STARTPAGE

PEOPLE

MARIE CURIE ACTIONS

International Incoming Fellowships (IIF)

Call: FP7-PEOPLE-2012-IIF

Optimizing Selectivity in C-H Functionalization Through Computational Design

"CHOPTOCOMP"

1. Work progress and achievements during the period

Introduction

The activation of inert C-H bonds lies at the heart of organic chemistry due to potential efficiency. In particular C-H activation using transition metal catalysis has made a profound impact on complex molecule synthesis, but the area remains important for future discovery. At present the utility of synthetic methods based on C-H activation is hampered by the inherent difficulty of being able to selectively functionalize a single C-H bond in the presence of many others. Thus the ability to perform predictably site-selective C-H functionalizations on a given C-H bond in a complex substrate would be transformative for chemical synthesis. The aim of this project is to perform computational studies on Pd-catalyzed C-H functionalization reactions, to uncover the inherent electronic or steric bias of substrate structures on the site-selectivity.

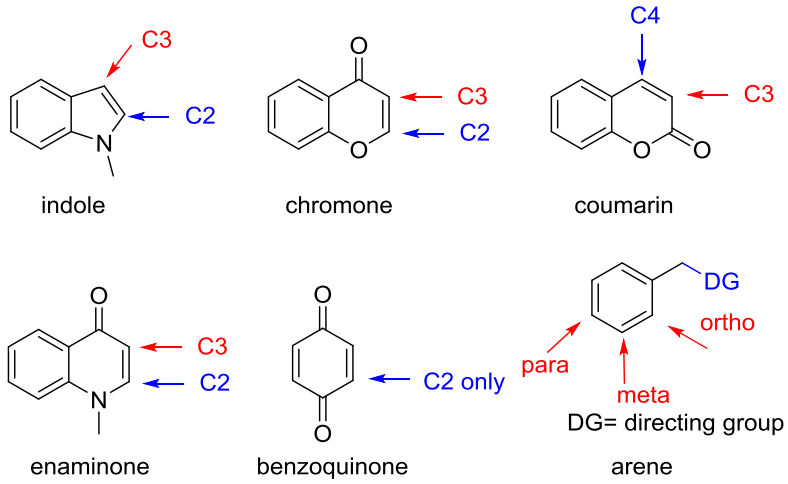


Figure 1. Substrate varieties for Pd-catalyzed C-H activation

Our calculations have performed using density functional theory (**ω**B97XD, M06 and M062x) to characterize the mechanisms and catalytic cycle for Pd-catalyzed arylation of aromatic and heteroaromatic substrates (indole, chromone, enaminone, benzoquinone, arene, in Figure 1), which state in the timeliness of **phase 1**. We have develop working models of reactivity and selectivity to deliver a greater understanding of the process (i.e. addressing some ligand effect), which will be used to generate predictions. The result will be a reliable predictive model with which to rationally design substrates and catalysts by modifying functional groups or ligands, shown in **phase 2** and **phase 3**.

Phase 1 completed

During the first several months of the project the researcher focused on the mechanism and regioselectivity of indole substrates for Pd-catalyzed C2 direct arylation with phenyl boronic acid [PhB(OH)2]. From the calculated pathways, four membered transmetalation is deemed to be less competitive than six-membered and crucially solvation helps to form polar-π interaction between solvent molecule and π system of indole to stabilize six-membered transition states, precomplexes and products. The favoured mechanism proceeds via concerted metalation-deprotonation (CMD) which is a reversible reaction. Following reprotonation and eventual C-H activation at C2, the reaction can accumulate at the low-energy, stable C2 aryl-palladium intermediate. The dissociation of the AcOH cis to C2 on the arylpalladium intermediate opens a coordination site on the square planar Pd, presenting ideal coordination geometry for incoming $PhB(OH)_2$. The transmetalation event with $PhB(OH)_2$ occurs via a six-membered solvated transition state which is more competitive in energy than the C3 regioisomer. Through calculation this is the shown to be the rate and selectivity determining step. The catalytic cycle concludes through a mono-ligated C2

reductive elimination TS that undergoes concerted three centered elimination to form a new C-C bond between N-methyl indole and phenyl, expelling Pd(0) and producing the C2 arylated product.

