Anti-Selective [3+2] (Hetero)annulation of Nonconjugated Alkenes via Directed Nucleopalladation

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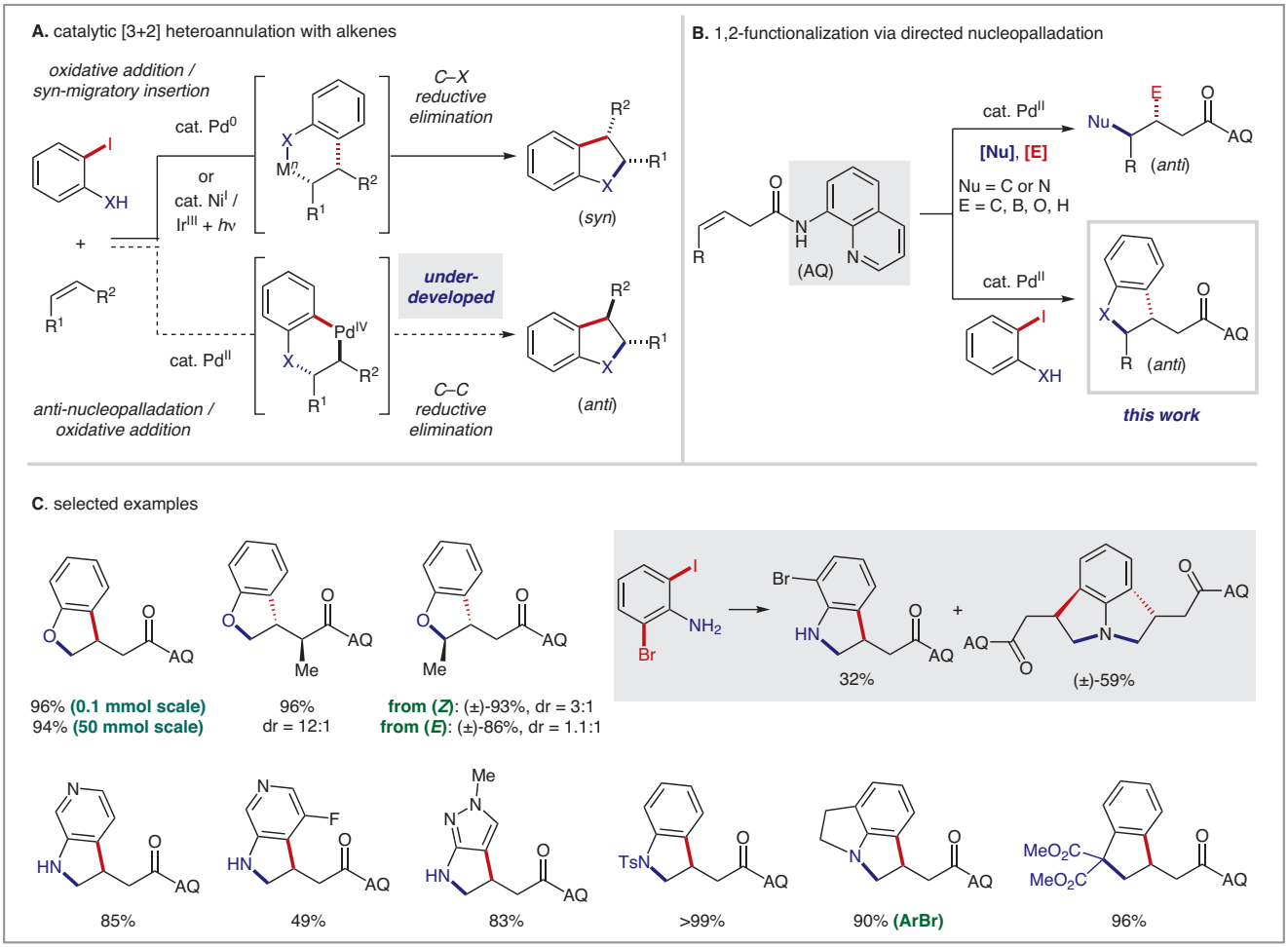
Carbo- and heterocyclic core structures – such as 2,3-dihydrobenzofurans, indolines, and indanes – are common motifs in bioactive and therapeutic molecules, as well as in natural products. Due to their usefulness, it remains important to identify efficient routes to access these compounds easily, quickly, and inexpensively. The groups of Dr. Indrawan J. McAlpine from Pfizer Oncology Medicinal Chemistry (San Diego, USA), Professor Peng Liu from the University of Pittsburgh (USA) and Professor Keary M. Engle from the Scripps Research Institute (La Jolla, USA) collaborated on the work leading to the publication of this paper in *Nature Communications*. Professor Engle said: "Based on the development of Larock-type (hetero)annulation reactions between ambiphilic aryl halides and alkenes over the past 30 years, as well as prior work in 8-aminoquinoline (AQ)-directed alkene 1,2-difunctionalization, we sought to develop an all-encompassing annulation process that could unite non-conjugated alkenes and a diverse collection of *O*-, *N*- and *C*-based coupling partners using a mechanistic approach distinct from prior (hetero)annulations, namely one that relies on an initial nucleo-



