

## Iron-Catalysed Asymmetric Carboazidation of Styrenes

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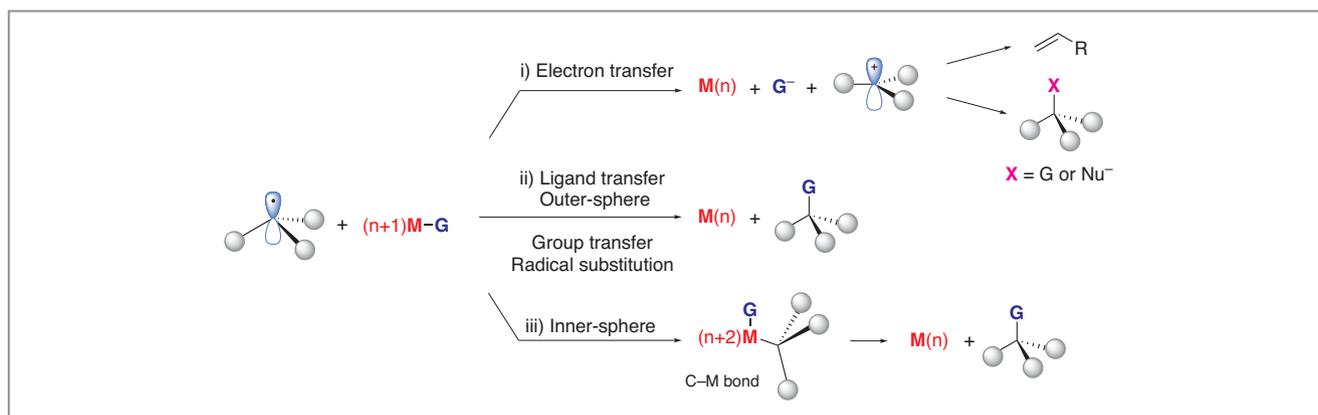
Professor Hongli Bao (Fujian Institute of Research on the Structure of Matter, Chinese Academy of Sciences, P. R. of China) recalls that one particular research question puzzled her at the onset of the research program that eventually led to the title paper: What will happen when a carbon radical meets a metal species? “Three scenarios are detailed in Professor Jay K. Kochi’s paper (Scheme 1),<sup>1</sup>” explains Professor Bao: “i) single-electron transfer from the radical to the metal–ligand (M–G) species, forming a carbon cation which is subsequently either deprotonated or attacked by nucleophiles in the reaction environment; ii) ligand (G) transfer from the metal species M–G to the radical without obvious interaction between two reactants; this process is also called outer-sphere group transfer or radical substitution mechanism by other chemists; iii) the radical combines with the M–G metal species forming a high-valent metal species M(n+2), which undergoes reductive elimination to deliver a product; the latter reaction mode is known as an inner-sphere pathway.”<sup>2</sup>

According to Professor Bao, among these three modes, normally the inner-sphere pathway is utilized in asymmetric synthesis, given that the C–M bond brings two coupling partners close in a chiral environment. She continued: “Conversely, due to the lack of moderate/strong interactions – e.g. covalent, dative, ionic, or hydrogen bonds – between two reaction partners, the stereocontrol through the outer-sphere pathway is extremely challenging, if not entirely impossible to achieve. But as Louis Pasteur once said: ‘*The universe is asymmetric and I am persuaded that life, as it is known to us, is a direct*

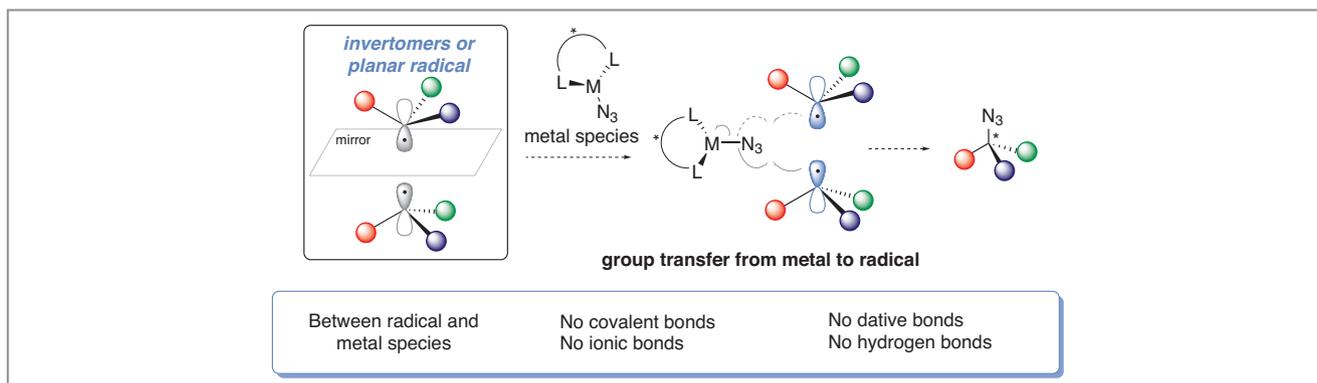
*result of the asymmetry of the universe or of its indirect consequences.*’ So, at the very beginning of the chirality-preference determination, a well-defined chiral environment with strong interaction was unlikely to exist and a weak interaction was therefore more likely to be a trigger.” Professor Bao and her research group are extremely interested in seeking to achieve stereocontrol in the outer-sphere radical reactions by harnessing weak interactions. Professor Bao said: “Before we began our exploration, there was only one successful precedent of stereoselective outcome involving a free untethered radical in enantioselective Kharasch addition reactions, which was reported by Professor Joseph Ready.<sup>3</sup>”

