Ruthenium(II)-Enabled *para*-Selective C–H Difluoromethylation of Anilides and their Derivatives

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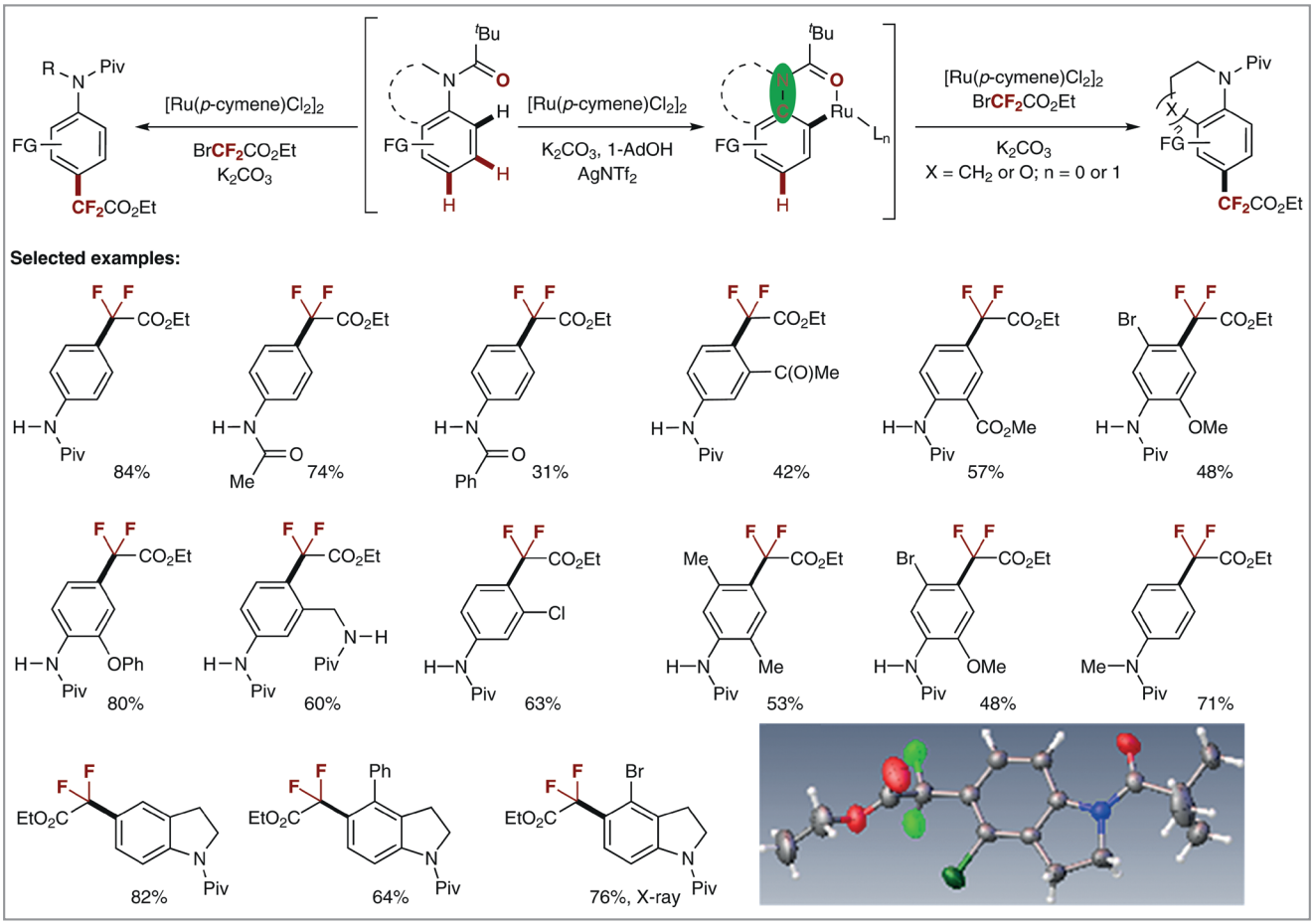
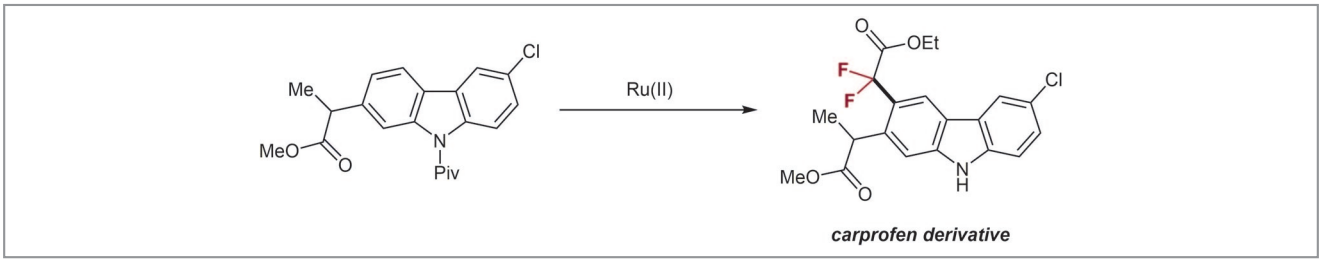
Highly regioselective functionalization of a C–H bond to construct complex synthetic structural units is an important and attractive process in synthetic chemistry. Especially, the highly site-selective introduction of fluorine atom(s) into aromatic rings is of particular value, because it can cause significant changes in the chemical and physical properties of biologically active compounds. However, effective strategies to achieve selective *para*-C–H functionalization of aniline derivatives are still limited in comparison with *ortho*-chelation cyclometalation processes, due to the large distance between the C–H bond and the transition-metal center. Until now, *para*-selective C–H functionalizations have been achieved by exploiting the inherent electronic properties of substrates, sterically hindered arenes or compounds with a directing group. However, these protocols are usually limited in terms of substrate scope and selectivity ratio. Recently, the research group of Professor Yingsheng Zhao at the Key Laboratory of Organic Synthesis of Jiangsu Province College of Chemistry, Chemical Engineering, and Materials Science, Soochow University (P. R. of China) developed a general approach for accomplishing the *para*-selective C–H dfluoromethylation of anilides, indolines, and quinolines by employing a ruthenium catalyst (Scheme 1).



