHC | N-Heterocyclic Carbene |
| NMR | Nuclear Magnetic Resonance |
| ONIOM | Our own N-layered integrated molecular orbital + molecular mechanics |
| PCM | Polarizable Continuum Model |
| PES | Potential Energy Surface |
| Ph | Phenyl |
| $^{i}$Pr | Isopropyl |
| QM | Quantum Mechanics |
| SDD | Stuttgart-Dresden effective core potential |
| $S_N2$ | Bimolecular nucleophilic substitution |

| | |
|---|---|
| THF | Tetrahydrofuran |
| TOF | Turnover Frequency |
| TON | Turnover Number |
| ZPE | Zero Point Energy |