Chlorodifluoromethane triggered formation of difluoromethylated arenes catalyzed by palladium

Subject Code: B02

With the support by the National Natural Science Foundation of China, a study by the research group led by Prof. Zhang Xingang (**张新刚**) from the Institute of Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences demonstrates the first direct catalytic difluoromethylations from $ClCF_2H$, which was published in *Nature Chemistry* (2017, 9: 918).

Owing to the unique properties of difluoromethyl group (CF_2H), difluoromethylated aromatic compounds are of increasing importance in pharmaceuticals, agrochemicals, and materials. As the most inexpensive and abundant industrial raw material used for the production of various fluorinated polymers (i. e. Teflon), $ClCF_2H$ is considered to be an ideal fluorine source for the difluoromethylation in terms of cost-efficiency and step economy. However, the direct introduction of CF_2H onto aromatics using $ClCF_2H$ remains a challenging topic and has not been reported. Difluoromethylated arenes can be prepared by deoxyfluorination of aromatic aldehydes with dialkylaminosulfur trifluorides, but this method is restricted by its modest functional group compatibility and cost. Recently, a milder approach by using preformed difluoromethylating reagents to access difluoromethylated arenes has been developed. In this case, all of the preformed reagents are expensive and require multiple steps to prepare from fluoroalkyl halides, such as $ClCF_2H$. Thus, direct introduction of CF_2H onto aromatics from inexpensive, simple, and abundant $ClCF_2H$ would provide a straightforward, cost-efficient, and useful alternative for the synthetic and medicinal chemistry community.

Zhang and his co-workers have established that the palladium-catalyzed difluoromethylation of aryl and heteroaryl boronic acids and esters with $ClCF_2H$ can efficiently access a variety of difluoromethylated aromatics. The reaction exhibits a remarkably broad substrate scope and was used for difluoromethylation of a range of pharmaceuticals and biologically active compounds. The ability to directly introduce a difluoromethyl group at metabolic positions of pharmaceuticals provides good opportunities to use $ClCF_2H$ for the synthesis and development new medicinal agents.

Preliminary mechanistic studies revealed that a palladium difluorocarbene intermediate is involved in the reaction. Although numerous metal-difluorocarbene complexes have been prepared and used to mediate the reactivity of difluorocarbene, the catalytic synthesis of difluoromethylated or difluoromethylenated compounds involving metal-difluorocarbene complexes has not received much attention and remains challenging. This new reaction therefore also opens the door to understand metal-difluorocarbene complex catalyzed reactions.

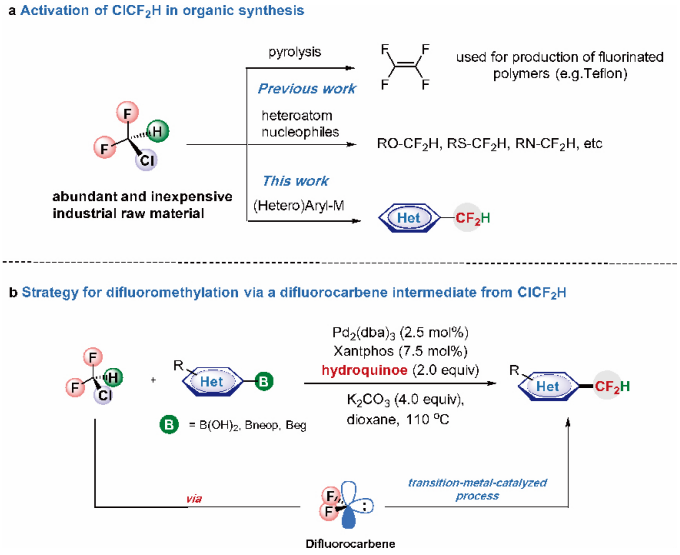

Figure A catalytic approach to difluoromethylated arenes using $ClCF_2H$.