

# Department of Organocatalytic Chemistry

Specially Appointed Professor: Keiji Maruoka



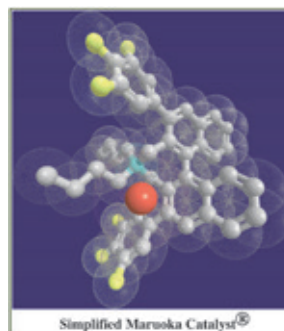
## Research Projects:

"Organocatalyst" has recently attracted considerable attention as the third catalyst in organic synthesis in addition to the conventional "biocatalyst" and "metal catalyst". In such an organocatalytic field, the design of "high-performance organocatalysts", if possible, enables the achievement of new reactivity and selectivity, hitherto not obtainable in the conventional "biocatalysts" and "metal catalysts". The aim of our research is to realize the rational design of high-performance organocatalysts, which is divided into four main categories consisting of "organobase catalysts", "organoacid catalysts", "organoacid/base bifunctional catalysts" and "organoradical catalysts". Throughout both the basic and applied researches in this project, we have developed the design and synthesis of a series of truly high-performance organocatalysts for practical organic transformations.



**1) Rational design of chiral phase-transfer catalysts:** A most important and significant aspect of our work is the impact it has had on the field of phase-transfer chemistry. We rationally designed and synthesized a series of chiral binaphthyl-modified spiro-type phase-transfer catalysts as "Maruoka Catalyst®" for asymmetric synthesis of various natural- and unnatural-type amino acid derivatives starting from simple glycine derivative. We further challenged the simplification of these phase-transfer catalysts with high catalytic activity, and finally succeeded to design super-active "Simplified Maruoka Catalyst®" (*i.e.*, S/C = 5,000~10,000) with virtually complete enantioselectivity. This catalyst is produced by Nagase & Co., Ltd. in a Kg-scale, and now commercially available from Sigma-Aldrich Co., Strem Co. and Kanto Chemical Co. In addition, Nagase & Co., Ltd. and Kishida Chemical Co., Ltd. have started the large-scale production of unnatural  $\alpha$ -alkyl and  $\alpha,\alpha$ -dialkyl amino acids (100 g~300 kg scale) as new pharmaceutical intermediates by using "Simplified Maruoka Catalyst®". Such large-scale production of unnatural amino acids is truly important because

about 20% (about 100 kinds) of the top-500 best selling medicines in the world markets utilize  $\alpha$ -amino acids as starting materials and pharmaceutical intermediates.



Our asymmetric phase-transfer chemistry has been successfully applied to asymmetric aldol reaction, Mannich reaction, conjugate addition, epoxidation, Strecker reaction, alkylation of  $\beta$ -keto esters, and diastereoselective terminal alkylation of peptides, etc.

### 2) Design of chiral bifunctional organocatalysts:

We designed an axially chiral hexamethoxybiphenyl amino acid catalyst to achieve the very high catalytic efficiency in the asymmetric direct aldol reaction. Based on the information, we succeeded to design an axially chiral binaphthyl-modified amino Tf-amide catalyst for hitherto unknown *anti*-selective asymmetric Mannich reaction of aldehydes with activated imines and *syn*-selective direct aldol reaction of two different aldehydes.

### 3) Design of chiral organo diacid catalysts:

Although the asymmetric hydrogen-bonding catalysis mainly relies on the use of thiourea, diol, and phosphoric acid as hydrogen-bonding donors, we newly designed axially chiral binaphthyl-modified dicarboxylic acids for asymmetric Mannich reaction of arylaldehyde *N*-Boc imines with diazoacetates; imino aza-enamine reaction of arylaldehyde *N,N*-dialkylhydrazones; and *trans*-selective aziridination of diazoacetamides with *N*-Boc imines.

### 4) Design of chiral organoradical catalysts:

We began our own organoradical chemistry by the generation of several iodanyl radical species from hypervalent iodine compounds under visible photocatalysis for site-selective functionalization of saturated hydrocarbons and selective generation of acyl radicals for selective C-C bond formation. We also achieved the design of chiral organothiol catalysts to generate chiral thiyl radicals for asymmetric (3+2) cyclization.

## Recent publications

- Design of N-Spiro  $C_2$ -Symmetric Chiral Quaternary Ammonium Bromides as Novel Chiral Phase-Transfer Catalysts: Synthesis and Application to Practical Asymmetric Synthesis of  $\alpha$ -Amino Acids, Ooi, T.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **2003**, 125, 5139-5151.
- An Organic Thiyl Radical Catalysed Enantioselective Cyclization, Hashimoto, T.; Kawamata, Y.; Maruoka, K. *Nature Chem.*, **2014**, 6, 702-705.
- A Chiral Electrophilic Selenium Catalyst for Highly Enantioselective Oxidative Cyclization, Kawamata, Y.; Hashimoto, T.; Maruoka, K. *J. Am. Chem. Soc.*, **2016**, 138, 5206-5209.