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 chemically inert C-H bonds offers the potential to transform simple starting materials into complex molecules with high efficiency. At present the utility of synthetic methods based on C-H activation, often involving transition metal catalysts, 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. The molecules upon which we have focussed our attention have been selected due their utility as pharmaceutical building blocks, thereby ensuring that the potential end-users of this research may be found inside and outside of academia.

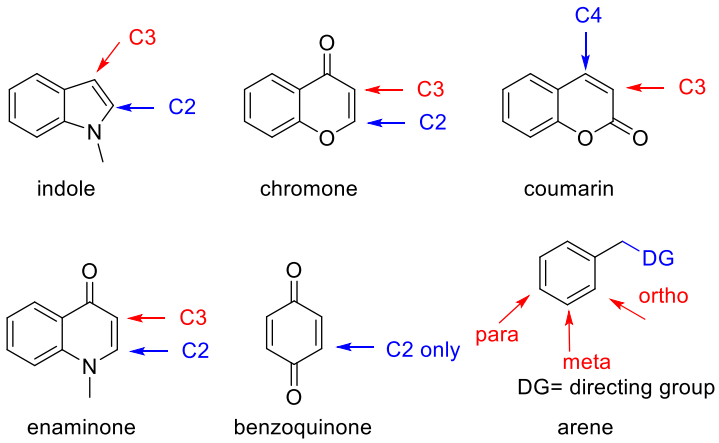


Figure 1. Substrates considered in CHOPTOCOMP for Pd-catalyzed C-H activation

We have performed a computational analysis 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, shown in Figure 1), as described by **objectives 1** and **2**. We have developed working models for reactivity and selectivity to deliver a greater understanding of the process, 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, as described by **objectives 3** and **4**.

Objective 1 Met: Computational mechanistic studies of Pd-catalyzed C-H activation

During the first twelve months of the project the researcher focused on the mechanism and regioselectivity of C-H functionalization of heteroaromatic substrates, including indoles. In particular, Pd-catalyzed arylation with phenyl boronic acid [$PhB(OH)_2$] was considered, which was subsequently expanded to consider a wider scope of synthetic methods including C-H arylation of heterocycles with unfunctionalized arenes and alkenes.

We observed the predominance of the concerted metalation-deprotonation (CMD) mechanism in Pd-catalyzed C-H activation of all heterocyclies considered, consistent with previous work (notably pioneered by MacGregor, Gorelsky and Maseras and others) for all-carbocyclic substrates. However, in the context of arylation reactions studied, this step was found to be independent of site-selectivity in nearly all examples, often being reversible. Regioselectivity results from either transmetalation, or carbopalladation steps as described below.

The favoured mechanism of heterocycle arylation by a boronic acid initially proceeds via a reversible, CMD step. Following reprotonation and eventual C-H activation at C2, the reaction accumulates at the low-energy, stable C2 aryl-palladium intermediate. The transmetalation event with $PhB(OH)_2$ occurs via a six-membered TS which is more competitive in energy than the C3 regioisomer. Through calculation this is the rate and selectivity determining step, which is consistent with the observed C2-product. The project considered a number of possible solvation environments, with implicit and explicit solvent models, and the results of DFT calculations were benchmarked against *ab initio* calculations which included scs-MP2 and CEPA-2 levels of theory.