“Our journey in this field began by studying radical azidation, which is a powerful approach to incorporate the nitrogen element,” explained Professor Bao (Scheme 2). She continued: “Although many achiral or racemic versions of radical azidations have been developed, the catalytic chiral radical azidation with high levels of enantiocontrol is unprecedented. Many previous studies on azidation reactions indicated that metal-catalyzed radical azidation often involves intermolecular transfer of an azido group from the metal catalyst to a carbon radical.<sup>4</sup> Such radical group transfer reactions do not involve interactions between metal species and radicals, therefore few believed that this type of transformation could be enantioselective.”

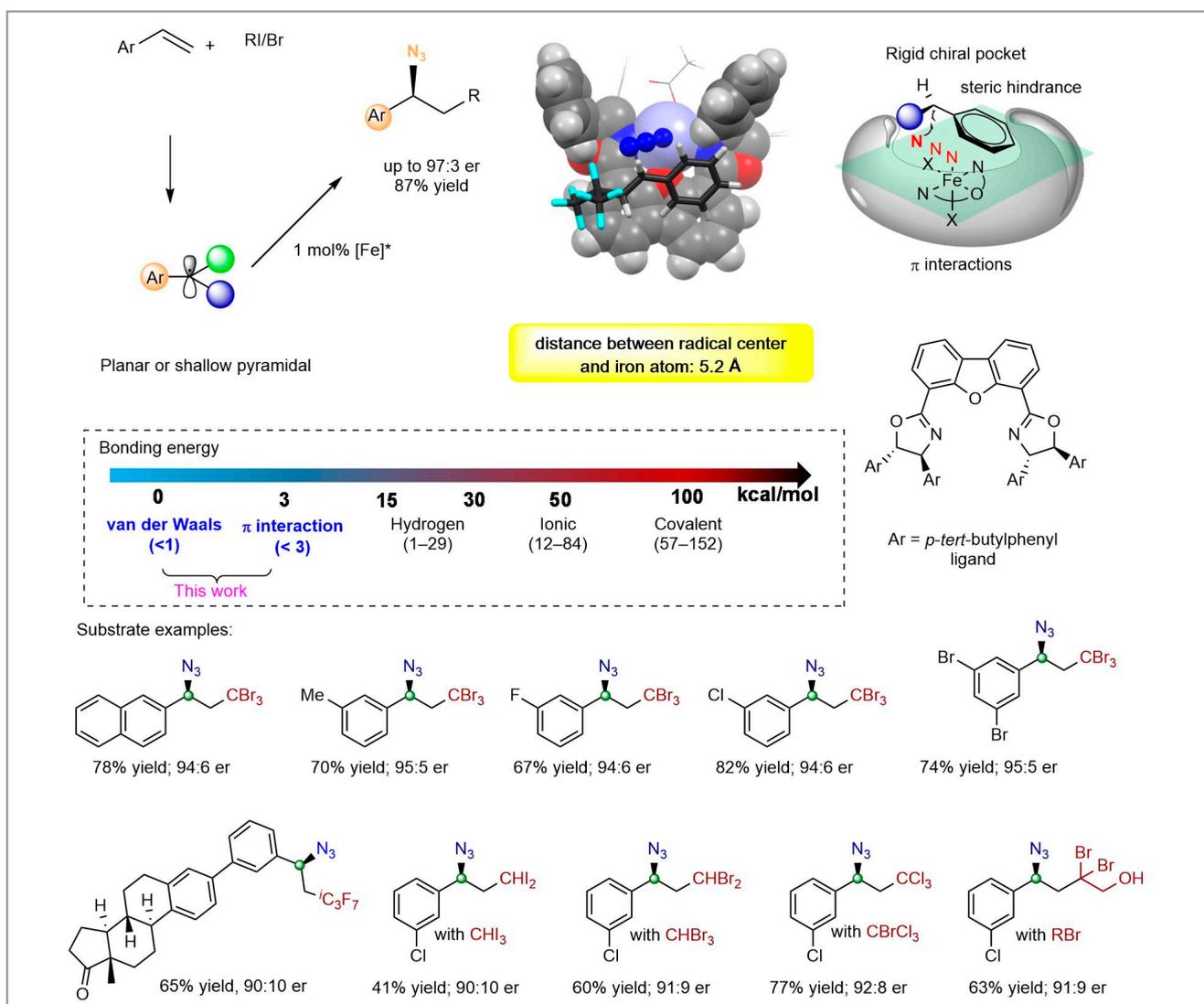
Professor Bao and Professor Xinhao Zhang (Peking University Shenzhen Graduate School, P. R. of China) thought differently. “We postulated that the rigid azido group may keep



