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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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*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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Abbreviations

Ar	Any aromatic group
B3LYP	Becke's three-parameter, Lee-Yang-Parr exchange-correlation functional
^t Bu	<i>tert</i> -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 _N 2	Bimolecular nucleophilic substitution

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