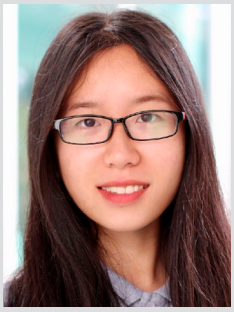
Scheme 1

palladation event, subsequent oxidative addition, and finally C(sp^3)–Ar reductive elimination, involving an overall Pd(II)/Pd(IV) redox couple."

At first, the three research groups were wary that the development of this reaction could end up facing insurmountable challenges. Professor Engle explained: "For example: (1) phenols and anilines have proven ineffective coupling partners in AQ-directed nucleopalladation reactions; (2) the strained transition states for intramolecular Pd(II)/Pd(IV) oxidative addition and reductive elimination appeared to be potentially high-energy; (3) competitive pathways arising from Heck- or Wacker-type oxidative alkene addition, hydrofunctionalization, or the alkene isomerization may diminish yield." He continued: "To our surprise and delight, however, the envisioned method was indeed viable (Scheme 1). Moreover, the substrate scope and the functional group tolerance of this reaction is impressive. In fact, this reaction system tolerates *ortho*-iodophenols, *ortho*-iodoanilines with or without protecting groups (such as *N*-acetyl, -tosyl, and -alkyl groups), various aminoiodopyridines, different carbon-based coupling partners, internal alkenes, and α-substituted alkenes." The authors found that good to excellent yields and diastereoselectivities were observed in most cases. The reaction was found to tolerate both air and moisture, and its performance did not require any special precautions. "Due to its operational convenience, the methodology can be easily scaled and gram quantities are obtained through simple work-up and purification. Unlike prior methods, where *syn*-oxy/aminopalladation is proposed to take place, in this reaction system an *anti*-nucleopalladation pathway is operative, as evidenced by single-crystal X-ray diffraction data from a representative product," remarked Professor Engle, who continued: "Importantly, the reaction tolerates both air and moisture and does not require any special precautions to perform. As a result, this methodology could be conveniently scaled up, allowing for isolation of 14.3 g of the desired product with minimal impurities after an operationally simple work-up and purification procedure."

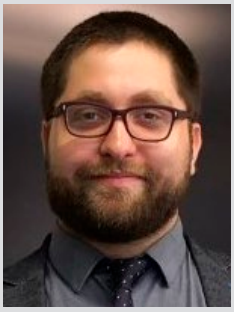
Professor Engle concluded: "Thanks to the joint efforts of three research groups, we have discovered a method that provides direct access to useful 2,3-dihydrobenzofurans, indolines, and indanes by employing ambiphilic aryl halide coupling partners and non-conjugated alkenyl amides. Mechanistic experiments and DFT studies shed light on the origins of diastereoinduction, anti-selectivity, and other fundamental aspects of this Pd(II)/Pd(IV) annulation process."

About the authors



H.-Q. Ni

Hui-Qi Ni was born and raised in Shanghai, P. R. of China. She earned her B.S. degree in 2019 from the University of Science and Technology of China, where she carried out undergraduate research under the direction of Prof. Xi-Sheng Wang. While completing her B.S., she also took two summer internships in the laboratories of Prof. Keary M. Engle (2017; Scripps Research, USA) and Prof. Neil K. Garg (2018; University of California Los Angeles, USA). She is currently pursuing a doctorate degree at Scripps Research (USA) under the tutelage of Prof. Keary M. Engle.



