OIST OKINAWA INSTITUTE OF SCIENCE AND TECHNOLOGY GRADUATE UNIVERSITY

Chemistry and Chemical Bioengineering Unit (Fujie Tanaka)

FY2012 Annual Report

Chemistry and Chemical Bioengineering Unit

Professor Dr. Fujie Tanaka, Associate Professor

Abstract

This unit develops efficient, concise, and safe chemical transformation methods and strategies for constructing small molecules bearing functional groups and/or chiral centers. This unit develops enzyme-like small organic molecule catalysts and protein catalysts to accelerate chemical transformations for the synthesis of functionalized designed molecules. This unit also develops strategies and tools for design and selection of highly efficient catalysts and chemical transformations. The studies undertaken by this unit advances the chemistry of catalysis and of molecular synthesis. The studies by this unit also accelerate creation of molecules used in investigation and control of cell functions and biological mechanisms and contribute to the development of new therapeutics, therapeutic strategies, and diagnostics.

1. Staff

- Dr. Akama, Hiroyuki, Researcher
- Dr. Chouthaiwale, Pandurang V., Researcher
- Dr. Cui, Hai-Lei, Researcher
- Dr. Forsyth-Norris, Andréa N., Researcher
- Dr. Johnson, Sherida, Researcher
- Dr. Katsuyama, Isamu, Researcher
- Dr. Nomura, Hiroshi, Researcher
- Ms. Oda, Motoko, Technician
- Ms. Yamashiro, Kaori, Research Administrator (~ 2012 May)
- Ms. Koki, Sawako, Research Administrator (2012 June ~ 2013 February)
- Ms. Kiriyama, Tomoko, Research Administrator (2013 March ~ 2013 May)
- Ms. Kohatsu, Tomo, Research Administrator (2013 May ~)

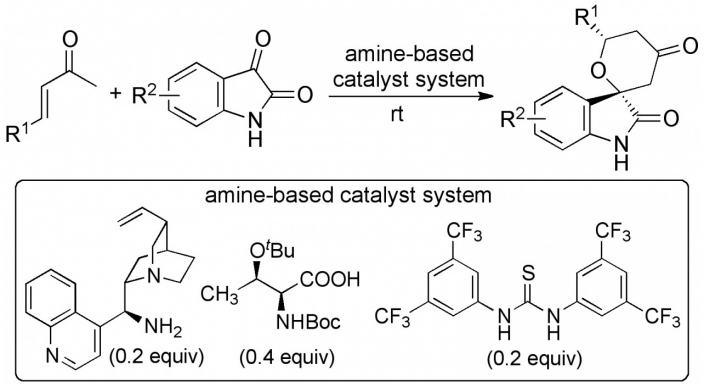
2. Activities and Findings

2.1. Organocatalysis

This unit has been developing small organic molecule catalysts (organocatalysts) and organocatalytic molecular transformation methods useful for the synthesis of designed functionalized molecules under mild conditions in a minimal number of steps, minimizing the need of protection and deprotection steps.

The main focus of this unit 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.

One of the achievements of this unit was the development of catalytic asymmetric hetero-Diels-Alder reactions that provide functionalized spirooxindole tetrahydropyranones with high diastereo- and enantioselectivities (Scheme 1) (Cui & Tanaka, *Chem. Eur. J.* 2013, 19, 6213). Novel amine-based catalyst systems have been developed to perform the reactions using enones as reactants. Substituted tetrahydropyranones are important for the syntheses of bioactive molecules. The developed reactions provide concise, atom-economical routes to substituted spirooxindole tetrahydropyranones.



