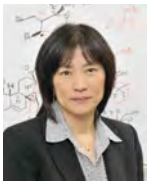
Synthetic Organic Chemistry Laboratory（2021）
Chief Scientist: Mikiko Sodeoka (D.Phar.)



(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 methylation and acylation. We are working on the development of new methods for analyzing chemical modification of proteins, and their application of the design of selective inhibitors. We are also working on the 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.

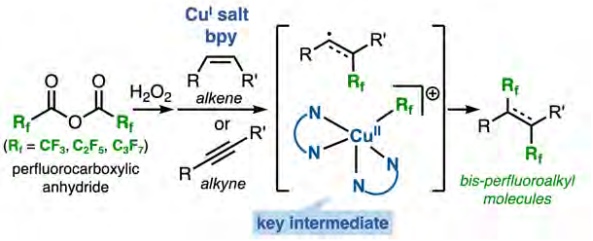
(2) Current research activities (FY2021) and plan (until Mar. 2025)

(A) Development of methodology to efficiently synthesize biologically active compounds

Reflecting the growing importance of environmentally friendly chemical processes, catalytic reactions with high atom-economy have attracted much attention in modern organic chemistry. We have been working on the development of unexplored metal-catalyzed reactions, particularly focusing on atom-economical proton-transfer reactions as well as novel reactions for the synthesis of organofluorine compounds, as useful organic transformations for the synthesis of complex bioactive molecules. We have also focused on exploring new strategies for synthetic derivatizations of highly fictionalized products that can be obtained by our original catalytic reactions.

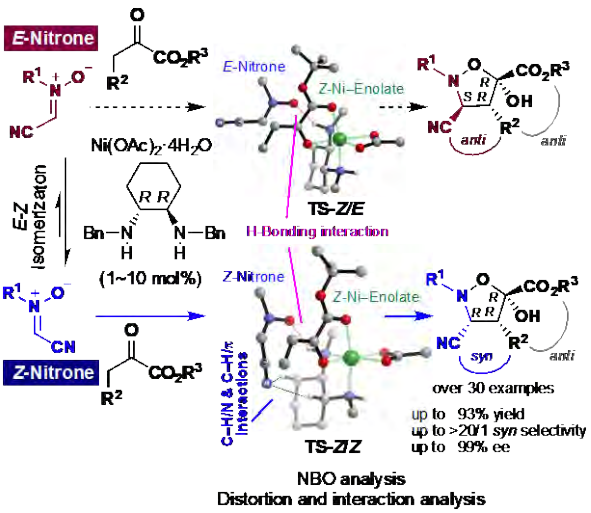
1) Development of synthetic methods for fluorinated compounds

We developed an efficient synthetic method for unique molecules bearing two perfluoroalkyl (R_f) groups. 1,2-Bis-perfluoroalkylation reaction of alkenes or alkynes with diacyl peroxides prepared in situ from perfluorocarboxylic anhydrides by using a copper complex was found to smoothly proceed.



2) Transition metal-catalyzed asymmetric reactions

We have previously reported the development of Ni-catalyzed (3 + 2) cycloaddition of cyclic *E*-nitrones with α-ketoesters, enabling to selective access to the *anti*-addition adducts. This year, we successfully developed the *Z*-nitrone selective (3 + 2) cycloaddition of *E*/*Z* isomerizable nitrile conjugated nitrones (*C*-CN-nitrones) and α-keto ester enolates, providing the *syn*-addition adducts. Our experimental and computational investigations suggest that the CH/N and CH/π interactions between the nitryl group in the nitrone and ligand play key roles in selectively recognizing the *Z*-nitrone to promote the *syn*-addition.



3) Aerobic oxidative transformations

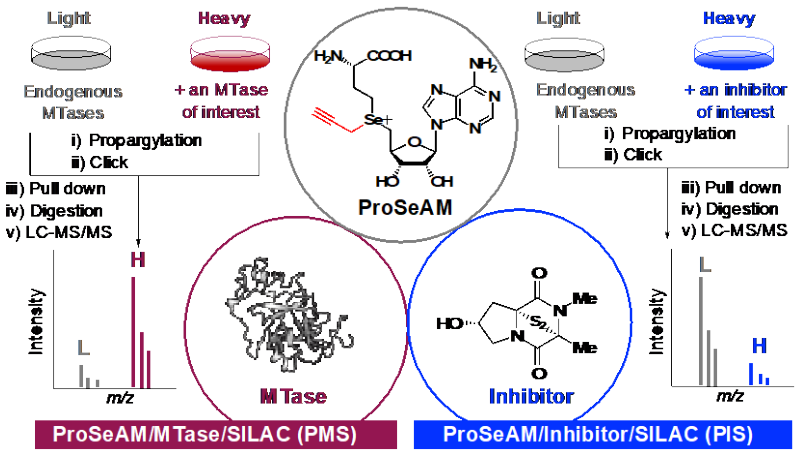
We have been working on the development of oxidative transformation with persistent *tert*-carbon radicals under aerobic conditions. This year, we focused on expanding the substrate scope of the aerobic cross-dehydrogenative coupling reaction between the oxindole monomers and catechols.

Future plan, 1) We will continuously develop new fluoroalkylation reactions. 2) We will focus on not only showcasing the reaction development, but also providing a basis underlying the design of transition metal

catalysts with the use of Earth-abundant metal through a series of mechanistic studies. 3) We will explore a new class of aerobic oxidative transformations using persistent radicals in even more complicated selectivity and energetic settings.