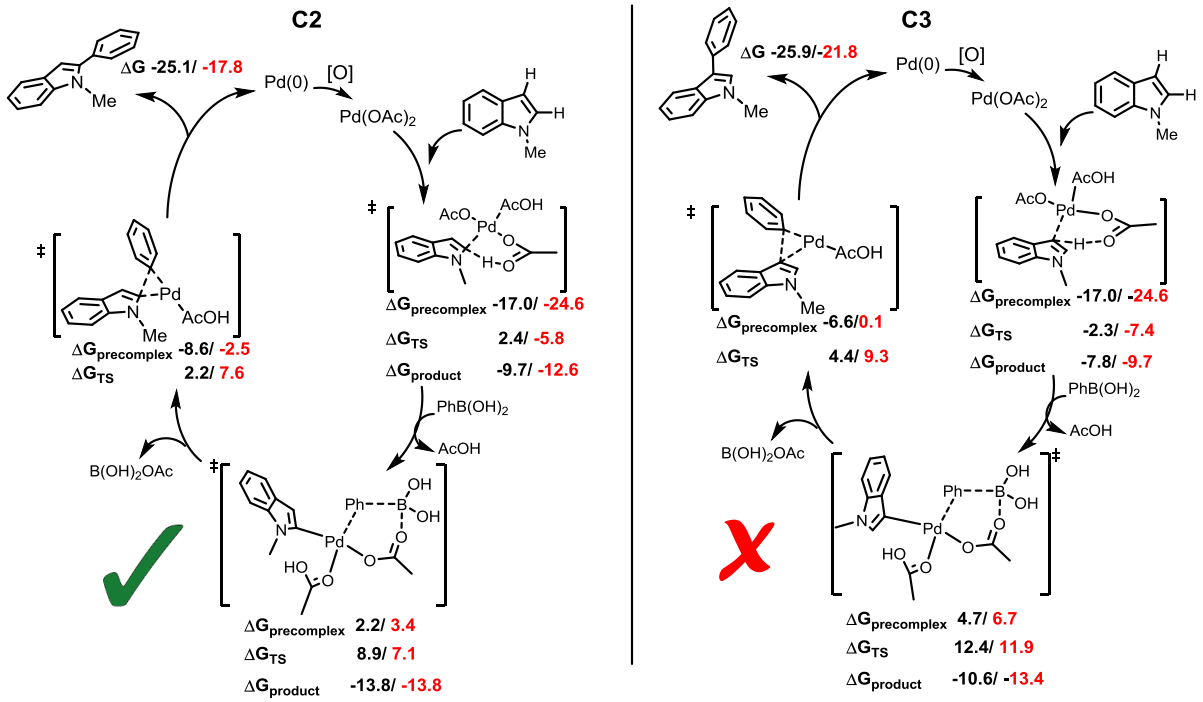


Figure 1 Computed catalytic cycles for the direct arylation at C2 and C3 of N-methyl indole. Selectivity is determined through a six-membered solvent assisted transmetalation TS. All values in kcal/mol. Calculations conducted at ωB97XD/6-31g(d)/LANL2DZ//6-311+G(d,p)/LANL3TZ (black) and ωb97xd/6-31g(d)//m062x/6-311+G(d,p)/LANLTZ (red)

Substrates extension

After understanding the mechanism of aromatic indole, we extended substrates to the reaction involving non aromatic ring systems such as chromone, enaminone, benzoquinone substrates. We present the energetics for all of the transition structures with $Pd(OTFA)_2$ Focusing on the CMD energetics, there is a marked separation according to whether the position undergoing activation is electron rich or electron deficient: the latter group describes the C2-positions of chromone or enaminone along with benzoquinone, and their corresponding barriers are all kinetically unfeasible and ca. 10 kcal/mol higher than for their more electron rich counterparts. Inspection of the electrostatic potential for each of these substrates confirms that the positions of greater electron density undergo C–H activation more easily. For enaminone and chromone the C3-position also provides the greatest atomic orbital contribution to the HOMO and also carries a substantially greater negative charge than at C2 from natural population analysis. The site-selectivity of C–H activation can thus be clearly related to the innate polarization of these substrates. Unlike (hetero)aromatic systems, the greater C=C bond localization in the substrates studied here enables a competitive carbopalladation pathway to occur. The inherent polarization of the C=C bond in chromone and enaminone, and the sites of HOMO/LUMO coefficients act to favor C2-arylation (Figure 3C) since the metal is delivered to the more electron-rich position in concert with C–C formation.

discussed so far in Figure 3, organized sequentially by their relative stability.

