Synthetic Organic Chemistry Laboratory
Chief Scientist: Mikiko Sodeoka (D.Phar.)

(0) Research field

CPR Subcommittee**:** Chemistry, Biology
Keywords: Transition Metal Chemistry, Fluorine Chemistry, Bioactive Molecules, Chemical Biology

(1) Long-term goal of laboratory and research background

Our laboratory focuses on the following research areas based on synthetic organic chemistry: 1) development of new reactions and methodologies for the efficient synthesis of bioactive molecules, 2) design and synthesis of molecules having unique biological activity, 3) biological researches using these unique molecules as biological probes. Our research interests encompass from novel synthetic methods using transition metal-catalysts for fluorine-containing molecules and chiral compounds to the design and synthesis of intracellular signal transduction modulators and their application to cell biology research. In particular, we are focusing on enzymes in charge of chemical modification of proteins, such as phosphorylation and methylation. We are working on design and synthesis of selective inhibitors of such enzymes as well as development of new methods for analyzing chemical modification of proteins. Development of new chemical methodology for identification of target protein/binding site of small bioactive molecules and for their imaging. Clarification of the unknown molecular mechanism of cell death (necrosis) by using our original cell death control molecules is also currently underway.

(2) Current research activities (FY2019) and plan (until Mar. 2025)

In this fiscal year, we achieved to develop a carbo-trifluoromethylation reaction that enables simultaneous introduction of a trifluoromethyl group and the construction of a tetrahydrocarbazole skeleton, as a novel method for synthesizing new fluorine-containing compounds. We have also developed a cross-coupling reaction of dimer-derived persistent tertiary-carbon radical with azo-compounds, providing a facile synthetic entry to structurally complex heterocycles having vicinal all-carbon quaternary centers. We established the synthetic route of natural products Spectomycin A1 and A2, and then we revealed their stereochemistry and structure-activity relationship of SUMOylation-inhibitory activity. In addition, we have also developed IM-93, a water-soluble derivative of IM-54, which was previously developed as an inhibitor of necrosis induced by oxidative stress. We also examined the inhibitory activity of IM-93 against various types of necrosis. As a result, IM-93 was found to inhibit ferroptosis and NETosis, which were related to lipid peroxides, but not necroptosis and pyroptosis, which activate inflammatory responses.

We will continuously develop new fluoroalkylation reactions and cross-coupling reactions. We will also continue the research on the regulation mechanism of necrosis by developing novel analysis methods.

