

Rhodium-Catalyzed Atroposelective C–H Arylation: Efficient Synthesis of Axially Chiral Heterobiaryls

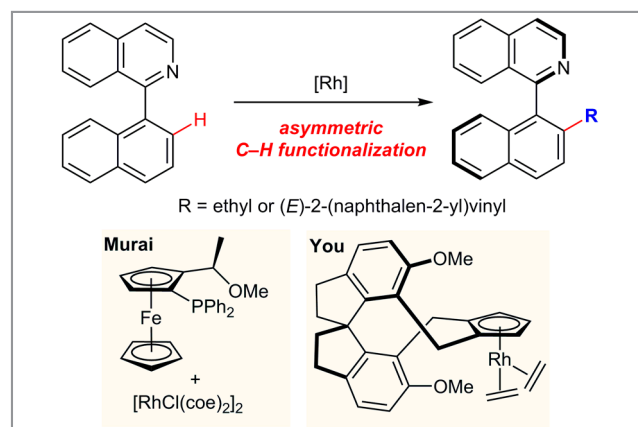
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Axially chiral biaryls are important scaffolds that exist widely in natural products and pharmaceuticals, and are also utilized as privileged ligands and catalysts in asymmetric synthesis. Thus, the development of novel methods for the efficient asymmetric synthesis of axially chiral biaryls, enabled by transition-metal catalysis or organocatalysis, has attracted enormous interest in the chemical community. The group of Professor Shu-Li You from the Shanghai Institute of Organic Chemistry (SIOC, P.R. of China) has been interested in the synthesis of axially or planar chiral molecules through transition-metal-catalyzed asymmetric C–H functionalization reactions for some time. “Recently, transition-metal catalyzed asymmetric C–H functionalization reactions have received much attention for their great potential in efficient and straightforward synthesis of axially chiral biaryls. As there are numerous applications of axially chiral pyridine-derived ligands/catalysts in asymmetric catalysis, it is highly desirable to develop efficient methods for their asymmetric synthesis,” said Professor You. “Although palladium-catalyzed asymmetric Suzuki coupling, reported recently by Fernández, Lassaletta and co-workers, represents a powerful strategy for the asymmetric synthesis of axially chiral aryl pyridines(isoquinolines) (*J. Am. Chem. Soc.* **2013**, *135*, 15730–15733), catalytic asymmetric synthesis with high enantioselectivity and efficiency via atroposelective C–H functionalization strategy (*Tetrahedron: Asymmetry* **2000**, *11*, 2647; *J. Am. Chem. Soc.* **2016**, *138*, 5242–5245) remains a challenging topic (Scheme 1).” Recently, Professor You and his group developed an efficient method for facile synthesis of axially chiral heterobiaryls with high enantioselectivities via atroposelective C–H arylation reactions.

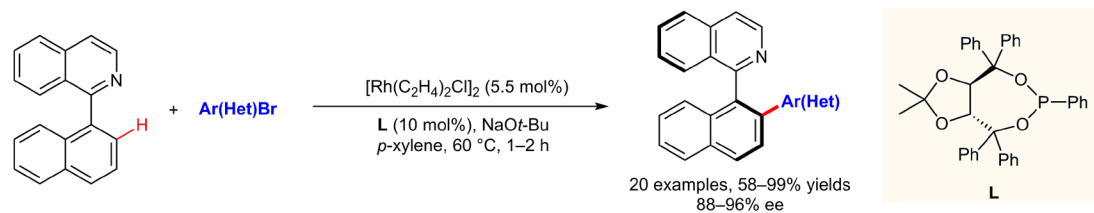
Professor You explained: “Five years ago, we reported the direct asymmetric C–H olefination of aryl benzo[*h*]isoquinolines using the Cramer catalyst (*Angew. Chem. Int. Ed.* **2014**, *53*, 13244–13247), but moderate enantioselectivities were obtained with aryl pyridines (isoquinolines). At the same time, we also developed the Pd(II)-catalyzed asymmetric C–H iodination of aryl-substituted pyridine *N*-oxides via kinetic resolution, but only moderate *s*-values were afforded (*ACS Catal.* **2014**, *4*, 2741–2745). Later on, we introduced the SCp ligand in Rh(III)-catalyzed asymmetric C–H olefination (*J. Am. Chem. Soc.* **2016**, *138*, 5242–5245) and the enantioselectivi-

ties could be significantly improved. However, the substrate scope was relatively narrow, and low enantioselectivities were observed for 1-(naphthalen-1-yl)isoquinoline. It has been a long-standing problem to synthesize axially chiral pyridine(isoquinoline) by C–H functionalization reaction in a highly enantioselective manner.”