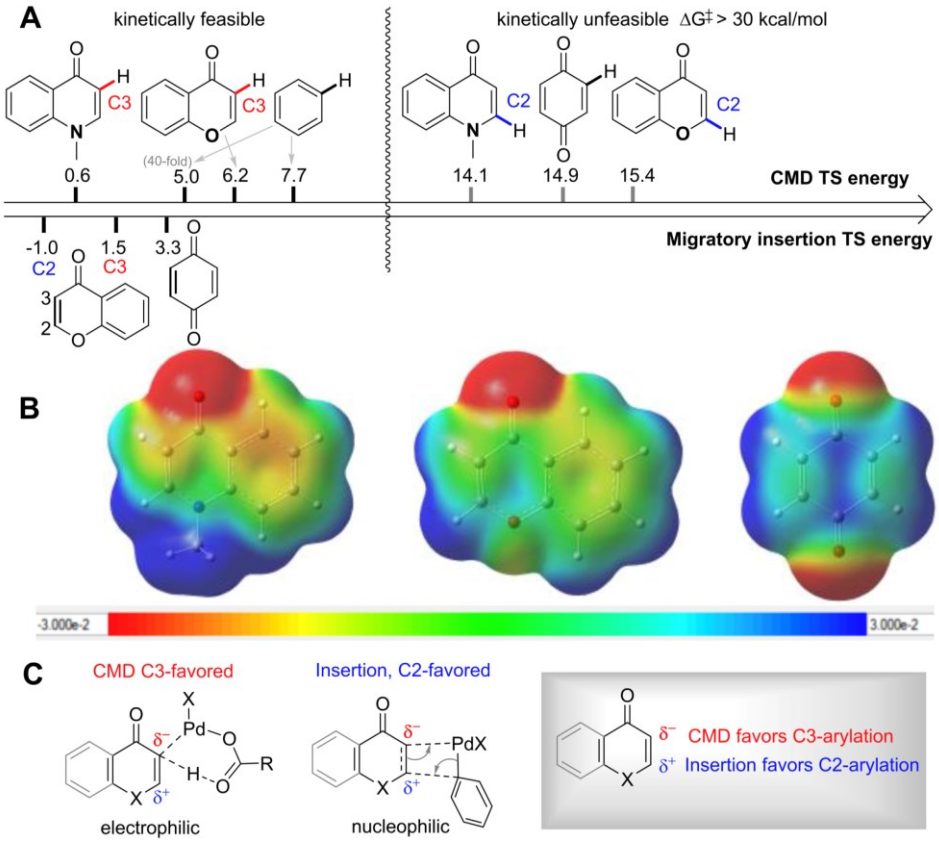
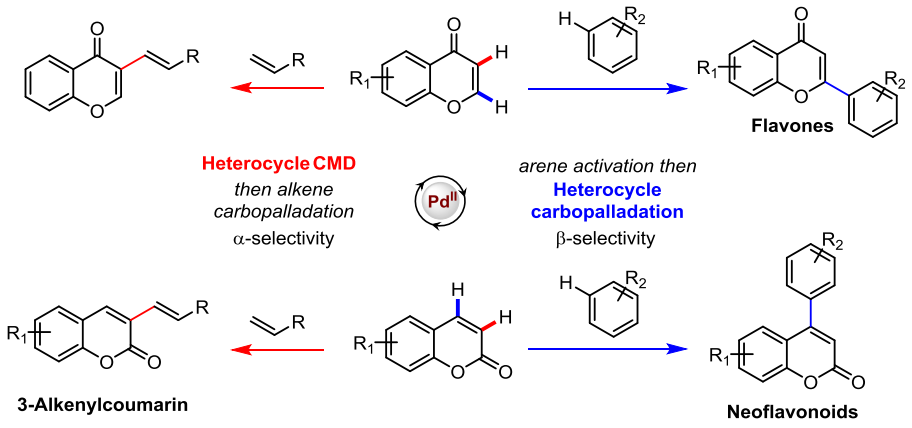


Figure 3. A: Energy of key transition states for site-selectivity; B: electrostatic potential map (ESP) with iso-value=0.001 ;C: favorable site-selectivity in the reaction.