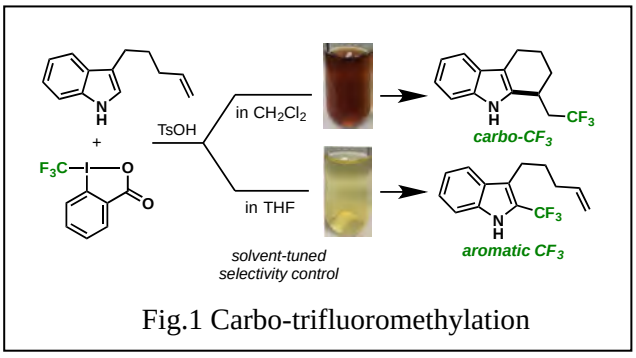

Fig.1 Carbo-trifluoromethylation

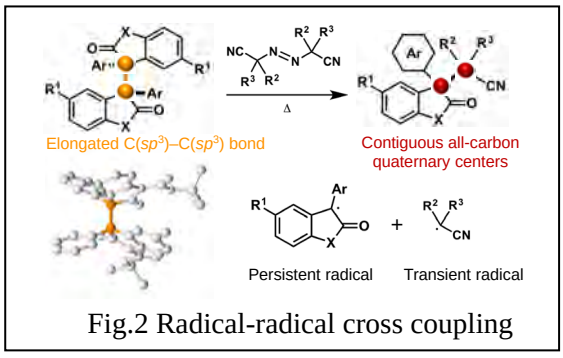

Fig.2 Radical-radical cross coupling

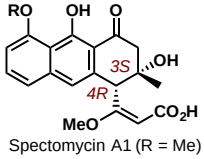

Fig.3 Structures of Spectomycin A

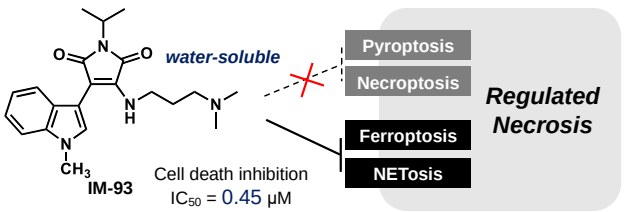

Fig.4 Cell death inhibitor IM-93

(3) Members as of March, 2020

(Chief Scientist)
Mikiko Sodeoka

(Senior Research scientist)
Kosuke Dodo, Yoshihiro Sohtome

(Research Scientist)
Shintaro Kawamura

(Technical Scientist)
Miwako Asanuma

(Special Postdoctoral Researcher)
Syusuke Egoshi

(Postdoctral Researcher)
Shuhei Nakao, Subha Bakthavatsalam

(Technical Staff)
Naoki Terayama, Mai Akakabe

(Visiting Technician)
Kanae Saito

(Assistant)
Izumi Saito

(Part-time Worker)
Xiuling Wang

(Student Trainee)
Rikako Ohnishi, Yusuke Mitani, Miyuki Kurokawa, Namika Makino, Ryo Nishiyama

(Vice Chief Scientist)
Hiroyuki Koshino (Unit Leader of Center for Sustainable Resource Science)

(4) Representative research achievements

1. "Development of a water-soluble indolylmaleimide derivative IM-93 showing dual inhibition of ferroptosis and NETosis", K. Dodo, E. Kuboki, T. Shimizu, R. Imamura, M. Magarisawa, M. Takahashi, T. Tokuhiro, S. Yotsumoto, K. Asano, T. Suda, M. Tanaka, and M. Sodeoka, ***ACS Med. Chem. Lett.*** 10, 1272 (2019).
2. "Synthesis of All Stereoisomers of RK460 and Evaluation of Activity and Selectivity as Abscisic Acid Receptor Antagonists", Y. Mikame, K. Yoshida, D. Hashizume, G. Hirai, K. Nagasawa, H. Osada and M. Sodeoka, ***Chem. Eur. J.*** 25, 3496 (2019).
3. "Synthesis of All Stereoisomers of Monomeric Spectomycin A1 and A2, and Evaluation of Their Protein SUMOylation-Inhibitory Activity", Y. Nomura, F. Thuaud, D. Sekine, A. Ito, S. Maeda, H. Koshino, D. Hashizume, A. Muranaka, T. Cruchter, M. Uchiyama, S. Ichikawa, A. Matsuda, M. Yoshida, G. Hirai, and M. Sodeoka, ***Chem. Eur. J.*** 25, 8387 (2019).
4. "Control of site selectivity in trifluoromethylation of alkenes bearing a pendant indolyl group: synthesis of CF_3-containing tetrahydrocarbazoles", R. Murakami, D. Sekine, Y. Aoki, S. Kawamura, and M. Sodeoka, ***Tetrahedron*** 75, 1327 (2019).
5. "Cross-Coupling Reaction of Dimer-derived Persistent Tertiary Carbon-Centered Radicals with Azo Compounds", R. Ohnishi, M. Sugawara, M. Akakabe, H. Koshino, Y. Sohtome, and M. Sodeoka, ***Asian J. Org. Chem.*** 8, 1017 (2019).

Laboratory Homepage
https://www.riken.jp/en/research/labs/chief/synth_org_chem/index.html
http://soc.riken.jp/index-e.html