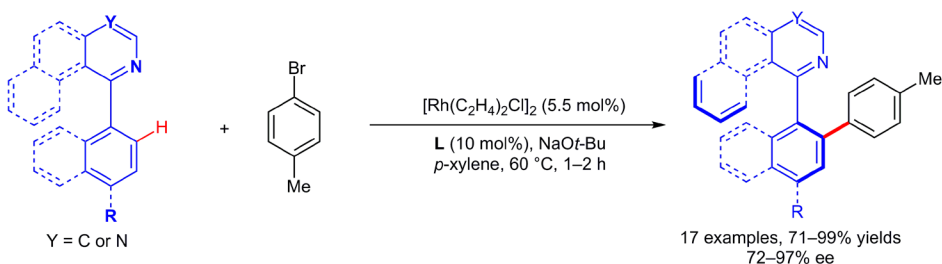
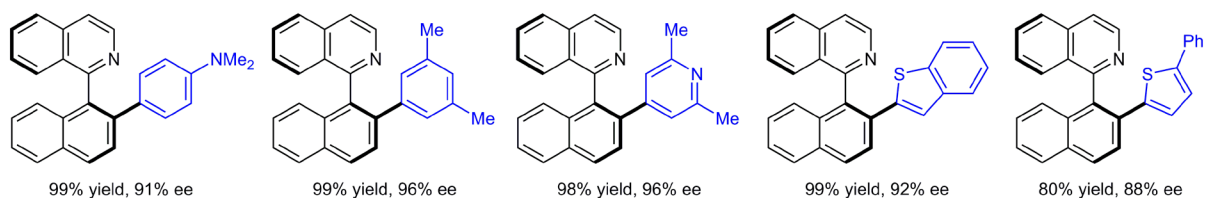
Professor You further explained: “Dr. Zhong-Jian Cai, a former postdoc in our lab, found that rhodium(I)/TADDOL-derived monodentate phosphonite catalytic system, introduced by the Glorius group (*Angew. Chem. Int. Ed.* **2018**, *57*, 9950–9954), worked well in the asymmetric C_{sp²}-H arylations of ferrocenes. Encouraged by these results, Dr. Qiang Wang, another talented postdoc working in the same fume hood, investigated the Rh-catalyzed C–H arylation of 1-(naphthalen-1-yl)isoquinoline.” Dr. Qiang Wang remarked: “Initially, the reaction under Glorius’ conditions using aryl iodides as arylating reagents only gave low yields (10–15%) in this transformation. Later on, Dr. Zhong-Jian Cai and Mr. Chen-Xu Liu, a graduate student in Professor You’s lab, synthesized many different types of ligands. These ligands were found inefficient in the Rh-catalyzed C–H arylation of 1-(naphthalen-1-yl)isoquinoline despite several months of optimization work.” Professor You continued: “Considering the halide effect in transition-metal catalysis (*Angew. Chem. Int. Ed.* **2002**, *41*, 26–47), we tried to revisit this reaction using aryl bromides as aryl-



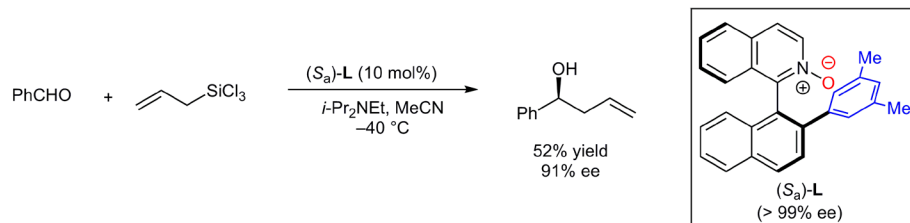
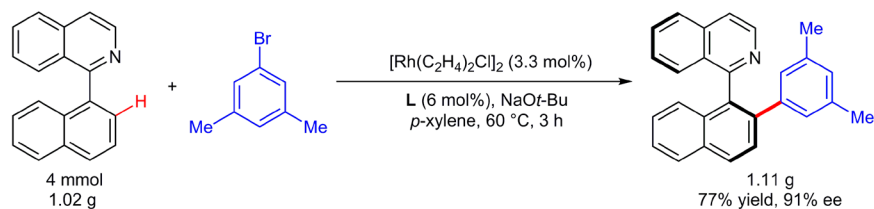
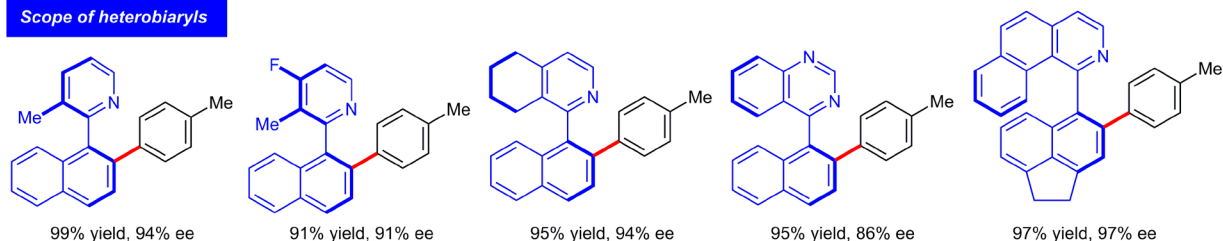
Scheme 1 Previously reported rhodium-catalyzed asymmetric C–H functionalization of 1-(naphthalen-1-yl)isoquinoline



Scope of aryl and heteroaryl bromides



Scope of heterobiaryls

Scheme 2 Selected substrate scope, a gram-scale reaction and application of chiral *N*-oxide as a catalyst in the allylation of aldehyde

ating reagents. To our delight, the efficiency of Rh-catalyzed C–H arylation of 1-(naphthalen-1-yl)isoquinoline was dramatically improved. Then Dr. Qiang Wang quickly identified the optimal conditions for this reaction.”