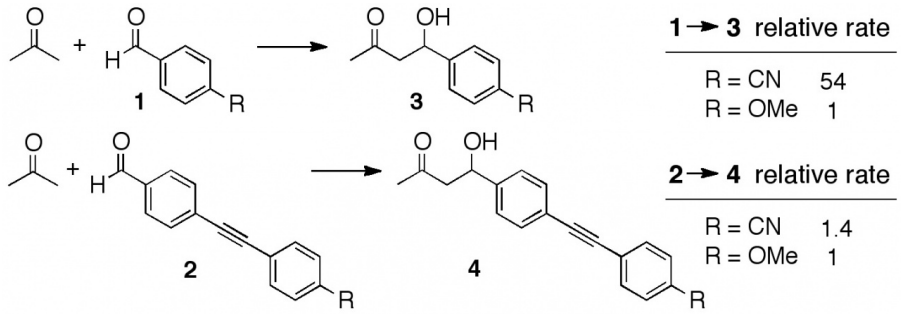
Scheme 1

2.2. Fluorescence-based reaction monitoring systems

This unit has 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. Use of fluorogenic substrates provides a straightforward method of reaction monitoring because reaction progress is directly observed as an increase in fluorescence.

To allow efficient monitoring of reaction progress assays with fluorogenic substrates, the reactivity of substrates is critical. 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 the substituent effect.

To aid the development of fluorogenic substrates, the substituent effect on 4-(phenylethynyl)benzaldehydes was compared with that on simple benzaldehyde. The results indicated that electronic features of substituents are significantly less influential in a diphenylacetylene system than in a simple benzene system (Scheme 2) (Katsuyama, Chouthaiwale, Cui, Ito, Sando, Tokiwa & Tanaka, *Tetrahedron* 2013, 69, 4098). That is, when diarylacetylene derivatives are used as fluorogenic substrate core structures, design of functions of the molecules can be the main focus, as reactivity does not depend on substituent.



Scheme 2

3. Publications

3.1. Journals

1. Cui, H.-L. & Tanaka, F. Catalytic enantioselective formal hetero-Diels-Alder reactions of enones with isatins to give spirooxindole tetrahydropyranones. *Chemistry - A European Journal* **19**, 6213-6216, doi:10.1002/chem.201300595 (2013).
2. Katsuyama, I., Chouthaiwale, P. V., Cui, H.-L., Ito, Y., Sando, A., Tokiwa, H. & Tanaka, F. Substituent-dependent reactivity in aldehyde transformations: 4-(phenylethynyl)benzaldehydes versus simple benzaldehydes. *Tetrahedron* **69**, 4098-4104, doi:10.1016/j.tet.2013.03.056 (2013).
3. Mase, N., Takabe, K. & Tanaka, F. Fluorogenic probes for chemical transformations: 9-anthracene derivatives for monitoring reaction progress by an increase in fluorescence. *Tetrahedron Letters* **54**, doi:10.1016/j.tetlet.2013.06.010 (2013).

