

Trends in Organic Synthesis Chemistry Research

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2.1 Introduction

The DNA sequence of genome, the blueprint of life, has been deciphered in human and other various organisms, and structural and functional analyses of proteins are currently in progress as post-genome research. Compounds that affect proteins or other functional molecules *in vivo* play critical roles in the post-genome research. For example, a compound acting specifically on a certain protein becomes a valuable reagent in biological science research. Moreover, most pharmaceuticals, which can be considered as compounds possessing many added values, can be synthesized through organic synthesis chemistry. Therefore, improving the capacity of organic synthesis chemistry in our country should contribute to the achievement of more outcomes from the post-genome research, as well as to the continuous release of novel chemical products from Japan to the world.

It has been considered that the current standard of organic synthesis chemistry has reached a level enabling total syntheses (synthesis using easily available starting materials) of compounds with quite complex structures, but tasks still remain, such as cost reduction or inhibition of by-products. For some compounds with complex structures such as Taxol, an anti-cancer drug, total synthesis techniques have been established, but their cost-performances are too low compared to other synthesis techniques. Furthermore, when chemically synthesizing certain kinds of useful substances, 3,000 times higher amounts of by-products are emitted besides the target substance, applying a heavy load on the environment. As a consequence, the development of new energy-

saving reaction systems inhibiting the production of by-products are expected for synthesizing compounds that are essential for disease treatment or productive activities. In general, the introduction of a catalyst into a reaction system is expected not only to reduce the energy required but also to permit only the desired reaction to proceed among several potential reactions. Therefore, the development of a new reaction system is often accompanied by the development of a new catalyst.

In this report, we will introduce the recent research achievements in the area of organic synthesis chemistry and discuss the future long-term trends.

2.2 Main achievements in organic synthesis chemistry

2.2.1 Progress in organic chemistry and the Nobel Prize

Table 1 shows a list of Nobel Prize winners who have received the awarded for work in the area of organic chemistry since 1950.^[1] Their efforts over these 50 years have made feasible the accurate syntheses of organic compounds. This is not limited to simple compounds, which can be prepared on industrial scales with low costs; it also applies to compounds with extremely complex structures, which can be synthesized on small, laboratory scales (in mg scales) at the expense of cost and time.

The organic chemistry research in our country has constantly retained its high level, which has been proven by the recent award of Nobel Prizes in Chemistry to Japanese researchers for two consecutive years.

The following sections will introduce the Wittig

Table 1: Winners of the Nobel Prize in Chemistry for the Area of Organic Chemistry since 1950.

Year awarded	Winner(s)	Works awarded
1950	Diels, Otto, Paul Hermann (Germany) Alder, Kurt (Germany)	Diene synthesis
1955	Du Vigneaud, Vincent (U.S.)	Synthesis of peptide hormone
1963	Ziegler, Karl (Germany) Natta, Giulio (Italy)	Chemistry of high polymers
1965	Woodward, Robert Burns (U.S.)	Modern organic chemistry theories
1969	Barton, Sir Derek H. R. (U.K.) Hassel, Odd (Norway)	Concept of conformation and its application in chemistry
1973	Fischer, Ernst Otto (West Germany) Wilkinson, Sir Geoffrey (U.K.)	Organometallic catalysts
1975	Cornforth, Sir John Warcup (U.K.) Prelog, Vladimir (Switzerland)	Stereochemistry of enzyme-catalyzed reactions
1979	Brown, Herbert C. (U.S.) Wittig, Georg (West Germany)	Use of boron- and phosphorus-containing compounds in organic synthesis
1981	Fukui, Kenichi (Japan) Hoffmann, Roald (U.S.)	Frontier orbital theory
1984	Merrifield, Robert Bruce (U.S.)	Chemical synthesis on a solid matrix
1987	Cram, Donald J. (U.S.) Lehn, Jean-Marie (France) Pedersen, Charles J. (U.S.)	Host-guest chemistry
1990	Corey, Elias James (U.S.)	Development of the theory and methodology of organic synthesis
1992	Marcus, Rudolph A. (U.S.)	Theory of electron transfer reactions in chemical syntheses
1994	Olah, George A. (U.S.)	Carbocation chemistry
2000	Heeger, Alan J. (U.S.) MacDiarmid, Alan G. (U.S.) Shirakawa, Hideki (Japan)	Discovery and development of conductive polymers
2001	Knowles, William S. (U.S.) Noyori, Ryoji (Japan) Sharpless, K. Barry (U.S.)	Development of chirally catalyzed hydrogenation reactions Development of chirally catalyzed oxidation reactions

