Young Career Focus: Dr. Jackson D. Leow (National Tsing-Hua University, Hsinchu, Taiwan)

Background and Purpose. ***SYNFORM*** will from time to time meet young up-and-coming researchers who are performing exceptionally well in the arena of organic chemistry and related fields of research, in order to introduce them to the readership. This ***SYNSTORY*** with a Young Career Focus presents Dr. Jackson D. Leow (National Tsing-Hua University, Hsinchu, Taiwan).

BIOGRAPHICAL SKETCH

Dr. J. D. Leow

Jackson D. Leow was born in Singapore in 1981. He received both his undergraduate and Ph.D. degrees from the National University of Singapore (NUS) under the tutelage of Professor Choon-Hong Tan in 2005 and 2009, respectively. His efforts led to the discovery of chiral bicyclic guanidine as a proton shuttle molecular machine for enantioselective protonation and isomerization reactions. In between, he worked at S*Bio Pharma and accumulated industrial experience in drug discovery. From 2010–2012, he pursued his postdoctoral studies with Professor Jin-Quan Yu at The Scripps Research Institute in San Diego (USA). There, he was engaged in research at the forefront of activating inert *meta*-C–H bonds, solving one of the most challenging problems in organic synthesis. He established the concept of directed remote *meta*-C–H functionalization which was published in *Nature*. Following that, he returned to Singapore to work at the Agency for Science, Technology and Research (A*STAR). As a research scientist II, he led a small research team as project leader. He assumed the position of Assistant Professor at the National Tsing Hua University of Taiwan in 2013. His works attracted an average of 58 citations per paper. They were recognized with numerous awards including the Thieme Chemistry Journal Award (2014), Marquis Who's Who in the World (2014), A*STAR postdoctoral fellowship (2010), and Kiang Ai Kim scholarship (2006). He is an elected Fellow of the World Technology Network as well as the Global Young Academy (GYA). His current research focuses on developing new catalytic processes to control radicals in organic synthesis.

INTERVIEW

SYNFORM | *What is the focus of your current research activity?*

Dr. J. D. Leow | My current research activity focuses on developing new catalytic processes. Ideally, they should proceed with excellent efficiency, selectivity, and eco-friendliness. From this perspective, classic radical reactions rarely fulfill these criteria. They have been known since their discovery by Professor Moses Gomberg in 1900. They are very reactive, resulting in poor regioselectivity and stereoselectivity. We aim to tap into their unique high reactivity profile while modulating them such that they do not react at random sites. We take on this challenge by using contemporary approaches such as transition-metal catalysis and organocatalysis.

SYNFORM | *When did you get interested in synthesis?*

Dr. J. D. Leow | My high school aspiration was to become a chemist. I am grateful and thankful that I had inspirational chemistry teachers during the formative years of my education. During my undergraduate studies, I chanced upon Professor K. C. Nicolaou's "Classics in Total Synthesis I". I was greatly fascinated by the monumental works of various legendary organic synthetic chemists such as Professor Robert B. Woodward and Professor E. J. Corey. On the other hand, I found them daunting and overwhelming. Luckily, I met a wonderful advisor, Professor Tan, when I started my undergraduate research with him. He has never failed to support and encourage me all these years. I found a sense of achievement and satisfaction whenever a new reaction was discovered. Since I started my undergraduate research in synthesis, I have never looked back. The irony is that I have yet to attempt a total synthesis project. I hope we can apply our new reaction methodologies to the total synthesis of natural products in the near future.

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SYNFORM | *What do you think about the modern role and prospects of organic synthesis?*

Dr. J. D. Leow | Carbon is an important element that resulted in the origin of life. It is omnipresent in our daily life, such as food, clothes, plastics, etc. Organic synthesis remains prevalent in our modern society as we advance to the technological era. We have seen the importance of the role that organic synthesis played in the enhancement of living standards. It has become an indispensable tool in industries such as petrochemicals, pharmaceuticals, flavors, fragrances, agrochemicals and others. In the past 13 years or so, this has been recognized with the award of Nobel prizes in the fields of asymmetric synthesis, olefin metathesis, and palladium-catalyzed cross-couplings. We will continue to experience revolutionary technological advancements, which offer greater reaction efficiency and greener solutions. Some of the upcoming exciting areas are asymmetric organocatalysis, transition-metal-catalyzed C–H bond activation, and photoredox catalysis.