(B) Development of small molecules to analyze and control protein methylation

Protein methylation, catalyzed by protein methyltransferases (MTases) using *S*-adenosyl-L-methionine (SAM) as a methyl donor, is an important class of the post translational modifications. However, it is still difficult to draw comprehensive protein methylome maps of MTases to determine their substrates and methylation sites. Our collaborative team has already developed a chemical strategy with the use of propargylic *Se*-adenosyl-L-selenomethionine (ProSeAM) as a SAM analogue for enriching the native methylome.



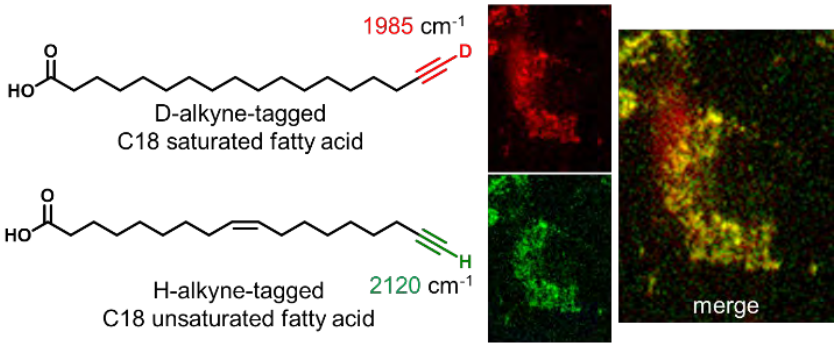
We have currently applied the ProSeAM-based protein labeling to the stable isotope label-based quantification, SILAC (stable isotope labeling by amino acids in cell culture). This year, we provided our overviews both for MTase substrate discovery (PMS: ProSeAM/MTase/SILAC) and inhibitor profiling (PIS: ProSeAM/MTase/SILAC), as a personal Account. We also investigated the identification of unprecedented protein substrates.

Future plan, We plan to expand our chemical methylome analysis to identify unprecedented biological functions of protein methylation.

(C) Development of Novel Raman Probes

We previously developed the method named as "Alkyne-tag Raman Imaging (ATRI)" to observe small biomolecules in cells. To expand this imaging technique, we have been developing novel Raman tags by using deuterium from the last fiscal year.

In this fiscal year, we found the vibrational frequency of terminal alkyne was blue-shifted by approximately 135 cm^{-1} upon deuteration. Furthermore, by using deuterated alkynes and terminal alkynes as Raman tags, we achieved the dual Raman imaging of intracellular localization of C18 saturated fatty acids (stearic acid, C18:0) and C18 unsaturated fatty acids (oleic acid, C18:1), which have almost the same chemical structure.



Future plan, We will continue to find functional groups showing unique Raman signals and develop novel Raman probes.

(3) Members

(Chief Scientist)
Mikiko Sodeoka
(Senior Research scientist)
Kosuke Dodo, Yoshihiro Sohtome, Shintaro Kawamura
(Research Scientist)
Rajiv Kumar Verma, Syusuke Egoshi
(Postdoctral Researcher)
Subha Bakthavatsalam, Kota Koike
(Technical Staff)
Naoki Terayama, Mai Akakabe
(Visiting Technician)
Kanae Saito, Koshi Harada
(Assistant)
Izumi Saito
(Part-time Worker)
Xiuling Wang
(Vice Chief Scientist)
Hiroyuki Koshino (Unit Leader of Center for Sustainable Resource Science)

(4) Representative research achievements

1. "Dynamics in Catalytic Asymmetric Diastereoconvergent (3 + 2) Cycloadditions with Isomerizable Nitrones and α-Keto Ester Enolates", Tetsuya Ezawa, Yoshihiro Sohtome, Daisuke Hashizume, Masaya Adachi, Mai Akakabe, Hiroyuki Koshino, Mikiko Sodeoka, **J. Am. Chem. Soc. 143**, 9094-9104 (2021).

2. "1,2-Bis-perfluoroalkylations of Alkenes and Alkynes with Perfluorocarboxylic Anhydrides via The Formation of Perfluoroalkylcopper Intermediates", Takuma Tagami, Yuma Aoki, Shintaro Kawamura, Mikiko Sodeoka, **Org. Biomol. Chem. 19**, 9148-9153 (2021).

3. "Deuteration of terminal alkynes realizes simultaneous live cell Raman imaging of similar alkyne-tagged biomolecules", Syusuke Egoshi, Kosuke Dodo, Kenji Ohgane, Mikiko Sodeoka, **Org. Biomol. Chem. 19**, 8232-8236 (2021).

4. "A decade of alkyne-Tag Raman imaging (ATRI): Applications in biological systems", Subha Bakthavatsalam, Kosuke Dodo, Mikiko Sodeoka, **RSC Chem. Biol. 2**, 1415-1429 (2021).

5. "Propargylic *Se*-adenosyl-L-selenomethionine: A Chemical Tool for Methylome Analysis", Yoshihiro Sohtome, Tadahiro Shimazu, Yoichi Shinkai, Mikiko Sodeoka, **Acc. Chem. Res. 54**, 3818-3827 (2021).

Supplementary

Group photo of RIKEN Synthetic Organic Chemistry Laboratory

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