Source: Authors' own compilation

reaction as a typical reaction of organic synthesis chemistry, and Taxol, an anti-cancer drug, as an example of organic compounds with extremely complex structures whose total syntheses have been reported recently. The subsequent sections will cover the versatile research on novel chiral catalysts, represented by asymmetric hydrogenation, the work of a 2001 Nobelist Dr. Ryoji Noyori, and asymmetric carbon-carbon bond generation.

2.2.2 A typical reaction of organic synthesis chemistry

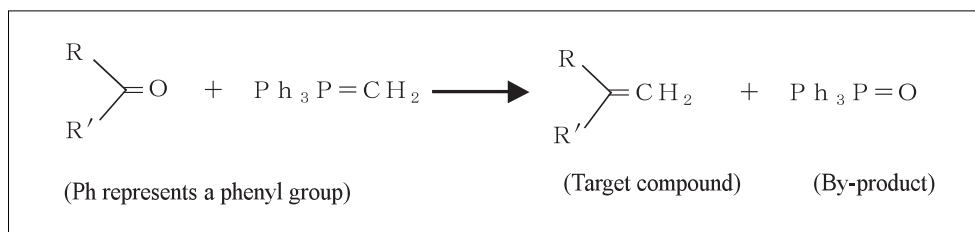
In the area of organic synthesis chemistry, Dr. Wittig was awarded the Nobel Prize in 1979, for developing an efficient reaction called "Wittig reaction" in 1953 (Figure 1). Wittig reaction employs phosphorus ylide ($\text{Ph}_3\text{P}=\text{CH}_2$) for specifically generating double bonds in carbonyl

groups via the generation of carbon—carbon bonds. The reaction is frequently employed for manufacturing various pharmaceuticals and perfumes.

In the second half of the 20th century, the area of organic synthesis chemistry progressed with emphasis on chemical yield improvement. Here, the generation of by-products was not considered a big problem, even if they were generated at amounts equal to the target products, as in the Wittig reaction.

2.2.3 Example of compounds with complex structures ~synthesis of Taxol~

Taxol is a compound having a complex structure as shown in Figure 2. It is found in the barks of yew trees (*Taxus brevifolia*) in trace amounts and acts as an anti-cancer drug effective for breast or uterine cancer. In the Charts of the present

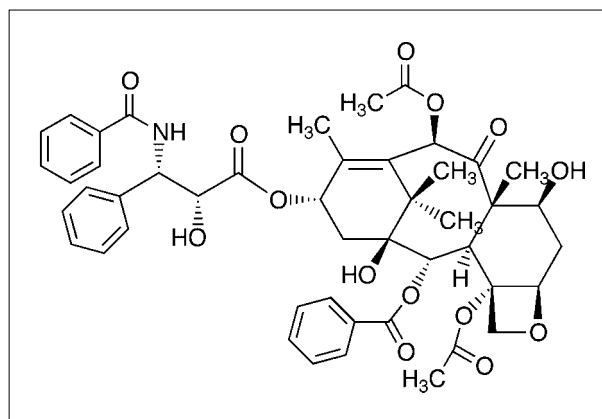
Figure 1: Wittig reaction

Source: material prepared by Professor Masakatsu Shibasaki of the Graduate Course of Pharmacy, Graduate School of Tokyo University

report, chemical bonds are represented by either bold solid lines or dotted lines. The bold solid lines are bonds that are positioned toward this side of the sheet, while the dotted lines are those positioned away to the other side of the sheet. As can be seen from Figure 2, Taxol has a sterically complex structure. Since the amount of Taxol required for treating one patient corresponds to 3 yew trees, the isolation of Taxol from plants is not suitable as a manufacturing process for a pharmaceutical product.

