Computation-based Strategy for the Development of Fluoroalkylation Reactions with Difluorocarbene

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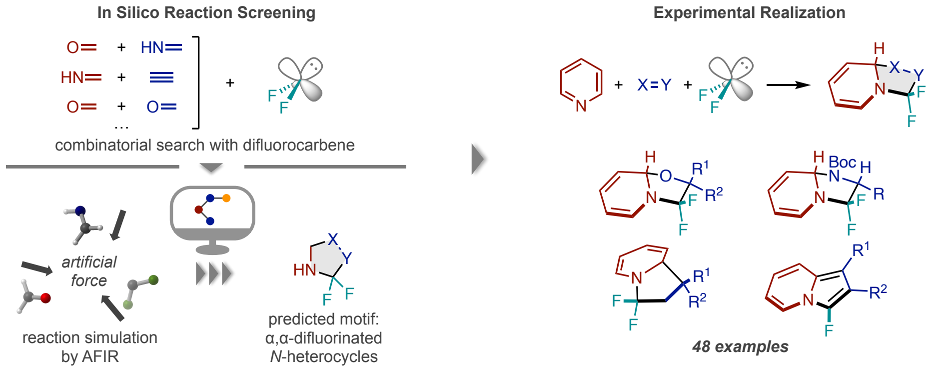
Keywords: Quantum Chemical Calculations; Reaction Development; Fluoroalkylation; Difluorocarbene; Dearomatization

Quantum chemical calculations have been an indispensable tool in synthetic methodology development. The progress of computational methods as well as computer technology has enabled the systematic exploration of reaction pathways, and their current primary role is to gain the mechanistic insight into established reactions. In this context, our group has developed an artificial force induced reaction (AFIR) method, an automated reaction path search algorithm that can explore the possible reaction pathways from single input structure. This method can create reaction path networks comprising computationally estimated reaction intermediates and products without any prior knowledge of organic transformations, showcasing its ability to predict even unknown chemical processes.[1]

Here, we report a strategy that leverages computational reaction simulations for the development of three-component reactions with difluorocarbene using the AFIR method. Difluorocarbene, an electrophilic carbene species useful not only for incorporating the difluoromethylene unit into organic molecules but also in the calculations due to its relatively small character, is used for in silico combinatorial reaction screening with two unsaturated compounds containing C=O, C=N, C=C, or C≡C bonds. These simulations suggested that the less explored three-component cycloaddition of methanimine, difluorocarbene, and the other unsaturated component would proceed preferentially to furnish α,α-difluorinated *N*-heterocyclic skeletons. Based on the computational results, we realized the identified reaction mode experimentally, leading to a diverse dearomative cycloaddition of pyridines with difluorocarbene and a series of unsaturated compounds (aldehydes, ketones, imines, alkenes, and alkynes).[2]



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2) H. Hayashi, H. Katsuyama, H. Takano, Y. Harabuchi, S. Maeda, T. Mita *Nat. Synth.* **2022**, *1*, 804.