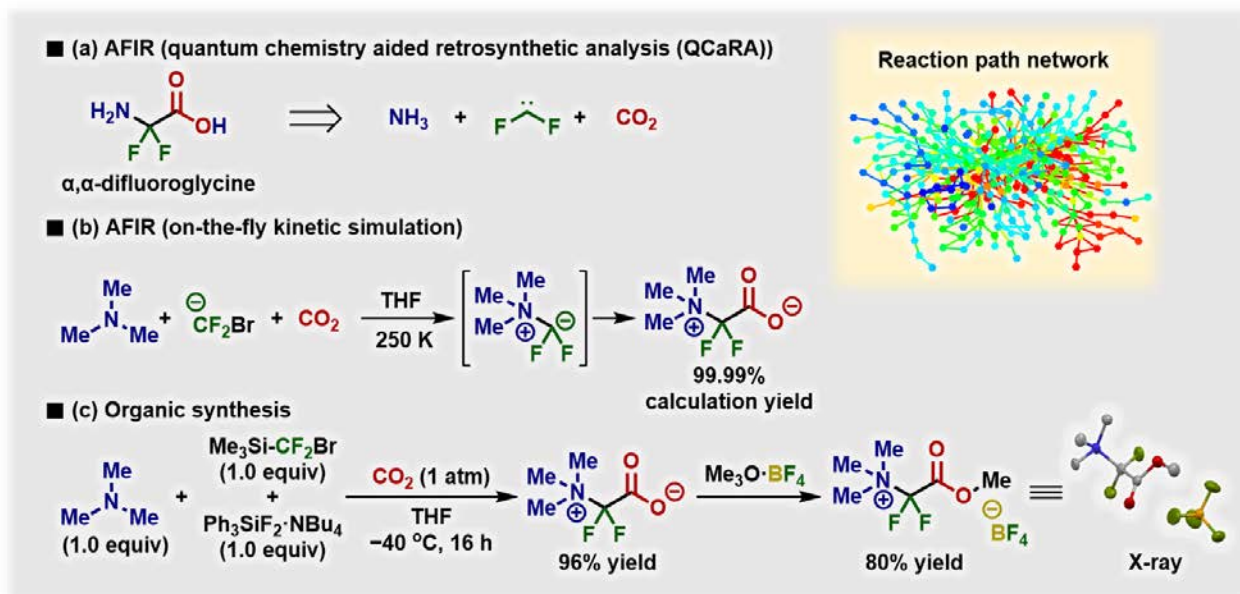


Report for Interdisciplinary research startup

1. Name of project leader: Tsuyoshi Mita
2. Project title: 反応経路探索を用いた新反応開発融合研究 / Development of a new reaction using the reaction path search
3. Report

The current trial-and-error approach to the development of new reactions is time-consuming and inefficient. A core technology of ICRoDD in Hokkaido University, Japan uses “reaction path search methods” using the AFIR (Artificial Force Induced Reaction) method in combination of machine learning, proposing possible experimental parameters such as starting materials and catalysts, etc. To develop a bioisostere of amino acids, we planned to synthesize an α,α -difluoroglycine derivative, which is the most simple α -fluorinated α -amino acid. We first retro-synthesized α,α -difluoroglycine by AFIR, proposing three basic and simple starting materials such as NR_3 (amine), $:\text{CF}_2$ (difluorocarbene), and CO_2 (carbon dioxide). Subsequently, when NMe_3 ($\text{R} = \text{Me}$) and $^-\text{CF}_2\text{Br}$, which is a reasonable difluorocarbene precursor, were used as reactants in further calculation, $\text{Me}_3\text{N}^+-\text{CF}_2-\text{CO}_2^-$ was obtained via three component assembly in 99.99% yield. Encouraged by this promising result, we conducted the chemical synthesis of a difluoroglycine derivative. As a result, $\text{Me}_3\text{N}^+-\text{CF}_2-\text{CO}_2\text{Me}\cdot\text{BF}_4^-$ was obtained in 80% yield after methyl esterification. It took only two months to complete the synthesis, which has emphasized the power of AFIR.

I set up our new mix lab as a chief by the support of this interdisciplinary research fund, which is mostly used for experimental tools, glassware, and chemical reagents. I also advertised our research activities at the 14th International Conference on Cutting-Edge Organic Chemistry in Asia (ICCEOCA-14) held in Niseko, Hokkaido, Japan, September 26-29th, 2019.



4. Research achievements
- 1) Tsuyoshi Mita*, Yu Harabuchi, and Satoshi Maeda* “Discovery of a Synthesis Method for a Difluoroglycine Derivative Based on a Path Generated by Quantum Chemical Calculations” *Chem. Sci.* **2020**, *11*, DOI: 10.1039/D0SC02089C.
- 2) Tsuyoshi Mita, Young Researcher's Award in Ube Industries Foundation, Japan “Development of Novel Organic Reactions Guided by Quantum Chemical Calculations”.
- 3) Tsuyoshi Mita, Yu Harabuchi, and Satoshi Maeda “Synthesis of Fluorinated Amino Acids by Three Component Coupling Reaction” The 100th CSJ (The Chemical Society of Japan) Annual Meeting, 3G3-30 (oral), Noda Campus, Tokyo University of Science, Chiba, Japan, March, 24th 2020.