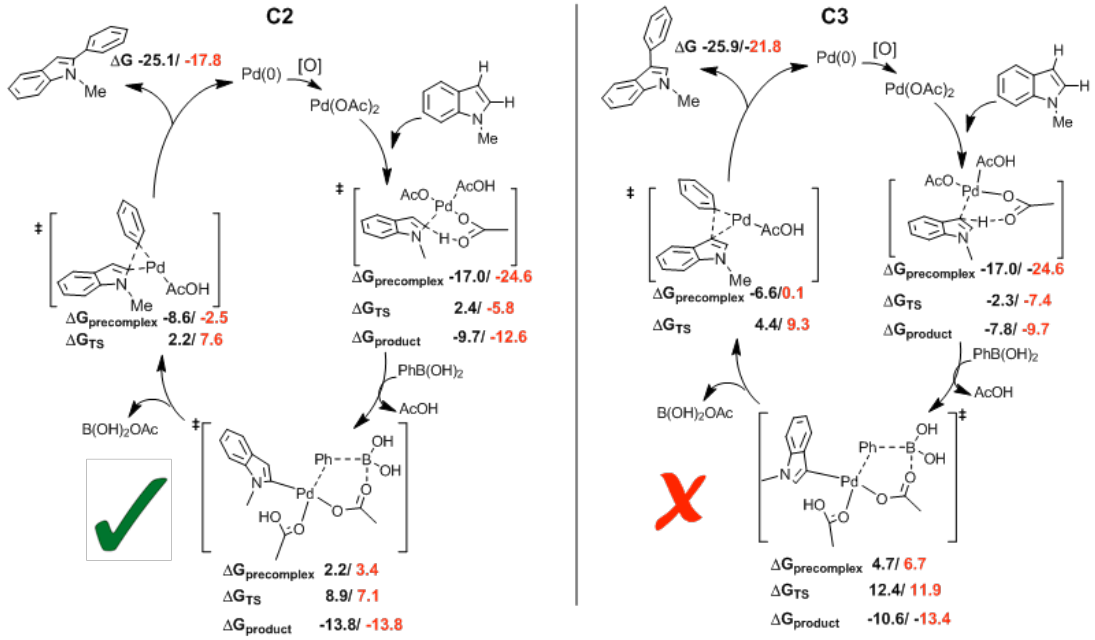


Figure 2. Computed catalytic cycles for the direct arylation at C2 and C3 of N-methyl indole. Calculations conducted at ωB97XD/6-31g(d)/LANL2DZ//6-311+G(d,p)/LANL3TZ (black) and ωb97xd/6-31g(d)//m062x/6-311+G(d,p)/LANLTZ (red)

Objective 2 Met: Consideration of substrate and catalyst effects upon selectivity

We extended computational study to consider substrates containing ring systems, such as chromone, enaminone, benzoquinone substrates. The presence of nitrogen and oxygen atoms in these rings mean that they are representative of many pharmaceutical building blocks currently used. We discovered a marked separation in the ease of C-H activation 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 all symmetric C-H positions of benzoquinone, and their corresponding barriers are all kinetically

unfeasible and *ca.* 10 kcal/mol higher than for their more electron rich counterparts. This is an interesting result, since the CMD mechanism is still the operative pathway of these activations. 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.

Objective 3 Met: Correlations of Reactivity and selectivity

This work therefore led us to develop a model for site-selectivity in C–H activation based on substrate polarization of these substrates. Greater C=C bond localization in the substrates studied here also enables a competitive carbopalladation pathway to occur. Here, the inherent polarization of the C=C bond in chromone and enaminone, and the sites of HOMO/LUMO coefficients favor C2-arylation (Figure 3C) since the metal is delivered to the more electron-rich position in concert with C–C formation.