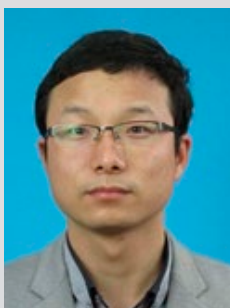
Professor You continued: “One of the most exciting parts of this methodology is that the reaction is extremely efficient. The reaction conditions are mild and the starting materials are readily available (Scheme 2). Heteroaryl bromides, such as pyridine, thiophene, benzofuran are well tolerated. Good to excellent yields and enantioselectivities are obtained. Moreover, 2-aryl pyridines, quinazolines and benzo[*h*]isoquinolines are efficient coupling partners. What’s more, the gram-scale reaction with relatively low catalyst loading further highlights the

potential utility of this method. In addition, a chiral *N*-oxide from one-step oxidation of the product could act as an efficient catalyst for asymmetric allylation of benzaldehyde with allyltrichlorosilane.”

Professor You concluded: “We have developed an efficient and highly enantioselective synthesis of axially chiral heterobiaryls, which is enabled by rhodium(I)-catalyzed atropo-selective C–H arylation of heterobiaryls. We expect that our study will provide a straightforward method for the synthesis of axially chiral pyridine(isoquinoline)-derived ligands and catalysts. The products obtained herein provide an excellent platform for this purpose.”

Mattia Fanello

About the authors



Dr. Q. Wang

for 18 months. In July 2018, he joined Prof. Shu-Li You’s group for his postdoctoral studies after being awarded the Initiative Postdocs Supporting Program. His current research interests are transition-metal-catalyzed asymmetric C–H bond functionalization.

Qiang Wang was born in Hubei (P. R. of China), in 1990. He received his BSc from Central China Normal University (CCNU, P. R. of China). He subsequently carried out his doctoral studies at the same university under the supervision of Prof. Wen-Jing Xiao and Prof. Liang-Qiu Lu, receiving his PhD in 2018. During his graduate studies, he joined the group of André M. Beauchemin (University of Ottawa, Canada) as a visiting PhD student

University, IN (USA), working in the research group of Prof. Mingji Dai.



C.-X. Liu

Chen-Xu Liu was born and grew up in Xuzhou, Jiangsu Province (P. R. of China). He received his bachelor’s degree (2017) in applied chemistry from Donghua University (P. R. of China) under the supervision of Prof. Yong-Fen Xu and now he is a PhD candidate in the group of Prof. Shu-Li You. His research interests focus on the construction of new chiral skeletons via asymmetric C–H bond functionalization.



Dr. Z.-J. Cai

P. R. of China) as a postdoctoral fellow studying transition-metal-catalyzed asymmetric C–H bond functionalization reactions. Zhong-Jian is currently a postdoctoral scholar at Purdue

Zhong-Jian Cai was born and raised in Ganzhou, Jiangxi (P. R. of China). He received a B.A. in chemistry from Nanchang University (P. R. of China), where he worked in the research group of Prof. Sen Lin. He obtained his Ph.D. from Soochow University (P. R. of China), working under the direction of Prof. Shun-Jun Ji. Following his doctoral work, he joined the laboratory of Prof. Shu-Li You at the Shanghai Institute of Organic Chemistry (SIOC,



Prof. Dr. Q. Gu

and at Georg-August-University of Göttingen (Germany) with Prof. Lutz Ackermann from 2012 to 2013. In 2011, he joined SIOC as an associate professor. His current research interests include asymmetric catalysis and C–H bond functionalization.

Qing Gu received his BSc in chemistry from East China University of Science and Technology (ECUST, P. R. of China) in 2001. He obtained his Master’s degree and PhD in organic chemistry from ECUST in 2005 and 2008 under the co-supervision of Prof. Qi-Lin Zhou and Prof. Xin-Yan Wu. He carried out his postdoctoral studies at the Shanghai Institute of Organic Chemistry (SIOC, P. R. of China) with Prof. Shu-Li You from 2009 to 2011

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Prof. S.-L. You

Shu-Li You was born in Henan (P. R. of China) and received his BSc in chemistry from Nankai University (P. R. of China) in 1996. He obtained his PhD from the Shanghai Institute of Organic Chemistry (SIOC, P. R. of China) in 2001 under the supervision of Prof. Li-Xin Dai before conducting postdoctoral studies with Prof. Jeffery Kelly at The Scripps Research Institute (USA).

From 2004, he worked at the Genomics Institute of the Novartis Research Foundation (USA) as a PI before returning to SIOC as a Professor in 2006. He is currently the director of the State Key Laboratory of Organometallic Chemistry. His research interests mainly focus on asymmetric C–H functionalization and catalytic asymmetric dearomatization (CADA) reactions.