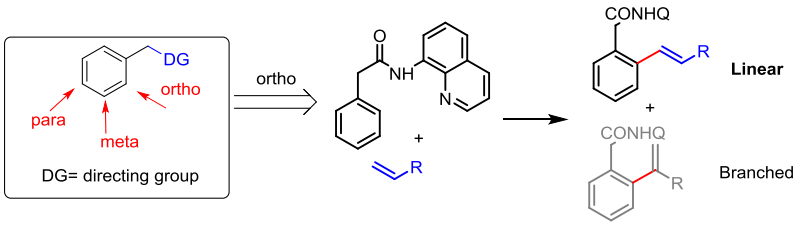
Scheme 1. Experimental regioselectivities of the arylation and alkenylation of chromone and coumarin substrates are in accord with the computational model.

The scope of our newly developed mechanistic model is applicable to other substrates and Pd-catalyzed functionalizations, so that we can predict regioselectivity in the arylation and alkenylation for chromone and other heteroamatic substrates, such as coumarins (Scheme 1). Based on the inherent polarization of chromone and coumarin substrates we predict that C-H activation of both substrates will occur preferentially at the enone α-position, and that carbopalladation will deliver the aryl group preferentially to the β-position. Alkenylation is thus expected to result in α-selectivity since heterocyclic CMD-activation dictates selectivity: indeed, experimentally this is the sole regioisomer for each substrate. Conversely, arylation is expected to result in β-selectivity as carbopalladation by the arylpalladium intermediate dictates selectivity, which is seen experimentally for both substrate. Our model is consistent

with experimental isotopic labeling studies, which show the C3 (α)-position of coumarin to be most susceptible towards palladation. A significant level of deuterium incorporation (41% D after 12 h) is observed at this position in the presence of D2O (20 equiv). The calculated MOs and ESP map of coumarin confirm that the polarization is in a similar sense as the other enolones considered, and can thus be used to make tangible predictions of regioselectivity for real catalytic reactions. Finally, this phase lead us to publish one paper (*Chem. Sci.* **2016**, *7*, 3900-3909.)

Phase 2 Reactivity and selectivity

Based on our calculations for aromatic indole and substrates extension of C-H activation, we could be able to address the mechanism of more challenge issues which is to combine the C-H activation with other tandem reaction such as Mizoroki-Heck reaction (Scheme 2). React position could be in ortho-, meta- and para- for C-H activation of arene which highly depended on the directing group whilst the region-selectivity of alkene group would lead to generate final linear or branched product.



Scheme 2. Combine Pd-catalyzed C-H activation with other tandem reactions

Our initial calculation is to model Pd-catalyzed aryl C-H olefination with alkenes. Calculated results show that CMD pathways is fast in neutral pathway of C-H activation with assistance of bidentate directing group (N-quinolinyl) see Figure 4, and Heck type pathway is rate and regio-selective determining step (including cabopalladation and β-H elimination) undergoing the cationic pathway, see figure 5.