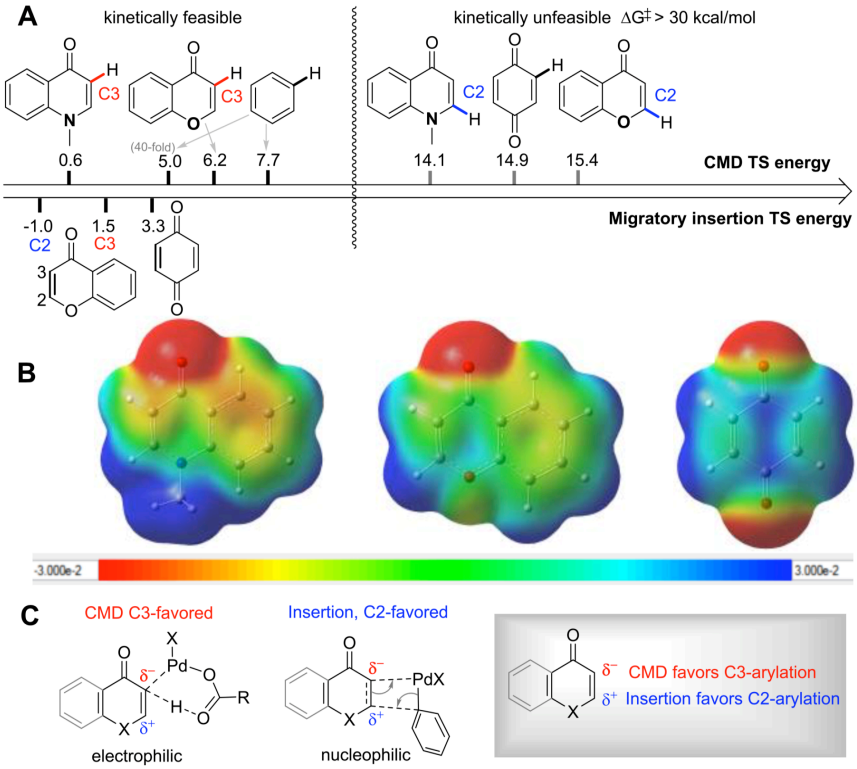
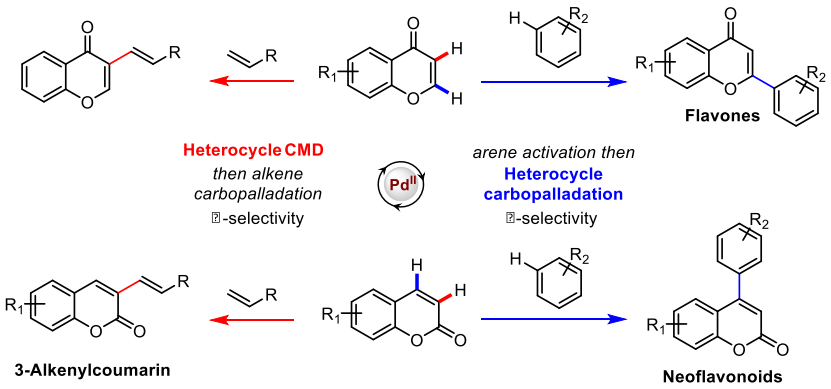


Figure 3. A: Energy of key transition states for site-selectivity; B: electrostatic potential map (ESP) with iso-value=0.001 ;C: favorable site-selectivity in the reaction.



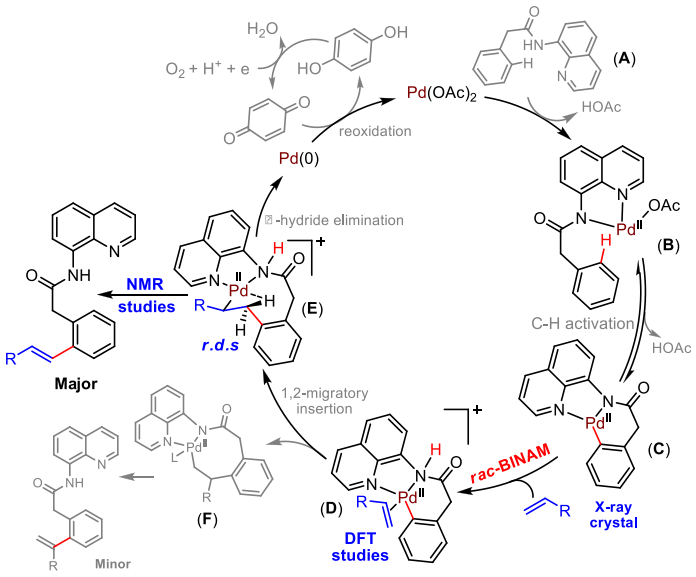
Scheme 1. Experimental regioselectivities of the arylation and alkenylation of chromone and coumarin substrates are in accord with the computational model.

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 D_2O (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 (Open Access) paper (*Chem. Sci.* **2016**, *7*, 3900-3909.)