I. Kevlishvili

Ilia Kevlishvili was born in Tbilisi, Republic of Georgia. He obtained a B.A. degree in chemistry and mathematics at the Franklin & Marshall College (USA) in 2012. Currently, he is a member of the Prof. Peng Liu group at the University of Pittsburgh (USA) as a fifth-year doctoral student. His research interests are transition-metal-catalyzed reaction mechanisms and computation-guided catalyst design.

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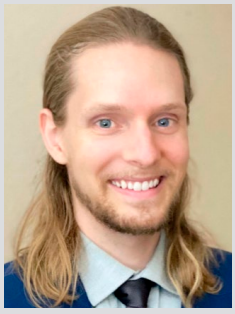
Dr. S. Yang

Shouliang Yang grew up in Shandong Province, P. R. of China, and he received his B.S. from Inner Mongolia University (P. R. of China) in 2009. He pursued his graduate studies under the guidance of Professor Zhen Yang at Peking University (P. R. of China) and earned his Ph.D. in 2014. Then, he took up a postdoctoral position in the laboratory of Professor Dale L. Boger at Scripps Research (USA) and worked on total synthesis and structure modification of vinblastine. In January 2018, he joined the medicinal chemistry department at Pfizer, La Jolla (USA) and began his new career in drug discovery.

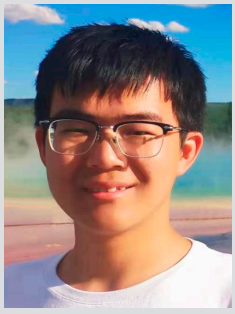
M. Tran-Dubé

Michelle Tran-Dubé was born in San Diego, California (USA). She received her B.S. at the University of California, Irvine (USA) in 2001 where her research was on nucleophilic addition to tetrahydrofuran oxocarbenium ion intermediates in Prof. Keith Woerpel's laboratory. She then received her M.S. in 2003 at Boston College (USA) in Prof. Scott Miller's laboratory researching the development of peptide-based and amino acid based asymmetric catalysts. In 2003, she returned to southern California where she currently works as a medicinal chemist at Pfizer in La Jolla (USA).



A. M. Romine

Andrew M. Romine is originally from Philadelphia, Pennsylvania (USA). He received his B.S. in chemistry and business, economics, and management in 2016 from the California Institute of Technology (USA) where he performed research supervised by Prof. G. Jeffrey Snyder (2013) and Prof. Robert H. Grubbs (2015–2016). While completing his B.S., he also attended a research program at ICIQ (Spain) under the supervision of Prof. Vladimir V. Grushin (2014). Andrew is currently an NSF fellow and fifth-year doctoral student at Scripps Research (USA) working with Prof. Keary M. Engle.



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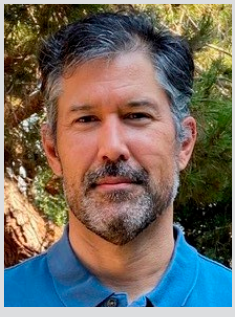

Dr. I. J. McAlpine

Indrawan J. McAlpine was born in Chicago (USA) and grew up in the far northern suburb of Libertyville, Illinois (USA). He obtained his B.S. in chemistry in 1991 at the University of Illinois, Urbana-Champaign (USA). He obtained his Ph.D. in 1998 at the University of California, Los Angeles (USA) with Prof. Robert Armstrong. He went on to complete an NIH postdoctoral study with Prof. Stuart Schreiber at Harvard University (USA). In 2000, he then became a medicinal chemist at Agouron/Warner-Lambert (USA) which was bought out by Pfizer in that same year. He is currently a Research Fellow in Oncology Medicinal Chemistry at Pfizer in La Jolla, CA (USA).

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Prof. K. M. Engle

Keary M. Engle was born and raised in western Michigan (USA). He was educated at the University of Michigan (USA), the Max-Plank-Institut für Kohlenforschung (Germany), the Scripps Research Institute (USA), the University of Oxford (UK), and the California Institute of Technology (USA). He began his independent career as an Assistant Professor at Scripps Research in 2015 and was promoted to Professor in 2020. His laboratory pursues basic science research in homogeneous catalysis with the goal of inventing useful new organic reactions.

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