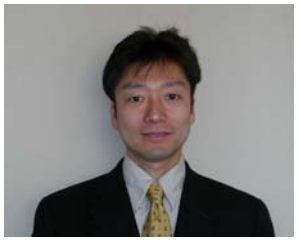
【Grant-in-Aid for Young Scientists(S)】

Biological Sciences (Medicine, dentistry, and pharmacy Ⅰ)



Title of Project：Streamlining Organic Synthesis Based on the Development of New Asymmetric Catalysis; Expansion of Pharmaceutical Leads

Motomu Kanai

(The University of Tokyo,Graduate School of Pharmaceutical Sciences, Associate professor)

Research Area：Pharmacy

Keyword：Asymmetric Synthesis

【Purpose and Background of the Research】

Main aims of this project are to expand the structural diversity of pharmaceutical leads and to facilitate drug discovery based on the development of environmentally friendly synthetic methods. The pharmaceutical science, a unity of molecular science and life science, is one of the most important research fields for our future. The number of pharmaceutical leads is limited, however, due to the inability of current organic synthesis to supply enough amounts of structurally diverse molecules. This project aims at overcoming such limitations by developing general catalytic asymmetric methods to produce new pharmaceutical leads.

【Research Methods】

1. Highly efficient asymmetric carbon-carbon bond-forming reactions promoted by chiral soft metal-conjugated base catalysts

The basic concept to achieve the goal described above is "*soft metal-conjugated base catalysis*". Through the interaction of soft metals (such as Cu, Fe, Mn, or Co) with π-electrons of nucleophilic substrates, such as nitriles, olefins, aromatic compounds, and alkynes, α-protons of π-bonds should be selectively acidified. Soft metal-based nucleophiles generated from stable organic molecules through chemoselective deprotonation should react with various electrophiles. Thus, carbon-carbon bond-formation occurs via proton transfer from pre-nucleophiles to products. Chirality control of these direct reactions should be possible by introducing chiral ligands to soft metals.

2. Highly efficient synthesis of pharmaceuticals and their leads

Using the original asymmetric catalyses, efficient synthesis of anti-tuberculosis R207910, anti-influenza Releza, and an important intracellular signaling molecule inositol 1,4,5-trisphosphate will be achieved. Targets are not limited to the already-existing drugs. An array of artificial polyketide molecules should be rapidly synthesized through iterative direct catalytic asymmetric aldol reactions. New pharmaceutical leads will be identified taking advantage of the origical catalytic asymmetric reactions.

【Expected Research Achievements and Scientific Significance】

By extending our original concept of "soft metal-hard anion conjugated asymmetric catalysis" to catalytic asymmetric carbon-carbon bond-formation with high atom economy, complex molecule synthesis will be streamlined. Moreover, the developed method should allow for the improvement of quality and diversity of pharmaceutical leads, leading to the facilitation of drug discovery.

【Publications Relevant to the Project】

- Tomita, D.; Yamatsugu, K.; Kanai, M.; Shibasaki, M. "Enantioselective Synthesis of SM-130686 Based on the Development of Asymmetric Cu(I)F-Catalysis to Access 2-Oxindoles Containing a Tetrasubstituted Carbon" *J. Am. Chem. Soc.* **2009**, *131*, in press.
- Yamatsugu, K.; Yin, L.; Kamijo, S.; Kimura, Y.; Kanai, M.; Shibasaki, M. "A Synthesis of Tamiflu by Using a Barium-Catalyzed Asymmetric Diels–Alder-Type Reaction" *Angew. Chem., Int. Ed.* **2009**, *48*, 1070–1076.

【Term of Project】 FY2009-2013

【Budget Allocation】 86,100 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.f.u-tokyo.ac.jp/~kanai/index.html