The total synthesis of Taxol was first reported in 1994 in the *Journal of the American Chemical Society*. This report attracted great attention as a study demonstrating the possibility of synthesizing complex-structured chemicals. However, the technique presented in the study barely enabled the synthesis of about 10 mg of Taxol in a high-tech laboratory for organic synthesis chemistry. The total synthesis required too much cost, which was fatal as a process for manufacturing pharmaceuticals. Later, a technique for producing Taxol through organic synthesis in fewer steps was developed using an intermediate material (baccatin). Baccatin can be isolated in a relatively large amount from leaves of a shrub named European yew (*Taxus baccata*), and this technique is currently used for Taxol production.

Furthermore, the partial modification of the total synthesis of Taxol has enabled the synthesis of an anti-cancer drug that is superior to Taxol. The clinical trials for this "novel Taxol" are currently in progress. So far, this novel compound cannot be synthesized from baccatin. This is a good example demonstrating that even for a naturally existing compound, the establishment of an organic synthesis technique is extremely important for the subsequent research in areas such as

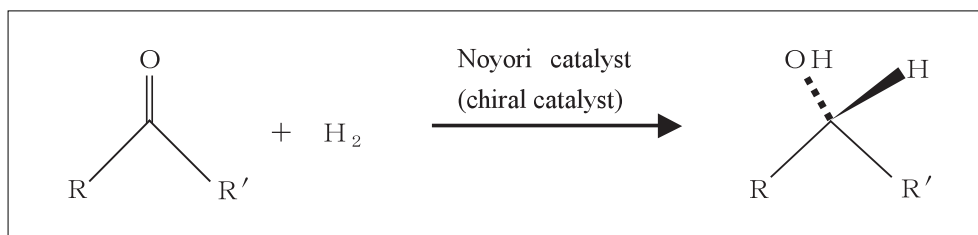
Figure 2: Structural formula of Taxol

pharmaceutical chemistry.

2.2.4 Asymmetric catalytic reaction ~asymmetric hydrogenation~

Most molecules are "asymmetric," having two forms that are mirror images of each other, just like a person's right hand and left hand. For some asymmetric molecules, only one of the mirror-image forms is biologically useful while the other is harmful. A considerable number of pharmaceutical products are known to have such "asymmetric" structures, and the difference between the two forms may lead to a matter of life and death in some cases. Therefore, it is crucial to make the two forms separately.

In 2001, Dr. Ryoji Noyori was awarded the Nobel Prize in Chemistry for his work "BINAP — Development of Chirally Catalyzed Hydrogenation based on Transition Metal Complex". Dr. Noyori developed a versatile catalytic molecule that enables the synthesis (asymmetric synthesis) of only one of the two enantiomers in asymmetric hydrogenation (Figure 3). The results from his research are applied to the industrial production of antibiotics and antibacterial agents.^[1]

Figure 3: Example of chirally catalyzed hydrogenation


Source: material prepared by Professor Masakatsu Shibasaki of the Graduate Course of Pharmacy, Graduate School of Tokyo University

2.2.5 Asymmetric Carbon

—Carbon bond generation

Because the bonds between carbon atoms form the skeletal structure of every organic compound, carbon—carbon bond generation is the central subject of organic synthesis. Particularly great attention is paid to asymmetric carbon—carbon bond generation, i.e., the asymmetric synthesis (separate production of “right hands” and “left hands”) of carbon—carbon bond generation. An example of such asymmetric carbon—carbon bond generation is a reaction known world-wide as “Mukouyama reaction,” which was developed by Dr. Mitsuteru Mukouyama, a professor emeritus of Tokyo University. Mukouyama reaction is described in Figure 4 through an example generating the target product from acetone and aldehyde.