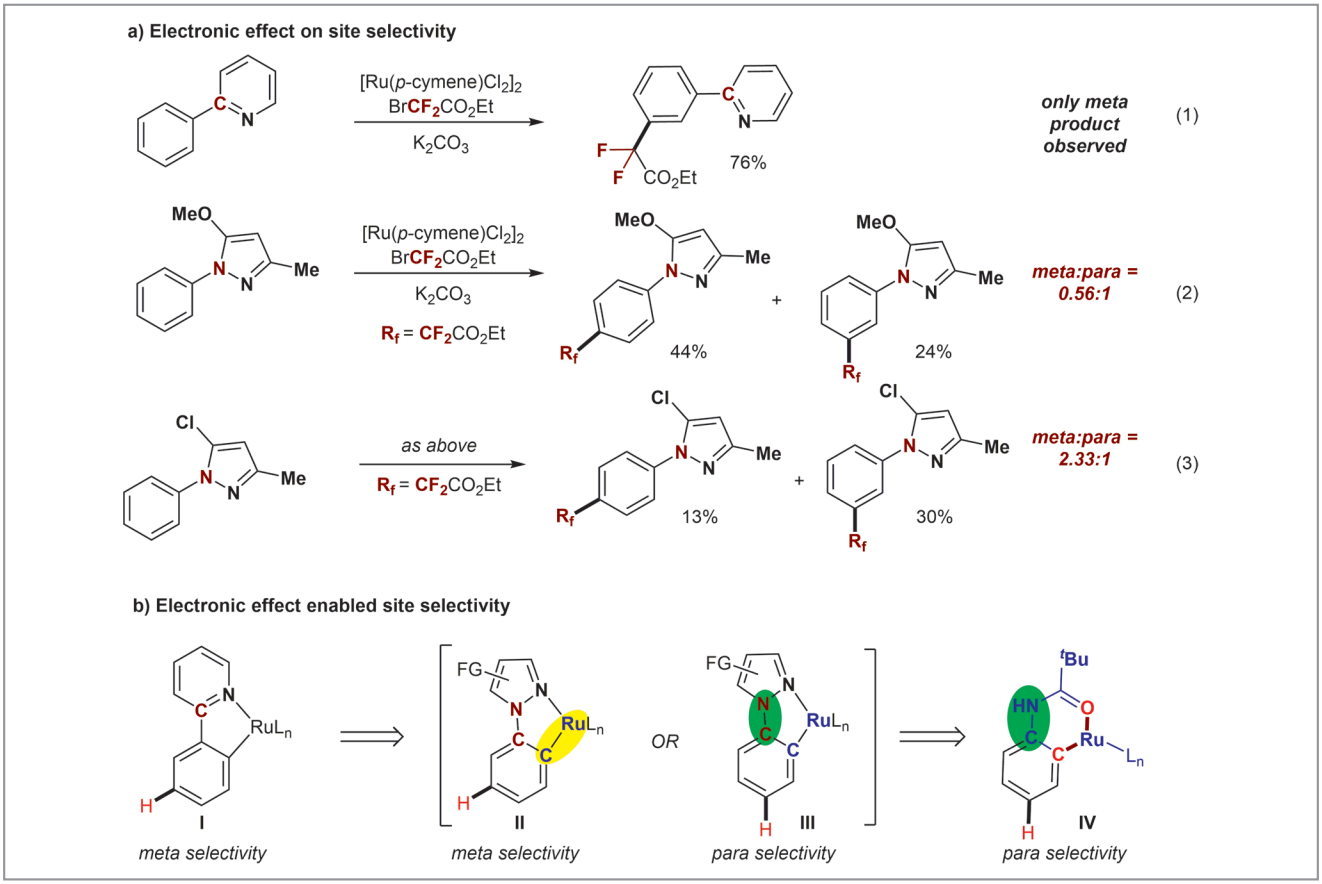
Scheme 1 Ruthenium-enabled *para*-selective difluoromethylation