Objective 4 Met: Applications of Computation to Ligand and Reaction 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 generated by this project phase has been used to improve understanding and direct synthetic optimization.

In the arena of C-H activation, this stage of the project has considered the potential of covalently attached groups to direct the metal catalyst to the desired position of functionalization. In collaboration with experimentalists (Prof. D Maiti, IIT) we have investigated the mechanism of ortho-directed C-H activation in the coupling of aromatic amides with alkenes. In the context of ligand design, we were able to extend the use of computations to successfully predict ligand effects in transition-metal catalyzed transformations.



Scheme 3 Established mechanism of C-H olefination

The proposed ligand design work had been carried out through collaboration with experimentalists Professor Ed Anderson in the University of Oxford. We have investigated the mechanism and selectivity in the asymmetric reaction of ynamide substrates using DFT calculations. And from experimentalists we have obtained selectivity values for a series of structurally-related phosphoramidites which is very useful in ensuring the resulting model is generally applicable. Combining both experimental and computational studies, we are able 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.

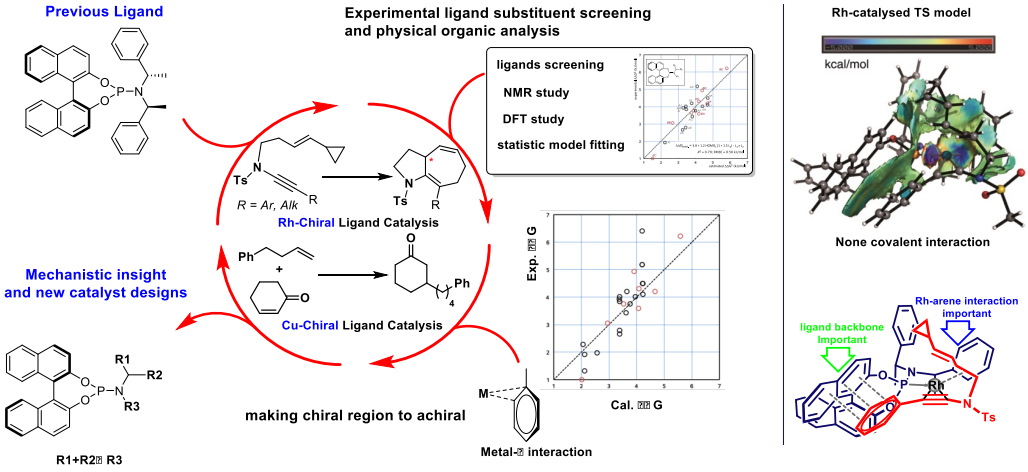


Figure 4. Computational ligand design for cycloisomerization and conjugate addition.

Following our success of design phosphoramidite ligand in Rh-catalysed asymmetry cycloisomerization, we continue to our effort on additional application to other reaction that is Cu-catalysed conjugate additions (collaboration with Prof. Stephen Fletcher in University of Oxford). Due to complex reaction systems, several new statistic models will be used to correlate experimental observation based on our understanding of metal-ligand and substrate interaction. Elucidation of the important interactions has been achieved by

studying the effects of ligand-structural variation on both the catalyst structure and resulting enantioselectivity, through a combination of experimental and theoretical techniques for this conjugate addition. These studies illustrate the ability of quantitative structure-selectivity relationships to provide both models for asymmetric induction and catalyst structural hypotheses that may be further probed by experiment and computation. Collectively, such an approach leads to the rational modification/simplification of chiral ligands for more effective catalysts

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. An extra two papers are in revision or preparation.