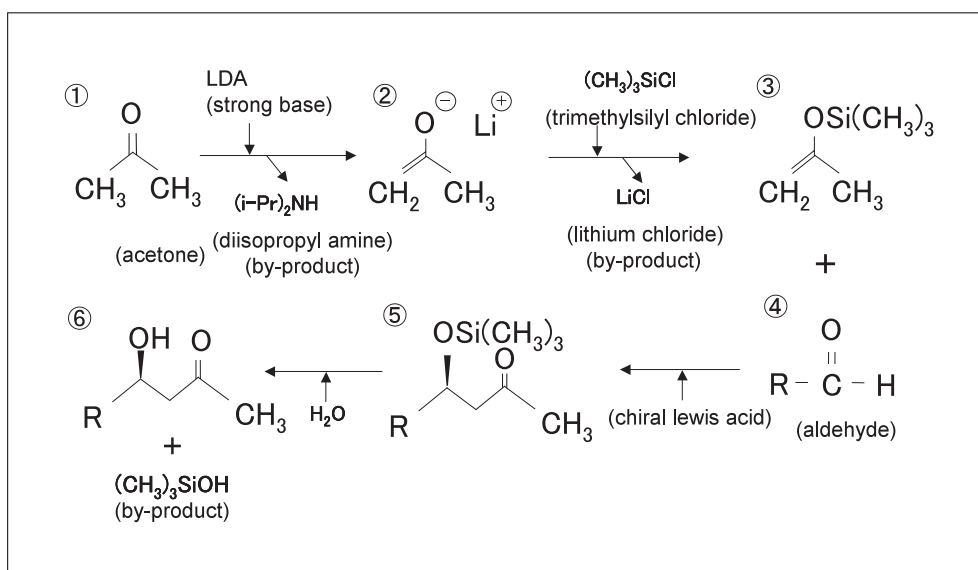
Mukouyama reaction is an outstanding research result with high originality. As a next step, one of the most important research subjects in the world

today is the development of a new versatile reaction system or catalyst for efficiently performing asymmetric carbon—carbon bond generation in one step (Figure 5).

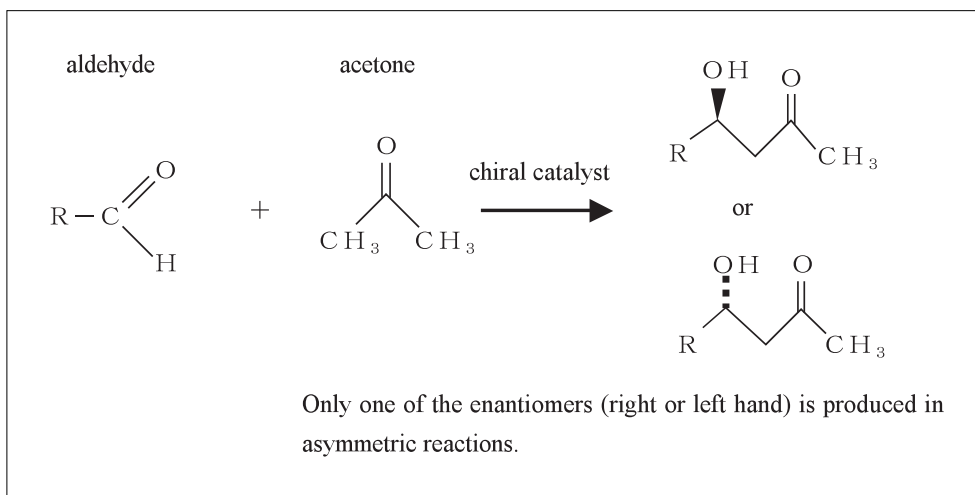
2.3 Long-term trends in organic synthesis chemistry research

The current standard of organic synthesis chemistry has already reached a level enabling syntheses of compounds with complex structures. Needless to say, the most important subject is to develop techniques for reducing costs and inhibiting by-product generation.