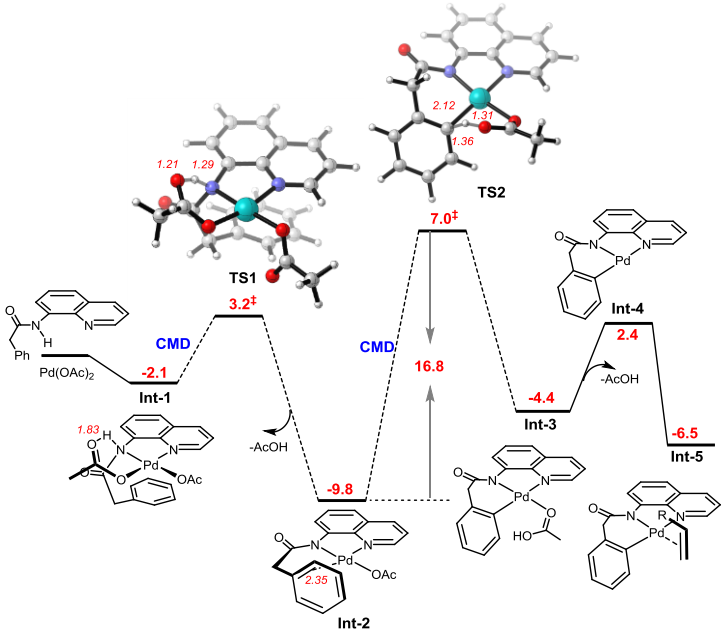


Figure 4. Two calculated CMD steps of ortho-palladation of the phenyl group to form palladacycle. All the energy except specific notice were shown in free energy (kcal/mol) at CPCM-ωB97XD/def2-QZVPP// ωB97XD/6-31G*/Lanl2DZ level of theory.

These calculation results can rationalize the control the regio-selectivity (linear vs. branched product) in carbopalladation step, and the kinetic isotopic effect (KIE) for β-H elimination. We finally unravel the nature of alkene preference for activated and unactivated alkene that is because of different distortion energy. And cationic pathways highly stabilize for the relevant transition states of both alkenes (about 5 kcal/mol). This mechanistic finding may provide a new perspective for controlling reactivity for unactivated species (Scheme 3). A paper is prepared and ready to be submitted soon.

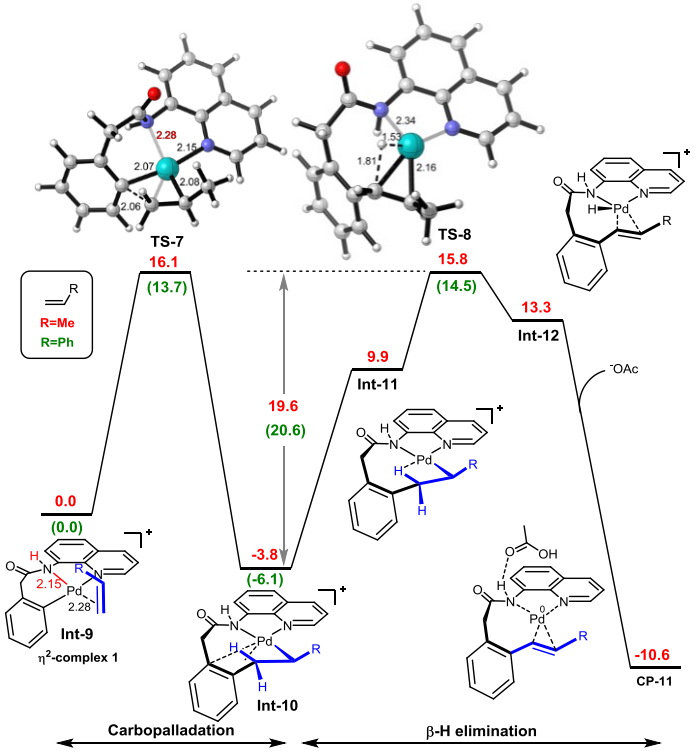
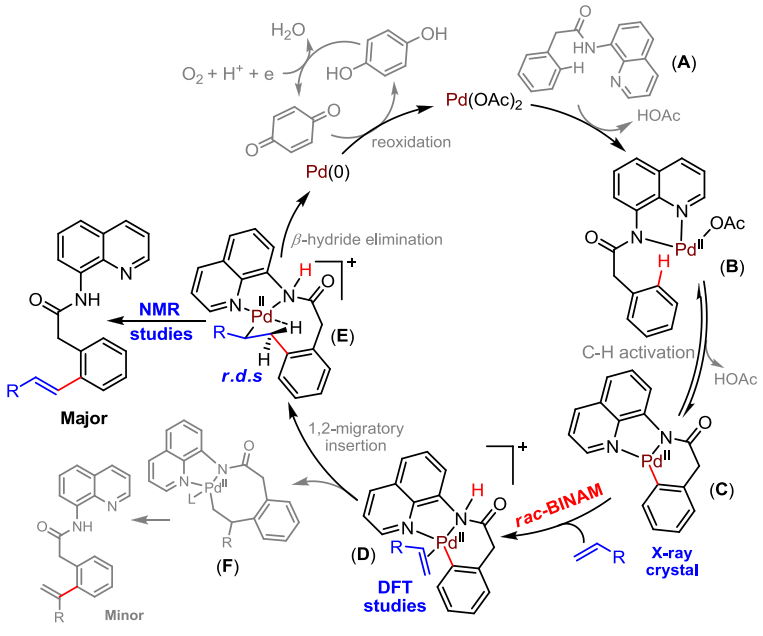


