

Z-Enamide Synthesis by Stereoselective Radical Fluoroalkylation Reaction

(¹RIKEN Center for Sustainable Resource Science, ²RIKEN Cluster for Pioneering Research)

○Takuma Tagami,¹ Daisuke Sekine,² Yuma Aoki,¹ Shintaro Kawamura,^{1,2} Mikiko Sodeoka^{1,2}

Keywords: Z-Enamides; Stereoselective Reaction; Radical Reaction; Allylic Fluoroalkylation; Metallacycle Intermediates

Z-Enamides are important motif as synthetic building blocks and bioactive molecules. Thus, stereoselective Z-enamide synthesis has long been studied. The methods based on polar reactions have been established, whereas radical approaches to Z-enamide synthesis is rarely known due to difficulty of the controlling stereochemistry. The previous stereoselective synthesis involving radical species required directing group on the substrate, such as inducing intramolecular hydrogen bonding and steric repulsion of the substituents, which strongly limited the substrate scope. Therefore, a typical method for controlling the stereoselectivity is highly demanded in the radical-involving Z-enamide synthesis to expand their chemical space, because radical reactions usually allowed to introduce unique functional groups that is difficult to be achieved by polar reactions.

In this work, we developed a novel method for Z-enamide synthesis by stereoselective radical fluoroalkylation of *N*-allylamides, which does not require the directing substituents. The fluoroalkylated Z-enamides were obtained by copper-catalyzed reaction of *N*-allylamides with diacyl peroxides that were prepared from fluorinated carboxylic anhydrides and urea·H₂O₂ in-situ and employed as a perfluoroalkyl radical source. This method could introduce various fluoroalkyl groups (R_f) by changing fluorinated carboxylic anhydrides, and also apply to a late-stage functionalization of bioactive molecules. Furthermore, the obtained products were derivatized to various *N*-containing fluoroalkyl molecules in order to prove their utility as a building block. In addition to the reaction development, its mechanistic studies including kinetic experiments were performed to elucidate the origin of the unusual Z-selectivity outcome. The details will be discussed in the presentation.