From the point of environmental conservation, it will be important to develop industrial techniques based on the standpoint of “Green Chemistry” (a movement involving a wide range of areas including basic/applied chemistry and chemical technology/industry, which aims at the establishment of a sustainable chemical

Figure 4: Example of Mukouyama reaction (asymmetric albol reaction)


Source: material prepared by Professor Masakatsu Shibasaki of the Graduate Course of Pharmacy, Graduate School of Tokyo University

Figure 5: Example of efficient generation of asymmetric carbon-carbon bond (asymmetric aldol reaction)

Source: material prepared by Professor Masakatsu Shibasaki of the Graduate Course of Pharmacy, Graduate School of Tokyo University

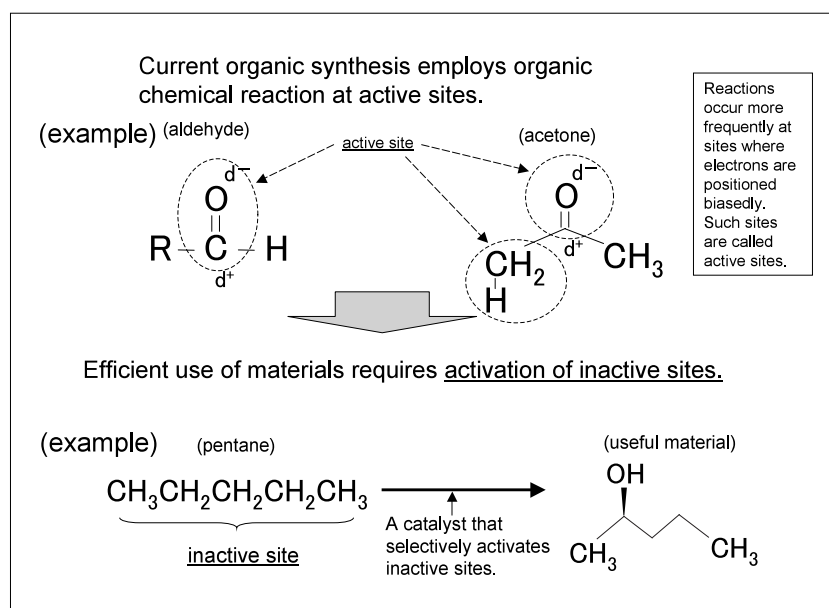
technology system suitable for future society).^[2] Furthermore, people may live in a closed system such as outer space in the future, and such possibility must also be taken into consideration. Here, we will introduce some examples of reactions that are expected to be developed in the future in the area of organic synthesis chemistry.

2.3.1 Development of reaction systems that selectively activates specific inactive sites

Current organic synthesis chemistry utilizes organic chemical reactions taking place at active sites (functional groups) such as aldehydes, ketones and hydroxyl groups. If catalysts that

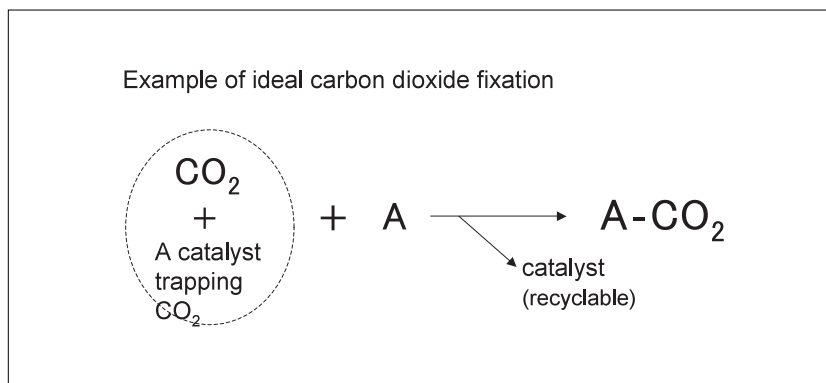
promote selective activation of specific inactive sites in various compounds were to be developed, it would be possible to produce useful substances using resources or compounds that are rarely used today. One example is a reaction which introduces functional groups such as hydroxyl groups ($-\text{OH}$) into selective sites in a saturated hydrocarbon compound such as pentane (Figure 6).