Figure 5. The calculated energy profile of tandem Heck reaction in cationic process. The energies of calculated model with propene and styrene were shown in red and green, respectively.



Scheme 3 Established mechanism of C-H olefination

Further challenges remain in designing the suitable tether directing groups to control the regio-selectivity (ortho-, meta- and para- for C-H activation of arene) on the phenyl ring. More calculations is therefore required to address this important field.

Phase 3 Potential ligand design

Demand for higher efficiency, economy, and selectivity in the synthesis of novel molecular scaffolds drives organic chemistry. The development of modular chiral ligands has led to the discovery of several transition metal:ligand complexes that catalyze various reactions with impressive levels of enantioselectivity. However, discovery of the appropriate chiral ligands for a desired transformation remains a formidable task. This is especially true for reactions where detailed mechanistic data are yet to be uncovered. Computational understanding of the mechanism of catalyst-control can lead to improved understanding and guide synthetic effort. The asymmetric transformation upon which we will focus is to be achieved through the use of modular, chiral phosphoramidite ligands (molecules which bind to a transition metal centre), and computational insights will be used to develop qualitative and quantitative models of selectivity that will be used in the design of greater levels of selectivity (Figure 6). Related crystal structures of cationic transition-metal: chiral phosphoramidite complexes point to the existence of metal-arene interactions in the solid state: we will also address the relevance of such interactions to catalysis, and the importance for stereo-selectivity which could be applied to organic reactions.

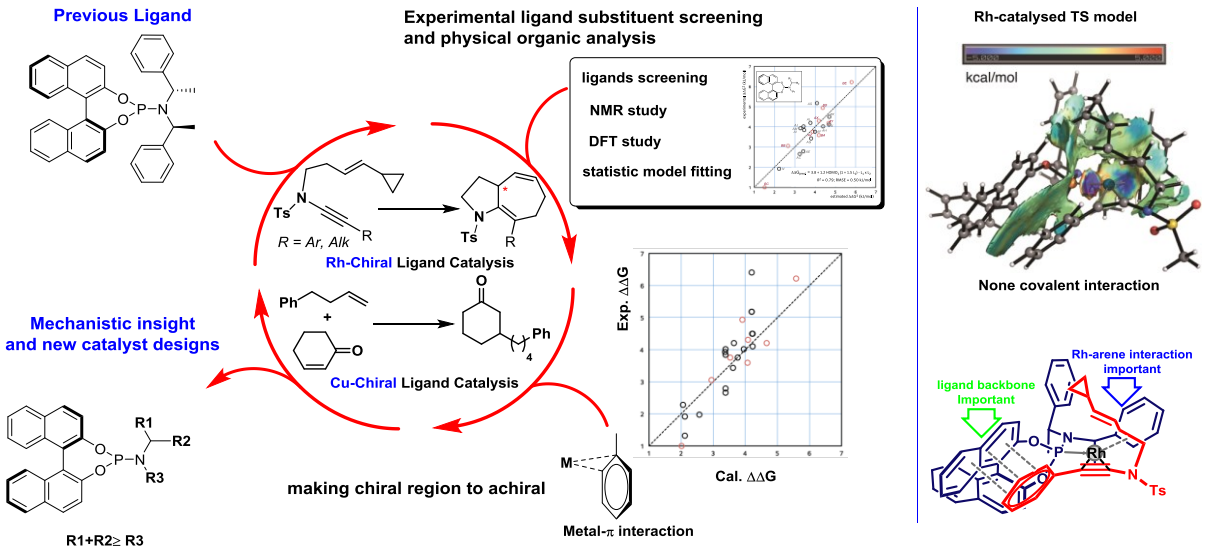


Figure 6. Computational ligand design process for cycloisomerization and conjugate addition