"We have focused on highly site-selective transition-metal-catalyzed C–H functionalization reactions since we set up our group in 2013," explained Professor Zhao. He continued: "Although transition-metal-catalyzed C–H activation reactions are one of the most powerful and efficient strategies in directly installing a functional group into an organic compound, the challenge of installing fluorine functional groups, such as the highly site-selective introduction of a CF_2 group on aromatic rings, still remains unsolved. In this work, our major contribution to this area is the discovery that ruthenium can selectively promote *para*-selective C–H difluoromethylation of anilides and their derivatives." The new method developed by Professor Zhao provides a direct and efficient approach to the synthesis of *para*-difluoromethylated anilides with broad substrate scope and good functional group tolerance.

"The difluoromethyl group (CF_2) is well known for improving the metabolic stability of biologically active molecules and for being a bioisosteric replacement of oxygen atoms," said Professor Zhao, who added: "One of the most important applications of C–H functionalization is that it can be used to directly functionalize known drugs, which may lead to the discovery of new drugs. For example, a difluoromethyl-



Scheme 2 Synthesis of carprofen derivative



Scheme 3 Preliminary mechanism studies

ated derivative of carprofen, which is a non-steroidal anti-inflammatory drug, can be easily prepared with this new method (Scheme 2)".

Professor Zhao also emphasized: "Although the exact mechanism of the ruthenium(II)-enabled *para*-selective C–H difluoromethylation of anilides and their derivatives is still uncertain, based on initial experiments (Scheme 3) we can speculate that an aryl-ruthenium species generated through directed *ortho*-metalation undergoes the reaction with radicals or electrophiles at the position *para* to the N–C center to give net *para*-functionalized products. The probable rationale for this N–C-enabled *para*-selective difluoromethylation is that the weakly coordinating nitrogen center reduces the *para*-directing ability of the Ru–C bonds. This in turn leads to a prevalence of the *para*-directing effect of anilides, indolines, and tetrahydroquinolines towards electrophiles, overriding the *para*-inducing effect of the Ru–C bonds."

Professor Zhao concluded: "An efficient approach to the synthesis of difluoromethylated anilides and its derivatives has been disclosed via a highly *para*-selective ruthenium(II)-catalyzed C–H difluoromethylation reaction. In the future, we are looking into the development of a general highly site-selective C-H activation reaction of aromatic rings. In particular, we are aiming to find a new C–H activation method which could directly introduce a fluorinated group into organic molecules, especially in pharmacologically active compounds. In the long-term, we hope our work will deliver outstanding contributions to the development of new drugs."

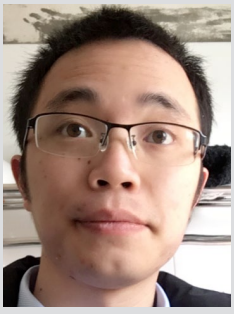
About the authors

Prof. Y. Zhao

Yingsheng Zhao received his B.Sc. degree from Southwest University (P. R. of China) in 2003 and his Ph.D. degree under the supervision of Professor Aiwen Lei at Wuhan University (P. R. of China) in 2008. He then worked as a postdoctoral fellow in the laboratory of Professor Noyori and Professor Saito from October 2008 to September 2010 at Nagoya University (Japan). From 2010 to 2012, he worked with Professor Chen at Penn State University (USA) as a postdoctoral fellow. In November 2012, he started his independent career as an associate professor at the College of Chemistry, Chemical Engineering and Materials Science of Soochow University (P. R. of China). His research interests lie in developing highly site-selective C–H functionalization reactions.

C. Chen

Changpeng Chen received his B.Sc. in 2013 from Qingdao Agricultural University (P. R. of China). He then joined Professor Yingsheng Zhao's group and received his Master's Degree from Soochow University (P. R. of China) in 2016. After that, he continued working in Professor Xiaoming Zeng's group as a Ph.D. candidate at Xi'an Jiaotong University (P. R. of China). His research interests focus on Cr-catalyzed regioselective cross-coupling reactions, hydrogenations and development of novel cyclic monoamine carbenes.



C. Yuan

Chunchen Yuan received his B.Sc. in 2015 from Wenzheng College of Soochow University (P. R. of China). He then joined Professor Yingsheng Zhao's group at Soochow University in 2015. After that, he continued working in Professor Zhao's and Professor Xiaoguang Bao's group as a Ph.D. student at Soochow University in 2017. His research interests focus on selective functionalizations of arene C–H bonds.

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