Studies on the site-specific activation of inactive sites are gradually making progress, realizing such reaction in a limited number of systems. However, it seems that much more time will be required before reactions such as those represented in

Figure 6: Selective activation of specific inactive sites

Source: material prepared by Professor Masakatsu Shibasaki of the Graduate Course of Pharmacy, Graduate School of Tokyo University

Figure 7: Example of carbon dioxide fixation by organic synthesis chemistry



Source: material prepared by Professor Masakatsu Shibasaki of the Graduate Course of Pharmacy, Graduate School of Tokyo University

Figure 6 can be put into practice.

2.3.2 Development of a carbon dioxide fixation system

Figure 7 illustrates a reaction that allows a trace amount of carbon dioxide at a level equivalent to that in the air (approximately 0.03%) to form a complex compound with the catalyst, and, subsequently, to be fixed in substance A. If such reaction were to be developed, carbon dioxide present in the air can be used as a substitute for carbonous materials such as petrol that may be exhausted in the future. The development of such reaction is also important from the point of reducing the carbon dioxide level in the environment. However, such reaction cannot be realized, since there is no catalyst that can distinguish and bind carbon dioxide at a level of approximately 0.03%.

The fixation of carbon dioxide in the air is mainly studied by researchers in the area of biomimetics who are attempting to mimic photosynthesis. This

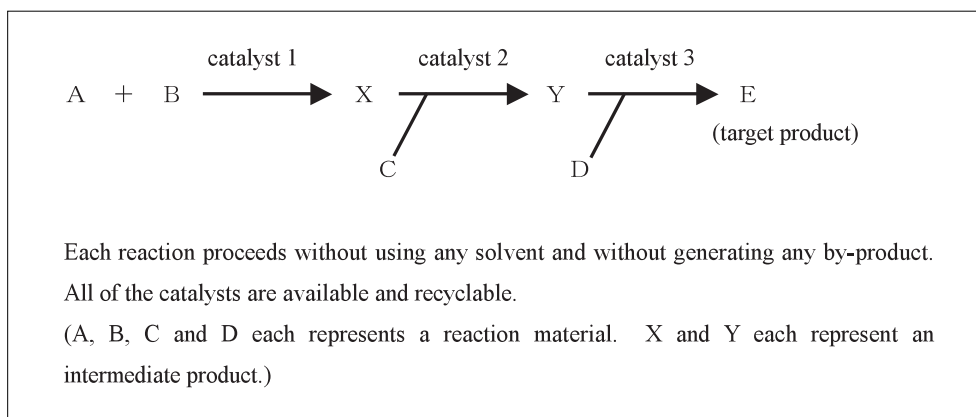
reaction is assumed to take many years before its realization, but once a catalyst that can capture carbon dioxide in the air is discovered, the research may progress radically.

2.3.3 Example of ideal organic synthesis chemical reaction

Generally, organic synthetic reaction requires hundreds or thousands of times as much organic solvents as the reaction product. To solve this problem, researchers are working on the development of organic synthetic reaction in water that requires no organic solvent. This research area is expected to grow more and more in the future. The ultimate goal is to carry out organic synthetic reactions in the absence of any solvent, and, therefore, researchers must contemplate on the development of such reaction systems.

One of the ideal forms of organic synthesis chemical reaction involves chemical syntheses of useful substances without emitting any by-

Figure 8: Example of the ideal form of organic synthesis chemistry reaction



Source: material prepared by Professor Masakatsu Shibasaki of the Graduate Course of Pharmacy, Graduate School of Tokyo University

product. In order to realize this, various catalysts must be available for promoting reactions without using any solvent (solvent-free) or generating any by-product (Figure 8).

