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Gui-Juan Cheng

Mechanistic Studies
on Transition
Metal-Catalyzed C–H
Activation Reactions Using
Combined Mass
Spectrometry and Theoretical
Methods

Doctoral Thesis accepted by
Peking University, Beijing, China

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Supervisor's Foreword

With the incredible development of theoretical methods and computer hardware, computational chemistry has become a practical and essential tool in understanding reaction mechanism. When facing realistic questions raised from flask, communication between theory and experiment is critical. Applications of computational chemistry are also facilitated by aids of various experimental techniques providing mechanistic insights. In this thesis, Dr. Gui-Juan Cheng investigated reaction mechanism with computational chemistry and mass spectrometry. In particular, a novel approach combining ion-mobility mass spectrometry and theoretical calculations was introduced as an addition to the toolbox for mechanistic study.

This dissertation focuses on the topic of C–H activation. Selective functionalization of ubiquitous C–H bonds provides an efficient synthetic strategy and experienced a remarkable development in recent years. Dr. Gui-Juan Cheng conducted detailed and systematic studies on a series of prominent C–H activation reactions which are recognized as breakthroughs in this field. The critical issues including the active form of catalyst, the role of ligand and additives, the origins of regio- and enantio-selectivity were investigated.

Several new mechanisms have been established in this dissertation. Chapter 2 proposes an unprecedented dimeric Pd₂(OAc)₄ or PdAg(OAc)₃ as the possible active catalyst for C–H activation. It successfully accounts for the experimentally observed *meta*-selectivity, and expands our understanding of the active form of palladium catalyst. Chapters 3 and 4 reveal the role of mono-N-protected amino acid (MPAA) ligands in Pd-catalyzed C–H bond functionalization and uncover a novel C–H activation model which accounts for the improved reactivity and selectivity. Further work obtains experimental supports for the novel C–H activation mechanism and proposes a chirality-relay model which successfully predicts the enantioselectivities of a range of asymmetric C–H activation reactions. Chapter 5

involves a sp^3 C–H cross-dehydrogenative coupling reaction and provides details of mechanistic profiles. Overall, the studies of this dissertation provide deeper mechanistic understandings as well as novel C–H activation models and offers guidance for optimizing or designing ligands and reactions.

Shenzhen, China
March 2017

Prof. Yun-Dong Wu

Parts of this thesis have been published in the following journal articles:

1. Yang, Y.-F.[†]; **Cheng, G.-J.**[†]; Liu, P.; Leow, D.; Sun, T.-Y.; Chen, P.; Zhang, X.; Yu, J.-Q.; Wu, Y.-D.; Houk, K. N. Palladium-Catalyzed Meta-Selective C–H Bond Activation with a Nitrile-Containing Template: Computational Study on Mechanism and Origins of Selectivity. *J. Am. Chem. Soc.* **2014**, *136*, 344. ([†]: co-first author)
2. **Cheng, G.-J.**; Yang, Y.-F.; Liu, P.; Chen, P.; Sun, T.-Y.; Li, G.; Zhang, X.; Houk, K. N.; Yu, J.-Q.; Wu, Y.-D. Role of N-Acyl Amino Acid Ligands in Pd (II)-Catalyzed Remote C–H Activation of Tethered Arenes. *J. Am. Chem. Soc.* **2014**, *136*, 894.
3. **Cheng, G.-J.**; P.; Chen, P.; Sun, T.-Y.; Zhang, X.; Yu, J.-Q.; Wu, Y.-D. A Combined IM-MS/DFT Study on Pd(MPAA)-Catalyzed Enantioselective C–H Activation: Relay of Chirality through a Rigid Framework. *Chem. Eur. J.* **2015**, *21*, 11180.
4. **Cheng, G.-J.**; Song, L.-J.; Yang, Y.-F.; Zhang, X.; Wiest, O.; Wu, Y.-D. Computational Studies on the Mechanism of the Copper-Catalyzed sp³-C–H Cross-Dehydrogenative Coupling Reaction. *ChemPlusChem* **2013**, *78*, 943.

