Synthesis of Tetra-Substituted Trifluoromethyl-3,1-Benzoxazines by Transition-Metal-Catalyzed Decarboxylative Cyclization of N-Benzoyl Benzoxazinones

Invited for this month’s cover are the group of Norio Shibata at Nagoya Institute of Technology (Japan). The cover picture is inspired by the diversity in the ocean also in cyberspace. In the present research, we can synthesize diverse heterocyclic molecules having a trifluoromethyl group in a single step by changing the N-substitution. You can see more variations of trifluoromethyl heterocycles in several papers by our group. Read the full text of their Communication at 10.1002/open.202000360.

Who designed the cover?
Miss Mami Shibata, a Japanese painter, created the cover. She contributed 20 of our scientific cover designs, including four covers of ChemistryOpen. The original title is “the ocean of pixel,” and she modified it for the cover picture. The cover image is inspired by the diversity in the ocean also in cyberspace. In the present research, we can synthesize diverse heterocyclic molecules having a trifluoromethyl group in a single step by changing the N-substitution. You can see more variations of trifluoromethyl heterocycles in several papers by our group. Please visit our website, http://www.ach.nitech.ac.jp/~organic/shibata/publications.html#01.

What are the main challenges in the broad area of your research?
Since my first academic position in the late 1990s, Toyama Medical and Pharmaceutical University, Japan, I have been in the field of organofluorine chemistry. The world of synthetic
fluorine chemistry has dramatically progressed in particular fluorination (F) and trifluoromethylation (CF₃) reactions during my career. The enantioselective reaction at sp³-carbon centers under the asymmetric catalysis, coupling reaction at sp²-carbon centers under transition metal catalysis, radical and electron-transfer reactions under photocatalytic conditions are milestone representatives. The C–H fluoro-functionalization protocols have been rapidly achieved in the last decade. Moreover, the research of fluoro-functional groups has been expanded; not only F and CF₃ but also CF₂H, SCF₂, SCF₃, OCF₃, SF₅ groups and more.

Despite these marvelous periods of synthetic fluorine chemistry in the last three decades, medicinal fluorine chemistry is somewhat behind. Although fluoro-pharmaceuticals and fluoro-agrochemicals significantly have supported our lives, the mechanistic biological perspective of organofluorine molecules is still obscure. In 2020, we were encouraged that one of the effective drugs for COVID-19 is dexamethasone, the oldest fluoro-pharmaceutical. We hope we would realize the rational design of fluoro-pharmaceuticals and agrochemicals soon.

What other topics are you working on at the moment?
We are working on the historically controversial drug thalidomide. Thalidomide is a notorious molecule due to teratogenicity but now is the blockbuster for treating erythema nodosum leprosum and multiple myeloma. We disclosed fluorinated thalidomide more than 20 years ago to elucidate the mechanism of action of thalidomide’s teratogenicity. Interestingly, the fluorinated thalidomide does not show teratogenicity, while the activity for multiple myeloma remains. Now we found a key neosubstrate of thalidomide teratogenicity by a collaboration project. We hope the safe, non-teratogenic thalidomide will be developed shortly.