OIST OKINAWA INSTITUTE OF SCIENCE AND TECHNOLOGY GRADUATE UNIVERSITY

Chemistry and Chemical Bioengineering Unit (Fujie Tanaka)

FY2011 Annual Report

Chemistry and Chemical Bioengineering Unit (Tanaka Unit)

Professor: Dr. Tanaka, Fujie

Abstract

We develop efficient, concise, and safe chemical transformation methods and strategies for constructing small molecules bearing functional groups and/or chiral centers. We develop enzyme-like small organic molecule catalysts and protein catalysts to accelerate chemical transformations for the synthesis of functionalized designed molecules. We also develop strategies and tools for design and selection of highly efficient catalysts and chemical transformations. Through our studies, we advance chemistry of catalysis and of construction of molecules. Our research accelerates creation of molecules necessary for the investigation and control of cell functions and biological mechanisms and contributes to the development of new therapeutics, therapeutic strategies, and diagnostics.

1. Staff

Dr. Akama, Hiroyuki, Researcher
Dr. Chouthaiwale, Pandurang, Researcher
Dr. Cui, Hai-Lei, Researcher
Dr. Katsuyama, Isamu, Researcher
Dr. Nomura, Hiroshi, Researcher
Ms. Oda, Motoko, Technician
Ms. Yamashiro, Kaori, Research Administrator

2. Collaborations

Theme: Development of methods for creation of molecules that modulate biofunctions
Type of collaboration: Joint research
Researcher: Professor Dr. Takeo Kawabata, Institute for Chemical Research, Kyoto University

3. Activities and Findings

3.1. Organocatalysis

Development of efficient chemical transformation methods for the creation of molecules that provide desired functions impacts biomedical research and a wide array of fields that require designer organic molecules.

In traditional synthesis, functional groups and heterocyclic moieties must be properly protected before certain transformations to prevent undesired reactions and these protecting groups must subsequently be removed.

Protection and deprotection methods depend on functional groups and heterocyclic moieties presenting in the molecule to be synthesized. Thus, synthesis of a set of molecules by traditional means often results in complicated, long multi-step routes that are time consuming and that generate considerable chemical waste.

In Nature, on the other hand, many enzymes catalyze chemical transformations under mild conditions without need of protection of functional groups; in many enzyme-catalyzed reactions, functional groups and heterocyclic moieties are not affected when these groups are not the targeted reaction sites. Enzymes are excellent catalysts in terms of catalytic efficiency, stereoselectivity, and substrate specificity.

We have been developing enzyme-like small organic molecule catalysts (organocatalysts) and organocatalytic molecular transformation methods useful for the synthesis of designed functionalized molecules under mild conditions without need of protection and deprotection steps. Whereas use of enzymes is often limited to catalyzing molecular transformations of the enzymes' substrates, our developing catalysts and molecular transformation methods are not as restricted as Nature's enzymes.

The main focus of our study has been the development of amine and amino acid catalysts and enamine-based reaction methods, in which enamine intermediates are generated in situ from aldehydes and ketones with catalysts. In one catalyst design strategy, we have synthesized pyrrolidine derivatives bearing acid functional groups. Using these catalysts, we have been developing bond-forming transformation methods including aldol, Mannich, Michael, and Diels-Alder reaction methods. We are also developing reaction methods that combine these reactions in one pot to concisely construct functionalized, complex molecules. In addition, we are investigating key factors and mechanisms that control product formations, reaction velocities, and stereoselectivities.

3.2. Fluorescence-based reaction monitoring systems

We have been developing concise fluorescence-based assay methods to monitor bond-forming and bond-breaking reaction progress on a small scale to facilitate the development of catalysts and catalyzed chemical transformation methods. Most of our assay systems use fluorogenic substrates; use of fluorogenic substrates provides a straightforward method of reaction monitoring because reaction progress is directly observed as an increase in fluorescence. Assay methods with fluorogenic substrates allow detection of reaction progress in early stages of reactions to evaluate catalysts and molecular transformation methods.

In reaction progress assays with fluorogenic substrates, tuning reactivity of substrates is one of the important points to appropriately analyze reaction progress. Reactivity of fluorogenic substrates often depends on fluorophores and substituents attached to the fluorophores within the substrates. When substituents are selected based on design of fluorescence features, resulting fluorogenic substrates may not show appropriate chemical reactivity because of substituent effect. To overcome this problem, we have developed a fluorogenic substrate system in which reactivities of substrates are tuned within a narrow range while varying fluorescence features. Our strategy to control molecular reactivity yet varying fluorescence features should be useful for not only designing new fluorogenic substrates but also creating other fluorescence-based probes.

4. Publications and Presentations

Tanaka, F., Enamine-based organocatalytic reactions, Special Lecture Session, Tokai Regional Section of The Pharmaceutical Society of Japan, Gifu Pharmaceutical University, Gifu, Japan, September 16, 2011.

Tanaka, F., Asymmetric synthesis of functionalized molecules using amino acid catalysts, The 42th Research

Meeting, Astellas Foundation for Research on Metabolic Disorders, Tokyo, Japan, October 15, 2011.

5. External Funding

Astellas Foundation for Research on Metabolic Disorders
Asymmetric synthesis of functionalized molecules using amino acid catalysts
PI: Tanaka, Fujie
Novemver 2010 – December 2011
Total costs 1,000,000 yen

Astellas Foundation for Research on Metabolic Disorders
Development of organocatalytic reactions using properties of nitrogen within catalysts
PI: Tanaka, Fujie
November 2011 – December 2012
Total costs 1,000,000 yen