

Catalytic C–H Arylation of Aliphatic Aldehydes Enabled by a Transient Ligand

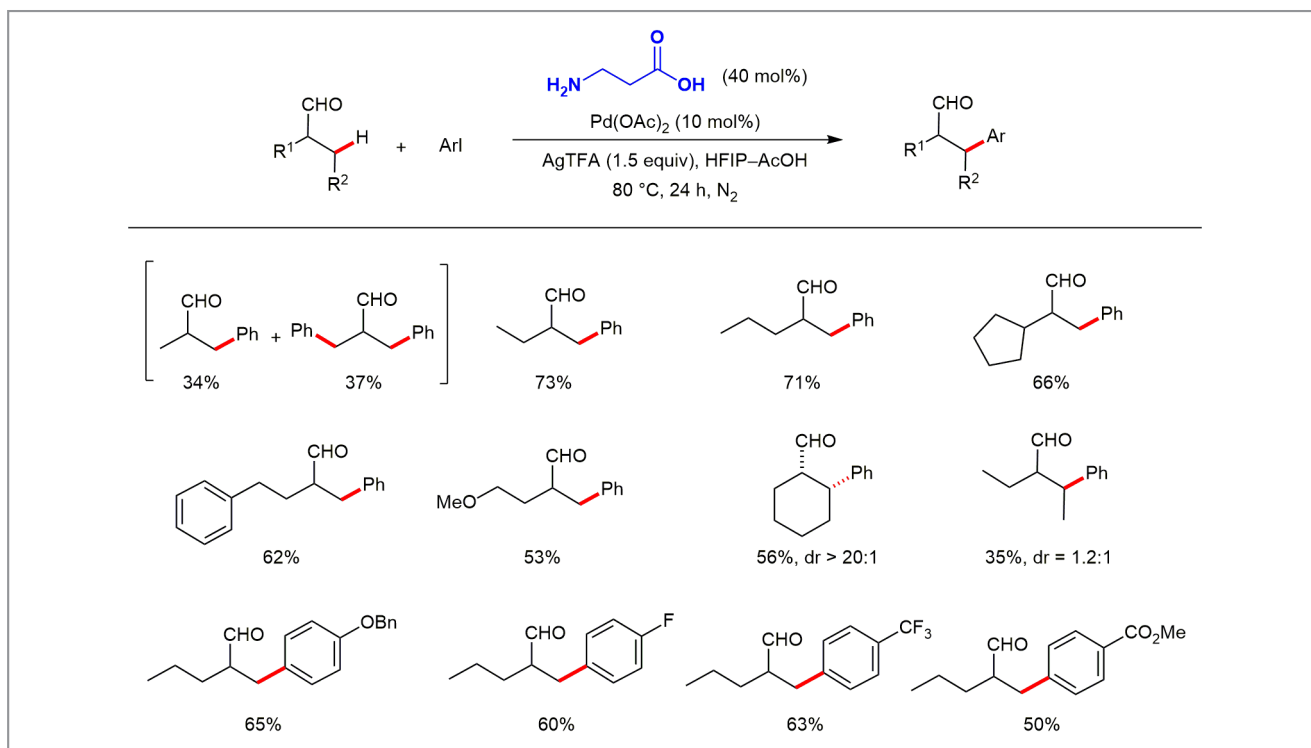
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In recent years, significant progress on transition-metal-catalyzed site-selective C–H bond activation has been achieved by introducing directing groups on substrates.¹ However, this method has inherent limitations: the process of construction of the original substrates and removal of the directing groups diminishes the efficiency and/or compatibility of the reactions. Therefore, there is a demand for developing a process without installing a directing group. The groups of Professor Guigen Li from Nanjing University (P. R. of China) and Professor Haibo Ge from Indiana University–Purdue University Indianapolis (IUPUI, USA) are aiming to design a specific catalyst as a transient directing group that can bind reversibly to the substrate and the metal center. Professor Ge said: “Some previous literature indicates that the reversible imine linkage was effective in Rh- or Pd-catalyzed selective C–H bond functionalization reactions.² Very recently, our group reported the di-

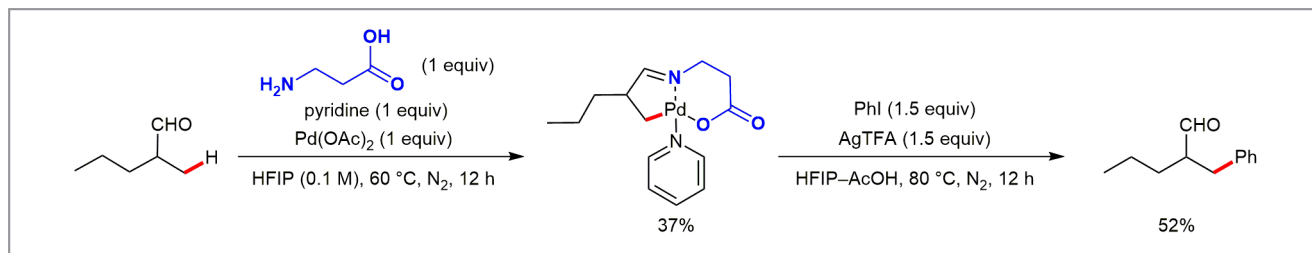
rect palladium-catalyzed γ -arylation of primary alkylamines with glyoxylic acid as a transient directing group.³”

He continued: “However, the direct β -functionalization of aliphatic aldehydes has not yet been discovered. Based on our previous results, we believe that the arylation of unactivated β -C–H bonds of aliphatic aldehydes is feasible using metal catalysts by employing appropriate amine compounds as transient directing groups.”