3.2. Oral and Poster Presentations

1. Tanaka, F. Organocatalytic molecular transformations catalyzed by amino acids: Design of catalysts and control of reactions, in The 1st Research Meeting, MEXT Grant-in-Aid for Scientific Research on Innovative Areas “Advanced Molecular Transformations by Organocatalysts”, Kyoto, Japan (2012), 2012.06.08-2012.06.09.
2. Tanaka, F. Enamine-Based Catalysis: Synthesis of Amino Acids and Sugars, in The Second Asian Chemical Biology Conference (ACBC2012), Okinawa, Japan (2012), 2012.07.04-2012.07.06, international conference, invited talk.
3. Tanaka, F. Development of organocatalytic reactions using properties of nitrogen within catalysts, in The 43rd Research Meeting, Astellas Foundation for Research on Metabolic Disorders, Tokyo, Japan (2012). 2012.10.20.
4. Tanaka, F. Enamine-based organocatalytic reactions: Design of catalysts and strategies for the development of catalysts, in The 5th Symposium on Organocatalysis (and The 2nd Symposium, MEXT Grant-in-Aid for Scientific Research on Innovative Areas “Advanced Molecular Transformations by Organocatalysts”), Tokyo, Japan (2012), 2012.10.26-2012.10.27.
5. Chouthaiwale, P. V. & Tanaka, F. Amino acid-catalyzed reactions of pyruvates: One-pot aldol condensation-Michael addition-cyclization sequence, in The Twelfth International Kyoto Conference on New Aspects of Organic Chemistry (IKCOC-12), Kyoto, Japan (2012), 2012.11.12-2012.11.16, international conference.
6. Cui, H.-L. & Tanaka, F. Amine-catalyzed asymmetric construction of quaternary carbon centers, in The Twelfth International Kyoto Conference on New Aspects of Organic Chemistry (IKCOC-12), Kyoto, Japan (2012), 2012.11.12-2012.11.16, international conference.
7. Tanaka, F. Synthesis of sugar derivatives and sugar-related molecules for the search of bioactive molecules, in Symposium, Okinawa Intellectual Cluster Program “Exploration Research on The Development of Pharmaceuticals and Their Candidates Using Bioresources and Networks in Okinawa”, Okinawa, Japan (2012), 2012.12.19.
8. Tanaka, F. Synthesis of sugar derivatives for screening of bioactive molecules, in The 1st Committee Meeting, Okinawa Intellectual Cluster Program “Exploration Research on The Development of Pharmaceuticals and Their Candidates Using Bioresources and Networks in Okinawa”, Okinawa, Japan (2013), 2012.2.12.
9. Cui, H.-L. & Tanaka, F. Enantioselective formal cycloadditions catalyzed by amine-based catalysts that afford functionalized tetrahydropyranones, in The 133rd Annual Meeting of the Phermaceutical Society of Japan, Yokohama, Japan (2013), 2013.03.27-2013.03.30.
10. Chouthaiwale, P. V. & Tanaka, F. Amino acid-catalyzed reactions of pyruvates: One-pot aldol

condensation-Michael addition-cyclization sequence, in Advanced Molecular Transformations by Organocatalysts 1st International Conference & 6th Symposium on organocatalysis, Otsu, Japan (2013), 2013.05.27-2013.05.28, international conference.

11. Cui, H.-L. & Tanaka, F. Catalytic enantioselective formal hetero-Diels-Alder reactions of enoneswith isatins to give spirooxindole tetrahydropyranones, in Advanced Molecular Transformations by Organocatalysts 1st International Conference & 6th Symposium on Organocatalysis, Otsu, Japan (2013), 2013.05.27-2013.05.28, international conference.
12. Tanaka, F. Synthesis of sugar derivatives for screening of bioactive molecules, in The 1st Committee Meeting (H25), Okinawa Intellectual Cluster Program “Exploration Research on The Development of Pharmaceuticals and Their Candidates Using Bioresources and Networks in Okinawa”, Okinawa, Japan (2013), 2013.06.20.

4. Intellectual Property Rights

Two (2) provisional patent applications

5. External Funding

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

2. Grant-in-Aid for Scientific Research on Innovative Areas “Advanced Molecular Transformations by Organocatalysts” from
   The Ministry of Education, Culture, Sports, Science and Technology, Japan
   Enamine-based organocatalytic molecular transformations: Development of highly efficient catalysts
   PI: Tanaka, Fujie
   Direct costs 3,600,000 yen (Total costs 4,680,000 yen)
   April 2012 – March 2013

3. Okinawa Intellectual Cluster Program “Exploration Research on The Development of Pharmaceuticals and Their
   Candidates Using Bioresources and Networks in Okinawa”
   Synthesis of sugar derivatives for screening of bioactive molecules
   PI: Tanaka, Fujie
   Direct costs 1,710,318 (Total costs 2,155,000 yen)
   August 2012 – March 2013

6. Seminars

6.1. Seminar

Date: May 23, 2013
Venue: OIST campus Lab 1
Speaker: Professor Robert H. E. Hudson, Department of Chemistry, The University of Western Ontario, Canada