The proposed work could be carried out through collaboration with experimentalists in the University of Oxford or with international collaborations. From experimentalists we have obtained selectivity values for a series of structurally-related phosphoramidites which will be very useful in ensuring the resulting model is generally applicable. Insights derived from the computed transition structures will also be used to establish the role of metal-arene coordination in asymmetric catalysis, both rate and selectivity, with phosphoramidite ligand. Theoretical reaction analysis provided insight into the reaction pathway and, crucially, led to a theory-guided ligand design that enhanced the required rate and selectivity of these processes. This phase lead us to publish two papers, one research paper in Nature Communications 2016, 7, 10109. and the other review paper in Acc. Chem. Res. 2016, 49, 1042–1051.

Publications:

1. Hao Wang, Zibo Bai, Tangqian Jiao, Zhiqiang Deng, Huarong Tong, Gang He*, **Qian Peng*,** and Gong Chen*.Palladium-Catalyzed Amide-Directed Enantioselective Hydrocarbo-functionalization of Unactivated Alkenes Using a Chiral Monodentate Oxazoline Ligand. *J. Am. Chem. Soc.* **2018,** *140*, 3542-3546**.**
2. **Qian Peng*,** Zengwei Wang, Snezana D. Zaric, Edward N. Brothers, and Michael B. Hall*.Unraveling the Role of a Flexible Tetradentate Ligand in the Aerobic Oxidative Carbon-Carbon Bond Formation with Palladium Complexes: A Computational Mechanistic Study. *J. Am. Chem. Soc.* **2018**, *140*, 3929-3939**.**
3. Jian-Qiang Huang, Wei Liu, Bao-Hui Zheng, Xiu Yan Liu, Zhen Yang, Chang-Hua Ding,* Hao Li, **Qian Peng,*** and Xue-Long Hou*. Pd-Catalyzed Asymmetric Cyclopropanation Reaction of Acyclic Amides with Allyl and Polyenyl Carbonates. Experimental and Computational Studies for the Origin of Cyclopropane Formation. *ACS Catalysis* **2018**, 8, 1964.
4. Meng-Yang Hu, Qiao He, Song-Jie Fan, Zi-Chen Wang, Luo-Yan Liu, Yi-Jiang Mu, **Qian Peng*** and Shou-Fei Zhu*，Ligands with 1,10-phenanthroline scaffold for highly regioselective iron-catalyzed alkene hydrosilylation. *Nature Communication* **2018***.* 9, 221.
5. Jia-Jia Suo, Juan Du, Qing-Rong Liu, Di Chen, Chang-Hua Ding*, **Qian Peng***, and Xue-Long Hou*, Highly Diastereo- and Enantioselective Palladium-Catalyzed [3 + 2] Cycloaddition of Vinyl Epoxides and α,β-Unsaturated Ketones. *Org. Lett.*, **2017**, *19*, 6658.
6. Ruchuta Ardkhean#, Philippe M. C. Roth#, Rebecca M. Maksymowicz, Alex Curran, **Qian Peng***, Robert S. Paton*, and Stephen P. Fletcher*, Enantioselective conjugate addition catalyzed by a copper-phosphoramidite complex: Computational and experimental exploration of asymmetric induction. *ACS Catalysis* **2017**, 7, 6729.
7. Arghya Deb, Avijit Hazra, **Qian Peng***, Robert S. Paton*, Debabrata Maiti*, Detailed Mechanistic Studies on Palladium Catalyzed Stereoselective C–H Olefination with Aliphatic Alkenes: A Significant Influence of Proton Shuttling. *J. Am. Chem. Soc.* **2017**, *136*, 763-775**.**