Publications resulting from the Project:

1. **Qian Peng*,** Robert S. Paton, "Catalytic Control in Cyclizations: from Computational Mechanistic Understanding to Selectivity Prediction" *Acc. Chem. Res.* ***2016***, *49,* 1042-1051.
2. Hwanho Choi, Minsik Min, **Qian Peng***, Dahye Kang, Robert S. Paton, and Sungwoo Hong, "Unraveling Innate Substrate Control in Site-Selective Palladium-Catalyzed C–H Heterocycle Functionalization" *Chem. Sci.* **2016**, 7,3900-3909 (*Open Access Article*).
3. Robert Strack, **Qian Peng***, Aroonroj Mekareeya, Robert.Paton***** and Edward Anderson*****, "Computational Ligand Design in Enantio- and Diastereoselective Ynamide [5+2] Cycloisomerization" *Nature Communication* **2016***. 7:10109 (Open Access Article).*
4. **Qian Peng***, Fernanda Duarte, Robert S. Paton, **"**Computing Organic Stereoselectivity – from Concepts to Quantitative Calculations and Predictions" *Chem. Soc. Rev.* **2016**, *in revision*.

In preparation:

1. Qian Peng, Philippe M. C. Roth, Rebecca M. Maksymowicz, Alex Curran, Robert S. Paton, and Stephen P. Fletcher, Computational approach to develop phosphoramidite ligand applied to copper catalysed asymmetry conjugate addition. Will be submitted in **2016.**
2. Arghya Deb, Qian Peng*, Avijit Hazra, Robert S. Paton, Debabrata Maiti, Unactivated Aliphatic Alkenes in Palladium Catalyzed Stereoselective C–H Olefination, Will be submitted in **2016.**

Progress in Research Training

Skills and Techniques

During the two years, the researcher developed several skills and techniques. The researcher developed for example his knowledge in computational chemistry, and developed his skills in calculation software (i.e. Gaussian) and analytical techniques such as NMR and mass spectrometry by collaborations with experimental groups. Moreover, the researcher also had developed his skills in management of project involving the development of Rh- and Cu-catalyzed asymmetric reaction, which was quite different from his previous experience in computational chemistry. He has not only demonstrated his independence in conducting projects and in strategizing which topics to study, but also succeeded to obtain two small seed fundings (i.e. SCG Innovation) and NSCCS for computational CPU hours as co-PI. For his future career development, he had attended "the Joliot-Curie Conference" which allowed him to learn the knowledge of career progression and importance of one's network. During the Fellowship, he has developed supervision skills and has participated in the drafting of manuscripts for publication and in the prepration of grants for computing access and research funds.

Communication and Presentation Skills

The Fellow attended regular seminar and group meeting in Oxford and UK to develop his communication skills. And the project has been presented in poster/oral by the researcher

during seminars and conferences including the worldwide international meetings for several times:

1. CRC-SU Joint International Symposium, Stockholm, Sweden, October **2014**
2. UK Catalyst Conference 2015, Loughborough, January **2015**
3. The 15th ICQC, Beijing, China, June **2015**
4. The OMCOS18, IUPAC International Symposium, Sitges-Barcelona, Spain, July **2015**.
5. The 17th International Symposium on homogeneous and Heterogeneous Catalysis, Utrecht, Netherlands, July 2015
6. The 15th European Symposium on Organic Reactivity (ESOR 2015), Kiel, Germany, August, **2015**
7. ACS national regional meeting, San Diego, CA, USA, March, **2016.**
8. Challenges in Organic Chemistry (ISACS19), Irvine, CA, USA, March, **2016**.
9. Girona Seminar on "Predictive Catalysis: Transition-Metal Reactivity by Design", Spain, April, **2016.**
10. The 23rd IUPAC Conference on Physical Organic Chemistry, Australia, July, **2016**.
11. The 20th International Symposium on Homogeneous Catalysis, Japan, July, **2016**.

Dr Peng had received talk Award of "Nature Chemistry" and "Organic Chemistry Frontiers" at Girona Seminar in Spain. Very recently, Dr Peng was awarded CSA-Trust grant for attending The 23rd IUPAC Conference on Physical Organic Chemistry, Australia. These opportunities have no doubts improved his communication and presentation skills to build his research network.

Student Supervision

The researcher successfully particpated in the day-to-day supervision and mentoring of juinor co-workers, including Miss Sophie Mathew-Jones (Part II student), Ruchuta Ardkhean (graduate student), özlem sarı (visiting PhD student).