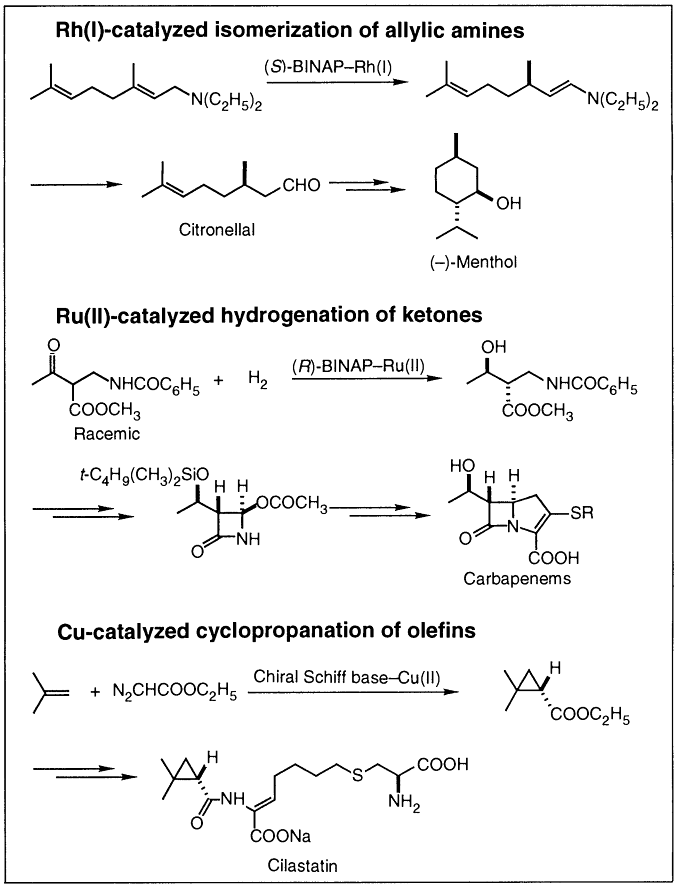
Organic Synthesis: Current Status in Japan

Ryoji Noyori

Organic synthesis not only produces important substances in an economical way but also greatly facilitates fundamental research in other scientific fields. Current trends in organic synthesis are not much different between Japan and other parts of the world. In modern synthetic organic chemistry, either basic or applied, the major efforts are in five areas: (i) invention of efficient synthetic methods (reactions, reagents, and catalysts); (ii) synthesis of molecules that are architecturally interesting; (iii) cost-effective preparation of important compounds; (iv) discovery and creation of artificial substances having significant properties or functions; and (v) understanding of biological phenomena or physiological functions at the molecular level.

Whether for industrial production or at research laboratories, organic synthesis must be truly efficient. Large-scale chemical production must not only have economical merit, but modern processes should also be safe, energy-saving, frugal in the use of resources, and the environmental impact should be minimal. In the 1950s, synthesis of organic compounds with a high degree of complexity of the three-dimensional structure was an art (*1*); only truly ingenious chemists were able to construct such molecular architectures. Currently, however, synthetic chemists are guided by systematic, rather than trial-and-error approaches, to prepare complicated organic compounds in a rational way (*2*). This trend has been accelerated by the acquisition of a series of new organometallic-aided preparative methods which selectively effect a redox process, carbon-carbon bond formation, or functional group transformation (*3*).

Some innovative synthetic methods can remarkably shorten the overall scheme of preparation of complex compounds (*4*). As a consequence, the potential of organic synthesis has now risen to a new stage; this discipline occupies not only an important place in chemistry but is dynamically linked with interdisciplinary sciences and technologies that are inherently chemical in nature. In particular, research (rather than production) to find fine chemicals and materials of a high added value is of growing importance, and multidisciplinary efforts are crucial for the accomplishment. Development of highly sophisticated therapeutic agents as well as investigations solving certain biological problems, for example, requires simultaneous cooperation of synthetic chemists and experts of other areas such as biochemistry, biology, pharmacology, and medicine. Accordingly chemical synthesis, normally performed on a multi-gram scale, must be expeditious and flexible, thereby adhering to the programs of personal or institutional cooperative research.



