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Reaction simulation by quantum chemical calculations for multicomponent reactions with difluorocarbene

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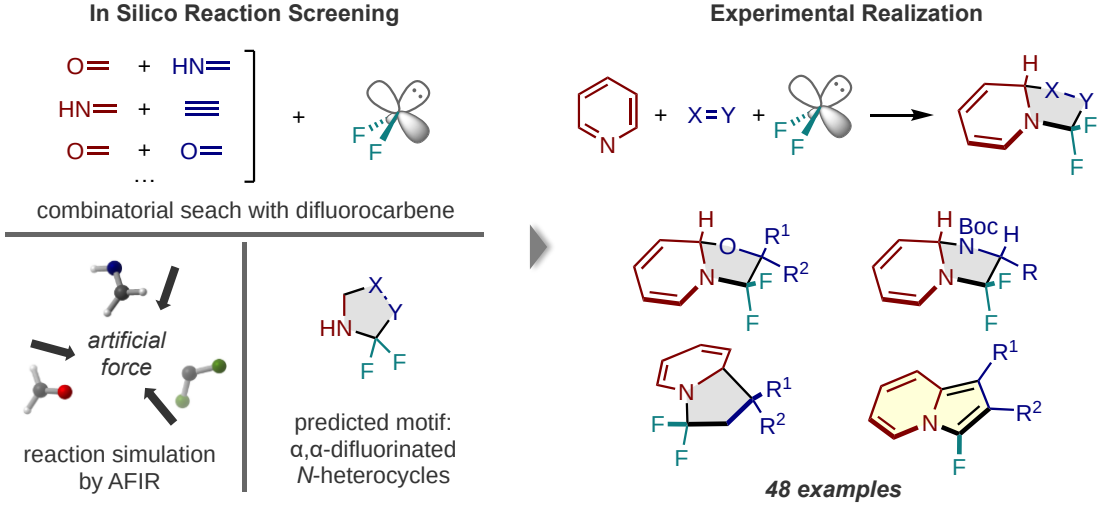
Over the years, computational chemistry has become essential for analyzing the structure and properties of molecules. In organic chemistry, quantum chemical calculations play an important role in obtaining mechanistic insight into chemical reactions. In this context, we have developed the artificial force induced reaction (AFIR) method, which leverages an artificial force on the input molecules to induce molecular transformations during the calculations in order to explore all theoretically possible reaction pathways.[1] This method is potentially applicable not only for mechanistic studies of known chemical reactions, but also for predictions of reactions in which the products or pathways are uncertain.

Here, we report a strategy for developing multicomponent reactions based on the results of computational reaction simulations. In silico screening of multicomponent reactions with difluorocarbene using the AFIR method suggested that cycloadditions between an azomethine ylide and a variety of coupling partners would proceed to generate the corresponding α,α-difluorinated *N*-heterocyclic compounds. The predicted reaction was successfully realized experimentally, leading to a multicomponent *N*-difluoroalkylative dearomatization of pyridines involving a pyridinium ylide-mediated 1,3-dipolar cycloaddition with a diverse range of electrophiles such as aldehydes, ketones, imines, alkenes, and alkynes. Moreover, the performance of the present cycloaddition could be explained by comparing the energy barrier of the desired pathway with that of the competitive undesired pathway, which was also identified by the AFIR search.[2]



Reference

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