After extensive investigations, 3-aminopropanoic acid was proven to be the most suitable transient directing group in the process of Pd-catalyzed arylation of unactivated β -C–H bonds of aliphatic aldehydes. “As expected, this reaction exhibited excellent functional group compatibility and site-selectivity. In the process, functionalization of the unactivated β -C–H bonds of methyl groups was favored over the β -methylene, γ - or δ -methyl C–H bonds,” said Professor Ge. He continued:



Scheme 1 Selected substrate scope of palladium-catalyzed direct β -arylation of aliphatic aldehydes



Scheme 2 Synthesis of the [5,6]-bicyclic palladium complex and the subsequent arylation reaction

“Moreover, unactivated secondary sp^3 carbons could also be functionalized (Scheme 1). More importantly, β -arylation of n -pentanal could also be accomplished in this catalytic cycle by using 3-amino-3-methylbutanoic acid as the transient directing group. Furthermore, the control experiments indicated that dehydrogenation of aliphatic aldehydes was not involved in this process and a [5,6]-bicyclic palladium complex might be the intermediate in the catalytic cycle. After a multitude of attempts, the [5,6]-bicyclic palladium complex was finally isolated by employing pyridine as an auxiliary ligand, and the desired arylated product was also captured from the reaction of palladium intermediate with iodobenzene successfully (Scheme 2).”

Professor Ge concluded: “We hope that further detailed mechanistic studies of this reaction will provide us more insights in developing novel transient directing groups to extend both the substrate and reaction scopes.”

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About the authors



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Ke Yang was born in Jiangsu Province (P. R. of China). He completed his B.S. and M.S. degrees at Jiangsu Normal University (P. R. of China). Next, he received his Ph.D. from Nanjing University (P. R. of China) under the supervision of Professor Yan Zhang. In 2014, he became a postdoctoral fellow at Nanjing University with Professor Guigen Li. In 2015, he joined the group of Professor Haibo Ge at IUPUI (USA). His research interests involve novel transition-metal-catalyzed C–H bond functionalization reactions.



Q. Li

Qun Li was born in Hubei Province (P. R. of China) and received his B.S. degree from Wuhan University of Technology (P. R. of China) in 2012. In 2013, he became a graduate student under the supervision of Professor Guigen Li at Nanjing University (P. R. of China). His main research interest is transition-metal-catalyzed methodologies.

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Yongbing Liu was born in 1984 in Hengyang (P. R. of China). In 2008, he received his bachelor's degree from Xiangtan University (P. R. of China). After obtaining his M.S. degree in organic chemistry from the same university in 2011, he moved to the Institute of Chemistry, Chinese Academy of Sciences (Beijing, P. R. of China) where he worked on the development of new strategies for borane-catalyzed hydrogenation under the guidance of Professor Haifeng Du. He finished his Ph.D. studies in 2014 and then joined the Ge group as a postdoctoral researcher in November 2014. He is currently studying novel organic transformations based on transition-metal-catalyzed C–H activation.



Prof. G. Li

Guigen Li was born in 1962 in Jiangsu (P. R. of China). He received his B.S. in 1984 at Jiangsu Normal University (P. R. of China) and M.S. in 1987 at Nankai University (P. R. of China) under the direction of the late Professor Zhenheng Gao. After he graduated from Nankai, he was immediately recruited as a faculty member at Nanjing University (P. R. of China) in July 1987 where he worked for three years. He came to the USA in 1990 and received his Ph.D. in 1995 at the University of Arizona (USA) with Professor Victor J. Hruby, and conducted his postdoctoral research on the asymmetric catalytic aminohydroxylation reaction (AA) at the Scripps Research Institute (USA) with Professor

K. Barry Sharpless until summer 1997. He joined Texas Tech University (USA) in August 1997 as an Assistant Professor and was promoted to Associate Professor in 2002 and to Full Professor in 2006. Currently, he holds an adjunct Professorship and Director position at the Institute of Chemistry & BioMedical Sciences (ICBMS) at Nanjing University (P. R. of China) and is an innovation team member at Shanghai Institute of Organic Chemistry (SIOC, P. R. of China). So far, he has trained over 40 graduates and 60 undergraduates in his research and achieved over 270 publications (H-index 45). His research interests are on establishing new synthetic concepts/technologies, new reagents (chiral and achiral), new methodologies and related mechanisms. He is also interested in bioorganic and medicinal chemistry.



Prof. H. Ge

Haibo Ge was born in Yancheng, Jiangsu (P. R. of China). He received his Ph.D. in medicinal chemistry from The University of Kansas (Lawrence, USA) in 2006 with Professor Gunda Georg. He then moved to The Scripps Research Institute (La Jolla, USA) for his postdoctoral studies with Professor Dale Boger. In 2009, he began his independent academic career at the Department of Chemistry and Chemical Biology at Indiana University–Purdue University Indianapolis (IUPUI, USA). Research in his group is mainly focused on the development of novel methods towards carbon–carbon and carbon–heteroatom bond formation through transition-metal-catalyzed C–H functionalization. Additionally, his group is working on the synthesis and structure–activity relationship studies of anticancer and antibacterial agents.