List of Publications

1. Rummelt, S.; **Cheng, G.-J.**; Gupta, P.; Thiel, W.; Fürstner, A. Hydroxyl-Directed Ruthenium Catalyzed Alkene/Alkyne Coupling: Increased Scope, Stereochemical Implications and Mechanistic Rationale. *Angew. Chem. Int. Ed.* **2017**, *56*, 3599.
2. Xie, Y.; **Cheng, G.-J.**; Lee, S.; Kaib, P.; Thiel, W.; List, B. Catalytic Asymmetric Vinylogous Prins Cyclization: A Highly Diastereo- and Enantioselective Entry to Tetrahydrofurans. *J. Am. Chem. Soc.* **2016**, *138*, 14538.
3. Zhong, X.-M. [†]; **Cheng, G.-J.** [†]; P.; Chen, P.; Zhang, X.; Yu, Wu, Y.-D. Mechanistic Study on Pd/Mono-N-protected Amino Acid Catalyzed Vinyl-Vinyl Coupling Reactions: Reactivity and E/Z Selectivity. *Org. Lett.* **2016**, *18*, 5240. ([†]:co-first author)
4. **Cheng, G.-J.**; P.; Chen, P.; Sun, T.-Y.; Zhang, X.; Yu, J.-Q.; Wu, Y.-D. A Combined IM-MS/DFT Study on Pd(MPAA)-Catalyzed Enantioselective C-H Activation: Relay of Chirality through a Rigid Framework. *Chem. Eur. J.* **2015**, *21*, 11180.
5. **Cheng, G.-J.**; Zhang, X.; Chung, L. W.; Xu, L.; Wu, Y.-D. Computational Organic Chemistry: Bridging Theory and Experiment by Mechanistic Understanding of Chemical Reactions. *J. Am. Chem. Soc.* **2015**, *137*, 1706.
6. Zhou, F. [†]; **Cheng, G.-J.** [†]; Yang, W. [†]; Long, Y.; Zhang, S.; Wu, Y.-D.; Zhang, X.; Cai, Q. Enantioselective Formation of Cyano-Bearing All-Carbon Quaternary Stereocenters: Desymmetrization by Copper-Catalyzed N-Arylation. *Angew. Chem. Int. Ed.* **2014**, *53*, 9555. ([†]: co-first author)
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9. **Cheng, G.-J.**; Song, L.-J.; Yang, Y.-F.; Zhang, X.; Wiest, O.; Wu, Y.-D. Computational Studies on the Mechanism of the Copper-Catalyzed sp³-C–H Cross-Dehydrogenative Coupling Reaction. *ChemPlusChem* **2013**, *78*, 943.
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11. Zhao, K.; **Cheng, G.-J.**; Yang, H.; Shang, H.; Zhang, X.; Wu, Y.-D.; Tang, Y. Total Synthesis of Incarvilleatone and Incarviditone: Insight into Their Biosynthetic Pathways and Structure Determination. *Org. Lett.* **2012**, *14*, 4878.
12. Yang, Y.-F.; **Cheng, G.-J.**; Zhu, J.; Zhang, X.; Inoue, S.; Wu, Y.-D. Silicon-Containing Formal 4π-Electron Four-Membered Ring Systems: Antiaromatic, Aromatic, or Not? *Chem. Eur. J.* **2012**, *18*, 7516.

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Abbreviations

Ar	Any aromatic group
CCS	Collision cross section
CDC	Cross-dehydrogenative coupling
CID	Collision induced dissociation
CMD	Concerted metallation and deprotonation
DFT	Density Functional Theory
DG	Directing group
<i>e.e.</i>	Enantiomeric excess
EHSS	Exact hard sphere scattering
ESI	Electrospray ionization
IM-MS	Ion mobility mass spectrometry
MECP	Minimum energy crossing point
MPAA	Mono-N-protected amino acid
MS	Mass spectrometry
PA	Projection approximation
PES	Potential Energy Surface
SET	Single electron transfer
TM	Trajectory method
TS	Transition state
TWIMS	Traveling wave ion mobility spectrometry
S _E Ar	Electrophilic aromatic substitution
<i>t</i> Bu	<i>Tert</i> -butyl
<i>i</i> Pr	Isopropyl
<i>o</i>	<i>Ortho</i>
<i>m</i>	<i>Meta</i>
<i>p</i>	<i>Para</i>
t _D	Drift time