**Scheme 1** Reaction pathways between carbon radicals and metal species



Scheme 2 Radical carbo-azidation reaction



Scheme 3 Mechanism and scope of the new radical azidation reaction of styrenes

two reaction partners at a distance of weak interactions,” said Professor Bao. She continued: “This system could then be an opportunity to design an asymmetric outer-sphere pathway. Two brave PhD students, Liang Ge and Huan Zhou, started to work on this project. To solve this problem, the chiral pocket-like catalyst, which contains a quasi-macrocyclic plain structure with an iron atom in the center and bulky groups on the side as steric hindrance, was designed and synthesized. With this catalyst, the first catalytic asymmetric radical carbo-azidation was accomplished. Feedstock chemicals such as  $\text{CBr}_4$ ,  $\text{CHI}_3$ ,  $\text{CHBr}_3$  and other alkyl bromides or iodides are suitable carbon sources, while the alkene substrate is limited to styrenes.<sup>5</sup>”

After achieving positive experimental results (Scheme 3), the group conducted mechanistic studies to verify whether this was truly a group transfer reaction. “Many people feel profoundly that enantioselectivity in metal-catalyzed radical reactions indicates instead an inner-sphere, high-valent-metal pathway,” said Professor Bao, who went on to explain: “The DFT studies by Dr. M. Chiou supported the proposed group transfer pathway and revealed the origin of the chirality control. This catalyst recognizes the carbon radical by  $\pi$  and van der Waals interactions whose bonding energies are very small and generally less than 3 kcal/mol. The capture of critical intermediates by HRMS studies and other experiments like radical clock also supported the proposed mechanism.”

“Many metal-catalyzed radical reactions undergo the group transfer mechanism, and the enantioselective control in these reactions is no longer mission impossible,” said Professor Bao, who concluded: “Our work should shed light on asymmetric radical reactions and may well lead to other enantioselective group transfer reactions.”

*Mattias Farnok*

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## About the authors



L. Ge

he is carrying out his Ph.D. studies in the same research group at FJIRSM.

**Liang Ge** graduated from Huainan Normal University (P. R. of China) in 2012 and received his Master’s degree in 2016 from Hefei University of Technology (HFUT, P. R. of China) under the guidance of Prof. Yougui Li. He studied as a visiting student at Fujian Institute of Research on the Structure of Matter (FJIRSM), CAS (P. R. of China), under the guidance of research Prof. Hongli Bao from 2014 to 2016. Currently,



Dr. H. Zhou

**Huan Zhou** obtained a BS degree in chemistry from Huaiyin Normal University (P. R. of China) in 2014. She did her PhD work under the supervision of Prof. Hongli Bao in 2019 at FJIRSM. Now, she is pursuing postdoctoral research in Prof. Xin-Yuan Liu’s research group at South University of Science and Technology (P. R. of China). Her research interest is transition-metal-catalyzed asymmetric radical involved reactions.



Dr. M. F. Chiou

**Mong-Feng Chiou** obtained his B.S. and Ph.D. degrees from Fu Jen Catholic University (P. R. of China) under the supervision of Prof. Wen-Shyan Sheu. His major studies are in the field of physical and computational chemistry, and his research interest is the reaction mechanism of metal-catalyzed organic chemistry for his postdoctoral studies.

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*Prof. X. Zhang*

**Xinhao Zhang** studied chemistry at the University of Science and Technology of China (P. R. of China), receiving his diploma in 2002. He did his PhD work under the supervision of Prof. Yun-Dong Wu at the Hong Kong University of Science and Technology (P. R. of China). After graduating in 2007, he received an Alexander von Humboldt Research Fellowship, and pursued postdoctoral research in Prof. Helmut Schwarz's research group at

Technische Universität Berlin (Germany). In 2011, he joined the faculty of Peking University Shenzhen Graduate School (P. R. of China) where he has focused on the understanding of reaction mechanisms in catalysis and developing promising catalysts by combining mass spectrometry and computational chemistry.

*Prof. H. Bao*

**Hongli Bao** received her B.S. degree in chemistry from the University of Science & Technology of China (P. R. of China) in 2002. She obtained her Ph.D. from the joint program of the Shanghai Institute of Organic Chemistry (P. R. of China) and the University of Science & Technology of China (P. R. of China) in 2008 with Professor Kuiling Ding and Professor Tianpa You. She joined the Tambar lab in 2009 and received the UT Southwestern Chilton Fellowship in Biochemistry in 2012. She started her independent career in 2014 at FJIRSM, Chinese Academy of Science. She is interested in developing new metal-catalyzed reactions and asymmetric catalysis.