SYNFORM | *Your research group is active in the area of organic synthesis, particularly C–H bond activation and catalysis. Could you tell us more about your research and its aims?*

Dr. J. D. Leow | I had a fruitful postdoctoral experience with Professor Yu at The Scripps Research Institute, which naturally trained me to be interested in the field of C–H bond activation. Direct functionalization of unactivated C–H bonds provides a fast and straightforward method for building up complexity in simple molecules. No additional step is required to preinstall the C–X handle and it represents an ideal step economy. However, complications arise when multiple C–H bonds are present in the target molecule, posing a challenge to achieve positional selectivity. For example, there are three different C–H sites on a monosubstituted arene. The regioselectivity is often clouded by the electronic and steric effects from the substituent. One of the classical methods to functionalize an arene C–H bond is the Friedel–Crafts reaction, in which it is heavily dependent on the electronic factor.

There has been a rapid development of α-chelating groups to direct the transition metal to the *ortho*-position of the arene ring. Using a weak coordination approach, *ortho*-C–H carbonylation of phenethyl alcohols was achieved in the presence of amino acid ligands to accelerate the reaction (*Chem. Sci.* **2011**, *2*, 967). This transformation provided an expedient route to 1-isochromanone motifs, which are common structural elements in natural products and other biologically active compounds (Figure 1). The synthesis of *para*-substituted biaryl compounds poses a significant challenge due to selectivity issues. A highly *para*-selective C–H/C–H cross-coupling of monosubstituted arenes was developed using an electrophilic fluorinating reagent as a bystanding oxidant (*J. Am. Chem. Soc.* **2011**, *133*, 13864).

Although proximity-driven reactivity has found broad applications, the activation of remote *meta*-C–H bonds is unfavorable due to the entropy effect of a large 12-membered ring. Recently, we have designed a class of removable nitrile-based templates tethered to the target arene. By squeezing the Pd and substrate together through steric effects, they are then able to interact with each other. The template makes a molecular U-turn while the nitrile group acts like a linear robotic arm. It swings the Pd out and around to reach the distal *meta*-C–H bonds (more than ten bonds away). This method can be used to functionalize a commercially available drug, Baclofen, to access novel *meta*-substituted molecules for drug screening in a single step. This work was published in the prestigious journal *Nature* (*Nature* **2012**, *486*, 518).

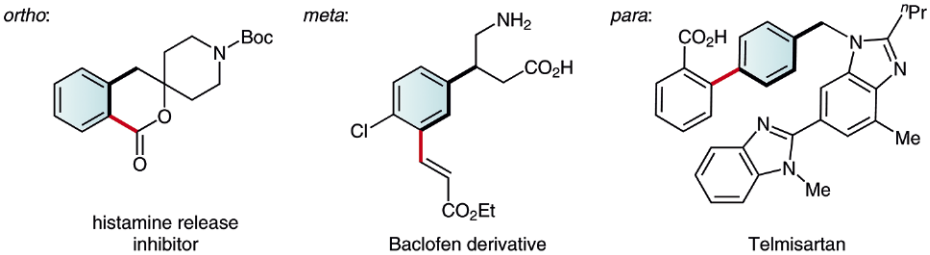

Figure 1 *Synthesis of novel drug leads via position-selective C–H bond functionalization*

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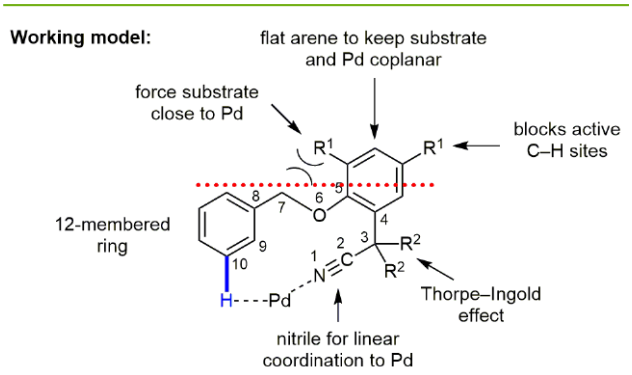

Figure 2

SYNFORM | *What is your most important scientific achievement to date and why?*

Dr. J. D. Leow | We are a newly set-up research group in the midst of intense exploration of new exciting chemistry with fervor. Our unpublished data show promising results that can possibly be important contributions to the chemistry community. We focus on unique catalyst and ligand designs that can dictate and tame the radicals towards our target reaction site. They are fine-tuned such that we can hit the sweet spot of our reactions. Our results greatly improve and expand the synthetic utility of radical chemistry. I hope our work will inspire fellow organic chemists to view existing challenges from different angles.

Matteo Zanda

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