For example, a solvent-free catalytic reaction is employed in a one-step reaction system for forming cyclohexane via the addition of hydrogen to hexane. However, it is difficult to apply the ideal synthesis method shown in Figure 8 to the synthesis of complex compounds that are formed via several steps. It will take many years before such methods become available.

2.4 Conclusion

2.4.1 Public interest in organic synthesis chemistry research

One of the important academic journals in the area of basic chemistry is the *Journal of the American Chemical Society (JACS)*. This journal published the first report on the total synthesis of Taxol.

Based on the JICST files (covering documents published since 1975), a database of documents in the area of science and technology, we have counted the number of papers written by the three 2001 Nobelists in Chemistry, Dr. Noyori, Dr. Sharpless and Dr. Knowles, published in *JACS*, *Science*, and *Nature* before May 13, 2002. *JACS* published 66 and 47 papers written by Dr. Noyori and Dr. Sharpless, respectively. On the other hand, *Science* published only five and two papers by Dr. Noyori and Dr. Sharpless, respectively, and *Nature* had no publications of the two Nobelists. Meanwhile, Dr. Knowles had four publications in *JACS* but none in *Science* or *Nature*. During this period, Dr. Knowles had only eight papers published in all the journals covered by the JICST files.

Furthermore, we calculated the proportions of papers in the areas of basic chemistry and organic chemistry (included in basic chemistry) published during the same period in *Science* and *Nature*. As a result, among a total of 17,159 papers published in *Science*, 910 (5.3%) were from the area of basic chemistry and merely 151 (0.9%) from organic chemistry. Meanwhile, among 20,197 papers published in *Nature*, 691 (3.4%) were from basic chemistry and merely 79 (0.4%) from organic

chemistry.

Since the Japanese media tend to cover mainly the works published in *Nature* and *Science*, the research results published in these two journals are easily propagated to the public. However, as mentioned above, organic synthesis chemistry is an area that does not appear very frequently in *Nature* or *Science*, so there is little chance for the research in this area to be covered by the media and attract public attention.

2.4.2 Expectations toward organic synthesis chemistry research

As mentioned earlier in the beginning of "Introduction," organic synthesis chemistry is an important research area in life science. Compounds that affect proteins or other molecules that function *in vivo* play extremely important roles in the post-genome research. For example, a compound acting specifically on a certain protein becomes a valuable reagent in biological science research. Moreover, most pharmaceuticals, which can be considered as compounds possessing many added values, can be synthesized through organic synthesis chemistry. Therefore, improving the capacity of organic synthesis chemistry in our country should contribute to the achievement of more outcomes from the post-genome research, as well as to the continuous release of novel chemical products from Japan to the world.

The current standard of organic synthesis chemistry has already reached a level enabling syntheses of compounds with complex structures. Needless to say, the development of a new, energy-saving reaction system inhibiting the generation of by-products is desirable from the viewpoint of Green Chemistry.

Consequently, one of the next goals in organic synthesis chemistry is to develop reaction systems for completing multi-step reactions in one step and to replace the existing reaction systems with low-cost systems. Since people may live in a closed system such as outer space in the future, we must also consider about such possibility on a long-term basis. Therefore, the establishment of solvent-free synthetic methods generating no by-product will become the long-range objective in this area.

Since the level of organic chemistry research in our country is one of the highest in the world, we must take the initiative in the research for achieving these goals.

References

- [1] Rensei Baba, The Century of Nobel Prize—History of Science and Nobel Prizes in Three Natural Science Areas, Chuko Shinsho, 2002 (in Japanese); Announcement of 2001 Nobelists in 3 Natural Science Areas—Dr. Ryoji Noyori, professor emeritus of the Graduate School of Nagoya University, wins the Nobel Prize in Chemistry, Kagaku Gijutsu Doukou (Science and Technology Trends) October 2001: 4-5 (in Japanese); Nobel Prize WebSite (<http://www.nobel.se/>).
- [2] Makoto Misono, Shunichi Murahashi edited, Green Chemistry, 2001 Kodansha Scientific (in Japanese).

Acknowledgments

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