Asymmetry at work. Three industrial applications of asymmetric catalysis, in which large amounts of either left- or right-handed molecules can be produced from a small amount of chiral source material.

An ideal chemical reaction would produce only the desired product possessing the specific shape in an absolute sense in a cost-effective and environmentally benign manner. However, only a limited number of practical methods classified into this category are now in hand. Because the efficacy of a biologically active compound, either natural or unnatural, often depends on chirality, incorporation of an efficient stereoselective reaction into the multi-step synthetic procedure is the pivotal issue. In addition, properties of certain solid-state materials and liquid crystals are also affected by the enantiomeric purities. As such, among the most exciting disciplines is *asymmetric catalysis*, which allows production of a large quantity of right- or left-handed compound from a very small amount of a chiral source (*5*). Metal complexes having a suitable chiral organic ligand repeatedly accelerate highly enantioselective organic reactions in the homogeneous phase, providing a general principle for the chemical multiplication of chirality. The chiral efficiency of the organometallic catalysts rival, or in certain cases even exceed, that of enzymatic transformations, realizing a long-sought dream of chemists.

The general potential of efficient asymmetric catalysis is apparent and its impact on pharmaceutical and agricultural technologies as well as material sciences is especially enormous. The role played by Japanese scientists, together with Western colleagues, in this topical field is particularly noteworthy. Three innovative industrial processes are being used in Japan (see figure), each of which originated from fundamental scientific research (*6*). Takasago International Co. is operating the BINAP-Rh catalyzed asymmetric isomerization of allylic amines for synthesis of optically active citronellal and menthol and also the BINAP-Ru catalyzed asymmetric hydrogenation of a functionalized ketone for the synthesis of an intermediate of carbapenem antibiotics [BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl, a phosphorus-based chiral organic ligand]. Asymmetric olefin cyclopropanation catalyzed by a chiral Schiff base–Cu complex is currently being used for the synthesis of Cilastatin, an in vivo stabilizer of carbapenems (Sumitomo Chemical Co. and Merck Sharp and Dohme Co.).

The author is in the Department of Chemistry, Nagoya University, Nagoya 464-01, Japan.

Good chemistry. During the past 5 years, the Ministry of Education, Science & Culture has designated Special Research projects, as well as group endeavors among 20 to 50 scientists for a period of 3 to 5 years.

Specially Promoted Research projects:	
Y. Harada (Univ. Tokyo)	Metastable Atoms
I. Ikemoto (Tokyo Metropolitan Univ.)	High-temperature Superconductors
N. Ise (Kyoto Univ.)	Colloidal Crystals
H. Iwamura (Univ. Tokyo)	Organic Ferromagnets
H. Kato (Kobe Univ.)	Dynamics of Excited Molecules
K. Maruyama (Kyoto Univ.)	Photosynthesis Modeling
A. Masuda (Univ. Tokyo)	Primeval Technetium
Y. Murakami (Kyushu Univ.)	Artificial Enzymes
R. Noyori (Nagoya Univ.)	New Synthetic Reactions
H. Ogoshi (Kyoto Univ.)	Molecular Recognition
H. Sakurai (Tohoku Univ.)	Organosilicon Materials
K. Tokumaru (Tsukuba Univ.)	Olefin Photoisomerization

Scientific Research of Priority Areas projects and their coordinators:	
K. Akiba (Hiroshima Univ.)	Unusual Valency of Main Group Elements
T. Goto (Nagoya Univ.) and K. Ogura (Tohoku Univ.)	Dynamic Natural Products Chemistry
T. Hata (Tokyo Inst. Tech.)	Nucleic Acids Chemistry
M. Hidai (Univ. Tokyo)	Activation of Small Molecules
E. Hirota (Graduate Univ. for Adv. Studies)	Free Radicals
K. Ito (Osaka City Univ.)	Molecular Magnetism
K. Morokuma (Okazaki Inst.)	Theory of Chemical Reactions
T. Mukaiyama (Sci. Univ. Tokyo)	Control of Complex Systems
S.-I. Murahashi (Osaka Univ.)	Reactive Organometallics
I. Murata (Osaka Univ.)	Design of Molecular Materials
Y. Ohashi (Tokyo Inst. Tech.)	Molecular Crystals
H. Ohtaki (Okazaki Inst.)	Non-equilibrium Processes in Solution
T. Osa (Tohoku Univ.)	Electroorganic Chemistry
E. Osawa (Toyohashi Univ. Tech.)	Carbon Clusters
T. Tsuruta (Sci. Univ. Tokyo)	New Materials
O. Yamauchi (Nagoya Univ.)	Bio-inorganic Chemistry
O. Yonemitsu (Hokkaido Univ.)	Asymmetric Synthesis

In Japan, as in some other countries, the academic community has a close relationship with the chemical and pharmaceutical industry. In 1942, the Society of Synthetic Organic Chemistry, Japan, was founded for the purpose of stimulating the activity of organic synthesis through the cooperation of academia and industry. This successful collaboration has resulted in mutual benefits for both academia and industry. A special commemorative edition, published this year on the occasion of the society's 50th anniversary (7), provides a deeper discussion of the past and present aspects of organic synthesis in Japan.

The Ministry of Education, Science & Culture has recognized the fundamental significance of many disciplines of chemistry and in the past 5 years has designated several projects as Specially Promoted Research (see table). Most of these principal investigators have made a pioneering achievement at the forefront of their respective research area. Notably, Sakurai devised a novel anionic polymerization of masked disilenes, which led to high-molecular-weight polysilanes, and synthesized persilyated pi-electron systems with unusual physical properties. Iwamura recently succeeded in the synthesis of an unprecedented non-acarbene ($S = 9$) and a 1.6 K nitroxide radical ferromagnet and also established a principle for the construction of molecular ferromagnets. In addition, the study of F. Toda (Ehime University) on solid-state organic reactions has produced a high level of selectivity in various intramolecular reactions in crystals with an unexpectedly wide generality. Supramolecular chemistry is also an exciting field, where T. Kunitake (Kyushu University) developed a series of weakly bound molecular assemblies possessing particular physical or chemical properties.

Great discoveries are often made accidentally by serendipitous scientists working individually. However, very few outstanding people have a sufficiently wide scientific view and enough knowledge and skills in different fields to work independently. Hence the Ministry of Education, Science & Culture encourages the organization of group research of a 3- to 5-year term composed of 20 to 50 scientists, where their technical cooperation or exchange of information is anticipated to advance a significant or rapidly growing, particularly interdisciplinary, scientific area. The results of these programs have been quite good for chemical research (see table).

The overall morale of the Japanese chemical community remains relatively high. The significance of chemistry in technology and eventually for the human welfare is recognized and appreciated by society. There is an acute problem, however (8). Although many industrial and non-academic national institutes have well-equipped laboratories for chemical research, the facilities and working conditions at major academic facilities are entirely outdated and urgently need complete renovation. This unattractive situation, caused by the financial straits of the past 10 years, will diminish the future supply of qualified young chemists to university and hence industry and elsewhere. Because the government now seriously recognizes this crisis, we expect a drastic improvement in the near future.

Our cultural background differs from that of scientists of other countries. For instance, our cultural tradition is characterized by the appreciation of harmony within a group and society, an influence of Confucianism, which in effect promotes various kinds of teamwork, if necessary, although this sometimes sacrifices the independence of individuals. Our research concepts and motivation of the projects may also be different from others. In years past, many young Japanese chemists went to Western countries as postdoctoral fellows to increase their experience. The direction of the personnel movement used to be one way but recently our academic laboratories have started to accommodate young foreign students and researchers from America, Europe, and other Asian countries. The combined efforts of our unique cultural and scientific tradition and the fruitful international exchange will continue to contribute to the progress of this important scientific realm.

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